Pulmonary Arterial Hypertension in Chronic Lung Disease

Kelly Fan, MD
Pulmonologist and Intensivist
Scripps Clinic Medical Group
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Disclosures

- None

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

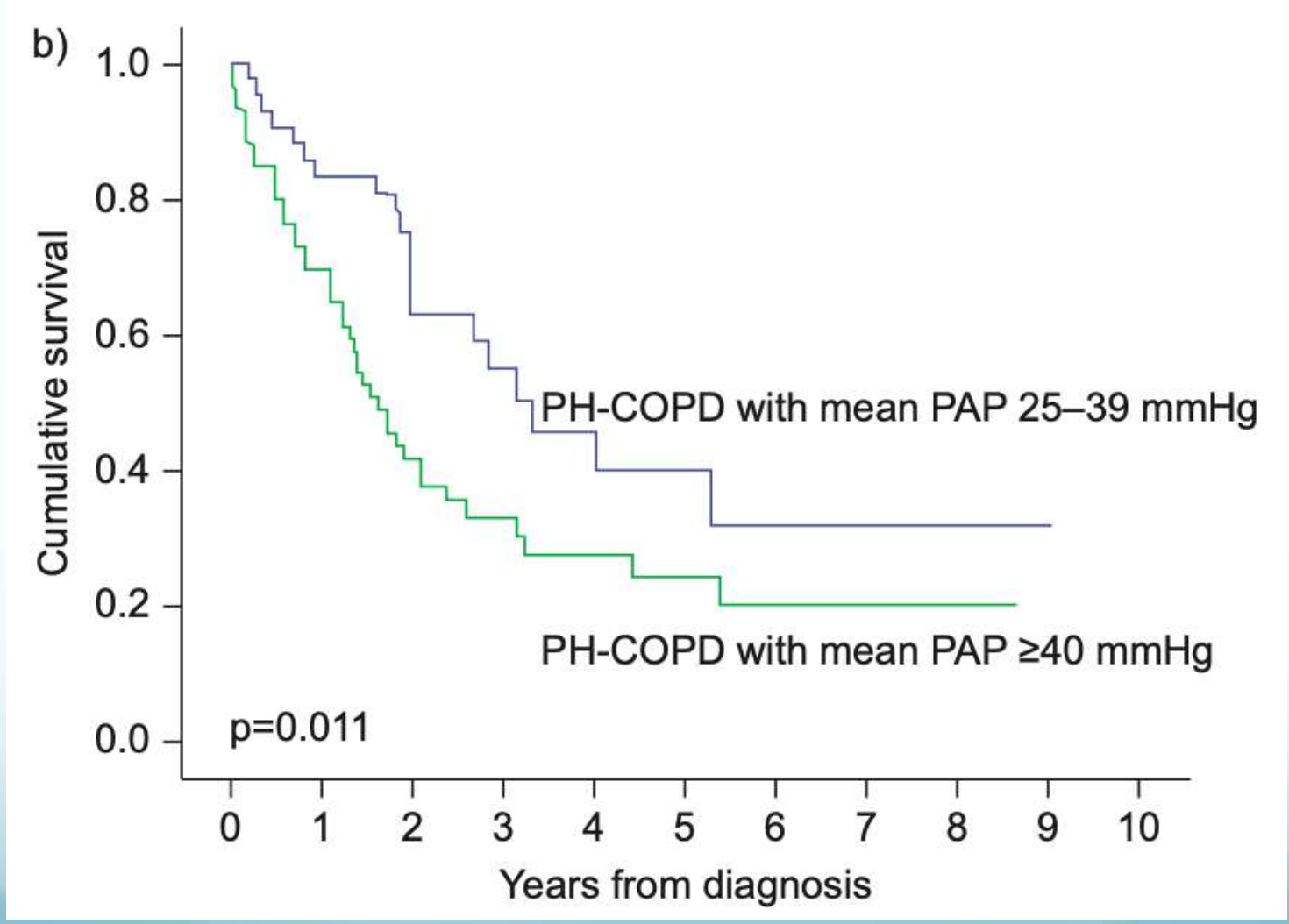
5 PH with unclear and/or multifactorial mechanisms (table 7)
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

Simonneau G, ERJ 2019

Outline of Talk

- Prognosis
- Diagnostic Workup
- Management

COPD-PH Prognosis



Hurdman J, ERJ 2013

IPF-PH Prognosis

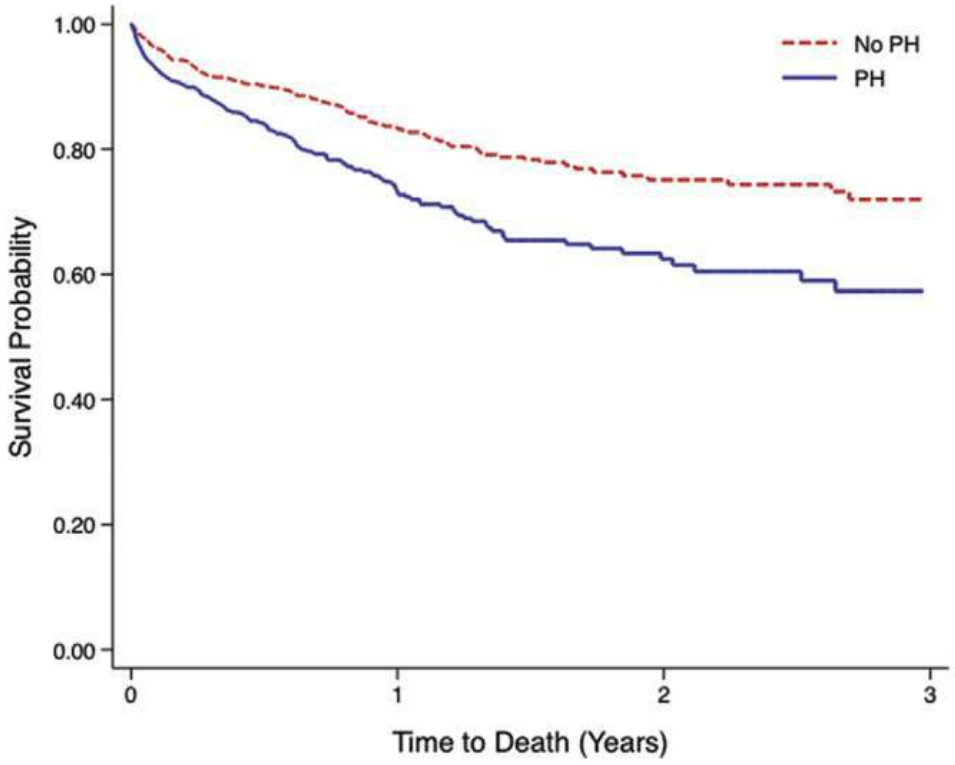
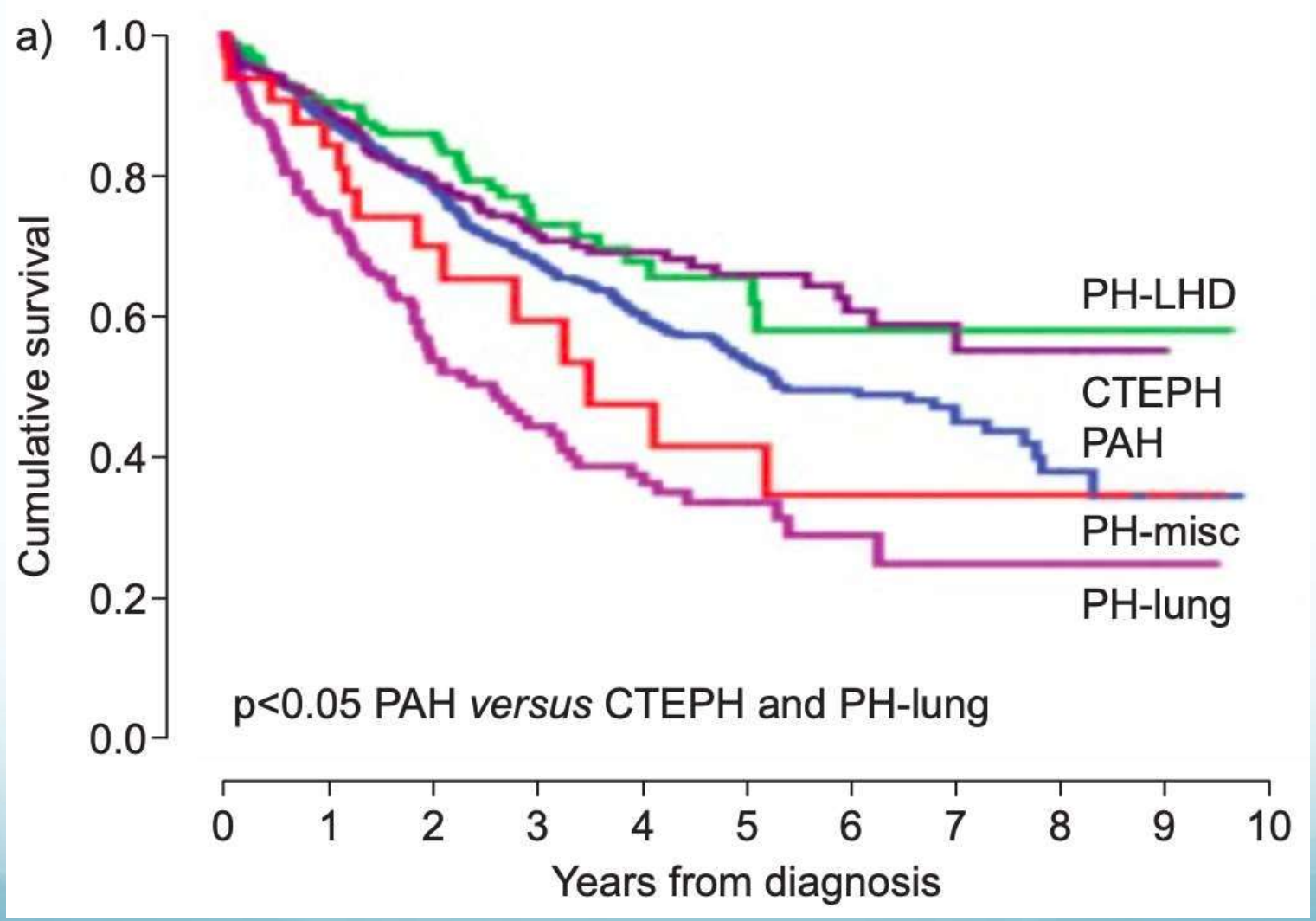


Fig 2. Kaplan-Meier survival functions comparing pulmonary hypertension (blue line) and no pulmonary hypertension (red line) in patients with idiopathic pulmonary fibrosis using mean pulmonary artery pressure 25 mm Hg or greater as the threshold ($n = 6{,}126$; log rank test χ^2 [$df = 1$] 40.44, $p < 0.001$).

Hayes D, Ann Thorac Surg 2016

Group 3 PH vs Other PH Groups



Hurdman J, ERJ 2012

COPD-PH Patient Characteristics

TABLE 1 Baseline characteristics

	COPD mean PAP 25–39 mmHg	COPD mean PAP ⩾40 mmHg	p-value
Subjects n	42	59	
Age years	67±11	70±9	0.092
Female	45	31	0.130
BMI kg·m^{-2}	28±8	27±6	0.520
Smoking			
Never-smoker	2	5	>0.05
Ex-smoker	78	83	>0.05
Current smoker	20	12	>0.05
Tobacco pack-years	45±28	38±28	0.295
Pulmonary function tests			
FEV1 % pred	51±28	65±23	0.006
FVC % pred	78±25	90±24	0.022
FEV1/FVC	0.51±0.18	0.59±0.18	0.041
*D*LCO % pred	40±20	27±13	0.001
CT scan			
Total emphysema score	5 (1–15)	9.5 (2–18)	0.191#
Total upper zone emphysema	3.5 (0–6)	5.5 (1–7)	0.214#
Total lower zone emphysema	0 (0–3)	0.5 (0–4)	0.178#
Total fibrosis score	0 (0–2)	0 (0–2.5)	0.509#
Total upper zone fibrosis	0 (0–0)	0 (0–0)	0.790#
Total lower zone fibrosis	0 (0–1.5)	0 (0–2)	0.330#

Hurdman J, ERJ 2013

IPF-PH Patient Characteristics

Table 1. Patient Characteristics With Pulmonary Hypertension Threshold of Mean Pulmonary Artery Pressure 25 mm Hg or Greater

	All[a] (n = 6,657)		Pulmonary Hypertension (n = 2,945)		No Pulmonary Hypertension (n = 3,187)		*p* Value	
Variable	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	*t* test	$\chi 2$
Male	4,475 (67.22)	…	2,022 (68.66)	…	2,112 (66.27)	…	…	0.046
Race	…	…	…	…	…	…	…	<0.001
White	5,296 (79.56)	…	2,285 (77.59)	…	2,598 (81.52)	…	…	…
Black	505 (7.59)	…	313 (10.63)	…	151 (4.74)	…	…	…
Other	856 (12.86)	…	347 (11.78)	…	438 (13.74)	…	…	…
Age, years	…	59.00 (9.56)	…	58.67 (9.38)	…	59.76 (8.74)	<0.001	…
Creatinine, mg/dL	…	0.88 (0.44)	…	0.89 (0.33)	…	0.88 (0.53)	0.784	…
Body mass index	…	27.43 (4.06)	…	27.95 (3.97)	…	27.04 (4.00)	<0.001	…
Supplemental oxygen, L	…	4.94 (4.63)	…	5.81 (5.00)	…	4.11 (3.96)	<0.001	…
FEV_1, % predicted[b]	…	50.98 (16.58)	…	50.31 (16.34)	…	51.44 (16.37)	0.340	…
FVC, % predicted[c]	…	47.04 (17.49)	…	49.28 (19.12)	…	45.28 (15.36)	<0.001	…
6MWD, feet	…	754.02 (504.80)	…	667.17 (472.88)	…	841.75 (509.02)	<0.001	…
Mean PAP	…	25.93 (10.27)	…	33.80 (9.13)	…	18.67 (3.96)	<0.001	…

Hayes D, Ann Thorac Surg 2016

Histopathologic Examination

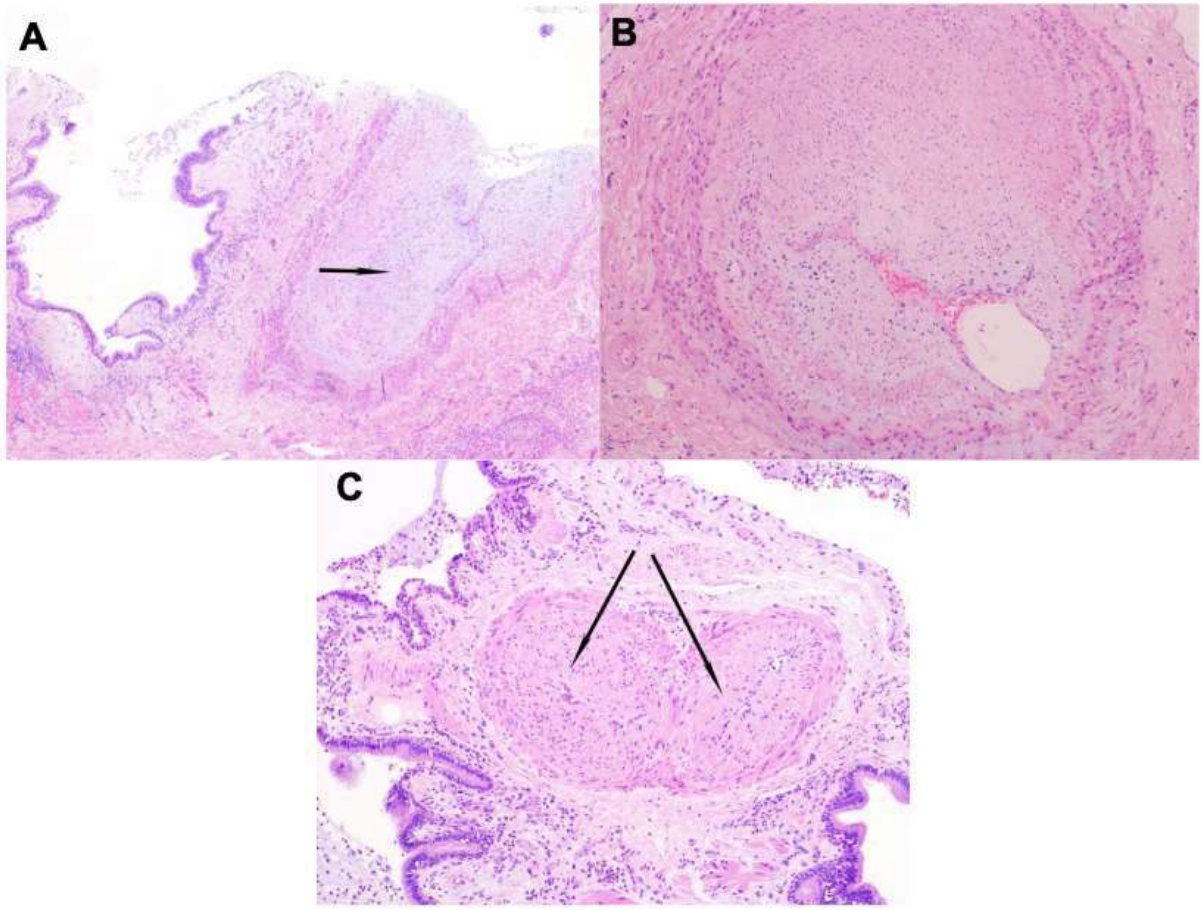
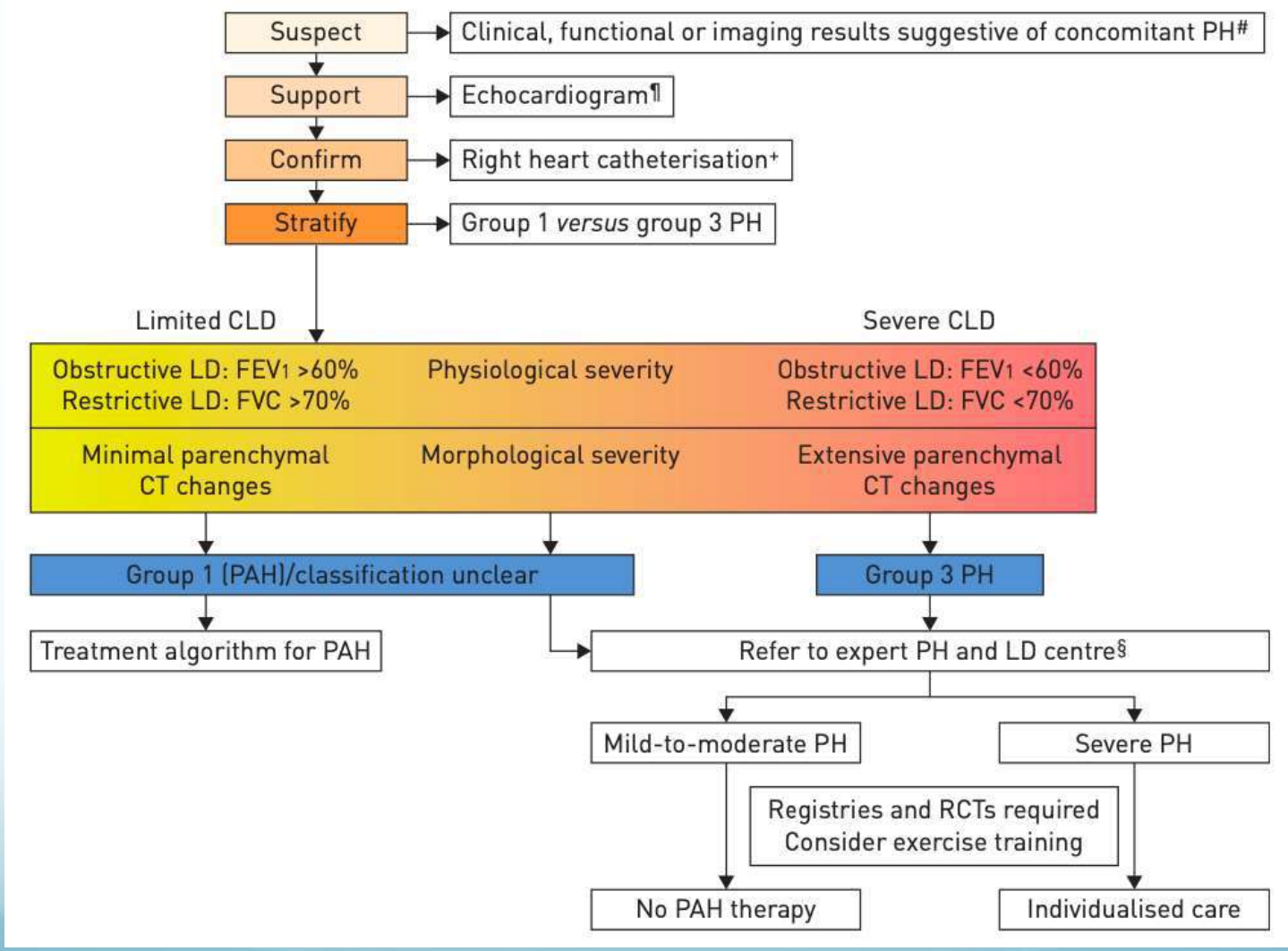


Figure 1 – *Histopathologic images from a patient with fibrotic interstitial lung disease and pulmonary hypertension. Large (A) and medium (B) pulmonary arteries show fibrointimal hyperplasia and myxoid change (arrow in A). C, Smaller arteries show marked medial hypertrophy (arrows). (Printed with permission from Haresh Mani, MD, Department of Pathology, Inova Fairfax Hospital).*

King CS, Chest 2020

Diagnostic Workup



Nathan SD, ERJ 2019

Clinical Findings

- Rapid decline in symptoms, pre-syncope, chest pain
- Loud P2, split second heart sound, elevated JVP, peripheral edema
- Mild obstructive/restrictive physiology on spirometry with significant decrease in DLCO
- Elevated NT-pro-BNP levels
- Right axis deviation on EKG

Nathan SD, ERJ 2019

CT Imaging

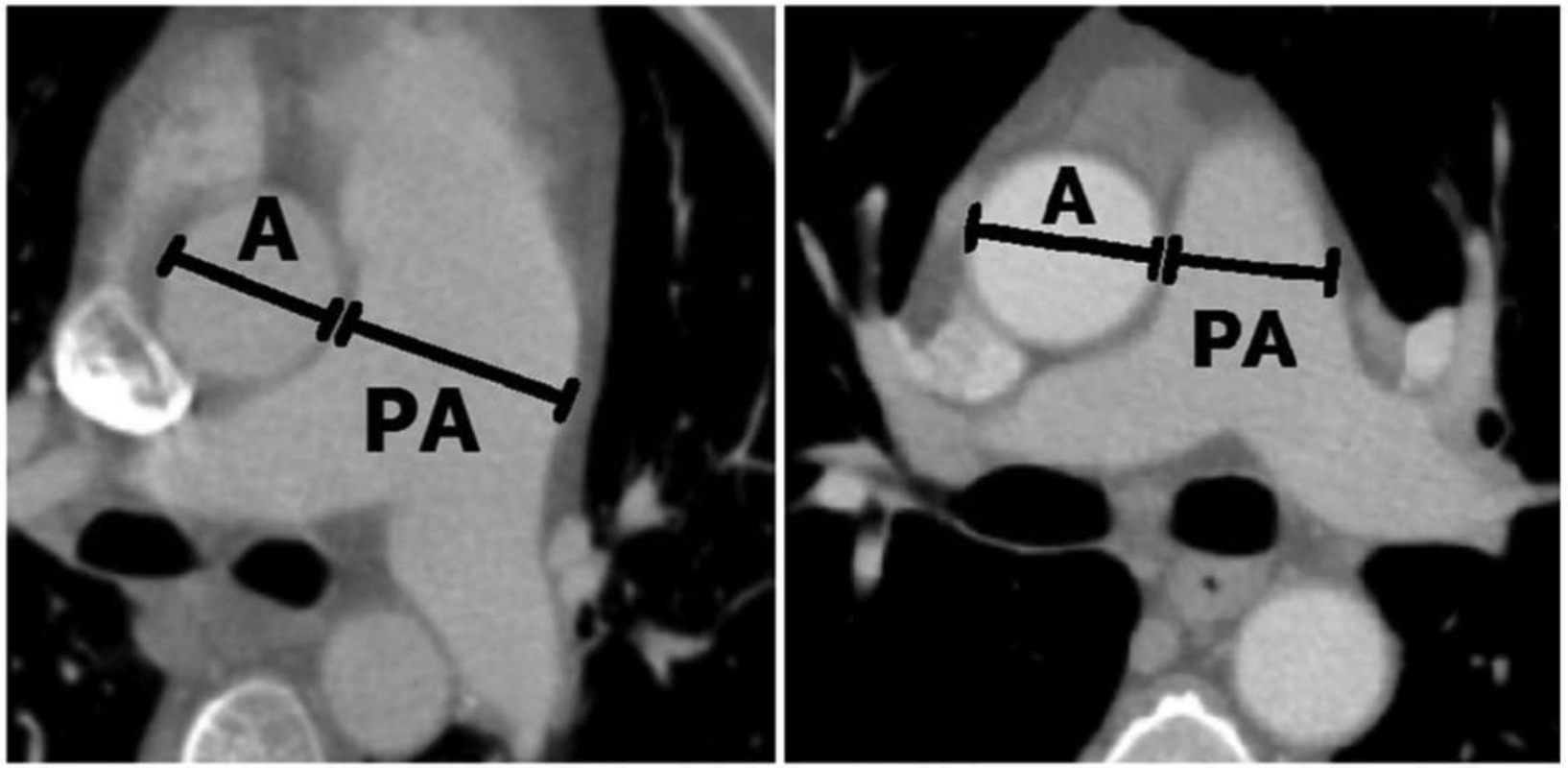


Figure 1.
Vessel measurements obtained from CT scans. (a) The diameter of an enlarged pulmonary artery (PA) from an IPAH patient (compare with the aorta (A) diameter). (b) An aorta and pulmonary artery diameter from a "normal" patient.

Corson N, Acad Radiol 2014

Echocardiogram

- Important to look at PA pressures and RV function
- In chronic lung disease patients, the tricuspid regurgitant jet may be difficult to visualize, which can over- or underestimate the RV systolic pressures compared to RHC
- Assessing RV function by looking at RV outflow tract diameter, tricuspid annular plane systolic excursion, and fractional area of change may be more accurate in diagnosing PH-ILD and predicting poor outcomes

Prins KW, J Am Heart Assoc. 2019

Indications for RHC

- Usually not indicated in patients with suspected mild PH
- Consider RHC when:

1. Clinical worsening not deemed attributable to ventilatory impairment
2. Severe PH or RV dysfunction is suspected based on echocardiogram
3. An accurate prognostic assessment is deemed important
4. Lung transplant workup
5. Rule out primary cardiac disease

Nathan SD, ERJ 2019

Interpretation of RHC

TABLE 1] Updated 6th World Symposium on Pulmonary Hypertension Definition of Group 3 PH

CLD	Definition
Without PH	mPAP ≤ 20 mm Hg or mPAP ≥ 21 mm Hg with PVR < 3
With PH	mPAP ≥ 21-24 mm Hg with PVR ≥ 3
With severe PH	mPAP ≥ 35 mm Hg or mPAP ≥ 25 mm Hg with cardiac index < 2.0 L/min/m^2

King CS, Chest 2020

Stratification

TABLE 3] Factors Favoring Group 1 vs Group 3 PH

Factor	Favors Group 1 Maladaptive Phenotype	Favors Group 3 Adaptive Phenotype
Clinical	• Presence of identified group 1 risk factor (CTD, HIV, family history, liver disease, congenital heart disease, etc)	• Absence of group 1 risk factors
PFT	• Mild restriction on PFTs • Low D_{LCO} in relation to restriction	• Severe restriction on PFT • D_{LCO} reduction proportional to restriction
CT imaging	• Mild fibrosis	• Severe fibrosis
Echocardiography	• Significant RV dysfunction	• Mild RV dysfunction
Hemodynamics	• Severe elevation of PAPs • Low cardiac index	• Mild elevations of PAPs • Preserved cardiac index

CTD = connective tissue disease; PAP = pulmonary artery pressure. See Table 1 and 2 legends for expansion of other abbreviations.

King CS, Chest 2020

Management Approach

- Optimize treatment of chronic lung disease
- LABA/LAMA/ICS and anti-fibrotics
- Airway clearance therapies
- Anti-inflammatory agents such as azithromycin and roflumilast
- Supplemental oxygen
- Pulmonary rehab and exercise
- Screen for sleep-disordered breathing and cardiac disease
- Consider lung transplant evaluation

King CS, Chest 2020

PAH Therapies in Group 3 PH

- PAH therapies have not been FDA approved for use in group 3 PH
- The poor performance of PAH-directed therapy in this population may be explained by vasodilatory effects that may exacerbate ventilation-perfusion abnormalities and worsen gas exchange in patients with lung disease
- Another potential concern is the development of pulmonary edema caused by vasodilation of pulmonary venoocclusive lesions
- Identify group 3 patients with PAH phenotype who are most likely to benefit from pulmonary vasodilator therapies

Nathan SD, ERJ 2019
King CS, Chest 2020

Prior Studies

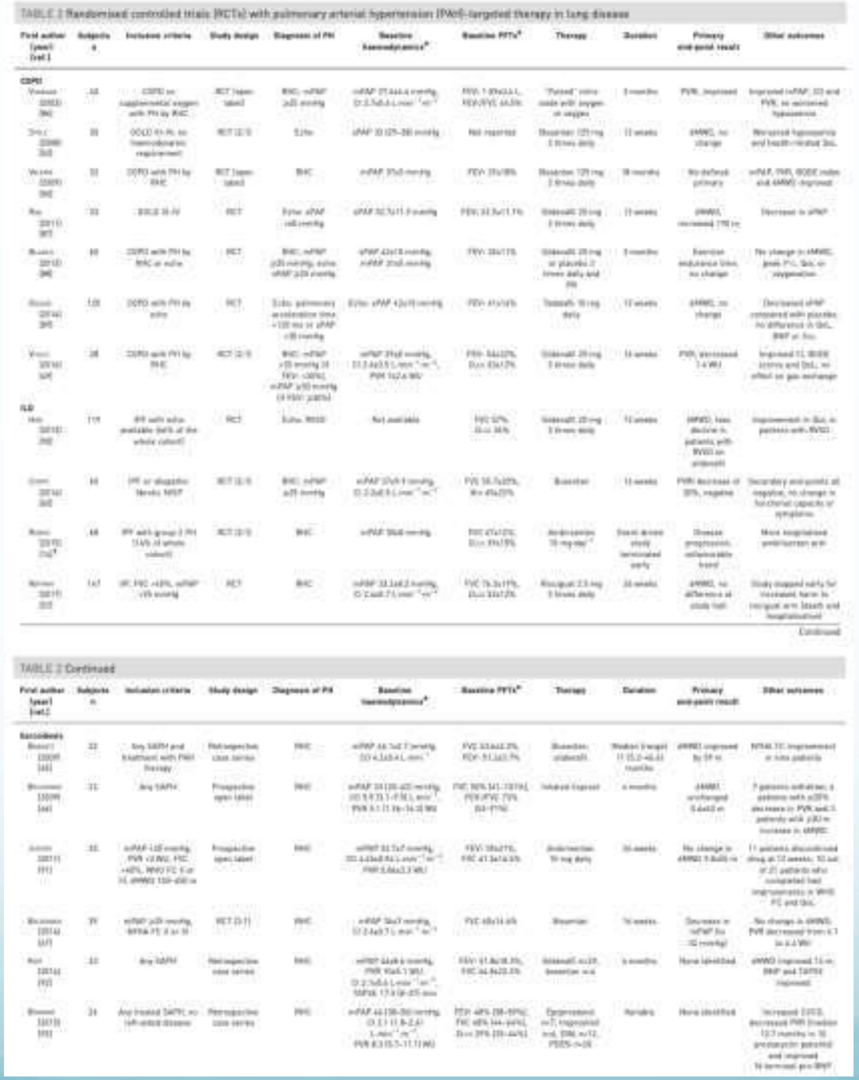


TABLE 2 Randomised controlled trials (RCTs) with pulmonary arterial hypertension (PAH)-targeted therapy in lung disease

First author (year) [ref.]	Subjects n	Inclusion criteria	Study design	Diagnosis of PH	Baseline haemodynamics	Baseline PFTs	Therapy	Duration	Primary end-point result	Other outcomes
COPD										

TABLE 2 Continued

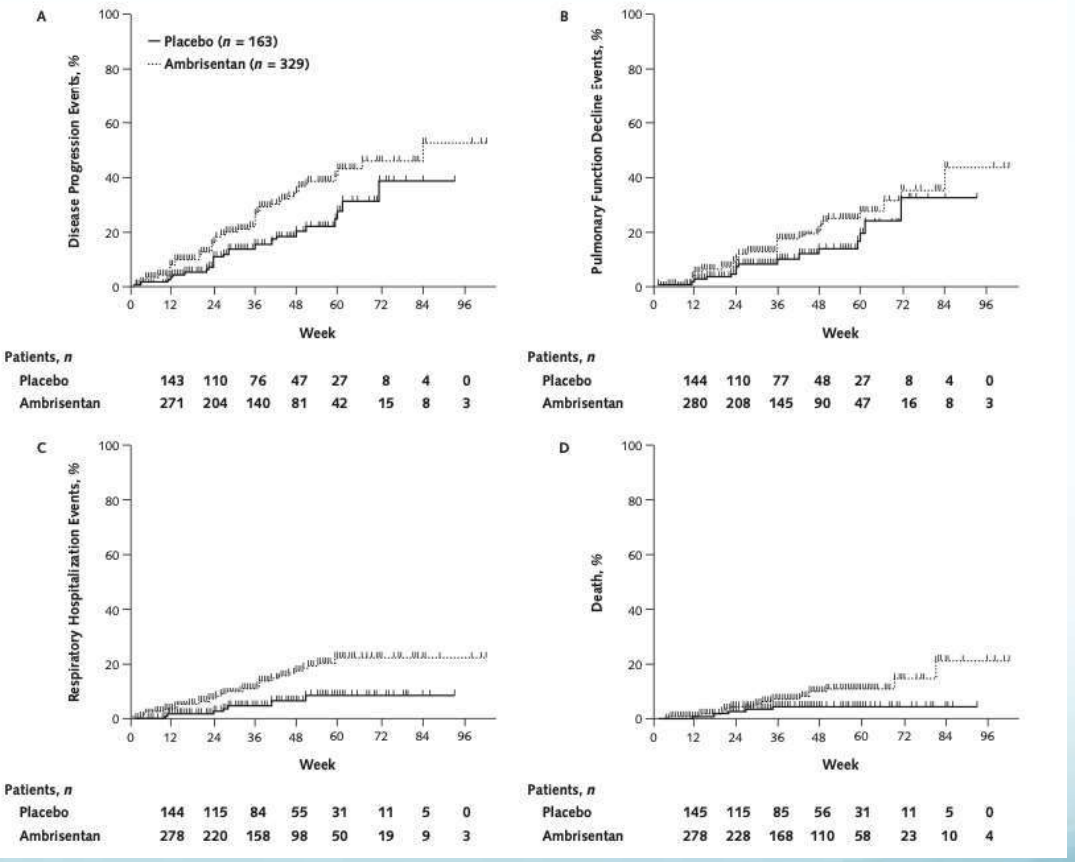
Nathan SD, ERJ 2019

ARTEMIS-IPF Trial

Table 1. **Baseline Characteristics of Study Participants**

Characteristic	Placebo (n = 163)	Ambrisentan (n = 329)
Mean age (SD), *y*	66.1 (7.1)	65.8 (7.4)
Male, *n (%)*	111 (68.1)	244 (74.2)
White, *n (%)*	145 (89.0)	293 (89.1)
Smoking status, *n (%)*		
Never	53 (32.5)	105 (31.9)
Current	5 (3.1)	7 (2.1)
Former	104 (63.8)	217 (66.0)
Pulmonary hypertension, *n (%)**	16 (9.8)	32 (9.7)
Mean pulmonary arterial pressure (SD), *mm Hg*	20.6 (8.0)	20.3 (6.3)
SLB-confirmed diagnosis of IPF, *n (%)**	76 (46.6)	154 (46.8)
Mean disease duration (SD), *y*	0.9 (1.2)	1.1 (1.4)
Mean FVC (SD), *% predicted*	69.9 (13.8)	68.7 (13.1)
Mean hemoglobin-adjusted D_{LCO} (SD), *% predicted*	45.6 (13.3)	42.0 (13.8)
Mean CPI score (SD)	50.6 (10.4)	53.0 (10.5)
Mean 6MWD (SD), *m*	420.5 (121.4)	410.4 (118.7)
Mean SGRQ score (SD)	40.5 (21.1)	44.5 (21.6)
Mean TDI score (SD)	7.6 (2.5)	7.3 (2.4)

Figure 3. **Kaplan–Meier plots for disease progression (*A*) (P = 0.010) and its components (lung function decline [*B*] [P = 0.109], respiratory hospitalizations [*C*] [P = 0.007], and death [*D*] [P = 0.100]), by treatment group.**



Raghu G, Ann Intern Med 2013

RISE-IIP Study

	Riociguat up to 2·5 mg (n=73)	Placebo (n=74)
Sex		
Male	50 (68%)	45 (61%)
Female	23 (32%)	29 (39%)
Mean age, years (SD)	68 (8)	69 (8)
Mean body mass index, kg/m² (SD)	30 (5)	28 (6)
Classification of IIP		
Idiopathic pulmonary fibrosis	54 (74%)	49 (66%)
Idiopathic nonspecific interstitial pneumonia	9 (12%)	14 (19%)
Respiratory bronchiolitis-interstitial lung disease	1 (1%)	0
Cryptogenic organising pneumonia	0	1 (1%)
Acute interstitial pneumonia	0	1 (1%)
Idiopathic lymphoid interstitial pneumonia	0	2 (3%)
Unclassifiable idiopathic interstitial pneumonias	9 (12%)	7 (9%)
WHO functional class		
II	16 (22%)	22 (30%)
III	50 (68%)	45 (61%)
IV	7 (10%)	7 (9%)
Mean 6-min walking distance, m (SD)	307 (80)	324 (66)
Haemodynamic parameters, mean (SD)		
Right atrial pressure, mm Hg	6·7 (4·0)	6·7 (4·5)
Mean pulmonary arterial pressure, mm Hg	33 (8)	33 (9)
Pulmonary vascular resistance, dyn·s·cm⁻⁵	391 (204)	418 (257)
Cardiac index, L/min/m²	2·6 (0·7)	2·6 (0·7)
Pulmonary artery wedge pressure, mm Hg	11 (3)	11 (3)
Systolic blood pressure, mm Hg	127 (17)	125 (18)
Diastolic blood pressure, mm Hg	77 (10)	76 (11)
Pulmonary function tests, mean (SD)		
FVC, % predicted	76·3% (19·1)	74·3% (15·7)
FEV_1, % predicted	75·5% (19·1)	75·1% (16·4)
FEV_1/FVC	0·81 (0·08)	0·82 (0·09)
Total lung capacity, % predicted	66·1% (14·6)	66·3% (12·0)
Diffusing capacity of the lung for carbon monoxide, % predicted	32% (12)	30% (11)
Resting blood gas analyses, mean (SD)		
PCO_2, mm Hg	36 (6)	37 (4)
PaO_2, mm Hg	67 (18)	69 (19)
SaO_2, % room air	91% (7)	92% (6)
History of tobacco smoking	3 (3%)	4 (5%)

Data are n (%) unless otherwise specified. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. IIP=idiopathic interstitial pneumonia. PaO_2=arterial partial pressure of oxygen. PCO_2=arterial partial pressure of CO_2. SaO_2=oxygen saturation measured by arterial blood gas analysis.

Table 1: Baseline patient characteristics

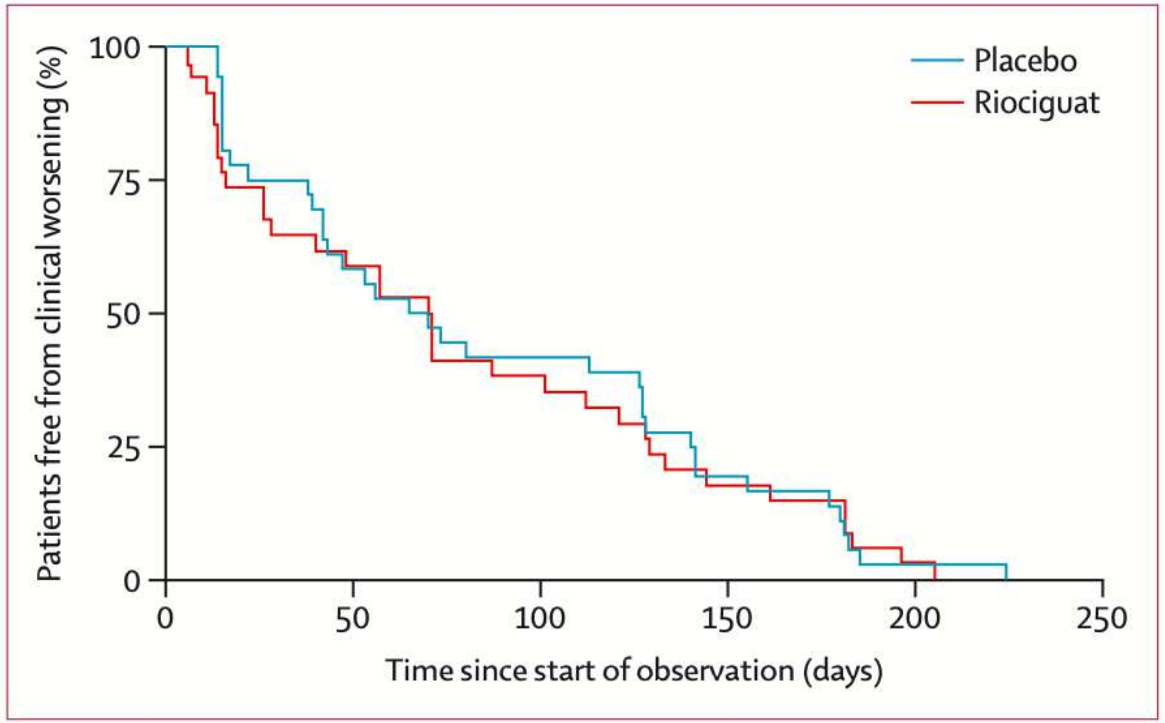


Figure 3: **Time to first clinical worsening event in the main study phase**

Nathan SD, Lancet Respir Med. 2019

RISE-IIP Study

	Main phase		Long-term extension phase*		Safety follow-up phase†	
	Riociguat up to 2·5 mg (n=73)	Placebo (n=74)	Riociguat up to 2·5 mg (n=32)	Former placebo (n=38)	Riociguat up to 2·5 mg (n=73)	Former placebo (n=74)
Any AE	65 (89%)	64 (86%)	29 (91%)	34 (89%)	40 (55%)	36 (49%)
Study drug-related AEs	29 (40%)	28 (38%)	12 (38%)	18 (47%)	1 (1%)	1 (1%)
AEs leading to study drug discontinuation	11 (15%)	3 (4%)	1 (3%)	4 (11%)	0	0
Any SAE	27 (37%)	17 (23%)	12 (38%)	21 (55%)	18 (25%)	14 (19%)
Study drug-related SAEs	5 (7%)	4 (5%)	3 (9%)	5 (13%)	1 (1%)	0
SAEs leading to study drug discontinuation	10 (14%)	1 (1%)	1 (3%)	2 (5%)	0	0
Deaths	8 (11%)	3 (4%)	1 (3%)	8 (21%)	3 (4%)	4 (5%)

Data are n (%). AE=adverse event. SAE=serious adverse event. *Both groups received riociguat up to 2·5 mg three times daily. †At study termination, all patients discontinued riociguat and immediately started the safety follow-up phase. The length of the safety follow-up ranged from 30 to 120 days.

***Table 2:* Summary of AEs by phase**

Nathan SD, Lancet Respir Med. 2019

STEP-IPF Study

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Sildenafil (N=89)	Placebo (N=91)
Age — yr	69.76±8.71	68.20±9.25
Female sex — no. (%)	14 (16)	16 (18)
Race — no. (%)†		
White	78 (88)	85 (93)
Black	5 (6)	1 (1)
Other	6 (7)	5 (5)
History of smoking — no. (%)	68 (76)	69 (76)
Time since diagnosis — yr	2.03±1.94	1.87±1.93
Supplemental use of oxygen during walk test — no. (%)	28 (31)	24 (26)
6-Minute walk distance — m		
First test	246.93±99.11	267.71±127.75
Second test	246.39±103.40	269.55±129.83
Score on Borg Dyspnea Index after walk test (range, 0–10)‡	3.82±1.95	3.33±1.73
Score on Shortness of Breath Questionnaire (range, 0–120)‡§	50.71±22.00	43.28±20.18
Total score on St. George's Respiratory Questionnaire (range, 0–100)‡	54.55±16.46	51.72±15.86
SF-36 (range for each subscale, 0–100)¶		
Aggregate physical score	33.17±9.19	34.84±8.69
Aggregate mental score	49.53±9.76	50.58±9.52
Score on EQ-5D¶		
Self-report questionnaire (range, −0.59 to 1.00)	0.71±0.24	0.74±0.19
Visual analogue scale (range, 0–100)	66.49±17.45	67.66±16.98
Forced vital capacity — % of predicted value	54.89±14.00	58.73±14.12
Carbon monoxide diffusion capacity — % of predicted value	25.81±6.03	26.73±6.16
Partial pressure of oxygen — mm Hg	66.22±12.22	69.88±12.85
Arterial oxygen saturation — %§	91.24±4.22	92.59±3.75

Idiopathic Pulmonary Fibrosis Clinical Research Network, NEJM 2010

STEP-IPF Study

Table 2. Change in Prespecified Secondary Outcomes at 12 Weeks.*

Characteristic	Sildenafil (N=89)	Placebo (N=91)	Absolute Difference†	P Value
	mean change (95% confidence interval)			
Dyspnea				
Score on Borg Dyspnea Index after walk test‡	0.04 (–0.30 to 0.37)	0.37 (0.04 to 0.70)	–0.34 (–0.81 to 0.14)	0.16
Shortness of Breath Questionnaire‡	0.22 (–3.10 to 3.54)	6.81 (3.53 to 10.08)	–6.58 (–11.25 to –1.92)	0.006
Quality of life				
St. George's Respiratory Questionnaire‡				
Total score	–1.64 (–3.91 to 0.64)	2.45 (0.17 to 4.72)	–4.08 (–7.30 to –0.86)	0.01
Symptoms score	–3.58 (–7.02 to –0.13)	2.15 (–1.30 to 5.61)	–5.73 (–10.61 to –0.85)	0.02
Activity score	–1.15 (–3.68 to 1.38)	2.49 (0.00 to 4.99)	–3.64 (–7.20 to –0.09)	0.04
Impacts score (social function)	–0.88 (–3.78 to 2.02)	2.82 (–0.03 to 5.67)	–3.70 (–7.76 to 0.37)	0.07

Table 3. Death and Acute Exacerbation.

Variable	Sildenafil (N=89)	Placebo (N=91)	P Value
Death from any cause — no (%)*			
12 wk	2 (2)	4 (4)	0.43
24 wk	3 (3)	9 (10)	0.08
28 wk	4 (5)	11 (13)	0.07
Acute exacerbation — no./total no. (%)			
Period 1	2/89 (2)	4/91 (4)	0.68
Period 2	1/78 (1)	3/83 (4)	0.62
All patients	3/89 (3)	7/91 (8)	0.33

Idiopathic Pulmonary Fibrosis Clinical Research Network, NEJM 2010

Sildenafil for COPD Patients

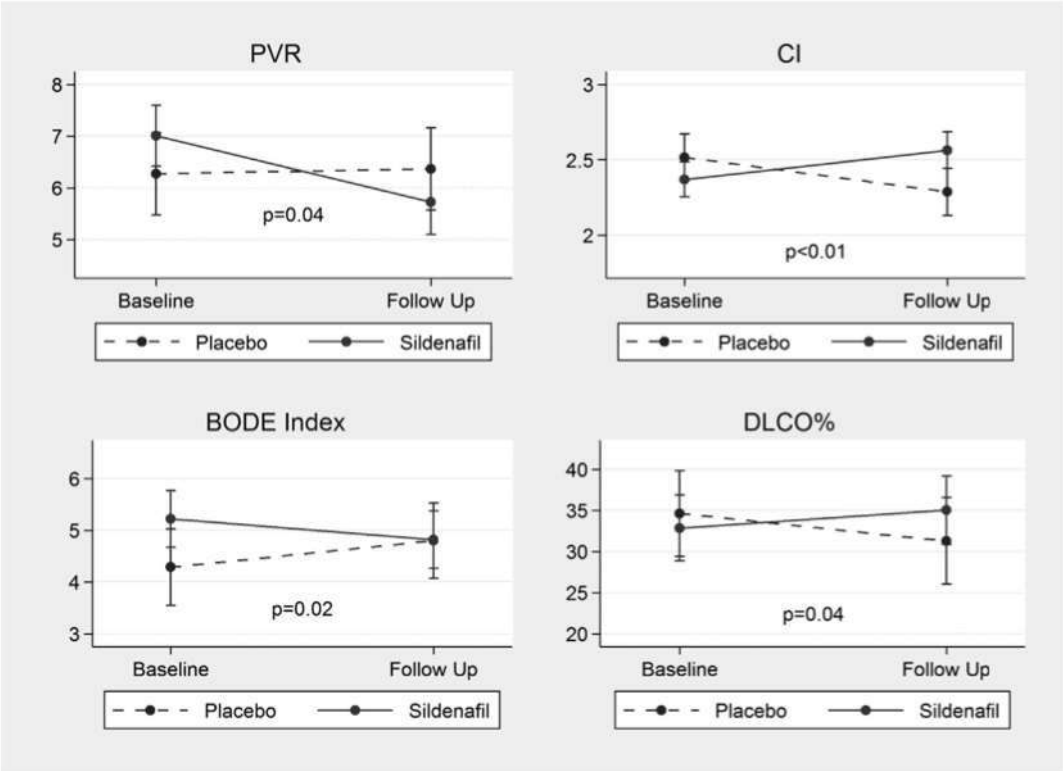


Figure 3 Primary and secondary end point variables significantly varied in patients treated with sildenafil (see also Tables 2–4). The error bars indicate the standard deviation. BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; CI, cardiac index; DLCO, diffusion capacity of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

Vitulo P, J Heart Lung Transplant 2017

INCREASE Trial

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
Female sex — no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) — yr	65.6 (26–90)	67.4 (36–85)	66.5 (26–90)
Age distribution — no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group — no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Hispanic or Latino ethnic group — no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis — yr	0.54±1.16	0.54±1.31	0.54±1.23
Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory — no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen — no. (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy — no. (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

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	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
6-minute walk distance, meters; mean (range)	254.1 (100-538)	265.1 (30-505)	259.6 (30-538)
Median	256.0	260.0	259.0
Pulmonary vascular resistance, Woods units; mean (range)	6.369 (3.11-18.05)	6.013 (3.06-17.62)	6.191 (3.06-18.05)
Median	5.570	5.060	5.275
NT-proBNP, pg/mL; mean (range)	1857.53 (10.2-21942.0)	1808.86 (23.0-16297.0)	1832.88 (10.2-21942.0)
Median*	550.50	420.80	503.85
Pulmonary arterial pressure, mmHg; mean (range)	37.2 (25-74)	36.0 (25-61)	36.6 (25-74)
Median	35.0	35.0	35.0
Pulmonary capillary wedge pressure, mmHg; mean (range)	10.1 (2-20)	9.6 (0-15)	9.8 (0-20)
Median	10.0	10.0	10.0
Pulmonary function tests			
FEV_1 % Predicted; mean (range)	63.9 (23, 120)	65.0 (22, 145)	
Median	63.0	63.0	
FVC % Predicted; mean (range)	62.5 (24, 130)	63.8 (20, 134)	
Median	60.0	61.0	
TLC % Predicted; mean (range)	62.9 (25, 126)	64.2 (30, 109)	
Median	62.0	62.5	
DLCO % Predicted; mean (range)	30.0 (5, 86)	28.1 (1, 86)	
Median	29.0	26.0	

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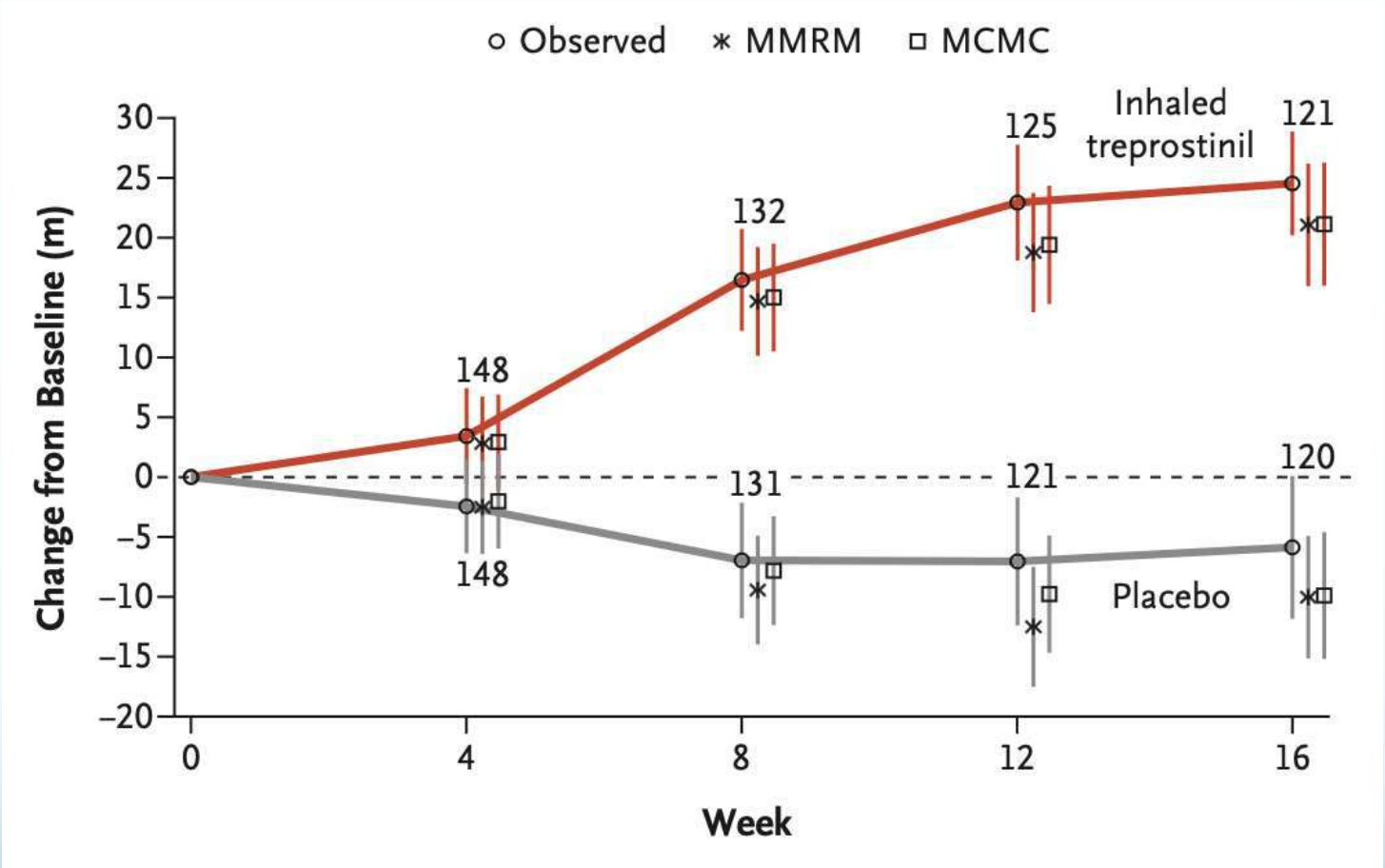

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Table 3. Summary of Adverse Events.

Variable	Inhaled Treprostinil (N=163)	Placebo (N=163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event — no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event — no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events — no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

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PAH Therapies in Group 3 PH

- Endothelin receptor antagonists: Avoid in ILD patients; Bosentan possibly safe in COPD-PH
- Guanylate stimulator: Riociguat associated with increased adverse events in ILD patients
- Phosphodiesterase-5 inhibitors: Generally safe, can consider as a bridge to transplant
- Prostacyclins: Promising data for inhaled treprostinil in ILD patients

Nathan SD, ERJ 2019
King CS, Chest 2020

Take Home Points

- Pulmonary hypertension in chronic lung disease is associated with increased mortality and worse outcomes
- A subset of group 3 PH patients exhibit a PAH phenotype
- Consider workup and RHC in patients with symptoms out of proportion to their ventilatory defects
- Once workup is complete, determine what contributes to pulmonary hypertension in the patient and how does pulmonary hypertension contribute to the patient's symptoms
- In chronic lung disease patients with the PAH phenotype, consider trial of PDE-5 or prostacyclin therapies or referral to a PH center

References

- Corson N, et al. CT-based pulmonary artery measurements for the assessment of pulmonary hypertension. Acad Radiol. 2014 Apr;21(4):523-30.
- Hayes Jr D, et al. Influence of Pulmonary Hypertension on Patients With Idiopathic Pulmonary Fibrosis Awaiting Lung Transplantation. Ann Thorac Surg. 2016 Jan;101(1):246-52.
- Hurdman J, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur Respir J. 2012 Apr;39(4):945-55.
- Hurdman J, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. Eur Respir J. 2013 Jun;41(6):1292-301.
- Idiopathic Pulmonary Fibrosis Clinical Research Network, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med. 2010 Aug 12;363(7):620-8.
- King CS and Shlobin OA. The Trouble With Group 3 Pulmonary Hypertension in Interstitial Lung Disease: Dilemmas in Diagnosis and the Conundrum of Treatment. Chest. 2020 Oct;158(4):1651-1664.

References

- Nathan SD, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019 Jan 24;53(1):1801914.
- Nathan SD, et al. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. Lancet Respir Med. 2019 Sep;7(9):780-790.
- Prins KW, et al. Clinical determinants and prognostic implications of right ventricular dysfunction in pulmonary hypertension caused by chronic lung disease. J Am Heart Assoc. 2019 Jan 22;8(2):e011464.
- Raghu G, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013 May 7;158(9):641-9.
- Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913.
- Vitulo P, et al. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial. J Heart Lung Transplant. 2017 Feb;36(2):166-174.
- Waxman A, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med. 2021 Jan 13. doi: 10.1056/NEJMoa2008470.