Pulmonary Hypertension Due to Left Heart Diseases

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Pulmonary hypertension (PH), a common complication of left heart diseases (LHD), negatively impacts symptoms, exercise capacity, and outcome. Although the true prevalence of PH-LHD is unknown, a subset of patients might present significant PH that cannot be explained by a passive increase in left-sided filling pressures. The term "out-of-proportion" PH has been used to identify that population without a clear definition, which has been found less than ideal and created confusion. We propose a change in terminology and a new definition of PH due to LHD. We suggest to abandon "out-of-proportion" PH and to distinguish "isolated post-capillary PH" from "post-capillary PH with a pre-capillary component" on the basis of the pressure difference between diastolic pulmonary artery pressure and pulmonary artery wedge pressure. Although there is no validated treatment for PH-LHD, we provide insights into management and discuss completed and randomized trials in this condition. Finally, we provide recommendations for future clinical trials to establish safety and efficacy of novel compounds to target this area of unmet medical need. (J Am Coll Cardiol 2013;62:D100–8) © 2013 by the American College of Cardiology Foundation

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), frequently occurring as a "symptom" of the underlying condition (1,2) and often related to disease severity. Pulmonary hypertension LHD is most common in patients with heart failure (HF), with preserved or reduced ejection fraction (EF) (1–3). When present, PH-LHD results in more severe symptoms and worse exercise tolerance and exerts a negative impact on outcome (1–3). Over the past 10 years, PH-LHD has been recognized as a growing problem in terms of definition and differential diagnosis but also of influence on outcome and therapy. Indeed, the differential diagnosis between pre- and post-capillary PH is

often challenging in patients with heart failure with preserved ejection fraction (HF-pEF). Compared with pulmonary arterial hypertension (PAH), patients with PH-LHD are more often older, female, with a history of systemic hypertension (4), and most, if not all, of the features of the metabolic syndrome (5).

The true prevalence of PH-LHD in HF remains unknown, due at least in part to the following: 1) current data are derived from either epidemiological studies in community-based HF populations (6–8) or tertiary HF referral centers (3); 2) the definition of PH was based on echocardiography, with a variety of cutoff values (6–8); 3) populations have been heterogeneous, in terms of symptoms, age, and level of EF; and 4) measurements of pulmonary arterial and left atrial filling pressures were not assessed by right (RHC) and/or left heart catheterization, with the exception of single-center reports (3–5). As a result, the prevalence of PH in LHD has been reported to range between 25% and 100% of the patients studied (Table 1).

This paper provides new hemodynamic definitions, terminology, and treatment insights of PH-LHD.

Definitions and Terminology

The current hemodynamic definition of PH-LHD combines a mean pulmonary artery pressure (mPAP) ≥25 mm Hg, a pulmonary artery wedge pressure (PAWP) >15 mm Hg, and a normal or reduced cardiac output (CO) (9). The transpulmonary pressure gradient (TPG) (i.e., the difference between mPAP and PAWP) is commonly used to distinguish "passive" PH (TPG ≤12 mm Hg) from "reactive" PH (TPG >12 mm Hg). However, this definition and the associated terminology have been unsatisfactory, to such extent that "out-of-proportion" PH-LHD has been often used to characterize a subset of patients with significant changes in the pulmonary circulation.

There are several reasons why we need a simple and workable definition for "out-of-proportion" PH in the context of LHD.

Understanding the determinants of PH-LHD. Irrespective of the origin of left heart disease, the first event leading to PH is a passive backward transmission of filling pressures, mainly driven by left ventricular (LV) diastolic function

(10,11). The resulting increase in PAWP might be enhanced by exercise-induced mitral regurgitation, together with a loss of left atrial compliance (12). The pulsatile load imposed by a chronically elevated PAWP might also play a role in the development of PH (13). In some patients, these purely mechanical components of venous congestion might trigger a superimposed component, combining pulmonary vasoconstriction, decreased nitric oxide (NO) availability, increased endothelin expression, desensitization to natriuretic peptide induced vasodilation, and vascular remodeling (2,14). At this stage, mPAP increases further, and this increase seems to be in excess of the elevation of PAWP (10,11). Finally, these changes might lead to pulmonary vascular disease, increased right ventricle (RV) afterload, and RV failure (Fig. 1).

Heterogeneity in terms of definition and terminology. Many legitimate attempts to distinguish the mechanical from the active component have been made, by using different terms such as passive versus reactive, fixed versus irreversible, unresponsive versus responsive, and out of proportion versus proportionate (1). These lead to unclear definitions, especially because the current definition of "passive" versus "reactive" PH (9) has been progressively substituted by "out-of-proportion" PH. This term has never been defined by any clear hemodynamic criteria, although it has been assumed that PH develops "out-of-proportion" to the raised PAWP.

Areas of confusion with PAH/pre-capillary PH. The lack of a clear definition of "out-of-proportion" PH causes confusion with PAH. As a result, it might encourage physicians to treat some patients suffering from PH-LHD with PAH-approved therapies, despite the lack of evidence (9). In contrast, complex surgery (transplantation, LV assist device, valve surgery) might be considered too high risk because of significant PH. Finally, vasoreactivity testing in PH-LHD is often performed without clear guidelines about which vasodilator should be used to perform testing and the expected changes in pulmonary vascular resistance (PVR)

Abbreviations and Acronyms

CO = cardiac output

Cpc-PH = combined post-capillary and pre-capillary PH

DPD = diastolic pressure difference

EF = ejection fraction

HF = heart failure

HF-pEF = heart failure with preserved ejection fraction

LHD = left heart disease

LV = left ventricle/ventricular

mPAP = mean pulmonary artery pressure

NO = nitric oxide

PAH = pulmonary arterial hypertension

PCWP = pulmonary capillary wedge pressure

PAWP = pulmonary artery wedge pressure

PDE5 = phosphodiesterase type 5

PH = pulmonary hypertension

PVD = pulmonary vascular disease

PVR = pulmonary vascular resistance

RCT = randomized controlled trial

RHC = right heart catheterization

RV = right ventricle

sGC = soluble guanylate cyclase

SV = stroke volume

TPG = transpulmonary gradient

VO$_2$ = oxygen consumption

Table 1	Prevalence of PH in HF (Selected Studies)							
First Author (Ref. #)	n	Type	Definition of PH	Population	EF	% Measurable TRV	Prevalence of PH	Corrected Prevalence of PH
Bursi (8)*	1,049	Echocardiography	TTG+RAP ≥35 mm Hg	Epidemiological		91%	79%	72%
Damy (51)*	1,380	Echocardiography	TTG ≥35 mm Hg	Hull HF clinic	26% preserved	26%	25%	7%
Lam (7)†	244	Echocardiography	TTG+RAP ≥35 mm Hg	Olmsted County HF survey	Only EF ≥50%	83%	83%	69%
Leung (52)†	455	Invasive	mPAP ≥25 LVEF 15%	Cath lab			52%	
Robbins (5)†	122	Invasive	mPAP ≥25 PAWP >15	PH reference center	Mixed	NA	23%	20%

See text for references. *All-comer patients with heart failure (HF); †patients from HF/pulmonary hypertension (PH) specialized centers.

Cath lab = catheterization laboratory; EF = ejection fraction; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; RAP = right atrial pressure (estimated from the inferior vena cava); TRV = tricuspid regurgitant jet velocity; TTG = transtricuspid gradient.

and/or TPG. As a consequence this might lead to the inappropriate use of PAH drug therapies.

Identification of different hemodynamic presentations. A simple way to clarify the definition would be to rely on a simple description of the potential hemodynamic presentations, as follows: 1) an elevated PAWP, but no significant change in the pulmonary circulation (i.e., absence of pulmonary vascular disease or vascular remodeling) (PVD); 2) an elevated PAWP, with PVD; 3) a previously elevated but meanwhile normalized PAWP, with persistence of PVD. The latter can be found in patients who have undergone forced diuresis in the presence of HF-pEF, atrial fibrillation and corrected valve disease.

A key issue is how to best describe "pulmonary vascular disease" or the "pre-capillary remodeling component" (and possibly also a "post-capillary remodeling component") of an initially purely passive phenomenon. In other words, how can we define a change in the pulmonary circulation that is not in relation with the increase in PAWP and that is measurable by RHC? Some key characteristics of such variables include the following: 1) it should reflect changes of the pulmonary circulation and be a clear marker of PVD;

Passive ↑ in mPAP ←---
- Loss of LA compliance
- Diastolic dysfunction
- Pulsatile load by PAWP
- Exercise-induced MR

Added component Further ↑ in mPAP ←---
- Endothelial dysfunction
- ↓ NO and ↑ ET-1 activity
- Vasoconstriction
- ↓ BNP induced vasodilation

Significant PVD RV failure Death ←---
- Vascular remodelling
- Decreased vascular compliance
- Blunted response to vasodilators

Figure 1 Mechanism of Pulmonary Hypertension Due to Left Heart Disease

2) it must be less dependent on (or as independent as possible of) the change in PAWP; 3) it should be minimally influenced by changes in blood flow and stroke volume (SV); and 4) it should reflect changes in compliance and take into account the distensibility of the pulmonary arteries.

Pulmonary vascular resistance, TPG, and the diastolic pressure difference (DPD) (defined as diastolic PAP—mean PAWP) have the advantage of being easily obtained from RHC. They might not all be suitable to describe the pre-capillary component of PH-LHD. The PVR is commonly used in clinical practice. It has the disadvantage of being a composite variable, with an interdependent numerator and denominator (changes in flow influence pressure in the pulmonary circulation). Therefore, it is highly sensitive to changes in both flow and filling pressures but does not reflect changes in the pulmonary circulation at rest (11,15).

At a constant SV, an increase of PAWP has a more pronounced effect on systolic PAP and mPAP than diastolic PAP (Fig. 2). This impact is even greater when SV increases. As a result, TPG is influenced by all determinants of mPAP, including flow, resistance, and left heart filling pressure (11,15). In contrast, diastolic PAP when compared with systolic pulmonary artery pressure and mPAP is less influenced by PAWP, which might be explained by a lower sensitivity to vessel distensibility (10,11). This is illustrated by a less steep slope of the diastolic pulmonary artery pressure/PAWP line compared with the same relationship with systolic and mPAP at any level of SV (Fig. 2). When reported as pressure differences, DPD seems to best approach the characteristics required to determine PVD.

In normal subjects, DPD lies in the 1-mm Hg to 3-mm Hg range, and in patients evaluated for cardiac disease (excluding shunts), the DPD remains ≤5 mm Hg in most cases (11,16).

In a retrospective study, 406 patients with PVR ≥200 dynes/s/cm^{-5} were compared with 406 subjects presenting with PVR <200 dynes/s/cm^{-5}. Patients were catheterized for evaluation of HF (n = 367), valvular regurgitation (n = 177), valvular stenosis (n = 244), and possible constrictive/restrictive physiology (n = 24) (16). In patients with PVR <200, PAPd and PAWP were similar, and
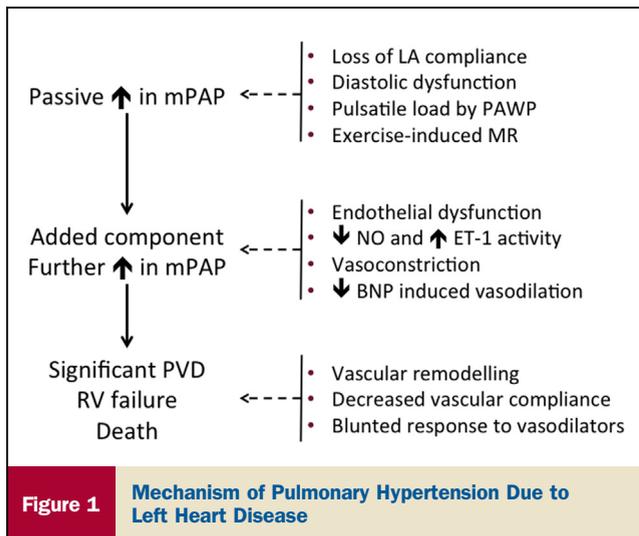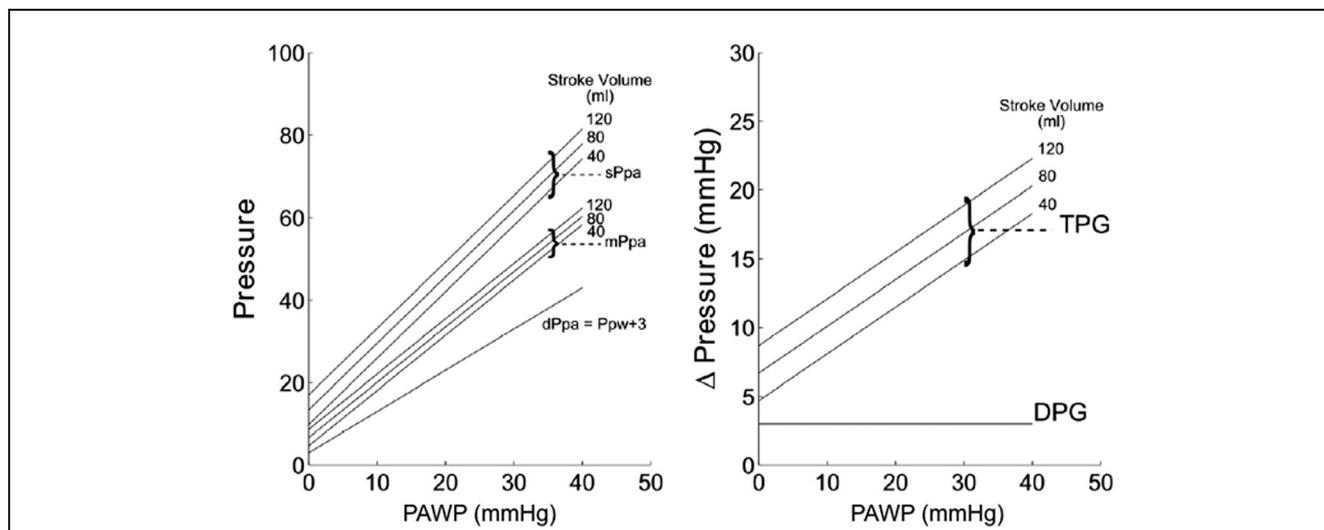
Figure 2   **Effect of PAWP and SV on Pulmonary Pressures**

Pulmonary artery wedge pressure (PAWP) is transmitted in a 1:1 ratio to diastolic pulmonary artery pressure (dPpa) and PAWP, both pressures being within a 3-mm Hg range. If PAWP is directly transmitted to dPpa, there is a non-proportional increase in systolic (sPpa) and mean (mPpa) pulmonary artery pressure, depending on (SV) **(left graph)**. The transpulmonary gradient (TPG) increases, but the dPpa-PAWP gradient is independent of both PAWP and SV **(right graph)**. If dPpa increases more than PAWP, the TPG increases. The dPpa-Ppw gradient increases linearly but slightly with PAWP but is independent of SV. Reproduced with permission from Naeije et al. (11).

DPD remained ≤5 mm Hg in 94% of the cases. When PVR increased, approximately one-half had DPD >5 mm Hg; however, a PAP ≤40 mm Hg was associated with an increased DPD >5 mm Hg in <20%.

This suggests that, when PH develops in heart diseases, DPD increases >5 mm Hg in one-half of the cases and that the increase in PAPd is somehow unrelated to the changes in PAWP. Therefore, the DPD might be seen as a potential marker of changes in the pulmonary circulation.

The role of the DPD in predicting outcome has recently been explored in a large cohort of patients referred to a single center for PH evaluation (17). In this retrospective study on 3,107 patients, the population was separated according to the current definition of "passive" versus "reactive" PH, the latter being referred to as "out-of-proportion" PH. Pulmonary hypertension due to LHD accounted for 35% of all cases of PH. More than one-half (55%) presented passive with PH-LHD, and 45% had "reactive" PH. By receiver-operating characteristic analysis, a DPD ≥7 mm Hg has been identified to independently predict outcome. The authors subsequently defined "out-of-proportion" PH as a TPG >12 mm Hg and a DPD >7 mm Hg, which represented 16% of the patients with PH-LHD. Patients with a TPG >12 mm Hg and a DPD ≥7 mm Hg had a worse median survival (78 months) compared with patients who presented with a DPD <7 mm Hg (101 months; p = 0.010). Survival in patients with an elevated TPG and DPD was similar to that reported for PAH (class I) patients. In addition, an elevated DPD was associated with more advanced pulmonary vascular remodeling in a small sample of patients who had lung biopsies. However, this study has important

limitations, including its retrospective nature, a bias in the population with patients presenting a negative DPD, and the unknown number of patients with a TPG <12 mm Hg but a DPD ≥7 mm Hg.

Recommendations. The term "out-of-proportion" PH should be abandoned in patients with post-capillary hemodynamic status, while recognizing the importance of describing the presence of a pre-capillary component in some cases of PH-LHD, without further implications in terms of reactivity, remodeling, or changes in the pulmonary circulation that cannot be assessed clinically.

We propose 2 types of PH-LHD, on the basis of the level of the DPD: "isolated post-capillary PH" (PAWP >15 mm Hg and DPD <7 mm Hg) and "combined post-capillary PH and pre-capillary PH" (PAWP >15 mm Hg and DPD ≥7 mm Hg. Cutoff values and the definition are shown in Table 2.

Gaps in evidence. Although based on a strong pathophysiological reasoning, the respective value of the TPG and the DPD should be further explored, including their role in predicting outcome. Multicenter data collection and analysis of established databases might be helpful to address the issue in an acceptable timeframe. A joint initiative with the International Society for Heart and Lung Transplantation might help to establish a common nomenclature and develop this in the specific context of heart transplantation and LV assist devices. This population is of interest, because patients with advanced HF are at much higher risk of presenting with a pre-capillary component of their PH.

The standardization and the relevance of testing the vasoreactivity of PH-LHD could be addressed in the context

Table 2	Proposed Definition and Classification of PH-LHD	
Terminology	**PAWP**	**Diastolic PAP – PAWP**
Isolated post-capillary PH	>15 mm Hg	<7 mm Hg
Combined post-capillary and pre-capillary PH	>15 mm Hg	≥7 mm Hg

Hemodynamic measurements are taken under resting conditions.
LHD = left heart disease; other abbreviations as in Table 1.

of the new nomenclature and be included in the previously described proposals. In line with the previous comments, this topic is of critical importance in the context of heart transplantation and mechanical circulatory support. Its relevance in other fields of cardiology (i.e., valvular heart disease, management of HF) is unknown.

The importance of fluid loading and exercise in uncovering PH due to LHD requires standardization and validation. Recent advances suggest that these tools might play a role in the differential diagnosis of PH, which has been discussed elsewhere and is beyond the scope of this manuscript.

The importance of the failing RV in the context of PH-LHD should be further explored. We believe that there might be a spectrum of clinical phenotypes in PH-LHD that might evolve from one to the other, from isolated post-capillary PH with little effect on the RV to more advanced disease where the failing RV is the key determinant of outcome.

Treatment Insights

The primary goal of therapy of PH-LHD must be to improve global management of the underlying condition before considering specific measures to treat PH. This includes repair of valvular heart disease and aggressive therapy for HF with reduced systolic function (18). Some patients might also benefit from nonspecific vasodilators such as nitrates and hydralazine, although evidence supporting this strategy is limited (18). In severe HF, optimizing volume status is of critical importance and might require invasive monitoring (19). In addition, the implantation of an LV assist device has been shown to lower pulmonary pressures through LV unloading without increasing the risk of post-implantation RV failure (20,21). Risk factors for cardiovascular diseases and features of the metabolic syndrome should be controlled (18). Concomitant disorders leading to PH should be identified and treated, including chronic obstructive pulmonary disease, sleep apnea syndrome, and pulmonary embolism. In contrast, there is no strong evidence-based recommendation for the treatment for HF-pEF (18).

The potential use of PAH therapies in PH-LHD is based on a sound pathobiological rationale. In patients with HF, endothelial dysfunction has been proposed as a cause of PH and hence as a target for treatment (14), supported by the presence of increased endothelin 1 activity (22,23) and

impaired NO-dependent vasodilation (24). In addition, direct LV myocardial effects might be more important in PH-LHD. For example, endothelin 1 has positive myocardial inotropic and lusitropic effects that might be blocked by receptor antagonists. In contrast, inhibition of phosphodiesterase type 5 (PDE5) attenuates LV remodeling and improves vascular, renal, and neuroendocrine function (25–27).

The rationale to use PAH therapies in PH-LHD has been supported by acute or short-term studies using prostanoids, endothelin receptor antagonists, and PDE5 inhibitors. Most of these studies consistently reported improvements in hemodynamic status, exercise capacity, and symptoms (28). However, the methodology (small sample size, single-center, unclear or no randomization process) does not provide enough evidence to support the use of these drugs in clinical management of patients.

Clinical trials with prostanoids and endothelin-1 antagonists. Several randomized controlled trials (RCTs) (Table 3) have been conducted with PAH-approved therapies (bosentan [29,30], epoprostenol [31]) or drugs acting on a pathway involved in the development of PH (darusentan [32,33]). These studies have the following in common: 1) almost all studies were performed in HF with systolic dysfunction, leading to disappointing results; 2) few required optimization of patient volume status before initiating therapy, which potentially led to drug-induced adverse events; 3) patients with valvular heart diseases were excluded; and 4) none of the studies stratified patients for the presence of PH, although some reported on invasive hemodynamic status (31,33). The results of these trials in HF were all negative (Table 3). Two RCTS (with epoprostenol [31] and high doses of bosentan [29]) had to be terminated before completion, due to either a trend toward higher mortality rate (31) or increased side effects (29) observed in the treated group.

Two RCTs assessed the safety and efficacy of bosentan on outcome in patients with systolic dysfunction (29,30). The REACH 1 (Research on Endothelin Antagonism in Chronic Heart Failure) trial (29) was interrupted due to an elevated rate of liver function test abnormalities, likely due to the high dose of bosentan used in the trial (500 mg bid). The second trial failed to demonstrate a benefit on mortality and hospital stay (30).

Two RCTs assessed the safety and efficacy of darusentan on invasive hemodynamic status (33) and outcome (32) in HF with systolic dysfunction. Although the study drug seemed to increase CO but not pulmonary capillary wedge pressure (PCWP) (33), it failed to reach the primary endpoint of decreasing clinical events and improving magnetic resonance imaging-derived indexes of LV function (32).

Clinical trials with PDE5 inhibitors. Before their use as part of the treatment regimen of HF, PDE5 inhibitors had been used to treat erectile dysfunction, with an encouraging safety profile (34). Acutely, sildenafil 25 to 50 mg has been shown to decrease PVR in the pre-transplant setting

Table 3	Completed RCTs Using Prostanoids and Endothelin Receptor Antagonists in HF				
Drug/Author Year	Study Acronym (Ref. #)	Patients	Design	Primary Endpoint	Results
Epoprostenol Califf 1996	FIRST (31)	n = 471 Severe HF	1:1 randomization event-driven mean dose 4 ng/kg/min	Survival	Early termination (trend to decreased survival in treated group)
Bosentan Packer	REACH-1 (29)	n = 174 Severe HF	2:1 randomization 26-week duration 500 mg bid	Change in clinical state	Early termination (drug-induced fluid retention in the treated group)
Kalra 2002	ENABLE (30)	n = 1,613 Severe HF	1:1 randomization 18-month duration 125 mg bid	Mortality + hospital stays	No effect
Darusentan Lüscher 2002	HEAT (33)	n = 179 NYHA III	3:1 randomization 3-week duration doses of 30, 100, 300 mg	Hemodynamic (changes in PAWP/CO)	Increased CO No change in PAWP
Anand 2004	EARTH (32)	n = 642 NYHA II–IV	5:1 randomization 6-month duration doses 10, 25, 50, 100, 300 mg	LV changes by MRI + clinical events	No effect

See text for references.

CO = cardiac output; HF = heart failure; LV = left ventricular; MRI = magnetic resonance imaging; NYHA = New York Heart Association functional class; PAWP = pulmonary artery wedge pressure; RCT = randomized controlled trial.

(35–37), to improve hemodynamic variables at rest (34,38) and exercise (38) and to improve peak oxygen consumption (VO$_2$) (34,38–40). The vasodilator capacities of sildenafil seem to be superior to prostaglandin E1. In a case-controlled prospective study, 22 patients with PVR >200 dynes/s/cm^{-5} received a single dose of 40 mg of sildenafil, compared with 24 matched control subjects (41). Acute administration of sildenafil was associated with a greater improvement in PVR and compliance compared with prostaglandin E1. Chronic administration of sildenafil has also been shown to improve pulmonary hemodynamic status before transplantation (37).

In a placebo-controlled study performed in patients with decreased LVEF, sildenafil has been shown to improve hemodynamic status and exercise tolerance after 12 weeks at a dose of 25 to 75 mg tid (38). The 20% decrease in PVR was mostly accounted for by an improvement in CO, whereas mPAP remained unchanged. Similar improvements in exercise tolerance were sustained up to 6 months with sildenafil 50 mg tid (42).

Although encouraging, the results of these RCTs should be treated with caution, because the studies were single-center and used a range of doses of sildenafil (from 25 to 75 mg tid) that were consistently higher than the doses approved to treat PAH.

Two multicenter clinical trials in PH-LHD are currently underway (Table 4), with sildenafil (NCT01616381) (43) and tadalafil (NCT01910389). Although these trials plan to include a well-defined population with PH due to systolic HF, the absence of RHC validation of PH might represent a significant limitation.

Guanylate cyclase stimulators. Riociguat is a novel soluble guanylate cyclase (sGC) stimulator that sensitizes sGC to endogenous NO and directly stimulates sGC independently of NO (44). Its vasodilatory effects might be associated with anti-fibrotic, anti-proliferative, and anti-inflammatory effects (44). Riociguat has recently been shown to improve 6-min walking distance in PAH (45) and chronic thromboembolic pulmonary hypertension (46).

In a multicentric placebo-controlled trial (47), 201 patients with PH due to systolic HF were randomized in 4 arms comparing 3 doses of riociguat (0.5, 1, and 2 mg tid) with placebo during 16 weeks. No effect on the primary endpoint (a change in mPAP after 16 weeks) was observed at any dose of riociguat compared with placebo.

A proof-of concept study to test the effects of riociguat in patients with PH associated with diastolic dysfunction (NCT01172756) has recently been completed, but results are not yet available (Table 4).

HF with preserved EF. Heart failure with preserved ejection fraction (HF-pEF) is a common cause of PH (1,2,7,9), and the latter is also associated with a worse outcome (7). In contrast with systolic HF, exposure of patients with HF-pEF to vasodilators is associated with a greater blood pressure reduction, a modest increase in CO, and a greater likelihood to decrease SV (48). Thus, there are fundamental differences in the 2 HF phenotypes, and this suggests that more pathophysiologically targeted therapies are needed in this setting. Therefore, it is anticipated that PAH therapies might have a different effect in patients with HF-pEF compared with other forms of HF.

Data on the use of PAH therapies in the context of HF-pEF with or without PH are scarce.

The effects of sildenafil on exercise capacity and clinical status have been studied in a recently published phase II trial (49). A total of 216 patients with HF-pEF were randomized to receive sildenafil (n = 113) or placebo (n = 103) administered orally at 20 mg tid for 12 weeks,

Table 4	Current Phase II/III Placebo-Controlled Randomized Trials in PH With LHD						
Drug Trial (Ref. #) Trial Number	n	Start	End	Duration	Primary Endpoint		Secondary Endpoints
HF With Reduced EF							
Riociguat LEPHT (47) (BAY63-2521)	201	Published (50)		16 W	Mean PAP		AE, PK, PVR, NT-pro BNP
Tadalafil PITCH-HF (NCT01910389)	2102			Up to 54 months	Time to CV death or 1st HF hospital stay		Biomarkers, exercise capacity, QoL
Sildenafil Sil-HF (43) (NCT01616381)	210	9/2012	6/2014	24 W	Patient Global Assessment and 6MWT		Qol, Kansas City questionnaire, AE
HF With Preserved EF							
Riociguat DILATE (BAY63-2521)	48	Recruitment completed		16 W	mPAP		AE, PK, PVR, NT-pro BNP

Available from ClinicalTrials.gov; accessed July 27, 2013.

AE = adverse events; CV = cardiovascular; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PK = pharmacokinetics; PVR = pulmonary vascular resistance; QoL = quality of life; 6MWT = 6-min walk test; other abbreviations as in Table 1.

followed by 60 mg tid for 12 weeks. In line with previous RCTs in HF due to reduced EF, there was no stratification for PH. After 24 weeks on a therapy regimen, there was no difference between groups in the primary endpoint, the change in peak VO_2. In addition, there was no difference in other relevant secondary endpoints, including outcome measurements.

In 1 placebo-controlled study that was performed in patients with PH induced by HF-pEF, sildenafil 50 mg tid improved exercise capacity and hemodynamic status after 6 months, with beneficial effects up to 1 year (50).

Recommendations. Vasoreactivity testing in PH-LHD should not be performed with selective pulmonary vasodilators (e.g., IV prostacyclin) in patients with PCWP >15 mm Hg, due to the risk of increased PCWP and pulmonary edema. The role of vasoreactivity testing remains to be explored further.

There is no new evidence supporting the use of PAH therapies in PH-LHD, due to the absence of studies specifically stratifying patients for PH and/or targeting this specific condition.

RCTs in PH due to left heart diseases. The history of trials to treat PH-LHD has yielded little evidence of clinical efficacy. In addition, much of the available evidence applies to HF (in which many drugs efficacious for PAH have failed) and without specific focus of the subgroup of patients with PH-LHD (for which data are scarce). Many reasons might explain why this field seems to be stagnant. Firstly, the population of HF is more heterogeneous than in PAH and more male, with older patients, and extensive background therapy resulting in complex polypharmacy. Secondly, the target population has not been properly defined. If all patients meeting the definition of PH-LHD were to be included in a trial, heterogeneity would be further increased by mixing patients with isolated post-capillary PH and patients with combined post-capillary with a pre-capillary component. The latter is felt to be the population of interest for future studies. Finally, the question of the most appropriate endpoint to assess for any intervention in the setting of PH-LHD is critical. It is acceptable and necessary for a proof-of-concept to assess safety first together with evidence of an efficacy signal based on a measurable clinical, exercise capacity, and/or hemodynamic improvement only. This would prompt larger, event-driven RCT with robust endpoints in event-driven trials for regulatory approval.

Recommendations for RCTs. POPULATION. Patients with PH due to HF-pEF and PH due to HF with reduced EF should be studied separately. Patients with uncorrected valvular heart diseases should be excluded. Patients with corrected valvular heart diseases might be studied as well.

Patients should be on optimal regimens of HF therapy and fluid balance before randomization.

Patients with combined post-capillary and pre-capillary PH should represent the target population. Recruitment should be based on RHC, although pre-screening by echocardiography might be considered.

ENDPOINT. A proof-of-concept study, including a placebo arm, should be conducted first to assess safety and record an efficacy signal (preferably hemodynamic and/or exercise capacity assessment). The latter could be either a change in DPD and/or peak VO_2 or ventilatory efficiency and/or increase in 6-min walking distance.

The population should ideally be similar in proof-of-concept and phase III studies (i.e., identified by invasive hemodynamic status, performed in the same clinical setting in patients on a regiment of optimized and stable therapy), although this approach might be challenging.

An outcome study should then be conducted, and a composite endpoint should be considered (a combination of cardiovascular mortality, hospital stay for worsening HF, and/or PH).

CHALLENGES. An invasive approach for recruiting in these trials is challenging, because many HF patients are not necessarily seen in highly specialized PH centers. It is of critical importance to properly characterize patients who might best benefit from the intervention.

In addition, invasive hemodynamic assessments are not part of standard of care in HF irrespective of EF, and right heart catheterization is even discouraged (18,19).

Recruitment might be delayed by the increasing off-label use of PDE5 inhibitors, the difficulties in performing collaborative studies between PH and HF centers, and potential exclusion of patients due to a high risk of drug-drug interaction.

Management of PH in LHD remains an unmet medical need lacking in an evidence-based approach. We believe that the revised definition of the nomenclature will help clinicians to better identify this growing population of patients that deserves special attention. Although still provisional, the proposed definition should be further validated by using clinical registries. There is currently no approved therapy for PH due to LHD. Nevertheless, we propose ideas that might help investigators to embark on clinical trials that might help to advance the field of PH in the near future.

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