Ipertensione polmonare e polmone (gruppo III)

50° Convegno di Cardiologia DG

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- Currently there is no specific therapy for PH associated with lung diseases.

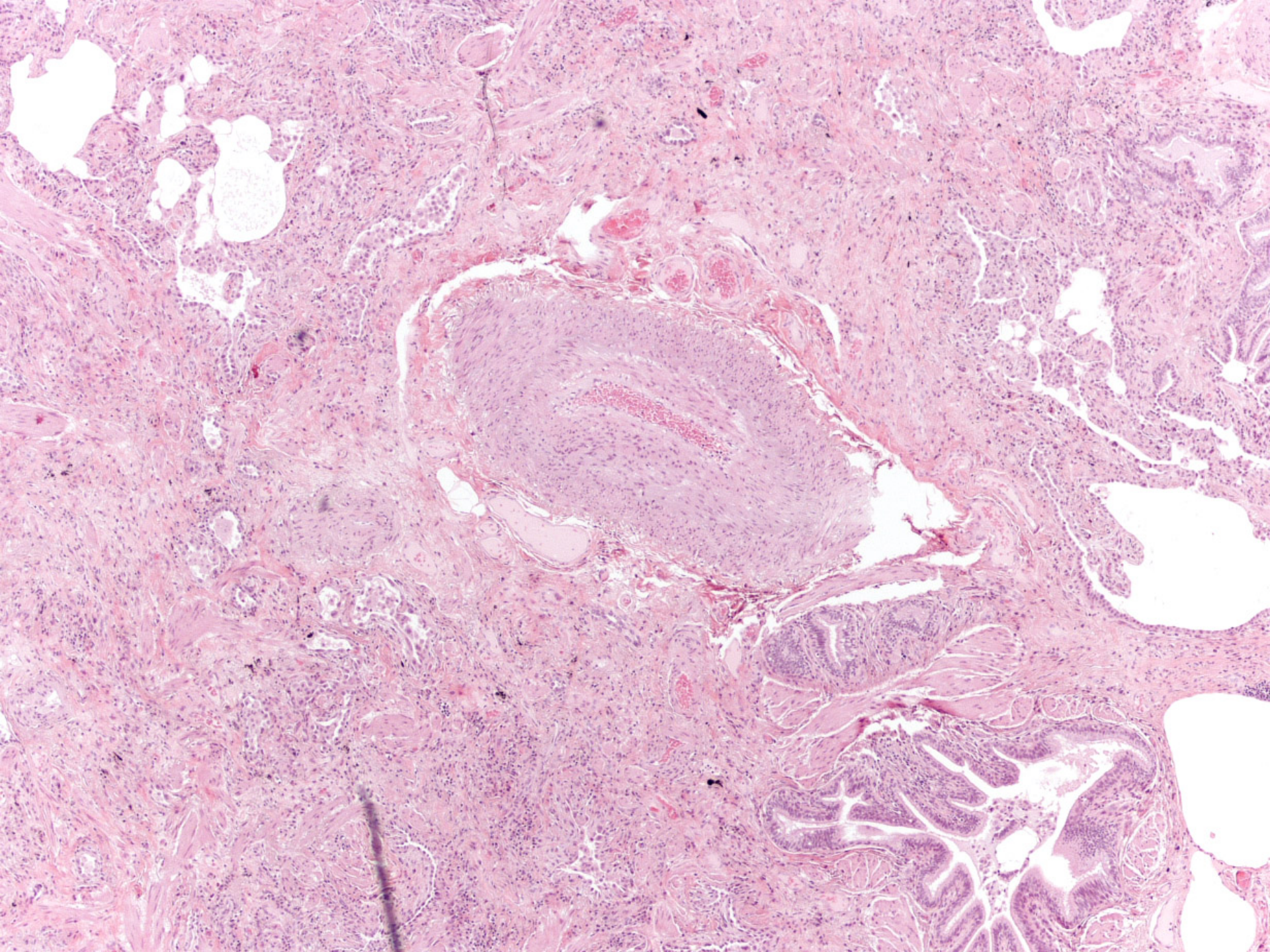
- Published experience with targeted PAH drug therapy is scarce, and so far there is no evidence from RCTs suggesting that PAH drugs result in improved symptoms or outcomes in patients with lung disease.

- The use of drugs approved for PAH is not recommended for patients with PH due to lung disease.

ESC/ERS 2015 Guidelines on PH

Disorders of the respiratory system and hypoxemia

- PH is generally mild or moderate (PAP < 30 mmHg), is not per se a predominant prognosis factor and not require specific therapeutic intervention (except oxygen therapy)
- Medial hypertrophy and mild intimal fibrosis



- The prevalence of PH in patients with ILD varies greatly as a function of the underlying disease and the diagnostic mode used to identify PH

- The most extensive data have been published in IPF

Author	Year	Patients	N	Diagnosis	Definition of PH	Prevalence, %
Leutche et al.	2004	IPF	28	RHC	mPAP>35 mmHg	21.4
Nadrous et al.	2005	IPF	88	Echo	sPAP>35 mmHg sPAP>50 mmHg	84 31
Hamada et al.	2007	IPF	70	RHC	mPAP>25 mmHg	8.1
Zisman et al.	2007	IPF	65	RHC	mPAP>25 mmHg	41.5
Patel et al.	2007	IPF	41	RHC	mPAP>25 mmHg +PCWP ≤15 mmHg	20
Shorr et al.	2007	IPF	2.5	RHC	mPAP>25 mmHg	46.1
Nathan et al.	2008	IPF	118	RHC	mPAP>25 mmHg	40.7
Song et al.	2009	IPF	131	Echo	sPAP>40 mmHg	25
Minai et al.	2009	IPF	148	RHC	mPAP>25mmHg mPAP>40mmHg	45.9 14.2
Kimura et al.	2012	IPF	101	RHC	mPAP > 20 mmHg	34,6

The incidence and prevalence of PH in IPF remain unclear, with widely varying estimates.

The differences reflect:

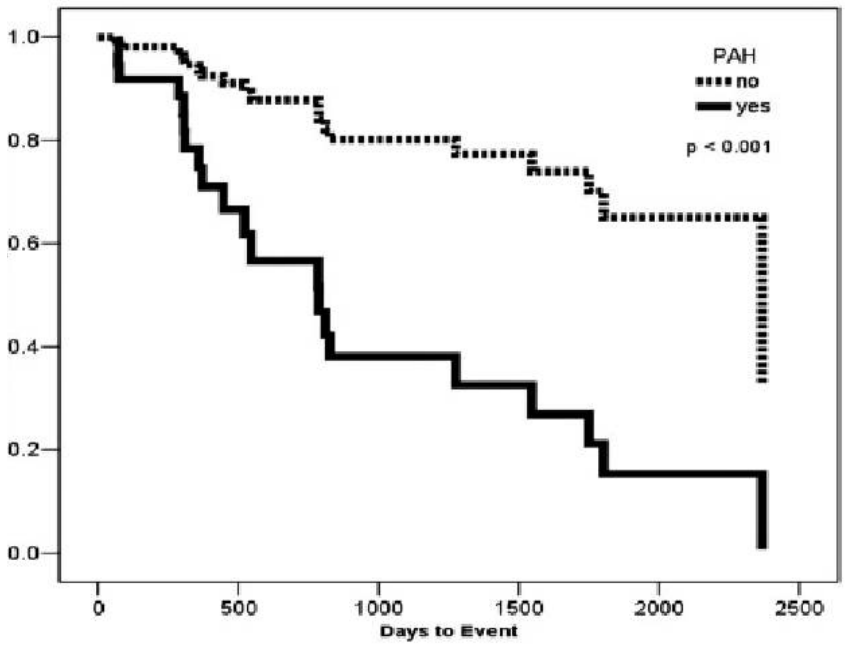
- varying patient populations
- varying underlying disease severity
- differing diagnostic modalities

Pulmonary hypertension in IPF

88 patients with IPF	PASP 0-34 mmHg (n=14)	PASP 35-49 mmHg (n=47)	PASP >50 mmHg (n=27)
Median survival	4.8y	4.1y	0.7y
1 year survival	100%	79%	44%
3 year survival	64%	61%	32%

Nadrous et al Chest 2005: 128;616-7

Pulmonary hypertension in IPF



Variables	MAP ≤ 25 mmHg (n= 10)	MAP > 25 mmHg (n= 24)	P value
MPAP, mmHg	18.2 ± 3.6	29.8 ± 5.1	NA
6MWT distance, m	365.9 ± 81.8	143.5 ± 65.5	< 0.001
SpO2 nadir on 6MWT, %	88.0 ± 3.5	80.1 ± 3.7	< 0.001
Mortality rate, %	37.5	70.0	0.003

Lettieri CJ et al. Chest 2006, 129:746-52

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883

Table 1 Demographic and clinical data of the study population (n = 66)

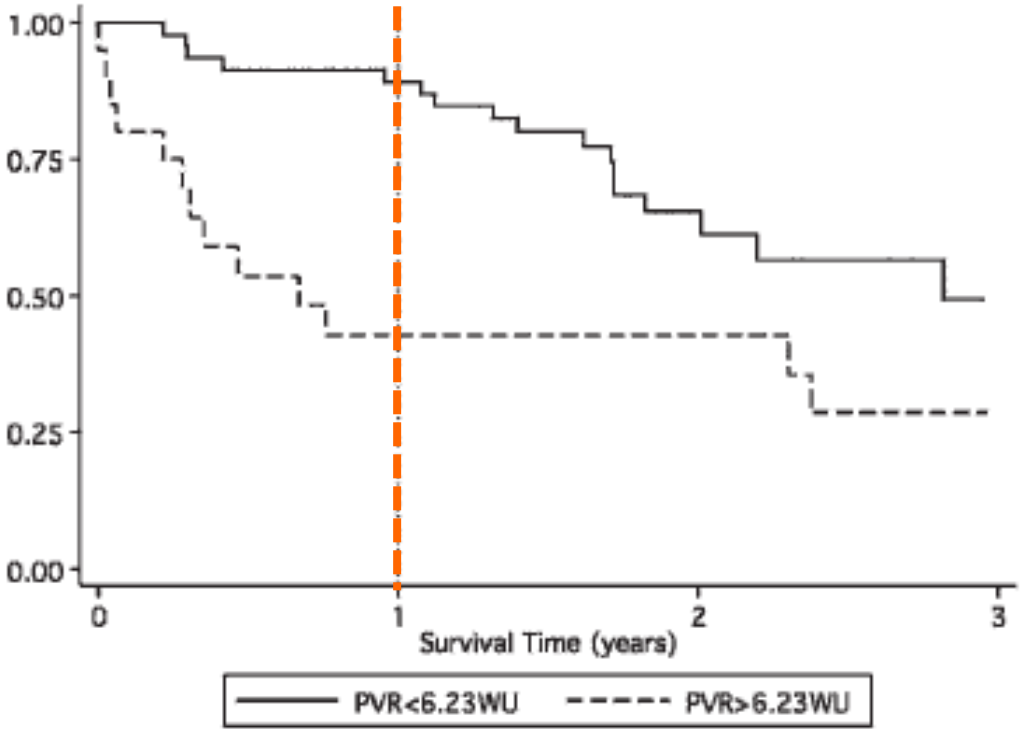
Parameters	No
Clinical parameters*	
Age (years)	57 (12)
Gender (F:M)	28:38
Smoking (pack years)	27 non-smokers, 31 ex-smokers, 7 current smokers, 1 unknown
Time from presentation (months)	33 (4–264)
WHO class	3 (1–4)
Working diagnosis (based on multidisciplinary consensus including lung biopsy when available)	IPF (n = 16) Idiopathic NSIP (n = 6) CTD-related fibrosis (n = 17) Sarcoidosis (n = 12) Other interstitial diseases (n = 15)
Biopsy diagnosis	n = 13 (20%)
Right heart catheter*	
mPAP (mm Hg)	33.6 (11.8)
mRAP (mm Hg)	5.9 (4.2)
mLAP (mm Hg)†	10.7 (5.1)
PVR (Wood units)	5.9 (4.3)
PVR index (Wood units/m²)	10.4 (7.1)
Cardiac output (l/min)	4.3 (1.2)
Cardiac index (l/min/m²)	2.3 (0.5)
Echocardiography	
RVSP (mm Hg, n = 48)	56 (24–102)
PAT (ms, n = 46)	100 (33–144)
Pulmonary function	
T_{LCO} % (n = 65)	29.6 (14.7)
K_{CO} % (n = 65)	52.0 (19.7)
TLC % (n = 61)	72.5 (20.2)
FEV_1 % (n = 62)	62.4 (23.3)
FVC % (n = 62)	67.9 (23.1)
Pao_2 (kPa, n = 61)	8.4 (2.2)
$Paco_2$ (kPa, n = 61)	5.0 (0.9)
CPI (n = 62)	56.9 (14.6)
6MWT (n = 42)	
End Spo_2 (%)	81.4 (8.4)
6MWT distance (m)	254.6 (128.1)

Table 2 Comparison of patients dying within 12 months with those surviving at 12 months

	Death within 12 months	Survival at 12 months	p Value*
mPAP (mm Hg)	39.0 (14.1)	31.7 (10.4)	0.03
PVR (WU)	9.4 (5.8)	4.6 (2.8)	<0.001
PVR index (WU/m²)	16.4 (9.7)	8.5 (4.8)	<0.001
mLAP (mm Hg)	12.2 (6.4)	9.5 (5.0)	0.11
Cardiac output (l/min)	3.8 (1.3)	4.4 (1.1)	0.06
PAT (ms)	69.4 (21.2)	99.5 (28.1)	0.005
Pao_2 (kPa)	7.4 (1.4)	8.8 (2.3)	0.03

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883



In severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF.

PVR is superior to other measurements at RHC and also to non-invasive tests (alone or in combination). These findings suggest that, in advanced lung disease, prognostic information that is only obtainable by RHC has important management implications

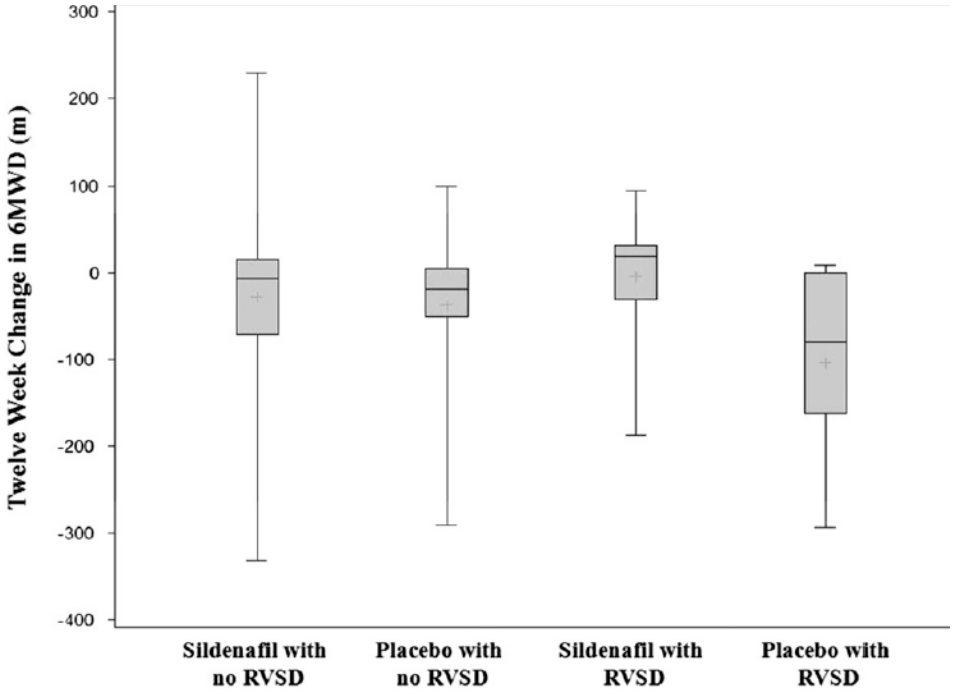
- The presence of PH in IPF is associated with higher mortality and its development contributes to the deterioration of IPF patients

Sildenafil in IPF with Right-sided Ventricular Dysfunction A substudy of STEP-IPF

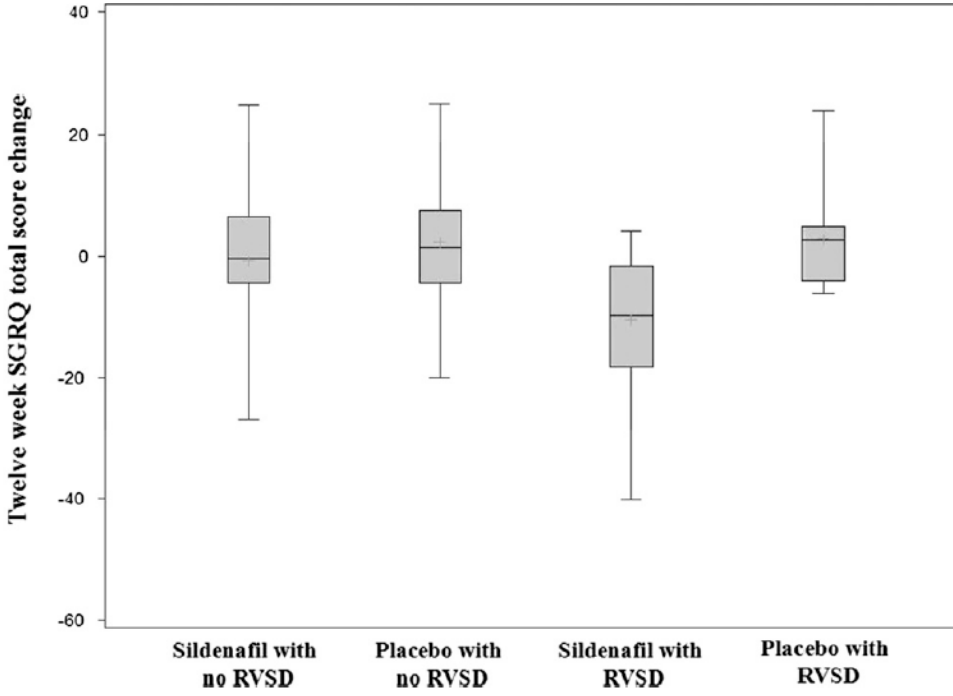
- Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, n 56; placebo, n 63)
- Right ventricular hypertrophy (RVH), right ventricular systolic dysfunction (RVSD), and right ventricular systolic pressure (RVSP) were assessed.
- Multivariable linear regression models estimated the relationship between RV abnormality, sildenafil treatment, and changes in 6MWD
- St. George's Respiratory Questionnaire (SGRQ), the EuroQol instrument, and SF-36 Health Survey (SF-36) from enrollment to 12 weeks.

Chest 2013; 143 (6): 1699-1708

Sildenafil in IPF with right-sided ventricular dysfunction
A sub-study of STEP-IPF



Change in 6MWD at 12 weeks by treatment and presence of RVSD



Change in SGRQ total score at 12 weeks by treatment and presence or RVSD

Patients with any evidence of RVSD treated with sildenafil demonstrated a 99.3 m greater 6MWD as compared with those treated with placebo.

Treatment with sildenafil in subjects with RVSD resulted in a significantly lower SGRQ total score

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

Hoeper MM. et al. Eur Respir J 2013;41: 853 - 860

TABLE 1 Baseline demographics and clinical characteristics of the patients

Patients n	22
Age years	60.5 (33.0–80.0)
White ethnicity	22 (100.0)
Male sex	14 (63.6)
BMI kg·m^{-2}	26±4
WHO functional class	
III	19 (86.4)
IV	3 (13.6)
6-min walk distance m	316±96
Underlying disease	
Idiopathic pulmonary fibrosis	13 (59.1)
Non-specific interstitial lung disease	5 (22.7)
Sarcoidosis	3 (13.6)
Systemic sclerosis	1 (4.5)
Pulmonary function	
TLC % pred	67±12
FVC % pred	67±20
FEV_1 % pred	67±17
D_{LCO}# mmol·min^{-1}·kPa^{-1}	2.7±1.5
Haemodynamics and blood gases	
Mean pulmonary artery pressure mmHg	40±10
Pulmonary vascular resistance dyn·s^{-1}·cm^{-5}	656±201
Cardiac output L·min^{-1}	4.3±1.4
Systolic blood pressure# mmHg	136±16
Heart rate¶ beats per minute	78±14
SpO_2 %	94±3
SvO_2¶ %	62±12
$PaCO_2$ mmHg	39±7

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

Hoeper MM. et al. Eur Respir J 2013;41: 853 - 860

Objective: to assess the safety, tolerability and preliminary efficacy of riociguat, in patients with PH-ILD

Design: open-label, uncontrolled pilot trial

Intervention: patients received oral riociguat (1.0–2.5 mg three times daily) for 12 weeks (n=22), followed by an ongoing long-term extension (interim analysis at 12 months) in those eligible (n=15)

Conclusions: Riociguat was well tolerated by most patients and improved cardiac output and PVR, but not mPAP. Further studies are necessary to evaluate the safety and efficacy of riociguat in patients with PH-ILD.

Efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) (RISE-IIP)

Phase 2 clinical study is terminated on 2016

The DMC recommended the study's immediate termination after observing that patients receiving riociguat were at a possibly increased risk of death and other serious adverse events as compared to patients receiving placebo

PH in chronic respiratory diseases management

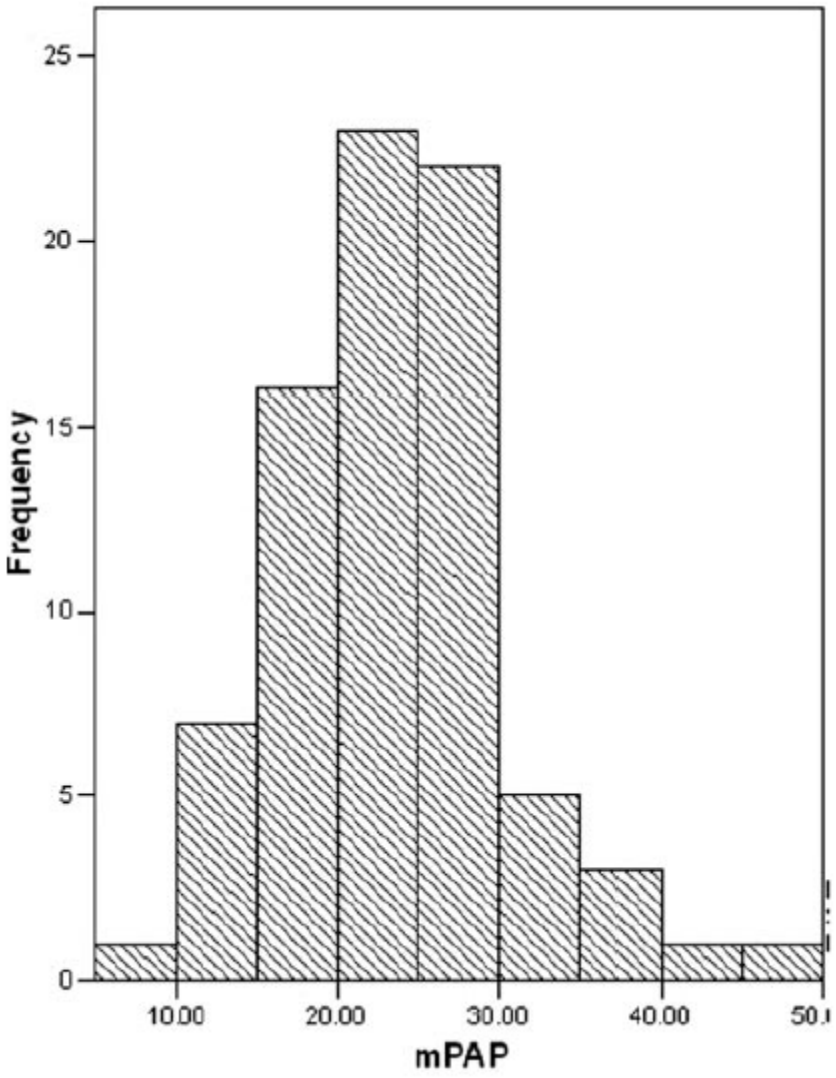
- **Long-term oxygen therapy**
  - Stabilisation or mild improvement of hemodynamics [1-4]
- Lung transplantation
- Drug therapy
  - No proven benefit of PAH-specific drugs (not recommended)
  - IPF regardless of PH : no benefit (bosentan, macitentan), deleterious (ambrisentan, riociguat), unclear benefit (sildenafil)
  - Possible improvement of hemodynamics with unclear clinical benefit and risk of deterioration of gas exchange [5-10]

1. MRC study, Lancet 1981; 1:681
2. NOTT study, Ann Intern Med 1980; 93: 391
3. Weitzenblum E et al, Am Rev Respir Dis 1985; 131: 493
4. Zielinski J et al, Chest 1998; 113: 65
5. Saadjian AY et al, Eur Respir J 1988; 1: 716
6. Agostoni P et al, Am Rev Respir Dis 1989; 139: 120
7. Melot C et al, Am Rev Respir Dis 1984; 130: 612
8. Bratel T et al, Eur Respir J 1990; 3: 46
9. Guenard H et al, In: Derenne JP et al, 1996; pp. 227–266
10. Ghofrani HA *et al.* Lancet 2002.

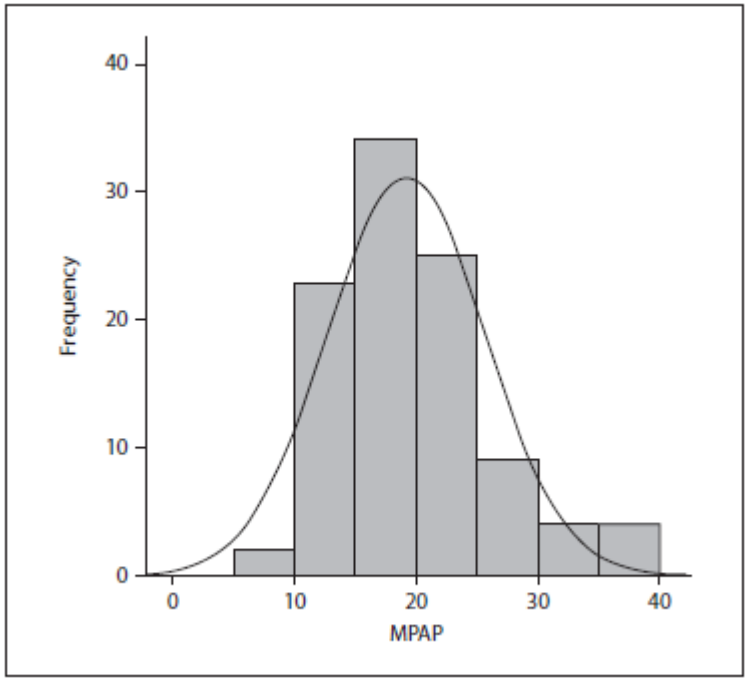
Haemodynamic classification of pulmonary hypertension due to lung diseases

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)

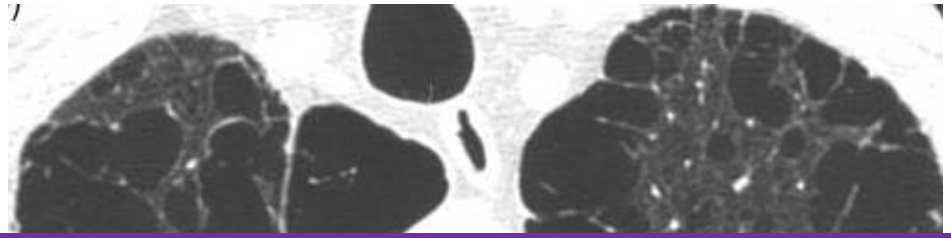
CI = cardiac index; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure; PAPm = mean pulmonary arterial pressure; PH = pulmonary hypertension.



Lettieri CJ et al. Chest 2006; 129:746-52



Kimura M et al. Respiration 2012



Combined pulmonary fibrosis and emphysema (CPFE)

Definition: Presence on HRCT of the chest of both:

- emphysema of the upper lobes (areas of abnormally low attenuation with a very thin wall [< 1 cm] or no wall),
- opacities suggestive of fibrosis of the lung bases (reticular opacities, basal and subpleural predominance, traction bronchiectasis, possibly honeycombing, with no or little ground glass opacities or consolidation).

PH in CPFE

PH is frequent in patients with the CPFE syndrome, with 47% of patients with estimated systolic right ventricular pressure ≥45 mmHg at echocardiography.

The risk of developing pulmonary hypertension is much higher in CPFE than in IPF without emphysema

The prognosis of CPFE is worse than that of IPF without emphysema, an outcome determined by severe pulmonary hypertension and not only by the presence of associated emphysema

PH in patients with CPFE

A retrospective multicentre study was conducted in 40 patients (38 males; age 68 ± 9 yrs; 39 smokers)

Dyspnoea was functional class II in 15%, III in 55% and IV in 30%. 6-min walk distance was 244±126 m. FVC was 86 ± 18%, FEV1 78 ± 19%, and DLCO 28 ± 16% of predicted.

PaO2 on room air was 56 ± 12 mmHg).

Mean pulmonary artery pressure was 40 ± 9 mmHg, cardiac index 2.5 ± 0.7 and pulmonary vascular resistance 521 ± 205.

Cottin V et al. Eur Respir J 2010; 35: 105

PH in patients with CPFE

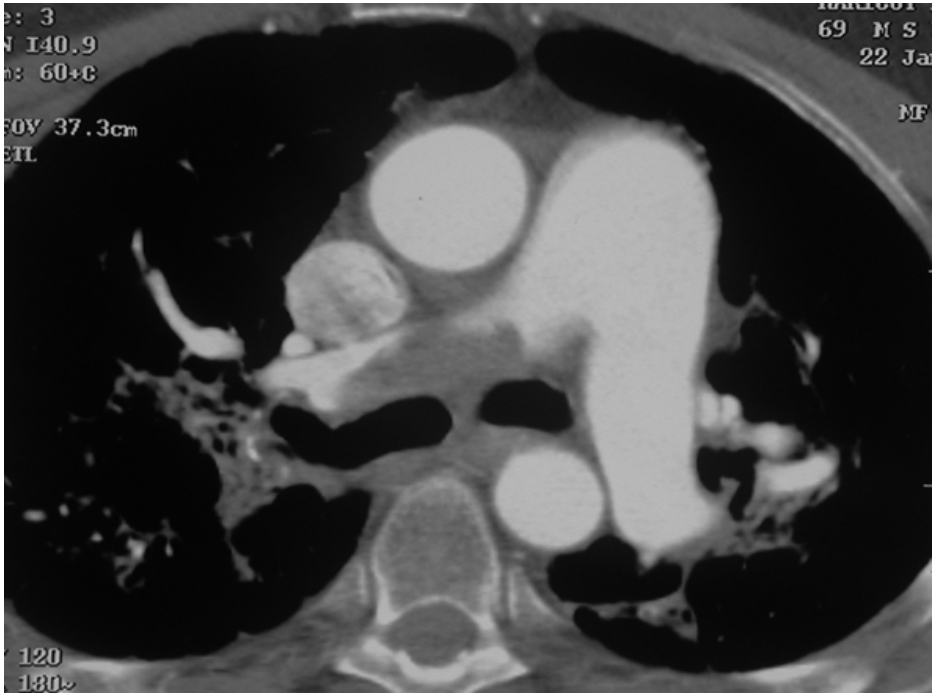
Although the efficacy of drugs specifically indicated in PAH has not been demonstrated in patients with pulmonary parenchymal disorders and associated out-of-proportion pulmonary hypertension, a large number of patients from were treated off-label on an individual basis, thereby providing some preliminary information on the efficacy and safety of pulmonary hypertension therapy in this condition.

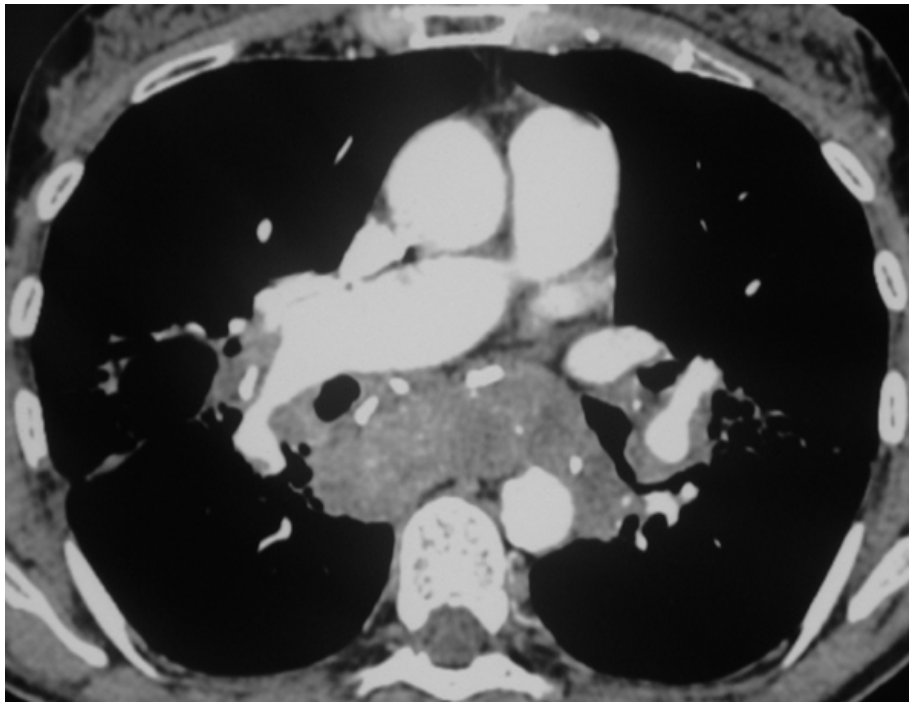
No significant effect of treatment was found on survival.

Cottin V et al. Eur Respir J 2010; 35: 105

Pulmonary vascular involvement in sarcoidosis

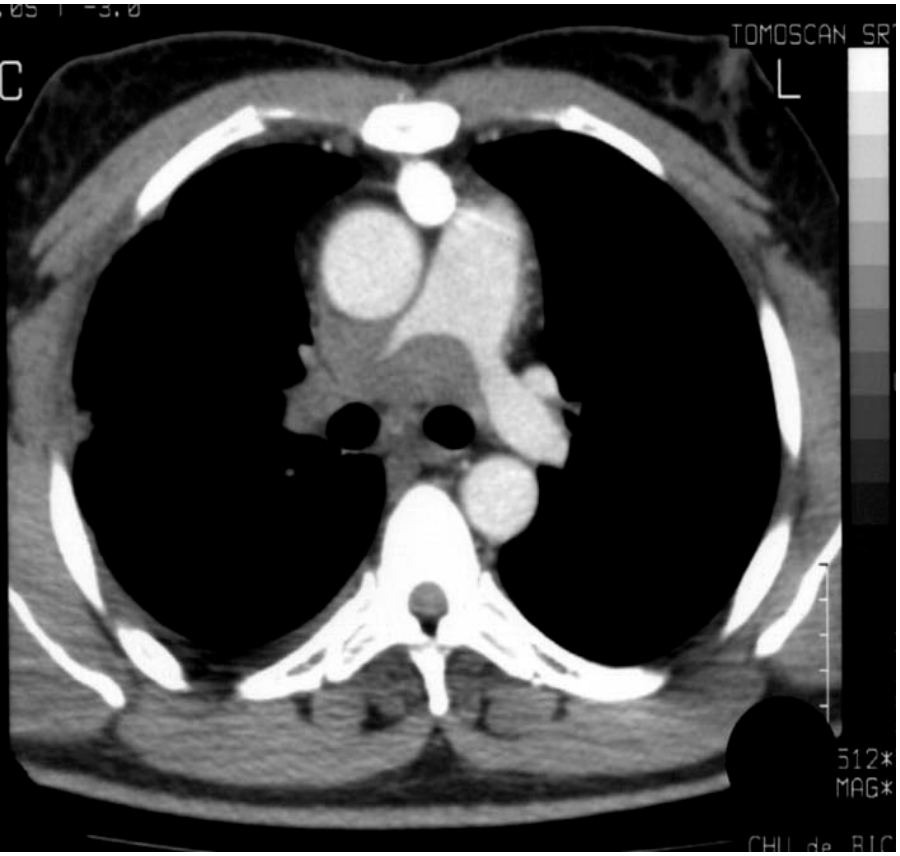
- Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis was detected in 4 out of 15 patients in stage IV

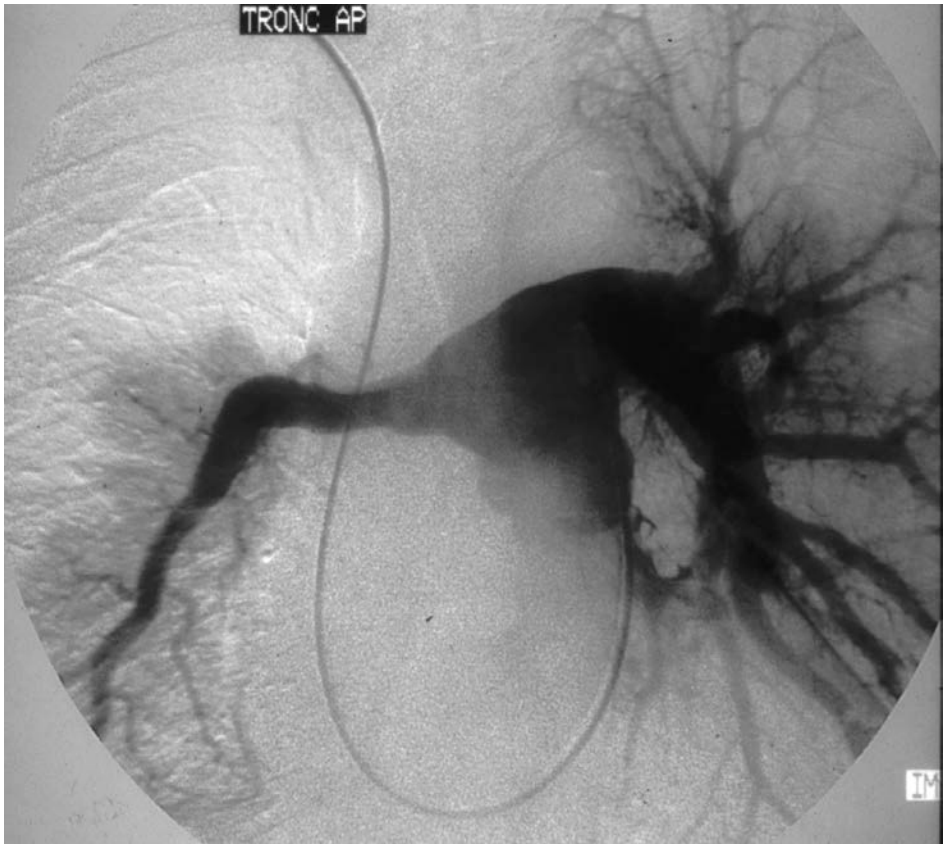




Nunes et al. Thorax 2006

Fibrosing mediastinitis in a cause of pulmonary hypertension in sarcoidosis





Pulmonary vascular involvement in sarcoidosis

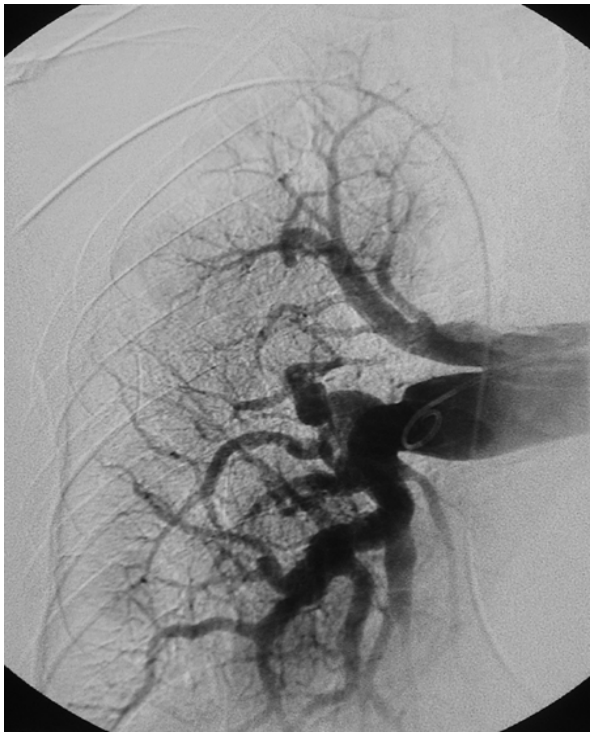
Precapillary pulmonary hypertension in the context of sarcoidosis may be due at least in part to:

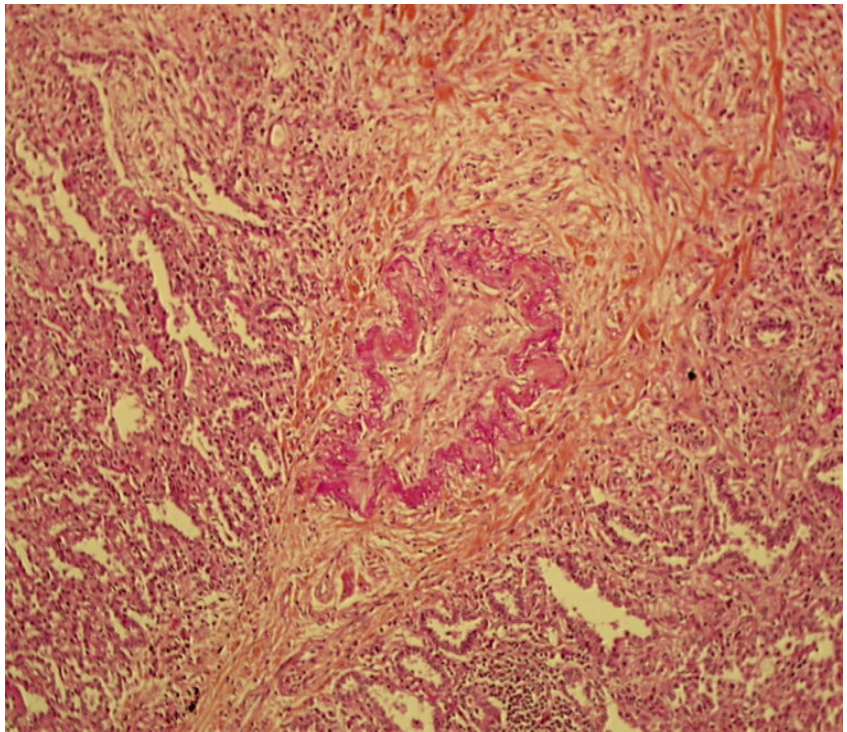
- ➔ Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis
- ➔ Destruction of the distal capillary bed by fibrotic process and resulting hypoxia (stage IV)
- ➔ Specific vasculitis, with infiltration of the walls of pulmonary arteries and/or veins by granulomas (steroid sensitive ?)

Nunes et al. Thorax 2006

Pulmonary vascular involvement in sarcoidosis

- Pulmonary hypertension in sarcoidois occurs in two very different settings
- In the absence of pulmonary fibrosis, PH appears to be related to a specific vasculopathy and may be steroid-sensitive
- In case of pulmonary fibrosis, the mechanism of PH is complex, but certainly involves at least in part a specific vasculopathy as PH is out of proportion with alterations in lung fuction. In these patients, physicians have to consider lung transplantation sooner than they would have solely on the basis of lung function

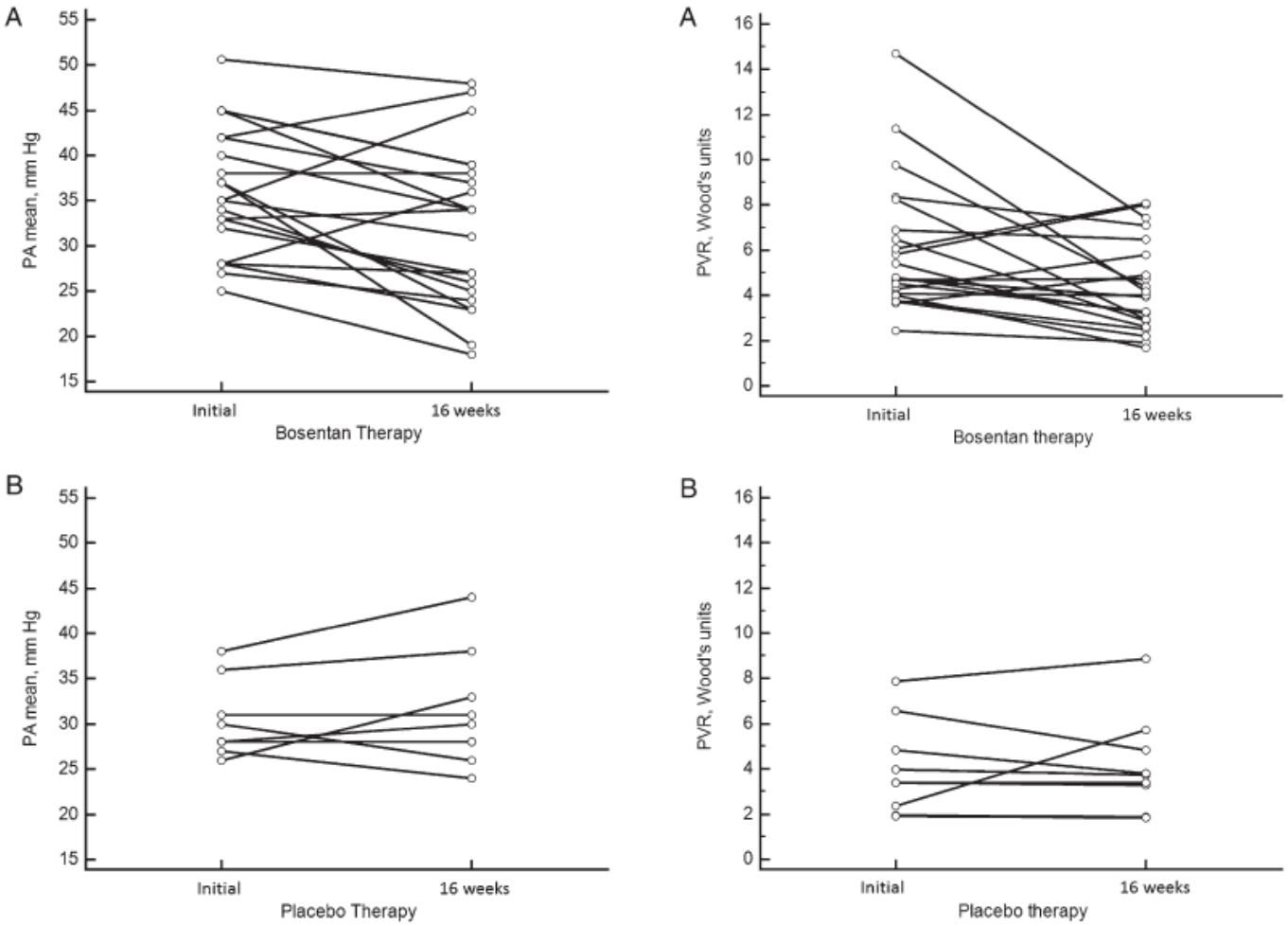




Original research

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension A Double-Blind Placebo Controlled Randomized Trial

Baughman RP, et al. Chest 2014; 145; S10



Original research

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension A Double-Blind Placebo Controlled Randomized Trial

Baughman RP, et al. Chest 2014; 145; S10

In conclusion, we found that 16 weeks of bosentan therapy in patients with SAPH is associated with a significant improvement in PA mean pressure and PVR. The level of improvement was similar to that reported in other WHO groups treated with bosentan. The treatment was well tolerated. The effect of treatment over longer periods will require further investigation.

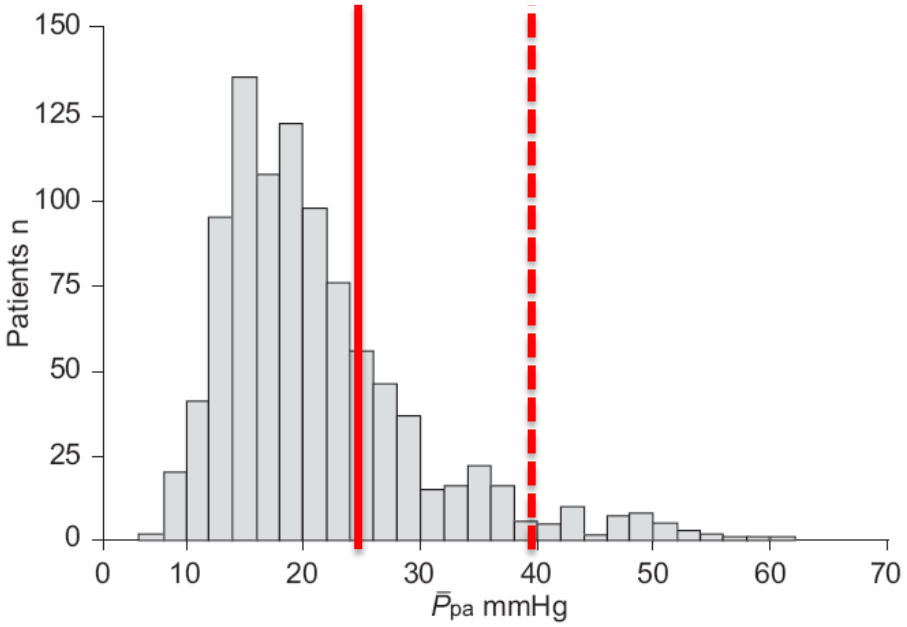
PH in COPD : methods and prevalence

Author	N	Design	FEV1	PaO_2 mmHg	DLCO %pred	PAP mmHg	CI L/min/m^2	PVR dyn·s·cm^{-5}	Definition of PH	Prevalence of PH. %
Burrows	50	Prosp.	37 %	NR	81	26	2.5	468	>25 mmHg	20
Weitzenblum	175	Prosp.	40 %	63	-	20	3.2	NR	>20 mmHg	-
Weitzenblum	93	Prosp.	41 %	66	-	19	3.6	NR	>20 mmHg	34
Oswald-Mammosser	84	Prosp. Pat. LTOT	36 %	52	-	27	-	NR	>20 mmHg	77
Scharf	120	Retrosp. Pat. NETT	27 %	66	27	26	2.9	193	>20 mmHg	91
Thabut	215	Retrosp. Candid. LVRS/LT	24 %	62	-		3.0	376[a]	>25 mmHg	50
Andersen	409	Retrosp. Candid. LT	23 %	63	25[b]	24	-	-	>25 mmHg	36
Cuttica	4930	Retrosp. Candid. LT	22 %	-	-	25	-	NR	>25 mmHg	30

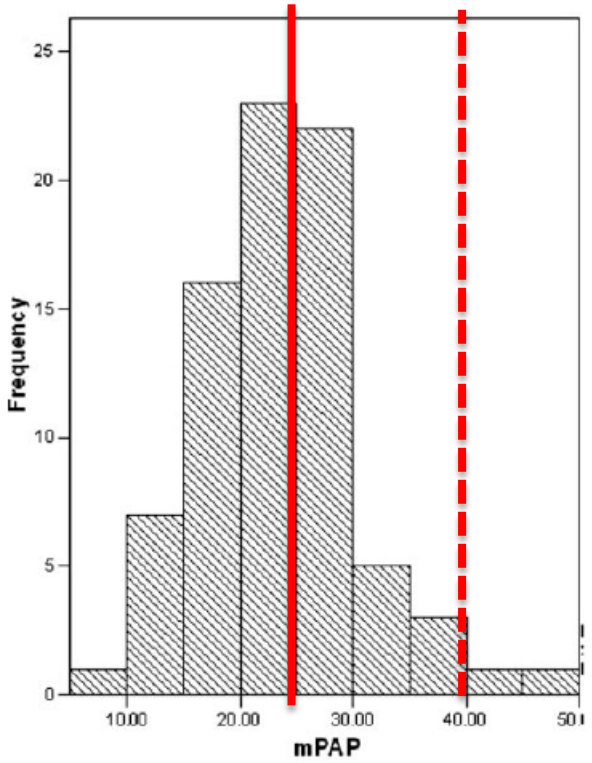
[a] PVR index; [b] patients with PH

PH in chronic respiratory diseases: hemodynamics

COPD



IPF



Chaouat A et al, Am J Respir Crit Care Med 2005; 172: 189

Lettieri CJ *et al, Chest* 2006;129:746

« Disproportionate PH » : cluster analysis

COPD

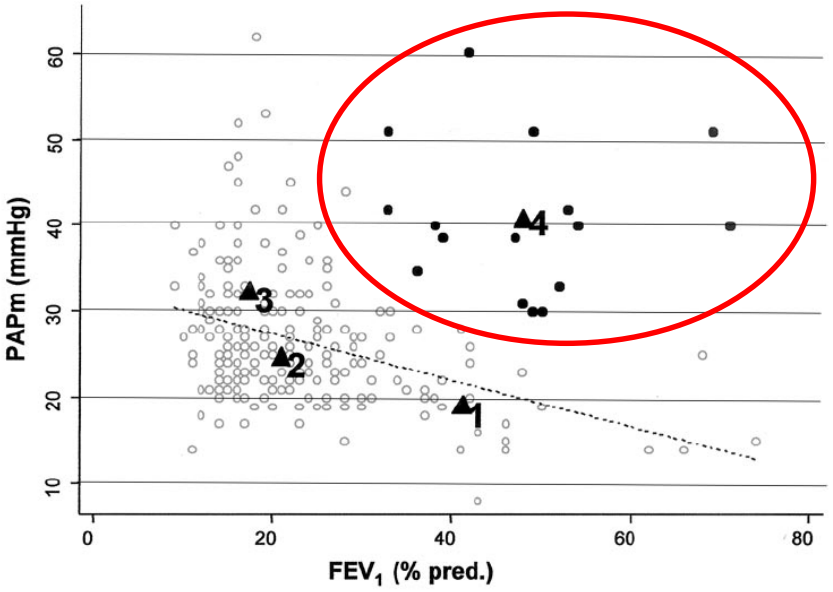
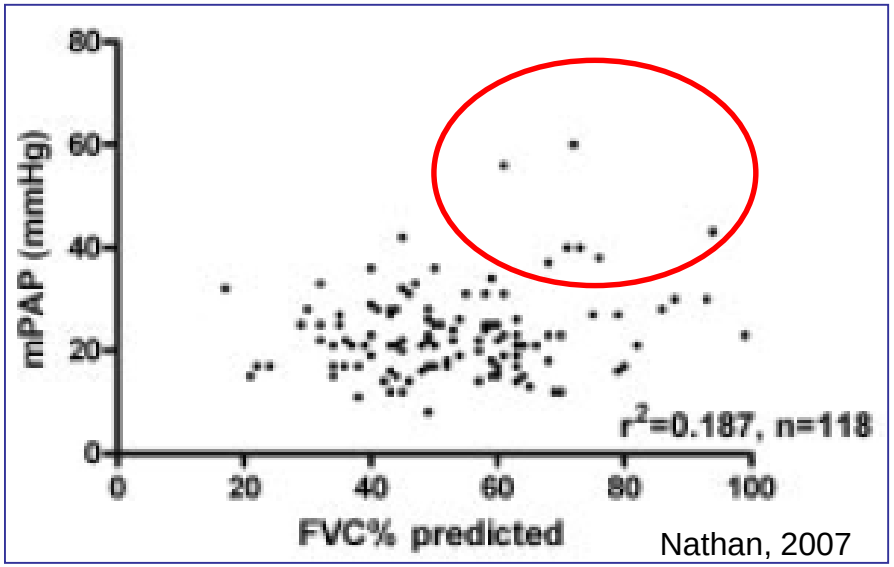


FIGURE 2. Characteristics of the four groups of patients disclosed by cluster analysis. Relationships between PAPm and FEV_1 are shown in groups 1, 2, and 3 (hollow circles) and group 4 (full circle). Triangles indicate the average of each group. A regression line is displayed.

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

IPF

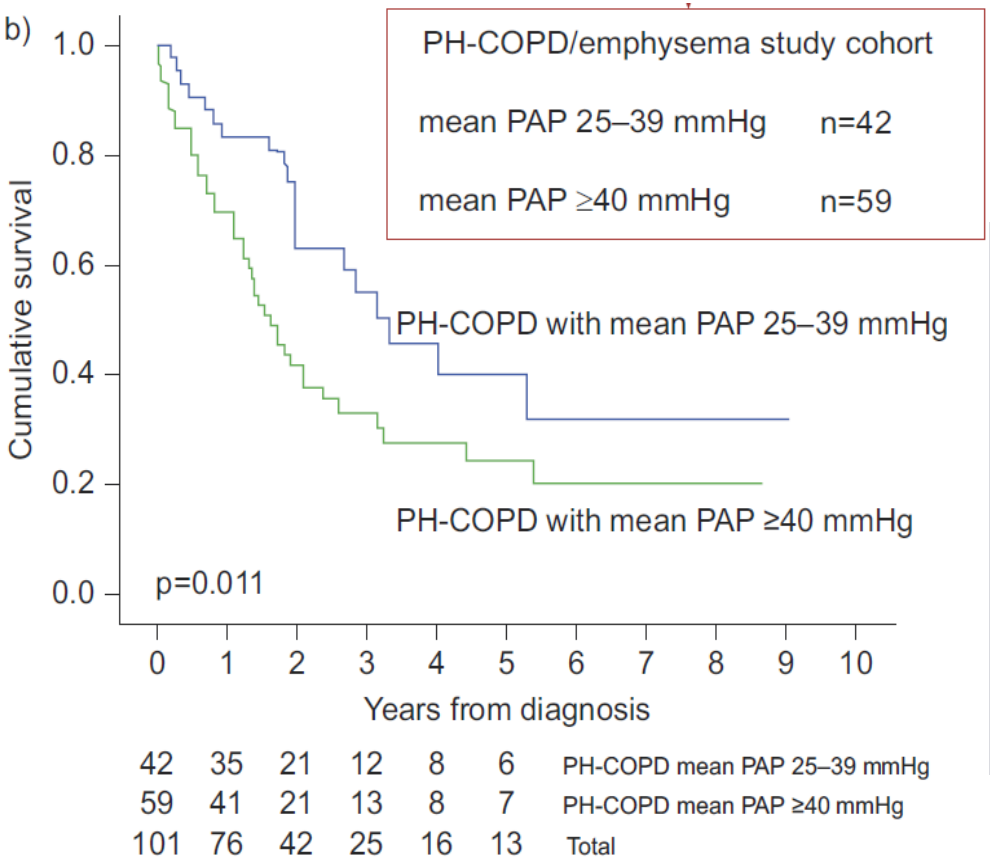


Nathan, 2007

Nathan SD Chest 2007;131:657

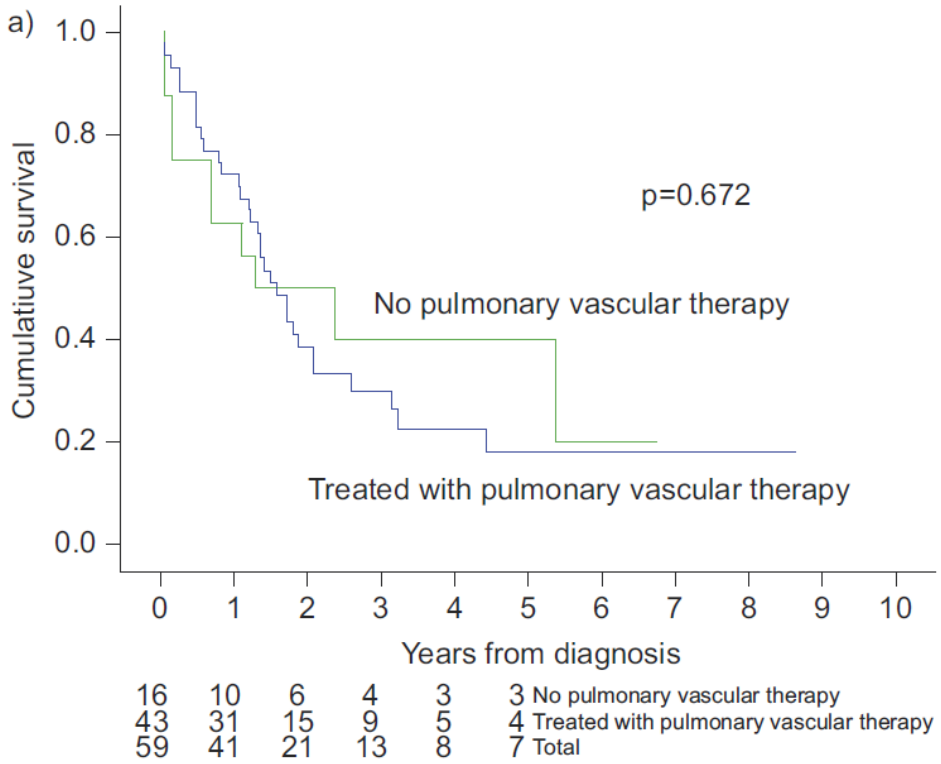
Pulmonary hypertension in COPD: results from the ASPIRE registry

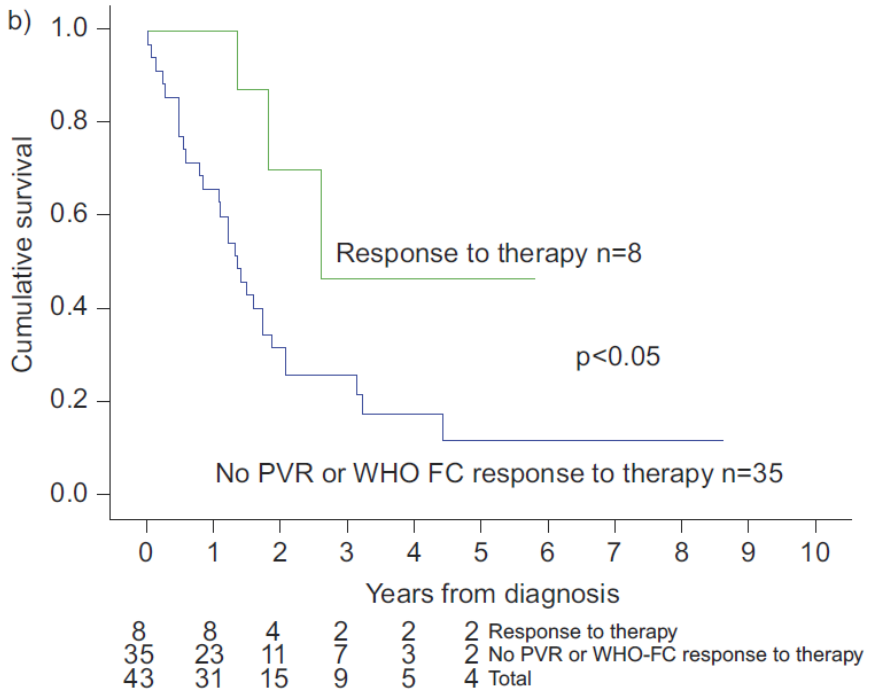
Judith Hurdman*, Robin Condliffe*,#, Charlie A. Elliot*,#, Andrew Swift#,¶, Smitha Rajaram¶, Christine Davies+, Catherine Hill+, Neil Hamilton*, Iain J. Armstrong*, Catherine Billings§, Lauren Pollard§, Jim M. Wild#,¶, Allan Lawrie$, Rod Lawson, Ian Sabroe*,#,## and David G. Kiely*,#**



	COPD mean PAP 25-39 mmHg	COPD mean PAP ≥ 40 mmHg	P
Mean RAP mmHg	8±4	12±5	0.001
Mean PAP mmHg	32±5	49±8	<0.001
CI L·min·m^{-2}	3.2±0.8	2.5±0.7	<0.001
PCWP mmHg	13±5	12±5	0.156
PVR dyn·s·cm^{-5}	303±168	755±377	<0.001
Sv_{O_2} %	67±8	63±8	0.051
Pulmonary function tests			
FEV_1 % pred	51±28	65±23	0.006
FVC % pred	78±25	90±24	0.022
FEV_1/FVC	0.51±0.18	0.59±0.18	0.041
D_{LCO} % pred	40±20	27±13	0.001

Eur Respir J 2013; 41: 1292–1301





43 received compassionate PH therapy
- PDE5i: n=31
- ERA: n=10
- Trepostinil sc: n=1
- Inhaled iloprost: n=1

Treated patients had more severe hemodynamics

Objective response to therapy in 7 / 43, based on improvements in WHO functional class (n=3) or a 20% fall in PVR (n=4/7)

Eur Respir J 2013; 41: 1292–1301

Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial

Vitulo P et al. J Heart Lung Transplant 2016

SPHERIC-1

An Italian multicenter, randomized, placebo-controlled double blind trial

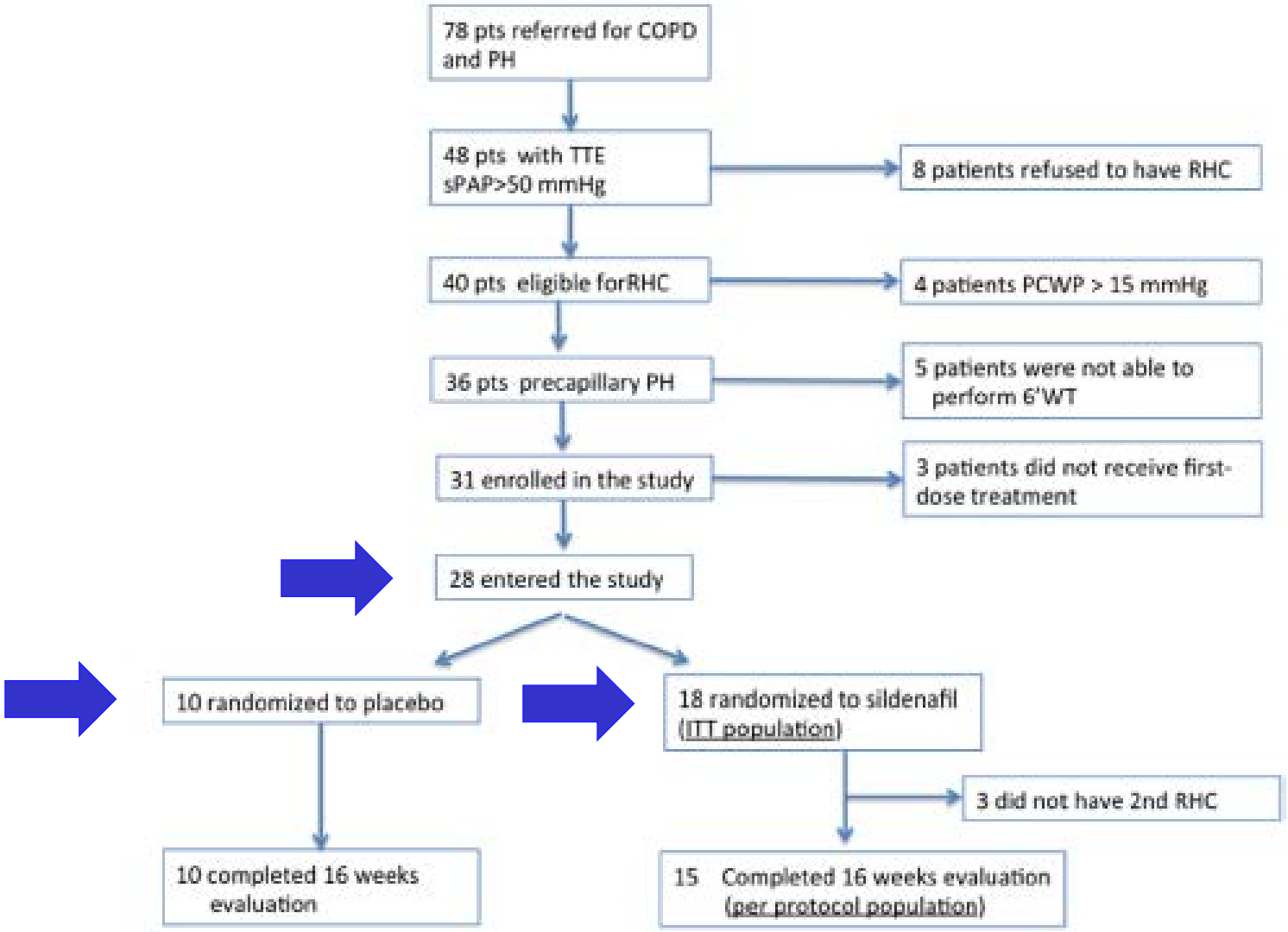
Patients were randomized to receive 20 mg sildenafil or placebo 3 times a day (ratio 2:1)

Duration of study: 16 weeks

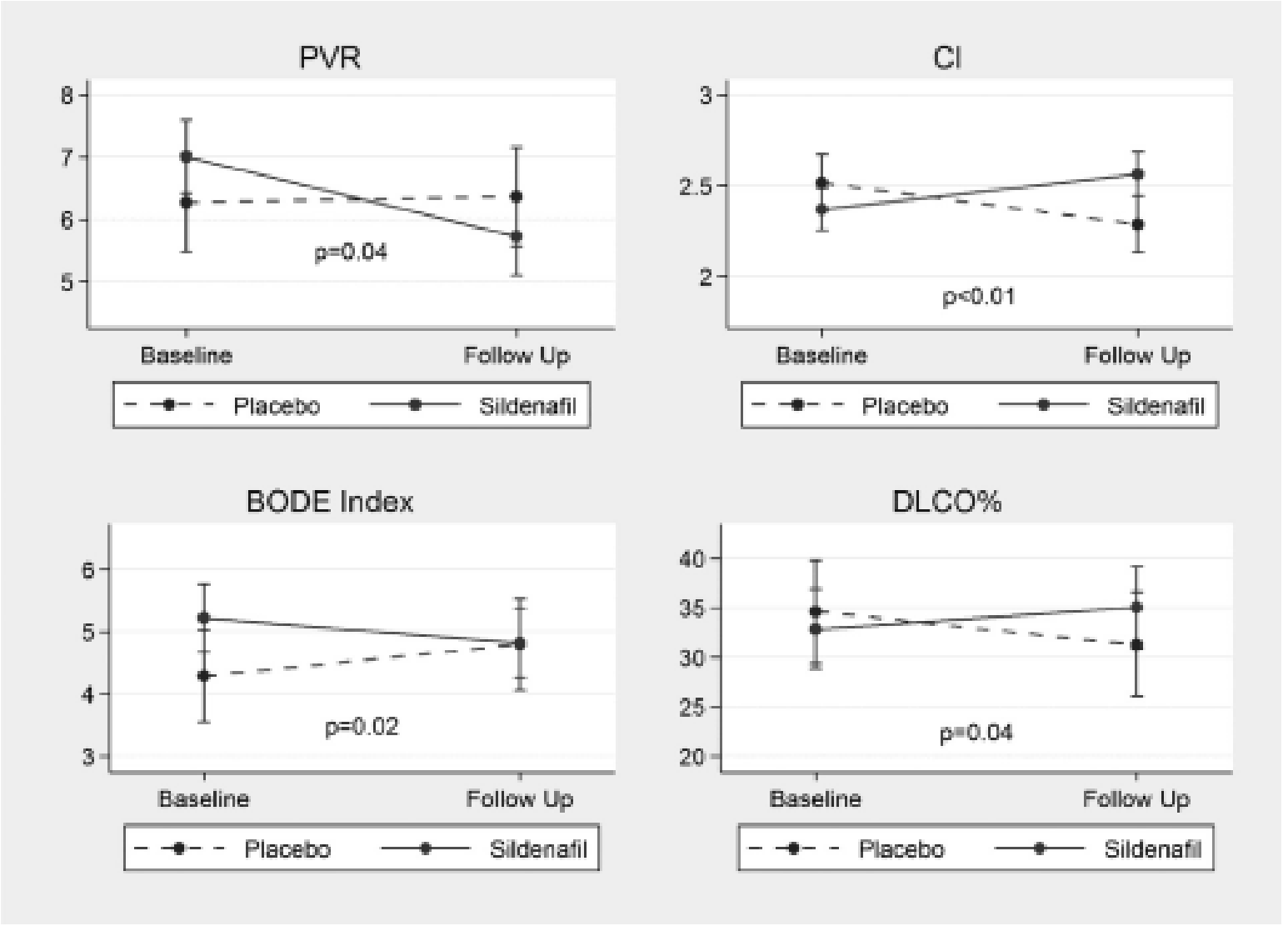
Primary endpoint: the reduction in pulmonary vascular resistance from baseline

Population: COPD patients (GOLD stage II and III) with associated pulmonary hypertension submitted to RHC, PFT, 6MWT, MMRC scale, ABG at time 0 and after 16 weeks of treatment.

SPHERIC-1


78 pts referred for COPD and PH
48 pts with TTE sPAP>50 mmHg
8 patients refused to have RHC
40 pts eligible forRHC
4 patients PCWP > 15 mmHg
36 pts precapillary PH
5 patients were not able to perform 6'WT
31 enrolled in the study
3 patients did not receive first-dose treatment
28 entered the study
10 randomized to placebo
18 randomized to sildenafil (ITT population)
3 did not have 2nd RHC
10 completed 16 weeks evaluation
15 Completed 16 weeks evaluation (per protocol population)

SPHERIC-1 - RESULTS



SPHERIC-1 - RESULTS

Table 2 Primary End Point and Hemodynamics of Patients Who Received the Last Dose of Sildenafil or Placebo (Intention-to-Treat Analysis)

Variable	Placebo ($n = 10$) Mean (SE)	Sildenafil ($n = 18$) Mean (SE)	Difference in change (95% CI)	p-value
PVR, WU				
Baseline	6.27 (0.79)	7.01 (0.59)		
Follow-up	6.36 (0.79)	5.72 (0.62)		
Change	0.09	−1.29	−1.38 (≤ −0.05)	0.04
Total PVR, WU				
Baseline	9.21 (0.95)	9.70 (0.70)		
Follow-up	9.34 (0.95)	8.03 (0.74)		
Change	0.13	−1.67	−1.80 (≤ −0.21)	0.03
RAP, mm Hg				
Baseline	9.00 (1.24)	7.28 (0.92)		
Follow-up	8.20 (1.24)	8.56 (1.00)		
Change	−0.80	1.28	2.08 (≥ −0.86)	NS
mPAP, mm Hg				
Baseline	39.10 (2.85)	39.33 (2.13)		
Follow-up	36.70 (2.85)	35.49 (2.28)		
Change	−2.40	−3.84	−1.44 (≤ 4.44)	NS
Cardiac index, liters/min/m^2				
Baseline	2.5 (0.2)	2.4 (0.1)		
Follow-up	2.3 (0.2)	2.6 (0.1)		
Change	−0.2	0.2	0.4 (≥ 0.2)	0.004
Stroke volume index, ml/m^2				
Baseline	33.2 (2.3)	29.4 (1.7)		
Follow-up	30.3 (2.3)	34.1 (1.8)		
Change	−2.9	4.7	7.6 (≥ 3.7)	0.0007
SVR, WU				
Baseline	2.89 (0.41)	2.73 (0.31)		
Follow-up	3.33 (0.42)	2.48 (0.33)		
Change	0.44	−0.25	−0.69 (≤ −0.24)	0.006
Heart rate, beats/min				
Baseline	77.8 (3.3)	82.0 (2.4)		
Follow-up	76.5 (3.3)	75.3 (2.6)		
Change	−1.3	−6.7	−5.4 (≤ 1.13)	0.09

SPHERIC-1 - RESULTS

Table 4 BODE Score With Individual Components of Patients Who Received the Last Dose of Sildenafil or Placebo (Intention-to-Treat Analysis)

Variable	Placebo ($n = 10$) Mean (SE)	Sildenafil ($n = 18$) Mean (SE)	Difference in change (95% CI)	p-value
BODE index				
Baseline	4.29 (0.74)	5.22 (0.55)		
Follow-up	4.80 (0.73)	4.82 (0.56)		
Change	0.51	−0.40	−0.92 ($\leq$ −0.20)	0.02
6MWT, m				
Baseline	308.5 (31.7)	229.2 (23.6)		
Follow-up	297.3 (32.0)	237.3 (24.2)		
Change	−11.2	8.1	−19.3($\geq$ −8.99)	NS
BMI, kg/m^2				
Baseline	24.93 (1.71)	27.22 (1.27)		
Follow-up	25.64 (1.71)	27.47 (1.28)		
Change	0.71	0.25	−0.46 ($\leq$ 0.11)	0.09
MMRC scale				
Baseline	2.31 (0.28)	3.00 (0.20)		
Follow-up	2.40 (0.27)	2.49 (0.21)		
Change	0.09	-0.51	−0.60 ($\leq$ −0.31)	0.03
FEV_1, % predicted				
Baseline	48.41 (7.11)	54.38 (5.30)		
Follow-up	45.63 (7.11)	54.60 (5.35)		
Change	−2.78	0.21	2.99 ($\geq$ −1.58)	NS

SPHERIC-1
Adverse events

- Only in five patients and they were mild to moderate and icluded headache, diarrhea, flushing, limb pain, myalgia, peripheral edema and dyspnea

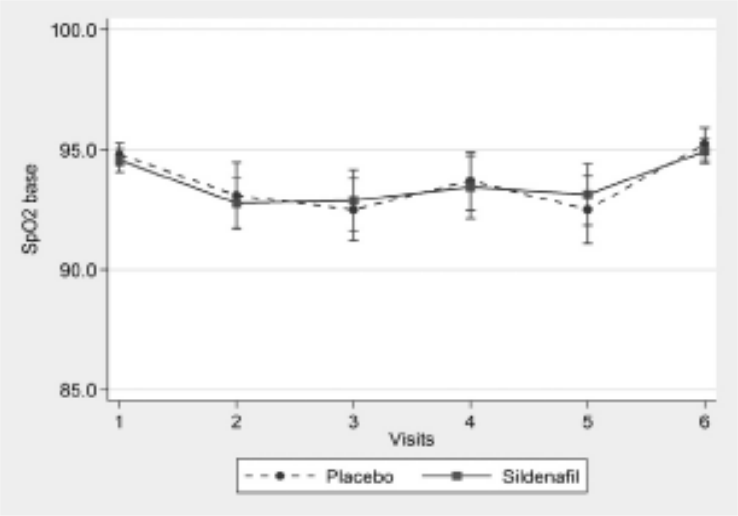


Figure 4 Trend of rest peripheral capillary oxygen saturation (Spo_2) at the scheduled visits

Absence of a detrimental effect of sildenafil on gas exchange (alveolar-arterial O2 gradient and Pao2)

SPHERIC-1 - CONCLUSIONS

Sildenafil (20 mg three times a day) improves PVR, CI and DLCO in PH-COPD patients, in absence of detrimental effect on gas exchange

No improvement in 6MWT-distance

The main limitation of the study is the small sample size

No information on sildenafil dose titration were reported

Another limitation is due the short observation time

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