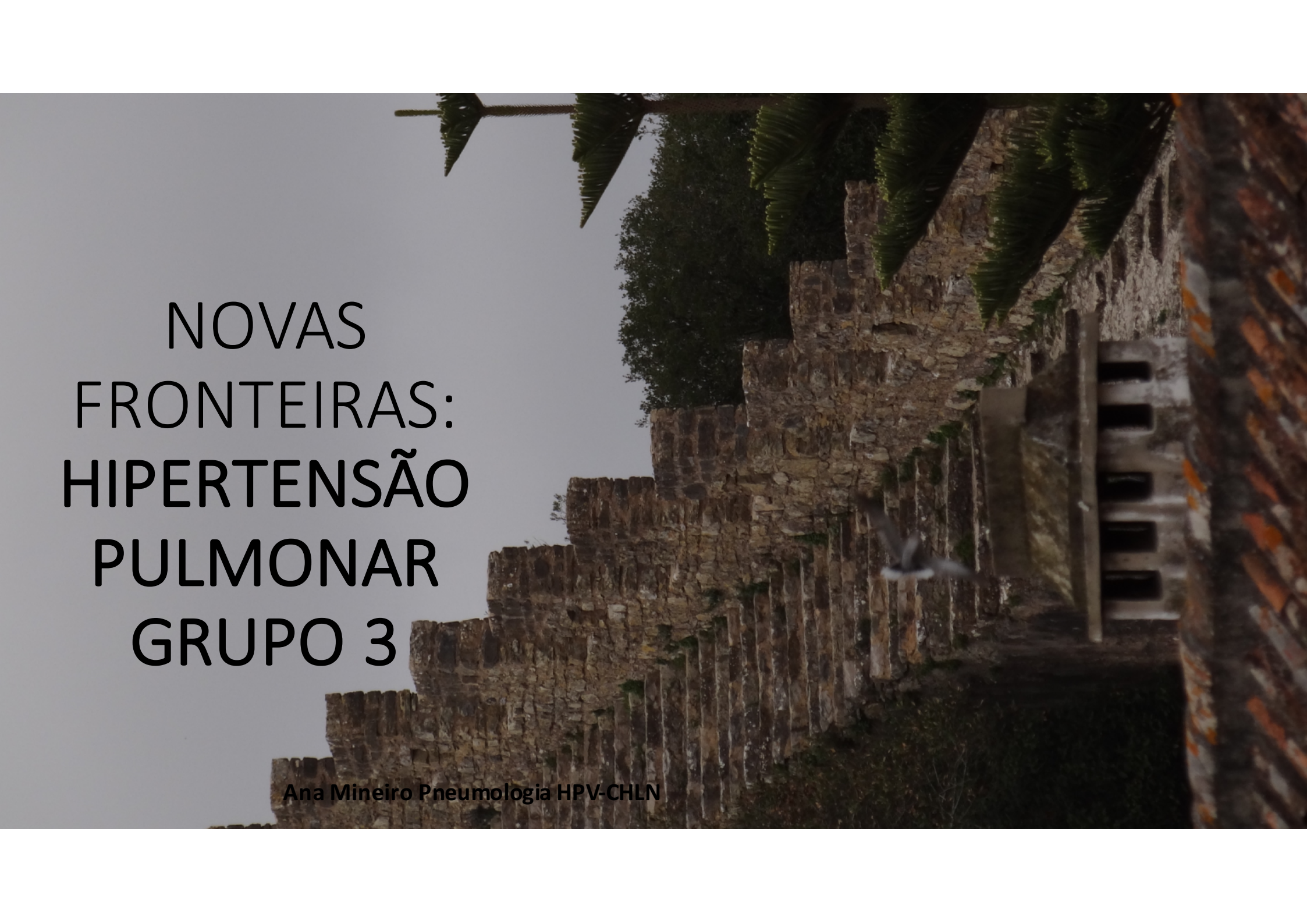


The background of the slide is a photograph of ancient stone ruins, likely Mayan or Aztec, featuring stepped pyramids and walls made of large, rectangular stone blocks. A bird is captured in mid-flight in the center of the image. The scene is set against a clear, light blue sky. The text is overlaid on the left side of the image.

NOVAS FRONTEIRAS: HIPERTENSÃO PULMONAR GRUPO 3

Ana Mineiro Pneumologia HPV-CHLN

Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et al.⁵)

I. Pulmonary arterial hypertension
I.1 Idiopathic I.2 Heritable I.2.1 BMPR2 mutation I.2.2 Other mutations I.3 Drugs and toxins induced I.4 Associated with: I.4.1 Connective tissue disease I.4.2 Human immunodeficiency virus (HIV) infection I.4.3 Portal hypertension I.4.4 Congenital heart disease (Table 6) I.4.5 Schistosomiasis
I'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
I'.1 Idiopathic I'.2 Heritable I'.2.1 EIF2AK4 mutation I'.2.2 Other mutations I'.3 Drugs, toxins and radiation induced I'.4 Associated with: I'.4.1 Connective tissue disease I'.4.2 HIV infection
I". Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies 2.5 Congenital /acquired pulmonary veins stenosis
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung diseases (Web Table III)
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension 4.2 Other pulmonary artery obstructions 4.2.1 Angiosarcoma 4.2.2 Other intravascular tumors 4.2.3 Arteritis 4.2.4 Congenital pulmonary arteries stenoses 4.2.5 Parasites (hydatidosis)
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Table 33 Recommendations for pulmonary hypertension due to lung diseases

Recommendations	Class ^a	Level ^b	Ref. ^c
Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease	I	C	403, 405
Referral to an expert centre is recommended ^d in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction	I	C	
The optimal treatment of the underlying lung disease, including long-term O ₂ therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases	I	C	169
Referral to PH expert center should be considered for patients with signs of severe PH/severe RV failure for individual-based treatment	IIa	C	
RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial)	III	C	169
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III	C	411–416

CTEPH = chronic thromboembolic pulmonary hypertension;

PAH = pulmonary arterial hypertension; PH = pulmonary hypertension;

RHC = right heart catheterization.

^aClass of recommendation.

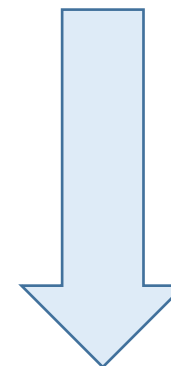
^bLevel of evidence.

^cReference(s) supporting recommendations.

^dThis recommendation does not apply to patients with end-stage lung disease who are not considered candidates for lung transplantation.

Estudos:

- Escasso numero de doentes
- Populações diversas/mistas
- Diferentes definições de HP
- Diferentes objetivos



Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.



The End

Utilização de terapêutica específica no grupo 3

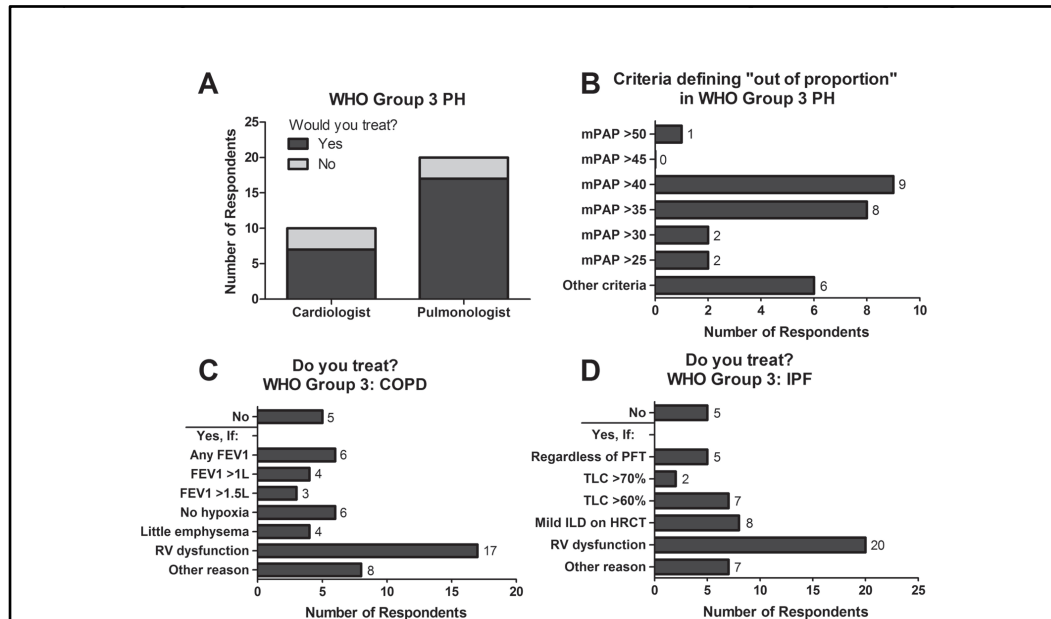


Figure 3. Use of pulmonary arterial hypertension (PAH)-directed therapy in World Health Organization (WHO) group 3 pulmonary hypertension (PH). A, Number of physicians who would utilize PAH-directed therapy for WHO group 3 patients by treating physician specialty. There is no difference by treating specialty in the proportion reporting that he or she would treat WHO group 3 PH (Fisher's exact test, $P = 0.37$). B, Criteria used to define out-of-proportion PH in WHO group 3. Mean pulmonary arterial pressure (mPAP) of >35 or >40 mmHg is reported most commonly as the hemodynamic definition of out of proportion in group 3 PH. C, D, Factors influencing the decision to treat with PAH-approved therapy in patients with chronic obstructive pulmonary disease (COPD; C) and idiopathic pulmonary fibrosis (IPF; D). Other criteria reported for COPD patients included pretransplantation status ($n = 2$), relatively severe PH for degree of parenchymal lung disease as assessed by imaging or pulmonary function testing ($n = 7$), and as a last resort when other medical therapy is maximized ($n = 2$). FEV₁: forced expiratory volume in 1 second; RV: right ventricle; PFT: pulmonary function testing; TLC: total lung capacity; ILD: interstitial lung disease; HRCT: high-resolution computed tomography imaging.

Use of pulmonary arterial hypertension-approved therapy in the treatment of non-group 1 pulmonary hypertension at US referral centres
Pulm Circ 2015;5(2):356-363.

	Baseline Group 3 PH (n = 2236)	Controls (n = 2236)	Follow-up Group 3 PH (n = 2236)	Controls (n = 2236)
Diagnostic procedures				
Echocardiography	1679 (75.1)	518 (23.2)	1678 (75.0)	441 (19.7)
Stress echocardiography	313 (14.0)	176 (7.9)	212 (9.5)	150 (6.7)
Other radiography	107 (4.8)	77 (3.4)	79 (3.5)	59 (2.6)
Electrocardiography	1779 (79.6)	1264 (56.5)	1777 (79.5)	1160 (51.9)
Computerized tomography	1001 (44.8)	693 (31.0)	1030 (46.1)	567 (25.4)
Angiography	385 (17.2)	187 (8.4)	385 (17.2)	122 (5.5)
RHC	144 (6.4)	15 (0.7)	135 (6.0)	6 (0.3)
MRI	39 (1.7)	17(0.8)	52 (2.3)	29 (1.3)
Other exercise testing	452 (20.2)	89 (4.0)	574 (25.7)	84 (3.8)
Therapeutic treatment				
Vena cava procedure	0	0	19 (0.9)	2 (0.09)
Ventilation perfusion	76 (3.4)	12 (0.5)	58 (2.6)	2 (0.09)
Oxygen therapy	1 (0.04)	1 (0.04)	3 (0.1)	2 (0.09)
Pharmacotherapy				
Oral anticoagulants	366 (16.4)	33 (1.5)	495 (22.1)	41 (1.8)
Diuretics	704 (31.5)	442 (19.8)	853 (38.2)	456 (20.4)
Calcium channel blockers	1273 (56.9)	714 (31.9)	1447 (64.7)	722 (32.3)
Digoxin	800 (35.8)	624 (27.9)	853 (38.2)	621 (27.8)
PAH-approved pharmaceuticals ^a	366 (16.4)	33 (1.5)	495 (22.1)	41 (1.8)
Prostacyclin analogues	19 (0.9)	0	34 (1.5)	0
ERAs	182 (8.1)	0	226 (10.1)	0
PDE5 inhibitors ^b	279 (12.5)	33 (1.5)	394 (17.6)	41 (1.8)

Values are expressed as No. (%)

ERA endothelin receptor antagonist, MRI magnetic resonance imaging, PDE5 phosphodiesterase type-5, PH pulmonary hypertension, RHC right heart catheterization

^aIncludes unique patients with ≥ 1 pharmaceutical claim for prostacyclin analogues, endothelin receptor antagonists, and/or PDE5 inhibitors

^bPDE5 inhibitors include those indicated for pulmonary arterial hypertension (PAH), as well as those for other indications or used off-label

Healthcare burden of pulmonary hypertension owing to lung disease and/or hypoxia
BMC Pulmonary Medicine (2017) 17:58

Grupo 3

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)

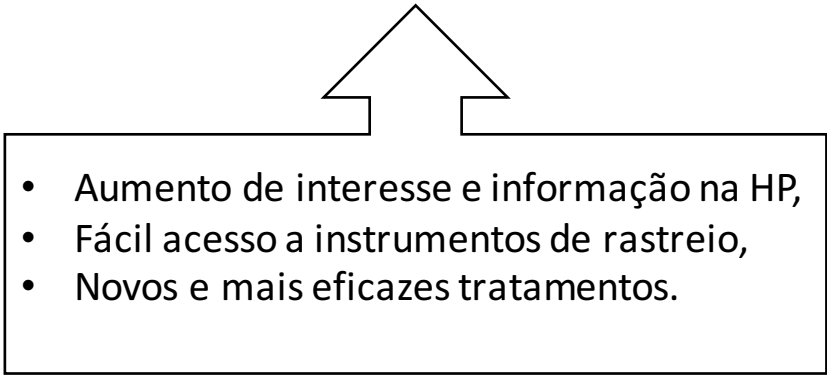
CI = cardiac index; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure; PAPm = mean pulmonary arterial pressure; PH = pulmonary hypertension.

Panorama atual da HAP: idade

Registry	Time period	Age years	Female	1-year survival
US NIH registry	1981–1988	36 ± 15	63	68
French registry [#]	2002–2003	52 ± 15	62	89
US REVEAL	2006–2009	50 ± 15	80	88
PH registry of the UK and Ireland ^{#,¶}	2001–2009	50 ± 17	70	93
COMPERA ⁺	2007–2011	65 ± 15	60	92
New Chinese registry	2008–2011	38 ± 13	70	92
Czech registry	2000–2007	52 ± 17	65	89 [¶]

Data are presented as mean ± SD or %, unless otherwise stated. NIH: National Institutes of Health; REVEAL: Registry to Evaluate Early and Long-term PAH Disease Management; PH: pulmonary hypertension; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension. [#]: included idiopathic pulmonary arterial hypertension (PAH), familial/heritable PAH and anorexigen-associated PAH; [¶]: incident population; ⁺: countries involved included Austria, Belgium, Germany, Italy, the Netherlands, Switzerland and the UK.

Eur Respir Rev 2014; 23:450–457

- 
- Aumento de interesse e informação na HP,
 - Fácil acesso a instrumentos de rastreio,
 - Novos e mais eficazes tratamentos.

Panorama atual da HAP: idade

Doentes incluídos prospectivamente à data do diagnóstico entre Janeiro de 2001 e Dezembro de 2009;

Casos incidentes de HP idiopática, hereditária e associada a anorexígenos .

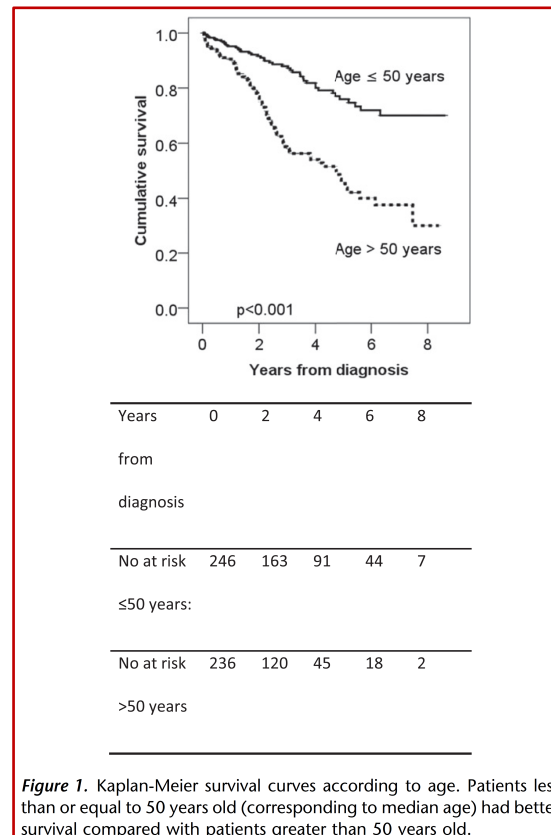
Baseline Characteristics	All Cases	Age ≤ 50	Age > 50	P Value*
Age, yr (n = 482)	50.1 (17.1)	36.5 (9.3)	65.1 (8.3)	<0.001
Sex, % female (n = 482)	69.9% (337)	73.2% (180)	66.5% (157)	0.112
Ethnicity, % nonwhite (n = 424)	12.3% (52)	15.4% (34)	8.9% (18)	0.041
Symptoms (n = 437)				
Peripheral edema	30.9% (135)	23.5% (52)	38.4% (83)	0.001
Syncope	22.7% (99)	33.5% (74)	11.6% (25)	<0.001
Presyncope	11.9% (52)	14.9% (33)	8.8% (19)	0.048
Duration of symptoms, mo, median (IQR) (n = 404)	18 (9–36)	12 (6–24)	24 (12–36)	<0.001
Functional class (n = 456)				
I and II	15.5% (72)	19.7% (45)	11.9% (27)	0.031
III	66.7% (304)	65.9% (151)	67.4% (153)	
IV	17.5% (80)	14.4% (33)	20.7% (47)	
Smoking history (n = 361)				
Current smoker	14.4% (52)	16% (28)	12.9% (24)	<0.001
Ex-smoker	41.3% (149)	30.9% (54)	51.1% (95)	
Never smoker	44.3% (160)	53.1% (93)	36% (67)	
Comorbidities (n = 455)				
IHD	12.1% (58)	1.3% (3)	24.2% (55)	<0.001
Hypertension	26.6% (121)	11% (25)	42.3% (96)	<0.001
Atrial fibrillation	5.3% (24)	0% (0)	10.6% (24)	<0.001
Diabetes	14.3% (65)	5.3% (12)	23.3% (53)	<0.001
Hypothyroidism	11.6% (53)	7.5% (17)	15.9% (36)	0.005
6MWD, m (n = 260)	292.4 (123)	330 (118.7)	246.1 (112.2)	<0.001
Pulmonary function				
% FEV ₁ (n = 350)	85.3 (14.7)	85.5 (13.6)	85.1 (15.8)	0.785
% FVC (n = 346)	94 (16.4)	91.2 (14.6)	96.7 (17.6)	0.002
% TLC (n = 204)	95.4 (13.9)	96.3 (13.4)	94.4 (14.3)	0.324
% DL _{CO} (n = 331)	62 (20.9)	67 (17.6)	56.7 (22.8)	<0.001
Hemodynamics				
mRAP, mm Hg (n = 439)	10.1 (6)	10 (5.8)	10.2 (6.1)	0.738
PASP, mm Hg (n = 427)	86.2 (21.1)	88.7 (22.6)	83.8 (19.2)	0.016
PADP, mm Hg (n = 424)	34.7 (12.3)	38.6 (12.9)	31.1 (10.5)	<0.001
mPAP, mm Hg (n = 457)	54.1 (13.9)	57.2 (14.9)	51 (12.2)	<0.001
PAOP, mm Hg (n = 408)	9.2 (3.5)	8.8 (3.5)	9.5 (3.5)	0.035
TPG, mm Hg (n = 404)	44.4 (13.7)	47.8 (14.5)	41.3 (12.2)	<0.001
SvO ₂ , % (n = 395)	61.5 (9.5)	62.5 (10.3)	60 (8.6)	0.053
CO, L·min ⁻¹ (n = 410)	4 (1.5)	4 (1.5)	4 (1.5)	0.830
CI, L·min ⁻¹ ·m ⁻² (n = 366)	2.1 (0.7)	2.1 (0.7)	2.1 (0.7)	0.683
PVR, WU (n = 395)	12.8 (6.3)	13.9 (6.7)	11.8 (5.8)	0.001
PVRI, WU·m ² (n = 355)	23.1 (10.3)	24.8 (11.2)	21.5 (9.1)	0.003

Definition of abbreviations: 6MWD = 6-minute walk distance; CI = cardiac index; CO = cardiac output; % DL_{CO} = % predicted diffusion capacity of carbon monoxide; IHD = ischemic heart disease; IQR = interquartile range; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PADP = pulmonary artery diastolic pressure; PAOP = pulmonary artery occlusion pressure; PASP = pulmonary artery systolic pressure; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; SvO₂ = mixed venous oxygen saturation; TPG = transpulmonary gradient; WU = Wood units.

Data expressed as % (n) or mean (SD) unless otherwise stated.

* Comparisons are for age less than or equal to 50 versus age greater than 50 years.

Panorama atual da HAP: idade



DPOC com HP grave: quantos são?

- Entidade rara:
 - 0.83 a 1.1 % (PmAP > 40 mmHg)^{1,2}
 - 5% (PmAP > 35 mmHg)³

1) Chaouat et al, Am J Respir Crit Care Med Vol 172. pp 189–194, 2005

2) Stevens D et al. Am J Respir Crit Care Med Vol 172. pp 189–194, 2005

3) Scharf SM et al. Am J Respir Crit Care Med 2002;166:314–322.

DPOC com HP grave: quem são?

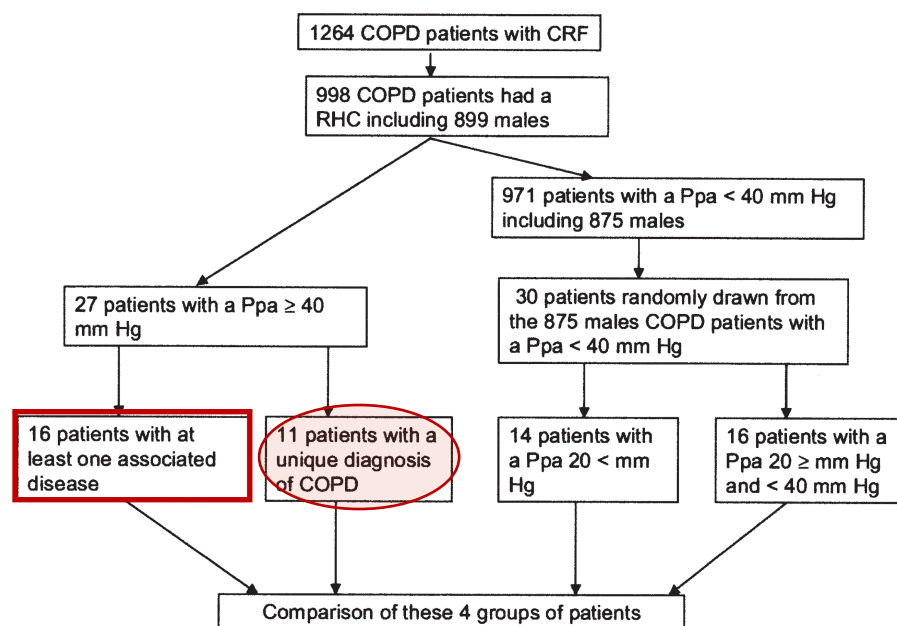


Figure 1. Study profile. COPD = chronic obstructive pulmonary disease; CRF = chronic respiratory failure; Ppa = pulmonary artery mean pressure; RHC = right heart catheterization.

TABLE 5. DEMOGRAPHICS, RESPIRATORY FUNCTION, AND EMPHYSEMA SCORE

Variable Median (IQR)	Severe PH without Associated Disease (n = 11)	Severe PH with Associated Disease (n = 16)	Control Subgroup, Ppa < 20 mm Hg (n = 14)	Control Subgroup, Ppa ≥ 20 mm Hg (n = 16)	p Value, Kruskal-Wallis Test
Age, yr	67 (62–68)	61 (56–68)	62 (53–75)	66 (63–73)	= 0.255
BMI, kg/m ²	26 (21–30)	26 (22–33)	22 (19–28)	25 (21–28)	= 0.400
Tobacco, pack-yr	44 (40–60)	40 (40–50)	45 (30–55)	50 (40–60)	> 0.5
Dyspnea, grade/5	4.0 (3.5–4.0)*†	4.0 (3.0–4.0)	3.0 (2.0–3.0)	3.0 (2.5–3.0)	< 0.001
VC, % predicted	86 (74–95)†	66 (57–91)	73 (65–80)	65 (56–70)	= 0.021
FEV ₁ , % predicted	50 (44–56)†	41 (35–63)	35 (29–50)§	27 (23–34)	< 0.001
FEV ₁ /VC, %	49 (39–53)†	49 (43–55)	39 (31–52)	34 (26–38)	= 0.001
TLC, % predicted	97 (83–115)	83 (74–92)	95 (88–114)	105 (94–121)	> 0.5
DL _{CO} , ml/min/mm Hg	4.6 (4.2–6.7)**‡	10.4 (8.2–16.6)	13.0 (11.0–17.0)	10.3 (8.9–12.8)	= 0.005
ES	16 (8–22)‡	5 (4–9)	13 (6–20)	19 (14–24)	< 0.001

Definition of abbreviations: BMI = body mass index; DL_{CO} = diffusion capacity for carbon monoxide; ES = emphysema score; IQR = interquartile range; PH = pulmonary hypertension; Ppa = pulmonary artery mean pressure; TLC = total lung capacity.

* p < 0.01, severe PH without associated disease versus control group; Ppa < 20 mm Hg.

† p < 0.01, severe PH without associated disease versus control group; Ppa ≥ 20 mm Hg.

‡ p < 0.01, severe PH without associated disease versus severe PH with associated disease.

§ p < 0.05, control group, Ppa < 20 mm Hg, versus control group, Ppa ≥ 20 mm Hg.

DPOC com HP grave: qual o prognóstico?

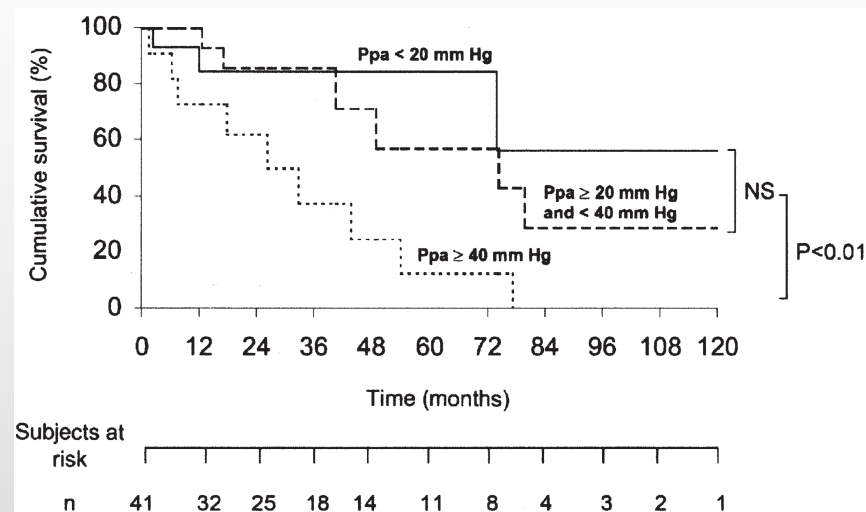


Figure 3. Survival of patients with COPD and no other detectable cause of pulmonary hypertension. The probability of survival of each group according to the Ppa was estimated using the Kaplan-Meier method and compared using the log-rank test. Eleven patients with a Ppa of 40 mm Hg or greater, 16 patients with Ppa of less than 40 mm Hg and 20 mm Hg or greater, and 14 patients with Ppa less than 20 mm Hg were at risk at baseline. NS = not significant.

DPOC com HP grave: histologia

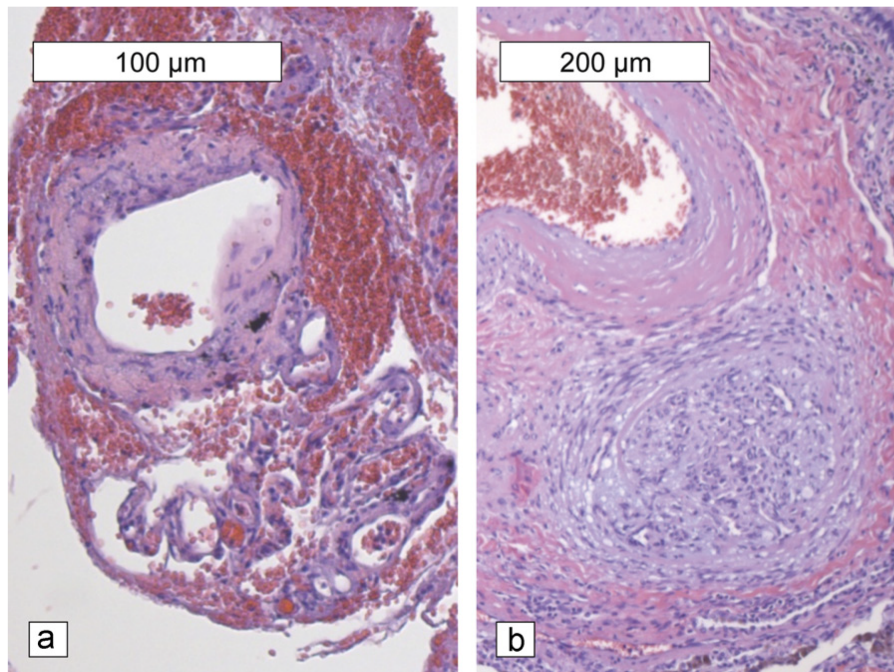


Figure 3 Generalized chronic dilatation with medial and intimal fibrosis and prominent plexiform lesions. (a) Patient with chronic obstructive pulmonary disease Heath and Edwards Grade 5. (b) Heath and Edwards Grade 5 lesion from a patient with idiopathic pulmonary arterial hypertension. There are no histopathologic hallmarks to discriminate between the two specimens.

Table 1 Heath and Edwards Grading Scheme for Hypertensive Pulmonary Vascular Disease With Progressive Structural Changes^{15,16}

Grade	Hypertensive pulmonary vascular disease
1	Distal extension of muscle into distal arterioles and medial thickening of muscular arteries
2	Medial hypertrophy with cellular intimal proliferation in small muscular arteries
3	Progressive fibrous vascular occlusion, concentric intimal fibrosis
4	Progressive generalized arterial dilatation with plexiform lesions
5	Chronic dilatation with medial and intimal fibrosis, prominent plexiform lesions, angiomatoid lesions, pulmonary hemosiderosis
6	Necrotizing arteritis

DPOC com HP grave: resumo de características

- **Fenótipo específico:**

- Fumadores
- Mais hipoxémicos com marcada dessaturação no esforço,
- Frequentemente hipocápnicos,
- Diminuição acentuada da DLCO face à alteração dos débitos/alts radiológicas,
- Maior mortalidade.

- **Alterações histológicas semelhantes à HAP.**

O mesmo fenótipo... noutros grupos

- Diminuição acentuada da DLCO* **na HAP** (1,2,3):
 - Mais velhos,
 - Fumadores,
 - > Mortalidade.
- Diminuição acentuada da DLCO* **na IC com Fej preservada** (4):
 - Fumadores,
 - > Mortalidade.

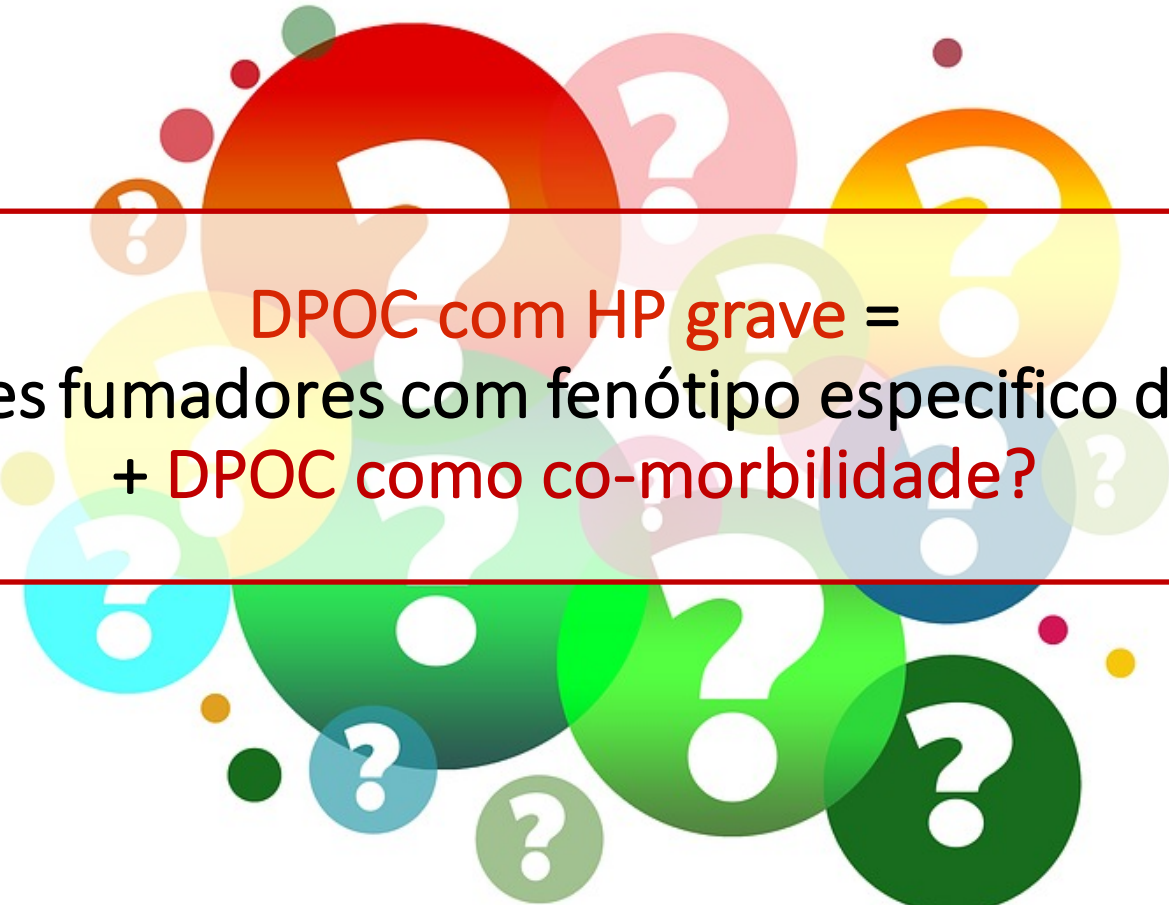
*DLCO<45%

1) Eur Respir J 2013; 42: 1575–1585

2) J Heart Lung Transplant 2010;29:181–7

3) Eur Respir Rev 2014; 23: 450–457

4) JACC Heart Failure 2016; 6: 441-449

The background features a cluster of overlapping circles in various colors including red, orange, yellow, green, blue, and pink. Many of these circles contain a white question mark. There are also smaller solid-colored dots scattered around the main cluster.

DPOC com HP grave =
doentes fumadores com fenótipo específico de HAP
+ DPOC como co-morbilidade?

Terapêutica DLCO/HP grave: definição de objetivos

- Prova de marcha?
 - Doentes mais velhos, com co-morbilidades que limitam a prova,
 - Atingir classe funcional I ou II pode não ser realista.
- Outros parâmetros independentes preditores de mortalidade na DPOC/HP grave?
 - Resistências vasculares pulmonares,
 - Índice Cardíaco,
 - SvO₂,
 - PAD,
 - DLCO.

Eur Respir J 2013;41: 1292–1301

Eur Respir J 2015;46: 1378–1389

Aspire registry: Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre)

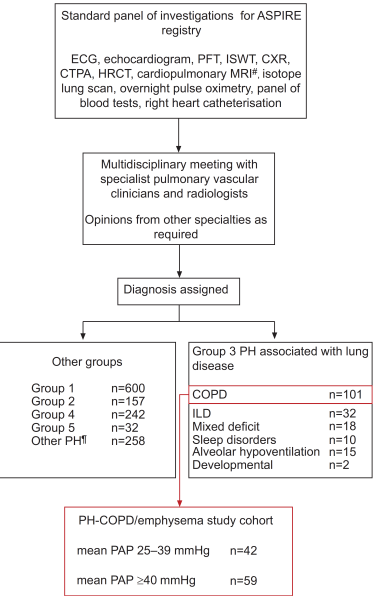
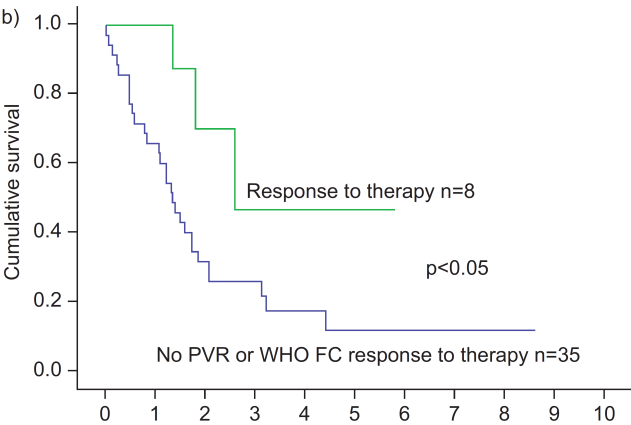


FIGURE 1. Diagnostic pathway. ASPIRE: Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre; PFT: pulmonary function testing; ISWT: incremental shuttle walking test; CXR: chest radiograph; CTPA: computed tomography pulmonary angiogram; HRCT: high-resolution computed tomography of the thorax; MRI: magnetic resonance imaging; PH: pulmonary hypertension; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PAP: pulmonary artery pressure. *: cardiopulmonary MRI was used routinely from 2004 onwards. *: Other PH included: PH multiple diagnoses n=38, PH inclusion criteria not met n=85, PH lung with connective tissue disease n=102 and PH owing to heart disease and connective tissue disease n=33.

TABLE 3 Therapy of patients with pulmonary hypertension (PH) associated with chronic obstructive pulmonary disease (COPD)		
	COPD mean PAP 25-39 mmHg	COPD mean PAP ≥40 mmHg
Subjects n	42	59
COPD therapy at presentation		
Inhaled steroid/LABA combination	53	51
Inhaled steroid	10	14
LABA	10	10
Long-acting antimuscarinic	48	51
Long-term oral prednisolone	10	14
Mucolytic	5	12
Theophylline	14	15
Oxygen therapy		
>15 h·day ⁻¹	64	85
Nocturnal	5	3
Maximal PH therapy		
None	83.4	27.1
Oral monoRx	14.3	64.4
Oral comb.	0	5.1
Prostanoid monoRx	0	1.7
Prostanoid comb.	2.4	1.7

Data are presented as %, unless otherwise stated. Prostanoid therapy was with nebulised or i.v. iloprost or s.c. treprostinil. PAP: pulmonary artery pressure; LABA: long-acting β-agonist; oral monoRx: oral monotherapy; oral comb.: combination of phosphodiesterase-5-inhibitor and endothelin receptor antagonist; prostanoid monoRx: prostanoid monotherapy; prostanoid comb.: prostanoid in combination with any other targeted therapy(ies).



Long-term Effect of Vasodilator Therapy in Pulmonary Hypertension due to COPD: A Retrospective Analysis

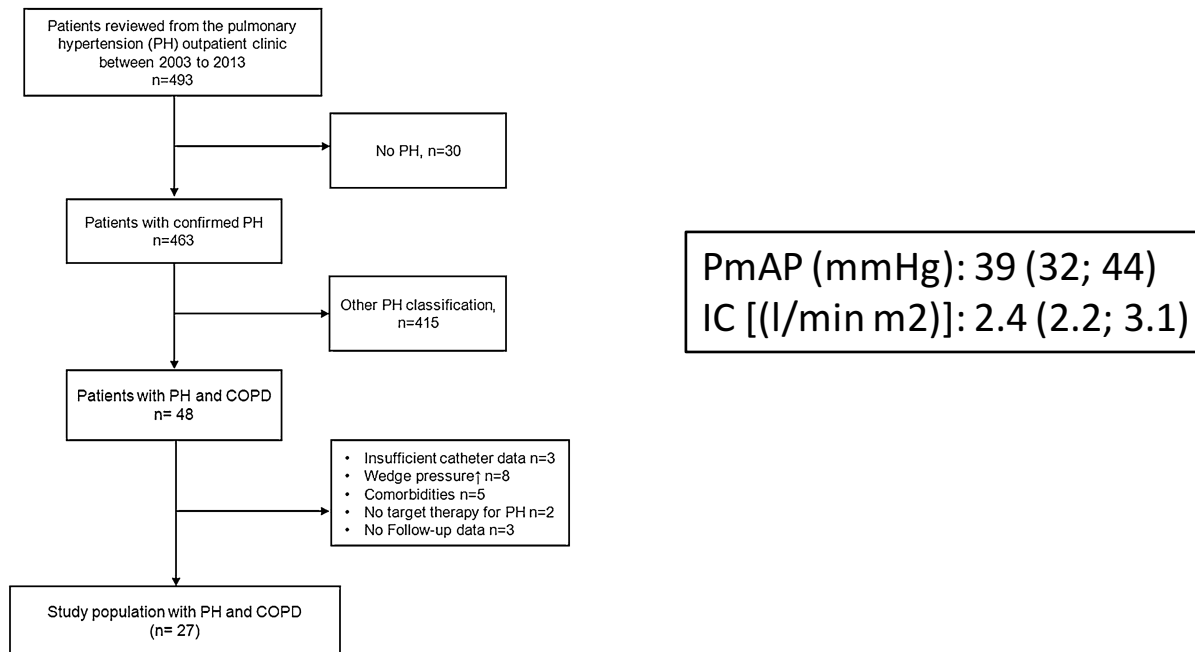


Fig. 1 Patient flow. *COPD* chronic obstructive pulmonary disease, wedge pressure pulmonary artery occlusion pressure. Target therapy: parenteral prostanoids, endothelin receptor antagonists (ERA) and phosphodiesterase-5 inhibitors (PDE5I)

Table 2 Pulmonary hypertension- target therapies started at baseline and maximal therapy

	Number (%)
PH-target therapies started at baseline	
Prostanoid inhaled	5/27 (18.5)
ERA (endothelin receptor antagonist)	8/27 (30)
PDE5I (phosphodiesterase type 5 inhibitor)	14/27 (52)
Maximal PH-target therapies over whole period	
Prostanoid inhaled	10/27 (37)
Prostanoid subcutaneous	2/27 (7.5)
Prostanoid intravenous	3/27 (11.5)
ERA (endothelin receptor antagonist)	15/27 (55.5)
PDE5I (phosphodiesterase type 5 inhibitor)	25/27 (93)

Long-term Effect of Vasodilator Therapy in Pulmonary Hypertension due to COPD: A Retrospective Analysis

Table 3 Course of characteristics under therapy

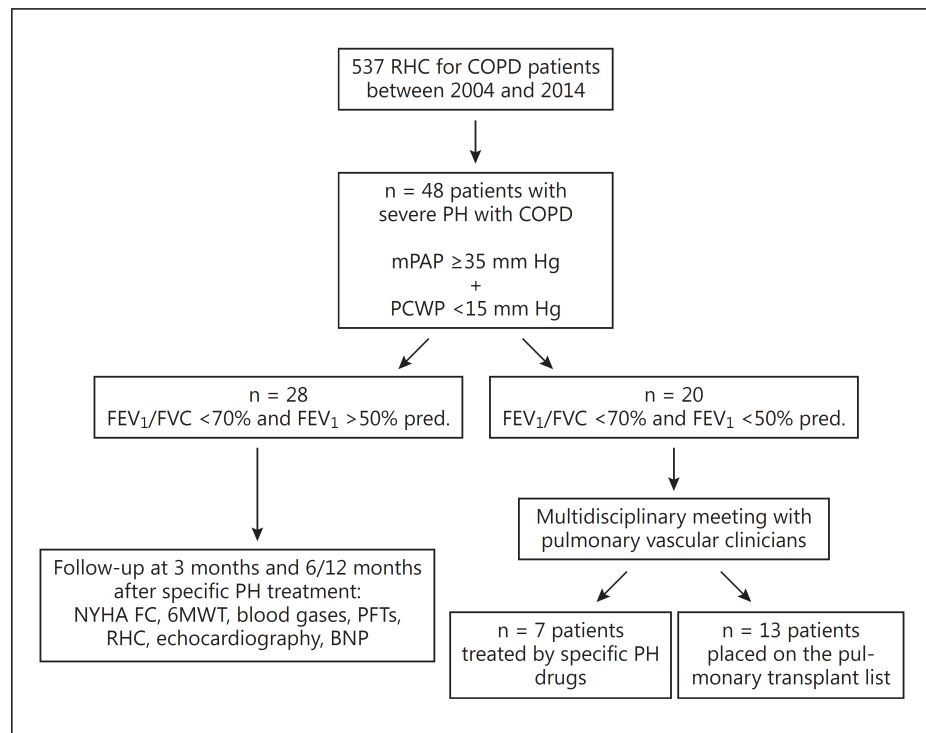
Characteristics	3 months	<i>n</i>	<i>p</i> value	6 months	<i>n</i>	<i>p</i> value	12 months	<i>n</i>	<i>p</i> value	24 months	<i>n</i>	<i>p</i> value
nnnNYHA functional class	3 (2; 4)	23	0.020	3 (2; 3.5)	17	0.008	3 (4; 2)	21	0.429	3 (2; 4)	15	0.655
6 min walk distance (m)	395 (338.5; 472)	25	0.005	414 (285; 492)	19	0.006	396 (308; 497)	23	0.011	434 (277; 508)	16	0.163
Borg scale	4 (4; 5)	23	0.303	4 (4; 5)	17	0.315	4.5 (4; 6.25)	22	0.736	5 (4; 6)	16	0.971
Resting peripheral oxygen saturation (%)	90 (84; 95)	22	0.286	90 (87.5; 94)	17	0.775	91 (86.5; 94)	21	0.358	89 (86; 91)	15	0.156
Peak exercise peripheral oxygen saturation (%)	83 (75.5; 88)	22	0.014	81 (76; 87)	17	0.014	82 (80; 88.5)	21	0.116	83.5 (73; 89.5)	16	0.039
Resting heart rate (min ⁻¹)	85 (80.5; 92.5)	21	0.408	84 (74.5; 104)	16	0.979	84 (77; 94)	21	0.689	84 (72.5; 95)	16	0.272
Peak exercise heart rate (min ⁻¹)	120 (106; 136)	21	0.053	120 (105; 131.5)	17	0.063	121 (102; 132.5)	21	0.104	116 (102; 134)	16	0.100
LHFQ total	37 (20; 59.5)	13	0.058	38 (28; 52)	11	*	36 (23.5; 48)	13	0.367	18.5 (6; 31)	8	*
LHFQ physical subscore	18 (11; 26)	13	0.440	20 (15; 24)	11	*	19 (14.5; 22)	13	0.504	10.5 (4.25; 17)	8	*
LHFQ emotional subscore	6 (3; 14)	13	0.156	5 (2; 13)	11	*	5 (2; 13)	13	0.502	1 (0; 4.5)	8	*
NT-pro-BNP (ng/l)	594 (167; 1,178)	18	0.078	525 (198; 1,340)	12	*	294 (148; 1,450)	19	0.938	769 (184; 1,951)	12	*
Tricuspid pressure gradient (mmHg)							45 (43.5; 60.50)	24	0.181	50.5 (39; 66)	8	*

Data given as median (quartiles)

NYHA new york heart association, *LHFQ* the minnesota living with heart failure questionnaire (higher values associated with worse quality of life), *NT-pro-BNP* N-terminal pro b-type natriuretic peptide

* Data available for less than 13 patients, hence the *p* values are not displayed

Pulmonary Arterial Hypertension-Specific Drug Therapy in COPD Patients with Severe Pulmonary Hypertension and Mild-to-Moderate Airflow Limitation



PAH-specific therapy	Baseline (n = 28)	3 months (n = 27)	6/12 months (n = 24)
ERA monotherapy	23	16	13
PDE-5I monotherapy	1	3	1
Oral bitherapy	1	6	9
Prostanoid monotherapy	1	0	0
Prostanoid in combination	0	1	2
Triple therapy	1	1	2
CCB	1	0	0

Data are the number of patients treated in each category. CCB = Calcium channel blocker. Oral monotherapy: PDE-5I or ERA. Oral bitherapy: PDE-5I and ERA. Prostanoid monotherapy: nebulized iloprost or intravenous epoprostenol. Prostanoid in combination: prostanoid in combination with any other targeted therapy/therapies. Triple therapy: combination of PDE-5I and ERA and prostanoid.

Pulmonary Arterial Hypertension-Specific Drug Therapy in COPD Patients with Severe Pulmonary Hypertension and Mild-to-Moderate Airflow Limitation

	Baseline (n = 28)	3 months (n = 28)	6/12 months (n = 16)	p value ¹
mPAP, mm Hg	44.1±8.7	43.4±8.35	39.43±6.56	n.s.
CO, l/min	4.8±1.2	5.4±1.1	5.9±0.9	0.018
CI, l/min/m ²	2.5±0.7	2.9±0.6	3.2±0.6	0.003
PVR, Wood unit	8.4±4.2	6.7±3	5±1.7	0.008
RAP, mm Hg	7.4±4.2	8.7±5	8±3.3	n.s.
SvO ₂ , %	57.5±10	55.9±9.2	58.8±9	n.s.
PaO ₂ , mm Hg	49.6±9.5	46.7±7.4	49.2±7.9	n.s.
A-a O ₂ , mm Hg	57.6±12.3	60.5±8.7	56.9±11.7	n.s.
PaCO ₂ , mm Hg	34.1±5.5	34.2±5.3	35±8.5	n.s.
6MWD, m	259.2±104	268.3±112.8	274.1±107.9	n.s.
NYHA class III or IV	22	21		

Data are presented as the mean ± SD. RAP = Right atrial pressure; PaCO₂ = arterial carbon dioxide tension.

¹ Kruskal-Wallis test for nonparametric data followed by the Mann-Whitney test (p value for the comparison between baseline and second follow-up at 6/12 months).

Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease

Table 1. Biometric and functional features of patients.

	Units	Bosentan	Best care + placebo	p
Age	years old	66 ± 9	65 ± 10	n.s.
Height	cm	165 ± 8	167 ± 10	n.s.
Body mass index	kg/cm ²	27 ± 4	25 ± 5	n.s.
Male:female	N:N	13: 3	12: 4	n.s.
Ex-smokers	%	100	100	n.s.
Under LTOT	%	40	40	n.s.
FVC	%	49 ± 18	53 ± 15	n.s.
FEV1	%	37 ± 18	39 ± 17	n.s.
TLC	%	132 ± 6	128 ± 9	n.s.
TICO	%	34 ± 7	36 ± 61	n.s.
PAP	mmHg	37 ± 5	36 ± 5	n.s.
PAP effort	mmHg	45 ± 7	43 ± 9	n.s.
PAP NO 20ppm	mmHg	35 ± 5	33 ± 5	n.s.
BODE	U	6.6 ± 2.8	7 ± 3	n.s.

Under LTOT, percentage of patients receiving long term oxygen therapy at a rate able to keep SaO₂ > 90% for 24 h/day; PAP effort, PAP under a workload of 40 W; PAP NO20 ppm, PAP under inhalation of NO at 20 ppm, BODE, BODE index. n.s., no significant difference between patients treated by bosentan and best care.

Table 2. Functional values observed in patients affected by COPD with PH in a stable state after 18 months of therapy using bosentan and BCS or BCS alone.

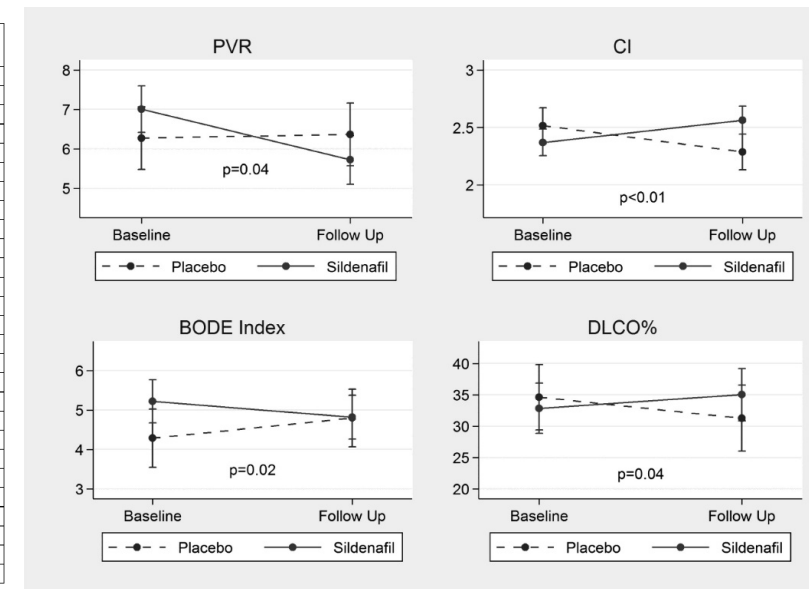
	Units	Bos + BCS	Aft18 m.	p	BCS	Aft18m.	p
FVC	%	49 ± 18	52 ± 16	n.s.	53 ± 15	51 ± 14	n.s.
FEV1	%	37 ± 18	41 ± 16	n.s.	39 ± 17	37 ± 15	n.s.
PaO2	mmHg	57 ± 10	61 ± 8	n.s.	58 ± 9	55 ± 12	n.s.
PaCO2	mmHg	46 ± 8	45 ± 6	n.s.	46 ± 9	48 ± 10	n.s.
PAP	mmHg	37 ± 5	31 ± 6	0.002	36 ± 5	38 ± 7	n.s.
C.I.	L/m/m2	2.8 ± 0.7	3.0 ± 0.8	n.s.	2.8 ± 0.6	2.6 ± 0.7	n.s.
PVR	dynes s/cm ⁵	442 ± 192	392 ± 180	0.0115	420 ± 170	435 ± 189	n.s.
6MWD	M	257 ± 118	321 ± 122	0.0027	270 ± 150	250 ± 170	n.s.
WHO	Grade	3.2 ± 0.8	2.75 ± 1.2	.05	3 ± 1	3 ± 1	n.s.
St George	U	43 ± 13	46 ± 13	n.s.	45 ± 11	43 ± 13	n.s.
BODE	U	6.6 ± 2.8	5.5 ± 3	0.002	7 ± 3	7 ± 4	n.s.
N	N	16	16		16	16	

FVC, forced vital capacity as percentage of normal standards; FEV1, forced expired volume in 1 s as percentage of normal standards; Aft 18 m, same values measured after 18 months of therapy using bosentan (Bos) and best care support (BCS) by means of theophylline, b2 + inhaled steroids inhalants, diuretics and oxygen; n.s., no significant difference between baseline values and measurement after 18 months; p, level of significance of null hypothesis.

SPERIC 1: SILDENAFIL IN SEVERE PULMONARY HYPERTENSION ASSOCIATED WITH COPD

Table 1. Demographics, pulmonary function test, and functional capacity of patients who assumed at last 1 dose of sildenafil/placebo: comparison at baseline.

	Placebo n=10	Sildenafil n=18	p-value
Gender, male (%)	80.0	72.2	ns
Age, years	64.1 ± 11.0	66.4 ± 6.5	ns
BMI	24.9 ± 4.8	27.2 ± 6.2	ns
FI_{O2}, %	26.3 ± 7.1	28.3 ± 7.2	ns
PaO₂, mmHg	74.4 ± 14.9	74.2 ± 14.3	ns
PaCO₂, mmHg	44.5 ± 9.0	40.3 ± 5.2	ns
AaO₂ Gradient, mmHg	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
DLCO%, 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
MRC scale, units	2.3 ± 0.7	3.0 ± 0.9	0.07
Hemodynamics			
RAP, mmHg	9.0 ± 2.6	7.3 ± 3.9	ns
mPAP, mmHg	39.1 ± 12.5	39.3 ± 7.6	ns
PCWP, mmHg	12.2 ± 2.9	10.9 ± 2.9	ns
CI, L/min/m ²	2.5 ± 0.7	2.4 ± 0.5	ns
SVI, mL/m ²	33.2 ± 9.9	29.4 ± 7.6	ns
TPVR, 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
HR, b/m	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; AaO₂ Gradient: alveolar-arterial gradient; BMI: body mass index; CI: cardiac index; DLCO: diffusing capacity of the lung for carbon monoxide; FEV₁: forced expiratory volume in 1 second; FI_{O2}: fraction of inspired oxygen; FVC: forced vital capacity; HR: heart rate; mPAP: mean pulmonary arterial pressure; MRC: Medical Research Council scale; PaCO₂: partial pressure of carbon dioxide in arterial blood; PaO₂: partial pressure of oxygen in arterial blood; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SVR: systemic vascular resistance; TLC: total lung capacity; TPVR: total pulmonary vascular resistance.

Estudos na terapêutica da HP grave na DPOC

- São escassos, raríssimos multicêntricos/aleatorizados/controlados,
- Incluem poucos doentes,
- Diferentes objetivos e metodologias dificultam comparações,
- Esquemas sub-terapêuticos...

No entanto, sem efeitos adversos significativo...

DPOC com HP grave: “conclusões”

- Entidade rara,
- Fenótipo específico,
- Mecanismo fisiopatológico independente da hipoxemia/perda de área de trocas perdida,
- Lesões vasculares semelhantes à HP idiopática.

DPOC com HP grave: “conclusões”

- Mortalidade elevada:
 - Sobrevida a 1 ano: 70%,
 - Sobrevida a 3 anos: 33%.
- Fenótipo particular do grupo 1 em que a DPOC é co-morbilidade?
- Excluir outras causas de HP e tratar... como grupo 1...



CONTINUA...

Resumo:

	RCP	n	CF	PM 6`	BODE	RVP	IC	sobrevida
Valerio et al.	x	16	+	+	+	+		
Vitulo et al.	x	15			+	+	+	
Hurdman et al.		43						+/-
Calcinu et al.		28	-	-		+	+	
Fossati et al		27	+	+				

RCP: estudo randomizado, controlado, prospectivo; n: numero de doentes; CF: classe funcional
PM 6`: prova de marcha 6 min; RVP: resistências vasculares pulmonares; IC: índice cardíaco;
B: IMC; **O**: obstrução, FEV1; **D**: dispneia mMRC; **E**: exercício, PM6.