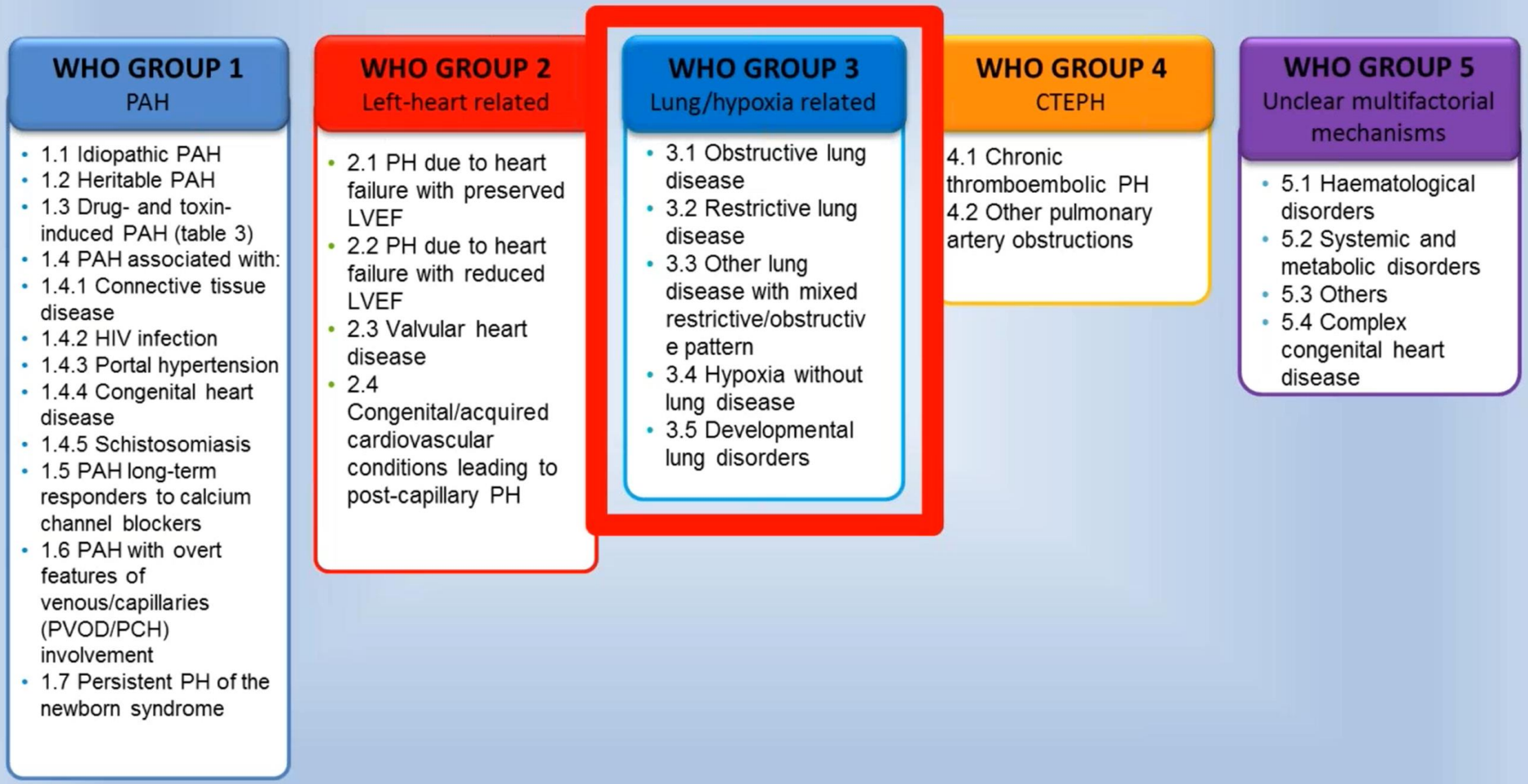
폐혈관 School 2021
SC 컨벤션

Pulmonary Hypertension due to Lung Disease (Group 3)

2021-04-24

명지병원 호흡기내과
최원일

Classification of Pulmonary Hypertension



Simonneau G et al. *J Am Coll Cardiol.* 2013;62(suppl):D34-D41.

ERJ Jan 2019 10.1183/13993003.01913-2018

Introduction

- CLD-associated PH (CLD-PH) is clearly linked with reduced functional status and worse outcomes

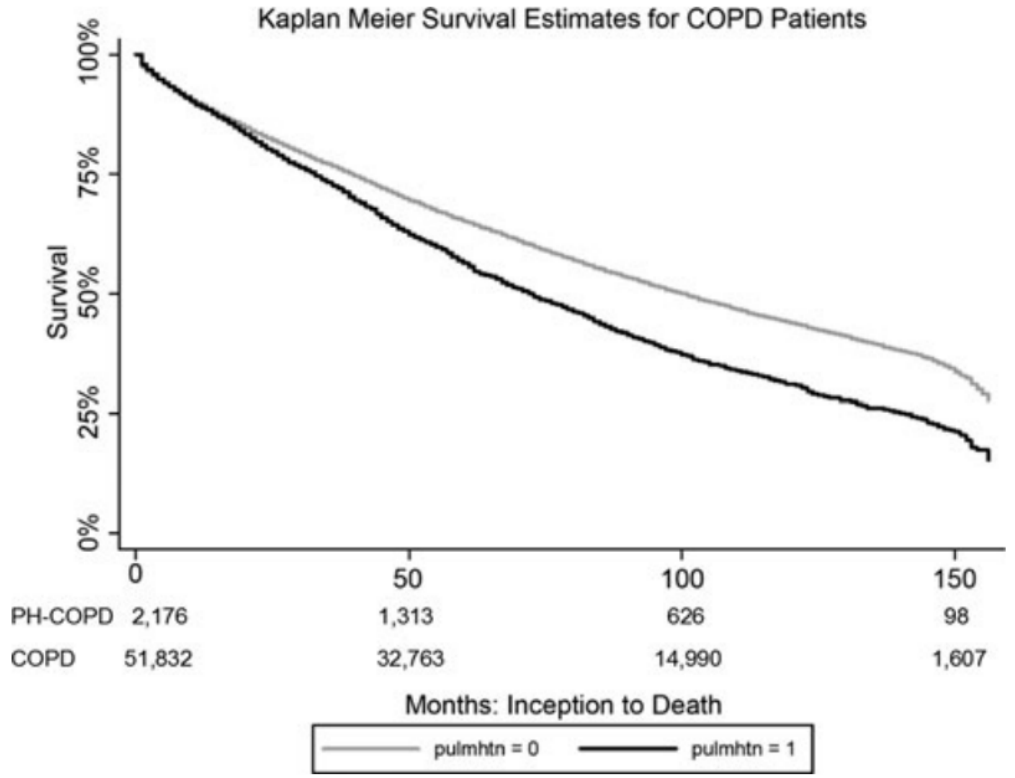


Figure 2. Survival curve for veterans with COPD, with and without PH, over 12 years.

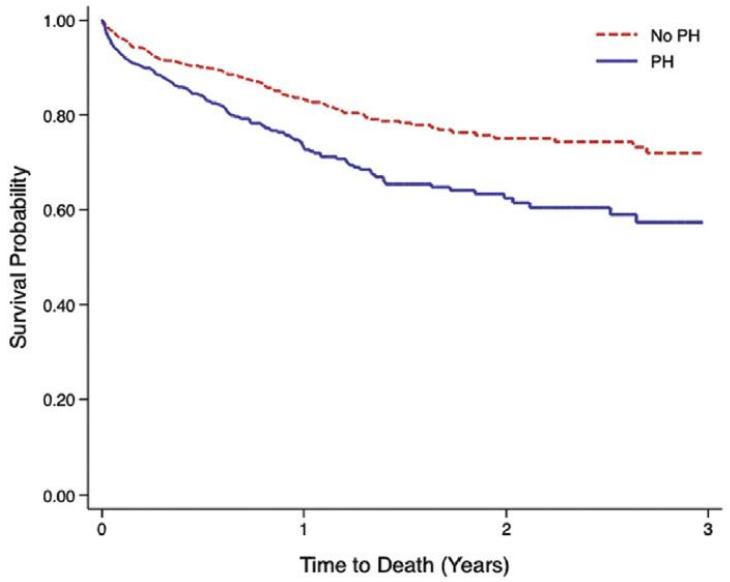


Fig 2. Kaplan-Meier survival functions comparing pulmonary hypertension (blue line) and no pulmonary hypertension (red line) in patients with idiopathic pulmonary fibrosis using mean pulmonary artery pressure 25 mm Hg or greater as the threshold ($n = 6{,}126$; log rank test χ^2 [$df = 1$] 40.44, $p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

COPD 2017; 14: 484–489
Ann Thorac Surg 2016; 101: 246–252.

Introduction

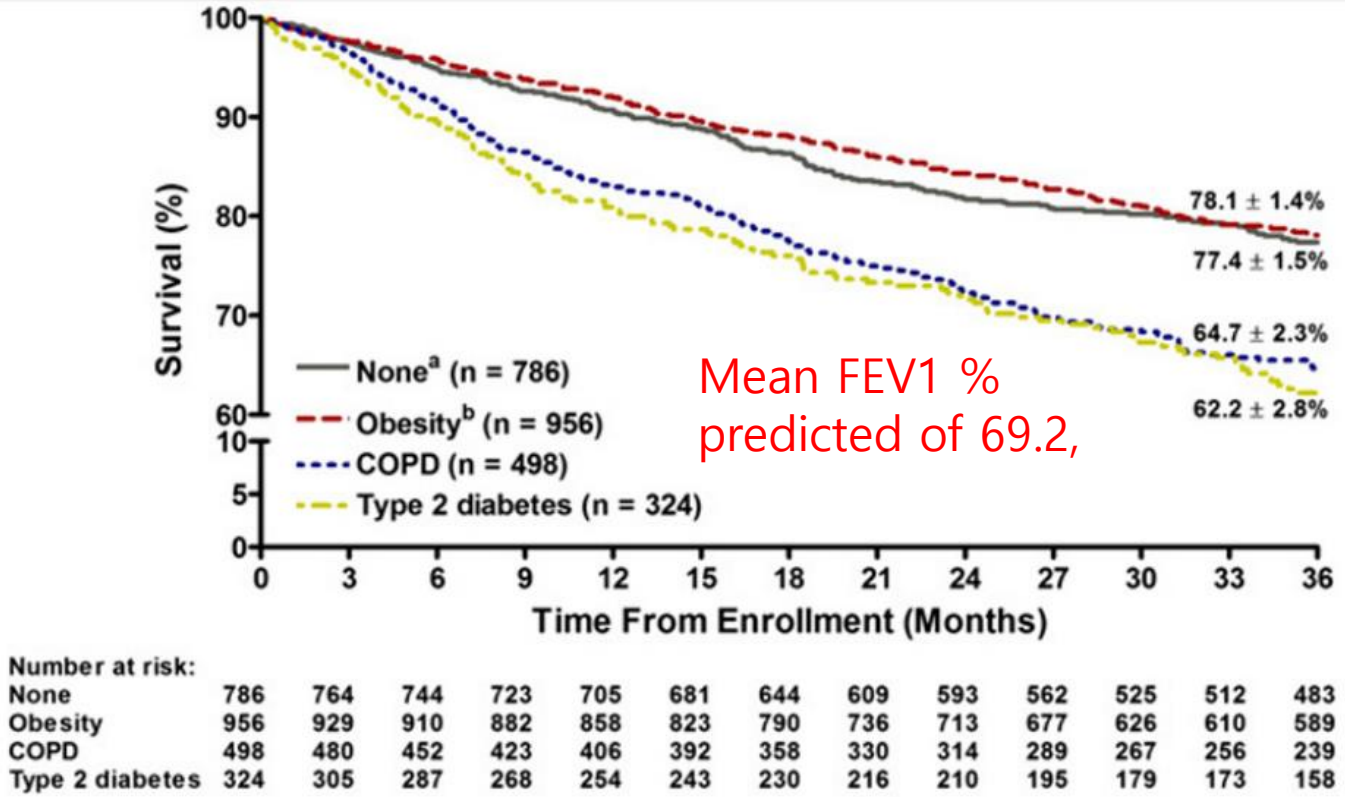


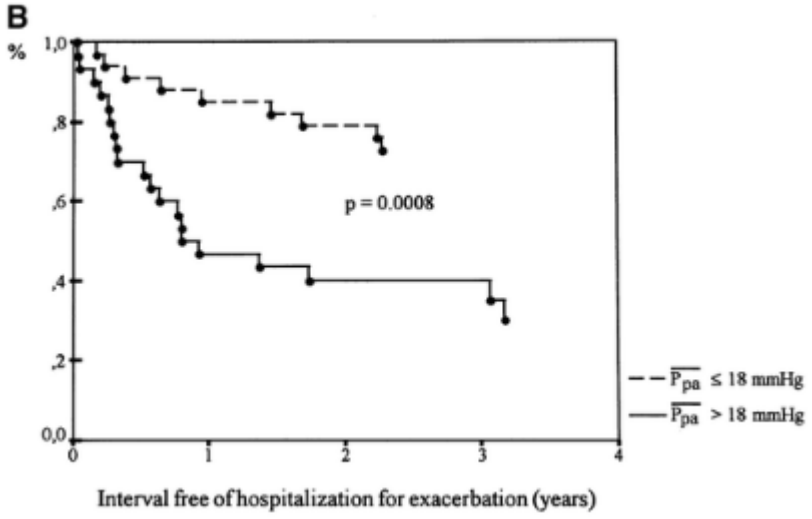
FIGURE 3. Three-year survival from enrollment in patients with pulmonary arterial hypertension stratified by comorbid conditions. Patients with the comorbidity of diabetes or COPD had the

- Even in patients who fulfil diagnostic criteria for group 1 pulmonary arterial hypertension (PAH), the presence of minor lung disease affects survival.

Chest 2013; 144: 169–176

Introduction

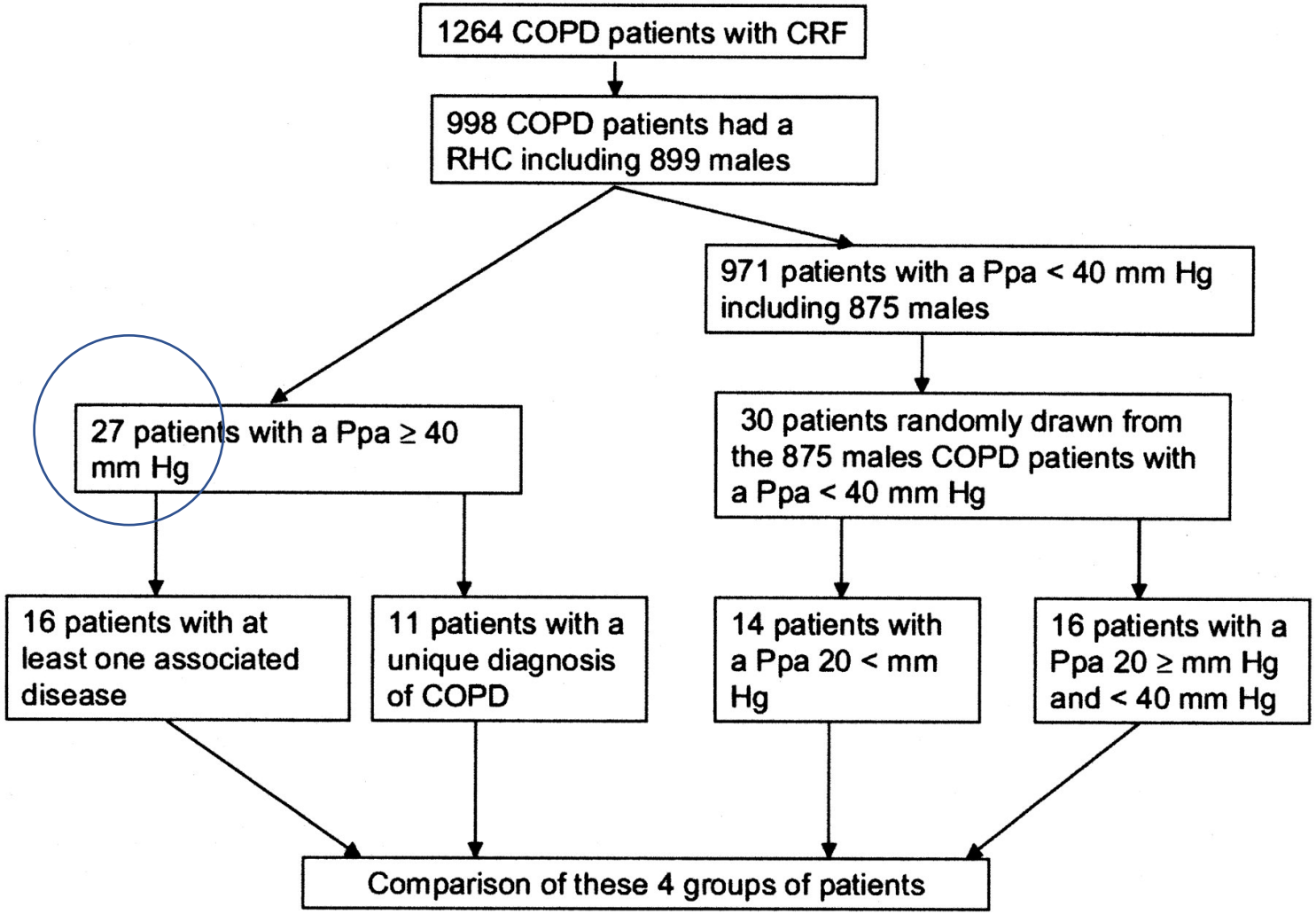
- Moreover, there is data suggesting that mean pulmonary arterial pressure (mPAP) ≥25 mmHg is associated with worse outcome in CLD-PH.



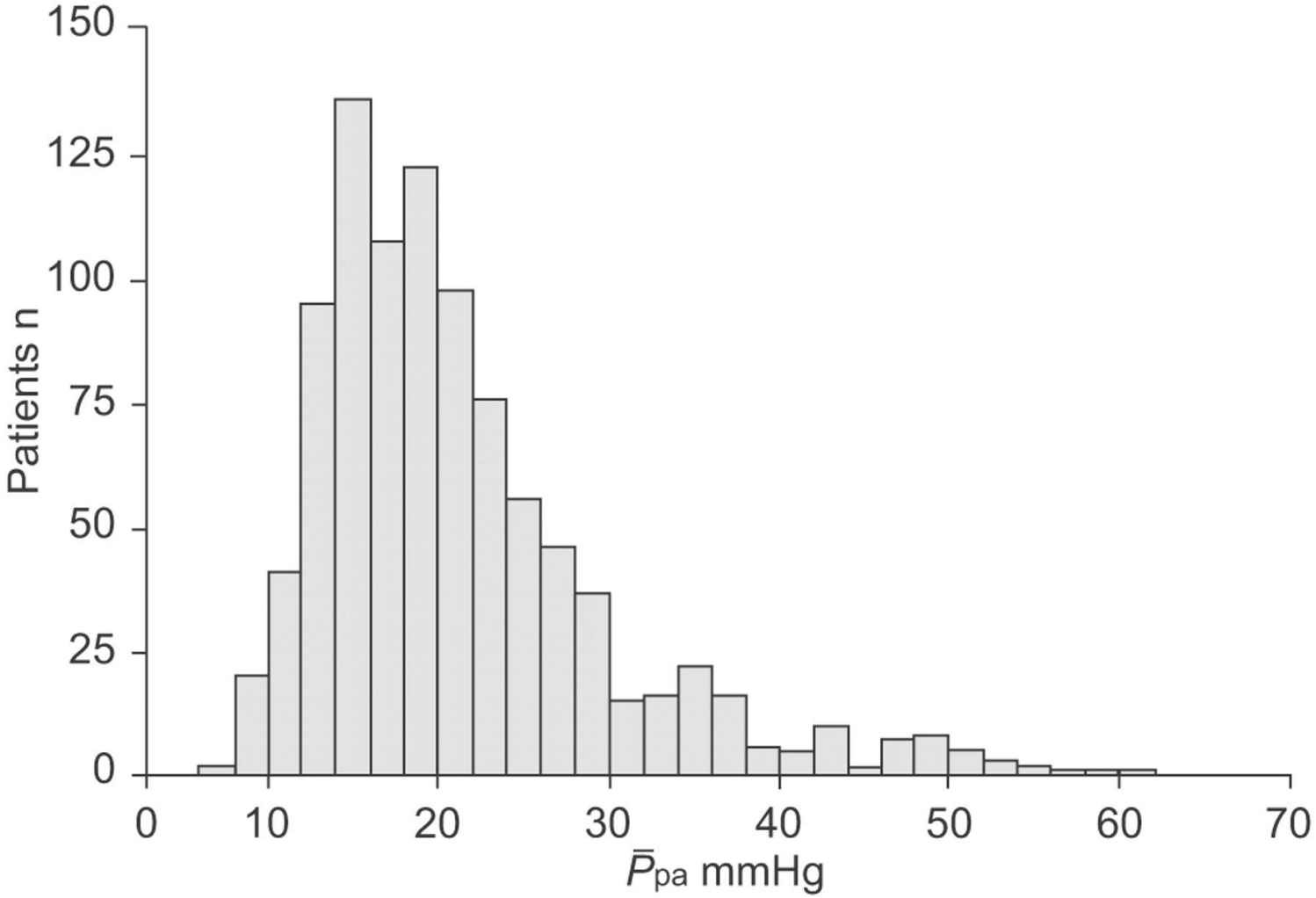
Chest 2007; 131: 650–656.
Am J Respir Crit Care Med 1999; 159: 158–164

Epidemiology and clinical relevance of PH in COPD

Am J Respir Crit Care Med 2005 172189-194.



998 chronic obstructive pulmonary disease (COPD) patients with a mild to very severe airflow limitation



European Respiratory Journal 2008 32: 1371-1385

COPD, a rapid rise in mPAP during moderate exercise

Table 3—*Exercise Hemodynamic and Gas Exchange Parameters*

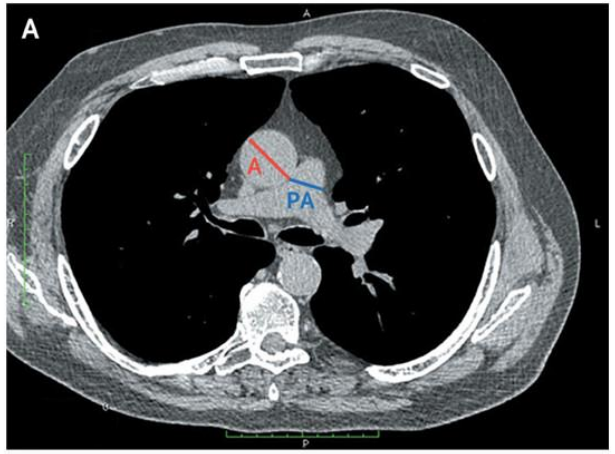
	No PH		Moderate PH		Severe PH		
Parameter	Rest	Exercise	Rest	Exercise	Rest	Exercise	*P* for Interaction
Cardiac index, L/m^2	3.2 ± 0.7	5.5 ± 1.7	3.3 ± 0.8	4.9 ± 4.5	2.5 ± 0.4	3.3 ± 1.0[a,b]	< .01
SVI, mL/m^2	40 ± 12	49 ± 11	40 ± 11	43 ± 11	31 ± 11[c,d]	32 ± 9[a,d]	.07
mPAP, mm Hg	19 ± 3	35 ± 11	31 ± 4[a]	52 ± 13[a]	51 ± 9[a,e]	69 ± 11[a,e]	.42
Sa_{O_2}, %	94 ± 3	91 ± 5	88 ± 5[c]	79 ± 8[a]	90 ± 5[c]	80 ± 9[a]	< .001
Sv_{O_2}, %	69 ± 4	48 ± 10	65 ± 7	41 ± 8[c]	55 ± 10[a,e]	30 ± 5[a,b]	.50
Pa_{CO_2}, mm Hg	38 ± 5	41 ± 6	45 ± 10	49 ± 10	37 ± 10	35 ± 10[b]	< .01

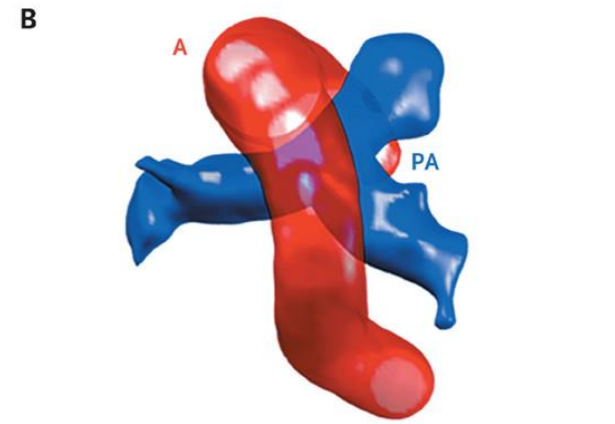
Data are presented as mean ± SD. SVI = stroke volume index; Sv_{O_2} = mixed venous oxygen saturation. See Table 1 and 2 legends for expansion of other abbreviations.

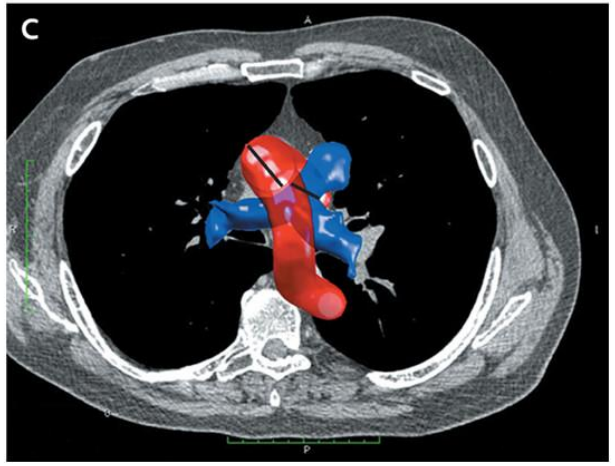
CHEST 2012; 142(5):1166–1174

Pulmonary Arterial Enlargement and Acute Exacerbations of COPD

- Pulmonary artery enlargement (a PA:A ratio of >1), as detected by CT, was associated with severe exacerbations of COPD.

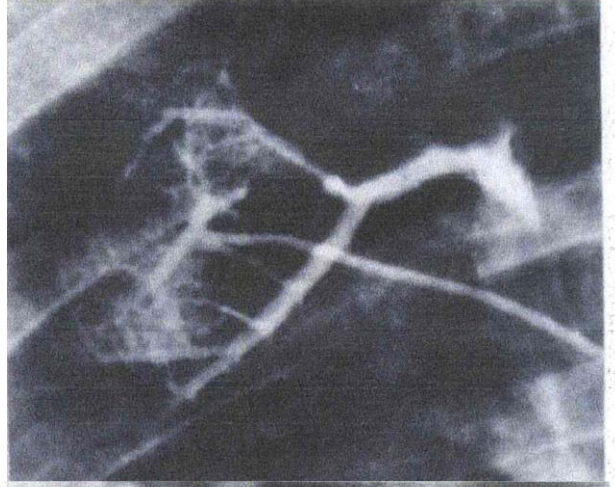


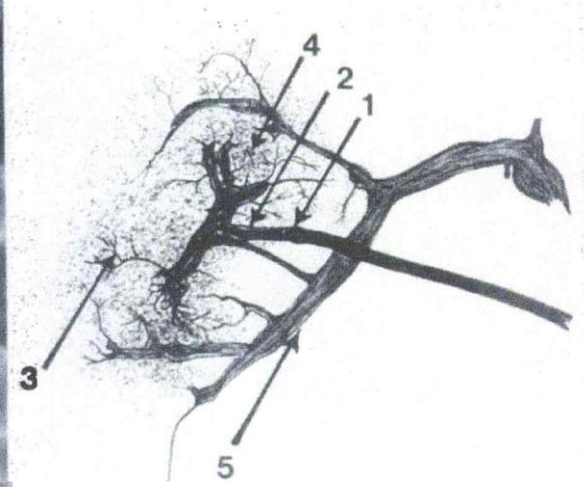




N Engl J Med 2012; 367: 913–921.

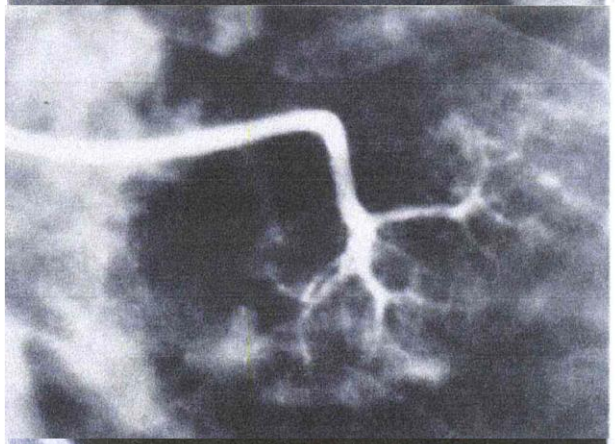
Healthy lung

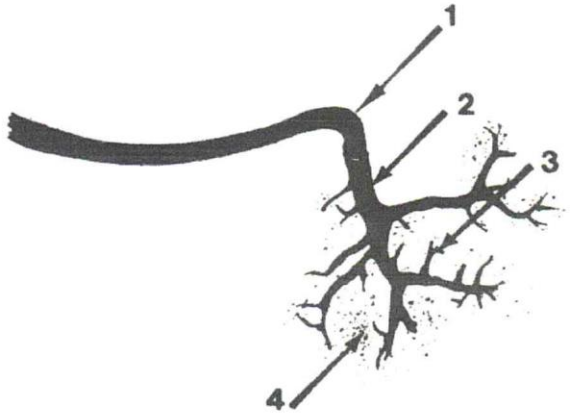




1. Wedged cath
2. Centrilobular artery
3. Branches
4. Capillary background
5. Paralobular veins

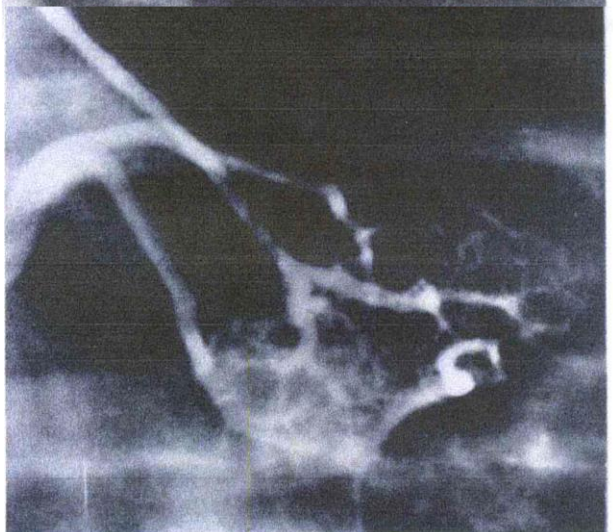
Severe emphysema

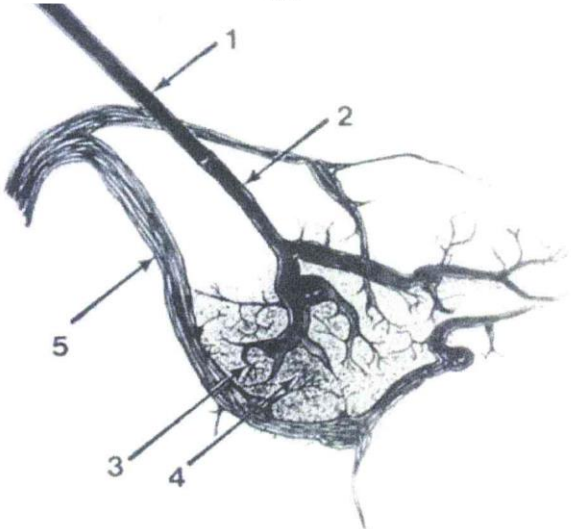




1. Wedged cath
2. Centrilobular artery
3. Markedly Branches ↓↓
4. Capillary background ↓↓

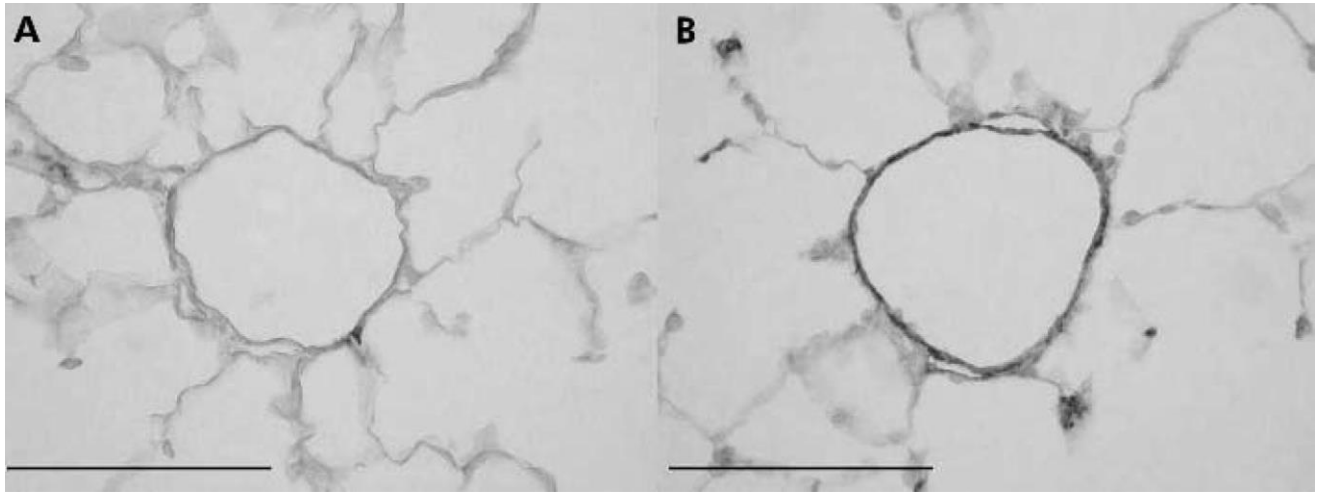
Chronic bronchitis





1. Wedged cath
2. Centrilobular artery
3. Branches ↔
4. Capillary background ↔ ↓

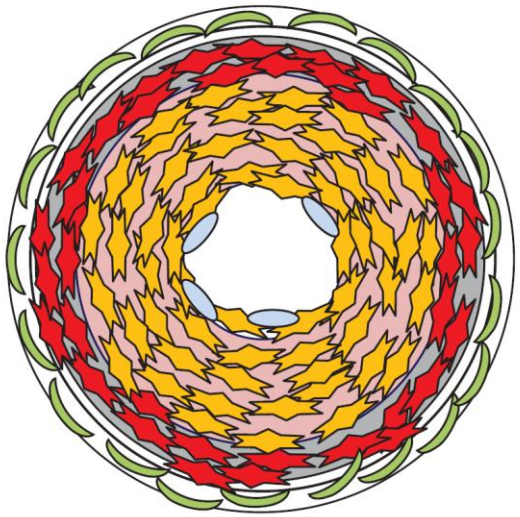
CHEST 1977; 74 :6



Muscularisation of the small, normally partially muscularised arteries adjacent to the alveolar ducts, cigarette smoke (B) for 6 months in guinea pigs

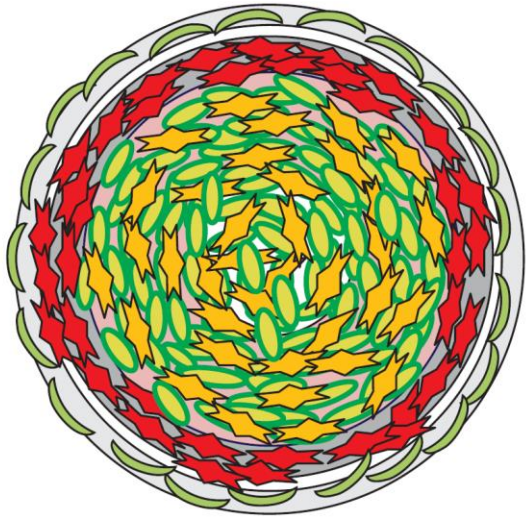
Thorax 2005

COPD

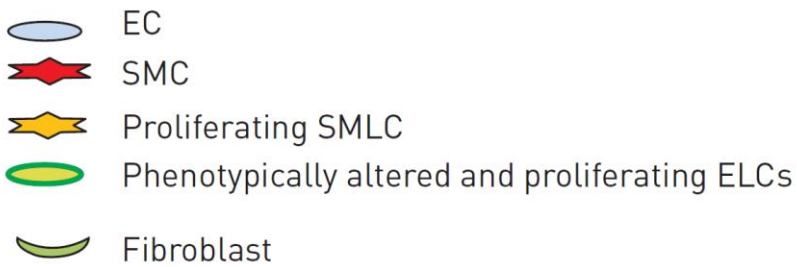


Neointimal lesion with proliferating SMLCs

IPAH



Plexiform lesion



Eur Respir Rev 2014

Epidemiology and clinical relevance of PH in IPF and other IIPs

- In IPF, mPAP ≥25 mmHg has been reported in 8–15% of patients upon initial work-up, with greater prevalence in advanced (30–50%) and end-stage (>60%) disease.

Respiration 2013; 85: 456–463
Eur Respir J 2015; 46: 1370–1377
Eur Respir J 2007; 30: 715–721.

Epidemiology and clinical relevance of PH in IPF and other IIPs

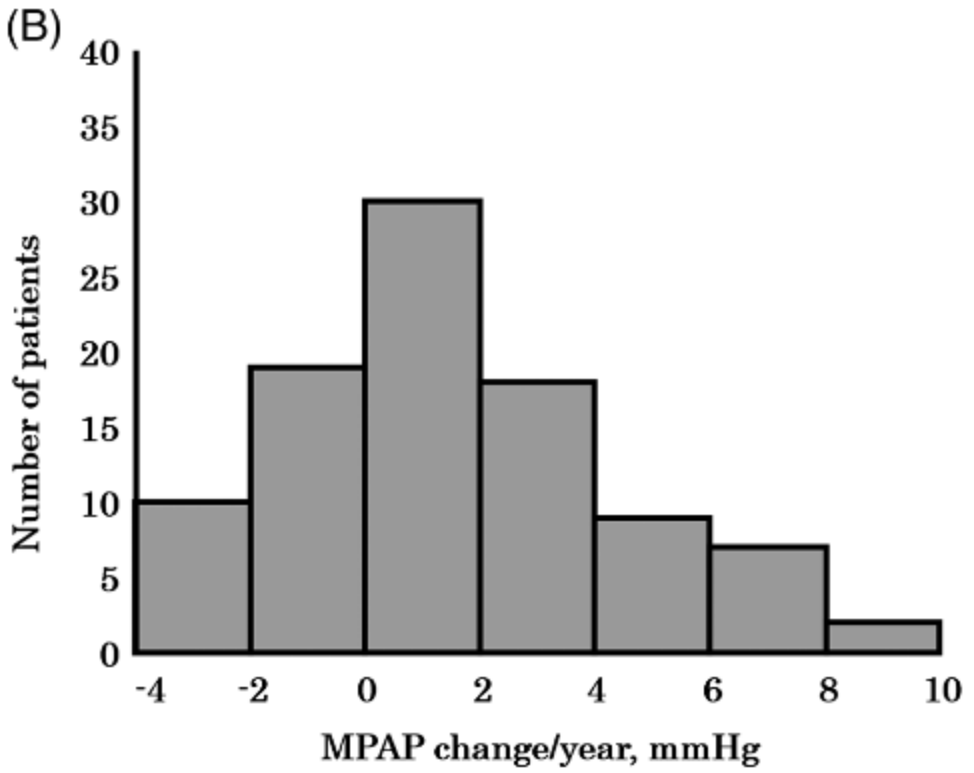
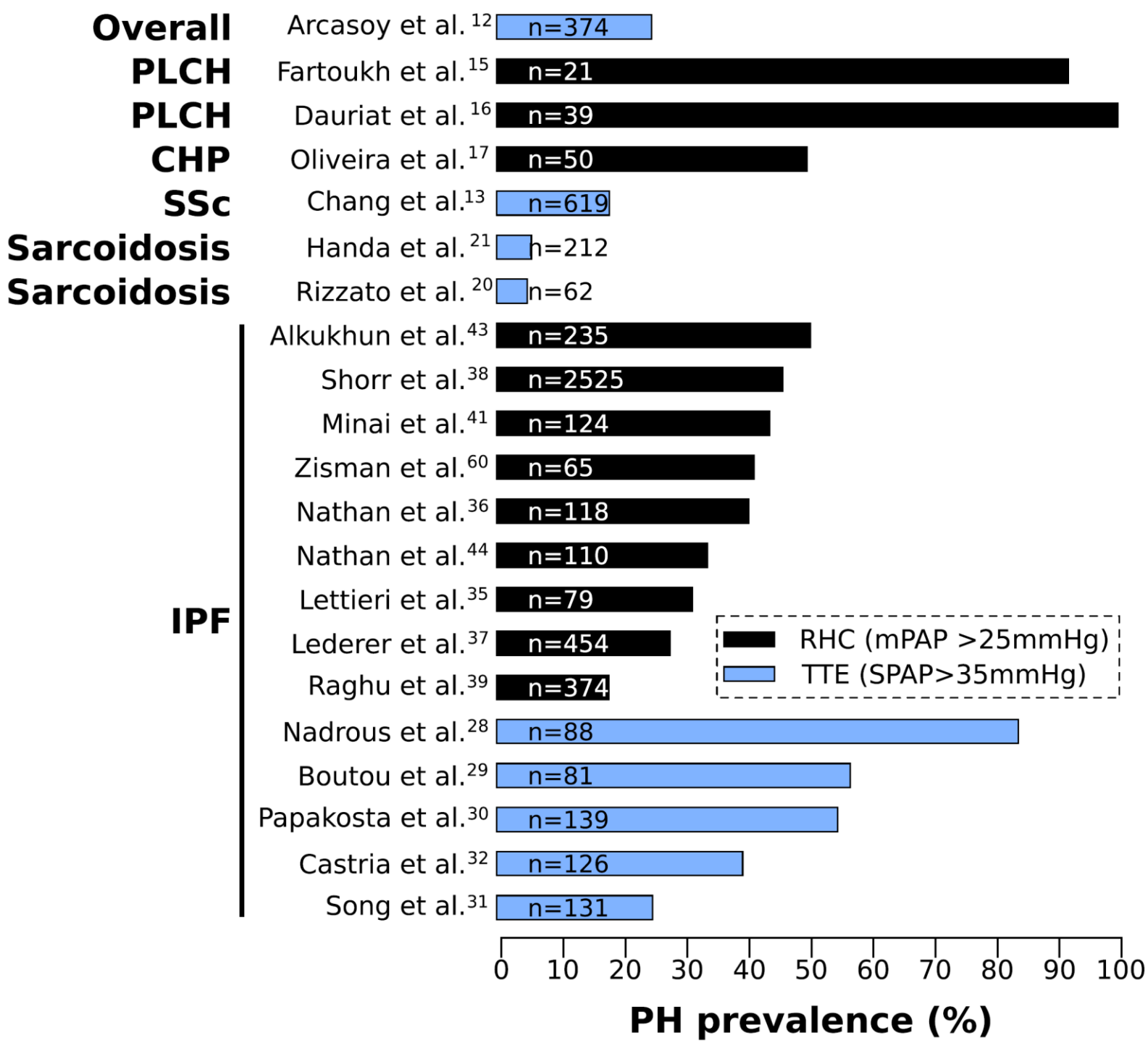


Figure 2 (A) Distribution of the mean pulmonary arterial pressure (MPAP) at baseline and at follow-up. The *P*-value was

- One longitudinal study suggested that mPAP increases by around 1.8 mmHg per year, but rapid progression of PH has also been reported in late-stage IPF patients.

Respirology 2017; 22: 986–990.


Overall
Arcasoy et al. [12]
n=374
PLCH
Fartoukh et al. [15]
n=21
PLCH
Dauriat et al. [16]
n=39
CHP
Oliveira et al. [17]
n=50
SSc
Chang et al. [13]
n=619
Sarcoidosis
Handa et al. [21]
n=212
Sarcoidosis
Rizzato et al. [20]
n=62
IPF
Alkukhun et al. [43]
n=235
Shorr et al. [38]
n=2525
Minai et al. [41]
n=124
Zisman et al. [60]
n=65
Nathan et al. [36]
n=118
Nathan et al. [44]
n=110
Lettieri et al. [35]
n=79
Lederer et al. [37]
n=454
Raghu et al. [39]
n=374
Nadrous et al. [28]
n=88
Boutou et al. [29]
n=81
Papakosta et al. [30]
n=139
Castria et al. [32]
n=126
Song et al. [31]
n=131
RHC (mPAP >25mmHg)
TTE (SPAP>35mmHg)
0
10
20
30
40
50
60
70
80
90
100
PH prevalence (%)

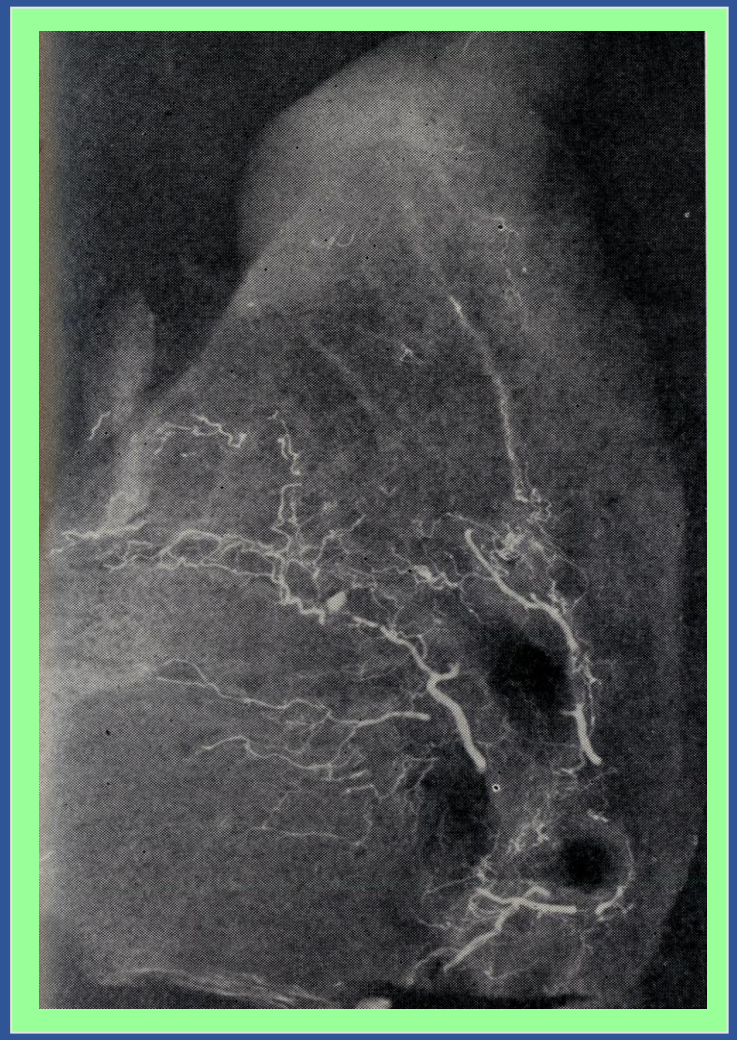
Combined pulmonary fibrosis and emphysema, and other lung diseases

- Patients with CPFE are particularly prone to develop PH, with estimates suggesting a prevalence of 30–50%.
- The PH appears to contribute to the functional limitation in CPFE and is associated with poor survival.

Eur Respir J 2010; 35: 105–111.
Chest 2009; 136: 10–15.

Angiogenesis in IPF

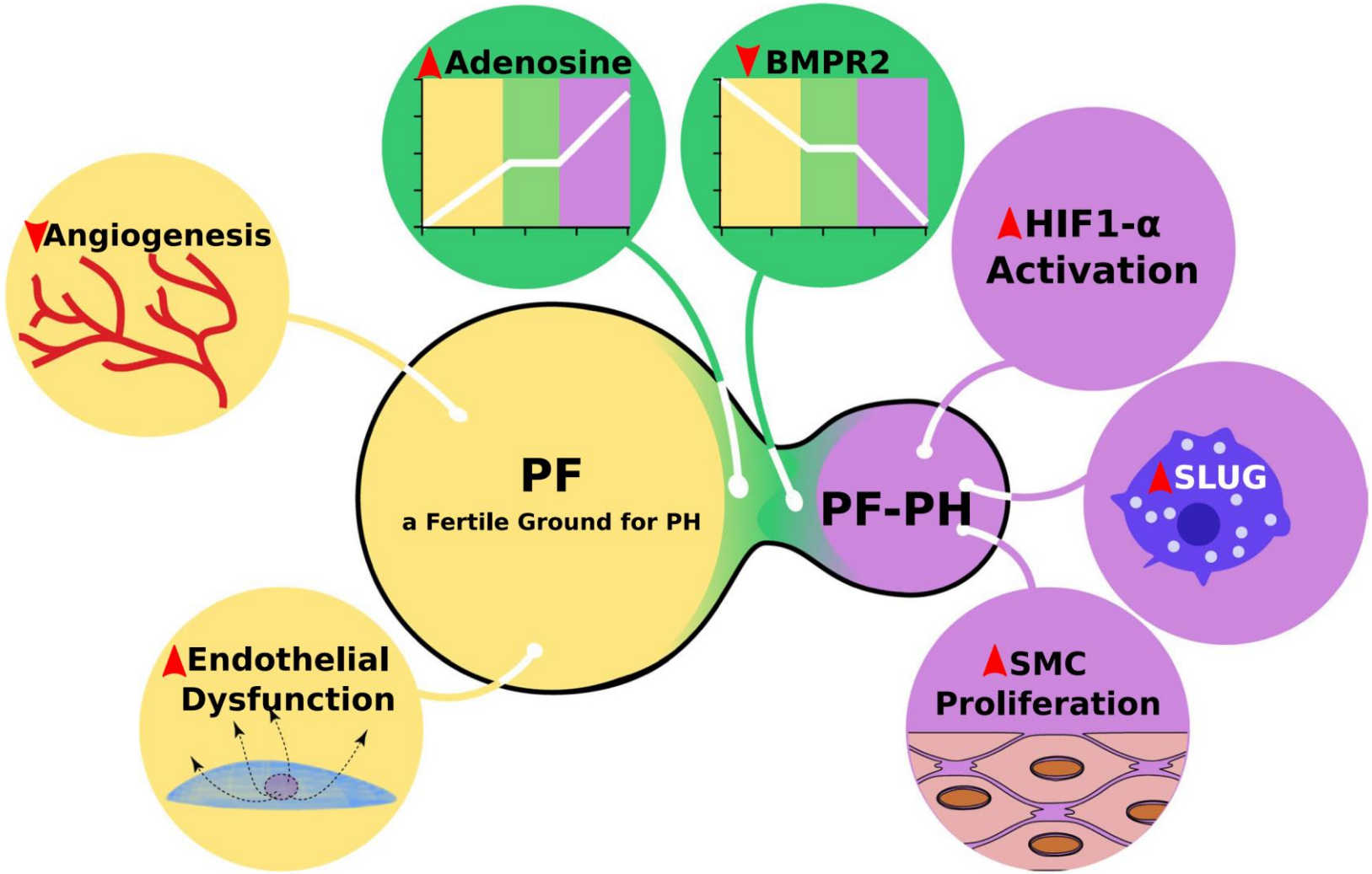
Normal



IPF patient

Turner-Warwick M

Pulmonary hypertension secondary to pulmonary fibrosis: molecular insights



Respir Res 2020

Detection of PH in CLD

Figure 1. Evaluation of pulmonary hypertension (PH) in chronic lung disease (CLD).

1) symptoms and signs (dyspnoea out of proportion, loud P2, signs of right heart failure, right axis deviation on ECG, elevated natriuretic peptide levels);

2) pulmonary function test abnormalities (low D_{LCO}(*e.g.* <40% of predicted), elevated %FVC/%D_{LCO} ratio (low K_{CO}));

3) exercise test findings (including decreased distance, decreased arterial oxygen saturation or increased Borg rating on 6-min walk test and decreased circulatory reserve, preserved ventilatory reserve on cardiopulmonary exercise testing);

4) imaging findings (extent of LD, enlarged pulmonary artery segments, increased pulmonary artery/aorta diameter ratio >1 on CT).

Nathan SD, et al. Eur Respir J 2018

Detection of PH in CLD

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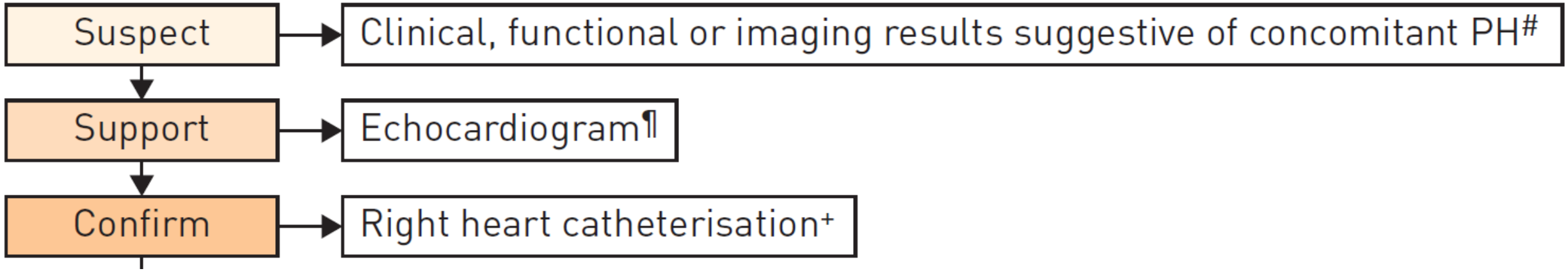


¶: signs supporting the diagnosis of PH include elevated systolic pulmonary arterial pressure and signs of right ventricular dysfunction. However, echocardiography measures are only suggestive and have limited accuracy in patients with CLD.

+: strongly consider referring the patient to a PH expert center.

Nathan SD, et al. Eur Respir J 2018

When to perform RHC

- RHC *should be performed*
  1. Significant PH is suspected
  2. Management will likely be influenced by RHC results, including referral for transplantation, inclusion in clinical trials or registries, treatment of unmasked left heart dysfunction, or compassionate use of therapy.
- RHC *may be considered* when
  1. Clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are not deemed attributable to ventilatory impairment.
  2. An accurate prognostic assessment is deemed sufficiently important.

Nathan SD, et al. Eur Respir J 2018

Measurement of Pulmonary Arterial Pressure

ORIGINAL ARTICLE
COPD AND PULMONARY VASCULAR DISEASES

Measuring central pulmonary pressures during exercise in COPD: how to cope with respiratory effects

Bart G. Boerrigter[1], Aaron B. Waxman[2], Nico Westerhof[1], Anton Vonk-Noordegraaf[1] and David M. Systrom[2]

Affiliations: [1]Dept of Pulmonary Diseases, VU University Medical Center, Amsterdam, the Netherlands. [2]Dept of Pulmonary and Critical Care Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA.

Eur Respir J 2014

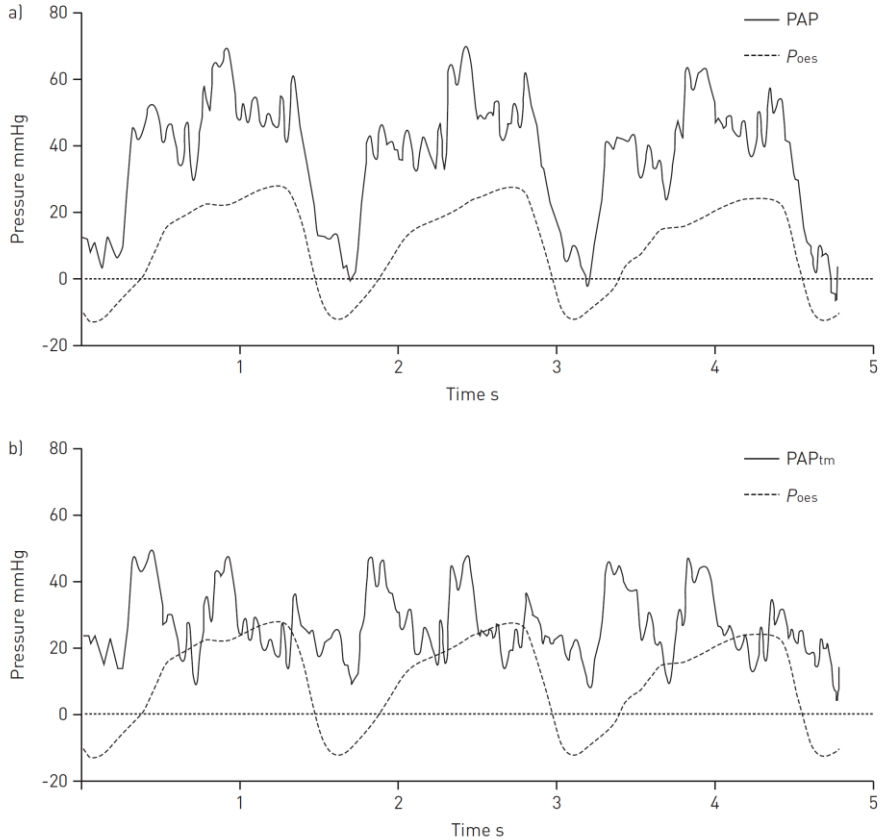
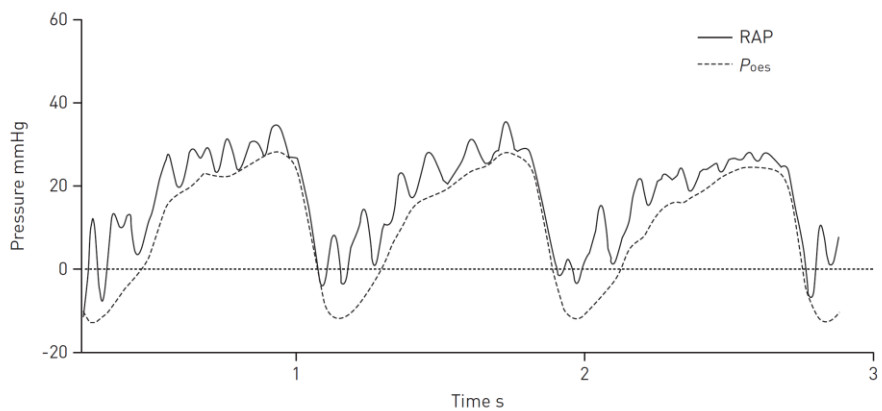


FIGURE 1 Example of pulmonary artery pressure (PAP) a) before and b) after (transmural PAP (PAP_{tm})) continuous correction for oesophageal pressure (P_{oes}) at maximal exercise in a patient with severe chronic obstructive pulmonary disease (forced expiratory volume in 1 s $\leqslant$30% predicted).



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Measuring central pulmonary pressures during exercise in COPD: how to cope with respiratory effects

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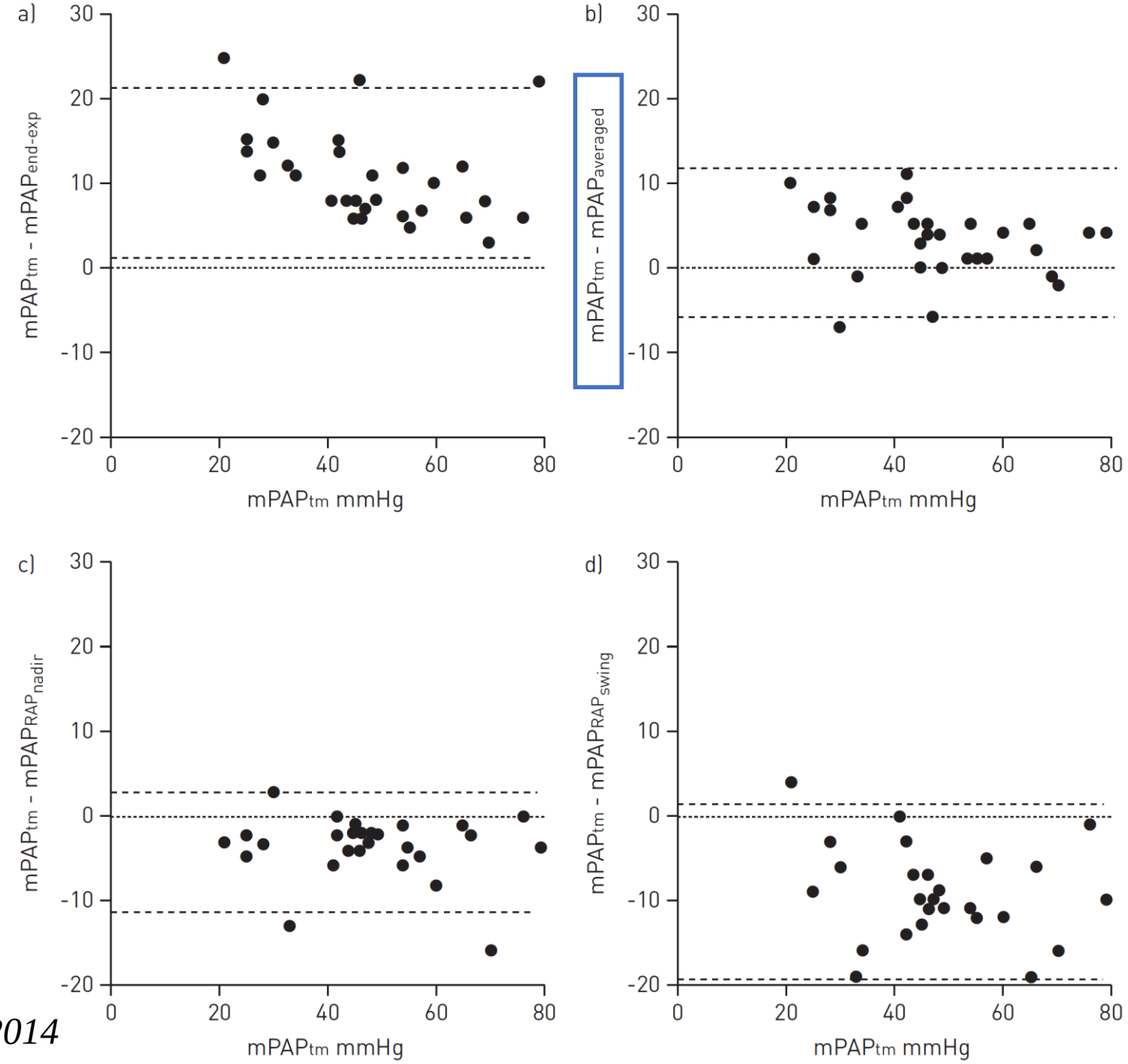
Affiliations: [1]Dept of Pulmonary Diseases, VU University Medical Center, Amsterdam, the Netherlands. [2]Dept of Pulmonary and Critical Care Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA.

- Bland–Altman analyses of the difference between mean pulmonary artery pressure (mPAP) and transmural mPAP (mPAPtm) plotted versus the mPAPtm.
- Transmural mPAP (mPAPtm) (calculated as mPAP - Poes)



Eur Respir J 2014

Pressure measurements during RHC

- As a result of exaggerated changes in intrathoracic pressures during the breathing cycle in patients with lung disease, a floating average over several breaths (without a breath hold) is suggested for measurement of mean pressures, including the pulmonary capillary wedge pressure.

Nathan SD, et al. Eur Respir J 2018

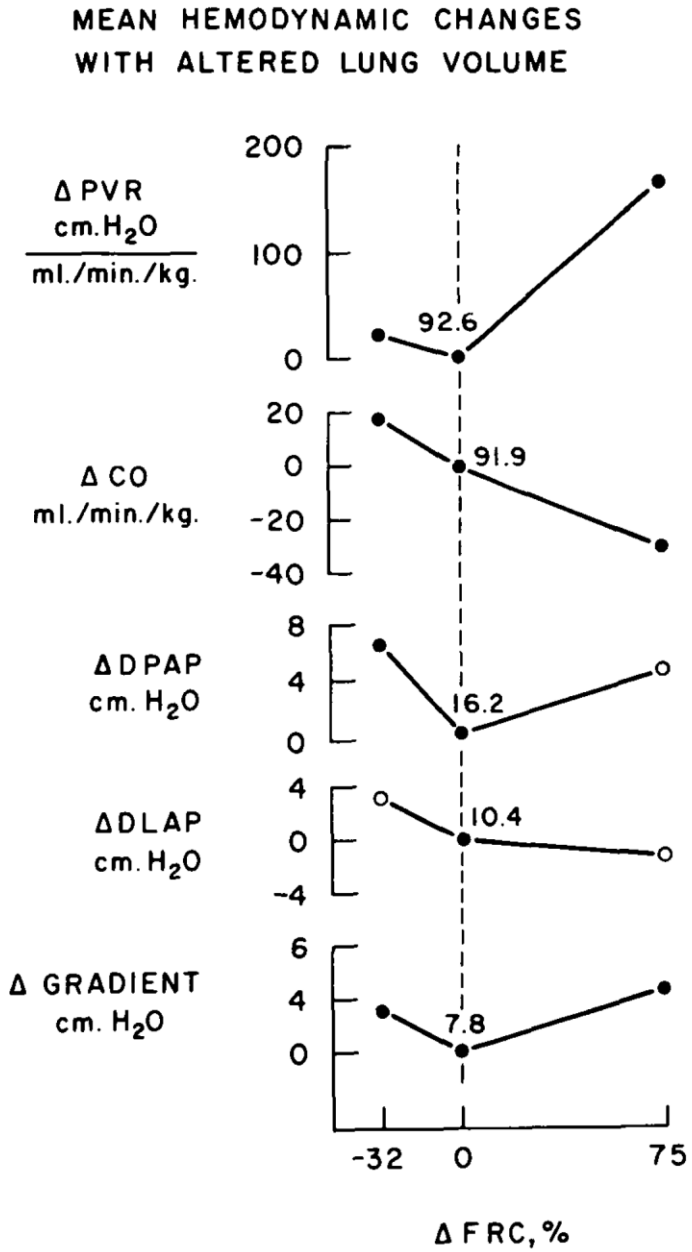


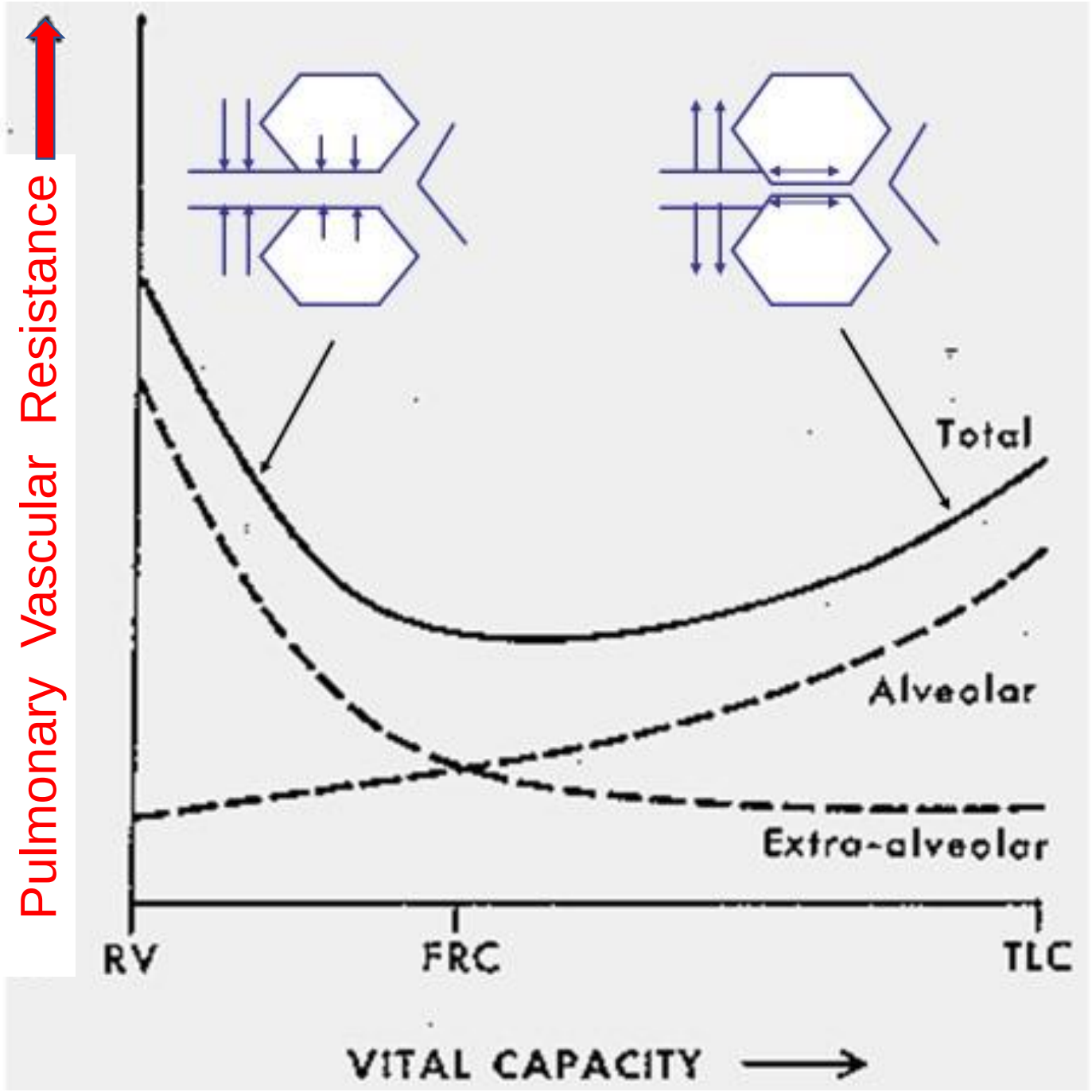
Figure 3

Summary of results. Changes (Δ) in pulmonary vascular resistance (PVR), cardiac output (CO), distending or transmural pulmonary artery pressure (DPAP), left atrial pressure (DLAP), and

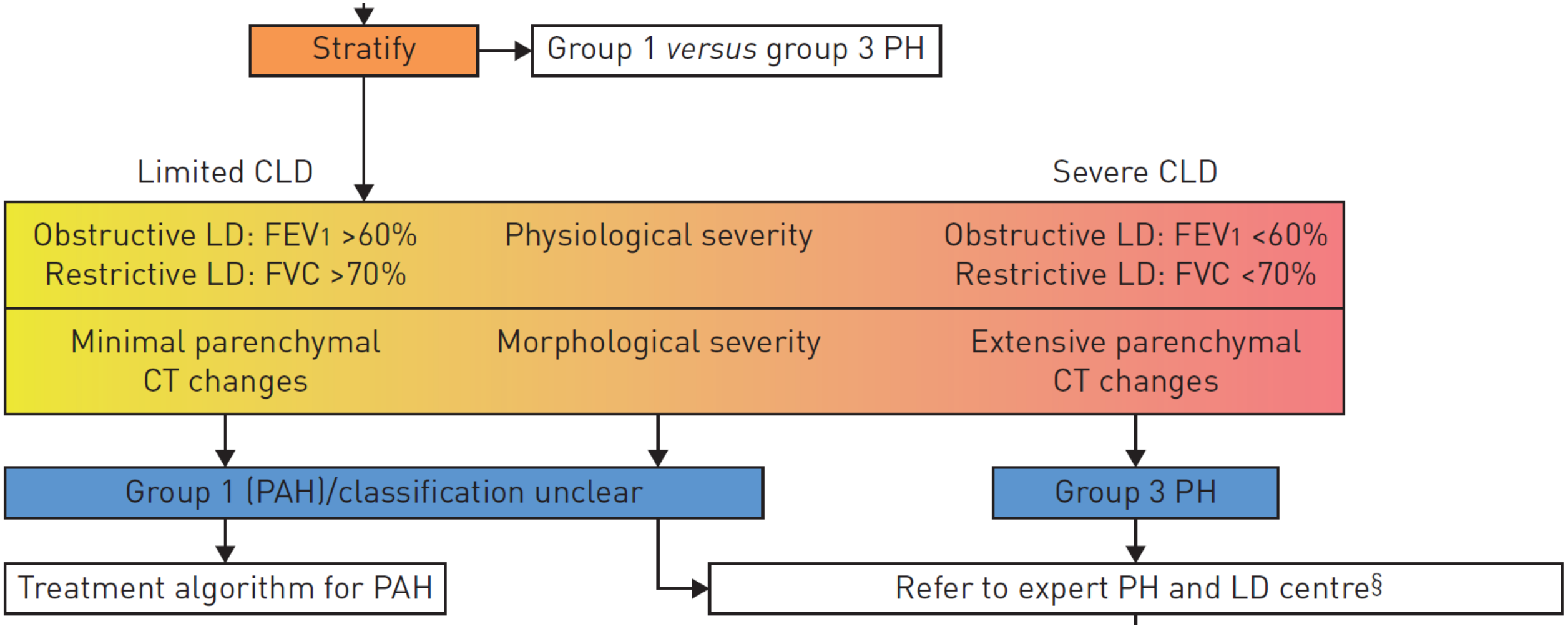
Relation Between Lung Volume and Pulmonary Vascular Resistance

By Daniel H. Simmons, M.D., Ph.D., Leonard M. Linde, M.D., Joseph H. Miller, M.D., and Ronald J. O'Reilly, M.D.

Circulation Research 1961


Pulmonary Vascular Resistance
Total
Alveolar
Extra-alveolar
RV
FRC
TLC
VITAL CAPACITY

Detection of PH in ILD



§: expert centres should comprise multidisciplinary teams.

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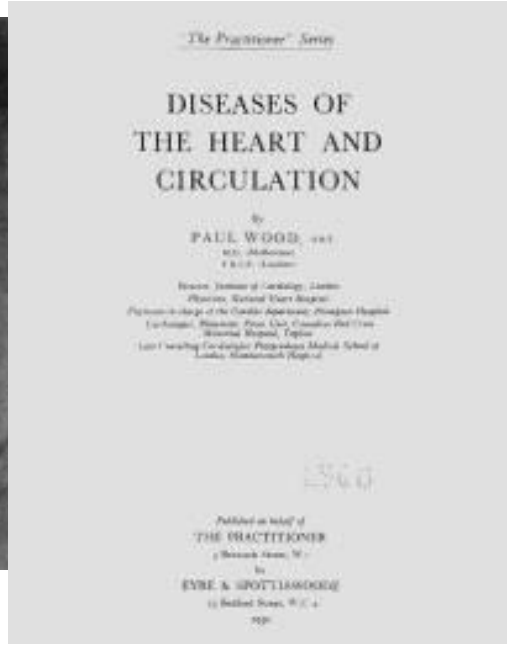
The hemodynamic definition of PH

« The normal pulmonary blood pressure in a series of 60 n ormal controls studied at the Brompton Hospital ranged fro m 8/2 to 28/14 mmHg Pulmonary hypertension is defined b y Pap >30/15, mean 20 mmHg, and the normal PVR is < 1 unit … In practice, serious PH usually means much higher Pap

A cut-off of 25 mmHg seems reasonable

PVR = (Pap – Pla)/Q

Pap = Q x PVR + Pla



Paul Wood, Br Heart J 1958; 20: 557-570

The definition for PH in the context of CLD-PH:

Definition	Characteristics	Reference
CLD without PH	• mPAP <21 mmHg or, • mPAP 21–24 mmHg with pulmonary vascular resistance (PVR) <3 Wood Units (WU).	Eur Respir J 2019; 53: 1801913 Isolated post-capillary PH (Group 2, 5)
CLD with PH	• mPAP 21–24 mmHg with PVR ≥3 WU, or • mPAP 25–34 mmHg	Eur Respir J 2019; 53: 1801913
CLD with severe PH	• mPAP ≥35 mmHg • mPAP ≥25 mmHg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$)	J Am Coll Cardiol 2013; 62: D109–D116.

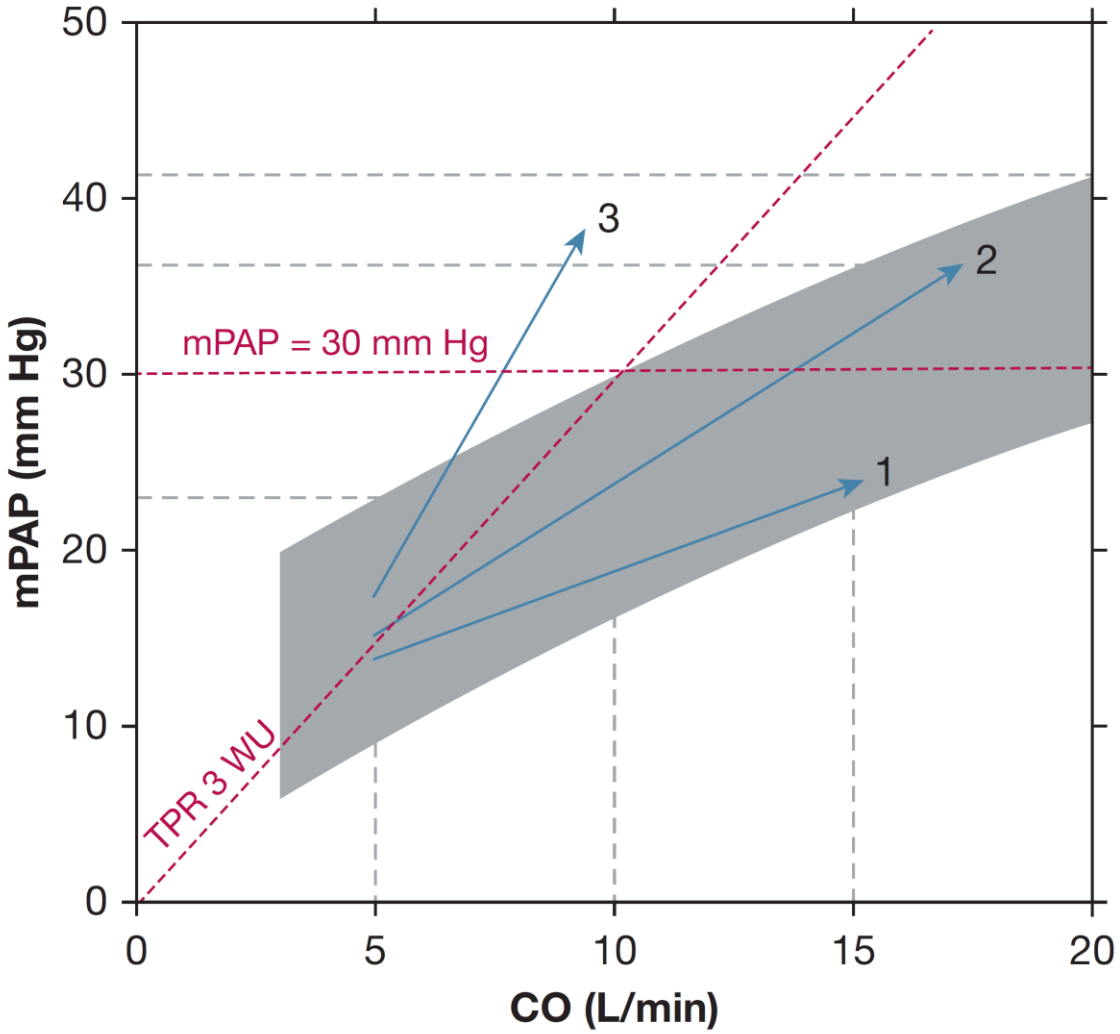
Nathan SD, et al. Eur Respir J 2018

Circulation
Volume 118, Issue 21, 18 November 2008, Pages 2183-2189
https://doi.org/10.1161/CIRCULATIONAHA.108.787101

Exercise-Induced Pulmonary Arterial Hypertension

James J. Tolle, MD; Aaron B. Waxman, MD, PhD; Teresa L. Van Horn, BA;
Paul P. Pappagianopoulos, MEd; David M. Systrom, MD

- ***Conclusions—*** Exercise-induced PAH is an early, mild, and clinically relevant phase of the PAH spectrum.



CHEST 2018; 154(1):10-15

Treatment of PH due in CLD: evidence for appropriate risk–benefit balance of PAH-targeted therapy

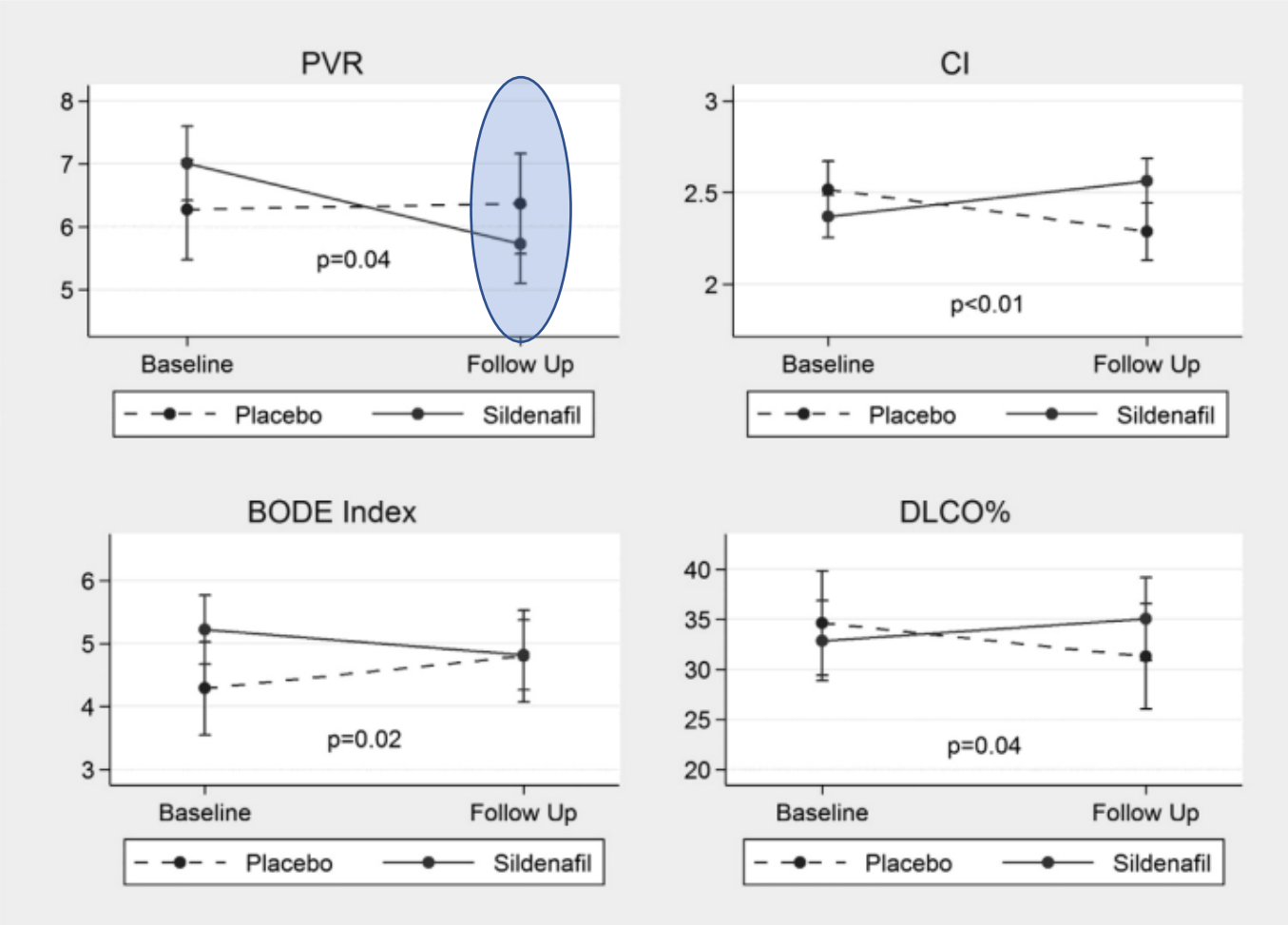
Eur Respir Rev 2017; 26: 160080.

RCT with PAH-targeted therapy in COPD

Year	Subject (n)	Inclusion	Dx of PH	Baseline hemodynamics	Baseline PFT	Therapy	Duration	Primary end point	Outcomes
2008	30	GOLD III–IV; no haemodynamic require	Echo	sPAP 32 (29–38) mmHg	Not reported	Bosentan 125 mg 2 times daily	12 wks	6MWD, no change	Worsened hypoxaemia and health-related QoL
2009	32	COPD with PH by RHC, open label	RHC	mPAP 37±5 mmHg	FEV1 37±18%	Bosentan 125 mg 2 times daily	18 months	No defined primary	mPAP, PVR, BODE index and 6MWD improved
2014	120	COPD with PH by echo	Echo: pulmonary acceleration time <120 ms or sPAP >30 mmHg	Echo: sPAP 42±10 mmHg	FEV1 41±16%	Tadalafil 10 mg daily	12 weeks	6MWD, no change	Decreased sPAP; no difference in QoL, BNP or SaO2
2016	28	COPD with PH by RHC	RHC: mPAP >35 mmHg (if FEV1 <30%), mPAP ⩾30 mmHg (if FEV1 ⩾30%)	mPAP 39±8 mmHg, CI 2.4±0.5 L·min−1·m−2, PVR 7±2.6 WU	FEV1 54±22%, DLCO 33±12%	Sildenafil 20 mg 3 times daily	16 weeks	PVR, decreased 1.4 WU	Improved CI, BODE scores and QoL; no effect on gas exchange

COPD: Effect on pulmonary hemodynamics

Sildenafil Treatment for Severe PH in COPD



- Beneficial hemodynamic effects with long-term PAH therapy, assessed by RHC, have been demonstrated with both sildenafil and bosentan.

J Heart Lung Transplant 2017; 36: 166–174

COPD: Effect on pulmonary hemodynamics

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

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

Ther Adv Respir Dis 2009; 3: 15–21.

COPD: Effect on exercise tolerance, symptoms and quality of life

- The effect of PAH-targeted therapy on exercise capacity and QoL in patients with COPD-PH is less apparent.
- Two meta-analyses failed to show significant improvement in 6-min walk distance (6MWD), whereas a third reported an improvement in 6MWD in COPD patients with demonstrated PH

J Thorac Dis 2015; 7: 309–319.
Pulm Circ 2017; 7: 145–155.
J Korean Med Sci 2013; 28: 1200–1206.

COPD Summary

- Mild-to-moderate pulmonary hypertension is a common in COPD
  - PH is associated with increased risks of exacerbation and decreased survival in COPD.
- Sildenafil may improve hemodynamics and exercise capacity in severe COPD-PH
- Current data may not support therapy with bosentan in COPD-PH patients
- COPD-PH should be evaluated in randomized clinical trials

RCT with PAH-targeted therapy in IPF

Year	Subject (n)	Inclusion	Dx of PH	Baseline hemodynamics	Baseline PFT	Therapy	Duration	Primary end point	Outcomes
2013	119	IPF with Echo	Echo: RVSD	N/A	FVC 57% DLCO 26%	Sildenafil 20mg tid	12 wks	6MWT, less decline RVSD	Improve QOL in RVSD patients
2014	60	IPF or idiopathic fibrotic NSIP	RHC: mPAP ≥ 25 mmHg	mPAP 37±9.9 mmHg, CI 2.2±0.5	FVC 55.7±20%, KCO 45±22%	Bosentan	16 wks	20% PVRI ↓, negative	Secondary end-points all (-)
2015	68	IPF with group 2 PH (14% of cohort)	RHC	mPAP 30±8 mmHg	FVC 67±12%, DLCO 39±15%	Ambrisentan 10 mg QD	Event-driven, terminated early	Disease progression, Unfavourable trend	More hospitalized ambrisentan arm
2019	147	IIP, FVC >45%, mPAP >25 mmHg	RHC	mPAP 33.2±8.2 mmHg, CI 2.6±0.7	FVC 76.3±19%, DLCO 32±12%	Riociguat 2.5 mg tid	26 weeks, study stopped early	6MWD, no difference at study halt	Riociguat arm (death ↑ and Hospitalisation ↑)

Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study

Steven D Nathan, Jürgen Behr, Harold R Collard, Vincent Cottin, Marius M Hoeper, Fernando J Martinez, Tamera J Corte, Anne M Keogh, Hanno Leuchte, Nesrin Mogulkoc, Silvia Ulrich, Wim A Wuyts, Zhen Yao, Francis Boateng, Athol U Wells*

- Diagnosed with a major idiopathic interstitial pneumonias
- **Major Inclusion criteria**
  - FVC ≥45%
  - 6MWD ≥150 m and ≤450 m
  - PH confirmed by RHC with mPAP ≥25 mmHg and PCWP ≤15 mmHg at rest
  - Systolic blood pressure ≥95 mmHg and no signs or symptoms of hypotension
  - WHO functional class II-IV disease
- **Major Exclusion criteria**
  - Known significant left heart disease: Symptomatic coronary artery disease or LVEF <45%
  - Active state of hemoptysis or pulmonary hemorrhage
  - Difference >15% between the eligibility and the baseline 6MWD
  - FEV_1/FVC <0.65 after bronchodilator administration
  - Approved IPF drug initiated within 3 months prior to screening

	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%)

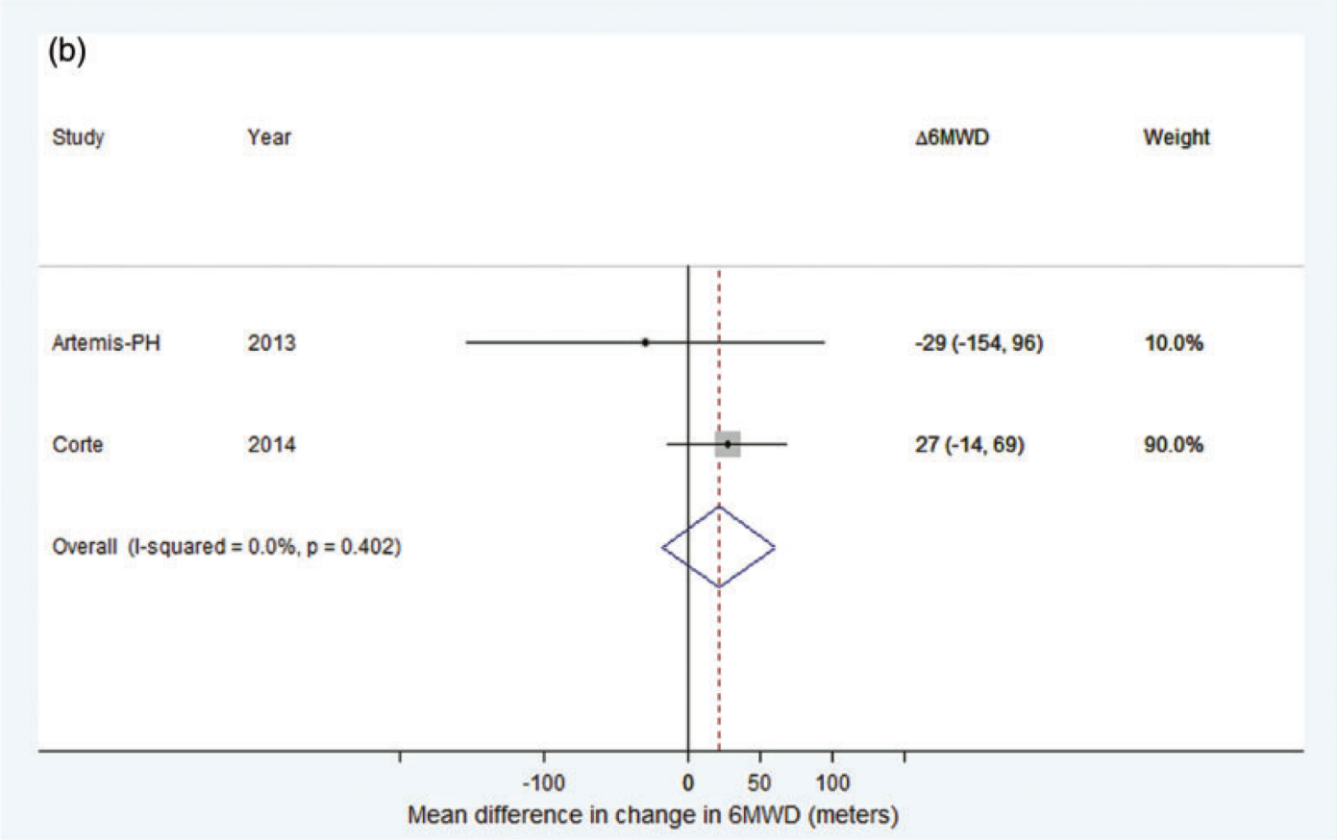
Data are n (%). AE=adverse event. SAE=serious adverse event. *Both groups received riociguat up to 2·5 mg three times daily. †At study termination, all patients discontinued riociguat and immediately started the safety follow-up phase. The length of the safety follow-up ranged from 30 to 120 days.

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

Lancet Res Med 2019;7:780-790

ILD-PH: **Effect on exercise tolerance**

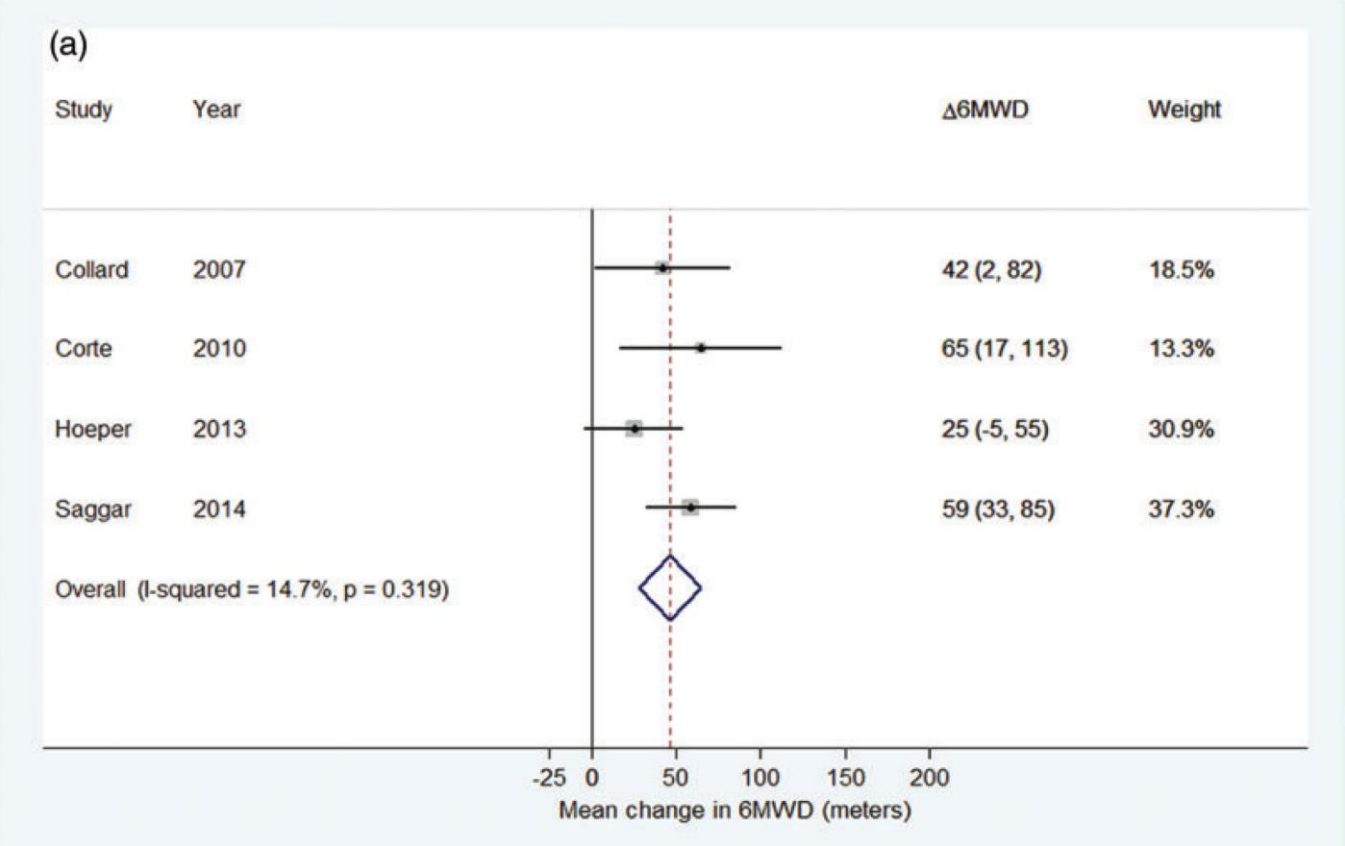
Chronic use of PAH-specific therapy in World Health Organization Group III Pulmonary Hypertension: a systematic review and meta-analysis



- Difference in 6MWD comparing placebo to PAH specific therapy from two randomized controlled studies. There was not a significant difference in 6MWD (21.6 m; 95% CI, –17.8 – 61.0).

Pulmonary Circulation 2017; 7(1) 145–155

ILD-PH: **Effect on exercise tolerance**



- In contrast, open-label studies with sildenafil, riociguat and treprostinil did show significant improvements in 6MWD, with an average increase of 46 m over baseline.

Pulmonary Circulation 2017; 7(1) 145–155

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*

- The STEP-IPF study, which was enriched for underlying IPF-PH by the inclusion of patients with DLCO <35% of predicted.

N Engl J Med 2010

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)
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
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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

	Parameter	Results	p-Value
Primary Endpoint	Proportion of patients with ≥ 20% increase in 6 mwt	10% (Sildenafil) vs 7% (Place bo)	0.39
Secondary endpoints	Arterial oxygen saturation	Δ+1.22 favoring sildenafil	0.05
	DLCO (% pred value)	Δ+1.55 favoring sildenafil	0.04
	Shortness of breath questionnaire	Δ-5.68 favoring sildenafil	0.006
	QoL (St. George Resp Questionnaire)	Δ-4.08 favoring sildenafil	0.01
	Death and acute exacerbations	No significant difference	n.s.

Sildenafil 20mg tid for 12 weeks

ILD-PH: **Effect on exercise tolerance**

- The largest observational study to date of severe IIP-PH patients (n=151) found that the improvement in 6MWD at 6 months in response to PAH therapy was equivalent to that seen in IPAH patients.

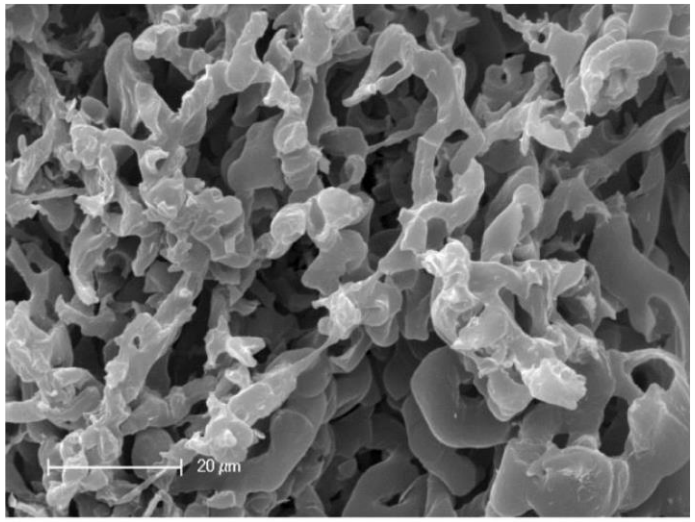
Table 3. Changes in 6 min walking distance (6MWD) from baseline to the first follow-up visit in patients with idiopathic pulmonary arterial hypertension (IPAH) and patients with pulmonary hypertension associated with idiopathic interstitial pneumonia (PH-IIP).

	Total	IPAH	PH-IIP	p
6MWD improvement ≥20 m	58.8%	59.5%	54.2%	0.530
6MWD improvement ≥30 m	52.7%	53.8%	45.8%	0.353
6MWD improvement ≥40 m	44.5%	45.9%	35.4%	0.213
6MWD improvement ≥50 m	35.7%	36.4%	31.3%	0.522
Worsening in 6MWD	26.6%	26.3%	29.2%	0.726
No change in 6MWD (change 0–19 m)	14.6%	14.2%	16.6%	0.661

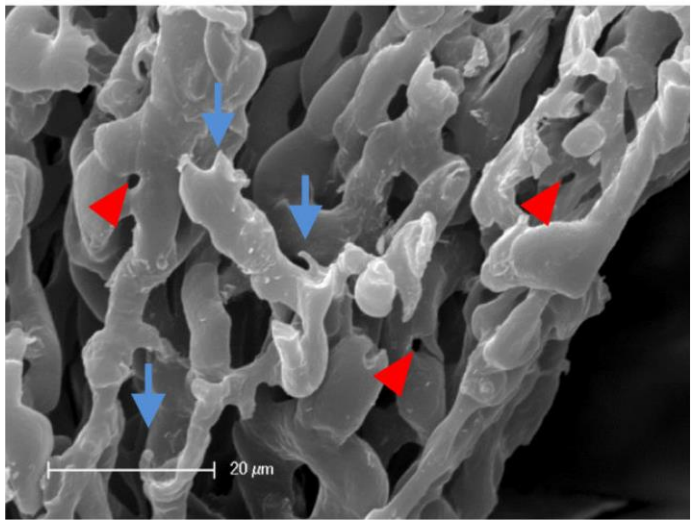
PLoS One 2015; 10: e0141911.

Nintedanib and vasculature experiment

Bleomycin



Bleomycin + Nintedanib



Angiogenesis. 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nintedanib + Sildenafil (N=137)	Nintedanib + Placebo (N=136)
Age — yr	70.3±8.6	70.0±7.9
Male sex — no. (%)	110 (80.3)	106 (77.9)
Weight — kg	73.7±17.7	74.2±15.5
Time since diagnosis of IPF — yr	2.2±1.9	2.1±1.8
Emphysema — no. (%)†	51 (37.2)	45 (33.1)
Nintedanib treatment status — no. (%)		
Not previously treated	76 (55.5)	87 (64.0)
Currently treated	56 (40.9)	46 (33.8)
Previously treated	5 (3.6)	3 (2.2)
Any echocardiographic sign indicative of right heart dysfunction — no. (%)	61 (44.5)	56 (41.2)
FVC		

CONCLUSIONS

In patients with IPF and a $D_{L_{CO}}$ of 35% or less of the predicted value, nintedanib plus sildenafil did not provide a significant benefit as compared with nintedanib alone. No new safety signals were identified with either treatment regimen in this population of patients. (Funded by Boehringer Ingelheim; INSTAGE ClinicalTrials.gov number, NCT02802345.)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nintedanib + Sildenafil (N=137)	Nintedanib + Placebo (N=136)
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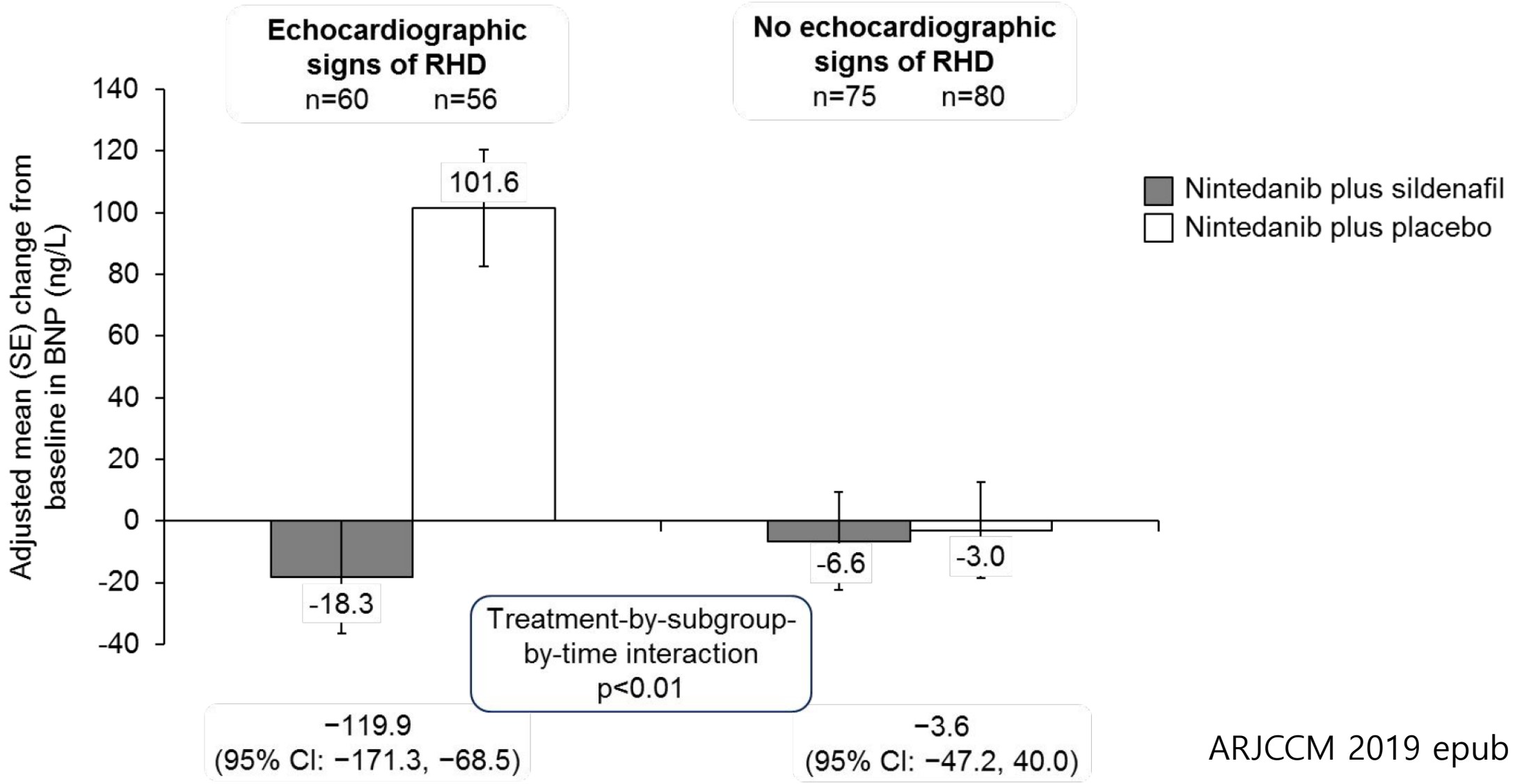
Time since diagnosis of IPF — yr	2.2±1.9	2.1±1.8
Emphysema — no. (%)†	51 (37.2)	45 (33.1)
Nintedanib treatment status — no. (%)		
Any echocardiographic sign indicative of right heart dysfunction — no. (%)	61 (44.5)	56 (41.2)
FVC		
Mean — ml	2246±749	2181±786
Percentage of predicted value	67.9±19.3	66.1±18.7
FEV_1:FVC	0.82±0.08	0.84±0.08
D_{LCO} — % of predicted value‡	25.8±6.8	25.6±7.0
SGRQ total score§	56.7±18.5	54.0±17.9
UCSD-SOBQ score¶	60.3±26.1	56.5±25.2
EQ-5D VAS score‖	55.8±17.9	60.0±17.8

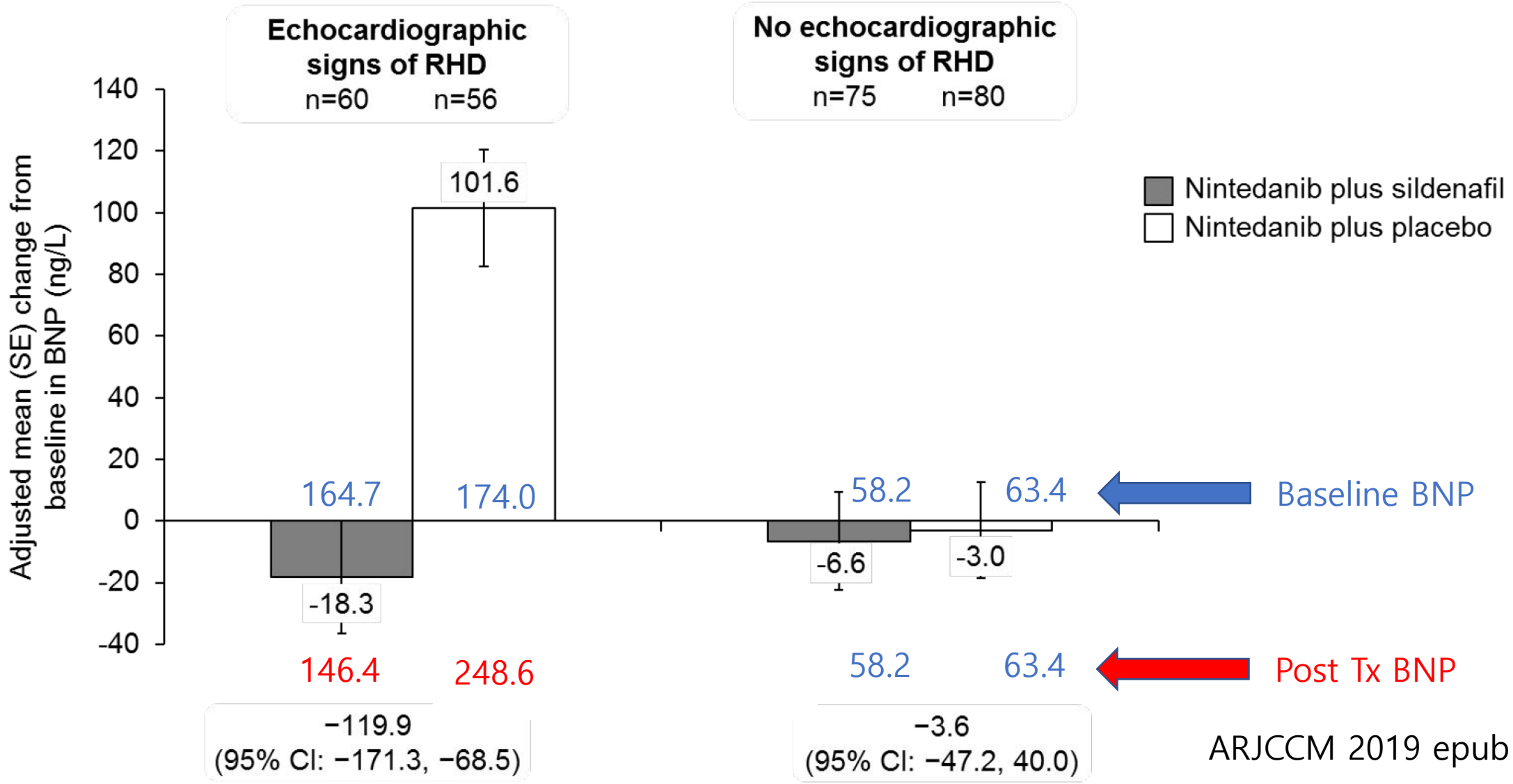
Any echocardiographic sign indicative of right heart dysfunction — no. (%) 61 (44.5) 56 (41.2)

Figure 3. Changes from baseline in BNP at week 24 by presence/absence of echocardiographic signs of RHD at baseline



ARJCCM 2019 epub

Figure 3. Changes from baseline in BNP at week 24 by presence/absence of echocardiographic signs of RHD at baseline



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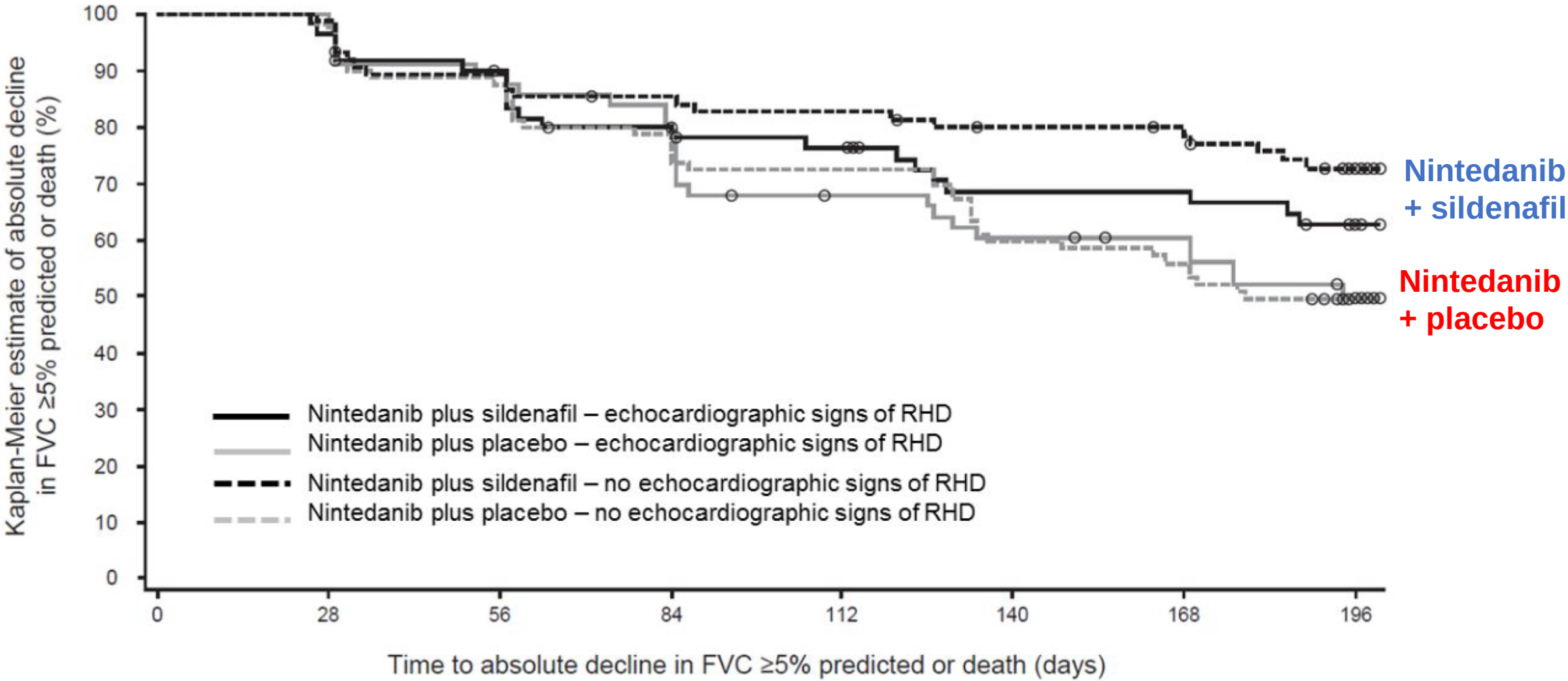

Kaplan-Meier estimate of absolute decline in FVC ≥5% predicted or death (%)
100
90
80
70
60
50
40
30
20
10
0
0
28
56
84
112
140
168
196
Time to absolute decline in FVC ≥5% predicted or death (days)
Nintedanib plus sildenafil – echocardiographic signs of RHD
Nintedanib plus placebo – echocardiographic signs of RHD
Nintedanib plus sildenafil – no echocardiographic signs of RHD
Nintedanib plus placebo – no echocardiographic signs of RHD
Nintedanib + sildenafil
Nintedanib + placebo

ARJCCM 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

This article was published on January 13, 2021, at NEJM.org.

N Engl J Med 2021;384:325-34.
DOI: 10.1056/NEJMoa2008470

Phase 3, multicenter, randomized (1:1), double-blind, placebo-controlled, 16-week, parallel-group (inhaled treprostinil / placebo) study

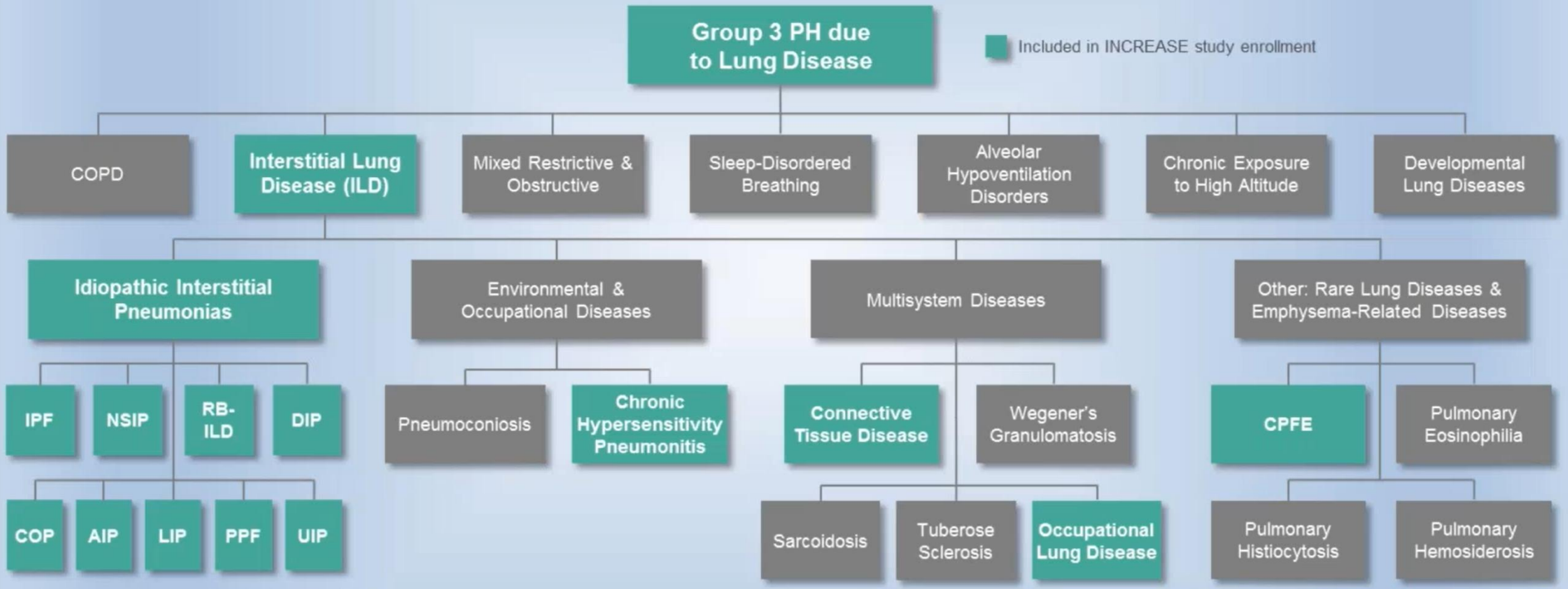
Key Inclusion Criteria

- Confirmed diagnosis of Group 3 PH based on CT within 6 months prior to randomization and demonstrated evidence of diffuse parenchymal lung disease; subjects had any form of ILD or CPFE
- Right heart catheterization within 1 year prior to randomization with the following documented parameters:
  - **PVR >3 WU and**
  - **PCWP ≤15 mmHg and**
  - **mPAP ≥25 mmHg**
- Baseline 6MWD ≥100 m
- Subjects on a chronic medication for underlying lung disease (i.e., pirfenidone, nintedanib, etc.) were on a stable and optimized dose for ≥30 days prior to randomization
- Subjects with Group 3 connective tissue disease had a Baseline forced vital capacity <70%

Key Exclusion Criteria

- Diagnosis of PAH or PH for reasons other than Group 3 PH-ILD
- Use of any PAH-approved therapy, including: prostacyclin therapy, IP receptor agonist, endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, or soluble guanylate cyclase stimulator within 60 days of randomization (or during the study)
- Evidence of clinically significant left-sided heart disease as defined by:
  - **PCWP >15 mmHg**
  - **Left ventricular ejection fraction <40%**
- Receiving >10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline
- Initiation of pulmonary rehabilitation within 12 weeks prior to randomization
- Acute pulmonary embolism within 90 days of randomization

INCREASE Eligible Study Population

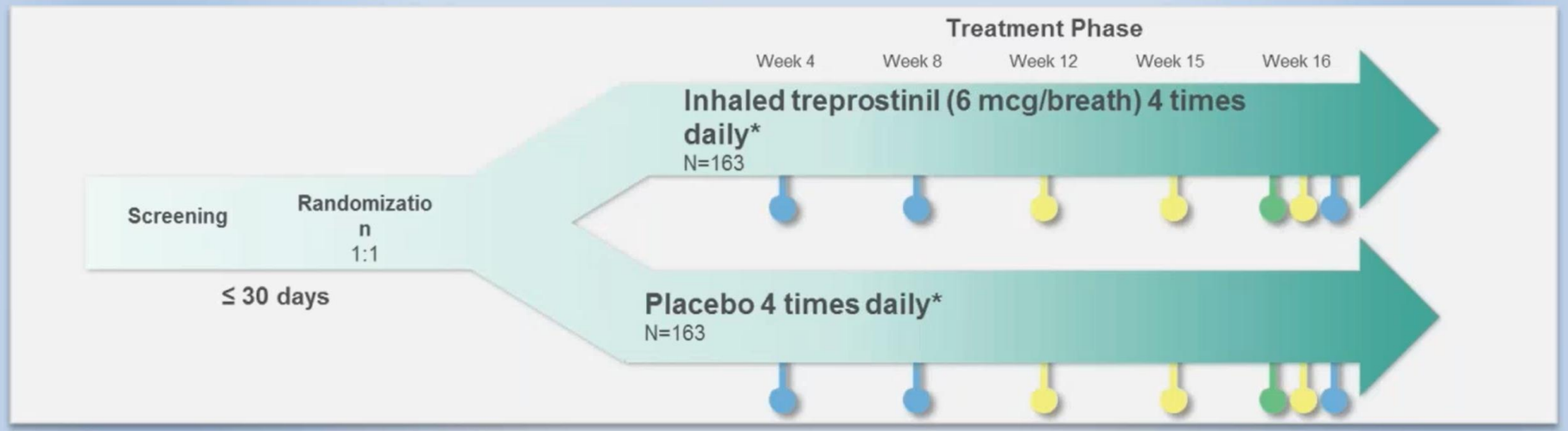


AIP: Acute interstitial pneumonitis; COP: Cryptogenic organizing pneumonia; CPFE: Combined pulmonary fibrosis and emphysema; DIP: Desquamative interstitial pneumonia; IPF: Idiopathic Pulmonary Fibrosis; LIP: Lymphoid Interstitial pneumonia; NSIP: Nonspecific interstitial pneumonia; PPF: Pleuroparenchymal fibroelastosis; RB-ILD: Respiratory bronchiolitis-associated interstitial lung disease; UIP: Unclassifiable interstitial pneumonia.

1. Simonneau G, et al. J Am Coll Cardiol. 2013;62(25):D34-41. 2. Bourke SJ. Postgrad Med J. 2006;82:494-499. 3. "Interstitial Lung Disease" www.erswhitebook.com – accessed December 2015.

INCREASE – Study Procedures

Timeline of Study Endpoint Assessments



* All subjects initiated study drug at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours). Dose escalations (additional 1 breath 4 times daily) could occur up to every 3 days, with a target dose of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, as clinically tolerated.

- Primary endpoint measure - 6MWD at peak exposure from Baseline to Week 16
- Secondary endpoint measures - Change in peak 6MWD Baseline to Week 12; Change in plasma concentration NT-proBNP Baseline to Week 16; Change in trough 6MWD from Baseline to Week 15.
- Exploratory endpoint measures

6MWD: six-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide.

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)

Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16

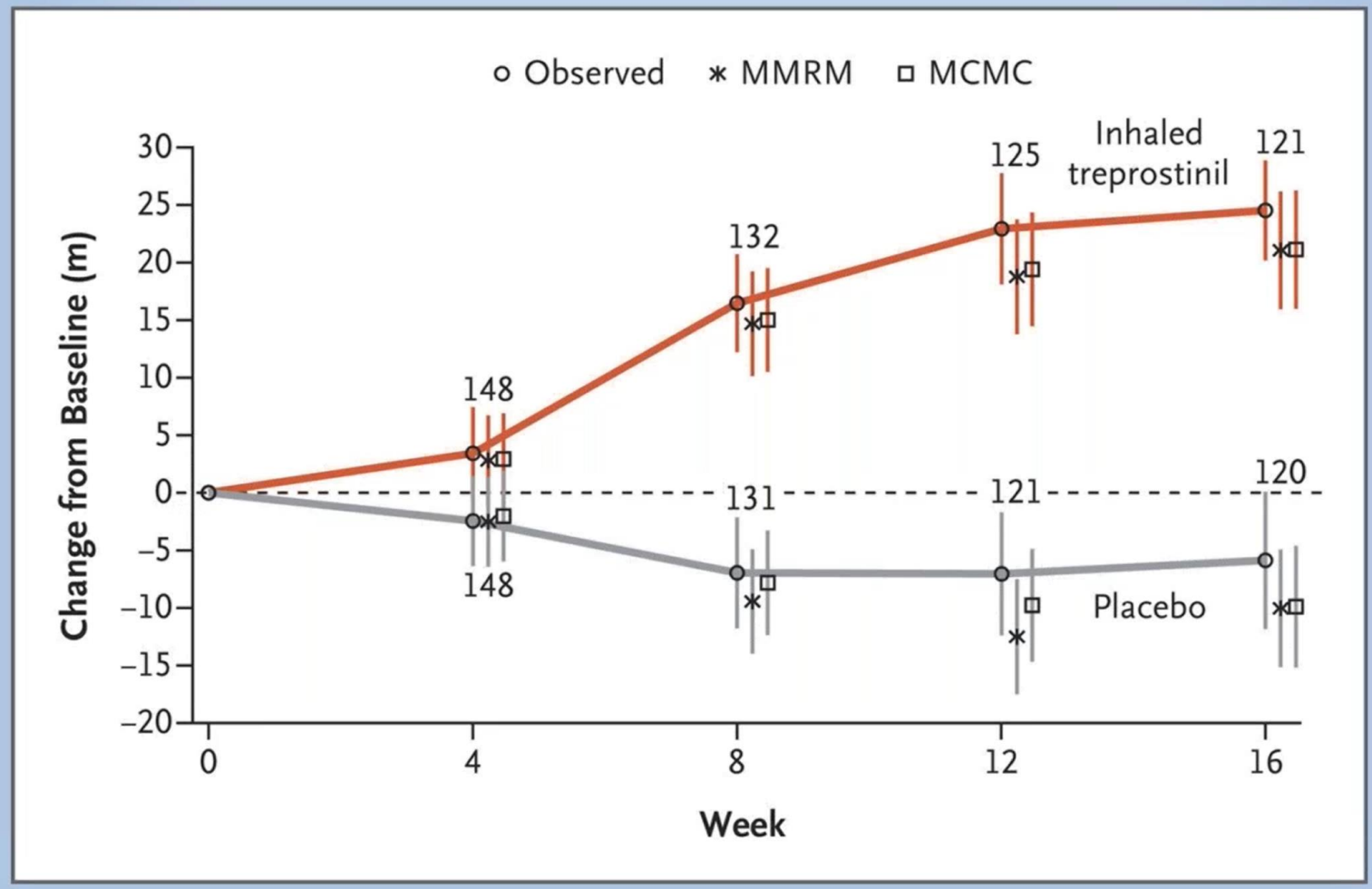


Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

ILD-PH Summary

- Precapillary PH is common in IPF
- Usually mild-to-moderate severity PH (mean PAP 25-35 mmHg), with preserved right ventricular function
- When present, PH is associated with greater mortality and worse clinical course
- The current guideline suggests riociguat and ambrisentan are contraindicated in ILD-PH
- Nintedanib and Sildenafil therapy may stabilize BNP in IPF patients with RHD.
- Severe PH (mPAP ≥ 35 mmHg) may be found in a minority of patients, with similarities with idiopathic PAH; this subgroup therapy used in PAH should be evaluated in randomized clinical trials
- Current data does support therapy with inhaled Treprostinil in ILD-PAH including CPFE patients.

Conclusion: Diagnosis

- CLD-PH
  - IPF with FVC <70% of predicted,
  - COPD with FEV1 <60% of predicted
  - Accompanying less severe PH (mPAP 20–24 mmHg with PVR ⩾3 WU, or mPAP 25–34 mmHg), these groups represent the majority of patients presenting with CLD-PH.

Conclusion: Treatment

- Treatment in sildenafil was well tolerated CLD-PH
- Sildenafil may have clinically meaningful outcomes including improvements in NT-proBNP, hemodynamic, and exercise capacity in some subgroup of CLD-PH
- Treatment with inhaled treprostinil was well tolerated
- Inhaled treprostinil improves 6MWT in ILD-PH
- Inhaled treprostinil support and additional treatment avenue in ILD-PH

경청해 주셔서 감사합니다

Q&A