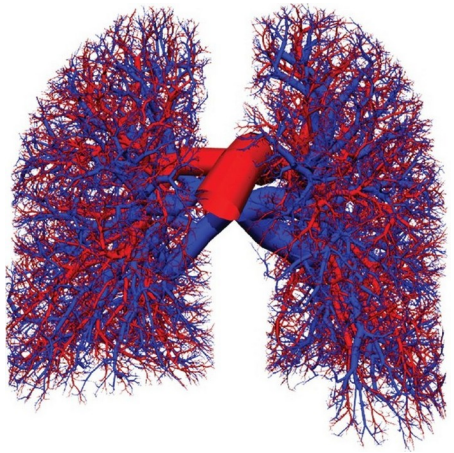

Pulmonary Vascular Disease Program

Brigham and Women's Hospital

Harvard Medical School

Pulmonary hypertension associated with interstitial lung disease

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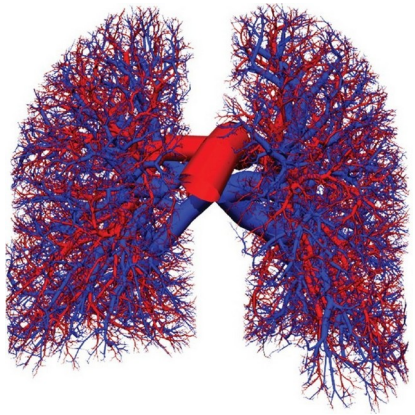
BWH BRIGHAM AND WOMEN'S HOSPITAL

PVDOMICS

CCC PHA Center of Comprehensive Care

HARVARD MEDICAL SCHOOL

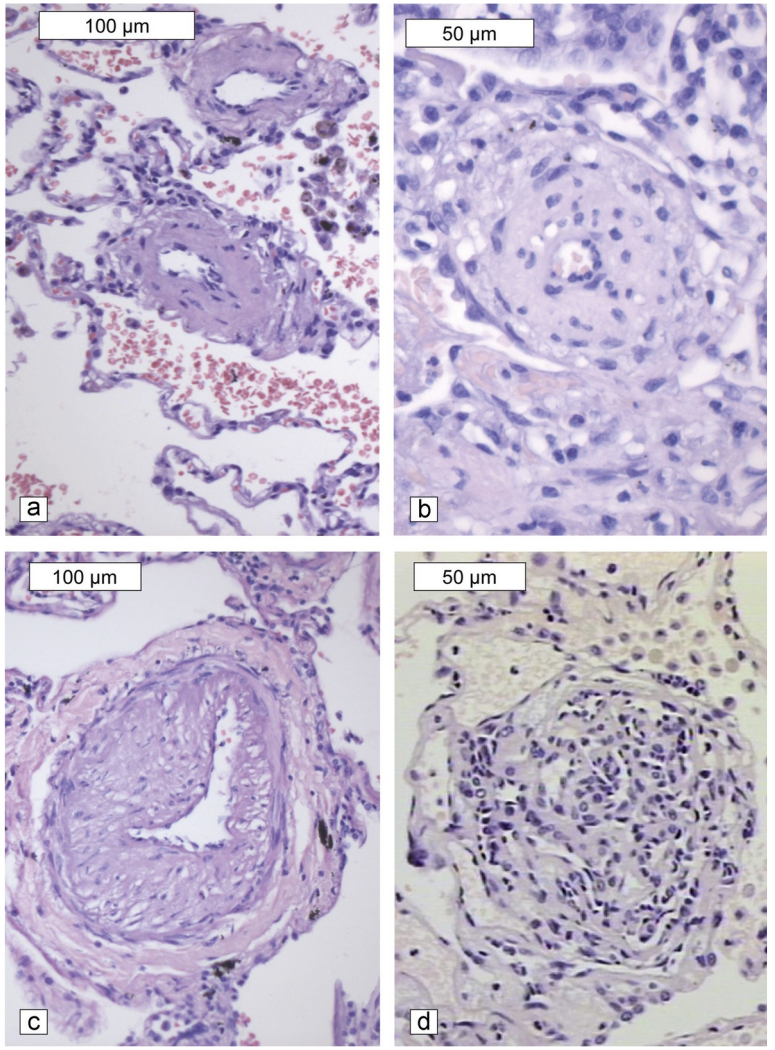


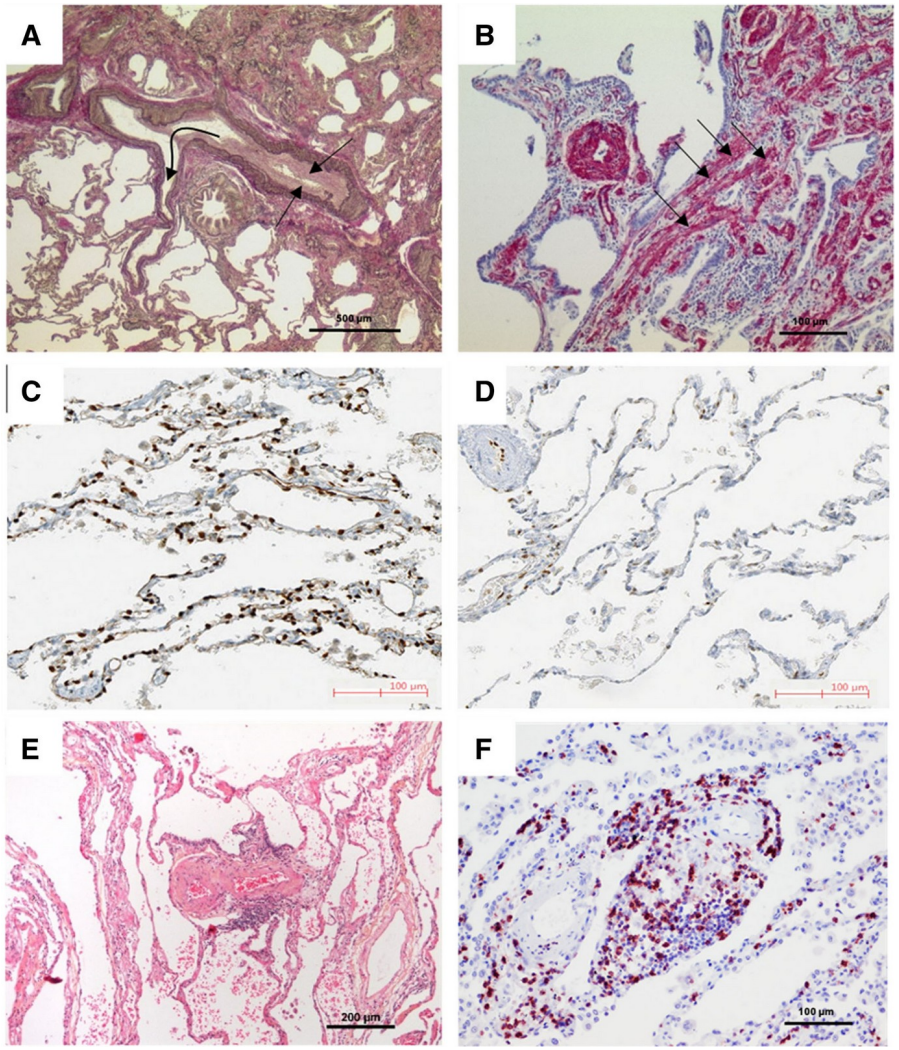
Disclosures

- United Therapeutics – Investigator, Study PI, Steering Cmt Chair
- Acceleron/Merck – Investigator, and Steering Committee member
- Aria-CV – PI
- Insmed – Chair, DSMB
- Janssen R&D – Investigator Initiated Grant
- R01HL158077 – Co-I
- R01HL160025 – Co-I
- PVDomics – Co-PI

Group 3 PH- Statement of the Problem

- WHO Group-3 PH is frequently encountered and adversely affects patients' quality of life and survival.
- Pulmonary vascular remodeling is a component of advanced lung disease and probably reflects the inflammatory nature of the disease

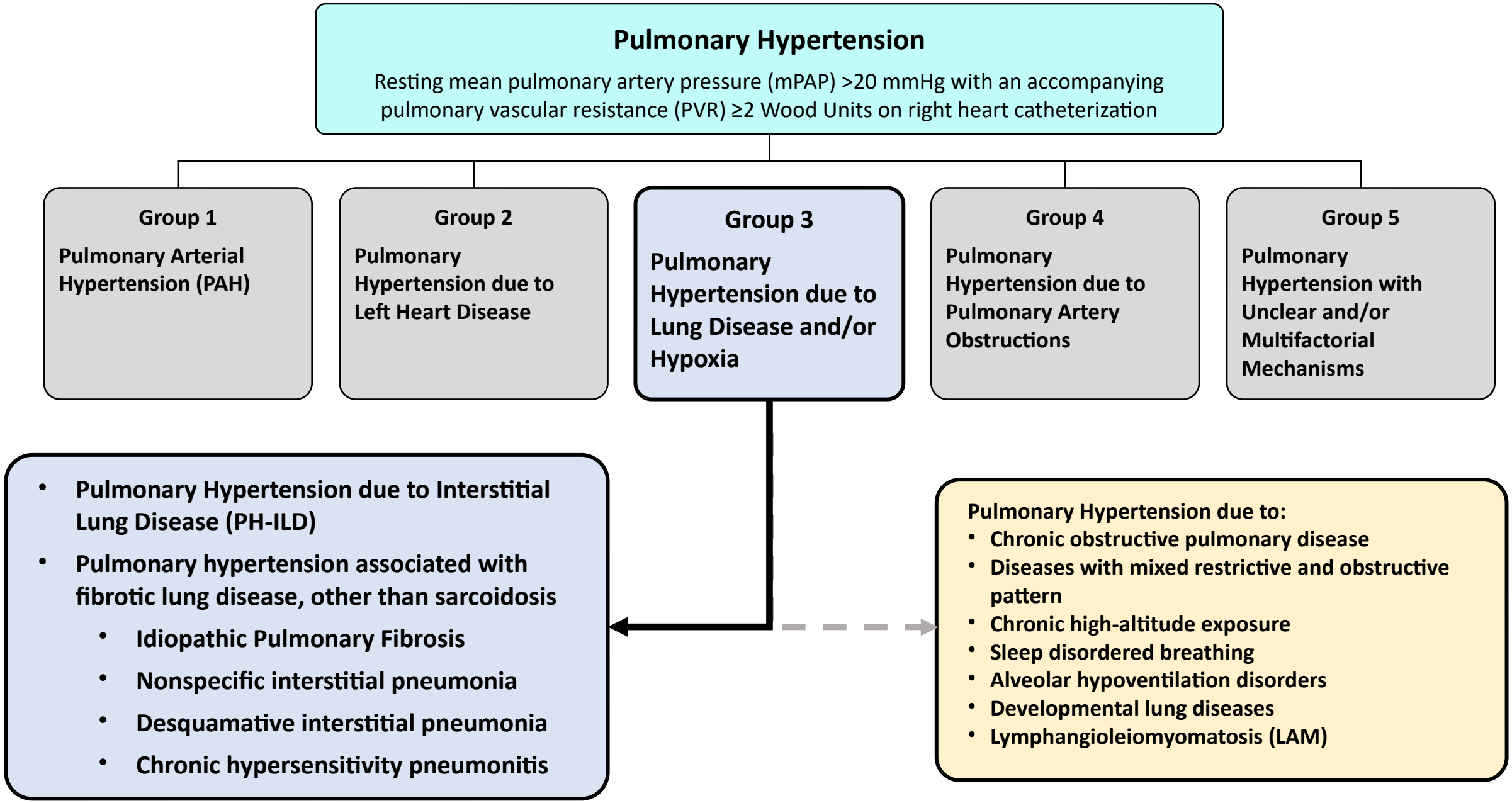




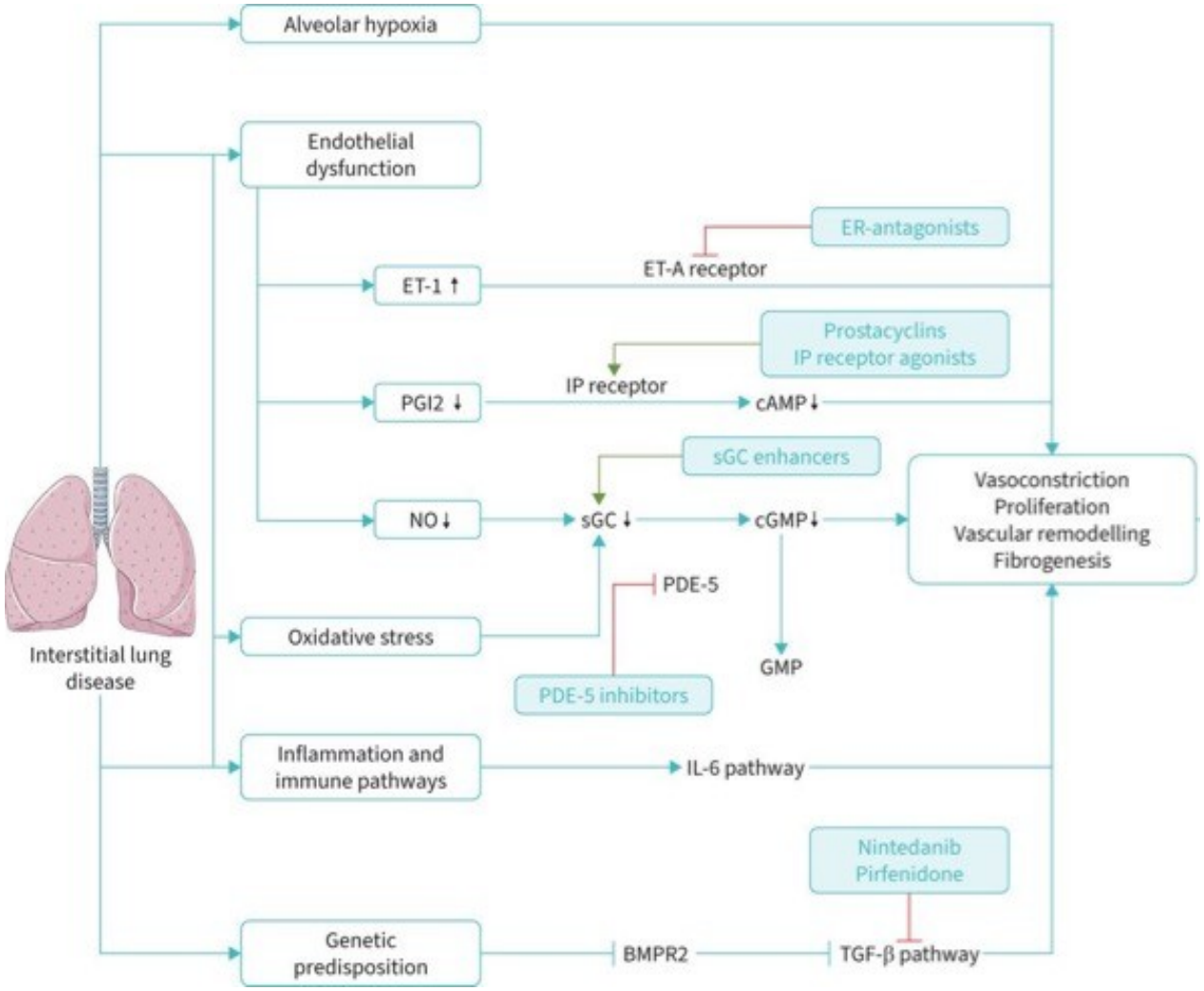
BRIGHAM AND WOMEN'S HOSPITAL

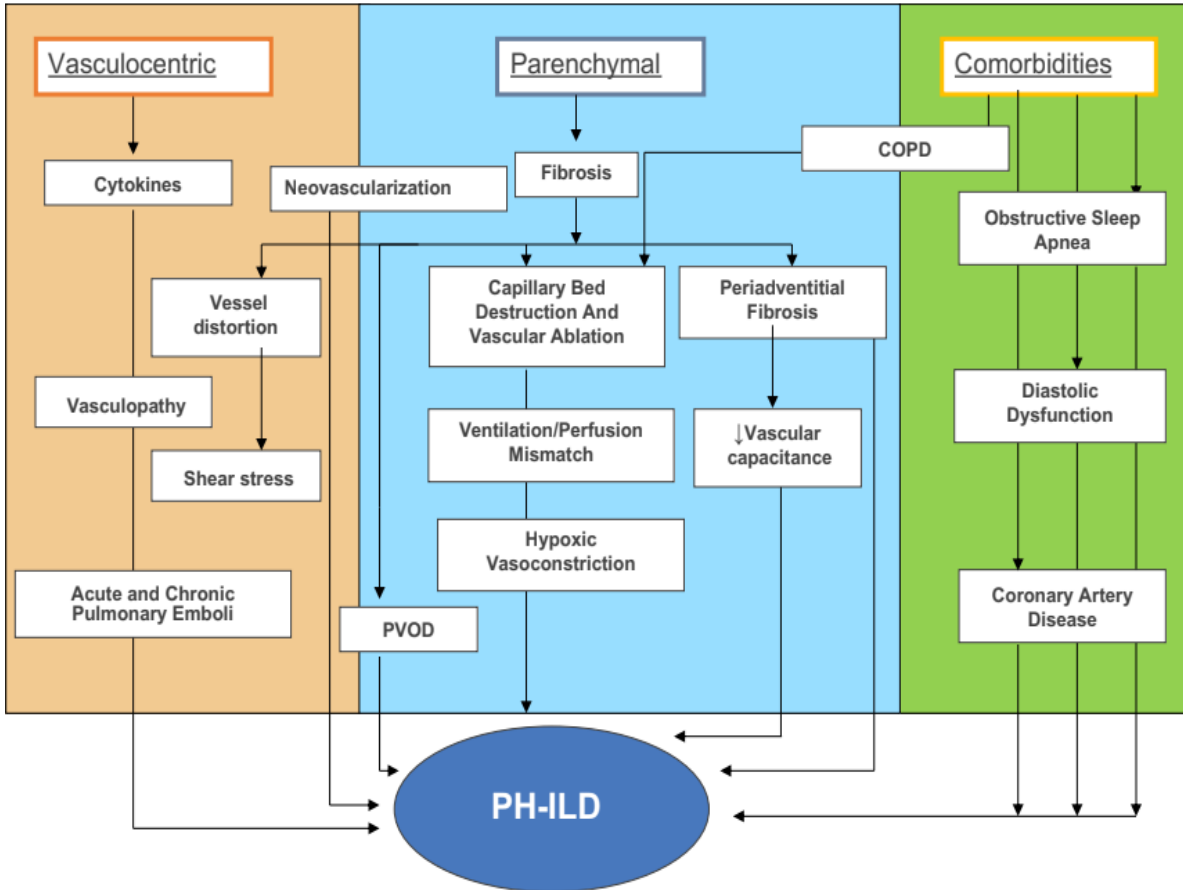
The Journal of Heart and Lung Transplantation 2013; 32:347-354,
Circ Res 2022 Apr 29;130(9):1404-1422.

HARVARD MEDICAL SCHOOL


Pulmonary Hypertension
Resting mean pulmonary artery pressure (mPAP) >20 mmHg with an accompanying pulmonary vascular resistance (PVR) ≥2 Wood Units on right heart catheterization
Group 1
Pulmonary Arterial Hypertension (PAH)
Group 2
Pulmonary Hypertension due to Left Heart Disease
Group 3
Pulmonary Hypertension due to Lung Disease and/or Hypoxia
Group 4
Pulmonary Hypertension due to Pulmonary Artery Obstructions
Group 5
Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms
• Pulmonary Hypertension due to Interstitial Lung Disease (PH-ILD)
• Pulmonary hypertension associated with fibrotic lung disease, other than sarcoidosis
• Idiopathic Pulmonary Fibrosis
• Nonspecific interstitial pneumonia
• Desquamative interstitial pneumonia
• Chronic hypersensitivity pneumonitis
Pulmonary Hypertension due to:
• Chronic obstructive pulmonary disease
• Diseases with mixed restrictive and obstructive pattern
• Chronic high-altitude exposure
• Sleep disordered breathing
• Alveolar hypoventilation disorders
• Developmental lung diseases
• Lymphangioleiomyomatosis (LAM)

Complex and Interrelated Pathophysiology of PH-ILD

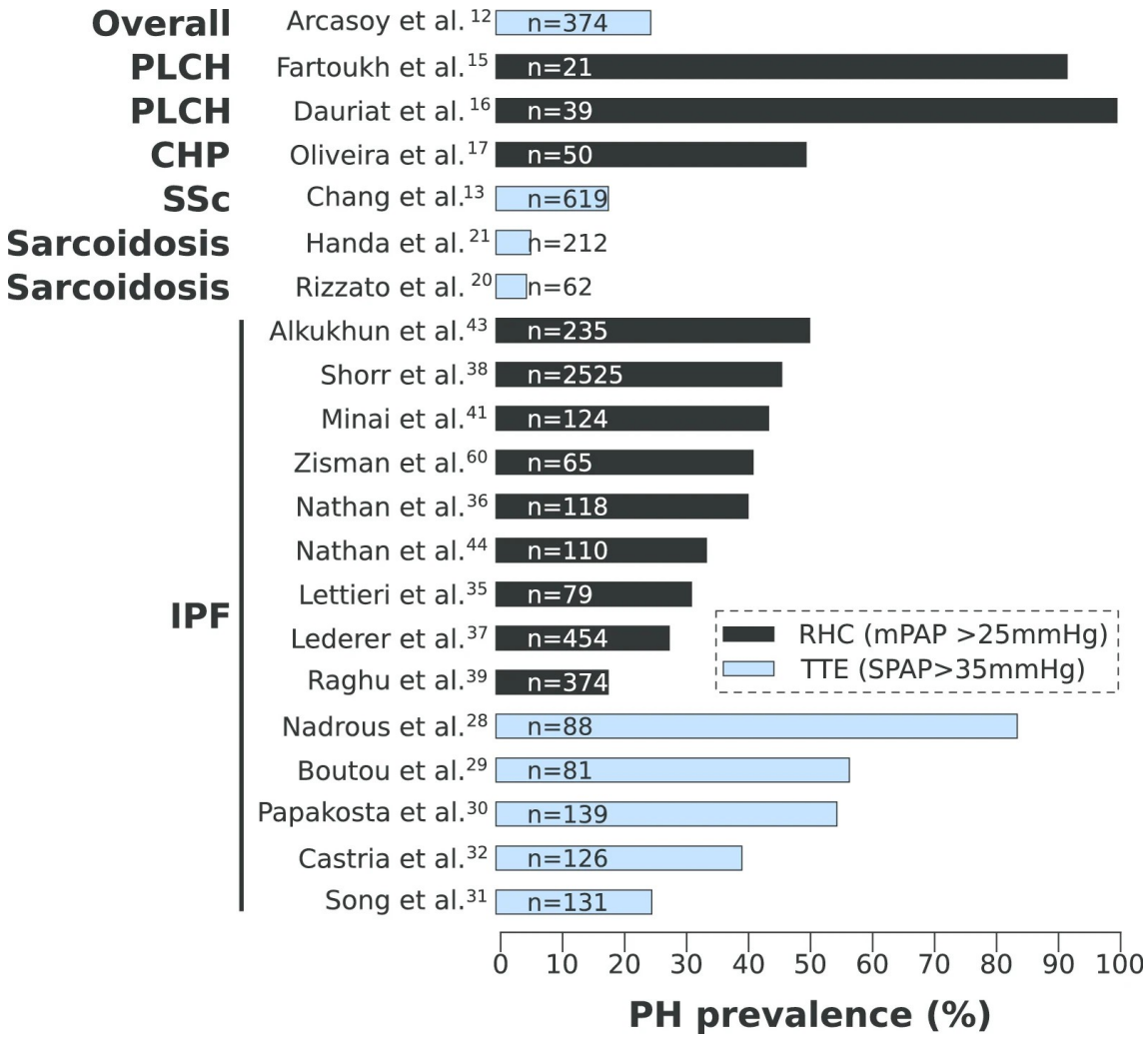




Behr J and Ryu JH, *Eur Respir J.* 2018;51(6):1800430. Shlobin OA, et al. *Chest.* 2017;151(1):204-214.
Sebastiaan Dhont et al. ERJ Open Res 2022;8:00272-2022

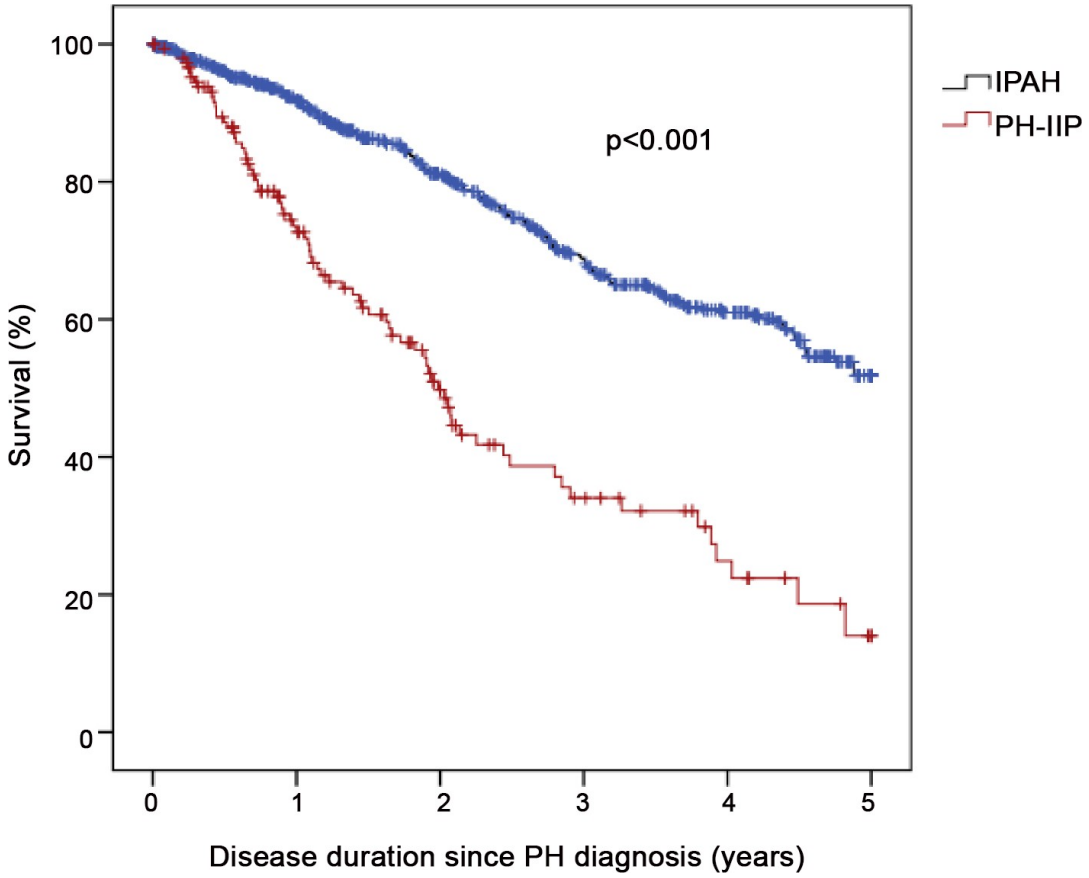
Prevalence of PH in patients with pulmonary fibrosis

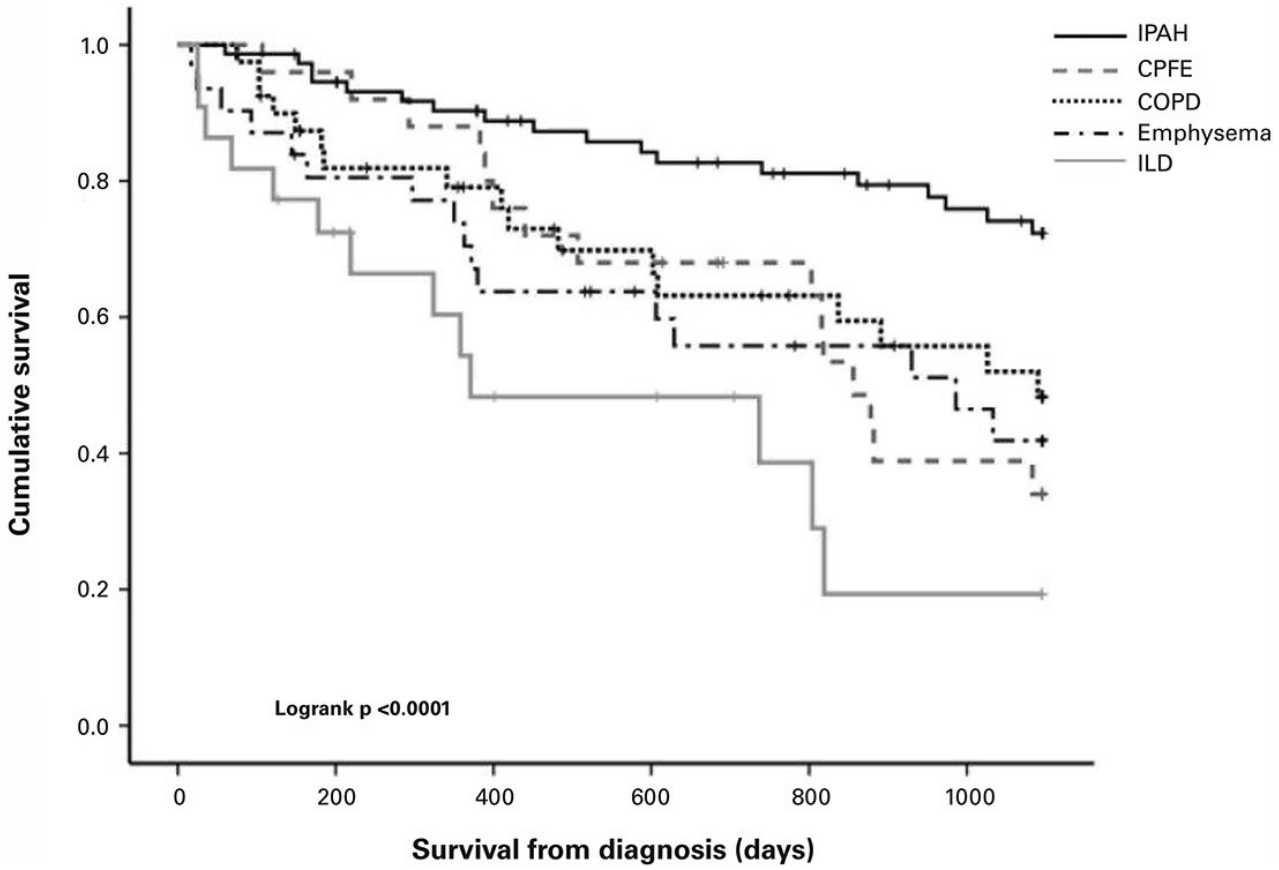
- Prevalence of ILD (US population-based study)
  - 80.9 per 100,000 men and 67.2 per 100,000 women
    - 31.5 new cases/100,000 men per year and 26.1/100,000 women per year
- Precise prevalence of PH in patients with ILD is difficult to establish
  - Most of the studies are from case reports and retrospective series
  - Annual incidence of Idiopathic Pulmonary Fibrosis (IPF) estimated as 6.8–8.8 cases per 100,000 population using narrow case definitions, and as 16.3–17.4 cases per 100,000 population using broad case definitions
- In early stages of the disease or at diagnosis, up to 15% of ILD already have PH
  - As ILD advances, frequency of PH continues to rise, beyond 50%



Am J Respir Crit Care Med 1994;150:967–972. Respir Med. 2012 Jun;106(6):875-82. Can. Respir. J. 2017;2017:1430350. Eur. Respir. J. 2007;30:715–721 *Respir Res* **21**, 303 (2020). https://doi.org/10.1186/s12931-020-01570-2.

Impact of PH-Chronic Lung Disease

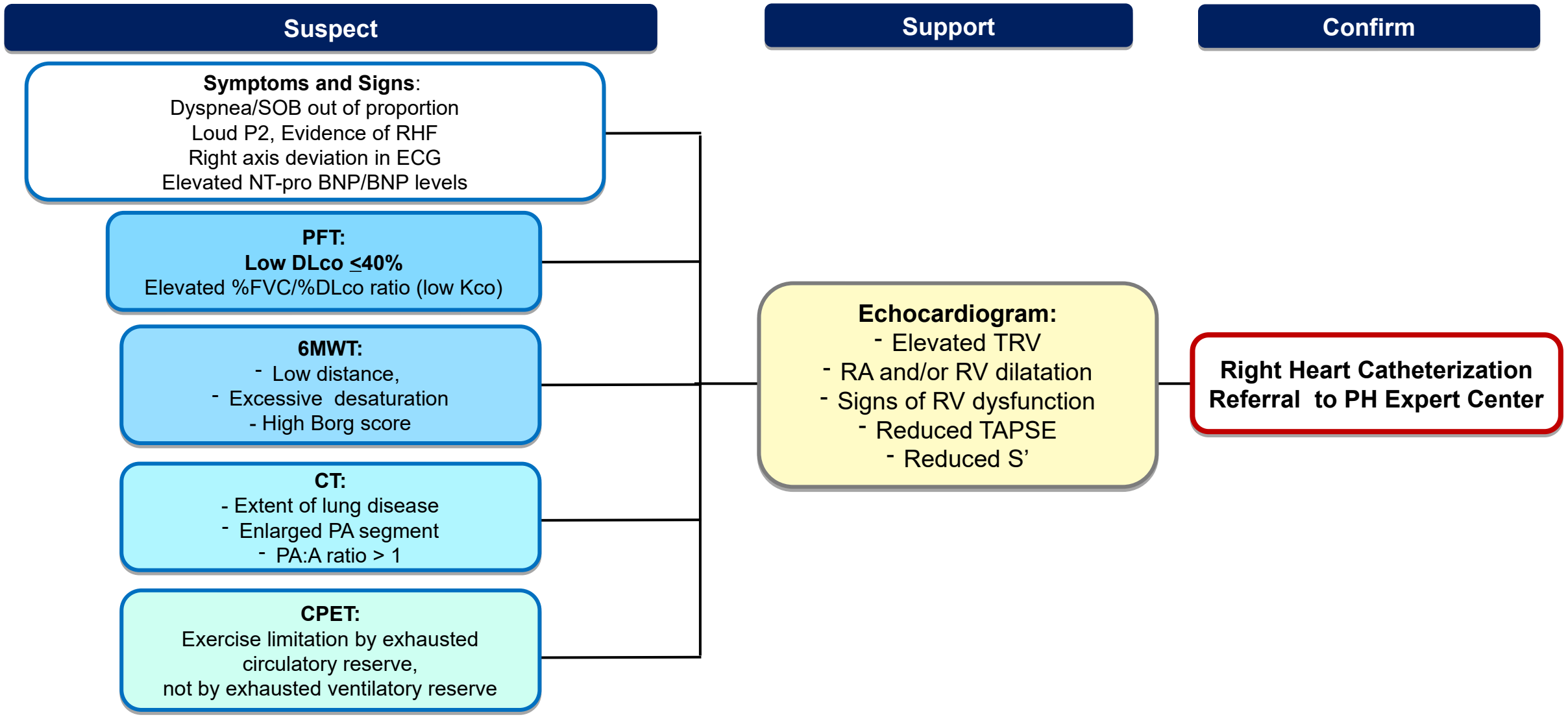




PLOS ONE 10(12): e0141911

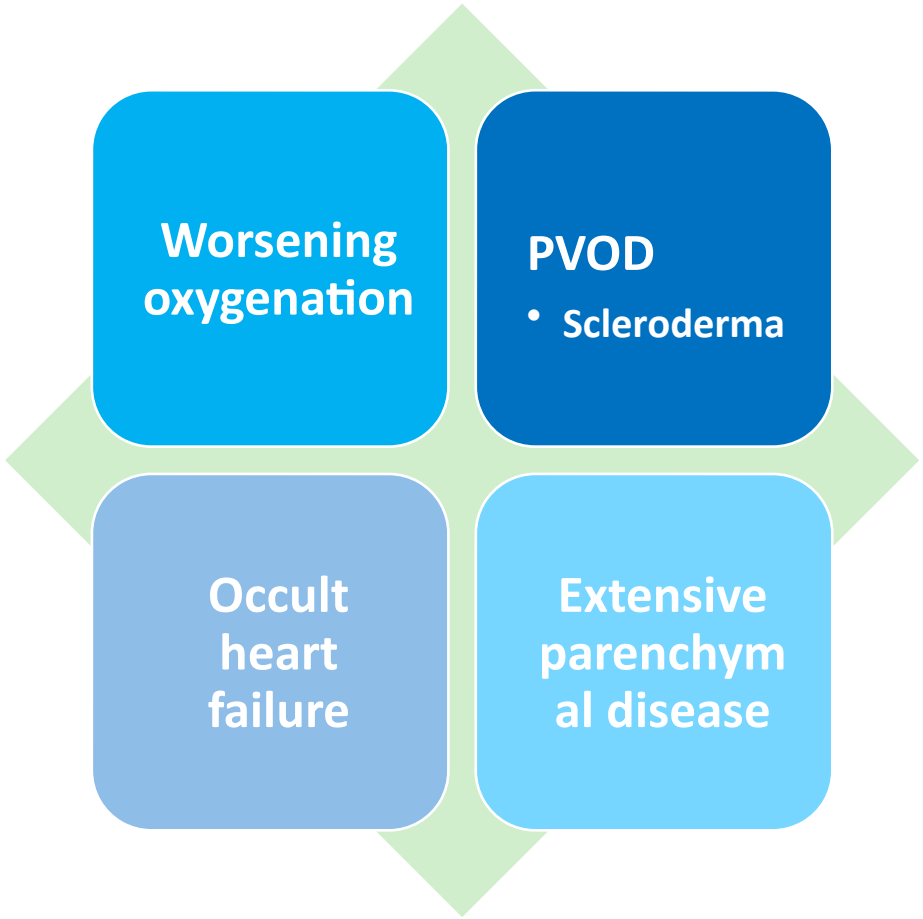
Eur Respir J. 2015;46(5):1378–89

Algorithm for Diagnosis of PH-ILD



Nathan S et al. *Eur Respir J*. 2019;53(1):1801914.

Caveats to Using PAH-specific Therapy in PH-ILD



- ETRAs have suffered from poor study design
  - General trend was worsening gas exchange without improvement in functional capacity.
- PDE-5i have shown some promise
  - Improved 6MWD, QOL, RV Function, and PVR
  - Worsening V/Q in some reports
- Prostacyclin's have shown promise
  - Improved PVR, CO, RV function
  - Worsening V/Q in some studies

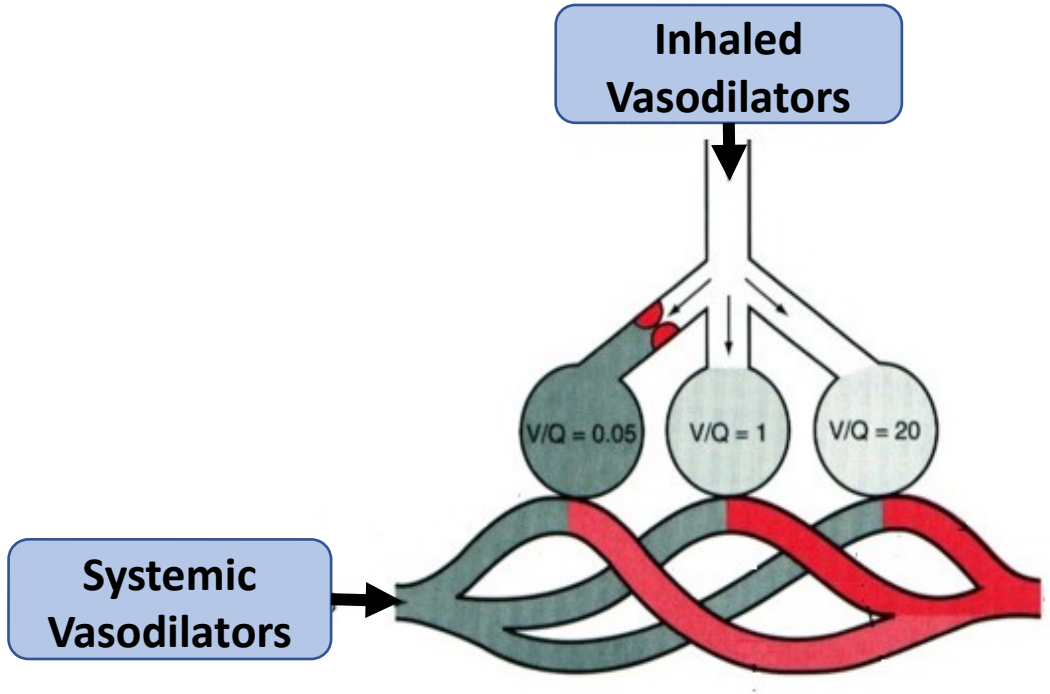
Circulation, 107(25):3230–3235, 2003; AMJRCCM 181(3):270-278, 2010; Chest 143(6):1699–1708, 2013; Respirology 19(5):700–706, 2014; ERJ 31(4):759-764; Chest 131(3):897-899, 2007; Clinical Physiology, 13(5):497–506, 1993; Internal Medicine, 50(20):2341–2346, 2011; Thorax, 69(2):123–129, 2014; The American Journal of Medicine, 65(6):896–902, 1978; Medical Journal of Australia, 182(12):621–626, 2005

Difficulties in Conducting Clinical Trials for PH-ILD

- Disappointing results from multiple clinical trials of pulmonary vasodilator therapy in ILD
  - Most trials enrolled patients with PH diagnosed on the basis of diffusion capacity and/or echocardiography criteria instead of hemodynamic parameters
  - Few trials focused specifically on severe PH-ILD
- PH-ILD trials are difficult to complete
  - Rarity and short life expectancy of patients
  - Hesitation among clinicians to enroll patients for placebo-controlled trials

Rational for Inhaled Therapy

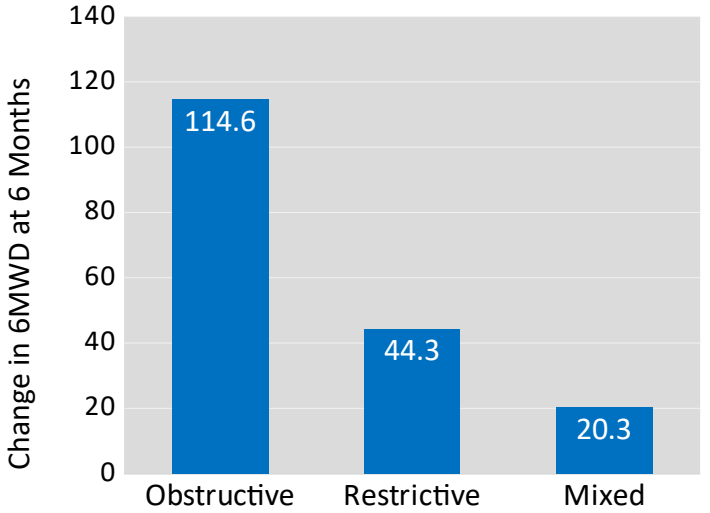
- Treatment with systemic pulmonary vasodilators may result in worsening V/Q imbalance.
- Inhaled therapy is delivered directly to well ventilated lung units preserving V/Q, and reducing undesirable alterations in perfusion
- Potential for increased efficacy and decreased systemic side effects

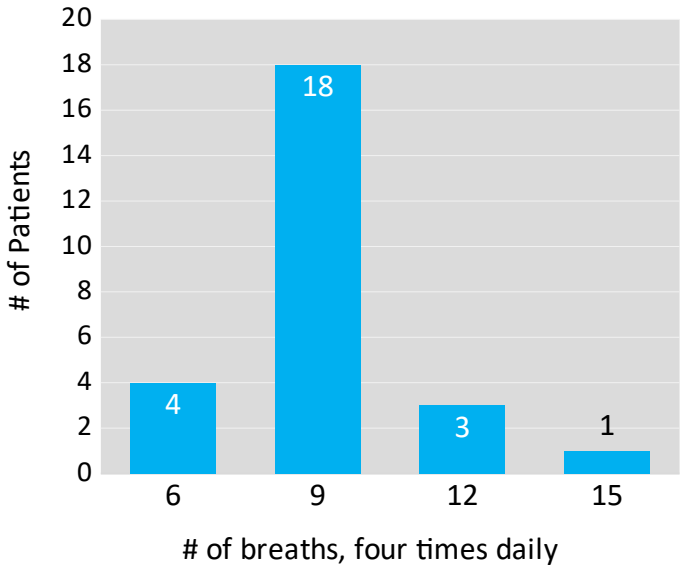


Preliminary Evidence

Retrospective Analysis of Inhaled Treprostinil in Group 3 Pulmonary Hypertension

- 26 patients completed 6 months of treatment; 2 patients discontinued due to adverse events and 2 due to lack of efficacy.
- 21 patients had 6MWD data at baseline (mean 228.5m) and 6 months (mean 289.4m):
  - Mean increase at 6 months was 60.85 ± 92.60 m, significant median improvement of 45 m (p=0.0019); and
  - Patients with obstructive lung disease had the greatest improvement in 6MWD.
- WHO FC and BDI remained stable throughout the duration of the study.





Adverse Event	# Patients
Cough	**12**
Headache	**5**
Leg swelling	2
Chest pain	1
Nausea	1
Throat irritation	1
Jaw pain	1
Flushing	1
GI upset	1

Agarwal M, Waxman A. Poster presented at ISHLT, 2015. M. Faria Urbina et al. Lung, 2018, April 196(2), 139-146

INCREASE – Study Design and Inclusion Criteria

Phase 3, multicenter, randomized (1:1), double-blind, placebo-controlled, 16-week, parallel-group (inhaled treprostinil / placebo) study (NCT02630316)

Key Inclusion Criteria

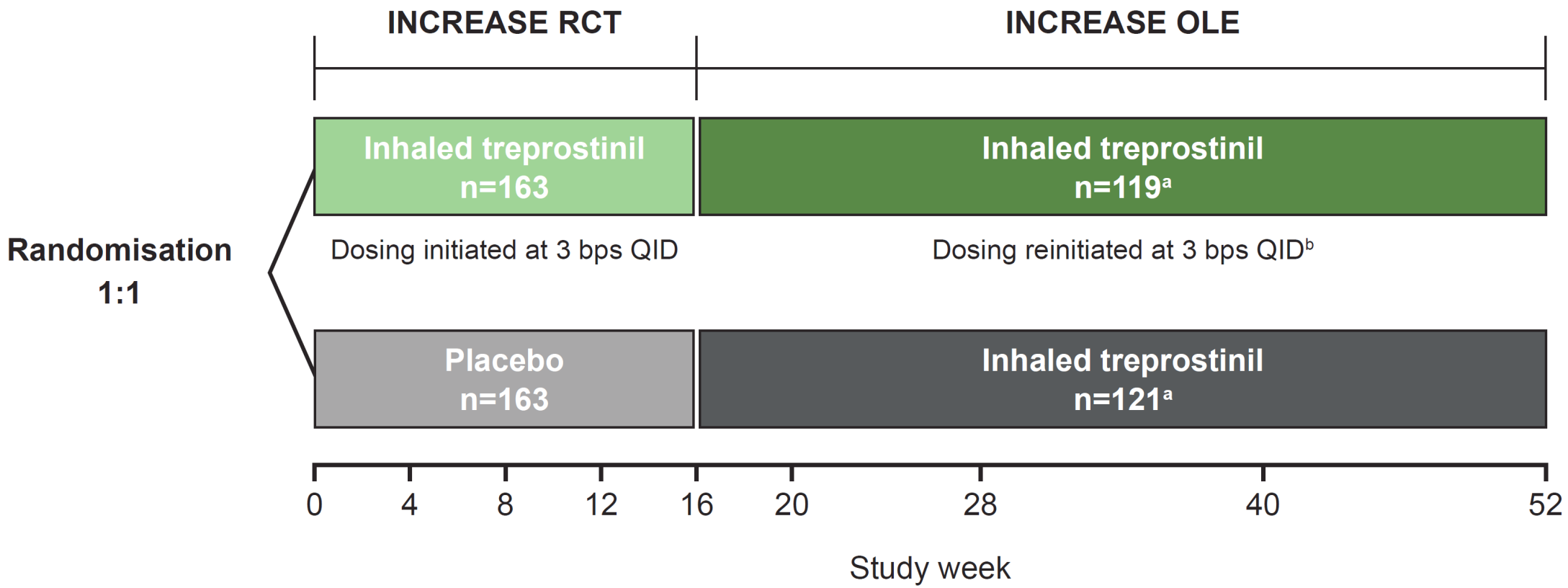
- Confirmed diagnosis of Group 3 PH based on CT within 6 months prior to randomization and demonstrated evidence of diffuse parenchymal lung disease. Subjects had any form of ILD or CPFE
- Right heart catheterization within 1 year prior to randomization with the following documented parameters:
  - **PVR >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, 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

N Engl J Med. 2021 384:325-334

INCREASE Study Schema



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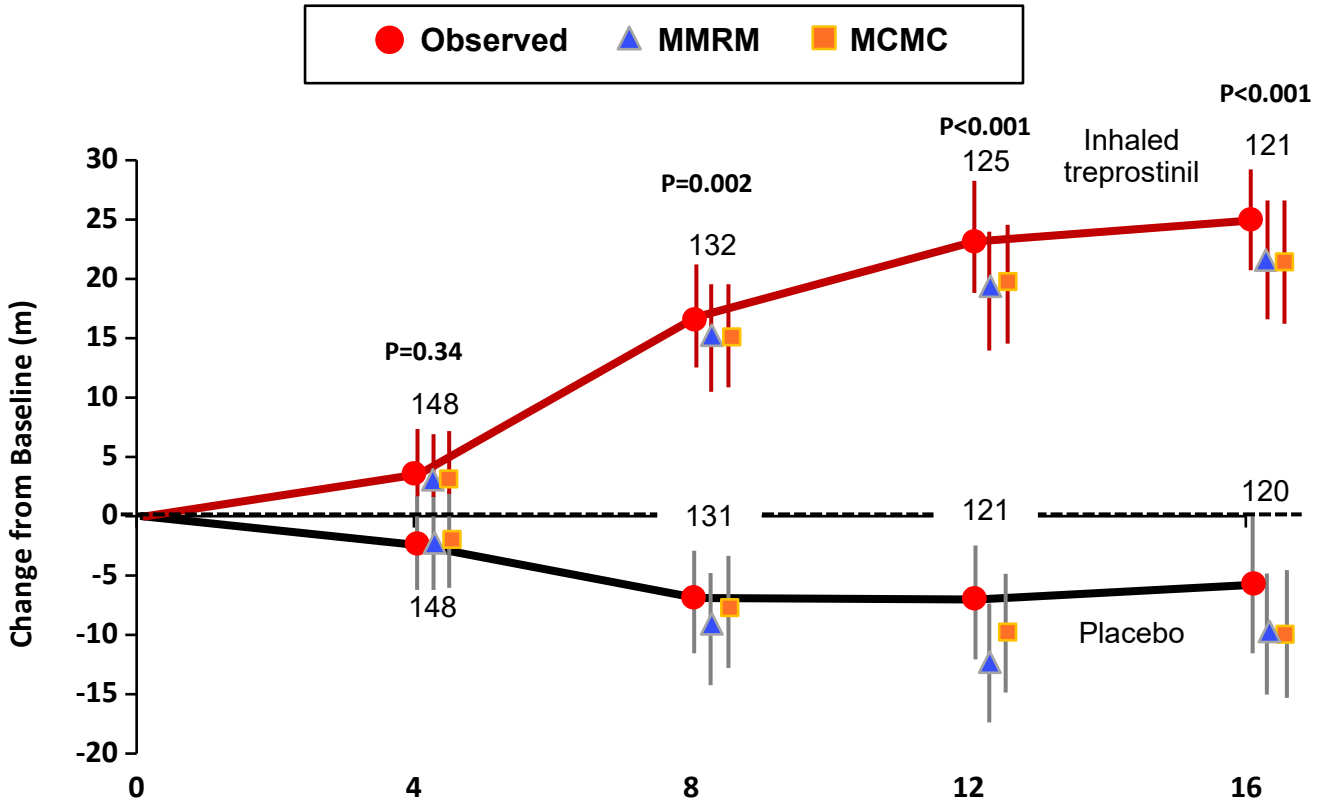
6MWD Results Through Week 16

At Week 16, inhaled treprostinil patients had a placebo-corrected difference from Baseline in peak 6MWD of 31.12 meters

(95% CI: 16.85, 45.39; P<0.001).



Inhaled Treprostinil Dose

Median 11 breaths/ session

57% achieved 10-12 breaths/session

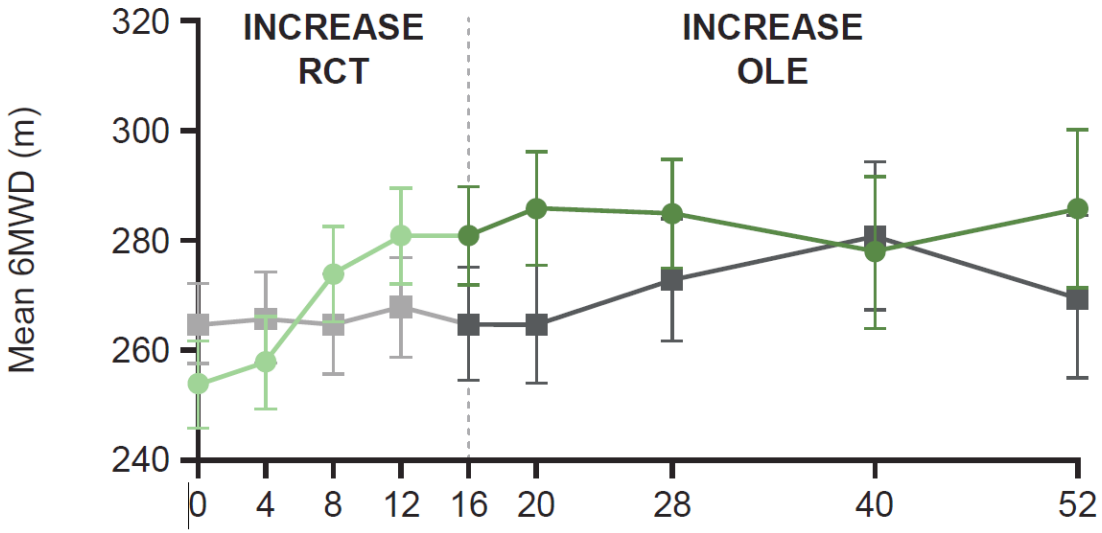
Inhaled Treprostinil Dose

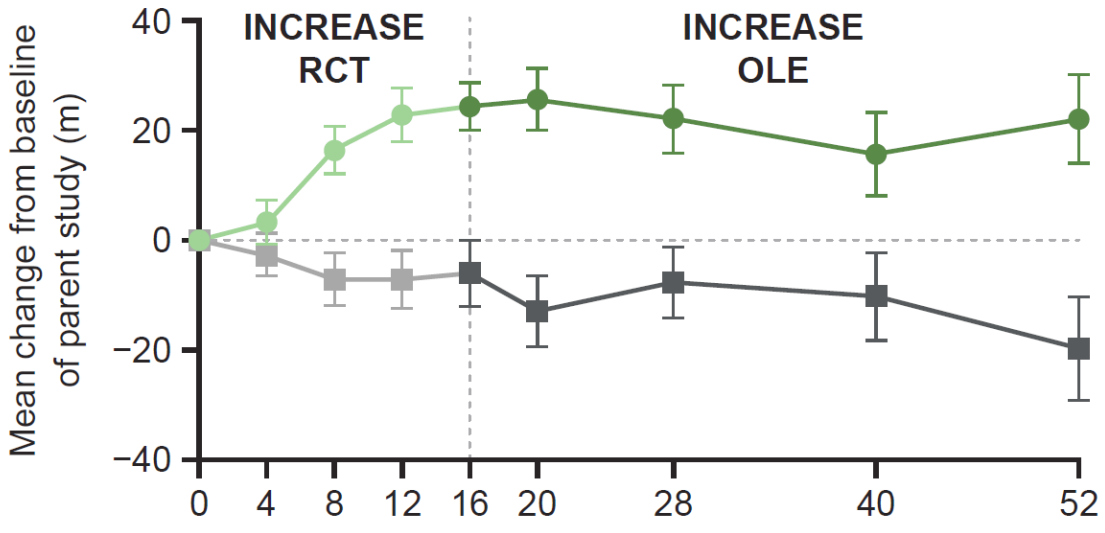
Median 12 breaths/ session

57.8% achieved 10-12 breaths/session

Mixed Model Repeated Measurement and Markov chain Monte Carlo Method treatment effect is provided.
6MWD, 6-Minute Walk Distance; m, meter.

6-MWD





Inhaled treprostinil in RCT									
n=	163	148	132	125	121	110	100	77	68
Placebo in RCT									
n=	163	148	131	121	120	102	89	62	55

Inhaled treprostinil in RCT									
n=	163	148	132	125	121	110	100	77	68
Placebo in RCT									
n=	163	148	131	121	120	102	89	62	55

- Inhaled treprostinil
- Inhaled treprostinil in RCT→inhaled treprostinil in OLE
- Placebo
- Placebo in RCT→inhaled treprostinil in OLE

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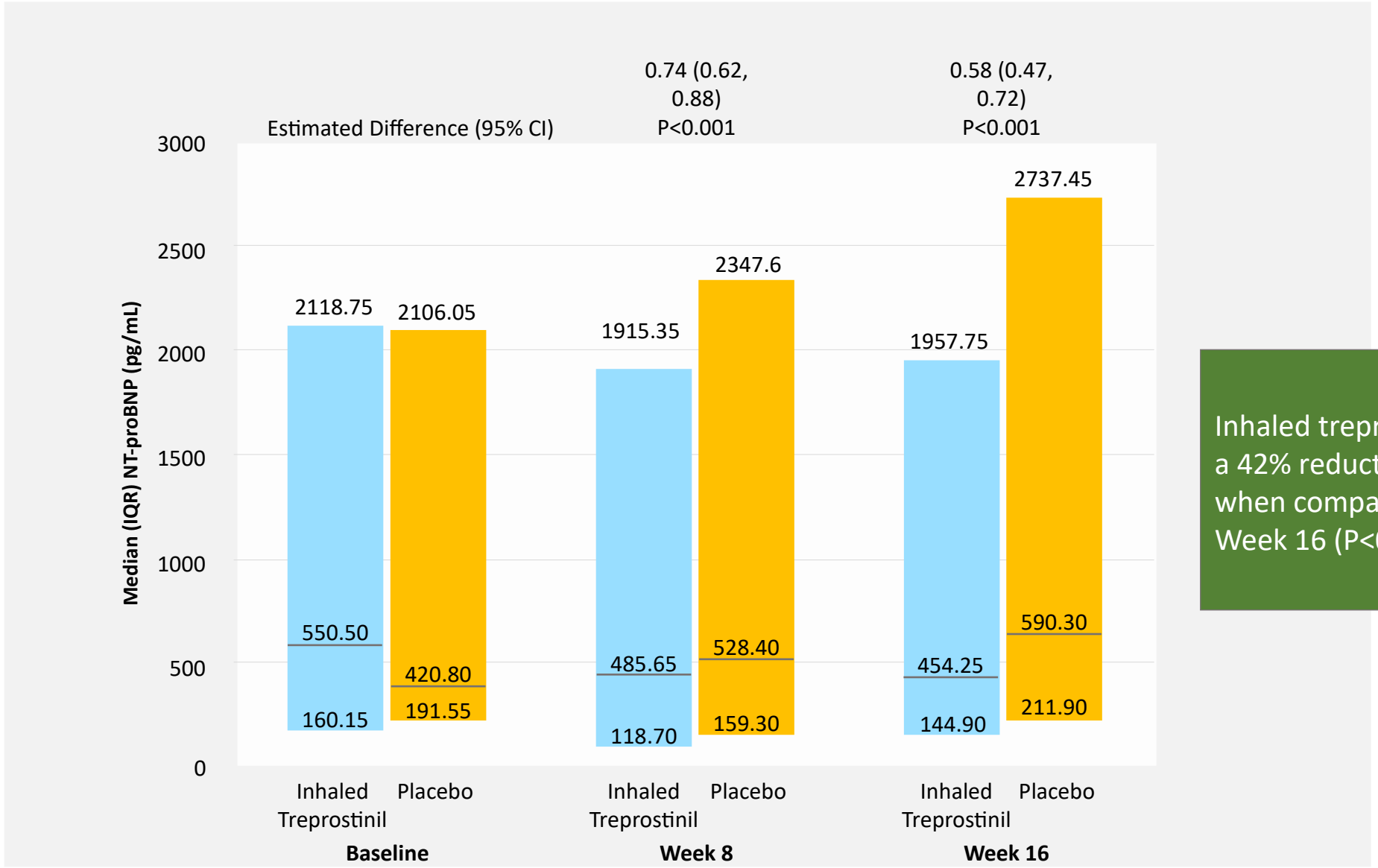
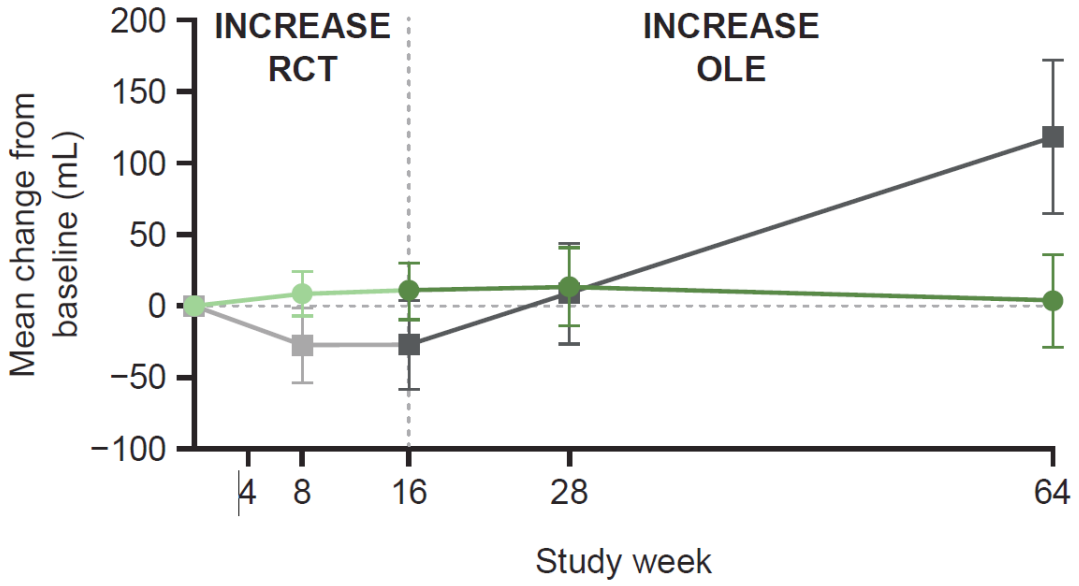
NT-proBNP Results by Study Visit



Inhaled treprostinil resulted in a 42% reduction in NT-proBNP when compared to placebo at Week 16 (P<0.001)

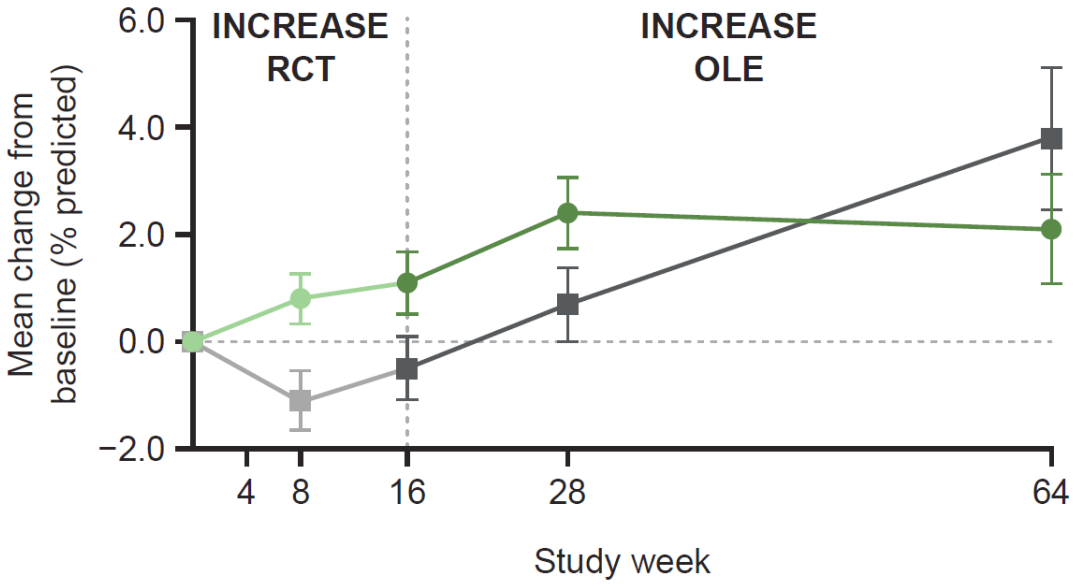
Change in FVC

a) Change in FVC (mL)



Inhaled treprostinil in RCT						
	n=	162	141	129	100	46
Placebo in RCT						
	n=	161	140	124	97	67

b) Change in FVC (% predicted)



Inhaled treprostinil in RCT						
	n=	162	141	129	100	46
Placebo in RCT						
	n=	161	140	124	97	67

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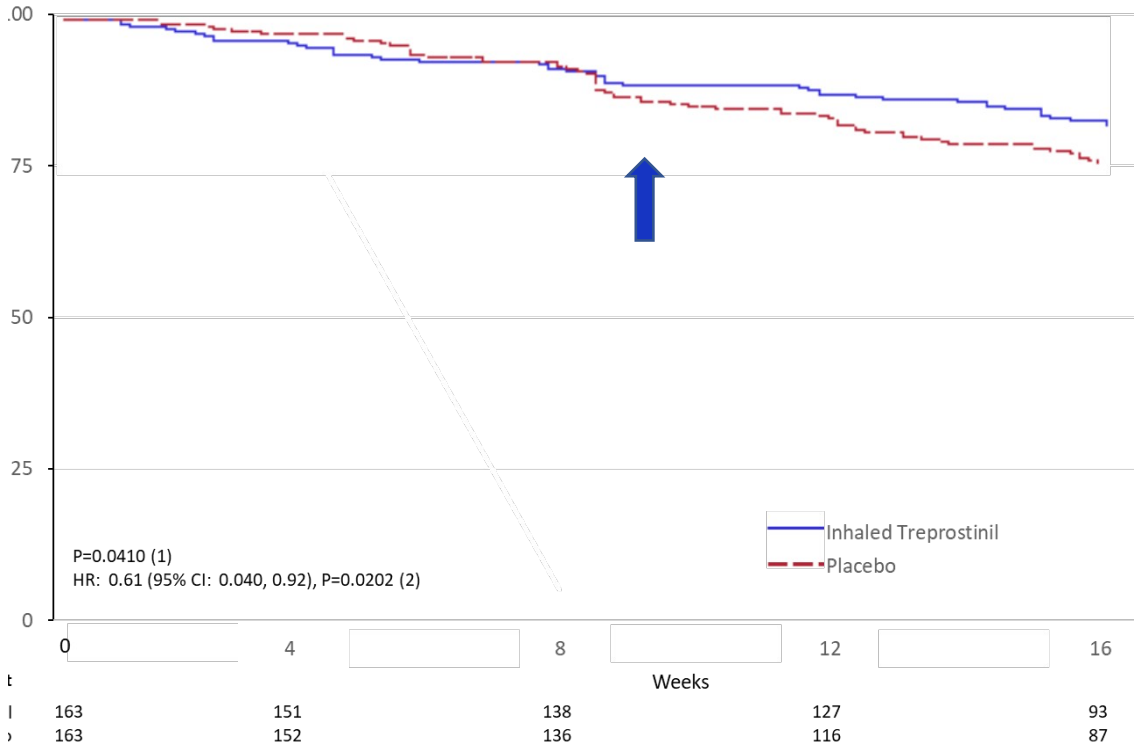
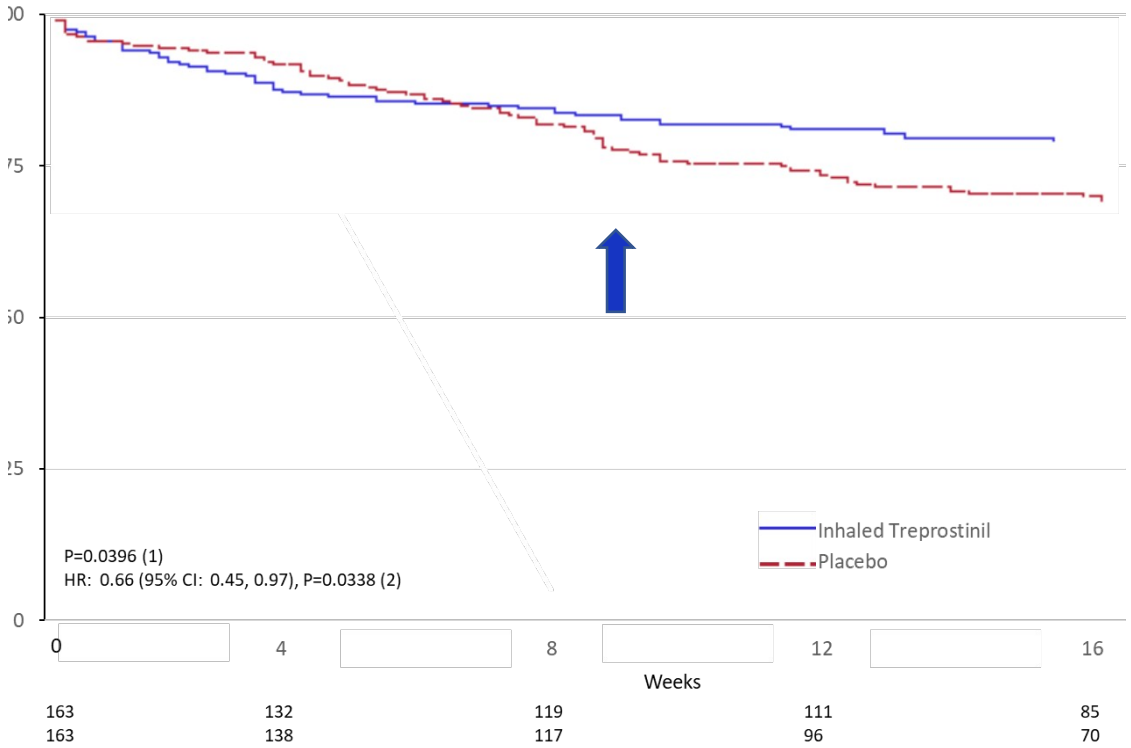
Time to Exacerbation of Underlying Lung Disease



Time to Clinical Worsening Events



Exacerbation: acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality
TTCW: death, need for and/or worsening-related listing for lung and/or heart transplant, need to initiate an approved PAH SOC rescue therapy, PAH-specific hospitalization, or functional deterioration (worsened WHO Functional Class AND 15% decrease in 6MWD)

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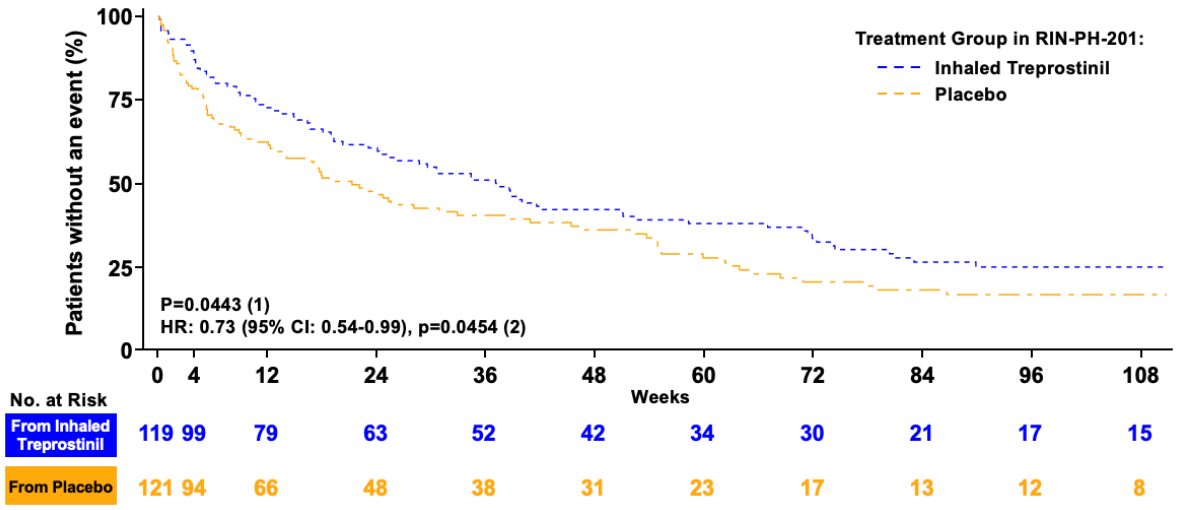
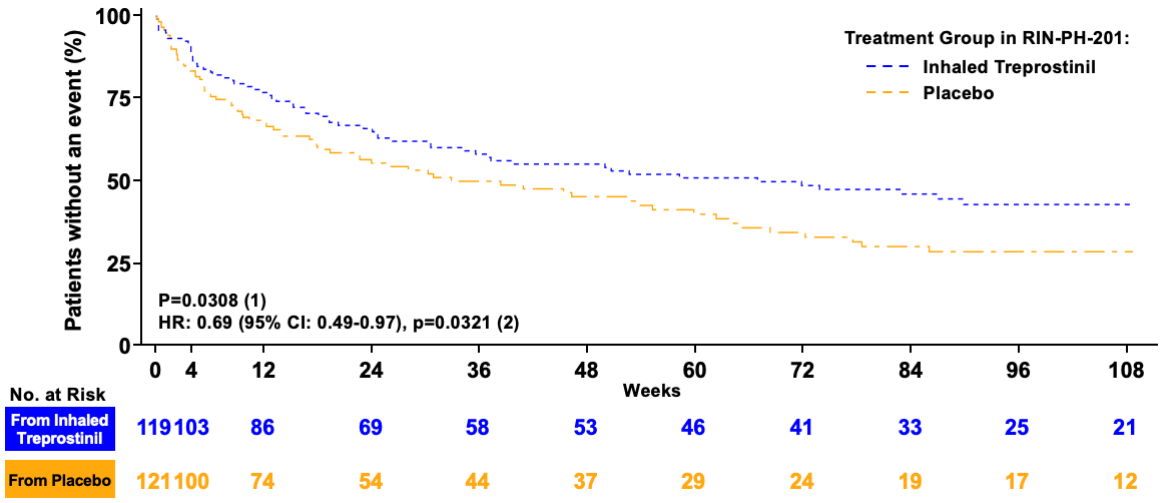
Event-free Survival in INCREASE Study Open-label Extension

Time to Event for Event-free Survival



Time to Exacerbation of Lung Disease



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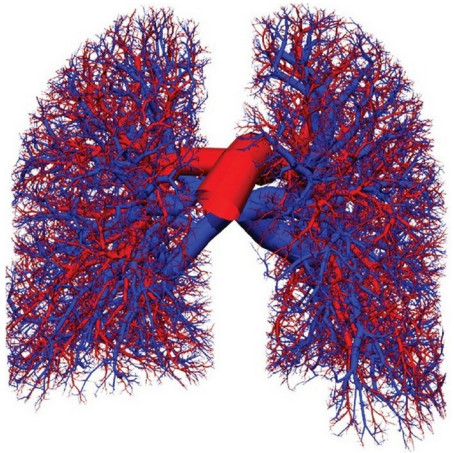
Conclusions

- Patients experienced significant improvements in exercise capacity (6MWD) as early as 8 weeks, with effects sustained throughout.
- Patients demonstrated improvements in other clinically meaningful outcomes, including improvements in NT-proBNP, FVC, and decreased risk of clinical worsening and exacerbation of underlying lung disease.
- Improved event-free survival and reduced exacerbation rate.
- Treatment with inhaled treprostinil was well tolerated.
- Think about, diagnose it, and treat it
  - Encourage early diagnosis and treatment

N Engl J Med. 2021 384:325-334 , Sci Rep. 2018;8(1):1087; Pulm Circ. 2019;9(4):2045894019881954; The Lancet Respir Med. 2021 Jun 29:S2213-2600



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Thank you

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Baseline Characteristics

- A total of 326 patients were enrolled in the study.
- The most common PH-ILD etiologies included:
  - Idiopathic interstitial pneumonia (45%)
  - Idiopathic pulmonary fibrosis (28%)
- 14% of patients were on single background therapy with pirfenidone and 9% on nintedanib
- The median dose of inhaled treprostinil achieved at Week 8 and Week 16 were 10 and 12 breaths per session, respectively.

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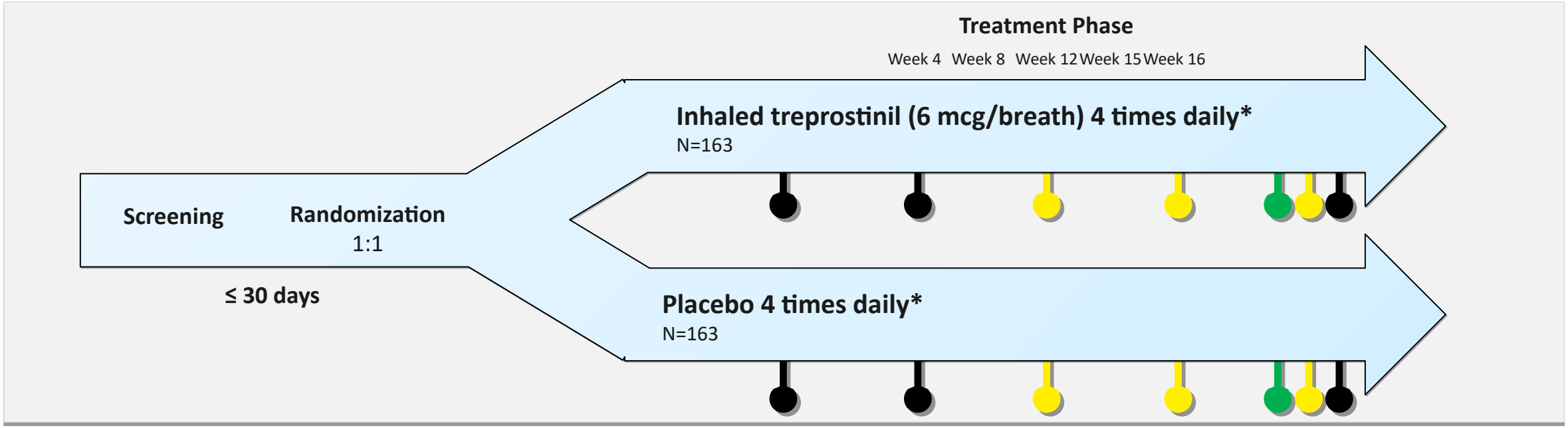
Incidence of Adverse Events in the OLE

AE	Former Inhaled Treprostinil Group (n=119)	Former Placebo Group (n=121)	Overall (n=242)
Cough	18.5%	35.5%	26.9%
Dyspnea	25.2%	27.3%	26.0%
Headache	10.1%	27.3%	18.6%
Diarrhea	16.8%	14.0%	15.3%
Dizziness	15.1%	14.9%	14.9%
Upper respiratory tract infection	16.8%	11.6%	14.0%
Fatigue	15.1%	11.6%	13.2%
Nausea	15.1%	11.6%	13.2%
Acute respiratory failure	13.4%	11.6%	12.4%
Pneumonia	11.8%	12.4%	12.4%

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

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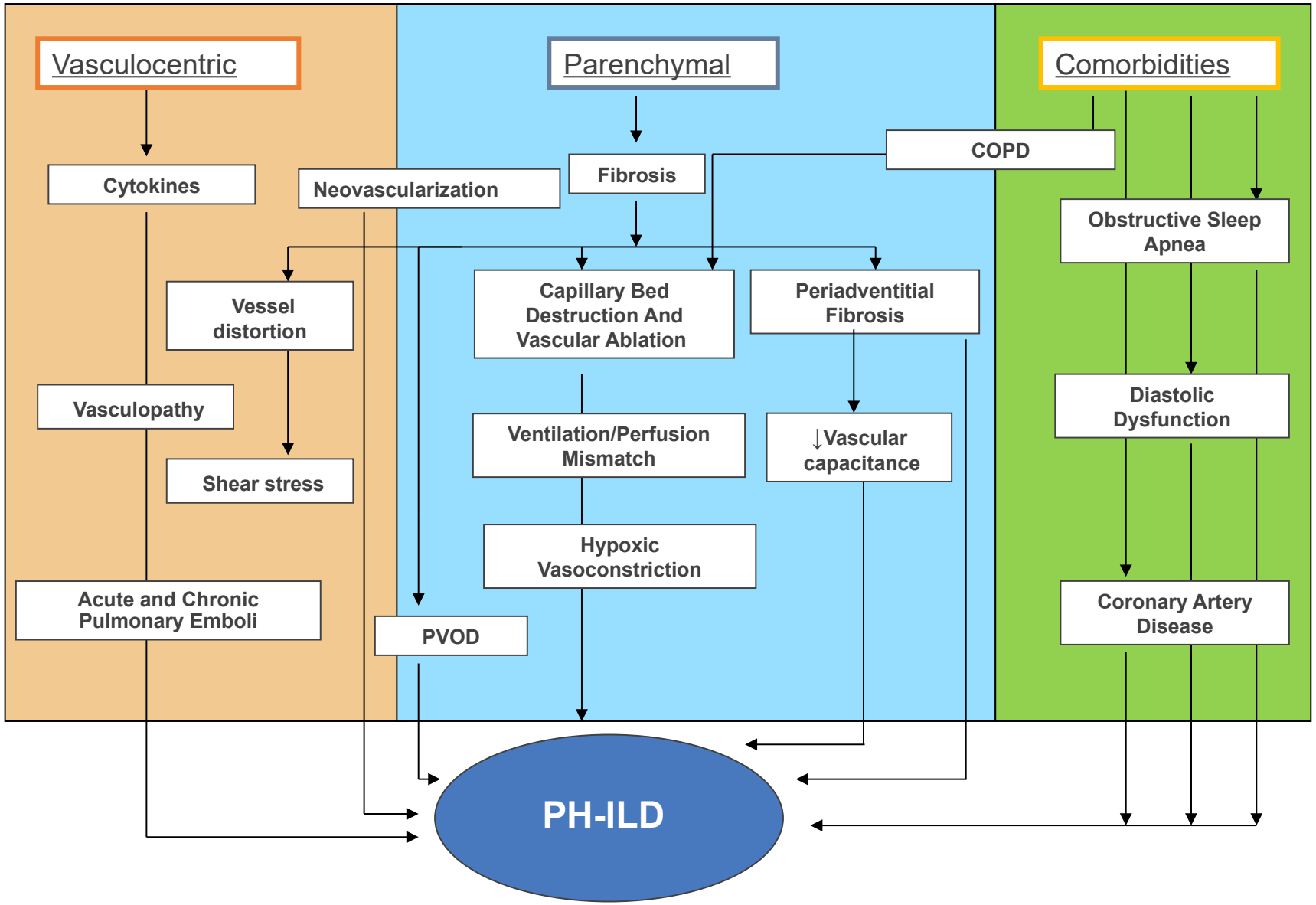
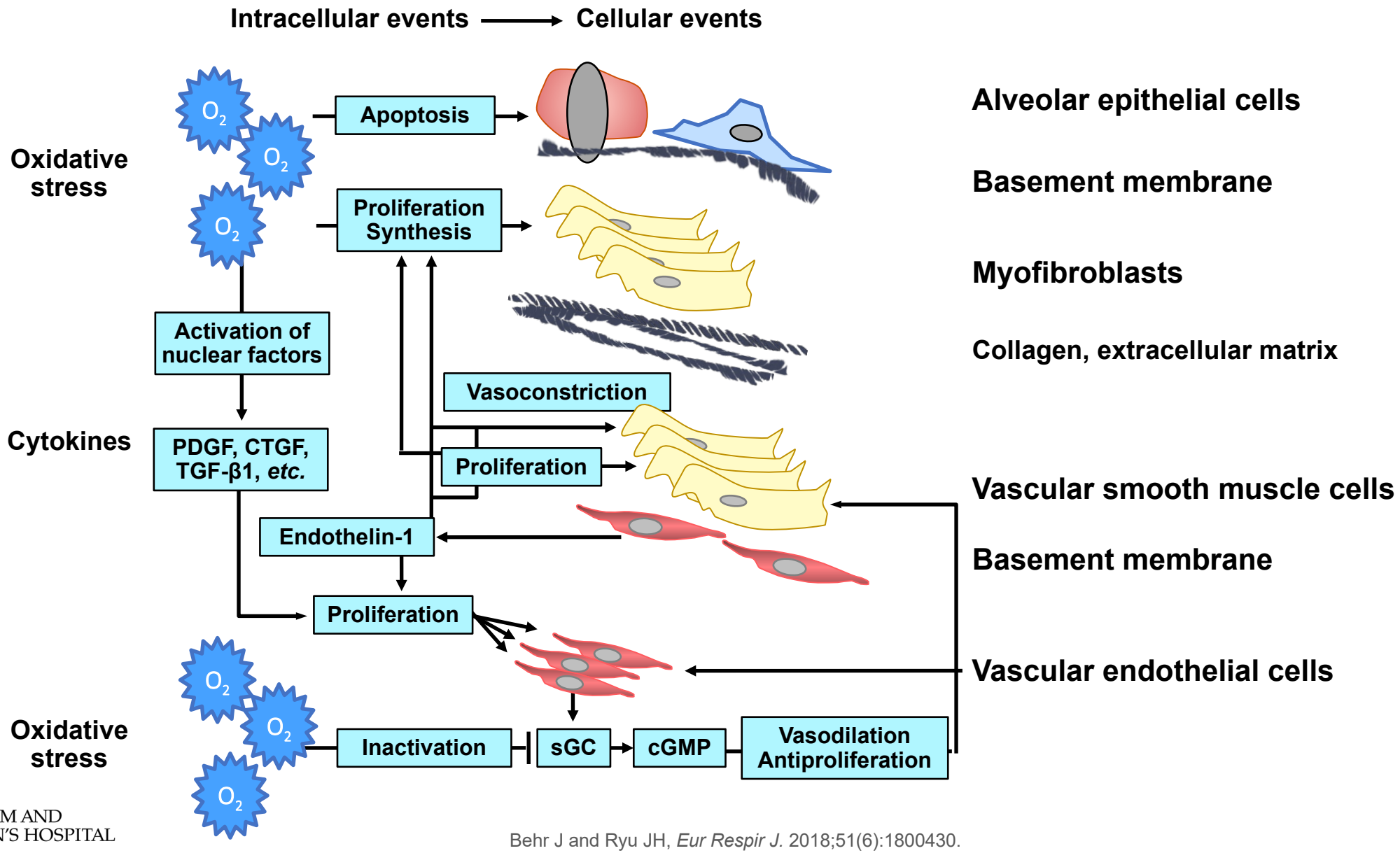
Complex and Interrelated Pathophysiology of PH-ILD



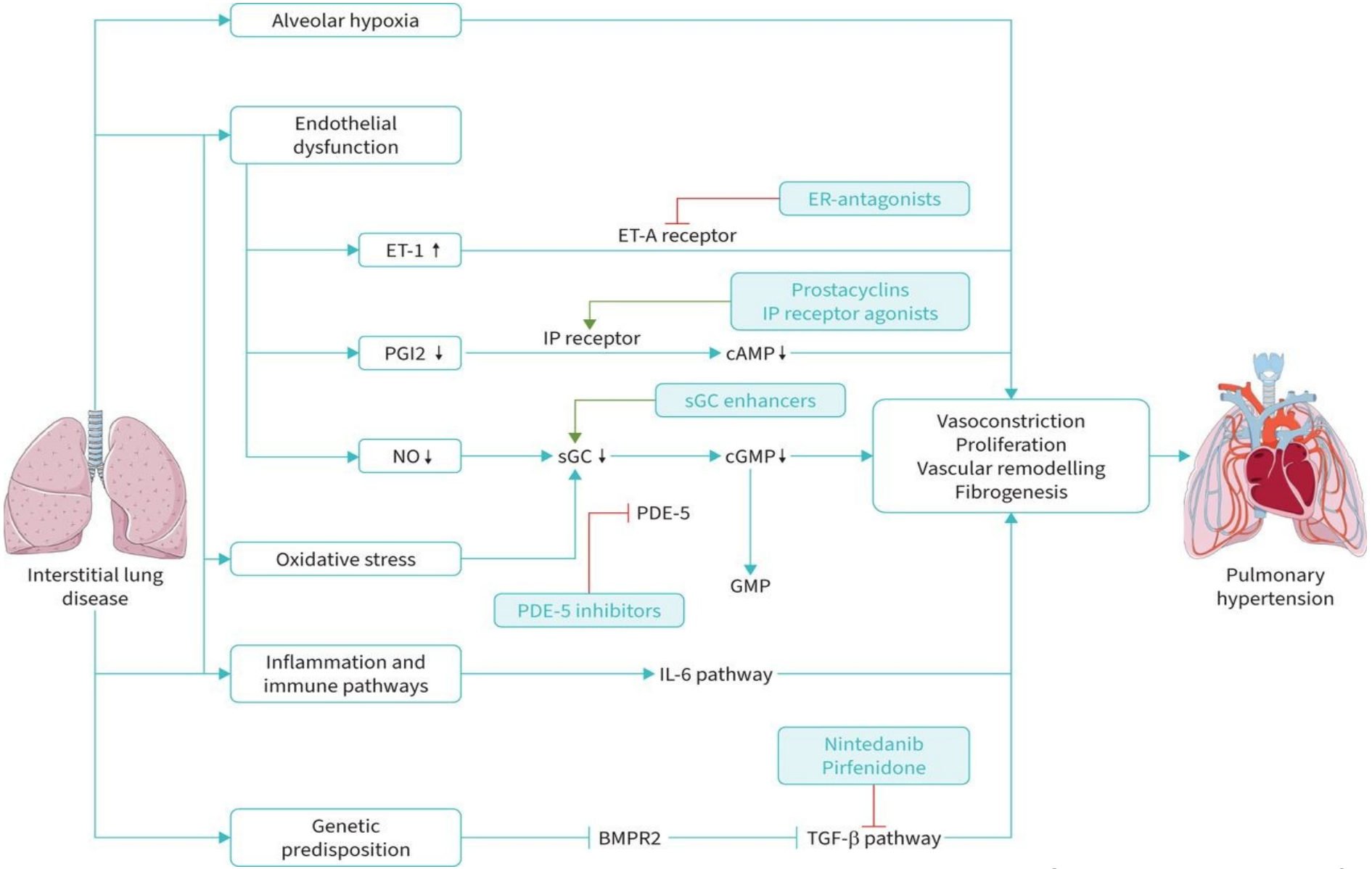
Shlobin OA, et al. *Chest.* 2017;151(1):204-214.

Cellular Events in PH-ILD



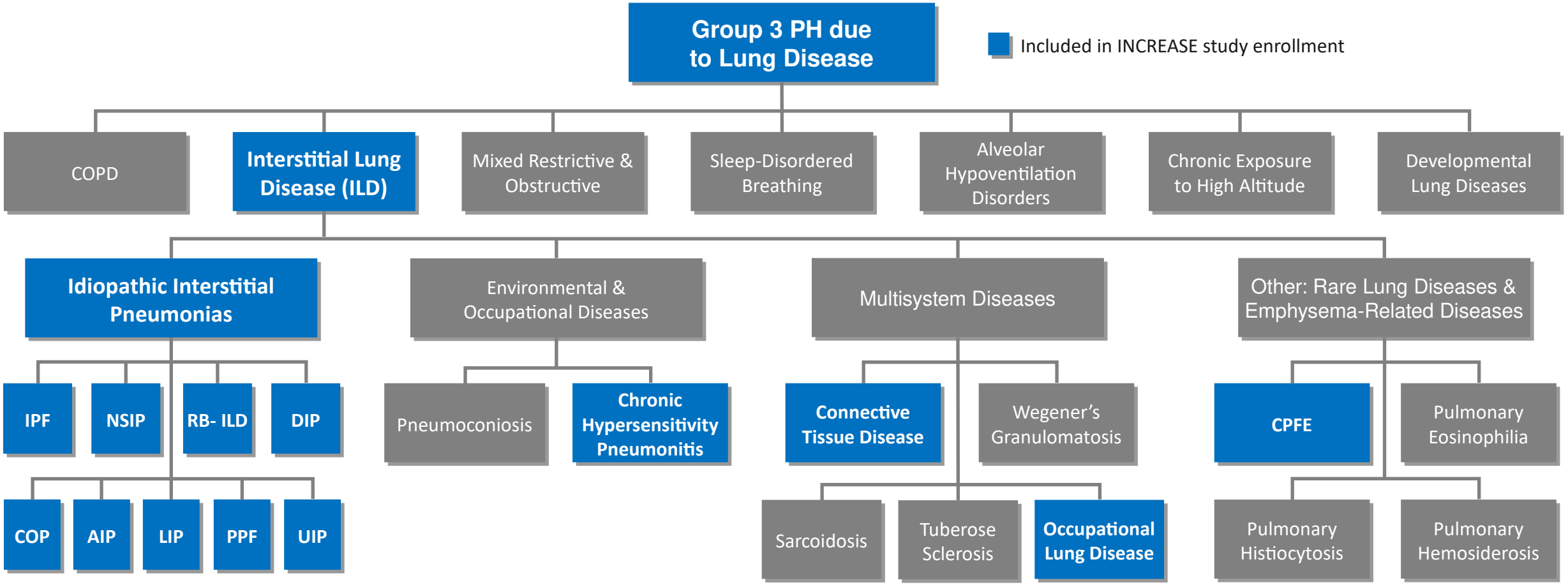
Behr J and Ryu JH, *Eur Respir J.* 2018;51(6):1800430.

The high co-incidence of interstitial lung disease and pulmonary hypertension can be explained by shared pathophysiology concerning parenchymal and vascular remodelling.

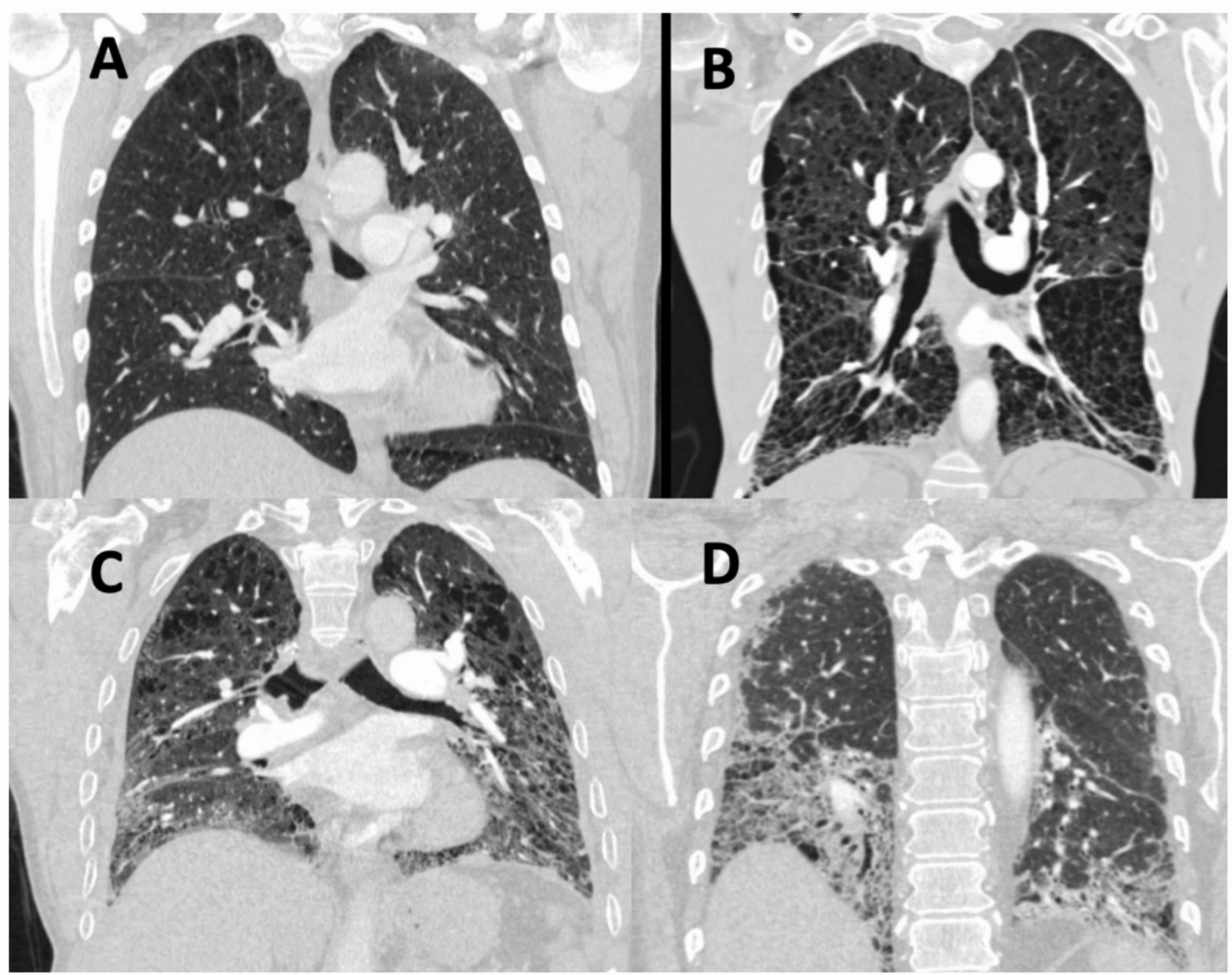


Sebastiaan Dhont et al. ERJ Open Res 2022;8:00272-2022

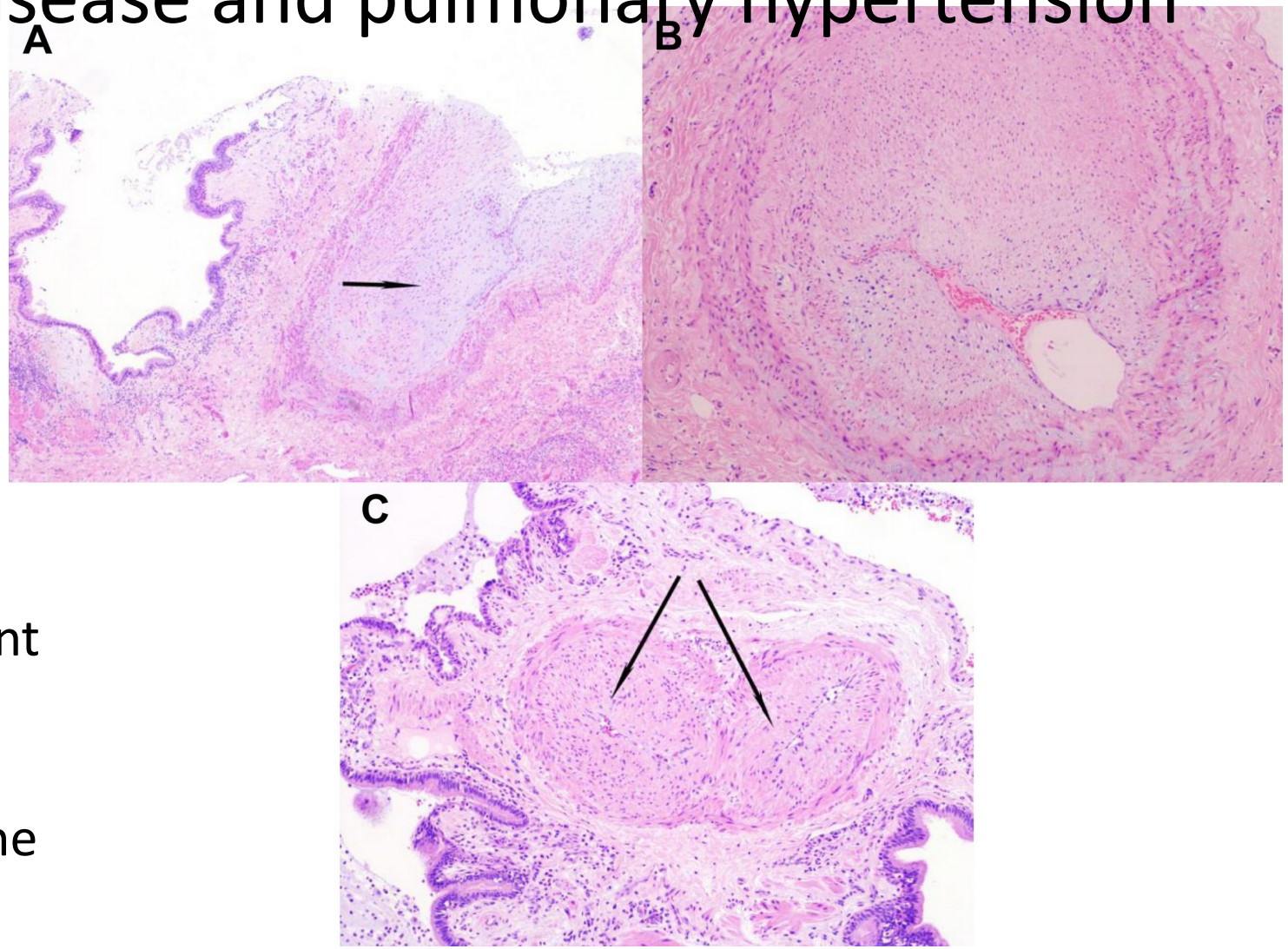
INCREASE Eligible Study Population



N Engl J Med. 2021 384:325-334


A
B
C
D

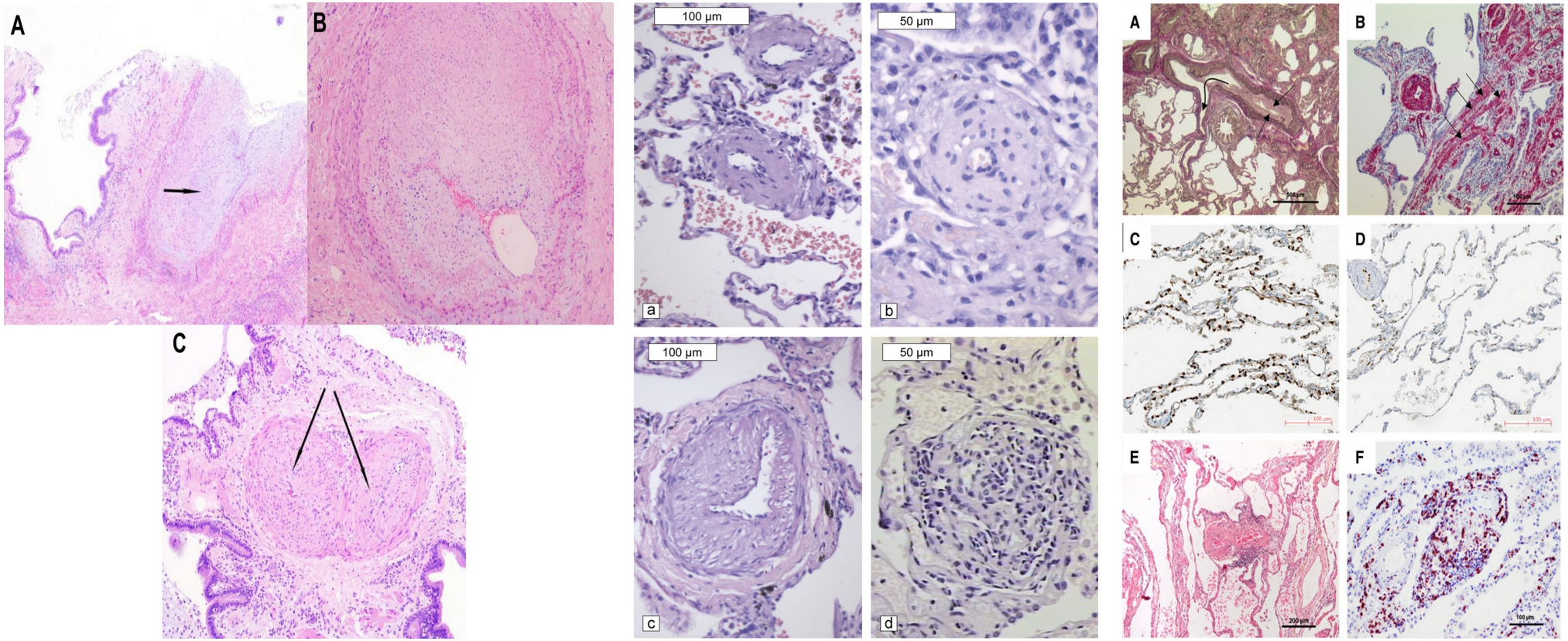
Histopathologic images from a patient with fibrotic interstitial lung disease and pulmonary hypertension



Pulmonary vascular remodeling is a component of advanced lung disease and probably reflects the inflammatory nature of the disease

CHEST 2020 1581651-1664DOI: (10.1016/j.chest.2020.04.046)

Histopathologic changes with fibrotic interstitial lung disease and pulmonary hypertension



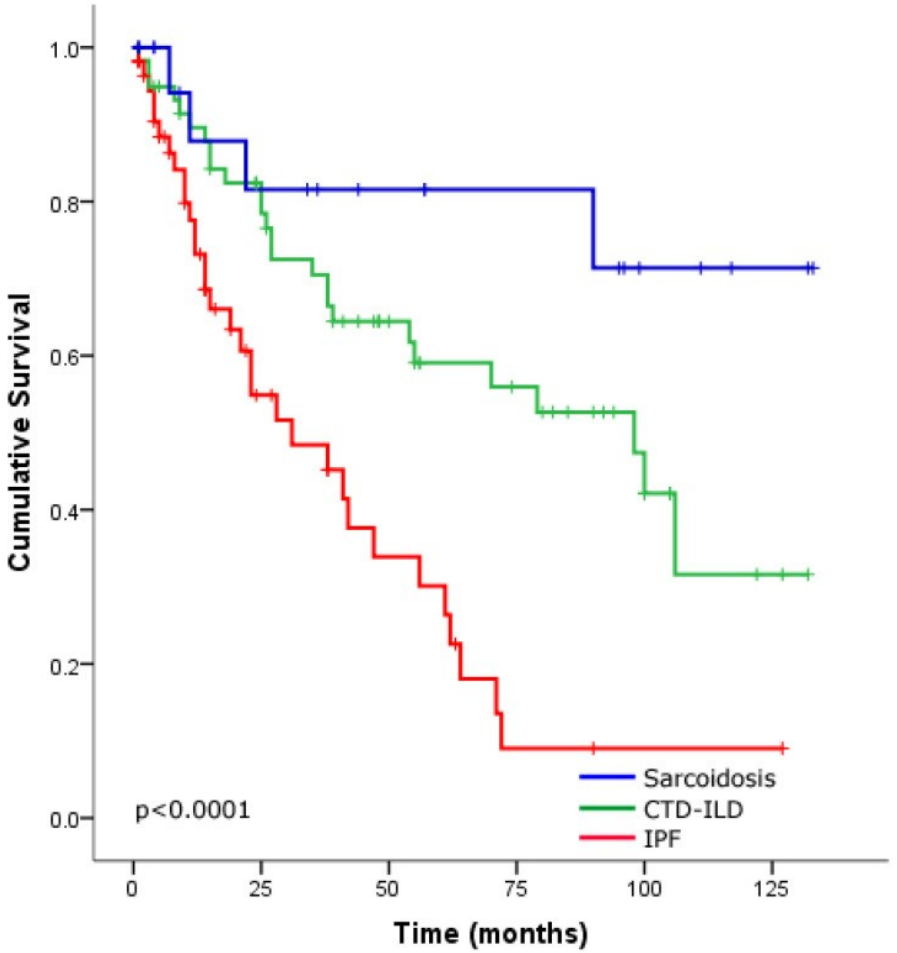
The Journal of Heart and Lung Transplantation 2013; 32:347-354,
Circ Res 2022 Apr 29;130(9):1404-1422.
CHEST 2020 Oct. 158(4): 1651-1664

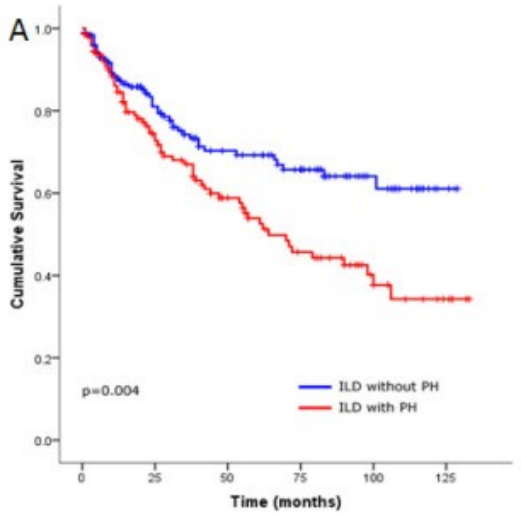
Epidemiology of PH-ILD

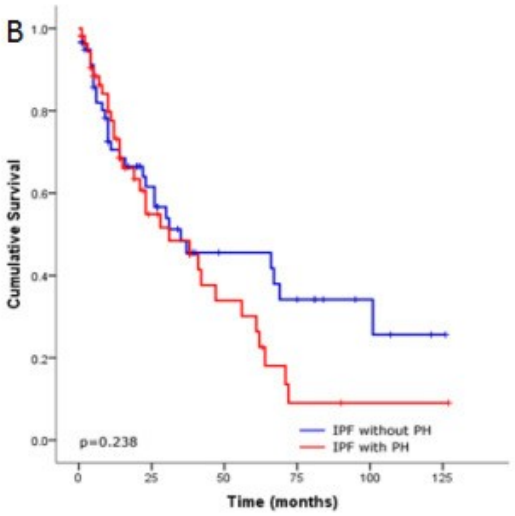
- Prevalence of ILD (US population-based study)
  - 80.9 per 100,000 men and 67.2 per 100,000 women
    - 31.5 new cases/100,000 men per year and 26.1/100,000 women per year
- Precise prevalence of PH in patients with ILD is difficult to establish
  - Most of the studies are from case reports and retrospective series
  - Annual incidence of Idiopathic Pulmonary Fibrosis (IPF) estimated as 6.8–8.8 cases per 100,000 population using narrow case definitions, and as 16.3–17.4 cases per 100,000 population using broad case definitions
- In early stages of the disease or at diagnosis, up to 15% of ILD already have PH
  - As ILD advances, frequency of PH continues to rise, beyond 50%

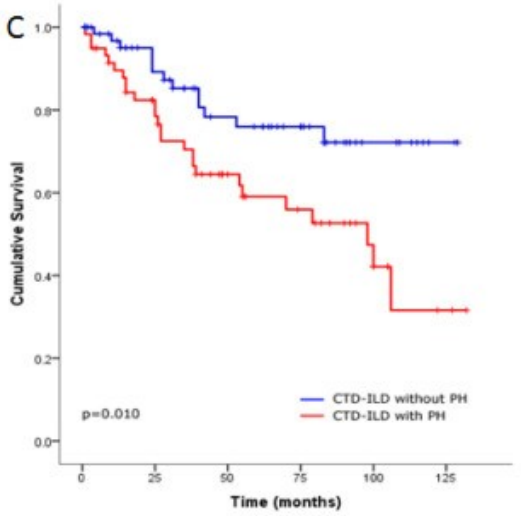
Am J Respir Crit Care Med 1994;150:967–972. Respir Med. 2012 Jun;106(6):875-82. Can. Respir. J. 2017;2017:1430350. Eur. Respir. J. 2007;30:715–721.

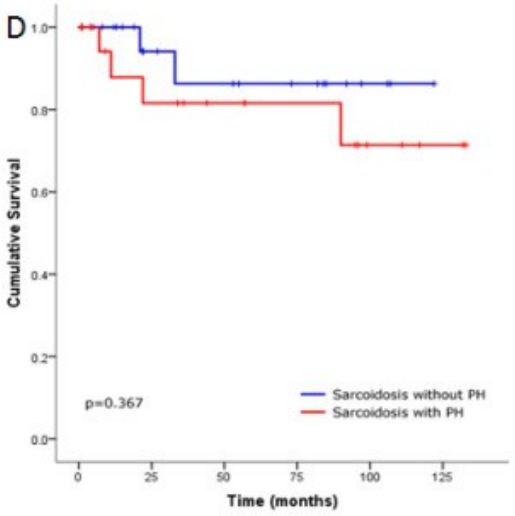
Prognosis in Pulmonary Hypertension and Chronic Lung Disease



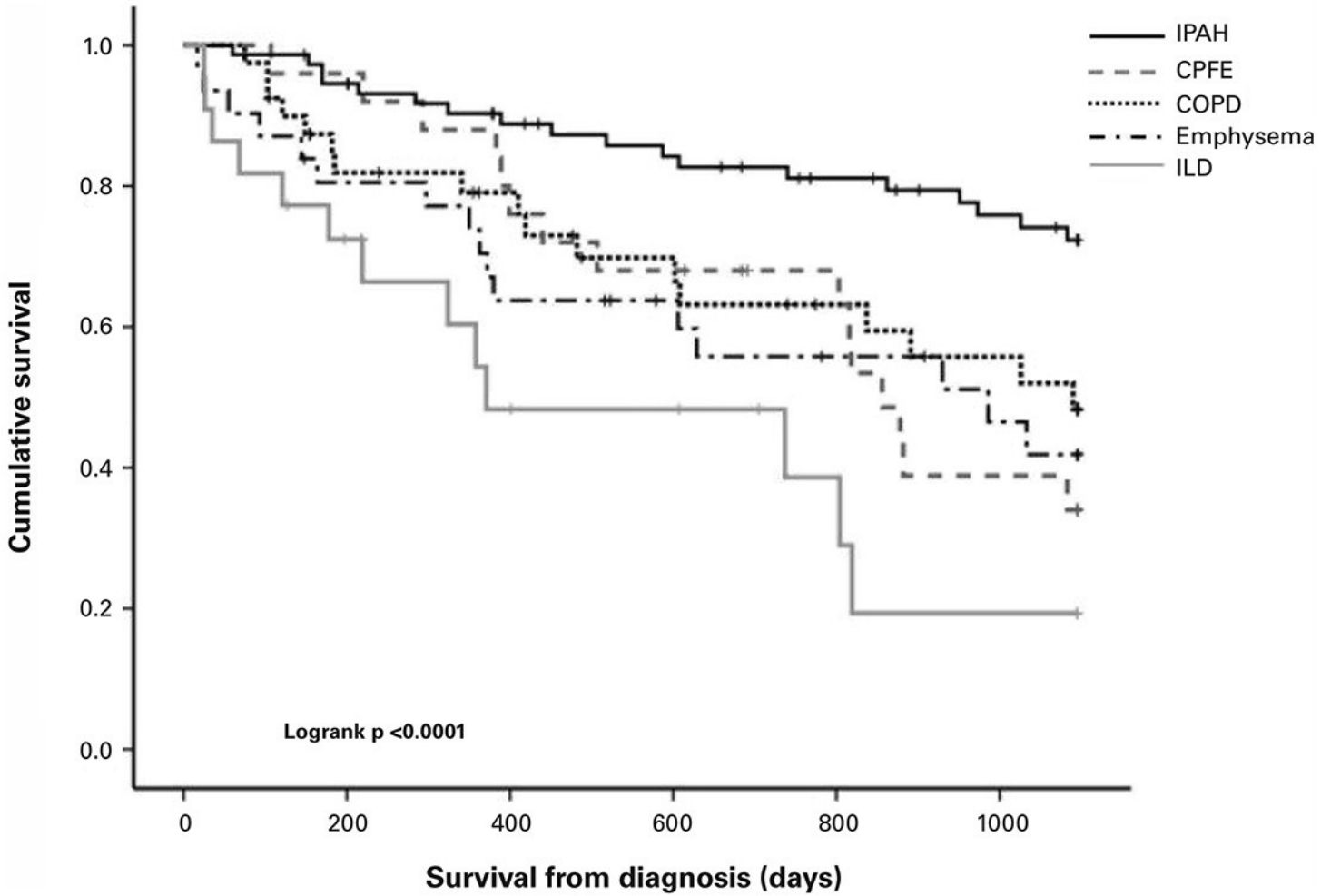








European Respiratory Journal, vol. 41, no. 6, pp. 1292–1301, 2013;
Chest, vol. 129, no. 3, pp. 746–752, 2006



Eur Respir J. 2015;46(5):1378–89

Endothelin Receptor Antagonists in ILD

Bosentan

BUILD trials failed to demonstrate improvements in functional status and in slowing disease progression

B-PHIT study in RHC-confirmed PH-ILD showed no improvements in hemodynamics, functional capacity, or symptoms

Macitentan

MUSIC trial did not show improvements in functional status and in slowing disease progression

Ambrisentan

ARTEMIS-IPF was terminated early for lack of efficacy and potential harm

- appeared to be associated with an increased risk for disease progression and respiratory hospitalizations

ARTEMIS-PH focusing on RHC-confirmed PH-IPF was terminated early

- a subgroup analysis of 10% of patients with PH in ARTEMIS-IPF showed no positive sign of efficacy

Caution against the use of endothelin receptor agonists is recommended in PH-ILD based on these studies.

IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; PH-ILD, pulmonary hypertension due to ILD; RHC, right heart catheterization.

King CS, Shlobin OA. *Chest.* 2020;158(4):1651-1664.

Nitric Oxide pathway in ILD

- Addition of sildenafil to pirfenidone did not provide a treatment benefit
- RISE-IIP study of riociguat terminated early for increased rates of serious adverse events and death in the treatment group
  - Failed to demonstrate improvement in 6MWT distance in patients treated with riociguat
- Sildenafil plus nintedanib in patients with IPF over 24-weeks showed no benefit

N Engl J Med. 2018;379(18):1722-1731.
Lancet Respir Med. 2021;9(1):85-95.
Lancet Respir Med. 2019;7(9):780-790

Sildenafil in PH-ILD

- STEP-IPF trial
  - population of patients with advanced IPF enriched for PH by means of reduced DLco criteria
- Failed to demonstrate a difference in the primary end point of a ≥ 20% increase in 6MWT distance
- Trend toward a mortality benefit at 24 weeks in the treatment arm (*P = .07*)
- Sildenafil improved a number of secondary end points
  - quality-of-life measures
  - arterial oxygen saturation
  - DLco
- Available data seem to demonstrate that use of sildenafil in PH-ILD is unlikely to be harmful and may be beneficial

N Engl J Med. 2010;363(7):620-628.

Treatment of PH in CLD

- ETRAs have suffered from poor study design
  - General trend was worsening gas exchange without improvement in functional capacity.
- PDE-5i have shown some promise
  - Improved 6MWD, QOL, RV Function, and PVR
  - Worsening V/Q in some reports
- Prostacyclin's have shown promise
  - Improved PVR, CO, RV function
  - Worsening V/Q in some studies

Circulation, 107(25):3230–3235, 2003; AMJRCCM 181(3):270-278, 2010; Chest 143(6):1699–1708, 2013; Respirology 19(5):700–706, 2014; ERJ 31(4):759-764; Chest 131(3):897-899, 2007; Clinical Physiology, 13(5):497–506, 1993; Internal Medicine, 50(20):2341–2346, 2011; Thorax, 69(2):123–129, 2014; The American Journal of Medicine, 65(6):896–902, 1978; Medical Journal of Australia, 182(12):621–626, 2005