PNEUMOLOGIA 2018

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Ipertensione polmonare: cosa sta cambiando dopo Nizza 2018

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Nice 2013 definition

COPD / DPLD without PH (PAP < 25 mmHg)

COPD / DPLD with PH (PAP >/= 25 mmHg; with supplemental O_2 if needed)

COPD / DPLD with severe PH (PAP >/= 35 mmHg; supplemental O_2)*

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

Nice 2018 definition

CLD without PH: mPAP <21 mmHg, or mPAP 21-24 with PVR <3 WU

CLD with PH: mPAP 21-24 mmHg with PVR >3 WU, or mPAP 25-34 mmHg (CLD-PH)

CLD with severe PH: mPAP >35 mmHg or mPAP >25 mmHg with low cardiac index (< 2.0 L/min/m2) *;

Rationale CLD with severe PH: - at this level hemodynamics contribute to exercise limitation

- minor subpopulation with “vascular phenotype” (in COPD < 3%)

- optimal target population in future RCT addressing PH in chronic lung disease

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

Clinical Classification of Pulmonary Hypertension

1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

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 abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Simonneau G, et al. J Am Coll Cardiol 2009 & 2014

Group 3 - PH due to lung disease and/or hypoxia

1.Obstructive pulmonary disease
- 1.COPD
- 2.Bronchiolitis obliterans

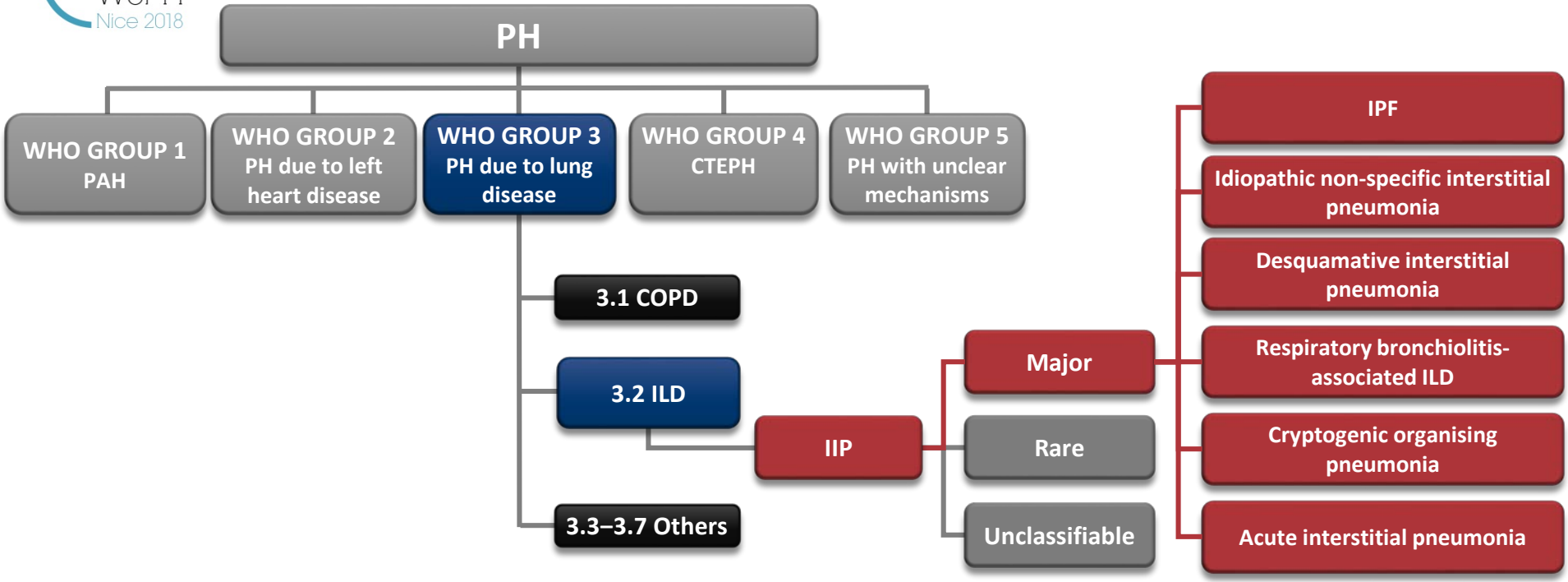
2.Interstitial Lung Diseases
- 1.Idiopathic interstitial pneumonias
- 2.Chronic hypersensitivity pneumonitis
- 3.Occupational lung diseases

3.Other lung diseases with mixed restrictive /obstructive pattern
- **1.Sarcoidosis**
- 2.Combined pulmonary fibrosis and emphysema
- **3.Cystic fibrosis and non-cystic fibrosis bronchiectasis**
- **4.Lymphangioleiomyomatosis**
- 5.Other destructive lung diseases

4.Alveolar hypoxia without lung disease
- 1.Sleep-disordered breathing
- 2.Chest wall abnormalities
- 3.Obesity-hypoventilation syndrome
- 4.Other alveolar hypoventilation disorders
- 5.Chronic exposure to high altitude

5.Developmental
- 1.Congenital lung disorders
- 2.Bronchopulmonary dysplasia

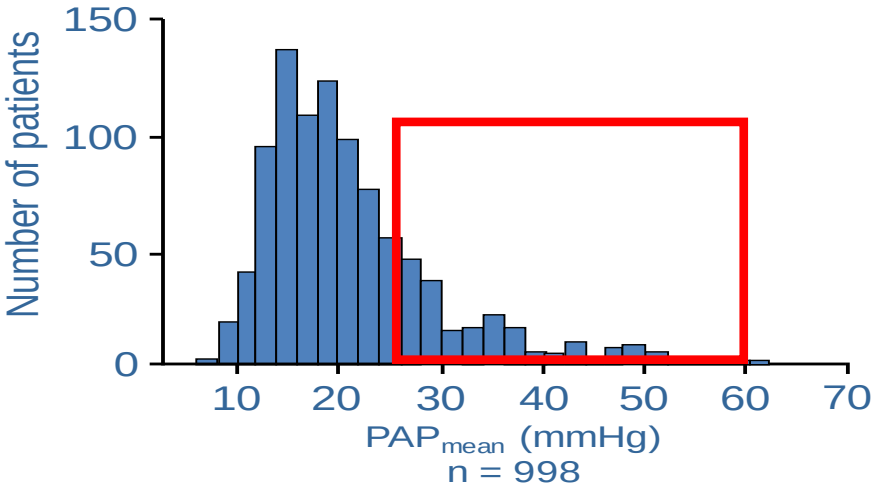
Overview interstitial lung diseases



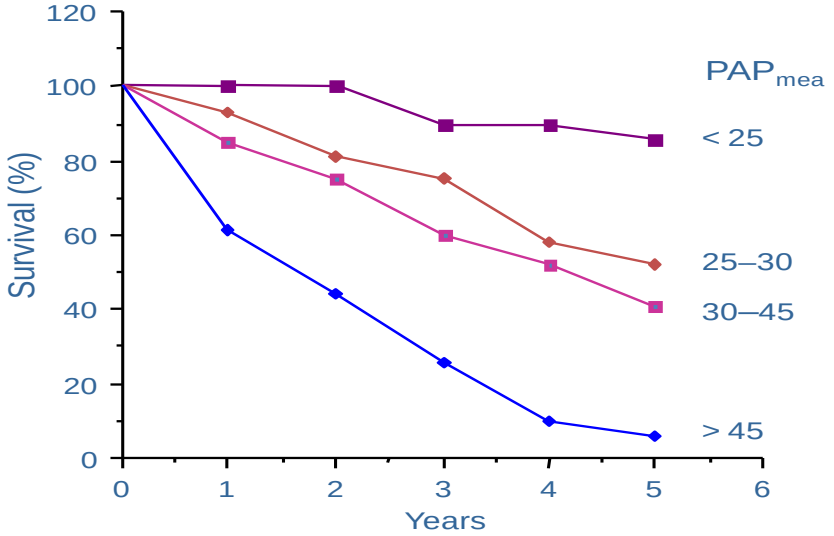
Epidemiology and clinical relevance of PH in chronic obstructive lung disease (COPD)

- High prevalence of mild PH in severe COPD
- 1 – 3 % of GOLD IV patients have mPAP > 35 – 40 mmHg
- Specific "*pulmonary vascular phenotype/unique cluster*" of COPD
- First evidence that specific genetic signatures are linked to this "vascular phenotype" in COPD
- Aspire Registry: patients with more severe PH have less severe airway obstruction
- Further PAP increase upon exercise
- PH strong predictor of hospitalization, exacerbation and mortality in COPD
- Hemodynamics stronger predictor of mortality than FEV1

Spectrum of PH in COPD



Impact on mortality



Nat Rev Cardiol 2011

Role of PH in exercise limitation in COPD

Ventilatory limitation in COPD + no/moderate PH

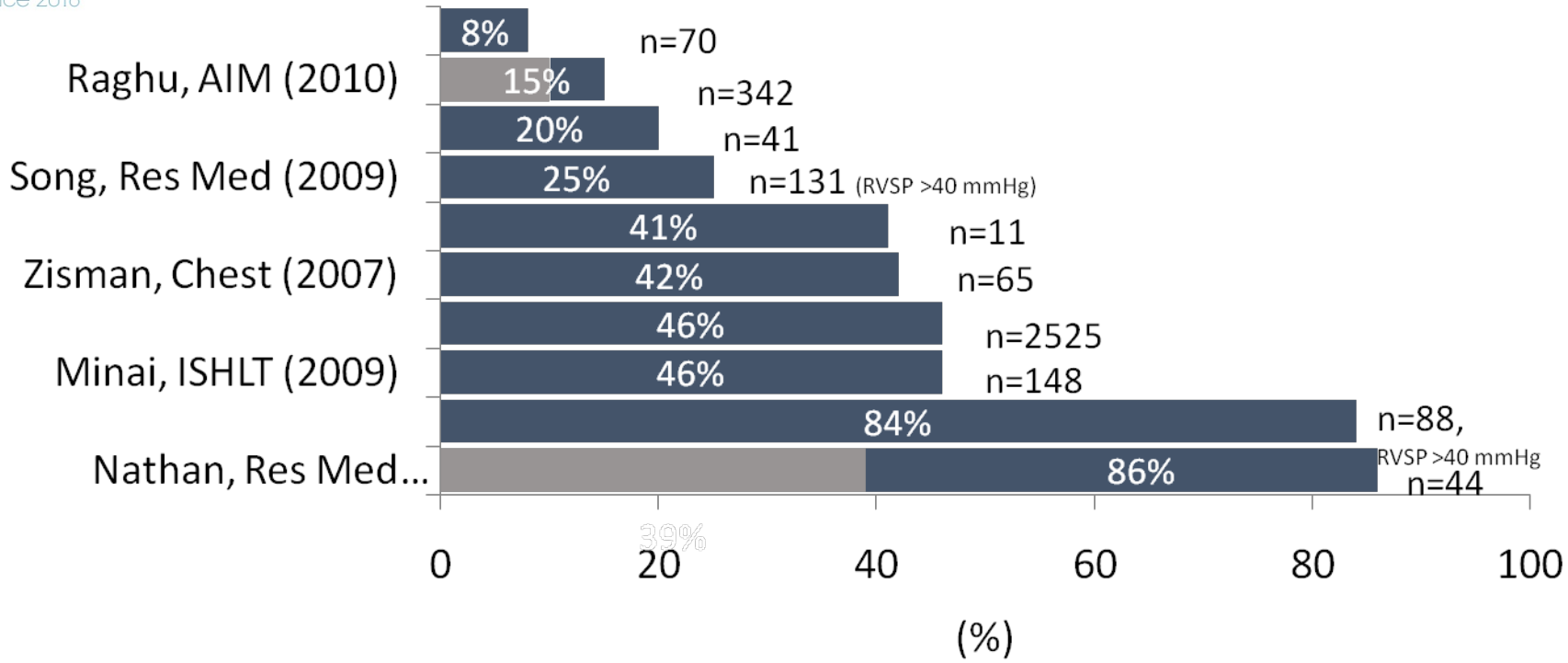
- $PaCO_2\uparrow$
- Exhausted breathing reserve
- Reserve in SvO_2
- Normal CO/VO_2 slope

Circulatory limitation in COPD + severe PH (> 35 mmHg)

- SvO_2 at lower limit
- CO/VO_2 slope reduced
- Low PaCO2
- Breathing reserve

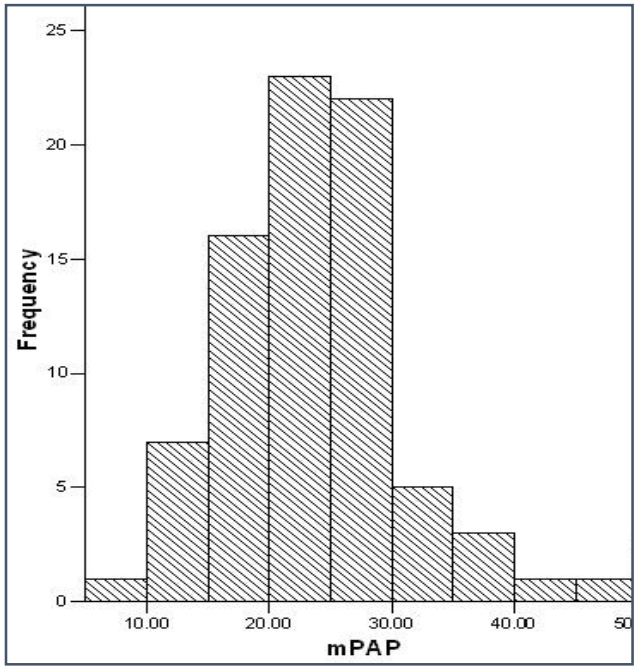
B.G. Boerrigter …A. Vonk Noordegraaf, CHEST 142:1166-1174, 2012

Prevalence of PH in IPF

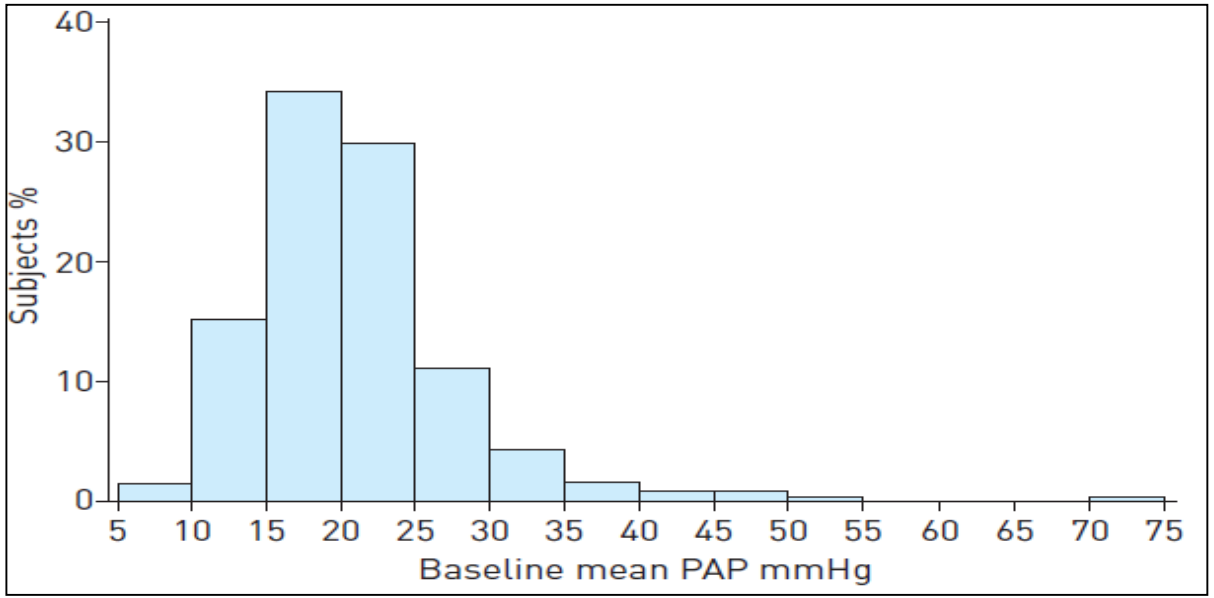


IPF, idiopathic pulmonary fibrosis; RVSP, right ventricle systolic pressure.

Distribution of PA pressures in IPF



Chest. 2006;129:746-752.



Raghu et al, ERJ 2015

PH in IPF: No correlation with Restriction

	N	FVC%	DL_{CO}%	mPAP (mmHg)	Patients with PH	%
FVC range						
> 70%	16	80.4	43.2	29.7	10	62.5
60-69%	26	63.1	41.1	22.1	7	26.9
50-59%	23	54.6	31.1	23.2	10	43.5
40-49%	31	44.8	32.5	22.9	13	41.9
< 40%	22	32.0	22.1	21.6	8	36.4

Chest 2007;131:657-663.

« Disproportionate PH » : cluster analysis

COPD

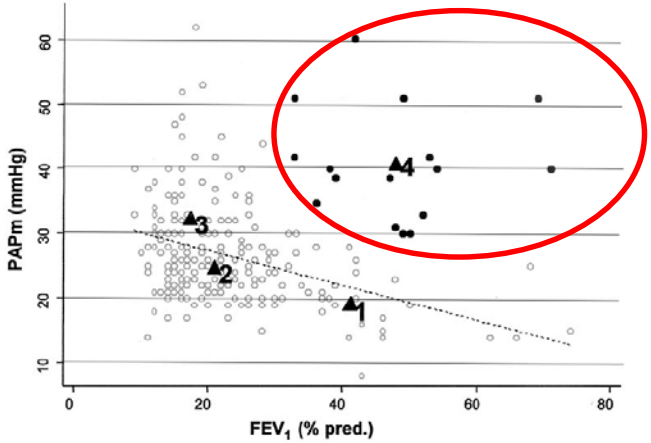
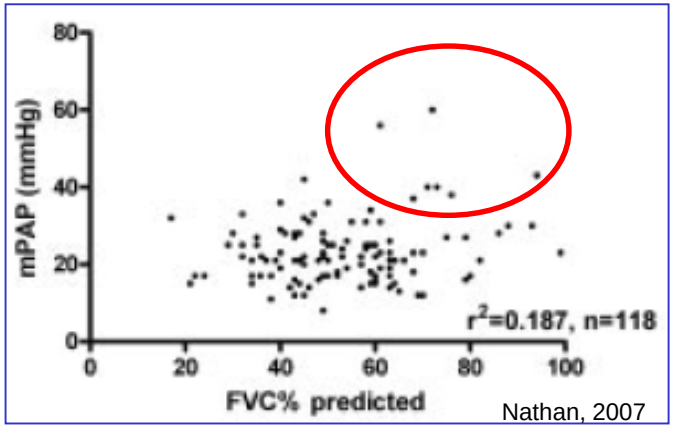


FIGURE 2. Characteristics of the four groups of patients disclosed by cluster analysis. Relationships between PAPm and FEV_1 are shown in groups 1, 2, and 3 (hollow circles) and group 4 (full circle). Triangles indicate the average of each group. A regression line is displayed.

Thabut G et al, *Chest* 2005;127:1531

IPF

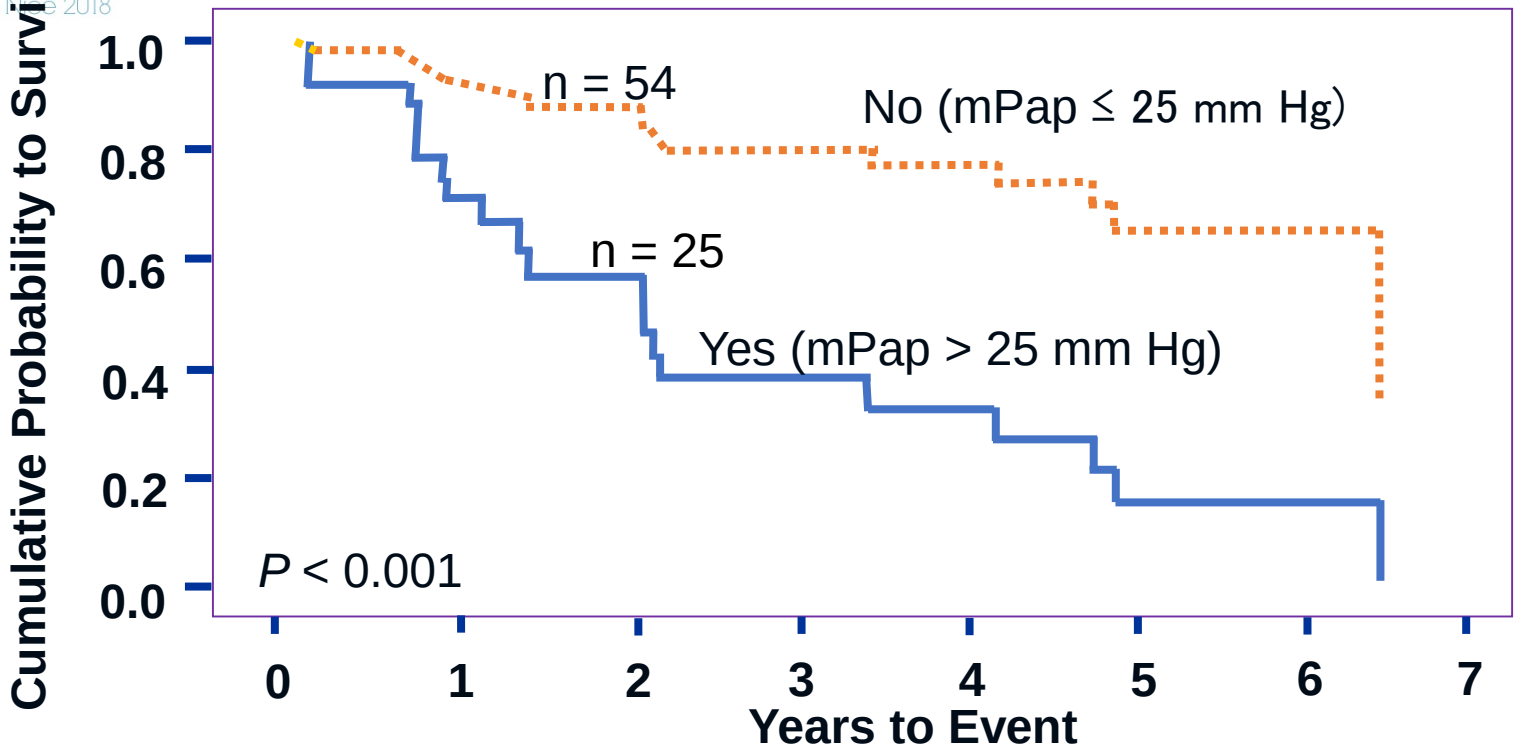


Nathan, 2007

Nathan SD Chest 2007;131:657

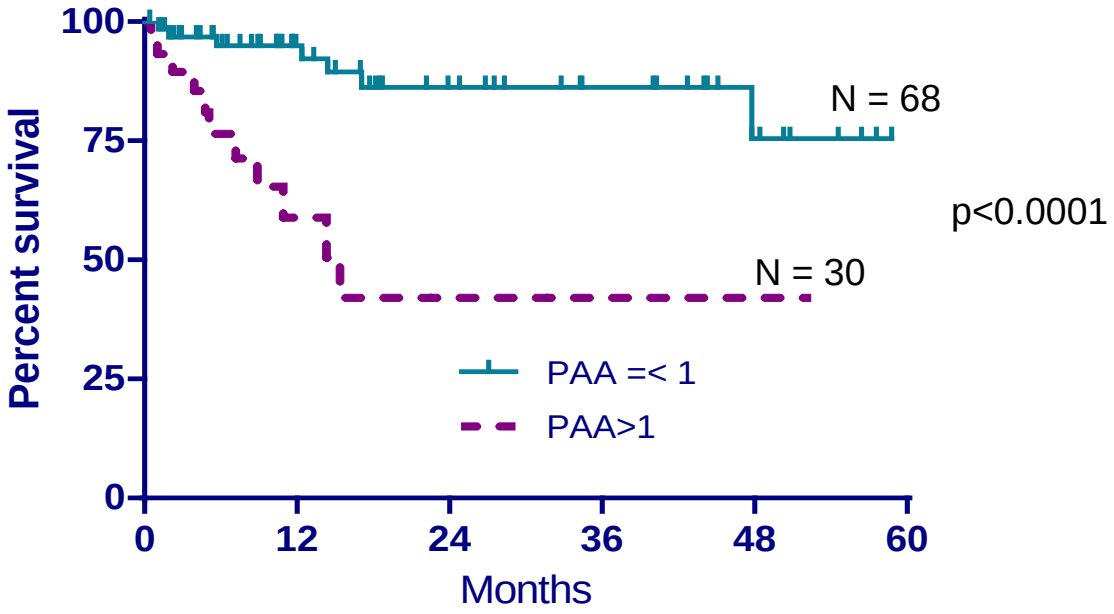
Mean Pulmonary Artery Pressure:

Prognostic Value in IPF



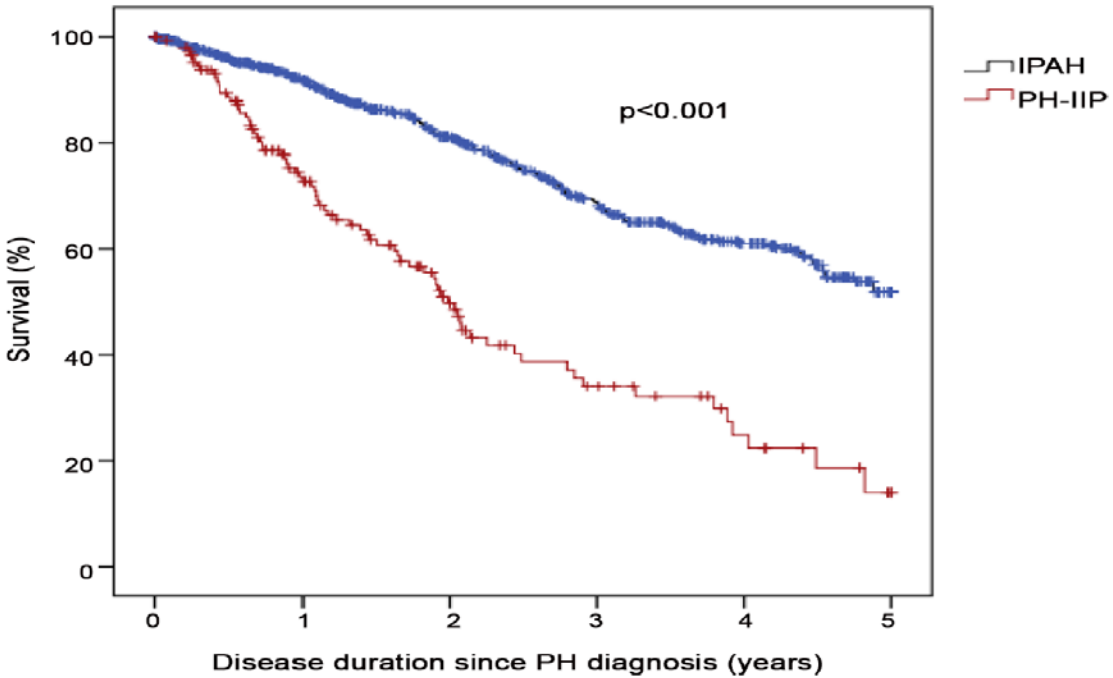
Chest 2006;129:746-752.

PA size predicts outcomes in IPF



Eur Respir J 2016;47:1445-1451

Survival: IPAH vs PH-IIP



Hoeper et al, PLOS ONE 2015

Role of PH in exercise limitation in IPF

Development of **severe PH** in IPF (mPAP >/= 35 - 40 mmHg) is linked with

- lower exercise capacity
- lower DLCO and arterial oxygenation
- desaturation upon exercise independent of lung function tests

Evidence for **circulatory impairment in severe PH-IPF** as similarly shown for severe PH-COPD

(AK Boutou et al, Respirology 16:451, 2011; OA Minai et al, Respir Med 106:1613, 2012; CU Andersen et al, Respir Med 106:875, 2012; Gläser S, Respir Med 2009;103:317)

Epidemiology and clinical relevance of PH in fibrotic lung disease

- High mPAP values of > 25 mmHg in 30 – 50 % of advanced IPF
- PH strong predictor of hospitalization/mortality in IPF
- PH in IPF reduces 6MWD independent of lung function

PH due to lung disease and/or hypoxia

Lung Diseases

- Epidemiology

- Assessment and Definition

- Therapy

Hypoventilation/High Altitude

Recommendations for Future Direction

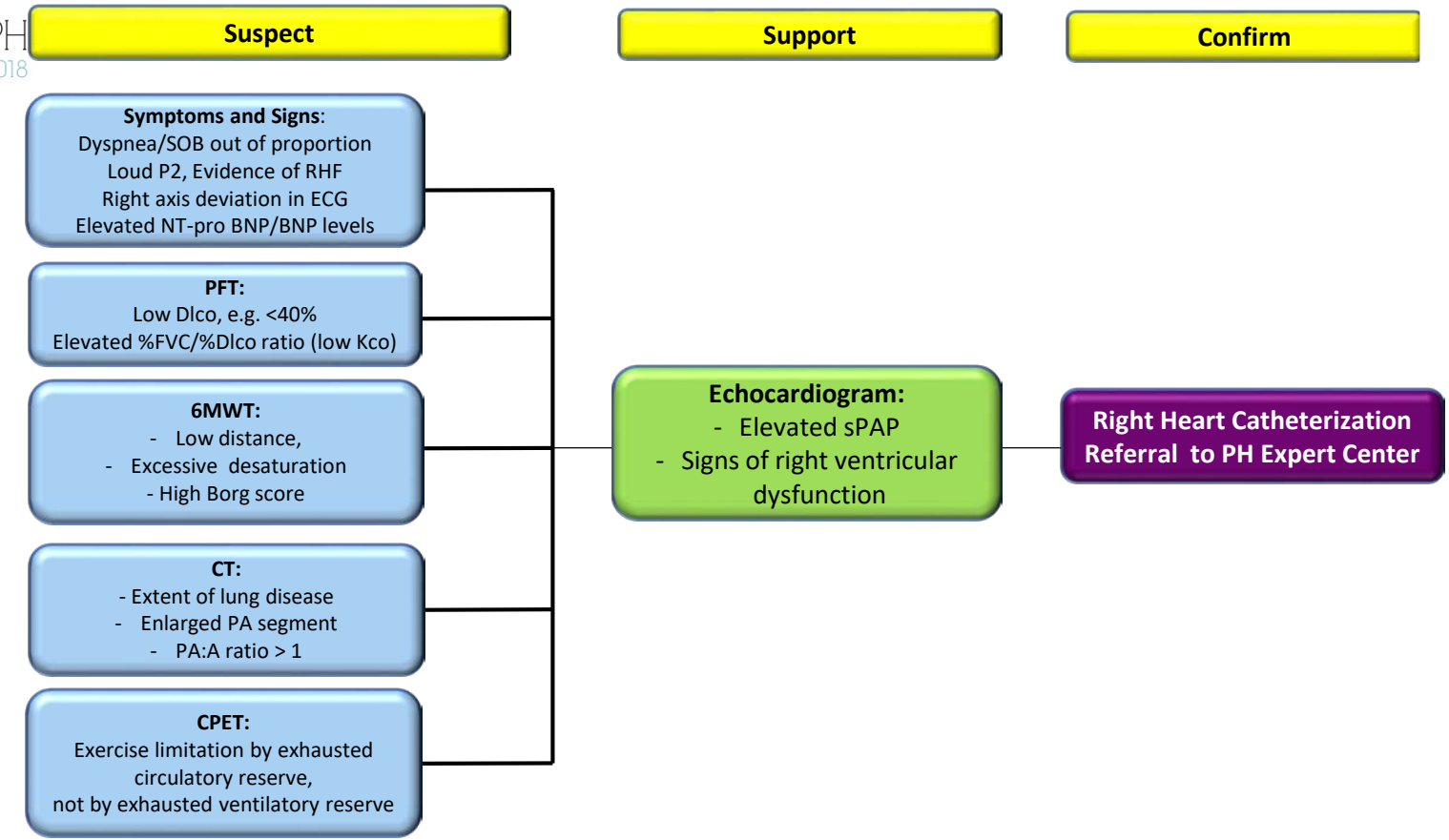
Right heart catheterization in chronic lung disease

RHC remains the **gold standard** for the diagnosis of PH

- suspicion for underlying PH does not always mandate RHC
- RHC **should be performed** in patients with chronic lung disease
  - 1) evaluation for lung transplantation
  - 2) suspicion of left ventricular systolic/diastolic dysfunction
  - 3) Severe PH is suspected and further therapy or inclusion in clinical trials or registries are being considered.
- RHC **may be considered**:
  - 1) clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are disproportionate to ventilatory impairment
  - 2) when an accurate prognostic assessment is deemed sufficiently important

Technique: averaging of pressure values over several respiratory cycles

Algorithm for Diagnosis of PH in Patients in Known Lung Disease



6th WSPH Nice 2018

Definition:

Group 1 versus group 3 patients ?

Criteria favoring Group 1 (PAH) versus Group 3 (PH due to Lung Disease) PH

Criteria favoring Group 1 (PAH)	Testing	Criteria favoring Group 3 (PH due to Lung Disease)
Extent of lung disease		
Normal or mildly impaired: FEV1 >60% pred. (COPD) FVC >70% pred. (IPF) Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severe impairment: FEV1 <60% pred. (COPD) FVC <70% pred. (IPF) Diffusion capacity “corresponds” to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High resolution CT scan**	Characteristic airway and/or parenchymal abnormalities
Hemodynamic Profile		
Moderate to severe PH	Right heart catheterization Echocardiogram	Mild to moderate PH
Ancillary Testing		
Present	Further PAH risk factors (as e.g. HIV, connective tissue disease, BMPR2 mutations, ...)	Absent
Features of exhausted circulatory reserve –Preserved breathing reserve –Reduced oxygen pulse –Low CO/VO2 slope –Mixed venous oxygen saturation at lower limit –No change or decrease in PaCO2 during exercise	Cardiopulmonary exercise test*** (particularly relevant in COPD)	Features of exhausted ventilatory reserve –Reduced breathing reserve –Normal oxygen pulse –Normal CO/VO2 slope –Mixed venous oxygen saturation above lower limit –Increase in PaCO2 during exercise

Predominant hemodynamic profile

Predominant obstructive/restrictive profile

PH due to lung disease and/or hypoxia

Lung Diseases

- Epidemiology

- Assessment and Definition

- Therapy

Treatment of PH in lung diseases –

evidence for appropriate benefit to

risk ratio of PAH approved drugs?

General

- Treatment of underlying disease
- No established vascular therapy except for LOT in COPD
- Rationale for use of PAH approved therapy?
  - PH contributes to limitation of exercise capability?
  - PH contributes to shortage of life expectancy?
  - Vascular abnormalities contribute to bronchial/ parenchymal disease progression?

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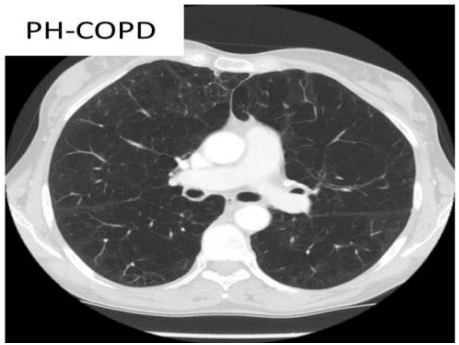
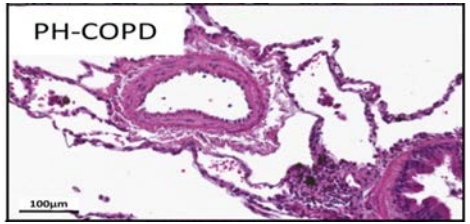
Therapeutic Trials focusing on PH in COPD

A



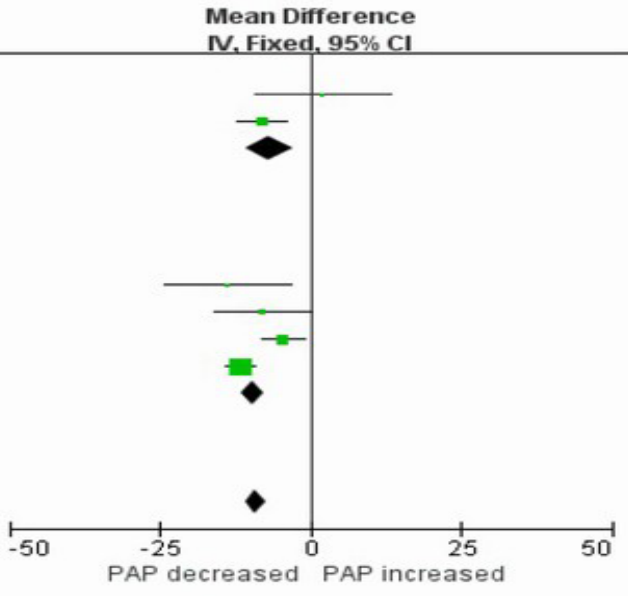


Meta-analyis: Chen et al, J Thorac Dis 2015

Meta-analyis: Prins et al. Pulm Circ 3/2017

Meta-Analysis: PH targeted therapy in COPD

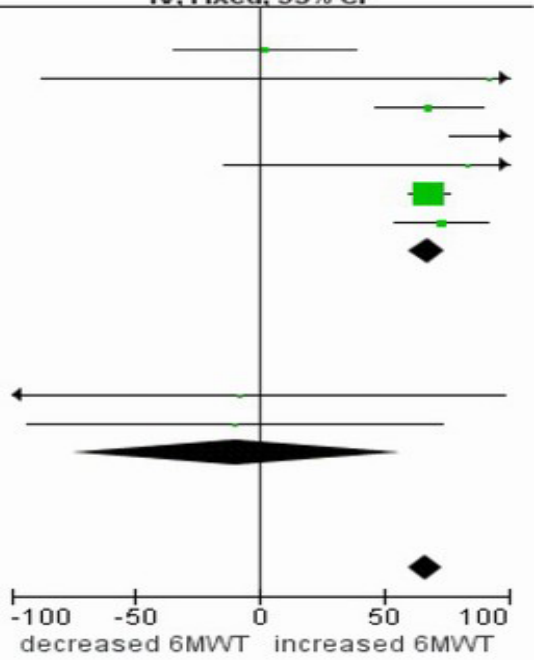
Study or Subgroup	PH specific drug Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.1.1 Bosentan								
Stolz 2008	-2	9.3	14	-4	15.4	9	2.3%	2.00 [-9.18, 13.18]
Valerio 2009	-6	5.6	16	2	6.2	16	16.9%	-8.00 [-12.09, -3.91]
Subtotal (95% CI)			**30**			**25**	**19.1%**	**-6.82 [-10.66, -2.97]**
Heterogeneity: Chi² = 2.71, df = 1 (P = 0.10); I² = 63%								
Test for overall effect: Z = 3.48 (P = 0.0005)								
3.1.2 Sildenafil								
Huangpu 2011	-21.69	21.1	30	-7.94	20.85	30	2.5%	-13.75 [-24.36, -3.14]
Rao 2010	-11.7	10.5	15	-3.8	12.8	18	4.5%	-7.90 [-15.85, 0.05]
Zhang 2012	-9.3	7.2	36	-4.7	7.9	35	22.8%	-4.60 [-8.12, -1.08]
Zhen 2011	-18	5.3	30	-6.3	3.9	30	51.0%	-11.70 [-14.05, -9.35]
Subtotal (95% CI)			**111**			**113**	**80.9%**	**-9.55 [-11.42, -7.68]**
Heterogeneity: Chi² = 11.57, df = 3 (P = 0.009); I² = 74%								
Test for overall effect: Z = 10.00 (P < 0.00001)								
Total (95% CI)			**141**			**138**	**100.0%**	**-9.02 [-10.71, -7.34]**
Heterogeneity: Chi² = 15.85, df = 5 (P = 0.007); I² = 68%								
Test for overall effect: Z = 10.52 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.57, df = 1 (P = 0.21), I² = 36.1%								



Chen et al, J Thorac Dis 2015

Meta-Analysis: PH targeted therapy in COPD

Study or Subgroup	PH specific drug Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 confirmed PH								
Blanco 2013	23	71	29	21	74	31	3.6%	2.00 [-34.69, 38.69]
Harris 2010	90.53	163.06	5	-1.83	126.1	5	0.1%	92.36 [-88.32, 273.04]
Huangpu 2011	129	49	30	61	37	30	10.0%	68.00 [46.03, 89.97]
Rao 2010	191	127	15	39	87	18	0.8%	152.00 [76.20, 227.80]
Valerio 2009	64	120	16	-20	161	16	0.5%	84.00 [-14.39, 182.39]
Zhang 2012	108.5	15.9	36	40.3	19.4	35	70.7%	68.20 [59.94, 76.46]
Zhen 2011	113	42.1	30	40	33.2	30	13.1%	73.00 [53.81, 92.19]
Subtotal (95% CI)			**161**			**165**	**98.9%**	**67.24 [60.26, 74.23]**
Heterogeneity: Chi² = 17.54, df = 6 (P = 0.008); I² = 66%								
Test for overall effect: Z = 18.86 (P < 0.00001)								
1.1.2 unconfirmed PH at rest								
Lederer 2012	0	81	5	8	81	4	0.4%	-8.00 [-114.50, 98.50]
Stolz 2008	-10	88	20	0	120	10	0.7%	-10.00 [-93.78, 73.78]
Subtotal (95% CI)			**25**			**14**	**1.1%**	**-9.24 [-75.08, 56.61]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 0.27 (P = 0.78)								
Total (95% CI)			**186**			**179**	**100.0%**	**66.39 [59.44, 73.34]**
Heterogeneity: Chi² = 22.66, df = 8 (P = 0.004); I² = 65%								
Test for overall effect: Z = 18.73 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.12, df = 1 (P = 0.02), I² = 80.5%								



Chen et al, J Thorac Dis 2015

Chen et al: COPD with mPAP > 35 mmHg: 6MWD + 67.2 m (p < 0.001)

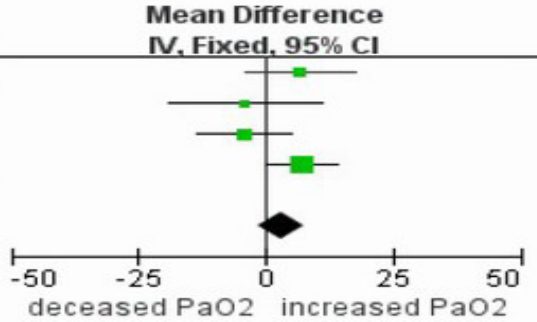
Prins et al: overall PH-COPD: 6MWD + 42.7 m (ns)

Meta-Analysis: PH targeted therapy in COPD

Study or Subgroup	PH specific drug Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Blanco 2013	-1.5	17	24	-8.3	21.1	25	19.2%	6.80 [-3.91, 17.51]
Lederer 2012	1	11.3	5	5	11.3	4	10.0%	-4.00 [-18.86, 10.86]
Stolz 2008	-4.5	9.4	20	-0.4	13.5	10	25.3%	-4.10 [-13.43, 5.23]
Valerio 2009	4	9.2	16	-3	10.8	16	45.5%	7.00 [0.05, 13.95]
Total (95% CI)			**65**			**55**	**100.0%**	**3.06 [-1.63, 7.75]**

Heterogeneity: $Chi^2 = 4.83$, $df = 3$ ($P = 0.18$); $I^2 = 38\%$

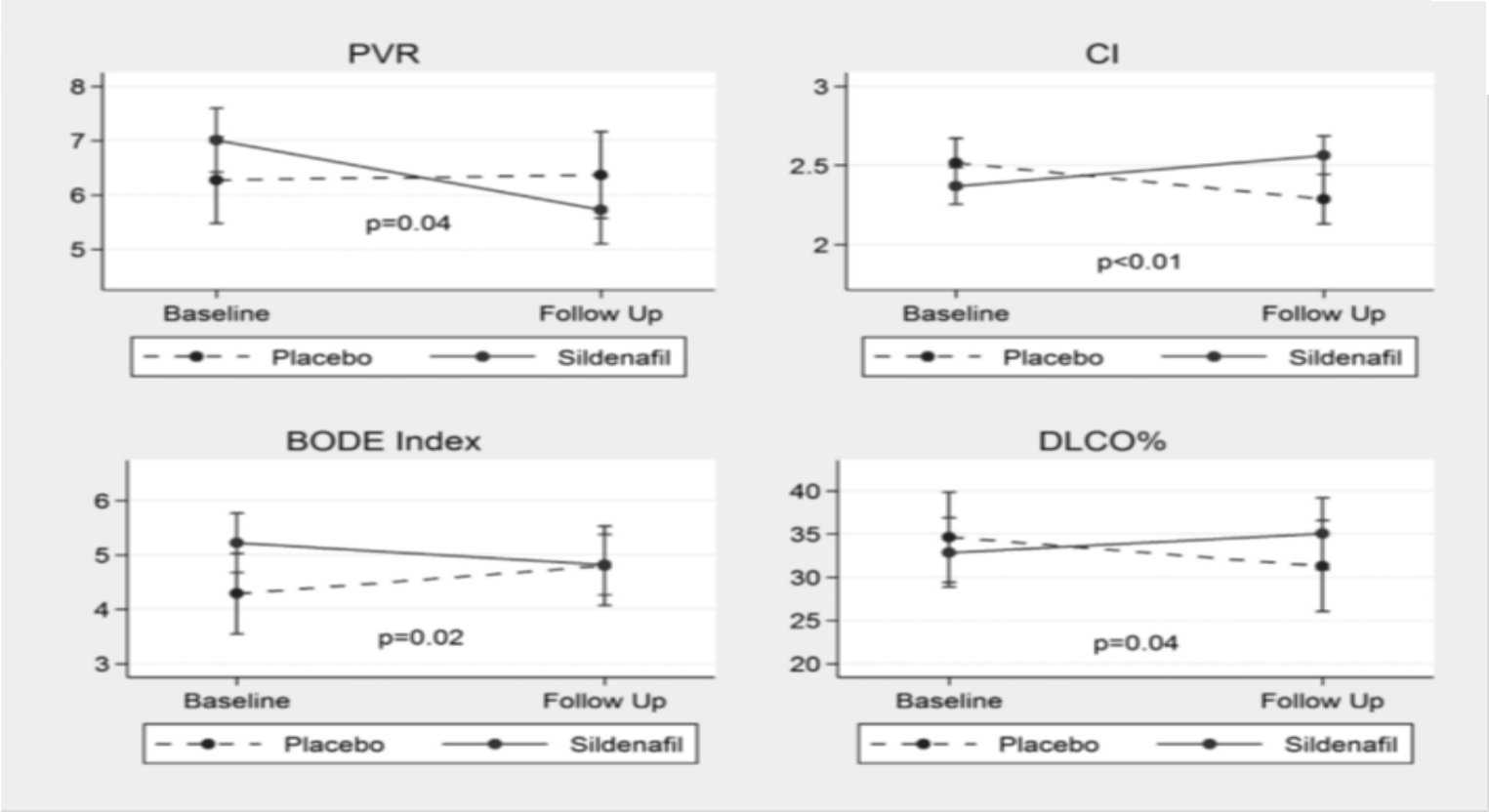
Test for overall effect: $Z = 1.28$ ($P = 0.20$)



Chen et al, J Thorac Dis 2015

Sildenafil in severe PH-COPD (mPAP > 35 mmHg):

A randomized controlled multicenter clinical trial



18 sildenafil,10 controls; 16 week randomized controlled trial

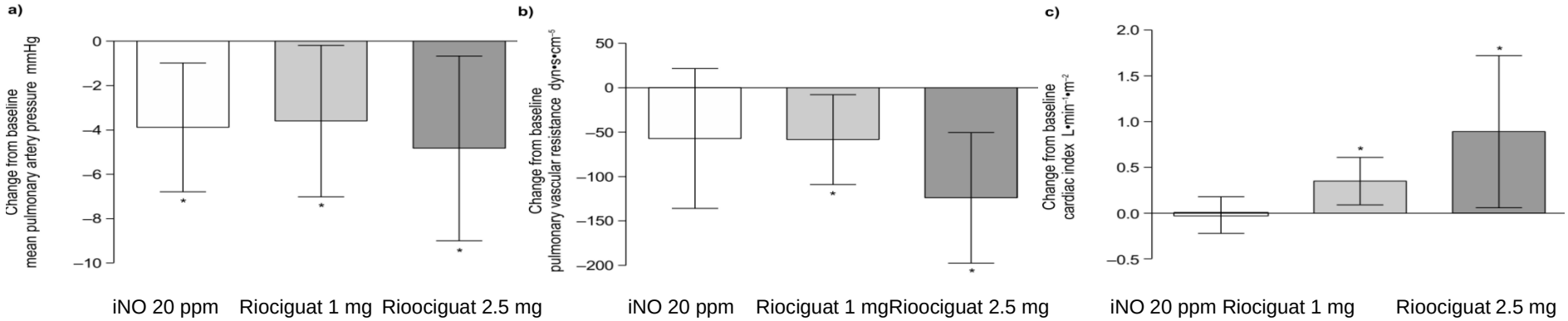
Vitulo et al, J Heart Lung Transplant 2017

Riociguat in PH-COPD (acute testing)

Short-term riociguat administration in PH-COPD patients

(mean mPAP = 28 / 32 mmHg)

- Hemodynamic improvement
- Very moderate decrease in paO2, estimated as clinically not relevant
- No change in lung function testing
- well tolerated



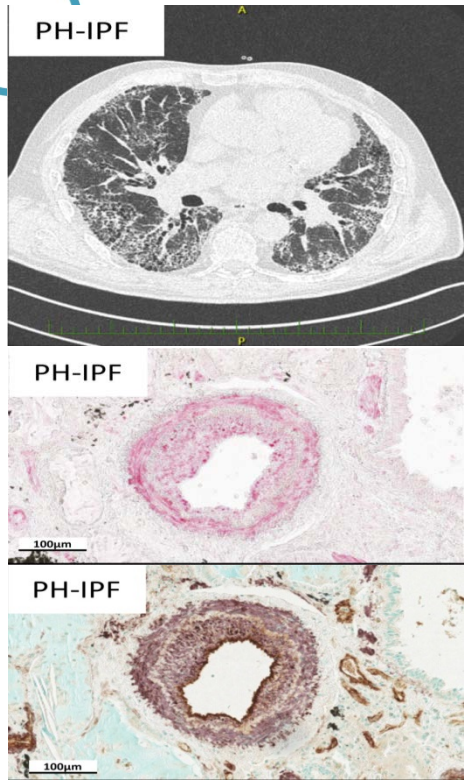
Ghofrani et al, Pulmonary Circulation 5:296-304, 2015

PAH targeted therapy in COPD

Conclusion from 2 meta-analyses and recent small trials

- Improved **hemodynamics** noted in the majority of studies, in particular in **severe PH-COPD** (mPAP > 35 mmHg)
- Preliminary evidence that this may translates into improvement of **exercise tolerance and quality of life,** in particular in severe PH-COPD
- **Gas exchange** may initially deteriorate (differences between inhalative and systemic route of application), with minor relevance upon long-term use
- **Large RCTs are missing** – should focus be on the "**vascular phenotype COPD**" (mPAP > 35 mmHg, circulatory exercise limitation)
- This does not preclude to focus on COPD patients with lower mPAP being enrolled in future studies

Therapeutic Trials focusing on PH in ILD



NO / Prostanoids

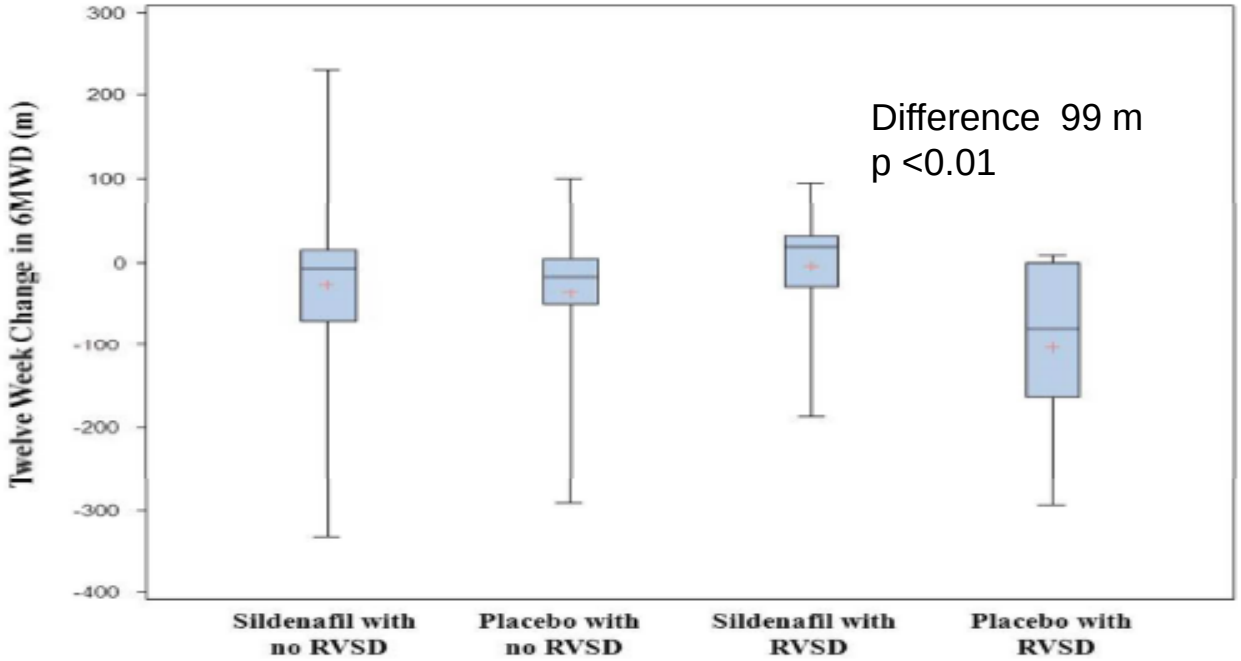
ERA

PDE 5 inhibitors

Riociguat

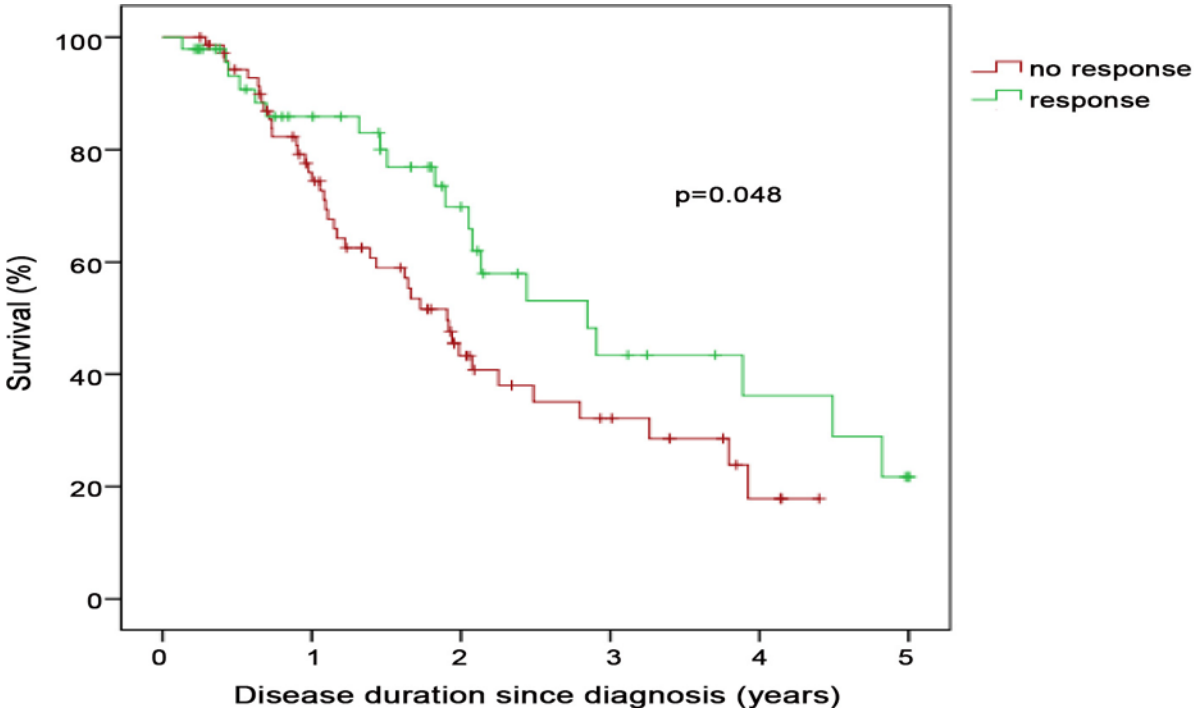
Sildenafil in IPF – STEP-IPF Trial

Change in 6MWD at 12 weeks by treatment and presence of right ventricular systolic dysfunction (RVSD)



Han et al, Chest 2013

COMPERA Registry: response to sildenafil in PH-IIP



Hoeper et al, PLOS1, 2015

Stratification by clinical response at first follow-up defined of onset of sildenafil treatment:

6 MWD + >/= 20 m

or

NYHA class+ 1

Total number: 121

“Response”: 48

“No response”: 73

Pirfenidone and sildenafil

- A phase IIb multicenter, randomized, double-blind placebo controlled study to evaluate the **efficacy**, **safety and tolerability** of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and intermediate or high probability of group 3 pulmonary hypertension
- Clinical phase: II b

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Clinical Trial Paper

Sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: A Phase IIb, randomised, double-blind, placebo-controlled study – Rationale and study design

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ABSTRACT

Background: Pulmonary hypertension (PH) is commonly observed in patients with advanced idiopathic pulmonary fibrosis (IPF). Despite the availability of therapies for both IPF and PH, none are approved for PH treatment in the context of significant pulmonary disease. This study will investigate the use of sildenafil added to pirfenidone in patients with advanced IPF and risk of PH, who represent a group with a high unmet medical need.

Methods: This Phase IIb, randomised, double-blind, placebo-controlled trial is actively enrolling patients and will study the efficacy, safety and tolerability of sildenafil or placebo in patients with advanced IPF and intermediate or high probability of Group 3 PH who are receiving a stable dose of pirfenidone. Patients with advanced IPF (diffusing capacity for carbon monoxide ≤40% predicted) and risk of Group 3 PH (defined as mean pulmonary arterial pressure ≥20 mm Hg with pulmonary arterial wedge pressure ≤15 mm Hg on a previous right-heart catheterisation [RHC], or intermediate/high probability of Group 3 PH as defined by the 2015 European Society of Cardiology/European Respiratory Society guidelines) are eligible. In the absence of a previous RHC, patients with an echocardiogram showing a peak tricuspid valve regurgitation velocity ≥2.9 m/s can enrol if all other criteria are met. The primary efficacy endpoint is the proportion of patients with disease progression over a 52-week treatment period. Safety will be evaluated descriptively.

Discussion: Combination treatment with sildenafil and pirfenidone may warrant investigation of the treatment of patients with advanced IPF and pulmonary vascular involvement leading to PH.

Primary endpoint

- The primary efficacy endpoint is will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:
  - Relevant decline in 6MWD of at least 15% from baseline (as defined per protocol), respiratory –related non-elective hospitalization, or all cause mortality

Key inclusion criteria

For the purpose of this study, patients have to present with:

Advanced IPF

(defined as a measurable %DLCO≤40% at screening)

AND

Intermediate or high probability of Group 3 PH

(defined as a mPAP≥ 20 mmHg with PAWP≤15 mmHg) on a previous RHC of acceptable quality

OR

In the absence of a previous RHC, patients with ECHO intermediate or high probability of PH, as defined by the 2015 ESC/ERS guidelines (peak TVR ≥ 2.9 m/s), will be considered eligible for the study

Efficacy and Safety of Nintedanib When Co-administered With Sildenafil in Idiopathic Pulmonary Fibrosis Patients With Advanced Lung Function Impairment

Nintedanib and sildenafil

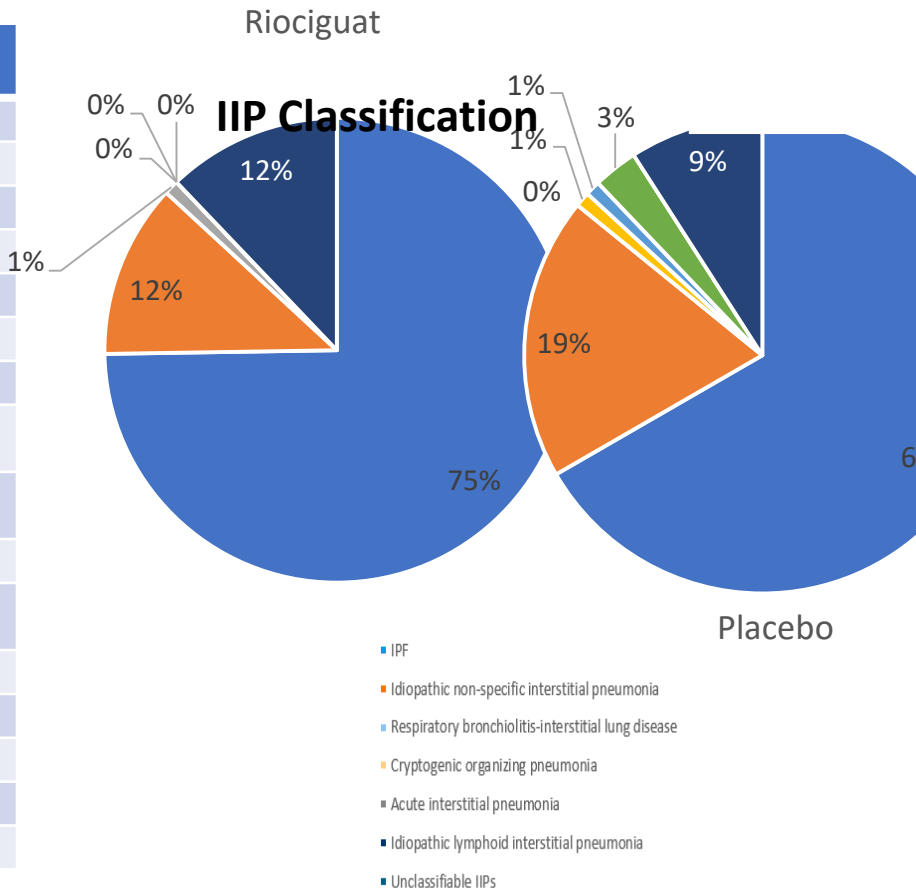
- A 24-week, double-blind randomized parallel group study evaluating the **efficacy and safety** of oral nintedanib co-administered with oral sildenafil
- Clinical phase: III b
- **Objective:** To assess efficacy and safety of concomitant treatment with nintedanib and sildenafil in IPF patients with advanced lung **function impairment**

Nintedanib and sildenafil

- 300 patients to be included, ≥ 40 years and with DLCO ≤ 35%
- Randomization 1:1
- Nintedanib 150 mg bid with the possibility to reduce to 100 mg bid to manage adverse events or placebo and sildenafil 20 mg tid
- 24 weeks of randomized treatment
- **Primary Endpoint**: Change from baseline in SGRQ total score at week 12

Riociguat: the RISE-IIP: Patient characteristics

Parameter	Riociguat up to 2.5 mg tid (n=73)	Placebo (n=74)
Female, n (%)	23 (32)	29 (39)
White race, n (%)	63 (86)	63 (85)
Age, years	68 (8)	69 (8)
Body mass index, kg/m^2	30 (5)	28 (6)
WHO FC II/III/IV, %	22/68/10	30/61/9
6MWD, m	307 (80)	324 (66)
Right atrial pressure, mmHg	6.7 (4.0)	6.7 (4.5)
Mean pulmonary arterial pressure, mmHg	33.2 (8.2)	33.5 (9.4)
Pulmonary vascular resistance, dyn·s·cm^{-5}	390.7 (204.5)	417.9 (256.9)
Cardiac index, L/min/m^2	2.6 (0.7)	2.6 (0.7)
Pulmonary capillary wedge pressure, mmHg	10.6 (3.2)	10.6 (3.0)
FVC, % predicted	76.3 (19.1)	74.3 (15.7)
FEV_1, L/s	2.0 (0.6)	1.9 (0.6)
FEV_1/FVC	0.8 (0.1)	0.8 (0.1)
Total lung capacity, L	4.1 (1.2)	3.8 (1.1)
DLCO, %	32.0 (11.8)	30.5 (10.9)



Riociguat: the RISE-IIP: Safety

AE, n (%)	Main phase		LTE phase[a]		Safety follow-up phase[b]	
	Riociguat up to 2.5 mg tid (n=73)	Placebo (n=74)	Former riociguat (n=32)	Former placebo (n=38)	Former riociguat up to 2.5 mg tid (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)**

- **Most deaths during the main phase occurred in patients receiving riociguat**
- **Most deaths in the LTE phase occurred in former placebo patients who switched to riociguat**

Riociguat: the RISE-IIP: Safety

	Main phase		LTE phase[b]		Safety follow-up phase[c]	
SAE, n (%)[a]	Riociguat up to 2.5 mg tid (n=73)	Placebo (n=74)	Former riociguat (n=32)	Former placebo (n=38)	Former riociguat (n=73)	Former placebo (n=74)
Any SAE	**27 (37)**	**17 (23)**	**12 (38)**	**21 (55)**	**18 (25)**	**14 (19)**
IPF	4 (5)	3 (4)	3 (9)	1 (3)	1 (1)	2 (3)
Right ventricular failure	1 (1)	2 (3)	1 (3)	2 (5)	1 (1)	1 (1)
Pneumonia	4 (5)	1 (1)	0	4 (11)	0	0
Interstitial lung disease	1 (1)	1 (1)	0	2 (5)	3 (4)	1 (1)
Pulmonary fibrosis	1 (1)	1 (1)	0	2 (5)	1 (1)	1 (1)
Respiratory failure	0	1 (1)	0	4 (11)	0	0

- **SAEs were experienced by more patients receiving riociguat compared with placebo in the main phase**
- **Most SAEs in the LTE phase were experienced by former placebo patients who switched to riociguat**

Secondary efficacy endpoint: clinical worsening in main treatment phase

Clinical worsening events[a] in main treatment phase	Patients, n (%)[b]	
	Riociguat up to 2.5 mg tid (n=73)	Placebo (n=74)
>15% decrease in 6MWD due to worsening of cardiopulmonary status	9 (12)	17 (23)
All-cause mortality	1 (1)	0
Need for hospitalization due to worsening of cardiopulmonary status attributable to progression of disease (including but not limited to increased shortness of breath or increased leg swelling)	15 (21)	7 (9)
Worsening of WHO FC	9 (12)	12 (16)
No clinical worsening event	**39 (53)**	**38 (51)**

- No significant difference in overall clinical worsening with riociguat vs placebo

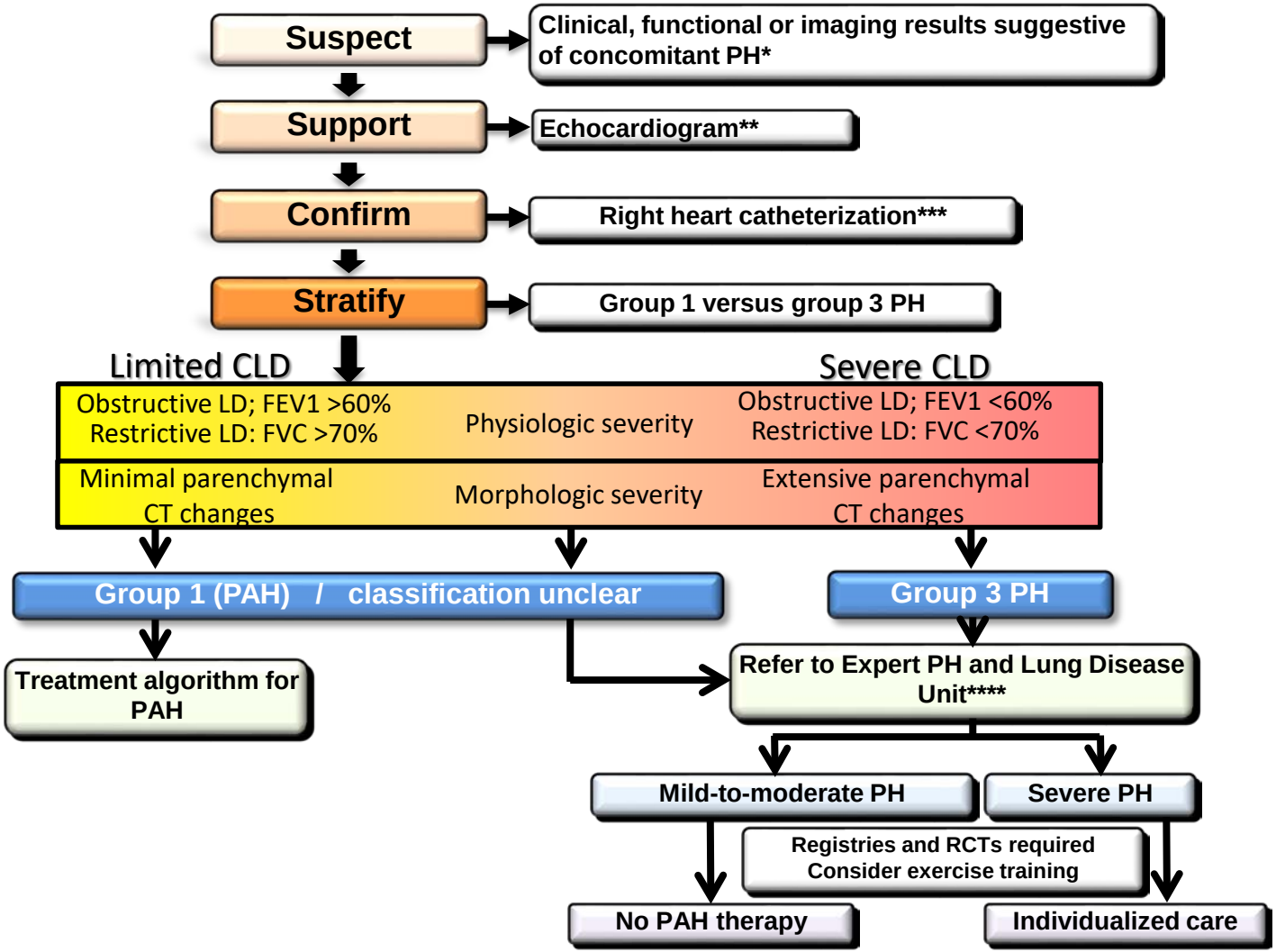
[a]First occurrence of all-cause mortality, worsening of WHO FC, >15% decrease in 6MWD, or hospitalization due to worsening cardiopulmonary status attributable to progression of disease
[b]Patients could experience more than one event

RISE-IIP: Conclusion

- RISE-IIP was terminated early at the request of the Data Monitoring Committee based on an unfavourable risk:benefit ratio due to:
  - The higher number of deaths and SAEs which occurred with riociguat treatment
  - Lack of efficacy demonstrated by riociguat in patients with PH-IIP
- The mechanism underlying this disadvantageous effect of ricioguat in IIP are still elusive (CPFE?)
- The use of riociguat in patients with **PH-IIP** is discouraged

Overall conclusion IIP-PH

- No evidence for the use of ERAs in IIP-PH with ambrisentan contraindicated in IPF.
- Riociguat is contraindicated in IIP-PH.
- The data on the use of sildenafil and prostanoid therapy in IIP-PH is too limited for any current recommendation, but further RCTs are encouraged


Suspect
Clinical, functional or imaging results suggestive of concomitant PH*
Support
Echocardiogram**
Confirm
Right heart catheterization***
Stratify
Group 1 versus group 3 PH
Limited CLD
Severe CLD
Obstructive LD; FEV1 >60%
Restrictive LD: FVC >70%
Physiologic severity
Obstructive LD; FEV1 <60%
Restrictive LD: FVC <70%
Minimal parenchymal CT changes
Morphologic severity
Extensive parenchymal CT changes
Group 1 (PAH) / classification unclear
Group 3 PH
Treatment algorithm for PAH
Refer to Expert PH and Lung Disease Unit****
Mild-to-moderate PH
Severe PH
Registries and RCTs required
Consider exercise training
No PAH therapy
Individualized care