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Review Article

The current best drug treatment for hypertensive heart failure with preserved ejection fraction[#]

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ABSTRACT

More than 90 % of patients developing heart failure (HF) have hypertension. The most frequent concomitant conditions are type-2 diabetes mellitus, obesity, atrial fibrillation, and coronary disease. HF outcome research focuses on decreasing mortality and preventing hospitalization for worsening HF syndrome. All drugs that decrease these HF endpoints lower blood pressure. Current drug treatments for HF are (i) angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or angiotensin receptor neprilysin inhibitors, (ii) selected beta-blockers, (iii) steroidal and non-steroidal mineralocorticoid receptor antagonists, and (iv) sodium-glucose

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; CCD, chronic coronary disease; CHARM, candesartan in heart failure assessment of reduction in mortality and morbidity; CHF, congestive heart failure; CONSENSUS, cooperative North Scandinavian Enalapril survival study; DELIVER, dapagliflozin in heart failure with mildly reduced or preserved ejection fraction; DHP-CCB, dihydropyridin-calcium channel blocker; EMA, European medical agency; EMPEROR PRESERVED, empagliflozin in heart failure with a preserved ejection fraction; EMPEROR REDUCED, empagliflozin in heart failure with a reduced ejection fraction; ESH, European society of hypertension; FDA, food and drug administration; FIGARO-DKD, finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease; FIDELIO-DKD, finerenone in reducing kidney failure and disease progression in diabetic kidney disease: FINEARTS-HF, finerenone in heart failure patients; HF, heart failure; HFpEF, heart failure with a preserved ejection fraction; HFmrEF, hear failure with a medium range ejection fraction; HFrEF, heart failure with a reduced ejection fraction; I-PRESERVE, irbesartan in heart failure with preserved ejection fraction; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NEP, neutral endopepdidase; NP, natriuretic peptide; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York heart association; PARADIGM-HF, comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure Trial; PARAGON, prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker global outcomes in HFpEF; PEP-CHD, perindopril vs. placebo in congestive heart disease; PCSK9, proprotein convertase subtilisin/kexin type 9; RALES, randomized aldactone evaluation study; RAS, renin-angiotensin-system; RCT, randomized clinical trial; SPIRIT-HF, spironolactone in the treatment of heart failure; SPIRRIT, spironolactone initiation registry randomized interventional trial in heart failure with preserved ejection fraction; SCORED, sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk; SENIORS, study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure; SGLT2I, sodium-glucose-cotransporter-2-inhibitor; siRNA, small interfering RNA; SOLVD, studies of left ventricular dysfunction; SOLOIST-WHF, sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening heart failure; TOPCAT, treatment of preserved cardiac function heart failure with an aldosterone antagonist; TRANSFORM-HF, comparative effectiveness of torsemide versus furosemide in heart failure.

[#] As recommended by the 2023 European Society of Hypertension Guidelines [71]

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Mineralocorticoid receptor antagonist
Sodium-glucose-cotransporter-2-inhibitor

cotransporter 2 inhibitors. For various reasons, these drug treatments were first studied in HF patients with a reduced ejection fraction (HFrEF). Subsequently, they have been investigated in HF patients with a preserved left ventricular ejection fraction (LVEF, HFpEF) of mostly hypertensive etiology, and with modest benefits largely assessed on top of background treatment with the drugs already proven effective in HFrEF. Additionally, diuretics are given on symptomatic indications. Patients with HFpEF may have diastolic dysfunction but also systolic dysfunction visualized by lack of longitudinal shortening. Considering the totality of evidence and the overall need for antihypertensive treatment and/or treatment of hypertensive complications in almost all HF patients, the principal drug treatment of HF appears to be the same regardless of LVEF. Rather than LVEF-guided treatment of HF, treatment of HF should be directed by symptoms (related to the level of fluid retention), signs (tachycardia), severity (NYHA functional class), and concomitant diseases and conditions. All HF patients should be given all the drug classes mentioned above if well tolerated.

1. Introduction

Heart failure (HF) affects 2.4 % of the American population and is expected to rise to 3 % by 2030 [1]. The prognosis of HF remains poor, with 5-year mortality above 50 % [2,3]. The fact that ACEIs or angiotensin receptor blockers (ARBs), selected beta-blockers, mineralocorticoid receptor antagonists (MRAs), and diuretics, improved the prognosis in HF patients with a reduced ejection fraction (HFrEF), did not exclude the possibility that these drugs had similar beneficial prognostic effects in patients with HF and a preserved EF (HFpEF). Most HF patients are given these drugs anyway because of hypertension and/or the HF itself with apparent clinical benefits [4–7]. Thus, it was too late to do studies in untreated HFpEF patients without these drugs. Additionally, more refined echocardiographic measures of systolic LV function within the preserved LVEF range showed reduced LV mid-wall shortening, stroke volume, and global longitudinal strain. Longitudinal axis shortening could be partly or completely missing as a sign of extensive systolic dysfunction [8–10].

The event rate in the RCTs in HFpEF was lower than in the corresponding RCTs of patients with HFrEF, suggesting difficulties in excluding from RCTs patients with normal to supra-normal LVEF who did not have HF and could not expect to benefit substantially of the HF medications [11–19]. Therefore, several initial RCTs in HFpEF were too small, had inadequate statistical power, and results were difficult to interpret.

In the present article we aim to review the randomized clinical trials (RCTs) that have been performed of drug effects in patients with HFpEF. Fig. 1 is summarizing current 2023 algorithm for up-titration of medication recommended by the European Society of Hypertension (ESH) and Fig. 2 illustrates a hexagon with overview of the drug classes that are available and recommended by ESH partly for treatment of HFpEF

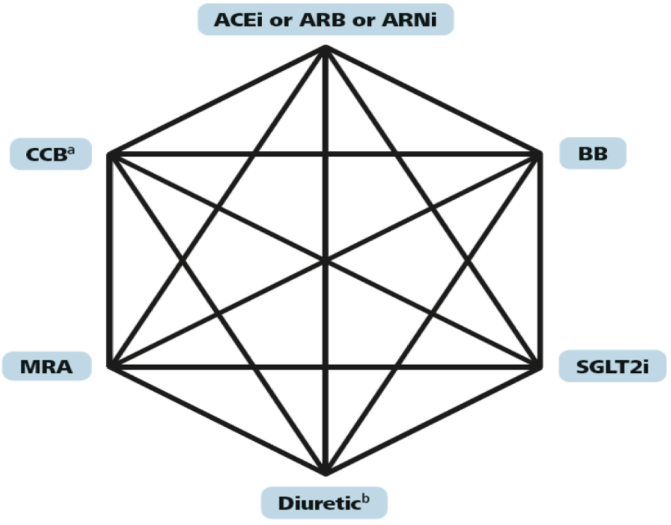

Fig. 2. Hexagon summarizing drug classes recommended by ESH [71] in the treatment of patients with heart failure with preserved ejection fraction. SGLT-2 inhibitors have a specific indication in heart failure patients beyond BP control. Abbreviations of drug classes are defined in a paragraph provided in the first part of the article.
(a) CCB preferably amlodipine can be added to the other drugs if still needed to control blood pressure.
(b) Thiazide or thiazide alike diuretic if limited fluid retention and loop-diuretic if needed and always in patients who have suffered pulmonary edema or who suffers from poor renal function.

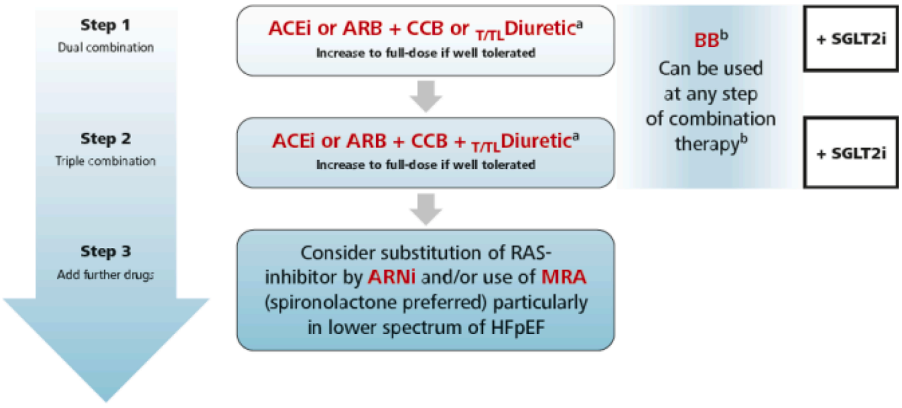

Fig. 1. Schematic overview of recommended drug treatment by ESH [71] of patients with heart failure with preserved ejection fraction (HFpEF). SGLT-2 inhibitors have a specific indication in heart failure patients beyond BP control.
Abbreviations of drug classes are defined in a paragraph provided in the first part of the article.
(a) Thiazide or thiazide alike diuretic if limited fluid retention and loop-diuretic if needed and always in patients who have suffered pulmonary edema or who suffers from poor renal function.
(b) Preferably beta-blockers shown to lower mortality in heart failure with reduced ejection fraction.

per see and partly to control the high blood pressure in most of these patients.

2. Current drug treatment of heart failure in patients with a preserved ejection fraction

The objectives of HF treatment are to increase survival, reduce hospitalizations for worsening HF, and improve quality of life. The current American [20] and European [21] HF guidelines have developed specific treatment recommendations for patients with HFrEF. In contrast, patients with a mildly reduced and a midrange LVEF, HFmrEF, and HFpEF, respectively, have been recommended symptomatic supportive care due to supposed lack of evidence.

The treatment recommendations for HFrEF include renin-angiotensin-system (RAS)-inhibitors, beta-blockers, MRAs, and SGLT2Is. The scientific basis for using these drug classes, "cornerstones", in HFrEF, are discussed in the guidelines [20,21]. Bisoprolol, carvedilol, metoprolol, and nebivolol are included because these beta-blockers have been proven to reduce mortality in HFrEF [22]. Hypertensive patients with severe HF may have low blood pressure (BP) because of very high total peripheral vascular resistance and may need careful in-hospital up-titration [20,21].

2.1. Evidence of ACE-Inhibitor treatment in HFpEF

Clinical evidence of ACEI benefit in HFpEF is limited for various reasons outlined above. Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [4] required increased heart size on chest X-ray and thus a mixture of HFrEF and HFpEF. Patients with HF after myocardial infarction, and hypertensive LV hypertrophy were included in the CONSENSUS population. It took 20 years from the publication of CONSENSUS [4] and 15 years after Studies of Left Ventricular Dysfunction (SOLVD) [5] before Perindopril vs. Placebo in Congestive Heart Disease (PEP-CHF) [13] investigated the prognostic effect of ACEI in HFpEF.

PEP-CHF was a prospective RCT (Table 1) with older patients but with fewer participants than planned ($n = 852$) and was hampered by challenges regarding the study design and statistical power [13]. The investigators overestimated the event rate and underestimated the discontinuation rate with event rate lower than expected, widespread drop-out and drop-in rates, and a very high rate of open-label ACEI use. Although PEP-CHF did not enroll the planned number of participants, the 1-year interim analysis showed a borderline significant effect on a composite of mortality and hospitalization for HF worsening. This finding was driven by the pre-specified secondary endpoint of HF hospitalization. PEP-CHF likely showed such strong results because patients included after echocardiography had confirmed cardiac disease that could explain HFpEF. The PEP-CHF investigators gave open ACEI treatment to one-third of the participating patients including patients in the control group [13]. Such liberal use of ACEI treatment contributed strongly to minimizing the visible effect of the study drug.

2.2. Evidence of angiotensin receptor blocker treatment in HFpEF

The effects of ARBs on cardiovascular mortality and morbidity in HFpEF investigated candesartan in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study [11] and irbesartan in Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) [23] (Table 1). Both trials had weak statistical power at the outset because of high rates of background use of other HF medications at baseline, which increased further during the trials [23].

Borderline significance ($p = 0.051$) was achieved in favor of candesartan in the CHARM study after pre-specified adjustments for covariates. There was a weak trend in I-PRESERVE, with Kaplan Meier curves diverging, apparently favoring irbesartan after two years. The investigators later published retrospective analyses displaying significant beneficial results on the main endpoints [24,25]. Our interpretation is that treatment with ARB has prognostic beneficial effects in HFpEF despite heavy background medication with HF drugs.

Table 1
Characteristics of patients with heart failure and preserved ejection fraction in randomized studies of drug treatment.

Characteristics at baseline		CHARM (2003)	PEP-CHF (2006)	I-PRESERVE (2008)	TOPCAT (2014)	PARAGON (2019)	EMPEROR PRESERVED (2021)	DELIVER (2022)
Age (years)		67 ± 11	75	72 ± 7	68.7	72 ± 8	71 ± 9	71 ± 9
Women (%)		40	55.5	60	51.5	52	45	43
Body mass index (kg/m^2)		29.3 ± 5.9	27.5 (25.1–30.0)	29.7 ± 5.3	31 [27–36]	30.2 ± 4.9	29.8 ± 5.8	29.8 ± 6.1
Systolic blood pressure (mmHg)		136	139	136	130	131	131 ± 15.5	125 ± 15
Left ventricular ejection fraction (%)		41–49 (35 %) 50–59 (35 %)	64.5	59.5	56	57.5	54.3	54 ± 8
New York Heart Association class (%)	**I**	–	75.5	–	3	3	0.1	–
	II	61		21.5	63	77	81.5	75.2
	III	38	24.5	76.5	32.5	19.5	18	24.4
	IV	1.5		3	0.4	0.4	0.3	0.3
N-terminal pro-brain natriuretic peptide (pg/mL)		–	335–453	320–360	887–1017	910	970	1387–1408/ 704–729
Co-morbidity (%)	**Atrial fibrillation**	29	21	29	32–51	33	51	56–57
	Diabetes mellitus	28	20.5	27.5	13–34	43	49	44.8
	Hypertension	64	79	88.5	95	95	90	88.6
	Previous myocardial infarction	44	26	23	22–40	22.5	–	-
Concomitant (%)	**ACE- inhibitor/ Angiotensin receptor blocker**	19	1/3 of patients (in trial)	25.5	Most patients	86	80 %	73 %
Concomitant (%)	**Mineralocorticoid-receptor antagonist**	11.5	10	15	–	26	37	43
Concomitant (%)	**Beta-blocker**	56	55	59	83	80	87	83

Study acronyms are defined in a paragraph provided in the first part of the article. ACE=angiotensin converting enzyme

2.3. Evidence of angiotensin receptor blocker neprilysin inhibitor treatment in HFpEF

Dual-acting Renin-Angiotensin-system (RAS) and neprilysin inhibitors exploit RAS blockade by augmenting natriuretic peptides' salutary actions [26,27]. LCZ696 is the first-in-class ARNI. It consists of the prodrug AHU377 (sacubitril), and the ARB valsartan combined in one molecule in equal moieties. The effect of sacubitril-valsartan in patients with HFpEF was investigated in the Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker Global Outcomes in the HFpEF (PARAGON—HF) trial [28] with valsartan rather than placebo as the comparator (Table 1). However, 95 % of patients received a diuretic and 75 % a beta-blocker at baseline. Despite the intrinsically effective comparator, valsartan, and the inclusion of a predominance of patients with NYHA Class II (not-so-severe HF), PARAGON—HF showed borderline significant results favoring ARNI ($p = 0.058$). After subsequent review and taking into consideration the benefits in HFrEF in the Prospective Comparison of ARNI with ACEI to Determine the Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM) [17], suggesting benefit across a wide range of LVEF, FDA approved sacubitril-valsartan as a treatment for HF with "up to normal" LVEF. Additionally, the reno-protective properties of ARNI were superior to those of other RAS inhibitors – a further benefit for the HFpEF population, in which renal dysfunction is common [29].

2.4. Evidence of diuretic treatment in HFpEF

The primary intention of diuretics is to prevent hospitalization due to congestion, in addition to the potential blood pressure-lowering effect. Loop diuretics are particularly beneficial in those with renal impairment and patients with severe HF with a history of pulmonary edema and other forms of severe fluid retention. The Comparative Effectiveness of Torsemide Versus Furosemide in Heart Failure (TRANSFORM-HF Trial) tested the hypothesis that torsemide was superior to furosemide in treating HF [30,31]. This randomized trial enrolled 2859 patients with HF regardless of LVEF during HF hospitalization. During a median of 17.4 months, all-cause deaths occurred in 26.1 % of patients in the torsemide group and 26.2 % in the furosemide group.

Differences in outcomes between hydrochlorothiazide or thiazide-like diuretics such as indapamide or chlorthalidone have never been shown in either HF or hypertension. A recent comparison in hypertension was neutral [32].

2.5. Evidence of beta-blocker treatment in HFpEF

Most patients (55–87 %) enrolled in HFpEF RCTs used open-label beta-blocker [22]. The SENIORS trial with nebivolol [33] included HF patients not based on LVEF and demonstrated a beneficial beta-blocker effect independent of LVEF [34]. The effect on all-cause mortality or cardiovascular hospital admission showed an overall HR of 0.86, and in the subgroup possessing LVEF ≥35 %, HR was 0.82. Apart from this single RCT, the published literature is based on observational cohorts and their meta-analyses. A meta-analysis on beta-blockers in HFmrEF and HFpEF (LVEF >40 %) showed that beta-blocker use was associated with reduced mortality [35], and beta-blockers have beneficial effects in HFpEF patients who are in sinus rhythm [36]. A specific reason for the beneficial role of beta-blockers in HFpEF is the increased sympathetic activity also in this form of HF [37]. Another aspect of beta-blockers in HF is their effect on increasing natriuretic peptide (NP) concentrations, likely because of their heart rate-reducing properties [38]. Thus, it is unclear how the increase in NPs contributes to their benefits and whether NPs can be used for monitoring HF progression during beta-blocker treatment.

2.6. Evidence of steroidal and non-steroidal mineralocorticoid receptor antagonists in HFpEF

The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial [14] was performed with study sites in America, as well as in Russia and Georgia [14]. The lack of significant effect of the study drug on the primary endpoint was clouded by the retrospective finding that there were substantial regional differences affecting the trial results [14]. Reanalysis of the data displayed a significant effect of the study drug on the primary endpoint in the subgroup in America with event rate as expected. In contrast, the event rate in Russia and Georgia was low and comparable to the general population. FDA reversed course on this matter based on the results from the American subset of the study (TOPCAT Americas). An FDA advisory committee recommended that the totality of evidence from TOPCAT supports a new indication for spironolactone. The Cardiovascular and Renal Drugs Advisory Committee decided that TOPCAT (Table 1) provides "sufficient evidence to support any indication" [39].

Spironolactone In The Treatment of Heart Failure (SPIRIT-HF) and Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction (SPIRRIT) are two ongoing trials comparing spironolactone to placebo in reducing the rate of the composite endpoint of recurrent HF hospitalizations and cardiovascular death in symptomatic HF patients (NYHA II-IV) with mid-range (LVEF 40–49 %) or preserved LVEF (≥50 %) [40].

In Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) [41,42] ($n = 7347$), the primary composite endpoint was cardiovascular and the secondary endpoint was a composite of kidney events (kidney failure, sustained ≥40 % eGFR decline, or renal death). In Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) [41,43] ($n = 5734$), primary and secondary endpoints were the reverse. Among the enrolled patients, >95 % had treated hypertension, 46 % had a history of cardiovascular disease, and 7 % had a history of HF. Yet, in terms of cardiovascular outcomes, a reduction in the primary cardiovascular endpoint was obtained, but a secondary benefit of finerenone was a significant reduction in hospitalizations for HF (HR = 0.78, 0.66–0.92, $p = 0.003$). Thus, further evidence obtained from HF patients is needed. The Finerenone in Heart Failure Patients (FINEARTS-HF) [44,45] is an ongoing study to evaluate the efficacy and safety of finerenone in patients with HF (NYHA II-IV) and LVEF ≥ 40 %.

2.7. Evidence of sodium-glucose cotransporter 2 inhibitor in HFpEF

Effects on cardiovascular mortality and hospitalization in HFpEF has been established through two randomized controlled trials (Table 1); Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR PRESERVED) [18] and Dapagliflozin in Heart failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) [46]. EMPEROR-PRESERVED investigated the effect of empagliflozin in HFpEF and found a significant reduction of the composite endpoint of cardiovascular mortality or hospitalization - a significant slowing of the decline in kidney function and an improvement in quality of life [18]. FDA and EMA expanded the approval of empagliflozin for HF last year, making it independent of LVEF. Subsequently, DELIVER demonstrated a positive effect of dapagliflozin on the composite primary outcome of worsening HF or cardiovascular death in patients with HFmrEF and HFpEF and a significant improvement in quality of life [46].

A significant reduction in the composite endpoint was demonstrated with the dual SGLT1–2 inhibitor sotagliflozin in HF patients with an LVEF ≥50 % and type 2 diabetes in a pooled analysis of 739 patients from the Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) and Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials [47,48]. These are subgroup analysis results in 8

% of the number of enrolled patients from trials that were not specifically HFpEF trials and were both stopped prematurely.

A meta-analysis of all SGLT2I Trials investigated the effects of these drugs on renal function [49–51] in 13 trials and 90,409 participants, 82.7 % with type-2 diabetes and 17.3 % without diabetes. Allocation to an SGLT2I reduced the risk of kidney disease progression by 37 % in patients with and without diabetes. In the four chronic kidney disease trials, reductions were similar irrespective of primary kidney diagnosis and SGLT2I reduced the risk of composite acute kidney injury and cardiovascular death or hospitalization for HF by 23 % and the risk of cardiovascular death by 14 %. Relative risk reductions were similar in patients with and without diabetes, and results were similar irrespective of baseline renal function [51].

2.8. Drug treatment of patients with HF: should we still make a difference according to the level of left ventricular ejection fraction?

Considering the totality of evidence HF drug therapy should not be based on LVEF but rather on other aspects of HF, such as presenting symptoms related to the level of fluid retention, signs like tachycardia, severity (NYHA functional class) and in almost all patients, concomitant diseases such as hypertension, type-2 diabetes, obesity, atrial fibrillation, coronary disease, and chronic kidney disease [52].

3. Baseline and achieved blood pressure in the RCTs in patients with HFpEF

For most of the drugs included in Figs. 1 and 2 the evidence on target BP values in HFpEF derives at least partly from trials that needed to achieve BP control. Yet, the question remains complex for several reasons, one of which is that about 90 % of HFpEF patients in the RCTs of various drugs had hypertension (Table 1) and their BP was uncontrolled at baseline (Table 2) because ≥130 mmHg is considered uncontrolled hypertension in heart failure patients. Another is that in HFpEF it is particularly difficult to recognize the BP-dependent and independent role in the effects of the treatments studied. Nevertheless, it is our opinion that the evidence provided by the RCTs reviewed in our Ms. supports the conclusion that the available RCTs show that treatments with these drugs are indicated, whether it is for prevention of heart failure in patients with high risk, BP control and for treatment of heart failure *per se*. They also concur to suggest that this is the case in both HFrEF and HFpEF, and that ejection fraction has limited importance in the clinical characterization of heart failure patients.

We have summarized the available information regarding the BP to be achieved in the RCTs of HFpEF with new drugs in Table 2. In all trials treatment with new drugs was associated with a BP reduction that, although being somewhat greater when baseline BP was higher, averaged only 3–6 mmHg systolic. A greater BP lowering effect, however, could hardly be expected, considering that, as shown in Table 1, on average the patients were already on several antihypertensive drugs (RAS blockers, calcium-antagonist, and diuretics), and it is hard to expect more BP reduction than was achieved when the experimental drug is the 3rd, 4th or 5th with a BP-lowering potential to be administered. Other information is that in the RCTs on HFpEF patients the new drugs caused more hypotensive episodes while no clue was obtained as to whether the BP reduction had a role in the protective effects, or the benefits were entirely due to BP-independent protective properties. Thus, current knowledge on the relationship between reduction of outcomes and BP in treated HFpEF patients is severely limited. Due to the short BP range explored and other confounding factors optimal BP targets are unknown, and this is the case also for the existence of phenomenon such as the "J-curve" effect or, alternatively, the concept that the lower is the achieved BP the better it is for the patient.

4. Other important aspects when considering outcomes of RCTs in patients with HFpEF

4.1. Left ventricular ejection fraction

While LVEF helps to categorize HF into pathophysiological

Table 2
Durations of trials, event rates and blood pressures achieved during treatment in the randomized trials of patients with heart failure with preserved ejection fraction reported in Table 1.

Duration of trials, event rates and achieved BPs		CHARM (2003)	PEP-CHF (2006)	I-PRESERVE (2008)	TOPCAT (2014)	PARAGON (2019)	EMPEROR PRESERVED (2021)	DELIVER (2022)
Duration of trials (months)		36.6	26.2	49.5	21.6	35	26.6	27.6
Event rates	**HF hospitalization control arm**	18.3 %	53 (n)	314 (n)	245 (n) 14.5 %	797 (n)	352 (n) 11.8 %	418 (n) 13.3 %
	HF hospitalization drug intervention arm	15.9 %	34 (n)	291 (n)	206 (n) 12 %	690 (n)	259 (n) 8.6 %	329 (n) 10.5 %
	Mortality control arm	11.3 % (CV)	17 (n) (CV)	226 (n)	176 (n) 10.2 %	212 (n) (CV) 8.9 %	244 (n) 8.2 %	261 (n) 8.3 %
	Mortality drug intervention arm	11.2 % (CV)	10 (n) (CV)	221 (n)	160 (n) 9.3 %	204 (n) (CV) 8.5 %	219 (n) 7.3 %	231 (n) 7.4 %
BPs reached during treatment or changes in BPs (mmHg)	**SBP control arm (mmHg)**	–	138 135	−0.2 (at 6)	–	–	–	–
	SBP drug intervention arm (mmHg)	−6.9 (more at 6 months)[#]	(at 12 months)[*]	−3.8 (at 6 months) (persisted)	Significantly lower than in control arm	−4.5 (3.6–5.4) (more at 8 months)[§]	Hypotension more common	0.71 (0.60–0.81)[§] in patients with >128 at start
	DBP control arm (mmHg)	–	- -	−0.2 (at 6 months	–	–	–	–
	DBP drug intervention arm (mmHg)	−2.9 (more at 6 months)[*]		−2.1 (at 6 months) (persisted)	–	–	–	–

Study acronyms are defined in a paragraph provided in the first part of the article. BP = blood pressure, SBP = systolic BP, DBP = diastolic BP, CV = cardiovascular.
[#] $P < 0.0001$,.
[*] $P < 0.03$ between active treatment and placebo or control,.
[§] 95 % Confidential Intervals (CIs).

phenotypes, its influence on treatment recommendations is limited. First, the prognostic value of LVEF mainly applies to severely impaired ventricles [53–55], in which the LVEF measurements are highly operator-dependent and reproducible only for experienced echocardiographers [56]. LVEF is a characterization of the stroke volume (SV) expressed as a fraction of the LV end-diastolic volume (LVEDV). The level of LVEDV is essential to translate SV expressed as a percentage, LVEF, into absolute SV. LVEF is influenced by both preload (diastolic) and afterload (systolic) and cannot be interpreted as an index of contractility without knowledge of LV loads; the structural changes leading to increases or decreases in LVEDV will influence the LVEF at a given level of contractility and SV.

Thus, low LVEF may be present even when stroke volume is (sub) normal, depending on the LV dilatation. Further, mitral regurgitation and tethering of the papillary muscles are associated with LV dilatation, resulting in secondary mitral regurgitation, reducing stroke volume, and increasing LVEF [57]. Other confounding factors associated with the prognostic value of LVEF are the degree of LV hypertrophy and LV afterload (systolic BP) [58]. Moreover, LVEF is a dynamic parameter even under stable conditions. Clarke et al. [59] estimated the LVEF-based HF-phenotype transition probabilities at follow-up in patients with a primary discharge diagnosis of HF and $\geq$2 LVEF measurements separated by at least 30 days; the probabilities for HFpEF to HFrEF-transition were 45 % and 50 % at one and two years, respectively. Likewise, the probabilities for HFrEF to HFpEF-transition were 18 and 20 %. Therefore, the guidelines may be ill-guided using EF cut-off values.

4.2. Natriuretic peptides and selection of patients with heart failure

Elevated NPs have, over the last decade, been incorporated as a selection criterion of HFpEF RCTs to address the deficiencies of HF ascertainment in HFpEF trials.

The importance of NTproBNP has been shown in a reevaluation of the PARAGON data, in a subgroup analysis comparing results from patients enrolled due to elevated NPs with patients enrolled due to hospitalization [60,61]. The inclusion of elevated NPs led to a significant treatment effect on the primary endpoint, in contrast to inclusion based on previous hospitalization. A reanalysis with a similar result was carried out on data from TOPCAT [62]. In mild or severe chronic kidney disease leading to hypervolemia, the sensitivity of NTproBNP as a diagnostic marker of HF may be limited [63,64].

Further, too strict requirements regarding the detection of elevated NTproBNP, ensuring the HF diagnosis and improving statistical power may not necessarily be ideal in clinical practice. Patients who have suffered decompensated HF but have not been diagnosed with elevated NTproBNP may be misclassified and not be given adequate drug treatment. However, statistical power to show drug effects has been week in the RCTs of HFpEF patients mainly because of the large fractions of patients already treated with foundational drug treatments.

4.3. Potential treatment effects in various phenotypes of HFpEF

Though hypertension is the most common risk factor for HFpEF (Table 1), there are several closely related conditions, including type-2 diabetes, obesity, atrial fibrillation, and coronary disease. Coronary heart disease is a disease of epicardial arteries caused by atherosclerosis with a major contribution from hypertension due to systemic high wall tension. In HFpEF, coronary disease causes HF by chronic ischemia, which is different mechanism than transmural myocardial infarctions leading to HFrEF. Atrial fibrillation develops in hypertension and HFpEF due to poor electrical contact in dilated and fibrotic atria. Furthermore, obesity leads to eccentric LV hypertrophy due to chronic volume overload and may be of interest in the search for phenotypes that may respond to specific therapeutic drug interventions which may improve outcomes in HFpEF.

HFpEF related to hypertension mainly is related to LV hypertrophy of the concentric LV type [65]. With most intensive drug treatment of hypertension, systolic BP <130 mmHg caused by antihypertensive drug treatment is related to increased cardiac and all-cause mortality [66,67], in parallel with the development of HF caused by ischemia and poor contractility or by sudden onset atrial fibrillation. Along the same lines, diabetic myocardial disease is dominated by extensive damage to the arterioles and capillaries. While in type-2 diabetes there may be hypertrophic remodeling of the arterioles, and in hypertension, eutrophic remodeling, the two conditions frequently appear together, and the capillaries show thickening of the basement membrane, reduced lumen diameter, and smaller area [68–70].

4.4. Treatment with statin and acetylsalicylic acid in hypertension and heart failure

As summarized in the 2023 European Society of Hypertension Guidelines [71] people with hypertension and elevated cardiovascular risk should be treated with a moderate dose of a statin, whereas hypertensive patients classified as having a high or very high cardiovascular risk, thus fulfilling the criteria for intensive LDL-cholesterol-lowering treatment, the required lower LDL-cholesterol goals for cardiovascular prevention should be attained by up-titrating statins to the maximally tolerated dose. Ezetimibe should be added if LDL-cholesterol control is not achieved and PCSK9 inhibitors or siRNA may be considered in very high-risk patients to attain the LDL-cholesterol target [71]. In secondary prevention [71], use of antiplatelet therapy, usually low-dose acetylsalicylic acid (aspirin) is required, because in patients with established cardiovascular disease, low-dose aspirin is associated with clinically important reductions of major cardiovascular events although with an increase of bleeding risk, especially from the gastrointestinal tract.

5. Conclusions

Heart failure (HF) should primarily be prevented by treatment of hypertension, type-2 diabetes mellitus, obesity, atrial fibrillation, coronary heart disease and any other cardiac disease. Foundational drug treatments of heart failure are RAS-inhibitor (ACEI or ARB) or ARNI, MRA, and SGLT2-inhibition, usually beta-blockers, and diuretics are given to treat symptoms caused by fluid retention (Figs. 1 and 2). Low ejection fraction as marker of systolic dysfunction has since late 1980′s been used to diagnose HF and select patients to RCTs and document the efficacious drug treatments. More advanced echocardiography or magnetic resonance imaging usually shows that HF patients with normal or supranormal EF also have advanced systolic dysfunction for example by poor longitudinal contractility. Seven RCTs of the drug classes, proven to work in HFrEF, have investigated hospitalization and mortality in HFpEF with apparently modest beneficial effects; however, these additional drug effects have been on top of the foundational drug classes for HFrEF. Thus, the totality of evidence points to effects of all the drug classes irrespective of EF, and patients should be titrated with one choice from all drug classes if well tolerated (Fig. 1). All drugs lower blood pressure, but in severe cases of HF the titrations should be carried out whether hypertension is still present or not, because total peripheral vascular resistance is very high. For the patients with the most severe HF, buildup of such drug regimen should be performed stepwise with patients in hospital.

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Aurora Rist: Writing – original draft. **Kaja Sevre:** Writing – original

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Declaration of Competing Interest

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