PAH targeted therapy in PH-ILD: Con

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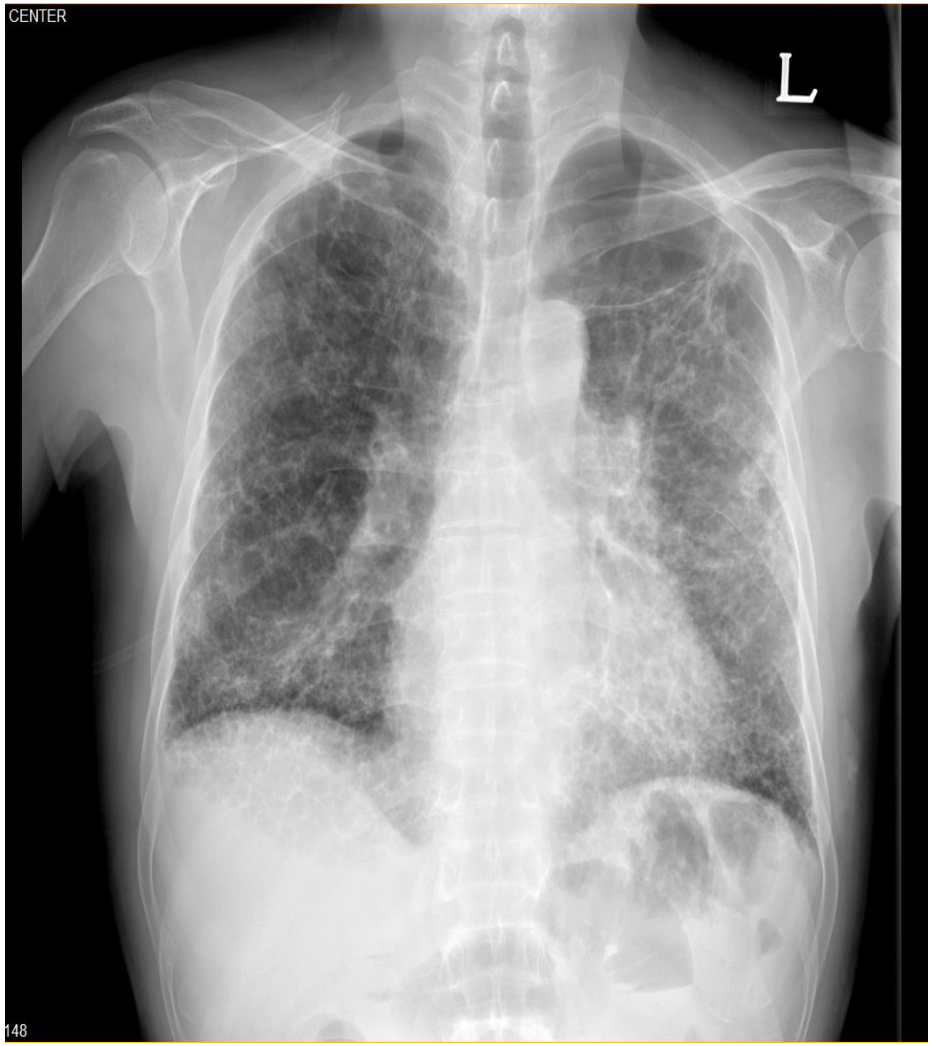
63/M patients with CPFE

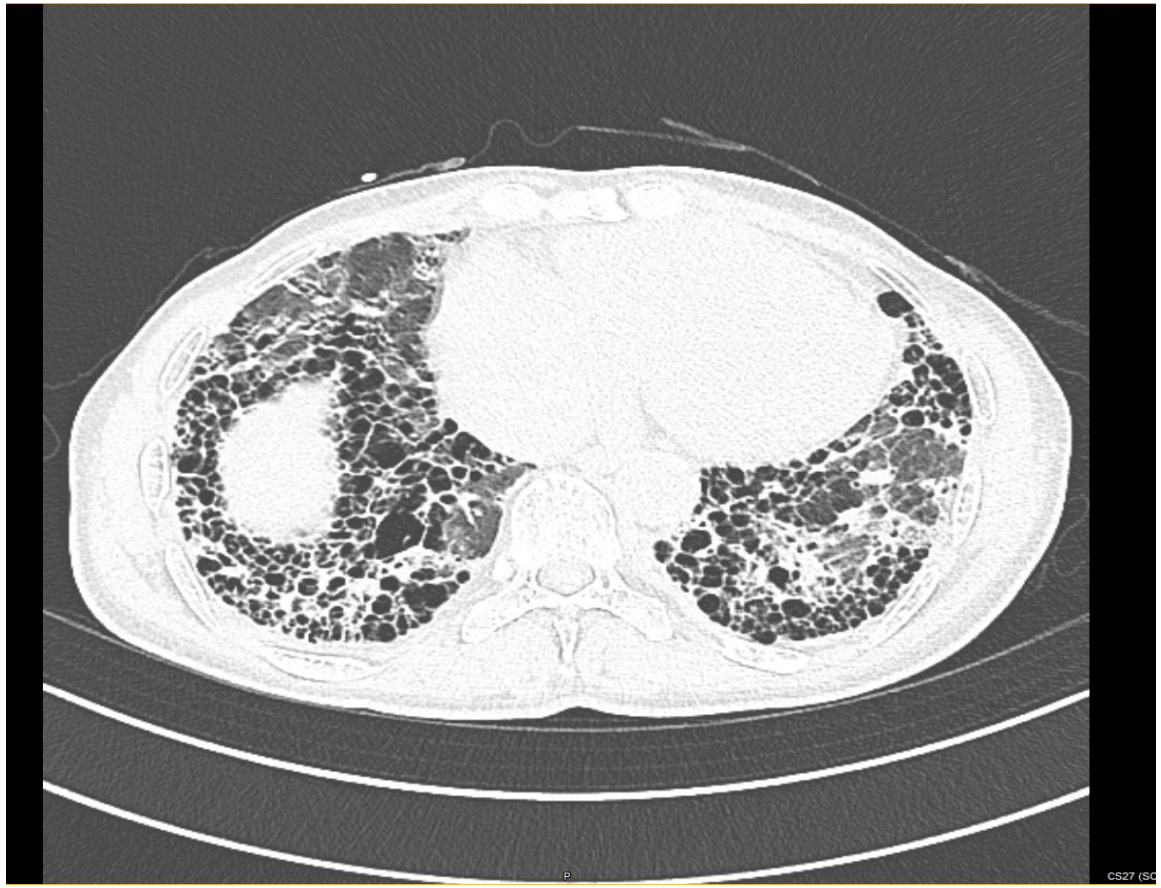


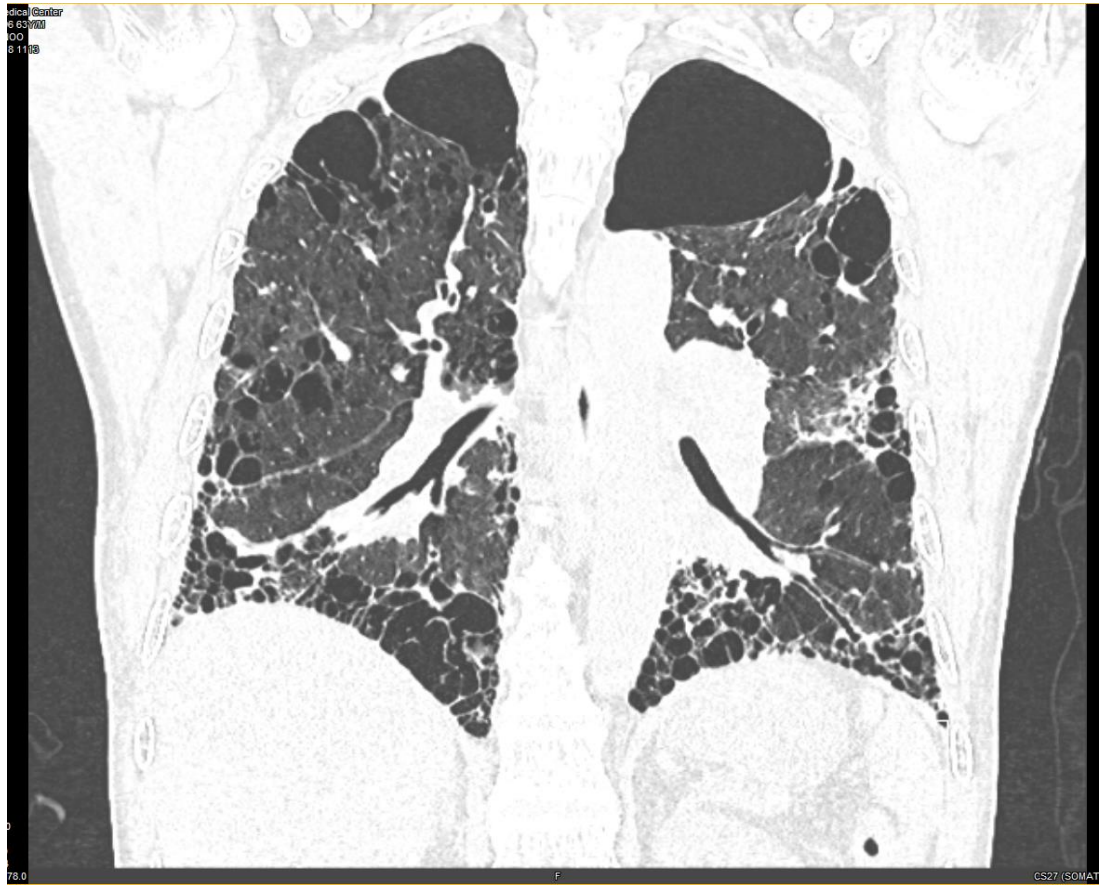
FVC	52% pred.
DLco	25% pred.

6MWT 168m (95- 82%)

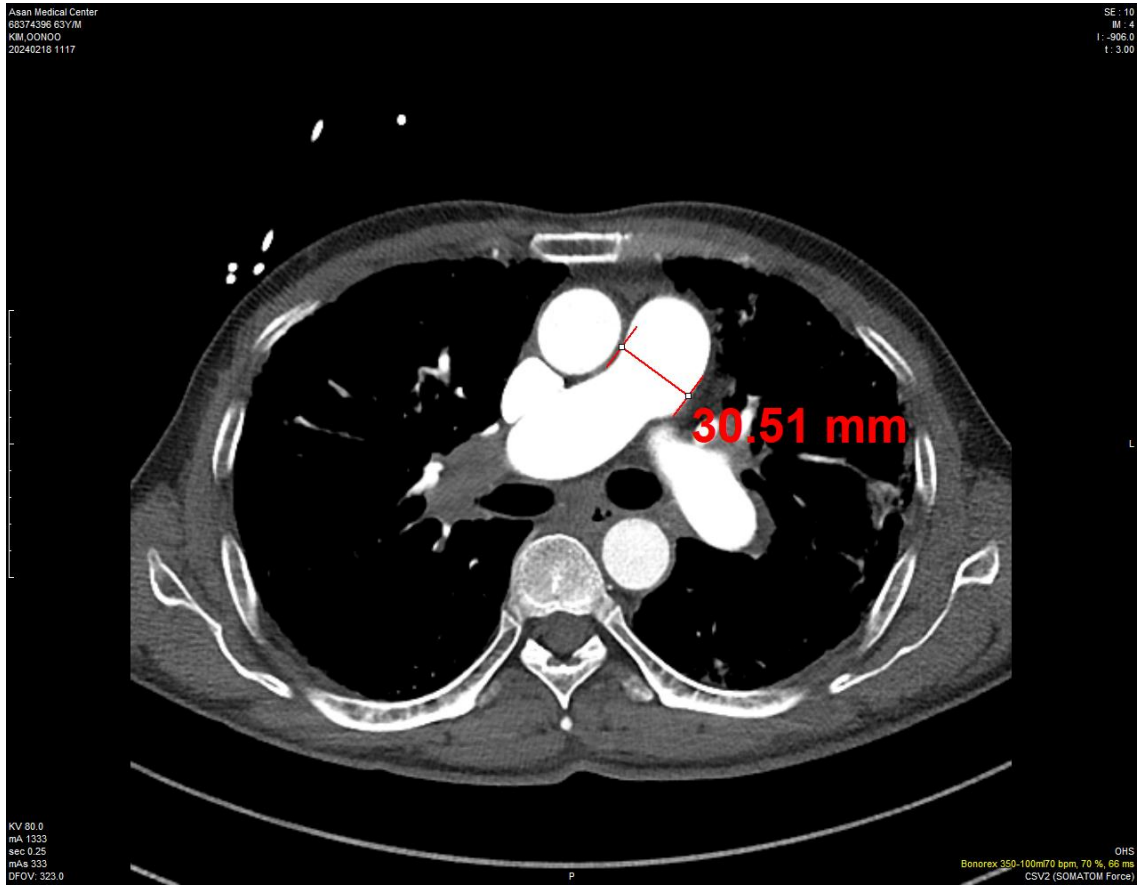
BNP 340 pg/mL

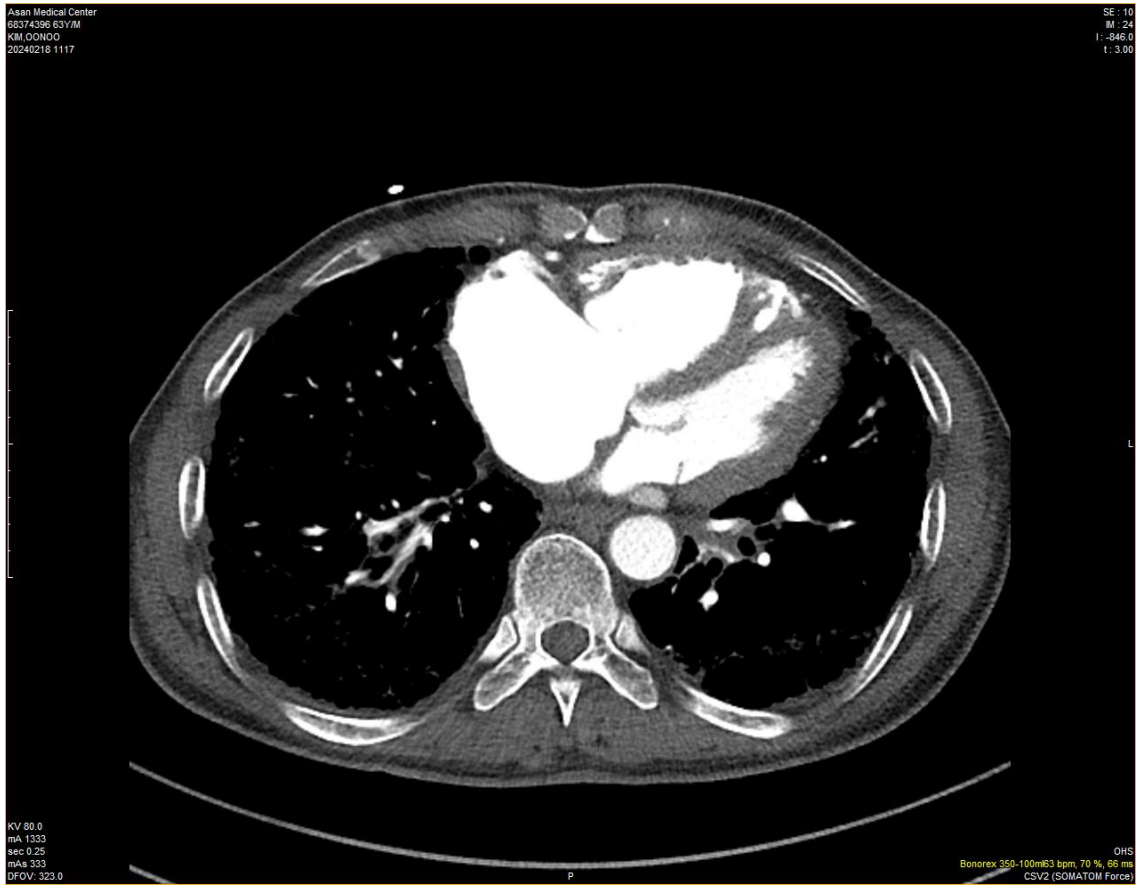
63/M patients with CPFE





Cardiac CT


Asan Medical Center
68374396 63Y/M
KIM,OONOO
20240218 1117
SE : 10
IM : 4
I : -906.0
t : 3.00
30.51 mm
L
KV 80.0
mA 1333
sec 0.25
mAs 333
DFOV: 323.0
P
OHS
Bonorex 350-100ml70 bpm, 70 %, 66 ms
CSV2 (SOMATOM Force)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68374396 63Y/M
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SE : 10
IM : 24
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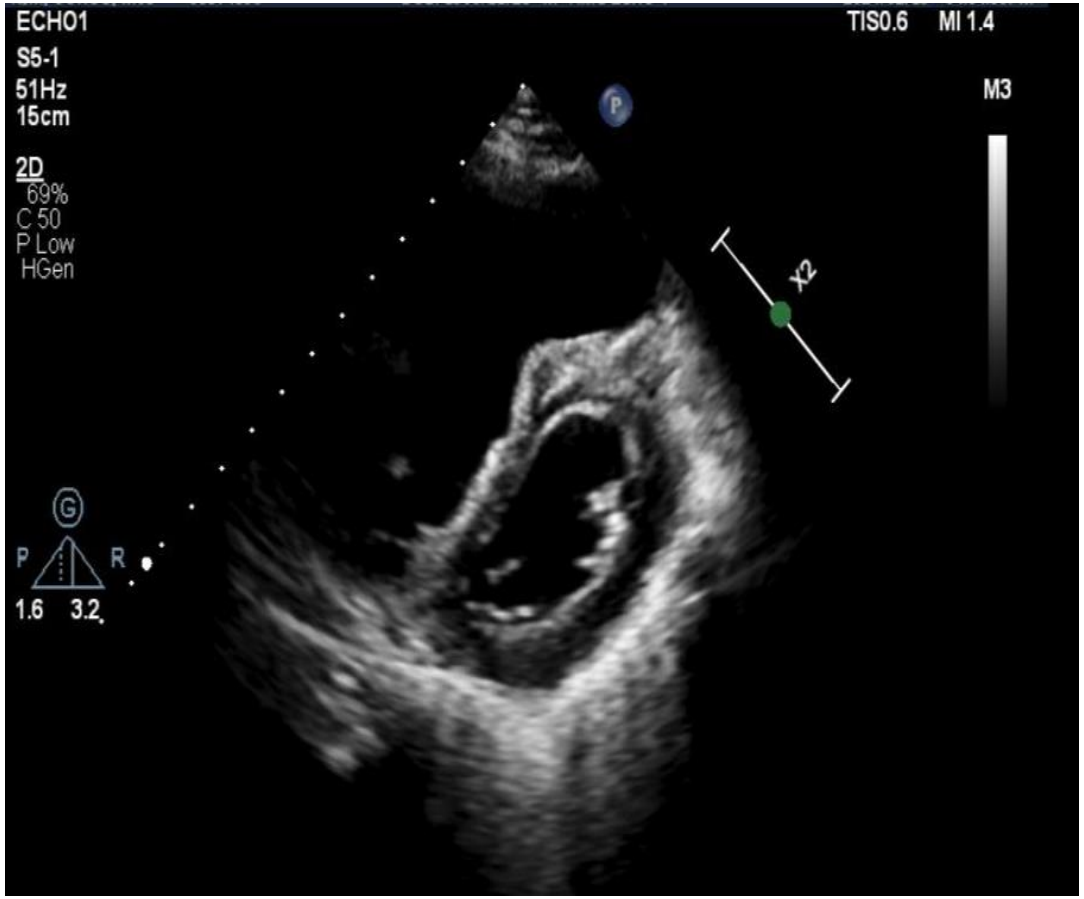
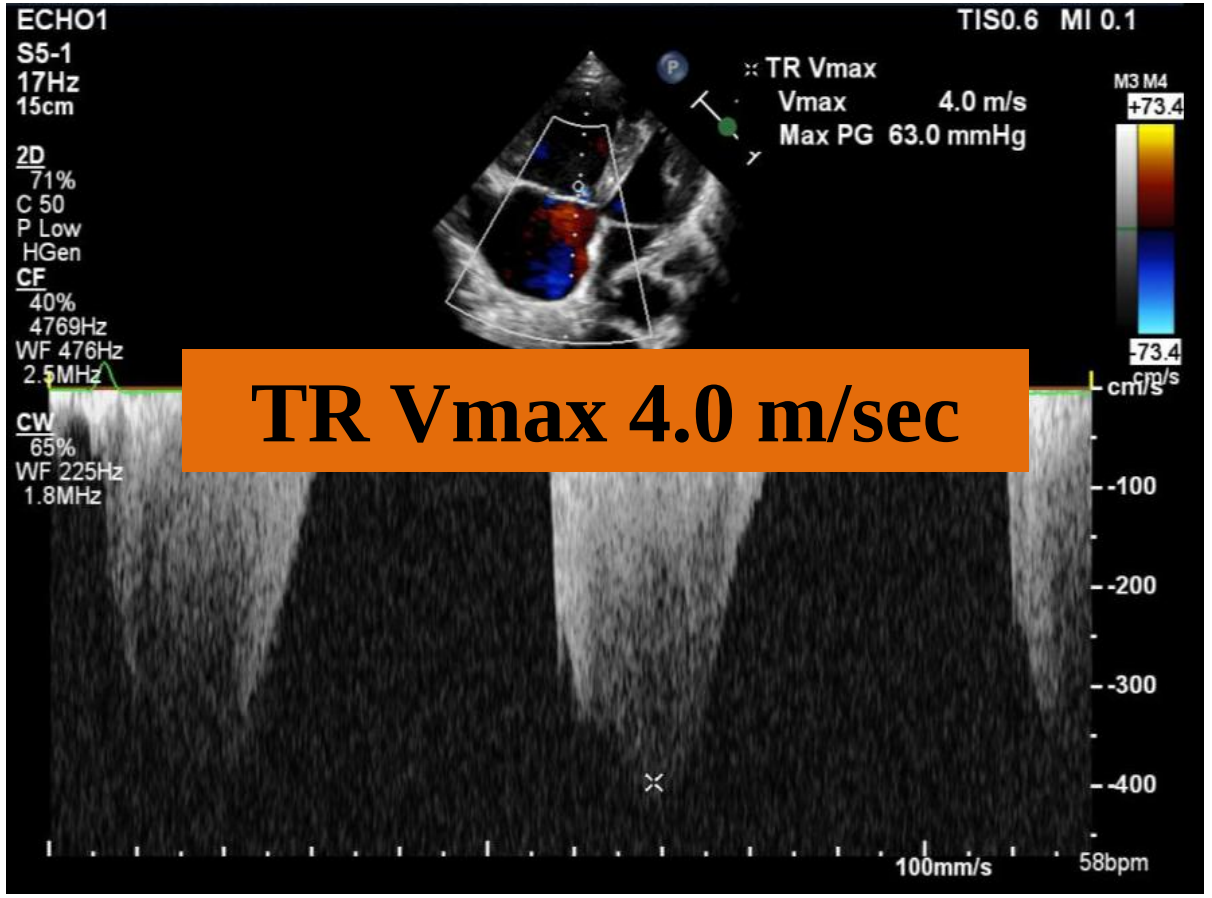
OHS
Bonorex 350-100ml63 bpm, 70 %, 66 ms
CSV2 (SOMATOM Force)

Echocardiogaphy





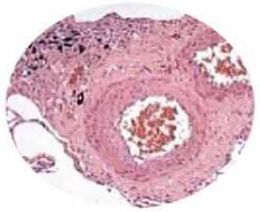
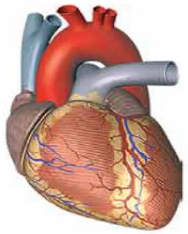
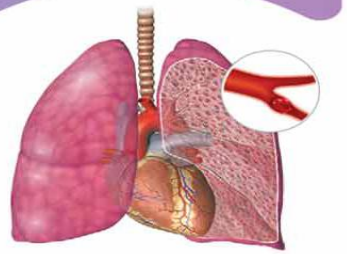
Diagnostic and therapeutic considerations

1. **Whether to do RHC or not ?**

2. **Whether to prescribe PAH target agents ?**

3. **Which PAH target agents ?**

Clinical classification of PH

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders
Therapeutic Strategies				
Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

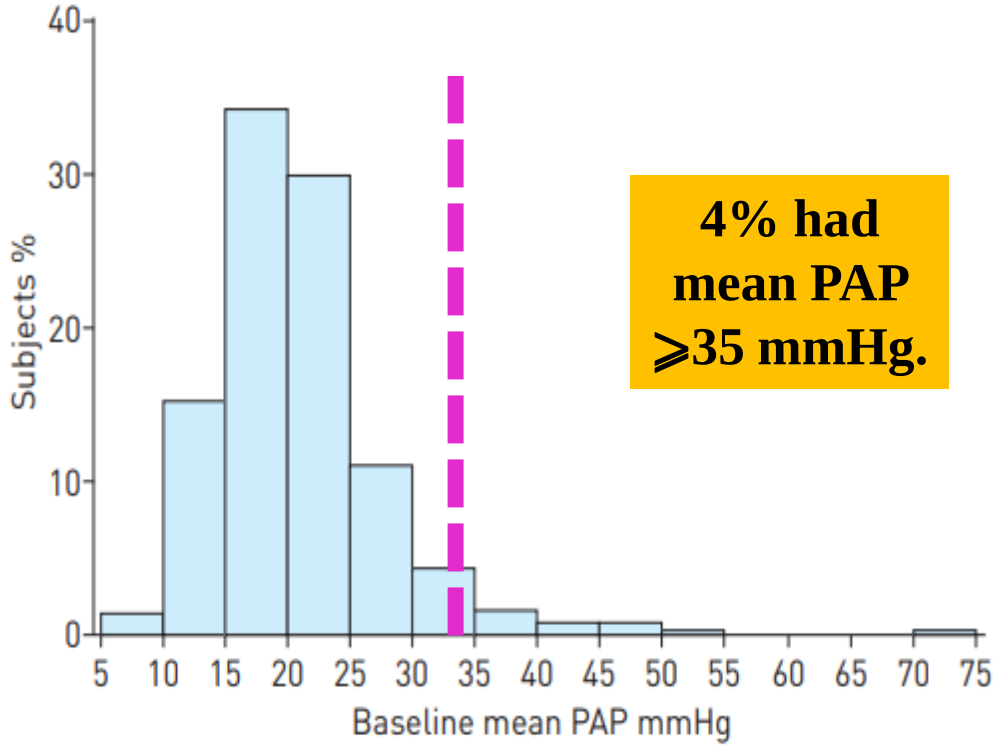
ESC ERS

Definition of PH in chronic lung disease

Terminology	2015 ESC/ERS guideline	2022 ESC/ERS guideline
No PH	Mean PAP <25mmHg	Mean PAP ≤ 20mmHg
Non-severe PH	**Mean PAP ≥ 25mmHg**	**Mean PAP > 20mmHg** **PVR ≤5WU**
Severe PH	**Mean PAP ≥ 35 mmHg, or** mean PAP ≥ 25mmHg in the presence of a low cardiac output (CI < 2.5L/min, not explained by other causes)	**Mean PAP > 20mmHg** **PVR >5 WU**

Mean PAP in patients with IPF

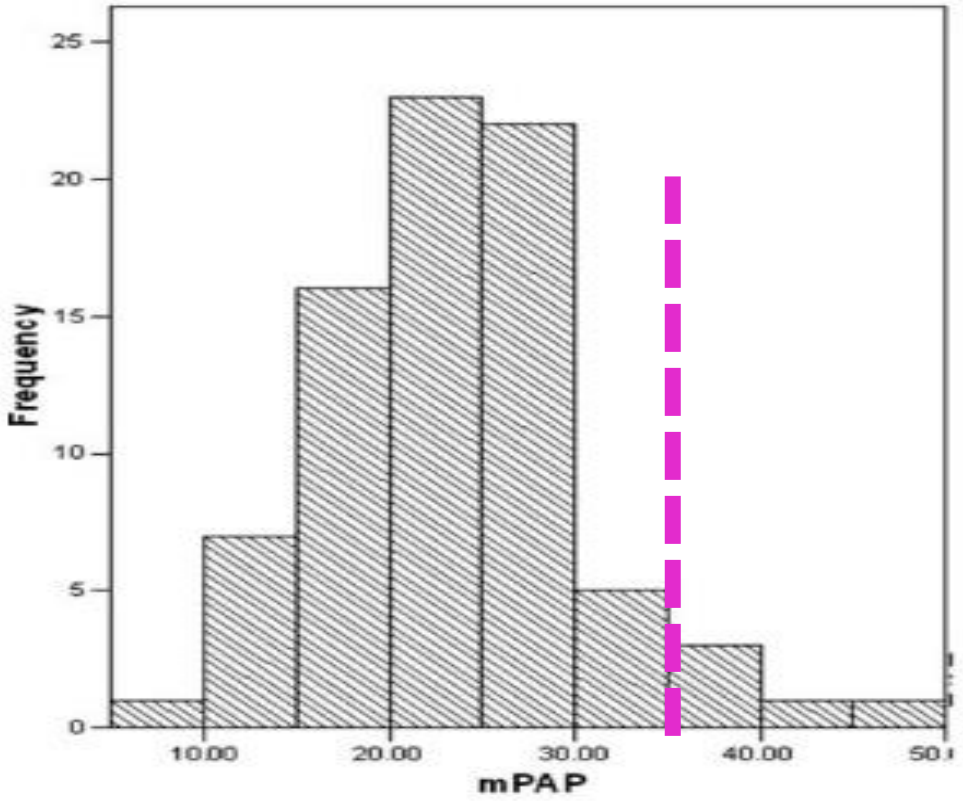
488 patients with mild-to-moderate IPF in ARTEMIS-IPF trial



4% had mean PAP ⩾35 mmHg.

Raghu G, et al. Eur Respir J 2015; 46: 1247–1250

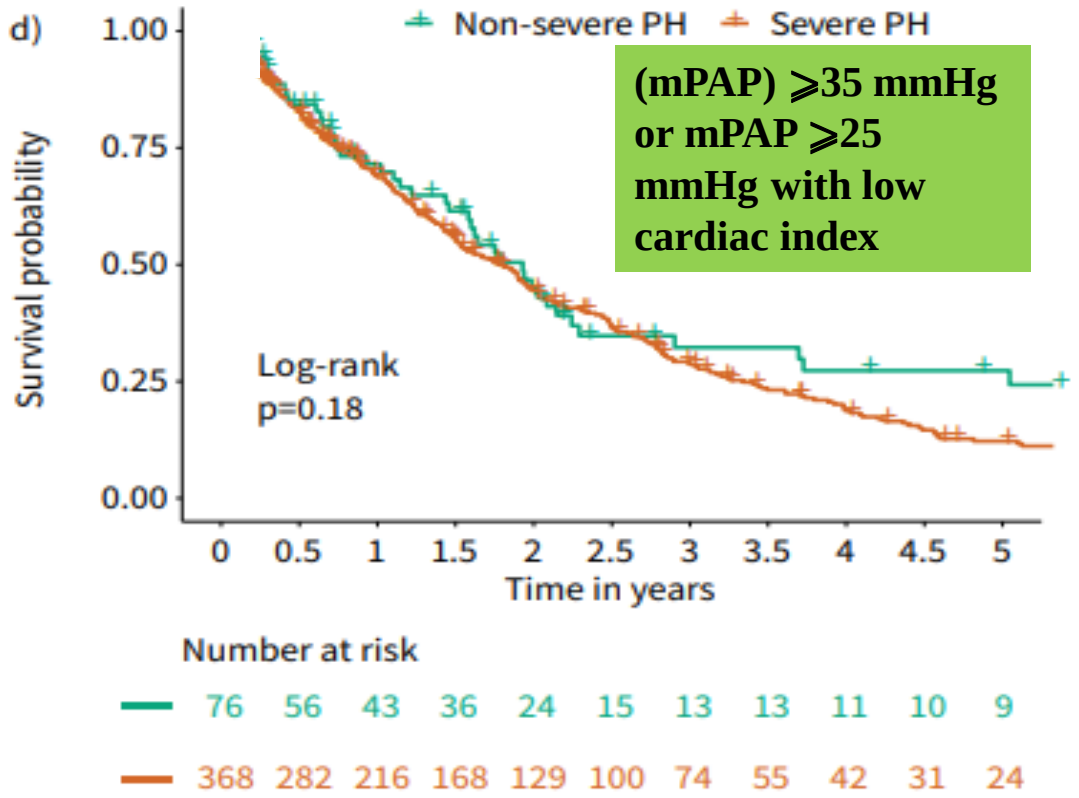
79 IPF patients with severe IPF who listed for lung transplantation

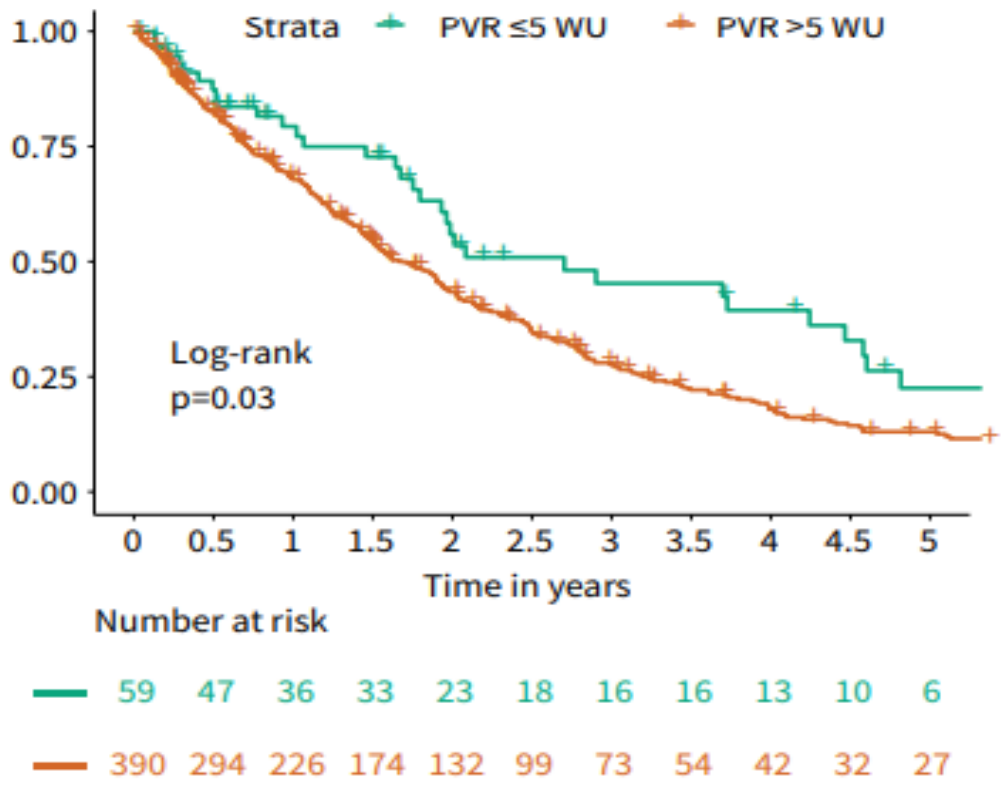


Lettieri CJ, et al. CHEST 2006; 129:746 –752

PVR is stronger prognostic factor than mean PAP in patients with PH-ILD

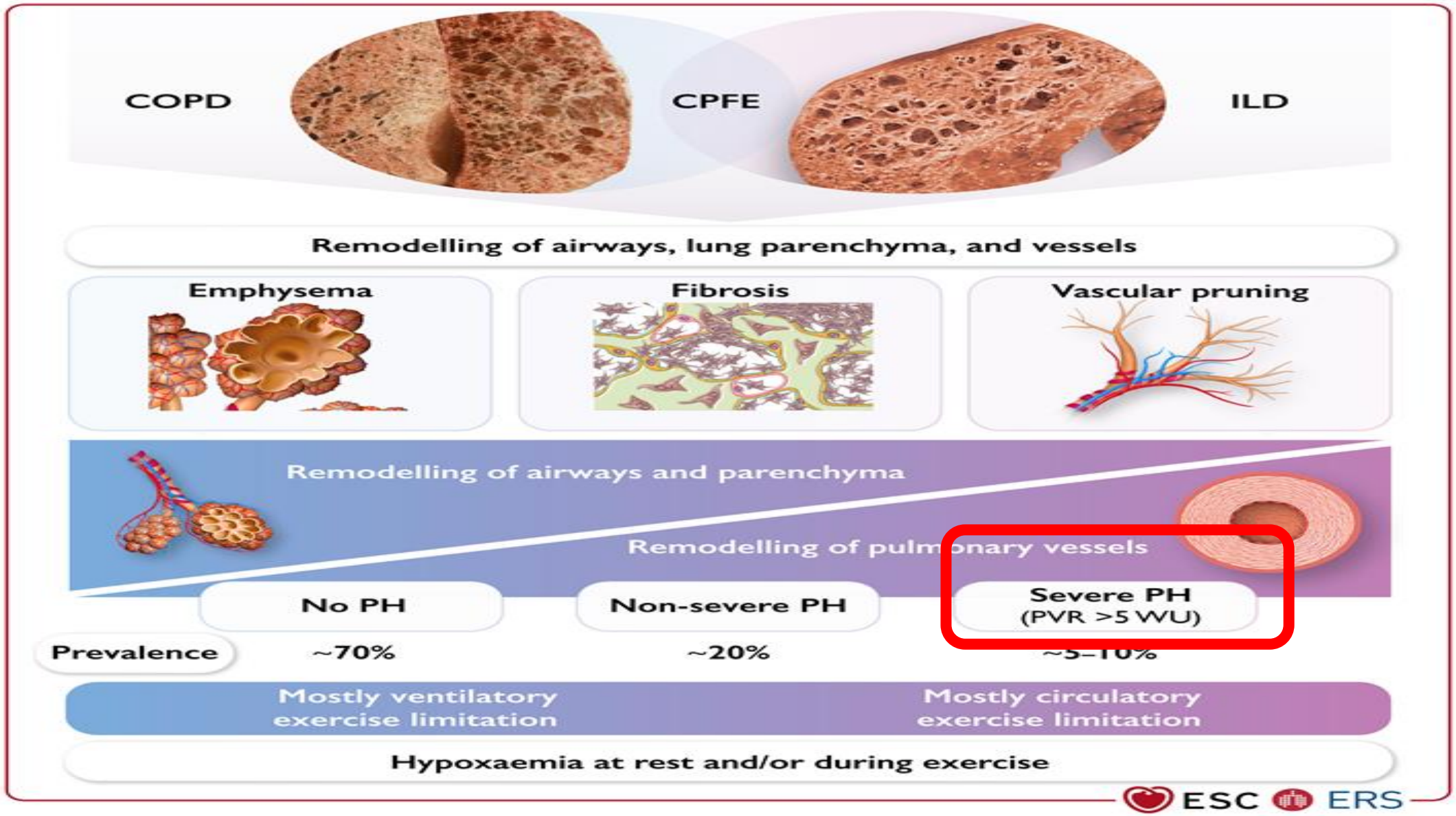
➢ 449 patients with PH-ILD in the COMPERA registry



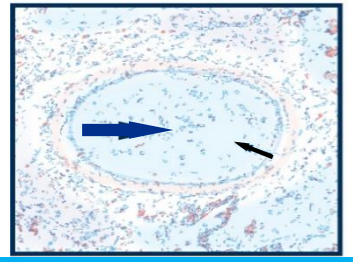


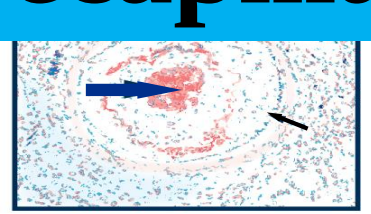
Olsson KM, et l. Eur Respir J 2021; 58: 2101483

Pathophysiology of PH-LD

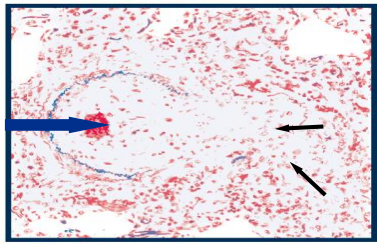


Vascular changes in IPAH

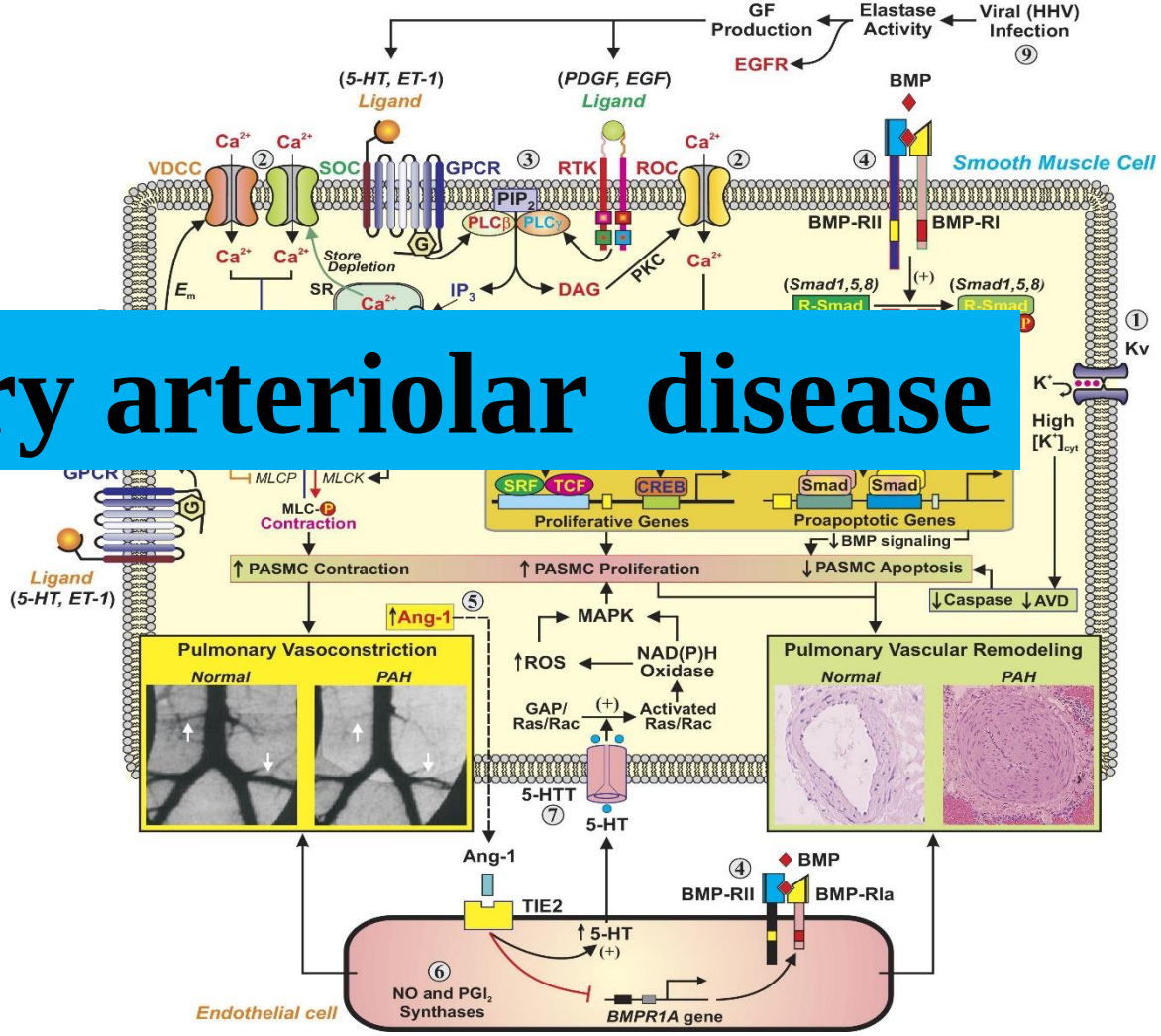




Medial hypertrophy

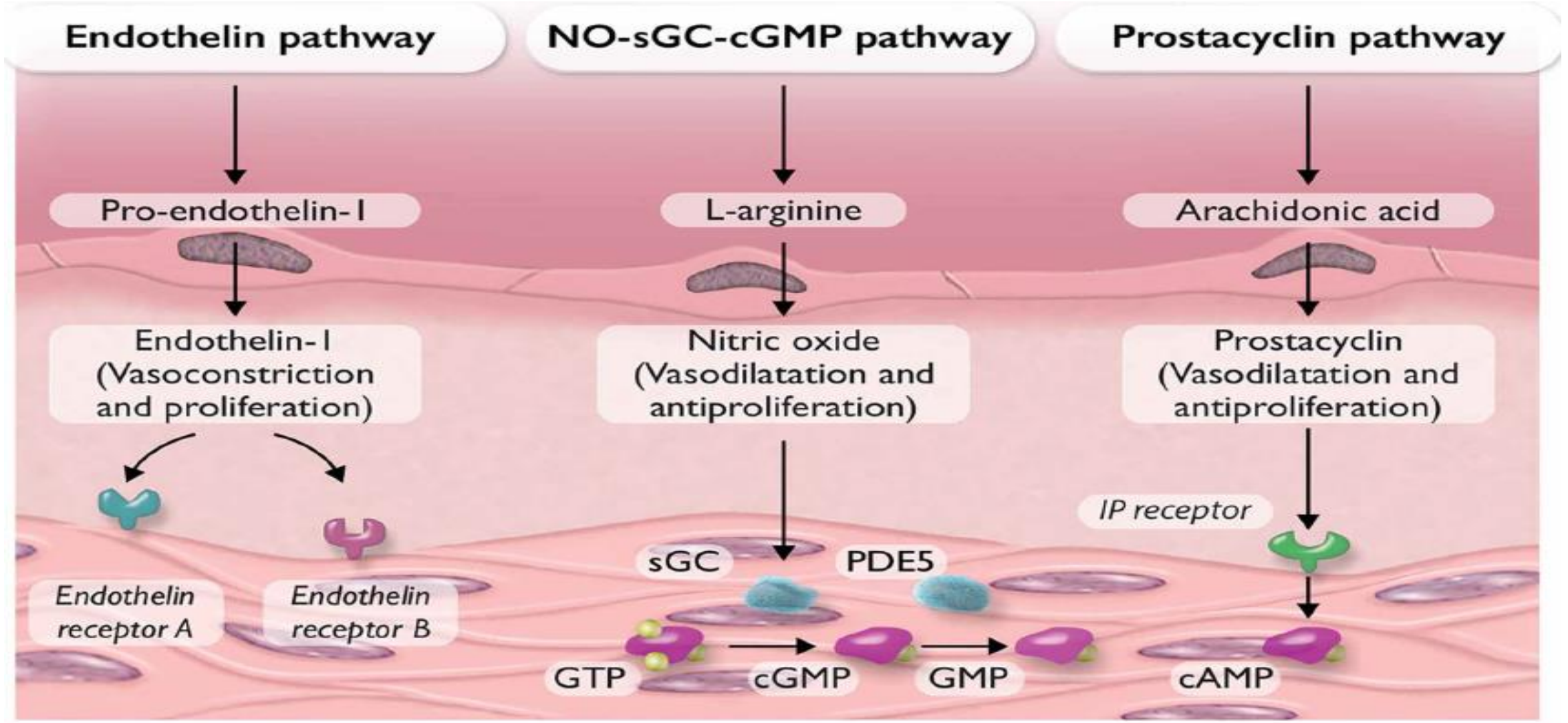


Plexiform lesions

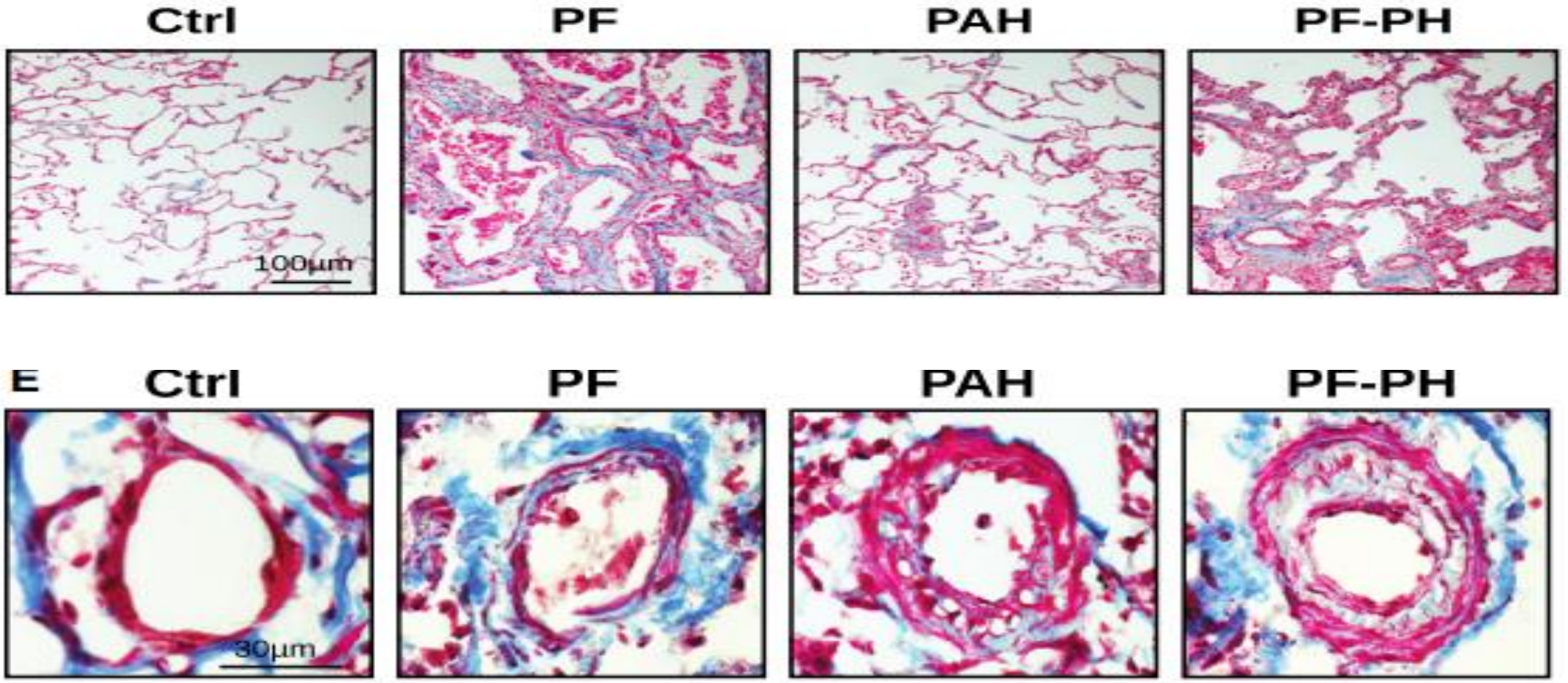


Diffuse precapillary arteriolar disease

3 main therapeutic pathways in PAH

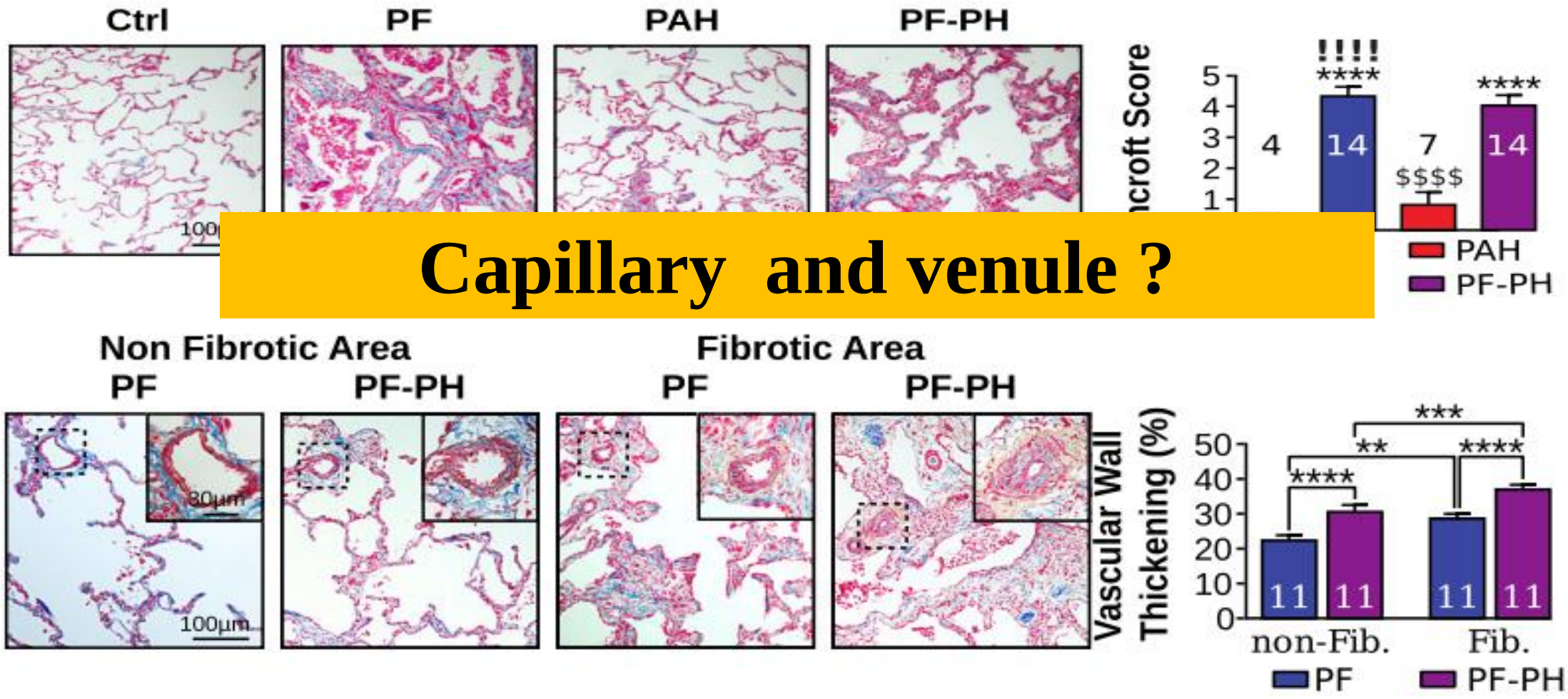


Vascular remodeling in PF, PAH and PF-PAH



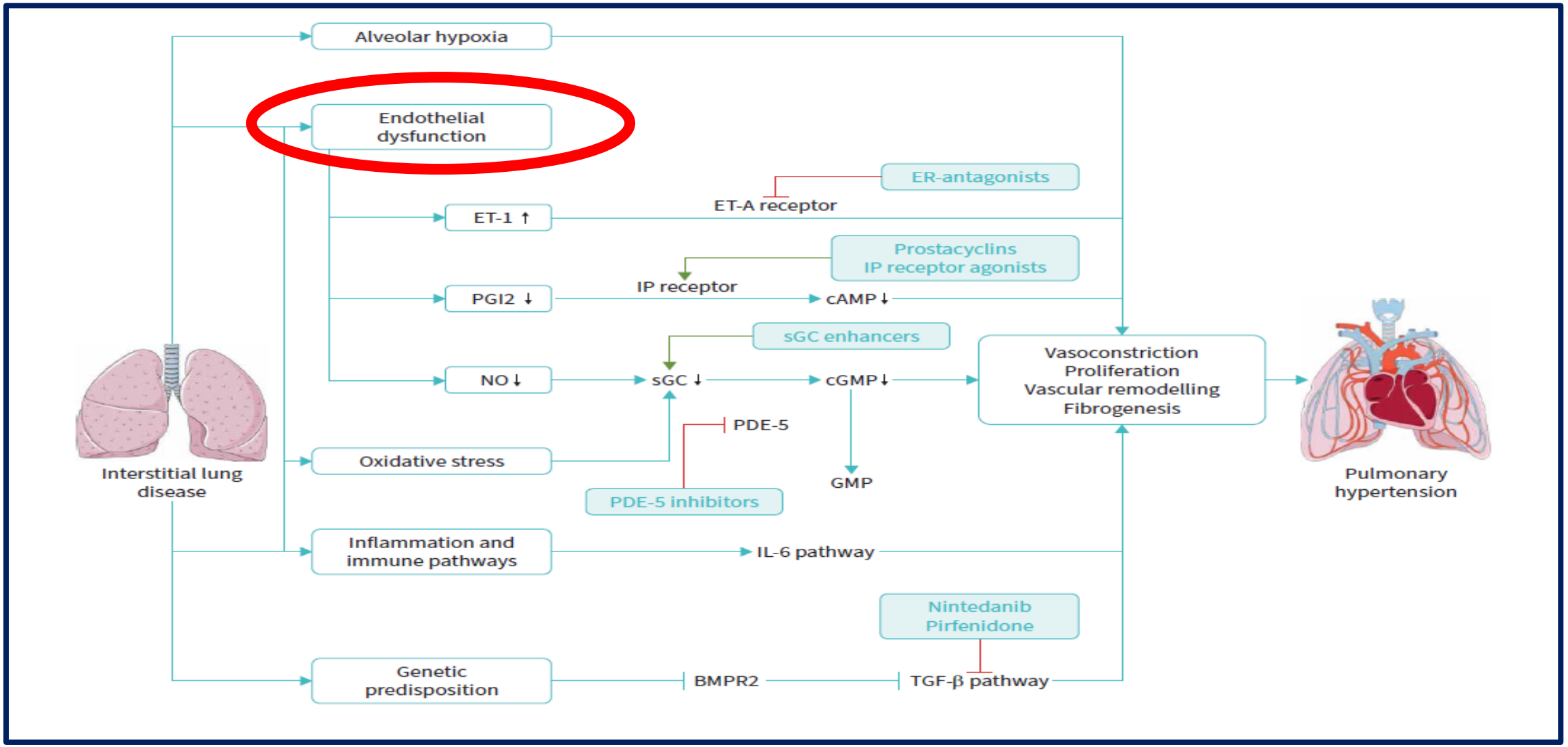
Ruffenach G, et al. EMBO Mol Med. 2019 Sep;11(9):e10061.

Vascular wall thickening in PH due to pulmonary fibrosis



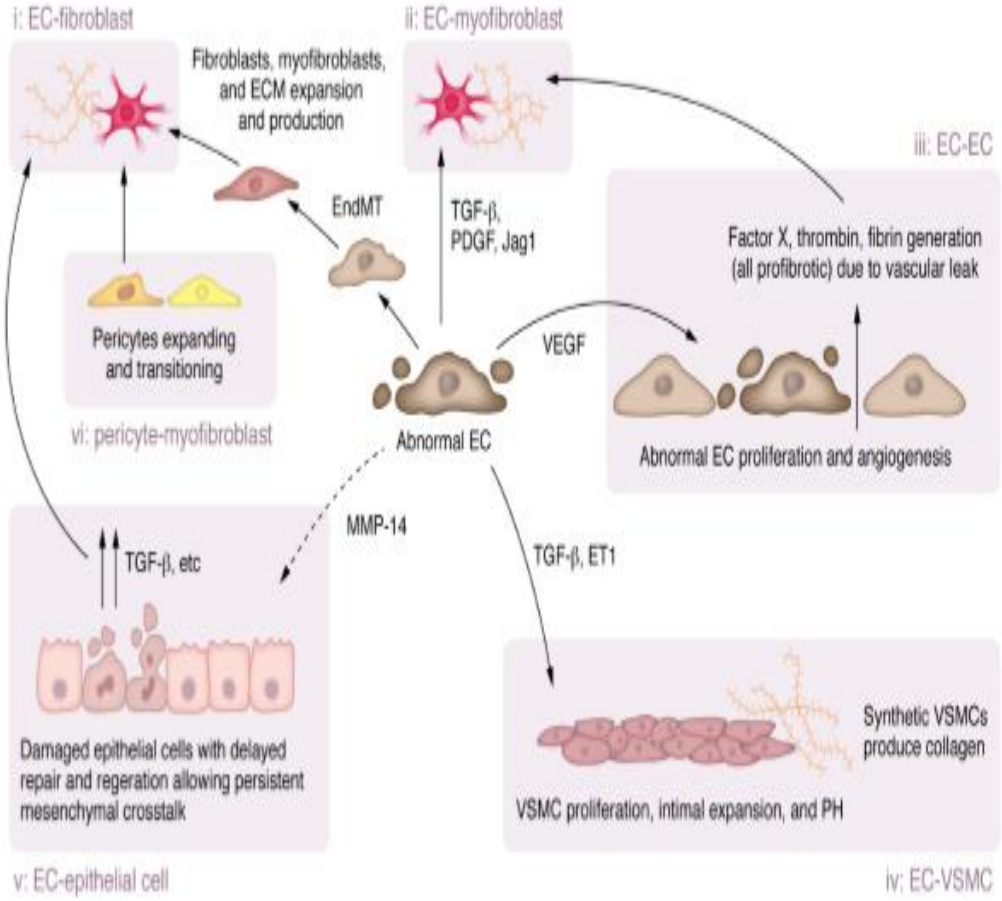
Ruffenach G, et al. EMBO Mol Med. 2019 Sep;11(9):e10061.

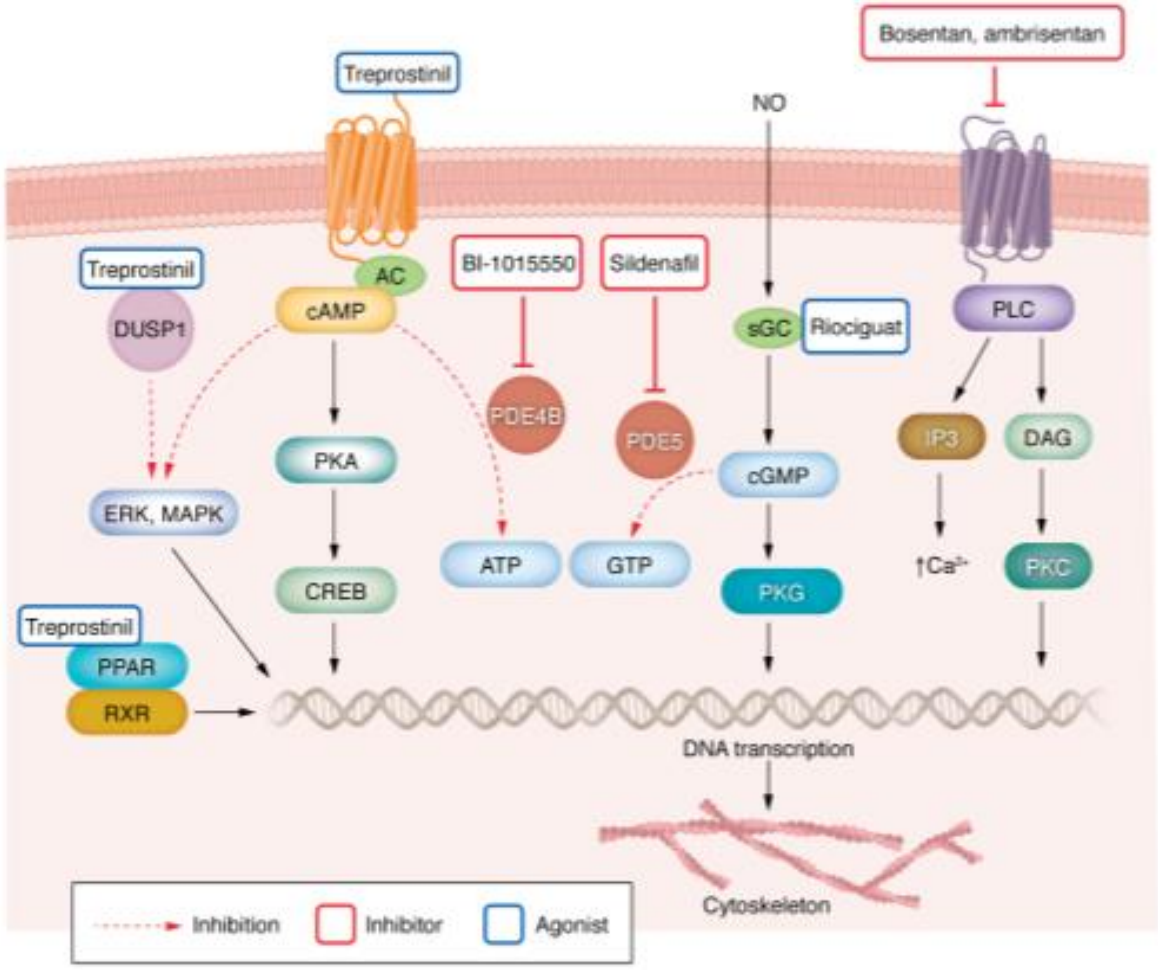
Pathogenesis of PH in ILD



Dhont S, et al. ERJ Open Res 2022; 8: 00272-2022

Vascular and endothelial contributions to IPF

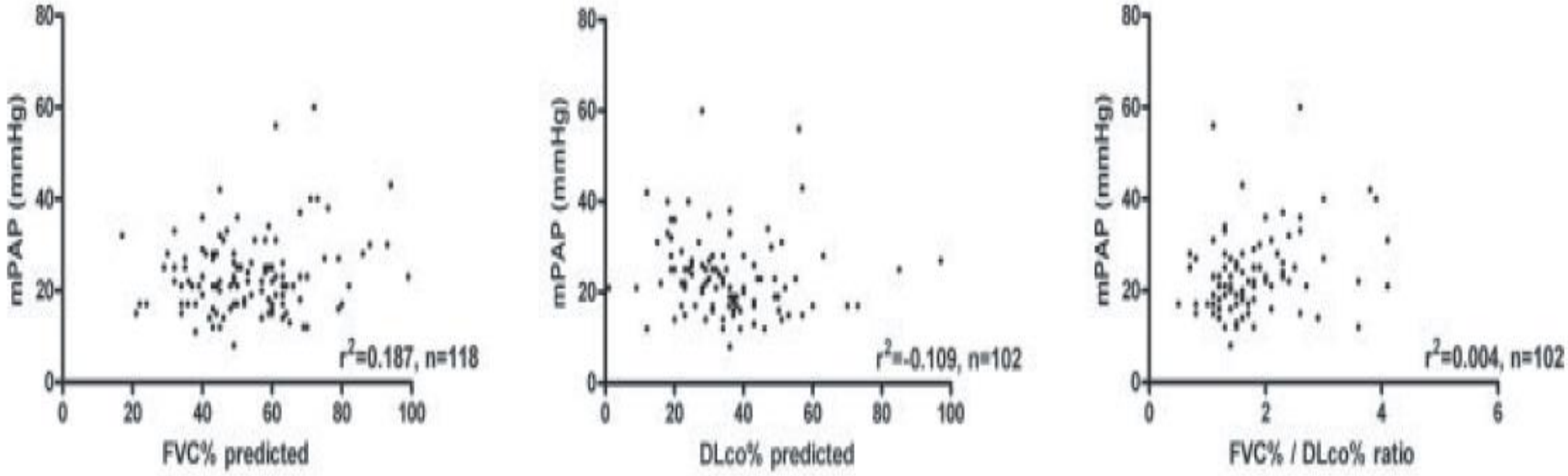




May J, et al. J Clin Invest. 2023;133(18):e172058.

mPAP and PFT in patients with IPF

There was no significant correlation between FVC%, DLco%, and the ratio of the two with mPAP

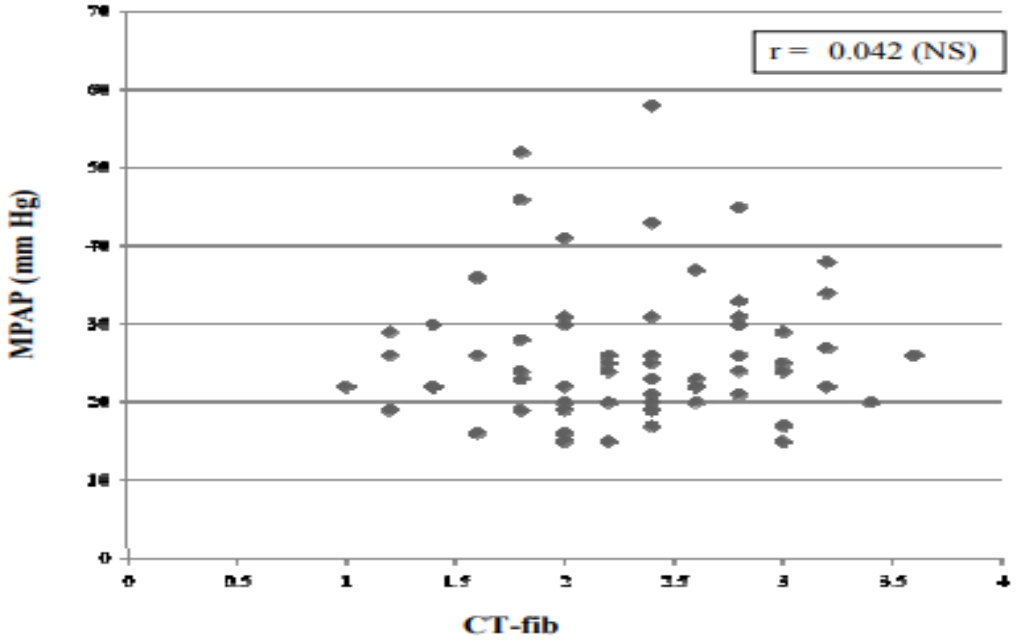


Nathan SD, et al. CHEST 2007; 131:657–663

Relationship between CT fibrosis score and measured mPAP in patients with advanced IPF

65 patients with advanced IPF

mPAP did not correlate with CT-based measurements of lung fibrosis, and these variables did not differ between those with and without PH.



Variables	No.	*r*	p Value*
CT-fib	65	0.042	0.74
WCT-fib	65	0.022	0.86
MCT-fib	54	0.004	0.97
CT-alv	65	0.153	0.22
WCT-alv	65	0.171	0.17
CT-hc	65	0.009	0.94
WCT-hc	65	0.025	0.84
CT-tot	65	0.009	0.38
WCT-tot	65	0.119	0.34

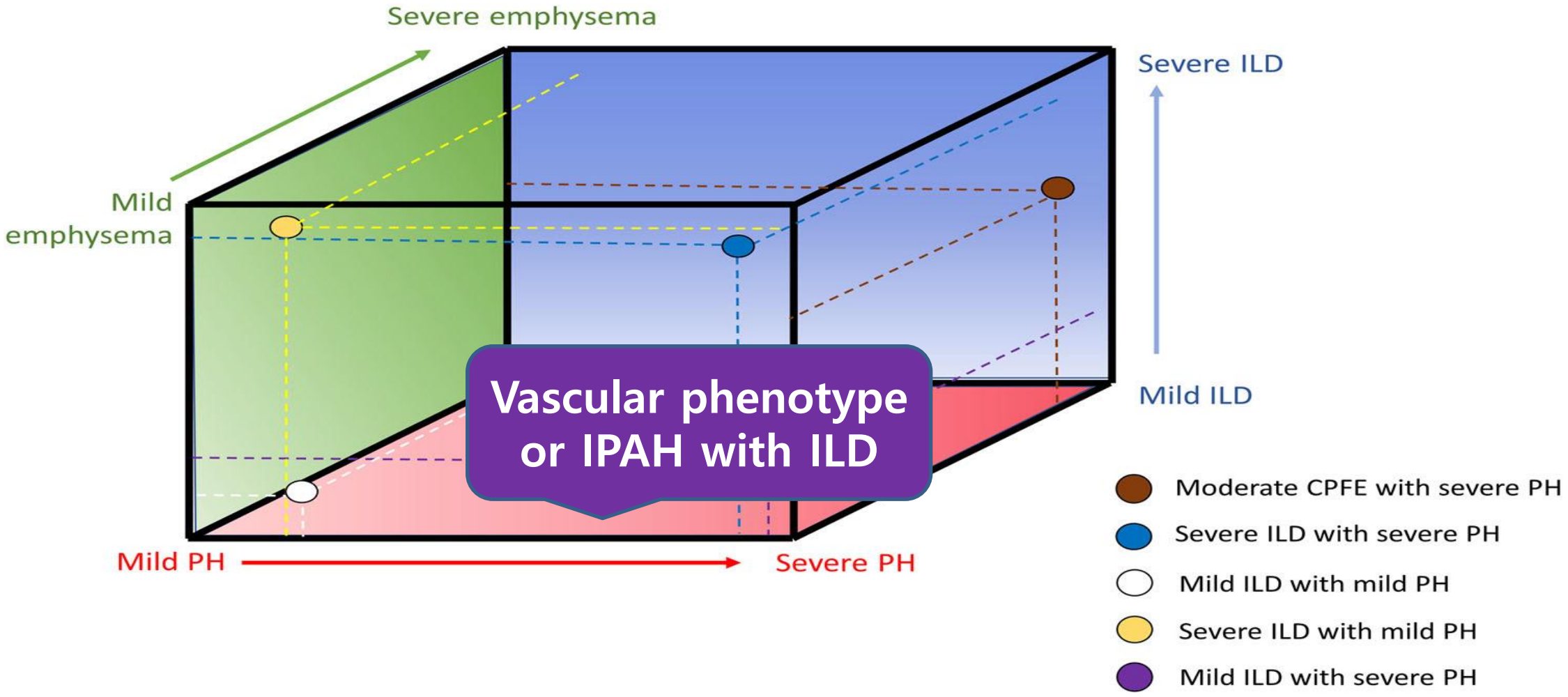
Zisman DA, et al. CHEST 2007; 132:773–779

Moderate PH versus severe PH-ILD

Parameters	mPAP > 25mmHg (n=932)	mPAP > 40mmHg (n=231)	P value
Age	**53.4**	**49.9**	**0.040**
BMI, kg/m^2	28.7	27.7	<0.001
FEV_1, % predicted	50.0	51.5	<0.001
FVC, % predicted	**48.4**	**51.4**	**0.020**
6MWD < 45m	13.9	21.1	0.010
CI L/min/m	**2.8**	**2.5**	**0.82**
PCWP, mmHg	**12.1**	**14.0**	**<0.001**
Any need for O_2	**86.0**	**92.8**	<0.001
O2 used L/min^{-1}	**2.9**	**3.5**	<0.001
Comorbid illness			
COPD	**15.7**	**16.2**	**0.030**
HTN	**21.6**	**22.8**	**0.040**

Shorr AF, et al. Eur Respir J 2007; 30: 715–721

Phenotypes of PH-ILD



Picccari L, et al. Pulmonary Circulation. 2023;13:e12213

Not all PH in patients with ILD is PAH !

Retrospective analysis of 157 patients with ILD-PH

	Pre-capillary PH (n=125)	Post-capillary PH (n=32)	P value
Age	68	68	0.730
Male	90	25	0.485
ILD-GAP score	**5**	**4**	**0.063**
FVC, % predicted	65.9	68.2	0.439
DLco, % predicted	**33.6**	**40.5**	**0.025**
PaO_2, Torr	**64.8**	**72.8**	**0.001**
6MWD, m	**385**	**465**	**0.071**
Lowest SpO_2, %	**70**	**76**	**0.014**
BNP, pg/mL	**24.3**	**31.3**	**0.350**
RVSP, mmHg (echo)	**47**	**37**	**0.103**
Mean PAP, mmHg	**28**	**28**	**0.970**
PVR, WU	**3.7**	**1.7**	**<0.001**
PAWP, mmHg	**10**	**18**	**<0.001**

Teramachi R, et al. Respir Investig. 2021; 59:342-349.

Indications for RHC

1) Proper diagnosis or exclusion of PH in candidates for surgical treatments (transplant, lung volume reduction)

2) suspected PAH or CTEPH

3) episodes of right ventricular failure

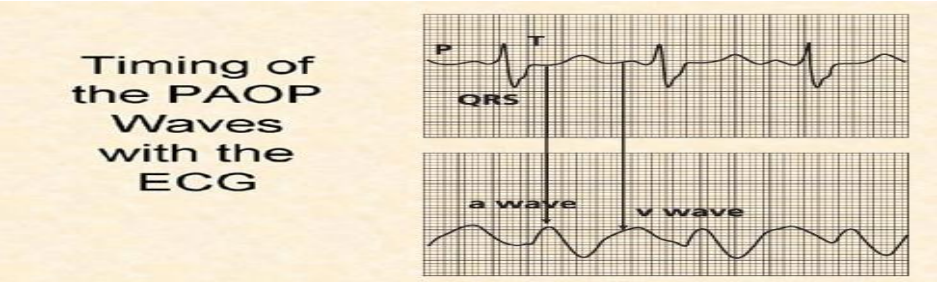
4) inconclusive echocardiographic findings in cases with a high level of suspicion and potential therapeutic implications.

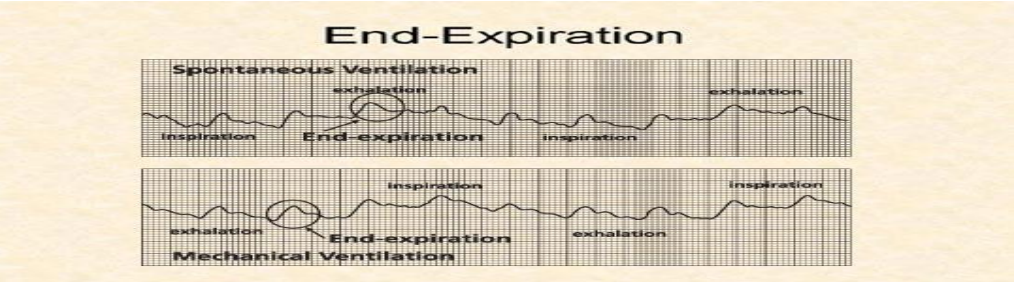
Challenges for using RHC

Challenges to proper use	Potential Consequences
Inability to perform procedure Not adhering to recommendations for accurate measurement of hemodynamics	Unable to make a definitive PAH diagnosis and **possibly mis-categorizing between groups 1 and 2 PH**
Relying on computer-generated pressure measurements in lieu of manual waveform interpretations	
Inaccuracy of measuring left-sided filling pressures (PAWP or LVEDP)	
Inability to perform acute vasodilator testing when IPAH suspected	Not detecting acute vaso-responders who can be successfully treated with calcium channel blockers

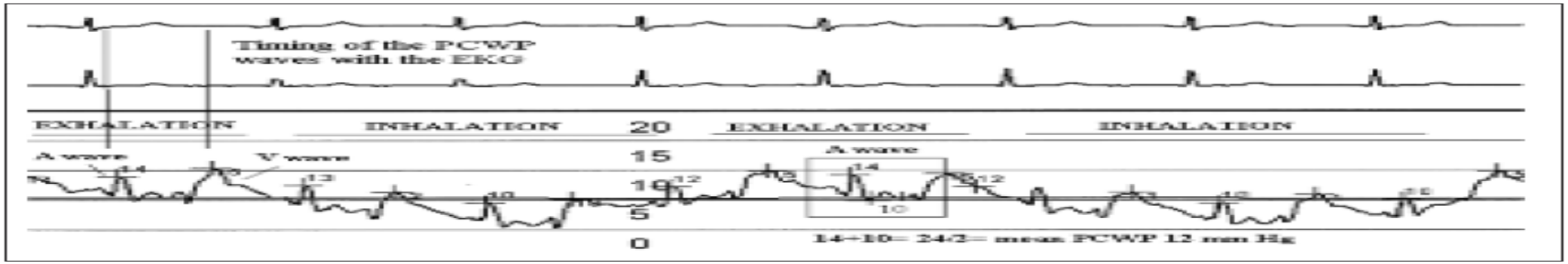
Measurement of PAWP

1) **Identification of the A wave during exhalation**
(right before the beginning of the pressure decline)





2) **Average the top and bottom values of the A wave**

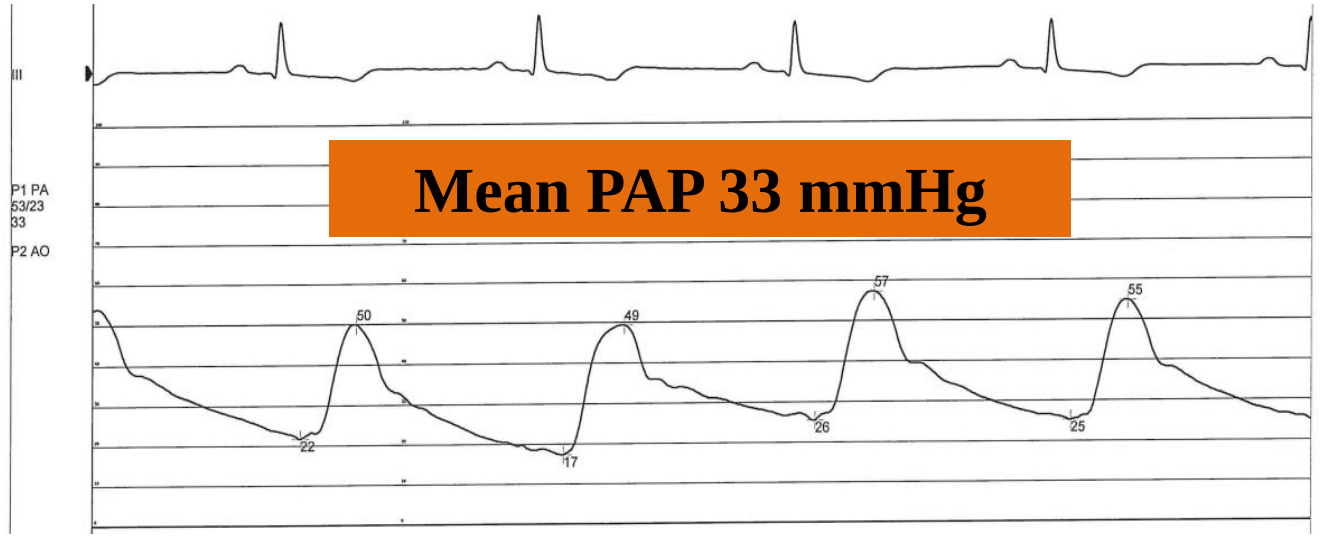


63/M IPF patients; mean PAP and PAWP

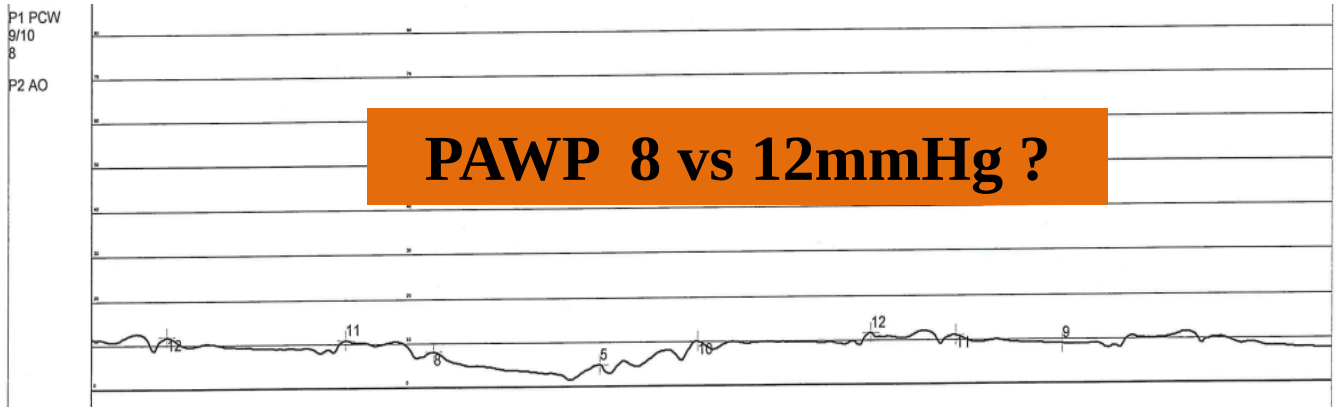
			Baseline			Vasoreactivity Test ▪ adenosine ( ) ▪ Oxygen ( )		
			Max	Min	Mean	Max	Min	Mean
Hemoglobin (g/dL)			15.9					
Heart Rate (bpm)			55					
Aorta	Pressure		104	66	80			
	Saturation		100					
LV	Pressure							
	Saturation							
SVC	Saturation		71.7					
IVC	Saturation		78.7					
RA	Pressure		11	8	6			
	Sat.	High RA						
		Middle RA	71.9					
		Low RA						
RV	Pressure		57	2	13			
	Saturation							
PA	MPA	Pressure	53	23	33			
		Saturation	69.1					
	RPA	Pressure						
		Saturation						
	LPA	Pressure	54	20	32			
		Saturation						
	Lt. PAWP	Pressure	9	10	8			
		Saturation						
	Rt. PAWP	Pressure						
		Saturation						
LA	Pressure				8			
	Saturation							
PV	Pressure							
	saturation							
Transpulmonary Pressure Gradient*					25			0
Diastolic pulmonary Pr. gradient**					15			0
Mixed Venous O2 Saturation(%)			73.45			0.00		
Assumed O2 Consumption (ml/m			210.58			0.00		

*Mean MPA preussure – Mean LA Pressure (PAWP)

**Diastolic MPA preussure – Mean LA Pressure (PAWP)



Mean PAP 33 mmHg



PAWP 8 vs 12mmHg ?

Measurement of cardiac output

❖Fick method

$$CO\ (L/m) = \frac{\text{oxygen consumption (mL } O_2\text{/m)}}{\text{arteriovenous oxygen difference (mL of } O_2\text{/L)}}$$

- **Direct Fick method: gold standard method**

- **Indirect Fick method: inaccurate estimate of O_2 consumption**

❖Thermo-dilution method

- At least 3 measurements within 10% of each other
- limitations in severe TR and congenital heart defect
- **must be performed by trained personel**

63/M IPF patients; cardiac output

Fick method

Flow

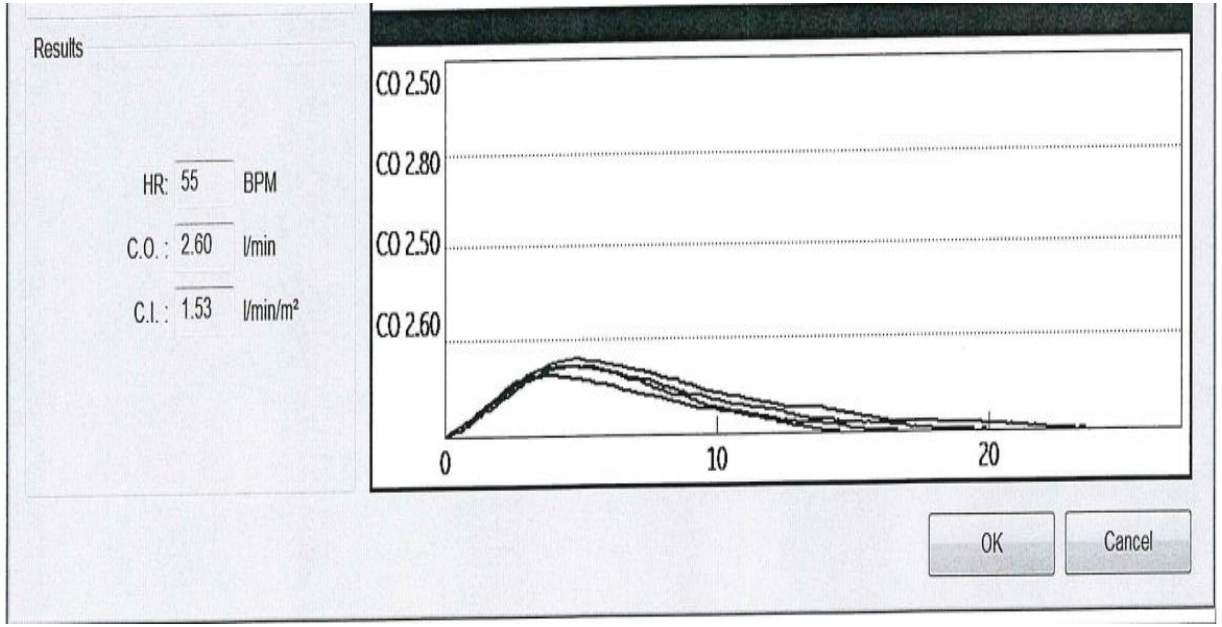
PBF(Qp) (L/min)	3.15	#DIV/0!
SBF(Qs) (L/min)	3.67	#DIV/0!
Cardaic Index (L/min/M^2)	2.18	#DIV/0!
Qp/Qs	0.86	#DIV/0!

Resistance

PVR (Wood units)	7.93	#DIV/0!
SVR (Wood units)	20.17	#DIV/0!
PVRI (dyn s cm^{-5}m^{-2})	1069.09	#DIV/0!
SVRI (dyn s cm^{-5}m^{-2})	2719.02	#DIV/0!
Rp/Rs	0.39	#DIV/0!

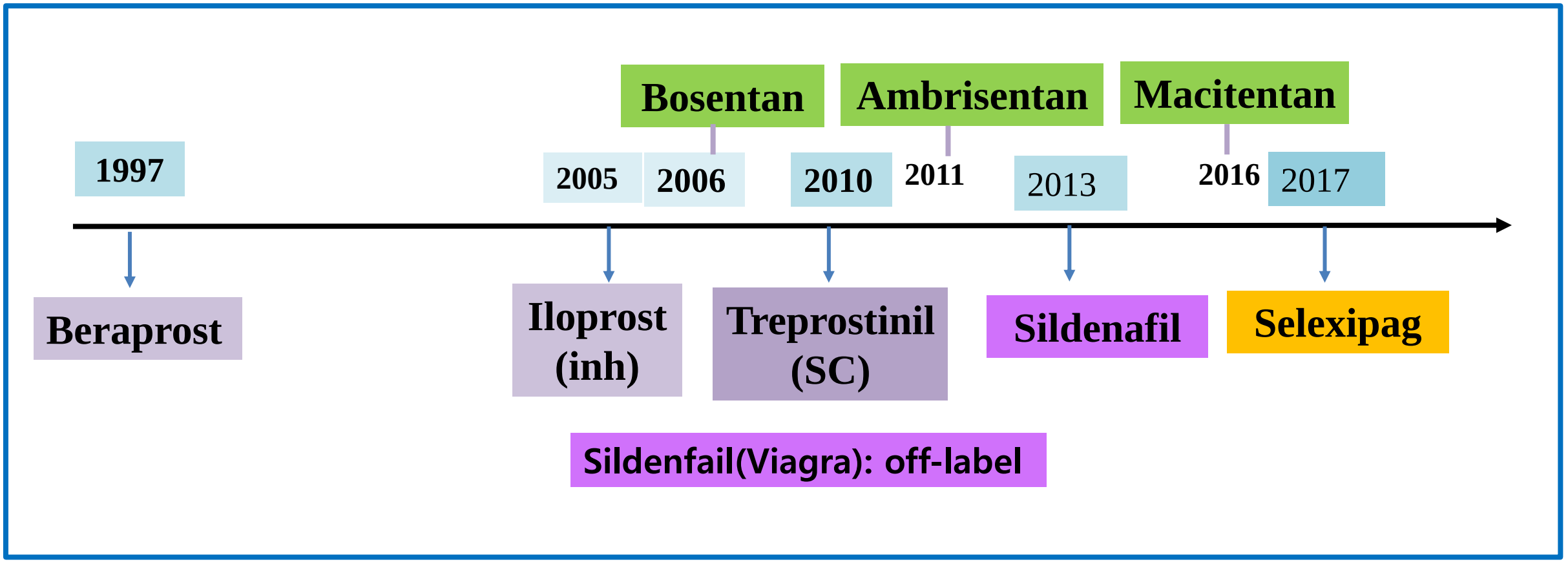
Stroke Volume Index(SVI)	39.58646898	#DIV/0!
Right Ventricular Stroke Work Index (RVSWI)	1068.834662	#DIV/0!

Thermo-dilution method



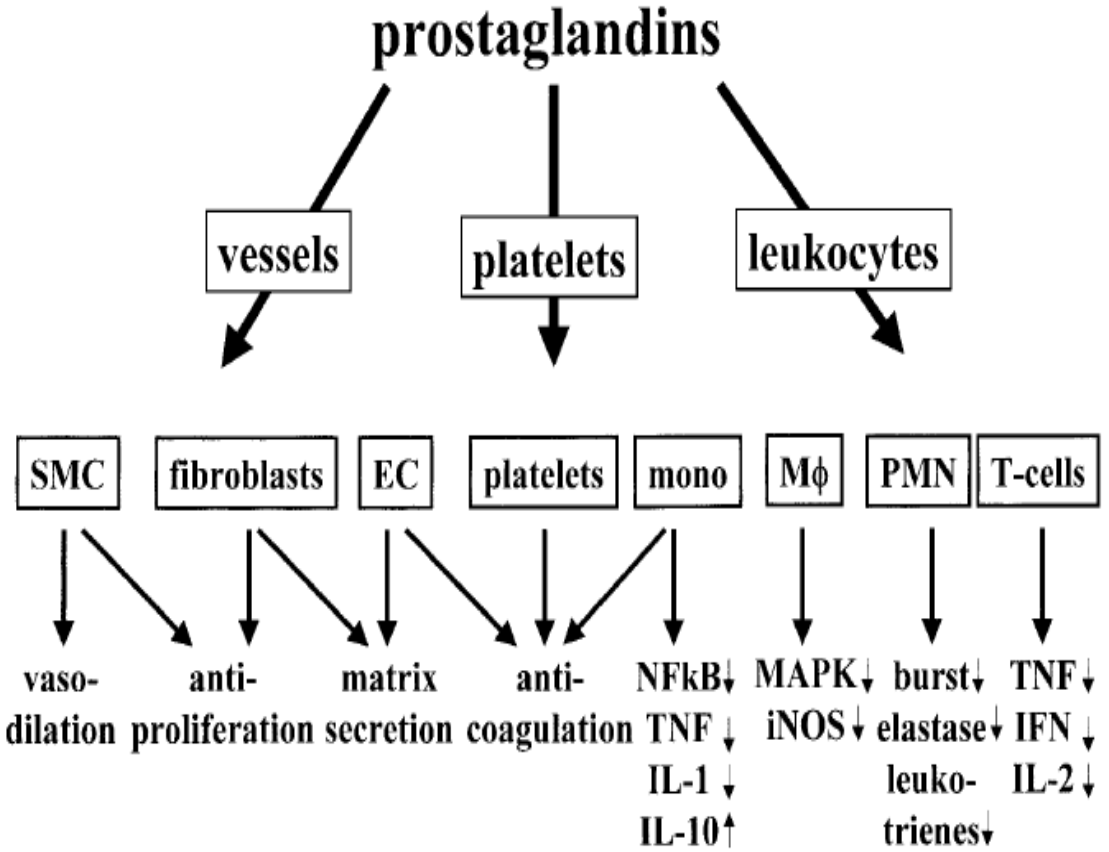
PVR: (33-12)/3.67 = 5.72 WU vs (33-8)/2.60 = 9.61 WU

PAH drug approval in South Korea



Pharmacologic properties of prostacyclins

- Potent vasodilator
- Anti-platelet effect
- Anti-proliferative
- Anti-inflammatory
- Inotropic effect

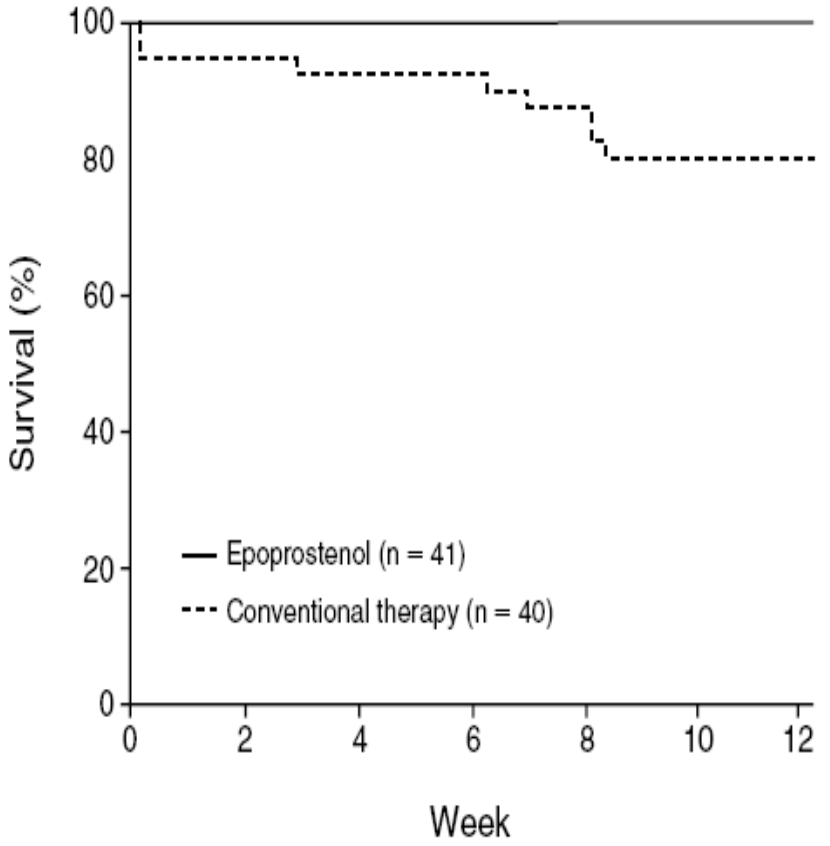


Olscewski H et al. J Lab Clin Med 2001; 138: 287–297

Epoprostenol

- "Gold standard" for FC IV PAH

- The only PAH therapy with a survival benefit for patients with PAH that has been demonstrated in a single RCT.



Barst et al. N Engl J Med 1996;334:296-301

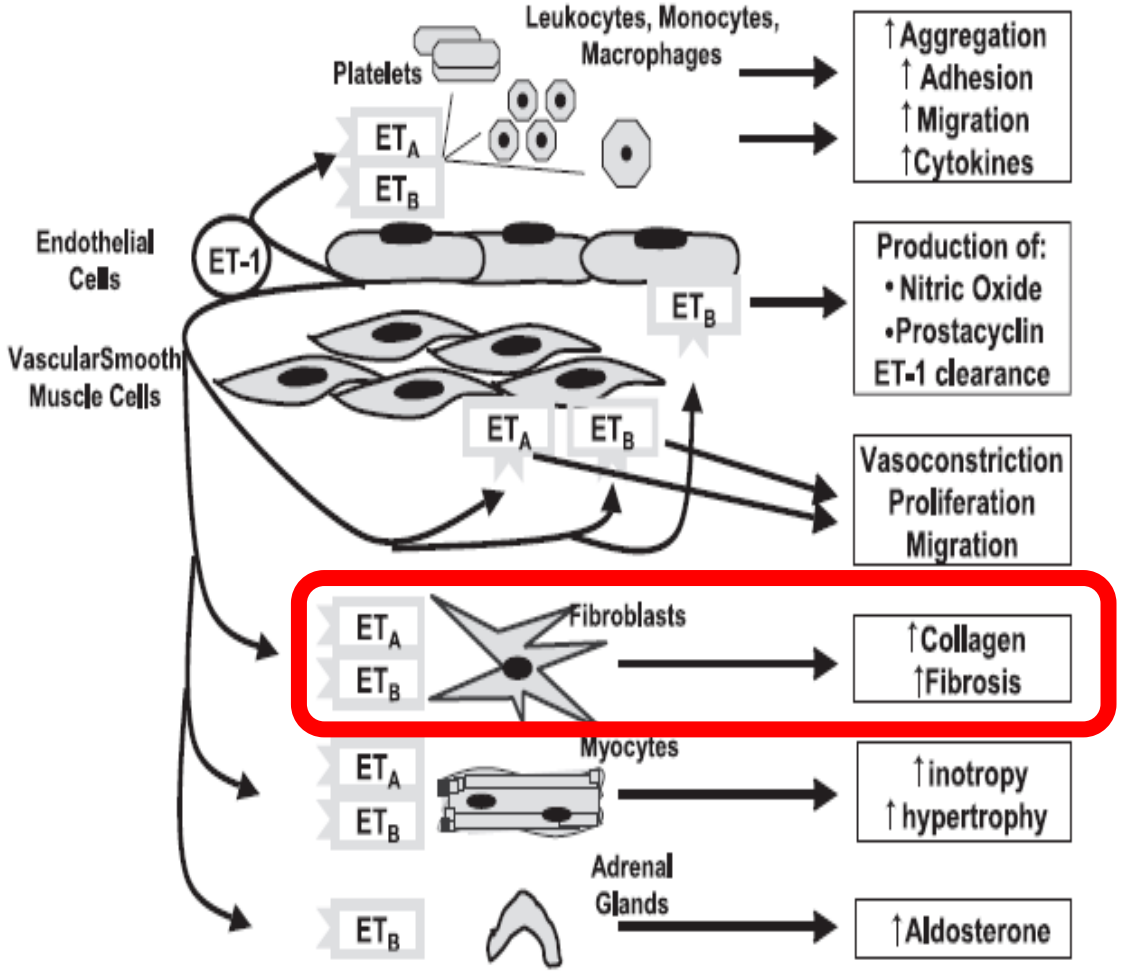
Effects of endothelin

ET_A–mediated effects

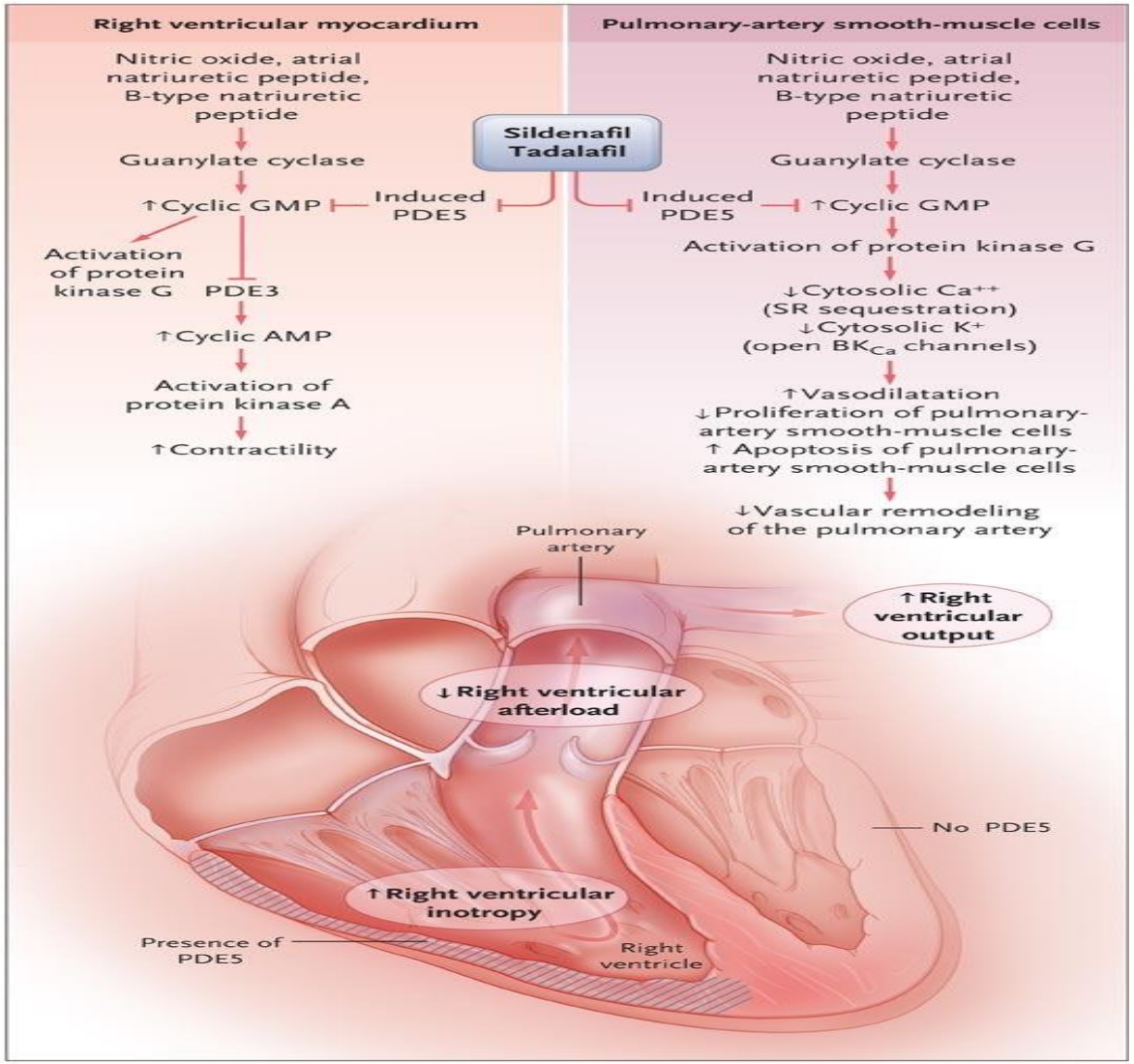
-vasoconstriction
- proliferation, hypertrophy
- cell migration
- fibrosis

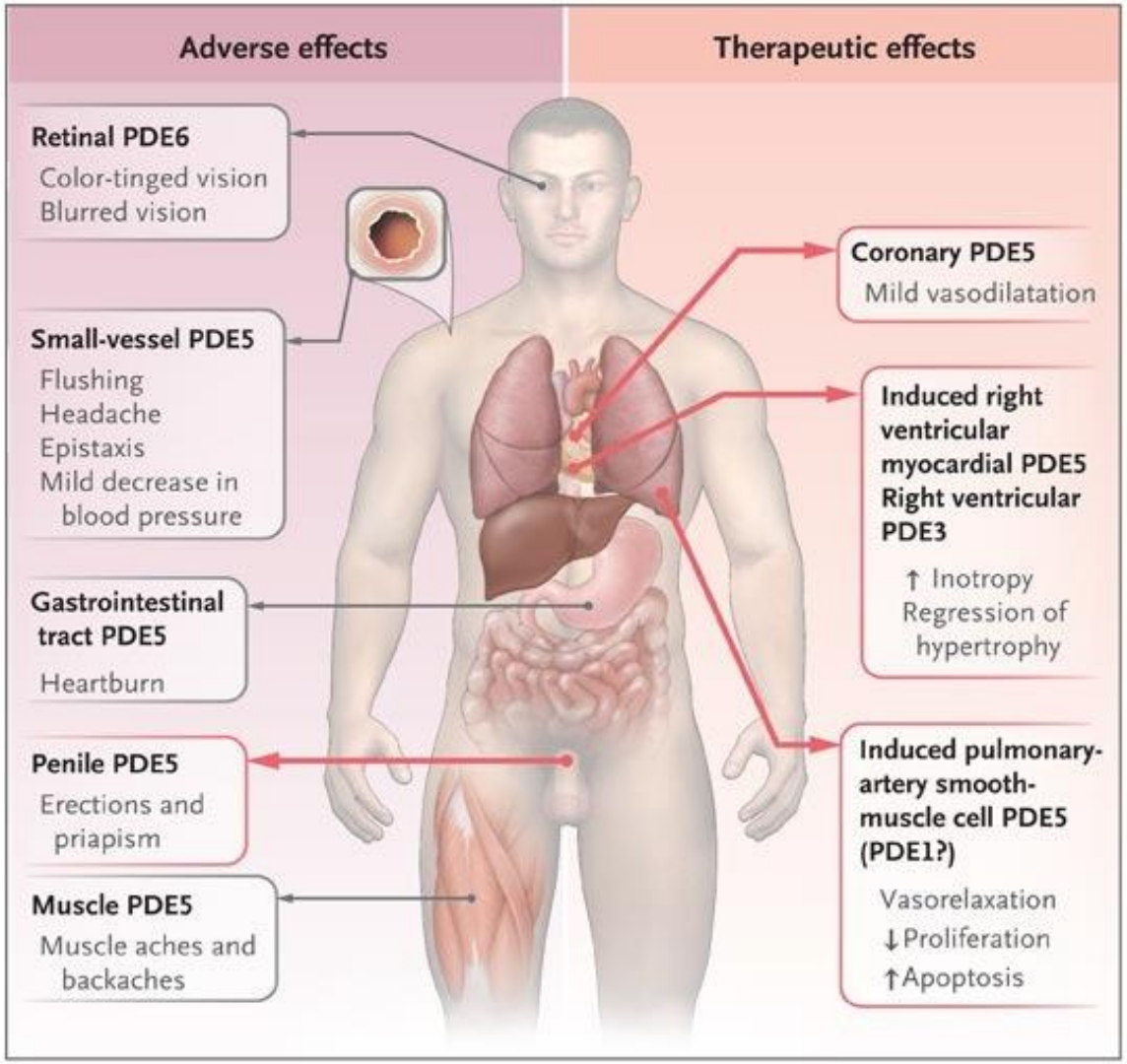
ET_B-mediated effect

- release of NO and PGI
- ET-1 clearance
- inhibits ET converting enzyme



Phosphodiesterase (PDE)-5 Inhibitors for PAH



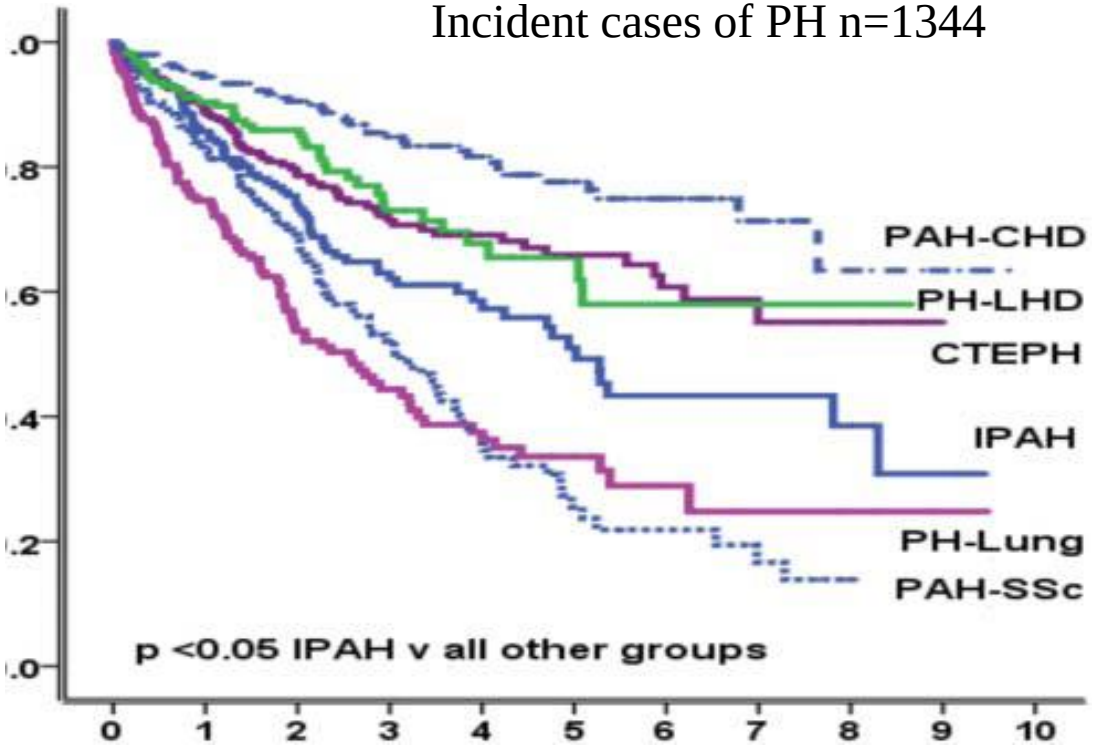


Archer SL, et al. N Engl J Med 2009;361:1864-71

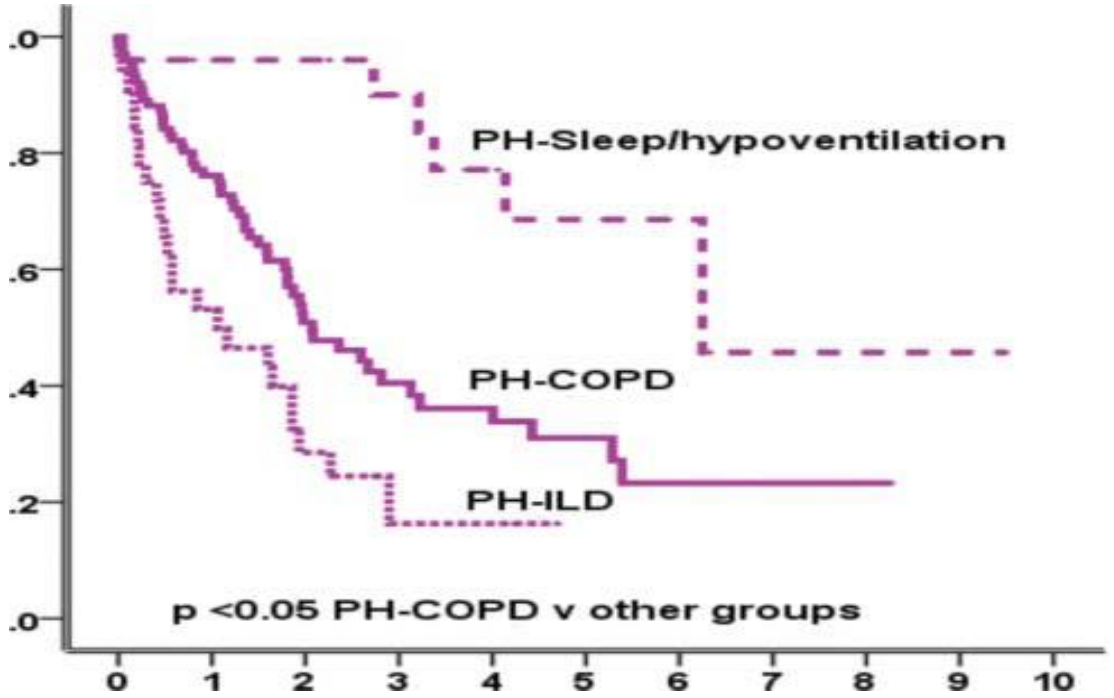
Survivals in PH-LD: the ASPIRE registry

3 year survival
IPAH (68%) vs PH-Lung (44%)

Incident cases of PH n=1344



3 year survival
PH-sleep/hypoventilation (90%)
PH-COPD (41%)
PH-ILD (16%)



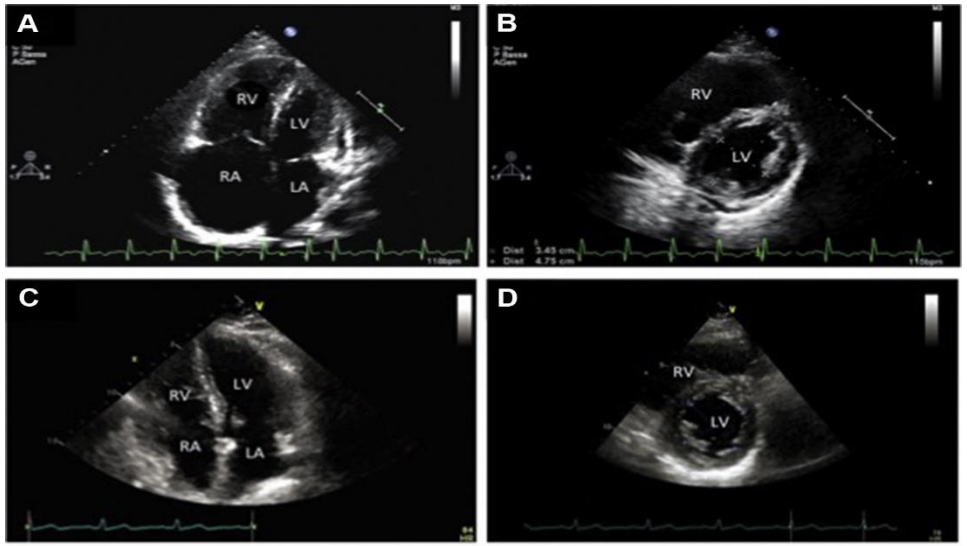
Hurdman et al. Eur Respir J. 2012

Right Heart Reverse Remodeling by Upfront Triple Combination Therapy in PAH

21 patients with newly diagnosed high-risk IPAH were treated upfront with a combination of ambrisentan, tadalafil, and subcutaneous treprostinil

Variable	Baseline	Follow-Up	Change (%)	*P* Value
Right-sided atrial area, cm^2	29 ± 3	21 ± 2	−8 (−28)	< .001
RV end-diastolic area, cm^2	28 ± 2	20 ± 3	−8 (−29)	< .001
RV end-systolic area, cm^2	21 ± 2	12 ± 2	−9 (−43)	< .001
Fractional area change, %	27 ± 4	40 ± 5	13 (63)	< .001
LV eccentricity index	1.5 ± 0.1	1.2 ± 0.1	−0.3 (−20)	< .001

Variable	Baseline	Follow-Up	Change (%)	*P* Value
RAP, mm Hg	13 ± 3	5 ± 2	−8 (−62)	< .001
mPAP, mm Hg	60 ± 9	42 ± 5	−18 (−30)	< .001
PAWP, mm Hg	8 ± 2	9 ± 3	1 (12)	.545
Cardiac input, $L/min/m^2$	1.8 ± 0.3	3.5 ± 0.8	1.7 (94)	< .001
PVR, WU	16.4 ± 4.4	5.5 ± 1.3	−10.9 (−69)	< .001
Svo_2, %	56 ± 6	70 ± 7	14 (25)	< .001



	Baseline	Follow-up
PVR (WU)	17.9	6.1
RVEDA (cm^2)	26	17
RVESA (cm^2)	19	10
LV-EI	1.5	1.1
REVEAL 2.0	11	7

D'Alto M, et al. CHEST 2020; 157(2):376-383

Bosentan in IPF without PH: BUILD-1

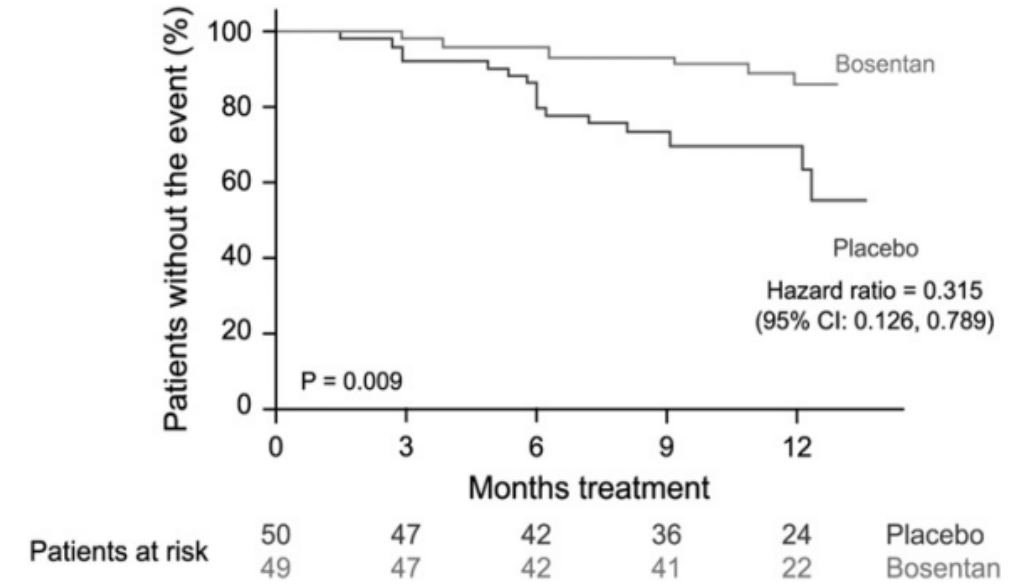
- Study design: Double blinded, placebo controlled RCT
- Inclusion: IPF made within 3years before enrollment
- **Exclusion: FVC < 50% pred., DLco < 30% pred., echocardiographic evidence of PH, etc.**

Primary outcome: 6MWD

Characteristic	Bosentan (*n* = 71)	Placebo (*n* = 83)
Baseline, m		
Mean ± SD	375 ± 92	372 ± 74
Median	397	387
Up to Month 12 (m)		
Mean ± SD	323 ± 164	338 ± 162
Median	390	369
Change,* m		
Mean ± SD	−52 ± 121	−34 ± 127
Median	−23	−9
Treatment effect		
Mean ± SD		−18 ± 20
Median		−17
P value		0.226

* Change from baseline up to Month 12.

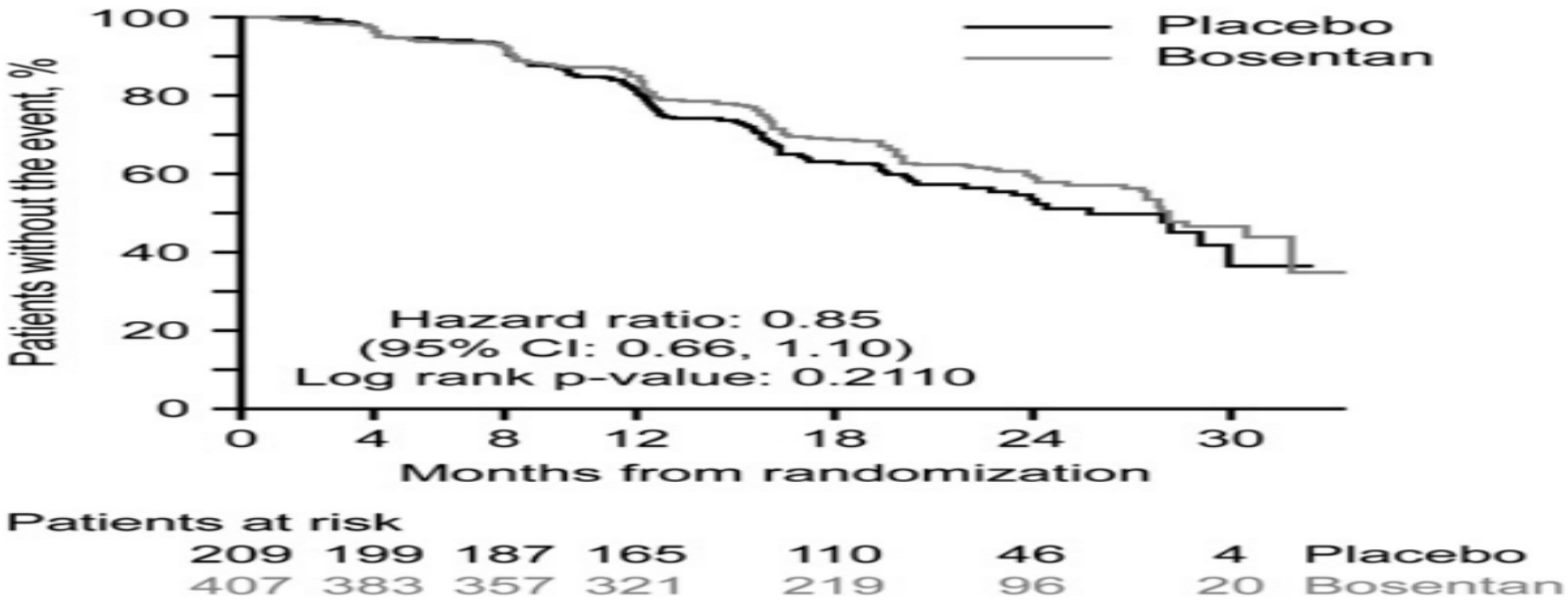
Subgroup analysis in patients with SLB: time to disease progression or death



King TE, et al. Am J Respir Crit Care Med. 2008; 177:75-81

Bosentan in IPF: BUILD-3

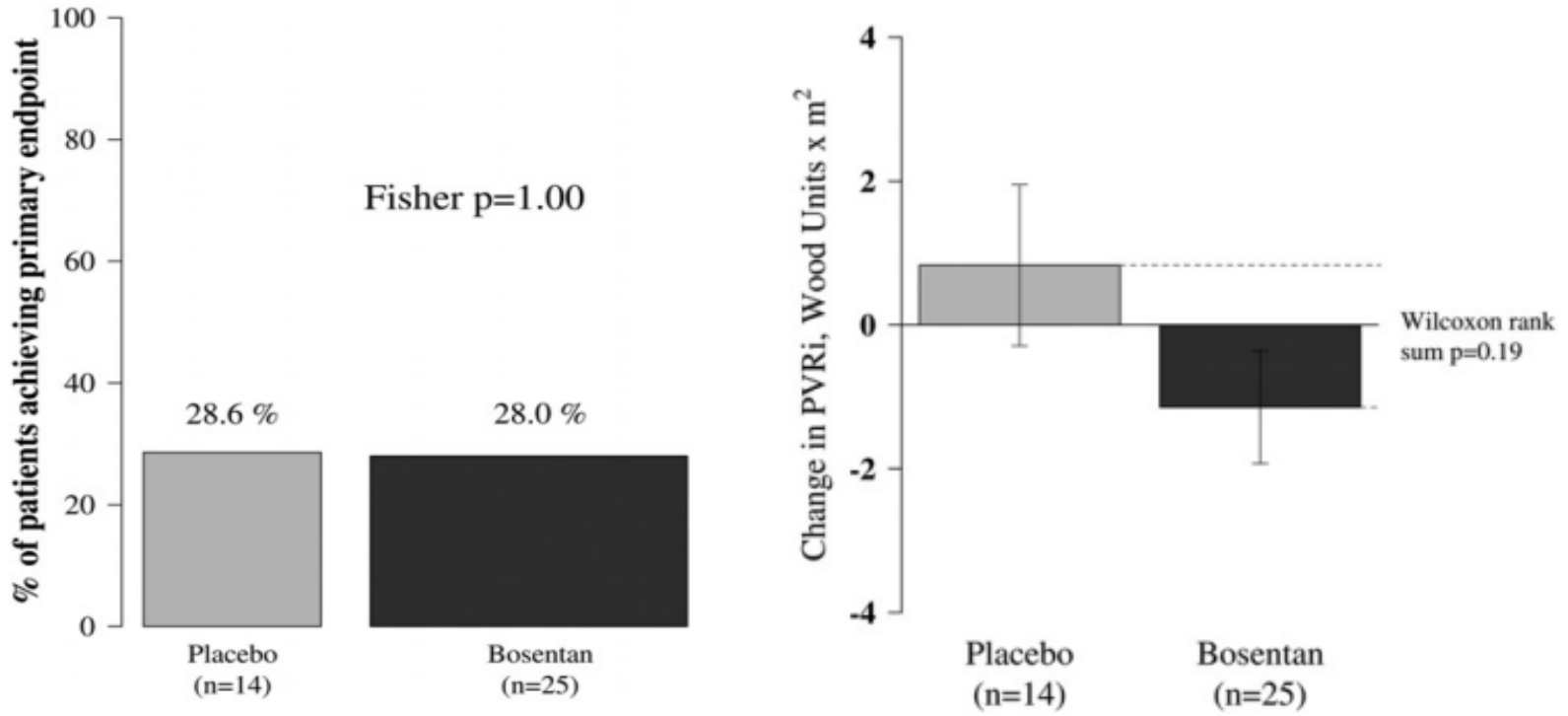
- Study design: **event-driven morbidity and mortality RCT**
- Inclusion: **IPF confirmed by surgical lung biopsy**
- **Exclusion: Extensive honeycombing on HRCT, FVC < 50% pred., DLco < 30% pred., etc.**



King TE, et al. Am J Respir Crit Care Med. 2011; 92-99

Bosentan in fibrotic IIP with PH

- The BPHIT study : Double blinded, placebo controlled RCT
- Inclusion: **60 patients with RHC confirmed PH**
- Primary outcome: **proportion of PVRI change > 20% over 16 weeks**



Corte TJ, et al. Am J Respir Crit Care Med Vol 2014;190: 208–217

Ambrisentan in IPF: The ARTEMIS-IPF study

Study design: DB, placebo-controlled. Event-driven RCT
Inclusion criteria: Patients with IPF aged 40 to 80 years with **minimal or no honeycombing on HRCT**
Primary endpoint: time to disease progression

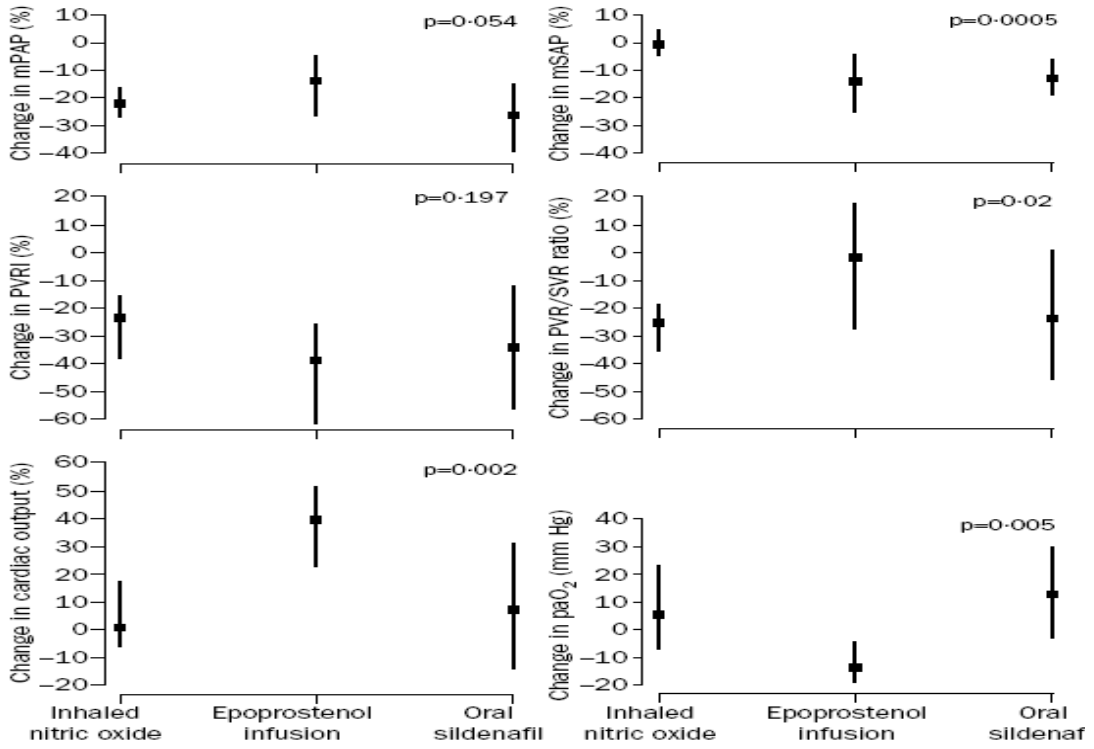
End Point	Placebo (n = 163)		Ambrisentan (n = 329)		Log-Rank P Value	Kaplan–Meier Estimate (95% CI) at Week 52, %			Hazard Ratio (95% CI)‡	P Value
	Events, n	Proportion (95% CI)*	Events, n	Proportion (95% CI)*		Placebo (n = 163)	Ambrisentan (n = 329)	Difference†		
Disease progression	28	17 (12 to 24)	90	27 (23 to 33)	0.010	22 (15 to 32)	39 (32 to 47)	17 (5 to 28)	1.74 (1.14 to 2.66)	0.011
Lung function decline	19	12 (7 to 18)	55	17 (13 to 21)	0.109	14 (8 to 23)	25 (19 to 32)	11 (−17 to 39)	1.53 (0.84 to 2.78)	0.112
Respiratory hospitalization	9	6 (3 to 10)	44	13 (10 to 18)	0.007	9 (4 to 17)	20 (15 to 26)	11 (4 to 23)	2.59 (1.14 to 5.89)	0.009
Death	6	4 (1 to 8)	26	8 (5 to 11)	0.100	5 (2 to 11)	11 (7 to 17)	6 (4 to 34)	2.08 (0.75 to 5.76)	0.108

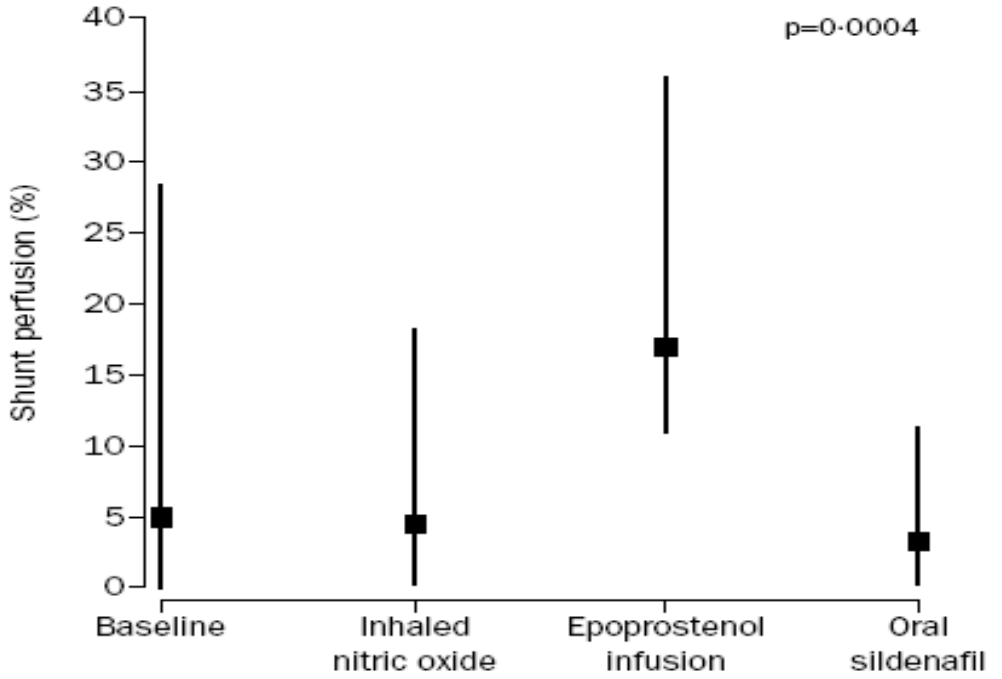
The study was terminated prematurely because of lack of efficacy, a worse outcome was observed in terms of disease progression.

Raghu et al. Ann Intern Med. 2013;158:641-649

Sildenafil in severe PH-IPF

- 16 IPF patients with mPAP > 35 mmHg





Sildenafil leads to preferential pulmonary artery vasodilation in well-ventilated lung tissue and may improve V/Q matching and gas exchange in IPF.

Ghofani HA et al. Lancet 2002

Sildenafil in severe IPF

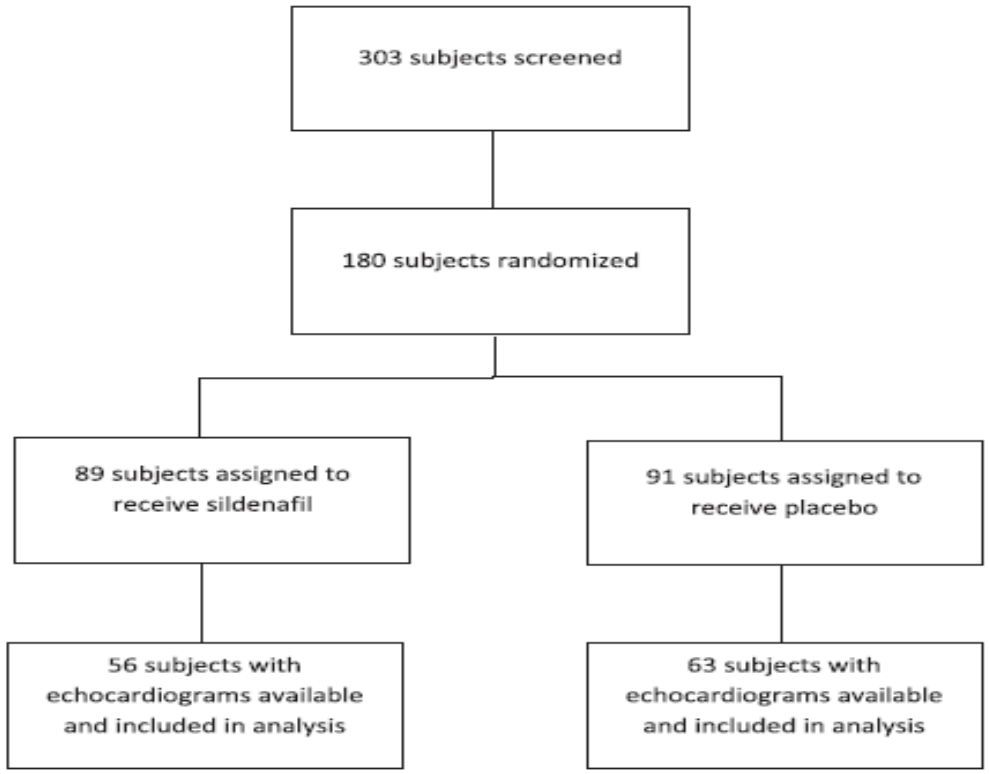
- **The STEP-IPF study** : **12 week,** double blinded, RCT
- Inclusion: **180 patients with advanced IPF (DLCO < 35% predicted)**
- Primary outcome: **proportion of 6MWD change > 20%**

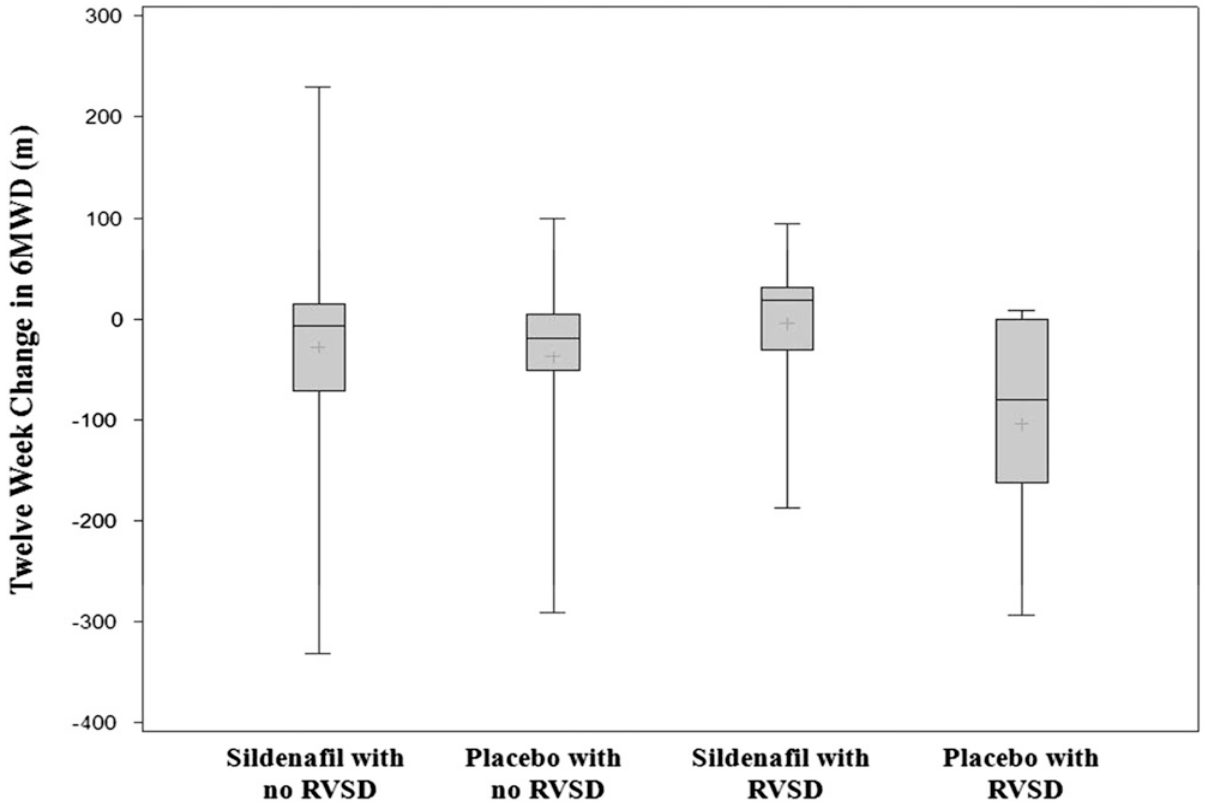
Endpoint	Sildenafil (N = 89)	Placebo (N = 91)	*P*-value
6MWD improvement ≥ 20% (Primary)	9/89 (10%)	6/91 (7%)	0.39
ΔDL_{CO} (%)	−0.33	−1.87	0.04
ΔPPO_2 (mm Hg)	−0.63	−3.64	0.02
ΔSOB Questionairre	0.22	6.81	0.006
ΔSGRQ (QOL)	−1.64	2.45	0.01

IPF Clinical Research Network. N Engl J Med. 2010

Sildenafil in patients with IPF and RV dysfunction

- **A subgroup analysis of the STEP-IPF study**





Han MK et al. CHEST 2013; 143(6):1699–1708

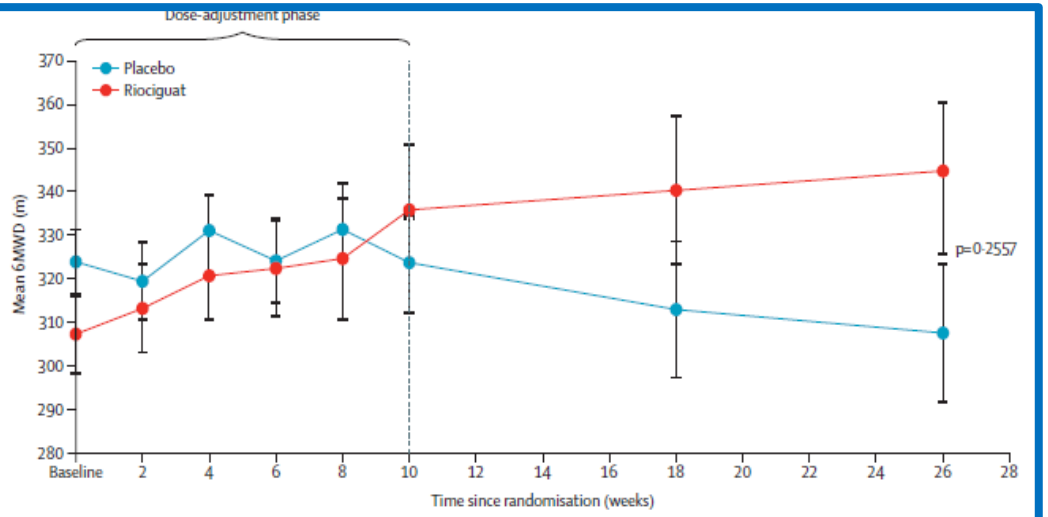
Riociguat in PH-IIP: RISE-IIP trials

Study design: 26 weeks, DB, placebo-controlled RCT

Inclusion: 147 IIP patients, FVC> 45% pred. 6MWD 150-450m, **PAH confirmed by RHC**

Primary outcome: change in 6MWD

	Main phase	
	Riociguat up to 2·5 mg (n=73)	Placebo (n=74)
Any AE	65 (89%)	64 (86%)
Study drug-related AEs	29 (40%)	28 (38%)
AEs leading to study drug discontinuation	11 (15%)	3 (4%)
Any SAE	27 (37%)	17 (23%)
Study drug-related SAEs	5 (7%)	4 (5%)
SAEs leading to study drug discontinuation	10 (14%)	1 (1%)
Deaths	8 (11%)	3 (4%)

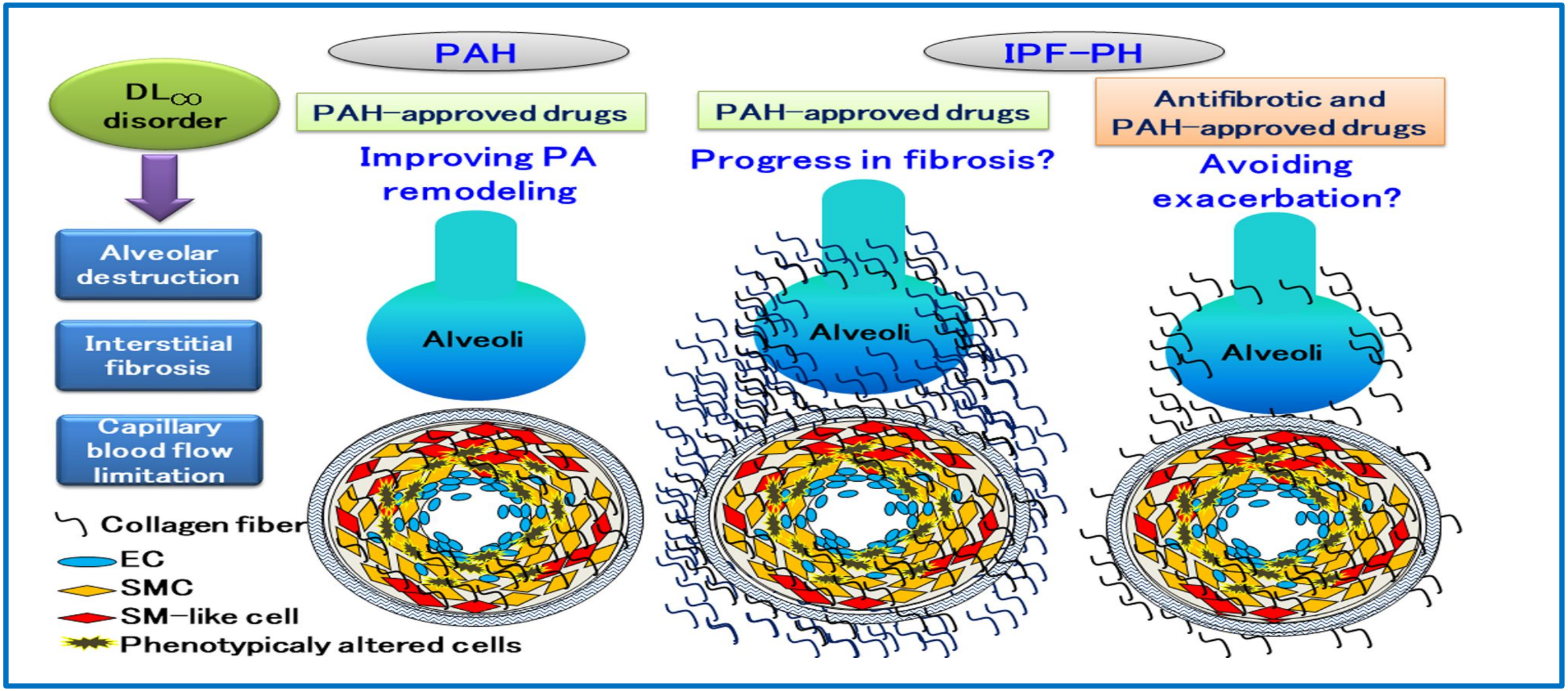


Number of patients															
Placebo	74	73	66	60	53	50	..	..	..	40	..	..	..	38	..
Riociguat	73	69	64	57	48	43	..	..	..	34	..	..	..	31	..
Mean (SD) absolute 6MWD, m															
Placebo	324 (66)	320 (77)	331 (68)	324 (77)	332 (78)	324 (81)	..	..	..	313 (100)	..	..	..	308 (98)	..
Riociguat	307 (80)	313 (87)	321 (81)	323 (86)	325 (97)	336 (99)	..	..	..	340 (101)	..	..	..	345 (107)	..

The study was terminated early owing to increased serious AEs and mortality in riociguat group

Nathan SD et al. Lancet Respir Med 2019; 7: 780–9

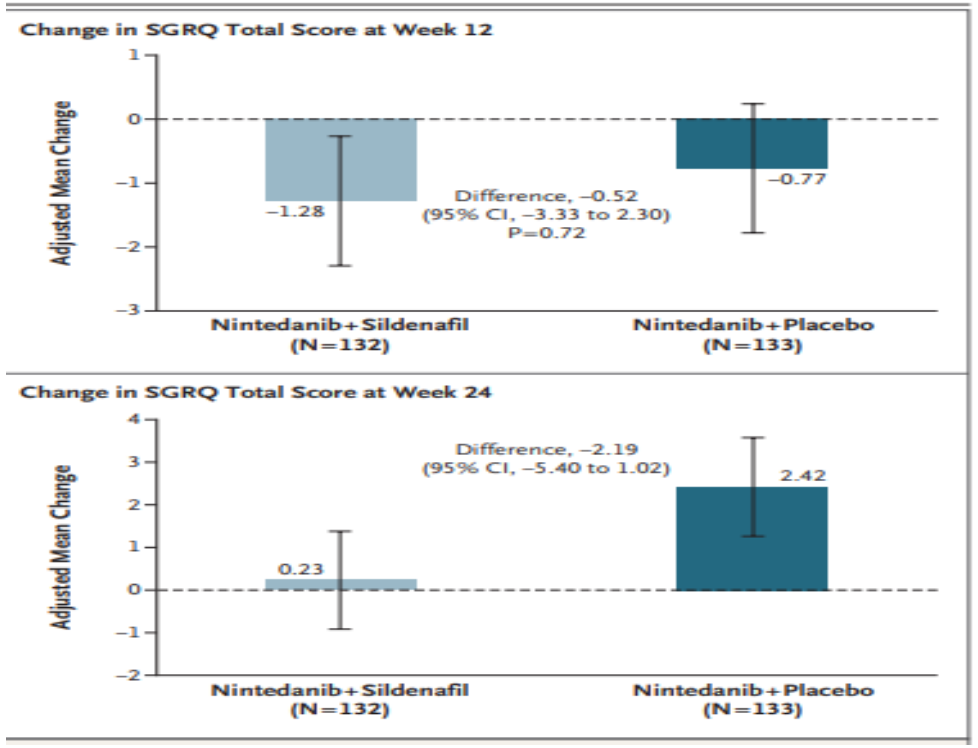
PAH targeted and anti-fibrotic drugs in PH-ILD

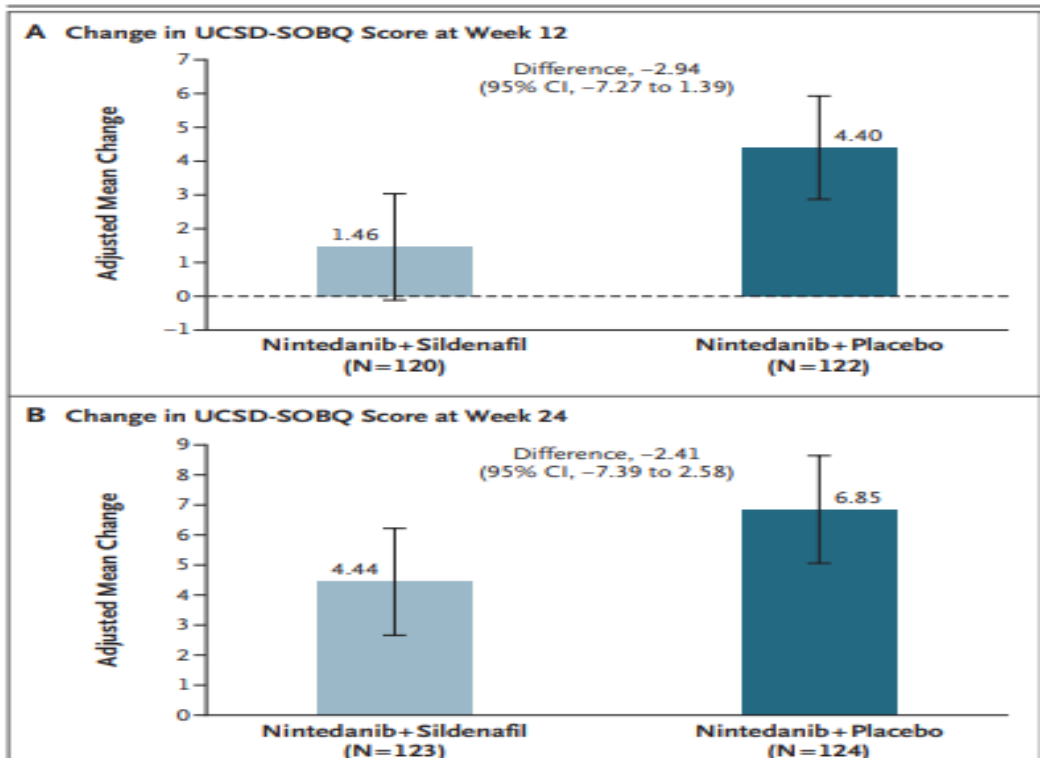


Sakao S , et al. J Am Heart Assoc. 2019;8:e013310.

Nintedanib plus sildenafil in severe IPF: The INSTAGE trial

- **Inclusion : Advanced IPF (DL_{CO} < 35% predicted)**
- **Primary endpoint: Change in SQRQ score at week 12**



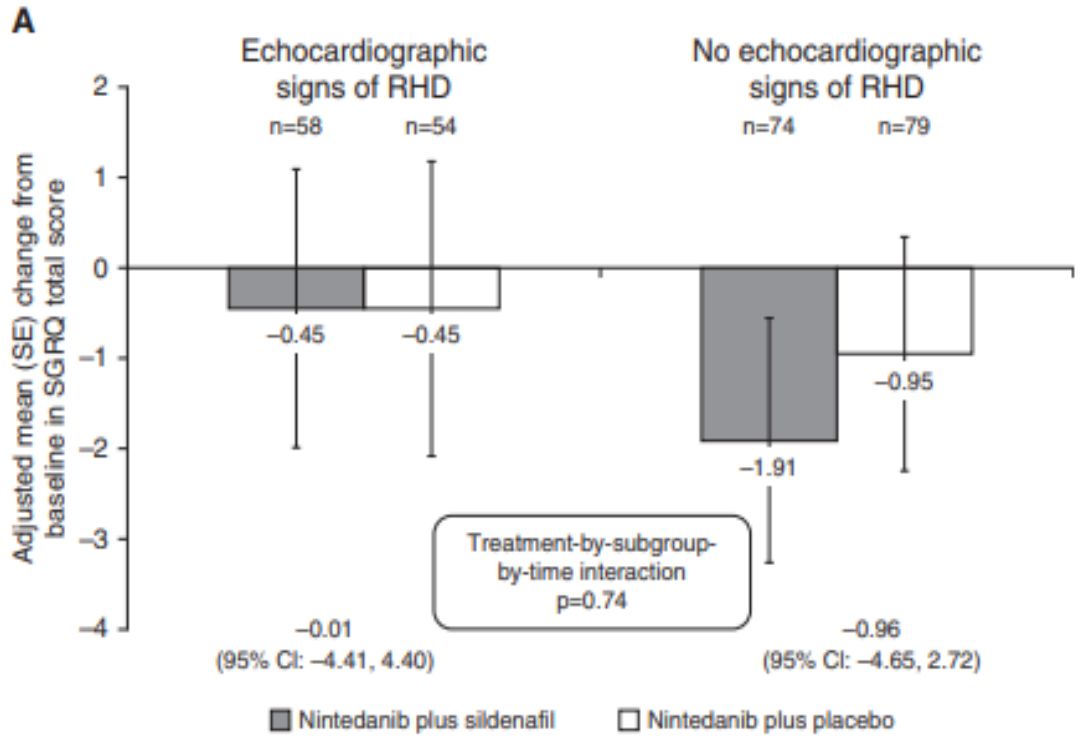


Kolb M, et al. N Engl J Med 2018;379:1722-31

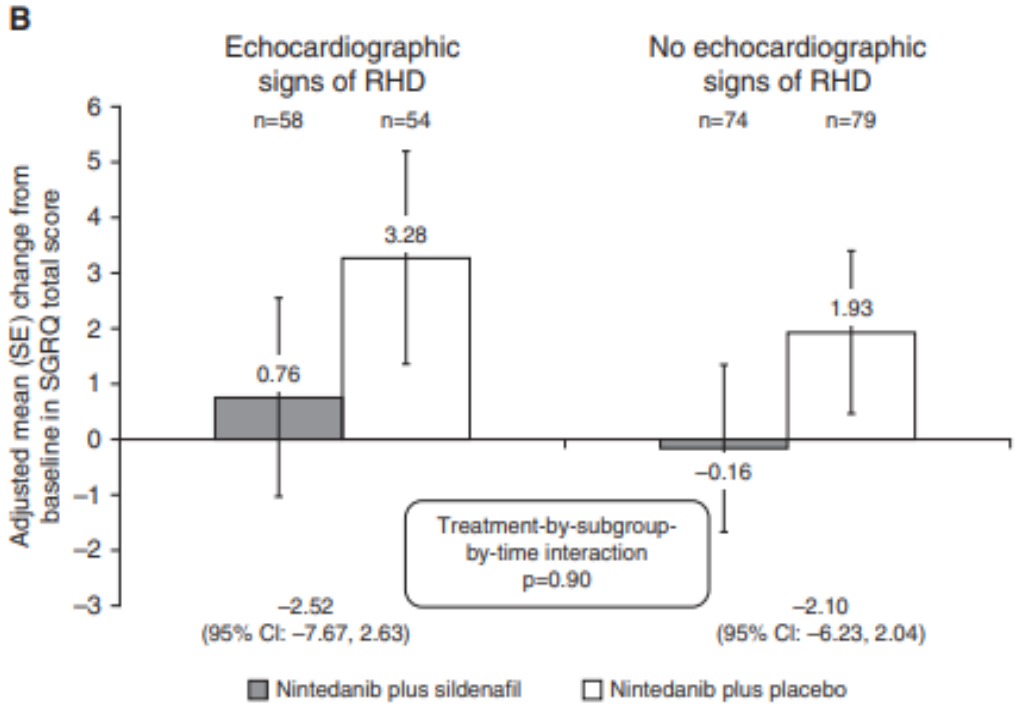
Nintedanib plus sildenafil in severe IPF with RV dysfunction

- **A pre-specified subgroup analysis of the INSTAGE study (119/180)**

(A) Week 12



(B) Week 24



Behr J, et al. Am J Respir Crit Care Med 2018; 200: 1505–1512

Sildenafil added to pirfenidone in patients with advanced IPF and risk of PH: A Phase IIb, RCT

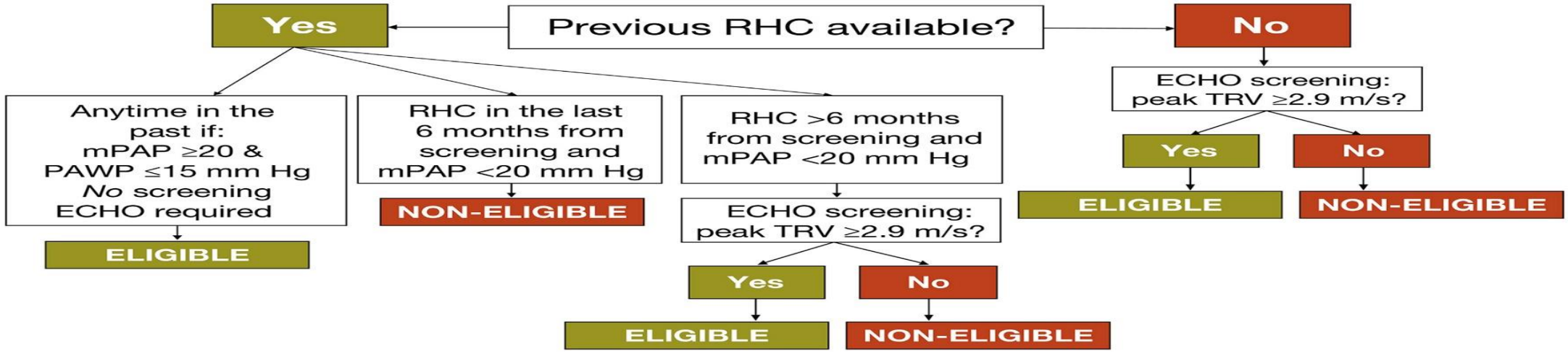
A

Advanced IPF
defined as a measurable %DLco ≤40% at screening

and

Risk of Group 3 PH
defined by
mPAP ≥20 mm Hg with PAWP ≤15 mm Hg on a previous RHC
or
Intermediate/high probability of Group 3 PH
as defined by the 2015 ESC/ERS guidelines [17]
In the absence of a previous RHC, patients with an ECHO showing a peak TRV ≥2.9 m/s will be considered eligible, assuming all other eligibility criteria are met

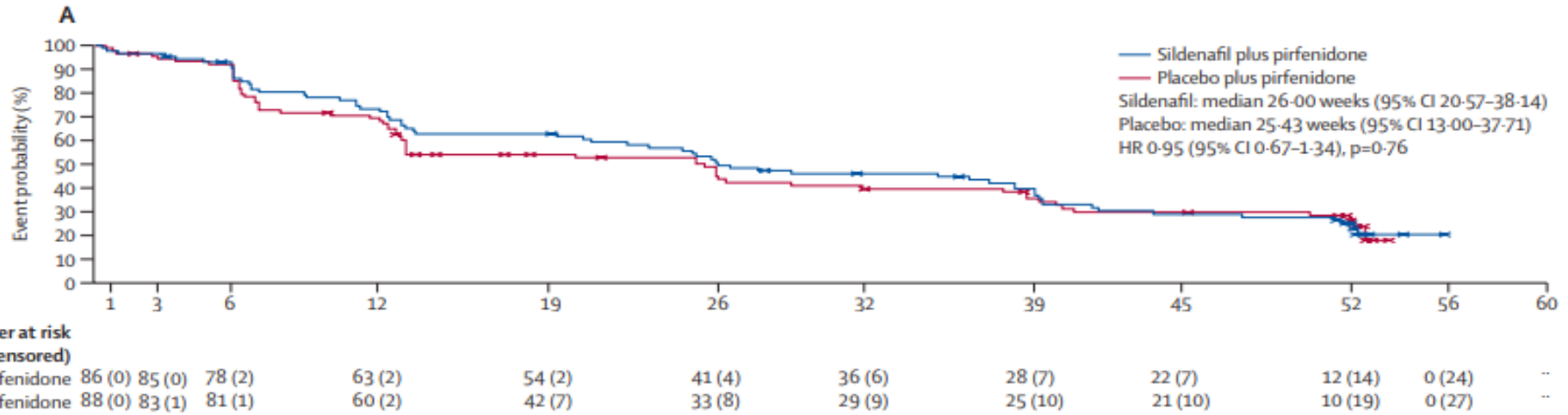
B



Behr J, et al. Respiratory Medicine 2018; 138:13–20

Sildenafil added to pirfenidone in patients with advanced IPF and risk of PH: A Phase IIb, RCT

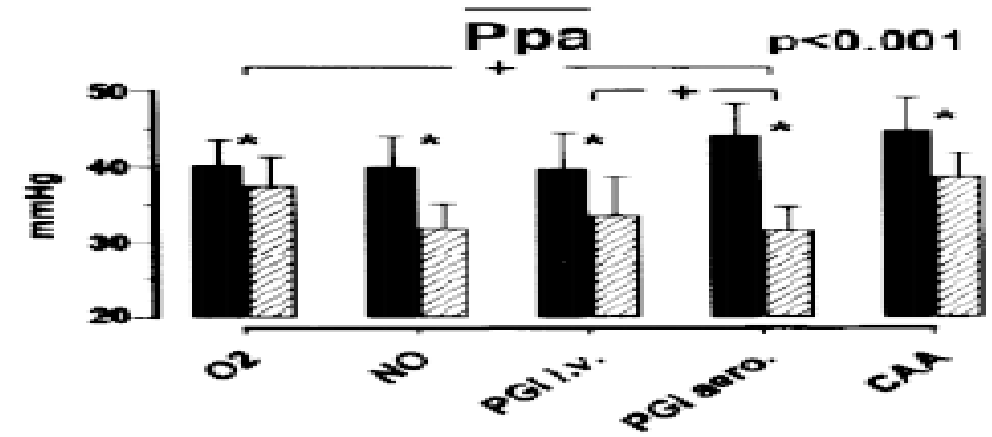
The composite primary endpoint : disease progression, defined as either a relevant decline in 6MWD, respiratory-related admission to hospital, or all-cause mortality, after 52 weeks

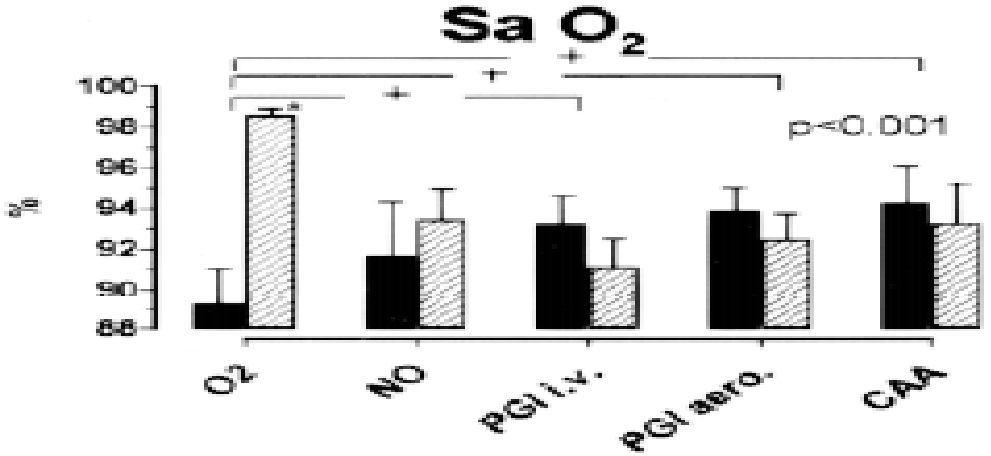


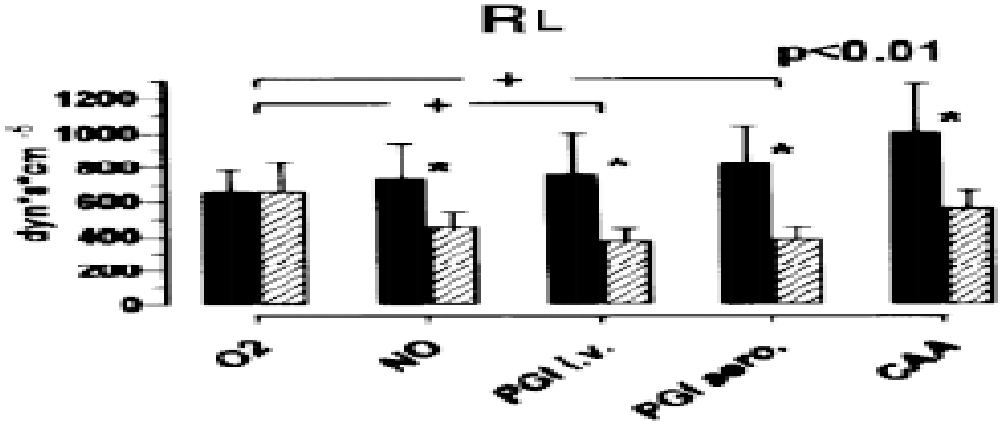
	Pirfenidone plus sildenafil (n=88)	Pirfenidone plus placebo (n=89)	Between-group difference	p value
FVC, mL (95% CI)	−145·0 (−231·3 to −58·6)*	−93·0 (−184·7 to −1·4)†	−51·9 (−159·5 to 55·6)	0·34
NT-proBNP, pg/mL (95% CI)	568·8 (81·6 to 1056·0)‡	775·4 (254·2 to 1296·6)§	−206·6 (−920·0 to 506·9)	0·56
6-min walk distance, m (95% CI)	−80·1 (−107·1 to −53·1)¶	−68·6 (−97·6 to −39·7)‖	−11·5 (−49·5 to 26·5)	0·55

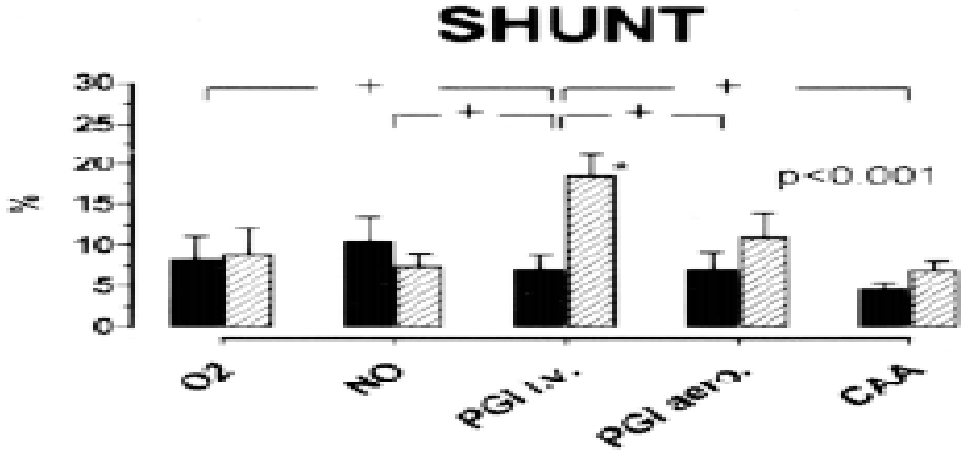
Behr J, et al. Lancet Respir Med 2021; 9: 85–95

IV and inhaled prostacylin in PH-lung fibrosis









Olschewski H. AM J RESPIR CRIT CARE MED 1999;160:600–607

Inhaled treprostinil in PH-ILD: INCREASE trial

- Multicenter, randomized, DB, placebo-controlled, 16-week trial
- Inclusion criteria : **Group 3 PH by RHC** and FVC <70% pred.
- Primary endpoint: difference in peak 6-minute walk distance

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)

Wasman A, et al. N Engl J Med 2021;384:325-34.

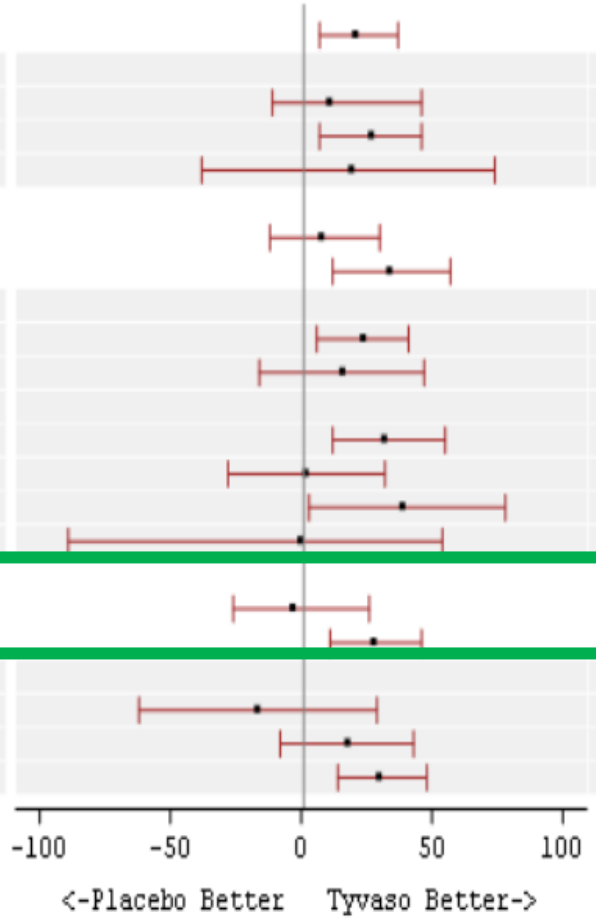
Inhaled treprostinil in PH-ILD: INCREASE trial

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		

Wasman A, et al. N Engl J Med 2021;384:325–34.

Subgroup analysis of primary efficacy endpoint

Subgroup	Tyvaso # of Patients	Placebo # of Patients	H-L Estimate (95% CI)	p-value
Overall	163	163	21.0(7.0, 37.0)	0.0043
Age Group				
<65 years old	64	48	11.0(-11.0, 46.0)	0.3203
65 - <80 years old	83	100	27.0(7.0, 46.0)	0.0111
>=80 years old	16	15	19.5(-38.0, 74.0)	0.9457
Sex				
Male	78	95	8.0(-12.0, 30.0)	0.4877
Female	85	68	34.0(12.0, 57.0)	0.0010
Baseline 6MWD Category				
<=350 meters	136	133	24.0(6.0, 41.0)	0.0084
>350 meters	27	30	16.0(-16.0, 47.0)	0.2697
PH-ILD Etiology				
IIP	65	81	32.0(12.0, 55.0)	0.0030
CPFE	42	40	2.0(-28.0, 32.0)	0.8742
CTD	40	32	39.0(3.0, 78.0)	0.0317
Other	16	10	0.0(-89.0, 54.0)	0.3607
Baseline PVR Category				
<4 WU	32	34	-3.0(-26.0, 26.0)	0.7345
>=4 WU	131	129	28.0(11.0, 46.0)	0.0019
Maximum Study Drug Dose				
4-6 breaths	6	2	-16.5(-62.0, 29.0)	0.8481
7-9 breaths	37	24	18.0(-8.0, 43.0)	0.2875
>=10 breaths	78	94	30.0(14.0, 48.0)	0.0006



Female
IIP, CTD-ILD
≤350m
≥ 4WU

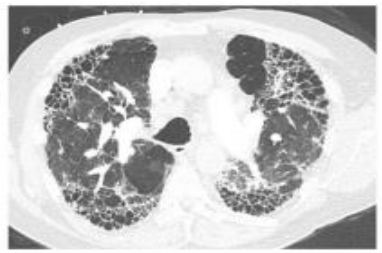
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214324s000lbl.pdf

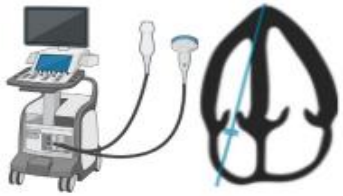
2022 ESC/ERS recommendations for PH-LD

Recommendations	Class[a]	Level[b]
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I	C
Inhaled treprostinil may be considered in patients with PH associated with ILD [734]	IIb	B
The use of ambrisentan is not recommended in patients with PH associated with IPF [740]	III	B
The use of riociguat is not recommended in patients with PH associated with IIP [181]	III	B
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]	III	C

Recommendations	GRADE		Class[a]	Level[b]
	Quality of evidence	Strength of recommendation		
PDE5is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	IIb	C
The use of PDE5is in patients with ILD and non-severe PH is not recommended	Very low	Conditional	III	C

Expert recommendations for PH-LD





ILD with Suspected PH

Refer to Expert Centre Right Heart Catheterization

mPAP >20 mm Hg AND PAWP ≤15 mm Hg

NO

STOP

NOT Pre-capillary PH

Yes

PVR > 5 WU

NO

STOP

ILD with Non-Severe PH

PDE5i Not Recommended

Yes

ILD with Severe PH

May consider :

Inhaled Treprostinil
OR
Individualized trial of PDE5i

5-10%
May consider

90-95% PAH target agent is not indicated

Weatherald J and Humbert M. Respirology 2024;28:212-214