Severe Pulmonary Hypertension Associated with COPD: Hemodynamic Improvement with Specific Therapy

Anne Girard^a Stephane Jouneau^{a,d} Céline Chabanne^b Chahéra Khouatra^e
Morgane Lannes^c Julie Traclet^e Ségolène Turquier^e P. Delaval^{a,d}
J.-F. Cordier^{e,f} Vincent Cottin^{e,f}

^aService de Pneumologie, Centre de Compétences des Maladies Pulmonaires Rares, Centre de Compétences de l'Hypertension Pulmonaire, ^bService de Cardiologie, Centre de Compétences de l'Hypertension Pulmonaire, ^cDépartement d'Information Médicale, Hôpital Pontchaillou, Université de Rennes 1, ^dIRSET UMR 1085, Université de Rennes 1, Rennes, ^eService de Pneumologie, Centre National de Référence des Maladies Pulmonaires Rares, Centre de Compétences de l'Hypertension Pulmonaire, Hôpital Louis Pradel, and ^fInra, UMR754, Université de Lyon, Université Claude Bernard Lyon 1, Lyon, France

Key Words

Pulmonary hypertension · Chronic obstructive pulmonary disease · Right heart catheterization · Echocardiography · Endothelin receptor antagonists · Phosphodiesterase-5 inhibitors

Abstract

Background: There is no recommendation for treating pulmonary hypertension (PH) when associated with chronic obstructive pulmonary disease (COPD). **Objective:** To evaluate the effect of PH-specific therapy in patients with COPD. **Methods:** All successive patients with severe PH [mean pulmonary arterial pressure (mPAP) ≥ 35 mm Hg] and COPD, who received specific PH medication and who underwent right heart catheterization at baseline and after 3–12 months of treatment, were analyzed from a prospective database. **Results:** Twenty-six patients were included with a median follow-up of 14 months. Mean forced expiratory volume in 1 s was $57 \pm 20\%$ of predicted, and mean forced expiratory

volume in 1 s/forced vital capacity was $47 \pm 12\%$. Dyspnea was New York Health Association classification stage (NYHA) II in 15%, NYHA III in 81% and NYHA IV in 4%. First-line treatments were endothelin receptor antagonists in 11 patients, phosphodiesterase-5 inhibitors in 11 patients, calcium blocker in 1 patient, combination therapy in 3 patients including 2 with a prostanoid. After 6 ± 3 months, pulmonary vascular resistance decreased from 8.5 ± 3 to 6.6 ± 2 Wood units ($p < 0.001$), with significant improvement of cardiac index from 2.44 ± 0.43 to 2.68 ± 0.63 liters $\times$ min $\times$ m⁻² ($p = 0.015$) and mPAP from 48 ± 9 to 42 ± 10 mm Hg ($p = 0.008$). There was no significant difference in dyspnea, 6-min walking distance, echocardiographic parameters or N-terminal pro-brain natriuretic peptide levels. There was no significant difference in arterial oxygen saturation after 3–12 months of treatment. **Conclusions:** Specific PH medications may improve hemodynamic parameters in COPD patients with severe PH. Appropriate prospective randomized studies are needed to evaluate the potential long-term clinical benefit of treatment.

© 2015 S. Karger AG, Basel

Introduction

Chronic obstructive pulmonary disease (COPD) is expected to be the 4th leading cause of death in the world in 2030 [1]. COPD can cause pulmonary hypertension (PH), especially in patients with hypoxemia, with the mean pulmonary arterial pressure (mPAP) slowly increasing over years [2], causing increased morbidity and mortality [3–5]. Thirty to 70% of patients with COPD have PH, depending on the PH definition and stage of disease [4, 6, 7], but only <5% of them have severe PH [6, 8], recently defined in the setting of chronic respiratory diseases by an mPAP ≥ 35 mm Hg and/or cardiac index (CI) < 2 liters $\times$ min $\times$ m² [9]. The pathophysiology of PH associated with COPD (COPD-PH) is not well established [10]. In the study by Chaouat et al. [8], severe PH was present in a subgroup of patients with mild airway obstruction and severe hypoxemia with very low diffusing capacity for carbon monoxide. Pulmonary artery vasoconstriction induced by alveolar hypoxia is considered to contribute to mild to moderate PH in COPD [11, 12], but cigarette smoke [13] and inflammation (i.e. IL-6) [14] may also play a role. Pulmonary arterial remodeling may be involved especially in severe PH [15]. Endothelin-1 plasma levels are elevated, and exhaled NO levels are decreased in COPD-PH as compared to COPD without PH and healthy controls [16]. Therefore, in addition to long-term supplemental oxygen therapy, which is the cornerstone of treatment in COPD-PH [17], recent studies have investigated specific PH medications in COPD [18–25], with various inclusion criteria [e.g. COPD with or without PH; PH diagnosed with echocardiography or with right heart catheterization (RHC)], and with conflicting results. Recent recommendations state that PH therapy is not indicated in the setting of COPD-PH, and advocate for studies to evaluate the potential benefit of therapy in patients with COPD and severe PH [9]. The aim of this study was to investigate whether specific PH therapy may improve hemodynamic or functional parameters in patients with COPD and severe PH.

Materials and Methods

Patients

From January 2006 to October 2012, data from all consecutive patients with COPD and severe PH seen at two referral centers (University Hospitals of Lyon and Rennes, France) were retrieved from the Registry of the French Network of Pulmonary Hypertension. It is a retrospective analysis of prospective registry data. All patients underwent an RHC. Precapillary PH was defined by mPAP ≥ 25 mm Hg with pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg [9]. Severe PH was defined by mPAP > 35

mm Hg and/or CI < 2 liters $\times$ min $\times$ m². The diagnosis of COPD was based on a smoking history ≥ 10 pack-years and a post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity < 0.7 [26]. All patients were receiving optimal treatment for COPD as per guidelines [26]. The study was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine – Société de Pneumologie de Langue Française (CEPRO).

Assessments

RHC was performed as described [27]. Cardiac output (CO) was measured with the standard thermodilution technique. A non-encouraged 6-min walk test was performed according to recommendations [28]. Echocardiography was performed with evaluation of estimated systolic right ventricular pressure based on right ventricular-atrial gradient, CO, CI, tricuspid annular plane systolic excursion and pericardial effusion. Right ventricular ejection fraction (RVEF) was measured using planar equilibrium radionuclide angiography, with intravenous injection of 925 MBq (25 mCi) of ^{99m}Tc-pertechnetate, following injection of 5 mg of stannous pyrophosphate for in vivo red blood cell labelling. Chronic thromboembolic PH was ruled out by V/Q scan and CT angiography. Treatment was left at the discretion of the physician, as per international and national guidelines [29, 30] and availability in France at the time of therapy initiation, allowing the individual use of PH-specific therapy in patients with COPD-severe PH, with severe exercise capacity and/or dyspnea considered to be related primarily to the pulmonary vascular disease, and with follow-up evaluation of the risk:benefit ratio. The choice of phosphodiesterase-5 inhibitors (PDE5i), endothelin receptor antagonists (ERA) and prostanoids as monotherapy or in combination was left to the treating physician of the PH center.

Statistical Analysis

SPSS 17.0 software (SPSS Inc., Chicago, Ill., USA) was used for all statistical analyses. Data were expressed as mean $\pm$ standard deviation. Characteristics of patients included and excluded were compared with a Fisher's exact test or a Mann-Whitney U test, as appropriate. Student's t test or Wilcoxon test for paired samples was used to compare quantitative variables before and after PH medication when appropriate. The McNemar test and sign test were used for the analysis of binary and ordinal variables, respectively.

Results

Baseline Characteristics

Out of 51 patients with COPD-PH, 26 patients met inclusion criteria and were included (fig. 1). The baseline characteristics of the 18 patients who could not be included in the analysis because of lack of adequate follow-up assessment were not significantly different from those of the population included in the study, although 6-min walking distance (6MWD) tended to be lower (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000431380).

Fig. 1. Flow chart describing patient inclusion.

The main baseline characteristics are listed in tables 1 and 2. Almost all patients were male (25 of 26), and 89% were ex-smokers. Most of the patients (85%) were New York Health Association classification stage (NYHA) III–IV. The mPAP was 48 ± 9 mm Hg with a mean PAWP of 10 ± 3 mm Hg, including 20 (77%) patients with mPAP ≥ 40 mm Hg and 16 patients (62%) with mPAP ≥ 45 mm Hg. Three patients were COPD GOLD 1, 14 were COPD GOLD 2, 6 were COPD GOLD 3 and 3 were COPD GOLD 4. All patients were receiving long-acting bronchodilators.

Two patients with emphysema had α_1 -antitrypsin (AAT) deficiency. One of them with an SZ protease inhibitor phenotype, AAT serum level of 0.28 g/l and FEV₁ of 1.05 l (30% of predicted) received AAT supplementation therapy. The other one, with a ZZ phenotype, AAT serum level of 0.40 g/l and FEV₁ of 0.86 l (26%) did not receive AAT supplementation therapy.

Hemodynamic Evaluation

The follow-up RHC performed 6 ± 3 months after the baseline initiation of therapy demonstrated a significant hemodynamic improvement (table 3). The pulmonary vascular resistance (PVR) decreased by 20% or more in 50% of the patients (fig. 2).

Noninvasive Evaluation

No significant difference was found in NYHA functional class. A nonsignificant numerical increase in 6MWD and a trend toward decrease in N-terminal pro-brain natriuretic peptide serum level were observed (table 4). There was no change in echocardiographic parameters. The RVEF measured by planar equilibrium radionuclide angiography significantly increased with therapy.

Respective Effect of Bosentan and Sildenafil

An exploratory analysis did not suggest any difference in treatment response between patients who received a PDE5i or an ERA as first-line PH therapy (online suppl. table 2).

Table 1. Baseline clinical and functional characteristics

Subjects	26
Male	25 (96)
Age, years	66±11
BMI	26±5
Smoking	
Ex-smoker	23 (89)
Current smoker	3 (11)
Tobacco pack-years	44±31
Comorbidities	
Ischemic heart disease	9 (35)
Pulmonary embolism	1 (4)
Sleep apnea syndrome	4 (15)
Diabetes	6 (23)
Dyspnea NYHA functional class	
I	0
II	4 (15)
III	21 (81)
IV	1 (4)
Chest pain	1 (4)
Syncope	0
Pulmonary functions	
FEV ₁ , l	1.65±0.64
FEV ₁ , % predicted	57±20
FEV ₁ /FVC, %	47±12
FVC, l	3.50±0.85
FVC, % predicted	90±20
TLC, l	6.72±1.68
TLC, % predicted	103±25
RV/TLC, %	50±18
RV/TLC, % predicted	112±31
DLco, %	29±16
6MWD, m	212±104
<i>First-line PH treatment after baseline evaluation</i>	
ERA	11 (42)
PDE5i	11 (42)
Combination therapy	3 (12)
ERA/PDE5i + prostanoid	2 (8)
ERA + PDE5i	1 (4)
Calcium blocker	1 (4)

Data are presented as mean ± SD, or n (%). BMI = Body mass index; FVC = forced vital capacity; TLC = total lung capacity; DLco = diffusing capacity of the lungs for carbon monoxide; RV = residual volume.

Table 3. Hemodynamic assessment (n = 26)

	Before treatment	After treatment	p
PVR, Wood units	8.5±3	6.6±2	<0.001
mPAP, mm Hg	48±9	42±10	0.008
CI, l × min ⁻¹ × m ⁻²	2.44±0.43	2.68±0.63	0.015
PAWP, mm Hg	9.7±2.8	9.4±2.9	0.68

Data are presented as mean ± SD.

Table 2. Baseline hemodynamics and noninvasive characteristics

Patients	26
Right heart catheterization	
Systolic PAP, mm Hg	76±14
Diastolic PAP, mm Hg	31±8
Mean PAP, mm Hg	48±9
PAWP, mm Hg	10±3
RAP, mm Hg	9±5
CO, l × min ⁻¹	4.6±0.98
CI, l × min × m ⁻²	2.43±0.42
PVR, Wood units	8.5±3.0
Echocardiography	
Estimated systolic PAP, mm Hg	64±17
TAPSE, mm	19±5
Pericardial effusion	4 (17)
CO, l × min ⁻¹	4.64±1.29
CI, l × min × m ⁻²	2.48±0.78
Biology	
NT-pro-BNP, ng × l ⁻¹	3,205±4,250
Planar radionuclide angiography	
RVEF, %	22±6

Data are presented as mean ± SD or n (%). RAP = Right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; NT-pro-BNP = N-terminal pro-brain natriuretic peptide.

Latest Assessment

Fifteen patients with severe PH at RHC had 2 follow-up assessments or more, with a mean overall follow-up of 18.9 ± 12.2 months from baseline to last RHC. A significant and consistent improvement was observed in PVR (p = 0.006) and in mPAP (p = 0.039) at the last evaluation visit as compared to baseline (table 5). The change in CI was only marginally significant between last evaluation and baseline. There was no improvement in NYHA functional class.

Arterial Oxygenation and Safety

Most of the patients were already on long-term nasal supplemental oxygen before initiation of PH treatment, and overall, oxygenation was not significantly altered by PH-specific therapy in the whole study population. In 2 of 26 patients who received an ERA, the treatment of PH had to be modified or discontinued because of worsening of dyspnea and arterial oxygenation. The arterial partial pressure of oxygen (PaO₂) was unchanged (from 7.68 ± 1.33 kPa at baseline to 8.05 ± 2.43 kPa at last visit, p = 0.98). The pulsed oxygen saturation (SpO₂) did not change significantly either (from 91.5 ± 3.1% at baseline to 92.4 ± 2.6% after the first evaluation, p = 0.06), with

Fig. 2. Evaluation of hemodynamic parameters before, after specific treatment at 6 ± 3 months ($n = 26$) and at the last assessment at 18.9 ± 12.2 months ($n = 15$).

overall no change in oxygen supplementation. Moreover, in a subgroup of 10 patients who were evaluated with the exact same level of oxygen supplementation before treatment initiation and at the first evaluation, SpO_2 increased significantly (from 91 ± 3.1 to $93 \pm 2.4\%$, $p = 0.01$) (fig. 3); among them, 5 patients were treated with a PDE5i, 3 with an ERA, 1 with a calcium blocker and 1 with a combination therapy. One patient developed cardiogenic shock while receiving combination therapy with an ERA and a PDE5i; this event was considered secondary to the underlying hemodynamic state and not to PH-specific therapy.

Discussion

In this exploratory study, we found that specific PH therapy improved hemodynamic parameters in patients with COPD and severe PH after a mean of 6 ± 3 months. However, no significant change was found in functional class or 6MWD, and therefore the potential clinical benefit of therapy was unclear. Treatment was associated with improvement in RVEF evaluated with radionuclide angiography; no significant changes in echocardiographic parameters were found. The tolerance of treatment was generally good, with worsening in oxygenation leading to treatment discontinuation in only 2 of 26 patients; however, additional long-term safety data need to be accumulated.

No benefit of PH therapy has been demonstrated in COPD patients, and specific PH therapy is therefore not recommended in subjects with PH associated with chronic respiratory disease [9]. Treatment is only considered on an individual basis in specialized centers, in the setting of clinical studies or registries, thereby prospectively accumulating knowledge about the potential effect of therapy. Patients in this study had severe dyspnea and limitation to exercise capacity, and all agreed to receive compassionate therapy despite being informed of absence of evidence for treatment efficacy in this setting and of the possibility of adverse events including worsening of oxygenation.

Because the limitation to exercise capacity in patients with COPD-PH is multifactorial [31], we anticipated that treating the pulmonary vascular component of disease may not significantly impact on functional class or 6MWD, and therefore we focused on the hemodynamic effect of therapy as a primary assessment. Furthermore, we studied a group of patients who fulfilled the recent definition of severe PH associated with COPD as proposed by the World Symposium on PH [9], with an mPAP

Table 4. Noninvasive assessment

	Patients	Before treatment	After treatment	p
Dyspnea NYHA functional class	26			0.344
I		0	0	
II		4 (15)	9 (35)	
III		21 (81)	15 (58)	
IV		1 (4)	2 (8)	
6MWD, m	19	234±92	276±108	0.078
NT-pro-BNP, ng × l ⁻¹	15	3,722±4,494	2,270±3,019	0.078
Estimated systolic PAP, mm Hg	15	64±16	67±16	0.62
CO, l × min ⁻¹	10	4.68±1.58	5±1.34	0.481
CI, l × min ⁻¹ × m ⁻²	10	2.53±1.00	2.65±0.73	0.611
TAPSE, mm	13	20±5.0	20±4.8	0.847
Pericardial effusion	21	4 (15)	6 (23)	1
RVEF, %	13	23±7	28±7	0.033

Data are presented as mean ± SD or n (%). TAPSE = Tricuspid annular plane systolic excursion; NT-pro-BNP = N-terminal pro-brain natriuretic peptide.

Table 5. Efficacy of PH medication at the last assessment

	Patients	Before	Last assessment	p
Hemodynamic parameters	15			
PVR, Wood units		9.4±3.3	6.6±2.8	0.006
Mean PAP, mm Hg		50.7±10.3	43.1±12.7	0.039
CI, l × min ⁻¹ × m ⁻²		2.4±0.4	2.72±0.52	0.064
Dyspnea NYHA functional class	15			0.219
I		0	0	
II		3 (20)	3 (20)	
III		12 (80)	8 (53)	
IV		0	4 (27)	
6MWD, m	8	226±118	246±135	>0.05
Echocardiographic parameters				
Estimated systolic PAP, mm Hg	6	68.7± 16.0	68.8±26.3	>0.05
CO, l × min ⁻¹	8	5.1±1.6	4.7±1.1	>0.05
CI, l × min ⁻¹ × m ⁻²	8	2.8±0.9	2.6±0.6	>0.05
TAPSE, mm	6	19.8±6.5	19.0±6.1	>0.05
Pericardial effusion	9	4 (15.4)	1 (3.8)	>0.05
Blood test				
NT-pro-BNP, ng × l ⁻¹	8	5,192±5,643	3,306±3,118	>0.05
Planar radionuclide angiography				
RVEF, %	6	24.7±5.4	32.3±12.1	>0.05

Data are presented as mean ± SD or n (%). TAPSE = Tricuspid annular plane systolic excursion; NT-pro-BNP = N-terminal pro-brain natriuretic peptide.

≥35 mm Hg and/or CI ≤2 liters/min/m², reasoning that vascular disease may be prominent in such patient population. COPD was generally of moderate severity in our study population, with a mean FEV₁ of 57% of predicted, contrasting with a mean diffusing capacity of only 29% of

predicted. Therefore, patients in the present study corresponded to those described by Chaouat et al. [8] as having COPD with disproportionate precapillary PH, who have severe PH, and milder obstructive ventilator pattern and shorter survival as compared to those with COPD and no

Fig. 3. Effects of specific PH therapy on oxygenation at 6 ± 3 months. **a** PaO₂ in 26 patients, who generally remained on similar levels of supplemental oxygen. **b** Arterial oxygen saturation (SpO₂) in the same 26 patients. **c** SpO₂ in a subgroup of 10 patients who were evaluated with the exact same level of oxygen supplementation before treatment initiation and at the last evaluation.

PH or mild PH. Patients in our series did not have chronic hypoventilation, which when present should be the main objective of management, even in the presence of severe PH [32, 33]. None of the patients had endoscopic lung volume reduction, which may improve hemodynamic parameters in patients with severe emphysema and PH [34].

PH-specific therapy was followed by significant improvement in hemodynamic parameters that persisted at the last assessment after a mean of 18.9 ± 12.2 months from baseline (i.e. diagnosis of severe precapillary PH and initiation of therapy). Although no significant improvement was demonstrated in clinical, functional or echocardiographic parameters, RVEF significantly improved with therapy, and a trend was observed toward greater 6MWD (234 ± 92 to 276 ± 108 m, $p = 0.078$), suggesting that PH treatment may at least not be detrimental in COPD with severe PH.

Our results compare rather favorably to recent data from another prospective registry [25], in which 43 patients with COPD-PH received a PDE5i ($n = 31$), an ERA ($n = 10$), or a prostanoid ($n = 2$) as compassionate therapy. Objective improvement defined by a decrease in functional class or a 20% decrease in PVR was observed in 3 and 4 patients, respectively; however, follow-up RHC was performed in only 7 of 43 patients, limiting the interpretation of hemodynamics. PH treatment was not associated with a survival benefit. We hypothesize that the more striking hemodynamic response observed in our study may be related to the severity of PH in all patients.

Data regarding PH therapy in COPD-PH are scarce. In another nonrandomized study of patients with COPD-PH [19], bosentan therapy was followed by significant

improvement in hemodynamics and 6MWD, with especially favorable effect in those with COPD stage GOLD III or IV. Benefit from PH therapy has been reported in isolated cases [35–37]; however, initiation of therapy was sometimes concomitant with supplemental oxygen supplementation, limiting interpretation of data. The short-term use of sildenafil [20–22] or inhaled iloprost [24] were found to improve hemodynamics; however, with unclear clinical benefit. In a randomized controlled trial, treatment with sildenafil did not improve the outcome of a rehabilitation program in COPD patients with moderately increased pulmonary pressures [38].

The risk of worsening oxygenation is considered a limitation to the use of PH-specific therapy in patients with COPD [9]. In one study of patients with severe COPD and without severe PH at rest, the oral administration of the ERA bosentan for 12 weeks resulted in deterioration of hypoxemia [18]. In another study of patients with COPD and moderately severe PH, an acute challenge with the PDE5i sildenafil impaired arterial oxygenation through inhibition of hypoxic vasoconstriction, despite hemodynamic improvement [21]. A less detrimental effect on oxygenation may be obtained with aerosolized iloprost [24]; however, no data are available regarding the clinical benefit of prolonged treatment. Worsening of oxygenation led to treatment discontinuation in only 2 of our 26 patients, and assessment of changes in PaO₂ and SaO₂ in the whole group did not demonstrate any significant difference (with a trend toward improved oxygenation in those who were assessed with identical conditions of supplemental oxygen therapy). We speculate that PH-specific therapy may result in different consequences on oxygenation according to the presence and severity of

PH. Consistent with this hypothesis, a recent systematic review of PH-specific therapy in COPD patients found no significant change in oxygenation in patients with COPD who received PH therapy, with improvement in exercise capacity observed only in subjects with COPD-PH [39].

Limitations to this study include the nonrandomized design and the small sample size related to the rarity of COPD with severe PH [8] and to the relatively stringent inclusion criteria (e.g. repeated RHC following PH-specific therapy). Only patients with follow-up RHC were included; however, excluded cases did not differ at baseline from those included in the study. A thorough exploration of exercise physiology evaluating the ventilatory and the circulatory reserves, which could potentially contribute to identify subjects with limitation to exercise capacity mostly due to PH [31], was not performed. Although patients were prospectively included in the French PH registry, the present exploratory analysis was not an open-label clinical trial, therefore with missing data, absence of power calculation and some degree of heterogeneity regarding the drug used and management in oxygen supplementation. Potential differences in the risk:benefit ratio when using ERAs or PDE5i in this patient population and patient-related outcome parameters could not be evaluated. A potential effect on survival could not be evaluated. A detailed evaluation of ventilation-perfusion mismatch was not performed, and further studies are needed to evaluate the tolerability of PH-specific therapy in this patient population. It is conceivable that presence of COPD may have caused difficulties in acquiring reliable echocardiographic parameters [40], whereas radionuclide measurement of RVEF better evaluated the improvement in right ventricular function.

In conclusion, the present study suggests that PH-specific therapy may improve hemodynamics in patients with

COPD and severe PH, and challenges existing data that it may worsen oxygenation in a majority of patients. In the absence of proven benefit, expensive PH-specific therapy cannot be recommended. This study further supports that prospective placebo-controlled randomized studies are warranted to evaluate the potential clinical benefit and tolerance of PH-specific therapy in patients with COPD-PH and especially severe PH, with particular emphasis on oxygenation, quality of life and long-term outcome.

Acknowledgements

The authors wish to thank Prof. G. Simonneau, Prof. M. Humbert and Prof. O. Sitbon (Paris, France), who coordinate the French PH registry; Prof. J.F. Mornex (Lyon, France) for fruitful discussions and clinical care; Mrs. S. Zeghmar (Lyon, France) and L. Rotat (Paris, France) for data extraction. This study was funded by PHRC national 2009.

Disclosure Statement

Dr. Girard reports nonfinancial support from Mundipharma, nonfinancial support from Novartis, nonfinancial support from Pfizer while conducting the study. Dr. Jouneau has nothing to disclose. Dr. Chabanne has nothing to disclose. Dr. Khouatra has nothing to disclose. Dr. Lannes has nothing to disclose. Dr. Traclet has nothing to disclose. Dr. Turquier has nothing to disclose. Dr. Delaval has nothing to disclose. Dr. Cordier reports personal fees from Boehringer Ingelheim, personal fees from Intermune, personal fees from Actelion, personal fees from Pfizer, personal fees from GSK, outside the submitted work. Dr. Cottin reports personal fees from Actelion, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Gilead, personal fees from GSK, personal fees from Intermune, personal fees from Novartis, personal fees from Roche, personal fees from Sanofi, outside the submitted work; Dr. Cottin's wife is an employee of Sanofi Pasteur.

References

- 1 Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
- 2 Weitzenblum E, Loiseau A, Hirth C, Mirhom R, Rasaholinjanahary J: Course of pulmonary hemodynamics in patients with chronic obstructive pulmonary disease. *Chest* 1979;75:656–662.
- 3 Weitzenblum E, Hirth C, Ducolone A, Mirhom R, Rasaholinjanahary J, Ehrhart M: Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981;36:752–758.
- 4 Andersen KH, Iversen M, Kjaergaard J, Mortensen J, Nielsen-Kudsk JE, Bendstrup E, Videbaek R, Carlsen J: Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2012;31:373–380.
- 5 Oswald-Mammoser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, Kessler R: Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest* 1995;107:1193–1198.
- 6 Thabut G, Dauriat G, Stern JB, Logeart D, Levy A, Marrash-Chahla R, Mal H: Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 2005;127:1531–1536.
- 7 Cuttica MJ, Kalhan R, Shlobin OA, Ahmad S, Gladwin M, Machado RF, Barnett SD, Nathan SD: Categorization and impact of pulmonary hypertension in patients with advanced COPD. *Respir Med* 2010;104:1877–1882.

- 8 Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, Ehrhart M, Kessler R, Weitzenblum E: Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:189–194.
- 9 Seeger W, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galie N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiery JL: Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013;62:D109–D116.
- 10 Chaouat A, Naeije R, Weitzenblum E: Pulmonary hypertension in COPD. *Eur Respir J* 2008;32:1371–1385.
- 11 Timms RM, Khaja FU, Williams GW: Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Ann Intern Med* 1985;102:29–36.
- 12 Skjorten I, Hilde JM, Melsom MN, Hansteen V, Steine K, Humerfelt S: Pulmonary artery pressure and PaO₂ in chronic obstructive pulmonary disease. *Respir Med* 2013;107:1271–1279.
- 13 Keusch S, Hildenbrand FF, Bollmann T, Halank M, Held M, Kaiser R, Kovacs G, Lange TJ, Seyfarth HJ, Speich R, Ulrich S: Tobacco smoke exposure in pulmonary arterial and thromboembolic pulmonary hypertension. *Respiration* 2014;88:38–45.
- 14 Chaouat A, Savale L, Chouaid C, Tu L, Sztrymf B, Canuet M, Maitre B, Housset B, Brandt C, Le Corvoisier P, Weitzenblum E, Eddahibi S, Adnot S: Role for interleukin-6 in COPD-related pulmonary hypertension. *Chest* 2009;136:678–687.
- 15 Carlsen J, Hasseriis Andersen K, Boesgaard S, Iversen M, Steinbruchel D, Bogelund Andersen C: Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2013;32:347–354.
- 16 Carratu P, Scoditti C, Maniscalco M, Seccia TM, Di Gioia G, Gadaleta F, Cardone RA, Dragonieri S, Pierucci P, Spanevello A, Resta O: Exhaled and arterial levels of endothelin-1 are increased and correlate with pulmonary systolic pressure in COPD with pulmonary hypertension. *BMC Pulm Med* 2008;8:20.
- 17 Zielinski J, Tobiasz M, Hawrylkiewicz I, Sliwinski P, Palasiewicz G: Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. *Chest* 1998;113:65–70.
- 18 Stolz D, Rasch H, Linka A, Di Valentino M, Meyer A, Brutsche M, Tamm M: A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J* 2008;32:619–628.
- 19 Valerio G, Bracciale P, Grazia D'Agostino A: Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2009;3:15–21.
- 20 Rietema H, Holverda S, Bogaard HJ, Marcus JT, Smit HJ, Westerhof N, Postmus PE, Boonstra A, Vonk-Noordegraaf A: Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J* 2008;31:759–764.
- 21 Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodriguez-Roisin R, Roca J, Barbera JA: Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med* 2010;181:270–278.
- 22 Lederer DJ, Bartels MN, Schluger NW, Brogan F, Jellen P, Thomashow BM, Kawut SM: Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. *COPD* 2012;9:268–275.
- 23 Dernaika TA, Beavin M, Kinasewitz GT: Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. *Respiration* 2010;79:377–382.
- 24 Boeck L, Tamm M, Grendelmeier P, Stolz D: Acute effects of aerosolized iloprost in COPD related pulmonary hypertension – a randomized controlled crossover trial. *PLoS One* 2012;7:e52248.
- 25 Hurdman J, Condliffe R, Elliot CA, Swift A, Rajaram S, Davies C, Hill C, Hamilton N, Armstrong IJ, Billings C, Pollard L, Wild JM, Lawrie A, Lawson R, Sabroe I, Kiely DG: Pulmonary hypertension in COPD: results from the ASPIRE registry. *Eur Respir J* 2013;41:1292–1301.
- 26 Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347–365.
- 27 Sitbon O, Humbert M, Jais X, Ios V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G: Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005;111:3105–3111.
- 28 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
- 29 Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43–S54.
- 30 Sitbon O, Humbert M, Simonneau G: Treatment for pulmonary arterial hypertension under the new French hospital financing system. Recommendations of the Pulmonary Vascular Diseases Working Group of the French Society of Pulmonary Medicine. *Presse Med* 2005;34:1456–1464.
- 31 Boerrigter BG, Bogaard HJ, Trip P, Groepenhoff H, Rietema H, Holverda S, Boonstra A, Postmus PE, Westerhof N, Vonk-Noordegraaf A: Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. *Chest* 2012;142:1166–1174.
- 32 Held M, Walthelm J, Baron S, Roth C, Jany B: Functional impact of pulmonary hypertension due to hypoventilation and changes under noninvasive ventilation. *Eur Respir J* 2014;43:156–165.
- 33 Cottin V, Lorillou M, Khouatra C, Traclet J, Nesme P, Cordier JF: Pulmonary hypertension specific therapy in patients with chronic respiratory insufficiency. *Eur Respir J* 2014;44:821–822.
- 34 Kontogianni K, Gerovasili V, Gompelmann D, Schuhmann M, Heussel CP, Herth FJ, Eberhardt R: Effectiveness of endobronchial coil treatment for lung volume reduction in patients with severe heterogeneous emphysema and bilateral incomplete fissures: a six-month follow-up. *Respiration* 2014;88:52–60.
- 35 Hegewald MJ, Elliott CG: Sustained improvement with iloprost in a COPD patient with severe pulmonary hypertension. *Chest* 2009;135:536–537.
- 36 Lasota B, Skoczynski S, Mizia-Stec K, Pierzchala W: The use of iloprost in the treatment of 'out of proportion' pulmonary hypertension in chronic obstructive pulmonary disease. *Int J Clin Pharm* 2013;35:313–315.
- 37 Cottin V, Khouatra C, Lazor R, Canu P, Cordier JF: Pulmonary hypertension therapy and COPD: still many questions to be answered. *Eur Respir J* 2009;33:450–452, author reply 2–3.
- 38 Blanco I, Santos S, Gea J, Guell R, Torres F, Gimeno-Santos E, Rodriguez DA, Vilaro J, Gomez B, Roca J, Barbera JA: Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. *Eur Respir J* 2013;42:982–992.
- 39 Park J, Song JH, Park DA, Lee JS, Lee SD, Oh YM: Systematic review and meta-analysis of pulmonary hypertension specific therapy for exercise capacity in chronic obstructive pulmonary disease. *J Korean Med Sci* 2013;28:1200–1206.
- 40 Andersen CU, Mellekjaer S, Nielsen-Kudsk JE, Sonderskov LD, Laursen BE, Simonsen U, Hilberg O: Echocardiographic screening for pulmonary hypertension in stable COPD outpatients and NT-proBNP as a rule-out test. *COPD* 2012;9:505–512.