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PH associated with COPD -

from Cor Pulmonale to the treatment of PH-COPD

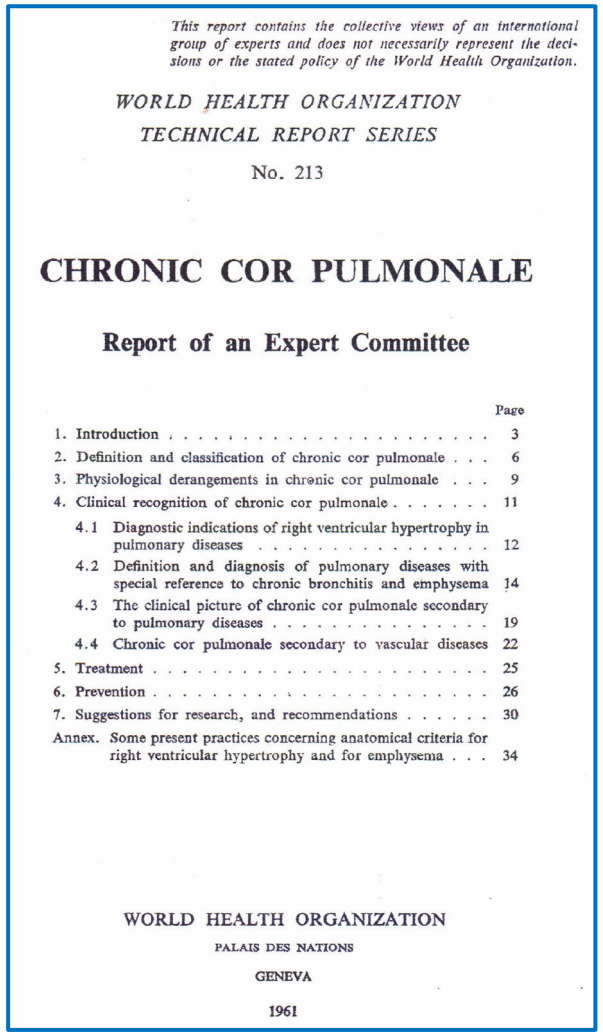
Gabor Kovacs

Disclosure Statement

Medical University of Graz

- Personal fees and non-financial support
  - Astra Zeneca, Janssen, Bayer, GSK, MSD, Boehringer Ingelheim, Novartis, Chiesi, Vitalaire, Ferrer, AOP
- Financial support for investigator initiated trials
  - Janssen, Boehringer Ingelheim

1961: WHO Report on Chronic Cor Pulmonale



This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

WORLD HEALTH ORGANIZATION
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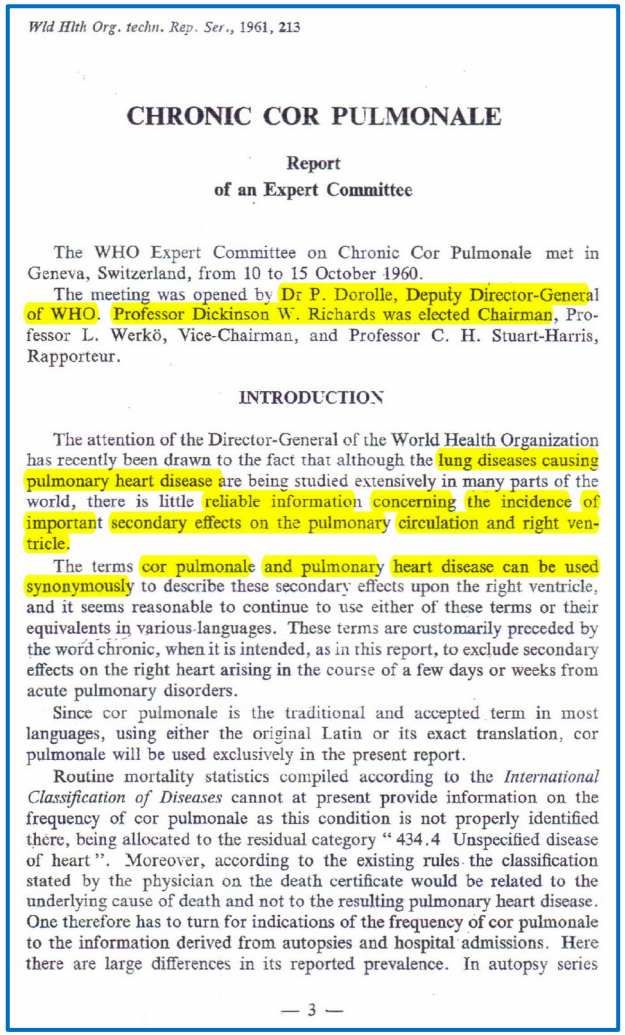
No. 213

CHRONIC COR PULMONALE

Report of an Expert Committee

WORLD HEALTH ORGANIZATION
PALAIS DES NATIONS
GENEVA
1961



CHRONIC COR PULMONALE

Report
of an Expert Committee

The WHO Expert Committee on Chronic Cor Pulmonale met in Geneva, Switzerland, from 10 to 15 October 1960.

The meeting was opened by Dr P. Dorolle, Deputy Director-General of WHO. Professor Dickinson W. Richards was elected Chairman, Professor L. Werkö, Vice-Chairman, and Professor C. H. Stuart-Harris, Rapporteur.

INTRODUCTION

The attention of the Director-General of the World Health Organization has recently been drawn to the fact that although the lung diseases causing pulmonary heart disease are being studied extensively in many parts of the world, there is little reliable information concerning the incidence of important secondary effects on the pulmonary circulation and right ventricle.

The terms cor pulmonale and pulmonary heart disease can be used synonymously to describe these secondary effects upon the right ventricle, and it seems reasonable to continue to use either of these terms or their equivalents in various languages. These terms are customarily preceded by the word chronic, when it is intended, as in this report, to exclude secondary effects on the right heart arising in the course of a few days or weeks from acute pulmonary disorders.

Since cor pulmonale is the traditional and accepted term in most languages, using either the original Latin or its exact translation, cor pulmonale will be used exclusively in the present report.

Routine mortality statistics compiled according to the *International Classification of Diseases* cannot at present provide information on the frequency of cor pulmonale as this condition is not properly identified there, being allocated to the residual category "434.4 Unspecified disease of heart". Moreover, according to the existing rules the classification stated by the physician on the death certificate would be related to the underlying cause of death and not to the resulting pulmonary heart disease. One therefore has to turn for indications of the frequency of cor pulmonale to the information derived from autopsies and hospital admissions. Here there are large differences in its reported prevalence. In autopsy series

Definitions of chronic cor pulmonale have been put forward by many authors in clinical, functional or morbid anatomical terms. A clinical definition is considered unsatisfactory, since the chief clinical manifestation is heart failure, which may be long delayed. A functional definition in terms of pulmonary hypertension or raised pulmonary vascular resistance provides an unsatisfactory basis. This is because vascular resistance is difficult to measure and is variable, and hypertension may be evanescent, may only occur on exercise, and may decline in the terminal phase of the disease. The Committee therefore prefers a definition based upon morbid anatomy, for this provides the only characteristic common to all patients at all stages of the disease.

Chronic cor pulmonale is defined as :

"Hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease."

Cor Pulmonale & Pulmonary Hypertension

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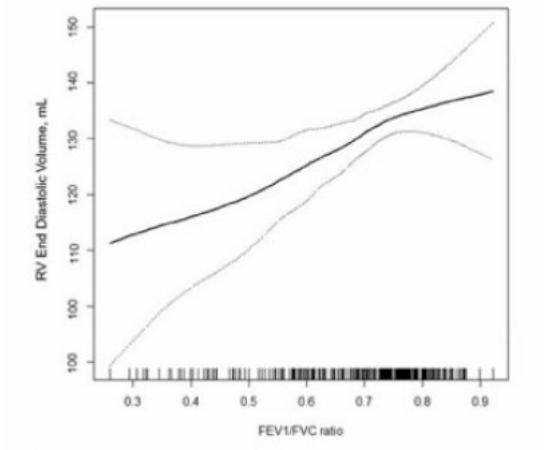
The term "cor pulmonale" is still very popular in the medical literature, but its definition varies and there is presently no consensual definition. Forty years ago an expert committee of the World Health Organization[1] defined cor pulmonale as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs . . .". This pathological definition is in fact of limited value in clinical practice. It has been proposed to replace the term "hypertrophy" by "alteration in the structure and function of the right ventricle". It has also been proposed to define clinically cor pulmonale by the presence of oedema in patients with respiratory failure. Finally, as pulmonary arterial hypertension is "the sine qua non" of cor pulmonale,[2] we believe that the best definition of cor pulmonale is : pulmonary arterial hypertension resulting from diseases affecting the structure and/or the function of the lungs; pulmonary arterial hypertension results in right ventricular enlargement (hypertrophy and/or dilatation) and may lead with time to right heart failure.

A new diagnostic classification of pulmonary hypertension was developed by a group of experts in 1998[3] and is presented on table 1. In our opinion cor pulmonale corresponds to the third part of this classification (pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia) and must be distinguished from pulmonary venous hypertension (part 2), and also from primary pulmonary hypertension (part 1) and from thromboembolic pulmonary hypertension (part 4).

Weitzenblum Heart 2003.

Cor Pulmonale parvus



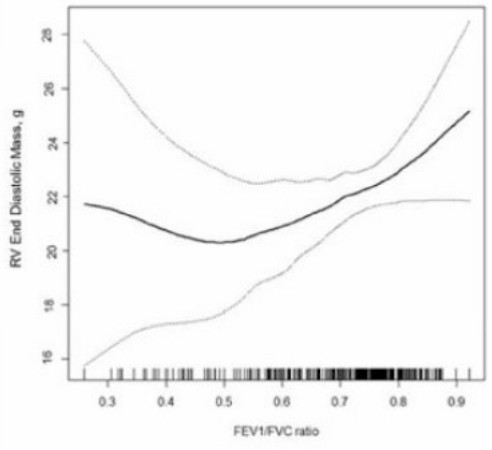
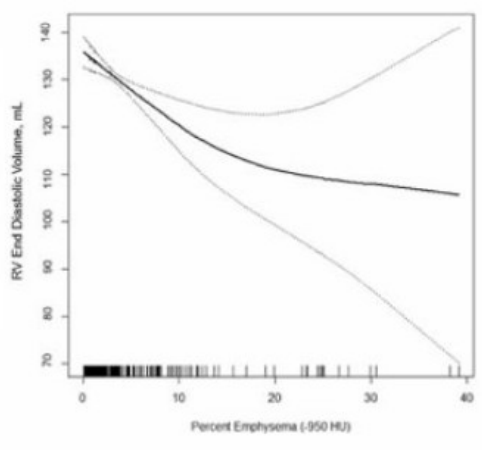


Figure 1. Multivariate Relationships between the Ratio of the Forced Expiratory Volume in One Second to Forced Vital Capacity and Right Ventricular End-Diastolic Volume and Mass

Smoothed regression plot of the relationship (solid line) of the ratio of the forced expiratory volume in one second to forced vital capacity with right ventricular end-diastolic volume (Panel A) and mass (Panel B) and 95% confidence intervals (dashed lines). The plots were obtained from regression models adjusted for age, sex, race/ethnicity, cohort, height, weight, smoking status, pack-years, hypertension, and sleep apnea. The hash marks denote data points.



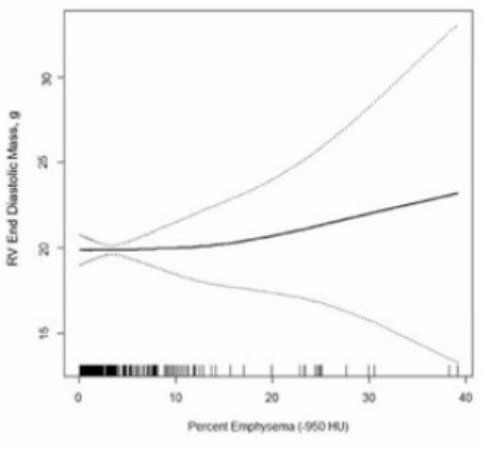


Figure 2. Multivariate Relationships between Percent Emphysema and Right Ventricular End-Diastolic Volume and Mass

Smoothed regression plot of the relationship (solid line) of percent emphysema with right ventricular end-diastolic volume (Panel A) and mass (Panel B) and 95% confidence intervals (dashed lines). The plots were obtained from regression models adjusted for age, sex, race/ethnicity, cohort, height, weight, smoking status, pack-years, hypertension, sleep apnea and mAs. The hash marks denote data points.

traditional cardiac sequelae than the "emphysema" subphenotype (35, 36). We showed that increasing centrilobular and paraseptal emphysema were associated with smaller RV volumes, whereas panlobular emphysema was not. Therefore, rather than being inconsistent with the classic paradigm of *cor pulmonale*, our findings may reflect the current phenotype of COPD in the general population in the US and may not apply to selected patients with severe chronic bronchitis or marked gas trapping.

Kawut et al. JACC 2014.

Cor Pulmonale - multifactorial development

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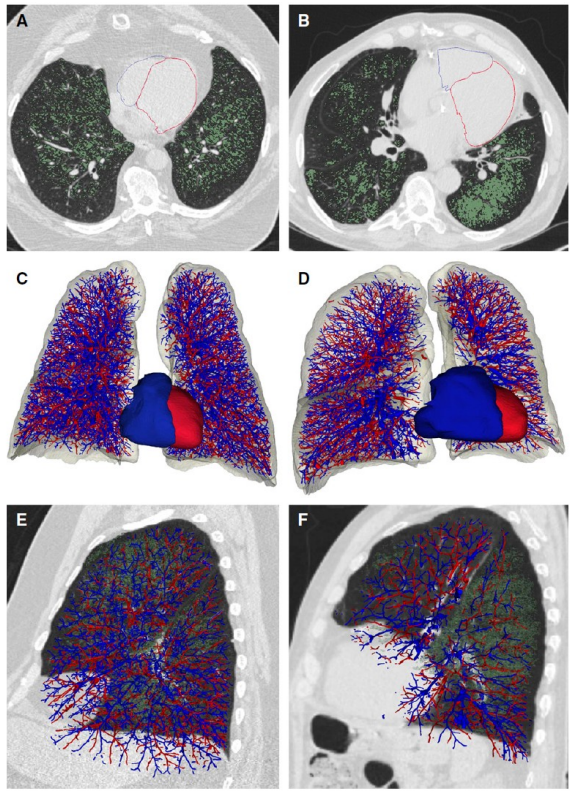
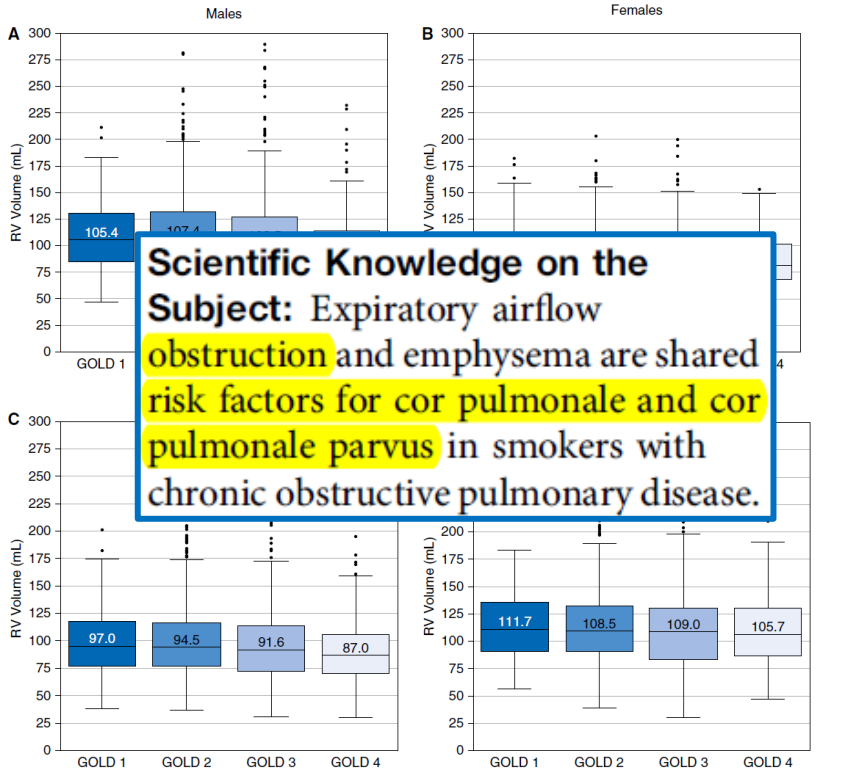
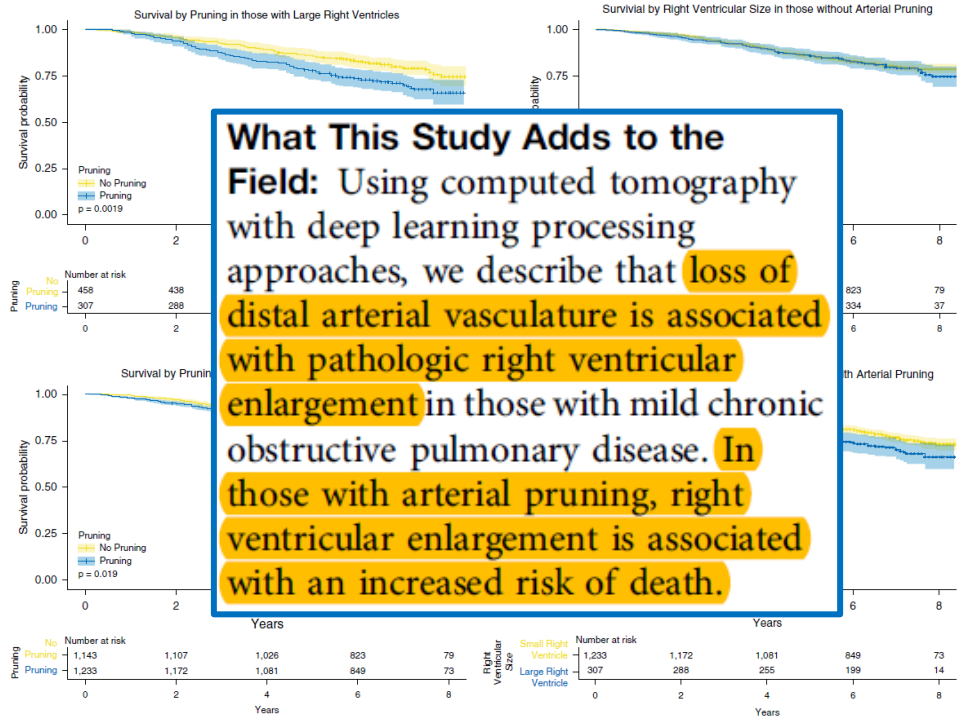


Figure 1. Pulmonary vasculature and right (blue) and left (red) ventricular reconstructions from computed tomography images for two subjects with approximately 20% emphysema on computed tomography scan. (*A*, *C*, and *E*) Subject 1 with 19% emphysema and relative preservation of the distal arterial vascular volume (arterial volume for vessels less than 5 mm^2 in cross-section = 131 ml). (*B*, *D*, and *F*) Subject 2 with 18% emphysema and relative loss of the distal arterial vascular volume (arterial volume for vessels less than 5 mm^2 in cross-section = 70.8 ml). (*A* and *B*) Axial images of the epicardial surface of the right ventricle (RV), which is outlined in blue and the epicardial surface of the left ventricle, which is outlined in red. Emphysema is depicted in green. (*C* and *D*) Frontal view of the arterial (blue) and venous vasculature and the surface model of the epicardial (myocardium and chamber) RV volume (blue) and epicardial (myocardium and chamber) left ventricular volume (red). The epicardial (myocardium and chamber) RV volume of Subject 1 is 58.9 ml and the epicardial (myocardium and chamber) RV volume for Subject 2 is 140 ml. (*E* and *F*) Sagittal views of the arterial (blue) and venous (red) vasculature of the left lung demonstrating the relative loss of distal arterial vascular volume. Emphysema is shown in green.



Scientific Knowledge on the Subject: Expiratory airflow obstruction and emphysema are shared risk factors for cor pulmonale and cor pulmonale parvus in smokers with chronic obstructive pulmonary disease.

Figure 2. Median (and interquartile range) epicardial (myocardium and chamber) right ventricular volume by sex (top two panels) or race (bottom two panels) and Global Initiative for Chronic Obstructive Lung Disease stage. GOLD = Global Initiative for Chronic Obstructive Lung Disease; RV = right ventricular.

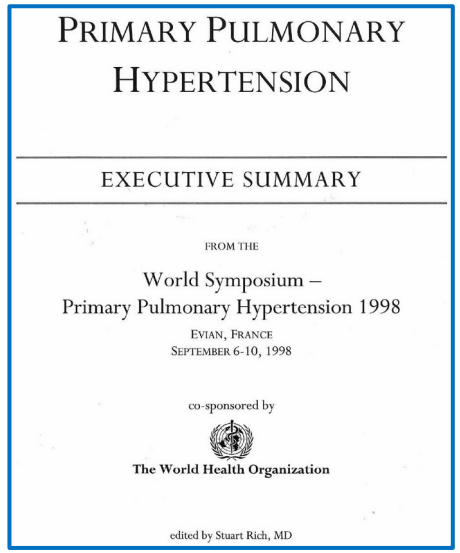


What This Study Adds to the Field: Using computed tomography with deep learning processing approaches, we describe that loss of distal arterial vasculature is associated with pathologic right ventricular enlargement in those with mild chronic obstructive pulmonary disease. In those with arterial pruning, right ventricular enlargement is associated with an increased risk of death.

Figure 3. (Top left) Survival in those participants with right ventricular (RV) enlargement with and without arterial pruning. (Top right) Survival by RV size in those without arterial pruning. (Bottom left) Survival by the presence or absence of arterial pruning in those without enlarged RVs. (Bottom right) Survival in small versus large RV size in those with arterial pruning. An enlarged right ventricle (epicardial [myocardium and chamber] RV volume) is defined as those in the highest quartile of RV volume compared with those in the bottom three quartiles. Pruning is defined as those with an arterial volume for vessels less than 5 mm^2 in cross-section less than the median.

Washko et al. AJRCCM 2019.

PH-Lung: Classification



PRIMARY PULMONARY HYPERTENSION

EXECUTIVE SUMMARY

FROM THE

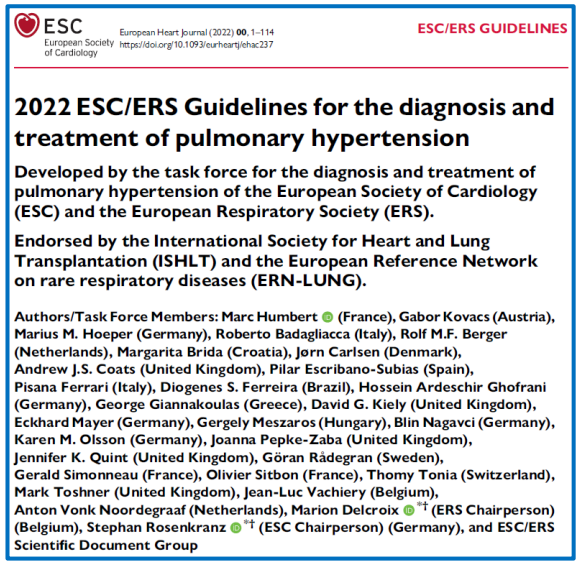
World Symposium –
Primary Pulmonary Hypertension 1998

EVIAN, FRANCE
SEPTEMBER 6-10, 1998

co-sponsored by

The World Health Organization

edited by Stuart Rich, MD



ESC European Society of Cardiology

European Heart Journal (2022) 00, 1–114
https://doi.org/10.1093/eurheartj/ehac237

ESC/ERS GUIDELINES

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Developed by the 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 the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG).

Authors/Task Force Members: Marc Humbert (France), Gabor Kovacs (Austria), Marius M. Hoeper (Germany), Roberto Badagliacca (Italy), Rolf M.F. Berger (Netherlands), Margarita Brida (Croatia), Jørn Carlsen (Denmark), Andrew J.S. Coats (United Kingdom), Pilar Escribano-Subias (Spain), Pisana Ferrari (Italy), Diogenes S. Ferreira (Brazil), Hossein Ardeschir Ghofrani (Germany), George Giannakoulas (Greece), David G. Kiely (United Kingdom), Eckhard Mayer (Germany), Gergely Meszaros (Hungary), Blin Nagavci (Germany), Karen M. Olsson (Germany), Joanna Pepke-Zaba (United Kingdom), Jennifer K. Quint (United Kingdom), Göran Rådegran (Sweden), Gerald Simonneau (France), Olivier Sitbon (France), Thomy Tonia (Switzerland), Mark Toshner (United Kingdom), Jean-Luc Vachiery (Belgium), Anton Vonk Noordegraaf (Netherlands), Marion Delcroix *† (ERS Chairperson) (Belgium), Stephan Rosenkranz *† (ESC Chairperson) (Germany), and ESC/ERS Scientific Document Group

3. Pulmonary Hypertension Associated with Disorders of the Respiratory System and/or Hypoxemia
   - 3.1 Chronic Obstructive Pulmonary Disease
   - 3.2 Interstitial Lung Disease
   - 3.3 Sleep Disordered Breathing
   - 3.4 Alveolar Hypoventilation Disorders
   - 3.5 Chronic Exposure to High Altitude
   - 3.6 Neonatal Lung Disease
   - 3.7 Alveolar-Capillary Dysplasia
   - 3.8 Other

GROUP 3 PH associated with lung diseases and/or hypoxia

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

Humbert et al. EHJ 2022, ERJ 2022.

PH-Lung: Pathophysiology of PH in COPD?

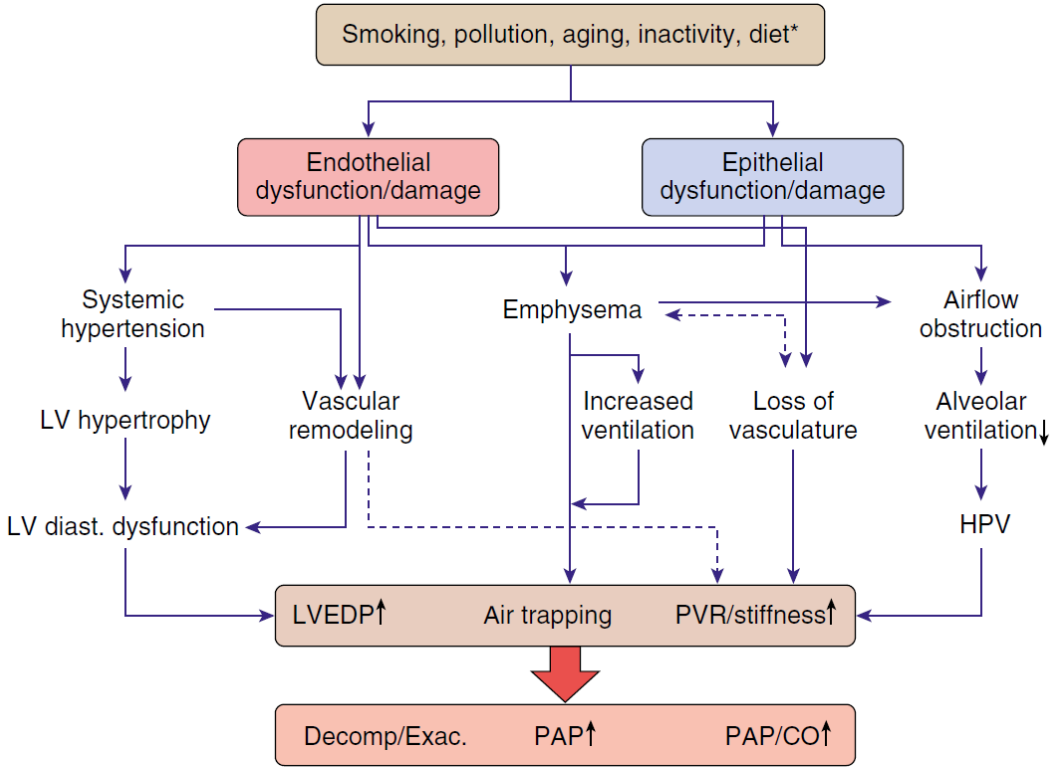
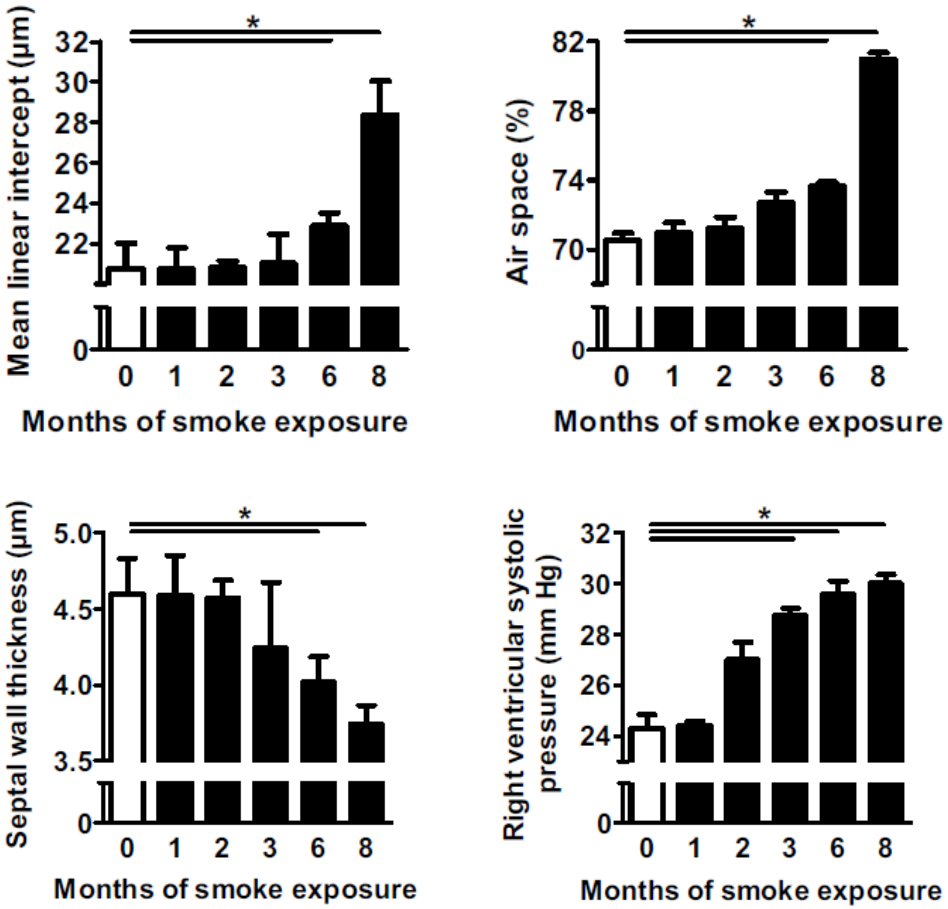
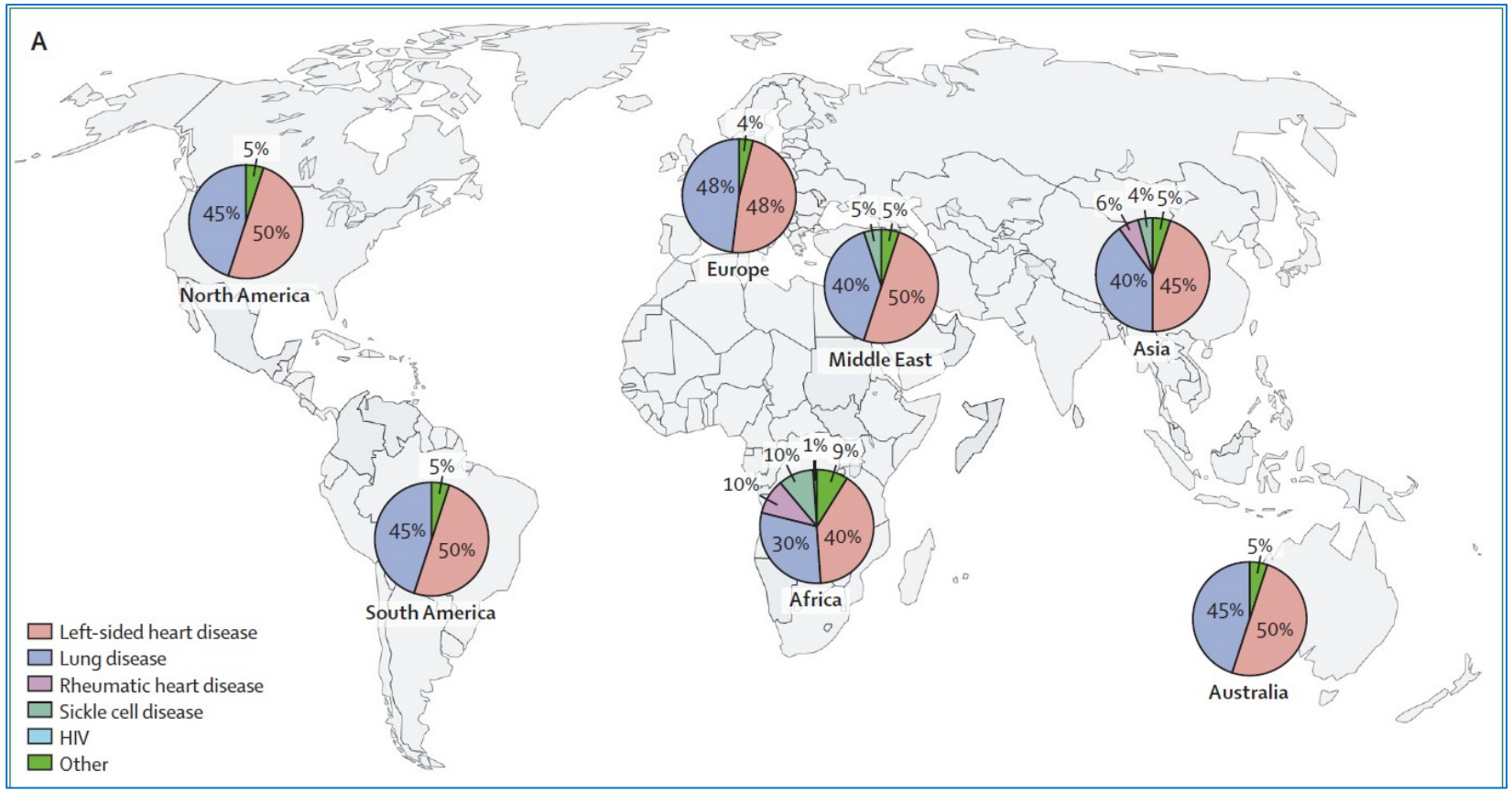


Figure 1. Emergence of epithelial and endothelial dysfunction and interaction of cardiac, thoracic, and pulmonary vascular factors contributing to the development of pulmonary hypertension in COPD. *From Reference 34. CO = cardiac output; HPV = hypoxic pulmonary vasoconstriction; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance. Illustration by Birck Cox.



Kovacs et al. AJRCCM 2018, Seimetz et al. Cell 2011.

PH-Lung Epidemiology: Relative Frequency



Hoeper et al. Lancet RM 2016.

PH-Lung Epidemiology: Prevalence of COPD

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TABLE 4 Nonduplicated pooled prevalence estimates for chronic obstructive pulmonary disease by category

	Estimates	Cases	Total population	Prevalence %	Pooled prevalence %	p-value#
Overall	37	111261	4123646	8.9 (2.1–26.4)	7.6 (6.0–9.5)	
Age						
<40 yrs	9	1074	25362	2.7 (0.8–10.6)	3.1 (1.8–5.0)	<0.0001
⩾40 yrs	34	4933	46095	9.7 (1.8–29.7)	9.9 (8.2–11.8)	
40–64 yrs	23	2793	30942	7.6 (1.8–28.7)	8.2 (6.5–10.3)	
⩾65 yrs	11	2140	15153	15.0 (4.8–29.7)	14.2 (11.0–18.0)	
Smoking status						
Smoker	17	3133	24122	15.2 (5.1–39.7)	15.4 (11.2–20.7)	<0.0001
Ex-smoker	16	1240	14521	12.7 (2.8–27.7)	10.7 (8.1–14.0)	
Never-smoker	16	1235	32542	3.9 (0.7–14.6)	4.3 (3.2–5.7)	
Sex						
Male	27	16480	327293	11.0 (2.5–28.0)	9.8 (8.0–12.1)	0.0002
Female	27	12024	356398	5.0 (1.8–25.2)	5.6 (4.4–7.0)	
WHO region						
Africa	0	0	0			0.7768
Americas	3¶	2666	27599	4.5 (3.2–14.0)	4.6 (2.8–7.6)	
Eastern Mediterranean	0	0	0			
Europe	28	104773	4015455	8.3 (2.1–26.4)	7.4 (5.9–9.3)	
South-East Asia	2+	747	6044	12.5 (7.1–17.9)	11.4 (4.4–26.4)	
Western Pacific	4§	3075	74548	10.6 (3.0–18.2)	9.0 (3.0–24.1)	
Study setting						
Urban	12	4096	44153	10.3 (3.6–26.4)	10.2 (7.4–13.9)	0.0438
Mixed	21	105571	4075965	4.9 (2.3–17.8)	6.1 (4.9–7.7)	
Rural	4	437	3482	8.4 (2.1–18.3)	8.0 (3.9–15.8)	
Study quality						
Good	15	23539	583658	6.8 (3.2–18.3)	6.8 (5.2–8.9)	0.6958
Average	13	6434	124960	7.1 (2.1–14.6)	6.7 (4.5–9.8)	
Poor	9	80131	3414982	10.5 (2.3–26.4)	9.9 (4.2–21.6)	

Data are presented as n. Prevalences are presented as median (range) and pooled prevalences as pooled prevalence estimate (95% confidence interval). WHO: World Health Organization. #: heterogeneity between strata calculated using Q statistic (*e.g.* males *versus* females); ¶: Canada and USA; +: Thailand and India; §: China, Japan and South Korea. Heterogeneity within each stratum, as calculated by the Q statistic, was significant for all strata with more than one estimate ($p<0.0001$).

Halbert et al. ERJ 2006.

PH-Lung Epidemiology: Prevalence of PH-COPD

	Year of inclusion	Number of participants	Proportion of females (%)	Age (years)	Lung function: FEV_1/FVC, or predicted FEV_1 (%)	Arterial blood gases: PaO_2, $PaCO_2$ (mm Hg)	Patients with pulmonary hypertension (%)	Effect of pulmonary hypertension on survival
Weitzenblum et al; France[105]	1968–72	175	1%	60 (range 36–82)	FEV_1/FVC 40% (11%)	63 (10), 40 (6)	PAPm >20 mm Hg in 35·4%, PAPm >30 mm Hg in 9·7%	4 year survival 71·8% when PAPm <20 mm Hg *vs* 49·4% when PAPm >20 mm Hg (p<0·01)
Scharf et al; USA[106]	..	120	39%	66 (6), evaluation for lung volume reduction surgery	Predicted FEV_1 27% (7%)	66 (10), 42 (6)	PAPm >20 mm Hg in 91%, PAPm >35 mm Hg in 5%	..
Sims et al; USA[107]	1991–2003	362	53%	56 (5), evaluation for transplantation	Predicted FEV_1 20% (5%)	62 (12), 51 (10) pulmonary hypertension group	PAPm ≥25 mm Hg and PAWP ≤15 mm Hg in 23%	..
Minai et al; USA[108]	..	797	35%	67 (6)	Predicted FEV_1 26% (7%) (pulmonary hypertension group)	61 (9), 43 (6) pulmonary hypertension group	PAPm ≥25 mm Hg in 38%, severe pulmonary hypertension in 2·2%*	..
Cuttica et al; USA[109]	1997–2006	4930	54%	56 (6), pulmonary hypertension group, evaluation for transplantation	Predicted FEV_1 22% (10%)	..	PAPm ≥25 mm Hg and PAWP ≤15 mm Hg in 30%	Adjusted hazard ratio for death associated with the presence of pulmonary hypertension 1·27 (95% CI 1·04–1·55)
Portillo et al; Spain[110]	..	139	4%	63 (8)	Predicted FEV_1 41% (16%)	69 (12), 40 (6)	PAPm ≥25 mm Hg in 18%, PAPm ≥35 mm Hg in 3%	..
Vizza et al; Italy[111]	1993–1995	168	62%	54 (6), evaluation for transplantation	Predicted FEV_1 20% (6%)	59 (12), 46 (11)	PAPm ≥25 mm Hg in about 50%	..
Thabut et al; France[112]	1988–2002	215	21·4%	55 (··), evaluation for transplantation or LVRS	Predicted FEV_1 24·3% (··)	66 (13), 41 (7) lung volume reduction surgery cohort	PAPm >25 mm Hg in 50·2%, PAPm >35 mm Hg in 13·5%	..
Chaouat et al; France[113,114]	1990–2002	998	10%	67 (62–68)	Predicted FEV_1 50% (44–56)	46 (41–53), 32 (28–37)	PAPm >20 mm Hg in about 50%, PAPm ≥35 mm Hg in 5·8%, PAPm ≥40 mm Hg in 1%	3 year survival about 88% in patients with PAPm <20 mm Hg *vs* about 38% in patients with PAPm ≥40 mm Hg (p<0·01)
Oswald-Mammosser et al; France[115]	1976–1992	84	10·7%	63 (··)	FEV_1/FVC 36% (11%)	52 (5), 45 (8)	PAPm >20 mm Hg in 77%, PAPm >30 mm Hg in 37%	5 year survival 62·2% when PAPm ≤25 mm Hg *vs* 36·3% when PAPm >25 mm Hg (p<0·001)
Andersen et al; Denmark[116]	1991–2010	409	61%	54 (7), evaluation for transplantation	Predicted FEV 23% (7%)	63 (12), 49 (11) pulmonary hypertension group	PAPm ≥25 mm Hg in 35·7%, PAPm ≥35 mm Hg in 3·9%, PAPm ≥40 mm Hg in 1·5%	5 year survival 63% when PAPm <25 mm Hg *vs* 37% when PAPm ≥25 mm Hg (p=0·016)

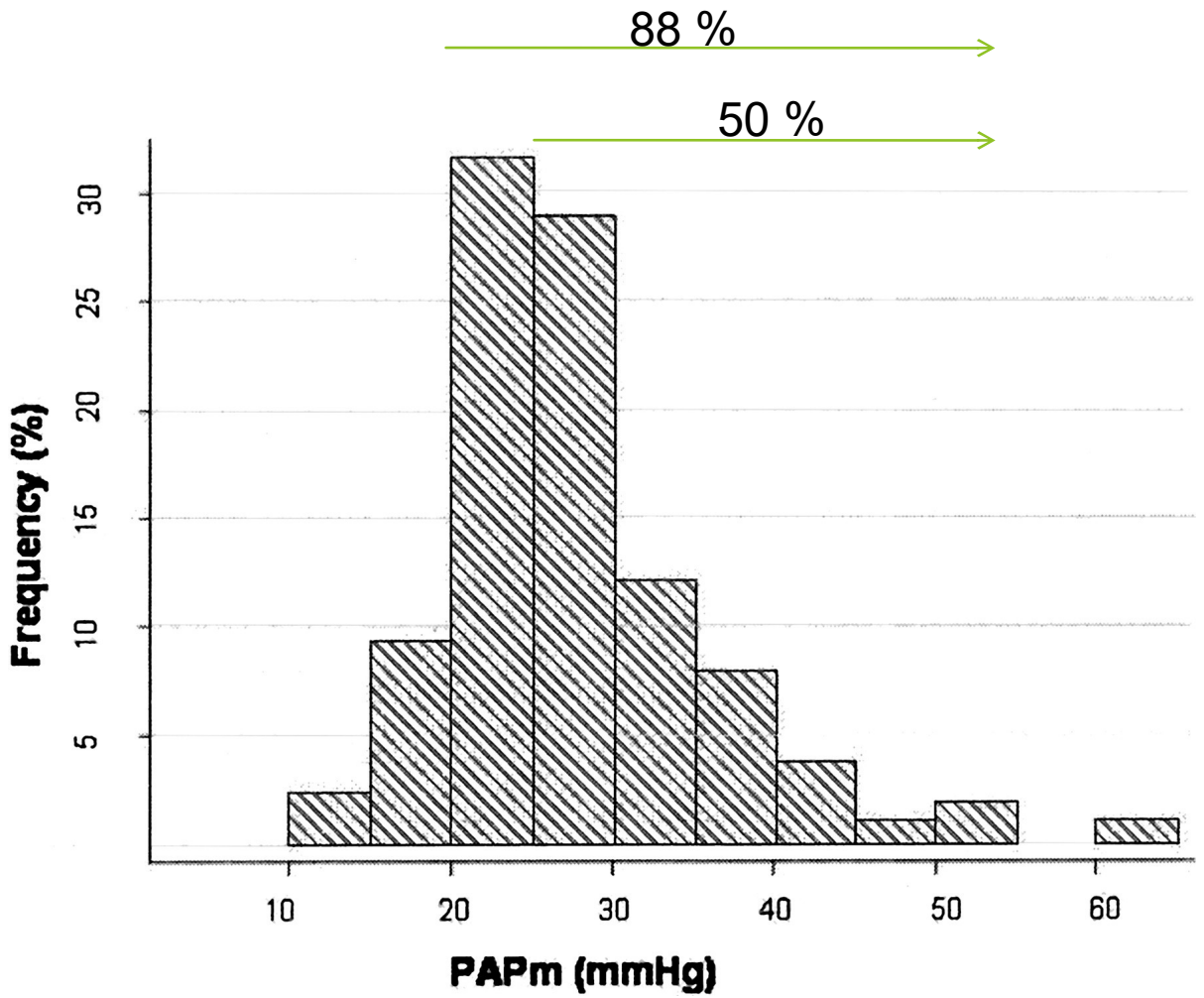
Data are mean (SD) or median (IQR). FEV_1=forced expiratory volume in the first second. FVC=forced vital capacity. PaO_2=partial pressure of oxygen in arterial blood. $PaCO_2$=partial pressure of carbon dioxide in arterial blood. PAPm=mean pulmonary arterial pressure. PAWP=pulmonary arterial wedge pressure. *Severe pulmonary was defined by a PAPm ≥35 mm Hg or a PAPm ≥25 mm Hg with pulmonary vascular resistance >480 dyn·s·cm^{-5} or cardiac index <2 L/min per m^2.

Table 3: Right heart catheter-based studies on pulmonary hypertension in patients with chronic obstructive pulmonary disease

Assuming a global COPD prevalence (disease severity stage II or higher) of 10% in the 2·5 billion adults that are 40 years or older and estimating a pulmonary hypertension prevalence of 10% in these patients,[117] about 25 million individuals aged 40 years or older might be affected worldwide by pulmonary hypertension due to COPD. Again, these numbers have to be interpreted with caution as they are based on assumptions rather than population-based studies.

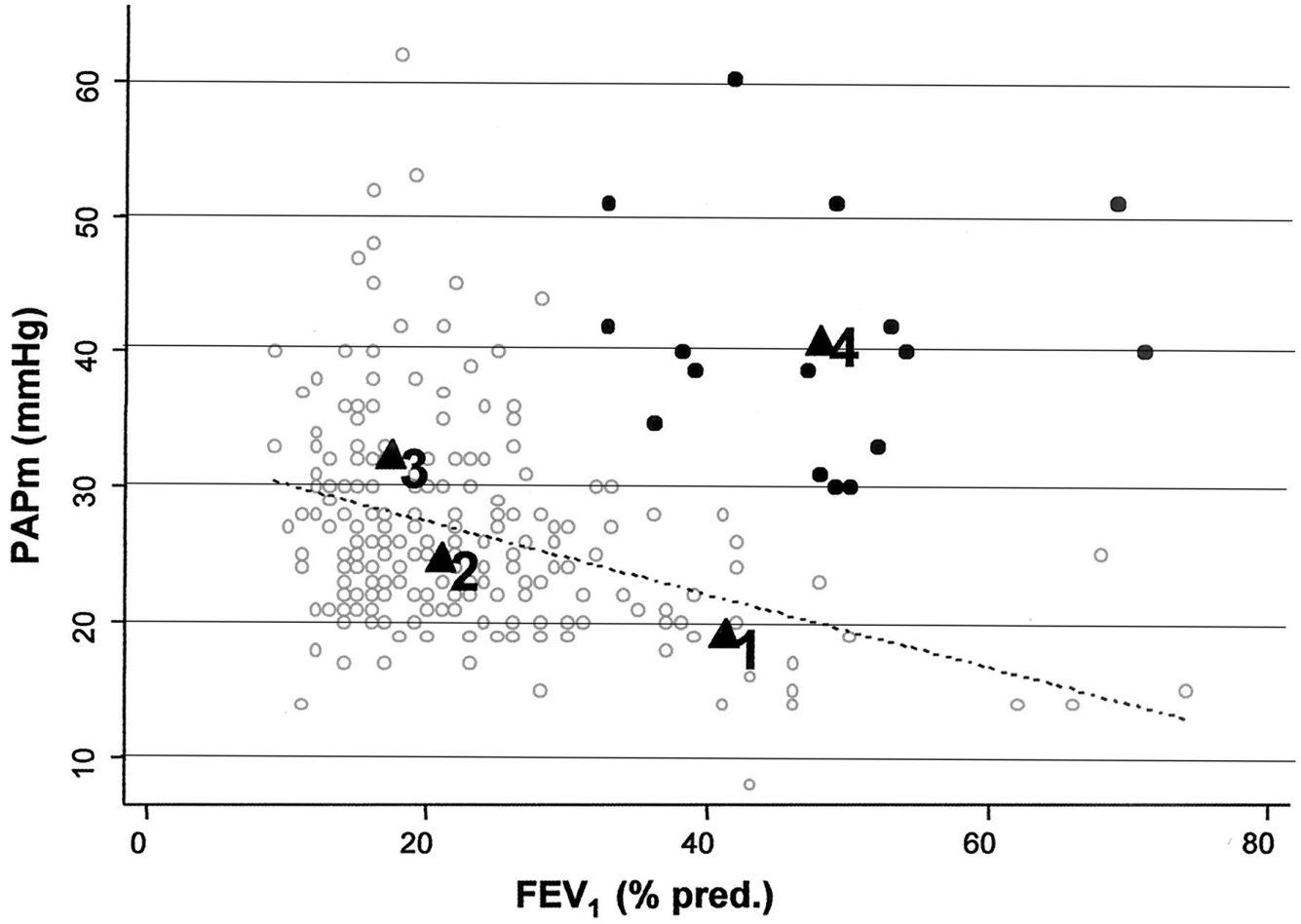
Hoeper et al. Lancet RM 2016.

PH-Lung Epidemiology: Prevalence of PH in severe COPD



Thabut et al. Chest 2005.

PH-Lung Epidemiology: PAPm vs. FEV_1 in COPD



Cluster „4“:
N=16
mean FEV1= 49%
mean PAP= 40mmHg
mean pO2= 46mmHg

Thabut et al. Chest 2005.

PH-Lung: Pulmonary Vascular Phenotype in COPD?

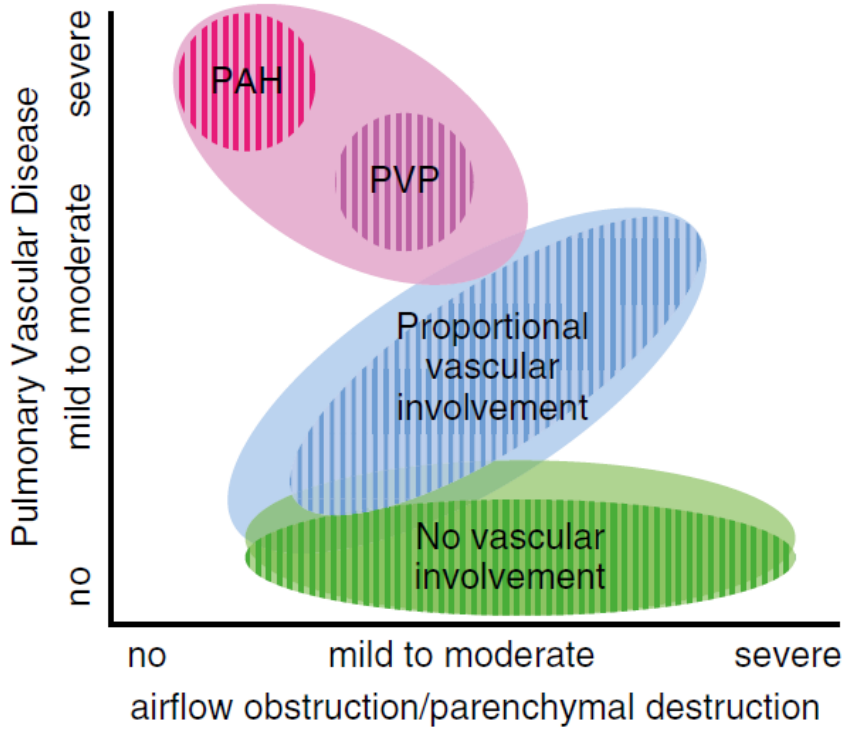
Medical University of Graz

PULMONARY PERSPECTIVE

Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease

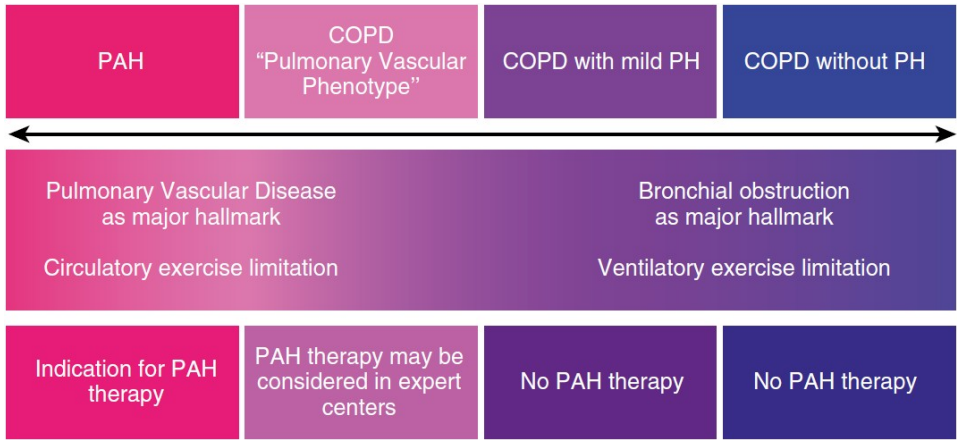
Is There a Pulmonary Vascular Phenotype?

Gabor Kovacs[1,2], Alvar Agusti[3,4], Joan Albert Barberà[3,4], Bartolome Celli[5], Gerard Criner[6], Marc Humbert[7], Don D. Sin[8,9], Norbert Voelkel[10], and Horst Olschewski[1,2]



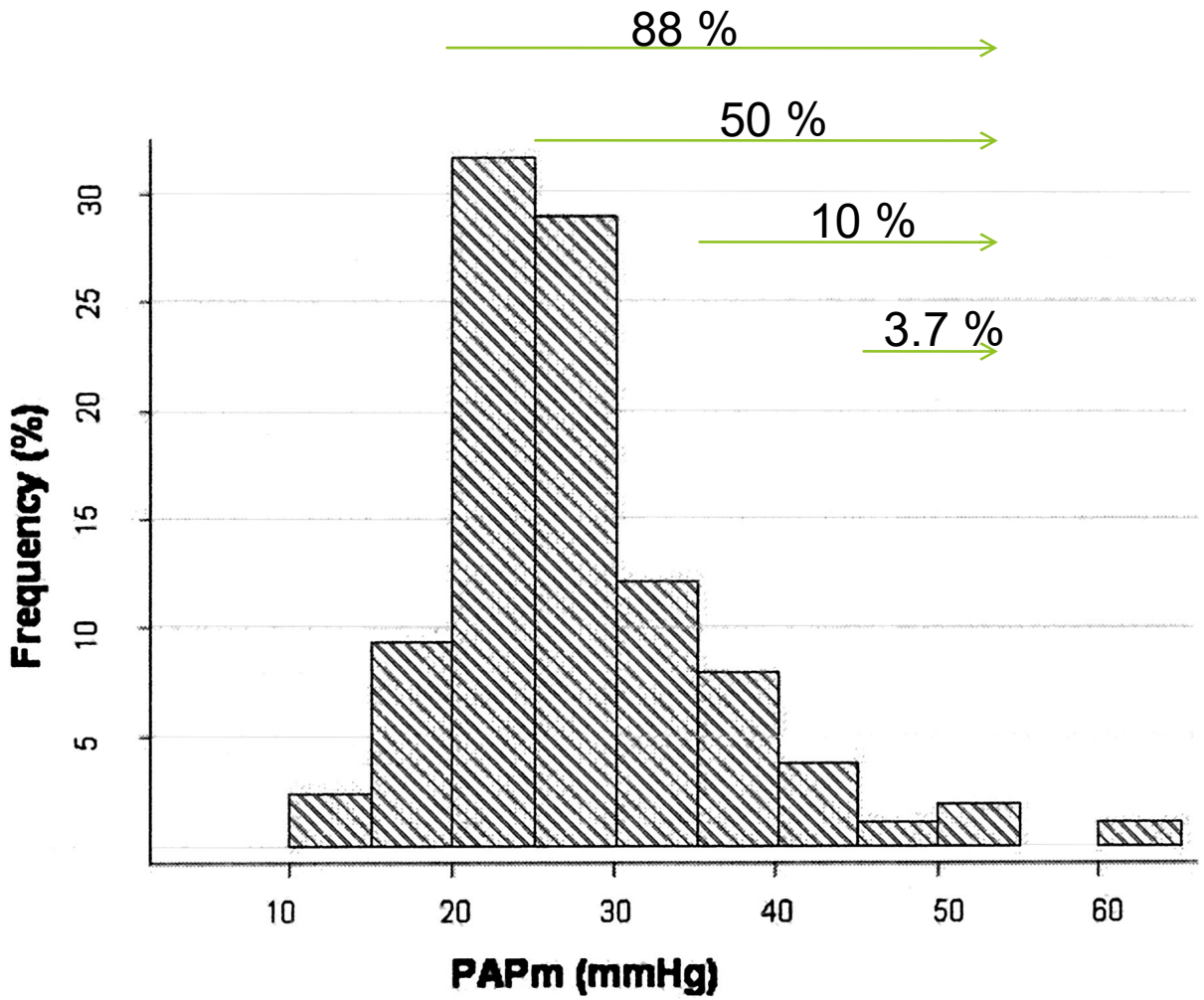
Major Characteristics of Patients with COPD with the "Pulmonary Vascular Phenotype"

- Severe precapillary pulmonary hypertension*
- Moderate airflow limitation
- No or very mild hypercapnia
- Very low D_{LCO} (<45% predicted)
- Circulatory exercise limitation



Kovacs et al. AJRCCM 2018.

PH-Lung: Concept of severe PH-Lung



Thabut et al. Chest 2005.

PH-Lung: Concept of severe PH-Lung

Medical University of Graz

The most recent NETT data on PH in patients with pulmonary emphysema was presented by Minai et al. in May 2010 during the American Thoracic Society's annual convention. 1,866 patients had been enrolled making this series one of the largest in this patient population. All patients underwent echocardiographic assessment; systolic pulmonary arterial pressure (PA pressure) ≥45 mmHg was determined as cut-off value. No further investigation was carried out in patients with a systolic PA pressure <45 mmHg (n = 1,069; 57%), while patients with a systolic PH pressure ≥45 mmHg underwent right heart catheterization. This procedure confirmed PH with a PAPm of ≥25 mmHg in 302 (38%) patients, which once more underlines the insufficient accuracy of determining PA pressure with echocardiography (see below). Prespecified criteria for severe pulmonary hypertension were (i) PAPm >35 mmHg, or (ii) PAPm ≥25 mmHg with a cardiac index <2.0 l/min/m^2, or (iii) pulmonary vascular resistance (PVR) >6 Wood units (corresponding to 480 dyn s cm^{-5}). According to these criteria, 18 (2.2%) patients had severe PH, including only one patient with a PAPm >35 mmHg (Minai O et al. ATS 2010). Surprisingly, in this population the presence of PH did not affect the survival rates after 1, 2 and 5 years (p = 0.19 for patients with a PAPm ≥25 mmHg versus <25 mmHg).

The German consensus group agreed to adopt the above-mentioned definition of severe PH from the NETT registry in a modified, stricter form (Table 2). Although this definition has been derived from patients

Table 2
Criteria for the presence of severe pulmonary hypertension in patients with chronic lung disease*.

At least 2 of the following criteria must be met:
1. Mean PA pressure (PAPm) >35 mmHg
2. PAPm ≥25 mmHg with limited cardiac output (CI <2.0 l/min/m^2)
3. Pulmonary vascular resistance (PVR) >480 dyn s cm^{-5}

*As a rule, these criteria only apply if other causes of PH (e.g. chronic thromboembolic PH or left ventricular failure) have been excluded.

Hoeper et al. Int J Cardiol 2011.

PH-Lung: Concept of severe PH-Lung

Medical University of Graz

PH was defined as resting mean pulmonary artery pressure (mPAP) $\geq$25 mmHg [7], pre-capillary PH as mPAP $\geq$25 mmHg and pulmonary artery occlusion pressure (PAOP) $\leq$15 mmHg, post-capillary PH as mPAP $\geq$25 mmHg and PAOP $>$15 mmHg, and severe PH was defined as a mPAP $>$35 mmHg or mPAP $\geq$25 mmHg with pulmonary vascular resistance 480 dynes/s/cm^{-5} or cardiac index $<$2 L/min/m^2 based on the Cologne Consensus definition [8].

Minai et al. Res Med 2014.

PH-Lung: Concept of severe PH-Lung

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Pulmonary Hypertension in Chronic Lung Diseases

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ESC/ERS GUIDELINES

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)

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It is suggested that the term "out of proportion" be abandoned and that the following definitions for COPD, IPF, and CPFE (measurements undertaken at rest with supplemental oxygen if needed) be used:

1. COPD/IPF/CPFE without PH (mPAP <25 mm Hg);
2. COPD/IPF/CPFE with PH (mPAP ≥25 mm Hg; PH-COPD, PH-IPF, and PH-CPFE); and
3. COPD/IPF/CPFE with severe PH (mPAP ≥35 mm Hg or mPAP ≥25 mm Hg with low CI (<2.0 l/min/m^2); severe PH-COPD, severe PH-IPF, and severe PH-CPFE).

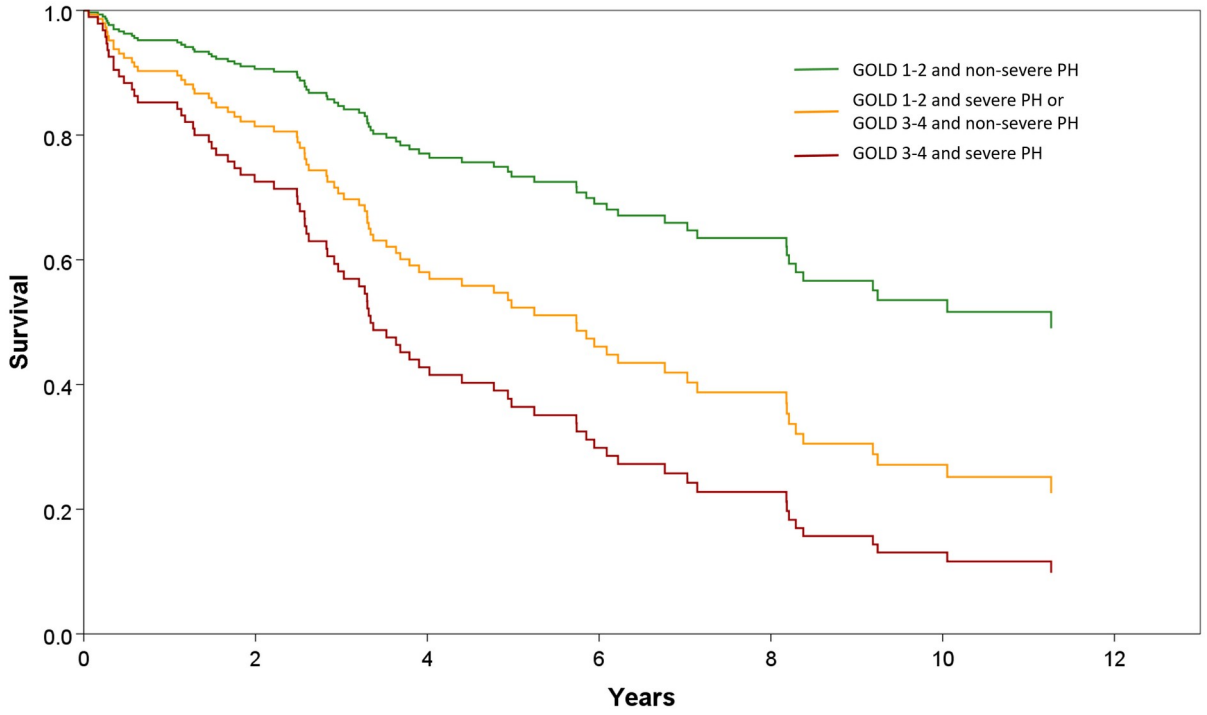
Table 32 Haemodynamic classification of pulmonary hypertension due to lung disease[9]

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

CI = cardiac index; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure; PAPm = mean pulmonary arterial pressure; PH = pulmonary hypertension.

Seeger et al. JACC 2013, Galie et al. ERJ 2015, EHJ 2016.

PH-Lung: Concept of severe PH-Lung



At risk:						
GOLD 1-2 and non-severe PH	42	41	23	18	14	9
GOLD 1-2 and severe PH or GOLD 3-4 and non-severe PH	70	52	28	20	14	9
GOLD 3-4 and severe PH	30	18	11	7	4	2

Kovacs et al. Chest 2022.

PH-Lung Epidemiology: Prognosis of PH-COPD & severe PH-COPD

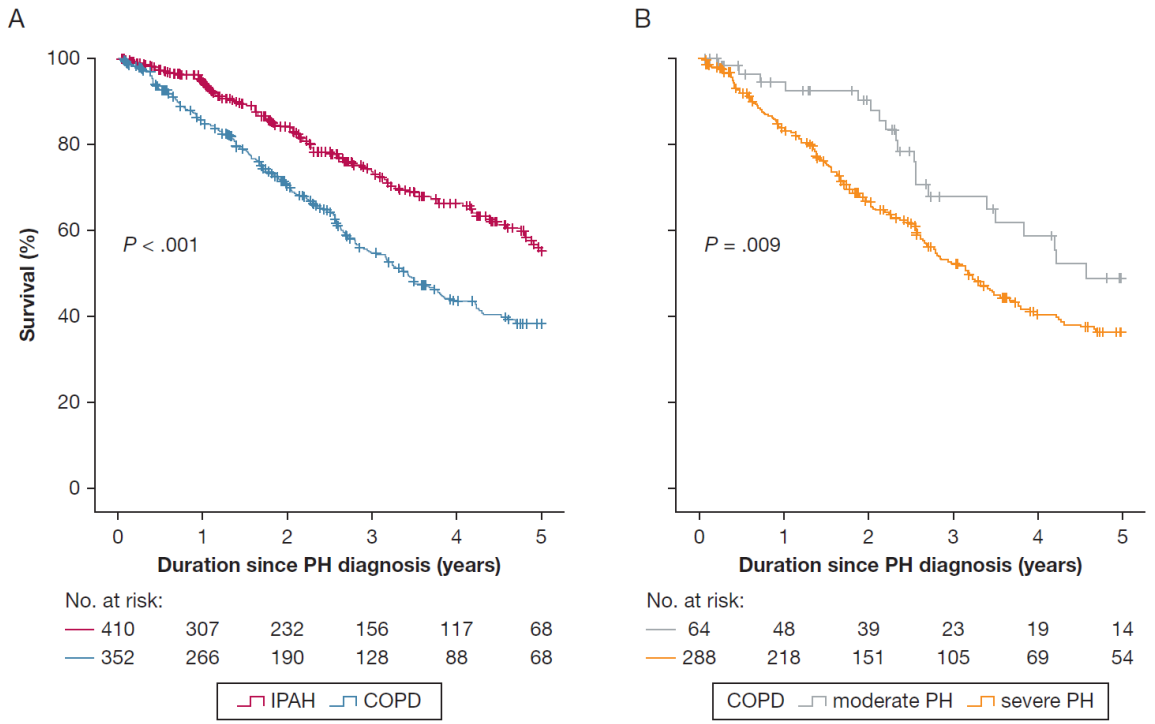


Figure 2 – *A, B, Kaplan-Meier plots showing 5-year survival free from lung transplantation of patients with IPAH and PH in COPD (A) and severe and moderate PH in COPD (B). IPAH = idiopathic pulmonary arterial hypertension; PH = pulmonary hypertension.*

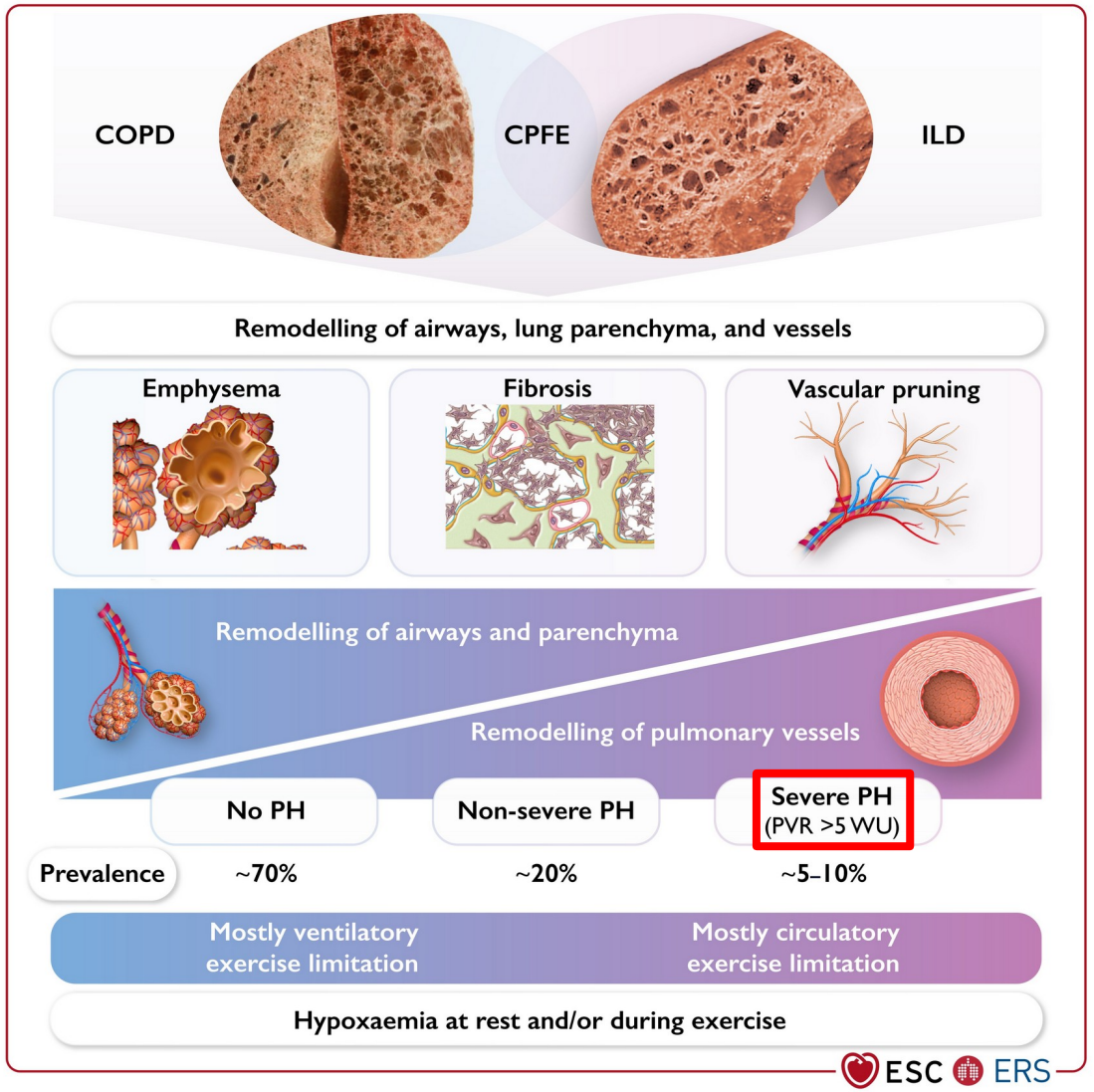
TABLE 4] Multivariate Cox PH Regression Model of Predictors for Death or Lung Transplantation in the PH in COPD Cohort for the Original Data and the Multiple Imputed Data Set

	Original Data (n = 211)		Pooled Imputed (n = 351[a])	
Variable	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.

Vizza et al. Chest 2020.

PH-Lung: Concept of severe PH-Lung



EUROPEAN RESPIRATORY JOURNAL
RESEARCH LETTER
K. ZEDER ET AL.

Elevated pulmonary vascular resistance predicts mortality in COPD patients

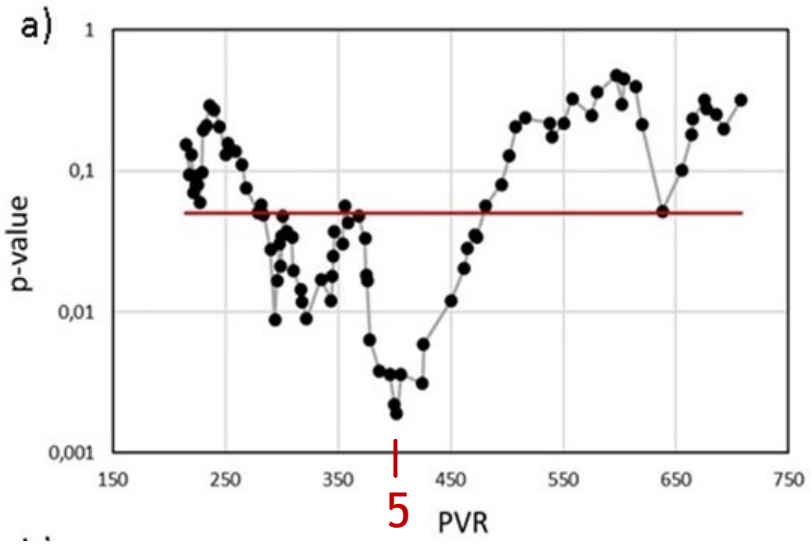
EUROPEAN RESPIRATORY JOURNAL
RESEARCH LETTER
K.M. OLSSON ET AL.

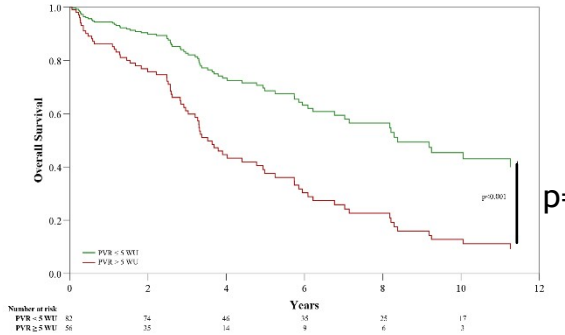
Pulmonary vascular resistance predicts mortality in patients with pulmonary hypertension associated with interstitial lung disease: results from the COMPERA registry

Humbert et al. EHJ 2022, ERJ 2022.

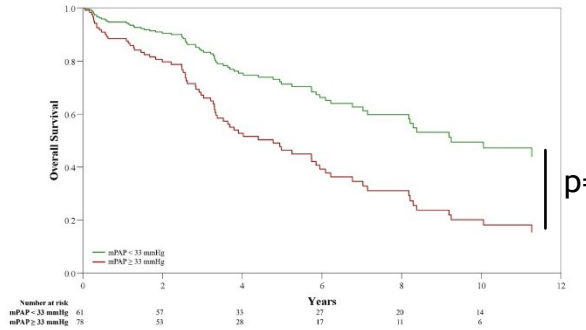
PH-Lung: Concept of severe PH-Lung

- Retrospective Analysis of n=139 COPD patients
- Cox-Regressios corrected for Age, Sex and FEV_1
- Primary Endpoint: Mortality
- Regression Analysis to identify best hemodynamic cut-offs for Mortality



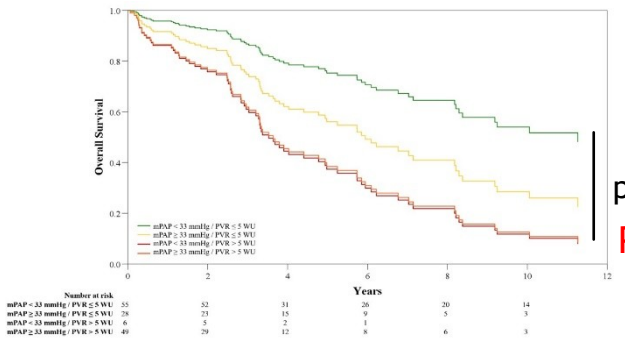


PVR 5 WU



mPAP 33mmHg

p=0.001



mPAP 33mmHg, PVR 5 WU

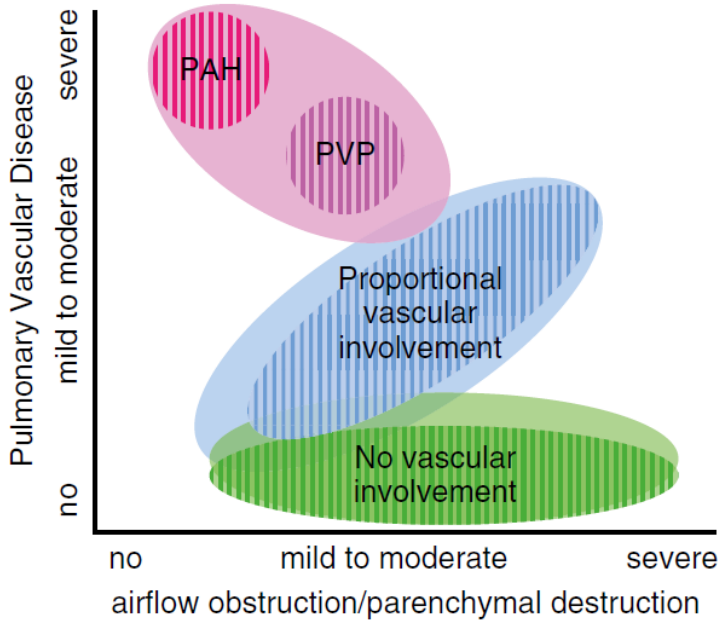
p=0.001

PVR > 5, independent of mPAP

Zeder et al. ERJ 2022.

PH-Lung: Concept of severe PH-Lung

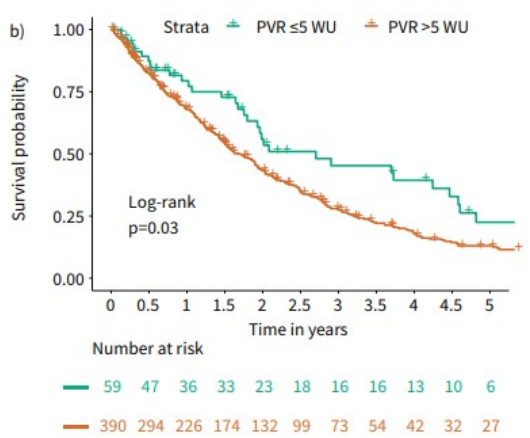
	mPAP 33-44		
	PVR ≤ 5	**PVR > 5**	**p-value**
N	26	21	
Age, yrs	66 [62- 73]	70 [68 - 74]	0.123
Sex, Male : Female	13 : 13	16 : 5	0.066
packyear	15.0 [0 - 30]	3.0 [0.0 - 37.5]	0.404
GOLD 1/2/3/4, N	0/12/11/3	3/14/3/1	**0.031**
Right heart catheterization:			
Heart rate, bpm	74 [68 - 83]	71 [6 - 77	0.243
mPAP, mmHg	36 [35 - 40]	40 [37 - 42	**0.041**
PAWP, mmHg	13 [10 - 18]	10 [6 - 10]	**<0.001**
RAP, mmHg	8 [6 - 12]	6 [4 - 7]	**0.010**
PVR, WU	3.7 [3.0 - 4.4]	7.6 [6 - 8.4]	**<0.001**
CI, L/min/m²	3.3 [2.7 - 3.6]	2.3 [2.1 - 2.5]	**<0.001**
Pulmonary function parameters:			
FVC, %pred	68.8 [53.7 - 82.5]	83.8 [68.8 - 93.0]	**0.040**
FEV1, %pred	48.2 [34.5 - 61.2]	61.5 [54.2 - 74.6]	**0.005**
FEV1/FVC, %	59.6 [47.8 - 65.6]	62 [55.1 - 68.0]	0.140
TLC, %pred	96.9 [90.3 - 119.7]	99.8 [92.3 - 112.4]	0.685
DLCOcSB, %pred	58.7 [34.9 - 78.2]	54.3 [39.0 - 72.0]	0.693
DLCOcVA, %pred	67.5 [44.6 - 102.9]	72.4 [40.1 - 84.4]	0.761
Exercise capacity, laboratory			
6MWD, m	360 [223 - 376]	278 [210 - 335]	0.064
NT-pro BNP, pg/ml	829 [221 - 1728]	1283 458 - 2537	0.247

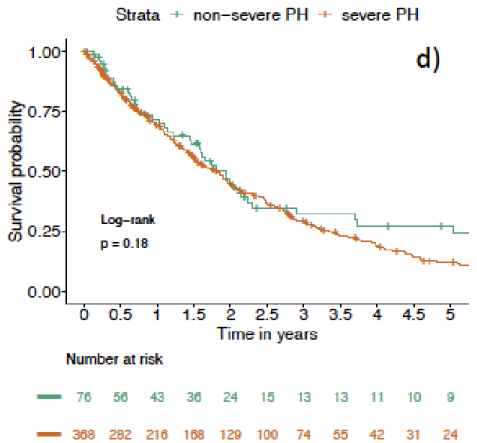


Zeder et al. ERJ 2022, Kovacs et al. AJRCCM 2018.

PH-Lung: Concept of severe PH-Lung

- Retrospective Analysis of “COMPERA”; 2006 - 2021
- N=449 patients with PH-ILD
- mPAP ≥ 25mmHg and PAWP ≤ 15mmHg
- Variables associated with Mortality: age, male sex, low TLC, high PVR
- mPAP, PAWP, CO, FVC, FEV_1: not associated with Mortality





information than mPAP or other haemodynamic variables. In Zeder *et al.* [3]’s analysis of patients with PH-COPD, PVR >5 WU was the best prognostic cut-off value, while in our analysis of patients with PVR-ILD, the best discrimination between survivors and non-survivors was seen at PVR >8 WU. However, our analysis also showed that mortality increased significantly with PVR >5 WU. At the same time, the current mPAP-based definition of severe PH in chronic lung disease was not found to be prognostic in the present analysis. Based on these findings, while bearing in mind the limitations of this and previous analyses, we believe that PVR >5 WU should be used to define the presence of severe PH in patients with chronic lung disease.

Olsson et al. ERJ 2022.

PH-COPD: Therapy

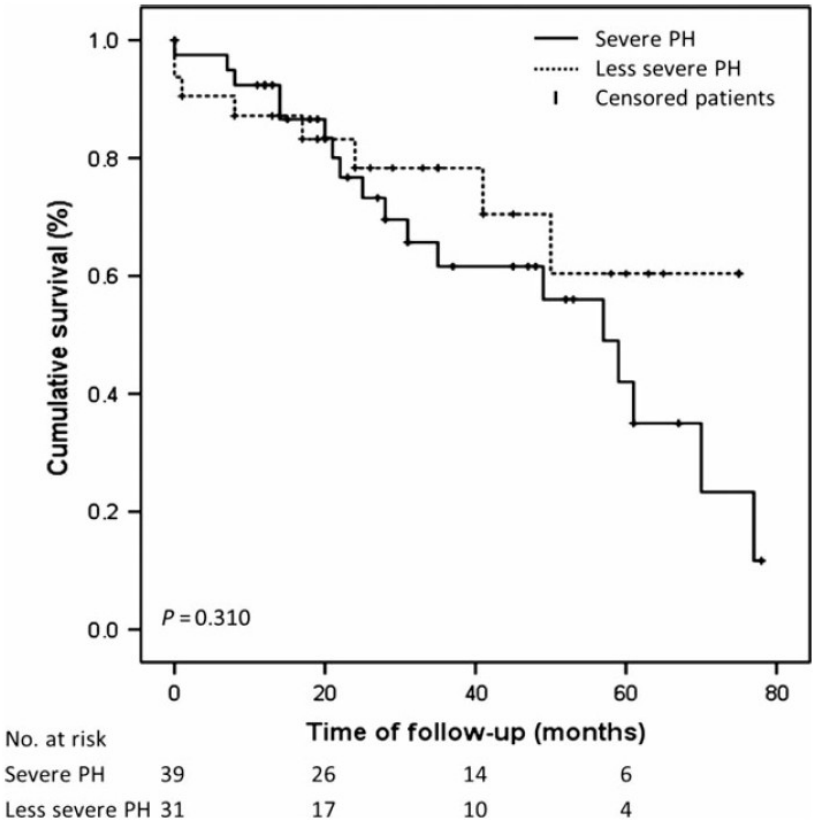


Figure 2 Cumulative survival according to pulmonary hypertension severity in all patients. PH, pulmonary hypertension.

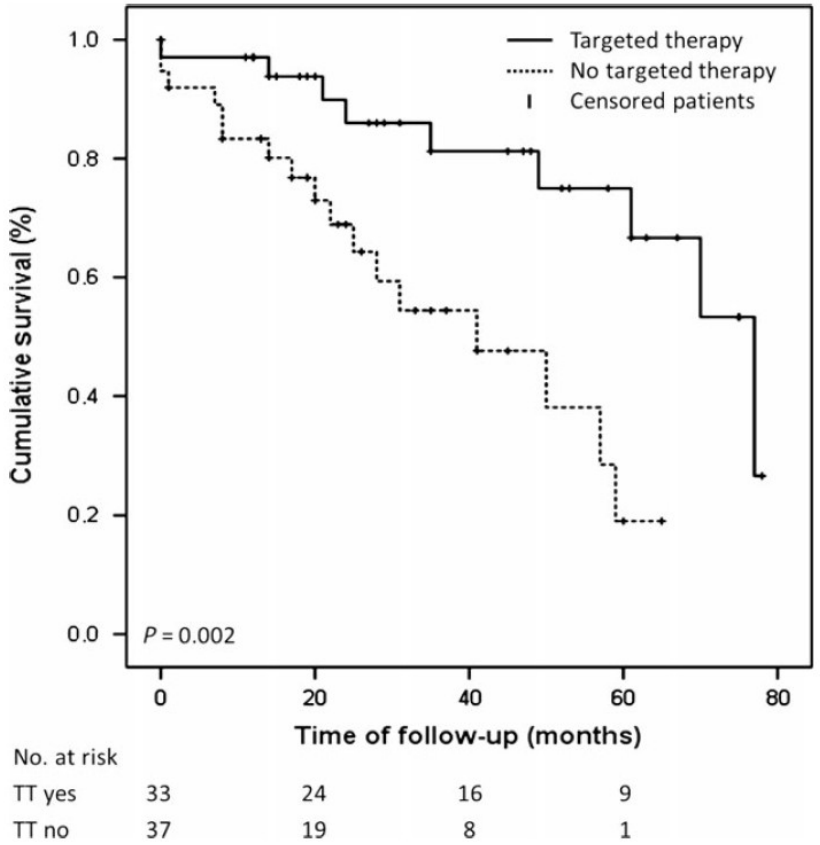


Figure 3 Cumulative survival according to the use of targeted therapy in all patients. TT, targeted therapy; targeted therapy refers to endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs.

Table 2 Effect of targeted therapy on survival according to subgroups

Group	n	HR (95% CI)	*P* value
All	72	0.262 (0.106, 0.649)	0.004
Severe PH	40	0.182 (0.061, 0.540)	0.002
Less severe PH	32	0.255 (0.030, 2.138)	0.208
Obstructive lung disease	29	0.235 (0.047, 1.160)	0.075
Restrictive lung disease	27	0.285 (0.059, 1.378)	0.118
Radiological diagnosis	16	0.220 (0.036, 1.345)	0.101
Phosphodiesterase 5-inhibitors	29	0.495 (0.212, 1.158)	0.105
Endothelin receptor antagonists	11	0.359 (0.105, 1.235)	0.104

CI, confidence interval; HR, hazard ratio; PH, pulmonary hypertension.

Lange et al. Cardiovasc Ther 2014.

PH-COPD: Therapy

Table 1 Demographics, Pulmonary Function Test Results, and Functional Capacity of Patients Who Assumed at Least One Dose of Sildenafil or Placebo: Comparison at Baseline

Variable[a]	Placebo ($n = 10$)	Sildenafil ($n = 18$)	p-value
Male gender, %	80.0	72.2	NS
Age, years	64.1 ± 11.0	66.4 ± 6.5	NS
BMI, kg/m^2	24.9 ± 4.8	27.2 ± 6.2	NS
F_{IO_2}, %	26.3 ± 7.1	28.3 ± 7.2	NS
Pa_{O_2}, mm Hg	74.4 ± 14.9	74.2 ± 14.3	NS
Pa_{CO_2}, mm Hg	44.5 ± 9.0	40.3 ± 5.2	NS
A-a O_2 gradient, mm Hg	57.5 ± 55.0	77.1 ± 54.1	NS
Pulmonary function test			
FEV_1, % predicted	48.4 ± 25.3	54.4 ± 22.4	NS
FEV_1/FVC, %	0.53 ± 0.17	0.52 ± 0.13	NS
TLC, % predicted	97.1 ± 17.8	101.2 ± 25.1	NS
D_{LCO} %, predicted	34.6 ± 23.0	32.8 ± 12.2	NS
Functional capacity			
6MWT, m	308.5 ± 99.6	229.2 ± 101.4	0.06
BODE Index, units	4.7 ± 2.0	5.2 ± 2.5	NS
MMRC scale, units	2.3 ± 0.7	3.0 ± 0.9	0.07
Hemodynamics			
RAP, mm Hg	9.0 ± 2.6	7.3 ± 3.9	NS
mPAP, mm Hg	39.1 ± 12.5	39.3 ± 7.6	NS
PCWP, mm Hg	12.2 ± 2.9	10.9 ± 2.9	NS
Cardiac index, liters/min/m^2	2.5 ± 0.7	2.4 ± 0.5	NS
Stroke volume index, ml/m^2	33.2 ± 9.9	29.4 ± 7.6	NS
Total PVR, WU	9.2 ± 3.3	9.7 ± 3.1	NS
PVR, WU	6.3 ± 3.1	7.0 ± 2.6	NS
SVR, WU	23.7 ± 8.5	21.4 ± 5.7	NS
Heart rate, beats/min	77.8 ± 15.8	82.0 ± 10.9	NS
SF-36 general health, units	44.6 ± 18.6	36.5 ± 16.1	NS

6MWT, 6-minute walk test; A-a O_2 gradient, alveolar-to-arterial gradient; BMI, body mass index; D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; F_{IO_2}, fraction of inspired oxygen; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; MMRC, Modified Medical Research Council; NS, not significant; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Pa_{O_2}, partial pressure of arterial oxygen; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance; TLC, total lung capacity; PVR, pulmonary vascular resistance.

[a]Continuous data are shown as mean ± standard deviation and categoric data as indicated.

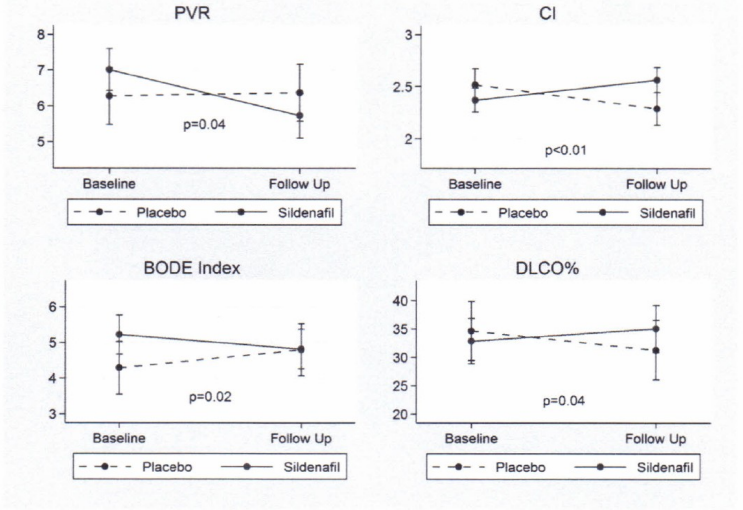


Figure 3 Primary and secondary end point variables significantly varied in patients treated with sildenafil (see also Tables 2–4). The error bars indicate the standard deviation. BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; CI, cardiac index; D_{LCO}, diffusion capacity of the lung for carbon monoxide; PPVR, peripheral pulmonary vascular resistance.

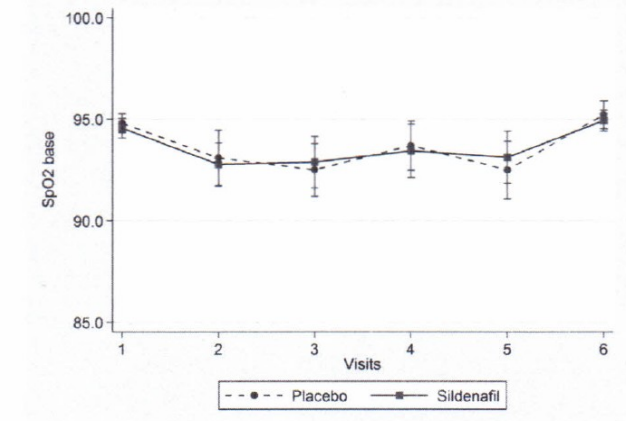
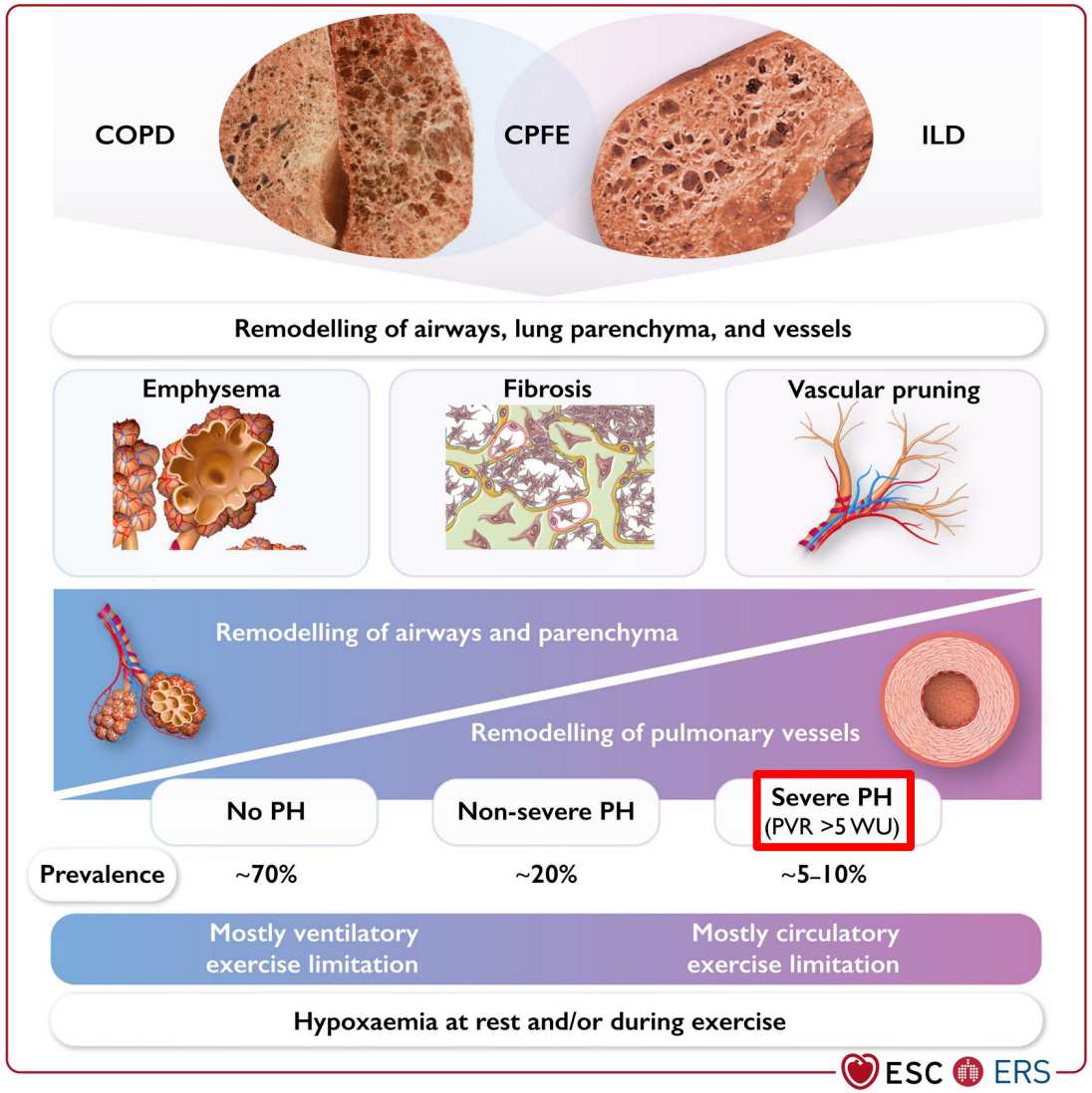


Figure 4 Trend of rest peripheral capillary oxygen saturation (Spo_2) at the scheduled visits

Vitulo et al. JHLT 2016.

Haemodynamic definitions of PH: severe PH-Lung



Recommendations	Class[a]	Level[b]
If PH is suspected in patients with lung disease, it is recommended that echocardiography[c] be performed and the results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging	I	C
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I	C
In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[d]	I	C
In patients with lung disease and severe PH, an individualized approach to treatment is recommended	I	C
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation	I	C
In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I	C
Inhaled treprostinil may be considered in patients with PH associated with ILD[734]	IIb	B
The use of ambrisentan is not recommended in patients with PH associated with IPF[740]	III	B
The use of riociguat is not recommended in patients with PH associated with IIP[181]	III	B
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]	III	C

Humbert et al. EHJ 2022, ERJ 2022.

PH-Lung: Group 1 vs. Group 3 PH

Medical University of Graz

Table 1 Differential Diagnosis Between Group 1 (PAH) and Group 3 (PH Due to Lung Disease) PH

Criteria Favoring Group 1 (PAH)	Parameter	Criteria Favoring Group 3 (PH Due to Lung Disease)
Normal or mildly impaired	Ventilatory function	Moderate to very severe impairment
FEV1 >60% predicted (COPD)		FEV1 <60% predicted (COPD)
FVC >70% predicted (IPF)		FVC <70% predicted (IPF)
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan*	Characteristic airway and/or parenchymal abnormalities
Features of exhausted circulatory reserve		Features of exhausted ventilator reserve
Preserved breathing reserve		Reduced breathing reserve
Reduced oxygen pulse		Normal oxygen pulse
Low Co/Vo_2 slope		Normal Co/Vo_2 slope
Mixed venous oxygen saturation at lower limit		Mixed venous oxygen saturation above lower limit
No change or decrease in $PaCo_2$ during exercise		Increase in $PaCo_2$ during exercise

*As to CT diagnosis, parenchymal changes linked to PVOD are to be discriminated from those associated with DPLD.† Features of exhausted circulatory reserve are also noted in severe PH-COPD and severe PH-IPF, but are then accompanied by major lung function and CT abnormalities.

Co/Vo_2 = cardiac output/oxygen consumption ratio; COPD = chronic obstructive pulmonary disease; CT = computed tomography; DPLD = diffuse parenchymal lung disease; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; $PaCo_2$ = partial pressure of carbon dioxide in arterial blood; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease.

Table 2 Management of PH in the Setting of Chronic Lung Disease

Underlying Lung Disease	mPAP <25 mm Hg at Rest	mPAP ≥25 and <35 mm Hg at Rest	mPAP ≥35 mm Hg at Rest*
COPD with FEV1 ≥60% of predicted IPF with FVC ≥70% of predicted CT: absence of or only very modest airway or parenchymal abnormalities	No PH No PAH treatment recommended	PH classification uncertain No data currently support treatment with PAH-approved drugs	PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3) Refer to a center with expertise in both PH and chronic lung disease
COPD with FEV1 <60% of predicted IPF with FVC <70% of predicted Combined pulmonary fibrosis and emphysema on CT	No PH No PAH treatment recommended	PH-COPD, PH-IPF, PH-CPFE No data currently support treatment with PAH-approved drugs	Severe PH-COPD, severe PH-IPF, severe PH-CPFE Refer to a center with expertise in both PH and chronic lung disease for individualized patient care because of poor prognosis; randomized controlled trials required

*Lower PA pressures may be clinically significant in COPD/DPLD patients with depressed cardiac index or right ventricular dysfunction.

CPFE = combined pulmonary fibrosis and emphysema; mPAP = mean pulmonary artery pressure; other abbreviations as in Table 1.

Seeger et al. JACC 2013.

PH-Lung: Group 1 vs. Group 3 PH

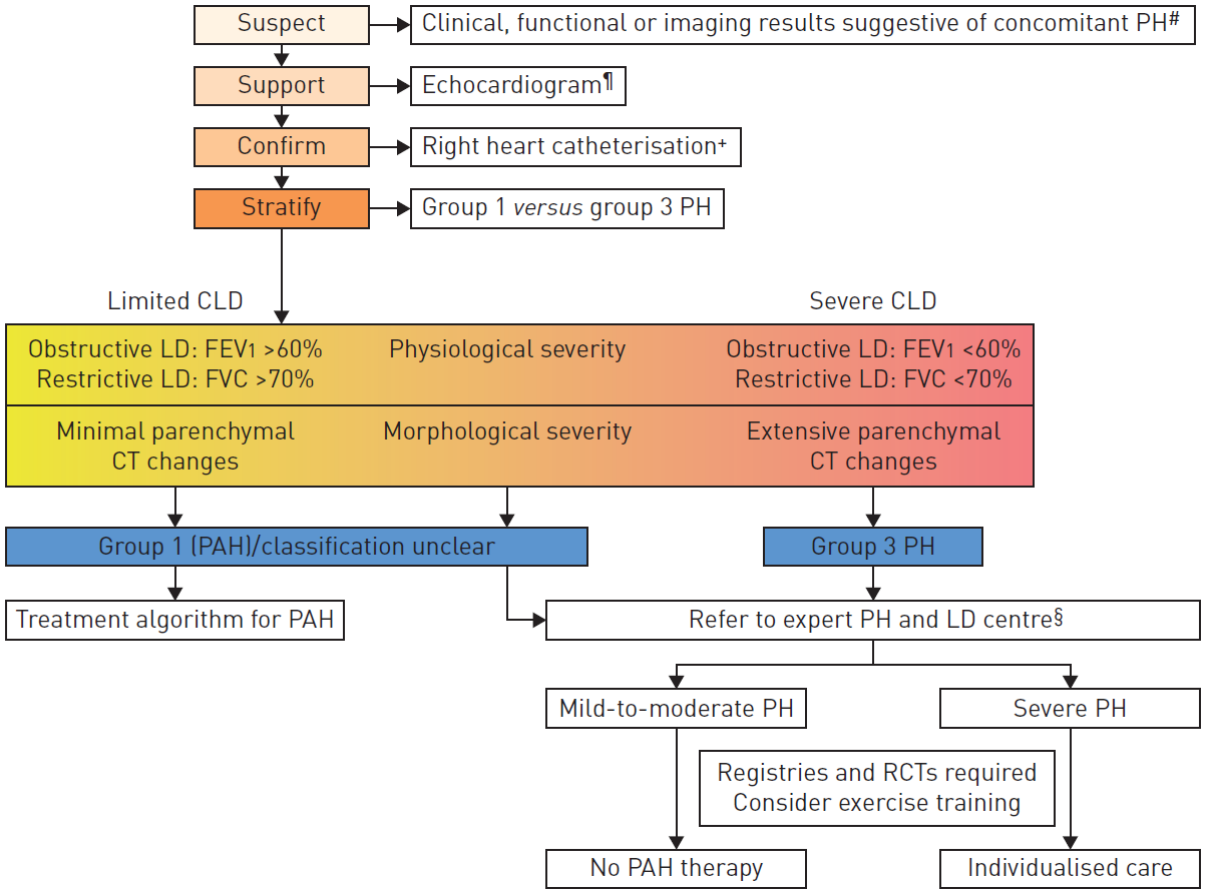


Table 14 Characteristic diagnostic features of patients with different forms of pulmonary hypertension

Diagnostic tool	Characteristic findings/ features	Group 1 (PAH)	Group 2 (PH associated with left heart disease)	Group 3 (PH associated with lung disease)	Group 4 (PH associated with pulmonary artery obstructions)
5.1.1 Clinical presentation	Clinical features	Variable age, but young, female patients may be predominantly affected.[a161] Clinical presentation depends on associated conditions and phenotype See *Section 5.1.1*	Mostly elderly patients, female predominance in case of HFpEF.[161] History and clinical findings suggestive of LHD	Mostly elderly patients, male predominance.[161] History and clinical findings suggestive of lung disease. Smoking history common	Variable age, but elderly male and female equally affected. History of VTE (CTEPH may occur in the absence of a VTE history). Risk factors for CTEPH See *Section 10.1*
	Oxygen requirement for hypoxaemia	Uncommon, except for conditions with low DLCO or right-to-left shunting	Uncommon	Common, often profound hypoxaemia in severe PH	Uncommon; common in severe cases with predominantly distal pulmonary artery occlusions
5.1.3 Chest radiography		RA/RV/PA size ↑ Pruning of peripheral vessels	LA/LV size ↑ Cardiomegaly Occasional signs of congestion (interstitial oedema/Kerley lines, alveolar oedema, pleural effusion)	Signs of parenchymal lung disease	RA/RV/PA size ↑ Number and size of peripheral vessels ↓ Occasional signs of pulmonary infarction
5.1.4 Pulmonary function tests and ABG	Spirometry/PFT impairment	Normal or mildly impaired	Normal or mildly impaired	Abnormal as determined by the underlying lung disease	Normal or mildly impaired
	DLCO	Normal or mild-to-moderately reduced (low DLCO in SSc-PAH, PVOD, and some IPAH phenotypes)	Normal or mild-to-moderately reduced, especially in HFpEF	Often very low (<45% predicted)	Normal or mild-to-moderately reduced
	Arterial blood gas PaO_2 $PaCO_2$	Normal or reduced Reduced	Normal or reduced Usually normal	Reduced Reduced, normal, or increased	Normal or reduced Normal or reduced
5.1.5 Echocardiography		Signs of PH (increased sPAP, enlarged RA/RV) Congenital heart defects may be present See *Section 5.1.5*	Signs of LHD (HFrEF, HFpEF, valvular) and PH (increased sPAP, enlarged RA/RV) See *Section 8*	Signs of PH (increased sPAP, enlarged RA/RV) See *Section 5.1.5*	Signs of PH (increased sPAP, enlarged RA/RV) See *Section 5.1.5*
5.1.6 Lung scintigraphy	Planar – SPECT V/Q	Normal or matched	Normal or matched	Normal or matched	Mismatched perfusion defect
5.1.7 Chest CT		Signs of PH or PVOD See *Section 5.1.7*	Signs of LHD Pulmonary oedema Signs of PH	Signs of parenchymal lung disease Signs of PH	Intravascular filling defects, mosaic perfusion, enlarged bronchial arteries Signs of PH
5.1.11 Cardiopulmonary exercise testing		High VE/VCO_2 slope Low $P_{ET}CO_2$, decreasing during exercise No EOV	Mildly elevated VE/VCO_2 slope Normal $P_{ET}CO_2$, increasing during	Mildly elevated VE/VCO_2 slope Normal $P_{ET}CO_2$,	High VE/VCO_2 slope Low $P_{ET}CO_2$, decreasing during

Nathan et al. ERJ 2019; Humbert et al. ERJ 2022, EHJ 2022.

PH-Lung: Group 1 vs. Group 3 PH

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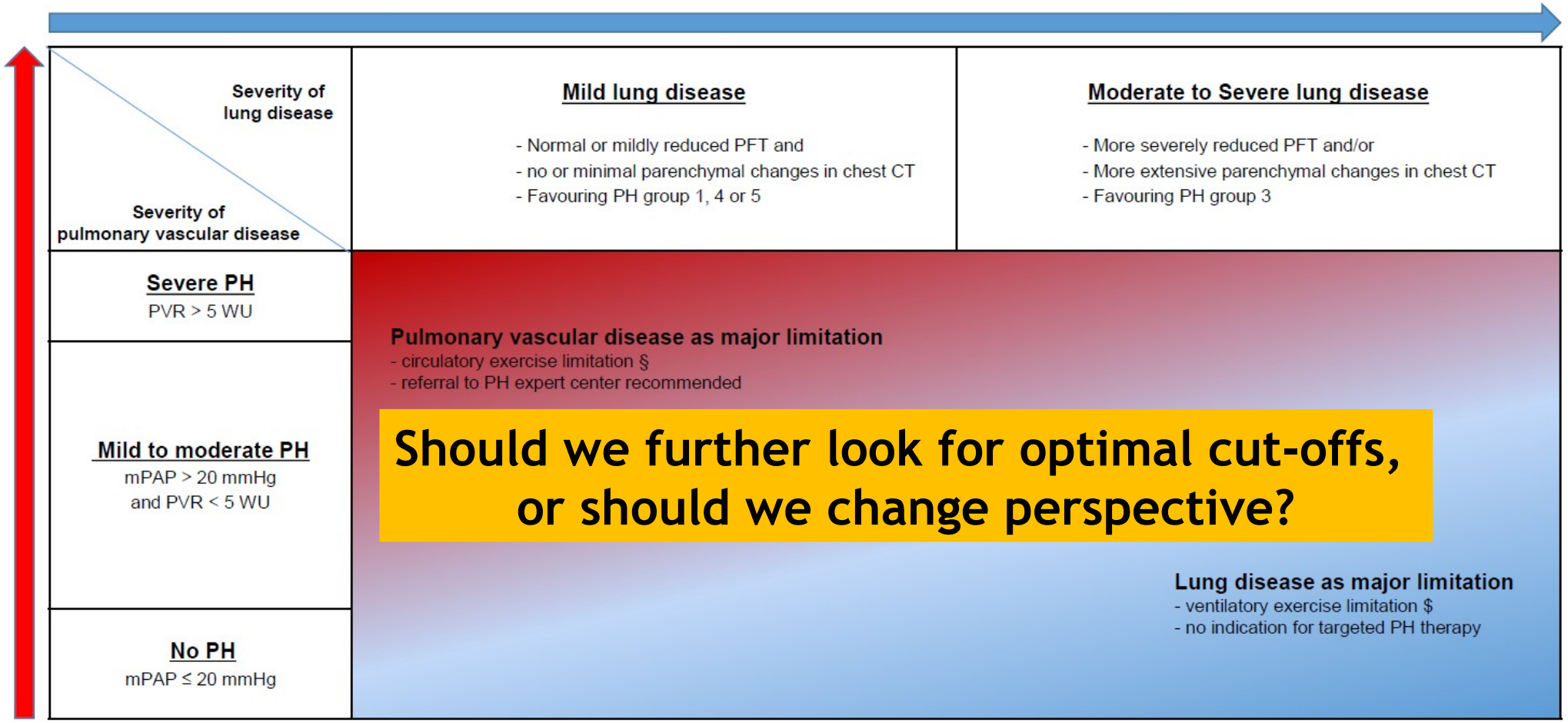

PH-Lung: Group 1 vs. Group 3 PH

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Table 1 Patient Characteristics at the Time of IPAH Diagnosis

Characteristic	Cluster 1 $n = 106$	Cluster 2 $n = 301$	Cluster 3 $n = 434$	p-value[a]	All $n = 846$
Age, years (median, Q1–Q3)	45 (31–61)	75 (68–80)	72 (64–78)	<0.001	72 (61–78)
Female sex, *n* (%)	80 (76)	296 (98)	121 (28)	<0.001	497 (59)
BMI, kg/m^2 (mean ± SD)	24.2 ± 3.2	30.7 ± 7.2	29.1 ± 5.9	<0.001	29.1 ± 6.5
Smoking habits					
Former/current smokers, *n* (%)	33 (31)	0 (0)	343 (79)	<0.001	376 (44)
Pack years (median, Q1–Q3)	16 (10–28)	—	33 (20–50)	<0.001	30 (15–50)
WHO FC				<0.001	
I/II, *n* (%)	20 (19)	20 (7)	25 (6)		65 (8)
III, *n* (%)	75 (72)	215 (72)	311 (76)		601 (74)
IV, *n* (%)	9 (9)	63 (21)	72 (18)		144 (18)
6MWD, m (mean ± SD)	386 ± 119	268 ± 114	276 ± 108	<0.001	287 ± 118
BNP, ng/l (median, Q1–Q3)	129 (81–259)	206 (92–299)	278 (112–468)	0.183	206 (101–371)
NT-proBNP, ng/l (median, Q1–Q3)	1,313 (524–2,480)	1,579 (676–3,520)	1,835 (634–3,592)	0.065	1,614 (631–3,460)
Hemodynamics					
RAP, mm Hg (mean ± SD)	7 ± 5	8 ± 5	8 ± 4	0.026	8 ± 5
mPAP, mm Hg (mean ± SD)	49 ± 14	40 ± 11	43 ± 11	<0.001	42 ± 12
PAWP, mm Hg (mean ± SD)	8 ± 3	10 ± 3	9 ± 4	<0.001	9 ± 3
CI, l/min/m^2 (mean ± SD)	2.1 ± 0.7	2.0 ± 0.6	2.1 ± 0.7	0.471	2.1 ± 0.7
PVR, dyn·s·cm^{-5} (mean ± SD)	948 ± 463	727 ± 398	730 ± 380	<0.001	756 ± 404
SvO_2, % (mean ± SD)	64 ± 10	64 ± 8	62 ± 8	<0.001	63 ± 8
Pulmonary function and blood gases					
TLC, % predicted (mean ± SD)	99 ± 16	93 ± 17	92 ± 17	<0.001	93 ± 17
FVC, % predicted (mean ± SD)	92 ± 17	83 ± 18	80 ± 20	<0.001	82 ± 20
FEV1, % predicted (mean ± SD)	87 ± 17	80 ± 19	75 ± 20	<0.001	78 ± 19
DLCO, % predicted (mean ± SD)	69 ± 15	56 ± 22	47 ± 21	<0.001	53 ± 22
DLCO <45% predicted, *n* (%)	0 (0)	101 (34)	231 (53)	<0.001	332 (40)
paO_2, mm Hg (mean ± SD)	77 ± 17	65 ± 11	61 ± 12	<0.001	65 ± 14
$paCO_2$, mm Hg (mean ± SD)	33 ± 4	36 ± 6	36 ± 7	<0.001	35 ± 6
Comorbidities					
Arterial hypertension, *n* (%)	0 (0)	251 (83)	320 (74)	<0.001	571 (68)
Coronary heart disease, *n* (%)	0 (0)	58 (19)	153 (35)	<0.001	211 (25)
Diabetes mellitus, *n* (%)	0 (0)	106 (35)	154 (36)	<0.001	260 (31)
BMI ≥30 kg/m^2, *n* (%)	0 (0)	149 (50)	170 (39)	<0.001	319 (38)
At least 1 comorbidity	0 (0)	283 (94)	396 (91)	<0.001	679 (81)
Number of comorbidities				<0.001	
0, *n* (%)	106 (100)	18 (6)	38 (9)		162 (19)
1, *n* (%)	0 (0)	93 (31)	138 (32)		231 (28)
2, *n* (%)	0 (0)	116 (38)	139 (32)		255 (30)
3, *n* (%)	0 (0)	57 (19)	95 (22)		152 (18)
4, *n* (%)	0 (0)	17 (6)	25 (6)		41 (5)
History of atrial fibrillation, *n* (%)	8 (8)	109 (36)	108 (25)	<0.001	225 (27)

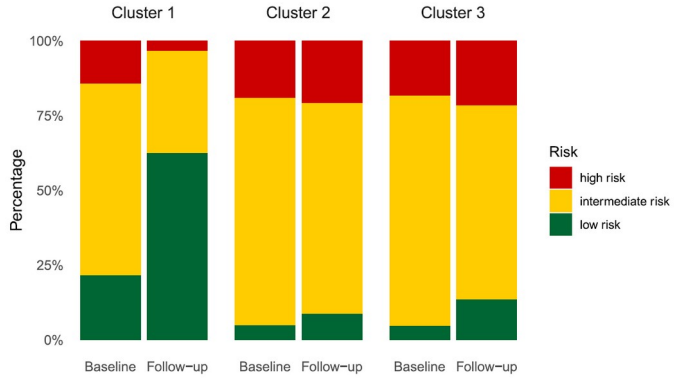


Figure 3 Risk as determined by the Swedish/COMPERA approach at baseline and follow-up in the 3 clusters. COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension.

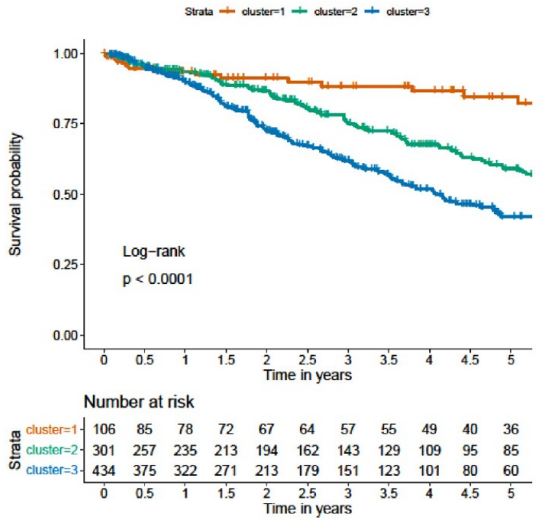
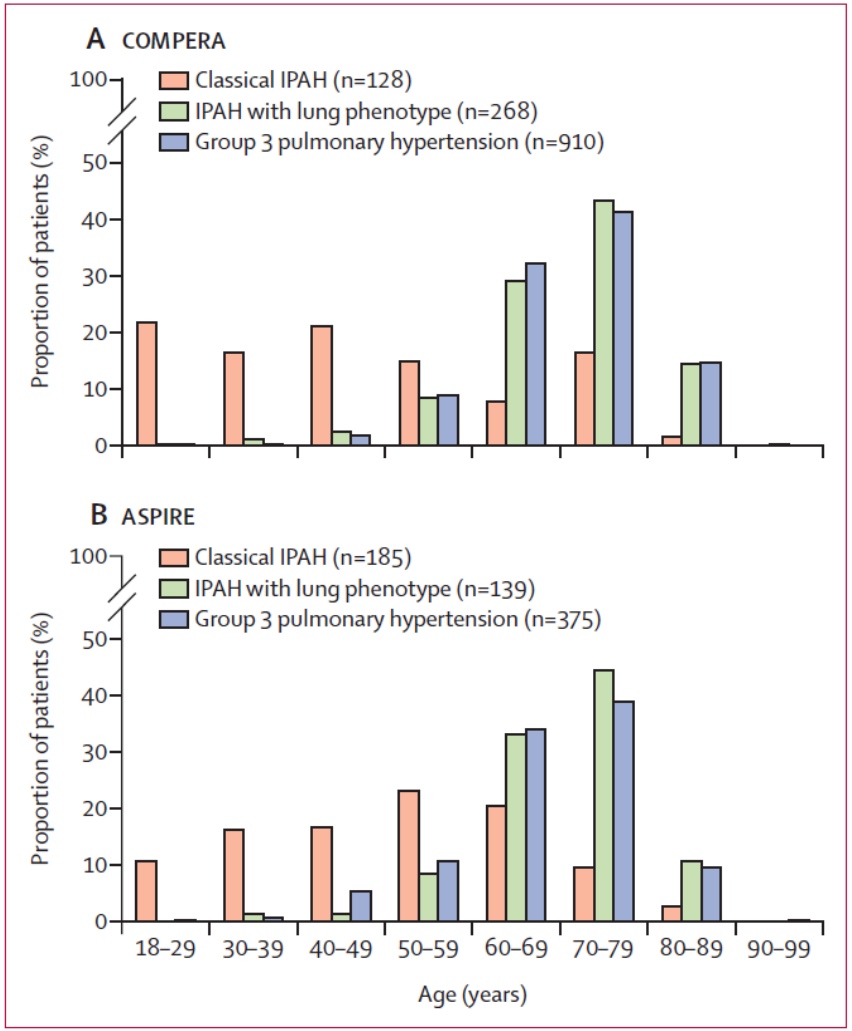


Figure 4 Kaplan-Meier survival estimates according to clusters.

Hoeper et al. JHLT 2020.

PH-Lung: Group 1 vs. Group 3 PH



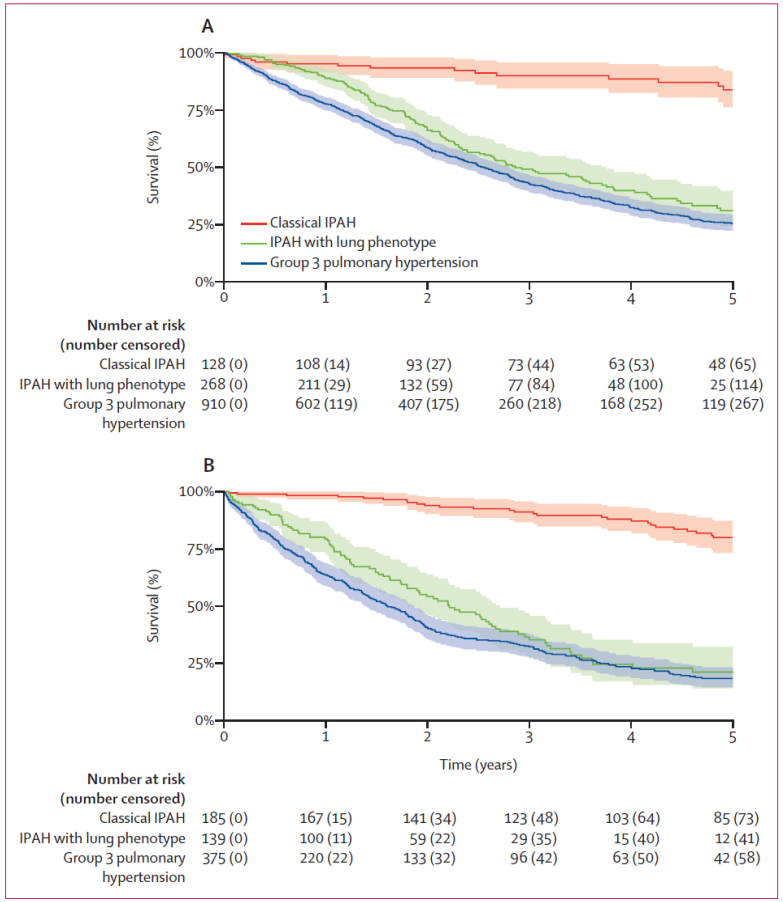


Figure 4: **Kaplan-Meier survival estimates for patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 pulmonary hypertension in COMPERA (A) and ASPIRE (B)**
ASPIRE=Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre.
COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension.
IPAH=idiopathic pulmonary arterial hypertension.

<u>IPAH with lung phenotype:</u> DLCO < 45%, Smoking history

Hoeper et al. Lancet Resp Med 2022.

PH-COPD: to make life even more complicated…

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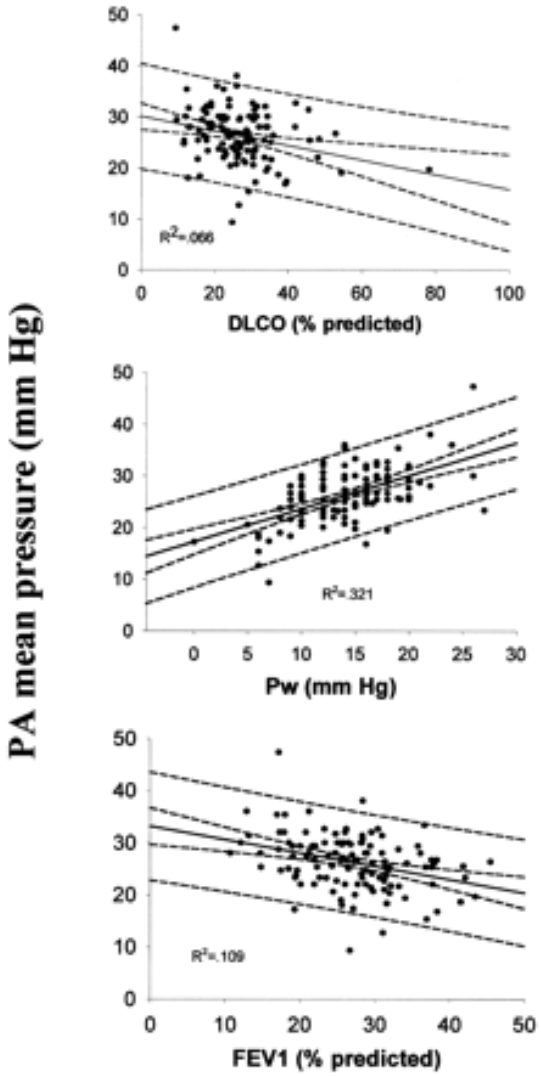
- COPD is frequently associated with left heart disease that may contribute to PH
- COPD exacerbations may lead to significant increase of PAP
- Methodological concerns at the assessment of PAP in COPD

PH-COPD: the role of left heart disease



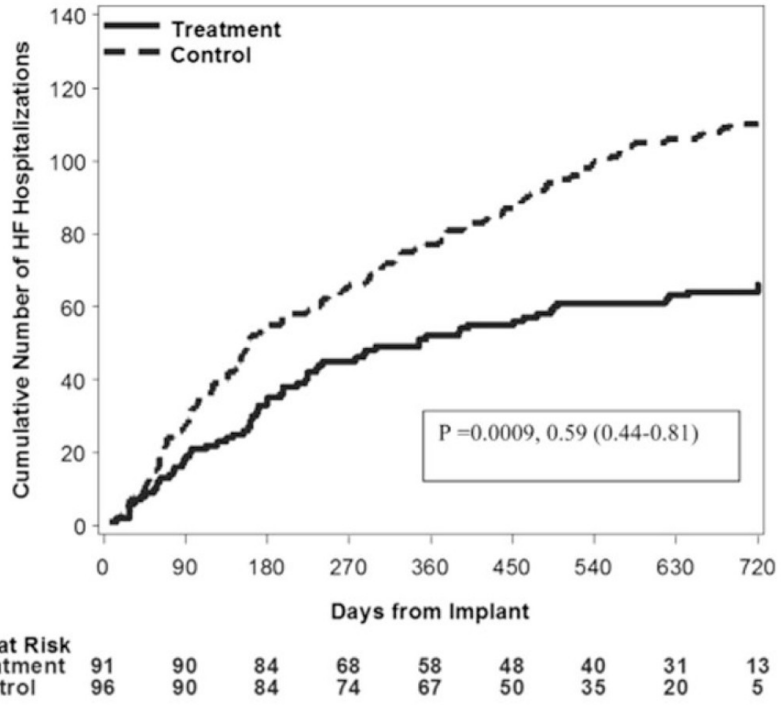


Fig. 1.
Cumulative heart failure (HF) hospitalizations after implantation in subjects with chronic obstructive pulmonary disease. *P* value, hazard ratio (treatment vs control), and 95% confidence interval were derived with the use of the Andersen-Gill model.

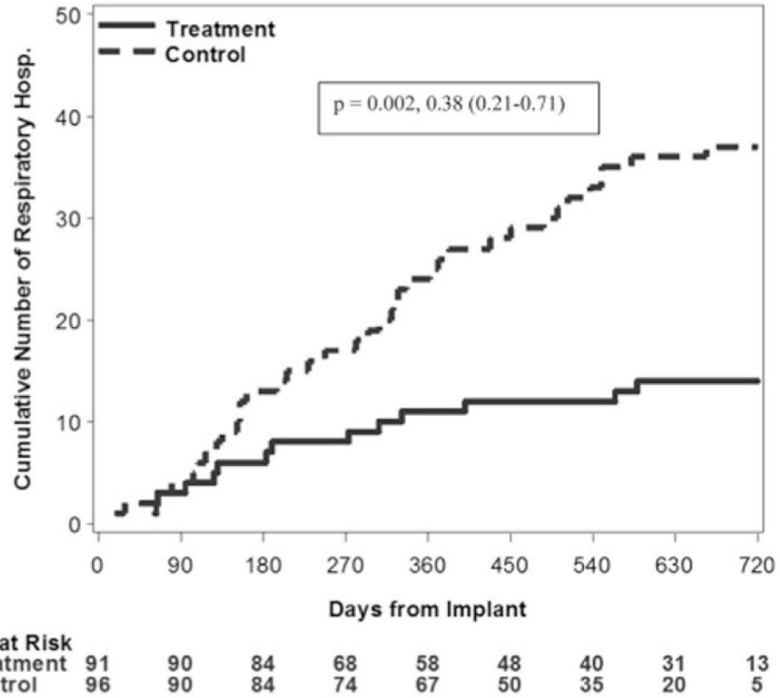


Fig. 3.
Cumulative respiratory hospitalizations after implantation in subjects with chronic obstructive pulmonary disease. P value, hazard ratio (treatment to control), and 95% confidence interval were derived with the use of the Andersen-Gill model.

Scharf et al. AJRCCM 2002, Krahnke et al. J Card Fail. 2015.

PH-COPD: the role of exacerbations

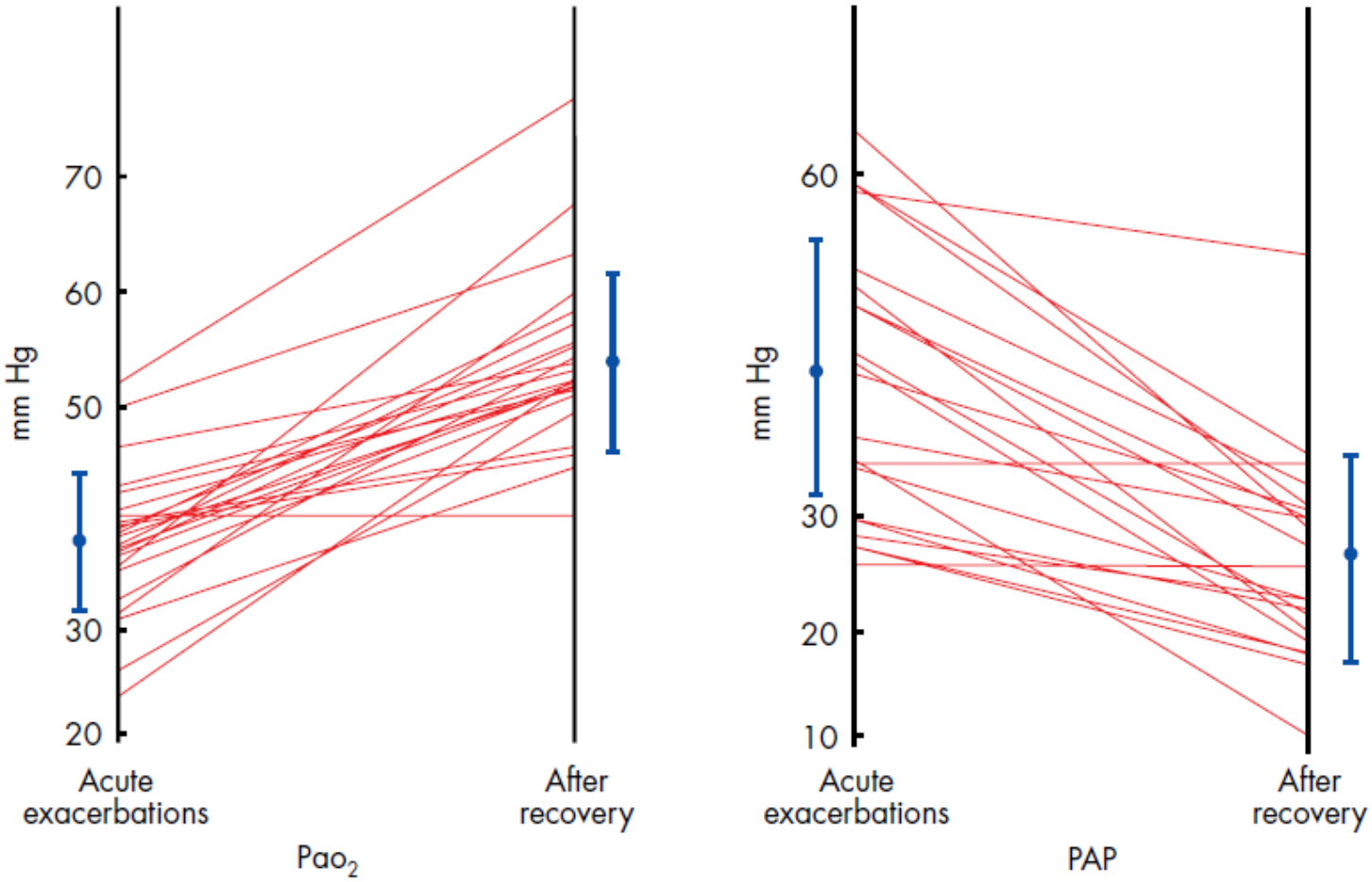


Figure 2 Evolution of arterial oxygen tension (Pa_{O_2}) and mean pulmonary artery pressure (PAP) in a series of chronic obstructive pulmonary disease patients investigated during acute exacerbations and after recovery. The pronounced improvement in Pa_{O_2} (from mean 38 mm Hg to 53 mm Hg) is accompanied by a profound decrease in PAP (from mean 44 mm Hg to 27 mm Hg).

Weitzenblum Heart 2003.

PH-COPD: methodological concerns for the assessment of PAP

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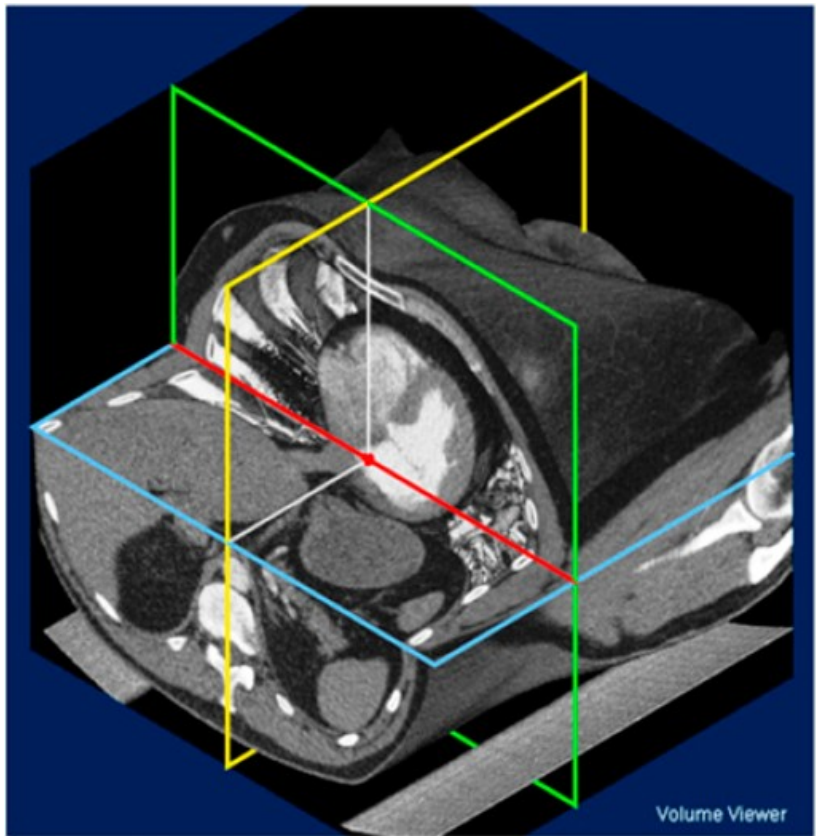

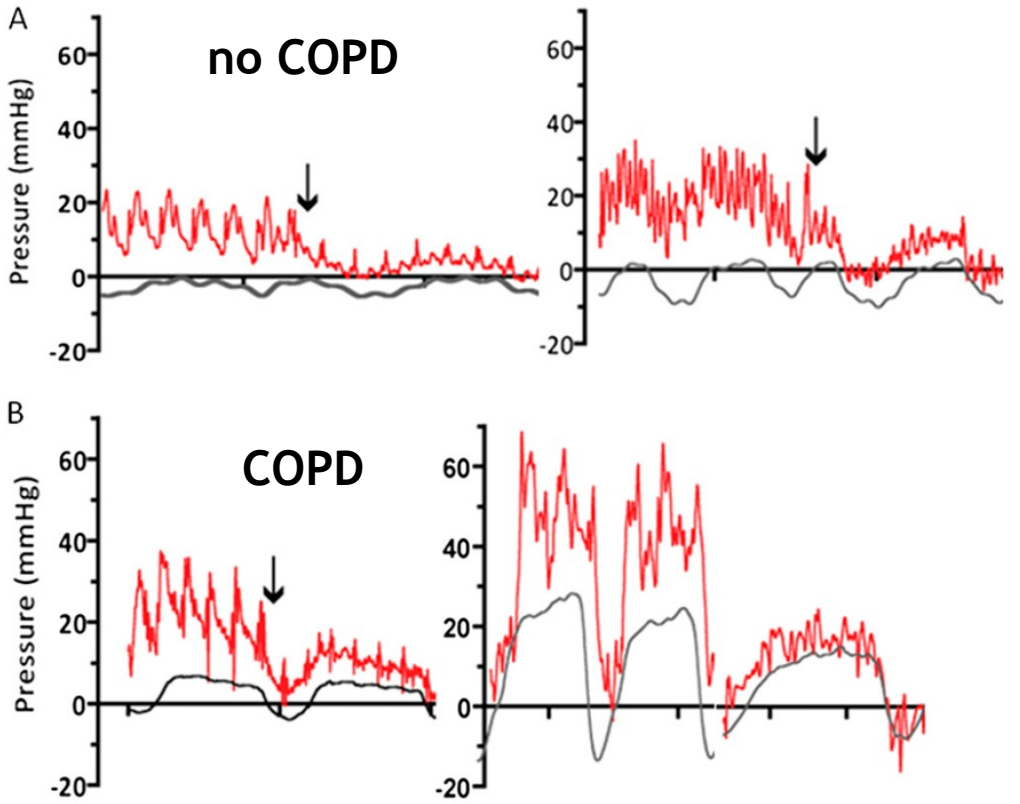

Figure 2. (*A*) Pulmonary artery pressure (*red line*) followed by pulmonary artery wedge pressure (*arrow*) in a normal subject at rest (*left*) and during exercise (*right*). Pleural pressure (*black line*) is on average negative with respiratory swings, which are amplified during exercise. (*B*) Pulmonary artery pressure (*red line*) followed by pulmonary artery wedge pressure (*arrow*) in a patient with chronic obstructive pulmonary disease at rest (*left*) and during exercise (*right*). Pleural pressure (*black line*) shows respiratory swings, which appear transmitted to pulmonary vascular pressures. Reprinted by permission from Reference 30.

Kovacs et al. AJRCCM 2014.

Summary

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- PH-COPD is frequent
- PH-COPD and especially severe PH-COPD is associated with poor prognosis
- No approved therapies for PH-COPD: unmet medical need
- The right therapy for the right patient
  - Severe PH
  - Inhalative application
  - No severe emphysema, no relevant left heart disease
- Methodological concerns should be addressed

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Questions?

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PH-Lung Epidemiology: Prognosis of PH-COPD & severe PH-COPD

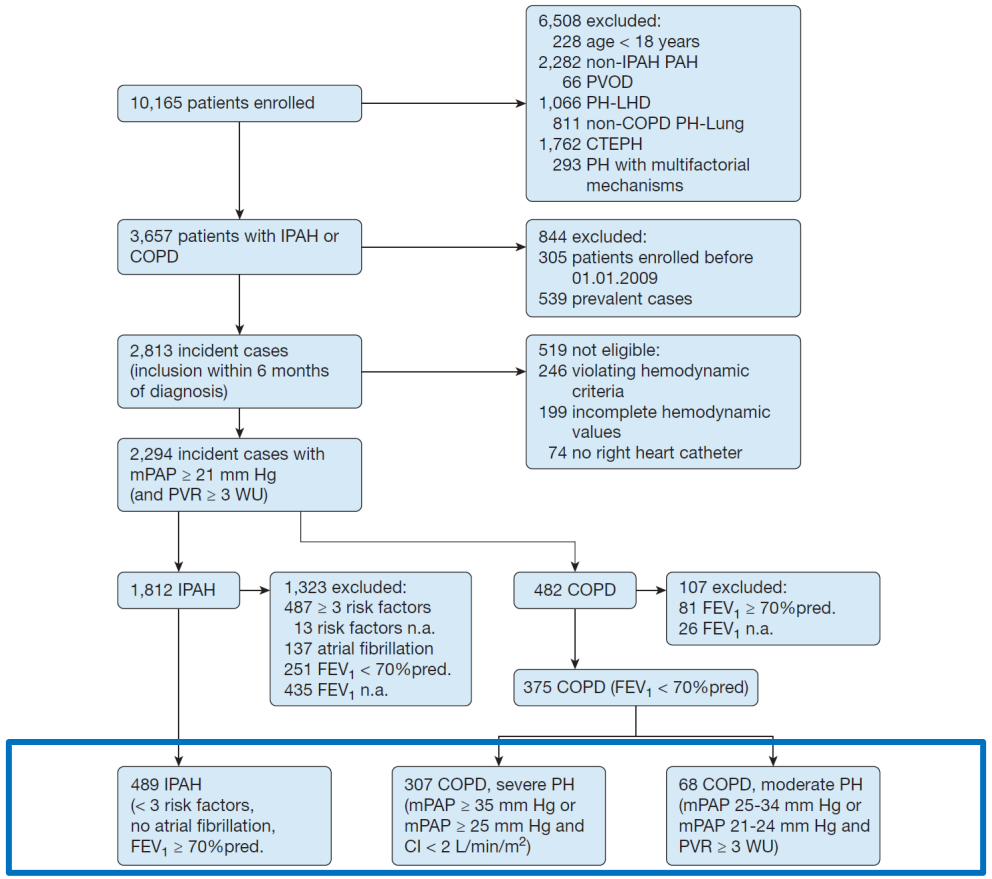

Figure 1 – *Flow chart showing patient selection from the COMPERA database. CI = cardiac index; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; LHD = left heart disease; mPAP = mean pulmonary arterial pressure; n.a. = not assessed; PAH = pulmonary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

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

Characteristic	IPAH (n = 489)	COPD (n = 375)	*P* Value	PH in COPD		
				Moderate (n = 68)	Severe (n = 307)	*P* Value
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)						
Pa_{O_2}, mm Hg	70 ± 26	55 ± 10	< .001	55 ± 9	54 ± 10	.65
Pa_{CO_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.

Vizza et al. Chest 2020.

PH-COPD: Therapy

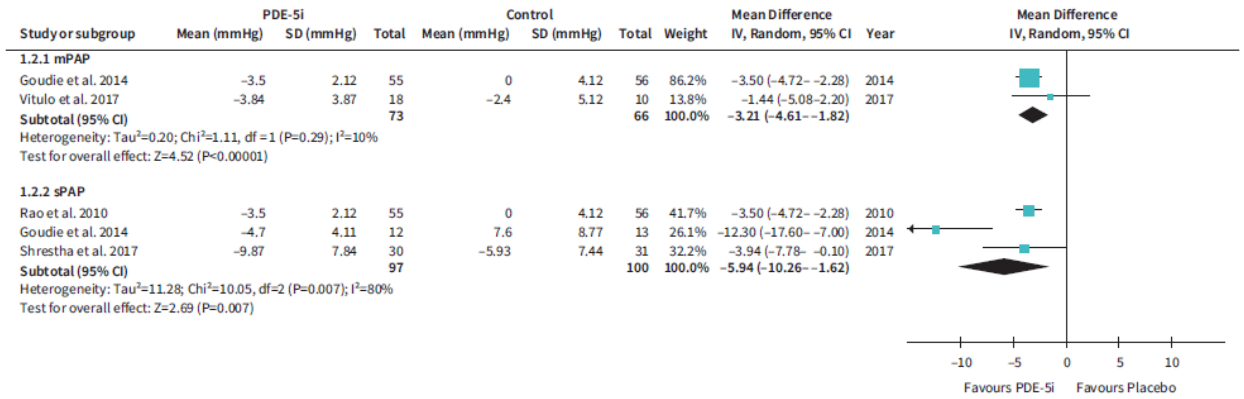

FIGURE 2 The effect of treatment with phosphodiesterase type 5 inhibitors (PDE-5i) on mean pulmonary artery pressure (mPAP; upper panel) and systolic pulmonary artery pressure (sPAP; lower panel) in COPD-associated pulmonary hypertension. Note: mPAP was measured by right heart catheterisation (Vitulo 2017) or estimated from echo measurement of sPAP (Goudie 2014). IV: inverse variance.

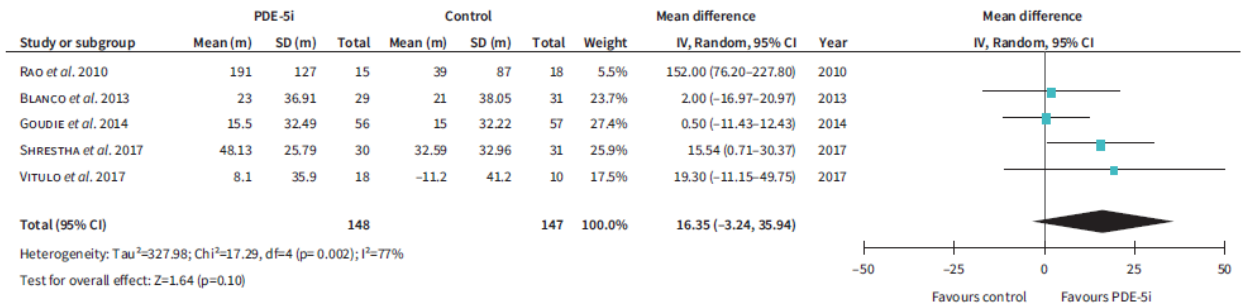

FIGURE 3 The effect of treatment with phosphodiesterase type 5 inhibitors (PDE-5i) on 6-min walk distance in patients with COPD-associated pulmonary hypertension (PH). Note: PH was diagnosed either by right heart catheterisation (Vitulo 2017) or by echocardiogram in the other studies. IV: inverse variance.

Arif et al. ERJOR 2022.

PH-COPD: Therapy

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TABLE 3 Summary of outcomes in treatment of COPD-associated pulmonary hypertension (PH)

Treatment	PH outcomes		Clinical outcomes				
	Cardiopulmonary haemodynamic	RV function	Symptoms	Functional capacity	HRQoL	Hospitalisation	Survival
Oxygen (n=4)							
LTOT (n=8)	+	NA	NA	NA	NA	NA	+
NOT (n=2)	+/–	NA	NA	NA	NA	NA	0
CCBs (n=4)							
Nifedipine (n=3)	0	NA	+	NA	NA	NA	0
Felodipine (n=1)	+	NA	NA	0	NA	NA	NA
PH-targeted therapy (n=9)							
PDE type 5 inhibitors							
Sildenafil (n=5)	+	NA	+/–	+/–	+/–	NA	NA
Tadalafil (n=1)	+	NA	0	0	0	NA	NA
ERA							
Bosentan (n=2)	+/–	NA	+	+/–	+	NA	NA
Ambrisentan (n=1)	NA	+	+/–	0	NA	NA	NA
Statins (n=6)							
Atorvastatin (n=4)	+	0	NA	0	NA	NA	NA
Rosuvastatin (n=1)	+	0	0	+	0	NA	NA
Pravastatin (n=1)	+	NA	+	+	NA	NA	NA

RV: right ventricular; HRQoL: health-related quality of life; LTOT: long-term oxygen therapy; NOT: nocturnal oxygen therapy; CCB: calcium channel blocker; PDE: phosphodiesterase; ERA: endothelin receptor antagonist. Clinically relevant effects: +: significant; +/–: uncertain; 0: none; NA: not assessed.

Arif et al. ERJOR 2022.

PH-COPD: Therapy

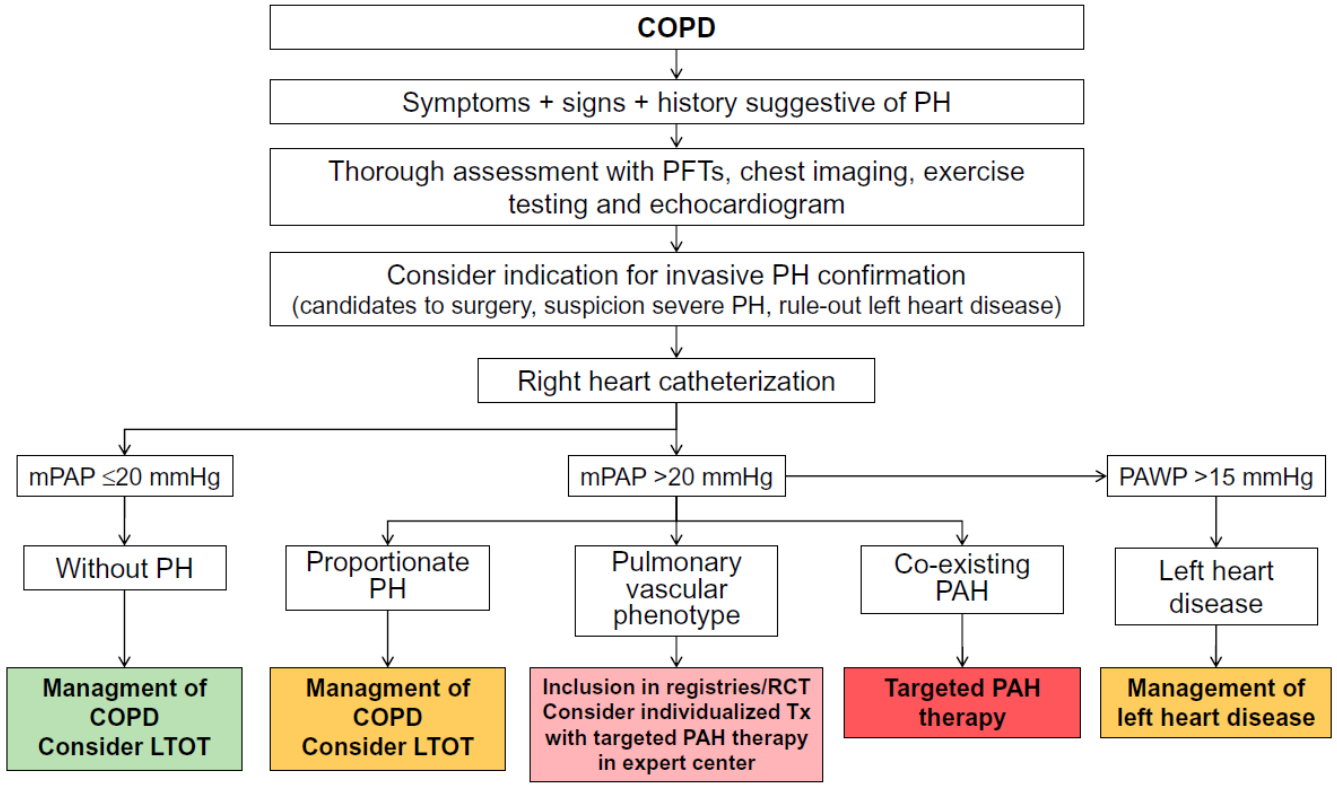

Figure 4 Diagnosis and management of pulmonary hypertension in COPD.
Abbreviations: COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; LTOT, long-term oxygen treatment; RCT, randomized controlled trials; Tx, treatment; PAH, pulmonary arterial hypertension.

Blanco et al. Int J COPD 2020.

PH-Lung: The right treatment for the right patients

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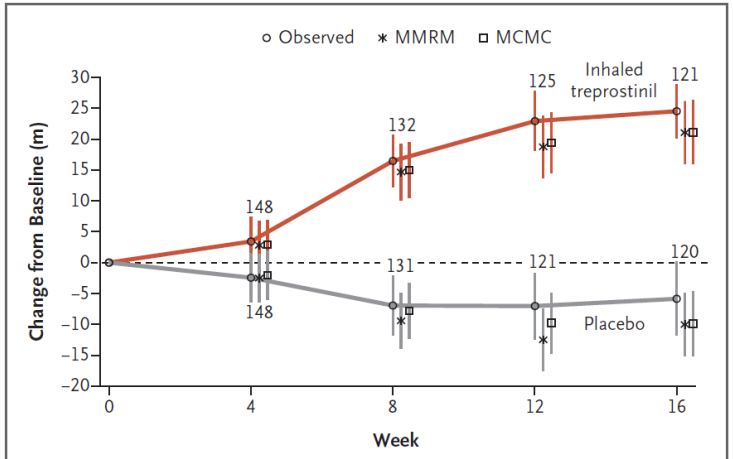
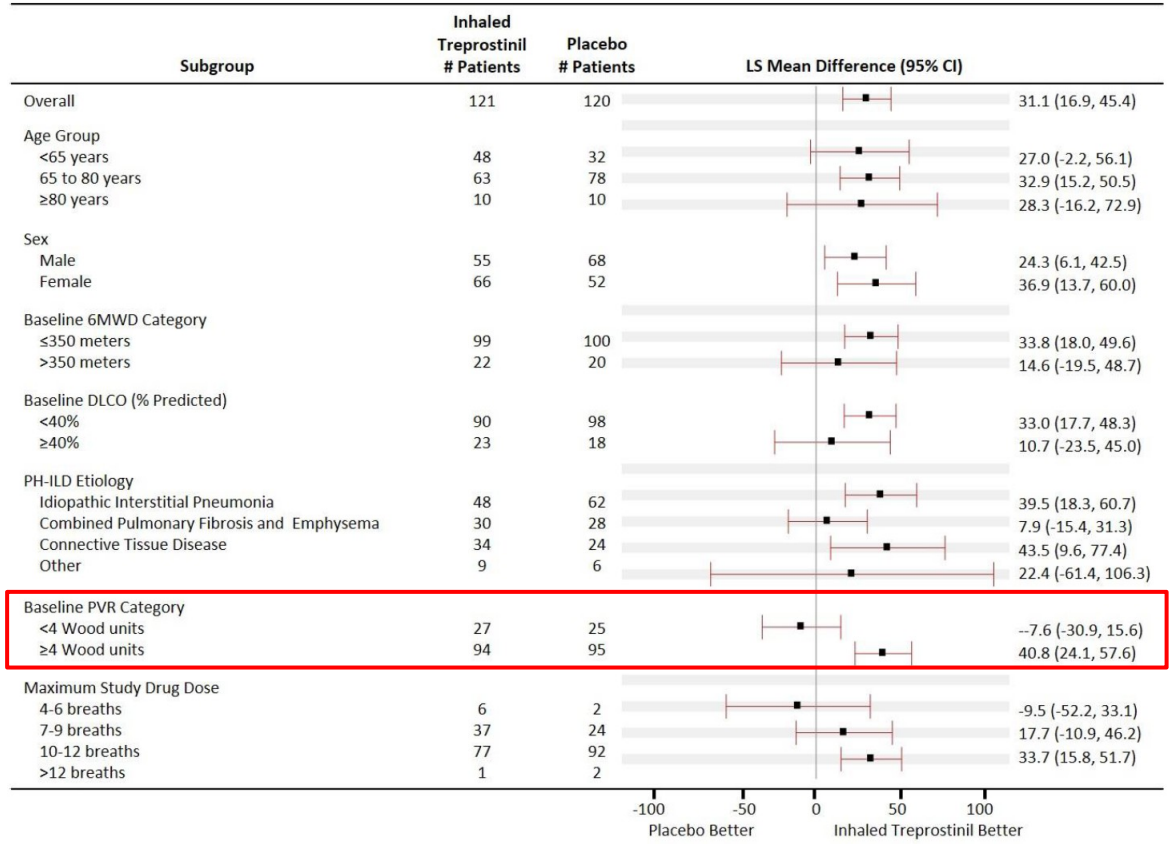


Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

Shown are mean (±SE) changes from baseline (dashed line) in peak 6-minute walk distance over the 16-week trial period. The data shown are for patients with available data (observed) as well as for the results of two analysis methods used to account for missing data. The values shown at each data point indicate the number of patients assessed at that time point. The primary analysis used mixed-model repeat-measurement (MMRM) methods, with the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed with the use of a multiple imputation approach with a multivariate normal imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model included treatment group, all scheduled visits, patient's sex, and patient's age at randomization. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Figure S2. Forest Plot on Subgroup Analyses of Peak 6-Minute Walk Distance (meter) at Week 16.



Waxman et al. NEJM 2021.

PH-COPD: The right treatment for the right patients

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- Patients with more severe PH
- Patients with no severe Emphysema
- Inhalative therapy to avoid V/Q mismatch?

PH-COPD: Therapy

Medical University of Graz

Table 1 Comparison of Baseline Characteristics at Study Start in the HRCT Subgroup and the Overall RISE-IIP Study Population

	Overall RISE-IIP population ($n = 147$)		RISE-IIP HRCT subgroup ($n = 65$)		RISE-IIP no HRCT subgroup ($n = 82$)	
	Riociguat up to 2.5 mg tid ($n = 73$)	Placebo ($n = 74$)	Riociguat up to 2.5 mg tid ($n = 35$)	Placebo ($n = 30$)	Riociguat up to 2.5 mg tid ($n = 38$)	Placebo ($n = 44$)
Female, *n* (%)	23 (32)	29 (39)	9 (26)	10 (33)	14 (37)	19 (43)
Age, years	68 (8)	69 (8)	68 (7)	68 (10)	68 (9)	69 (7)
Body mass index, kg/m^2	29.8 (5.1)	28.5 (5.9)	28.7 (4.7)	27.4 (4.8)	30.7 (5.4)	29.2 (6.6)
Classification of IIP, *n* (%)						
IPF	54 (74)	49 (66)	26 (74)	19 (63)	28 (74)	30 (68)
Idiopathic NSIP	9 (12)	14 (19)	4 (11)	6 (20)	5 (13)	8 (18)
Respiratory bronchiolitis-ILD	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Cryptogenic organizing pneumonia	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (2)
Acute interstitial pneumonia	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (2)
Idiopathic LIP	0 (0)	2 (3)	0 (0)	1 (3)	0 (0)	1 (2)
Unclassifiable IIPs	9 (12)	7 (9)	4 (11)	4 (13)	5 (13)	3 (7)
WHO FC II/III/IV, %	22/68/10	30/61/9	20/71/9	33/57/10	24/66/11	27/64/9
6MWD[a], m	307.0 (80.0)	324.0 (66.0)	313.8 (83.1)	336.7 (72.7)	313.6 (77.0)	326.0 (60.7)
Hemodynamics						
RAP, mm Hg	6.7 (4.0) $n = 71$	6.7 (4.5) $n = 73$	6.2 (4.4) $n = 34$	7.2 (3.8)	7.1 (3.6) $n = 37$	6.4 (4.9) $n = 43$
mPAP, mm Hg	33.2 (8.2)	33.5 (9.4)	33.5 (9.1)	31.9 (8.2)	32.9 (7.3)	34.5 (10.1)
Diastolic PAP, mm Hg	22.0 (6.8)	22.6 (7.5)	22.6 (7.4)	21.6 (7.1)	21.5 (6.1)	23.3 (7.8)
Systolic PAP, mm Hg	55.6 (13.4)	55.2 (14.8)	55.4 (14.8)	52.6 (12.5)	55.7 (12.1)	56.9 (16.2)
PVR, dyn.s.cm^{-5}	390.7 (204.5) $n = 72$	417.9 (256.9) $n = 72$	409.2 (258.2) $n = 34$	355.3 (187.0) $n = 29$	374.2 (142.0)	460.2 (289.4) $n = 43$
Cardiac index, L/min/m^2	2.6 (0.7) $n = 72$	2.6 (0.7) $n = 69$	2.7 (0.7) $n = 34$	2.8 (0.7) $n = 29$	2.5 (0.6)	2.5 (0.7) $n = 40$
PAWP, mm Hg	10.6 (3.2)	10.6 (3.0) $n = 73$	10.4 (3.0)	10.7 (2.9)	10.9 (3.5)	10.6 (3.1) $n = 43$
Pulmonary function tests						
FVC, %	76.2 (19.1)	74.3 (15.7)	74.7 (17.1)	73.0 (17.0)	77.6 (21.0)	75.2 (14.9)
FEV_1, %	75.5 (19.1)	75.1 (16.4)	74.7 (17.8)	76.2 (16.8)	76.2 (20.4)	74.4 (16.3)
FEV_1:FVC	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)
TLC, %	66.1 (14.6) $n = 71$	66.3 (12.0)	65.7 (13.5) $n = 34$	64.6 (12.1)	66.4 (15.7) $n = 37$	67.4 (11.8)
DL_{CO}, %	32.0 (11.8) $n = 69$	30.5 (10.9) $n = 71$	31.7 (11.9) $n = 33$	30.5 (11.4) $n = 29$	32.3 (12.0) $n = 36$	30.5 (10.7) $n = 42$

Abbreviations: 6MWD, 6-min walking distance; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LIP, lymphoid interstitial pneumonia; mPAP, mean pulmonary artery pressure; NSIP, non-specific interstitial pneumonia; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; tid, 3 times daily; TLC, total lung capacity; WHO FC, World Health Organization functional class.

Data are mean ± standard deviation unless otherwise stated.

[a]Mean of the maximum values from 3 6MWD measurements taken at baseline.

RISE-IIP (all participants: n=147)

- With HR-CT: n=65/147 (44%)
  - CPFE: n=41/65 (63%)
- Mortality in patients
  - With CPFE: 29% (12/41)
  - Without CPFE: 13% (3/24)

Nathan et al. JHLT 2021.

PH-COPD: Therapy

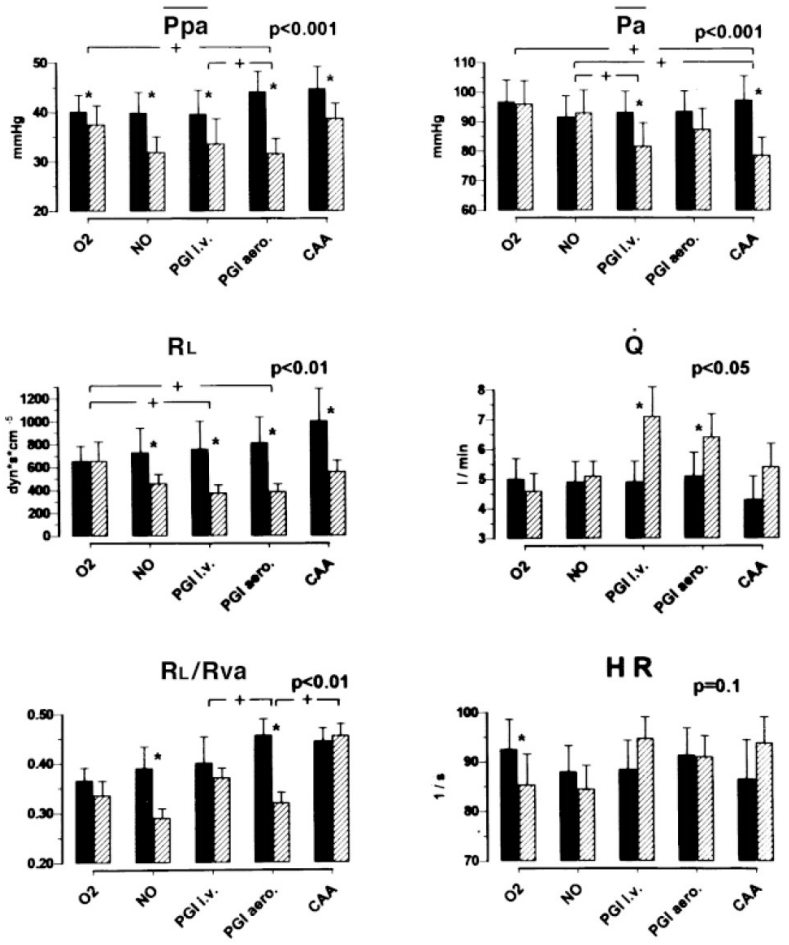

Figure 2. Acute responses to oxygen, NO, intravenously administered and inhaled prostacyclin (PGI i.v. and PGI aero, respectively), and calcium antagonists (CAAs). *Dark columns* and *light columns* give mean values ± SE before and after drug administration, respectively, for mean pulmonary artery pressure ($\overline{Ppa}$), pulmonary vascular resistance (R_L), ratio of pulmonary to systemic vascular resistance (R_L/Rva), mean systemic arterial pressure ($\overline{Pa}$), cardiac output ($\dot{Q}$), and heart rate (HR). For statistics *see* Figure 1.

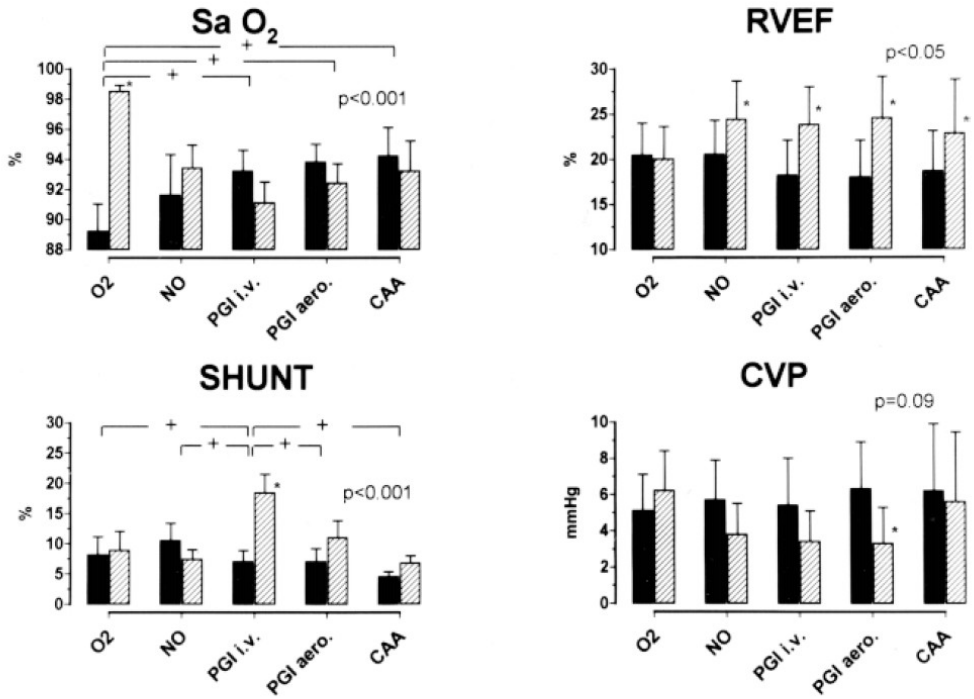

Figure 1. Acute responses to oxygen, NO, intravenously administered and inhaled prostacyclin (PGI i.v. and PGI aero, respectively) in eight patients, and to calcium antagonists (CAAs) in six patients. *Dark columns* and *light columns* give mean values ± SE before and after drug administration, respectively, for arterial oxygen saturation (Sa_{O_2}), right-to-left shunt flow (as a percentage of pulmonary blood flow; SHUNT), right ventricular ejection fraction (RVEF), and central venous pressure (CVP). p = significance level for differences in the responses to the various agents (ANOVA for the intrapair differences); * = significant difference pre- and postapplication, $p < 0.05$; + = significant linear contrast between responses to different agents (Scheffé test, $p < 0.05$).

Olschewski et al. AJRCCM 1998.

PH-Lung: Group 1 vs. Group 3 PH

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	Classical IPAH	Classical IPAH vs IPAH with a lung phenotype p value	IPAH with a lung phenotype	IPAH with a lung phenotype *vs* group 3.1 or 3.2 pulmonary hypertension p value	Group 3.1 or 3.2 pulmonary hypertension
COMPERA					
Number of patients	128	..	268	..	910
Age, years	45 (32–60)	<0·0001	72 (65–78)	0·89	71 (65–77)
Sex					
Female	99 (77%)	<0·0001	95 (35%)	0·71	336 (37%)
Male	29 (23%)	..	173 (65%)	..	574 (63%)
Comorbid conditions					
Body-mass index ≥30 kg/m²	0	<0·0001	86 (32%)	0·0023	194 (23%)
Hypertension	0	<0·0001	183 (70%)	0·53	506 (68%)
Coronary heart disease	0	<0·0001	110 (42%)	0·17	270 (37%)
Diabetes	0	<0·0001	94 (36%)	0·011	206 (27%)
Atrial fibrillation	7 (6%)	0·033	36 (14%)	0·58	106 (12%)
Pulmonary hypertension therapy type	..	<0·0001	..	<0·0001	..
Monotherapy	81 (63%)	..	220 (82%)	..	871 (96%)
Combination therapy	47 (37%)	..	48 (18%)	..	37 (4%)
ASPIRE					
Number of patients	185	..	139	..	375
Age, years	52 (38–64)	<0·0001	71 (65–76)	0·049	69 (63–74)
Sex					
Female	133 (72%)	0·0009	75 (54%)	0·0032	148 (39%)
Male	52 (28%)	..	64 (46%)	..	227 (61%)
Oral monotherapy	40 (24%)	..	43 (31%)	..	165 (44%)
Oral combination	79 (47%)	..	72 (52%)	..	22 (6%)
PPA ± oral therapy	29 (17%)	..	21 (15%)	..	7 (2%)

IPAH with lung phenotype: DLCO < 45%, Smoking history

Hoeper et al. Lancet Resp Med 2022.

PH-Lung: Group 1 vs. Group 3 PH

Medical University of Graz

	Classical IPAH (n=185)	Classical IPAH *vs* IPAH with a lung phenotype p value	IPAH with a lung phenotype (n=139)	IPAH with a lung phenotype *vs* group 3.1 or 3.2 pulmonary hypertension p value	Group 3.1 or 3.2 pulmonary hypertension (n=375)
CT available	109 (59%)	0·59	86 (62%)	0·48	219 (58%)
CT fibrosis, any present	9 (8%)	<0·0001	26 (30%)	0·0093	102 (47%)
CT fibrosis by severity	..	<0·0001	..	<0·0001	..
None	100 (93%)	..	60 (71%)	..	117 (57%)
Mild	6 (6%)	..	21 (25%)	..	21 (10%)
Moderate	1 (1%)	..	4 (5%)	..	33 (16%)
Severe	0	..	0	..	36 (17%)
CT emphysema, any present	15 (14%)	<0·0001	42 (49%)	0·070	132 (60%)
CT emphysema by severity	..	<0·0001	..	<0·0001	..
None	94 (89%)	..	44 (52%)	..	87 (41%)
Mild	11 (10%)	..	22 (26%)	..	21 (10%)
Moderate	1 (1%)	..	16 (19%)	..	62 (30%)
Severe	0	..	3 (4%)	..	40 (19%)

Data are n (%). Statistical comparisons were made by Pearson's χ^2 test or Fisher's exact test. Percentages for fibrosis and emphysema severity were calculated for those patients who had their severity score available in their original report (appendix pp 4–5). IPAH=idiopathic pulmonary arterial hypertension.

Table 2 **Lung parenchymal abnormalities on chest CT (ASPIRE)**

IPAH with lung phenotype: DLCO < 45%, Smoking history

Hoeper et al. Lancet Resp Med 2022.