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PULMONARY HYPERTENSION (JR KLINGER, SECTION EDITOR)

Management of Pulmonary Hypertension in the Context of Heart Failure with Preserved Ejection Fraction

Elie Kozaily[1] · Ecem Raziye Akdogan[1] · Natalie Stringer Dorsey[2] · Ryan J. Tedford[1,3]

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Abstract

Purpose of Review To review the current evidence and modalities for treating pulmonary hypertension (PH) in heart failure with preserved ejection fraction (HFpEF).

Recent Findings In recent years, several therapies have been developed that improve morbidity in HFpEF, though these studies have not specifically studied patients with PF-HFpEF. Multiple trials of therapies specifically targeting the pulmonary vasculature such as phosphodiesterase (PDE) inhibitors, prostacyclin analogs, endothelin receptor antagonists (ERA), and soluble guanylate cyclase stimulators have also been conducted. However, these therapies demonstrated lack of consistency in improving hemodynamics or functional outcomes in PH-HFpEF.

Summary There is limited evidence to support the use of pulmonary vasculature-targeting therapies in PH-HFpEF. The mainstay of therapy remains the treatment of the underlying HFpEF condition. There is emerging evidence that newer HF therapies such as sodium-glucose transporter 2 inhibitors and angiotensin-receptor-neprilysin inhibitors are associated with improved hemodynamics and quality of life of patients with PH-HFpEF. There is also a growing realization that more robust phenotyping PH and right ventricular (RV) function may hold promise for therapeutic strategies for patients with PH-HFpEF.

Keywords Pulmonary hypertension · Heart failure with preserved ejection fraction · Diastolic heart failure

Introduction

Heart failure with preserved ejection fraction (HFpEF) is at least as common as heart failure with reduced ejection fraction (HFrEF) and generally carries a similar prognosis with a high burden of morbidity and mortality [1]. The prevalence of HFpEF is only projected to increase [2, 3]. Pulmonary hypertension (PH) is frequently co-morbid with HFpEF. The prevalence of PH in HFpEF may be up to 80% [4], yet its definition and prevalence vary widely between studies [3, 5]. PH-HFpEF is classified under the World Symposium on Pulmonary Hypertension (WSPH) group 2 PH, or PH due to left heart disease. The latter is defined hemodynamically as mean pulmonary artery pressure (mPAP) > 20 mmHg along with pulmonary artery wedge pressure (PAWP) > 15 mmHg [6]. It is further subclassified as isolated post-capillary pulmonary hypertension (IpcPH) when PVR < 2 Woods Unit (WU) or combined pre- and post-capillary pulmonary hypertension (CpcPH) when PVR ≥ 2WU [7]. The recent lowering of both the mPAP as well as PVR cut points was based on large populations studies of normative data [8]. IpcPH is more prevalent than CpcPH, with some studies reporting IpcPH at least twice as prevalent [9, 10]. CpcPH, however, is associated with pulmonary congestion, worse right ventricle (RV) function, more impairment in oxygen delivery with hypoxemia during exertion [9, 11], and ultimately higher risk of mortality [11].

Because PH is both a marker of disease severity in HFpEF and has hemodynamic characteristics shared with pulmonary arterial hypertension (PAH), it naturally follows that targeting the pulmonary vasculature may constitute a

✉ Ryan J. Tedford
TedfordR@musc.edu

1 Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC 29425, USA

2 Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

3 Advanced Heart Failure & Transplant Fellowship Training Program, Medical University of South Carolina (MUSC), 30 Courtenay Drive, BM215, MSC592, Charleston, SC 29425, USA

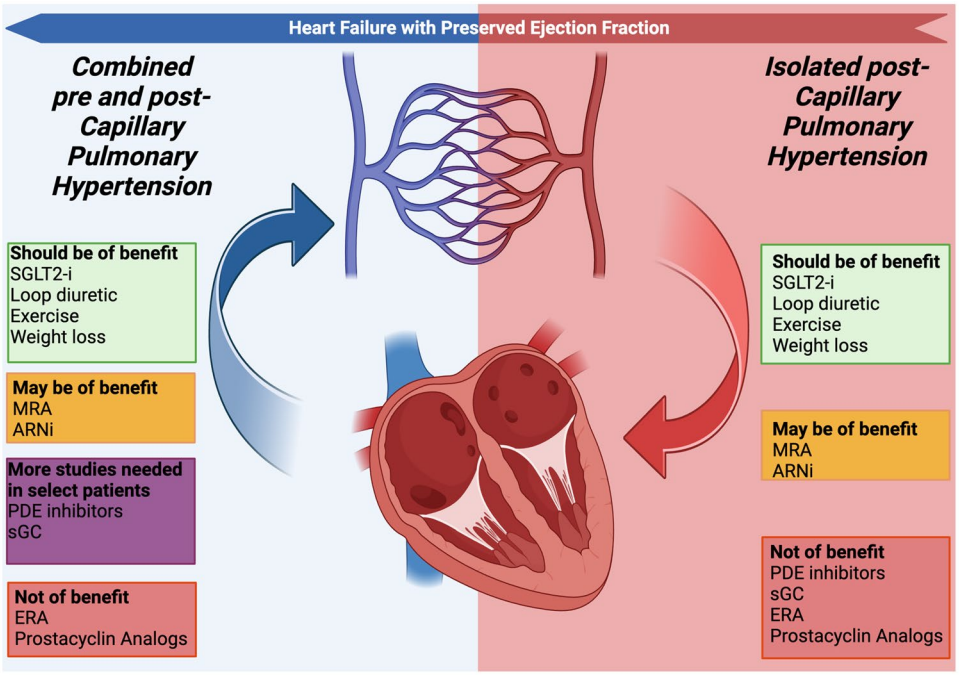

Fig. 1 Therapeutic options for Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction (HFpEF). Created with Biorender.com

therapeutic target in patients with HFpEF. The goal of this review is to provide an update on the management of PH in the context of HFpEF (Fig. 1).

Management of PH in HFpEF

The first goal of treating PH in HFpEF is to target the underlying heart failure syndrome and its potential causes. HFpEF is associated with multiple comorbidities such as type 2 diabetes mellitus, systemic hypertension, atrial fibrillation (AF), obstructive sleep apnea (OSA), and obesity. Controlling these comorbidities with dietary modification, weight loss, aerobic exercise, and even drug therapy improves outcomes in HFpEF [3].

Loop Diuretics

In the ACC/AHA heart failure guidelines, loop diuretics have a class I indication to achieve and maintain euvolemia [12]. Normalization of left heart filling pressures will also lead to a reduction in pulmonary pressures. Additionally, reduction in left heart filling pressures results in both an increase in pulmonary artery compliance (calculated as the ratio of stroke volume to pulmonary artery pulse pressure) and a decrease in PVR—the net effect is a reduction of RV afterload [13]. RV function is a critical determinant of mortality in HFpEF [14]. The benefits of loop diuretics on PH were demonstrated in studies that involved pulmonary artery (PA) pressure monitoring devices (cardioMEMS) and tailored diuresis. Titrating loop diuretics based on PA pressure reduced HF hospitalizations [15, 16].

Even though some small studies suggested the benefits of torsemide compared with other loop diuretics on myocardial fibrosis and ventricular remodeling [17, 18], there are no studies to compare between different loop diuretics in the context of PH-HFpEF. The recently published open-label, pragmatic clinical trial TRANSFORM-HF (Torsemide Comparison With Furosemide for Management of Heart Failure) compared torsemide and furosemide in $N = 2859$ patients with heart failure of which 25% had HFpEF. There was no difference in hospitalization rates at 12 months, regardless of LVEF [18]. The trial did not specifically account for PH.

Therefore, loop diuretics should be used as needed for volume management in patients with PH-HFpEF. No current evidence suggests the superiority of one loop diuretic over the other in this context.

The utility of cardioMEMS to guide diuresis in PH associated with left heart disease was described in a subsequent analysis of the CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients). Benza et al. found that patients with PH (17.5% with preserved LVEF) had a significant 36% decrease in HF hospitalizations but a non-significant difference in mortality [19]. This reduction in HF hospitalizations was consistent across subgroups of patients with PVR ≥ 3 WU and PVR < 3 WU. Assmus et al. investigated the effects of cardioMEMS using the MEMS-HF data where 35% of patients with PH had preserved LVEF [20]. The authors

observed a significant and comparable reduction in HF hospitalizations in patients with IpcPH (55% reduction) and CpcPH (63% reduction) as well as a meaningful improvement in health-related quality-of-life surveys.

Mineralocorticoid Receptor Antagonists

The use of mineralocorticoid receptor antagonists (MRA) is currently given a class IIB recommendation in the ACC/AHA heart failure guidelines for treating HFpEF [12]. Spironolactone for the treatment of HFpEF was studied in a randomized, double-blind, placebo-controlled trial of $N=3445$ patients with HFpEF (TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist). Spironolactone was associated with reduction in HF hospitalizations but did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or HF hospitalization [21]. Notably, a post hoc analysis examined the regional differences in outcomes in participants from the Americas (USA, Canada, Brazil, and Argentina) to participants from Eastern Europe (Russia and the Republic of Georgia) [22]. As compared to placebo, spironolactone reduced primary outcome in the Americas but not in Russia/the Republic of Georgia. This was accompanied with an overall low event rate of primary outcome for both spironolactone and placebo in participants from Russia/the Republic of Georgia 2.5 and 2.3 per 100 patient-years, respectively, compared to 10.4 and 12.6 per 100 patient-years in the Americas, respectively. In addition, an analysis of spironolactone metabolite in the urine revealed the absence of urine metabolite was more common in subjects from Russia and the Republic of Georgia (30% vs 3%) casting doubts over compliance with the trial drug [23].

While MRA may be considered for treatment of HFpEF regardless of the presence of PH [3], there is some evidence to suggest MRA may have direct impacts on the pulmonary vasculature. MRA has been shown to reverse aldosterone inhibiting effect on endothelin-type B in endothelial cells within pulmonary vessels. Endothelin-type B has a major vasodilatory effect on pulmonary artery endothelial cells [24, 25]. An experimental animal study showed that spironolactone and epleronone did not reduce PA pressure or reverse vascular remodeling, yet higher drug levels correlated with lower RV systolic pressures and lower PVR in rats with PAH and RV dysfunction. Notably, there was no significant difference between spironolactone and epleronone [26]. The potential benefit of MRA on PAH was investigated in a retrospective review of four large databases ($N=1229$ patients). The authors did not find survival nor clinical benefit with MRA [24]. A large retrospective study by Lahm and colleagues [27] found that MRA use did not improve survival but was rather a marker of disease severity in patients with PH due to left heart disease.

In summary, while spironolactone showed benefits for the treatment of HFpEF, its potential benefit in PH-HFpEF is only speculative based on the reversal of the aldosterone vasoconstricting effect on pulmonary vessels.

Angiotensin Receptor-Neprilysin Inhibitors (ARNi)

The mortality benefit of Angiotensin-converting enzyme inhibitors (ACE-I) and Angiotensin receptor blockers (ARB) are well known in patients with HFrEF [12]. However, their effectiveness in HFpEF did not yield comparable results across various clinical trials, giving ARB a class IIB recommendation in the ACC/AHA guidelines for the treatment of HFpEF, benefiting mostly patients with a LVEF at the lower end of the spectrum [12, 28–30]. Yet, the possible benefit of ACE-I or ARB in PH-HFpEF is derived from a large retrospective Veterans Affair study that reported that ACE-I or ARB use in PH, especially group 2 PH, was associated with lower mortality [27].

The role of Angiotensin Receptor-Neprilysin Inhibitor (ARNi) in HFpEF is controversial. It is currently a class IIB recommendation in the ACC/AHA guidelines [12]. The PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF with preserved ejection fraction) was a randomized, double-blind, active-comparator trial [31]. After a run-in phase which excluded 925 patients, $N=4822$ patients were randomly assigned to ARNi or ARB. ARNi failed to show statistical superiority over ARB with the primary endpoint of total HF hospitalizations and cardiovascular death ($P=0.06$). In a post hoc analysis combining the data of PARAGON-HF and PARADIGM-HF (Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial), the authors identified a group of patients with lower LVEF (women with LVEF < 60% and men with LVEF < 45%) who are more likely to benefit from ARNi [32]. Unfortunately, data on the presence of PH nor RV function was not presented in either analysis.

Over the past couple of years, evaluation of ARNi in the treatment of PH has gained interest given its potential effect on pulmonary vascular vasodilation and remodeling. This effect was suggested in a PH rat model which found that a 6-week course of ARNi reduced pulmonary vascular thickness, RV pressure, and RV hypertrophy and reduced collagen deposition compared to placebo [33]. Moreover, the combination of ARNi and bosentan (an endothelin receptor antagonist) had more improvement in PH and pulmonary vascular remodeling compared to bosentan (or ARNi) alone [34]. In an attempt to delineate the impact of ARNi on PH associated with left heart disease, a meta-analysis by Zhang and colleagues reviewed

$N=875$ patients with HFrEF in ten retrospective observational studies. The authors observed a reduction in mPAP (weighted mean difference, 2.92 mm Hg; 95% CI, 0.66–5.19 mm Hg; $P<0.05$), a reduction in PA systolic pressure (PASP), and an increase in tricuspid annular plane systolic excursion TAPSE after initiation of ARNi. Findings were suggestive of an effect of ARNi on PH and RV not exclusively dependent on improvement in left heart function [35].

Codina and colleagues also sought to examine ARNi in PH associated with HFpEF [36]. In this single-arm, investigator-initiated, interventional study, $N=14$ ambulatory patients with CardioMEMS were followed over a total of 18 weeks divided into 3 periods of 6 weeks each, pre-ARNi, ARNi-ON, and ARNi-OFF. Between pre-ARNi vs ARNi-ON, mPAP significantly decreased by 4.99 mmHg [95% CI, −5.55 to −4.43]. When ARNi was stopped (ARNi-OFF), mPAP significantly increased by +2.84 mmHg [95% CI +2.26 to +3.42]. Similarly, ARNi met the secondary endpoints of increasing 6MWD compared to pre-ARNi and ARNi-OFF periods, reducing B-line on ultrasound (no significant worsening with ARNi-OFF), and improving quality of life assessed by KCCQ and EuroQol-visual analogue scales (with significant worsening of KCCQ with ARNi OFF). Notably, loop diuretic management did not differ between periods.

Overall, the role of ARNi in treating HFpEF remains controversial to date but recent observations of their potential benefit on PH-HFpEF warrant further and larger cohort investigations. Given their impact on systemic blood pressure, care should be taken to avoid systemic hypotension, particularly in the setting of PH and RV dysfunction.

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)

SGLT2i are now considered a mainstay therapy for HFpEF [37]. Two large randomized controlled trials, EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) showed that SGLT2i reduced cardiovascular death and heart failure-related hospitalizations, regardless of the presence of diabetes mellitus [38–41]. The mechanisms behind the therapeutic benefit of SGLT2i are not well understood. Although there is clearly a component of natriuresis, SGLT2i may reduce myocardial fibrosis and result in myocardial remodeling. In patients with diabetes, SGLT2i reduce diastolic filling pressure and have a favorable effect on vascular stiffness [42]. In addition, the use of SGLT2i in patients with diabetes had a favorable effect on kidney function, weight loss, and hypertension control which all have beneficial effects on the course of HFpEF.

Some experimental observations also suggest SGLT2i could have a favorable effect on the pulmonary vasculature. Uthman and colleagues found that empagliflozin and dapagliflozin reduced reactive oxygen species (ROS) and restored nitric oxide (NO) availability in endothelial cells in a study on human coronary arteries [43]. In an experimental rat model, Dai and colleagues found that dapagliflozin reduced the pathological process of pulmonary vascular remodeling by inhibiting inflammasome pathway mainly toll-like receptor 4/nuclear transcription factor-κB/NACHT, LRR, and PYD domain-containing protein 3 (TLR4/NF-κB/NLRP3) [44].

A recent randomized controlled trial by Nassif and colleagues examined the impact of empagliflozin compared to placebo on PA pressures by studying patients with cardioMEMS devices [45]. The study included 65 patients of which 50% had HFpEF. Compared to placebo, empagliflozin 10 mg daily reduced PA diastolic, systolic, and mPAP as early as the first week. The improvement was sustained through pre-specified follow-up intervals (weeks 8 and 12). Even though subgroup analysis was limited by a small sample size, the decrease in PA pressures was comparable in HFrEF and HFpEF. Notably, loop diuretic use was also comparable between empagliflozin and placebo groups implying that PA pressure lowering happened independently of SGLT2i "diuretic" effect. The CAMEO-DAPA trial (Evaluation of the Cardiac and Metabolic Effects of Dapagliflozin in Heart Failure With Preserved Ejection Fraction) was a phase II, prospective, double-blind study that aims to compare dapagliflozin 10 mg daily to placebo in patients with HFpEF and elevated PAWP during exercise [46••]. Borlaug and colleagues found that treatment with dapagliflozin led to reductions in both resting PAWP (−3.5 mm Hg [95% CI, −6.6 to −0.4]; $P=0.029$) and exercise PAWP (−5.7 mm Hg [95% CI, −10.8 to −0.7]; $P=0.027$). This reduction in pressure was accompanied by beneficial effects on plasma volume and body weight.

In summary, just like for the treatment of HFpEF, SGLT2i seem to have reproducible benefits on PH-HFpEF and hold promise in treating PH-HFpEF with larger studies needed.

Atrial Fibrillation

Left atrial (LA) myopathy and AF may arise from LA enlargement, a consequence of elevated filling pressures in HFrEF. LA myopathy/AF in HFpEF may also be related to systemic or local inflammatory processes such as obesity and epicardial fat [47]. In the early stages of HFpEF, there is a decrease in LA compliance and reservoir function followed by a decrease in LA contractility with ensuing LA enlargement. With AF, LA pressure further increases, both increasing pulmonary artery pressure [48].

In experimental studies, SGLT2i led to reduction in atrial fibrosis and cardiac electrical remodeling [44]. A more recent retrospective study also observed that SGLT2i

use in patients with type 2 diabetes mellitus reduced the recurrence of AF after AF catheter ablation [49].

While observations derived from larger trials suggest a trend favoring rhythm control for AF in the setting of HF, this benefit is not consistent across all studies [47, 50]. Considering timing of therapy since AF onset, one study showed that adopting an early rhythm control strategy (< 1 year since AF onset) over less strict rhythm control reduced the composite outcome of cardiovascular death, stroke, hospitalization for acute coronary syndrome or worsening HF (5.7 per 100 patient-years vs 7.9 per 100 patient-years, $P = 0.03$) [45]; whereas, another study demonstrated no difference between pharmacologic rhythm or rate control in terms of survival or cardiovascular hospitalization in patients with AF onset within 6 months of enrollment [51]. Notably, when considering a rate control strategy for AF in patients with HFpEF, a more lenient approach may be favored over a strict rate control given possible harm that translates into reduction in functional capacity with no mortality benefit with the more strict approach [52]. When it comes to rhythm control strategies for AF in HFpEF, data derived from larger trials show some trend favoring catheter ablation over pharmacologic rhythm control [53, 54].

In a more recent randomized, prospective, single-blinded, controlled trial dedicated to AF in the setting of HFpEF, Chieng et al. compared catheter ablation versus medical therapy for management of AF in $N = 31$ patients with HFpEF [55]. After a 4-week run-in period where all participants underwent antiarrhythmic therapy to achieve an AF ventricular rate of less than 100 beats per minute, participants were randomized 1:1. With the caveat of the relatively small sample size of the study, catheter ablation led to reduction in primary endpoint which was peak exercise PAWP at 6 months. While right atrial (RA) pressure was also reduced in the catheter ablation group, peak PA pressure was unchanged from baseline. Additionally, there was an improvement in peak O2 consumption and MLHF (Minnesota Living with Heart Failure) and a decrease in N-terminal pro–B-type natriuretic (NT pro-BNP) peptide levels. Very interestingly, following catheter ablation, 50% of the patients no longer met the exercise PAWP criteria for HFpEF, suggesting the potential benefits of ablation in patients with AF and HFpEF.

In summary, although robust data for management of AF in the setting of PH-HFpEF is lacking, a rhythm control strategy, particularly catheter ablation, may be appropriate in some cases. The decision should be individualized and follow the ACC/AHA guidelines in addressing AF with HF [12] until more data emerge.

Obesity

The use of drug therapy in addressing obesity in HFpEF was cemented in the recently published randomized, double-blind, placebo-controlled STEP-HFpEF [56]. Patients ($N = 529$) with body mass index ≥ 30 kg/m^2 were randomized to semaglutide 2.4 mg once weekly vs usual care. Semaglutide is a glucagon-like peptide 1 receptor agonist approved for weight loss [57]. At 52 weeks, patients who received semaglutide met the dual primary endpoint of improved functional status assessed by the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; 16.6 vs 8.7 in placebo) and body weight loss (−13.3% vs −2.6% in placebo). Similarly, the semaglutide cohort met secondary endpoints by improving 6-min walking distance (6MWD) and hierarchical composite outcome of death, heart failure events, differences in the change in the KCCQ-CSS and 6MWD, and the change in the C-reactive protein level with a win ratio of 1.72 (95% confidence interval (CI), 1.37 to 2.15; $P < 0.001$). Serious adverse events were more common in the placebo group (26.7% vs 13.3%). The most common serious adverse event in the semaglutide group was gastrointestinal events which was the main reason for discontinuation of semaglutide. Whether the benefits observed in STEP-HFpEF were all secondary to weight loss versus other mechanisms remain unknown. Significant weight loss can be realized through bariatric surgery. Recent observations suggest that bariatric surgery in patients with obesity and PH led to reduction in pulmonary pressures and improved RV function by echocardiographic assessment [58, 59]. While bariatric surgery led to fewer cardiac ischemic events and in-hospital mortality in patients with PH, bariatric surgery was associated with higher odds of atrial fibrillation and acute pulmonary embolism [60].

Obstructive Sleep Apnea

OSA remains prevalent and underdiagnosed in patients with HF [61]. It is associated with increased mortality, HF readmissions, and healthcare costs in patients with HFpEF [62]. HFpEF and OSA share mutual risk factors and comorbidities such as obesity and hypertension. Multiple mechanisms like increased arterial stiffness and impaired diastolic function could explain the relationship between OSA and HFpEF. Most of all, hypoxemia associated with OSA not only triggers systemic inflammation but also promotes pulmonary vasculature constriction and remodeling, both of which constitute a link between PH and HFpEF. In addition, sleep-related hypoxia (oxygen saturation < 90%) was shown to be associated with RV dysfunction in patients with PAH [63].

When it comes to addressing OSA in patients with PH-HFpEF, positive airway pressure (PAP) was shown to improve diastolic function markers such as left atrial volume index, early mitral inflow velocity/mitral annular early diastolic velocity (E/E') in patients with HFpEF [64]. Moreover, PAP was shown to reduce pulmonary systolic pressures in patients with PH [65]. In a recent retrospective propensity-matched study of $N = 4327$ patients with HFpEF and OSA (25.6% with PH), Cistulli et al. report that those who were adherent to PAP devices had a 26% decrease in emergency department visits and a 57% decrease in hospitalizations compared to the year before PAP initiation [66]. Of note, PAP adherence was defined as ≥ 4 h/night for > 70% of nights over a consecutive period of 30 days, in the first 90 days of therapy. Similarly, PAP-adherent patients had fewer health care resource use compared to nonadherent patients.

Pulmonary Vasculature Targets

With the increase in PVR in the context of CpcPH, therapies targeting pulmonary vasculature, like in PAH, have been of keen interest. Pathways that are known to lead to pulmonary vasculature remodeling include increased endothelin-1 (ET-1) production, reduced prostacyclin, and NO production as well as reduced soluble guanylate cyclase (sGC) activity in pulmonary vascular endothelium [67]. Targeting these pathways could have hypothetical benefits on the pre-capillary component of CpcPH in patients with HFpEF.

Prostacyclin Analogs

Prostacyclin analogs can cause pulmonary vascular vasodilation with clear benefits in patients with pulmonary arterial hypertension [68]. While these drugs showed benefits in PAH, the FIRST (Flolan International Randomized Survival Trial) trial found that epoprostenol (*Flolan*) infusion in patients with HF with LVEF < 25% was associated with worse mortality, prompting early termination [69]. Unfortunately, 20 years later, the SOUTHPAW (Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects With Pulmonary Hypertension and Heart Failure With Preserved Ejection Fraction—ClinicalTrials.gov Identifier–NCT03037580) study, which aimed to evaluate the effect of oral treprostinil on change in 6MWD in patients with CpcPH, was terminated prematurely due to slow enrollment.

Endothelin Receptor Antagonists

Endothelin receptor antagonists (ERA) are approved for the treatment of PAH. ET-1—which leads to pulmonary vasoconstriction—is elevated in HF and higher levels are associated with worse outcomes including mortality [70]. The role of ERA in HFpEF has been investigated in several randomized trials (Table 1). In a randomized trial, sitaxsentan met its primary endpoint of improving exercise capacity in patients with HFpEF by increasing treadmill time (90 s vs 37 s, $P = 0.03$). Sitaxsentan was similar to placebo in terms of secondary endpoints including change in NYHA (New York Heart Association) functional class, death, or HF hospital stay as well as adverse reactions. Notably, the study did not account for the presence of PH [71]. A subsequent randomized, placebo-controlled trial studied bosentan in patients with HFpEF and PH diagnosed by right heart catheterization (RHC) with mPAP > 25 mmHg, PAWP > 15 mmHg at rest [72]. Compared to placebo, bosentan treatment did not improve 6MWD over 12 weeks. Additionally, bosentan did not improve NT pro-BNP, echocardiographic, hemodynamic parameters, nor quality of life.

The MELODY-1 trial (Macitentan in subjects with combined prE- and post-capiLlary pulmOnary hypertension due to left ventricular DYsfunction) failed to show the benefit of macitentan over placebo on the composite outcome of fluid retention or worsening NYHA class in patients with CpcPH, of which 76% had HFpEF [73]. Macitentan and placebo had comparable reduction in PVR. MELODY-1 was one of the first trials to enroll a patient population with clear evidence of a pre-capillary PH component [74]. Importantly, macitentan led to numerically more serious adverse events related to edema and volume overload. A larger follow-up study was terminated early (SERENADE; ClinicalTrials.gov–Identifier NCT03153111). In the existing SERENADE data, there was no difference in primary or secondary endpoints between macitentan and placebo, but as seen in MELODY-1, numerically more serious adverse events in macitentan compared to placebo (40.9% vs 32.4%), mainly fluid retention and electrolytes disturbances. With this higher rate of adverse events and lack of benefit on NT-proBNP or functional status, the subsequent SERENADE open label aiming to further assess long-term safety and efficacy was closed (Clinicaltrials.gov Identifier–NCT03714815).

In summary, ERA should not be used in the treatment of PH-HFpEF and may be associated with harm.

Table 1 Randomized controlled trials

Author–date	Intervention (comparator)	Population size (*N*)	Inclusion criteria	Outcomes (follow-up duration)	Findings	Adverse reactions
Endothelin receptor antagonist in HFpEF						
Zile et al. (2014) [71] NCT00303498	Sitaxsentan 100 mg/day vs placebo	$N=192$ ($n=128$ sitaxsentan vs placebo $n=64$)	HF NYHA II or III and an LVEF ≥ 50%. *(Not specifically addressing PH)*	At 24 weeks, the primary endpoint was an increase in treadmill time. Secondary outcomes were change in E/e', LV mass, Minnesota Living with Heart Failure questionnaire, NYHA functional class, deaths, or HF hospital stay.	Sitaxsentan increased median treadmill time (90 s vs 37 s, $P=0.03$). No significant difference in secondary outcomes.	Similar rate of adverse reactions between Sitaxsentan and placebo No serious adverse reactions were noted
Koller et al. (2017) [72] BADDHY trial NCT00820352	Bosentan 65 mg bid × 4 weeks then 125 mg bid × 8 weeks vs placebo	$N=20$ ($n=9$ bosentan vs $n=11$ placebo)	18–75 yo, HFpEF with PH defined as mPAP > 25 mmHg and PAWP > 15 mmHg at rest on RHC, 6 MWD between 150 and 450 m	At 12 weeks end of intervention then at an additional 12 weeks follow-up (non-interventional phase), the primary endpoint was 6MWD at 12 weeks Secondary endpoint, 6MWD at 24 weeks, NT-proBNP, Echo, RHC, body weight, QoL MLHFQ; SF36	No difference in outcomes in bosentan vs placebo	Bosentan may have worsened 6MWD in the non-interventional phase by overloading LV
Vachiéry et al. (2018) [73] MELODY-1 trial NCT02070991	Macitentan 10 mg once daily vs placebo	$N=63$ ($n=31$ macitentan vs $n=32$ placebo)	> 18 yo, LVEF ≥ 30% NYHA II-III with 6MWD 150 m—optimized and stabilized on diuretics. CpcPH confirmed by RHC (mPAP ≥ 25 mmHg, PAWP > 15 mmHg and < 25 mmHg, PVR at rest ≥ 3 WU and DPG ≥ 7 mmHg). Patients stratified by LVEF ≥ 50% vs LVEF < 50%	At 12 weeks, the primary composite of significant fluid retention or worsening in NYHA class from baseline up to the end of treatment, adverse events, PVR, NT-proBNP	Non-statistically significant higher rate of primary composite outcome in macitentan, driven by significant fluid retention Similar improvement in PVR in macitentan and placebo Non-significant reduction in NT-proBNP in macitentan	More AE in the macitentan group is mainly related to edema and volume overload
Voors et al. (2022) (Not published yet, results on clinicaltrials.gov) SERENADE trial NCT03153111	Macitentan 10 mg once daily vs placebo	$N=142$ (71 macitentan vs 71 placebo)	> 18 yo, LVEF ≥ 40% NYHA II-III on at least one diuretic, elevated NT-proBNP, pulmonary vascular disease, or RV dysfunction. *(Not specifically addressing PH)*	At 24 weeks, the primary outcome was a change in NT-proBNP, secondary outcome KCCQ score, the accelerometer assessed the proportion of time spent in light to vigorous physical activity. Number of patients with HF at 52 weeks.	No difference in macitentan vs placebo in lowering NT-proBNP and no effect on HF outcomes	Higher rate of serious AE in macitentan compared to placebo (40.85% vs 32.39%)
The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway sGC in HFpEF						
Bonderman et al. (2014) [83] DILATE-1 NCT01172756	Riociguat 0.5 mg vs riociguat 1 mg vs riociguat 2 mg vs placebo	$N=39$ (8 riociguat 0.5 mg vs 8 riociguat 1 mg vs 10 riociguat 2 mg vs 13 placebo)	≥ 18yo, HFpEF (LVEF ≥ 50%) with PH with controlled symptoms including stable diuretic therapy ≥ 7 days, optimized medical therapy. PH is defined by RHC mPAP ≥ 25 mmHg, PAWP > 15 mmHg at rest.	At 6 h, the primary endpoint was a peak decrease in mPAP; secondary outcomes included other hemodynamic and echo parameters and safety	No change in mPAP at 6 h. Significant decrease in systolic BP and RV end-diastolic area and increase in stroke volume. No effect on PAWP, PVR.	AE mild/moderate-In riociguat 2 mg, $n=3$ drop in MAP and $n=1$ drop in CO (total 30%) vs placebo 15% had a drop in CO
Pieske et al. (2017) [85] SOCRATES-PRESERVED NCT01951638	Vericiguat fixed 1.25 mg vs fixed 2.5 mg vs up-titrated to 5 mg vs up-titrated to 10 mg target doses vs placebo (randomized 1:1:1:1:1)	$N=477$ (96 each of vericiguat group vs 93 placebo)	> 18yo, HFpEF LVEF ≥ 45%, NYHA II-IV, elevated NT-proBNP or BNP within 4 weeks of ADHF. *(Not specifically addressing PH)*	At 12 weeks, two primary endpoints: 1/change in NT-proBNP 2/change in left atrial volume. Secondary endpoints patient-reported outcomes using KCCQ	No change in NT-proBNP or left atrial volume Vericiguat [2.5–5 mg] and [5–10 mg] improved KCCQ scores compared to placebo.	Comparable adverse events across vericiguat groups and placebo
Armstrong et al. (2020) [86] VITALITY-HFpEF NCT03547583	Vericiguat up-titrated to 15 mg once daily vs vericiguat 10 mg once daily vs placebo (randomized 1:1:1)	$N=789$ (264 vericiguat 15 mg vs 263 vericiguat 10 mg vs 262 placebo)	> 45 yo, HFpEF with NYHA II-III LVEF ≥ 45%, elevated NT-proBNP or BNP, within 6 months of ADHF. *(Not specifically addressing PH)*	At 24 weeks, the primary endpoint was functional outcome using KCCQ, secondary endpoint was 6MWD	No improvement in KCCQ nor 6MWD in vericiguat 15 mg or vericiguat 10 mg compared to placebo	Comparable frequency of AE between 3 groups. Symptomatic hypotension and syncope are slightly more prevalent in the vericiguat groups compared to placebo

Table 1 (continued)

Author–date	Intervention (comparator)	Population size (*N*)	Inclusion criteria	Outcomes (follow-up duration)	Findings	Adverse reactions
Udelson et al. (2020) [97] CAPACITY-HFpEF NCT03254485	Praliciguat 40 mg daily vs placebo	*N* = 181 (91 praliciguat vs 90 placebo)	≥45 yo, LVEF ≥ 40%, HFpEF evidenced by hospitalization ADHF, echo or hemodynamics findings of HFpEF. With ≥ 2/4 of the following conditions a/w NO deficiency: diabetes, hypertension, obesity, or advanced age (≥ 70 y). *(Not specifically addressing PH)*	At 12 weeks, the primary endpoint was the change from baseline in peak O2 consumption. Secondary endpoints were the change in 6MWD, ventilatory efficiency (ventilation/CO2 production on CPET), and number of CPET responders (patients with a peak O2 improvement ≥ 1.5 mL/kg/min)	No improvement in primary or secondary endpoints.	The rate of serious AE is similar in praliciguat vs placebo Praliciguat had more hypotension, dizziness, and headache compared to placebo.
Dachs et al. (2022) [84] DYNAMIC NCT02744339	Riociguat 0.5 mg titrated up to 1.5 mg TID vs placebo	*N* = 114 randomized – 88 completed (58 riociguat vs 56 placebo)	18–80 yo, symptomatic PH-HFpEF (LVEF ≥ 50%, WHO-FC II-IV, mPAP ≥ 25 mmHg at rest, and PAWP > 15 mmHg at rest	At 26 weeks, the primary endpoint was a change in CO at rest from baseline. Secondary endpoints PVR, SVR transpulmonary pressure gradient (TPG), and PCWP; change in serum levels of NT-proBNP, and improvements by ≥ 1 WHO-FC; 6MWD, EQ-5D, MLHFQ.	Significant increase in CO (stable HR); a significant decrease in PVR and TPG but no improvement in clinical symptoms.	More dropouts in the riociguat group No serious AE, but more frequent in Riociguat: peripheral edema, dyspnea, hypotension. No death related to riociguat
PDE5 Inhibitors HFpEF						
Guazzi et al. (2011) [75] NCT01156636	Sildenafil 50 mg TID vs placebo for 52 weeks	*N* = 44 (22 sildenafil vs 22 placebo)	HFpEF–LVEF ≥ 50%, sinus rhythm, pulmonary artery systolic pressure ≥ 40 mmHg (echo estimation), and no hospitalization in the 6 months preceding recruitment	At 6 and 12 months, the primary endpoint was a change in pulmonary hemodynamics mPAP and RV performance	Sildenafil is associated with a statistically significant decrease in mPAP Sildenafil associated with decreased in SBP and DBP—also increased CI and decreased PAWP at 6 and 12 months Sildenafil associated with significant lowering of RA pressure, RV end-diastolic pressure, at 6 months	None mentioned
Andersen et al. (2013) [98] SIDAMI trial NCT01046838	Sildenafil 40 mg TID for 9 weeks vs placebo	*N* = 70 (35 sildenafil, 35 placebo)	Male or nonpregnant females aged ≥ 50 years with a recent documented MI, diastolic dysfunction, and LVEF ≥ 45% on echocardiography performed within 48 h of the MI were enrolled. *(Not specifically addressing PH)*	At 9 weeks, the primary endpoint was PAWP at rest and during exercise Secondary endpoints were CI and mPAP	No differences in PAWP between the two groups (at rest and during peak exercise). Sildenafil was associated with an increase in CI (rest and peak exercise) and LV end-diastolic volume index, and a decrease in systemic vascular resistance index and DBP.	Dyspepsia, headache, dyspnea
Redfield et al. (2013) [77] RELAX Trial NCT00763867	Sildenafil 20 mg TID for 12 weeks followed by 60 mg TID for 12 weeks vs placebo	*N* = 216 (113 sildenafil vs 103 placebo)	Patients with HF with LVEF ≥ 50%—NYHA II-IV on stable medical therapy *(Not specifically addressing PH)*	At 24 weeks, the primary endpoint was a change in peak O2 consumption. Secondary endpoint was a change in 6MWD and a 3-tier hierarchical composite clinical status score (tier 1 time to death; tier 2 time to cardiovascular or cardiorenal hospitalization; tier 3 change in MLHFQ from baseline in participants alive without cardiovascular or cardiorenal hospitalization)	Sildenafil therapy did not alter peak O2 consumption, exercise capacity, quality of life, clinical status, LV remodeling, diastolic function parameters, or PASP compared to placebo. Sildenafil was associated with a decrease in renal function and an increase in NT-pro-BNP, endothelin-1, and uric acid levels.	Sildenafil-treated patients had a higher incidence of "vascular" adverse events, which included (but were not limited to) headache, flushing, and hypotension.
Hoendermis et al. (2015) [76] NCT01726049	Sildenafil 20 mg TID × 2 weeks and then titrated to 60 mg TID × 10 weeks vs placebo	*N* = 52 (26 sildenafil vs 26 placebo)	Patients ≥ 18 with symptomatic HFpEF (EF ≥ 45%) with NYHA class II-IV symptoms and pulmonary hypertension as measured by RHC (PAP > 25, PAWP > 15)	At 12 weeks, the primary endpoint was a change in mPAP after treatment Secondary endpoints were a change in mean PAWP, CO, and peak oxygen consumption	No significant changes in mPAP with sildenafil. No difference in secondary endpoints between placebo and sildenafil.	More patients in the treatment group experienced respiratory tract infection, headache, and hypotension.

Table 1 (continued)

Author–date	Intervention (comparator)	Population size (*N*)	Inclusion criteria	Outcomes (follow-up duration)	Findings	Adverse reactions
Liu et al. (2017) [99] NCT01726049 Complementary study of the previous trial by Hoendermis et al. (2015) [76]	Sildenafil 20 mg TID × 2 weeks then up-titrated to 60 mg TID for 10 weeks vs placebo (total of 12 weeks)	N = 52 (26 sildenafil vs 26 placebo)	Patients were adult males or females, with HFpEF (LVEF ≥ 45%) and NYHA functional class II-IV and pulmonary hypertension (mean PAP > 25 mmHg and mean PAWP > 15 mmHg), diagnosed by RHC	Changes in cardiac structure and function (echocardiogram), functional exercise testing, KCCQ, and other lab parameters such as Hgb, C-reactive protein, HgbA1c, and renal function	Sildenafil did not improve the mentioned parameters.	As discussed in the cell above.
Belyavskiy et al. (2020) [78] NCT01201257849	Sildenafil 25 mg TID for 3 months followed by 50 mg TID for 3 months vs placebo	*N* = 50 (30 sildenafil vs 20 placebo)	Patients with HFpEF (LVEF > 50%) and NYHA functional class II-III. CpcPH determined by echocardiography (LV diastolic dysfunction grade II/III) and pulmonary artery systolic pressure > 40 mmHg. Pre-capillary pulmonary hypertension determined by PVR > 3 wood units and/or transpulmonary gradient (TPG) > 15 mmHg	At 6 months, the primary endpoint was exercise capacity measured as change in 6MWD Secondary endpoints were a change in NHYA functional class, exercise duration/maximal achieved workload during cycle ergometry, and changes in mitral E/e' ratio and PASP during diastolic stress echo Pre-specified endpoints: impact of sildenafil on LV, RV structure/function, and NT-proBNP	Sildenafil is associated with an increase in 6MWD + 50 m (95% CI, 36 to 64 m). Sildenafil i associated with an increase in exercise duration and improvement in NYHA class. Sildenafil low dose: improvements in pulmonary hemodynamics (PVR, TPG, and ACT-RVOT) in the first 3 months Sildenafil higher dose: no further significant effects for the remaining 3 months of therapy. Sildenafil improved RV size and contractility, but changes developed gradually regardless of treatment dose at 6 months.	None were experienced, specifically no symptomatic hypotension, facial flushing, or vision changes
PASSION trial (Terminated early) EudraCT 2017-003688-37	Tadalafil 20 mg up-titrated to 40 mg after 4 weeks vs placebo	*N* = 356	Age ≥ 18 years with HFpEF and combined post- and pre-capillary pulmonary HTN as assessed by RHC (PAWP or LVEDP > 15 mmHg, mean PAP ≥ 25 mmHg and PVR > 3 WU during the past 12 months.	At 24 weeks, the primary endpoint was event-free survival Secondary endpoints were changes in NYHA functional class, 6MWD, serum NT pro-BNP, serum bilirubin, GFR, and quality of life	The trial was terminated early due to a manufacturer's drug recall	
PDE3 inhibitors in PH and HFpEF						
Nanayakkara et al. (2020) [82] MilHFPEF Study ACTRN12616000619448	Extended-release oral milrinone (14 mg BID) vs placebo for 43 days	*N* = 23 (12 milrinone vs 11 placebo)	Age ≥ 18 years, NYHA class III, LVEF ≥ 50%, with HFpEF on stable heart failure therapy 2 weeks prior to screening *(Not specifically addressing PH)*	At ~4 weeks, the primary safety endpoint was clinically significant arrhythmia)—efficacy of milrinone using KCCQ and 6 MWD	The Milrinone group experienced a statistically significant improvement in KCCQ and quality of life. Overall, no significant changes in 6MWD. No significant changes were seen in terms of NT-proBNP, HR, eGFR, or E/e' on the echocardiogram.	1 HF hospitalization in a patient in the placebo group, but no adverse events in the treatment group
Cilostazol for HFpEF CLIP-HFpEF NCT05126836	100 mg cilostazol BID × 2 separated weeks (separated by placebo weeks) for a total of 4 weeks	*N* = 25, crossover assignment	Age > 18 yrs, LVEF ≥ 50% (< 2 years), diagnosis of HFpEF or shortness of breath with NYHA II-IV, and findings of HFpEF (imaging, echo, NT-proBNP) *(Not specifically addressing PH)*	At 4 weeks, the primary endpoint quality of life was measured using the KCCQ Secondary endpoint is NT-proBNP at week 1 and week 3	Currently ongoing	

6MWD 6-minute walking distance, *ADHF* Acute decompensated heart failure, *ACT-RVOT* Accelartion time right ventricle outflow tract, *BP* Blood pressure, *CO* Cardiac output, *CI* Cardiac index, *DBP* Diastolic BP, *E/e'* Early filling velocity/early mitral annular velocity, *eGFR* Estimated glomerular filtration rate, *HFpEF* Heart failure with preserved ejection fraction, *Hgb* Hemoglobin, *HgbA1c* Hemoglobin A1c, *HR* Heart rate, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *LV EF* Left ventricle ejection fraction, *LVEDP* Left ventricle end-diastolic pressure, *MAP* Mean arterial pressure, *MI* Myocardial infarction, *mPAP* Mean pulmonary artery pressure, *NO* Nitric oxide, *NYHA* New York Heart Association Functional class, *PASP* Pulmonary artery systolic pressure, *PAWP* Pulmonary artery wedge pressure, *PVR* Pulmonary vascular resistance, *RA* Right atrium, *RHC* Right heart catheterization, *RV* Right ventricle, *SBP* Systolic BP, *SVR* Systemic vascular resistance

Nitric Oxide Pathway

The proinflammatory conditions associated with HFpEF—like obesity and insulin resistance—lead to microvascular inflammation involving endothelial cells. The increase in oxidative stress leads to reduction in NO which in turn leads to reduction in intracellular cyclic guanosine 3′,5′-monophosphate (cGMP) production by soluble guanylate cyclase (sGC). The cGMP is broken down by phosphodiesterase (PDE) mainly PDE type 5 (PDE-5). The reduction in cGMP leads to reduction in vascular compliance and increased stiffness culminating in increased PVR. Multiple trials have examined PDE-5 inhibitors and sGC stimulators in HFpEF, but fewer in PH-HFpEF.

Phosphodiesterase Inhibitors

The most studied PDE inhibitor subclass is PDE-5 inhibitors, mainly sildenafil. PDE-3 inhibitors such as milrinone have recently become of interest as well, as these drugs have vasodilatory properties by increasing cyclic adenosine monophosphate levels (cAMP).

PDE-5 Inhibitors

Given both success in PAH and animal studies, significant excitement centered around the use of PDE-5 inhibitors in PH-HFpEF (Table 1). In a single-center, double-blind, placebo-controlled trial, patients with PH-HFpEF (EF > 50% and PH diagnosed by echocardiography) were randomized to sildenafil 50 mg three times a day vs placebo [75]. Patients who received sildenafil had a significant decrease in systemic blood pressure as well as a decrease in mPAP and PVR at 6 and 12 months. In addition, sildenafil substantially increased cardiac index and reduced RA and RV end-diastolic pressure from baseline and compared to placebo. These positive findings were unfortunately not replicated in a subsequent double-blind, placebo-controlled trial where sildenafil treatment over 12 weeks did not meet its primary endpoint of reducing mPAP in patients with PH-HFpEF with NYHA class II to IV [76]. The lack of benefit was observed in patients with higher PVR (> 240 dynes/s/cm^{-5} reflective of CpcPH) as well as in patients with lower PVR (≤ 240 dynes/s/cm^{-5} reflective of IpcPH), the latter of which were the majority of patients. Sildenafil did not reduce PAWP, RA, or RV pressure and did not improve cardiac output. Compared to placebo, sildenafil also did not improve peak oxygen consumption.

A larger study of patients with HFpEF also failed to show improvements in peak oxygen consumption [77]. The study did not specifically account for the presence of PH, yet baseline echocardiographic assessment showed that median PASP was 41 mmHg with interquartile range [33–51]. Furthermore, sildenafil did not improve 6MWD nor quality of life.

The impact of sildenafil on 6MWD as a primary endpoint was further delineated in a single-center, randomized, placebo-controlled trial [78]. Patients with HFpEF and CpcPH were randomized in a 3:2 ratio to receive either sildenafil or placebo for 6 months. CpcPH was derived using an echocardiogram as PASP > 40 mmHg, PVR > 3 WU, and/or transpulmonary gradient (TPG) > 15 mmHg. Contrary to the findings of the RELAX trial, Belyavskiy and colleagues found that 6MWD increased by +50 m (95% CI, 36 to 64 m) in the sildenafil group at 6 months, whereas no significant improvement was seen in the placebo group +18 m (95% Cl −6 to +41 m). In addition, sildenafil improved NYHA functional class (more patients went from NYHA II and III to NYHA I) and increased exercise duration at 6 months compared to baseline +75 s (95% Cl +23 to +130 s). Moreover, sildenafil reduced PVR and PASP. Kramer and colleagues investigated both sildenafil and tadalafil in a retrospective analysis of $N = 40$ patients with HFpEF and CpcPH who received either drug for 12 months; their findings supported that PDE-5 inhibitors had positive effects on 6MWD, World Health Organization functional class, and resulted in fewer HF hospitalizations [79].

In most trials where safety was assessed, sildenafil and placebo had similar rates of total adverse events [76, 77]. Sildenafil had more common vascular adverse events including hypotension, headache, flushing, and dizziness. For instance, in the RELAX trial, vascular events were 20% in sildenafil vs 8% placebo ($P = 0.011$) even though the change in systemic mean arterial pressure was comparable in both groups. Serious adverse events tended to occur more commonly in sildenafil groups without reaching statistical significance [76, 77]. The notable exception to this is the SIOVAC (Sildenafil for Improving Outcomes After Valvular Correction) study which enrolled patients with persistent PH 1 year after valvular surgery (91% mitral interventions). In this study, patients with mPAP ≥ 30 mmHg were randomized to receive sildenafil vs placebo. Compared to placebo, the sildenafil cohort had a worse composite clinical score (any cause of death, HF hospitalization, WHO functional class, or changes in global self-assessment) [80]. The presence of elevated PVR did not modify the findings.

The ESC/ERS PH guidelines currently give no recommendations regarding the use of PDE-5 inhibitors for significant CpcPH. However, use in IpcPH is a class III recommendation (should not be used) [81].

PDE-3 Inhibitor

Milrinone, a PDE-3 inhibitor, increases cAMP therefore increasing myocardial inotropy and reducing systemic vascular resistance. In a relatively small trial, Nanayakkara and colleagues examined the safety and benefit of extended-release oral milrinone in $N=23$ patients with HFpEF and NYHA III symptoms without specifically accounting for the presence of PH [82]. Milrinone was overall safe with no significant decrease in systemic blood pressure or increase in HR. Compared to placebo, milrinone had a significantly greater improvement in KCCQ score ($+10\pm13$ vs -3 ± 15; $P=0.04$) including the quality of life subdomain. Similarly, milrinone improved 6MWD (10 ± 62 m) compared to placebo (-42 ± 77 m) without reaching statistical significance ($P=0.092$). There was no significant decrease in NT-proBNP and no improvement in filling pressure on the echocardiogram. A randomized, crossover trial assessing cilostazol on functional status and NT-proBNP in patients with HFpEF and NYHA II-IV is currently ongoing (ClinicalTrials.gov Identifier–NCT05126836).

Soluble Guanylate Cyclase Stimulators

In a double-blind, randomized, placebo-controlled, parallel-group phase 2a study, three doses of riociguat 0.5 mg, 1 mg, and 2 mg were compared to placebo in patients with HFpEF and PH defined by RHC, mPAP ≥ 25 mmHg, PAWP > 15 mmHg at rest [83]. Elevated PVR was not an inclusion criterion. The aim of the study was to explore the acute hemodynamics effects of riociguat. At 6 h, there was no difference between 2 mg riociguat and placebo in the primary endpoint of decreasing peak mPAP. While riociguat 2 mg did not impact PAWP, PVR, or TPG, riociguat led to a significant increase in stroke volume and cardiac index (+0.4 L/min/m^2; 95% CI 0.2 to 0.7; $P=0.001$) without affecting heart rate. In addition, riociguat 2 mg was associated with decreased systemic vascular resistance, systolic (−11.7 mmHg; 95% CI −22.4 to −0.9) and diastolic blood pressure (−6.3 mmHg; 95%CI −11.8 to −0.7), and RV end-diastolic area. Adverse events of riociguat were consistent with a drop in mean arterial pressure below 60 mmHg, yet, patients did not present with symptoms of hypotension. More recently, the DYNAMIC trial was conducted, though was terminated prematurely due to enrollment issues. In this trial, riociguat (up to 1.5 mg three times daily) resulted in an increase of cardiac output (by 0.37 ± 1.26 L/min) at 26 weeks compared with placebo (-0.11 ± 0.92 L/min)—(least-squares mean difference, 0.54 L/min; $P=0.014$) [84]. Riociguat was also associated with mild reductions in TPG and PVR. However, there was no difference in 6MWD, QOL measures, NT-proBNP, or WHO functional class. Drug-related adverse events, including hypotension, were more common in the riociguat arm as was the dropout rate. Thus, it remains unclear if the modest hemodynamic benefits of riociguat are clinically relevant.

Two randomized, placebo-controlled trials examined the impact of vericiguat on functional capacity in HFpEF using patient-reported outcomes, without accounting for the presence of PH. In the SOCRATES-PRESERVED trial (vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF), vericiguat failed to meet the two primary endpoints of improving NT-proBNP or decreasing LA volume, yet higher doses of vericiguat [2.5–5 mg] and [5–10 mg] led to meaningful increase in KCCQ [85]. However, in the larger VITALITY-HFpEF trial (Effect of Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction) involving $N=789$ patients, two different doses of vericiguat (10 mg and 15 mg) failed to improve KCCQ and 6MWD at 24 weeks compared to placebo [86].

Although most large studies have only enrolled HFpEF patients, there is no compelling evidence (Table 1) to suggest the benefits of sGC stimulators in PH-HFpEF.

Sotatercept

Sotatercept is a fusion protein that inhibits certain members of the transforming growth factor β family; this action is thought to promote apoptosis and reduce inflammation within the pulmonary vasculature. Sotatercept recently showed dramatic benefits in PAH patients on dual PAH therapy in the STELLAR study [87••]. Compared to placebo, sotatercept resulted in an increase in 6MWD (40.8 m) compared to placebo. Eight of the nine secondary endpoints also favored sotatercept. Nonserious bleed was the most common adverse event, occurring in 21.5% of the sotatercept group and in 12.5% in placebo. Sotatercept is currently being investigated for CpcPH due to HFpEF in the CADENCE study (ClinicalTrials.gov Identifier–NCT04945460).

Pulmonary Artery Denervation

Pulmonary artery denervation (PADN), a catheter-based technique, aims to abolish baroreceptor reflex in PA and its bifurcations. Zhang and colleagues compared PADN to sildenafil plus sham PADN in $N=98$ patients with CpcPH in HF of which 39% had HFpEF [88]. Compared to sildenafil plus sham, PADN reached its primary endpoint of increasing 6MWD (83 m vs 15 m; $P<0.001$) at 6 months. PADN also

improved mPAP and lowered PVR and PAWP at 6 months. PADN had less clinical worsening (16.7% vs 40%; $P=0.014$) and less worsening of HF (14.6% vs 36%; $P=0.016$). The PADN procedure was mostly safe. The recent 3-year follow data was also promising [89]. These aspects are currently being investigated in the ongoing TReatment of Pulmonary Hypertension Group II (TROPHY-II) Study (ClinicalTrials.gov Identifier–NCT03611270). More data is certainly needed to determine the safety and efficacy of this therapy in PH-HFpEF.

Is Targeting the Pulmonary Vasculature the Right Approach?

Despite enthusiasm to specifically target the pulmonary vasculature, it remains possible that this approach has limited efficacy. For example, higher ET-1 levels in volunteers free of cardiovascular disease appear protective of future heart failure events and LV dilation/function [90]. Thus, it remains possible that the development of pre-capillary PH occurs principally to reduce LV preload. However, Omote et al. observed during exercise that patients with CpcPH had a higher incidence of pulmonary congestion quantified by Kerley B lines on ultrasound, lower arterial oxygen saturation, and more ventilation–perfusion mismatch when compared with IpcPH. Lung congestion was inversely proportional to PVR at rest in patients with CpcPH [9]. It remains unknown, however, if these patients would have even more congestion in the absence of an elevated PVR.

The role of vasodilator testing (inhaled NO or nitroprusside) during an invasive hemodynamic assessment to understand the link between the elevation in PVR and HFpEF is an important concept. Al-Naamani and colleagues found that testing with iNO in patients with PH-HFpEF (IpcPH and CpcPH included) was well tolerated, with half of the patients having an increase in PAWP between 1 and 16 mmHg. While only a small minority met the criteria for a positive response to iNO, the responders were more likely to be women and obese patients. A positive response to iNO was not a predictor of survival [91]. The most recent retrospective single-center experience showed that iNO in patients with CpcPH reduced PVR by 1.1 ± 1.4 WU and increased PAWP by 1.3 ± 3.7 mmHg. There was no significant difference in the effect of iNO on patients thought to have predominantly PAH with component of left heart disease compared to those thought to have left heart disease with pre-capillary component. While a more increased PAWP was associated with more decrease in PVR, this effect of iNO was not correlated with a tolerance to PAH-specific medications [92].

Other Therapies

Levosimendan has PDE-3 inhibiting properties, activates potassium channels, and sensitizes myofilaments to calcium. In phase 2 clinical trial including $N=37$ patients with HFpEF with NYHA class II-III, and PH defined by RHC (mPAP > 35 mmHg, PAWP > 20 mmHg), once weekly levosimendan injection for 6 weeks failed to meet its primary end point of reducing exercise PAWP (–1.4 mm Hg; 95% CI, –7.8 to 4.8; $P=0.65$). Yet, compared to placebo, levosimendan reduced PAWP measured across all exercise stages ($P=0.047$) and improved 6MWD ($P=0.033$) [93]. The potential benefits of levosimedan seemed more related to venodilation and reduction in stressed blood volume than the inotropic properties of the drug [94].

Early animal studies showed that in a rodent model of PH-HFpEF with features of metabolic syndrome, oral nitrite, and metformin reduced pulmonary arterial pressures and improved pulmonary vascular remodeling by activating the SIRT3-AMP-Activated Protein Kinase pathway [95]. Nitrite which is transformed into nitric oxide was tested as an inhaled, nebulized treatment for HFpEF. In a multicenter, double-blind, placebo-controlled, 2-treatment, crossover trial of $N=105$ patients with HFpEF, inhaled nitrite over 4 weeks did not improve the primary outcome of improving mean peak oxygen consumption compared to placebo (13.5 vs 13.7 mL/kg/min; $P=0.27$) [96]. Inhaled nitrite did not meet secondary endpoints such as increasing daily activity levels, improving KCCQ-12, or decreasing NT pro-BNP. Several ongoing studies are exploring this therapy with different delivery methods. Metformin is also currently under investigation (ClinicalTrials.gov Identifier–NCT03629340) as the potential therapy for PH-HFpEF.

Conclusion

With the increasing prevalence of HFpEF, the quest for new therapies is ongoing. The importance of characterizing PH in the context of HFpEF is critical for prognosis and has implications for therapeutic strategies. Prior investigations of PAH therapies have not shown consistency in improving HF outcomes or functional status in patients with PH-HFpEF. Ongoing and future studies targeting a well-defined phenotype of patients with PH-HFpEF, such as CpcPH with RV dysfunction, as well as developing therapies that better target the underlying HFpEF condition may ultimately prove to be beneficial.

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