CHEST

# Pulmonary Hypertension in Patients With COPD

## Results From the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)

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**BACKGROUND:** Pulmonary hypertension (PH) in COPD is a poorly investigated clinical condition.

**RESEARCH QUESTION:** Which factors determine the outcome of PH in COPD?

**STUDY DESIGN AND METHODS:** We analyzed the characteristics and outcome of patients enrolled in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) with moderate or severe PH in COPD as defined during the 6th PH World Symposium who received medical therapy for PH and compared them with patients with idiopathic pulmonary arterial hypertension (IPAH).

**RESULTS:** The population included incident patients with moderate PH in COPD (n = 68), with severe PH in COPD (n = 307), and with IPAH (n = 489). Patients with PH in COPD were older, predominantly male, and treated mainly with phosphodiesterase-5 inhibitors. Despite similar hemodynamic impairment, patients with PH in COPD achieved a worse 6-min walking distance (6MWD) and showed a more advanced World Health Organization functional class (WHO FC). Transplant-free survival rates at 1, 3, and 5 years were higher in the IPAH group than in the PH in COPD group (IPAH: 94%, 75%, and 55% vs PH in COPD: 86%, 55%, and 38%; $P = .004$). Risk factors for poor outcomes in PH in COPD were male sex, low 6MWD, and high pulmonary vascular resistance (PVR). In patients with severe PH in COPD, improvements in 6MWD by ≥ 30 m or improvements in WHO FC after initiation of medical therapy were associated with better outcomes.

**INTERPRETATION:** Patients with PH in COPD were functionally more impaired and had a poorer outcome than patients with IPAH. Predictors of death in the PH in COPD group were sex, 6MWD, and PVR. Our data raise the hypothesis that some patients with severe PH in COPD may benefit from PH treatment. Randomized controlled studies are necessary to explore this hypothesis further.

**TRIAL REGISTRY:** ClinicalTrials.gov; No.: NCT01347216; URL: www.clinicaltrials.gov

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**KEY WORDS:** COPD; pulmonary hypertension; survival; treatment

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**ABBREVIATIONS:** 6MWD = 6-min walking distance; BNP = brain natriuretic peptide; COMPERA = Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; $D_{LCO}$ = diffusing capacity of the lung for carbon monoxide; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PDE5-i = phosphodiesterase-5 inhibitor; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WHO FC = World Health Organization functional class

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Pulmonary hypertension (PH) is a frequent finding in advanced COPD; its prevalence in selected populations (candidates for lung transplantation or volume reduction surgery) is around 50%.[1-4] In these patients, PH is usually mild to moderate, as defined by a mean pulmonary arterial pressure (mPAP) of 21 to 34 mm Hg, but about 6% to 8% of these patients demonstrate severe PH (mPAP $\geq$ 35 mm Hg or mPAP $\geq$ 25 mm Hg in the presence of low cardiac output).[5] The clinical importance of PH associated with COPD has been documented in several studies that demonstrated the independent prognostic role of PH in this population.[3,6-8]

It is unclear whether patients with PH in COPD may benefit from treating the pulmonary vascular disease component. So far, only small randomized controlled studies have been performed using targeted therapies approved for pulmonary arterial hypertension (PAH) in PH in COPD, with heterogeneous results.[9-12] The main limitations of most of these studies include lack of power and poor selection of the populations studied (ie, patients with COPD and normal or mildly elevated pulmonary pressure). Although the role of PH therapy in patients with PH in COPD remains undefined, PAH therapies sometimes are used in these patients.[13]

To obtain more information on the population with PH in COPD, we analyzed data from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), an ongoing, investigator-initiated, noninterventional, prospective European-based registry that enrolls patients with all forms of PH.[14] The aim of the present study was to describe the clinical characteristics and outcomes of a large population of patients with PH in COPD treated with targeted therapy (1) to compare the outcomes of these patients with a population with idiopathic PAH (IPAH), (2) to study the factors predicting survival in patients with PH in COPD, (3) to compare patients with moderate and severe PH in COPD based on the latest recommendations from the 6th PH World Symposium, and (4) to describe the response to PH-targeted therapy.

## Take-home Points

**Research Question:** Which are the clinical characteristics of PH in COPD patients and what are their impacts on outcome?

**Results:** Compared with patients with IPAH, patients with PH in COPD have similar hemodynamic impairment but worse effort capacity and survival. Risk factors for death in PH in COPD are male sex, high age, low 6MWD, and high PVR. In patients with severe PH in COPD (mPAP $\geq$ 35 mm Hg), improvements in 6MWD by $\geq$ 30 m or improvements in WHO FC after initiation of medical therapy are associated with better survival.

**Interpretation:** Patients with PH in COPD have a poorer prognosis than patients with IPAH. Predictors of death in patients with PH in COPD are related to sex, age, effort capacity, and pulmonary vascular impairment. Some patients with severe PH in COPD may benefit from PH treatment. Randomized controlled studies are necessary to explore this hypothesis further.

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## Methods

### Setting and Participants

COMPERA is a PH registry that was launched in July 2007 and continues to enroll patients (www.clinicaltrials.gov Identifier: NCT01347216). Currently, 62 PH centers from 12 countries (Austria, Belgium, Germany, Greece, Hungary, Italy, Latvia, Lithuania, The Netherlands, Slovakia, Switzerland, and the United Kingdom) participate, with 84% of the patients coming from German centers. Documentation is internet based and includes demographics (age, sex), height and weight, type of PH according to the Dana Point classification,[15] date of the initial cardiac catheterization, World Health Organization functional class (WHO FC), 6-min walking distance (6MWD), hemodynamics, pulmonary function and blood gases, selected laboratory variables, including N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) and detailed information about medications for PH. The participating centers enter all of their eligible patients on a consecutive basis. Data are collected at the time of diagnosis (baseline) and at least in 6-month intervals or whenever the patient has a predefined clinical event (death, lung transplantation, PH-related hospitalization, deterioration in functional class, any unscheduled change in PH therapy, or other serious adverse events). Out-of-range data or missing values are queried automatically during data entry. As of July 2020, source data had been monitored randomly onsite in 44 of 62 participating centers (71%). The cutoff date for the present analysis was August 1, 2020; at that time, 10,165 patients had been enrolled into the database.

Inclusion criteria for the present analysis were a diagnosis of IPAH or PH in COPD, age of $\geq$ 18 years, and availability of data from right heart catheterization at diagnosis showing mPAP of $>$ 20 mm Hg and mean pulmonary arterial wedge pressure of $\leq$ 15 mm Hg, and, for IPAH, pulmonary vascular resistance (PVR) of $>$ 3 Wood units. Patients were incident cases, that is, the PH diagnosis had been made $\leq$ 6 months before inclusion. The diagnosis of IPAH or PH in COPD was made in each center in accordance with the European Respiratory Society and European Society of Cardiology guidelines[15] and the 6th World Symposium on Pulmonary Hypertension recommendations.[16] Patients with PH in COPD were included based on the investigator-based diagnosis and a postbronchodilator $FEV_1$ of $\leq$ 0.7 of the predicted value.

According to the 6th World Symposium on Pulmonary Hypertension recommendations,[5] the COPD population was divided in two groups based on hemodynamics at diagnosis: (1) moderate PH in COPD, defined as mPAP of 25 to 34 mm Hg or mPAP of 21 to 24 mm Hg with PVR of $\geq$ 3 Wood units; (2) and severe PH in COPD, defined as mPAP of $>$ 35 mm Hg or mPAP of $\geq$ 25 mm Hg with low cardiac index ($<$ 2.0 L/min/m$^2$)

The registry was approved by the institutional review boards of all contributing centers and written informed consent was obtained from all participating patients before start of documentation. Guidelines on good pharmacoepidemiologic practice (GPP) and data protection guidelines are followed. Study details may be seen at www.COMPERA.org. COMPERA is registered at ClinicalTrials.gov (Identifier: NCT01347216).

### Definition of Therapeutic Response

To assess the impact of PH therapy, we evaluated the clinical response from baseline to the first follow-up (after 6 $\pm$ 3 months of therapy). Clinical improvement was defined arbitrarily by an increase in 6MWD of $\geq$ 30 m[17] or an improvement in WHO FC.

### Statistical Analysis

Categorical data were displayed as number of patients and respective relative frequency (percentage) and were compared with the $\chi^2$ test or Fisher exact test, respectively. For continuous data, normally distributed data were displayed as mean $\pm$ SD; otherwise, median and interquartile range were shown. Group differences for normally distributed data were tested with a two-sided *t* test; otherwise, a two sided Mann-Whitney *U* test was used. The primary outcome was transplant-free survival, which was compared using Kaplan-Meier estimates and the Breslow test. Patients with more than 5 years of follow-up were censored after 60 months. Survival was ascertained by patient visits to the centers or—if that was not possible—by phone calls to the patients, their relatives, or their local physicians. A sensitivity analysis was performed with censoring patients at the time of treatment discontinuation. Patients lost to follow-up were censored at the time of the last visit. To identify predictors of death or transplantation, single-variable Cox regression analyses were followed by multivariate Cox regression analysis. Baseline variables preselected based on clinical reasoning and previous studies were age, BMI, sex, 6MWD, mPAP, right atrial pressure, cardiac index, PVR, $FEV_1$, diffusing capacity of the lung for carbon monoxide ($D_{LCO}$), NT-proBNP (log10 transformed), and WHO FC. As a result of left truncation, mPAP was considered only as a dichotomized variable ($<$ 35 mm Hg vs $\geq$ 35 mm Hg). Because of a high number of missing and imputed values, $D_{LCO}$ and NT-proBNP were not included in the multivariate model. Multiple imputation with 10 runs was applied to missing values at baseline, and results of both the original data and pooled results of the imputed data are shown. P values $<$ .05 were considered significant; no adjustment was made for multiple testing.

## Results

After applying the inclusion and exclusion criteria, 489 patients with IPAH, 307 patients with severe PH in COPD, and 68 patients with moderate PH in COPD were eligible for this analysis (Fig 1). Table 1 summarizes the clinical and hemodynamic characteristics of the populations. Overall, patients with PH in COPD predominantly were male and older than patients with IPAH. Compared with patients with IPAH, patients with PH in COPD showed more severe airflow obstruction, lower $D_{LCO}$, lower $Pa_{O_2}$, and higher $Pa_{CO_2}$. Furthermore, patients with PH in COPD, particularly patients with severe PH in COPD, demonstrated worse 6MWD and more advanced functional class. Patients with severe PH in COPD showed hemodynamic impairment similar to that of patients with IPAH, whereas patients with moderate PH in COPD showed—per definition—lower mPAP, PVR, and preserved cardiac index.

Table 2 summarizes the use of PH drugs at baseline: most of the patients with PH in COPD initially were treated with oral monotherapy (mainly phosphodiesterase-5 inhibitors [PDE-5i]) whereas in

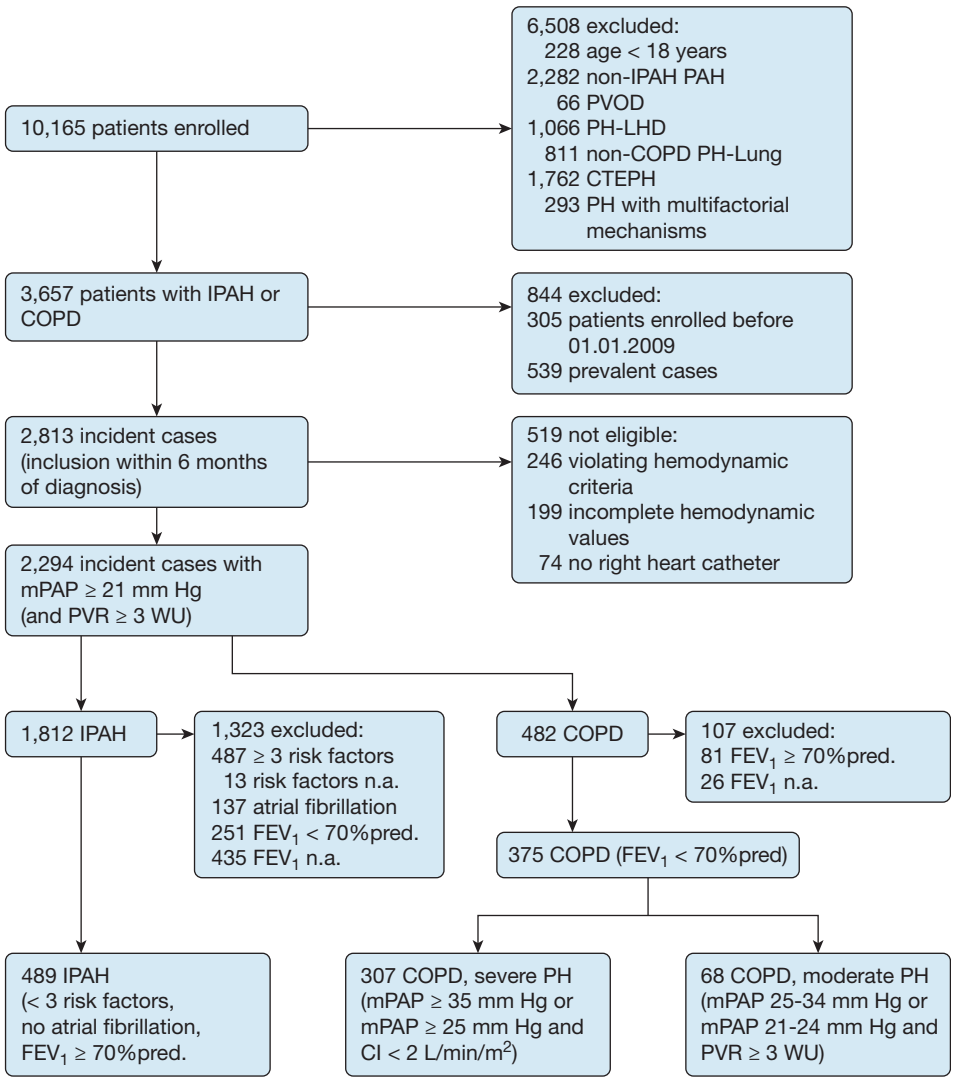


Figure 1 – *Flow chart showing patient selection from the COMPERA database. CI = cardiac index; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; LHD = left heart disease; mPAP = mean pulmonary arterial pressure; n.a. = not assessed; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVOD = pulmonary venoocclusive disease; PVR = pulmonary vascular resistance; WU = Wood units.*

patients with IPAH, monotherapy was less common, with a higher proportion of patients receiving endothelin receptor antagonists.

Treatment discontinuations were more frequent in the moderate PH in COPD group (7/64 [10.9%]) than in the IPAH group (27/410 [6.6%]) and the severe PH in COPD group (15/288 [5.2%]). In patients with IPAH, 63% of discontinuations were the result of lack of tolerability and 7% were the result of efficacy failure; in patients with severe PH in COPD, lack of tolerability and efficacy failure accounted for 47% and 47%, respectively, of drug discontinuations. In patients with moderate PH in COPD, the respective numbers were 29% and 57%.

### *Transplant-Free Survival*

At least one follow-up documentation was available for 410 patients with IPAH (84%) and 352 patients (288 with severe PH and 64 with moderate PH) with PH in COPD (94%). During follow-up, 102 deaths (24.9%) and six lung transplantations (1.5%) occurred in the IPAH group and 161 deaths (45.7%) and four lung transplantations (1.1%) occurred in the PH in COPD group. In the severe PH in COPD group, 141 deaths (49.0%) and four lung transplantations (1.4%) occurred. In the moderate PH in COPD group, 20 deaths (31.3%) and no lung transplantations occurred. Estimated transplant-free survival probabilities at 1, 3, and 5 years in the IPAH group were 94%, 74%, and 57%, which was

**TABLE 1** ] Demographic and Baseline Characteristics of the Patients in the Study

| Characteristic | IPAH (n = 489) | COPD (n = 375) | *P* Value | PH in COPD | | *P* Value |
|---|---|---|---|---|---|---|
| | | | | Moderate (n = 68) | Severe (n = 307) | |
| Female sex | 308 (63) | 153 (41) | < .001 | 34 (50) | 119 (39) | .102 |
| Age, y | 61.7 ± 17.9 | 68.4 ± 9.2 | < .001 | 68.5 ± 8.4 | 68.4 ± 9.3 | .96 |
| 6MWD, m | 326 ± 133 | 247 ± 110 | < .001 | 282 ± 111 | 239 ± 108 | .008 |
| BMI, kg/m$^2$ | 27.1 ± 5.9 | 26.2 ± 6.1 | .027 | 25.8 ± 5.6 | 26.2 ± 6.2 | .62 |
| WHO FC | … | … | < .001 | … | … | .002 |
| I | 1 (0.2) | 0 | … | 0 | 0 | … |
| II | 86 (18) | 10 (3) | … | 3 (4) | 7 (2) | … |
| III | 331 (68) | 260 (69) | … | 57 (84) | 203 (66) | … |
| IV | 43 (9) | 87 (23) | … | 5 (7) | 82 (27) | … |
| Unknown | 28 (6) | 18 (5) | … | 3 (4) | 15 (5) | … |
| Lung function tests | | | | | | |
| TLC, % predicted | 98 ± 16 | 107 ± 24 | < .001 | 108 ± 25 | 106 ± 24 | .66 |
| FVC, % predicted | 93 ± 16 | 67 ± 21 | < .001 | 69 ± 21 | 67 ± 21 | .64 |
| $FEV_1$, % predicted | 90 ± 15 | 45 ± 14 | < .001 | 46 ± 14 | 45 ± 14 | .60 |
| $D_{LCO}$, % predicted | 55 ± 22 | 30 ± 15 | < .001 | 31 ± 15 | 29 ± 15 | .41 |
| Arterial blood gases (room air values only) | | | | | | |
| $Pao_2$, mm Hg | 70 ± 26 | 55 ± 10 | < .001 | 55 ± 9 | 54 ± 10 | .65 |
| $Paco_2$, mm Hg | 33 ± 6 | 41 ± 9 | < .001 | 42 ± 8 | 41 ± 9 | .36 |
| Right heart catheter | | | | | | |
| RAP, mm Hg | 7.2 ± 4.3 | 7.7 ± 4.6 | .13 | 5.3 ± 3.6 | 8.3 ± 4.6 | < .001 |
| mPAP, mm Hg | 46 ± 13 | 40 ± 10 | < .001 | 30 ± 3 | 43 ± 10 | < .001 |
| PAWP, mm Hg | 8.7 ± 3.4 | 9.4 ± 3.3 | .001 | 8.4 ± 3.9 | 9.7 ± 3.2 | .018 |
| PVR, Wood units | 10.5 ± 5.4 | 7.7 ± 3.2 | < .001 | 5.1 ± 2.6 | 8.3 ± 3.0 | < .001 |
| Cardiac index, L/min/m$^2$ | 2.2 ± 0.6 | 2.3 ± 0.7 | .001 | 2.7 ± 0.5 | 2.3 ± 0.7 | < .001 |
| $SvO_2$, % | 63 ± 9 | 64 ± 8 | .036 | 68 ± 6 | 63 ± 9 | < .001 |
| Laboratory results | | | | | | |
| BNP, pg/mL | 299 (84-578) | 111 (39-311) | .004 | 60 (26-178) | 120 (44-489) | .023 |
| NT-proBNP, pg/mL | 1,263 (455-3,187) | 1,157 (378-2,830) | .31 | 487 (158-1,235) | 1,395 (454-3,043) | < .001 |

Data are presented as No (%), mean ± SD, or median (interquartile range), unless otherwise indicated. 6MWD = 6-min walking distance; BNP = brain natriuretic peptide; $D_{LCO}$ = diffusing capacity of the lung for carbon monoxide; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; $SvO_2$ = mixed venous oxygen saturation; TLC = total lung capacity; WHO FC = World Health Organization functional class.

**TABLE 2** ] PH Drug Treatment Within 3 Months After Diagnosis

| Therapy at Inclusion | IPAH (n = 489) | PH in COPD (n = 375) | *P* Value | PH in COPD | | *P* Value |
|---|---|---|---|---|---|---|
| | | | | Moderate (n = 68) | Severe (n = 307) | |
| ERA monotherapy | 52 (11) | 10 (3) | < .001 | 1 (2) | 9 (3) | .70 |
| PDE-5i monotherapy | 253 (52) | 346 (92) | < .001 | 62 (91) | 284 (93) | .80 |
| PCA monotherapy | 0 | 3 (1) | .081 | 1 (1) | 2 (1) | .45 |
| Other monotherapy[a] | 45 (9) | 3 (1) | < .001 | 0 | 3 (1) | 1.00 |
| ERA + PDE-5i | 92 (18) | 4 (1) | < .001 | 0 | 4 (1) | 1.00 |
| Other double-combination therapies | 29 (6) | 8 (2) | .006 | 3 (4) | 5 (2) | .16 |
| Triple-combination therapy | 18 (4) | 1 (0.3) | .001 | 1 (2) | 0 | .18 |

Data are presented as No. (%), unless otherwise indicated. ERA = endothelin-receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; PCA = prostacyclin analog; PDE-5i = phosphodiesterase-5 inhibitor; PH = pulmonary hypertension.
[a]Includes soluble guanylate cyclase stimulators (IPAH 2.7%, COPD 0.5%) and calcium channel blockers (IPAH 6.5%, COPD 0.3%).

significantly better than the respective transplant-free survival rates in the PH in COPD group (86%, 55%, and 38%; $P < .001$). The difference in transplant-free survival remained statistically significant when adjusted for age and sex ($P = .004$). When censoring patients who discontinued PH therapy, the results remained similar: survival rates at 1, 3, and 5 years were 95%, 75%, and 57% in the IPAH group and 86%, 56%, and 39% in the PH in COPD group, respectively ($P < .001$) (e-Fig 1). Comparing the transplant-free survival rates between the two PH in COPD groups, patients with severe PH in COPD experiences worse outcomes than patients with moderate PH in COPD, with estimated survival probabilities at 1, 3, and 5 years of 84%, 52%, and 36% compared with 95%, 68%, and 49%, respectively ($P = .009$) (Fig 2). These differences remained statistically significant when patients were censored at the time of treatment discontinuation: survival rates were 94%, 68%, and 47% in the moderate PH in COPD group and 84%, 53%, and 38% in the severe PH in COPD group, respectively ($P = .018$) (e-Fig 1).

In the univariate Cox regression analysis, baseline variables associated with transplantation or death in those with PH in COPD were higher age, low 6MWD, high mPAP, high PVR, and high NTpro-BNP (Table 3). In the multivariate approach, male sex, low 6MWD, and high PVR remained associated independently with transplant-free survival; however, sex and PVR were statistically significant only in the imputed multivariate model, not in the original multivariate model, the latter based on much smaller numbers of patients (Table 4).

### *Response to Therapy and Survival*

At follow-up, 6MWD was available in for 209 patients with IPAH (42.7%) and 160 patients with PH in COPD (42.7%). WHO FC assessment was collected for 285 patients with IPAH (58.3%) and for 246 patients with PH in COPD (65.6%). The frequency of 6MWD improvement of ≥ 30 m from baseline was similar in the PH in COPD group compared with the IPAH group (46.9% vs 52.6%; $P = .294$), with considerable differences between the severe PH in COPD group and the moderate PH in COPD group (51.6% vs 31.6%; $P = .04$). WHO FC improved by ≥ 1 class in 35.8% of patients with IPAH and in 28.5% of patients with PH in COPD ($P = .078$), with no difference based on traditional statistical thresholds in severe PH in COPD compared with moderate PH in COPD (30.4% vs 19.0%; $P = .188$).

Associated with a response to therapy in the PH in COPD group were a low 6MWD and a high WHO FC at baseline, whereas pulmonary function and hemodynamics did not differ between responders and nonresponders. In the IPAH group, younger age, higher $D_{LCO}$, higher mPAP, lower $PCO_2$, and higher WHO FC were associated with response to therapy (e-Table 1).

Stratifying the patients with PH in COPD based on clinical response at 6 months, we found that patients who met the criteria of a clinical improvement experienced a better transplant-free survival than patients who did not meet this criterion (Fig 3A). This observation was restricted to patients with severe PH in COPD (Fig 3B, 3C).

## Discussion

The present study describes the characteristics and outcome of patients with PH in COPD treated with medications approved for PAH. Our results show that patients with PH in COPD achieved a worse clinical

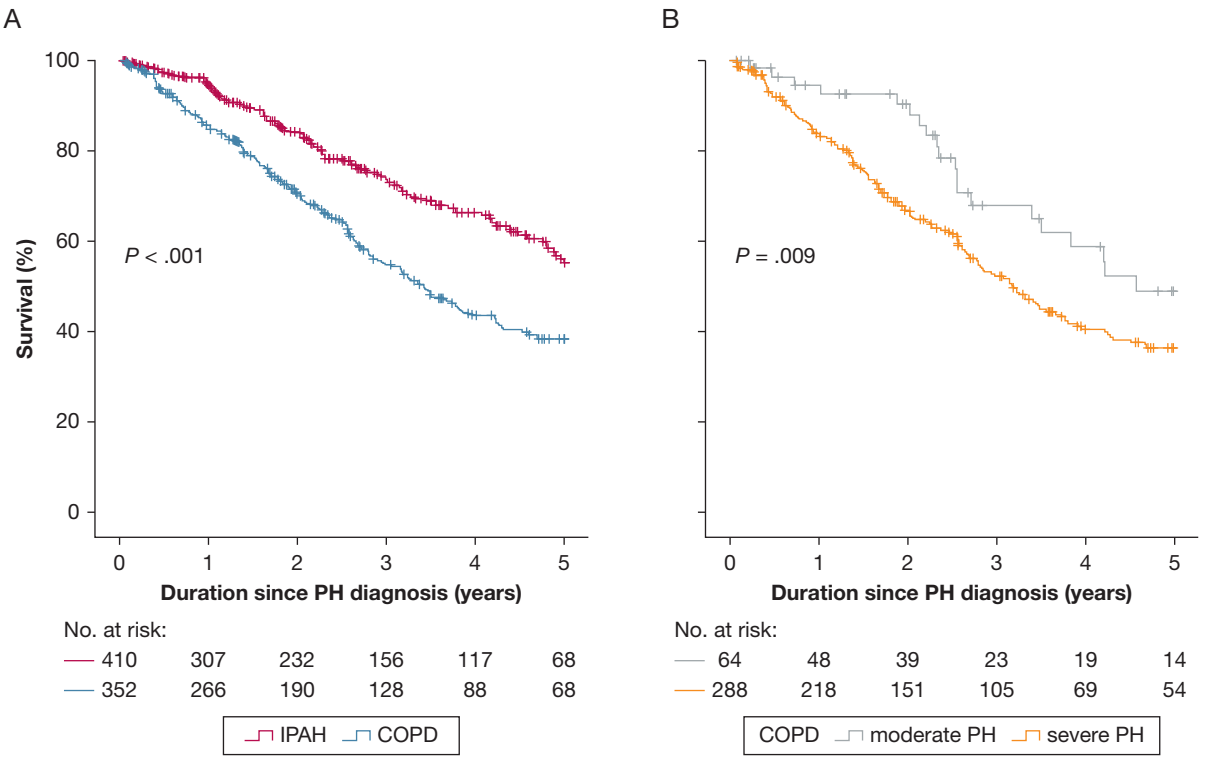


Figure 2 – *A, B, Kaplan-Meier plots showing 5-year survival free from lung transplantation of patients with IPAH and PH in COPD (A) and severe and moderate PH in COPD (B). IPAH = idiopathic pulmonary arterial hypertension; PH = pulmonary hypertension.*

status and a lower transplant-free survival than patients with IPAH, despite similar hemodynamic impairment. The risk of transplantation or death in patients with PH in COPD was not related to the degree of airflow obstruction, but rather to male sex, low 6MWD, and high PVR. Patients with severe PH in COPD achieved worse outcomes than patients with moderate PH in COPD, providing evidence that the distinction between moderate and severe PH in COPD, as proposed during the latest PH world symposium, has clinical relevance.[5] In addition, our data raise the possibility that some patients with severe PH in COPD may benefit from treatment with PAH medications.

The COPD population in the present series consisted mainly of patients with severe PH. The hemodynamic profile of these patients was similar to that of patients with IPAH. These findings suggest the presence of a severe pulmonary arteriopathy.[18]

Despite similar hemodynamic impairment, patients with severe PH in COPD showed a worse effort tolerance and worse prognosis than patients with IPAH, even when adjusted for age and sex. The mortality rate was around 12% per year in patients with severe PH in COPD, that is, about twice the observed mortality rate in the IPAH population. These findings are in line with previous observations.[13,19,20] It remains unclear whether the survival differences between these entities result from differences in the underlying diseases, comorbidities, or different treatment patterns.

These observations underscore the need for better treatment options in patients with PH in COPD. Drugs approved for the treatment of PAH have been explored in patients with PH in COPD, but with inconsistent and mostly negative results. Bosentan, an endothelin receptor antagonist, not only failed to improve exercise capacity, but also caused a deterioration in gas exchange and functional status in patients with advanced COPD and mild PH.[9] In a similar population, tadalafil, a PDE-5i, showed no effect on effort capacity and quality of life.[11] In a dose comparison study evaluating the acute hemodynamic effects of sildenafil, another PDE-5i, Blanco and colleagues[21] showed a significant reduction in mPAP at rest and during exercise with an impairment of gas exchange at rest, but not during exercise. In two other studies in patients with COPD with borderline or mild PH, sildenafil failed to demonstrate an improvement in effort capacity.[10,22,23]

**TABLE 3** ] Univariate Cox Regression Model of Predictors for Death or Lung Transplantation in the PH in COPD Cohort for the Original Data and the Multiple Imputed Dataset

| Variable | Original Data | | Pooled Imputed Dataset (n = 351[a]) | | Imputed Values |
|---|---|---|---|---|---|
| | Risk Ratio (95% CI) | *P* Value | Risk Ratio (95% CI) | *P* Value | |
| 6MWD, per 10 m | 0.97 (0.96-0.99) | < .001 | 0.97 (0.96-0.98) | < .001 | 22.4 |
| Age at inclusion, per 5 y | 1.11 (1.02-1.21) | .011 | 1.11 (1.02-1.21) | .011 | 0.0 |
| BMI, per 1 kg/m$^2$ | 0.97 (0.94-0.995) | .022 | 0.98 (0.96-1.01) | .165 | 8.5 |
| Cardiac index, per 0.5 L/min/m$^2$ | 0.89 (0.80-0.99) | .040 | 0.91 (0.82-1.01) | .075 | 7.4 |
| $D_{LCO}$, per 10% predicted | 0.88 (0.77-1.01) | .073 | 0.88 (0.78-1.00) | .055 | 38.9 |
| $FEV_1$, per 10% predicted | 0.98 (0.88-1.10) | .772 | 0.98 (0.88-1.10) | .772 | 0.0 |
| NT-proBNP, log10 transformed | 1.50 (1.09-2.06) | .012 | 1.37 (1.02-1.82) | .035 | 43.2 |
| WHO FC (reference, II) | | .207 | | | 4.5 |
| III | 1.84 (0.59-5.78) | .296 | 1.94 (0.61-6.21) | .262 | 4.5 |
| IV | 2.27 (0.71-7.24) | .166 | 2.46 (0.76-7.96) | .135 | 4.5 |
| PVR, per 1 Wood unit | 1.07 (1.03-1.11) | .001 | 1.07 (1.03-1.11) | .001 | 4.5 |
| RAP, per 3 mm Hg | 1.07 (0.98-1.17) | .108 | 1.07 (0.98-1.17) | .120 | 5.4 |
| mPAP ≥ 35 mm Hg | 1.39 (1.02-1.90) | .038 | 1.39 (1.02-1.90) | .038 | 0 |
| Male sex | 1.19 (0.89-1.58) | .236 | 1.19 (0.89-1.58) | .236 | 0 |

Data are presented as percentage, unless otherwise indicated. 6MWD = 6-min walking distance; $D_{LCO}$ = diffusing capacity of the lung for carbon monoxide; mPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; PVR = pulmonary vascular resistance; RAP = right atrial pressure; WHO FC = World Health Organization functional class.
[a]One patient was censored before the first event (death).

A main drawback of these studies is that most of the enrolled patients had mild or moderate PH. Thus, it may not be surprising that PH-targeted therapy did not result in improvement in hemodynamics or exercise capacity. In fact, in a study that included only patients with severe PH in COPD, sildenafil demonstrated significant improvements in hemodynamics and BMI, airflow obstruction, dyspnea, and exercise capacity in COPD index without significant deterioration in $Pa_{O_2}$ compared with placebo.[12]

In the present series, most of the patients in the PH in COPD cohort were treated with PDE5-i. After 6 months,

**TABLE 4** ] Multivariate Cox PH Regression Model of Predictors for Death or Lung Transplantation in the PH in COPD Cohort for the Original Data and the Multiple Imputed Data Set

| Variable | Original Data (n = 211) | | Pooled Imputed (n = 351[a]) | |
|---|---|---|---|---|
| | Risk Ratio (95% CI) | *P* Value | Risk Ratio (95% CI) | *P* Value |
| 6MWD, per 10 m | 0.96 (0.94-0.98) | .001 | 0.97 (0.95-0.98) | < .001 |
| Age at inclusion, per 5 y | 1.07 (0.96-1.19) | .244 | 1.08 (0.98-1.18) | .106 |
| BMI, per 1 kg/m$^2$ | 0.96 (0.92-0.99) | .019 | 0.97 (0.94-1.00) | .060 |
| Cardiac index, per 0.5 L/min/m$^2$ | 0.93 (0.79-1.10) | .388 | 1.03 (0.91-1.17) | .630 |
| $FEV_1$, per 10% predicted | 1.02 (0.88-1.19) | .754 | 0.97 (0.86-1.10) | .669 |
| WHO FC (reference, II) | | | | |
| III | 0.61 (0.13-2.82) | .529 | 1.40 (0.40-4.91) | .594 |
| IV | 0.44 (0.08-2.28) | .327 | 1.33 (0.37-4.81) | .666 |
| PVR, per 1 Wood unit | 1.05 (0.97-1.14) | .198 | 1.06 (1.00-1.12) | .042 |
| RAP, per 3 mm Hg | 0.99 (0.87-1.12) | .852 | 1.06 (0.96-1.17) | .275 |
| mPAP ≥ 35 mm Hg | 1.17 (0.72-1.89) | .530 | 1.18 (0.82-1.70) | .366 |
| Male sex | 1.40 (0.95-2.05) | .092 | 1.54 (1.12-2.11) | .008 |

6MWD = 6-min walking distance; mPAP = mean pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; WHO FC = World Health Organization functional class.
[a]For number of imputed values, see Table 3.

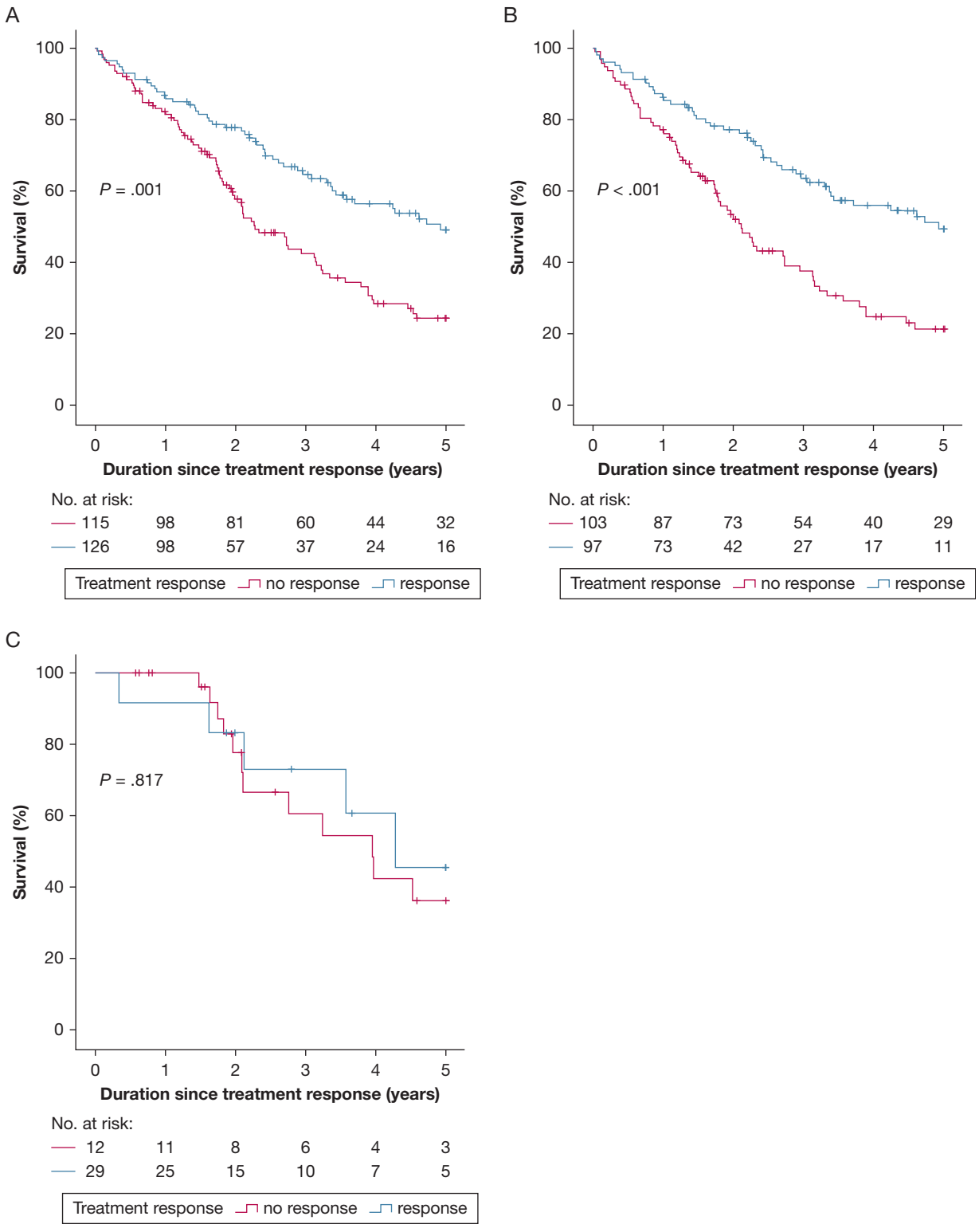


Figure 3 – *A-C, Kaplan-Meier plots showing 5-year survival free from lung transplantation of patients with PH in COPD with and without treatment response defined as improvement in WHO FC or 6MWD ≥ 30 m at 6 months: total (A), patients with severe PH (B), and patients with moderate PH (C). 6MWD = 6-min walking distance; PH = pulmonary hypertension; WHO FC = World Health Organization functional class.*

46.9% of the patients showed improvement in 6MWD of ≥ 30 m, and 28.5% showed an improvement in WHO FC (16.2% showed improvements in both criteria).

These numbers compared well with the present IPAH cohort and are consistent with the abovementioned data from Vitulo and colleagues.[12]

Another potentially relevant finding of the present study is the observed association of a clinical response to PH therapy and transplant-free survival in patients with severe PH in COPD. Our results suggest that patients with severe PH in COPD with a clinical response to PH-targeted therapy (herein identified arbitrarily as an improvement in 6MWD of $\geq$ 30 m or improvement in WHO FC) achieved a better transplant-free survival compared with patients who did not meet this responder criterion. Of note, this observation was restricted to the subgroup of patients with severe PH in COPD. In addition, patients with moderate PH in COPD showed a higher rate of PH drug discontinuations compared with patients with severe PH in COPD or IPAH. These aspects may be of potential relevance when designing future trials in this patient population.

Our findings are in line with previous observations by Hurdman and colleagues[19] in a series of 43 patients with severe PH in COPD. In that study, a decline in PVR of $>$ 20% or improvement in WHO FC after initiation of PH drugs identified patients with a better survival compared with patients who did not respond. Taken together, these observational experiences suggest that some patients with severe PH in COPD may benefit from drug therapy targeting PH and support the need for randomized controlled trials in this area.

### *Study Limitations*

The main limitations of the present study are related to the intrinsic nature of a registry and include lack of standardized assessment of the lung disease, missing values for some variables, and lack of systematic assessment of hemodynamics and blood gases during follow-up. Only a limited number of PFT data were captured in the electronic database, and data on imaging were not available, so we cannot exclude the possibility that some patients were misclassified. In addition, none of the patients with PH in COPD received no medical therapy targeting PH. Hence, the study had no control group and selection bias cannot be excluded. In terms of efficacy of medical interventions, registry data have to be viewed as hypothesis generating. As such, our data do not provide evidence that PH drugs are beneficial in patients with PH in COPD, and they are not intended to encourage physicians to use these drugs outside the setting of clinical trials.

## Interpretation

In the present series, patients with PH in COPD had a poorer prognosis than patients with IPAH. The risk of death in patients with PH in COPD was predicted by male sex, a low 6MWD, and high PVR. Our data suggest that PH-targeted drug therapy in patients with COPD and severe PH may improve exercise tolerance and WHO FC in a subgroup of patients and that patients with COPD and PH who respond to therapy may have a better prognosis than patients who do not show clinical improvement. These findings need to be explored further in prospective, randomized controlled clinical studies.

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**Additional information:** The e-Figure and e-Table can be found in the Supplemental Materials section of the online article.

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