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REVIEW ARTICLE

Drug Therapy for Acute and Chronic Heart Failure with Preserved Ejection Fraction with Hypertension: A State-of-the-Art Review

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Abstract

In this comprehensive state-of-the-art review, we provide an evidence-based analysis of current drug therapies for patients with heart failure with preserved ejection fraction (HFpEF) in the acute and chronic phases with concurrent hypertension. Additionally, we explore the latest developments and emerging evidence on the efficacy, safety, and clinical outcomes of common and novel drug treatments in the management of HFpEF with concurrent hypertension. During the acute phase of HFpEF, intravenous diuretics, mineralocorticoid receptor antagonists (MRAs), and vasodilators are pivotal, while in the chronic phase, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have proven effective in enhancing clinical outcomes. However, the use of calcium channel blockers in HFpEF with hypertension should be approached with caution, owing to their potential negative inotropic effects. We also explored emerging drug therapies for HFpEF, such as sodium–glucose co-transporter 2 (SGLT2) inhibitors, angiotensin receptor–neprilysin inhibitor (ARNI), soluble guanylate cyclase (sGC) stimulators, novel MRAs, and ivabradine. Notably, SGLT2 inhibitors have shown promise in reducing heart failure hospitalizations and cardiovascular mortality in patients with HFpEF, regardless of their diabetic status. Additionally, ARNI and sGC stimulators have demonstrated potential in improving symptoms, functional capacity, and quality of life. Nonetheless, additional research is necessary to pinpoint optimal treatment strategies for HFpEF with concurrent hypertension. Furthermore, long-term studies are essential to assess the durability and sustained benefits of emerging drug therapies. Identification of novel targets and mechanisms underlying HFpEF pathophysiology will pave the way for innovative drug development approaches in the management of HFpEF with concurrent hypertension.

Key Points

This review discusses drug trials for treating heart failure with preserved contractility with high blood pressure, including how well these drugs work during both immediate and long-term phases of the condition.

New drug treatments for heart failure with preserved contractility with high blood pressure show promise in enhancing outcomes, but more research is needed to identify the most effective methods and long-term advantages of these therapies.

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1 Introduction

Heart failure (HF) is a significant global health concern, affecting approximately 1–3% of the worldwide population [1]. Among its various types, HF with preserved ejection fraction (HFpEF) poses a major challenge with unmet clinical needs in cardiology in the 21st century [2]. Approximately 50% of patients with HF have HFpEF [3], although this can range from 30% to 75% depending on the definition used [4], rendering it a prevalent condition with substantial clinical implications. This is supported by the CHART-1 and CHART-2 studies where HFpEF accounted for 51% and 68% of the overall patient cohorts, respectively [5]. In Western countries, HFpEF represents a significant proportion of patients with HF, with a prevalence of 51% reported in OPTIMIZE-HF [6], 34% in EFHS-II [7], and 51% in ADHERE [8]. Notably, the HFpEF prevalence in Japan is in the range of 34–46% depending on the HFpEF definition and the mean age of the overall cohort [9–11].

The HFpEF prevalence is expected to rise owing to population aging [12], which poses a particular challenge for countries with a high proportion of older individuals, such as Japan. Globally, the highest percentage of older people is currently in Japan, with approximately 29% of the population aged ≥ 65 years in 2022 [13]. Furthermore, projections indicate a steady increase in the number of Japanese outpatients with left ventricular (LV) dysfunction, reaching 1.3 million patients by 2030 [14]. HFpEF is recognized as a growing epidemiological issue because of its high mortality rates, increasing treatment costs attributed to the high hospital admission rates, poor patient-reported outcomes, and the years lost in employment [15].

According to current international guidelines, HFpEF is defined by the presence of HF signs and symptoms, with a preserved LV ejection fraction (LVEF) of > 50% [16–18]. HFpEF is a clinical syndrome with the signs and symptoms of HF due to high LV filling pressures, despite normal or near-normal LVEF [19–21]. Additionally, structural cardiac abnormalities, such as interstitial fibrosis and concentric ventricular hypertrophy, and increased natriuretic peptide concentrations are often observed in patients with HFpEF [4]. However, it is important to note that approximately 20% of patients with HFpEF do not have elevated natriuretic peptide concentrations [18], and these patients are high risk in terms of mortality and HF readmissions [22]. The discrepancy in whether natriuretic peptide concentrations are increased can be attributed to various factors, including diverse underlying pathophysiological mechanisms in HFpEF, such as non-severe progression of cardiac remodeling and significant diastolic dysfunction, as well as underlying comorbidities, such as hypertension, valvular disease, atrial fibrillation, and obesity.

HFpEF has a multifactorial pathophysiology, with mechanisms varying depending on the underlying comorbidities, making its treatment challenging [23, 24]. The possible underlying causes and mechanisms of HFpEF and a detailed review of the specific HFpEF pathophysiology have been previously published [25]. A proinflammatory state induced by conditions such as hypertension, diabetes mellitus, chronic kidney disease (CKD), and age is considered a key contributor to the HFpEF pathological process [26]. These underlying conditions can lead to various cardiac abnormalities, including diastolic dysfunction [27, 28] and reduced cardiac output reserve [29–31], as well as non-cardiac abnormalities, such as reduced vasodilation [25] and arterial stiffness [32]. These abnormalities result in a broad spectrum of clinical signs and symptoms, including exercise intolerance, dyspnea, orthopnea, congestion, and edema [33].

Hypertension, which plays a pivotal role in HFpEF, is the leading cause of HFpEF development, with a prevalence ranging from 60 to 90% [18]. In the Framingham study, 91% of new HF cases were preceded by the development of hypertension [34]. Increased LV afterload due to hypertension can lead to LV hypertrophy and subsequent diastolic dysfunction [35]. In the hypertrophied myocardium, reduced capillary density, worsening coronary microcirculation resulting in myocardial ischemia, and altered electrical properties of the heart can affect overall cardiac function [36, 37]. Furthermore, LV mass and hypertrophy serve as independent predictors of cardiovascular risk, highlighting the importance of addressing LV hypertrophy [38–40] and hypertension as modifiable risk factors in patients with HFpEF.

Until recently, therapeutic recommendations for HFpEF have primarily focused on managing the underlying comorbidities and modifiable risk factors to reduce symptoms, stabilize patients, and minimize hospitalizations. However, the lack of targeted and preventive strategies introduces barriers to its optimal management [30, 35]. In addition to targeting the underlying comorbidities, such as hypertension, HFpEF drug therapy depends on whether HF is acute or chronic. The definitions of acute and chronic HFpEF are subject to controversy. Nevertheless, acute HFpEF can be characterized as a sudden or rapid onset of HF symptoms necessitating urgent therapy, which can manifest in patients with previously diagnosed HF, chronic HF (often referred to as 'acute-on-chronic HF'), or advanced/end-stage (stage D) chronic HF [41, 42]. Further elaboration on the definitions of acute and chronic HFpEF has been provided previously [43].

This comprehensive, state-of-the-art review, aims to provide an evidence-based analysis of the currently used drug therapies for acute and chronic HFpEF with a particular focus on patients with concurrent hypertension who are widely observed in the clinical setting. Additionally, the

review aims to explore the latest developments in emerging drug therapies that show promise for improving outcomes in patients with HFpEF. A summary of this information is provided in Fig. 1. By evaluating the existing evidence, we can gain valuable insights into the effectiveness of various drug treatments and their potential implications for clinical practice.

2 Current Drug Therapies for Acute and Chronic HFpEF with Hypertension

2.1 Current Drug Therapies for Acute HFpEF with Hypertension

The management of HFpEF in the acute phase with concurrent hypertension presents specific challenges, necessitating urgent or rapidly acting therapy. In this context, the primary treatment goals are symptom reduction and patient stabilization. Various drug therapies are used in the management of acute HFpEF with hypertension, including diuretics, vasodilators, inotropes, anti-hypertensives, and oxygen therapy. A comprehensive summary of these drug classes, pertinent trials, and their effects on blood pressure control and hypertensive complications is provided in Table 1. The following sections provide an in-depth analysis of the existing evidence regarding the effectiveness of each drug class in the management of acute HFpEF, with a specific emphasis on their effects on hypertensive complications and blood pressure control.

2.1.1 *Loop Diuretics*

Diuretics play a crucial role in the management of HFpEF, particularly in addressing the hallmark features of abnormal fluid distribution and fluid overload [44]. In the acute phase of HF, most patients present to the emergency department with symptoms of volume overload [45]. Loop diuretics, such as furosemide, are the primary treatment approach for reducing congestive symptoms associated with hypervolemia in patients with HFpEF [46]. Diuretics enhance sodium and water excretion in urine, effectively decreasing

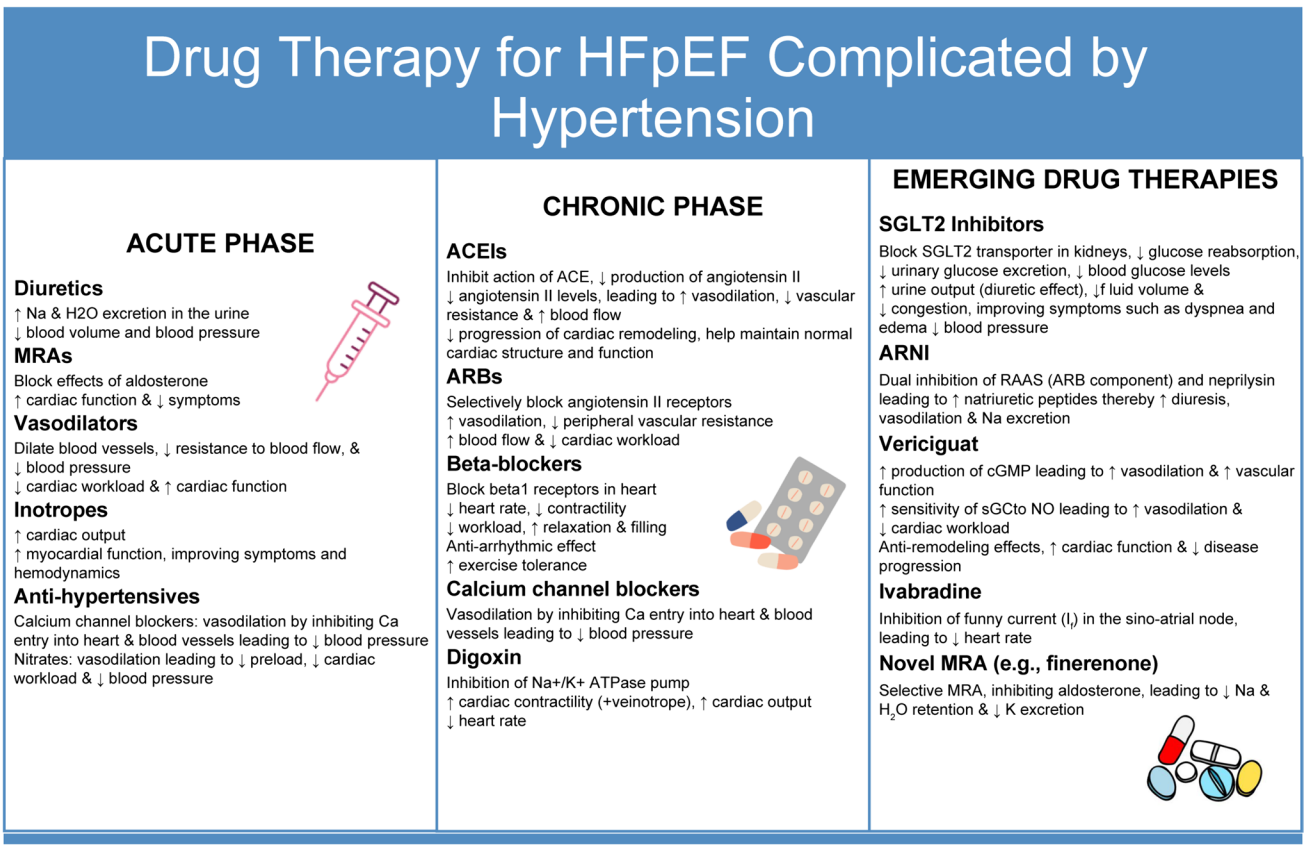

Fig. 1 Available drug therapies and their mechanisms of action in patients with HFpEF with concurrent hypertension. Many of these drug therapies are not currently guideline-recommended [16]. *ACE* angiotensin-converting enzyme, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *cGMP* cyclic guanosine monophosphate, *HFpEF* heart failure with preserved ejection fraction, *MRA* mineralocorticoid receptor antagonist, *RAAS* renin-angiotensin-aldosterone system, *sGC* soluble guanylate cyclase, *SGLT2* sodium–glucose co-transporter 2

Table 1 Summary of the most pertinent studies on drug therapies for patients with acute and chronic HFpEF with concurrent hypertension

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
Acute HFpEF with hypertension								
Diuretics	ESC: I ESC: IIa JCS/JHFS: I	AHA: Loop diuretics preferred in most patients with HF; thiazide diuretics may be considered in those patients complicated by hypertension [17]. ESC: Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms (class I recommendation). ESC: Combination of a loop diuretic with thiazide diuretic should be considered in patients with resistant edema who do not respond to an increase in loop diuretic doses (class IIa recommendation). JCS/JHFS: Use of diuretics to relieve symptoms of congestion in HFpEF [146]						

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
MRAs	Not reported	Not reported	TOPCAT sub-analysis [58]: higher risk of all-cause hospitalization, but not all-cause mortality in HFpEF	Not reported	Not reported	For all study participants ($N = 3445$): SBP 129–130 mmHg (118, 140) DBP 70–80 mmHg (62, 85)	Not reported	
			Aldo-DHF trial [61]: Spironolactone improved LV diastolic function but did not affect maximal exercise capacity, HF symptoms, or QoL	LVEF ≥ 50%	$N = 387$ (92%)	For all study participants ($N = 422$): SBP 135 mmHg DBP 79 mmHg	Compared with placebo, spironolactone significantly reduced SBP after 12 months. Placebo group mean: 137 (95% CI 135–139); spironolactone group mean: 128 (95%, CI 126–130). Difference: −8 (95% CI −11 to −5; $P < 0.001$)	
			TOPCAT sub-analysis [63] Spironolactone treatment in HFpEF patients is feasible with heterogeneous effects, showing positive effects in patients with high BMI and WBC while harmful in patients with low BMI and ALP	LVEF ≥ 45%	$N = 3029$ (91.5%)	For all study participants ($N = 3312$): SBP 129.3 ± 14 mmHg DBP 75.8 ± 10.7 mmHg	Not reported	
			Kresoja et al. 2023 [64]: Spironolactone treatment significantly reduced the occurrence of the primary outcome among responders (HR 0.42, 95% CI 0.22–0.78; $P = 0.008$ [Cox-regression]), but not among patients in the non-responder group (HR 0.88, 95% CI 0.59–1.31; $P = 0.52$ [Cox-regression]). This effect among responders was mainly driven by a reduction in mortality (P-log-rank = 0.028), while HF hospitalization only showed a non-significant trend (P-log rank = 0.085)	LVEF ≥ 50%	Aldo-DHF: $N = 387$ (92%) TOPCAT: $N = 3147$ (91%)	Not reported	Not reported	
			TOPCAT [65]: Spironolactone may be an effective add-on medication for patients with HFpEF with resistant hypertension taking ACEIs/ARBs, calcium channel blockers, and diuretics	Not reported	$N = 3146$ (91.4%)	Patients with HFpEF with resistant hypertension ($N = 1004$): SBP 134.2 ± 13.3 mmHg DBP 76.4 ± 11.2 mmHg Patients with HFpEF and without resistant hypertension ($n = 2437$): SBP 127.2 ± 13.7 mmHg DBP 75.5 ± 10.4 mmHg	In patients with HFpEF with resistant hypertension: SBP and DBP were significantly lower in the spironolactone group compared with the placebo group (SBP 129.3 [15.1] vs. 133.4 [16.9] mmHg; $P < 0.001$; DBP 73.8 [10.7] vs. 76.1 [11.1] mmHg; $P = 0.001$). In patients with HFpEF without resistant hypertension: SBP and DBP were significantly lower in the spironolactone group compared with placebo group (SBP 125.6 [15.8] vs. 127.8 [15.4] mmHg; $P = 0.001$; DBP 74.0 [10.3] vs. 75.5 [10.1] mmHg; $P < 0.001$). Difference in SBP in patients with HFpEF with resistant hypertension compared with those without resistant hypertension (−4.4 vs. −1.8 mm Hg; $P = 0.006$)	

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
Vasodilators	AHA: 3 (no benefit) ESC: IIb in acute HF JCS/JHFS: III	AHA: In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL is ineffective. ESC: In patients with acute HF and SBP > 110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. JCS/JHFS: Use of nitrates to improve prognosis and increase activities of daily living HFpEF [146]	NICHE [70]: In patients with chronic HF with renal failure (89% had concurrent hypertension), hydralazine–isosorbide dinitrate improved 6-MWD compared with standard of care at 6 months, with lower rates of HF hospitalization and mortality, but higher rates of hypotension	No restrictions	Hypertension in standard-of-care group: N = 20 (90.9%) Hypertension in H-ISDN group: N = 19 (86.4%)	SBP in standard-of-care group (N = 22): 147.0 ± 18.5 mmHg SBP in H-ISDN group (N = 22): 139.8 ± 23.6 mmHg	Not reported	
			NEAT HF-PEF trial [71]: Patients with HFpEF treated with isosorbide mononitrate were less active and did not have better QoL or submaximal exercise capacity than those who received placebo	LVEF ≥ 50%	Hypertension in placebo group: N = 54 (92%) Hypertension in isosorbide mononitrate group: N = 45 (88%)	SBP in placebo group (N = 59): 132 ± 18 mmHg SBP in isosorbide mononitrate group (N = 51): 129 ± 14 mmHg	SBP showed a significant decrease in patients who received isosorbide mononitrate compared with those who received placebo. Isosorbide mononitrate group (mean 125; 95% CI 122–128) Placebo group (mean 129; 95% CI 125–132) Treatment difference (mean −3.7; 95% CI −7.2 to −0.3; P = 0.04)	
			Zamani et al. 2017 [72]: Isosorbide dinitrate, with or without hydralazine, did not exert beneficial effects on reflection magnitude, LV remodeling, or submaximal exercise, and was poorly tolerated. These findings do not support the routine use of these vasodilators in patients with HFpEF	LVEF ≥ 50%	N = 40 (90.9%)	For all study participants (N = 44): SBP 126.8–146 mmHg DBP 69.3–79.2 mmHg	Isosorbide dinitrate did not reduce brachial SBP but tended to reduce central SBP (visit 2 vs. visit 1: −27.6 [95% CI −54.0 to −1.3]; visit 3 vs. visit 1: −30.4 [95% CI −58.2 to −2.6] mmHg; overall P = 0.051), although this reduction did not reach statistical significance	
			Chen et al. 2013 [73]: In participants with acute HF and renal dysfunction, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy	LVEF < 50% 26% of the patients: LVEF > 50%	80–88%	For all study participants (N = 360) SBP: 114–117 mmHg	Not reported	
			Schwartzenberg et al. [74]: In patients with HFpEF, nitroprusside reduced LV filling pressures to a greater degree than in patients with HFrEF, but improvements in stroke volume and cardiac output were lower in HFpEF. Pulmonary artery systolic pressure decreased more in HFpEF, despite similar reduction in pulmonary mean pressure and resistance, suggesting higher ventricular systolic elastance in HFpEF. Overall, patients with HFpEF experienced greater BP reduction, but less enhancement in cardiac output and stroke volume	Not specified	Hypertension in HFrEF group: N = 48/174 Hypertension in HFpEF group: N = 66/83	SBP in HFrEF group (N = 174): 113 (100–127) mmHg SBP HFpEF group (N = 83): 166 (144– 180) mmHg	HFpEF demonstrated a 2.6-fold greater decrease in systemic arterial pressure than HFrEF (P < 0.0001)	

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
Inotropes	ESC: IIb and III	ESC: Inotropic agents may be considered in patients with SBP < 90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function (class IIb recommendation). ESC: Inotropic agents are not recommended routinely because of safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion perfusion and maintain end-organ function (class III recommendation). ESC recommends infusion of milrinone at a rate of 0.375–0.75 ug/kg/min in patients with acute HF	Sengupta et al. 2020 [75]: Although cardiac output values at rest and during stress are different for bioreactance and echocardiography, a major advantage of bioreactance is its ability to continuously monitor key hemodynamic variables such as cardiac output, stroke volume, and heart rate. It is also patient friendly, and does not require a familiarization procedure and may have wider application, especially in cardiology settings where cardiac output monitoring is important	LVEF ≥ 50%	85%	For all study participants ($N = 20$): Echocardiography rest SBP 121.33 ± 8.34 mmHg and DBP 76.67 ± 4.88 mmHg Echocardiography peak stress test SBP 136.60 ± 23.43 mmHg and DBP 78.67 ± 9.15 mmHg Bioreactance rest SBP 117.87 ± 17.61 mmHg and DBP 69.33 ± 10.06 mmHg Bioreactance peak stress test SBP 125.47 ± 42.13 mmHg and DBP 71.53 ± 10.41 mmHg	Not reported	
			MilHFpEF trial [76]: Extended-release oral milrinone was well tolerated and associated with improved QoL in patients with HFpEF.	LVEF ≥ 50%	Hypertension in milrinone group: $N = 11$ (92%) Hypertension in placebo group: $N = 9$ (82%)	For all study participants ($N = 23$): SBP 126–156 mmHg DBP 58–81 mmHg	SBP was unchanged (treatment group −3 ± 18 vs. placebo +1 ± 12 mmHg; $P = 0.57$)	
Anti-hypertensives	Not reported	Not reported	Malesker et al. [78]: Nicardipine is a more effective anti-hypertensive agent than labetalol in an unselected group of patients who develop hypertension in the intensive care unit setting (approximately 12% of study patients had HF). An advantage of nicardipine compared with labetalol was its fewer adverse effects. Nicardipine was associated with less hypotension and bradycardia or atrioventricular block, resulting in a lower rate of drug discontinuation compared with labetalol	Not reported	76–82%	For all study participants ($N = 382$): SBP 171.8–173.5 mmHg DBP 100.9–102.4 mmHg	There were no significant differences in the magnitude of the average change in SBP or DBP between labetalol and nicardipine. The proportion of patients achieving BP targets was significantly greater with nicardipine (83%) than with labetalol (67%) ($P = 0.04$) and the proportion of patients requiring an alternate anti-hypertensive agent was significantly greater with labetalol than with nicardipine (31% vs. 17%; $P = 0.02$)	

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
Chronic HFpEF with hypertension								
MRAs	AHA: 2b in HFpEF ESC: IIb in acute HF JCS/JHFS: IIb	AHA: In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum [17]. ESC: In patients with acute HF, combination of loop diuretic with either thiazide diuretic or spironolactone may be considered in patients with resistant edema or insufficient symptomatic response [18]. Treatment alternatives for HFpEF are being revised. JCS/JHFS: Increasing the dose of MRAs to maximum tolerable level to reduce the risk of clinical events in HFpEF [146]	TOPCAT trial [62]: Spironolactone demonstrated a statistically nonsignificant effect in reducing CV mortality or HF hospitalization	LVEF ≥ 45%	Not reported	For all study participants ($N = 3445$): SBP: 130 mmHg DBP: 80 mmHg	At post-baseline visits, SBP was significantly lower in the spironolactone group	SPIRIT-HF (spironolactone) in patients with mid-range (LVEF 40–49%) or preserved (LVEF ≥ 50%) ejection fraction [147]

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
ACEIs	AHA: 2b in patients with HFmrEF JCS/JHFS: IIb	AHA: Among patients with current or previous symptomatic HFmrEF (LVEF, 41–49%), use of evidence-based beta-blockers for HFrEF, ARNI, ACEIs, or ARBs, and MRAs may be considered, to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. JCS/JHFS: Increasing the dose of ACEIs/ARBs to maximum tolerable level to reduce the risk of clinical events in HFpEF [146]	PEP-CHF trial [83]: Conducted in patients with HF who had neither a low LVEF nor valve disease. This study was not sufficiently powered for its primary endpoint; however, improved symptoms and exercise capacity and fewer hospitalizations for HF in the first year were observed on perindopril, during which most patients were on assigned therapy, suggesting that it may be of benefit in this patient population	LVEF > 40%	79%	For all study participants ($N = 850$): Sitting SBP 138–140 mmHg Sitting DBP 80 (73–88) mmHg	Sitting SBP and DBP declined to a greater extent in patients assigned to perindopril. Mean (SD) SBP at 1 year were as follows: Placebo: 138 (18) Perindopril: 135 (18) Mean difference in change [95% CI]: −3 mmHg [25–0]; $P = 0.03$	
ARBs	AHA: 2b ESC: Not provided for HFpEF JCS/JHFS: IIb	AHA: In selected patients with HFpEF, the use of ARBs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum [17]. JCS/JHFS: Increasing the dose of ACEIs/ARBs to maximum tolerable level to reduce the risk of clinical events in HFpEF [146]	I-PRESERVE trial [67]: Irbesartan did not improve the outcomes of patients HFpEF	LVEF ≥ 45%	88%	For all study participants ($N = 4128$): SBP 136 ± 15 mmHg DBP 79 ± 9 mmHg	Between baseline and 6 months, BP decreased by a mean (± SD) of 3.8 ± 18.0 mmHg systolic and 2.1 ± 10.5 mmHg diastolic in the irbesartan group and by a mean of 0.2 ± 17.6 mmHg systolic and 0.2 ± 10.4 mmHg diastolic in the placebo group; the decrease observed in the two groups persisted for the trial duration	
			CHARM-PRESERVED trial [82]: Candesartan showed a moderate impact in preventing admissions for CHF among patients with HF and LVEF higher than 40%	LVEF > 40%	Hypertension in candesartan group: $N = 984$ (65·0%) Hypertension in placebo group: $N = 959$ (63·6%)	For all study participants ($N = 3023$): SBP 136 ± 18 mmHg DBP 77.8 ± 10 mmHg	By 6 months, the BP decreased from baseline by 6.9 mmHg systolic and 2.9 mmHg diastolic more in the candesartan group than in the placebo group ($P < 0.0001$)	

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
Beta-blockers	AHA: 2b in patients with HFmrEF ESC: Not provided for HFpEF JCS/JHFS: IIb	AHA: Among patients with current or previous symptomatic HFmrEF (LVEF, 41–49%), use of evidence-based beta-blockers for HFrEF, ARNI, ACEI, or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among the patients with LVEF on the lower end of this spectrum JCS/JHFS: Increasing the dose of beta-blockers to maximum tolerable level to reduce the risk of clinical events in HFpEF [146]	SWEDIC trial [96]: Treatment with carvedilol resulted in a significant improvement in *E/A* ratio in patients with HF due to a LV relaxation abnormality compared with patients who received matching placebo; this effect was observed particularly in patients with higher heart rates at baseline	LVEF > 45%	Hypertension in placebo group: $N = 31$ (62%) Hypertension in carvedilol group: $N = 33$ (70.2%)	Placebo group $N = 50$: SBP 150 mmHg DBP 90 mmHg Carvedilol group $N = 47$: SBP 155 mmHg DBP 89 mmHg	No significant change in SBP or DBP was observed between the two treatment groups	
			OPTIMIZE-HF trial (6-year follow-up) [100]: In patients with HFpEF and heart rate ≥ 70 beats/min, high-dose beta-blocker use was associated with a significantly lower risk of death	LVEF ≥ 50%	After propensity score matching ($N = 1280$) 79–81%	After propensity score matching ($N = 1280$): SBP 131–132 mmHg DBP 69 mmHg	Not reported	
			ELANDD trial [103]: Compared with placebo, six months treatment with nebivolol did not improve exercise capacity in patients with HFpEF; its negative chronotropic effect may have contributed to this finding.	LVEF > 45%	86%	For all study participants ($N = 1116$): SBP 133–134 mmHg DBP 78–81 mmHg	SBP decreased significantly from baseline in the nebivolol group, without a change in the placebo arm. Nebivolol group mean ± SD SBP at rest: baseline = 128 ± 17; 6 months = 122 ± 18, $P < 0.05$. Peak exercise: baseline = 176 ± 29; 6 months = 167 ± 31; $P < 0.05$	
			J-DHF trial [104]: Carvedilol did not improve the overall prognosis of patients with HFpEF; however, the standard dose, not the low dose, prescription might be effective	LVEF > 40%	80%	For all study participants ($N = 245$): SBP 133–134 ± 21 mmHg DBP 74–75 ± 14 mmHg	No significant differences in SBP or DBP were noted between the two groups (carvedilol vs. control)	
Calcium channel blockers	Not reported	AHA: Dihydropyridine calcium channel blockers may be used to treat hypertension in patients with elevated BP despite optimization of guideline-directed medical therapy	CONVINCE trial [109]: The study did not demonstrate equivalence of a controlled-onset extended-release verapamil-based anti-hypertensive regimen compared with a regimen beginning with a diuretic or beta-blocker. The effectiveness of calcium channel therapy in reducing the cardiovascular disease is similar but not better than that of diuretic or beta-blocker treatment	Not reported	100%	For all study participants ($N = 16602$): SBP 150.1 mmHg DBP 86.8 mmHg	Both regimens significantly lowered the BP. Over the entire follow-up period, SBP was reduced by 13.6 mmHg and DBP by 7.8 mmHg from baseline in the verapamil group. In the atenolol or hydrochlorothiazide group, SBP was reduced by 13.5 mmHg and DBP by 7.1 mmHg. The mean differences in BP change (verapamil minus atenolol or hydrochlorothiazide) were small for SBP (0.06 mmHg; 95% CI −0.44 to 0.56 mmHg) and DBP (0.67 mmHg; 95% CI 0.38–0.95 mmHg). At the last follow-up visit attended, an SBP < 140 mmHg and DBP of < 90 mmHg was achieved in 65.5% of the verapamil group and 65.9% of the atenolol or hydrochlorothiazide group	

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
Emerging drug therapies								
ARNI	AHA: 2b ESC: Not reported for HFpEF JCS/JHFS: IIb in HFpEF	AHA: In selected patients with HFpEF, ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum [17]. JCS/JHFS: Administration of ARNI for HFpEF may be considered [146]	PARAMOUNT [85]: In patients with HFpEF, sacubitril/valsartan reduced NT-proBNP to a greater extent than valsartan alone at 12 weeks and was well tolerated	LVEF ≥ 50%	92–95%	For all study participants ($N = 301$): Median sitting SBP 136 mmHg Median sitting DBP 78–80 mmHg	Not reported	PREMIER trial [93]: An ongoing study to assess the treatment effect of sacubitril valsartan vs. conventional therapy for HF) in patients admitted because of exacerbation of HF on NT-proBNP concentrations
			PARAGON-HF [88]: Sacubitril/valsartan did not result in a significantly lower rate of total hospitalizations for HF and death from cardiovascular causes among patients with HF and an ejection fraction of ≥ 45%	LVEF ≥ 45%	95%	For all study participants ($N = 4822$): SBP 130 ± 15 mmHg	The mean SBP at 8 months was 4.5 mmHg (95% CI 3.6–5.4) lower in the sacubitril/valsartan group than that in the valsartan group, but this difference was not correlated with the potential treatment effect	
			PARAGON-HF [89]: The primary outcome was a composite of total hospitalizations for HF and death from cardiovascular causes. Sacubitril–valsartan may be useful in treating apparent resistant hypertension in patients with HFpEF, even in those who continue to have an elevated BP despite treatment with at least four antihypertensive drug classes, including an MRA	LVEF ≥ 50%	100%	SBP in patients with apparent resistant hypertension ($N = 731$), non-resistant hypertension ($N = 1268$), and a controlled BP ($N = 2796$) were 149.2 (±11.0), 149.1 (±11.2), and 123.6 (±9.2) mmHg, respectively DBP in patients with apparent resistant hypertension, non-resistant hypertension, and a controlled BP were 78.7 (±10.7), 80.4 (±10.5), and 72.7 (±10.0) mmHg, respectively.	The reduction in systolic BP at weeks 4 and 16, respectively, was greater with sacubitril–valsartan vs. valsartan in patients with apparent resistant hypertension (−4.8 [−7.0 to -2.5] and 3.9 [−6.6 to −1.3] mmHg) and apparent MRA-resistant hypertension (−8.8 [−14.0 to −3.5] and −6.3 [−12.5 to −0.1] mmHg)	
			PARAGON-HF trial [90]: PP was an independent predictor of cardiovascular events in patients with HF with preserved ejection fraction enrolled in PARAGON-HF. Sacubitril/valsartan lowered PP compared with valsartan	LVEF ≥ 50%	> 93.6%	SBP based on pulse pressure quartiles were 122 (±10) [$N = 1085$], 131 (± 10) [$N = 1194$], 138 (±10) [$N = 1313$], and 151 (±13) mmHg [$N = 1204$], respectively. DBP were 80 (±10), 78 (±10), 76 (±10) and 72 (±11) mmHg, respectively.	One year after randomization, PP was significantly lower in the sacubitril/valsartan group compared with the valsartan group (3.0 mmHg decrease [95% CI 2.4–3.5]; $P < 0.001$)	
			ARNIMEMs-HF [91]: Sacubitril/valsartan significantly reduced mean pulmonary artery pressure in patients with HFpEF and pulmonary hypertension. Independent of loop diuretic management, together with improvement in functional capacity, lung congestion, and QoL	LVEF > 45%	$N = 12$ (85.7%)	For all study participants ($N = 14$) SBP 143 ± 14 mmHg DBP 77 ± 9 mmHg	Baseline SBP was 143 ± 14 mmHg, decreased to 133 ± 15 mmHg during ARNI On period ($P = 0.031$), and remained without significant changes during ARNI Off period (135 ± 22 mmHg, $P > 0.05$)	

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
SGLT2 inhibitors	AHA: 2a ESC: Not reported for HFpEF JCS/JHFS: I in patients with symptomatic HFrEF (not reported in HFpEF)	AHA: In patients with HFpEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality [17].	Bhatt et al. 2021 [113]: In patients with diabetes and recent worsening HF, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF than placebo	LVEF < 50%	Not reported	For all study participants ($N = 1222$): SBP 122 mmHg DBP 72 mmHg	Not reported	
			DELIVER trial [116]: Dapagliflozin reduced the combined risk of worsening HF or cardiovascular death among patients with HFpEF or HF with mildly reduced ejection fraction	LVEF > 45%	Not reported	Not reported	Not reported	
			EMPEROR-PRESERVED trial [118]: Empagliflozin significantly reduced HF hospitalization with a neutral effect on CV death	LVEF > 40%	Not reported	Not reported	Not reported	
Soluble guanylate cyclase stimulators	AHA: Not reported for HFpEF ESC: Not reported for HFpEF	Not reported	SOCRATES-PRESERVED trial [124]: Vericiguat was well tolerated, but did not change NT-proBNP and left atrial volume at 12 weeks compared with placebo; however, it was associated with improvements in QoL in patients with HFpEF	LVEF ≥ 45%	Not reported	For all study participants ($N = 477$): SBP 133 (14) mmHg	There was no change in BP in the highest target dose arm and no dose–response relationship for BP was observed. The largest difference in DBP at 12 weeks was between the placebo and 2.5 mg vericiguat groups (−4.1 mmHg; 95% CI −7.6 to −0.6 mmHg)	
			VITALITY-HFpEF trial [125]: Among the patients with HFpEF and recent decompensation, 24-week treatment with vericiguat at either 15-mg/day or 10-mg/day dosages compared with placebo did not improve the physical limitation score of the Kansas City Cardiomyopathy Questionnaire	LVEF ≥ 45%	92%	For all study participants ($N = 789$): SBP 129 mmHg, with > 70% above 120 mmHg DBP 73 mmHg	Mean changes in SBP at 24 weeks were −3.1 (SD, 14.94) mmHg in the 15-mg/day vericiguat group, −3.8 (SD 4.01) mmHg in the 10-mg/day vericiguat group, and −1.2 (SD 15.42) mmHg in the placebo group. There were no significant changes between the groups in DBP	
			Abuelazm et al. 2024 [128]: Vericiguat 10 mg was effective in reducing the composite CVS mortality and HF hospitalization, with an acceptable safety profile. This was only observed in HFrEF patients, but not in HFpEF patients. However, our data regarding other agents (riociguat and praliciguat) and HFpEF can be underpowered, warranting further RCTs to clarify vericiguat 10 mg place in HFrEF management guidelines and to investigate sGC stimulators for HFpEF in large-scale trials	Not reported	Not reported	Not reported	Not reported	

Table 1 (continued)

Drug class	Evidence level	Guidelines	Key studies and results	LVEF	Prevalence of hypertension	Baseline BP	Effect on BP	Ongoing studies
Ivabradine	AHA/ACC: Not reported ESC: Not reported JCS/JHFS: Not reported	AHA/ACC: Not reported for HFpEF ESC: Ivabradine should be considered in HFpEF for angina relief, but without foreseen benefit on HF endpoints. JCS/JHFS: Indication for ivabradine should be limited to HFrEF (not HFpEF)	EDIFY [131]: No improvement in exercise tolerance, 6-MWD, NYHA functional class, *E/e'*, or NT-proBNP	LVEF ≥ 45%	89 (93.7%) in Ivabradine group 73 (86.9%) in placebo group	For all study participants ($N = 179$): SBP: 132–133 (120–145) mmHg DBP 76–80 (70–85 mmHg	In the ivabradine group, 13/94 patients (13.8%) (compared with 9/84 [10.7%] in placebo) had uncontrolled BP; all of these patients had a hypertension history, and in most cases, worsening of this condition was reported	
			Kosmala et al. [132]: Significant improvement in exercise capacity	LVEF ≥ 50%	27 (90%) in Ivabradine group 24 (77%) in placebo group	For all study participants ($N = 61$): SBP 130–133 mmHg DBP 75–76 mmHg	No significant change in BP	
			Pal et al. [133]: Significant reduction in oxygen consumption and submaximal exercise capacity	LVEF ≥ 50%	HFpEF group: $N = 11$ (50%) Hypertensive group: $N = 22$ (100%)	For all study participants ($N = 44$): SBP 148–147 mmHg DBP 83–82 mmHg	No significant change in BP	
			Tóth et al. 2021 [135]: Ivabradine significantly improved LV performance in HFrEF, at the same time it exerted a tendency to have improved bradycardic effect in HFrEF	Baseline LVEF for HFrEF < 40% For HFpEF > 40%	Not reported	Not reported	Not reported	
Novel MRA								FINEARTS-HF (finerenone in patients with LVEF ≥ 40%) [139]
Antifibrotics			Lewis et al. 2021 [145]: Pirfenidone in comparison to placebo reduced myocardial extracellular volume. Among patients with HFpEF and myocardial fibrosis, administration of pirfenidone for 52 weeks reduced myocardial fibrosis	LVEF > 50	Pirfenidone group: $N = 39$ (83%) Placebo group: $N = 40$ (85%)	For all study participants ($N = 94$): SBP 134–139 mmHg		

6-MWD 6-min walk distance, *ACC* American College of Cardiology, *ACEI* angiotensin-converting enzyme inhibitor, *AHA* American Heart Association, *ALP* alkaline phosphatase, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor–neprilysin inhibitor, *BMI* body mass index, *BP* blood pressure, *CHF* chronic heart failure, *CI* confidence interval, *CV* cardiovascular, *CVS* cardiovascular, *DBP* diastolic blood pressure, *E/A* mitral ratio of peak early to late diastolic filling velocity, *E/e'* early mitral filling velocity/early diastolic mitral annular velocity ratio, *ESC* European Society of Cardiology, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *H-ISDN* hydralazine-isosorbide dinitrate, *HR* hazard ratio, *JCS* Japanese Circulation Society, *JHFS* Japanese Heart Failure Society, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association, *PP* pulse pressure, *QoL* quality of life, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SD* standard deviation, *sGC* soluble guanylate cyclase, *SGLT2* sodium–glucose co-transporter 2, *WBC* white blood cell

blood volume and blood pressure. Consequently, intravenous diuretics are commonly used in the treatment of patients with HFpEF in the acute phase with concurrent hypertension.

Patients with HFpEF have a narrow range of sensitivity to volume changes, with a fine line between hypervolemia, leading to congestive symptoms, and hypovolemia. The diuretic response can be evaluated by measuring the urinary potassium to creatinine ratio in patients with acute HFpEF [47]. Overly aggressive diuresis can potentially reduce the cardiac output, decrease renal function, and cause hypotension [48, 49]. In light of this, the ROPA-DOP trial investigated whether the combination of dopamine and furosemide could minimize worsening renal function in patients with HFpEF [50]. Furosemide was associated with renal impairment, and dopamine did not significantly affect creatinine levels, highlighting the persistent challenge of renal impairment associated with diuretic therapy. Another concern is the development of diuretic resistance with chronic loop diuretic use [51, 52], characterized by an inadequate reduction in edema despite the use of a maximal diuretic dose [53]. Moreover, clinicians should exercise caution when initiating loop diuretics or escalating the dose of loop diuretic in patients treated with other agents, such as sacubitril/valsartan [54] and empagliflozin [55] in patients with HFpEF, owing to the increased risk of volume depletion.

The use of intravenous diuretics in the acute phase of HFpEF can effectively alleviate symptoms of congestion associated with fluid overload, which may in turn lead to a reduction in blood pressure. However, chronic diuretic therapy may contribute to renal impairment, and overly aggressive diuresis can lead to hypotension. Therefore, the optimal balance between achieving an ideal fluid status and avoiding adverse effects necessitates careful consideration when administering diuretics in the treatment of HFpEF with concurrent hypertension. In patients with CKD, the administration of loop diuretic agents should be maintained at the lowest effective dose. Preferred alternatives include evidence-based agents with diuretic effects, such as mineralocorticoid receptor antagonists (MRAs) with careful serum potassium level monitoring, and sodium–glucose co-transporter 2 (SGLT2) inhibitors [56]. Thiazide diuretics may also be considered in combination with loop diuretics to enhance the effectiveness of diuretics [57].

In the TOPCAT trial that studied the usefulness of spironolactone, an MRA, in 3445 patients with HFpEF [58], a significant proportion of patients were receiving diuretic medications at baseline. Specifically, among the 1767 patients enrolled in the Americas, approximately 89% were receiving a diuretic at baseline, whereas in Georgia/Russia, approximately 74% were receiving a diuretic at baseline [58, 59]. A sub-analysis of the TOPCAT trial indicated that baseline diuretic use was associated with a higher risk of all-cause hospitalization, but not with all-cause mortality in patients with HFpEF. However, the sub-analysis did not report whether diuretic use led to changes in blood pressure [59].

2.1.2 MRAs

Aldosterone receptor blockade can be beneficial in patients with HF, as MRAs are believed to prevent many of the maladaptive effects of aldosterone on the cardiovascular system. For example, spironolactone is hypothesized to prevent the aldosterone-mediated collagen synthesis that contributes to LV remodeling [60].

In the Aldo-DHF trial, in patients with HFpEF, long-term therapy with spironolactone improved LV diastolic function but did not affect maximal exercise capacity, HF symptoms, or quality of life [61]. In the TOPCAT trial, spironolactone did not significantly reduce cardiovascular mortality, but it did significantly reduce HF hospitalization. Moreover, spironolactone significantly reduced systolic blood pressure (SBP) [62]. This was only apparent in the patient cohort from the Americas, who had a baseline SBP of 129 (118–138) mmHg, while those in Georgia/Russia had a baseline SBP of 130 (120–140) mmHg. With spironolactone, the average magnitude of SBP reduction was 4.2 mmHg and 0.6 mmHg in the patients from the Americas and Russia/Georgia, respectively [58]. These findings suggest that there may be regional variations in the blood pressure response to spironolactone. However, maximal exercise capacity, HF symptoms, and quality of life appear to be unaffected by spironolactone. Although there was a trend toward a reduction in cardiovascular mortality, the observations were not statistically significant; however, a reduction in HF hospitalization was observed with spironolactone in the TOPCAT trial, which is why MRAs have a class IIb recommendation in HFpEF [17].

Another study based on the results of the TOPCAT trial [63] evaluated the heterogeneous treatment effects of spironolactone in patients with HFpEF. The study revealed that spironolactone reduced the risk of cardiovascular death in those with a high body mass index (defined as > 31.71 kg/m^2) and a high white blood cell count (> 6.6 cells/μL), but it increased the risk of cardiovascular death in those with a low body mass index (defined as ≤ 31.71 kg/m^2) and low alkaline phosphatase (≤ 80 U/L), indicating that the response to spironolactone may vary among different patient populations.

A recent study used a machine-learning approach to identify responders and non-responders to spironolactone among patients with HFpEF. The derivation cohort was obtained from the Aldo-DHF trial, and the validation cohort was obtained from the TOPCAT trial. The machine-learning approach identified that early mitral filling velocity/early diastolic mitral annular velocity ratio (*E*/*e*') significantly

improved in spironolactone responders in the derivation cohort, and spironolactone significantly reduced the occurrence of the primary outcome (composite of cardiovascular mortality, aborted cardiac arrest, and HF hospitalization) among responders, but not among non-responders [64].

A secondary analysis of the TOPCAT trial also evaluated the benefits of spironolactone as an add-on therapy for patients with HFpEF with resistant hypertension (defined as an SBP ≥ 130 mmHg and/or a diastolic blood pressure ≥ 80 mmHg despite the use of an angiotensin-converting enzyme inhibitor [ACEI]/angiotensin receptor blocker [ARB], calcium channel blocker, and diuretic, or using ≥ 4 classes of anti-hypertensive medication). The risk of the composite of cardiovascular death, aborted cardiac arrest, or HF hospitalization was significantly lower in the group receiving spironolactone, whereas the risk of the composite outcome was not significantly different for patients without resistant hypertension. A significant interaction was observed between spironolactone and resistant hypertension in HFpEF. Therefore, the study suggested that spironolactone may be an effective add-on medication for patients with HFpEF with resistant hypertension [65].

2.1.3 Vasodilators

Vasodilators play a vital role in the management of HFpEF by addressing the relaxation impairment (diastolic dysfunction) that is characteristic of the condition. In HFpEF, the ability to tolerate rapid increases in afterload is reduced, which can lead to pulmonary edema. Direct vasodilators, such as nitroglycerin, hydralazine, and nesiritide, are used to dilate the blood vessels, which in turn reduces the blood pressure and afterload. This improves the cardiac output and diminishes the risk of pulmonary edema.

Although nitrates are commonly prescribed to enhance exercise capacity in patients with HFpEF, their clinical evidence is limited. Exercise limitation is a significant chronic symptom in HFpEF [66], prompting treatment with nitrates in approximately 15–50% of the patients [51, 67]. However, the risk of excessive hypotension must be considered. Practice guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) [17] and the Heart Failure Society of America (HFSA) [68] acknowledge a potential role for nitrates in alleviating HFpEF symptoms but highlight the risk of nitrate-induced hypotension in older patients with HFpEF. In the ACC/AHA 2022 guidelines, avoidance of routine use of nitrates is stated, with a class III recommendation [17]. Moreover, older patients with HFpEF often exhibit autonomic dysfunction, chronotropic incompetence, and altered baroreflex sensitivity. These factors can exacerbate the hypotensive responses to changes in hemodynamic load, subsequently increasing nitrate intolerance [69].

Studies evaluating the efficacy of vasodilators in HFpEF have yielded contradictory results. The NICHE trial suggested that the combination of hydralazine and isosorbide dinitrate may improve exercise capacity in HF (6-min walk test); however, this effect diminished after adjusting for baseline covariates. Nevertheless, the rates of HF hospitalization and mortality were lower with the combination of hydralazine and isosorbide dinitrate than with standard of care [70]. The study did not identify significant differences in cardiac structure and function, although the possibility of being underpowered was acknowledged. However, the NEAT-HFpEF trial, which evaluated the use of isosorbide mononitrate in patients with HFpEF, showed no significant difference in peak oxygen consumption between the isosorbide mononitrate and placebo groups. Compared with placebo, isosorbide mononitrate failed to demonstrate a significant improvement in exercise capacity [71]. Another study investigating isosorbide dinitrate, with or without hydralazine, failed to demonstrate beneficial effects on LV remodeling or submaximal exercise capacity, and suggested that it was poorly tolerated in patients with HFpEF. Consequently, routine use of vasodilators in HFpEF was not supported in that study [72]. The ROSE study evaluated whether the addition of low-dose nesiritide to diuretic therapy would enhance decongestion and preserve renal dysfunction in patients with HF regardless of ejection fraction; the addition of nesiritide had no effect on decongestion, renal function, or clinical outcomes [73]. Another study compared hemodynamic responses to nitroprusside in patients with HFpEF with those of patients with HF with reduced ejection fraction. The study demonstrated that the decrease in systemic arterial pressure with nitroprusside was greater in patients with HFpEF than in those with HF with reduced ejection fraction. The study concluded that patients with HFpEF experienced greater blood pressure reduction with nitroprusside [74].

Given the conflicting results on the benefits of vasodilators, further clarification is needed to determine whether the combination of isosorbide dinitrate and hydralazine enhances exercise capacity in patients with HFpEF, and to clarify the benefits that can be achieved with vasodilators generally in patients with HFpEF.

2.1.4 Inotropes

Inotropes, including dobutamine and milrinone, play a role in managing severe HFpEF by enhancing cardiac contractility and increasing cardiac output. These parameters can be measured by echocardiography and bioreactance methods, although the methods cannot be used interchangeably as they provide different cardiac output values at rest and during dobutamine stress tests. Bioreactance is advantageous because it can be used to continuously monitor key hemodynamic variables, including cardiac output, stroke volume,

and heart rate, and it demonstrates good test–retest reliability for estimating cardiac output and stroke volume at rest and after stress testing, such as with dobutamine, to evaluate cardiac function [75].

The MilHFpEF study investigated extended-release milrinone, a phosphodiesterase type III inhibitor, and found it to be well-tolerated by patients, with an improvement in their quality of life [76]. Regarding blood pressure control, another study investigated milrinone and observed a reduction in the mean pulmonary artery pressure from 23 ± 2 to 19 ± 4 mmHg; however, the mean arterial pressure remained unchanged. The study also demonstrated a decrease in LV filling pressure without any changes in the stroke volume, indicating an improvement in LV compliance [77]. These findings suggest that inotropic agents, such as milrinone, may effectively enhance cardiac function and contribute to symptom improvement in patients with HFpEF.

However, it is important to note that the 2022 ACC/AHA guidelines only recommend inotropes with a class IIa/IIb recommendation in patients with advanced HF who are awaiting mechanical circulatory support or heart transplantation, which is mostly (but not exclusively) patients with HF with reduced ejection fraction [17]. Moreover, the ROSE study tested the hypothesis that the addition of low-dose dopamine (inotrope) to diuretic therapy enhances decongestion and preserves renal function in patients with acute HF, regardless of ejection fraction. The addition of low-dose dopamine did not enhance decongestion or improve renal function when added to diuretic therapy, so this strategy was not supported [73].

Given the conflicting findings and the shortage of evidence on blood pressure control in patients with HFpEF with hypertension specifically, further research is needed to establish the benefits of inotropes and to better understand their impact on blood pressure control in the context of HFpEF with hypertension.

2.1.5 Anti-hypertensives

In the management of acute HFpEF, intravenous medications are commonly administered to address the challenges associated with afterload reduction and preload adjustment. In such cases, calcium channel blockers and nitrates are frequently used. Nitrates adjust the preload by expanding the venous pool and reducing the amount of blood returning to the heart. Calcium channel blockers exert their effects by dilating the blood vessels, leading to a decrease in the afterload and improved cardiac function. Intravenous beta-blockers are often administered in acute settings with the primary aim of lowering the heart rate and improving cardiac function. By blocking the action of catecholamines on beta-adrenergic receptors, beta-blockers slow heart rate, thereby improving filling and cardiac output. However, they may still have an impact on blood pressure, which varies depending on the hemodynamic status of the patient. In the chronic HF phase, oral beta-blockers are more commonly prescribed for long-term heart rate control and their additional benefits in managing blood pressure. The use of oral beta-blockers is described in more detail in the following sections.

A retrospective analysis comparing intravenous labetalol (beta-blocker) and intravenous nicardipine (calcium channel blocker) in the intensive care setting for patients with acute elevations in systolic or diastolic blood pressure suggested that nicardipine exhibits greater efficacy as an antihypertensive agent than labetalol. The use of nicardipine was associated with fewer adverse effects, such as bradycardia, hypotension, or atrioventricular block, and had lower discontinuation rates than labetalol [78]. These findings were supported by the multicenter randomized CLUE trial, which compared the safety and efficacy of Food and Drug Administration-recommended dosing of intravenous nicardipine with intravenous labetalol for the management of acute hypertension. Patients treated with nicardipine were more likely to achieve the target SBP range within 30 min than those treated with labetalol [79]. Note that these studies were conducted in a general hospitalized patient population with acute hypertension. Although patients with concomitant HF were included, the findings were not specific to the population of patients with HFpEF. Therefore, the applicability of these results to the management of hypertension in patients specifically diagnosed with HFpEF requires further investigation and clinical consideration.

2.2 Current Drug Therapies for Patients with Chronic HFpEF with Hypertension

In the chronic phase, the primary goals of HFpEF treatment are to enhance cardiac function, alleviate symptoms, and prevent long-term complications. The following sections present the management of HFpEF during the chronic phase, with particular emphasis on patients with concurrent hypertension. The commonly prescribed drug therapies in this context include ACEIs/ARBs, beta-blockers, and calcium channel blockers. In this section, we present a summarized overview of these drug classes, pertinent trials, and their effects on blood pressure control and hypertensive complications, as outlined in Table 1. The subsequent discussion explores the available evidence regarding the efficacy of these therapeutic agents in managing HFpEF, with particular focus on their impact on hypertensive complications and blood pressure control.

2.2.1 ACEIs/ARBs

ACEIs and ARBs contribute to HF management by targeting the renin–angiotensin–aldosterone system, effectively

reducing blood pressure, enhancing cardiac function through afterload reduction, and relieving the heart's workload. Although their benefits in patients with HF with reduced ejection fraction have been well established, showing reductions in morbidity and mortality [80, 81], in patients with HFpEF, the outcomes have been less promising across large-scale clinical trials. The CHARM-PRESERVED study demonstrated a moderate and borderline significant trend toward an 11% reduction in combined cardiovascular mortality or HF hospitalization with candesartan compared with the placebo [82]. The PEP-CHF trial, which evaluated perindopril, showed improvements in symptoms and exercise capacity but not in the combined all-cause mortality or cardiovascular hospitalization compared with the placebo [83]. Finally, the I-PRESERVE trial evaluating irbesartan did not demonstrate a significant reduction in cardiovascular hospitalization or all-cause mortality compared with placebo in patients with HFpEF [67]. Nonetheless, all three trials reported a significant decrease in blood pressure over time with the active drug compared with the placebo, highlighting the effectiveness of ACEIs/ARBs in blood pressure control [67, 82, 83].

2.2.2 ARNI

Angiotensin receptor–neprilysin inhibitor (ARNI) is a combination therapy comprising an ARB and a neprilysin inhibitor [84]. Currently, sacubitril/valsartan (LCZ696) is the only available ARNI. ARNI blocks the angiotensin II receptor and inhibits the breakdown of natriuretic peptides, leading to vasodilation, reduced sodium retention, and improved cardiac function.

In the phase II PARAMOUNT trial, sacubitril/valsartan demonstrated favorable effects in patients with HFpEF. It reduced the N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration, left atrial enlargement, and improved New York Heart Association (NYHA) functional class compared with valsartan alone. Moreover, sacubitril/valsartan demonstrated a significant reduction in systolic and diastolic blood pressure after 36 weeks of treatment compared with valsartan alone [85]. These findings were further supported by another study, which showed that sacubitril/valsartan reduced NT-proBNP concentration and heart rate, improved the signs and symptoms of HF, and led to improvements in NYHA functional class and *E*/*e*' [86]. The PIONEER-HF trial investigated the use of sacubitril/valsartan in patients with acute decompensated HF. It demonstrated that early initiation of sacubitril/valsartan following stabilization resulted in a significantly lower risk of cardiovascular death or HF rehospitalization compared with enalapril at 8 weeks [87].

The PARAGON-HF trial evaluated the efficacy of sacubitril/valsartan compared with valsartan alone in patients with HFpEF. Although the reduction in events with sacubitril/valsartan was not statistically significant, there was a 13% risk reduction, primarily driven by a 15% reduction in hospitalizations [88]. These positive outcomes led to the approval of sacubitril/valsartan as the first drug therapy indicated for the treatment of HFpEF in 2021.

In terms of blood pressure control, in the PARAGON-HF trial, patients in the sacubitril/valsartan group had a higher incidence of hypotension than those in the valsartan group. However, they were less likely to experience increases in creatinine and potassium levels, which are indicators of kidney function. At 8 months, the mean SBP was 4.5 mmHg lower in the sacubitril/valsartan group (approximately 130 mmHg) compared with the valsartan group (approximately 135 mmHg). However, this difference was not correlated with the potential treatment effect [88]. A recent post hoc analysis of the PARAGON-HF trial evaluated the effect of neprilysin inhibition on resistant hypertension (defined as an SBP $\geq$ 140 mmHg despite treatment with valsartan, a calcium channel blocker, and a diuretic) in patients with HFpEF. The reduction in SBP at weeks 4 and 16 was greater with sacubitril/valsartan than with valsartan alone in patients with resistant hypertension, and the proportion of patients with resistant hypertension who achieved SBP control by week 16 was 47.9% with sacubitril/valsartan and 34.3% with valsartan alone [89]. These findings suggest that the combination of sacubitril with valsartan may be particularly beneficial in patients with HFpEF with resistant hypertension.

Another study of data from 4796 patients with HFpEF from the PARAGON-HF trial first evaluated the influence of pulse pressure (an indicator of hypertension and arterial stiffness) on the PARAGON-HF primary endpoint of total HF hospitalizations and cardiovascular death, showing that patients in the highest pulse pressure quartile had a higher rate of the primary endpoint, total HF hospitalizations, and myocardial infarction than patients in the second pulse pressure quartile. Then, reductions in pulse pressure with sacubitril/valsartan treatment were associated with a decreased risk of the primary endpoint and total HF hospitalizations. One year after randomization, pulse pressure was significantly lower in the sacubitril/valsartan group than in the valsartan group. These findings suggest that pulse pressure is an independent predictor of cardiovascular events in patients with HFpEF, and that sacubitril/valsartan reduces pulse pressure to a greater degree than valsartan alone [90].

In the ARNIMEMs-HFpEF trial, sacubitril/valsartan improved functional capacity, lung congestion, and quality of life [91]. In addition, the trial demonstrated a significant reduction in mean pulmonary arterial pressure with sacubitril/valsartan, independent of loop diuretic management. The transition to sacubitril/valsartan resulted in a reduction in the mean pulmonary arterial pressure, by 4.99 mmHg, accompanied by significant improvements in 6-min walking distance and quality of life. Moreover, between the ARNI On

and ARNI Off periods, the mean pulmonary arterial pressure rebounded by + 2.84 mmHg [91]. In addition, a study by Burgdorf et al. reported a significant reduction in pulmonary arterial pressure after transitioning to sacubitril/valsartan in patients with HFpEF and pulmonary hypertension [92].

A phase IV, multicenter, prospective, randomized, open-label study assessing the effect of in-hospital initiation of sacubitril/valsartan on NT-proBNP in patients admitted with an acute exacerbation of HF (PREMIER) is currently enrolling patients in Japan [93]. The PREMIER study is anticipated to reach primary completion in May 2024.

2.2.3 Beta-Blockers

Beta-blockers, such as carvedilol and metoprolol, are frequently used in the management of HFpEF to effectively reduce heart rate and alleviate the workload on the heart. By reducing the sympathetic stimulation effects, oral beta-blockers can lower heart rate and decrease peripheral vascular resistance, thereby helping in the regulation of blood pressure. This dual mechanism renders them valuable in optimizing both heart rate and blood pressure control in patients with stable HF. Notably, a higher heart rate is associated with poor outcomes in patients with HFpEF who have sinus rhythm [94, 95].

In the SWEDIC trial, treatment with carvedilol demonstrated significant improvement in early filling/atrial filling ratio in patients with HF due to LV relaxation abnormalities; this effect was particularly pronounced in patients with higher heart rates at baseline. However, the study also acknowledged the limitations of Doppler echocardiographic indices in assessing LV diastolic dysfunction in this population [96]. The OPTIMIZE-HF registry did not identify a relevant prognostic effect of beta-blockers in older patients with HFpEF [5], potentially owing to underdosing [97] or the relatively short follow-up duration (median, 2.2 years) [98]. Additionally, the benefits of beta-blockers appeared to manifest after three years but not at the 1-year follow-up in patients with HFpEF in another study [99]. Six-year follow-up data from the OPTIMIZE-HF registry showed that high-dose beta-blocker therapy in patients with HFpEF and elevated heart rate (≥ 70 beats/min) was associated with a significantly lower risk of death, where the all-cause mortality rates were 63% and 68% in the matched patients receiving high-dose beta-blocker and no beta-blocker, respectively [100]. Similarly, in another study, the use of beta-blockers was associated with lower all-cause mortality but not with combined all-cause mortality or HF hospitalization [101]. A meta-analysis of randomized controlled trials showed a potential mortality reduction with beta-blockers in HFpEF, although statistical significance was not reached [102]. In the ELANDD study, nebivolol treatment for 6 months reduced the heart rate but did not enhance the exercise capacity or peak oxygen consumption in patients with HFpEF [103]. The J-DHF study, which enrolled Japanese patients with HFpEF, suggested that standard-dose carvedilol (> 7.5 mg/day) may be effective in reducing the composite outcome of cardiovascular death and unplanned HF hospitalization; however, the study was underpowered, and the findings were not conclusive [104].

Although beta-blockers demonstrate some promise in the management of HFpEF, the findings remain inconclusive and may be influenced by factors such as dosage and follow-up duration. Moreover, some clinicians suspect that beta-blockers may worsen HFpEF, particularly in patients with chronotropic incompetence, which is why this drug class does not currently carry any recommendation in existing guidelines and they are not the first choice for the treatment of hypertension in patients with HFpEF [17].

2.2.4 Calcium Channel Blockers

As stated in the AHA/ACC/HFSA guidelines, non-dihydropyridine calcium channel blockers, such as diltiazem and verapamil, have negative inotropic effects and are generally not well tolerated in HF owing to their myocardial depressant activity. However, second-generation dihydropyridine calcium channel blockers, such as amlodipine and felodipine, exhibit less myocardial depressant activity and can help in reducing peripheral vasoconstriction and LV afterload [17]. Non-dihydropyridine calcium channel blockers have a class III recommendation in stage B HF with an ejection fraction < 50%, and all calcium channel blockers are contraindicated in patients with HF with reduced ejection fraction [17]; however, there is no indication that they cause harm in patients with HFpEF; therefore, they may be used to control hypertension in this population.

Calcium channel blockers, including amlodipine and diltiazem, are commonly prescribed for hypertension, but their use in patients with chronic HFpEF and hypertension should be given lower priority compared with other medications, such as ACEIs/ARBs, ARNI, and MRAs. Findings from OPTIMIZE-HF showed that the primary composite endpoint of all-cause mortality and HF hospitalization occurred in 82% and 81% of patients with HFpEF who received and did not receive calcium channel blockers, respectively. Similar results were observed when patients were categorized according to the administration of amlodipine and non-amlodipine calcium channel blockers. These results suggest that the prescription of calcium channel blockers, regardless of the class, does not have an association with the composite endpoint or individual endpoints of all-cause mortality, HF hospitalization, and all-cause hospitalization in patients with HFpEF [105]. Primary HF prevention mainly depends on decreasing blood pressure [106]. While calcium channel blockers are effective for controlling blood

pressure in patients with hypertension, multiple studies have demonstrated that they may be less protective against HF development than other anti-hypertensive agents [107, 108]. For instance, the CONVINCE trial reported a 30% higher incidence of HF in patients treated with verapamil than in those treated with diuretics [109]. Furthermore, a meta-analysis of 18 randomized clinical trials revealed a 25% increase in HF risk among patients with hypertension using intermediate-acting dihydropyridine calcium channel blockers [110]. The significance of this evidence in guiding the selection of calcium channel blockers as anti-hypertensive agents and their impact on primary HF prevention warrants further research.

3 Emerging Drug Therapies for HFpEF

Despite substantial efforts to identify effective drug therapies for HFpEF, the findings of clinical trials remain controversial [61]. While some studies have shown improvements in certain parameters, such as hospitalization for HF and all-cause mortality, others have not demonstrated significant benefits. This reflects the complexity of HFpEF and the challenges in optimizing targeted treatments. Recent clinical trials have focused on identifying novel drug therapies specifically targeting HFpEF. The following sections outline some of these therapies and their effects.

3.1 SGLT2 Inhibitors

SGLT2 inhibitors act by inhibiting SGLT2 in the proximal tubule of the kidney, leading to increased urinary glucose excretion and subsequent reduction in blood glucose levels [111]. SGLT2 inhibitors were originally developed for blood glucose control in type 2 diabetes mellitus (T2DM), but they have recently demonstrated cardiovascular benefits in patients, regardless of diabetes mellitus status.

A recent meta-analysis of five randomized controlled trials concluded that SGLT2 inhibitors reduce the risk of cardiovascular death and HF hospitalization in patients with HF, irrespective of the ejection fraction or care setting [112]. The SOLOIST-WHF study evaluated the benefits of sotagliflozin in patients recently hospitalized for worsening HF. Although the main analysis reported results for all patients regardless of LVEF (encompassing patients with HFpEF, as well as other types), a subgroup analysis by LVEF ($\geq$ 50% vs. $<$ 50%) was performed, allowing deductions to be made on the benefits of this agent in HFpEF specifically. The subgroup analysis showed that the benefits of sotagliflozin on the primary endpoint of total deaths from cardiovascular causes and HF hospitalization were consistent between the main analysis and the subgroups stratified by LVEF. Specifically, the primary endpoint was significantly lower in those treated with sotagliflozin than in those treated with placebo [113].

Other clinical trials have evaluated the potential benefits of SGLT2 inhibitors in patients with HFpEF specifically. One study revealed that 12 weeks of dapagliflozin treatment resulted in significant improvements in patient-reported symptoms, physical limitations, and exercise function in patients with mildly reduced or preserved ejection fraction [114]. The DELIVER randomized controlled trial, which included over 6000 patients, revealed that over a median duration of 2.3 years, dapagliflozin lowered the combined risk of worsening HF or cardiovascular death in patients with mildly reduced or preserved ejection fraction [115]. A secondary analysis of the DELIVER trial examined the association of dapagliflozin with changes in individual components of the Kansas City Cardiomyopathy Questionnaire (KCCQ). The most significant improvements were observed in the frequency of lower limb edema, sleep limitation by dyspnea, and limitation in desired activities by dyspnea. Therefore, this analysis showed that dapagliflozin may reduce certain symptoms and improve physical limitation [116]. The EMPEROR-Preserved trial, in which patients with HFpEF were randomized to receive either placebo or empagliflozin, showed that empagliflozin reduced the risk of cardiovascular death and HF hospitalization [117, 118]. Collectively, these findings suggest that SGLT2 inhibitors are a promising therapeutic alternative for patients with HFpEF, offering potential benefits in terms of improving symptoms and physical limitation, as well as reducing the risk of cardiovascular events.

3.2 Soluble Guanylate Cyclase Stimulators

Vericiguat, a novel oral soluble guanylate cyclase (sGC) stimulator, has shown potential in reducing HF-associated oxidative stress and improving endothelial dysfunction [119–122]. However, the clinical evidence regarding the effectiveness of vericiguat as an sGC stimulator in patients with HFpEF has yielded conflicting results.

The phase II SOCRATES-PRESERVED trial showed that vericiguat, compared with placebo, improved the physical limitation score of the KCCQ in patients with worsening HF [123, 124]. Conversely, the VITALITY-HFpEF trial, which investigated the effects of vericiguat treatment over 24 weeks in patients with HFpEF following recent decompensation, did not demonstrate improvement in the KCCQ physical limitation score [125–127]. A recent network meta-analysis of eight randomized controlled trials with a total of 7307 patients showed that vericiguat did not reduce the composite of cardiovascular mortality and HF hospitalization in patients with HFpEF [128]. These conflicting findings highlight the need for further research to better understand the

role of sGC stimulators in the management of HFpEF and their potential implications for improving patient outcomes.

In terms of blood pressure control, the VITALITY-HFpEF trial demonstrated a mean change in SBP at 24 weeks of − 3.1 mmHg in the 15-mg/day vericiguat group, − 3.8 mmHg in the 10-mg/day vericiguat group, and − 1.2 mmHg in the placebo group; however, there were no significant changes in the diastolic blood pressure or heart rate [125]. In the SOCRATES-PRESEVED trial, no changes in blood pressure were observed in the highest target dose arm, and there was no dose–response relationship for blood pressure. At 12 weeks, the largest difference in diastolic blood pressure was between the placebo and 2.5 mg vericiguat groups (− 4.1 mmHg, 95% confidence interval [CI] − 7.6 to − 0.6 mmHg) [124].

3.3 Ivabradine

Ivabradine, a funny current (I_f) inhibitor, reduces heart rate without reducing cardiac inotropy [129] and may have some positive effects on cardiac fibrosis via upregulation of microRNA-133a, which targets connective tissue growth factor and collagen 1 in cardiac fibroblasts [130]. To date, two randomized controlled trials [131, 132] and one cross-over study [133] have been conducted to evaluate the usefulness of ivabradine in patients with HFpEF. However, the outcomes of these trials are, to some extent, conflicting.

In 2013, Kosmala et al. [132] published a study examining 61 patients treated with either ivabradine or placebo for 7 days before follow-up assessment. The ivabradine-treated group demonstrated a significant improvement in exercise capacity from baseline when compared with the placebo group. The EDIFY trial [131], which included 179 patients with HFpEF with eight months of follow-up, also examined changes in exercise tolerance, 6-min walk distance, and NYHA functional class. In contrast with the findings of Kosmala et al. [132], ivabradine did not lead to a significant improvement in exercise tolerance, and there was no improvement in the 6-min walk distance in the ivabradine-treated group. Moreover, most patients did not demonstrate an improvement in the NYHA functional class [131]. One possible explanation for this is that the patients in EDIFY had advanced HFpEF with extensive myocardial fibrosis, which reduces the stroke volume. This implies that the cardiac output depends to a greater extent on the heart rate (heart rate × stroke volume = cardiac output). Therefore, heart rate reduction with ivabradine in this context would be detrimental [134]. Furthermore, ivabradine failed to improve *E*/*e*' and reduce NT-proBNP concentration in the EDIFY trial [131].

In the cross-over study by Pal et al. [133], 22 patients with HFpEF with exercise limitation were administered ivabradine and placebo separately, each in blocks of 2 weeks. The results were compared with 22 matched volunteers with asymptomatic hypertension who underwent the same treatment regimen. Ivabradine significantly reduced oxygen consumption and submaximal exercise capacity in the HFpEF group. However, patients in this study had poor stroke volume reserve, which, along with heart rate reduction, could have led to the worsening in exercise capacity. In terms of blood pressure, ivabradine significantly reduced the resting heart rate without affecting the blood pressure or LVEF [133].

A meta-analysis evaluated the effects of ivabradine on heart rate reduction and LV functional improvement in patients with HFpEF. Ivabradine significantly decreased heart rate in HFpEF, but not LVEF or LV performance [135].

Along with this evidence showing the limited benefits of ivabradine in patients with HFpEF, it should be emphasized that in a large trial of ivabradine in patients with coronary artery disease without HF, a 20% increase in hospitalizations for HF was noted [136]. Therefore, the use of ivabradine in patients with HFpEF is not yet widely supported.

3.4 Novel MRA

Finerenone, a non-steroidal selective MRA, is currently being studied for the reduction of renal and cardiovascular adverse outcomes in patients with kidney disease and diabetes mellitus. The FIDELITY analysis, which comprised a prespecified pooled efficacy and safety analysis of the FIDELIO-DKD and FIGARO-DKD studies, concluded that finerenone reduced the risk of clinically significant kidney and cardiovascular outcomes in the spectrum of CKD when compared with placebo in patients with T2DM [137]. In this analysis, patients with CKD, T2DM, and hypertension had a higher prevalence of LV hypertrophy than patients without CKD. LV hypertrophy is a predictor of cardiovascular disease and associated morbidity and mortality. Of the 13,026 patients with CKD and T2DM analyzed in FIDELITY, 1250 patients had LV hypertrophy at baseline. Finerenone treatment consistently reduced the relative risk of the cardiovascular composite endpoint, both in cases with and without LV hypertrophy (28% in cases with LV hypertrophy vs. 11% in those without LV hypertrophy; $P_{\text{interaction}} = 0.11$). The relative risk reduction of the renal composite endpoint was also consistent across subgroups (44% in cases with LV hypertrophy vs. 20% in those without LV hypertrophy; $P_{\text{interaction}} = 0.18$). The relative risk of HF hospitalization, a component of the cardiovascular composite endpoint, was reduced in both subgroups (66% in patients with LV hypertrophy vs. 14% in those without LV hypertrophy), with the effect of finerenone being significantly greater in the population with LV hypertrophy ($P_{\text{interaction}} = 0.0024$) [138]. The cardiovascular and renal benefits of finerenone in a particularly vulnerable subgroup of patients with CKD and T2DM

highlight the potential cardiorenal protective benefits of this treatment alternative without the need for hospitalization.

The ongoing FINEARTS-HF trial (NCT04435626) is evaluating the effect of finerenone on the reduction of cardiovascular death and HF events in patients with HFpEF (LVEF of ≥ 40%). The study is planned to enroll 6000 participants, with estimated study completion in 2024 [139]. Finally, the ongoing three-arm, phase II CONFIDENCE trial (NCT05254002) will assess the efficacy and safety of finerenone plus empagliflozin (SGLT2 inhibitor) compared with either finerenone or empagliflozin alone in patients with CKD complicated by T2DM [140]. The primary objective of this study is to evaluate the superiority of concurrent finerenone and empagliflozin over empagliflozin or finerenone monotherapy with respect to lowering the urinary albumin to creatinine ratio.

3.5 Antifibrotics

Extracellular matrix expansion resulting from excessive collagen accumulation is frequently observed in patients with HFpEF, and data suggest that it plays an etiological role in HFpEF, with adverse effects on mechanical, electrical, and microvascular function [141–144]. In the randomized, double-blind, placebo-controlled, phase II PIROUETTE trial [145], the antifibrotic pirfenidone (which has no hemodynamic effect) was evaluated in terms of its safety and efficacy in patients with HFpEF (LVEF ≥ 45%) with myocardial fibrosis. The study showed that pirfenidone reduced myocardial extracellular volume compared with placebo; however, the benefits of this on HFpEF itself remain to be clarified.

4 Future Perspectives and Research Needs

Despite the advancements in management and treatment alternatives for patients with HFpEF, there are still several areas that require further research to optimize drug therapy for this patient population, particularly for those with concurrent hypertension. There are also certain groups of patients who may warrant particular consideration. Patients with comorbid hypertension have an increased likelihood of complications related to renal dysfunction, and a high level of awareness of cardiorenal interactions in such patients is required. SGLT2 inhibitors, which have shown evidence of benefit in the prognosis of patients with HFpEF, may be the most promising oral treatment alternative in the future. Furthermore, the cardiovascular and renal benefits of finerenone may be further emphasized in the future, along with its potential as a therapeutic agent for HFpEF in terms of cardiorenal protection, although the evidence remains to be established.

In an era of precision medicine, the effects of sex differences should also be considered in daily medical practice. Among the medical treatments described in this review, the PARAGON-HF study demonstrated the influence of sex differences on the treatment outcomes [88], but this is an area set for further development. Moreover, it is crucial to consider older populations; in an aging and hyper-aging society, developing a strong evidence base in such groups is increasingly important. Across various drug therapies, the tolerability and optimal dosing strategies of drugs may differ in this context. For example, there is no established evidence for the long-term prognostic benefit of SGLT2 inhibitors in patients with HFpEF. Especially in patients who have or who are progressing toward sarcopenia or frailty, the long-term benefits obtained with SGLT2 inhibitors may be diminished.

HFpEF is a heterogeneous condition with diverse underlying pathophysiological mechanisms. More research is needed to identify distinct subgroups within the HFpEF population for the development of tailored treatment strategies that benefit each subgroup. In addition, there is a continued need to explore novel therapeutic targets for HFpEF with concurrent hypertension. The current treatment alternatives for HFpEF primarily focus on managing comorbidities and symptoms, and there are limited therapies that directly target the underlying pathophysiological processes. Furthermore, investigating the role of novel drug classes may offer promising approaches for therapeutic intervention in patients with HFpEF with concurrent hypertension.

5 Conclusions

This comprehensive state-of-the-art review highlights the current drug therapies for patients with HFpEF with hypertension, with a focus on both the acute and chronic phases of HFpEF. In the acute phase of HFpEF, intravenous diuretics, MRAs, and vasodilators are essential for achieving rapid decongestion and alleviating symptoms. Additionally, carefully selected patients may benefit from calcium channel blockers to improve hemodynamic stability and reduce hospital readmissions. In the chronic phase, ACEIs and ARBs have shown efficacy in improving the clinical outcomes, including reducing hospitalizations and mortality rates. Nonetheless, caution should be exercised when considering calcium channel blockers because of their potential negative effects on cardiac contractility.

Regarding emerging drug therapies, SGLT2 inhibitors, ARNI, sGC stimulators, and novel MRAs offer promising strategies for the management of HFpEF with hypertension. SGLT2 inhibitors, in particular, have demonstrated the potential to reduce HF hospitalizations and cardiovascular mortality in patients with HFpEF, irrespective of their diabetic status. Moreover, ARNI and sGC stimulators

(vericiguat specifically) have shown potential in improving symptoms, functional capacity, and quality of life. However, further research employing long-term studies is needed to identify the optimal treatment strategies for HFpEF with concurrent hypertension. Additionally, the identification of novel targets and mechanisms underlying HFpEF pathophysiology will drive innovative drug development approaches in the management of patients with HFpEF with concurrent hypertension.

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Declarations

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