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REVIEW

Heart failure with preserved ejection fraction: current management and future strategies

Expert opinion on the behalf of the Nucleus of the "Heart Failure Working Group" of the German Society of Cardiology (DKG)

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Abstract About 50% of all patients suffering from heart failure (HF) exhibit a reduced ejection fraction (EF ≤ 40%), termed HFrEF. The others may be classified into HF with midrange EF (HFmrEF 40–50%) or preserved ejection fraction (HFpEF, EF ≥ 50%). Presentation and pathophysiology of HFpEF is heterogeneous and its management remains a challenge since evidence of therapeutic benefits on outcome is scarce. Up to now, there are no therapies improving survival in patients with HFpEF. Thus, the treatment targets symptom relief, quality of life and reduction of cardiac decompensations by controlling fluid retention and managing risk factors and comorbidities. As such, renin–angiotensin–aldosterone inhibitors, diuretics, calcium channel blockers (CBB) and beta-blockers, diet and exercise recommendations are still important in HFpEF, although these interventions are not proven to reduce mortality in large randomized controlled trials. Recently, numerous new treatment targets have been identified, which are further investigated in studies using, e.g. soluble guanylate cyclase stimulators, inorganic nitrates, the angiotensin receptor neprilysin inhibitor LCZ 696, and SGLT2 inhibitors. In addition, several devices such as the CardioMEMS, interatrial septal devices (IASD), cardiac contractility modulation (CCM), renal denervation, and baroreflex activation therapy (BAT) were investigated in different forms of HFpEF populations and some of them have the potency to offer new hopes for patients suffering from HFpEF. On the basic research field side, lot of new disease-modifying strategies are under development including anti-inflammatory drugs, mitochondrial-targeted antioxidants, new anti-fibrotic and microRNA-guided interventions are under investigation and showed already promising results. This review addresses available data of current best clinical practice and management approaches based on expert experiences and summarizes novel approaches towards HFpEF.

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Introduction

In the US, with 5.7 million adults suffering from heart failure (HF) in 2012 [1], total annual costs for HF-related therapy were estimated amounting to 60 billion dollars [2]. About a half of patients exhibit a reduced ejection fraction (i.e. EF < 40%; the so-called HFrEF), whereas the other half experiences symptoms of heart failure despite a preserved EF (i.e. EF ≥ 50%, the so-called HFpEF). For Europe, an estimated prevalence of 1% of HFpEF in the general population accounts for 3–4 millions of affected patients. In these patients, symptoms primarily originate from impaired filling of the left ventricle (LV). However, as some patients exhibit concomitant systolic impairment, an isolated diastolic dysfunction does not sufficiently characterize this syndrome. Isolated LV diastolic dysfunction is rare and most likely not the only problem, and can include over the time left atrial enlargement and dysfunction, pulmonary hypertension as well as right ventricular impairment. According to European recommendations, the following triad establishes the presence of HFpEF: (1) clinical symptoms of heart failure; (2) EF ≥ 50%; (3) diastolic dysfunction [3]. However, application of this "simple definition" both in clinical research and practice remains difficult [4]. We thus need more appropriate criteria to identify those patients, e.g. including information on stroke volume and its change during exercise [5] or abnormal echocardiographic strain values [6]. An important aspect in the management of patients with suspected HFpEF is the identification of common treatable aetiologies including risk factors, comorbidities and specific cardiomyopathies (Fig. 1).

HFpEF predominantly concerns older patients whose left ventricular diameter is small. However, numerous other cardiac (e.g. disturbed chronotropy, impaired ventricular coupling, and right ventricular impairment) and non-cardiac abnormalities (pulmonary, renal and metabolic comorbidities) may contribute to this syndrome, which is very heterogeneous with regard to its aetiology and phenotypes. Despite a "normal" EF, patients with HFpEF exhibit an impaired prognosis [7–9]. There are differences between the epidemiology and the aetiology of HFpEF and HFrEF. Patients with HFpEF are older, more often female, show less myocardial ischemic events, but display risk factors such as obesity, hypertension and diabetes mellitus [7–10]. Although there is hardly any difference between mortality and hospitalisation rates of HFpEF and HFrEF, both types of heart failure differ regarding to treatment response to neuroendocrine antagonists. While there is solid evidence on the prognostic effects of treatment with renin–angiotensin–aldosterone system (RAAS) blockers and beta-blockers in HFrEF, no such effects were yet demonstrated for these substance classes in patients with HFpEF. The reasons may lie in the incomplete understanding of its pathophysiology, and different definitions

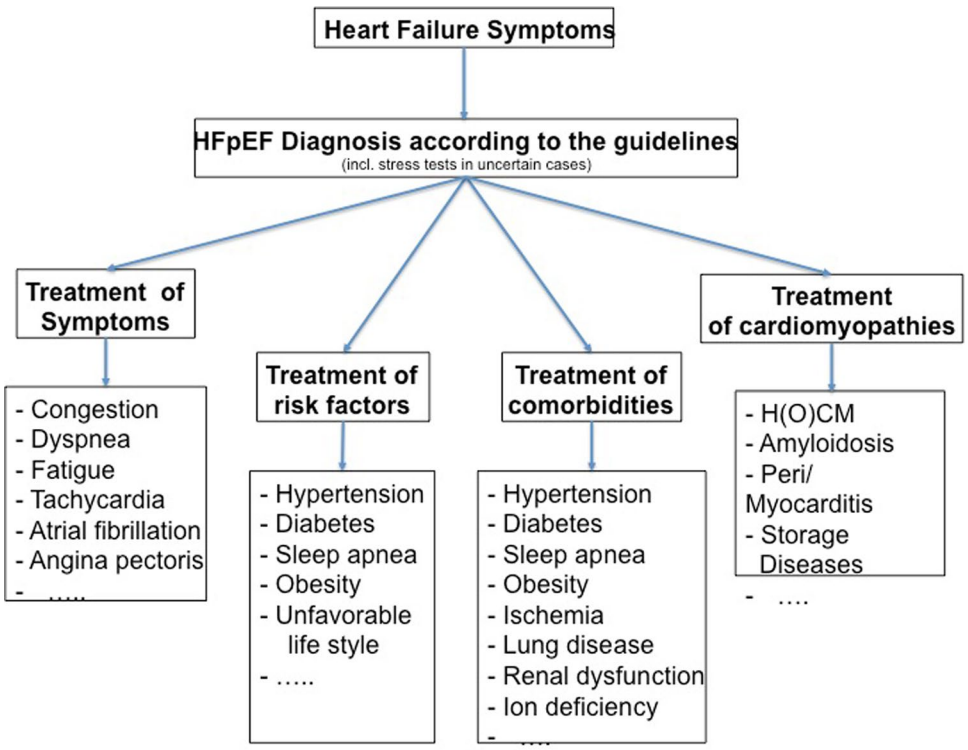

Fig. 1 Diagnostic and treatment targets of HFpEF

and classifications. The latest recommendation in this respect is to define HFpEF not as a solely cardiac disease, but as a systemic heterogeneous syndrome.

While there have been no breakthrough clinical trials showing a reduction in mortality, it is still important to develop management strategies for these patients to reduce risk factors, cardiac decompensations advents and to improve quality of life. This is in general agreement with the current ESC-heart failure guidelines, which lack of practical details [3, 4]. We aim to propose management strategies, helpful for decisions in the daily routine based on expert experiences. Thus, in this review paper, we (a) summarize the current recommendations for the management of HFpEF (Fig. 1), (b) discuss the implications on best clinical practice of studies investigating therapeutic approaches towards HFpEF (Fig. 2), and (c) present an overview on potential new innovative and disease-modifying treatment options for the future (Fig. 3).

Current management of risk factors, comorbidities and symptoms in HFpEF

HFpEF is accompanied by a large variety of risk factors and comorbidities (Fig. 1). Behind aging and female gender hypertension, obesity and diabetes mellitus belongs to the most important risk factors and comorbidities in HFpEF. A successful treatment of HFpEF requires a thorough understanding of these contributing entities, including also conditions such as cardiac ischemia, sleep apnoea, renal dysfunction, deconditioning, anaemia and iron deficiency, and sarcopenia. Older patients (> 67 years), with chronic kidney disease, pulmonary hypertension, right ventricular dysfunction and high filling indices are high-risk patients [11]. Death in HFpEF is attributable to non-cardiac causes in more than 60%, but only in less than 35% of patients with HFrEF. Hence, the current guidelines emphasize stringent cardiovascular risk management as the principal approach to improved symptoms and possibly prognosis, although hard evidence for this perspective is scarce [3, 4]. Despite the common mantra that HFpEF has no effective treatments, closer inspection of HFpEF clinical trials reveals that several of the drugs tested are associated with benefits in exercise capacity and quality of life, and reduction in heart failure hospitalization.

Comorbid conditions impose serious threats by triggering rehospitalisation in HFpEF [12]. This is particularly important for uncontrolled systolic and diastolic blood pressure [13], which explains the importance of angiotensin-converting enzyme inhibitors (ACEi), angiotensin-2 type-1 receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), diuretics, CCB and beta-blockers as pivotal preventive strategies. These substance classes can induce a regression of left ventricular

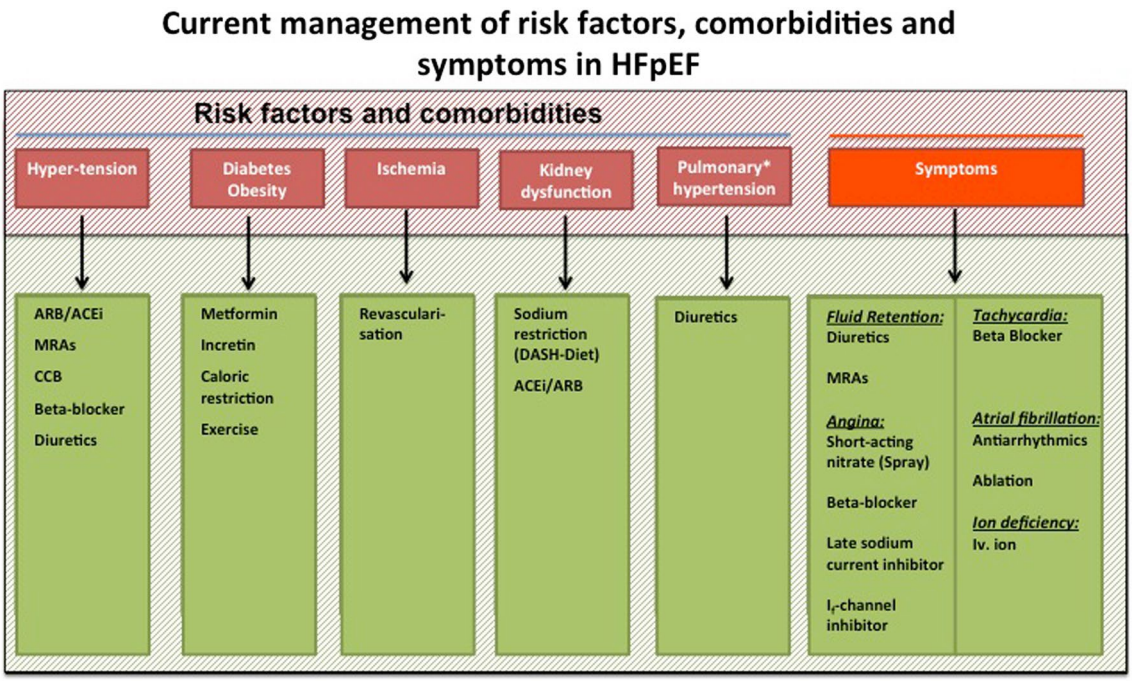

Fig. 2 Current management of risk factors, comorbidities and symptoms in HFpEF. *ARB* angiotensin receptor blocker, *ACEi* angiotensin-converting enzyme inhibitor, *MRA* mineralocorticoid receptor antagonist, *HFpEF* heart failure with preserved ejection fraction, *CCB* calcium channel blocker, *RF* risk factor; modified from [22]

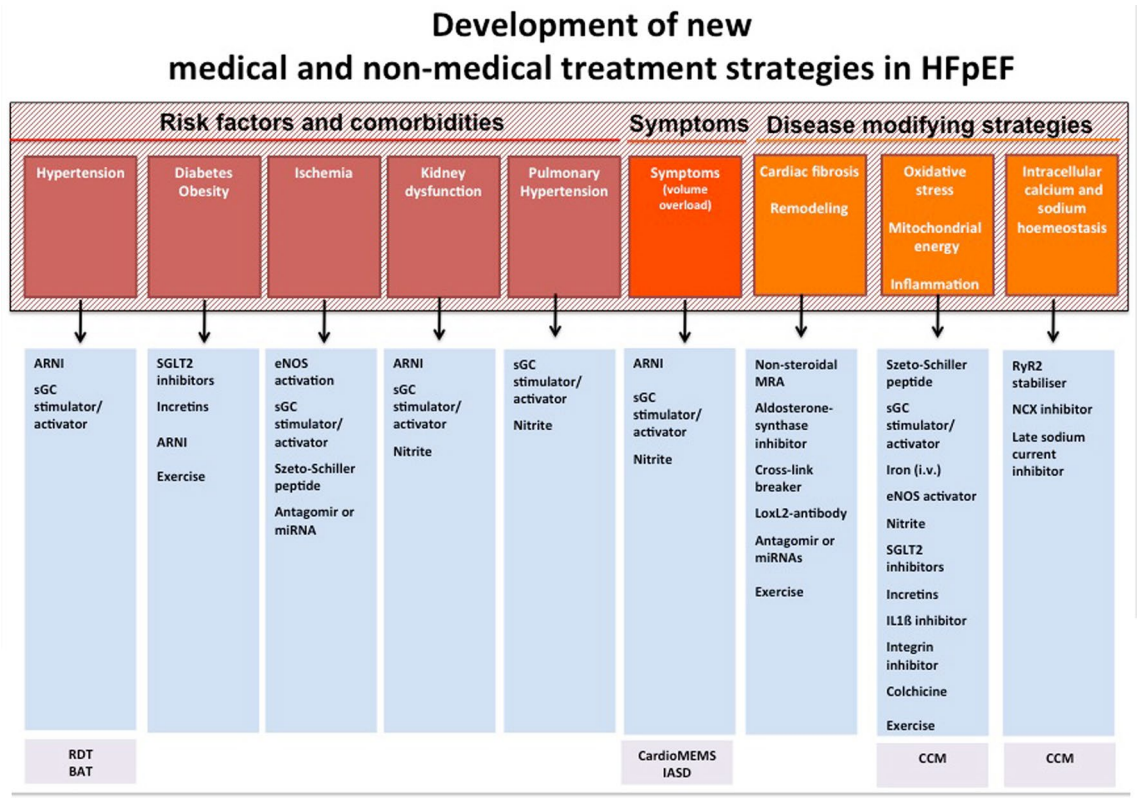

Fig. 3 Development of new medical and non-medical treatment strategies in HFpEF. *ARB* angiotensin receptor blocker, *ACEI* angiotensin-converting enzyme inhibitor, *MRA* mineralocorticoid receptor antagonist, *ARNI* angiotensin receptor and neprilysin inhibitor, *HFpEF* heart failure with preserved ejection fraction, *AGEs* advanced glycation end products, *SGLT2* sodium–glucose cotransporter-2, *sGC* soluble guanylate cyclase, *LOXl2* lysyl oxidase-like 2 antibody, *RyR2* ryanodine receptor 2, *IASD* interatrial septal device, *eNOS* endothelial NO-synthase, NCX: *CRT* cardiac resynchronization therapy, *iv* intravenously, *CCM* cardiac contractility modulation, *RDT* renal denervation therapy, *BAT* baroreflex activation therapy

hypertrophy, which in turn may ameliorate diastolic heart failure [14–16]. The selection of the anti-hypertensive drugs complies with the recommendations of the current hypertension guidelines [17]. However, it has not been shown that regression of a left ventricular hypertrophy improves long-term prognosis. Since myocardial ischemia can further worsen HFpEF, appropriate diagnostic measures and revascularization is needed. Obesity, diabetes mellitus, anaemia, sleep apnoea, pulmonary hypertension, obstructive lung disease, deconditioning, depression and kidney failure constitute important comorbidities disturbing the ventricular coupling with the vessel system. With respect to iron deficiency intravenously (CONFIRM-HF trial; [18]) but not orally (IRONOUT-HF study; [19]) administered iron to supplement reduced transferrin saturation improves symptoms and quality of life of patient with HFrEF [20]. Smaller studies in HFpEF populations showed that iron deficiency was prevalent in half of the patients, even in the absence of anaemia [21]. It is conceivable that patients with HFpEF who are treated for iron deficiency might also experience symptom improvement. Iron supplementation has been suggested to improve mitochondrial energy supply that is impaired in HFpEF.

In conclusion, the conditions listed may be causally involved in the development and/or accelerated progression of HFpEF [22]. Therefore, the comprehensive treatment approach to HFpEF should systematically screen for these conditions and include their optimization and—if appropriate—repeated monitoring into the management strategy (Fig. 1).

Diuretics

In HFrEF, fluid retention can be treated with diuretics. Mechanistically, patients with HFrEF and HFpEF differ regarding changes in total blood volume (TBV). TBV expansion in HFpEF is predominantly characterized by a red cell mass deficit, indicating that true anaemia (i.e. haemoglobin concentration < 12 mg/day) and a compensatory plasma volume expansion reflect the qualitative changes of TBV in most of the decompensated HFpEF patients [23]. Loop diuretics, thiazide and thiazide-like drugs are necessary to

overcome TBV expansion and congestion in both forms of HF [24].In the Hong Kong Diastolic Heart Failure Study [25], diuretic therapy significantly improved symptoms, and neither the ARB irbesartan nor the ACEi ramipril had a significant additional effect. However, diuretics in combination with RAAS (renin–angiotensin–aldosterone system) inhibitors marginally improved LV systolic and diastolic longitudinal LV function, and lowered NT-proBNP over a period of 1 year. Thus, diuretics appear indispensable for the improvement of symptom relief and belong to the current ESC guideline recommendations under these conditions, especially when post-capillary pulmonary hypertension occurs [24]. However, an excessive preload reduction by diuretics can lead to an under-filling of the left ventricle, and therefore to a reduction of stroke volume and cardiac output. This is particularly a problem in HFpEF patients with pronounced left ventricular hypertrophy and small ventricles including patients with cardiomyopathies such as hypertrophic cardiomyopathies (H(O)CM), storage diseases (amyloidosis) or cardiac inflammation (myocarditis) [26] (Fig. 1).

ACE inhibitor and AT1 receptor antagonists

Inhibition of neurohumoral activation by RAAS inhibitors is key principles in the treatment of dilated ventricles (with predominantly eccentric remodelling) in patients with HFrEF. In contrast, HFpEF is characterized by concentric remodelling, left ventricular hypertrophy and small ventricles [27]. However, treatment with RAAS inhibitors in HFpEF might improve diastolic function by counteracting left ventricular hypertrophy and fibrotic processes [28]. Three large studies investigated this pathophysiologic concept. In the PEP-CHF study [29], the ACEi perindopril showed no benefit on hospitalization or all-cause death. Uncertainty remains about the effects of perindopril on long-term morbidity and mortality in this clinical setting since this study had insufficient power for its primary endpoint. However, improved symptoms and exercise capacity and fewer hospitalizations for heart failure in the first year were observed in patients on perindopril, suggesting that it may benefit this patient population. In the CHARM Preserved study [30], the ARB candesartan reduced the hospitalisation risk but did not alter mortality. In the PRESERVE trial, the ARB irbesartan [31] did not improve mortality or hospitalisation risks after 50 months in HFpEF patients. However, in real life scenarios reflected by large registries, which include also more morbid HFpEF patients, the use of ACEI and ARBs was found to be effective [32, 33].

Since none of these agents improved hard clinical endpoints in HFpEF trials, as a consequence, current guidelines do not recommend the use of ACEi or ARB for the direct treatment of HFpEF [24], as long as they are not explicitly part of the regimen for their acknowledged effect on comorbidities such as hypertension [16] (Fig. 2).

Mineralocorticoid receptor antagonists (MRA)

Animal experiments showed that aldosterone is involved in the pathology of cardiac hypertrophy and fibrosis [34]. In the ALDO-HF study 25 mg spironolactone showed a slight reduction of blood pressure, significant improvements in diastolic LV function such as an *E*/*e′* reduction, decrease of left ventricular mass, and reduction of the NT-proBNP level, but no effects on exercise capacity as assessed by cardiopulmonary exercise testing (CPET) [35].

The investigators of the TOPCAT trial found that the incidence of the primary composite end point of death from cardiovascular causes, hospitalization for heart failure, or resuscitated cardiac arrest was not significantly lower in the spironolactone group than in the placebo group, but the incidence of hospitalization for heart failure was significantly lower in the spironolactone group [36]. However, significant differences in the clinical profiles, event rates, and responses to spironolactone were identified between the patients who were enrolled in the trial in the Americas (United States, Canada, Brazil, and Argentina) and the patients who were enrolled in Russia and Georgia, and these differences have aroused concerns about study conduct at the Russian and Georgian sites [37]. To further explore potential regional disparities in medication use, concentrations of canrenone (an active metabolite of spironolactone) were measured of 366 patients in the TOPCAT trial (206 patients from the United States and Canada and 160 patients from Russia). Analyses showed that canrenone concentrations were undetectable in a higher percentage of participants from Russia than from the United States and Canada (30 vs. 3%, $P < 0.001$) [38]. The findings suggest that the trial results obtained in Russia do not reflect the true therapeutic response to spironolactone, which is important since patients from countries such as the United States, Canada, Brazil, and Argentina met the primary endpoint of the study.

Based on these data, aldosterone antagonists are not generally recommended for patients with HFpEF today. Thereby, careful monitoring of potassium levels and renal markers is required to further clarify the role of aldosterone antagonism in HFpEF, the SPIRIT-HF phase III trial has been initiated by the German Centre for Cardiovascular Research (DZHK), to investigate the effects of spironolactone in well-characterized HFpEF patients. In addition, safety and efficacy of new aldosterone antagonists including dihydropyridine-like CCB, non-steroidal aldosterone antagonists, and aldosterone synthase inhibitors are under investigation [39–41].

Beta-blockers

High resting heart rate is a risk factor for adverse outcomes in patients with HFpEF [42]. The reduction of heart rate may improve the left ventricular filling time in abnormally stiff left ventricles and thus contribute to improved coronary perfusion. Therefore, heart rate control and maintenance of sinus rhythm with beta-blockers is considered favourable for patients prone to atrial fibrillation [43–46]. However, during exercise an adequate increase in heart rate is necessary to maintain cardiac output, especially when stroke volume is low, as shown as for HFpEF patients [47].

However, evidence for a general use of beta-blockers in patients with HFpEF is incoherent. In the SENIORS study [48], a pre-specified post hoc analysis showed that nebivolol improved the outcome of HFpEF patients to a similar degree as in HFrEF [49], although the echocardiographically measured diastolic function remained unaltered. In the ELLANDD study, the decrease of heart rate by nebivolol improved oxygen consumption but not load reserve or NYHA status [50]. Similar, registry data reported controversial results. In the OPTIMIZE registry [51], no benefits were seen with regard to mortality and rehospitalisation rates in patients having an EF > 40%. But the COHERE registry [52] as well as a recent meta-analysis found that beta-blockers reduced the mortality risk by 21% in HFpEF populations [53]. A report from the nation-wide Swedish registry showed that HFpEF patients treated with beta-blockers had a reduced total mortality, although no effect was observed regarding the combined endpoint of total mortality and heart failure-related hospitalisation [54]. Thus, studies are required to examine the role of beta-blockers in HFpEF more explicitly.

Current recommendations do not favour a general treatment recommendation for beta-blockers in HFpEF, as long as they are not indicated to optimise the therapy of comorbidities and symptoms including the control of ventricle frequency, angina pectoris or hypertension [55, 56]. If necessary, vasodilatory beta-blockers might be preferred agents. Chronotropic incompetence must be excluded before beta-blocker therapy is initiated.

If-channel inhibitor

Aside of its anti-ischemic properties, If channel inhibition using ivabradine may improve diastolic function by lowering sinus heart rate [57] and/or improving the function of the intracellular calcium ATPase SERCA2a [58]. Animal data suggested that the latter effect may occur independent of heart rate regulation [59]. Small studies in patients led to inconsistent results with respect to changes in E/e´ or peak VO2 [60, 61]. However, the recently finalized EDIFY study showed no influence on E/e´, exercise intolerance or NT-proBNP levels despite a heart rate reduction of 13% (mean HF about 63 bpm) after treatment with ivabradine [62]. Thus, ivabradine cannot be recommended for the primarily treatment of HFpEF. However, according to guidelines, ivabradine is useful in patients with angina pectoris and high heart rates despite ß-blocker therapy, independent of EF.

Calcium channel blockers

No large prospective trials investigated the effects of CCB in HFpEF [63]. In a recent retrospective analysis in hospitalized older patients with HFpEF, initiation of CCB had no effect on mortality or heart failure-related hospitalization, regardless of the class of CCB [64]. Thus, CCB for HFpEF cannot be generally recommended, but may be used for the optimisation of hypertension and angina symptoms [24].

Late sodium current inhibitors

Ischemia-triggered symptoms due to microvessel disease and vascular rarefication are considered pivotal pathophysiological principles of HFpEF [65, 66]. Preclinical data have shown that under ischemic conditions, an upregulation of the late sodium channels of myocytes may occur. This can lead to an increase of the intracellular calcium concentration, and therefore to a deceleration of diastolic relaxation [67, 68]. An inhibition of the late sodium current with drugs such as ranolazine or eleclazine might, therefore, improve diastolic function. In a first proof-of-concept study (RALI-DHF), intravenous administration of ranolazine in patients with HFpEF resulted in a reduction of the end-diastolic pressure [69]. However, a 14-day oral continuation of the therapy neither led to a continuous improvement of diastolic function nor to a decline of NT-proBNP levels or improvement of the load capacity. Further studies are necessary to investigate the role of ranolazine in HFpEF. Ranolazine is available for the treatment of patients with angina pectoris and may thus be tested for symptom relief in patients with HFpEF and typical or atypical angina pectoris.

Cardiac glycosides

The DIG study analysed treatment with digoxin or placebo in 980 patients with an EF of just over 45% [70]. After a median of 37 months, a trend towards the reduction of the hospitalisation rate was found in the digoxin group without any reduction in total or cardiovascular mortality. In patients suffering also from coronary artery disease, the mortality was increased.

However, patients with HFpEF often develop atrial fibrillation [71]. Cessation of the atrial contraction diminishes the left ventricular filling, and along with that decreases cardiac output and increases the risk for decompensation. Hence, restoration of sinus rhythm including ablation strategies and

pharmacologic interventions including class I, II or III antiarrhythmic drugs may improve clinical symptoms. If this is not possible, ventricular heart rate should be controlled using beta-blockers, heart rate lowering CCBantagonists or glycosides [55].

In conclusion, cardiac glycosides should not generally be used in HFpEF, but they may have a place in the control of atrial fibrillation [24]. Digitoxin, the agent preferably used in Germany, has not been systematically investigated in this regard.

Statins

The large GISSI-HF trial did not show a positive effect of rosuvastatin in HFrEF [72]. Statins can positively affect left ventricular hypertrophy and the development of fibrosis under experimental conditions [73]. A small study suggested that statins may improve mortality risk in HFpEF patients [74]. Similar, the results of a recent meta-analysis suggest a potential mortality benefit of statins in HFpEF. Further prospective and randomized controlled trials should be planned to confirm this observations [75]. While the ACCF/AHA HF guidelines support the use of statin therapy for patients with known atherosclerotic disease, statins are not recommended for the treatment of HFpEF alone, i.e. in the absence of other indications for their use.

Non-pharmacological therapy approaches in HFpEF

Exercise in HFpEF

Higher levels of physical activity (PA) in healthy subjects have been associated with a lower risk of adverse cardiovascular (CV) outcomes, including lower incident heart failure, with a well-described dose–response relationship. In a recent post hoc analysis of the TOPCAT study was shown that in patients with HFpEF, poor and intermediate baseline PA compared to ideal PA were associated with a twofold higher risk of HF hospitalization and mortality [76]. In the Ex-DHF pilot trial [77], 64 patients with HFpEF were treated either according to the current recommendations or were exposed to an additional dedicated training programme. After 3 months, patients in the intervention group exhibited an improved peak VO_2 and improved physical fitness. This was accompanied by an improvement of both diastolic and atrial function. Mechanistically, exercising can lead to an improvement of neurohormonal activation, including anti-inflammatory and anti-oxidative stress properties [78, 79]. The benefit of exercising was corroborated by a recent meta-analysis by Pandey et al. [80] and showed how safe and important training programs are for HFpEF patients.

Diet in HFpEF

In a very small study, 3 weeks of treatment with a salt-restricted DASH diet improved diastolic function, arterial stiffness, and ventricular–arterial coupling in 13 subjects with HFpEF [81]. Further, a 20-week caloric-restriction diet was feasible in obese HFpEF patients, and improved symptom burden, peak oxygen consumption, and quality of life. Quantitatively, the improvement in quality of life was greater with diet than exercise. The combination of diet with endurance exercise training appeared additive [82]. However, much larger studies are needed for any clinical recommendations.

The hope for new disease-modifying strategies

Novel strategies for the treatment of HFrEF are under investigation to prove whether they are sufficient to control disease progression and influence outcome rather than to control primarily risk factors comorbidities or symptoms. They include the regulation of energy and calcium homoeostasis, including anti-diabetic drugs, may be useful also in non-diabetic patients, matrix regulation, inflammation, angiogenesis, oxidative stress, and the cGMP axis (Fig. 3).

Targeting the NO-cGMP-PK-axis

In HFpEF, the intracellular nitrogen monoxide-cGMP-protein kinase (NO-cGMP-PK) signal cascade is disturbed [66]. The myocyte decline of cGMP appears to be a specific mechanism during HFpEF and differs from HFrEF [83]. A disorder in this signal cascade contributes to the development of concentric remodelling, increased cardiomyocyte stiffness by disturbances of regulation of titin and to an increase of fibrosis [3, 66]. This new concept has consequences for the development of new therapeutic options because it may be possible to mechanistically intervene with inorganic nitrates, phosphodiesterase-5 (PDE5) inhibitors, orally available soluble guanylate cyclase stimulators, or by angiotensin receptor neprilysin inhibitors (ARNI).

Organic nitrates and endothelial NO-synthase (eNOS) activators

Currently, direct NO-donators such as organic nitrates (isosorbide-nitrate) are not discussed favourably in the treatment of HFpEF due to their risk of a strong preload reduction and the possibility of tachyphylaxis. In a multicentre, double blind, crossover study, 110 patients with HFpEF were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate. Patients on isosorbide mononitrate were less active and did not have better quality of life or

submaximal exercise capacity compared to the placebo group [84]. Therefore, only short-acting nitrates are recommended to overcome angina symptoms in HFpEF. By contrast, eNOS activators like the eNOS transcription amplifier AVE3085 have been promisingly investigated in animal experiments [85] and await clinical testing.

Inorganic nitrates (nitrites)

In contrast to organic nitrates, the inorganic nitrate–nitrite pathway represents an important alternative route to restore NO signalling in HFpEF by increasing myocardial nitric oxide bioavailability [86]. Acute infusion of sodium nitrite reduced diastolic LV pressures and pulmonary artery pressures during exercise while restoring cardiac output reserve towards normal levels, without reducing systemic blood pressure. Part of this benefit was mediated by vasodilation, but evidence for a direct myocardial benefit, such as increased stroke work, was also observed [87]. Similar effects were seen by inhaled sodium nitrate [88]. Another recent study found that inorganic nitrate (precursor to nitrite), delivered as on a week of once-daily beetroot juice drink, improved submaximal exercise endurance [89]. INDIE and KNO3CKOUT-HFpEF are phase II trials testing inhaled or oral nitrites, respectively, in HFpEF.

Phosphodiesterase-5 inhibitors

PDE5-inhibition belongs to another strategy to simulate the cGMP system, which could lead to an improvement of cardiac relaxation and diastolic performance in HFpEF. This concept had been investigated in the RELAX-Trial [90], investigating elderly HFpEF patients without pulmonary hypertension. But none of the investigated endpoints of the study reached significance. A similar negative result was shown by the study from Hoendernis et al. investing patients with HFpEF and post-capillary hypertension [91]. However, sildenafil was effective in patients with severe combined post- and precapillary pulmonary hypertension (CpC-PH; diastolic pressure gradient > 7 mmHg) and preserved EF [92], a form of pulmonary hypertension detectable also at least in some forms of HFpEF [93, 94]. Whether this observed benefit is reproducible and drug specific is yet still to be determined. Registry data indicate predominantly PDE5 inhibitors are used in Cpc-PH-HFpEF but this do not represent a robust scientific evidence [95, 96].

Thus, sildenafil cannot be recommended in HFpEF patients without or post-capillary hypertension. The use of sildenafil in other forms of pulmonary hypertension, characterized by increased pulmonary vascular resistance, and HFpEF needs further investigations.

Angiotensin receptor neprilysin inhibitor

LCZ696 (sacubitril/valsartan), a water–salt complex consisting of the ARB valsartan and a neprilysin inhibitor is able to stimulate in the NO-cGMP-PK signal cascade. Inhibition of neprilysin prevents the degradation of numerous vasoactive peptides, including biologically active natriuretic peptides such as ANP, BNP and CNP. These peptides stimulate the formation of cGMP via specific receptors, and are therefore thought to be directly involved into the pathomechanisms of HFpEF. Natriuretic peptides exert anti-fibrotic, vasodilatory and natriuretic effects. Besides blood pressure reduction, the induction of diuresis by BNP can reduce volume overload and pulmonary pressure. In addition, neprilysin inhibition includes the prevention of glucagon degradation, which has a beneficial impact of the diabetic status and could offer an additional support for diabetic HFpEF patients [97]. This concept was investigated in the phase II PARAMOUNT trial [98]. A decline in NT-proBNP levels after 12 weeks, the primary endpoint, was observed in the LCZ696 group, and atrial volumes were reduced and NYHA functional class improved after 36 weeks. Currently, the PARAGON-HF trial further explores these encouraging findings investigating the effect of LCZ696 on mortality risk among patients with HFpEF.

Soluble guanylate cyclase (sGC) stimulators and activators

Stimulators and activators of sGC increase the enzymatic activity of sGC to generate cGMP independently of NO. This property might be relevant under conditions of diminished NO bioavailability. Clinical data on vericiguat and riociguat, direct sGC stimulators, appear promising as treatment strategies in heart failure [99, 100]. The DILATE-1 trial examined the use of riociguat in patients with post-capillary pulmonary hypertension (PH-HFpEF). While there was no effect on peak decrease in mean pulmonary artery pressure, riociguat increased stroke volume and cardiac index [100]. Recently, the results of SOCRATES-PRESERVED have been reported, showing no effect of vericiguat on a change of NT-proBNP and LAV at 12 weeks compared with placebo. However, the quality of life improved [101]. Further studies are on-going.

Cytokine inhibitors

Patients with HFpEF exhibit signs of chronic myocardial inflammation [102]. Endothelial activation enables immigration of activated inflammation cells that can activate the local cytokine cascade. Increased cardiac expression of TGFß stimulated formation of pro-inflammatory myofibroblasts, which release collagens and chemokines [103–105]. In the small D-HARD study, the effect of the interleukin-1

inhibitor anakinra was examined over a period of 14 days in 12 HFpEF patients, who had increased plasma C-reactive protein levels (> 2 mg/dl). In this study, load capacity and C-reactive protein levels improved compared to placebo [106]. Whether HFpEF patients without signs of systemic inflammation may benefit from such intervention remains to be shown. Similarly, new adhesion molecule antagonists targeting integrins (ICAM or VCAM) and colchicine are under investigation to prevent myocardial invasion of inflammatory cells.

Anti-diabetic drugs

In some HFpEF patients, chronically increased β-adrenergic stimulation and insulin resistance is present, leading to an unfavourably altered cardiac metabolism along with a compromised energy production [107]. A large proportion of patients with HFpEF suffer from diabetes mellitus [108]. Thiazolidines, incretins, and inhibitors of the sodium–glucose cotransporter-2 (SGLT2) may possibly represent an additional therapy option in the future for diabetic and non-diabetic HFpEF patients.

Thiazolidines

Pioglitazone, an agonist for the PPAR-y receptor, is able to improve myocardial energy production and glycolysis [109]. The PIRAMID study showed that in patients with uncomplicated type-2 diabetes myocardial glucose assimilation and diastolic function were improved after 24 weeks of therapy [110]. Further studies will be necessary to evaluate thiazolidine as therapeutic option also for HFpEF patients without diabetes mellitus. Currently, thiazolidine is contraindicated in patients with HFrEF and NYHA functional class II–IV.

Incretins

The glucagon-like peptide 1 (GLP-1) is a hormone of the incretin family that is released from the gastrointestinal tract after food intake [111]. GLP receptors have also been found in the heart [112]. Stimulation of myocardial GLP receptors leads to an increased cardiac glucose assimilation, thus activating myocyte glycolysis [113]. Two pharmacological strategies stimulate this metabolic pathway: (a) GLP-1 analogues such as exenatide, semaglutide, liraglutide; and (b) DPP-IV inhibitors such as sitagliptin, saxagliptin, or linagliptin. The latter are able to additionally stimulate the cGMP axis [114]. Exenatide improved cardiac diastolic function in diabetic patients [115, 116]. Two large phase-III trials showed a mortality risk reduction in diabetic patients with cardiovascular risks with semaglutide [117] and liraglutide [118]. Similarly, DPP-IV inhibitors are under investigation with respect to their effect on left ventricular diastolic function. In a small study focussing on non-diabetic patients with non-ischaemic cardiomyopathy, sitagliptin improved myocardial glucose utilization [119]. Linagliptin and sitagliptin improved diastolic function in diabetic HFpEF patients with chronic kidney disease [120]. However, in patients with reduced EF, increased basal BNP levels and renal dysfunction, DPP-IV inhibitors such as saxagliptin increased the rehospitalisation risk due to adverse effects on heart failure [121]. Further studies will show whether an incretin-based therapy approach with diabetic and/or non-diabetic patients and HFpEF can lead to improvements in symptom burden or mortality risk.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors

This drug class currently includes approved antihyperglycemic agents such as empagliflozin, dapagliflozin, and canagliflozin. Renal SGLT2 inhibition prevents glucose reabsorption and induces a diuretic effect by glycosuria. The EMPA-REG OUTCOME trial investigated the effects of empagliflozin in patients with type 2 diabetes and found an unexpected but strikingly consistent relative risk reduction in cardiovascular mortality (38%), hospitalization for heart failure (35%), and death from any cause (32%). Accordingly, it was hypothesized that mechanisms other than those observed in the trial, i.e. modest improvements in glycaemic control, glycosuria-induced diuresis, body weight, blood pressure and uric acid level, may play a role [122]. One possible explanation might be that under conditions of mild, persistent hyperketonaemia, such as those prevailing during treatment with SGLT2 inhibitors, β-hydroxybutyrate is freely taken up by the heart and oxidized in preference to fatty acids [123]. Such fuel selection may improve the transduction of oxygen consumption into work efficiency at the mitochondrial level. In addition, the haemoconcentration that typically follows SGLT2 inhibition enhances oxygen release to the tissues, thereby establishing a powerful synergy with the metabolic substrate shift. Empagliflozin is now recommended in diabetic heart failure patients by the ESC in combination with metformin (IIA recommendation; [24]). Studies are on-going in non-diabetic HFrEF (EMPEROR-HFrEF-Trial) and HFpEF (EMPEROR-HFpEF-Trial) patients.

Szeto–Schiller peptides

Heart failure represents a mismatch between ATP supply and demand. This mismatch may result from damaged mitochondria, decreased mitochondrial production of ATP including increased workload to the myocardium following ischemia, hypertension and diastolic dysfunction [124–126]. Current HF treatments rely on “energy sparing” by decreasing workload. Targeting mitochondrial

plasticity to improve ATP supply may provide an alternative approach. New mitochondria-targeted antioxidant peptides were developed that are able to restore the mitochondrial electron transport chain to optimize efficiency of electron transport and restore cellular bioenergetics [127, 128]. Modulation of myocardial energy balance and restoration of mitochondrial bioenergetics is possible by the so-called Szeto–Schiller (SS) peptides such as elamipretide (MTP-131, SS31), that binds the phospholipid cardiolipin and stabilizes the components of electron transport and ATP generation. Elamipretide is the first of these compounds that has entered clinical development and is studied in phase-II trials for HFrEF and HFpEF. However, elamipretide was not able to reduce infarct size in a phase-II trial in patients with acute ST-elevation myocardial infarction (EMBRACE STEMI study, [126]).

Cross-link breakers

Oxidative stress can lead to a formation of advanced glycation products (AEGs), whereby proteins and carbohydrates form a compound which leads to "cross-linking" with the extracellular matrix [129] and contributes to LV stiffness in HFpEF [130]. The so-called cross-link breaker alagebrium chloride was examined in a small study involving 23 older patients with HFpEF [131]. After 16 weeks, an improvement of the diastolic function was observed. However, due to drug toxicity, this approach is currently not further investigated.

Lysyl oxidase-like 2 (Loxl2) is an enzyme that cross-links collagen and has been shown to be essential for interstitial fibrosis and mechanical dysfunction of stressed hearts. Antibody-mediated inhibition of Loxl2 in mice has been shown to greatly reduce stress-induced cardiac fibrosis and chamber dilatation, improving systolic and diastolic functions [132]. Further studies are in preparation to prove different concept strategies of cross-link breaking in HFpEF.

Modulators of intracellular calcium homoeostasis

Disorders of the intracellular calcium homoeostasis contribute to diastolic dysfunction [133] via interference with the ryanodine receptor (RyR2) [134], the SERCA2a pathway, and the sodium–potassium pump [135]. The so-called *RyR2 stabilizers* like K201 improved diastolic function in experimental models [136] as did substances that are capable of inhibiting the Na^+/Ca^{2+} exchanger (NCX), e.g. SES0400 [137]. Strategies targeting SERCA2A are thought not only to improve diastolic function but also decrease myocardial hypertrophy [138]. Although these are sound pathophysiological concepts, their value in the clinical setting has not been explored.

MicroRNAs

MicroRNAs (miRNAs) are small non-coding RNA involved in RNA silencing and post-transcriptional regulation of gene expression. miRNA have been reported to influence genes that are important for HF [139] and different miRNA profiles were reported for patients with HFpEF compared to HFrEF (miR-30c, -146a, -221, -328, and -375; miR-125a-5p, -190a, -550a-5p, and -638) [140, 141]. However, the role of miRNAs as biomarkers in HFpEF is still not clear. Currently, the importance of miRNAs and/or certain inhibitors (antagomirs) are investigated as inducers of angioneogenesis or modifiers of fibrosis, e.g. inhibition of miRNA 21. For this molecule, anti-apoptotic and anti-fibrotic effects were shown in an animal experiment related to diastolic heart failure [142]. Further, miRNAs are presently being discussed as possible therapeutic targets for the treatment of HFpEF [143, 144].

Device therapy in HFpEF

Several device studies are on-going in HFpEF populations (Fig. 3)

Online monitoring

Increased pressures in the left atrium and the small circulation frequently cause the symptoms of HFpEF. Importantly, the rise in atrial and right-sided pressures can be detected prior to symptom deterioration or overt decompensation. Online haemodynamic monitoring could detect such early indicators of incipient decompensation.

The CardioMEMS device is a small pressure sensor and monitor, which is implanted into the pulmonary artery and calibrated in the course of a right-heart catheter procedure. After discharge, the patients record their pulmonary artery pressure via a cushion-based wireless radiofrequency transmitter. These values are online monitored by dedicated staff and may be used to adjust medication. In the CHAMPION trial, the use of CardioMEMS transmitted information lowered hospitalisation rates of NYHA III patients with either HFrEF or HFpEF [145]. In addition, data from a recent large real-world study reported that pulmonary pressure could be very effective targeted with this system by adapting especially the diuretic-based therapy [146–148].

Atrial shunt device

The reduction of increased left atrial pressure belongs to the principal haemodynamic objectives of treating HFpEF [149]. The hypothesis that a small, artificially induced left–right shunt might function as an overflow valve is based

on historical observations, showing that patients with an untreated mitral stenosis and concomitant atrial defect had better survival (Lutembacher syndrome [150]). In a small study of 11 HFpEF patients (EF ≥ 45%, PCP > 15 mmHg at rest, or PCP ≥ 25 mmHg during exercise), an interatrial septal device (IASD) was implanted in the septum using a catheter-based technique enabling a small shunt [151]. After 30 days, the filling pressure had fallen and mean NYHA classification improved. No patient developed pulmonary hypertension over this time. More recently, the REDUCE LAP-HF study analysed 68 HFpEF patients who underwent IASD implantation and showed that more than 50% of patients showed a reduction in wedge pressure at rest or during exertion [152]. These results need to be repeated in long-term trials.

Cardiac resynchronisation therapy (CRT)

Approximately 20% of HFpEF patients exhibit left ventricular asynchrony, which is associated with about 15% myocardial energy and contractility loss [153]. Unpublished results of an Asian study investigating about 130 HFpEF patients with mechanical asynchrony (regional level mechanical delay ≥ 65 ms) suggest that temporary stimulation with a CRT system may improve diastolic parameters. However, up to now patients with a narrowed QRS complex are not eligible for CRT.

Cardiac contractility modulation (CCM)

This device delivers a strong electrical current in the refractory period into the septum, thus triggering molecular remodelling which is thought to improve EF and optimise symptoms of symptomatic HFrEF patients. The effect seems to be more pronounced in patients with better EF (i.e. ≥ 35%) [154]. A recent case series found that early after initiating CCM treatment patients improved in NYHA classification, 6 min walking distance, quality of life, also exhibiting a significant reduction of the diastolic filling index (*E*/*e*′) and an improved EF reserve [155]. A clinical exploratory study, the CCM-HFpEF-Trial, has been initiated to further investigate the role of CCM in HFpEF.

Renal denervation

HFpEF is associated with an increased tone of the sympathetic nervous system (SNS). Reduction of blood pressure by renal denervation therapy (RDT) improved left ventricular hypertrophy and diastolic left ventricular function in a small series of patients with refractory hypertension [156]. This effect was prospectively investigated in the RDT-PEF study [157]. In this single-centre open trial, 25 patients with HFpEF were randomized (2:1) to RDT with the Simplicity™ catheter or continuing medical therapy. The primary endpoint was not met in that there were no differences between groups at 12 months for quality of life and markers for diastolic function. Some patients improved with respect to peak VO_2 although markers of macro- and microvascular function such as augmentation index or endothelial function, respectively, did not improve [158]. Up to now, the sustained clinical value of RDT remains unclear.

Baroreflex activation therapy (BAT)

BAT electrically stimulates the carotid sinus via an implanted electrode in close vicinity to the glomus caroticus. The device has originally been studied for the treatment of hypertension. Potential (long-term) benefits of such an approach include regression of left ventricular hypertrophy, normalization of the sympathovagal balance, and inhibition of the RAAS, arterio- and venodilation, and preservation of renal function. BAT had been successfully investigated in HFrEF showing an improvement of functional status, quality of life, exercise capacity, and BNP reduction [159]. The clinical utility of BAT in treatment of HFpEF needs further investigation [160].

Summary, expert opinion and conclusion

The management of and clinical research in patients with HFpEF remains an on-going challenge. Especially, since HFpEF is a heterogeneous syndrome. Therefore, clinical management and future clinical trials mandate an individualized, phenotype-specific approach instead of a "one-size-fits-all" strategy. Options to improve patients' symptoms and quality of life include control of fluid overload, heart rate, risk factors, and comorbidities (Figs. 1, 2). Comorbidities such as coronary artery disease, hypertension and diabetes mellitus must be stringently treated. Maintaining mobility and regular exercise should be implemented in the treatment plan and is the most effective treatment strategy in HFpEF. Diuretics and/or mineralocorticoid receptor antagonists can be used to stabilize the optimal volume status. RAAS inhibitors and (vasodilatory) beta-blockers are preferred to control blood pressure in euvolaemic patients. Beta-blockers should be avoided in patients with chronotropic incompetence [161].

Devices such as the CardioMEMS system seem to be extremely helpful for critical HFpEF patients with several decompensation episodes. But guiding patients by a telemedical approach asks for a specific organization structure of the clinic, which needs a significant reimbursement backup. Similarly, an atrial shunt device will be in our opinion a strategy for a limit group of severe HFpEF patients, only.

Recently, our understanding of the pathological processes involved in HFpEF has led to the discovery of new treatment targets and holds promise for more specific treatment options of HFpEF in the future (Fig. 3). Some strategies, such as LCZ696, have already been successfully studied in a phase-II trial [98]; other potential treatment targets, e.g. involving cGMP stimulation, mitochondria-targeted antioxidant peptides, new devices or the role of anti-diabetic drugs such as empagliflozin in normoglycaemic patients are currently investigated. The later offer the opportunity to develop more specific disease-modifying treatment strategies and to be able not only to treat comorbidities and symptoms. The future will show whether new treatment strategies including disease-modifying approaches are sufficient to improve outcome in HFpEF.

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Compliance with ethical standards

Conflict of interest CT: Steering Committee or Speaker honoraria from AstraZeneca, Novartis, Berlin Chemie, Servier, Bristol-Meyers Squibb GmbH, Roche, Boeheringer Ingelheim, Bayer Healthcare, Impulse Dynamics. CB: Speaker honoraria from Novartis, AstraZeneca. SF: Steering Committee or Speaker honoraria from AMGEN, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol-Meyers Squibb GmbH, Daiichi Sankyo, MSD, Novartis, Pfizer, Servier. MB: Steering Committee, Advisory Board and Speaker honoraria from AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Medtronic, Novartis, St. Jude, Servier, Vifor. LSM: Steering Committee, Advisory Board and Speaker honoraria Gilead, Berlin-Chemie, MSD, Böhringer, Zoll, Astra-Zeneca, Novartis, Sanofi, Servier, Daiichi-Sankyo, Edwards, Bayer Healthcare, Medtronic, Pfizer, Abbott. SS: Steering committee or advisory board or speaker honoraria for AMGEN, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Novartis, Pfizer, Servier. UL: Speaker honoraria from Amgen, Boehringer Ingelheim, MSD, Novartis, Sanofi, Servier. AL: none. BK: none. OB: none.

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