Treatment of patients with hypertension and heart failure with preserved ejection fraction (HFpEF): A call to action to identify the best medical therapy
Position paper by the European Society of Hypertension (ESH)

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Abstract

Hypertension constitutes a major risk factor for heart failure (HF) with preserved ejection fraction (HFpEF). HFpEF is a prevalent clinical syndrome with increased cardiovascular morbidity and mortality. Specific guideline-directed medical therapy (GDMT) for HFpEF is not established due to lack of positive outcome data from randomized controlled trials (RCTs) and limitations of available studies. Although available evidence is limited, control of blood pressure (BP) is widely regarded as central to the prevention and clinical care in HFpEF. Thus, in current guidelines including the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) Guidelines, blockade of the renin-angiotensin system (RAS) with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers provides the backbone of BP lowering therapy in hypertensive patients. Although superiority of RAS blockers has not been clearly shown in dedicated RCTs designed for HFpEF, we propose that this core drug treatment strategy is also applicable for hypertensive patients with HFpEF with the addition of some modifications. The latter apply to the use of spironolactone apart from the treatment of resistant hypertension and the use of the angiotensin receptor neprilysin inhibitor. In addition, novel agents such as sodium-glucose co-transporter-2 inhibitors, currently already indicated for high-risk patients with diabetes to reduce HF hospitalizations, and finerenone represent promising therapies and results from ongoing RCTs are eagerly awaited. The development of an effective and practical classification of HFpEF phenotypes and GDMT through dedicated high quality RCTs are major unmet needs in hypertension research and calls for action.

Key Words: heart failure, preserved ejection fraction, hypertension, heart failure hospitalization, mortality, drug recommendations

Condensed abstract

HFpEF is a prevalent clinical syndrome with increased cardiovascular morbidity and mortality, and hypertension constitutes one of its major risk factors. Specific guideline-directed medical therapy for HFpEF is not established. We propose that the core drug treatment strategy of the 2018 European Society of Cardiology/European Society of Hypertension guidelines is also applicable for hypertensive patients with HFpEF with some modifications including the use of spironolactone apart from the treatment of resistant hypertension, and the use of the angiotensin receptor neprilysin inhibitor. Trial results of novel drug agents and better understanding of classification of HFpEF are major unmet needs in hypertension research and calls for action.

List of Abbreviations

ABPM, Ambulatory blood pressure monitoring
ACEi, Angiotensin-converting enzyme inhibitor
ARB, Angiotensin receptor blocker
ARNi, Angiotensin receptor neprilysin inhibitor
BNP, Brain natriuretic peptide
BP, Blood pressure
CCB, Calcium channel blocker
CKD, Chronic kidney disease
FDA, Food and Drug Administration
GDMT, Guideline directed medical therapy
ESC, European Society of Cardiology
ESH, European Society of Hypertension
HF, Heart failure
HFpEF, HF with preserved ejection fraction
HFrEF, HF with reduced ejection fraction
HMOD, Hypertension mediated organ damage
LV, Left ventricle, left ventricular
LVEF, Left ventricular ejection fraction
LVH, Left ventricular hypertrophy
MRA, Mineralocorticoid-receptor antagonist
NYHA, New York Heart Association
RAS, Renin-angiotensin system
RCT, Randomized controlled trial
SBP, Systolic blood pressure
SGLT2, sodium-glucose co-transporter-2

Introduction

Heart failure (HF) represents a major and highly relevant clinical consequence of hypertension mediated organ damage (HMOD) [1]. Up to half of all patients presenting with HF have HF with preserved ejection fraction (HFpEF) and increasing evidence suggests that their risk of death and recurrent hospitalization is similar to patients with HF with reduced EF (HFrEF)[2]. The prevalence of hypertension among patients with HFpEF ranges between 55% and 90% and patients with HFpEF are more likely to present with a history of hypertension compared to those with HFrEF [3,4]. In a patient with an stablished diagnosis of HFpEF, hypertension, when present, may be the only cause or one of multiple aetiologies or comorbidities. Even though available evidence is limited, appropriate control of blood pressure (BP) is widely regarded as central to the prevention and clinical care of HFpEF patients [5-7].

In the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) Guidelines for the management of hypertension, a simplified core drug treatment algorithm is recommended for most hypertensive patients including patients with uncomplicated hypertension, HMOD, diabetes, and the elderly [1]. Guideline directed medical therapy (GDMT) includes a combination of a blocker of the renin-angiotensin system (RAS), i.e., an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), with a calcium channel blocker (CCB) or thiazide/thiazide-like diuretic as initial therapy for most patients [1]. In addition, the steroidal mineralocorticoid-receptor-antagonist (MRA) spironolactone is recommended as the preferred drug for treating patients with resistant hypertension, i.e., patients in whom BP control is not achieved with a triple combination of a RAS blocker, CCB and thiazide/thiazide-like diuretic[1,8]. Even though there are no specific pharmacologic options for HFpEF, based on the current guideline recommendations, a RAS blocker would also represent the backbone of therapy in hypertensive patients with HFpEF, while treatment with an MRA would apply only in case of resistant hypertension. Nevertheless, while the core algorithm of GDMT for hypertension appears appropriate for patients with HMOD including patients with left ventricular (LV) hypertrophy (LVH), its applicability for the treatment of HFpEF patients could be critically questioned [1].

Clear evidence for medical treatments that improve the course of HFpEF represents one of the major unmet needs in cardiovascular medicine which applies to an already large and increasing number of patients, most of whom are hypertensive. Thus, the optimal treatment

strategy for hypertensive patients with concomitant HFpEF is currently also unknown due to the paucity of positive outcome data derived from randomized controlled trials (RCTs) and methodological limitations of the available studies[9-11]. Importantly, there is no definite evidence for any drug treatment, including the use of BP-lowering drugs, to support clear improvements in cardiovascular outcomes and mortality in HFpEF patients[11]. Nevertheless, targeting the RAS is fundamental to the BP-lowering algorithm, as it is the cornerstone of pharmacological treatment across the cardiovascular continuum with a significant body of evidence supporting the use of RAS blockers in hypertensive patients [1,11,12]. However, definitive superiority for the use of a RAS blocker (ACEi or ARB) or an MRA (spironolactone) has not been shown in RCTs explicitly designed for HFpEF[10,11].

The current position paper by the ESH seeks to review some of the pathophysiological aspects of HFpEF of particular interest to hypertensive patients, re-examine medical options investigated in major HFpEF trials and propose a current framework for treatment and future research directions for patients with hypertension and HFpEF. In this regard, the BP-lowering therapy of hypertensive patients with concomitant HFpEF but also the options for management of HFpEF beyond BP control are discussed. It should be acknowledged that although the approach to control BP in hypertensive patients with HFpEF could be considered to be distinct from that of treating HFpEF per se, current drug choices for therapy in these two conditions are largely overlapping. Nevertheless, the proposed recommendations in the current document would primarily apply to patients with HFpEF and a preceding or new diagnosis of hypertension.

Pathophysiology of HFpEF in hypertension: Implications for treatment

HFpEF is a heterogeneous condition in terms of pathophysiological triggers and clinical presentation[9,13]. It has been suggested that different etiologies contribute to a common pathophysiological substrate but also that assigning patients to more specific clinical sub-phenotypes may allow the identification and development of more targeted treatment strategies [9,14-17]. Even though it remains unclear whether HFpEF is a distinct entity or an intermediate step from normal to reduced LV systolic function, the transition from preserved to reduced LV ejection fraction (LVEF) in hypertensive patients is commonly considered the result of poorly controlled long-term sustained hypertension or incident myocardial infarction[18,19]. Overall, the pathophysiology of HFpEF in hypertensive patients is complex and multifactorial (Figure 1), but certain vital issues merit consideration as they may have implications for treatment.

LVH and the limitations of the LVEF

The presence of LVH and/or LV diastolic dysfunction are considered cardinal features to establish the diagnosis of HFpEF, although they are not pathognomonic [5,6,20,21]. Echocardiographic data from large studies have shown that LVH may be absent in approximately half to three-fourths of patients with HFpEF [22,23]. Nevertheless, different types of remodelling patterns (including concentric and eccentric LVH and concentric remodelling) can be found in patients with hypertension with or without HFpEF [22-26]. The concentrically hypertrophied LV of the hypertensive patient, with preserved LVEF but with leftward/upward shifting of its pressure volume-relationship reflecting increased filling pressures at rest and/or exercise has often served as an archetype of the pathophysiology of HFpEF, despite its limitations [9,13].

The LVEF is a simple but notoriously preload- and afterload-dependent index that continues to serve as a convenient estimate of LV function, as well as for categorization of the failing heart, both in the clinical and research setting [27,28]. In clinical practice and RCTs, an arbitrary LVEF of less than 35% or 40% has been used to identify patients who have HF with reduced systolic function[5,6,27,28]. The use of a high LVEF cut-off of $\geqslant$50% compared to lower values, e.g. $\geqslant$40%, as a diagnostic criterion for HFpEF is recommended in recent guidelines [5]. However, a preserved LVEF does not exclude LV systolic function abnormalities, and, conversely, diastolic dysfunction mostly coexists with reduced LVEF [29,30].

The utility of the LVEF as a diagnostic tool for HFpEF is limited by the confounding effect of LVH. The LVEF is a parameter of chamber function and is used to express the stroke volume as a fraction of end-diastolic volume. In concentric chamber remodelling, the LVEF may appear increased due to a reduction in LV cavity volume and not due to increased contractility [31]. In addition, there is a difference between LV chamber function (i.e., fractional shortening or LVEF) and myocardial function (i.e., midwall shortening) [32]. As the myocardial contractile elements are located in the midwall, the estimation of LV systolic function depends on the distance from the endocardium to the midwall. When performing measurements for estimation of LV chamber function, the wall is considered infinitely thin. However, this is a misleading assumption in the case of concentric remodelling and LVH. As a result, a seemingly normal LVEF could coexist with depressed midwall shortening, lower cardiac output and higher peripheral resistance[32-35]. Accordingly, LV longitudinal strain, that serves as a proxy for subendocardial function, appears to be a more meaningful measure compared to LVEF to describe alterations in contractility [36]. In hypertensive LVH, longitudinal LV strain may be

affected despite an apparently normal LVEF [37,38]. Impairements in longitudinal LV strain can be more pronounced in patients with HFpEF, and may have implications regarding prognosis and response to treatment [39].

Right heart involvement

The importance of right heart involvement in the clinical syndrome of HFpEF should not be overlooked[40,41]. Elevated left atrial pressures lead to pulmonary hypertension that may be further worsened by superimposed development of increased pulmonary vascular resistance and impaired pulmonary arterial compliance[42]. An elevated pulmonary artery systolic pressure (>35mmHg) has been shown to effectively distinguish HFpEF patients from hypertensive subjects without HF [43]. Chronically increased pulmonary arterial pressures and the resultant right ventricular-pulmonary arterial coupling mismatch are main mediators of right ventricular dysfunction, observed in up to 50% of HFpEF patients and associated with a poor outcome[40,41,44]. Echocardiographic data in patients with a diagnosis of HFpEF and a previous history of pulmonary oedema or invasively confirmed increased filling pressures, showed that right ventricular systolic function and structure may deteriorate to a significantly greater extent over time when compared with the LV [45].

Ventricular-arterial interaction

Using traditional pressure-volume loop analysis, patients with HFpEF show greater ventricular and arterial stiffening compared to what is expected from hypertension or aging alone [46]. Their ratio may approximate its normal value and become less informative. Separate measurements of each component of the ratio with more sensitive markers of myocardial function (e.g. global longitudinal strain) and pulsatile arterial function (e.g. pulse wave velocity for arterial stiffness, augmentation index and reflection magnitude for wave reflections) have been recently recommended[47]. In particular, an increase in wave reflections may unfavourably increase late systolic load, which in turn impairs diastolic function [48].

Abnormalities in ventricular-arterial interaction in HFpEF may affect the clinical response and tolerance to commonly used BP-lowering drugs. Increased arterial stiffness, coupled with increased LV end-systolic elastance may lead to marked fluctuations in BP following changes in loading conditions or stroke volume [49]. The steep end-systolic pressure-volume relationships may thus lead to massive BP decreases without increasing stroke volume when vasodilators are used [50]. In addition, impaired chronotropic reserve along with reduced

stroke volume reserve limit the expected increase in cardiac output during exercise [51]. This phenomenon may be further exacerbated with drug-induced heart rate lowering [52].

The effect of age

The majority of patients with HFpEF are over 65 years old and female. The syndrome of HFpEF is often regarded as an exaggerated presentation of the aging heart (presbycardia). Older patients with HFpEF are more likely to be hypertensive, have lower body weight and exhibit more comorbidities compared to their younger peers [53]. Arterial and ventricular stiffening increase in parallel with age and in older hypertensive patients it is difficult to distinguish to what extent impaired LV diastolic parameters are due to aging per se or are resulting from chronically increased BP elevation, i.e. increased afterload [54]. This poses diagnostic challenges and implications for risk assessment. Impairment of LV relaxation parameters in elderly with otherwise normal hearts is frequent and may be even prognostically benign. As a consequence, some authors have suggested to use age-based values for indices of LV diastolic function [55]. Similarly, an increase in arterial stiffness and wave reflections, on top of the normal aging process, can be easily quantified and age- and sex-specific reference values for central pulsatile haemodynamics are available [56].

Kidney disease and the cardiorenal syndrome

Hypertension is a major risk factor for chronic kidney disease (CKD) which is a common comorbidity in patients with HFpEF [1]. In turn, CKD has been associated with increased risk of new-onset HFpEF and up to half of the patients with HFpEF have CKD defined as a glomerular filtration rate <60ml/min/1.73 m^2 [57]. There is evidence that CKD may be equally or even more strongly associated with mortality in patients with HFpEF than in those with HFrEF [58]. The association between CKD and HFpEF appears to be bidirectional [59]. The prevalence of LVH increases with worsening renal function [60], and patients with HFpEF and CKD have been suggested to have greater LV mass, more pronounced impairment of LV diastolic function, and poorer ventricular and atrial strain measurements compared to subjects with preserved kidney function [61]. Proposed mechanisms implicated in the pathophysiological interactions between the heart and kidney in HFpEF (i.e. the cardiorenal syndrome) include increased central venous and intra-abdominal pressures, RAS activation, oxidative stress, and chronic inflammation. It has been speculated that fibrosis could represent the unifying consequence of inflammation resulting from systemic diseases (such as hypertension or diabetes) and also promotes the

various expressions of the cardiorenal syndrome continuum, including the HFpEF phenotype [62].

Critical appraisal of major outcome trials in patients with HFpEF

Many well-designed landmark RCTs have provided robust evidence that ACEis, ARBs, beta-blockers, and MRAs significantly improve mortality and morbidity in HFrEF [5,6]. A common denominator of these medications is their ability to produce neurohormonal blockade and suppress the activated RAS and sympathetic nervous system. Activation of the RAS and aldosterone pathway is an essential component in the pathophysiology of hypertension, LVH, cardiac remodelling, and fibrosis, even though a direct causative contribution to HFpEF has not been demonstrated [9-12]. A number of trials have been conducted in patients with HFpEF to investigate if the observed efficacy of relevant established treatments in hypertension and HFrEF would extent to this patient group (Table 1) [63-69]. However, all these trials either failed or nearly missed to meet their primary endpoint, a finding that was surprising for most experts given the anticipated crucial role of the RAS in LVH and cardiac remodelling and the development of HF [7,11,12,70]. This has been also in contrast to the evidence of decreased mortality associated with the use of RAS blockers in observational studies [71,72].

It is recognized that the landmark RCTs deploying RAS blockade in HFpEF exhibited several weaknesses that may have underlied their failure as recently reviewed in detail (Table 2) [11]. It is important to note that in these studies BP was already overall well-controlled (<140/90 mmHg) at baseline, and there were substantial rates of concurrent treatment with other antihypertensive drugs. These factors may have impacted the effect size of the interventions [63-67,73,74]. It should also be considered that a substantial proportion of patients (e.g. elderly, people of Black ethnicity) do not respond or respond incompletely to RAS inhibition when used as first-line therapy or in combination drug therapy [75,76]. Finally, the extent of neurohormonal activation in HFpEF is less clear compared to HFrEF [77,78], and while aldosterone associates with LVH in hypertensive patients, this may not be the case with LV diastolic dysfunction [79]. In the following sections, a short overview of the design and limitations of major RCTs in hFpEF is presented.

Trials on RAS blockade

Candesartan in heart failure: assessment of reduction in mortality and morbidity study (CHARM-PRESERVED)

In the CHARM program, HF subgrouping was performed before randomization with patients with LVEF⩽40% allocated to CHARM-Added (candesartan vs. placebo added to standard treatment including ACEi) or CHARM-Alternative (if intolerant to ACEi) and patients with LVEF>40% allocated to CHARM-Preserved [80]. CHARM-Preserved included 3023 patients (65% with an LVEF⩾50%) of which two-thirds were hypertensive and almost half had experienced a myocardial infarction [63]. Ischemic heart disease as a cause of HFpEF was identified in 56% of patients. A reduction in the primary outcome (composite of cardiovascular death or first HF hospitalization) with candesartan compared to placebo failed to reach statistical significance; thus, the study was considered neutral. However, a trend for a reduction in HF hospitalizations was noted (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.72-1.01, *P*= 0.072) and fewer patients were hospitalized with HF in the candesartan group.

Specific points require consideration when examining the conclusions of CHARM-Preserved. From a design aspect, extensive non-randomized use of beta-blockers (56% at baseline), CCBs (31%), ACEis (20%), and spironolactone (12%) and notable discontinuation rates of allocated study medication may have weakened the observed effect in the ARB group. Also, controlling for a large number of baseline covariates identified a more substantial adjusted HR of 0.86 (95% CI 0.74-1.00, *P*=0.051) for the primary composite endpoint and an HR of 0.84 (95% CI 0.70-1.00, *P*=0.047) for HF hospitalization. An analysis utilizing a method that takes into account repeat hospital admissions rather than only time to first event documented a significant reduction in the composite of recurrent HF hospitalizations and cardiovascular death (rate ratio [RR] 0.75, 95% CI 0.62-0.91, *P*=0.003) [81]. The overall positive result of the CHARM program for the combined endpoint with no evidence of heterogeneity by LVEF implies some benefit with candesartan for the entire LVEF range met in HF [82]. The results of CHARM-Preserved have led experts to give a weak recommendation for the use of ARB to reduce hospitalizations in HFpEF [6].

Perindopril in elderly people with chronic heart failure study (PEP-CHF)

In the PEP-CHF study, a total of 850 patients aged ≥70 years (79% hypertensive) diagnosed with HF due to diastolic dysfunction based on clinical and echocardiographic criteria were

randomized to either perindopril 4 mg or placebo [64]. Treatment with diuretics as well as previous HF hospitalization were used to support the diagnosis further. No LVEF cut-off was set, but an LV wall motion index of <1.4 was used as an exclusion criterion serving as a proxy for reduced LVEF. All patients were followed until the last patient had completed at least one year of follow-up (median follow-up 2.1 years). There were an unexpected low event rate and a high rate of open-label ACEi use. After the one year visit, a significant number of patients stopped blinded treatment. At the end of the study 35% of patients in the perindopril group and 37% assigned to placebo were on open-label ACEi. Thus, the steering committee decided to cease recruitment before reaching the initial target of 1,000 participants due to the predicted lack of statistical power for analysis of the primary endpoint. The composite endpoint of total mortality and first HF hospitalization was not different between groups, with the obvious limitation that the low statistical power does not allow conclusions to be drawn. However, it was encouraging that within the first year, when most patients were on assigned therapy, treatment with perindopril was associated with improvements in symptoms and exercise capacity, and reductions in hospitalizations for HF (HR 0.63, 95% CI 0.41-0.97, *P*=0.033).

Irbesartan in heart failure with preserved ejection fraction study (I-PRESERVE)

I-PRESERVE studied the ARB irbesartan vs. placebo in 4133 patients with HFpEF (LVEF≥45%) who were aged ≥60 years and predominantly hypertensive (88%) [65]. Significant baseline symptoms and high rates of subsequent hospitalizations attested to an actual HF population. Hypertension was considered the primary cause of HFpEF in 64% of cases and coronary artery disease in one fourth. There was no difference in either the primary outcome (all-cause death and first cardiovascular hospitalization) or any of the secondary outcomes between groups.

There were significant limitations regarding the efficacy of irbesartan in patients with HFpEF. Use of ACEis was allowed if there was an indication other than hypertension, with a 33% cap in each participating centre. During the trial, use of non-randomized medication reached 73% for beta-blocker, 40% for ACEi, and 28% for spironolactone. The frequent non-randomized use of RAS-blockers, MRA, and beta-blockers may have produced a ceiling effect and prevented any added beneficial impact of irbesartan. Additionally, a high rate of discontinuation of the study drug, reaching 34% by the end of the study, was observed. The primary composite outcome was all-cause death or hospitalization for a cardiovascular cause (HF, myocardial infarction, unstable angina, arrhythmia, or stroke), making comparisons with other relevant studies less straight-forward. Finally, adjustment for baseline differences was not

performed. A recent exploratory analysis which adjusted for prognostic baseline variables routinely available in clinical practice, provided evidence of some significant benefit with irbesartan, documenting a HR of 0.89 (95% CI 0.80-0.99, *P*=0.033) for the primary composite and HR of 0.87 (95% CI 0.77-0.99, *P*=0.039) for the composite of cardiovascular death or HF hospitalization [83].

The role of neprilysin inhibition combined with angiotensin receptor blockade

Neprilysin inhibition has been a tempting therapeutic target for HFpEF in hypertensive patients because the resultant augmentation in natriuretic peptides is expected to enhance vasodilation, increase diuresis/natriuresis, activate guanylyl cyclase, improve myocardial relaxation and reduce LV fibrosis and hypertrophy [84,85]. Stand-alone neprilysin inhibition also increases angiotensin II levels and therefore needs to be combined with a RAS blocker. From a mechanistic point of view, it has been recently shown that soluble neprilysin levels are lower in patients with HFpEF compared to healthy controls [86]. However, this does not necessarily reflect the respective neprilysin activity [86]. Of note, angiotensin receptor neprilysin inhibitors (ARNis) are very effective antihypertensive drugs, and studies in hypertensive patients showed greater reductions in BP as well as LV mass with sacubitril/valsartan compared to ARB treatment [87,88]. The first-in-class ARNi sacubitril/valsartan has been shown to decrease the risk of HF hospitalization or cardiovascular death versus enalapril by 20% in patients with HFrEF [89]. A phase-II study documented greater reductions in NT-pro-Brain Natriuretic Peptide (BNP), left atrial size, BP and dyspnea with ARNi compared to valsartan in HF patients with LVEF>45% [90]. The Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction trial (PARAGON-HF) trial was a randomized, double-blind study that examined the safety and efficacy of ARNi versus stand-alone valsartan on the composite outcome of total hospitalizations for HF (first and recurrent) and cardiovascular mortality in 4822 symptomatic patients aged 50 years or older with LVEF≥45% (average 58%), LVH or left atrial enlargement, and increased natriuretic peptide levels [67]. Similar to patients in previous HFpEF trials, 96% of participants had hypertension, 43% had coronary artery disease, 43% had diabetes and 32% had atrial fibrillation.

In the PARAGON-HF trial, the reduction of the primary endpoint in the ARNi group narrowly failed to reach statistical significance (RR 0.87, 95% CI 0.75-1.01, *P*=0.06). There was, however, a marginally significant reduction in the number of total HF hospitalizations (RR 0.85, 95% CI 0.72-1.00, *P*=0.056). Additionally, an expanded composite endpoint combining the primary endpoint with urgent HF visits was also significantly reduced in the ARNi group

(RR 0.86, 95% CI 0.75-0.99, *P*=0.04) [91]. Prespecified subgroup analysis showed that patients with LVEF equal to or below the median (of 57%) as well as women derived a possible benefit (RR 0.78, 95% CI 0.64-0.95 and RR 0.73, 95% CI 0.59-0.90 for the primary endpoint respectively) [67,92]. A prespecified pooled analysis combining clinical trial data on HFrEF and HFpEF populations showed that the greatest risk reduction with ARNis vs. RAS inhibition alone is observed at lower levels of LVEF, but this benefit extends to a higher LVEF in women compared to men [93]. A post-hoc analysis showed that initiation of treatment with the ARNi early after hospitalization for HF might be accompanied by a more pronounced risk reduction [94]. The ARNi group also presented with significant improvements in quality of life scores and New York Heart Association (NYHA). Importantly, halving of the risk for a prespecified composite of renal events and worsening renal function (HR 0.50, 95% CI 0.33-0.77, *P*=0.001), with the treatment effect extending across the spectrum of baseline renal function, has been demonstrated [67,95]. Additionally, combination of MRA with ARNi rather than valsartan appears to be associated with less decline in renal function [96]. It is important to underline that PARAGON-HF evaluated two distinct RAS blocking strategies, one with the addition of neprilysin inhibition to valsartan, and the other with stand-alone valsartan as the active comparator. A putative placebo analysis of patient-level data from the major trials of ARNi and candesartan in HF patients suggested that there was indeed a clear treatment benefit of ARNi versus putative placebo for HF hospitalization or cardiovascular death across the full range of LVEF up to 60% [97].

The Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients trial (PARALLAX, NCT number: NCT03066804) was recently presented in the ESC Congress 2020. The trial studied the effects of ARNi in 2566 NYHA II-IV patients (97% hypertensive) with LVEF>40% (mean 56%), evidence of structural heart disease and increased NT-pro-BNP [98]. The study population was stratified into three groups based on background therapy with RAS blockers (ACEi vs. ARB vs. no RAS blocker). With the use of such a three-arm parallel-group design, sacubitril/valsartan was tested against enalapril, valsartan, or placebo. The ARNi versus standard medical therapy resulted in significant reductions in the surrogate marker of NT-pro-BNP at 12 weeks, but there was no additional benefit on 6-minute walk distance, quality of life, or NYHA class at 24 weeks [99]. A post-hoc analysis revealed an impressive 51% reduction in the exploratory endpoint of first HF hospitalizations at 24 weeks.

The role of MRAs

Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT)

The use of MRA has been of particular interest for the management of HFpEF, considering their known benefits with respect to endothelial function and cardiac remodelling, particularly fibrosis and stiffness, but also arterial stiffness [100-102]. A positive signal had been observed in the small RCT Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF), which showed an improvement in echocardiographic markers of LV diastolic function with spironolactone [103]. TOPCAT investigated the prognostic effect of spironolactone versus placebo in 3,445 predominantly hypertensive (91%) patients with HFpEF (LVEF≥45%) from the Americas (51%) and Russia/Georgia (49%) [66]. Patients were maintained on medical therapy with diuretics, beta-blockers, and ACEis or ARBs. Spironolactone was uptitrated from 15 mg to 45 mg daily. The mean follow-up was 3.3 years, and the primary outcome was a composite endpoint of cardiovascular death, aborted cardiac arrest and HF hospitalization. The total event rate was 18.6 and 20.4% in the spironolactone and placebo groups respectively, resulting in a non-significant trend for fewer events (HR 0.89, 95% CI 0.77-1.04, *P*=0.14) in favor of spironolactone.

Significant bias related to regional study conduct is strongly suspected of having influenced the actual trial results, even though the treatment-by-region interaction was not statistically significant. Firstly, patients in the Americas were more frequently enrolled based on increased BNP levels compatible with HF, whereas investigators in Russia/Georgia largely enrolled patients based on recent HF hospitalization, a stratum raising the risk of an erroneous diagnosis of HF [66]. Secondly, there were marked regional variations in event rates, which were overall greater and significantly different between groups in the Americas (27.3% in the spironolactone vs. 31.8% in the placebo group; HR 0.82, 95% CI 0.69-0.98, *P*=0.026) compared to Russia/Georgia (9.3% in the spironolactone vs. 8.4% in the placebo group; HR 1.10, 95% CI 0.79-1.51, *P*=0.576) [104]. Thus, the placebo group in Russia/Georgia had a markedly lower occurrence of the primary outcome than in the Americas (8.4% vs 31.8%), being as low as in a healthy population. Lastly, measurements of the serum concentration of the spironolactone metabolite canrenone in 366 patients who consented for the TOPCAT biorepository showed that an estimated 30% of subjects in Russia/Georgia randomized to spironolactone were not receiving or taking the drug [105].

Despite these shortcomings, in the entire population, treatment with spironolactone significantly reduced HF hospitalization rates (HR 0.83, 95% CI 0.69-0.99, *P*=0.04). In addition, in the Americas, spironolactone versus placebo resulted in significantly lower event rates for the primary composite, cardiovascular death and HF hospitalization [104]. Most importantly, in the BNP stratification analysis, spironolactone resulted in lower rates in the primary composite endpoint (HR 0.65, 95% CI 0.49-0.87, *P*=0.003) [106]. Taken the available data together, one could consider that TOPCAT showed the superiority of spironolactone in the patients with biomarker-confirmed HFpEF who took their assigned medication. Additionally, an analysis that examined outcomes across LVEF categories identified a greater estimated benefit of spironolactone at the lower end of the LVEF spectrum [107]. More light may be shed by the results of the ongoing Swedish Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction (SPIRRIT, NCT02901184) and the German Spironolactone In the Treatment of Heart Failure Trial (SPIRIT-HF, EudraCT: 2017-000697-11). The ongoing Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity and Mortality in Participants With Heart Failure and Left Ventricular Ejection Fraction Greater or Equal to 40% (FINEARTS-HF, NCT04435626) has been designed to evaluate the efficacy of the non-steroidal MRA finerenone to reduce cardiovascular death and HF events in patients with HF and an EF≥40%.

The role of beta-blockers and other heart rate lowering drugs

Data from clinical trials suggested that higher heart rates are associated with worse outcomes in HFpEF patients in sinus rhythm [108]. From a physiological standpoint, impaired LV relaxation is associated with reducing LV stroke volume with increasing heart rates [9,13]. Beta-blockers have been traditionally considered of potential benefit because heart rate lowering would be expected to improve early diastolic filling of the stiff hypertrophied LV and reduce myocardial oxygen demand. However, certain caveats need consideration [52]. Heart rate slowing may only prolong diastasis without affecting LV filling at rest. Conversely, prolonged diastolic filling increases ventricular volumes and pressures, increasing the ventricular load and wall stress, as suggested by increased natriuretic peptides observed in patients on beta-blockers [109]. This mechanism may be detrimental for the predominantly older population of HFpEF patients with limited physical activity. In addition, heart-rate slowing drugs may further aggravate chronotropic incompetence, and the limited chronotropic reserve may further impair exercise tolerance. There is a delicate balance between the increase in diastolic filling time and preservation of chronotropic reserve but at the expense of inefficient enhancement of relaxation

with tachycardia [9,51,52]. Finally, the weaker central systolic BP (SBP) reduction with beta-blockers compared to other antihypertensive drugs may provide an additional burden in this population [110].

Trial results on the effects of heart rate lowering in HFpEF patients have been mixed [111-113]. Of note, several relevant studies and meta-analyses have used the low LVEF cut-off of 40 or 45%, making the results difficult to interpret with respect to current HFpEF definitions [111-114]. In terms of intermediate endpoints, the randomized placebo-controlled Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with Diastolic Dysfunction study (ELANDD) failed to show any benefit of nebivolol in symptoms or exercise capacity among 116 patients with an LVEF >45% and evidence of diastolic dysfunction, most of which were hypertensive [115]. Even though the nitric oxide-releasing attributes of nebivolol may favorably affect aortic and ventricular compliance, the negative result was presumably associated with the concomitant inhibition of the heart rate response. Similarly, in HFpEF patients with a heart rate of ≥70 beats per minute, heart rate reduction with the I*f* channel inhibitor ivabradine failed to improve filling pressures and functional capacity and reduce NT-pro-BNP levels [116].

With respect to hard endpoints, The Beta-blockers in Heart Failure Collaborative Group recently pooled individual patient-level data from double-blind RCTs in HF in order to examine the effects of beta-blockers on all-cause and cardiovascular mortality according to LVEF [117]. A total of 17,312 patients from 11 major studies were included. Among patients in sinus rhythm at baseline, in the small group of 244 patients with HFpEF (LVEF>50%), with a baseline median SBP of 147 mmHg, treatment with beta-blockers showed no benefit in terms of all-cause and cardiovascular morbidity. This was in contrast to the substantial benefit observed in the larger groups of HF with reduced LVEF (<40%) and mid-range HF (LVEF 40-49%), although the low number of trial patients included in this LVEF category represents a limitation. An explorative analysis of the American data of the TOPCAT trial showed that among 1567 mostly hypertensive participants with LVEF >50%, baseline beta-blocker use was associated with a greater risk of HF hospitalization (HR 1.74; 95% CI 1.28-2.37) [118]. In the same study, a higher LVEF was also associated with a greater risk among patients receiving beta-blockers, while a sensitivity analysis confirmed the results among patients who continued or discontinued beta-blocker therapy during follow-up [118].

Potential of sodium-glucose co-transporter-2 inhibitors in HFpEF patients with and without diabetes

The sodium-glucose co-transporter-2 (SGLT2) is a low-affinity, high capacity glucose transport protein located in the proximal convoluted tubule of the nephron and responsible for renal glucose reabsorption [119]. Several SGLT2 inhibitors are approved for treatment of type 2 diabetes as they have a glucose-lowering effect with a low risk of hypoglycaemia [120,121]. LV diastolic dysfunction is frequent in diabetes, and shows a strong correlation with insulin resistance and hyperglycaemia [122,123]. HFpEF represents the most frequent form of HF in patients with diabetes and is particularly prevalent in older female patients with hypertension [124]. SGLT2 inhibitors display multiple modes of action with particular interest to diabetic patients with hypertension and HFpEF as they not only reduce blood glucose levels, but also decrease BP, lower body weight and exhibit renal protection [125,126]. There is also evidence that SGLT2 inhibitors may improve volume regulation, reduce arterial stiffness, inhibit cardiac fibrosis, reduce LV mass, improve cardiac energetics and improve diastolic function [126-131].

Use of SGLT2 inhibitors has been shown to significantly lower the risk for hospital admissions for HF in type 2 diabetes mellitus patients at high CV risk, who were mostly hypertensive [132-135]. The risk reductions for HF hospitalizations were consistent and in the range of 27% to 39% [132-135]. Data from the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) have supported the beneficial effect of SGLT2 inhibitors in HFrEF patients with and without type 2 diabetes [136,137]. A prespecified meta-analysis of these two single large-scale trials indicated consistent pooled treatment effects in HFrEF patients [138]. The benefit associated with SGLT2 inhibitors was primarily related to reducing HF hospitalizations, and, secondarily, to improved renal outcomes and decreased all-cause and cardiovascular death. Importantly, these benefits were seen regardless of age, sex, presence of diabetes and treatment with an ARNi [138].

Because of the consistent and convincing RCT data available for SGLT2 inhibitors, recent guidelines and position papers recommend SGLT2 inhibitors for patients with type 2 diabetes and established cardiovascular disease or multiple risk factors to prevent HF hospitalizations [120,121,125,139-142]. Similar recommendations extend to patients with HFrEF regardeless of the presence of diabetes [141,142]. Regarding HFpEF, the ongoing Empagliflozin Outcome trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved, NCT03057951) and Dapagliflozin Evaluation to Improve the Lives of

Patients With Preserved Ejection Fraction Heart Failure trial (DELIVER, NCT03619213) are of great interest as they are dedicated studies in HFpEF to assess the effect of empagliflozin and dapagliflozin on cardiovascular outcomes in patients with LVEF>40% with or without diabetes. Encouraging data were provided by the recently reported Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) RCT, which included patients with type 2 diabetes recently hospitalized for worsening HF (31% with an LVEF over 50%) [143]. Even though the trial was ended early because of loss of funding, it was shown that start of treatment with sotagliflozin around discharge of patients from hospital resulted in significantly lower risk for the primary end point of cardiovascular death and hospitalizations and urgent visits for HF. This treatment effect was consistent across subgroups of LVEF <50% or ≥50%.

Other treatment options

Many proof-of-concept studies, RCTs and observational analyses have examined other medical targets for HFpEF as recently reviewed [144,145]. Published results have either been disappointing (e.g. for organic nitrates) or requiring further investigation (statins, inorganic nitrates/nitrites, cytokine inhibitors, levosimendan). More trials examining novel treatments such as antifibrotic, anti-inflammatory, and anti-oxidant agents, as well as cell therapies, are under way (Table 3). A detailed description of these trials falls outside the scope of this paper but specific points merit a mention. Phosphodiesterase-5 inhibitors have not been shown to improve exercise capacity in HFpEF patients [146], but may be beneficial for some patients with combined pre- and post-capillary pulmonary hypertension. This concept is currently investigated in the Phosphodiesterase-5 Inhibition in Patients With HF With Preserved Ejection Fraction and Combined Post- and Pre-Capillary Pulmonary Hypertension study (PASSION, EudraCT: 2017-003688-37).

Device-based therapies are also investigated and atrial unloading with a transcatheter interatrial shunt device has been shown to safely reduce capillary wedge pressures [147]. Catheter-based renal denervation has been shown to reduce LV mass and improve diastolic function [148], and recent randomized sham-controlled trials in hypertensive patients with or without treatment showed significant reductions in office and ambulatory BP [149,150]. Even though a small, underpowered trial in HFpEF patients failed to show a benefit with renal denervation [151], more trials are required to reveal the role of this method for hypertensive patients with HFpEF.

Therapeutic approach and recommendations for the management of patients with hypertension and HFpEF

In addition to BP control, the treatment of hypertensive patients with HFpEF seeks to 1) minimize symptoms and improve functional capacity and quality of life, 2) slow progression of the disease, 3) reduce the risk of HF hospitalizations and, ultimately, 4) improve cardiovascular outcome and survival (Figure 2). As a crucial step, vigorous management of concomitant risk factors and comorbidities is recommended to improve symptoms and/or prognosis even if relevant data is scarce [5,6,144,145,152]. Currently, no treatment has convincingly been shown to reduce mortality. Noteworthily, in clinical practice this predominantly elderly hypertensive population may be often frail, a characteristic that has been associated with increased dependency, more hospital admissions, and greater mortality [153]. Therefore, secondary targets such as the reduction of hospitalizations and other patient-related outcomes, as, for example, improvements in quality of life metrics, are also important.

Regression of LVH and cardiovascular benefit

Treatment with all major antihypertensive drugs reduces LVH, although beta-blockers may be relatively less effective [70,154-157]. Several analyses from the Losartan Intervention for Endpoint reduction (LIFE) study have shown that in patients with hypertension, LVH regression induced by antihypertensive treatment was accompanied by improvements in indices of diastolic function and systolic performance [33,158]. Additionally, reduction in LVH was associated with lower rates of clinical endpoints including new-onset HF, independently of BP reduction [7,159]. Although similar evidence regarding LVH regression in patients with HFpEF is not yet established, the study data in hypertensive patients with LVH support that LV mass reduction should also be pursued in subjects with HFpEF using strategies that lower cardiac afterload, peripheral vascular resistance and central BP [7,155,156].

Blood pressure targets

No study has directly investigated the optimal BP target in hypertensive patients with HFpEF [160]. Current recommendations may therefore only be based on extrapolations from populations with and without HF [1,160-163]. In the major randomized trials investigating RAS blockers and MRA, baseline BP was overall controlled and this may explain why further clinically non-negligible reductions in BP in the active compared to the control group (Table 1) were not

accompanied by an identifiable decrease in cardiovascular endpoints [63-67]. For instance, in PARAGON-HF, the mean SBP at 8 months was lower by 4.5 mmHg in the ARNi arm compared to the valsartan group, a difference that was not associated with the treatment effect [67]. However, baseline and mean achieved SBP of 120-129 mmHg demonstrated the lowest risk for cardiovascular and renal outcomes [74]. An analysis of the TOPCAT trial in 1645 participants from the Americas examined whether BP-lowering was associated with outcomes [73]. In the trial, the baseline BP was on average 126/71 mmHg and the authors identified a J-shaped association with adverse events as a SBP around 135 mmHg was associated with the lowest risk. A 4.4 mmHg reduction in SBP was observed in the spironolactone arm compared to the control group at eight weeks. This reduction was similar across SBP quartiles and overall sustained throughout the follow-up period, but with limited association with the observed risk reductions [73]. In an analysis of all TOPCAT participants with multiple available SBP measurements, a U-shaped association between a measure of mean SBP obtained during follow-up and mortality was observed, with SBP values of 120-129 mmHg and 130-139 mmHg associated with a lower risk [164]. Also, in a TOPCAT secondary data analysis restricted to patients enrolled in the Americas, spironolactone was associated with greater BP reductions (by 6.1mmHg in SBP) and better BP control in HFpEF patients with characteristics of resistant hypertension. Importantly, the favorable effect of spironolactone on the primary outcome in patients with resistant hypertension was similar to those without resistant [165]. Finally, recent observational analyses from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure registry (OPTIMIZE-HF) provided some evidence that among older patients with HFpEF, a discharge SBP<120mmHg following hospitalization for HF may be associated with worse outcomes [166,167].

Indications for out-of-office BP measurements, namely ambulatory BP monitoring (ABPM) and home BP monitoring, include the diagnosis of white-coat, masked and resistant hypertension as well as the assessment of BP control and the nighttime BP phenotypes [1]. However, published data on out-of-office BP monitoring in hypertensive patients with HFpEF is limited. Recent small observational cohort studies in Japanese patients hospitalized with HFpEF suggested that a riser pattern (a nocturnal BP fall <0% as assessed by ABPM) could be associated with all-cause mortality and cardiovascular outcome [168,169]. The Ambulatory Blood Pressure in HFpEF Outcomes Global Registry (HFPEFGlobal, NCT04065620) is an ongoing observational cohort study designed to assess the association of BP parameters derived from 24-hour ABPM with cardiovascular outcomes, taking also into considerations confounders such as comorbidities, frailty and functional capacity.

No properly designed RCT has been conducted to address BP treatment targets in HFpEF, but many major RCTs in hypertension have included patients with HMOD and HFpEF and have consistently shown that BP-lowering treatment effectively prevents HF events [1,163]. Hypertensive patients with HFpEF belong to the high/very high risk category, and, in agreement with the current recommendations of the 2018 ESC/ESH guidelines, prompt initiation of BP-lowering treatment alongside lifestyle interventions is indicated. In patients aged >80 years, even though the BP threshold for interventions to lower BP is generally ≥160/90mmHg, antihypertensive treatment should also be considered when BP is ≥140/90. In patients younger than 65 years a target SBP in the range of 120-129 mmHg is recommended. [1]; For older patients (age ≥65 years), a target SBP of 130-139 mmHg should be pursued, but treatment decisions should be individualized based on tolerability, frailty, and comorbidities [1]. Accordingly, in older patients, inititation of combination therapy at the lowest available doses is recommended, while for the very old (>80 years), initiation of treatment with monotherapy may be appropriate. A target range between 70-79 mmHg for diastolic BP (DBP) applies to all patients with hypertension including those with HFpEF [1]. In line with current recommendations, it appears wise to avoid actively lowering BP to less than 120/70 mmHg, because the risk of harm may increase and outweigh the benefits [1,170].

Lifestyle changes

Even though there is limited evidence of the effect of different lifestyle measures in patients with HFpEF, promotion of lifestyle changes is recommended in order to improve BP control and possibly reduce cardiovascular events [Figure 2]. A large group of patients with HFpEF are obese and obesity is associated not only with insulin resistance and higher BP but also with reduced functional capacity and increased risk of developing HF [171]. A distinct phenotype of HFpEF patients with a body mass index (BMI) of ≥35kg/m^2 showing more marked concentric LV remodelling, increased plasma volume and greater biventricular filling pressures with exercise has been proposed [172]. Although the optimal body weight target for hypertensive patients with HFpEF has not been established and an obesity paradox has been described in HF, there is evidence of a beneficial effect of diet-induced weight loss on exercise capacity in obese patients with HFpEF [173]. Thus, the current ESC/ESH guideline 2018 recommendation for weight control to avoid obesity appears valid also for hypertensive patients with HFpEF [1].

The role of salt in the pathophysiology of fluid overload in HFpEF is unclear, and the evidence for salt restriction even for patients with HFrEF is weak [5,6,174]. In a small uncontrolled study of 13 hypertensive patients with HFpEF, a three-week restricted sodium intake within the

dietary approach to stop hypertension (DASH) diet led to improvements in LV diastolic function and arterial elastance [175]. Evidence for specific recommendations beyond the current guidelines [1] with respect to sodium intake in HFpEF patients is lacking and there may be variations of optimal sodium intake based on symptoms, renal function and ethnic origin. Until more data are available, the current general recommendation of salt restriction to <5 g per day should be followed in all hypertensive patients, including the ones with HFpEF, particularly those prone to volume overload in order to reduce congestive symptoms [1]. Hypertensive patients with HFpEF should also be advised to pursue a balanced diet rich in vegetables, legumes, whole grains, fresh fruits, low-fat dairy products, fish, and unsaturated fatty acids, and low in red meat and saturated fatty acids.

Regular exercise has been shown to improve cardiorespiratory fitness in patients with HFpEF and may as well affect prognosis. The Exercise Training in Diastolic Heart Failure pilot study (Ex-DHF) had shown that among 64 patients with HFpEF, a supervised combined endurance and resistance training program for three months was associated with improvements in peak VO_2, markers of diastolic function and reported physical functioning [176]. A post-hoc analysis of the TOPCAT trial showed that HFpEF patients who reported ideal physical activity as per current recommendations (≥150 min/week of moderate aerobic activity or ≥75 min/week of vigorous activity) had lower rates of HF hospitalization and mortality compared to those with poor or intermediate level physical activity [177]. In an RCT which included 100 older obese individuals with HFpEF, 20 weeks of caloric restriction lead to a mean decrease of body weight by 7 kg, and a three-times-weekly supervised aerobic session individually and additively increased peak oxygen consumption [173]. Data from meta-analyses further support the concept that exercise training improves exercise capacity and quality of life, with less convincing evidence of a direct action on myocardial systolic or diastolic function [178]. However, very recently, the three-armed RCT Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure (OptimEx-Clin) performed on 180 patients with HFpEF (LVEF> 50%) in NYHA class II or III documented no difference in peak oxygen consumption after 3 months of high-intensity interval versus moderate continuous training, while neither mode met the prespecified clinically important difference in peak $\dot{V}O_2$ compared with 1-time advice on physical activity according to guidelines [179].

Before prescribing an exercise program, baseline evaluation should include an exercise test (preferably cardiopulmonary exercise testing) in order to evaluate functional capacity, chronotropic reserve and BP response to exercise, monitor for ischemia or exercise-induced arrhythmia and accurately prescribe optimal exercise intensity. An exercise regimen tailored to

the needs and capacity of each patient, which usually combines moderate-intensity endurance (3-5.9 metabolic equivalents) and dynamic exercise (30-50% of one-repetition maximum) is recommended [180]. Consideration should be made to include inspiratory muscle training (to enhance functional capacity) and strength training (to reduce sarcopenia) especially in certain high-risk groups such as elderly, frail patients with multiple comorbidities [181]. Implementation of exercise in the context of a cardiac rehabilitation program may be considered depending on individual and resource settings, and patient preferences [180].

Drug therapy

The treatment goals in hypertensive patients with HFpEF are the control of BP per se, along with management of symptoms and improvement in prognosis. In Table 4, proposed recommendations for BP control in these patients and HFpEF-specific treatment are presented. It is suggested that, based on available data, the core drug treatment strategy of the 2018 ESC/ESH guidelines is also applicable for hypertensive patients with HFpEF (Figure 3) [1]. The following modifications of the core treatment algorithm could be considered in HFpEF patients (Table 4, Figure 3):

- **RAS blockers:** BP-lowering with a RAS blocker should be prescribed to all patients if not contraindicated. Apart from their BP-lowering action, available evidence supports a benefit in relation to LVH regression and diastolic function and has provided a positive signal for improvements in exercice capacity and decreases in HF hospitalizations in HFpEF patients [63-65,68-72,155,158,159,182,183]. Additionally, CKD and diabetes mellitus are common comorbidities in patients with HFpEF and RAS blockade has been well documented to reduce albuminuria and delay the progression of diabetic and non-diabetic CKD [1].
- **Diuretics:** The use of thiazide/thiazide-like diuretics is recommended in the current core treatment algorithm for BP control in hypertension, while loop diuretics are recommended in patients with glomerular filtration rates below 30ml/min/1.73m^2 [1]. The thiazide-like diuretics chlorthalidone and indapamide, in particular, have been shown to efficiently reduce the risk of HF in elderly populations [1]. A differential and transiently intensified use of diuretics in HFpEF patients, most commonly loop diuretics, as compared to hypertensive patients with uncomplicated hypertension is often required for volume unloading in order to manage symptoms and avoid hospital visits [5,6,184,185]. A (transient) combination of loop diuretics with a thiazide diuretic, may be required in refractory cases. The optimal dosing of diuretics in HFpEF has not been established. Excessive use should be avoided considering that many patients may be preload-sensitive [186]. In patients with advanced symptoms,

haemodynamic guidance with the use of a microsensor implanted in the pulmonary artery has been shown to significantly reduce hospitalizations [187]. Finally, the loop diuretic torasemide has been shown to improve diastolic function by positively affecting collagen cross-linking [188].

- **MRA:** Spironolactone is the best studied MRA in hypertension as well as HFpEF. While the use of low-dose spironolactone is recommended in patients with resistant hypertension [1,8,165], the addition of spironolactone should be considered earlier, and independently from the stage of BP control, to reduce hospitalizations for HF. Patients who may benefit more are those meeting the criteria of the TOPCAT trial (elevated BNP levels (BNP≥100 pg/ml or N-terminal-pro-BNP≥360 pg/ml, or hospital admission for HF within the previous 12 months), particularly those with a LVEF at the lower end of the spectrum [66,107]. Patients should be closely monitored for changes in potassium levels and renal function, and dosing of other diuretics should be adjusted based on clinical judgment (see Table 4 for further information regarding dosing). Very recently, the Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee voted in favor of expanding the indication of spironolactone for the reduction of HF hospitalization in HFpEF patients[189,190]. A better understanding of the biological alterations in HFpEF and improved clinical phenotyping of HFpEF patients may provide more tailored and compelling evidence on the specific population that will mostly benefit from MRA [191,192]. Accordingly, the heart 'Omics' in AGEing RCT (HOMAGE) examined the effects of spironolactone on people at increased risk of developing HF, who presented with features suggestive of clinically occult HFpEF. Spironolactone led to a significant decrease in systolic BP (by 10 mmHg) and NT-pro-BNP and improved echocardiographic markers of diastolic dysfunction, and, most importantly, appeared to favourably affect type-1 collagen turnover [192]. These findings are of particular interest, considering the role of myocardial fibrosis in patients with HFpEF and hypertension [193,194].
- **ARNi:** For the time being, the results from PARAGON-HF, and the most recent PARALLAX studies have not provided unequivocal evidence on the superiority of ARNi over stand-alone ARB in HFpEF [67,99]. However, additional data and post-hoc analyses suggest that certain patient groups, such as women and those with a LVEF at the lower end of the HFpEF spectrum may derive benefit [67,91-93]. Therefore, ARNIs should be considered as a replacement for conventional RAS blockers in these patient groups to reduce HF hospitalizations. It should also not be dismissed that ARNis represent a very efficacious BP-lowering drug which is, however, not approved for this indication [87,88,195]. Lastly, the same

FDA committee as above, after evaluating the totality of available evidence voted also for an expanded indication for ARNi for HFpEF in the lower LVEF range [196,197]. Following this positive recommendation, the FDA has approved an indication for sacubitril/valsartan to reduce the risk of cardiovascular mortality and HF hospitalizations in adults with chronic HF [198]. Importantly, the new label states that benefits are most clearly evident in patients with LVEF below normal, but does not provide a LVEF cut-off, underlining the importance of clinical judgement in deciding who to treat [198].

- **CCB:** In agreement with the general treatment algorithm, CCB appear as a valid choice in addition to RAS blocker therapy in patients with HFpEF, especially for younger patients or those free from clinical signs and symptoms of congestion. There is, however, limited data on the use of CCBs in HFpEF. Earlier small studies had shown improvements in diastolic function with non-dihydropyridine CCBs, but these results have not been examined in more recent trials [199]. The negative chronotropic and inotropic effect of non-dihydropyridine CCBs may be unsuitable for some patients, and regular follow-up to detect worsening LV function may be required. Non-dihydropyridine CCB are effective drugs for rate control in atrial fibrillation. The prognostic benefit of CCBs is unclear; in an analysis of 10570 patients over 65 years old hospitalized with HFpEF (LVEF≥40%), a new discharge prescriptions for CCB was not associated with improvements in mortality, regardless of the class of the CCB [200,201].
- **Beta-blockers:** In the 2018 ESC/ESH guidelines, beta-blockers are generally recommended at any treatment step when there is a specific indication in the core algorithm for patients with hypertension. However, while their use in HFrEF is clearly supported by a class I, level of evidence A indication, this does not apply to the HFpEF population [1,5,6,113]. On the contrary, there is even data supporting their cautious use in HFpEF patients, especially those with limited chronotropic reserve [51,52]. This contrasts with their frequent use in up to 80% of HFpEF patients as reflected in contemporary HFpEF studies (Table 1) [66,67]. Nevertheless, beta-blockers are effective antihypertensive agents and a very recent meta-analysis confirmed that treatment with beta-blockers results in significant reductions in cardiovascular endpoints, including heart failure events, that appear more pronounced among hypertensive patients [202]. In addition, an elevated heart rate has been associated with morbidity and mortality and a heart higher than 80 beats per minute has been included in the current ESC/ESH 2018 guidelines as a factor that influences cardiovascular risk [1,203]. Consequently, beta-blockers can be combined with any of the other major drug classes for BP control in HFpEF patients, especially those with other cardiac indications, e.g. angina,

post-myocardial infarction or arrhythmias including atrial fibrillation requiring heart rate control.

- **SGLT2 inhibitors:** Empagliflozin, canagliflozin, dapagliflozin, ertugliflozin and more recently sotagliflozin (a combined SGLT2 and SGLT1 inhibitor) have been consistently shown to reduce the risk of HF events in patients with diabetes mellitus and established cardiovascular disease or high cardiovascular risk [132-135]. They are therefore expected to be of significant benefit also for hypertensive patients with diabetes mellitus and HFpEF. When prescribing these medications, their BP-lowering and natriuretic effect should be taken into consideration, The results of upcoming RCTs shall provide more evidence on the role of these drugs in patients with HFpEF with or without diabetes.

Future directions

Phenotyping of HFpEF

Patients with HFpEF present with remarkable diversity in terms of predisposing factors, pathophysiologic mechanisms, clinical patient profiles and level of non-cardiac involvement [9,13-17,21]. Heterogeneity of HFpEF is already evident from the fact that not all HFpEF patients present with LVH or diastolic dysfunction [22-25]. Similarly, the fact that antifibrotic agents could be more effective in patients exhibiting a more pronounced fibrotic phenotype may partially explain why large trials of drugs targeting the RAS, which did not specifically include such patients, have failed to provide a solidly positive result [63-67,85,191-194,204-206]. Classification attempts based on epidemiological data, clinical characteristics, biological markers as well as machine-learning technology (phenomapping) have recently proven promising for identifying specific patient phenotypes who may benefit from more targeted treatment [14-17]. For instance, a combination of different clinical presentations and predisposing factors has provided twenty different HFpEF phenotypes that may be addressed in order to design individualized treatment [15]. The optimal approach in relation to phenotyping (e.g. pathophysiological vs clinical) and how this may translate to personalized treatment and improve outcomes is a main area of scientific interest [14-17]. For example, lately there has been evidence that the burden of atrial fibrillation in patients with HFpEF may mark a distinct phenotype with impaired atrial mechanics, abnormal ventricular interactions and a different prognosis [207]. In terms of future research, it may appear more effective to investigate medical treatments in specific sub-populations (e.g. patients with/without obesity or atrial fibrillation, with phenotypes derived

from machine learning-based clustering), rather than all-comers under the umbrella term of HFpEF [208].

Study methodologies and patient selection

A number of issues should be considered for future trials in patients with HFpEF. The taxonomy of HF has caused confusion with respect to interpretation of study results as well as treatment decisions. The current European definition of HFpEF requires an EF>50%, but a lower cut-off (e.g. >45% or >40%) has been used in most landmark studies [5,6]. Post-hoc analyses of major trials have suggested a greater treatment effect in those patients with an LVEF at the lower end of the HFpEF range (e.g. LVEF<50%), which has been labeled as mid-range HF [82,93,107]. Moreover, with speckle tracking echocardiography and measurement of longitudinal strain it is possible to identify HFpEF with concurrent LV systolic dysfunction, which has been associated with a worse outcome [36-39,209]. The first phase of ejection fraction, which corresponds to the percentage change in LV volume from end-diastole to peak ventricular fiber shortening, has also been shown to be impaired in hypertensive patients with diastolic dysfunction and could represent an early marker of systolic impairment despite a preserved LVEF [210]. Finally, following the recent approach of the FDA to the labelling of sacubitril/valsartan, where there was no mention of HF classification by LVEF [185], a new universal definition of HF may be contemplated [211-213]. This definition would be based on signs and symptoms, cardiac abnormalities and mode of presentation, further enriched by the etiology of HF (e.g. hypertensive HF), rather than nominal LVEF values[211,212].

The addition of an elevated BNP or NT-pro-BNP as a biomarker criterion may further ensure that patients genuinely have HFpEF. However, normal levels observed in symptom-free periods and obese individuals may falsely preclude some patients from being enrolled in trials. At the same time, comorbidities (such as CKD or bouts of recurrent atrial fibrillation) or pharmacological interventions (such as beta-blockade) may increase circulating levels. The identification of markers of maximal clinical response to currently available or future treatments is an important objective in order to shape the optimal treatment for each patient. In this direction, analyses of I-PRESERVE and TOPCAT have documented a greater prognostic benefit for irbesartan and spironolactone respectively, in patients with lower BNP levels who may have less advanced disease [91,214]. However, no interaction has been shown between baseline NT-pro-BNP and the treatment effect of ARNi in PARAGON-HF [215].

Conclusions

We propose that further high-quality studies with careful patient selection fulfilling criteria of the dominant - in terms of prevalence and etiology- hypertensive HFpEF phenotype, will provide more definite evidence (Table 5). The studies need to be sufficiently powered and the study design should take into account the limitations as well as lessons learned from previous trials. Given the large volume of research demonstrating the effectiveness of RAS-blockers and MRA in hypertension, HFrEF and other cardiovascular diseases, these drug classes currently appear to have a potential in hypertensive patients with HFpEF not yet sufficiently explored. It remains to be seen whether the positive results of major hypertension trials that have investigated the aforementioned pillars of current cardiovascular therapy indeed extend to this group of patients. Finally, the results of already ongoing or planned studies using newer therapies such as SGLT2 inhibitors or the non-steroidal MRA finerenone in HFpEF patients may further modify the recommendations for the medical therapy of HFpEF per se and mainly in patients with hypertension due to the BP-lowering potential of these drugs.

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Figure legends

Figure 1.

Hypertension and HFpEF. The pathophysiologic milieu of hypertension (panel A) sets the stage for the development of further functional and structural changes in HFpEF (panel B) that underlie the clinical phenotype of symptomatic HFpEF patients (panel C). Selected mechanisms, risk factors and comorbidities are listed, while several other abnormalities not shown may be involved in HFpEF. Some mechanisms may contribute to more than one pillar across the disease continuum. Certain abnormalities may be evident only during exercise. The impairment of systolic and diastolic reserve and ventricular-arterial coupling, in conjunction with changes in preload, afterload, heart rate and rhythm, is central to the generation of symptoms. Comorbidities variably contribute to abnormalities throughout the disease process.
RAS, renin-angiotensin-system; LV, left ventricle; NO, nitric oxide; ECM, extracellular matrix; cGMP, cyclic guanosine monophosphate; EF, ejection fracton; LVEDP, left ventricular end-diastolic pressure.

Figure 2.

Stepwise approach to the management of the hypertensive patient with HFpEF.
BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; OSA, obstructive sleep apnea; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.
* SBP targets should always be indiviualized, based on tolerability, particularly in frailer old or very old patients.

Figure 3.

Drug treatment strategy for patients with hypertension and HFpEF. The core treatment algorithm for drug treatment of the ESC/ESH 2018 guidelines adapted for hypertensive patients with HFpEF.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist; ARNi, angiotensin receptor neprilysin inhibitor; SGLT2, sodium-glucose co-transporter-2.

Table 1. Major randomized controlled trials in HFpEF

Trial, Year *N* Duration	**Study drug Mean dose**	**Patient characteristics**	**NYHA**	**Previous HF hospitalisation**	**Concurrent antihypertensive medications**	**Initial BP and HR (Means)**	**Decrease in BP compared to placebo group**	**Endpoints and unadjusted outcomes**
CHARM-Preserved [63], 2003 *N*= 3023 Median 37 months	Candesartan 25 mg	EF: 54 % Age: 64 yr. Women: 40 % BMI: 29 kg/m^2 HT: 64 % DM: 28 %	Range: II-IV III-IV: 38%	69%	Diuretic: 75% β-blocker: 56% CCB: 31% ACE-I: 20% Spiro.: 11%	136/78mmHg, 71bpm	↓6.9mmHg (systolic BP), ↓2.9mmHg (diastolic BP) at 6 months	*CV death & first HF hospitalization:* HR, 0.89; 95% CI 0.11-1.03; *P*= 0.12 *First HF hospitalization:* HR, 0.85; 95% CI 0.72-1.01; *P*= 0.072
PEP-CHF [64], 2006 *N*= 850 Mean 26 months	Perindopril 4 mg	EF: 64 % Age: 76 yr. Women: 56 % BMI: 28 kg/m^2 HT: 79 % DM: 21 %	Range: I-IV III-IV: 24%	100%	Diuretic: 100% β-blocker: 55% CCB: 33% ACE-I: 36% Spiro.: 10 %	139/80mmHg, 73bpm	Greater decrease in systolic and diastolic BP (values not available)	*All cause death & first HF hospitalization:* HR, 0.92; 95% CI 0.70-1.21; *P*= 0.55 *First HF hospitalization:* HR, 0.86; 95% CI 0.61-1.20; *P*= 0.37

I-PRESERVE [65], 2008 ***N*= 4128** **Mean 49.5 months**	Irbesartan 300 mg	EF: 59 % Age: 72 yr. Women: 60 % BMI: 30 kg/m^2 HT: 88 % DM: 27 %	Range: II-IV III-IV: 80%	44%	Diuretic: 90% β-blocker: 73% CCB: 40% ACE-I: 40% Spiro.: 28%	136/79mmHg, 71bpm	↓3.6mmHg (Systolic BP), ↓1.9mmHg (Diastolic BP) at 6 months	*All cause death & first CV hospitalization:* HR, 0.95; 95% CI 0.86-1.05; *P*= 0.35 *First CV hospitalization:* HR, 0.95; 95% CI 0.85-1.08; *P*= 0.44
TOPCAT [66,73], 2014 ***N*= 3445** **Mean 40 months**	Spironolactone 25mg	EF: 56 % Age: 69 yr. Women: 52 % BMI: 31 kg/m^2 HT: 91 % DM: 33 %	Range: II-IV III-IV: 33%	72%	Diuretic: 82% β-blocker: 78% CCB: 37% ACE-I: 84% Spiro.: N/A	130/80mmHg, 68 beats/min	↓4.4mmHg (Systolic BP) (Americas) at 8 weeks	*CV death & aborted cardiac arrest & first HF hospitalization:* HR, 0.89; 95% CI 0.77-1.04; *P*= 0.14 *First HF hospitalization:* HR, 0.83; 95% CI 0.69-0.99; *P*=0.04
PARAGON HF [67,74], 2019 ***N*= 4796**	Sacubitril/Valsartan 200mg	EF: 58 % Age: 73 yr. Women: 52 % BMI: 30 kg/m^2 HT: 95 %	Range: II-IV III-IV: 20%	48%	Diuretic: 95% β-blocker: 80% CCB: 37% ACE-I: N/A Spiro.: 26%	131/74mmHg, 70bpm	↓4.5mmHg (Systolic BP) at 8 months	*CV death & total HF hospitalization:* RR, 0.87; 95% CI 0.75-1.01; *P*= 0.06 *Total HF hospitalization:*

Median 35 months		DM: 43 %						RR, 0.85; 95% CI 0.72-1.00. *P*= 0.056

HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; HF, heart failure; BP, blood pressure; HR, heart rate or hazard ratio; EF, ejection fraction; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; CCB, calcium channel blocker; ACE-I, angiotensin converting enzyme inhibitor; CV, cardiovascular; CI, confidence intervals; RR, rate ratio.

Table 2. Parameters that may have affected study results in major randomized controlled trials in HFpEF
Different accepted cut-offs of left ventricular ejection fraction for inclusion in the study
Markers of confirmation of HFpEF (e.g. indices of diastolic function, structural heart disease, elevated biomarkers, prior HF hospitalization)
Blood pressure control at study entry
Selection of placebo vs active comparator for the control arm
Concurrent treatment with other antihypertensive/HF medication during follow-up
Selection of endpoints and composite outcomes (e.g., first vs. recurrent HF hospitalizations, urgent HF visits, total vs. cardiovascular mortality)
Other issues related to study conduct/data analysis (e.g., insufficient statistical power, early study termination, lack of adjustment for potential confounders, regional differences)
HFpEF, heart failure with preserved ejection fraction; HF, heart failure.

Table 3. Representative ongoing trials examining treatments in HFpEF						
Trial name	**Identifier**[a]	**Phase**	**Treatment**	**Sample size (Actual or estimated)**	**Follow-up for main endpoint**	**Main endpoint**
Mineralocorticoid receptor antagonists						
FINEARTS-HF	NCT04435626	3	Finerenone	5500	42 months	Number of CV deaths or HF hospitalizations
SPIRRIT-HFPEF	NCT02901184	3	Spironolactone	3200	5 years	CV death or first HF hospitalization
SPIRIT-HF	2017-000697-11	3	Spironolactone	1300	5 years	CV death or first HF hospitalization
Angiotensin receptor neprilysin inhibitors						
CNEPi	NCT03506412	4	Sacubitril/ Valsartan	40	5 weeks	Change in biomarkers that reflect neprilysin activity
PARAGLIDE-HF	NCT03988634	3	Sacubitril/ Valsartan	800	8 weeks	Proportional change in NT-pro-BNP
PERSPECTIVE	NCT02884206	3	Sacubitril/ Valsartan	592	3 years	Change in Global Cognitive Composite Score
PRISTINE HF	NCT04128891	3	Sacubitril/ Valsartan	60	12 months	Improvement in microvascular function and ischaemia
Beta-blockers						

CAYMUS HFpEF	NCT03948685	4	Carvedilol SR	300	24 weeks	Change in maximum NT-pro-BNP value
Preserve-HR	NCT03871803	4	Drug withdrawal	4	30 days	Change in peak VO2
Sodium-glucose co-transporter-2 inhibitors						
EMPEROR-Preserved	NCT03057951	3	Empagliflozin	5988	38 months	CV death or first HF hospitalization
EMPULSE	NCT04157751	3	Empagliflozin	500	90 days	Death or HF events or HF visits and change in KCCQ
DELIVER	NCT03619213	3	Dapagliflozin	6100	33 months	CV death rate or first HF hospitalization or urgent HF visit
DETERMINE-Preserved	NCT03877224	3	Dapagliflozin	504	16 weeks	Change in KCCQ and 6MWD
PRESERVED-HF	NCT03030235	4	Dapagliflozin	320	12 weeks	Change in KCCQ
Metformin						
PH-HFpEF	NCT03629340	2	Metformin	32	12 weeks	Mean pulmonary artery pressure during submaximal exercise
Inorganic nitrites/nitrates						
INABLE	NCT02713126	2	Sodium nitrite	100	12 weeks	Change in peak VO2
KNO3CK OUT HFPEF	NCT02840799	2	Potassium nitrate	76	12 weeks	Change in peak VO2 and total work during maximal-effort exercise test

ONOH	NCT02918552	2	Sodium nitrite	15	8 weeks	Change in peak VO2
PMED	NCT02980068	1	Oral nitrate	120	6 hours	Change in nitrite/nitrate level in urine/plasma, bacterial content of oral/gut microbiome
Soluble guanylate cyclase stimulators						
DYNAMIC	NCT02744339	2	Riociguat	114	26 weeks	Change in cardiac output
Phosphodiesterase-5 inhibitors						
PASSION	2017-003688-37	2	Tadalafil	372	24 weeks	All-cause death or first HF hospitalization
Endothelin receptor antagonists						
SERENADE	NCT03153111	2	Macitentan	143	24 weeks	Change in NT-pro-BNP levels
Prostacyclin derivatives						
ILO-HOPE	NCT03620526	4	Iloprost	34	15 minutes	Change in pulmonary capillary wedge pressure after exercise
Antifibrotic agents						
PIROUETTE	NCT02932566	2	Pirfenidone	129	12 months	Change in extracellular volume in cardiac magnetic resonance
B3- Adrenergic receptor agonists						
BETA3_LVH	NCT02599480	2	Mirabegron	297	12 weeks	Change in left ventricular mass index, E/e′
Calcium sensitizer						

HELP	NCT03541603	2	Levosimendan	38	6 weeks	Change in PCWP
Fatty acid β-oxidation inhibitor						
DoPING-HFpEF	2018-002170-52	2	Trimetazidine	25	12 weeks	Change in PCWP
Anti-hyperuricemic drugs						
AMETHYST	2019-004862-16	2	Verinurad+ allopurinol	435	32 weeks	Change in exercise capacity
Cell therapy						
CELL-pEF	NCT02923609	2	CD34+ cell therapy	30	12 months	Change in E/e′ assessed by cardiac magnetic resonance
Regress-HFpEF	NCT02941705	2	Allogeneic cardiosphere-derived cells	40	3 years	Safety profile during or post intracoronary delivery and during follow-up
Management of comorbidities/ exercise therapy						
Cardiac Rehab Effects in HFpEF	NCT04506606	-	Afferent block	50	1 hour	Femoral blood flow
FAIR-HFpEF	NCT03074591	2	Ferric carboxymaltose	200	12 months	Change in 6MWD
OPTIMIZE-HFPEF	NCT02425371	3	Management of comorbidities	410	2 years	Change in patient's well-being
PREFER-HF	NCT03833336	3	Ferric carboxymaltose	72	24 weeks	Change in 6MWD

Resistance Training in HFpEF	NCT02435667	-	Resistance Exercise Training	24	12 weeks	Bone density and strength, cardiopulmonary function, quality of life, blood biomarkers
Device therapies						
CCM-HFpEF	NCT03240237	Pilot	Cardiac contractility modulation	60	24 weeks	Change in KCCQ
CORolla	NCT02499601	-	CORolla® TransApical Approach	10	6 months	All-cause mortality and serious adverse events
GUIDE-HF	NCT03387813		CardioMEMS	3600	12 months	Change in all-cause mortality, total number of HF hospitalizations, IV diuretic visits
PREFECTUS	NCT03338374	-	Cardiac resynchronization therapy	10	12 weeks	Change in diastolic and systolic reserve index in echocardiography
RAPID-HF	NCT02145351	-	Rate adaptive atrial pacing	30	4 weeks	Change in VO2 at ventilator anaerobic threshold
REDUCE LAP-HF II	NCT03088033	-	Interatrial shunt device	608	12 months	CV death or first non-fatal stroke or HF admissions and change in KCCQ

HFpEF, heart failure with preserved ejection fraction; CV, cardiovascular death; HF, heart failure; NT-pro-BNP, NT-pro-brain natriuretic peptide; 6MWD, 6-minute walk distance; KCCQ, Kansas City cardiomyopathy questionnaire; PCWP, pulmonary capillary wedge pressure.
[a]Identifier corresponds to clinical trial identifier in ClinicalTrials.gov or the European Union Clinical Trials Register.

Table 4. Proposed recommendations for treatment of hypertensive patients with HFpEF		
Recommendations*	**Class**	**Level**
Recommendations for BP control		
Prompt initiation of BP-lowering treatment is recommended simultaneously with lifestyle interventions when BP is ≥140/90 mmHg [1].	**I**	**A**
Although initiation of BP-lowering treatment and lifestyle interventions in individuals aged >80 years is generally recommended when SBP is ≥160mmHg, antihypertensive treatment should be considered in patients with HFpEF at this age when BP is ≥140/90 mmHg and treatment is tolerated [1,5].	**IIa**	**C**
It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower, in most patients [1].	**I**	**A**
In patients < 65 years it is recommended that SBP should be lowered to a BP range of 120-129 mmHg [1].	**I**	**A**
In patients ≥65 years it is recommended that SBP should be targeted to a BP range of 130-139 mmHg [1].	**I**	**A**
A DBP target in the range of 70-79 mmHg is recommended [1].	**I**	**A**
The BP threshold for initiation of treatment and the BP targets need to be individualized based on tolerability, frailty, and comorbidities, particularly for the elderly (>65 years). Close monitoring of adverse effects is recommended [1].	**I**	**C**
For BP control, combination treatment is recommended for most patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACEi or an ARB) with a thiazide/thiazide-like diuretic or CCB [1].	**I**	**A**
It is recommended to initiate antihypertensive treatment with a two-drug combination, preferably in an SPC [1].	**I**	**B**

It is recommended that beta-blockers are combined with any of the other major drug classes for BP control, particularly when there are other specific clinical situations, e.g., angina, post-myocardial infarction, or heart rate control [1,200].	**I**	**A**
For BP control, addition of low-dose spironolactone[a], if tolerated, to existing BP-lowering therapy is recommended in patients with HFpEF and resistant hypertension [1,8,165].	**I**	**B**
HFpEF-specific recommendations		
Intensified use of diuretics, including loop diuretics, is recommended to relieve congestion and manage symptoms [5].	**I**	**C**
Irrespective from targeting BP, low-dose spironolactone[a] should be considered to reduce HF hospitalizations[b] [66,104,106].	**IIa**	**B**
Irrespective from targeting BP, use of sacubutril/valsartan (ARNi) as an alternative to ACE inhibitor or ARB should be considered to reduce worsening HF[c] [67,92-96].	**IIa**	**B**
SGLT2 inhibitors are recommended in hypertensive patients with diabetes mellitus to reduce the risk of HF hospitalization [125,132-135,139-143].	**I**	**A**
HFpEF, heart failure with preserved ejection fraction; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; RAS, renin-angiotensin system; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; SPC, single pill combination; HF, heart failure; ARNi, angiotensin receptor neprilysin inhibitor; SGLT2, sodium-glucose co-transporter-2 inhibitor.		
[a]The dose range for spironolactone in the PATHWAY-2 study in resistant hypertension was 25 mg with forced titration to 50 mg once daily [8]. The dose range for spironolactone in the TOPCAT study in HFpEF was 15 to 45 mg once daily (mean dose 25 mg) [66]. A cautious use is recommended, particularly because of the risk of hyperkalaemia, in patients with an eGFR < 45 ml/min/1.73m^2 or baseline potassium ≥4.5		

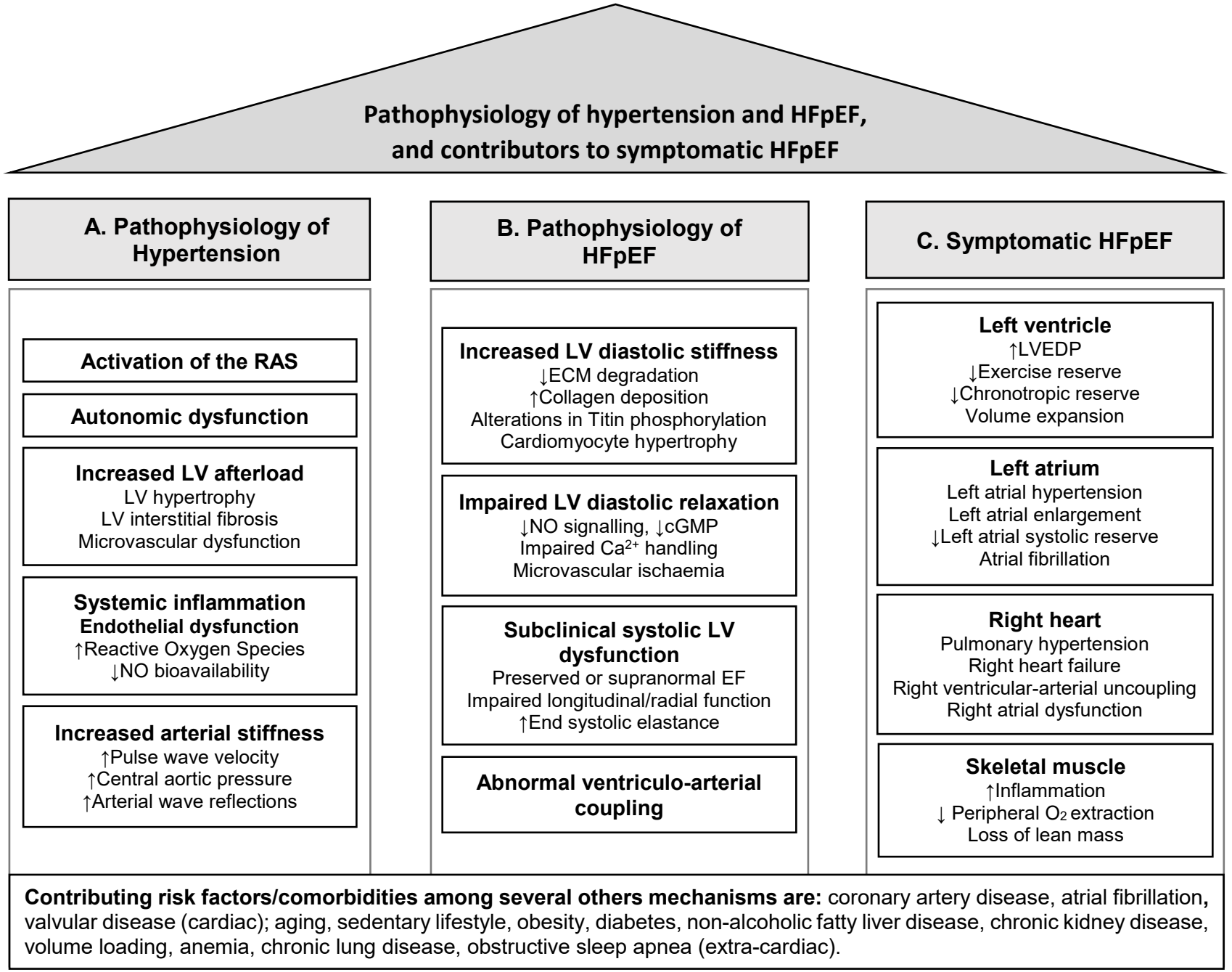
mmol/L based on PATHWAY-2 [8]. Patients with baseline potassium ≥5.0 mmol/L within the past two weeks or ≥5.5 mmol/L in the past six months, or with eGFR< 30 ml/min/1.73m^2 were excluded in TOPCAT [66].

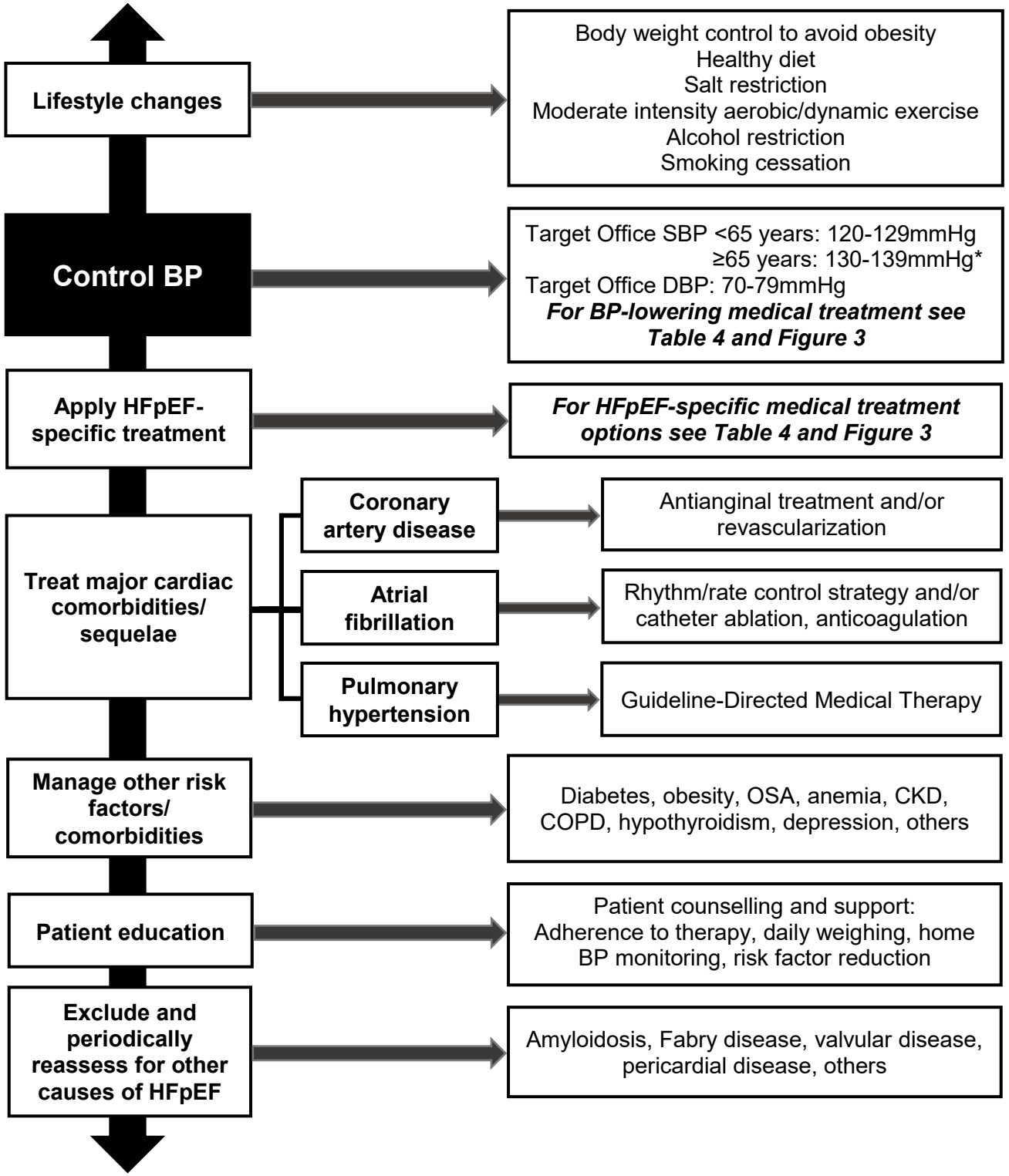
[b]A greater benefit of spironolactone was observed in patients with LVEF< 50% [66,107].

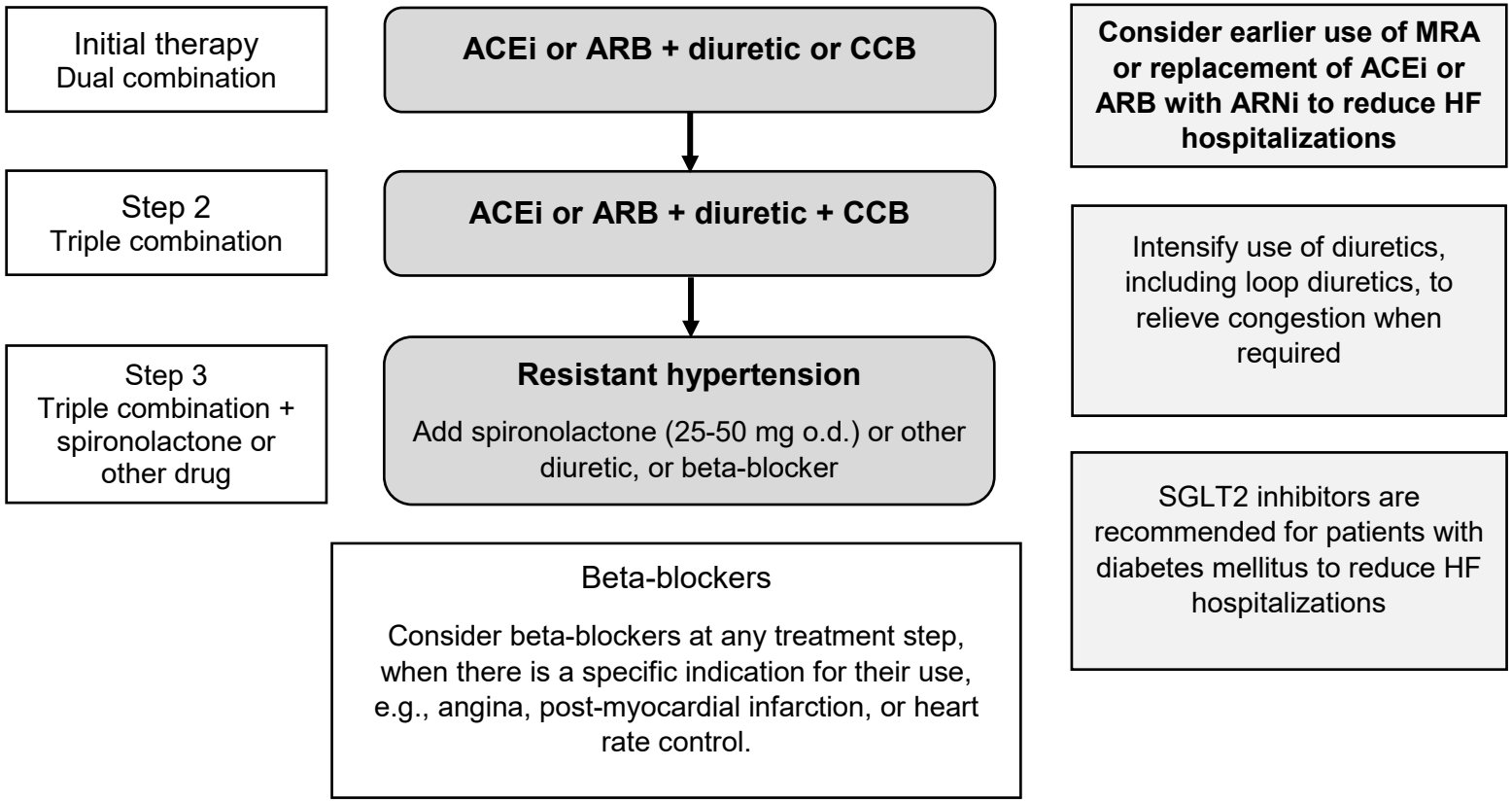
[c]A greater benefit of sacubutril/valsartan was observed in patients with LVEF≤ 57% [67,93].

*The 2018 ESC/ESH guidelines did not include dedicated recommendations for HFpEF. Accordingly, the following recommendations are based on a critical appraisal of the general recommendations in these guidelines, novel data and reports with potential impact on HFpEF in hypertension.

Table 5. Upcoming advances and expectations related to the management of HFpEF in hypertension
Establishment of most effective and practical classification of HFpEF patients (subphenotyping) to develop individualized and targeted therapies • Mechanistic/biological • Etiological • Clinical • Data-derived clustering
Optimization of study design to accurately include HFpEF patients • Utilization of a LVEF cut-off >50% • Consideration of subclinical systolic dysfunction • Utilization of undisputable markers of HFpEF (e.g. HF hospitalization, structural abnormalities, elevated biomarkers)
Determination of sex-related differences in disease presentation, prognosis and response to treatment
Determination of the role of atrial fibrillation in classification of HFpEF and disease course
Re-evaluation of established cardiovascular therapies (RAS blockade, MRA, ARNi) on specific HFpEF phenotypes, including patients with (uncontrolled) hypertension
Interpretation of the role of fibrosis and extracellular matrix homeostasis and the response to specific drug treatments
Identification of markers of greater response to certain pharmaceutical agents, with respect to symptoms and risk reduction
Trial results of promising therapies (SGLT2 inhibitors, sitagliptin, pirfenidone, mirabegron, others)
Clarification of the contribution of lifestyle measures and exercise therapy to quality of life and prognosis
HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; HF, heart failure; RAS, renin-angiotensin system; MRA, mineralocorticoid receptor antagonist; ARNi, angiotensin receptor neprilysin inhibitor; SGLT2, sodium-glucose co-transporter 2.


Pathophysiology of hypertension and HFpEF,
and contributors to symptomatic HFpEF
A. Pathophysiology of Hypertension
Activation of the RAS
Autonomic dysfunction
Increased LV afterload
LV hypertrophy
LV interstitial fibrosis
Microvascular dysfunction
Systemic inflammation
Endothelial dysfunction
↑Reactive Oxygen Species
↓NO bioavailability
Increased arterial stiffness
↑Pulse wave velocity
↑Central aortic pressure
↑Arterial wave reflections
B. Pathophysiology of HFpEF
Increased LV diastolic stiffness
↓ECM degradation
↑Collagen deposition
Alterations in Titin phosphorylation
Cardiomyocyte hypertrophy
Impaired LV diastolic relaxation
↓NO signalling, ↓cGMP
Impaired Ca2+ handling
Microvascular ischaemia
Subclinical systolic LV dysfunction
Preserved or supranormal EF
Impaired longitudinal/radial function
↑End systolic elastance
Abnormal ventriculo-arterial coupling
C. Symptomatic HFpEF
Left ventricle
↑LVEDP
↓Exercise reserve
↓Chronotropic reserve
Volume expansion
Left atrium
Left atrial hypertension
Left atrial enlargement
↓Left atrial systolic reserve
Atrial fibrillation
Right heart
Pulmonary hypertension
Right heart failure
Right ventricular-arterial uncoupling
Right atrial dysfunction
Skeletal muscle
↑Inflammation
↓ Peripheral O2 extraction
Loss of lean mass
Contributing risk factors/comorbidities among several others mechanisms are: coronary artery disease, atrial fibrillation, valvular disease (cardiac); aging, sedentary lifestyle, obesity, diabetes, non-alcoholic fatty liver disease, chronic kidney disease, volume loading, anemia, chronic lung disease, obstructive sleep apnea (extra-cardiac).


Lifestyle changes
Body weight control to avoid obesity
Healthy diet
Salt restriction
Moderate intensity aerobic/dynamic exercise
Alcohol restriction
Smoking cessation
Control BP
Target Office SBP <65 years: 120-129mmHg
≥65 years: 130-139mmHg*
Target Office DBP: 70-79mmHg
For BP-lowering medical treatment see Table 4 and Figure 3
Apply HFpEF-specific treatment
For HFpEF-specific medical treatment options see Table 4 and Figure 3
Treat major cardiac comorbidities/ sequelae
Coronary artery disease
Antianginal treatment and/or revascularization
Atrial fibrillation
Rhythm/rate control strategy and/or catheter ablation, anticoagulation
Pulmonary hypertension
Guideline-Directed Medical Therapy
Manage other risk factors/ comorbidities
Diabetes, obesity, OSA, anemia, CKD, COPD, hypothyroidism, depression, others
Patient education
Patient counselling and support: Adherence to therapy, daily weighing, home BP monitoring, risk factor reduction
Exclude and periodically reassess for other causes of HFpEF
Amyloidosis, Fabry disease, valvular disease, pericardial disease, others


Initial therapy
Dual combination
ACEi or ARB + diuretic or CCB
Consider earlier use of MRA or replacement of ACEi or ARB with ARNi to reduce HF hospitalizations
Step 2
Triple combination
ACEi or ARB + diuretic + CCB
Intensify use of diuretics, including loop diuretics, to relieve congestion when required
Step 3
Triple combination + spironolactone or other drug
Resistant hypertension
Add spironolactone (25-50 mg o.d.) or other diuretic, or beta-blocker
SGLT2 inhibitors are recommended for patients with diabetes mellitus to reduce HF hospitalizations
Beta-blockers
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g., angina, post-myocardial infarction, or heart rate control.