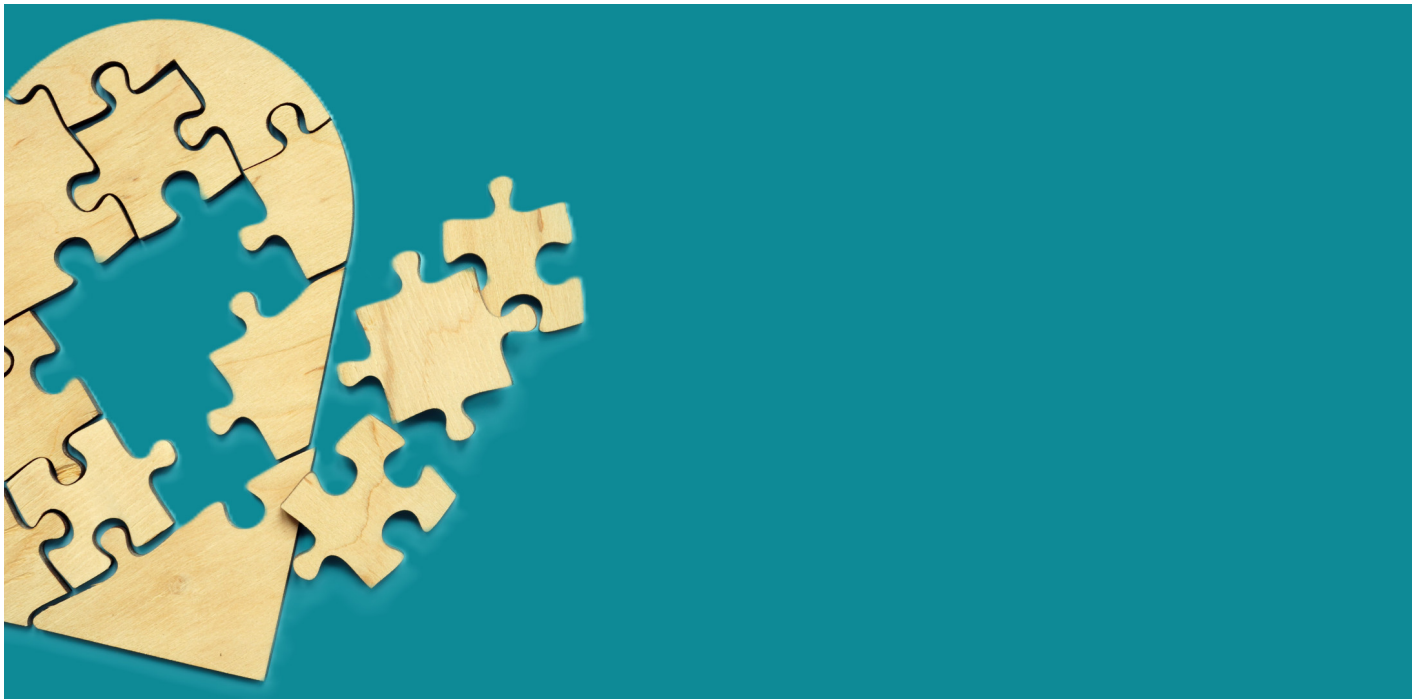




© Designer491 | Dreamstime.com

Treatment Update

Review on the Treatment of Heart Failure with preserved Ejection Fraction

Raffaele Zannoni^{a,b*}, Elia Rigamonti^{b*}, Maria Luisa De Perna^b, Giorgio Moschovitis^b

^a Department of Internal Medicine, Ente Ospedaliero Cantonale (EOC), Ospedale Regionale di Lugano, Switzerland

^b Department of Cardiology, Ente Ospedaliero Cantonale (EOC), Istituto Cardiocentro Ticino, Ospedale Regionale di Lugano, Switzerland

* shared first authorship

Definition and Epidemiology

According to the 2021 European Society of Cardiology (ESC) heart failure (HF) guidelines, heart failure with preserved ejection fraction (HFpEF) is defined as a clinical syndrome in which patients present with symptoms and/or signs of HF caused by structural and/or functional abnormality resulting in high left ventricular (LV) filling pressure at rest and/or exercise in presence of a left ventricular ejection fraction (LVEF) of $>50\%$ [1]. Importantly, there should not be a prior diagnosis of HF with mildly reduced, reduced (HFrEF), nor improved ejection frac-

tion [1, 2]. HFpEF is a heterogeneous clinical syndrome that includes multiple clinical phenotypes and is accompanied by numerous cardiovascular and non-cardiovascular comorbidities [1-3]. HFpEF has a rapidly increasing incidence and prevalence, accounts for about 50% of all new HF cases, has a significant impact on patient's quality of life (QoL) and is associated with a high risk for hospitalization and death. The mortality rate of HFpEF is comparable to that of HFrEF (fig. 1). It is of pivotal importance to implement strategies to adequately identify and manage patients with HFpEF because of its

severe socioeconomical and health burden [1, 2].

Diagnosis

A correct diagnosis is necessary for appropriate patient selection and treatment. We give an overview of the diagnostic process, highlighting some of its most challenging aspects.

Cardinal symptoms of HF include fatigue, breathlessness, exercise intolerance and fluid overload [1-3]. Unfortunately, there are many diseases that can cause similar symptoms (so called HFpEF mimickers), but re-

Abstract

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome that includes multiple clinical phenotypes and is accompanied by numerous cardiovascular and non-cardiovascular comorbidities. HFpEF is rapidly increasing in incidence and prevalence, accounting for approximately 50% of all new cases of heart failure. It has a significant impact on patients' quality of life and is associated with a high risk of hospitalization and death. The diagnosis of HFpEF is challenging, and many patients with HFpEF are likely to be unrecognized or misdiagnosed. So far, HFpEF management relies on patient education and treatment of comorbidities. However, the use of SGLT-2 inhibitors has recently demonstrated a significant reduction in the composite outcome of heart failure hospitalizations and cardiovascular mortality in HFpEF, and is now considered as the first-line therapy.

Keywords: Comorbidities; diagnostic challenge; heart failure with preserved ejection fraction; HFpEF phenotypes; multidisciplinary management; SGLT-2 inhibitors

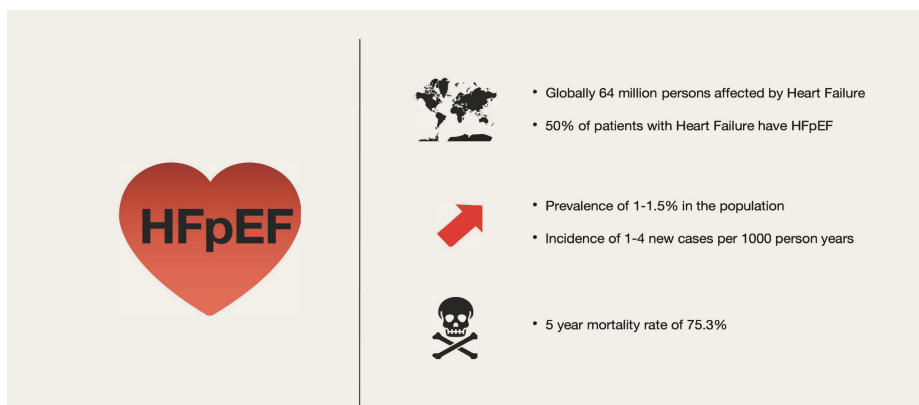


Figure 1: Epidemiology of heart failure with preserved ejection fraction (HFpEF). HFpEF prevalence and incidence are alarmingly rising over the last decades and it comes with a very high mortality [2, 4].

quire special investigations and specific therapies (fig. 2). Furthermore, the reliance on HF biomarkers such as brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-pro-BNP) can be misleading, as 30% of confirmed HFpEF patients have normal values. This applies especially to obese patients [1, 2, 4]. Also, some patients with HFpEF tend to be completely asymptomatic at rest and only experience symptoms or signs of HF during exercise, therefore limiting the echocardiographic detection value of elevated filling pressures if measured only at rest. Finally, it is important to remember that the gold standard for the diagnosis of HFpEF remains a right heart catheterization with confirmation of elevated pulmonary capillary wedge pressure (PCWP) at rest (>15 mm Hg), or during exercise (>25 mm Hg), and that this is usually only pursued when other diagnostic modalities have been inconclusive [1, 4]. For all these reasons, HF experts have recently proposed simple, non-invasive diagnostic algorithms to identify pa-

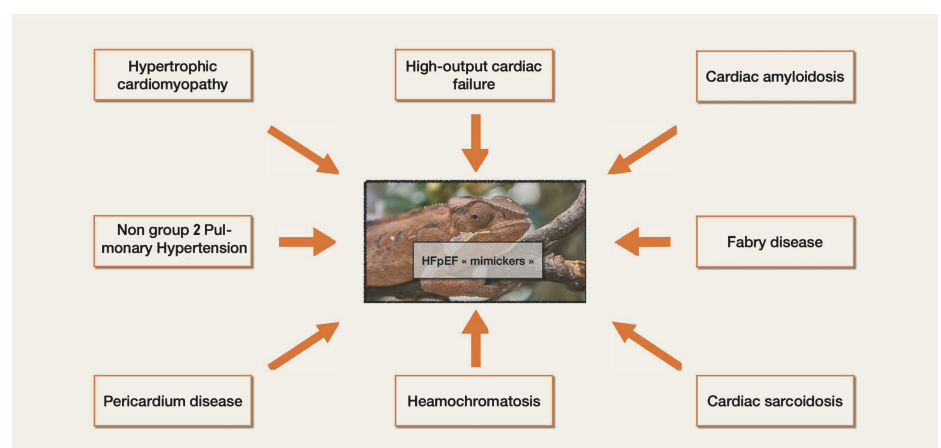


Figure 2: Differential diagnosis and principal “mimicker” pathologies of heart failure with preserved ejection fraction (HFpEF) [4].

tients with HFpEF: the H2FPEF score and the HFA-PEFF score [3-6].

The H2FPEF score is a clinically validated, diagnostic risk score for HFpEF built around six easily available clinical and echocardiographic variables creating a composite score ranging from 0 to 9. Each point

doubles the odds for HFpEF diagnostic probability, allowing an effective discrimination between patients with HFpEF and a comparator population of patients with exertional dyspnea not caused by HF [5].

The HFA-PEFF score works as a diagnostic pathway evaluating breathless patients for their symptoms, comorbidities, baseline laboratory tests (BNP, NT-pro-BNP) and echocardiography to help determine the probability of HFpEF. Patients with intermediate suspicion may proceed to advanced diagnostic modalities (stress echocardiography, invasive hemodynamic testing), while those with low or high diagnostic probability can be excluded or included for HFpEF diagnosis right away [6].

The Role of Comorbidities

HFpEF is a multifactorial disease associated with a large number of cardiovascular and non-cardiovascular comorbidities. The main comorbidities are obesity (up to 80% of HFpEF patients are obese or overweight), arterial hypertension (55-90%), atrial fibrillation (AF, 40%), coronary artery disease (66%), diabetes mellitus (DM, 40%), chronic kidney disease (22-59%), chronic obstructive pulmonary disease (33%), and anemia (50%) [1, 7, 8].

The role of these comorbidities in the HFpEF pathophysiology is a complex one (fig. 3). They participate actively in the pathogenesis of HFpEF by creating a chronic inflammatory state leading to mitochondrial, endothelial and myocyte dysfunction [9]. Chronic inflammation, indicated by elevated levels of circulating cytokines and adipokines, can lead to increased oxidative stress, disorganized intracellular (e.g., impaired autophagy pathways, titin hyperphosphorylation) and nitric oxide pathways, ultimately causing microvascular dysfunction, myocardial fibrosis and cardiac stiffness [9]. These mechanisms contribute to increasing LV filling pressures and an inefficient global cardiac function, suggesting that HFpEF may actually be a metabolic disease.

To illustrate the importance of comorbidities in HFpEF, some authors have identified a subset of comorbidity-driven HFpEF phenotypes, proposing a phenotype-based classification of HFpEF [2]. The most common and most accepted phenotype is the cardiometabolic-obesity HFpEF phenotype. This phenogroup is characterized by a high burden of comorbidities and heavy cardiac remodeling in patients presenting with obesity or overweight. Other phenotypes include atrial myopathy, hypertension, cardio-renal and autoimmune-inflammatory HFpEF [2, 10]. While it is important to clarify that even though an optimal elucidation and classification of HFpEF phenotypes hasn't been

reached yet, the classification into phenotypes may be a very important step towards appropriate detection, selection, and management of HFpEF patients, although it is not certain whether this classification is related to better treatment outcomes. We think that, at the moment, phenotype classification can be seen as an important starting point towards a better understanding of the disease.

Interestingly, HFpEF is associated with a higher burden of non-cardiovascular comorbidities than HFrEF [4]. This is reflected by the fact that patients with HFpEF are more frequently admitted to the hospital for non-cardiovascular reasons than patients with HFrEF. In addition, the HFpEF mortality appears to be heavily influenced by non-cardiovascular reasons in comparison to HFrEF [2, 4], highlighting the relevance of comorbidities on the overall health burden of HFpEF patients. Indeed, HFpEF treatment is characterized by a more heterogeneous response to medical therapy in comparison to the treatment of HFrEF, further underlining the idea that managing comorbidities should constitute an important therapeutic strategy in HFpEF treatment. In fact, an aggressive control of comorbidities could lead to a risk reduction for developing and/or worsening of HFpEF [11, 12].

Non-pharmacological Treatment

The first pillar in the management of HF patients, regardless of LVEF, is lifestyle management. Patients with HF (including those with HFpEF), are advised to be an integral part in the management of their disease. Patients are encouraged to implement self-education and self-care behaviors, implying that they are educated on their disease and the medications that they should take, as well as their correct administration, followed by a multidisciplinary treating team. Patients are encouraged to decrease their sodium intake to less than 5 g salt per day, to avoid excessive fluid intake, alcohol consumption and smoking, and learn to recognize the signs and symptoms of worsening HF and how to act accordingly. These self-care behaviors (class IA indication in European guidelines [1], class IA to IB-R in American guidelines [8]) have been associated with a reduction of HF hospitalizations (HFH), all-cause mortality, as well as improvement in QoL.

Another important aspect in self-care management is exercise training and dieting. This is extremely important, as many HFpEF patients are overweight or obese and suffer

from reduced exercise capacity, demonstrated by a substantial reduction in their exercise peak VO₂ capacity during cardiopulmonary exercise testing and maximal functional capacity expressed by metabolic equivalents of task. Exercise intolerance often manifests itself during normal low-intensity daily activities, dramatically decreasing the QoL [1, 2, 8]. From a pathophysiological point of view, exercise intolerance is thought to derive from impaired transport and utilization of oxygen caused by mitochondrial, microvascular and myocardial alterations, all of which are in turn sustained by the patient's many comorbidities. Strategies to tackle this issue revolve around aerobic exercise training and weight loss by caloric restriction dieting, as shown by Kitzman and colleagues who have demonstrated benefits in exercise capacity and in QoL measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) [13]. El Hajj and colleagues could demonstrate that an intensive lifestyle modification program (15-week management program with dieting and exercise prescription) led to significant weight loss in obese HFpEF patients (74% lost >5% of their baseline body weight), improving many metabolic parameters (e.g., glycated hemoglobin, hypercholesterolemia) [11]. Moreover, dieting and exercise protocols may even be associated with a reduction in diuretic therapy doses, antihypertensive agents and diabetes medications. Hummel and colleagues have demonstrated that the adoption of a hypocaloric and salt restricted diet (DASH diet) could improve the diastolic dysfunction in hypertensive HFpEF patients, with a reduction in arterial elastance and improvement of cardiac contractility and ventricular-arterial coupling (based on more efficient energy transfer between heart and arteries) [12]. These improvements are likely associated with the reduction of excess adiposity leading to a reduction in inflammation and its associated metabolic derangements. Also, cardiovascular rehabilitation programs after acute HF decompensation have shown to increase physical capacity, favoring a quicker return to normal life [1, 8]. Although cardiac rehabilitation has predominantly been studied in the HFrEF population, it has been showed that it also improves QoL in HFpEF patients, since it represents an outstanding opportunity for patients to develop awareness and empowerment about their disease in a controlled and educational program, and for the treating team to implement and/or uptitrate the disease-modifying therapy. This is the reason why some authors consider car-

diac rehabilitation the fifth pillar in HF treatment [14].

Finally, patients with HFpEF are strongly encouraged to be vaccinated against viral and bacterial respiratory pathogens, in particular *Streptococcus pneumoniae*, Influenza and COVID-19, for specifically the Influenza vaccination is associated with a reduction of all-cause mortality [1, 8].

Pharmacological Treatment

As stated by the recently uploaded 2023 ESC Focused Update of the ESC 2021 HF guidelines, the only pharmacological agent that significantly decreases both HFH and cardiovascular mortality in HFpEF patients are sodium-glucose linked transporter 2 inhibitors (SGLT2i), now with a new class IA indication [15]. Diuretics are recommended for individuals with fluid retention and HF symptoms (NYHA II-IV) with a class IC indication. Other drugs that may be considered are mineralocorticoid receptor antagonists (MRA) and angiotensin receptor-neprilysin inhibitors (ARNi) to decrease HFH in male patients with LVEF on the lower end of the “normal” LVEF range and in women, who appear to benefit across all range of LVEF, as well as angiotensin II receptor blockers

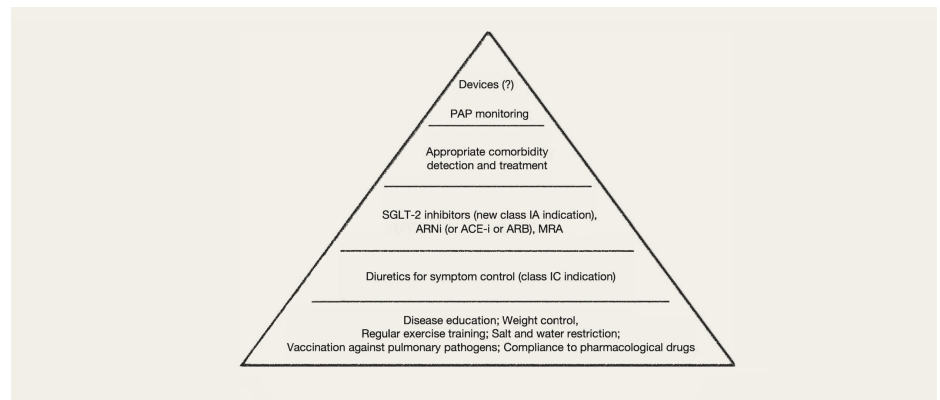


Figure 5: Management hierarchy of heart failure with preserved ejection fraction (HFpEF). From bottom to top, it is of pivotal importance to implement appropriate lifestyle measures to maintain good cardiovascular health and to reduce the burden of comorbidities [15, 16].

ACE-i: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor blocker; ARNi: Angiotensin receptor-neprilysin inhibitor; MRA: Mineralocorticoid receptor antagonist; PAP: Pulmonary artery pressure; SGLT-2: Sodium-glucose linked transporter 2.

(ARB) for patients who can't take ARNi (costs, intolerance) (fig. 4 and 5) [8, 16].

Diuretics for Volume Overload

Diuretic therapy remains the cornerstone for decongestion in patients with volume overload [1, 8, 15]. Usually, first-line therapy includes loop diuretics (e.g., furosemide,

torasemide, bumetanide) whereby type and dosing depend on the severity of congestion [1, 4]. Torasemide has a longer elimination half-life (6 vs. 2.7 h) and higher bioavailability than furosemide, but a recent open-label pragmatic trial (TRANSFORM-HF tri-

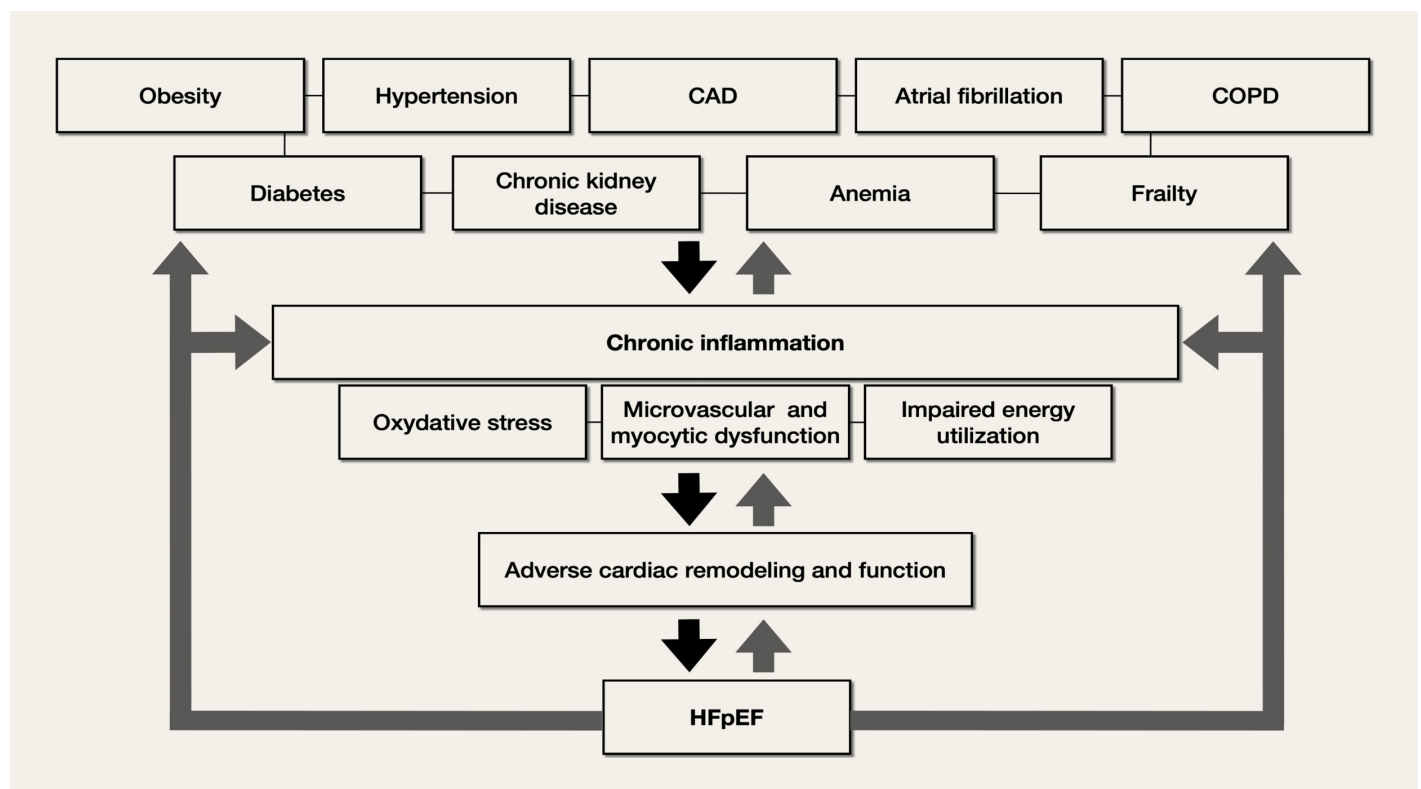


Figure 3: Pathogenesis hypothesis of heart failure with preserved ejection fraction (HFpEF). Many comorbidities provoke a proinflammatory state leading to sustained oxidative stress, microvascular dysfunction and impaired energy utilization through the disruption of intracellular energetic pathways, and ultimately to adverse cardiac remodeling with development of cardiac stiffness, impaired relaxation, and hypertrophy [9].

CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease.

al) comparing torasemide with furosemide in the management of HF, has shown no significant differences in rates of HFH after twelve months, regardless of baseline LVEF [17]. Carbonic anhydrase inhibitors (e.g., acetazolamide) represent a further therapeutic option to achieve optimal decongestion by reducing proximal tubular sodium reabsorption in addition to standard care. Indeed, the ADVOR study demonstrated that the introduction of acetazolamide on top of intravenous loop diuretics in patients hospitalized for acute HF resulted in a greater success in decongestion across the whole spectrum of LVEF [18].

Sodium-Glucose Linked Transporter 2 Inhibitors

Three recent randomized controlled trials highlighted the importance of SGLT2i in HF as they are nowadays considered a first-line therapy [15-21]. In the SOLOIST-HF trial, recently hospitalized patients with DM type 2 and either HFpEF or HFrEF were randomly assigned to sotagliflozin or placebo [19]. At 7.7 months follow-up, the primary endpoint of cardiovascular death and worsening of HF (defined as hospitalization or any urgent visit for HF) was lower in the sotagliflozin group (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.52-0.85). In the EMPEROR-preserved trial, recruiting 5988 patients with LVEF >40% and NYHA II-IV HF symptoms, the SGLT2i empagliflozin showed a benefit on the composite outcome of cardiovascular death, primarily driven by a reduction in HFH [20]. The following DELIVER

trial, studying 6263 patients with HF and LVEF >40% over a median follow-up of 2.3 years, showed that dapagliflozin reduced the combined primary clinical endpoint of worsening HF or cardiovascular death (HR 0.82, 95% CI 0.73-0.92), with a similar incidence of adverse events [21]. Indeed, the 2023 Focused Update of the ESC 2021 HF guidelines gives a class I indication and A level of evidence for SGLT2i in HFpEF to reduce HFH and cardiovascular death [15].

SGLT2i are formally contraindicated in patients with type 1 DM, a history of ketoacidosis or an estimated glomerular filtration rate <20 ml/min/m². Although it is not formally contraindicated, we also avoid SGLT2i in patients with recurrent genitourinary infections. The mechanisms behind the cardiac protection of SGLT2i, which were initially developed as oral antidiabetic drugs inhibiting glucose reabsorption in the renal proximal tubules, are not fully clarified yet. Proposed hypotheses include increased natriuresis, cross-action with the sodium-hydrogen exchanger, reduction in blood pressure without a compensatory sympathetic stimulation and thus without increase in heart rate, reduction in arterial stiffness and vascular resistance favoring better ventricular-arterial coupling, and metabolic effects such as loss of body weight, fat mass and lowering of serum uric acid levels. Moreover, SGLT2i promote lipolysis and ketogenesis thereby causing a reduction in epicardial fat, adipocy-

tokine-mediated inflammation and oxidative stress, cause a shift towards preferential fat oxidation (over glucose) in the cardiac muscle, and seem to attenuate atherosclerosis progression and adverse cardiac remodeling with a reduction of the left atrial and ventricular end diastolic and end systolic volume indexes [22].

Mineralocorticoid Receptor Antagonists

Drugs targeting the renin-angiotensin-aldosterone-system (RAAS) are a mainstay of the neurohormonal drug therapy for HFrEF by inhibiting the development of myocardial hypertrophy and fibrosis promoted by aldosterone. RAAS blocking agents (e.g., spironolactone) were evaluated in the TOPCAT trial and did not reduce the composite primary outcome of cardiovascular-related death, aborted cardiac arrest and HFH in patients with symptomatic HFpEF (defined as LVEF ≥45%) [23]. Nevertheless, a reduction in HF readmissions was observed. Moreover, a post hoc analysis restricted to patients enrolled in North and South America revealed a significant reduction in the primary combined endpoint among patients according to the elevated natriuretic peptide levels with big regional variations. In fact, event rates were dramatically lower in participants who were younger, with lower rates of AF and DM and lower levels of NT-proBNP, that were enrolled in Russia and Georgia with respect to

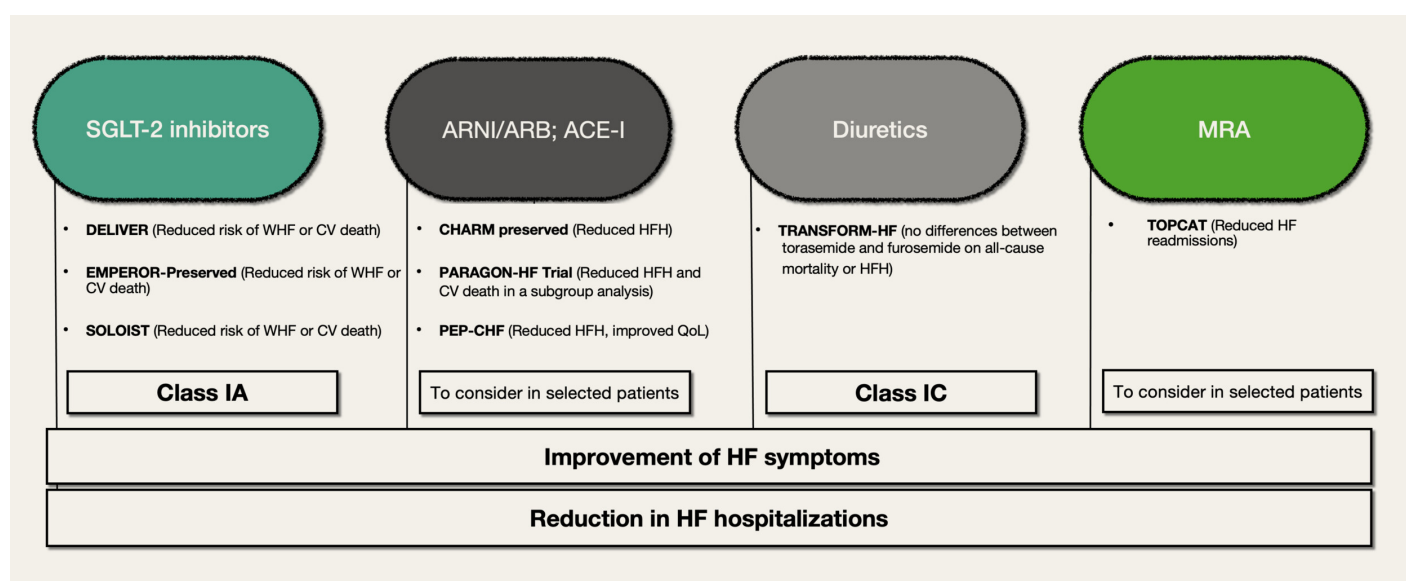


Figure 4: Pharmacological treatment of heart failure with preserved ejection fraction (HFpEF). According to the 2023 ESC Focused Update [15], sodium-glucose linked transporter 2 (SGLT-2) inhibitors have a class IA indication for HFpEF therapy and diuretics a class IC for decongestion. Angiotensin receptor-neprilysin inhibitors (ARNI), angiotensin II receptor blockers (ARB), angiotensin-converting-enzyme inhibitors (ACE-I) and mineralocorticoid receptor antagonists (MRA) can be considered in selected patients [16].

CV: Cardiovascular; HF: Heart failure; HFH: Heart failure hospitalizations; QoL: Quality of life; WHF: Worsening of heart failure.

American patients. This observation does underscore how challenging it may be to make the right diagnosis and appropriate patient inclusion or selection. It should be noted that adverse effects, such as renal failure and hyperkalemia, are common with MRAs (spironolactone, eplerenone) and demand a regular biochemical follow-up [8, 23]. More recent studies, such as the ongoing FIN-EARTS-HF trial (NCT04435626), want to further elucidate the role of the new non-steroidal MRAs (e.g., finerenone) in the treatment of HFpEF.

Angiotensin II Receptor Blockers and Angiotensin Receptor-Nephrilysin Inhibitors

Sacubitril/valsartan combines the inhibitory action on the RAAS with the blockade of neprilysin, the primary enzyme that degrades the BNP. In the PARAGON trial, Solomon, McMurray and colleagues could demonstrate that for the 4822 enrolled patients with HFpEF, sacubitril/valsartan did not significantly reduce the combined endpoint of cardiovascular death and HFH at the median follow-up of 35 months [24]. Nevertheless, subgroup analyses suggested heterogeneity in the treatment effect with a potential benefit for women (HR 0.73, 95% CI 0.59-0.90) and in patients with a LVEF between 45 and 57% (HR 0.78, 95% CI 0.64-0.95). These findings granted an extended indication for ARNIs from the Food and Drugs Administration in the treatment of chronic HF to reduce HFH and cardiovascular death [8, 16].

Specifically regarding ARBs, the CHARM-PRESERVED trial evaluated the response of 3023 patients with HF and LVEF $\geq$ 40% to add-on therapy with candesartan compared to placebo, showing no significant differences in regards to mortality, however a trend towards less HFH in the candesartan arm [25]. In the similar PEP-CHF trial, which recruited 850 HFpEF patients with a mean age of 76 years, comparing perindopril to placebo, patients treated with perindopril had fewer HFH and improved NYHA functional class [26]. However, the positive effect was lost over the complete follow-up of 2.1 years. Overall, 107 patients assigned to placebo and 100 patients assigned to perindopril group reached the primary endpoint (HR 0.919, 95% CI 0.700-1.208, $p=0.545$). At one-year follow-up, reductions in the primary outcome (HR 0.692, 95% CI 0.474-1.010, $p=0.055$) and HFH (HR 0.628, 95% CI 0.408-0.966, $p=0.033$) were observed and both, NYHA functional class ($p<0.030$) and 6-min corridor

walk distance ($p=0.011$) improved in the perindopril group. Uncertainty remains about the effects of perindopril on long-term morbidity and mortality in HFpEF since this study had insufficient power for its primary endpoint. However, improved symptoms, exercise capacity and fewer HFH in the first follow-up year were observed.

Other Therapies

The use of beta blockers is controversial. The meta-analysis of Cleland et al found no evidence of benefit in the subgroup of patients with HFpEF and sinus rhythm nor a consistent benefit in patients with AF and there was no reduction of all-cause mortality and cardiovascular death [27]. It is suggested to use beta blockers not primarily to treat HFpEF, but rather coronary syndromes or for heart rate control in cases of concomitant AF [8].

As discussed before, nitric oxide production pathways are deranged in HFpEF [9] and there were efforts to try and compensate for these metabolic abnormalities, but unfortunately, trials of agents targeting nitric oxide signaling (e.g., nitrates, sildenafil, guanylate cyclase stimulators) did not improve endpoints (HFH and mortality) nor the QoL (exercise capacity or symptoms) and therefore their use is not endorsed by the guidelines [1, 8].

Iron deficiency (with or without anemia) is a prevalent and important non-cardiac comorbidity of HFpEF contributing to exercise intolerance and reduced QoL [1, 2, 7-9]. Its management might be important to alleviate HF symptoms. To this day, most trials focus on iron deficiency in the HFrEF population and there are no clear guidelines regarding the treatment of iron deficiency in HFpEF patients, even though it is recognized that a screening for iron deficiency should be carried out in all patients with chronic HF regardless of LVEF [1, 8, 15]. Interesting clinical trials are ongoing to investigate the role of iron supplementation (specifically with ferric carboxymaltose) in the HFpEF population, namely the FAIR-HFpEF study (NCT03074591), the IRONMET-HFpEF (NCT04945707) and the PREFER-HF (NCT03833336), whose results are awaited with great anticipation.

Regarding the tight link between HFpEF and obesity, interesting treatment opportunities for weight loss with glucagon-like peptide-1 (GLP1) analogues (e.g., semaglutide) have been explored in the (very) obese HFpEF population in STEP-HFpEF trial, demonstrating that a weekly semaglutide in-

jection proved to be more effective than placebo for weight loss (13.3% vs 2.6%) after a 57 week period, as well as more effective in the improvement of QoL reflected by the KCCQ-CSS and 6-min walk test [28]. There was also a trend towards reduced HFH, but the trial was not adequately powered for conclusions on this outcome. Regarding the general principles of hyperlipidemia, the standard guidelines also apply to the HFpEF population.

Devices

Implantable hemodynamic monitoring, such as pulmonary artery pressure (PAP) monitoring, may be an effective strategy option to reduce HFH as demonstrated by the CHAMPI-ON trial, in which PAP-guided therapy lead to a decrease in recurrent HFH in selected NYHA II-IV symptomatic patients with prior multiple HFH despite optimal standard medical therapy [29]. Recently, the MONITOR-HF trial, recruiting 348 patients with a mean age of 69 years randomly assigned to hemodynamic monitoring through the CardioMEMSTM-HF system (Abbott, Abbott Park, North Chicago, US) or standard care, has shown a difference in the primary endpoint of KCCQ overall summary score at twelve months of 7.13 points (95% CI 1.51-12.75, $p=0.013$) between the groups [30].

It has been postulated that the placement of an interatrial shunt device may reduce left atrial pressure at rest and during exercise. However, in the REDUCE LAP-HF II trial, including 626 patients with HFpEF and a PCWP $\geq$ 25 mm Hg during exercise, the placement of the device did not lead to a significant decrease in mortality, HFH or change in QoL scores and was associated with higher risk of safety events [31].

Other devices, such as the CORolla[®] (CorAssist Cardiovascular Ltd, Haifa, Israel) [32], which is positioned in the left ventricle for applying an outward radial force on the LV endocardium, thus transferring energy from systole to diastole, or the mechanical unloading of the left atrium by PulseVADTM (Northern Research, Oslo, Norway) [33], are confined to initial animal tests.

Transitional and Follow-up Care

Follow-up care is considered as a particularly vulnerable phase. Two recent trials have highlighted the importance of implementing an earlier and more intensive follow-up after

acute HF. A hospital stay represents an opportunity for optimizing guideline-directed medical therapy (GDMT) in a safe environment, but current practices are disappointing. In STRONG-HF, which included 1078 patients hospitalized for acute HF (68% HFrEF), the high-intensity optimization approach led to 34% relative risk reduction in 180-day risk of HF readmissions or all-cause death [34]. All patients included in the high-intensity arm were discharged with at least half of the optimal doses according to GDMT, to reach the full dose within the next four weeks, if well tolerated. Of note, even patients with LVEF >40% benefited from optimization and rapid uptitration of medical therapy with a reduction in 180-day re-hospitalization or all cause death. The COACH trial, including nearly 2000 HFpEF patients, found that the incidence of any-cause death or hospitalization for cardiovascular causes was significantly reduced by using a validated risk score to guide clinical decision making about hospital admission coupled with rapid follow-up in a specialized HF clinic [35].

ESC HF guidelines as well as the American College of Cardiology expert consensus on decision pathways in HFpEF management strongly emphasize the importance of close and regular clinical follow-up as well as early initiation and rapid uptitration of HF GDMT [1, 8, 15, 16].

Conclusions

HFpEF is a heterogeneous multiple organ disease with an increasing prevalence and high mortality that represents a real diagnostic and therapeutic challenge. In the last decades, many advances have been brought to the field of HFpEF mainly illustrated by the increasing efforts to better recognize and characterize the disease through new diagnostic tools and phenotype classifications. Regarding the non-pharmacological treatment for HFpEF, emphasis is put on the management of comorbidities and patient education (fig. 5). For the pharmacological treatment, the classical HFrEF disease-modifying drugs have failed to show significant benefits in HFpEF patients regarding hard endpoints such as survival, likely due to the disease's heterogeneity. Nonetheless, based on recent trials which consistently confirmed a reduction of HFH or mortality in HFpEF patients through the use of SGLT2i, the ESC has endorsed their use as first-line therapy in HFpEF with a class IA indication. Regarding device therapy, PAP monitoring may be

a valid tool for reduction of morbidity but not mortality. Nevertheless, HFpEF remains a challenging disease and deserves a patient-centered multidisciplinary approach.

Correspondence

Dr. med. Giorgio Moschovitis
EOC, Cardiocentro Ticino Institute
Via Tesserete 48
CH-6900 Lugano
[giorgio.moschovitis\[at\]eoc.ch](mailto:giorgio.moschovitis[at]eoc.ch)

Conflict of Interest Statement

RZ, ER and MLDP have no potential conflicts of interest to declare.

GM received advisory board and speaker's fees from Astra Zeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Gebro Pharma, Novartis and Vifor, all outside of the submitted work.

Author Contributions

RZ, ER, MLDP, and GM were responsible for the manuscript conception (data and article gathering for the review, article structure and content), and writing. RZ is responsible for the making and adaptation of the article figures. All authors edited, reviewed and approved the final version of the report. GM is the recipient of the original invitation to write the article in Cardiovascular Medicine.

References

- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021 Sep;42(36):3599-726. Erratum in: *Eur Heart J*. 2021 Oct.
- Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. *J Am Coll Cardiol*. 2023 May;81(18):1810-34.
- Reddy YN, Kaye DM, Handoko ML, van de Bovenkamp AA, Tedford RJ, Keck C, et al. Diagnosis of Heart Failure With Preserved Ejection Fraction Among Patients With Unexplained Dyspnea. *JAMA Cardiol*. 2022 Sep;7(9):891-9.
- Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA*. 2023 Mar;329(10):827-38.
- Reddy YN, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation*. 2018 Aug;138(9):861-70.
- Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019 Oct;40(40):3297-317. Erratum in: *Eur Heart J*. 2021 Mar;42(13):1274.
- Teramoto K, Teng TK, Chandramouli C, Tromp J, Sakata Y, Lam CS. Epidemiology and Clinical Features of Heart Failure with Preserved Ejection Fraction. *Card Fail Rev*. 2022 Aug;8:e27.
- Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al.; Writing Committee Members; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *J Card Fail*. 2022 May;28(5):e1-167.
- Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013 Jul;62(4):263-71.
- Schiattarella GG, Alcaide P, Condorelli G, Gillette TG, Heymans S, Jones EA, et al. Immunometabolic Mechanisms of Heart Failure with Preserved Ejection Fraction. *Nat Cardiovasc Res*. 2022 Mar;1(3):211-22.
- El Hajj EC, El Hajj MC, Sykes B, Lamicq M, Zile MR, Malcolm R, et al. Pragmatic Weight Management Program for Patients With Obesity and Heart Failure With Preserved Ejection Fraction. *J Am Heart Assoc*. 2021 Nov;10(21):e022930.
- Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E,

- Zhu S, et al. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. *Circ Heart Fail*. 2013 Nov;6(6):1165-71.
- Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA*. 2016 Jan;315(1):36-46.
- Taylor RS, Dalal HM, Zwisler AD. Cardiac rehabilitation for heart failure: 'Cinderella' or evidence-based pillar of care? *Eur Heart J*. 2023 May;44(17):1511-8.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published online ahead of print 2023 Aug 25]. *Eur Heart J*. 2023 Oct;44(37):3627-39.
- Kittleson MM, Panjath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023 May;81(18):1835-78.
- Mentz RJ, Anstrom KJ, Eisenstein EL, Sapp S, Greene SJ, Morgan S, et al.; TRANSFORM-HF Investigators. Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized with Heart Failure: The TRANSFORM-HF Randomized Clinical Trial. *JAMA*. 2023 Jan;329(3):214-22.
- Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al.; ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*. 2022 Sep;387(13):1185-95.
- Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al.; SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021 Jan;384(2):117-128.
- Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021 Oct;385(16):1451-61.
- Solomon SD, McMurray JJ, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al.; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022 Sep;387(12):1089-98.
- Maeder MT, Rickli H, Brenner R, Scheler E, Buser M. Therapie der Herzinsuffizienz mit reduzierter Auswurfraction: Was ist neu in den Leitlinien 2021? [Therapy of Heart Failure with Reduced Ejection Fraction: What's New in the 2021 Guidelines]. *Praxis*. 2022;111(8):445-56.
- Pfeiffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015 Jan;131(1):34-42.
- Solomon SD, McMurray JJ, Anand IS, Ge J, Lam CS, Maggioni AP, et al.; PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019 Oct;381(17):1609-20.
- Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003 Sep;362(9386):777-81.
- Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure study. *Eur Heart J*. 2006 Oct;27(19):2338-45.
- Cleland JG, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJ, et al.; Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018 Jan;39(1):26-35.
- Kosiborod MN, Abildström SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al.; STEP-HFpEF Trial Committees

- and Investigators. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023 Sep;389(12):1069-84.
- 29 Abraham WT, Adamson PB, Bourge RC, Aaron MF, Constanzo MR, Stevenson LW, et al. CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011 Feb;377(9766):658-66. Erratum in: *Lancet*. 2012 Feb;379(9814):412.
- 30 Brugts JJ, Radhoe SP, Clephas PR, Aydin D, van Gent MW, Szymanski MK, et al.; MONITOR-HF investigators. Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): a randomised clinical trial. *Lancet*. 2023 Jun;401(10394):2113-2123. Erratum in: *Lancet*. 2023 Jun;401(10394):2112.
- 31 Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, et al.; REDUCE LAP-HF II investigators. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet*. 2022 Mar;399(10330):1130-40.
- 32 Feld Y, Reisner Y, Meyer-Brodnitz G, Hoefler R. The CORolla device for energy transfer from systole to diastole: a novel treatment for heart failure with preserved ejection fraction. *Heart Fail Rev*. 2023 Mar;28(2):307-14.
- 33 Gude E, Fiene AE. Can mechanical circulatory support be an effective treatment for HFpEF patients? *Heart Fail Rev*. 2023 Mar;28(2):297-305.
- 34 Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised trial. *Lancet*. 2022 Dec;400(10367):1938-52.
- 35 Lee DS, Straus SE, Farkouh ME, Austin PC, Taljaard M, Chong A, et al.; COACH Trial Investigators. Trial of an intervention to improve acute heart failure outcomes. *N Engl J Med*. 2023 Jan;388(1):22-32.