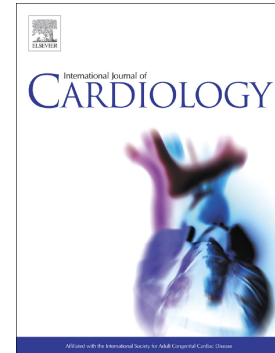


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Updated Recommendations of the Cologne Consensus
Conference 2018

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Pulmonary hypertension associated with left heart disease: Updated Recommendations of the Cologne Consensus Conference 2018

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Summary

In the summer of 2016, delegates from the German Society of Cardiology (DGK), the German Respiratory Society (DGP), and the German Society of Pediatric Cardiology (DGPK) met in Cologne, Germany, to define consensus-based practice recommendations for the management of patients with pulmonary hypertension (PH). These recommendations were built on the 2015 European Pulmonary Hypertension guidelines, aiming at their practical implementation, considering country-specific issues, and including new evidence, where available. To this end, a number of working groups was initiated, one of which was specifically dedicated to PH associated with left heart disease. In this context, the European Guidelines point out that the drugs currently used to treat patients with PAH (prostanoids, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, sGC stimulators) have not been sufficiently investigated in other forms of PH. However, despite the lack of respective efficacy data, an uncritical use of targeted PAH drugs in patients with PH associated with left heart disease is currently observed at an increasing rate. This development is a matter of concern. On the other hand, PH is a frequent problem that is highly relevant for morbidity and mortality in patients with left heart disease. In that sense, the distinction between isolated post-capillary pulmonary hypertension (IpcPH) and combined post- and pre-capillary pulmonary hypertension (CpcPH) and their proper definition may be of particular relevance. The detailed results and recommendations of the working group on PH associated with left heart disease, which were last updated in the spring of 2018, are summarized in this article.

Word count abstract: 249

Key words: pulmonary hypertension, left heart disease, heart failure, isolated post-capillary pulmonary hypertension (IpcPH), combined post- and pre-capillary pulmonary hypertension (CpcPH)

Introduction

Pulmonary hypertension (PH) due to left heart disease (PH-LHD; Nice group 2) is the most common form of PH and accounts for 48–80% of all cases [1–4]. PH-LHD can occur due to any type of left heart disease, including valvular heart disease and congenital heart disease, but it is most common in patients with heart failure and preserved (HFpEF) or reduced ejection fraction (HFrEF). PH-LHD is associated with more severe symptoms and a lower exercise tolerance, and also has a negative impact on prognosis [2–4]. Patients with PH-LHD – in particular those with HFpEF – are usually older, female, and have a higher prevalence of cardiovascular comorbidities and most, if not all, components of the metabolic syndrome [5–7].

Definitions, pathophysiology and classification

Patients with PH-LHD usually have post-capillary PH, which is defined by a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and a pulmonary arterial wedge pressure (PAWP) > 15 mmHg [2,3,8] (**Table 1**).

PH-LHD develops primarily due to the passive reverse transmission of elevated left-sided filling pressures into the pulmonary circulation. This is determined in particular by the diastolic function of the left ventricle (LV), but can be exacerbated by other components such as exercise-induced mitral regurgitation and loss of left atrial (LA) compliance [2,3,8]. However, chronic pulmonary venous congestion may trigger additional pathophysiological changes, including pulmonary vasoconstriction, reduced NO bioavailability, increased endothelin expression, desensitization to natriuretic peptide-induced vasodilation, and vascular remodeling [2–4,8,9]. These mechanisms may then lead to a further increase in mPAP in excess of PAWP elevation, which is associated with pulmonary vascular abnormalities, elevated right ventricular (RV) afterload, and finally right-sided heart failure [2,3,8]. Historically, the transpulmonary pressure gradient (TPG = mPAP - PAWP) was used to characterize the severity of post-capillary PH due to LHD in order to distinguish “passive” PH (TPG < 12 mmHg) from “reactive” or “out-of-proportion” PH (TPG ≥ 12 mmHg) [10]. However, this definition and the associated terminology proved unsatisfactory and were therefore abandoned, in particular because the TPG is influenced considerably by volume status and cardiac function, and has no prognostic significance for PH-LHD [11]. Instead, other hemodynamic parameters are considered, which (i) constitute markers of the disease [12], (ii) are influenced only slightly by filling pressure and stroke volume [13], and (iii) take into account the pulsatile nature of the pulmonary circulation [3,8]. Based on these considerations, the ESC/ERS guidelines introduced a new sub-classification: Depending on elevations of the diastolic pressure gradient (DPG; defined as the difference between diastolic PAP

and PAWP) and/or pulmonary vascular resistance (PVR), a distinction was made between “isolated post-capillary PH” (lpcPH) and “combined post- and pre-capillary PH” (CpcPH) (**Table 1**) [2,3,8].

Comments: *Although the pathophysiological differentiation between lpcPH and CpcPH is supported by recent work and is based on solid evidence [14,15], the hemodynamic definition proposed in the ESC/ERS guidelines is problematic because patients who meet only one of the two criteria (PVR; DPG) cannot be definitively classified. A recent analysis [16] revealed that this applied for 28.7% of patients with PH-LHD undergoing right heart catheterization, in whom only one of the variables was elevated. Furthermore, recent studies revealed that a PVR >3 WU was predictive of survival in patients with PH-LHD and outperformed other measures such as TPG or DPG (see also below) [17-19]. Given this new evidence, it appears appropriate to define CpcPH primarily by a PVR >3 WU, although a DPG ≥ 7 mmHg as well as a pulmonary arterial compliance (PAC) <2,3 ml/mmHg may also be considered. Nevertheless, further clarification is still needed in this regard.*

The clinical classification of PH-LHD is based on the underlying left heart disease (**Table 2**). The new ESC guidelines on heart failure distinguish between HFrEF (EF <40%), heart failure with mid-range ejection fraction (HFmrEF; EF 40–49%) and HFpEF (EF $\geq 50\%$) [20], all of which are commonly associated with PH. In addition, potential causes of post-capillary PH include left-sided valvular heart disease as well as congenital or acquired inflow or outflow tract obstructions of the left heart, congenital cardiomyopathy and pulmonary vein stenosis. Regardless of the underlying condition, the presence of either PH or right ventricular dysfunction in LHD is of prognostic significance.

2.1-2.2 Pulmonary hypertension due to heart failure

The true prevalence of PH due to heart failure is not known, primarily because the definition of PH in epidemiological studies is based on echocardiographic data with different definitions and thresholds, while invasive hemodynamic measurements have been documented in only a few single-center studies [2-4]. In HFrEF, the prevalence of PH confirmed by right heart catheterization was between 40% and 75% [11,21,22]. In patients with HFpEF, the prevalence of PH was in the range of 36% to 83%, based on echocardiographic criteria or invasive assessment [23-25]. The prognostic significance of PH in heart failure has been shown in numerous studies. One observational study [26] showed that, in patients with heart failure, pulmonary artery systolic pressure (PASP) as measured by echocardiography had a high predictive value for all-cause mortality and cardiovascular mortality, independent of known predictors of mortality. While numerous studies have consistently shown an inverse correlation between the presence of PH and survival rates, the combination of elevated PAP and reduced systolic RV function was associated with a particularly poor prognosis in patients with

HFrEF [13]. Likewise, the existence of PH in HFpEF is associated with a markedly higher mortality rate [20-22]. In addition, HFpEF patients commonly exhibit right ventricular (RV) dysfunction (measured as TAPSE [tricuspid annular plane systolic excursion] or RV-FAC [right ventricular fractional area change]), which is associated with an elevated PAP, especially in advanced disease, and also constitutes a strong predictor of mortality [27,28].

Comments: Hemodynamic parameters that have prognostic significance in PH due to heart failure include elevated PAWP, mPAP and PVR values, as well as reduced PA_c [11,17-19,22,29-34], while no significance was demonstrated for the TPG at a threshold of 12 mmHg [11]. Findings from recently published studies on the predictive value of the DPG in different heart failure populations yielded conflicting results [12,17-19,22,33,34]. This may be attributable to differing populations and methodological limitations [35]. Current data show that CpcPH is present in 12% to 38% of heart failure patients, depending on the definition (elevated DPG or PVR) [12,22,33,34]. When characterizing a pre-capillary component in PH-LHD, it may be advisable to consider all of the aforementioned measures. Exercise RHC parameters may provide additional prognostic information in HF patients, as ΔCO and $\Delta sPAP$ independently predicted transplant/assist device-free survival in patients with HFrEF [36]. In summary, available data consistently show that PH and RV dysfunction are common in heart failure and are associated with a poor outcome.

2.3 Valvular heart disease

Mitral stenosis – Mitral stenosis can be viewed as an established disease model for PH-LHD. Significant, long-term mitral valve stenosis is usually accompanied by clinically relevant PH. The fact that PH usually improves or even normalizes after the valve defect has been corrected clearly illustrates the potentially reversible nature of PH-LHD. However, concomitant PH appears to affect early and late outcomes following surgery for mitral stenosis [37].

Mitral regurgitation – In addition to structural mitral valve disease, functional mitral regurgitation is a frequent cause of PH, which is associated with elevated mortality rates, particularly in patients with HFrEF and dilated left atria/ventricles, but also in HFpEF [38]. Even exercise-induced PH and RV dysfunction are associated with a poor outcome in patients with asymptomatic mitral regurgitation [39,40]. Surgical or interventional treatment of the mitral valve, including catheter-based approaches such as MitraClip® or CardioBand®, lead to substantial improvements in pulmonary hemodynamics (reduction of the mPAP and PAWP – primarily by reducing the V wave and increasing cardiac index) [41] in patients with HFrEF and functional mitral regurgitation, which underscores the pathophysiological importance of mitral regurgitation as a cause of PH due to LHD. Nevertheless,

recent data from the TRAMI registry have shown that even moderate PH affects post-procedural survival in patients undergoing MitraClip® therapy [42].

Aortic valve stenosis – Symptomatic aortic valve stenosis is associated with PH in up to 65% of cases [43-48]. The extent of PH correlates with both the severity of stenosis and clinical symptoms. Furthermore, pre-operative PH (usually defined as PASP >60 mmHg) in patients with surgical valve replacements is associated with a higher complication rate and a poor long-term prognosis. Although PH is a risk factor for heart valve surgery, surgical correction usually results in substantial improvement of PH severity within weeks or months [43-48]. However, in some cases (particularly in patients with severe AS), PH may persist even after successful valve correction and determine the clinical symptoms and disease course. Even in patients with a transcatheter aortic valve implantation (TAVI), pre-interventional PH is associated with a poor prognosis [49]. Furthermore, a reduction of the PAP after TAVI measured using echocardiography correlates with a favorable outcome [50]. A study of 433 patients who underwent pre-interventional invasive hemodynamic assessment showed that pre-capillary PH and CpcPH (defined as DPG ≥ 7 mmHg), but not lpcPH, were associated with a significantly higher 1-year mortality after TAVI [51]. Moreover, persistence of PH post-TAVI is common, and even moderate PH is associated with higher all-cause mortality [52].

2.4 Congenital/acquired left heart inflow/outflow tract obstructions and congenital cardiomyopathies

The distinction between pulmonary arterial hypertension (PAH) and post-capillary PH is also relevant in the context of congenital heart disease (CHD). Especially in patients with left-sided valve defects or diastolic dysfunction of the ventricle supplying the systemic circulation, post-capillary PH should be considered. Examples of congenital conditions prone to develop post-capillary PH include congenital mitral stenosis, Shone complex (combination of left heart deformities, which include LV inflow and outflow, and the aortic arch), cor triatriatum, transposition of the great arteries after atrial switch with baffle stenoses, congenital stenosis of the LV outflow tract, and aortic isthmus stenosis. This distinction impacts treatment decisions, as targeted PAH therapy is not indicated in patients with lpcPH and may potentially even be harmful. While the current ESC/ERS guidelines prefer the DPG over the TPG when distinguishing lpcPH and CpcPH, in CHD, the TPG is still considered important and relevant, as standardized values for the DPG have not been established for patients with complex anatomy or those who have undergone a Fontan procedure (for details on group 2.4, see article on “Pulmonary hypertension in adults with congenital heart disease” in this supplement).

2.5 Congenital/acquired pulmonary vein stenosis

Congenital pulmonary vein stenosis is a rare condition that is observed in only <0.1% of newborns. Acquired pulmonary vein stenosis occurs primarily after interventional pulmonary vein isolation (PVI) for atrial fibrillation. The reported prevalence after PVI is 0.2–0.4% [53], and has become less frequent over time.

Diagnostics

With respect to treatment decisions, the distinction between pre- and post-capillary PH and the proper clinical classification of PH are of key importance, although this may be challenging. Signs of PH can be identified in patients with left heart disease by using a step-by-step approach (**Fig. 1**). Although no single parameter can reliably differentiate between PH-LHD and pre-capillary PH, the presence of multiple risk factors and clinical findings may be indicative of PH-LHD (**Table 3**). In addition to the patient's history, clinical presentation, ECG findings, echocardiographic signs and other imaging techniques, particularly non-specific symptoms, signs of right-sided heart failure, and PH-associated comorbidities such as sleep apnea, COPD, pulmonary embolism and risk factors for heart disease or PAH may raise the suspicion of PH-LHD.

During the diagnostic work-up, it is necessary to consider the results of both non-invasive (primarily echocardiography) and invasive testing (**Fig. 1**) [2,8]. A suspected diagnosis should be formulated on the basis of non-invasive measurements, which may provide a rationale for further invasive evaluation. The indications for right heart catheterization in PH-LHD, which should preferably be performed as an elective procedure in patients who are in stable condition and in a euvolaemic state, are shown in **Table 4**. If left heart disease is suspected, left heart catheterization may also be indicated, including measurement of LVEDP. Upon invasive hemodynamic assessment, it should be determined whether the findings are consistent with the suspected diagnosis. This appears to be particularly important to distinguish between PAH and PH-HFpEF in patients who are pre-treated with diuretics.

Comments: Characterizing patients with PH by phenotype

Achieving a proper distinction between PH-LHD and different forms of PAH is not trivial and may at times even be impossible. In patients with PH-LHD, hemodynamic assessment usually reveals post-capillary PH (PAWP >15 mmHg). However, a normal PAWP does not rule out left heart disease, particularly in patients being treated with diuretics, as such pre-treatment lowers left-sided filling pressure and may thus pseudo-normalize PAWP.

In patients with HFpEF and severe PH, it may be particularly challenging to decide whether PH occurs as a consequence of HFpEF, or whether PAH may be co-existent with (mild) LV diastolic dysfunction. In any case, invasive assessment of hemodynamics must be comprehensive and performed in accordance with current recommendations [54]. Usually, simultaneous left heart catheterization, including measurement of the LVEDP, is indicated in these patients as part of the diagnostic work-up. Measurement of PAWP and LVEDP should preferably be performed at end-expiration to avoid misclassifications [2,3,8]. When in doubt (borderline PAWP 13-15 mmHg, diuretic pretreatment, signs of left heart disease), a volume challenge or exercise testing during RHC may be considered to uncover occult LHD in patients with HFpEF and an artificially lowered PAWP. However, these tests have not been standardized, and there are no valid reference values (a threshold PAWP after volume challenge of 18 mmHg has been suggested [55]). Furthermore, it was demonstrated that patients with PAH may also exhibit an abnormal increase in PAWP during volume challenge [56].

A precise hemodynamic characterization including measurement of PAP, PAWP, and cardiac output, and calculation of TPG, DPG, and PVR, and the interpretation of these results in conjunction with non-invasively measured parameters and the overall clinical context are essential for patients with significant PH. For patients who formally exhibit “pre-capillary PH” but have cardiopulmonary comorbidities and risk factors for LHD, specific criteria were recently introduced to better describe the patients’ phenotype, referred to as “atypical PAH” or “PAH with comorbidities” (Table 5) [7,57]. This clinical presentation should ultimately be viewed as a mixed form of PH, which is frequently observed in elderly patients who typically display a moderately increased PVR.

When considering the various causes and determinants of PAP elevation, there is a spectrum of different phenotypes ranging from “classical PAH” and “PAH with comorbidities” at one end, to CpcPH and lpcPH, and finally to heart failure without PH and with normal RV function at the other end (Figure 2). In this sense, PH may be viewed as a pathophysiological continuum [7], where various mechanisms may contribute to the elevation of PAP. The consideration of these pathophysiological interrelations and phenotypes may inform treatment decisions in individual patients. Furthermore, in future, detailed phenotyping using cluster analyses of multiple phenotypical characteristics (“phenomapping”) that include the simultaneous consideration of clinical, laboratory, ECG and echocardiographic parameters, may also prove helpful to better characterize particularly the heterogeneous population of HFpEF patients [58,59].

Rationale treatment of PH-LHD

The ESC/ERS PH guidelines recommend that in patients with PH-LHD, treatment of the underlying left heart condition should be optimized before an assessment of PH is considered (I-B) [8]. This relates

primarily to the thorough correction of valve defects, and guideline-directed treatment of HFrEF that includes controlling cardiovascular risk factors [20]. In addition, comorbidities that may cause PH should be identified and treated (e.g. COPD, sleep apnea syndrome, pulmonary embolism). Selected patients may benefit from vasodilators such as nitrates or hydralazine, although the evidence for this is scarce, and a recent study (NEAT) showed negative effects for isosorbide mononitrate in patients with HFpEF [20,60]. In general, the use of “PAH-specific medications” is not recommended in patients with PH-LHD (III-C) (Table 6).

Comments:

Optimized treatment of heart failure (HF) in patients with PH-HF: In general, “optimized heart failure treatment” is considered thorough therapy of HFrEF in accordance with current heart failure guidelines [20]. In this context, both the use of the appropriate medications (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers or angiotensin receptor neprilysin inhibitors, beta blockers, mineralocorticoid receptor antagonists) and the achievement of the respective target dosages which were applied in clinical trials play a critical role. In addition, cardiac resynchronisation therapy (CRT, with a QRS interval of ≥ 130 ms) and heart rate control with ivabradine (sinus rhythm and heart rate >70 bpm) must also be considered. Furthermore, LV unloading by implanting LV assist devices (LVAD) usually results in a substantial reduction of PAP in patients with severe HFrEF and even “fixed PH”, without increasing the risk of post-procedural right heart failure [61-63]. Recent studies must be noted though, indicating that only about one-third of patients with fixed PH achieve normalization of PVR before transplant with either LVAD or inotropes [64], and decoupling of diastolic PAP and PAWP was identified as a prognostic factor after LVAD implantation [65].

Optimized treatment of patients with HFpEF or HFmrEF is more challenging because diuretics represent the only evidence-based recommendation for these populations (I-C) [20]. In view of hemodynamic adjustments in HFpEF patients, the use of interventional therapies is currently being tested. In a multicenter pilot study (REDUCE-LAP-HF) [66], an interatrial shunt device was implanted in 64 patients with HFpEF, aiming at mechanically reducing the elevated LA pressure. During the 6-month follow-up period, none of the patients had catheter-associated complications or serious cardiac or cerebral adverse events. The procedure resulted in improvements in NYHA functional class, 6-minute walk distance ($+32$ m) and mean PAWP at maximal exertion (32 ± 8 to 29 ± 9 mmHg).

It is important to note that in clinical trials of PH due to heart failure, one of the generally required inclusion criteria is optimized, guideline-oriented heart failure therapy that remained unchanged for at least 30 days prior to study enrolment and resulted in a stable clinical condition [67]. Despite these criteria, e.g. in studies evaluating riociguat in HFrEF, the rate of patients treated with β -blockers was

“only” 50% [67], although this is considered a Class I-A indication in the guidelines [20]. Likewise, the target dosages of heart failure medications are frequently not reached, both in routine clinical practice and in clinical trials [67-69].

Management of fluid volume: Since elevated filling pressures (“congestion”) in patients with heart failure are associated with higher hospitalization and mortality rates [70-72], proper volume control is of key importance. Independent of LVEF, in decompensating HF patients filling pressures usually increase at least 2 weeks prior to hospitalization [73]. Hence, an important goal of heart failure control is the avoidance and/or removal of excessive intra- and/or extravascular fluid, without causing additional neurohumoral activation or impairment of renal function. In cases of advanced heart failure, optimizing the volume status is a particularly important goal, which may require invasive monitoring [20,74].

Although clinical and non-invasive signs of congestion are often unreliable for estimating filling pressures, they can provide important clues (**Table 7**). Jugular vein distention (sensitivity 70%, specificity 79%), orthopnea, and peripheral edema moderately correlate with LVEDP and/or RAP [75]. Hemodynamic assessment remains the gold standard, but is not feasible for regular follow-up evaluations. The availability of implantable pressure sensors that continuously measure PAP as a surrogate of filling pressures enables heart failure specialists to continuously monitor filling pressures to help guide treatment decisions in HF [87]. Controlled studies have demonstrated the superiority of hemodynamically guided heart failure therapy (regardless of LVEF) over “guideline-directed standard of care”, even at heart failure expert centers [88]. In this context, it appears doubtful whether effective volume control was achieved in patients with a mean RAP of 23 ± 6 mmHg at the time of enrolment into a study that assessed the efficacy of sildenafil in patients with PH-HFpEF [89].

Recommendations for the use of targeted PH therapies depending on heart failure therapy:

In patients with PH-LHD and a pronounced pre-capillary component (high PVR and high DPG), treatment with pulmonary vasodilators (“targeted PH therapy”) may be considered as a therapeutic option on a case-by-case basis (**Table 6**). However, in patients with chronic heart failure, irrespective of the LVEF, this type of therapy should only be considered if the following requirements for optimized heart failure therapy have been met:

- *All reversible causes of heart failure and those that are treatable by non-pharmacological means (e.g. device-based, interventional, surgical) should have been excluded or treated.*
- *All evidence-based treatment approaches recommended in the guidelines should, if appropriate for the patient, be utilized in the described sequence [20].*
- *With regard to pharmacological therapies, the recommended target dosages should try to be attained and used, where possible. The proportion of patients achieving the target dose should be equivalent to the percentage reported in the respective clinical trials.*
- *Effective volume control, taking into account the neurohumoral activation and renal function, is a key treatment goal. Should this not be achievable by means of clinical and non-invasive measures, invasive hemodynamic assessment of the treatment goals may be considered.*

Once all of the above-mentioned points are addressed and remain stable for at least 12 weeks, invasive reassessment of hemodynamics may be considered. Only if PH persists and PVR remains elevated, consultation with a PH expert center should follow, and the use of targeted PH medications may be considered on an individual basis.

Targeted PAH therapy in PH-LHD

The use of targeted PAH medications in PH-LHD is generally not recommended in the ESC/ERS guidelines (III-C) [8]. However, in patients with PH-LHD comprising a pronounced pre-capillary component as indicated by an elevated PVR (and/or elevated DGP/reduced PA_c), individual treatment decisions at a specialized center with expertise in both HF and PH may be appropriate (IIa-C) (Table 5).

The rationale for the use of PAH therapies in PH-LHD is derived from small, short-term studies which demonstrated improvements in hemodynamic variables, exercise tolerance, and symptoms following treatment with prostanoids, ERAs and PDE-5 inhibitors [2,3,90]. However, these studies are characterized by considerable methodological limitations (small sample size, single-center, unclear or no randomization process), and there are no robust long-term data from randomized controlled studies to confirm the efficacy and safety of PAH therapies in PH-LHD. Moreover, there are numerous examples of neutral studies in this area [2,3,8]. Recent examples include the ENABLE and MELODY-1 studies, showing that the two ERAs bosentan and macitentan failed to improve clinical measures or outcome in patients with HFrEF or HFpEF, respectively, and in both studies ERA therapy was associated with an increased occurrence of fluid retention [91,92]. In addition, the SIOVAC trial has shown that the use of sildenafil was associated with an increased risk of clinical deterioration and worse outcome versus placebo in patients with PH after VHD intervention (aortic, mitral, or tricuspid) [93], thus indicating that such therapies may even be harmful in the context of LHD. When viewed

together, there is currently no new evidence that would justify the general use of PAH therapies in PH-LHD, and potentially harmful effects have to be considered. However, when interpreting the results of such studies, it should be noted that few studies in patients with heart failure have stratified the populations for the presence of PH, and studies performed in the context of PH-LHD have almost exclusively evaluated patients with lpcPH (with the exception of MERIT-1), while the consideration of pulmonary hemodynamics in PH-LHD and the distinction between lpcPH and CpcPH may be crucial.

Comments: *The therapeutic consequences of the current sub-classification of post-capillary PH (lpcPH versus CpcPH) are not yet clear. However, recent data suggest differences in response to targeted PAH therapies among these subtypes of post-capillary PH, as well as differential effects of the various drug classes among PAH medications. In this context, the importance of proper phenotyping and precise hemodynamic characterization especially of HFpEF patients with PH has recently been highlighted [94,95].*

lpcPH: *The randomized, placebo-controlled RELAX trial [96], which enrolled patients with HFpEF irrespective of the presence of PH, showed no advantage of sildenafil treatment versus placebo with respect to exercise capacity or other endpoints. In another RCT [97], in 52 HFpEF patients who predominantly exhibited lpcPH (mean DPG 1 mmHg, mean PVR 2.4 WU), sildenafil also failed to reduce the mPAP (primary endpoint) or improve any of the secondary endpoints. Based on these data, patients with lpcPH should not be treated with targeted PAH medications, especially not sildenafil.*

CpcPH: *Although the current sub-classification of PH-LHD did not yet exist at the time the study was conducted, an RCT [66] in HFpEF patients who met the hemodynamic criteria for CpcPH showed that sildenafil significantly reduced PVR and improved RV function compared with placebo. Consistently, recent data from the COMPERA registry [7] revealed that patients with HFpEF and CpcPH may benefit from targeted PH therapies, particular PDE-5 inhibitors (improvement of exercise tolerance, WHO functional class, and NT-proBNP levels), although the therapeutic effect was less pronounced than in patients with IPAH. Furthermore, treatment discontinuations (due to side effects and/or lack of efficacy) were higher among patients with PH-HFpEF, with ERA less well tolerated than PDE-5 inhibitors. The MELODY-1 study, investigating the ERA macitentan, showed no benefit and significantly more edemas than placebo in patients with CpcPH [92]. This, together with the distinct tolerability of drug classes in patients with PH-HFpEF observed in COMPERA [7], may be indicative of differences with respect to efficacy and tolerability among targeted PH therapies in patients with LHD.*

Specific recommendations for targeted PH therapy in CpcPH

Comments:

- *Thus far, even if patients with CpcPH display PH with a relevant pre-capillary component, they were excluded from clinical trials that investigated targeted PAH therapies because of their elevated left-sided filling pressure (PAWP >15 mmHg). Accordingly, data from randomized controlled trials are lacking, so that to date neither the safety nor the efficacy of PAH drugs have been sufficiently characterized in these patients. Consequently, such patients should be evaluated at expert centers, where treatment attempts may be considered in experienced hands if deemed necessary (IIa-C). Close monitoring is essential especially in the initial phase, and invasive follow-up assessments are advisable.*
- *In contrast to PAH, it is not yet known whether PAH-specific medications have a favorable effect on disease progression when used for CpcPH. Whenever possible, patients should be enrolled into randomized controlled trials.*
- *In light of the prognostic impact of PH and RV dysfunction in patients with LHD and preliminary evidence for the efficacy of targeted PAH therapies in CpcPH, especially in patients with HFpEF, treatment attempts may be appropriate in individual patients presenting with elevated PVR despite proper volume control. In such cases, PDE-5 inhibitors should be the preferred drug class. Treatment attempts should initially be restricted to a limited period of time (e.g. 3–6 months). Subsequently, after a thorough reevaluation, it must be decided whether there has been an objective clinical improvement that justifies continuation of this treatment. Otherwise, the treatment should be terminated. This approach should be discussed with the patient before starting the treatment, and the response to treatment should be documented over time.*
- *The indiscriminate use of targeted PAH medications for CpcPH in cases other than those described above is strongly discouraged.*
- *Clinical trials assessing targeted interventions in the context of PH-LHD should primarily focus on CpcPH, as an elevated PVR (and reduced PA_d) provides a rationale for a treatable target in the pulmonary circulation. Several clinical studies including a multicenter trial assessing sildenafil in PH-LHD (SiLHF; NCT01616381) are ongoing, and an outcome study testing the PDE5 inhibitor tadalafil versus placebo in patients with HFpEF and CpcPH (PASSION) is currently under way.*

References

- 1 Hoeper MM, Humbert M, Souza R et al. A global view of pulmonary hypertension. *Lancet Respir Med* 2016; 4: 306-322.
- 2 Rosenkranz S, Gibbs JSR, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J* 2016; 37: 942-954.
- 3 Vachiery JL, Adir Y, Barbera JA et al. Pulmonary hypertension due to left heart disease. *J Am Coll Cardiol* 2013; 62: D100-D108.
- 4 Fang JC, DeMarco T, Givertz MM et al. World Health Organization Pulmonary Hypertension Group 2: Pulmonary hypertension due to left heart disease in the adult—a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2012; 31: 913-933.
- 5 Thenappan T, Shah SJ, Gombert-Maitland M et al. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail* 2011; 4: 257-265.
- 6 Robbins IM, Newman JH, Johnson RF et al. Association of the metabolic syndrome with pulmonary venous hypertension. *Chest* 2009; 136: 31-36.
- 7 Opitz CF, Hoeper MM, Gibbs JSR et al. Pre-capillary, combined, and post-capillary pulmonary hypertension: A pathophysiological continuum. *J Am Coll Cardiol* 2016; 68: 368-378.
- 8 Galiè N, Humbert M, Vachiery JL et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67-119.
- 9 Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. *Circulation* 2000; 102: 1718-1723.
- 10 Galiè N, Hoeper M, Humbert M et al. Guidelines on diagnosis and treatment of pulmonary hypertension: the Task Force on Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and of the European Respiratory Society. *Eur Heart J* 2009; 30: 2493-2537.
- 11 Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction. *JACC Heart Fail* 2013; 1: 290-299.
- 12 Gerges C, Gerges M, Lang MB et al. Diastolic pulmonary vascular pressure gradient. A predictor of prognosis in out-of-proportion pulmonary hypertension. *Chest* 2013; 143: 758-766.
- 13 Naeije R, Vachiery JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. *Eur Respir J* 2013; 41: 217-223.
- 14 Assad TR, Hemnes AR, Larkin EK, et al. Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. *J Am Coll Cardiol* 2016; 68: 2525-2536.
- 15 Guazzi M, Naeije R. Pulmonary hypertension in heart failure: Pathophysiology, pathobiology, and emerging clinical perspectives. *J Am Coll Cardiol* 2017; 69: 1718-1734.
- 16 Gerges M, Gerges C, Lang IM. How to define pulmonary hypertension due to left heart disease. *Eur Respir J* 2016; 48: 553-555.
- 17 Palazzini M, Dardi F, Manes A, et al. Pulmonary hypertension due to left-heart disease: analysis of survival according to the hemodynamic classification of the 2015 ESC/ERS guidelines and new insights for future changes. *Eur J Heart Fail* 2018; 20: 248-255.

- 18** Caravita S, Dewachter C, Soranna D, et al. Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. *Eur Respir J* 2018; 51(4). pii: 1702427.
- 19** Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. *JAMA Cardiol* 2018; 3: 298-306.
- 20** Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 18: 891-975.
- 21** Ghio S, Gavazzi A, Campana C et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* 2001; 37: 183-188.
- 22** Tampakakis E, Leary PJ, Selby VN et al. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail* 2015; 3: 9-16.
- 23** Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction. A community-based study. *J Am Coll Cardiol* 2009; 53: 1119-1126.
- 24** Leung CC, Moondra V, Catherwood E, Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. *Am J Cardiol* 2010; 106: 284-286.
- 25** Shah AM, Shah SJ, Annand IS et al. Cardiac structure and function in heart failure with preserved ejection fraction: Baseline findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial (TOPCAT). *Circ Heart Fail* 2014; 7: 104-115.
- 26** Bursi F, McNallan SM, Redfield MM et al. Pulmonary pressures and death in heart failure: a community study. *J Am Coll Cardiol* 2012; 59: 222-231.
- 27** Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J* 2014; 35: 3452-3462.
- 28** Mohammed SF, Hussain I, Abou Ezzeddine OF et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation* 2014; 130: 2310-2320.
- 29** Pellegrini P, Rossi A, Pasotti M et al. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. *Chest* 2014; 145: 1064-1070.
- 30** Dragu R, Rispler S, Habib M et al. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. *Eur J Heart Fail* 2015; 17: 74-80.
- 31** Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. *JACC Heart Fail* 2015; 3: 467-474.
- 32** Malhotra R, Dhakal BP, Eisman AS et al. Pulmonary vascular distensibility predicts pulmonary hypertension severity, exercise capacity, and survival in heart failure. *Circ Heart Fail* 2016; 9: e003011
- 33** Gerges M, Gerges C, Pistrutto AM et al. Pulmonary hypertension in heart failure. Epidemiology, right ventricular function, and survival. *Am J Respir Crit Care Med* 2015; 192: 1234-1246.
- 34** Zotter-Tufaro C, Duca F, Kammerlander AA et al. Diastolic pressure gradient predicts outcome in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2015; 66: 1308-1310.
- 35** Chatterjee NA, Lewis GD. Characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: limitations of a solitary measurement. *JACC Heart Fail* 2015; 3: 17-21.

- 36** Rieth A, Richter MJ, Gall H, et al. Hemodynamic phenotyping based on exercise catheterization predicts outcome in patients with heart failure and reduced ejection fraction. *J Heart Lung Transpl* 2017; 36: 880-889.
- 37** Yang B, De Benedictus C, Watt T, et al. The impact of concomitant pulmonary hypertension on early and late outcomes following surgery for mitral stenosis. *J Thorac Cardiovasc Surg* 2016; 152: 394-400.
- 38** Bursi F, Barbieri A, Grigioni F et al. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. *Eur J Heart Fail* 2010; 12: 382-388.
- 39** Kusunose K, Popović ZB, Motoki H, Marwick TH. Prognostic significance of exercise-induced right ventricular dysfunction in asymptomatic degenerative mitral regurgitation. *Circ Cardiovasc Imaging* 2013; 6: 167-176.
- 40** Lancellotti P, Magne J, Dulgheru R, Ancion A, Martinez C, Pierard LA. Clinical significance of exercise pulmonary hypertension in secondary mitral regurgitation. *Am J Cardiol* 2015; 115: 1454-1461.
- 41** Gaemperli O, Moccetti M, Surder D et al. Acute haemodynamic changes after percutaneous mitral valve repair: relation to mid-term outcomes. *Heart* 2012; 98: 126-132.
- 42** Tigges E, Blankenberg S, von Bardeleben S, et al. Implication of pulmonary hypertension in patients undergoing MitraClip therapy: results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail* 2018; 20: 585-594.
- 43** Faggiano P, Antonini-Canterin F, Ribichini F et al. Pulmonary artery hypertension in adult patients with symptomatic valvular aortic stenosis. *Am J Cardiol* 2000; 85: 204-208.
- 44** Melby SJ, Moon MR, Lindman BR, Bailey MS, Hill LL, Damiano Jr RJ. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. *J Thorac Cardiovasc Surg* 2011; 141: 1424-1430.
- 45** Zuern CS, Eick C, Rizas K et al. Prognostic value of mild-to-moderate pulmonary hypertension in patients with severe aortic valve stenosis undergoing aortic valve replacement. *Clin Res Cardiol* 2012; 101: 81-88.
- 46** Zlotnick DM, Ouellette ML, Malenka DJ et al. Effect of pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. *Am J Cardiol* 2013; 112: 1635-1640.
- 47** Vahanian A, Alfieri O, Andreotti F et al., Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; 33: 2451-2496.
- 48** Roques F, Nashef SA, Michel P et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999; 15: 816-822.
- 49** Luçon A, Oger E, Bedossa M et al. Prognostic implications of pulmonary hypertension in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation: study from the FRANCE 2 registry. *Circ Cardiovasc Interv* 2014; 7: 240-247.
- 50** Sinning JM, Hammerstingl C, Chin D et al. Decrease of pulmonary hypertension impacts on prognosis after transcatheter aortic valve replacement. *EuroIntervention* 2014; 9: 1042-1049.
- 51** O'Sullivan CJ, Wenaweser P, Ceylan O et al. Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with severe symptomatic aortic valve stenosis

undergoing transcatheter aortic valve implantation. Insights from the new proposed pulmonary hypertension classification. *Circ Cardiovasc Interv* 2015; 8: e002358.

52 Masri A, Abdelkarim I, Sharbaugh MS, et al. Outcomes of persistent pulmonary hypertension following transcatheter aortic valve replacement. *Heart* 2018; 104: 821-827.

53 Arbelo E, Brugada J, Hindricks G et al. Atrial Fibrillation Ablation Pilot Study Investigators. ESC-EURObservational Research Programme: the Atrial Fibrillation Ablation Pilot Study, conducted by the European Heart Rhythm Association. *Europace* 2012; 14: 1094-1103.

54 Rosenkranz S, Behr J, Ewert R et al. Rechtherzkatheter-Untersuchung bei pulmonaler Hypertonie. *Dtsch Med Wochenschr* 2011; 136: 2601-2620.

55 D'Alto M, Romeo E, Argiento P, et al. Clinical relevance of fluid challenge in patients evaluated for pulmonary hypertension. *Chest* 2017; 151: 119-126.

56 Robbins IM, Hemnes AR, Pugh ME et al. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. *Circ Heart Fail* 2014; 7: 116-122.

57 Galiè N, Barbera JA, Frost A et al. Initial use of Ambrisentan plus Tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 379: 834-844.

58 Shah SJ, Katz DH, Selvaraj S et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* 2015; 131: 269-279.

59 Dalos D, Mascherbauer J, Zotter-Tufaro C et al. Functional status, pulmonary artery pressure, and clinical outcomes in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2016; 68: 189-199.

60 Redfield MM, Anstrom KJ, Levine JA et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015; 373: 2314-2324.

61 Patel ND, Weiss ES, Schaffer J et al. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. *Ann Thorac Surg* 2008; 86: 832-840.

62 Torre-Amione G, Southard RE, Loebe MM et al. Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support. *J Heart Lung Transplant* 2010; 29: 195-200.

63 Zimpfer D, Zrunek P, Roethy W et al. Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates. *J Thorac Cardiovasc Surg* 2007; 133: 689-695.

64 Al Kindi SG, Farhoud M, , et al. Left ventricular assist devices or inotropes for decreasing pulmonary vascular resistance in patients with pulmonary hypertension listed for heart transplantation. *J Cardiac Fail* 2017; 23: 209-215.

65 Imamura F, Chung B, Nguyen A, et al. Decoupling between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure as a prognostic factor after continuous flow ventricular assist device implantation. *Circ Heart Fail* 2017; 10: e003882.

66 Hasenfuß G, Hayward C, Burkhoff D et al. REDUCE LAP-HF study investigators. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet* 2016; 387: 1298-1304.

67 Bonderman D, Ghio S, Felix SB et al. Riociguat for Patients With Pulmonary Hypertension Caused by Systolic Left Ventricular Dysfunction: A Phase IIb Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Hemodynamic Study. *Circulation* 2013; 128: 502-511.

68 Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. *J Am Coll Cardiol* 2007; 50: 2136-2144.

- 69** Komajda M, Follath F, Swedberg K et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 2: Treatment. *Eur Heart J* 2003; 24: 464-474.
- 70** Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med* 2001; 345: 574-581.
- 71** Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J* 2007; 154: 260-266.
- 72** Ambrosy AP, Pang PS, Khan S et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013; 34: 835-843.
- 73** Zile MR, Bennett TD, St John Sutton M et al. Transition from chronic compensated to acute decompensated heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008; 118: 1433-1441.
- 74** Khush KK, Tasissa G, Butler J, McGlothlin D, De MT. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. *Am Heart J* 2009; 157: 1026-1034
- 75** Gheorghiade M, Follath F, Ponikowski P et al. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010; 12: 423-433.
- 76** Valente MA, Voors AA, Damman K et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J* 2014; 35: 1284-1293.
- 77** Rudski LG, Lai WW, Afilalo J et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685-713.
- 78** Pellicori P, Carubelli V, Zhang J et al. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. *JACC Cardiovasc Imag* 2013; 6: 16-28.
- 79** Stawicki SP, Adkins EJ, Eiferman DS et al. Prospective evaluation of intravascular volume status in critically ill patients: does inferior vena cava collapsibility correlate with central venous pressure?. *J Trauma Acute Care Surg* 2014; 76: 956-963.
- 80** Pimenta J, Paulo C, Mascarenhas J et al. BNP at discharge in acute heart failure patients: is it all about volemia? A study using impedance cardiography to assess fluid and hemodynamic status. *Int J Cardiol* 2010; 145: 209-214.
- 81** Maisel A, Mueller C, Adams Jr K et al. State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail* 2008; 10: 824-839.
- 82** Melenovsky V, Andersen MJ, Andress K, Reddy YN, Borlaug BA. Lung congestion in chronic heart failure: haemodynamic, clinical, and prognostic implications. *Eur J Heart Fail* 2015; 17: 1161-1171.
- 83** Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol* 2013; 62: 516-524.
- 84** Davila C, Reyentovich A, Katz SD. Clinical correlates of hemoconcentration during hospitalization for acute decompensated heart failure. *J Cardiac Fail* 2011; 17: 1018-1022.

- 85** Ng TM, Cao DX, Patel KA et al. Association of hyponatremia to diuretic response and incidence of increased serum creatinine levels in hospitalized patients with acute decompensated heart failure. *Cardiology* 2014; 128: 333-342.
- 86** Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. *J Am Coll Cardiol* 2015; 65: 480-492.
- 87** Adamson PB, Abraham WT, Aaron M et al. CHAMPION trial rationale and design: the long-term safety and clinical efficacy of a wireless pulmonary artery pressure monitoring system. *J Cardiac Fail* 2011; 17: 3-10.
- 88** Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Philip B Adamson PB for the CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet* 2016; 387: 453-461.
- 89** Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation* 2011; 124: 164-174.
- 90** Barnett CF, DeMarco T. Pulmonary hypertension associated with left-sided heart disease. *Heart Fail Clin* 2012; 8: 447-459.
- 91** Packer M, McMurray JJV, Krum H, et al. Long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure: Primary results of the ENABLE trials. *JACC Heart Fail* 2017; 5: 317-326.
- 92** Vachiéry JL, Delcroix M, Al-Hiti H, et al. Macitentan in pulmonary hypertension due to left ventricular dysfunction. *Eur Respir J* 2018; 51(2). pii: 1701886.
- 93** Bermejo J, Yotti R, García-Orta R, et al. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. *Eur Heart J* 2018; 39: 1255-1264.
- 94** Hoeper MM, Lam CSP, Vachiéry JL, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: A plea for proper phenotyping and further research. *Eur Heart J* 2017; 38: 2869-2873.
- 95** Borlaug BA, Obokata M. Is it time to recognize a new phenotype? Heart failure with preserved ejection fraction with pulmonary vascular disease. *Eur Heart J* 2017; 38: 2874-2878.
- 96** Redfield MM, Chen HH, Borlaug BA et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013; 309: 1268-1277.
- 97** Hoendermis ES, Liu LC, Hummel YM et al. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. *Eur Heart J* 2015; 36: 2565-2573.
- 98** Gheorghiade M, Greene SJ, Butler J et al. SOCRATES-REDUCED Investigators and Coordinators. Effect of Vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: The SOCRATES-REDUCED randomized trial. *JAMA* 2015; 314: 2251-2262.
- 99** Pieske B, , , et al. . SOCRATES-PRESERVED.

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Table 1 Hemodynamic definitions of post-capillary pulmonary hypertension (PH)

Definition	Characteristics ^a	Clinical groups
Post-capillary PH	mPAP ≥ 25 mmHg PAWP ≤ 15 mmHg	<ul style="list-style-type: none">• PH due to left heart disease• PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (IpcPH)*	PVR ≤ 3 WU ^b (and/or DPG <7 mmHg and/or PA _C ≥2.3 ml/mmHg)	
Combined post- and pre-capillary PH (CpcPH)*	PVR > 3 WU ^b (and/or DPG ≥ 7 mmHg and/or PA _C <2.3 ml/mmHg)	
DPG: diastolic pressure gradient, PA _C : pulmonary artery compliance, mPAP: mean pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, PVR: pulmonary vascular resistance, WE: Wood units.		

modified from [10]

^a All values measured at rest.

^b Wood units are preferable to dyn·s·cm⁻⁵.

* change from original guidelines

Table 2 Clinical classification of pulmonary hypertension due to left heart disease

2. Pulmonary hypertension due to left heart disease
2.1 Left-ventricular systolic dysfunction (heart failure with reduced ejection fraction; HFrEF)
2.1 Mild left-ventricular systolic dysfunction* (heart failure with mid-range ejection fraction; HFmrEF)
2.2 Left-ventricular diastolic dysfunction (heart failure with preserved ejection fraction; HFpEF)
2.3 Valvular heart disease (VHD)
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary vein stenosis

* updated based on [20]

Table 3 Factors which suggest the presence of pulmonary hypertension due to left heart disease (PH-LHD) in patients with suspected pulmonary hypertension [10]

Clinical presentation	Echocardiography	Other features
Age >65 years Symptoms of left heart failure History of CHD	<ul style="list-style-type: none"> Structural left heart disease: <ul style="list-style-type: none"> Diseases of the left heart valves LA enlargement (>4.2 cm) Bowing of the IAS to the right LV dysfunction (syst./diast.) Concentric LV hypertrophy and/or increased LV mass Doppler indices of increased LV filling pressure: <ul style="list-style-type: none"> Increased E/e' >Type 2–3 mitral flow abnormality 	<ul style="list-style-type: none"> ECG: <ul style="list-style-type: none"> LVH and/or LAHB AF/Afib LBBB Presence of Q waves Absence of "RV strain" Other imaging: <ul style="list-style-type: none"> Kerley B lines Pleural effusion Pulmonary edema LA enlargement
Features of the metabolic syndrome	Absence of: <ul style="list-style-type: none"> RV dysfunction Mid-systolic notching of the PA flow Pericardial effusion 	
History of heart disease (previous or current)		
Atrial fibrillation (persistent/permanent)		
AF/Afib: Atrial flutter/atrial fibrillation, CHD: coronary heart disease, IAS: interatrial septum, LA: left atrium, LAHB: left anterior hemiblock, LBBB: left bundle branch block, LV: left ventricle, LVH: left ventricular hypertrophy, PA: pulmonary artery, RV: right ventricle		

Table 4 Recommendations for right heart catheterization in patients with pulmonary hypertension due to left heart disease (PH-LHD) [10]

Recommendation	Class	Level
RHC is recommended in patients with congenital cardiac shunts to support decisions on surgical or interventional corrections.	I	C
RHC is recommended in patients with PH due to left heart disease or lung disease if organ transplantation is being considered.	I	C
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP.	IIa	C
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and to support treatment decisions.	IIb	C
LVEDP: left ventricular end-diastolic pressure, PAWP: pulmonary artery wedge pressure, PH: pulmonary hypertension, RHC: right heart catheterization		

Table 5 Characteristics used to differentiate “classical” pulmonary arterial hypertension (PAH) from “PAH with comorbidities” [57]

Parameter	Characteristics
Hemodynamic characteristics	<ul style="list-style-type: none"> • PVR <3.5 WU • PAWP 12–15 mmHg and PVR >3.5 but <6.0 WU
Risk factors for left heart disease*	<ul style="list-style-type: none"> • BMI ≥ 30 kg/m² • arterial hypertension • diabetes mellitus (any form) • known significant CHD
BMI: body mass index, CHD: coronary heart disease, PAWP: pulmonary artery wedge pressure, PVR: pulmonary vascular resistance, WU: Wood units	

* at least 3 risk factors must be present

Table 6 Recommendations for the management of pulmonary hypertension due to left heart disease (PH-LHD) [10].

Recommendation	Class	Level
Optimization of the treatment for the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease).	I	C
It is recommended that other causes of PH (i.e. COPD, SAS, PE, CTEPH) are identified and treated, where appropriate, before considering assessment of PH-LHD.	I	C
It is recommended that invasive assessments for PH are performed in patients on optimised volume status.	I	C
Patients with PH-LHD and a severe pre-capillary component, as indicated by a high DPG and/or high PVR, should be referred to an expert PH center for a complete diagnostic workup and an individualized decision regarding treatment.	IIa	C
The importance and role of vasoreactivity testing in PH-LHD is not established, except in patients who are candidates for heart transplantation and/or LVAD implantation.	III	C
The use of targeted PAH-approved therapies is not recommended in PH-LHD.	III	C
COPD: chronic obstructive pulmonary disease, CTEPH: chronic thromboembolic pulmonary hypertension, DPG: diastolic pressure gradient, LVAD: left ventricular assist device, PE: pulmonary embolism, PH: pulmonary hypertension, PH-LHD: pulmonary hypertension with left heart disease, PVR: pulmonary vascular resistance, SAS: sleep apnoea syndrome		

Table 7 Findings that indicate a requirement for additional fluid reduction in heart failure.

Investigation	Signs of excess fluid volume
Physical examination	Peripheral edema, anasarca, signs of ascites or pleural effusion, pulmonary rhonchi, jugular vein distention, S3 gallop [20,70,72,75]
Relative body weight	Current BW is clearly higher than the “dry weight” (known BW of the individual when volume status is balanced) [63, 64]
Sonography	Pleural effusion, ascites, inferior vena cava >2.1 cm and <50% variation during respiration [20, 77-79]
Laboratory test results	NT-proBNP and/or BNP level >125–150% of the value for the individual when volume status is balanced (“wet BNP”) [80,81], low hematocrit [82-84], low sodium level [85,86]
BW: body weight BNP: brain natriuretic peptide NT-proBNP: N-terminal pro-brain natriuretic peptide	

Figure Legends

Figure1 Algorithm to differentiate between pulmonary arterial hypertension (PAH) and pulmonary hypertension with left heart disease (PH-LHD) [2]. © Oxford University Press. <http://www.escardio.org>.

CO: cardiac output, Cpc-PH: combined post- and pre-capillary PH, CPET: cardiopulmonary exercise testing, DLCO: diffusing capacity for carbon monoxide, dPAP: diastolic pulmonary artery pressure, DPG: diastolic pressure gradient, ECG: electrocardiogram, HFmrEF: Heart Failure with mid-range Ejection Fraction, HFpEF: Heart Failure with preserved Ejection Fraction, HFrEF: Heart Failure with reduced Ejection Fraction, HR-CT: high-resolution computed tomography, Ipc-PH: isolated post-capillary PH, LHD: left heart disease, LuFu: lung function, LVEDP: left ventricular end-diastolic pressure, mPAP: mean pulmonary artery pressure, PA: pulmonary artery, PAP: pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, PH: pulmonary hypertension, PVP: right ventricular pressure, PVR: pulmonary vascular resistance, RAP: right atrial pressure, RVP: right ventricular pressure, sPAP: systolic pulmonary artery pressure, SvO₂: mixed venous oxygen saturation, TPG: transpulmonary pressure gradient, V/Q scan: ventilation/perfusion scan, WU: Wood units

Figure 2 Spectrum of phenotypes in pulmonary arterial hypertension (PAH) and pulmonary hypertension due to left heart disease (PH-LHD).

CpcPH: combined post- and pre-capillary PH, DPG: diastolic pressure gradient, HF: heart failure, IpcPH: isolated post-capillary PH, PA_c: pulmonary arterial compliance, PH: pulmonary hypertension, PVR: pulmonary vascular resistance, RV: right ventricle

Highlights

In the summer of 2016, delegates from the German Society of Cardiology (DGK), the German Respiratory Society (DGP), and the German Society of Pediatric Cardiology (DGPK) met in Cologne, Germany, to define consensus-based practice recommendations for the management of patients with pulmonary hypertension (PH). These recommendations were built on the 2015 European Pulmonary Hypertension guidelines, aiming at their practical implementation, considering country-specific issues, and including new evidence, where available. To this end, a number of working groups was initiated, one of which was specifically dedicated to PH associated with left heart disease. In this context, the European Guidelines point out that the drugs currently used to treat patients with PAH (prostanoids, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, sGC stimulators) have not been sufficiently investigated in other forms of PH. However, despite the lack of respective efficacy data, an uncritical use of targeted PAH drugs in patients with PH associated with left heart disease is currently observed at an increasing rate. This development is a matter of concern. On the other hand, PH is a frequent problem that is highly relevant for morbidity and mortality in patients with left heart disease. In that sense, the distinction between isolated post-capillary pulmonary hypertension (IpcPH) and combined post- and pre-capillary pulmonary hypertension (CpcPH) and their proper definition may be of particular relevance. The detailed results and recommendations of the working group on PH associated with left heart disease, which were last updated in the spring of 2018, are summarized in this article.

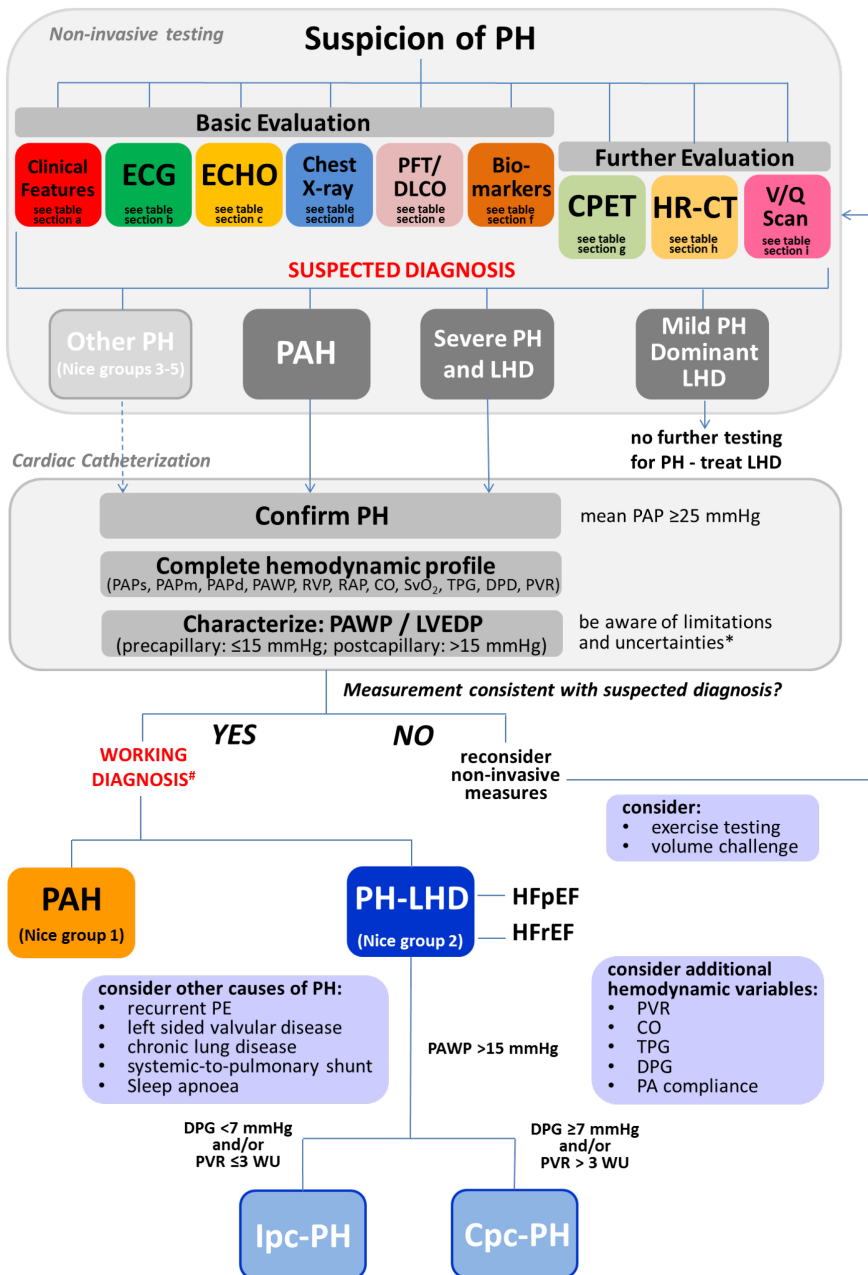


Figure 1

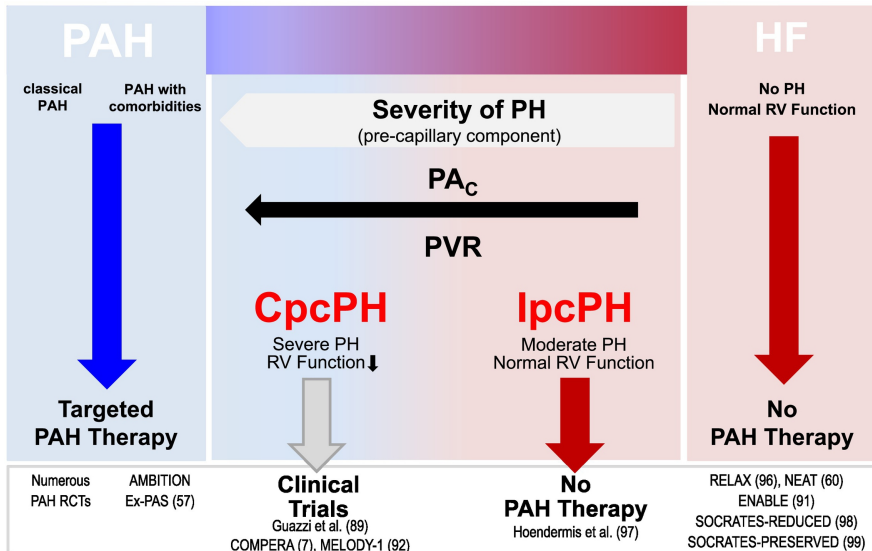


Figure 2