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

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It has been estimated that about 50% of all patients with heart failure (HF) symptoms have a reduced ejection fraction (HFrEF $\leq$40%). The others have been newly classified into HF with midrange EF (HFmrEF 40-50%) or preserved ejection fraction (HFpEF, EF $\geq$50%). The management of patients with HFpEF remains a challenge since evidence of therapeutic benefits is scarce. The presentation and pathophysiology of HFpEF is heterogeneous and HFpEF is better characterized as a syndrome. Although there are no persuasive and proven therapies for survival improvement of HFpEF patients, treatment of fluid retention, adjustment of heart rate and comorbidities do remain targets in the management for symptom relief and quality of life. For symptom control, renin-angiotensin-aldosterone inhibitors, diuretics, calcium antagonists and beta-blockers might be useful. Over the last few years, numerous new therapeutic targets have been investigated. Among those, the dysregulation of the NO-cGMP-PK's signalling pathway for HFpEF seems to represent a promising target. In addition, drugs such as the neprilysin inhibitor LCZ 696 or soluble guanylate cyclase stimulators vericiguat or riociguat are under investigation. Interventions targeting non-cardiac mechanisms or non-pharmacological interventions including physical exercise, diets, new antidiabetic or anti-inflammatory drugs, mitochondrial-targeted antioxidants, anti-fibrotic strategies, antagomirs, devices such as CARDIOMEMs, interatrial septal devices (IASD), cardiac contractility modulation (CCM), and renal denervation and baroreflex activation therapy (BAT) are studied.

Management and symptomatic therapy

Since HFpEF is accompanied by a heterogeneous comorbidities, successful treatment requires a thorough understanding of these contributing entities, including conditions like hypertension, sleep apnoea, obesity, renal dysfunction. Therefore a “one pill fits all” is unlikely to be successful in HFpEF. Death in HFpEF is attributable to non-cardiac causes in more than 60%, but only in less than 35% of patients with HFrEF. Hence, current guidelines emphasize stringent cardiovascular risk management as the principal approach to improved symptoms and possibly progrnosis, although hard evidence for this perspective is scarce [7, 6]. Along these lines, substance classes including angiotensin converting enzyme inhibitors (ACEi), angiotensin-2 type-1 receptor blockers (ARB), mineralocorticoid receptor blockers (MRA, diuretics, calcium channel blockers (CCB) and beta-blockers play an important role. They are utilized in the context of best clinical practice depending on the phenotype of HFpEF in an individual patient. A proposed guide for “precision medicine” in HFpEF is summarized in Fig 1.

Fluid retention:

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/d) and a compensatory plasma volume expansion reflects the qualitative changes of TBV in most of the decompensated HFpEF patients [10].Loop diuretics, thiazide and thiazide-like drugs are necessary to overcome TBV expansion and congestion in both forms of HF[11]**.** Differences among loop diuretics for the treatment of HFpEF could be of great potential interest, since smaller studies have suggested that torasemide, in contrast to furosemide, may have additional positive effects on collagen metabolism by inhibition of procollagen type I (PIP) [12]. The Hong Kong Diastolic Heart Failure Study [13] showed that the quality of life can be improved by a monotherapy with diuretics, and this effects was amplified when ACEi was added . Thus, diuretics appear indispensable for the improvement of symptom relief. According to the report of a small study, adding the vasopressin antagonist tolvaptan can be effective in severe cases accompanied by hyponatraemia[14]**.** 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.

Atrial contraction:

Patients with HFpEF are often intolerate to atrial fibrillation, especially when ventricular heart rate is high. Cessation of the atrial contraction diminishes the left ventricular filling and along with that, decreases cardiac output [15]. 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 or heart rate lowering calcium antagonists [8]. Theoretically, late sodium current-inhibitors like ranolazine or eleclazine may exhibit secondary antiarrythmic effects and may be considered in HFpEF patients with angina symptoms to maintain sinus rhythm. .

Treatment of comorbidities:

Comorbidities impose serious risk on rehospitalisation rates in HFpEF[16]. This is particularly important for systolic and diastolic blood pressure [17, 18]. Therefore ACEi, ARB, CCB, diuretics and beta-blockers are recommended to control blood pressure These substance classes can induce a regression of left ventricular hypertrophy, which in turn may ameliorate diastolic heart failure [19, 20]. The selection of the anti-hypertensive drugs complies with the recommendations of the current hypertension guidelines [21]. 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.

Intravenously, but not orally, given iron to supplement reduced ferritin saturation improves the symptomatology and quality of life of a patient having diminished heart failure [22]. In smaller studies, it has been shown that in HFpEF populations iron deficiency was prevalent in half of the patients, even though no anaemia was present [23]. It is theoretically possible that patients with HFpEF who are treated for iron deficiency might benefit and might experience symptom improvement. Iron supplementation has been suggested to improve mitochondrial energy supply that is impaired in HFpEF.

Obesity, diabetes mellitus, anaemia, iron deficiency, pulmonary hypertension, sleep apnoea, depression and kidney failure constitute important comorbidities disturbing the ventricular coupling with the vessel system. These conditions may be causally involved in the development and/or accelerated progression of HFpEF [24]. 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.

New developments among causal therapeutic strategies for HFpEF

Novel strategies for the treatment of HFrEF include the regulation of energy and calcium homoeostasis, matrix regulation, inflammation, angiogenesis, and oxidative stress (Fig. 2).

NO-cGMP-PK-activators

In HFpEF, the intracellular nitrogen monoxide-cGMP-protein kinase (NO-cGMP-PK) signal cascade is disturbed [60]. The myocyte decline of cGMP appears to be a specific mechanism during HFpEF and differs from HFrEF [61]. 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 [60, 6]. This new concept has consequences for the development of new therapeutic options, because it may be possible to mechanistically intervene with NO-donators, phosphodiesterase-5 inhibitors, by dipeptidyl peptidase 4 inhibitors (DPP-IV), orally available soluble guanylate cyclase stimulators like vericiguat or by neprilysin inhibition.

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 multicenter, 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 [62]. Therefore, only short-acting nitrates are recommend to overcome angina symptoms in HFpEF. By contrast, eNOS activators like the eNOS transcription amplifier AVE3085 have been promisingly investigated in animal experiments [63] and await clinical testing.

Inorganic nitrates, nitrites and beetroot juice

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 [64]. Acute infusion of sodium nitrite reduced diastolic LV pressures and pulmonary artery pressures during exercise while restoring cardiac output reserve toward 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 [65].

Similar effects were seen by inhaled sodium-nitrate [66]. 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 [67]. INDIE and KNO3CKOUT-HFpEF are phase II trials testing inhaled or oral nitrites, respectively, in HFpEF.

Angiotensin receptor and neprilysin inhibition (ARNI). LCZ696 (sacubitril/valsartan), a water-salt-complex consisting of the AT1 receptor antagonist valsartan and a neprilysin inhibitor, is able to stimulate in the NO-cGMP-PK signal cascadeis. Inhibition of neprilysin prevents the degradation of numerous vasoactive peptides, including biologically active natriuretic peptides like 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. This concept was investigated in the phase II PARAMOUNT trial [68]. 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.

Phosphodiesterase-5 inhibitors. Patients suffering from primary pulmonary hypertension often also have concomitant diastolic dysfunction [69]. In 44 patients with pulmonary hypertension and HFpEF (EF >50%) treatment with the phosphodiesterase-5 inhibitor sildenafil attenuated pulmonary pressure and improved diastolic function [70]. However, these results were not confirmed in the placebo-controlled RELAX study investigating elderly HFpEF patients without pulmonary hypertension [71]. Application of sildenafil among HFpEF patients without pulmonary hypertension can therefore not be recommended. To this end, further phase II studies with phosphodiesterase inhibitors in combination with endothelin antagonists (like ambrisentan and bosentan) are initiated aiming of improve diastolic function in patients with pulmonary hypertension (PH-HFpEF). Recently, the placebo-controlled BADDHY trial showed that bosentan in patients with PH-HFpEF had no beneficial effects and could even be detrimental [72].

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 riociguat and vericiguat, direct sGC stimulators, appear promising for HFrEF [73]. The DILATE-1 trial examined the use of riociguat in patients with HFpEF and pulmonary hypertension. Thirty-six HF patients with EF >50%, mean PAP ≥25 mmHg, and PAWP >15 mmHg were randomized to riociguat. While there was no effect on peak decrease in mean PAP, riociguat (2 mg dose) increased stroke volume and cardiac index, and decreased systolic blood pressure and right ventricular end-diastolic area. Further studies are ongoing to investigate the effects of this drug class in HFpEF [74].

Endothelin receptor (ET) antagonism

Inhibition of ET receptors is used for the treatment of pulmonary hypertension. Since ET_A receptors can increase left ventricular hypertrophy as well as matrix accumulation, the ET_A antagonist sitaxsentan was investigated in a phase-II study in 192 patients with HFpEF for a period of 24 weeks. Although exercise tolerance of the patients improved, diastolic function or left ventricular mass remained unaltered. Experimental studies suggest that the dual ET_A/ET_B antagonist macicentan improved diastolic function in a murine model of HFpEF [76]**.** Further studies on ET antagonism in HFpEF are ongoing [75].

Inflammation and cytokine inhibition

Patients with HFpEF exhibit signs of chronic myocardial inflammation [77]. 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 [78] [79] [80]. 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/l). In this study, load capacity and C-reactive protein levels improved compared to placebo [81]. 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) are under investigation as is the role of colchicine to prevent myocardial invasion of inflammatory cells.

Modulators of intracellular calcium homoeostasis

Disorders of the intracellular calcium homoeostasis contribute to diastolic dysfunction [82] via interference with the ryanodine receptor (RyR2) [83], the SERCA2a pathway, and the sodium-potassium pump [84]. So-called *RyR2 stabilizers* like K201 improved diastolic function in experimental models [85] as did substances that are capable of inhibiting the Na^+/Ca^{2+} exchanger (NCX), e.g. SES0400 [86]. Strategies targeting the functions SERCA2A are thought not only to improve diastolic function but also decrease myocardial hypertrophy [87]. While these are sound pathophysiological concepts, their value in the clinical setting has not been explored.

Modulation of myocardial energy balance and restoration of mitochondrial bioenergetics

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 [88]. A large proportion of patients with HFpEF suffers from diabetes mellitus. Thiazolinidine, 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. Another strategy includes the restoration of mitochondrial energy metabolism by so-called Szeto-Schiller (SS) peptides like elamipretide (MTP-131), a mitochondrial-targeting peptide that binds the phospholipid cardiolipin and stabilizes the components of electron transport and ATP generation.

Anti-diabetic drugs

Thiazolidine

Pioglitazone, an agonist for the PPAR-y receptor, is able to improve myocardial energy production and glycolysis [89]. 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 [90]. 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 gastro-intestinal tract after food intake [91]. GLP receptors have also been found in the heart [92]. Stimulation of myocardial GLP receptors leads to an increased cardiac glucose assimilation, thus activating myocyte glycolysis [93]. Two pharmacological strategies stimulate this metabolic pathway: a) GLP-1 analogues like exenatide, semaglutide, liraglutide; and b) DPP-IV inhibitors

such as sitagliptin, saxapliptin, or linagliptin. The latter are able to additionally stimulate the cGMP-axis [94]**.** Exenatide improved cardiac diastolic function in diabetic patients [95, 96]. Two large phase-III trials showed a mortality risk reduction in diabetic patients with cardiovascular risks with semaglutide [97] and liraglutide [98]. Similar, 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 assimilation [99]. Linagliptin and sitagliptin improved diastolic function in diabetic HFpEF patients with chronic kidney disease [100]**.** However, in patients with reduced EF, increased BNP-levels and renal dysfunction, DPP-IV inhibitors like saxagliptin increased the rehospitalisation risk due to adverse effects on heart failure [101]. 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 inhibitors

SGLT2 inhibitors. This class currently includes approved antihyperglycemic agents like empaglifozin, dapagliflozin, and canagliflozin. The EMPA-REG OUTCOME trial investigated the effects of empagliflocin 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, body weight, blood pressure and uric acid level, may play a role [102]**.** One possible explanation might be that under conditions of mild, persistent hyperketonemia, 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 [103]. Such fuel selection may improve the transduction of oxygen consumption into work efficiency at the mitochondrial level. In addition, the hemoconcentration 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; [11]). Studies are ongoing in non-diabetic HFrEF and HFpEF patients.

Szeto-Schiller (SS) 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 [104, 105]

[106]. 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 [107, 108]. The first of these compounds (SS-31; also named MTP-131, elamipretide) has entered into clinical development and is studied in phase II clinical 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, [106])**.**

Matrix regulation by "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 an interlinking "cross-link" with the extra-cellular matrix [109]. The so-called cross-link breaker alagebrium chloride was examined in a small study involving 23 older patients with HFpEF [110]. After 16 weeks, an improvement of the diastolic function was observed. Whether these results can be confirmed subsequently depends on further larger studies.

Lysyl oxidase-like 2 (Loxl2) is an enzyme that crosslinks collagen and which has been shown to be essential for interstitial fibrosis and mechanical dysfunction of pathologically 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 [111]. Further studies are ongoing to prove this anti-body under clinical conditions.

Micro-RNA regulation

Micro-RNAs (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 [112] 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) [113][114]. 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 [115]. Further miRNAs are presently being discussed as a possible therapeutic targets for the treatment of HFpEF [116].

Non-pharmacological therapy approaches in HFpEF

Exercise: In the Ex-DHF pilot trial [117], 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. These finding were corroborated by a recent meta-analysis by Pandey et al [118].

Diet: 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 [119]. 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 [120].

However, much larger studies are needed for any clinical recommendations.

<u>Device therapy for HFpEF</u>

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 use of CardioMEMS transmitted information lowered hospitalisation rates of NYHA III patients with either HFrEF or HFpEF [121]. The CardioMEMS system was approved recently for Europe and the US.

The LAPTOP device is a second system that measures left atrial pressure directly but its safety has been questioned due to complications during the implantation procedure which led to a premature termination of the trial..

Atrial shunt device.

The reduction of increased left atrial pressure belongs to the haemodynamic objectives of treating HFpEF [122]. 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 [123]). 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 [124]. After 30 days the filling pressure had fallen by 5 mmHg and mean NYHA classification had improved. No patient developed pulmonary hypertension over this time. More recently, the REDUCE LAP-HF study analysed 68 HFpEF patients (EF >40%, PCP >15 mm Hg at rest or PCP >25 mmHg during exercise) who underwent IASD implantation. After 6 months 52% of patients showed a reduction in PCP at rest, 58% had a lower PCP during exertion, and 39% fulfilled both criteria [125]. These encouraging results need to be repeated in long-term trials. Other companies are testing similar procedures with devices that include valves, which may become of great interest also in regard to the prevention of pulmonary hypertension.

Cardiac resynchronisation therapy (CRT).

Approximately 20% of HFpEF patients exhibit left ventricular asynchrony, which is associated with about 15% myocardical energy and contractility loss [126]. 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. Currently, a safety study in HFpEF patients with mechanical delay is being planned investigating the effect of so-called "fusion pacing", a new CRT pacing method ~~[127].~~

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 a better EF (i.e., ≥35%) [128]. A recent case series found that early after initiating CCM treatment patients improved in NYHA classification, 6 minute walking distance, quality of life, and showed a significant reduction of the diastolic filling index (E/e´) and in improvement in EF reserve [129]. A clinical phase-II trial investigating the effect of CCM in non-HFrEF patients, including a 2:1 HFpEF:HFmrEF randomization, has been initiated.

Renal denervation. HFpEF is associated with increased sympathetic nervous system (SNS) tone. 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 [130]. This effect was prospectively investigated in the RDT-PEF study [131]**.** 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 Minnesota Living with Heart Failure Questionnaire score, peakVO_2 at exercise, BNP, E/e', left atrial volume index or left ventricular mass index. However, a greater proportion of patients improved at 3 months in the RDT group with respect to peakVO_2. Since the study was underpowered, the value of RDT remains unclear.

Baroreflex activation therapy (BAT).

BAT electrically stimulates the carotid sinus via an implanted electrode sewn in the close vicinity of the glomus caroticus. The device has been inititally being 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, inhibition of the renin-angiotensin-aldosterone system, 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 [132]. The clinical utility of BAT in treatment of HFpEF needs further investigation [133].

Summary, expert opinion and conclusion

The management of and clinical research in patients with HFpEF remains an ongoing challenge. 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 patient’s symptoms and quality of life include control of fluid overload, heart rate, risk factors and comorbidities (Fig. 1). Comorbidities such as coronary artery disease and diabetes should be stringently treated. Maintaining mobility and regular exercise should be implemented in the treatment plan. Thiazide 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 [134].

Recently, our understanding of the pathological processes involved in HFpEF have led to the discovery of new treatment targets and may promise more specific treatment options for HFpEF in the future (Fig. 2). Some strategies, such as LCZ696, have already been successfully studied in phase II trials; other potential treatment targets, e.g. involving cGMP stimulation, mitochondria-

targeted antioxidant peptides, new devices or the role of anti-diabetic drugs like empaglifozin in normoglycaemic patients are currently investigated.

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