Pulmonary hypertension due to lung diseases

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TORINO DHU Thorax Innovation

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Disclosures

–**Actelion:** consultancy (current), board or advisory committee (current), speaker (current)
–**Bayer:** consultancy (current), board or advisory committee (current), speaker (current)
–**GSK:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
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–**Pfizer:** consultancy (current), board or advisory committee (current), speaker (current), research support (past)

Definition/ Hemodynamic classification

- Pre-capillary PH: mPAP ≥ 25 mm Hg and PAWP ≤ 15 mm Hg

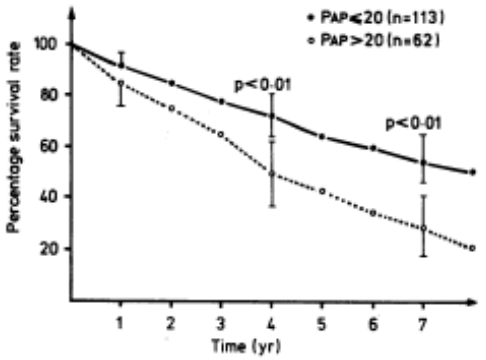
3. Pulmonary hypertension due to lung diseases and/or hypoxia	Terminology	Haemodynamics (right heart catheterization)
3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung diseases (Web Table III)	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/m^2, not explained by other causes)

Simonneau *et al. JACC* 2013

Galié *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH

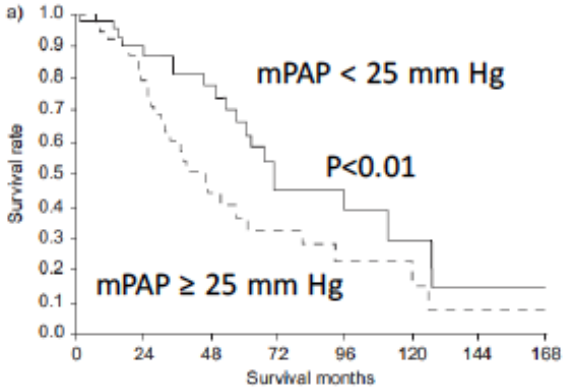
Prognostic factor of PH in chronic lung diseases

COPD



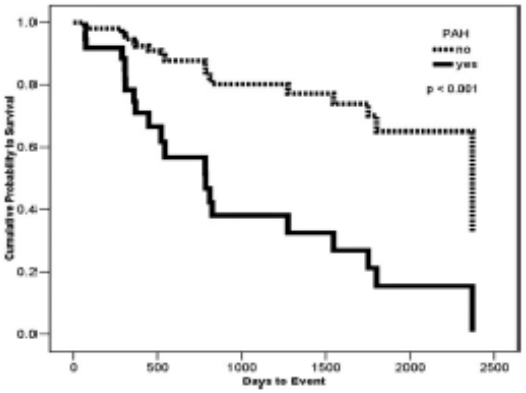
Weitzenblum *et al.*
Thorax 1981

COPD under LTOT



Oswald-Mammosser *et al.*
Chest 1995

IPF



Lettieri *et al.*
Chest 2006

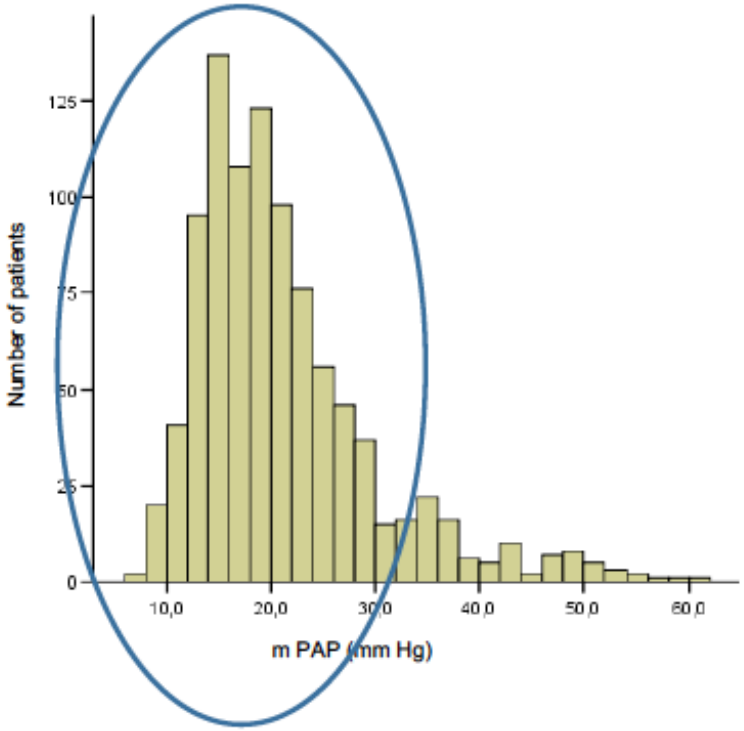
To characterize patients with lung disease and suspicion of severe PH

- Complete Lung Function Tests: spirometry, plethysmography and DLCO
- Chest CT
- Sleep study
- Echocardiography may not be enough to exclude HFpEF

Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease	I	C

Chronic Obstructive Pulmonary Disease

PH due to COPD: the usual case

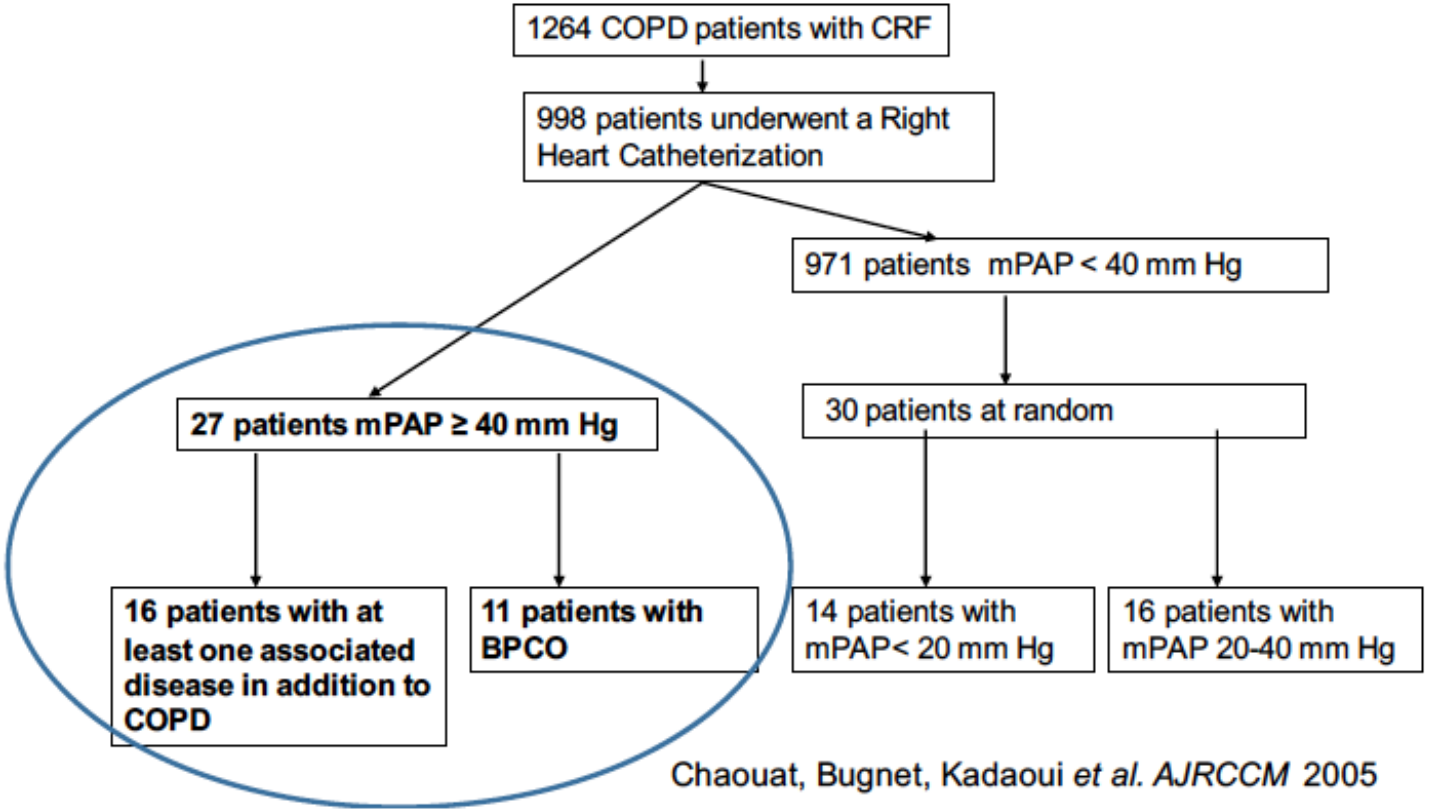


Chaouat, Bugnet, Kadaoui *et al. AJRCCM* 2005

- mPAP=(mean)20.3 ±(SD) 8.1mmHg
- ≈30% with a mPAP ≥ 25 mmHg
- 1,1%(CI 95% 0.55-1.96) with mPAP ≥ 40mmHg

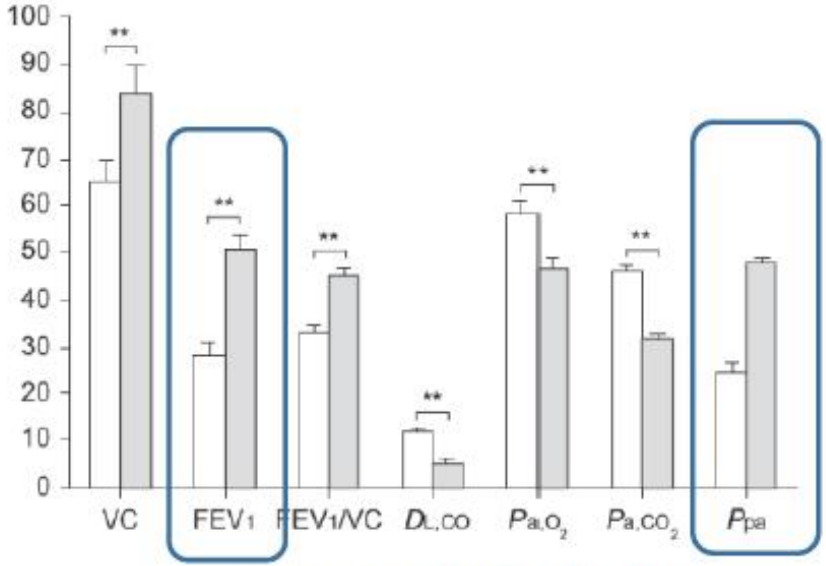
- 30 % of COPD patients with a PaO_2<70mmHg develop PH
- When PH is present PAP is mildly or moderately increased
- Progression is usually slow: 0.5 to 1.5 mmHg/y

Severe PH in COPD

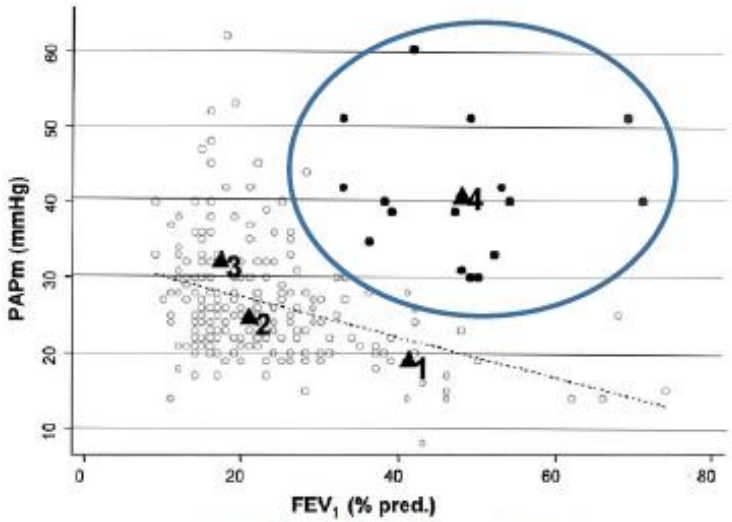


Chaouat, Bugnet, Kadaoui *et al. AJRCCM* 2005

Characteristics of severe PH in COPD without comorbidity



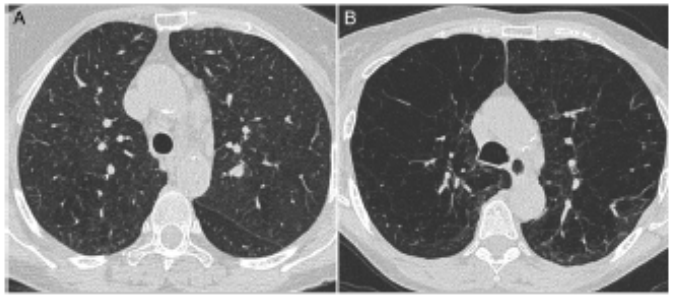
Chaouat *et al. AJRCCM* 2005



Thabut *et al. Chest* 2005

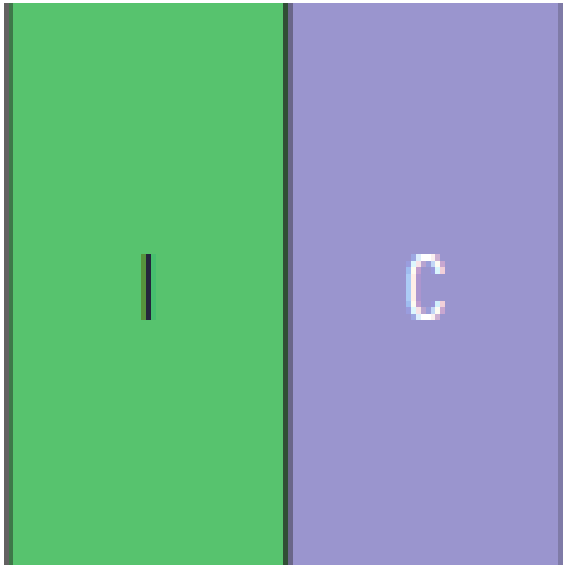
Hurdman *et al. Eur Respir J* 2013

Characteristics of severe PH in COPD without comorbidity



	No PH	Mod. PH	Sev. PH	
Aa PO_2 (mmHg)	32 ± 9	30 ± 9	57 ± 15*#	
PvO_2 (mmHg)	36 ± 2	36 ± 2	33 ± 3#	
LogSD Q	0.93 ± 0.22	0.88 ± 0.15	1.34 $	1.24 $

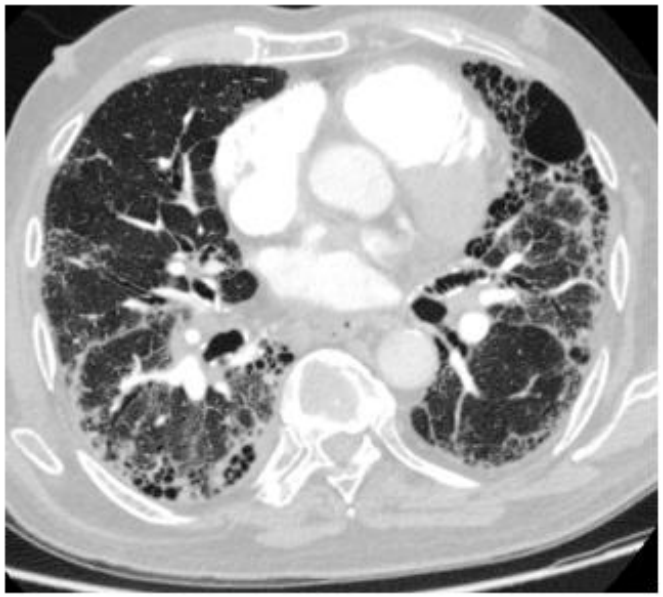
Referral to an expert centre is recommended[d] in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction

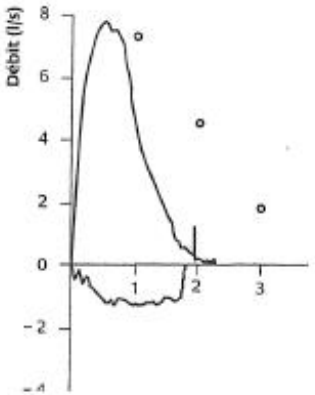


Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis

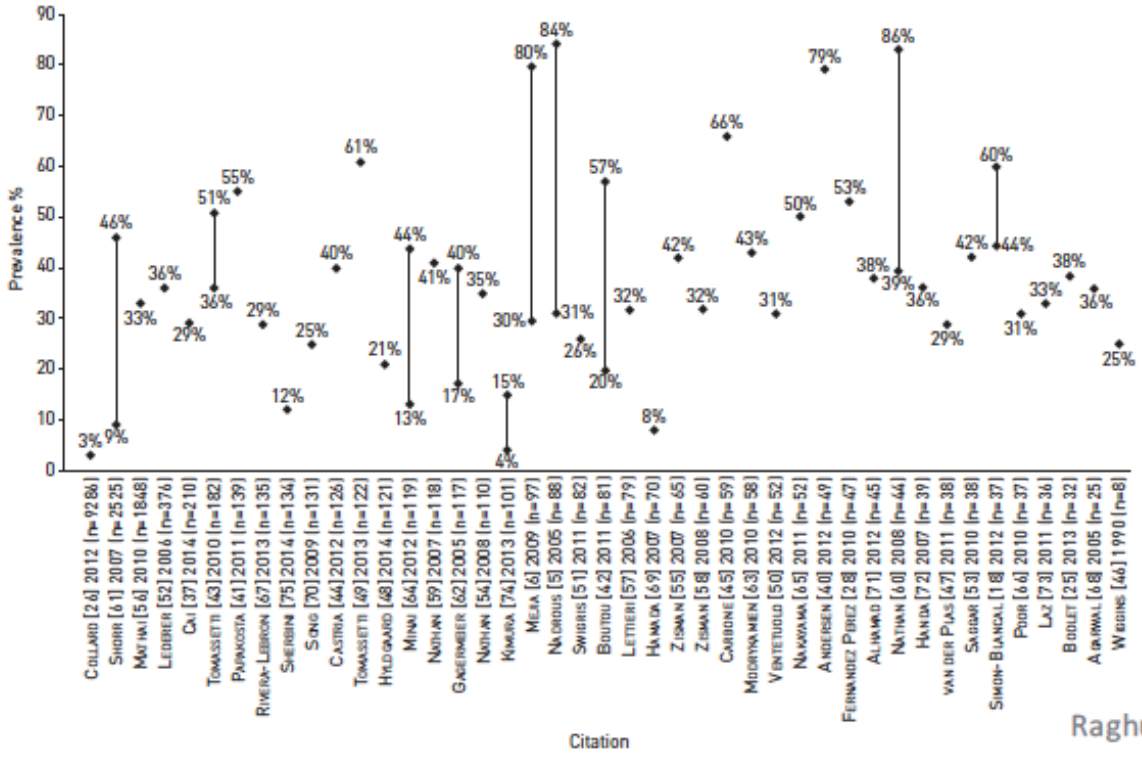
- « Among the most urgent questions are whether anti-pulmonary hypertension therapy is indicated for IPF-associated PH,… »





Wison and Raghu Editorial ERJ 2015 IPF guidelines

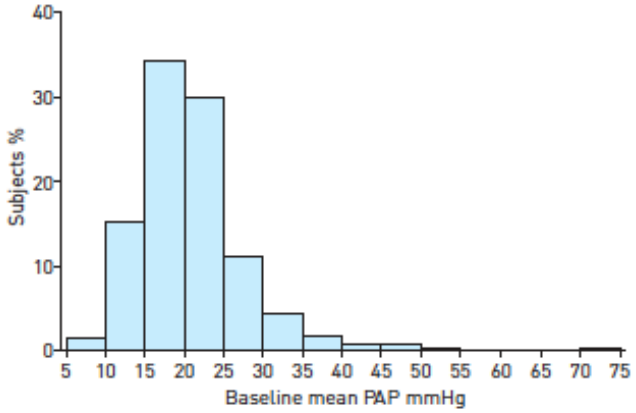
Prevalence of PH in IPF



Raghu *et al. Eur Respir J* 2015; 46: 1113–1130

IPF- associated PH

- 488 subjects
  - Group 3 PH, 14 %
  - Group 2 PH, 5 %
  - No PH, PAWP > 15 mmHg, 4 %
  - No PH, PAWP ≤ 15, 77 %



	FVC % predicted	D_{LCO}# % predicted	6MWD
Mean PAP			
Pearson coefficient	0.047	−0.16	−0.20
p-value	0.30	0.001	<0.001
Paired observations n	87	487	483

Raghu *et al. Eur Respir J* 2015; 46: 1370

Hemodynamic changes

	All subjects			Group 3# PH subjects		
	Ambrisentan	Placebo		Ambrisentan	Placebo	
		Mean±SD	n		Mean±SD	n
Change in mean PAP mmHg		0.4±5.85	44		−1.1±9.39	7
Change in cardiac output L·min^{-1}		−0.38±1.30	43		0.44±0.9	7
Change in PVR mmHg·L^{-1}·min		0.14±0.79	43		−0.51±1.56	7

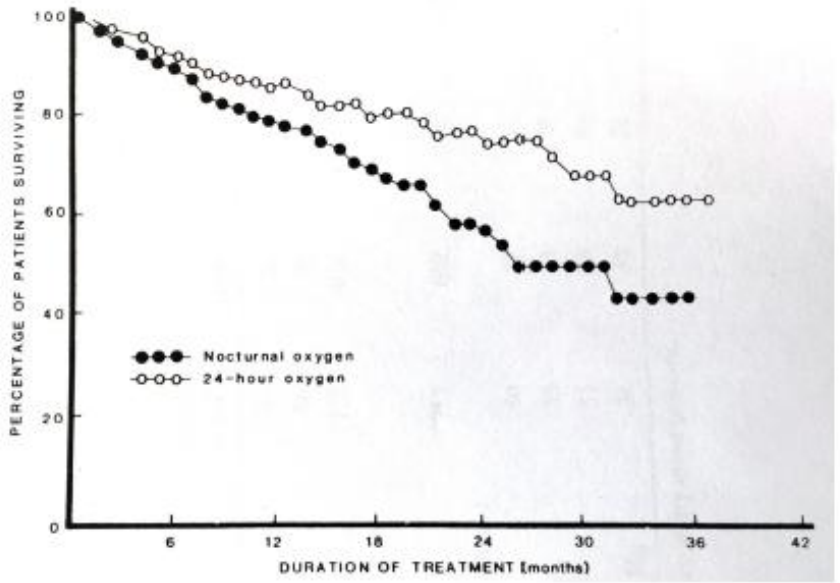
Raghu *et al. Eur Respir J* 2015; 46: 1370

Treatment of hypoxaemia/hypoventilation

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

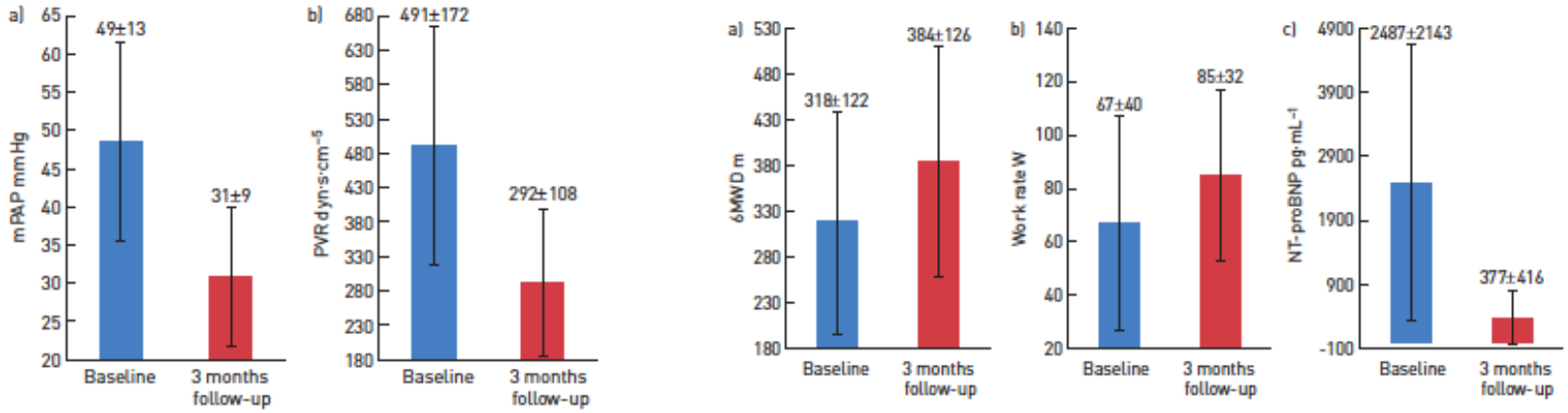
Long-Term Oxygen Therapy in patients with COPD

- Baseline mPAP 29 ± 10 mm Hg
- Delta mPAP
  - NOT: 0 ± 7 mm Hg, NS
  - COT: - 3 ± 11 mm Hg, p<0.001



Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980
Medical Research Council Working Party. Lancet 1981

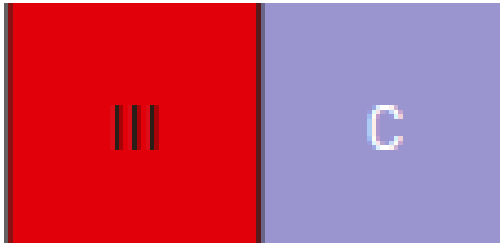
Correcting hypoxemia in alveolar hypoventilation syndrome: non invasive ventilation



Held *et al. Eur Respir J* 2014

Treatment with PAH-approved therapies

The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases

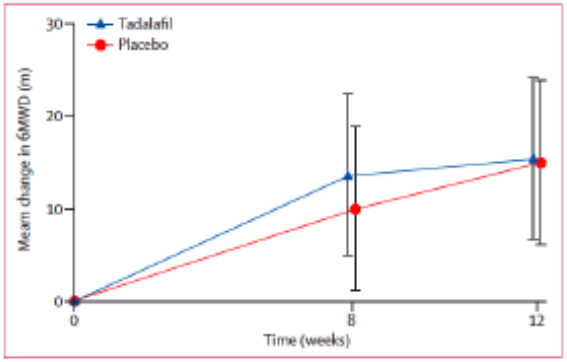


Tadalafil in patients with COPD: RCT

- mean placebo-corrected difference between the baseline and final 6MWD after 12 weeks

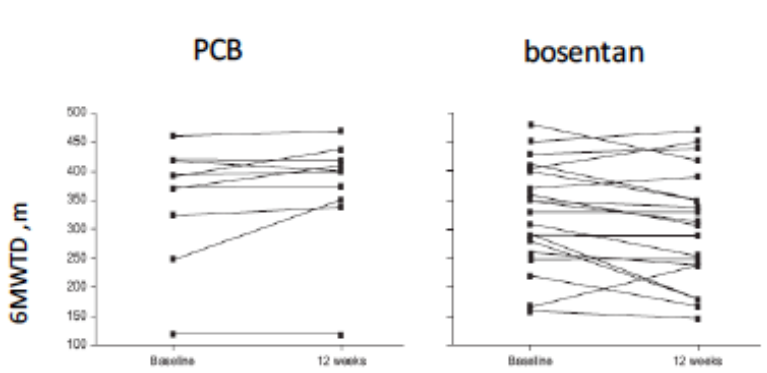
Median (IQR)	Tadalafil n=60	PCB n=60
Age (years)	68 (9)	70 (7)
Men	42 (70%)	40 (67%)
MRC dyspnea scale	3.4 (0.9)	3.4 (1.0)
FEV_1 (%)	41 (14)	40 (17)
RVSP (mmHg)	42 (9)	42 (10)
6-MWD (m)	354 (105)	341 (104)

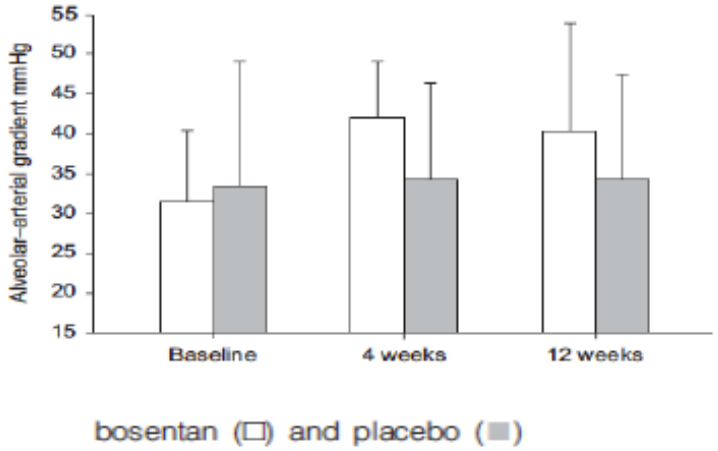
Goudie *et al. Lancet Respir Med* 2014



	Mean difference between groups (95% CI)	p value*
PAT (ms)	7·3 (0·9 to 13·6)	0·001
mPAP (mm Hg)†	−3·5 (−6·6 to −0·4)	0·025
PAT/RVET	0·02 (0·01 to 0·04)	0·008
RVSP (mm Hg)	−12·3 (−20·9 to −3·6)	0·007
TAPSE (mm)	1·1 (−1·1 to 3·3)	0·319

A randomized, controlled trial of bosentan in severe COPD (FEV_1 < 50 %): 12 weeks





Stolz D *et al. Eur Respir J* 2008; 32: 619

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

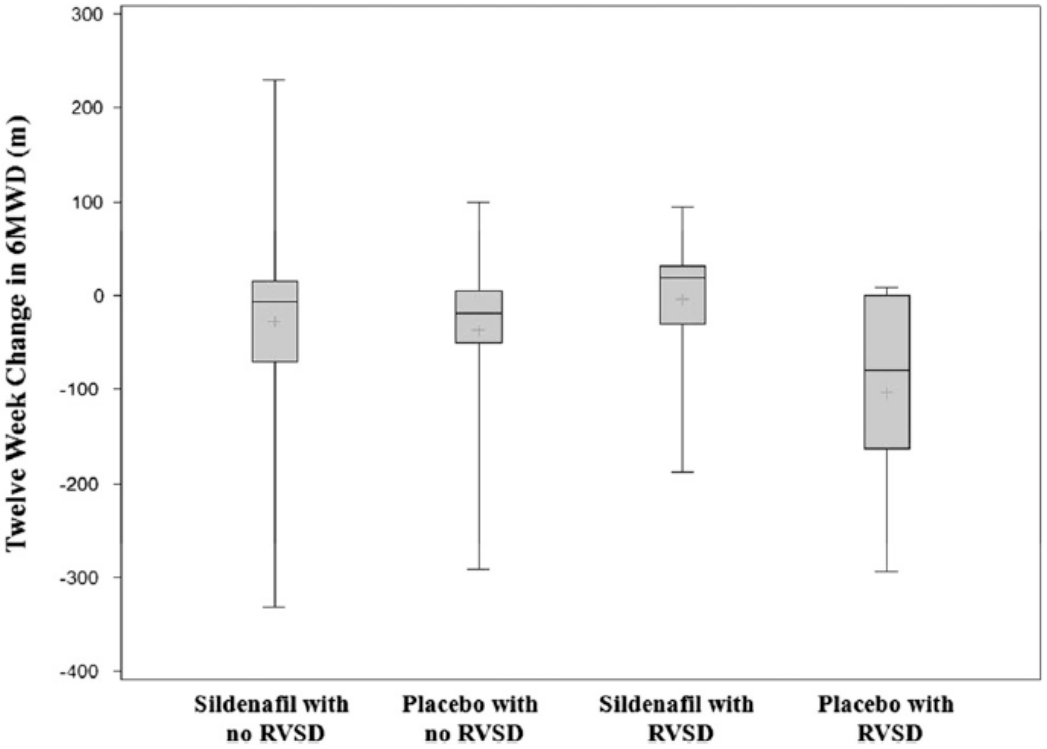
RESULTS

A total of 180 patients were enrolled in the study. The difference in the primary outcome was not significant, with 9 of 89 patients (10%) in the sildenafil group and 6 of 91 (7%) in the placebo group having an improvement of 20% or more in the 6-minute walk distance (P=0.39). There were small but significant differences in arterial oxygenation, carbon monoxide diffusion capacity, degree of dyspnea, and quality of life favoring the sildenafil group. Serious adverse events were similar in the two study groups.

N Engl J Med 2010;363:620-8.

Sildenafil Preserves Exercise Capacity in Patients With Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction

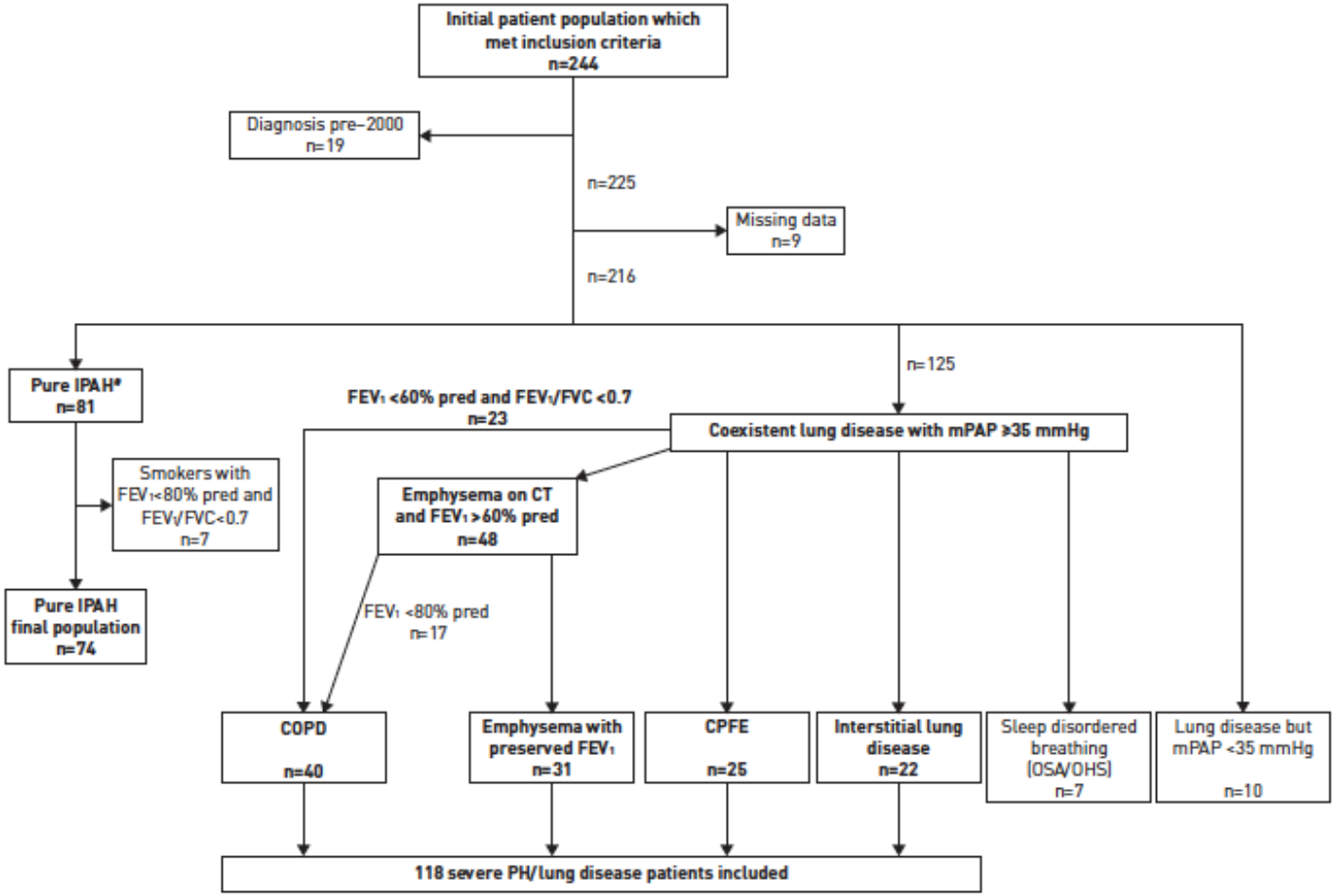
*MeiLan K. Han, MD; David S. Bach, MD; Peter G. Hagan, MD; Eric Yow, MS; Kevin R. Flaherty, MD, FCCP; Galen B. Toews, MD; Kevin J. Anstrom, PhD; and Fernando J. Martinez, MD, FCCP; for the IPFnet Investigators**



Han et al. Chest 2013

Severe pulmonary hypertension in lung disease: phenotypes and response to treatment

Melanie J. Brewis[1], Alistair C. Church[1], Martin K. Johnson[1,2] and Andrew J. Peacock[1,2]



Brewis et al. Eur Respir J 2015

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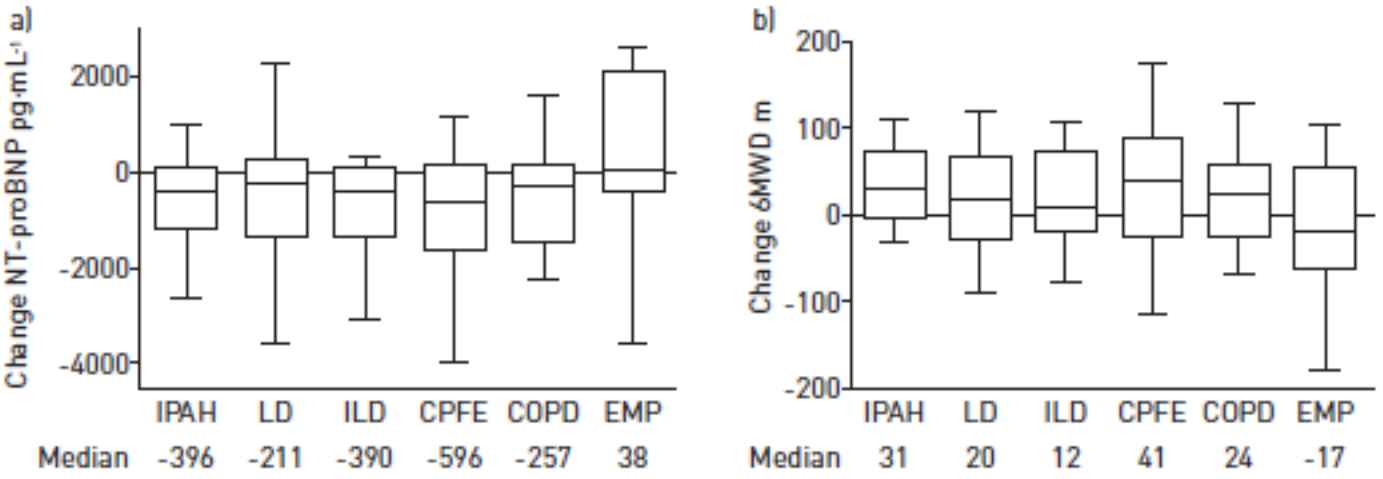


Conclusion

In comparison to IPAH patients, patients with severe PH associated with lung disease had poorer survival, which was driven by the ILD cohort and not abolished by adjusting for age. PH therapy did not lead to improvements in NYHA functional class or 6MWD; however, a reduction in NT-proBNP was seen. Survival and response to therapy may vary according to lung phenotype. Further studies with an untreated control group may establish if PH therapy has a role in delaying the progression of the pulmonary hypertension and improving survival.

Brewis et al. Eur Respir J 2015

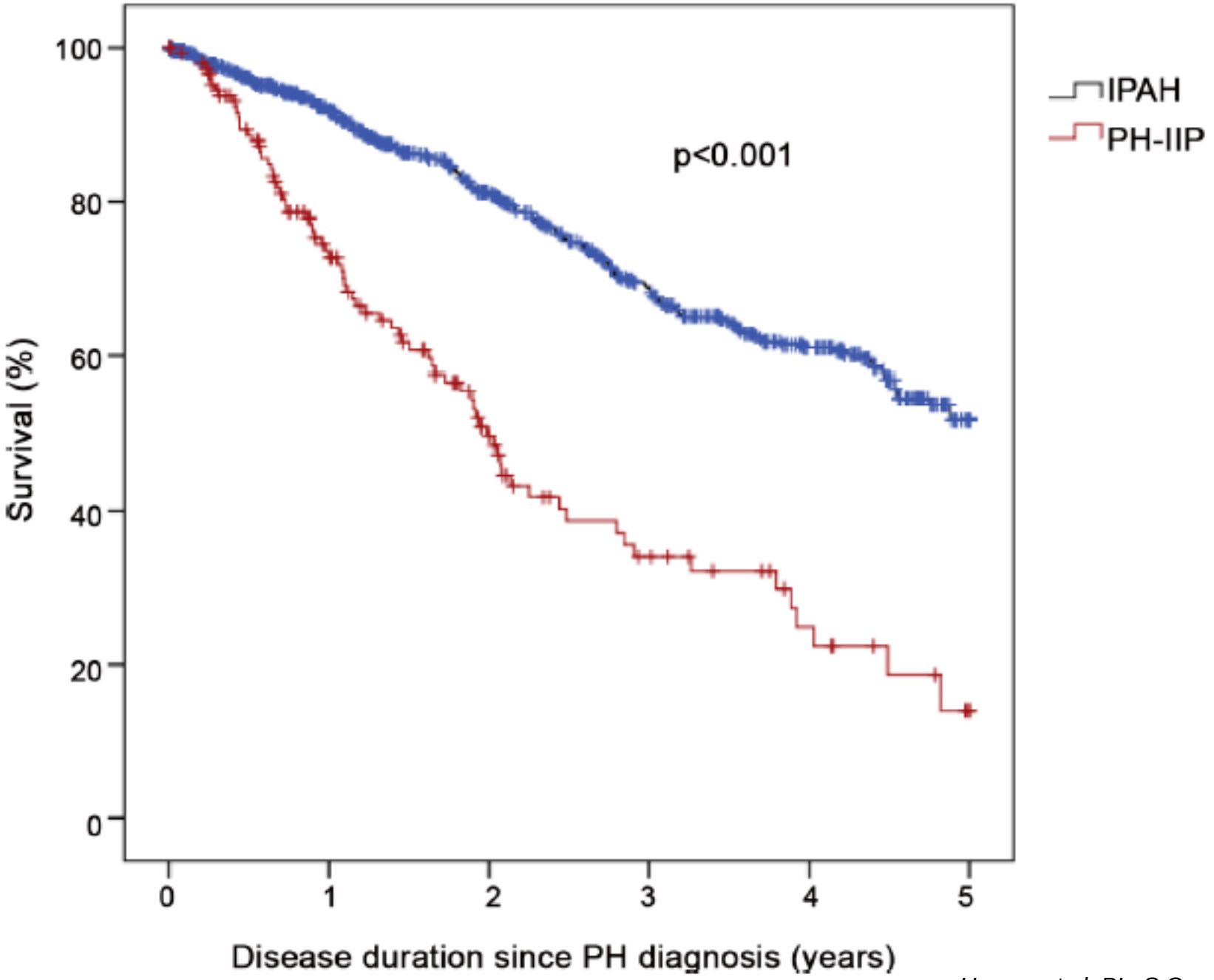
Pulmonary Hypertension in Patients with Chronic Fibrosing Idiopathic Interstitial Pneumonias

Marius M. Hoeper[1]*, Juergen Behr[2], Matthias Held[3], Ekkehard Grunig[4], C. Dario Vizza[5], Anton Vonk-Noordegraaf[6], Tobias J. Lange[7], Martin Claussen[8], Christian Grohé[9], Hans Klose[10], Karen M. Olsson[1], Thomas Zelniker[11], Claus Neurohr[2], Oliver Distler[12], Hubert Wirtz[13], Christian Opitz[14], Doerte Huscher[15], David Pittrow[16], J. Simon R. Gibbs[17]

Conclusions

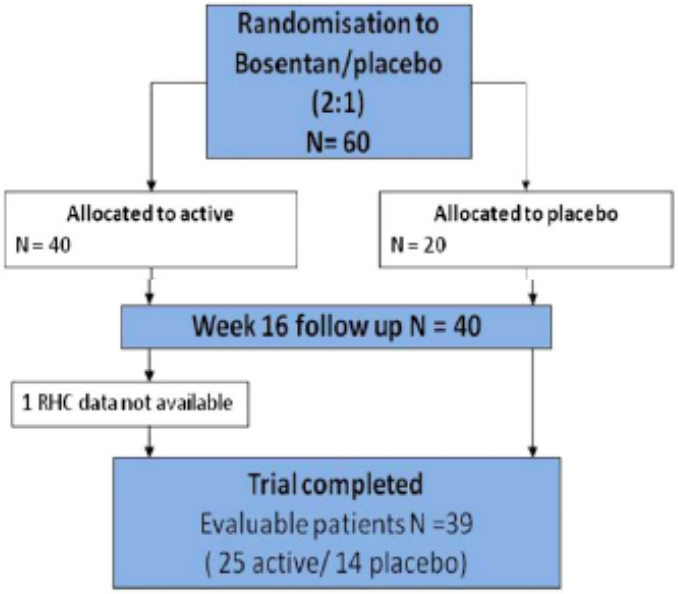
Patients with PH-IIP have a dismal prognosis. Our results suggest that pulmonary vasodilator therapy may be associated with short-term functional improvement in some of these patients but it is unclear whether this treatment affects survival.

Hoeper et al. PLoS One 2016



Hoeper et al. PLoS One 2016

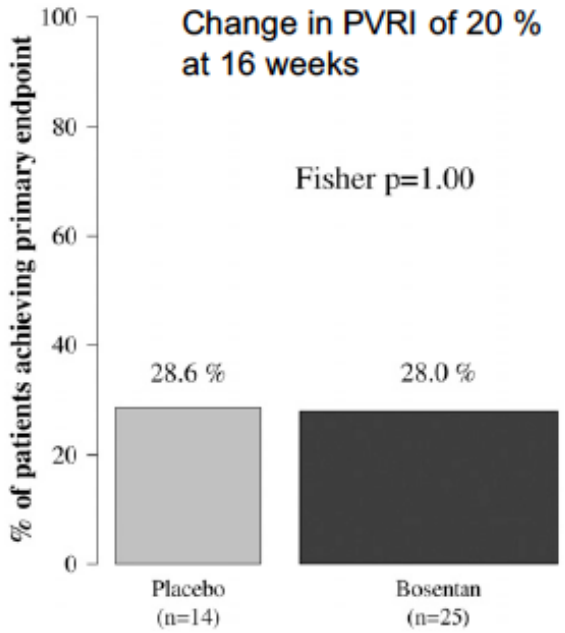
Bosentan in Pulmonary Hypertension Associated with Fibrotic Idiopathic Interstitial Pneumonia



	Bosentan (*n* = *40*)	Placebo (*n* = *20*)
Age	66.4 (9.2)	66.9 (9.3)
Male	27 (67.5%)	15 (75%)
WHO FC II/III/IV	2/17/21	2/9/9
6MWD, m	149.3 (99.6)	170.7 (97.0)
mPAP, mm Hg	37.2 (9.9)	33.5 (6.1)
mRAP, mm Hg	7.4 (5.4)	6.1 (5.4)
PVR, Wood units	7.4 (4.0)	6.0 (2.4)
PVR index, Wood Units/m^2	13.9 (7.5)	11.4 (4.5)
Cardiac index, L/min/m^2	2.2 (0.5)	2.2 (0.5)
D_{LCO}, % predicted	21.3 (9.6)	21.2 (7.5)
Kco, % predicted	45.1 (21.8)	48.8 (20.5)
FEV_1, % predicted	58.8 (20.8)	49.8 (19.8)
FVC%, % predicted	55.7 (19.8)	51.1 (24.0)
CPI	67.5 (8.6)	68.2 (7.9)

Corte T. *et al. AJRCCM* 2014

Bosentan in Pulmonary Hypertension Associated with Fibrotic Idiopathic Interstitial Pneumonia



Corte T. *et al. AJRCCM* 2014

	P Value
Δ PVR index	0.19
Δ mPAP, mm Hg	0.43
Δ mRAP, mm Hg	0.74
Δ Cardiac index, L/min/m^2	0.31
Δ SpO_2, %	0.74
Δ 6MWD, m	0.42
Δ 6MWT, dyspnea pre	0.98
Δ 6MWT, dyspnea post	0.51
Δ 6MWT, fatigue pre	0.71
Δ 6MWT, fatigue post	0.12
Δ CAMPHOR, symptom score	0.92
Δ CAMPHOR, activities score	0.94
Δ CAMPHOR, QOL score	0.96
Δ D_{LCO}, % predicted	0.96
Δ Kco, % predicted	0.54
Δ FVC, % predicted	0.96
Δ CPI	0.95
Δ BNP, pg/ml	0.32
Δ TAPSE, mm	0.56
Δ RV inlet size, mm	0.12

ARTEMIS-IPF

	All subjects				Group 3# PH subjects			
	Ambrisentan		Placebo		Ambrisentan		Placebo	
	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n
Change in mean PAP mmHg	−1.1±5.99	73	0.4±5.85	44	−5.3±4.27	12	−1.1±9.39	7
Change in cardiac output L·min^{-1}	0.56±1.45	72	−0.38±1.30	43	0.03±1.38	12	0.44±0.9	7
Change in PVR mmHg·L^{-1}·min	−0.41±1.19	72	0.14±0.79	43	−0.70±1.31	12	−0.51±1.56	7

Raghu *et al. Eur Respir J* 2015; 46: 1370

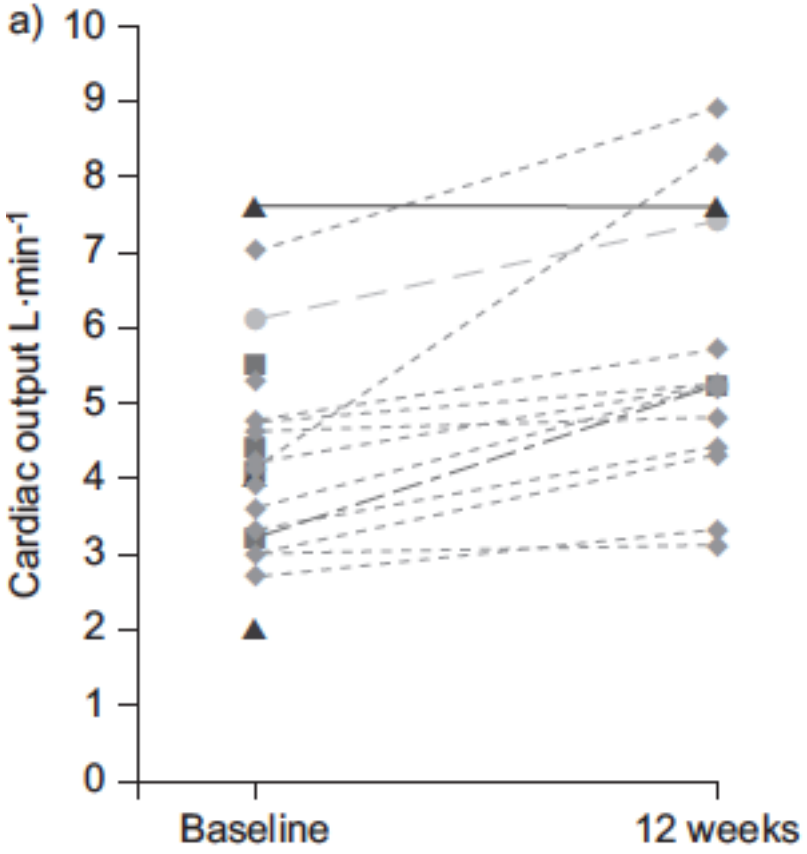
Limitation: The study was terminated early.

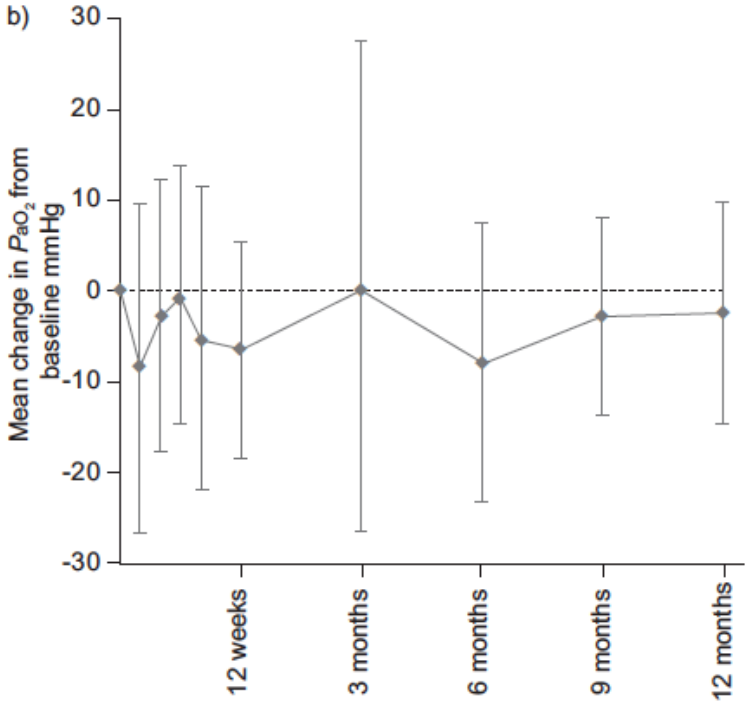
Conclusion: Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations.

Raghu et al. Ann Int Med 2016

Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial

Marius M. Hoeper*, Michael Halank[#], Heinrike Wilkens[¶], Andreas Günther[+], Gerrit Weimann[§], Irmingard Gebert[ƒ], Hanno H. Leuchte and Jürgen Behr[##]**





Hoeper et al. Eur Respir J 2013

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Marius M. Hoeper*, Michael Halank#, Heinrike Wilkens¶, Andreas Günther+, Gerrit Weimann§, Irmingard Gebert‡, Hanno H. Leuchte** and Jürgen Behr##

RISE-IIP:

The trial was terminated early on the basis of interim results that showed increased mortality and increased risk of serious adverse events in the riociguat group compared with the placebo

Hoeper et al. Eur Respir J 2013
Bayer Press release 2016

Task Force 11th Word symposium: PH due to Chronic Lung Diseases

- **Treatment of PH in COPD and ILD - evidence for appropriate benefit to risk ratio of PAH approved drugs?**

General

- No established vascular therapy except for LOT in COPD
- Vasodilators may improve cardiac output/PVR at the expense of a deterioration of gas exchange

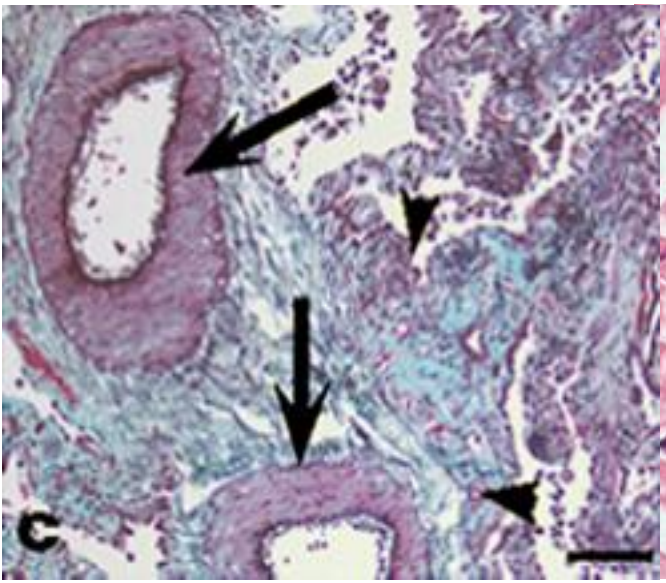
Concerns

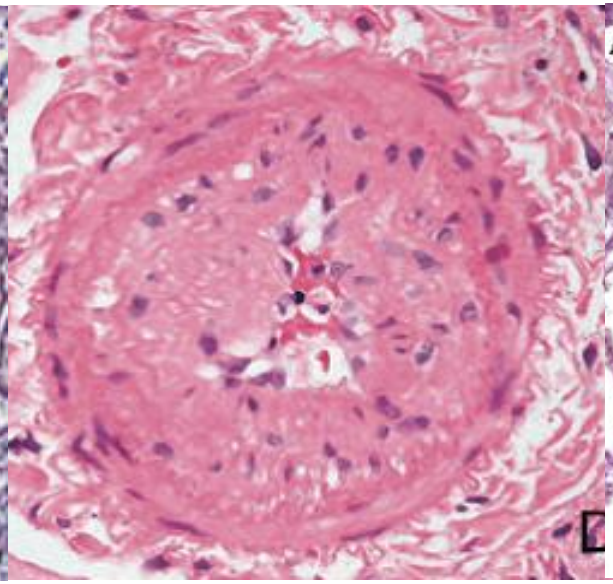
- Most if not all studies have failed
- ARTEMIS: Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations.
- RISE-IIP: The trial was terminated early on the basis of interim results that showed increased mortality and increased risk of serious adverse events in the riociguat group compared with the placebo

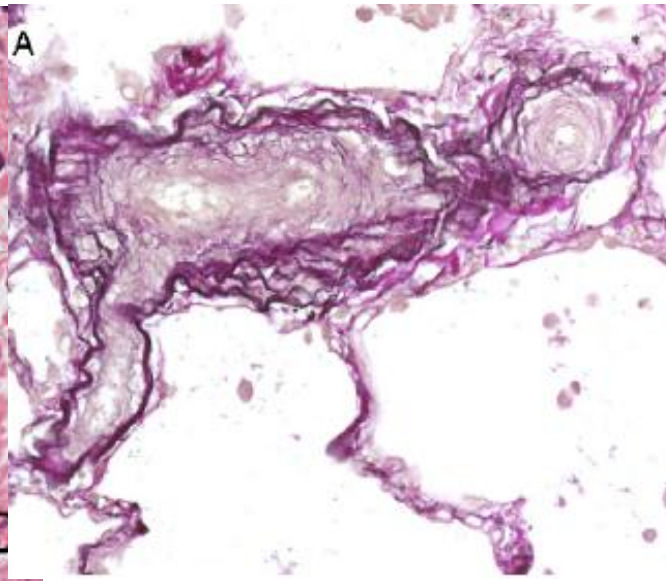
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III	C

PATHOLOGY

Lung samples from severe PH in the setting of chronic lung disease shows pulmonary artery remodeling and pulmonary venous involvements







Nathan, AJRCCM 2007, Patel, Chest 2007, Colombat Hum Pathol 2007

Task Force 11th Word symposium: PH due to Chronic Lung Diseases

- **Any specific/novel targets for future PH therapy in COPD ?**
  - Focus on **endothelial injury** which may underlie both COPD-associated pulmonary arterial remodeling and emphysema development (loss of septal capillaries) ?
  - Focus on **oxidative and nitrosative stress** to *prevent* and *reverse* these vascular abnormalities ?
  - Interference with senescence-associated **proliferative signaling** ?
- **Any specific/novel targets for future PH therapy in IPF ?**
  - Focus on gene sets and networks (gene profiling) related to **myofibroblast proliferation and vascular remodeling** in IPF *with* versus *without* major PH
  - Focus of **"bystander effects"** of IPF associated pro-proliferative and pro-scarring mediators (TGF-ß, PDGF, FGFs, chemokines, …)
  - Focus on a **shift of the angiostatic-angiogenetic balance** (VEGF, endothelial progenitor cells, …)
  - **Consider combination of drugs approved for PAH and IPF** ?

Conclusions

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

Recommendations	Class[a]	Level[b]	Ref.[c]
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

Recommendations	Class[a]	Level[b]	Ref.[c]
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III	C	411–416

Galié *et al. ESC/ERS Guidelines:* 2015

NICE

6TH

February 27-28
March 1, 2018

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION