

**In Chronic Cardiac Decompensation with Reduced Left Ventricular Ejection Fraction, Phosphodiesterase-5 Inhibition Exerts Significant Effects on some Clinical, Functional and Hemodynamic Outcomes: a Meta-Analysis**

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**Abstract**

**Background** In patients with pulmonary arterial hypertension, substantial clinical benefits have been reported with the use of phosphodiesterase-5 inhibitors(PDE5i) . Moreover, some studies would have proven useful effects of PDE5i also on the clinical picture of the pulmonary hypertension(PH) secondary to left-sided chronic heart failure(CHF).

**Methods** We performed a meta-analysis comprising randomized controlled trials ( RCTs) which had compared PDE5i ( mostly sildenafil) with placebo in CHF patients .

**Results** 14 studies, including 928 patients overall, were admitted to the meta-analysis. In heart failure with reduced left ventricular ejection fraction (HFREF), PDE5i, compared to placebo, significantly improved the composite of death and hospitalization (OR= 0.28; 95% CI: 0.10 to 0.74). They also improved peak VO<sub>2</sub> (difference in means [MD]: 3.76; 95% CI: 3.27 to 4.25), six-minutes walk distance (6MWD) (MD, 22.7 meters; 95% CI, 8.19 to 37.21) and pulmonary arterial systolic pressure (MD: -11.52 mmHg; 95% CI: -15.56 to -7.49).

Conversely, in CHF with preserved left ventricular ejection fraction (HFpEF), PDE5i were shown not to yield any beneficial effect concerning the investigated endpoints

**Conclusions** In HFREF, PDE5i were shown to improve the composite of death and hospitalization, as well as exercise capacity and pulmonary hemodynamics. Conversely, in HFpEF, no significant clinical, ergospirometric or hemodynamic betterment was achieved using PDE5i treatment.

**Key words:** sildenafil ; phosphodiesterase-5 inhibitors; chronic heart failure; meta-analysis

## MANUSCRIPT

### Background

The cardinal symptom of heart failure, i.e., the dyspnea, is largely attributable to pulmonary hypertension and congestion in the pulmonary vasculature(1). So it is crucial to emphasize the very important role that pulmonary hypertension plays in causing the

symptoms and the clinical picture of heart failure either right-sided or left-sided or biventricular. Pulmonary hypertension associated with left heart disease ( PH-LHD) coincides with the Group 2 of the most recent international classification of the pulmonary hypertension(2) (Tables 1 and 2). The favorable effects of phosphodiesterase - 5 ( PDE5) inhibitors, in particular sildenafil, in the treatment of pulmonary hypertension are mainly attributed to the action exerted on the pulmonary arteriolar -precapillary district ( so-called “precapillary pulmonary selectivity” of PDE5 inhibitors)(3-4). In other words, the benefit of PDE5i in treating heart failure may originate from its hemodynamic effect for the combined post- and pre-capillary PH (Cpc-PH), but not for the isolated postcapillary PH (Ipc-PH)(5).

## **Aims**

In the present article, in order to evaluate the effects exercised by sildenafil or other PDE5- inhibitors on some functional, hemodynamic or clinical end-points , a number of meta-analyses were separately conducted in patients with chronic heart failure with reduced( HFREF) or preserved (HFpEF) left ventricular ejection fraction , respectively.

## **Methods**

### **Study selection**

A systematic search using some related terms was conducted using the PubMed and Embase electronic archives. We limited our search to adults (>18 years old) and to randomized controlled trials( RCTs). The study was performed according to the guidelines and recommendations expressed in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [6] statement. Search terms firstly included “heart failure”, “sildenafil”, “vardenafil”, “tadalafil”, “avanafil”, “udenafil”, “phosphodiesterase 5

inhibitors”, “phosphodiesterase type 5 inhibitors”, “PDE5 inhibitors”, “cardiac dysfunction”, and “pulmonary hypertension”, variously combined by means of the Boolean operators AND and OR. Roots and variants of the search terms were also used. Studies had to be prospective RCTs . In each of the studies admitted to meta-analysis, a comparison had to be made between a group of CHF patients taking a PDE5 inhibitor and a second group assigned a placebo. Studies were incorporated in the meta-analysis provided that they had sufficient information about the explored hemodynamic and/or ergospirometric and/or clinical outcomes .

### **Study endpoints**

The included RCTs were assessed for the following outcomes: **exercise capacity** (peak VO<sub>2</sub> and 6-minutes walking distance [6MWD]), **cardiac performance** (left ventricular ejection fraction [LVEF, %]), **diastolic function** (E/e' ratio), and **pulmonary resistance** (mean pulmonary arterial pressure [mPAP, mmHg], pulmonary arterial systolic pressure [PASP, mmHg], pulmonary vascular resistance [PVR, dyn·sec/cm<sup>-5</sup>]). Clinical outcomes were assessed as all-cause death and hospitalization and adverse events.

### **Data extraction**

All authors participated in determining the eligibility of candidate trials. The search included publications up to June 2016 and no lower date limit was applied. Titles and abstracts of all identified citations were reviewed independently by two authors (R.D.V. and C.A.). Any candidate study was selected for further screening of the full text. Notably, it was decided that the studies selected for the meta-analysis should have included patients aged over 18 years. In addition, animal experimental studies as well as case

reports of PDE5i administration without a control group were eliminated from the meta-analysis. Similarly, all studies not written in English, duplicated studies, review articles, editorials and expert opinions were excluded.

### **Quality assessment**

The authors assessed the risk of bias for the recruited RCTs using the Cochrane Collaboration Risk of Bias Tool. The following risks of bias were evaluated: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data and 6) other bias.

**Statistical analysis** In the case of dichotomous variables, e.g., the composite of “death and hospitalizations” or adverse events, the effect size was expressed as odds ratio with a 95% confidence interval, using Mantel-Haenszel method as the weighting method.

When the endpoint was a continuous variable, such as “change in mean pulmonary arterial pressure (mPAP)” or “change in six min walking test”, the effect size was expressed as a difference in means (MD) with a 95% confidence interval, using inverse variance as the weighting method. Due to the large variety of patients, the effect size was calculated using a random effects model, even in case no heterogeneity was found.

Statistical heterogeneity across studies was tested using Cochran’s Q test and  $I^2$  statistic (coefficient of variability due to inter-study variability). Statistical analyses were performed using RevMan 5.3 software (available from the Cochrane Collaboration; <http://www.cochrane.org>) and Stata version 10 (Stata Corp LP, College Station, TX, USA).

## Results

In our meta-analyses, 14 studies were incorporated on the whole ( Figure 1 and Tables 3 and 4 ). Among them, 13 were RCTs (7-16,18-20) and one was a subgroup analysis (17). Patients affected by HFREF included in our meta-analysis were 555. All of them were derived from the pooling of 9 RCTs plus the afore-mentioned subanalysis study (Tables 3-4). Conversely, patients with HFpEF included in our meta-analysis were 373 on the whole. This value corresponds to the sum of the patients enrolled by 4 RCTs (8,11,14,19), specifically aimed to explore the effects of PDE5 inhibitors in HFpEF.

Therefore, a total of 928 patients with chronic heart failure were considered for the elaboration of the meta-analyses conducted in the course of our research. Among the included studies, 444 patients were assigned to sildenafil (with 443 patients assigned to placebo), and 21 patients were assigned to udenafil (with 20 patients assigned to placebo)( tables 3 and 4).

### **Clinical outcomes ( death and/or hospitalizations, adverse events)**

Seven RCTs of HFREF (7,12-13,15-16,18,20) reported clinical outcomes, with 5 hospitalization events occurring in the PDE5 inhibitor arm and 17 occurring in the control arm. These results indicate a significant benefit conferred by PDE5 inhibitors against hospitalization (OR= 0.28; 95% CI: 0.10 to 0.74;  $p = 0.03$ ; figure 2). Among the three RCTs concerning HFpEF that had included the endpoints of death and hospitalizations, one study ( 11) did not report any event, whereas the remaining two studies(14,19) signaled 16 hospitalization events on the whole occurring in the PDE5 inhibitor arm and 18 occurring in the control arm (OR= 0.81; 95% CI: 0.41 to 1.63;  $p = 0.64$ ; figure 2). During the follow-up period, five deaths were reported.

The occurrence of adverse events in these studies did not significantly differ between the PDE5i arm and the control arm (figure 3).

### **Exercise capacity and cardiac performance**

The use of PDE5 inhibitor significantly improved exercise capacity in patients with HFrEF (figures 4 and 5). In particular, among the six RCTs that had investigated the peak VO<sub>2</sub> in HFREF patients

(9-10,12-13,16,18) this parameter was improved by the use of PDE5 inhibitors (difference in means[MD]: 3.76; 95% CI: 3.27 to 4.25;  $p < 0.0001$ ; figure 4). Similarly, based on the results of two studies (7,18), in HFREF patients PDE5 inhibitor use yielded a significant betterment of six minute walk distance (6MWD) compared to placebo arm (MD, 22.7 meters; 95% CI, 8.19 to 37.21;  $p = 0.002$ ; figure 5). By contrast, in the RCTs of patients with HFpEF no benefit ensued from PDE5i use regarding exercise capacity as measured by cardiopulmonary exercise test or 6 MWD (figure 4 and figure 5).

As regards the assessment of LVEF in patients with HFREF, based on the results of 4 studies (10,13,16,18), the use of PDE5i was associated with a significant increase in LVEF compared to placebo (MD= 4.30%; 95% CI: 2.18% to 6.42%;  $P < 0.0001$ ; figure 6). By contrast, the use of PDE5i for HFpEF patients resulted only in a nonsignificant tendency for increased LVEF (MD= 2.28%; 95% CI: -0.35% to 4.91%;  $p = 0.10$ ; figure 6).

The use of PDE5i in HFrEF decreased mitral annular E/e' ratio, but did not significantly affect this parameter in HFpEF (figure 7).

### **Pulmonary resistance and pulmonary pressures( figures 8-9)**

For patients with HFREF, PDE5i caused a nonsignificant reduction in mPAP (MD: -6.73 mmHg; 95% CI: -14.37 to 0.91;  $p = 0.11$ ), while PASP was significantly reduced (MD: -11.52 mmHg; 95% CI: -15.56 to -7.49;  $p < 0.001$ ; figure 8).

The PDE5i-mediated improvement in pulmonary hemodynamic parameters for patients with HFREF was concordant among the RCTs. The use of PDE5i proved not to be associated with any significant improvement in pulmonary hemodynamics in patients with HFpEF( figures 8 and 9); however, the included RCTs showed very high heterogeneity ( $I^2$  :99% for both mPAP and PASP in HFpEF patients; figure 8).

## Discussion

The illustration of the various studies centered around the PDE5 inhibitor use in heart failure is far from simple. In addition, in order to explain the substantial failure of PDE5 inhibitors in HFpEF, you may need to refer to specific categories of hemodynamic profile regarding the pulmonary circulation . However, such an approach is only applicable to RCTs in which pulmonary catheterization was performed (5 out 13; see tables 3 and 4). Some aspects of this issue are highlighted below.

### **Favorable effects of PDE5 inhibitors in the subset of HFREF patients**

First, the PDE5 inhibitors have proven to improve the composite of death and hospitalizations compared to placebo in HFREF patients. This has to be emphasized because based on 7 studies ( 7,12-13,15-16,18,20) it testifies the existence of an important protective role of PDE5 inhibitors against the risk of death and hospitalizations in HFREF patients. Among the studies incorporated in the meta-analysis, sildenafil was used in 6 studies and udenafil in one , with a total of 460 patients investigated about the endpoint "death and hospitalizations" (see Figure 2).It should be noted that a significant effect on this "hard" endpoint was not achieved by any of the individual studies considered. (Notably, two



studies were not evaluable for the absence of events, i.e., lack of death or hospitalization both in the arm of PDE5i-treated patients and in the one of controls). Therefore, a statistically significant protective effect against death and / or hospitalizations (odds ratio = 0.28; 95% CI: 0.10-0.74) was inferred in HFREF patients exclusively on the basis of the overall analysis of the aggregate data . However, this result has to be reported with the due emphasis because it is a novelty, and because it helps us to propose with the due caution the PDE5 inhibitors , in particular sildenafil, as candidate drugs ready to be inserted into the group of drugs(ACE inhibitors, beta blockers, aldosterone receptor antagonists ) that on the basis of substantial clinical evidence are currently regarded capable of providing significant benefit to patients with HFREF in terms of increased survival and / or survival free from hospitalizations. Obviously further studies, again in the form of randomized controlled trials, are warranted to corroborate and validate the results of this meta-analysis. As regards the functional parameters (exercise capacity and cardiac performance), a very important and solid evidence in favor of the use of PDE5 inhibitors has emerged from our meta-analysis. Indeed a functional betterment, ensuing from the administration of PDE5i has been documented for the exercise capacity in HFREF patients. Indeed, based on six RCTs (9-10,12-13,16,18) with a total of 206 HFREF patients randomized to PDE5i or placebo, a substantial improvement in the peak VO<sub>2</sub> has been proven in the PDE5i-treated patients. In particular, three studies have evidenced a significant increase in peak VO<sub>2</sub>. Moreover, the analysis of aggregated data has confirmed the existence of a statistically significant meaning of the increase in peak VO<sub>2</sub> in the entire study population, related to the use of PDE5i (weighted mean difference = 3.76; 95% CI: 3.27 to 4.25).

Among patients with HFREF, the 6MWT has been assessed only in two studies, whose overall evaluation by means of metaanalysis has evidenced an increase in functional capacity in the PDE5i

arm( fig 5). Even the LVEF was improved compared to placebo in HFREF patients taking therapy with sildenafil ( figure 6).

In studies evaluating the measurements of the mean pulmonary pressure (mPAP [two studies], systolic pulmonary arterial pressure (PASP [four studies]) and pulmonary vascular resistance (PVR: two studies), a significant reduction was consistently detected across the studies for each of these indexes in HFREF patients treated with PDE5i compared to those taking placebo.

### **The functional, hemodynamic and clinical response of HFpEF patients to the PDE5 pharmacological inhibition: disappointing overall results, that deserve further research**

Differently from the substantially favorable response of HFREF patients to PDE5i administration, we didn't observe any significant and consistent benefits conferred by PDE5i treatment for patients with HFpEF. The reasons for this unsatisfactory response are at the moment unclear. In this regard, there are elements of significant perplexity in the fact that at least two studies (10,16) would have documented an improvement in diastolic function index known as E / e' ratio in patients with heart failure treated with sildenafil ( 10) or udenafil (16). In addition, the molecular and biochemical pathways of sildenafil and related drugs, such as detected in experimental animals, appear to actually be compatible with the hypothesis of a favorable effect by PDE5i on hemodynamic parameters and clinical outcomes of patients with HFpEF (21 ). Conversely, with regard to the relatively low efficacy of PDE5i on hemodynamic and spiro-ergometric parameters, as well as on clinical outcomes in patients with HFpEF, as evidenced by some studies included in our meta-analysis (14, 19),this might depend on a possible predominance of the cases of lpc-PH in these studies.This has been documented with certainty in the study by Hoendormis ES et al. (14), in which a condition of Cpc-PH, regarded as a crucial element for the

occurrence of a comprehensive and effective pharmacodynamic action of PDE5i (5,16) in the pulmonary hypertension related to left heart disease, was present only in 12% of cases. The fact that the HfpEF patients investigated in these studies were to be ascribed predominantly to the lpc-PH category might have played a crucial role in the generation of disappointing results.

Therefore, the thesis aimed to support a useful effect limited to the HFREF patients, due to an alleged lack of efficacy of the PDE5 inhibition in HFpEF patients should be regarded not adequately proven yet(22). In fact, the highlighted difference about the effects reported in the two echographic phenotypes might depend on a lower frequency of Cpc-PH profile in HFpEF patients rather than on a real critical role of the type of left ventricular dysfunction (HFREF or HFpEF) in determining the clinical efficacy of the PDE5 inhibitors.

Therefore, in order to verify the possible causes of the unsatisfactory results of PDE5 inhibitors in HFpEF, further studies, conducted by recruiting HFpEF patients belonging to the Cpc-PH category, would be warranted.

## **Conclusions.**

**The use of PDE5 inhibitors in patients with HFREF showed beneficial effects on pulmonary hemodynamics and exercise capacity. In addition, as regards the composite endpoint death / hospitalization, there was a significantly protective effect of PDE5 inhibitors, limited to the HFREF patients.**

Conversely, the use of PDE5 inhibitors in patients with HFpEF showed disappointing results.

In fact, in the case of HFpEF patients, no significant improvement was achieved for each of the investigated endpoints (either functional, hemodynamic or clinical ).

However, the hypothesis that the unfavorable results detected in HFpEF patients might have been caused by a not proper selection of the patient population( i.e., paucity of the cases of combined post-and precapillary pulmonary hypertension in the studies conducted so far ) should be taken into account. Thus, further studies with well - defined pulmonary hemodynamic profile, including an adequate number of HFpEF patients with CpcPH, would be warranted in order to better clarify the real therapeutic potential of PDE5 inhibitors even for treatment of HFpEF patients.

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<b>1. Pulmonary arterial hypertension</b>	<b>3. Pulmonary hypertension due to lung diseases and/or hypoxia</b>
1.1 Idiopathic	3.1 Chronic obstructive pulmonary disease
1.2 Heritable	3.2 Interstitial lung disease
1.2.1 BMPR2 mutation	3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
1.2.2 Other mutations	
1.3 Drugs and toxins induced	3.4 Sleep-disordered breathing
1.4 Associated with:	3.5 Alveolar hypoventilation disorders
1.4.1 Connective tissue disease	3.6 Chronic exposure to high altitude
1.4.2 Human immunodeficiency virus( HIV) infection	3.7 Developmental lung diseases
1.4.3 Portal hypertension	<b>4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions</b>
1.4.4 Congenital heart disease	4.1 Chronic thromboembolic pulmonary hypertension
1.4.5 Schistosomiasis	4.2 Other pulmonary artery obstructions
<b>1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</b>	4.2.1 Angiosarcoma
<b>1''. Persistent pulmonary hypertension of the newborn</b>	4.2.2 Other intravascular tumors
<b>2. Pulmonary hypertension due to left heart disease</b>	4.2.3 Arteritis
2.1 Left ventricular systolic dysfunction	4.2.4 Congenital pulmonary arteries stenoses
2.2 Left ventricular diastolic dysfunction	4.2.5 Parasites (hydatidosis)
2.3 Valvular disease	<b>5. Pulmonary hypertension with unclear and/or multifactorial mechanisms</b>
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
2.5 Congenital/acquired pulmonary veins stenosis	5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
	5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
	5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure( with/without dialysis), segmental pulmonary hypertension
<b>Table 1 Comprehensive clinical classification of pulmonary hypertension ( modified from Galie' N et al <sup>2</sup>)</b>	



<b>Table 2</b>		
<b>Definition</b>	<b>Characteristics</b>	<b>Clinical group(s)</b>
PH	mPAP $\geq$ 25 mm Hg	All
Pre-capillary PH	mPAP $\geq$ 25 mm Hg PCWP $\leq$ 15mm Hg	1) Pulmonary arterial hypertension 3)PH due to lung disease 4)Chronic thromboembolic PH 5)PH with unclear and/ or multifactorial mechanisms
Post-capillary PH	mPAP $\geq$ 25 mm Hg PCWP $>$ 15mm Hg	2) PH due to left heart disease 5)PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH ( Ipc-PH)	DPG $<$ 7 mm Hg and/or PVR $\leq$ 3WU	
Combined post-capillary and pre-capillary PH ( Cpc- PH)	DPG $\geq$ 7 mm Hg and/or PVR $>$ 3WU	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PCWP); mPAP = mean pulmonary arterial pressure; PCWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

**Table 3 Baseline features of included RCTs**

	Amin A (2013)	Andersen MJ (2013)	Behling A (2008)	Guazzi M (Circ Heart Fail 2011)	Guazzi M (Circulation 2011)	Guazzi M (2012)	Guazzi M (2007)	Hoendermis ES (2015)	Katz SD (2005)	Kim KH (2015)	Lewis GD (2008)	Lewis GD (2007)	Redfield MM (2013)	Webster LJ (2004)	
<b>Subjects randomized (n; PDE5i / Placebo)</b>	53/53	35/35	11/8	23/22	22/22	16/16	23/23	21/22	60/72	21/20	15/15	17/17	113/103	35/35	
<b>Drug name</b>	sildenafil	sildenafil	sildenafil	sildenafil	sildenafil	sildenafil	sildenafil	sildenafil	sildenafil	udenafil	sildenafil	sildenafil	sildenafil	sildenafil	
<b>Drug dosage</b>	25 mg bid for first 2 weeks; 50 mg tid for next 10 weeks	40 mg tid	50 mg tid	50 mg tid	50 mg tid	50 mg tid	50 mg bid	20 mg tid for first 2 weeks; 60 mg tid for next 10 weeks	25 / 50 / 100 mg	50 mg bid for first 4 weeks; 100 mg bid for next 8 weeks	25 to 75 mg tid	25 to 75 mg tid	20 mg tid for first 12 weeks; 60 mg tid for next 12 weeks	50 mg once daily	
<b>Inclusion criteria</b>	HFREF	Diastolic dysfunction after MI	HFREF	HFREF	HFpEF with PH	HFREF with PH and EOB	HFREF	HFREF	HFpEF with PH	CHF (HFREF) with ED	HFREF	HFREF with PH †	HFREF with PH	HFpEF	CHF (HFREF)
<b>Entry criteria</b>	<b>NHYA</b>	II-III	—	I-III	II-III	II-IV	III-IV	II-III	II-III	I-III	II-IV	II-IV	II-IV	II-IV	II-III
	<b>LVEF</b>	<35%	≥45%	≤40%	<40%	≥50%	<45%	≤45%	≥45%	≤40%	≤40%	<40%	<40%	≥50%	—
<b>Follow-up duration (months)</b>	3	2	1	12	12	12	6	3	3	3	3	3	6	1.5	
<b>Outcome measures</b>	BP, NYHA, 6MWT	Echo-, cardiac cath, CPET, 6MWT	Echo-, CPET, FMD	Echo-, CPET, BNP, QoL	Echo-, cardiac cath, QoL	CPET, cardiac cath	Echo-, CPET, FMD	Cardiac cath, CPET, Echo-	International index of erectile function	Echo-, CPET	Cardiac cath, CPET, ventriculography	CPET: peak VO2	Echo-, CMRI, CPET, 6MWT	International index of erectile function	

†Subanalysis of Lewis GD et al.

**Abbreviations:** CHF, chronic heart failure; HFREF, heart failure with reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; PH, pulmonary hypertension; EOB, exercise oscillatory breathing; MI, myocardial infarction; NYHA, New York Heart Association; PDE5i, phosphodiesterase type 5 inhibitor; CPET, cardiopulmonary exercise test; echo-, echocardiography; FMD, flow-mediated dilatation; BNP, B-type natriuretic peptide; QoL, quality of life; BP, blood pressure; 6MWT, six minutes walking test; CMRI, cardiac magnetic resonance imaging

**Table 4: Different impact of PDE5 inhibitors according to pulmonary hemodynamics**

	Amin A (2013)	Andersen MJ (2013)	Behling A (2008)	Guazzi M (Circ Heart Fail 2011)	Guazzi M (Circulation 2011)	Guazzi M (2012)	Guazzi M (2007)	Hoendermis ES (2015)	Kim KH (2015)	Lewis GD (2008)	Lewis GD (2007)	Redfield MM (2013)	
<b>Inclusion criteria</b>	HFREF	Diastolic dysfunction after MI	HFREF	HFREF	HFpEF with PH	HFREF with PH and EOB	HFREF	HFpEF with PH	HFREF	HFREF with PH †	HFREF with PH	HFpEF	
<b>Pulmonary hemodynamic parameters</b>	mPAP (mm Hg; PDE5i/placebo)	—	19/20	36.2/39.8*	24.6/25.2*	39/37	35/34	22.7/21.5*	35/35	27/28.2*	30/33	30/33	27/27*
	dPAP (mmHg; PDE5i / placebo)	—	14/15	—	—	31.6/29.7	—	—	20/21	—	—	—	—
	PCWP (mmHg; PDE5i / placebo)	—	12/13	—	—	22/21.9	21/20	—	19.9/20.8	—	18/19	18/19	—
	TPG (mmHg; PDE5i / placebo)	—	7/7	—	—	16.2/14.5	15.2/14.7	—	13/13	—	12/14	12/14	—
	DPG (mmHg; PDE5i / placebo)	—	2/2	—	—	9.6/7.8	—	—	2/-1	—	—	—	—
	PVR (dyn·s·cm <sup>-5</sup> ; PDE5i / placebo)	—	207/220	—	—	310.4/261.6	360/354	—	207/203	—	340/360	340/360	—
<b>Features of combined post- and pre-capillary PH (DPG ≥7 mmHg; PVR &gt;3 WU [&gt;240 dyn·s·cm<sup>-5</sup>])</b>	Not investigated	No	Not investigated	Not investigated	Yes	Yes	No	Mainly no (Cpc-PH in 12%)	Not investigated	Yes	Yes	Not investigated	
<b>Outcomes</b>	<b>Exercise capacity</b>	No change	No change	Improved	Improved	N/A	Improved	Improved	No change	Improved	Improved	Improved	No change
	<b>LV function</b>	N/A	Improved	No change	Improved	Improved	Improved	Improved	No change	Improved	N/A	Improved	No change
	<b>Pulmonary pressure</b>	N/A	No change	Reduced	Reduced	Reduced	Reduced	Reduced	No change	Reduced	Reduced	Reduced	No change

\* Converted from echocardiographic PASP by the following equation: mPAP (mmHg) = (0.61 × PASP [mmHg]) + 2 mmHg.[5] † Sub-analysis of 'Lewis GD et al., 2007

Legend: HFREF, heart failure with reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; PH, pulmonary hypertension; EOB, exercise oscillatory breathing; MI, myocardial infarction; mPAP, mean pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient; DPG, diastolic pulmonary gradient; PVR, pulmonary vascular resistance; N/A, not applicable

Improvement in exercise capacity was evaluated based on the changes in peak VO<sub>2</sub> and VE/VCO<sub>2</sub> slope evidenced by cardiopulmonary exercise test, or based on 6MWT. Improvement in LV