# PULMONARY HYPERTENSION IN PULMONARY FIBROSIS

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# Presentation Outline

Classification and Haemodynamic Definitions

Clinical Recognition and Diagnostic Assessment

Vascular Pathobiology Beyond Fibrosis

Pulmonary Vascular Phenotypes and Prognosis

Prediction Models: FORD and PHINDER

Therapeutic Evidence: INCREASE, TETON and Beyond

# A 2024 reclassification: group 3 is not one disease

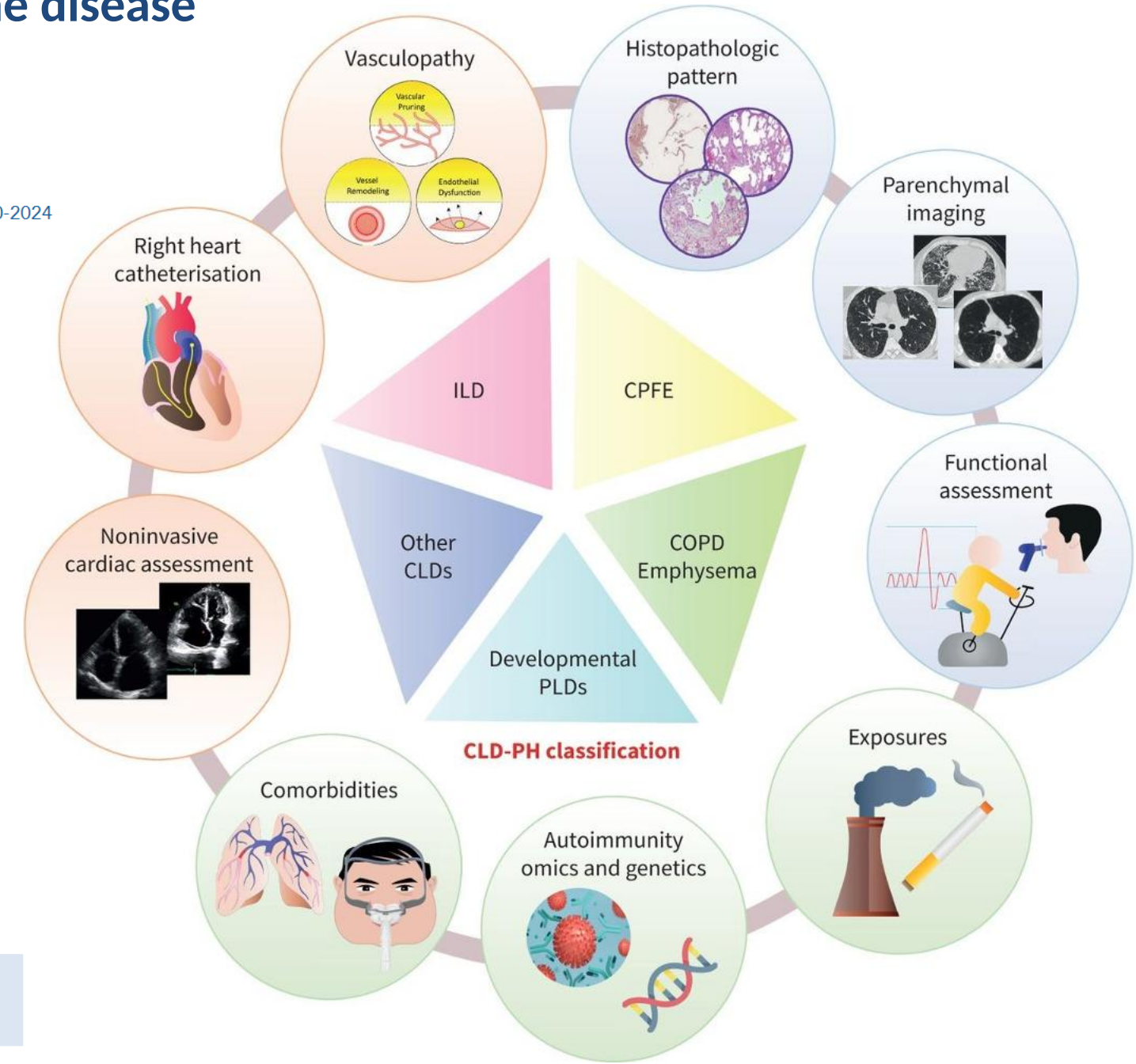
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## Pulmonary hypertension associated with lung diseases

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European Respiratory Journal 2024 64(4): 2401200; DOI: https://doi.org/10.1183/13993003.01200-2024

There are important pathogenic differences contributing to PH complicating different chronic lung diseases (CLDs), which is likely to impact how these entities respond to




ILD: Fibrotic, inflammatory or mixed phenotypes
What is the balance of ILD and vascular burden?

Is CPFE a separate treatment-response phenotype?
Preserved volumes may hide profound gas-transfer loss

# Definition of PH

ESC European Society of Cardiology
European Heart Journal (2022) 43, 3618–3731
https://doi.org/10.1093/eurheartj/ehac237

ESC/ERS GUIDELINES

**2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension**

## Haemodynamic definitions of pulmonary hypertension

| Definition | Haemodynamic characteristics |
|---|---|
| PH | mPAP >20 mmHg |
| Pre-capillary PH | mPAP >20 mmHg<br>PAWP ≤15 mmHg<br>PVR >2 WU |
| IpcPH | mPAP >20 mmHg<br>PAWP >15 mmHg<br>PVR ≤2 WU |
| CpcPH | mPAP >20 mmHg<br>PAWP >15 mmHg<br>PVR >2 WU |
| Exercise PH | mPAP/CO slope between rest and exercise >3 mmHg/L/min |

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## Clinical classification of pulmonary hypertension

**GROUP 1** Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

**GROUP 2** PH associated with left heart disease
- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction[b]
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

**GROUP 3** PH associated with lung diseases and/or hypoxia
- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

**GROUP 4** PH associated with pulmonary artery obstructions
- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions[c]

**GROUP 5** PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders[d]
- 5.2 Systemic disorders[e]
- 5.3 Metabolic disorders[f]
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

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PH associated with lung diseases and/or hypoxia (group 3, which includes ILD-PH)

**In patients with PH and chronic respiratory diseases, defining thresholds for classification is challenging.**

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# Definition, classification and diagnosis of pulmonary hypertension

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In patients with PH and chronic respiratory diseases, defining thresholds for classification is challenging. We suggest multimodal assessment of these subjects, including pulmonary function tests (PFTs), diffusion capacity of the lung for carbon monoxide ($D_{LCO}$) and high-resolution computed tomography (HRCT). HRCT should be performed especially in former or current smokers with strongly reduced $D_{LCO}$ (<45% predicted). For patients with significant abnormalities in pulmonary function or relevant parenchymal involvement in HRCT, particularly pulmonary fibrosis and/or emphysema, classification into group 3 PH should be favoured [31].

For patients with significant abnormalities in pulmonary function or relevant parenchymal involvement in HRCT, particularly pulmonary fibrosis and/or emphysema, classification into group 3 PH should be favoured.

# Suggested new subgroups of group 2 and 3 PH: clinical diagnoses

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| **Group 3: PH associated with lung diseases and/or hypoxia** |
|---|
| 3.1 COPD and/or emphysema |
| **3.2 Interstitial lung disease** |
| **3.3 Combined pulmonary fibrosis and emphysema** |
| **3.4 Other parenchymal lung diseases+** |
| 3.5 Nonparenchymal restrictive diseases: |
| 3.5.1 hypoventilation syndromes |
| 3.5.2 pneumonectomy |
| 3.6 Hypoxia without lung disease (*e.g.* high altitude) |
| 3.7 Developmental lung diseases |

Previous PH guidelines utilised classifications based on pulmonary function measurements, “obstructive lung diseases”, “restrictive lung diseases” and “lung diseases with mixed restrictive/obstructive pattern”, as subgroups of group 3 PH (PH associated with lung diseases and/or hypoxia).

**Potential future PH classifications**

The current clinical classification of PH is based on epidemiological and clinical considerations to categorise clinical conditions associated with PH according to their presentation, haemodynamic characteristics, and therapeutic management. As in other fields of contemporary medicine, future scientific advances may lead to more personalised PH classifications based on characteristics of pathophysiology, genetic background and therapy responses at an individual level. This may allow for a more customised approach in diagnosing and managing patients with PH and help to overcome current limitations that are derived from the relatively rigid structure of the clinical classification.

+PH associated with respiratory insufficiency and restriction that is not directly related to parenchymal lung pathology

# Common interstitial lung disease (ILD) subtypes associated with pulmonary hypertension

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## Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review

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| Subtype | Clinical definition |
|---|---|
| **Combined pulmonary fibrosis and emphysema** | Characterised by the presence of upper-lobe emphysema and lower-lobe fibrosis (often associated with idiopathic pulmonary fibrosis) [20]. |
| **Idiopathic interstitial pneumonias** | Characterised by the presence of fibrosis and inflammation; specific characteristics vary by subtype. Includes non-specific interstitial pneumonia, alveolar macrophage pneumonia (formerly desquamative interstitial pneumonia), respiratory bronchiolitis-associated interstitial lung disease, idiopathic diffuse alveolar damage (previously called acute interstitial pneumonia), cryptogenic organising pneumonia and lymphoid interstitial pneumonia [203]. |
| **Idiopathic pulmonary fibrosis** | Characterised by usual interstitial pneumonia pattern of progressive fibrosis [204]. |
| **Fibrotic hypersensitivity pneumonitis** | Caused by environmental antigens and characterised by sensitisation to these antigens, resulting in inflammation and fibrosis in the lungs with repeated exposures [205]. |
| **Systemic autoimmune rheumatic disease (connective tissue disease)-associated ILD** | Systemic autoimmune disorders that include rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, systemic lupus erythematosus and Sjögren's syndrome [206]. |
| **Systemic sclerosis** | Characterised by systemic fibrosis, inflammation, vasculopathy and immune system dysfunction; lung involvement is common, especially ILD [207]. |

# Suggested diagnostic approach to pulmonary hypertension (PH)

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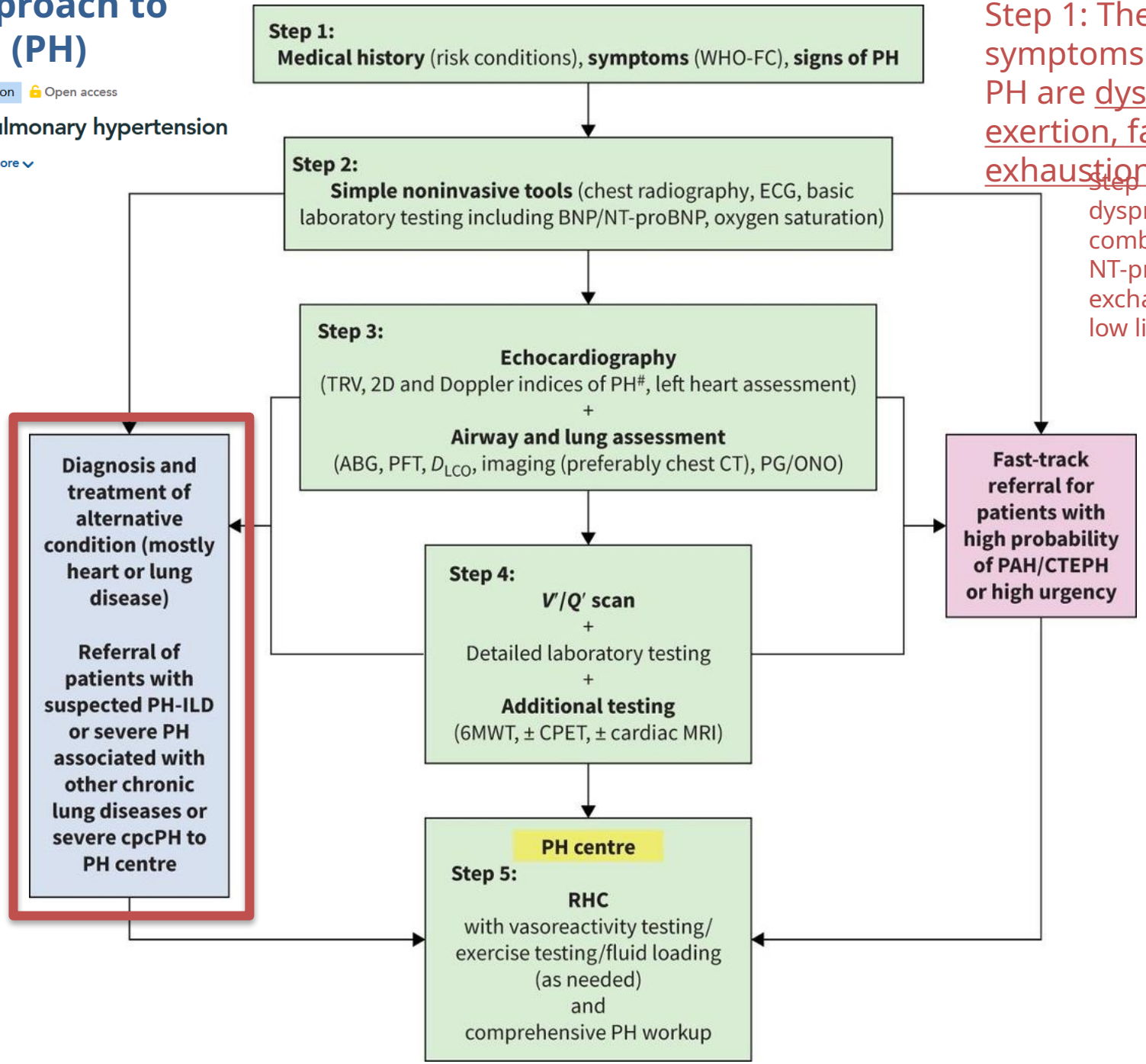
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Step 3: TRV >3.4 m·s$^{-1}$ suggests a high probability of PH, independent of additional signs of PH in echocardiography.

TRV values between 2.9 and 3.4 m·s$^{-1}$ are associated with an intermediate probability of PH, but the additional presence of further echocardiographic signs of PH result in high PH probability.

TRV ≤2.8 m·s$^{-1}$ is associated with low PH probability, but further echocardiographic signs of PH may increase PH probability to intermediate




Step 1: The most frequent symptoms in patients with PH are dyspnoea on exertion, fatigue and rapid exhaustion.

Step 2: In the absence of severe dyspnoea, a normal ECG in combination with normal BNP or NT-proBNP and normal gas exchange is associated with a low likelihood of PH

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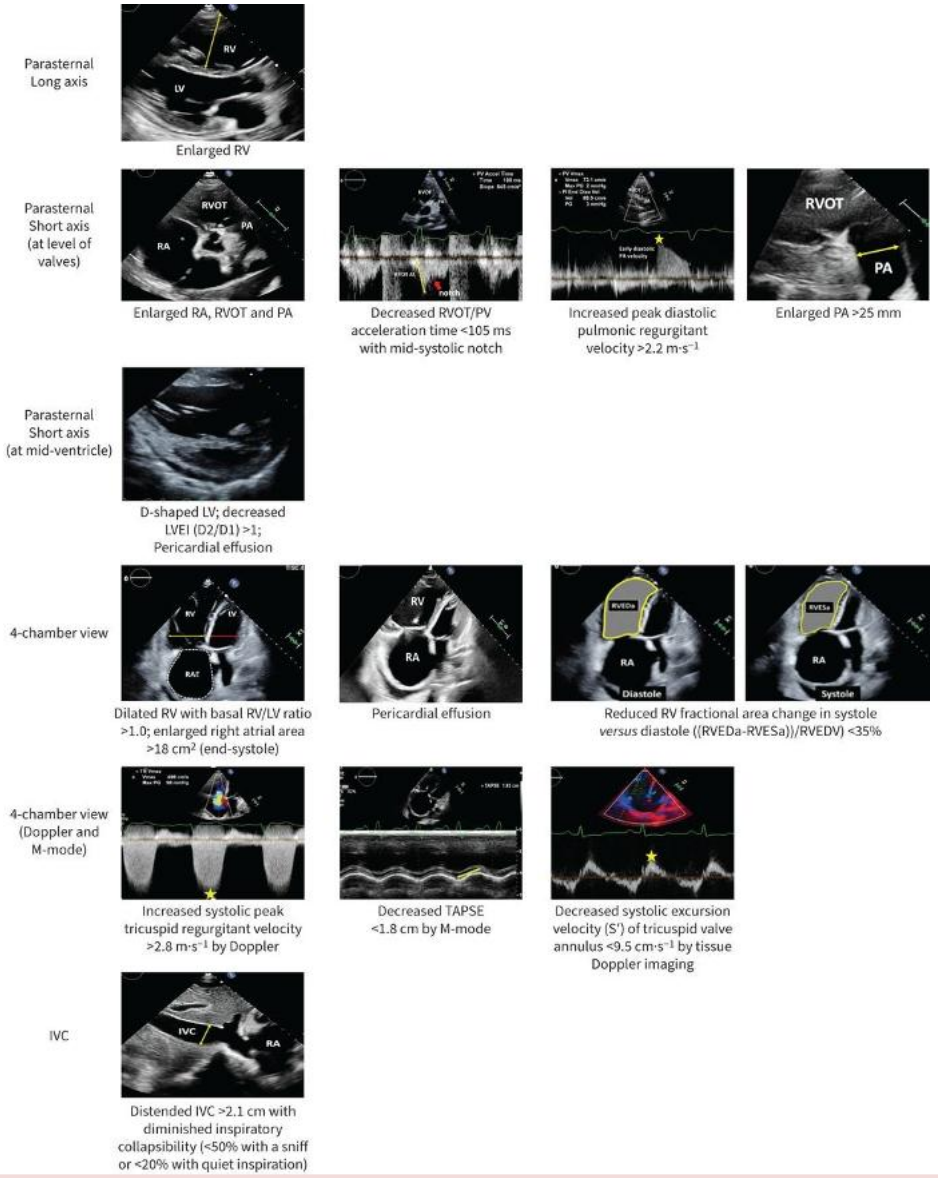
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### Additional echocardiographic signs suggestive of pulmonary hypertension (PH)

| | |
|---|---|
| **Ventricles** | RV/LV basal diameter/area ratio >1.0 |
| | Flattening of interventricular septum (LVEI >1.1 in systole and/or diastole) |
| | TAPSE/sPAP ratio <0.55 mm·mmHg$^{-1}$ |
| **PA** | RVOT AT <105 ms and/or mid-systolic notching |
| | Early diastolic pulmonary regurgitation velocity >2.2 m·s$^{-1}$ |
| | PA diameter>AR diameter; PA diameter >25 mm |
| **IVC and RA** | IVC diameter >21 mm with decreased inspiratory collapse |
| | RA area (end-systole) >18 cm$^2$ |




TRV to evaluate the probability of PH was recommended by the 2022 European Society of Cardiology/European Respiratory Society guidelines and recently endorsed by the 7th World Symposium on Pulmonary Hypertension

# CT images from a patient with PH associated with ILD

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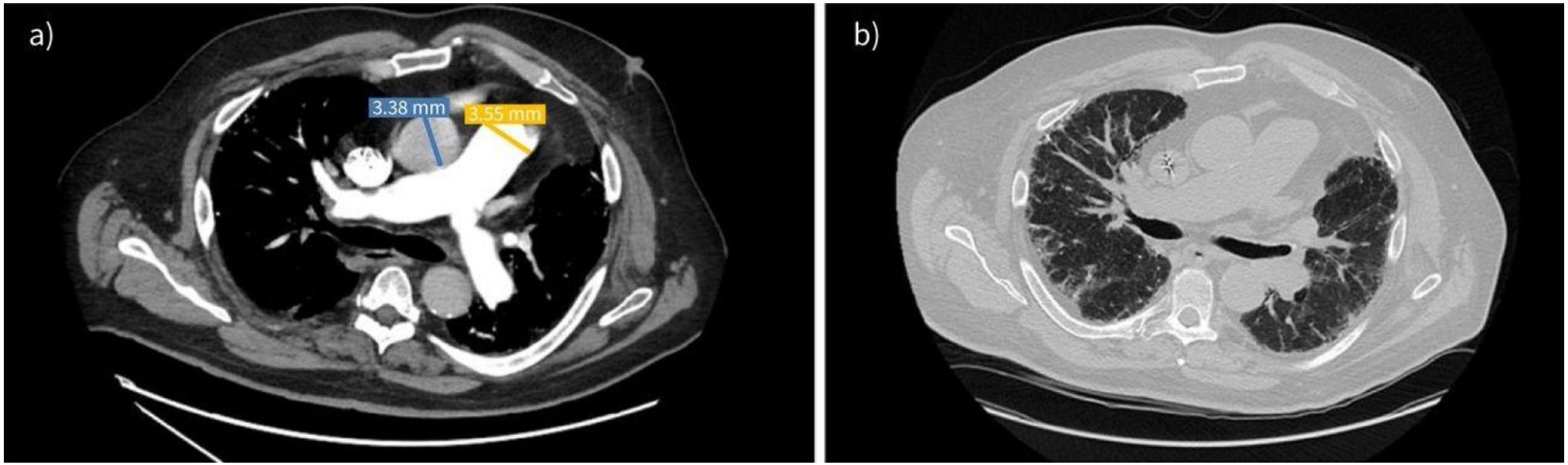
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A pulmonary artery/aorta ratio >1 on non-gated CT is more reliable than pulmonary artery diameter alone. When combined with echocardiographic estimates of systolic PAP, the predictive value improves

İmaging can also show enlargement of the right heart chambers, which is indicative of PH




CT from a patient with idiopathic pulmonary fibrosis and haemodynamically confirmed PH showing:
a) a pulmonary artery/aorta ratio >1 and
b) fibrotic interstitial changes.

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The 2022 ESC/ERS PH guidelines recommend the referral of patients with suspected severe PH associated with lung disease to a PH centre and an individualised approach to treatment, if severe PH is confirmed. In addition, inhaled treprostinil may be considered for the treatment of patients with PH associated with interstitial lung disease

In step 3, respiratory investigations are suggested as well. This inclu
(preferably chest computed tomography (CT)), and polygraphy or o
syndromes. Patients with PAH usually have normal or slightly reduced partial pressure of oxygen. More severe reductions
should raise suspicion for significant airflow obstruction, parenchymal lung disease, right-to-left shunt, PVOD or hepatic disease. Partial pressure of arterial carbon dioxide is typically normal or decreased in PAH due to alveolar hyperventilation, and PFT is usually normal or shows only mild abnormalities [71, 72]. More severe abnormalities suggest the presence of significant airway or parenchymal lung disease. A low $D_{LCO}$ (<40% predicted) in patients with PH is frequently associated with parenchymal lung disease or PVOD; therefore, chest HRCT should be performed in these patients [27].

Chest CT is the preferred imaging modality in patients with PH as compared to chest radiography.

Signs of PH in chest CT include an enlarged pulmonary artery diameter and its ratio to the aorta, and enlarged right heart chambers

Patients with interstitial lung disease and suspected PH should also be referred to a PH expert centre.

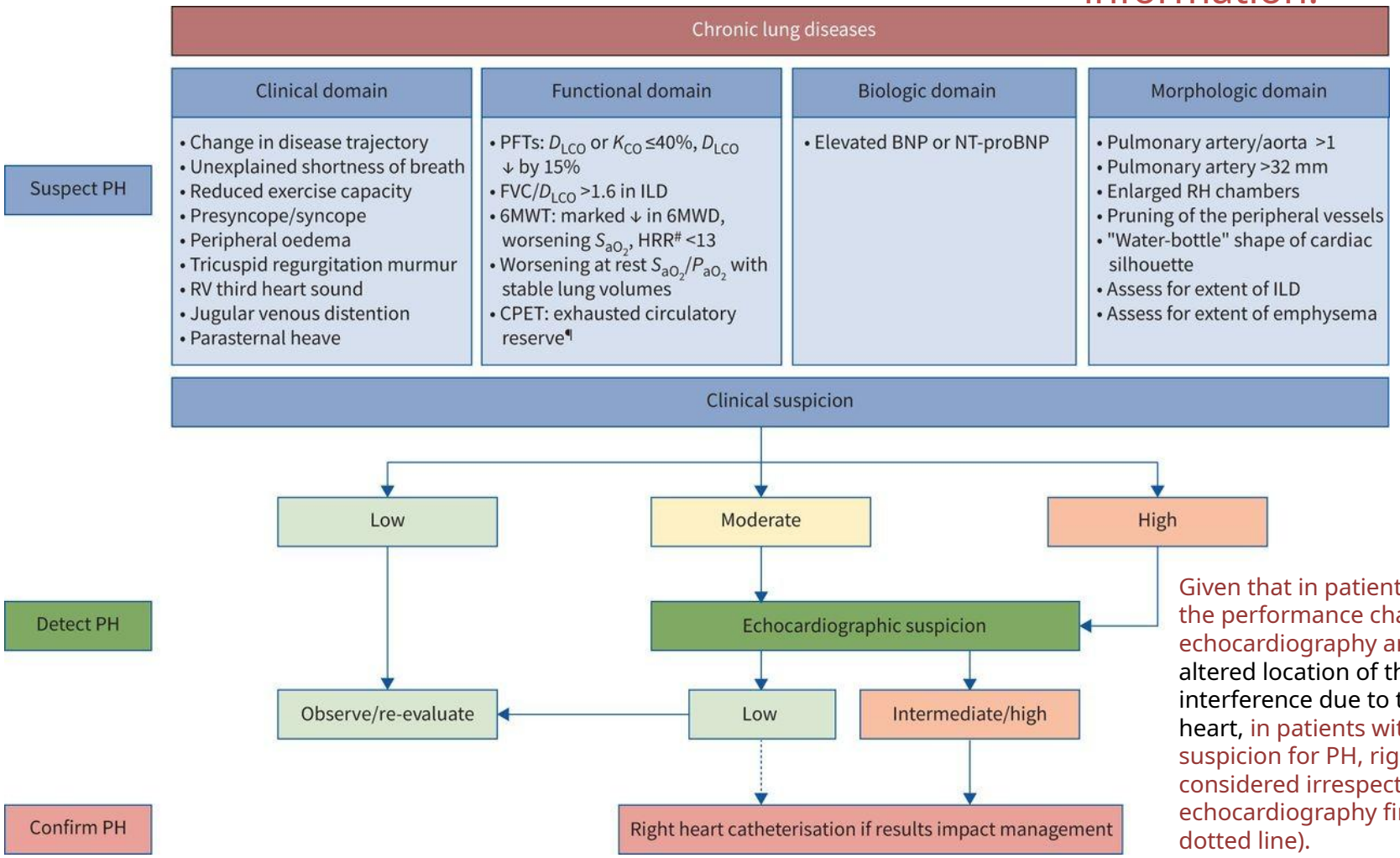
# Diagnostic algorithm for PH in the setting of COPD and ILD.

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## Pulmonary hypertension associated with lung diseases

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The decision to perform a right heart catheterisation should be predicated by a clinical or research need that would impact management and/or provide prognostic information.




Given that in patients with chronic lung diseases the performance characteristics of transthoracic echocardiography are worse due to poor windows, altered location of the heart in the chest cavity and interference due to the lung tissue overlying the heart, in patients with moderate or high clinical suspicion for PH, right heart catheterisation can be considered irrespective of the transthoracic echocardiography findings (as indicated by the dotted line).

Shlobin et al., ERJ 2024 – 7th WSPH

# Prevalence and Early detection of ILD-PH

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## Prevalence of ILD-PH

Estimates of PH in ILD subgroups may vary by as much as 20% depending on the diagnostic cut-off applied

A recent physician survey in Europe indicated that fewer than half of patients with suspected ILD-PH may be referred for confirmatory tests (*i.e.* echocardiography or RHC), leading to significant underestimation of disease prevalence

The results of cohort studies such as DeciPHer-ILD (NCT06388421), a real-world patient registry study, are eagerly awaited for insights into the clinical variables, treatments and clinical outcomes of patients with ILD-PH.

## Early detection of ILD-PH

Currently, there is no established screening approach for early detection of PH in the setting of ILD. Traditionally, PH in ILD has been diagnosed at advanced stages, often when patients present with clinical signs of right heart failure or during evaluation for lung transplantation.

PHINDER study (NCT05776225) has recently expanded participant recruitment to explore early detection strategies for ILD-PH

# Early detection of pulmonary hypertension (PH) in patients with underlying interstitial lung disease (ILD).

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#: initiation of discussions of lung transplant considerations at initial diagnosis of ILD-PH is suggested.

**PH detection is suggested at initial ILD diagnosis# and during follow-up, regardless of clinical suspicion**

### Clinical findings possibly due to PH:¶

- Worsening exertional dyspnoea, fatigue or palpitations
- Signs indicative of RHF
- Worsening $O_2$ saturation, decreased 6MWD, increased supplemental $O_2$ needs
- Elevated BNP/NT-proBNP
- $D_{LCO}$ decline >15%, $D_{LCO}$ <40% predicted, worsening (increasing) FVC/$D_{LCO}$, FVC/$D_{LCO}$ % predicted >1.6
- Disproportionate decline in $D_{LCO}$ related to FVC, and decline in 6MWD in the context of stable FVC

### Imaging: echocardiography or HRCT

- Echocardiography: right atrial enlargement, RV dilation/enlargement, TAPSE/sPAP ratio <0.55 mm·mmHg$^{-1}$, TRV+
- Chest CT: signs of RV enlargement, flattening or leftward bowing of interventricular septum, PA enlargement

- Confirmation of PH *via* RHC§
- Monitoring or re-evaluation as needed

§Severe ILD-PH is defined as PVR >5 WU

# Why does vascular disease become severe in some fibrotic lungs?

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**The severity of ILD based on radiography or PFTs may not correlate well with the severity of ILD-PH, suggesting that mechanisms beyond parenchymal fibrosis contribute to the development of PH**

A recent publication by KIM *et al*. highlights the heterogeneity observed in ILD.
Their single-centre study, which included 371 patients with RHC data available, highlighted that >50% of patients with $D_{LCO}$ ≤40% predicted or forced vital capacity (FVC)/$D_{LCO}$ % predicted ratio >1.5 still had potentially treatable PH (PVR >3 WU)

This underscores the need for more refined models and methods to predict the presence of PH in the setting of ILD.

# Pathogenesis of ILD-PH

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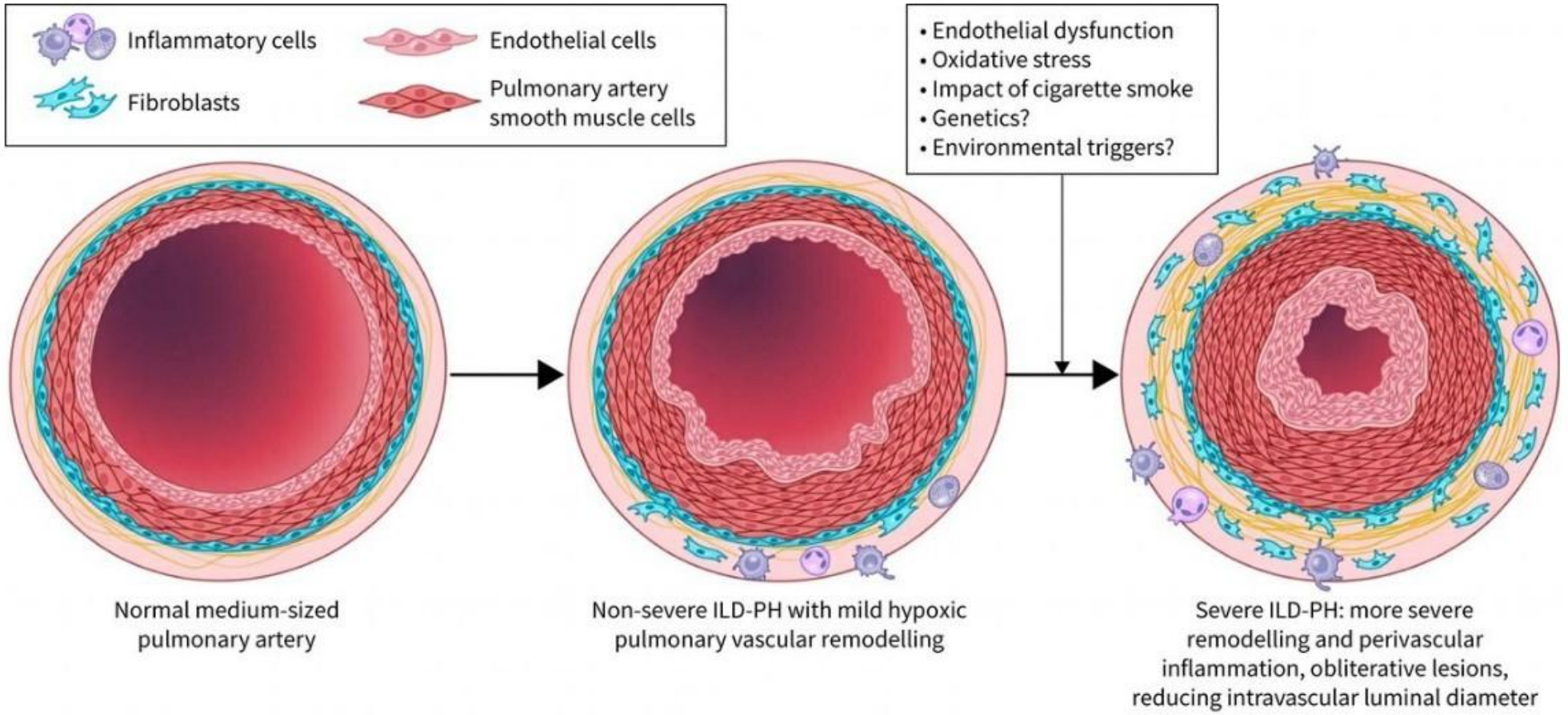
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Severe pulmonary vascular remodelling and perivascular inflammation can occur in ILD-PH, correlating with haemodynamic severity.

A pro-inflammatory, pro-proliferative, anti-apoptotic and profibrotic environment drives endothelial dysfunction and ultimately, global vascular remodelling.



# Pathogenesis of ILD-PH

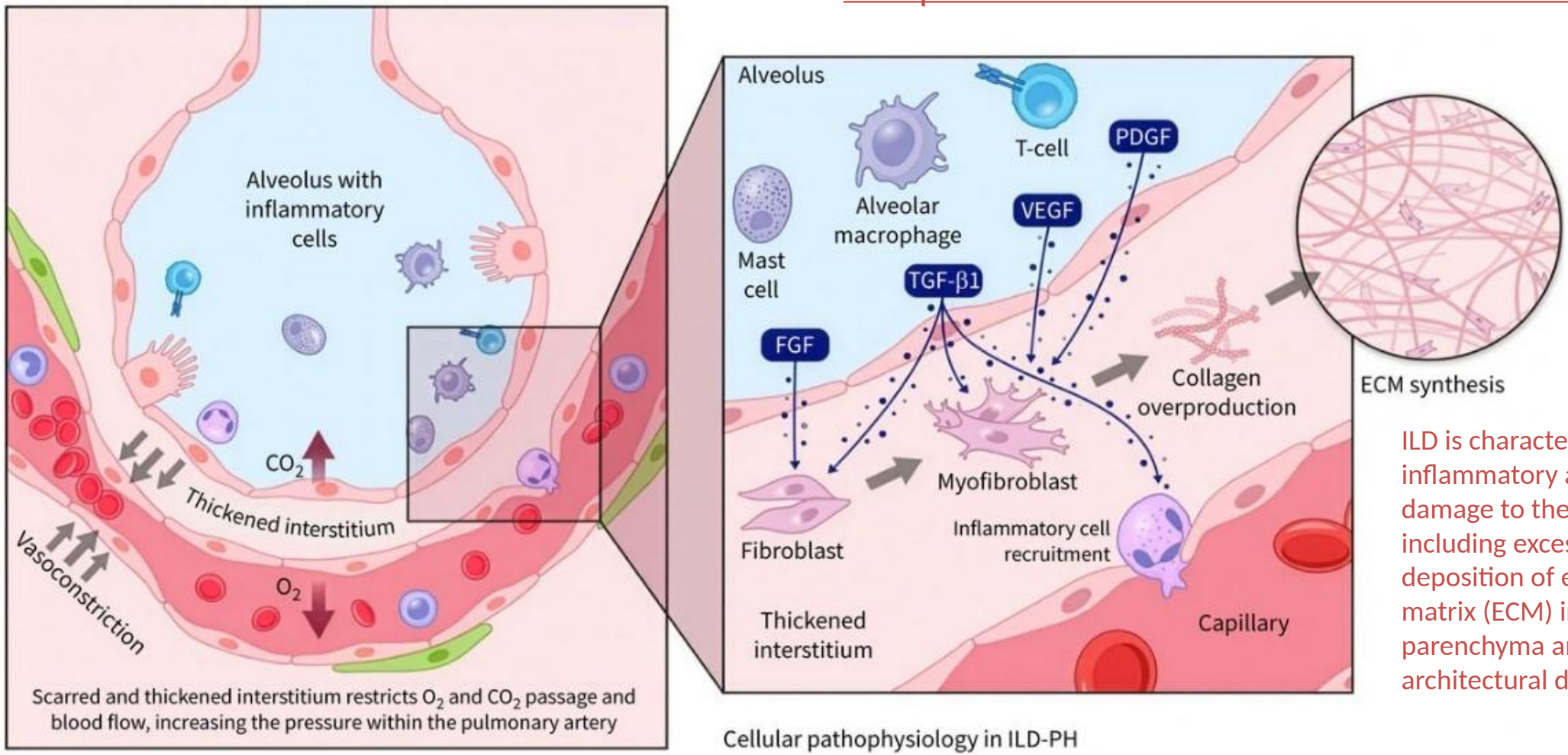
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The relationship between levels of fibrosis and PH severity is not linear, as indicated by a lack of clear correlation between lung function and CT fibrosis extent with invasive haemodynamics, suggesting independent mechanisms are also relevant.




Cellular pathophysiology in ILD-PH

ILD is characterised by inflammatory and fibrotic damage to the lungs, including excessive deposition of extracellular matrix (ECM) in the parenchyma and architectural destruction

$CO_2$: carbon dioxide; $O_2$: oxygen; FGF: fibroblast growth factor; TGF: transforming growth factor; VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor; ECM: extracellular matrix.

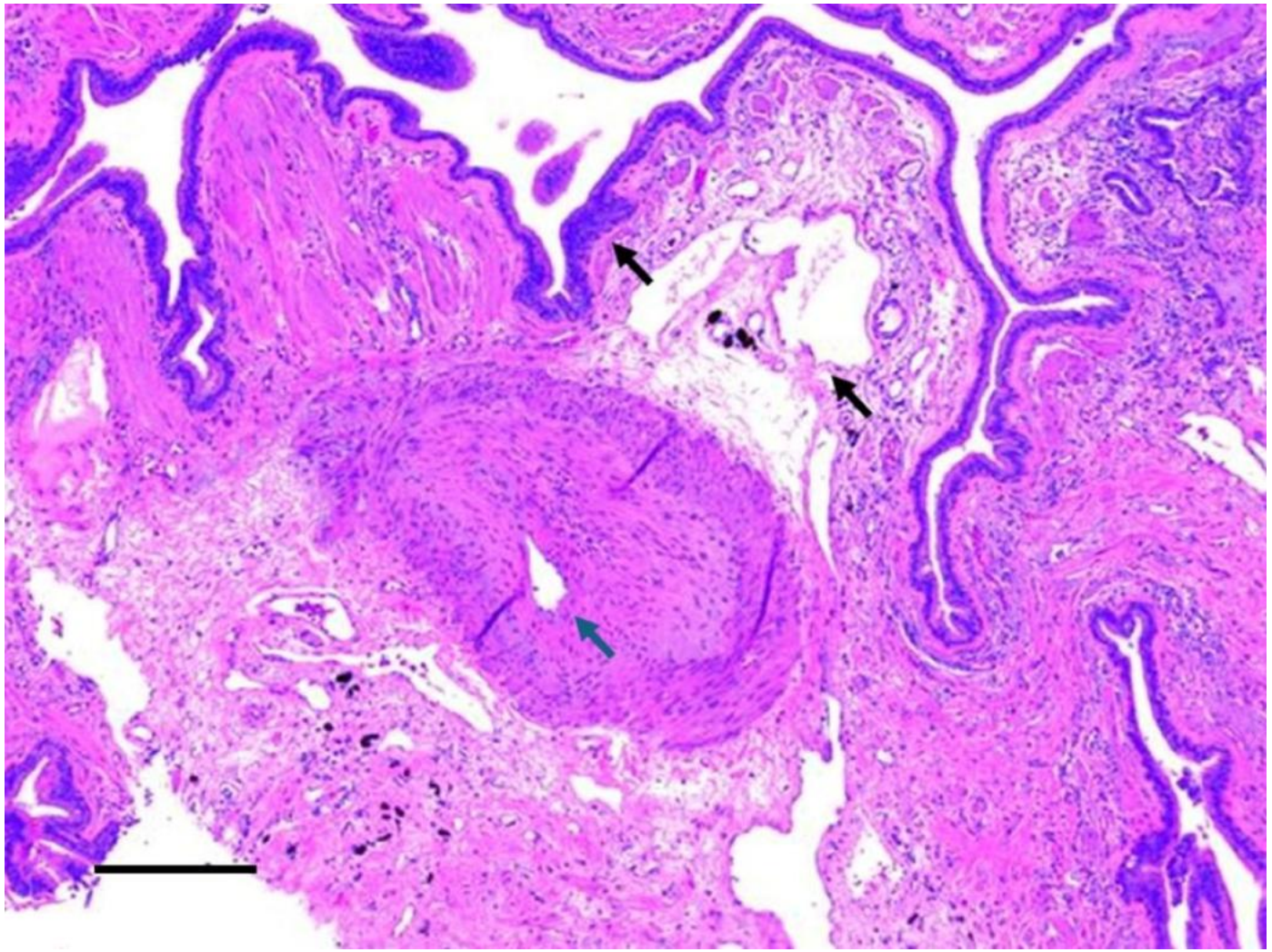
Histopathology

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- Histopathology photomicrograph from a patient with pulmonary hypertension associated with interstitial lung disease.
- Note: section of lung with interstitial fibrosis showing marked architectural distortion with metaplastic epithelial hyperplasia changes (black arrows).
- An artery with marked medial and intimal thickening and luminal reduction is also seen (teal arrow).

(Haematoxylin/eosin; scale bar: 100 µm.)

# Why does vascular disease become severe in some fibrotic lungs?

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## The vascular burden is not a linear function of parenchymal fibrosis.

Histopathology reveals multicompartment remodelling with marked spatial and temporal heterogeneity.

Integrate HRCT, DLCO, oxygenation and RHC — do not infer vascular severity from FVC alone.

| VASCULAR COMPARTMENT | PATHOLOGICAL FINDINGS | IMPLICATION FOR PH–ILD |
|---|---|---|
| **Small pulmonary arteries and arterioles** | Intimal and medial thickening, luminal narrowing and perivascular inflammation. | Pulmonary vascular resistance may increase out of proportion to fibrotic extent. |
| **Capillary and venous circulation** | Remodelling may extend to pulmonary capillaries, veins and lymphatic vessels. | Venous involvement may adversely affect tolerance of pulmonary vasodilators. |
| **Neoangiogenesis** | New vascular channels, including variable pulmonary–systemic anastomoses. | Potential additional mechanism contributing to hypoxaemia. |
| **Regional and temporal heterogeneity** | Vascular injury is patchy and need not progress synchronously with parenchymal disease. | Invasive haemodynamics reflect the net vascular burden; FVC and CT extent are imperfect surrogates. |

Raghu G et al. Eur Respir J. 2026;68:2502651. doi:10.1183/13993003.02651-2025

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## Severe pulmonary vasculopathy: beyond hypoxia alone

Severe ILD-PH reflects proliferative vascular disease, not simply loss of alveolar units.

| Pathobiological domain | Evidence / mediators | Biological implication |
|---|---|---|
| **Histopathology** | Marked arteriolar remodelling; rare PAH-like plexiform lesions | Vascular lesion burden may track haemodynamic severity |
| **Inflammatory signalling** | IL-1, IL-6, TNF-α and CCL5 (RANTES) | Endothelial activation and vascular inflammation |
| **Proliferative pathways** | PDGF, FGF2, TGF-β, endothelin-1, HIF-1α and VEGF | Smooth-muscle proliferation and disordered vascular repair |
| **Additional modifiers** | Tobacco smoke and viral insults; possible genetic susceptibility | Contributions to severe ILD-PH remain incompletely defined |

Raghu G et al. Eur Respir J. 2026;68:2502651. doi:10.1183/13993003.02651-2025

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## Hypoxia-related mechanisms: a graded vascular response

Hypoxic vasoconstriction supports V/Q matching acutely—but does not fully explain severe ILD-PH.

| Clinical setting | Mechanism | Haemodynamic implication |
|---|---|---|
| **Acute exacerbation** | Hypoxic vasoconstriction, alveolar injury and reduced compliance | Acute deterioration in pulmonary haemodynamics |
| **Sustained hypoxaemia** | HIF-1α activation; medial hypertrophy and arteriolar muscularisation | Often modest remodelling; severe PH implies additional mechanisms |
| **Nocturnal hypoxia / hypercapnia** | Intermittent hypoxic and ventilatory stress | Potential added vascular burden, especially with sleep disorders |
| **Exercise desaturation** | Increased pulmonary flow combined with hypoxic tone | Dynamic vascular stress and impaired exercise reserve |

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Ultimately, the overall reduction in perfusable vasculature in patients with ILD-PH, driven by remodelling of pulmonary arteries, loss of pulmonary vessels and impaired vasodilatory capacity, results in increased PVR.

This causes exercise limitation in patients with ILD-PH more due to cardiovascular dysfunction than ventilatory impairment.

In time, reduced pulmonary arterial compliance and increasing pulmonary arterial resistance impose limits on RV cardiac output and increase RV wall stress and consequently, myocardial oxygen demand.

Initially, adaptation of the right ventricle leads to hypertrophy.

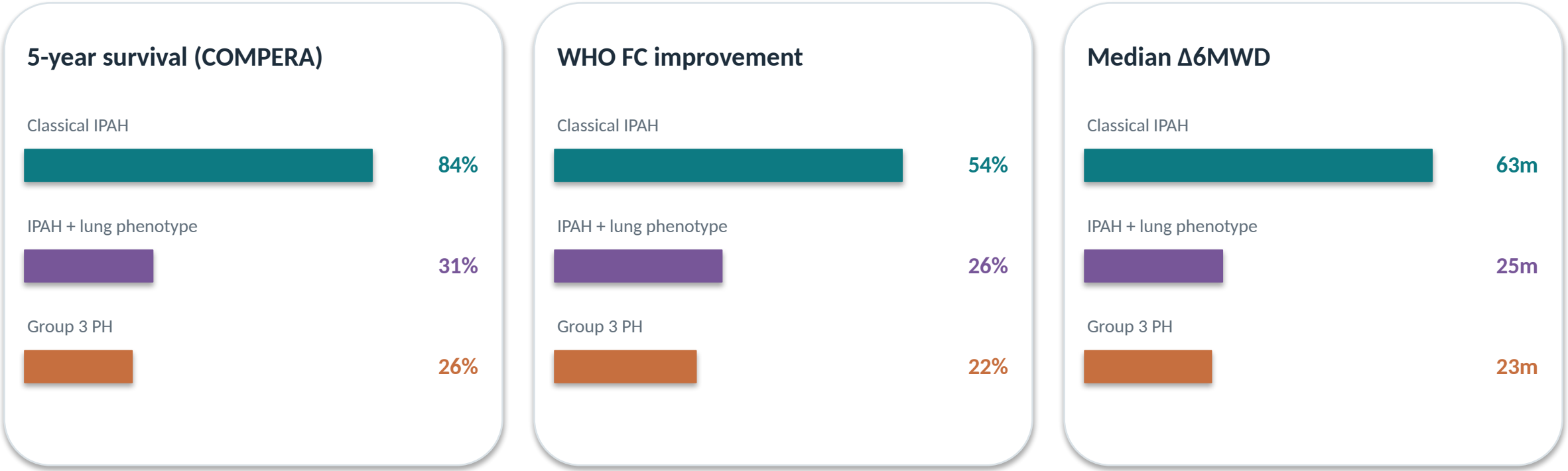
Eventually, the right ventricle dilates, establishing a maladaptive process resulting in RV uncoupling and failure, significant exercise limitation, and increased mortality.

The poorly compliant lung parenchyma also limits RV diastolic filling and therefore any adaptive increases in stroke volume. Together, these effects may lead to RV–pulmonary arterial uncoupling and progressive RV failure.

Hoeper M, Dwivedi K, Pausch C et al. Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. The Lancet Respiratory Medicine, 2022; 10, 937-948

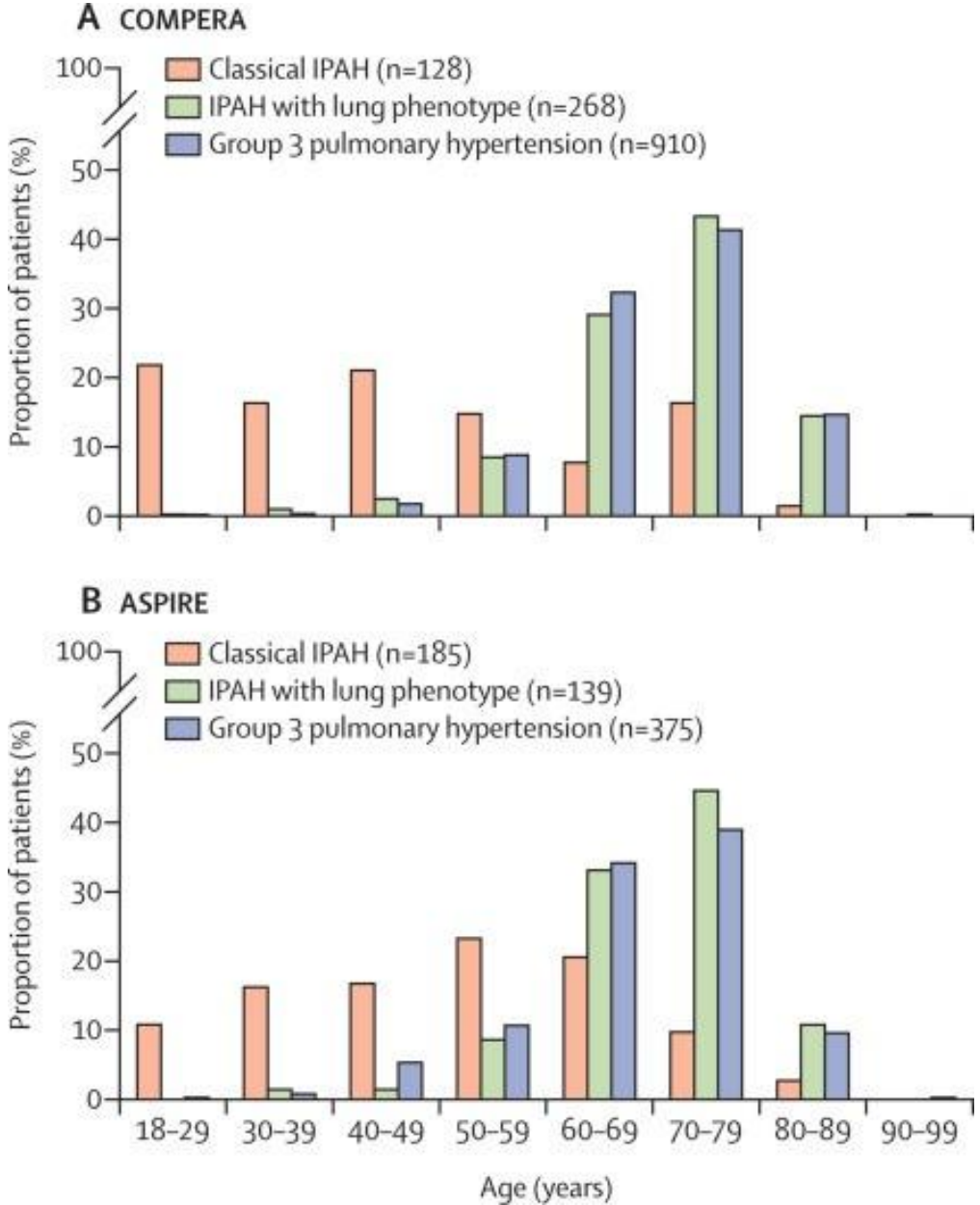
# The vascular phenotype: a spectrum, not a binary label

## COMPERA REGISTRY · CLASSIC IPAH VS IPAH LUNG PHENOTYPE VS GROUP 3 PH

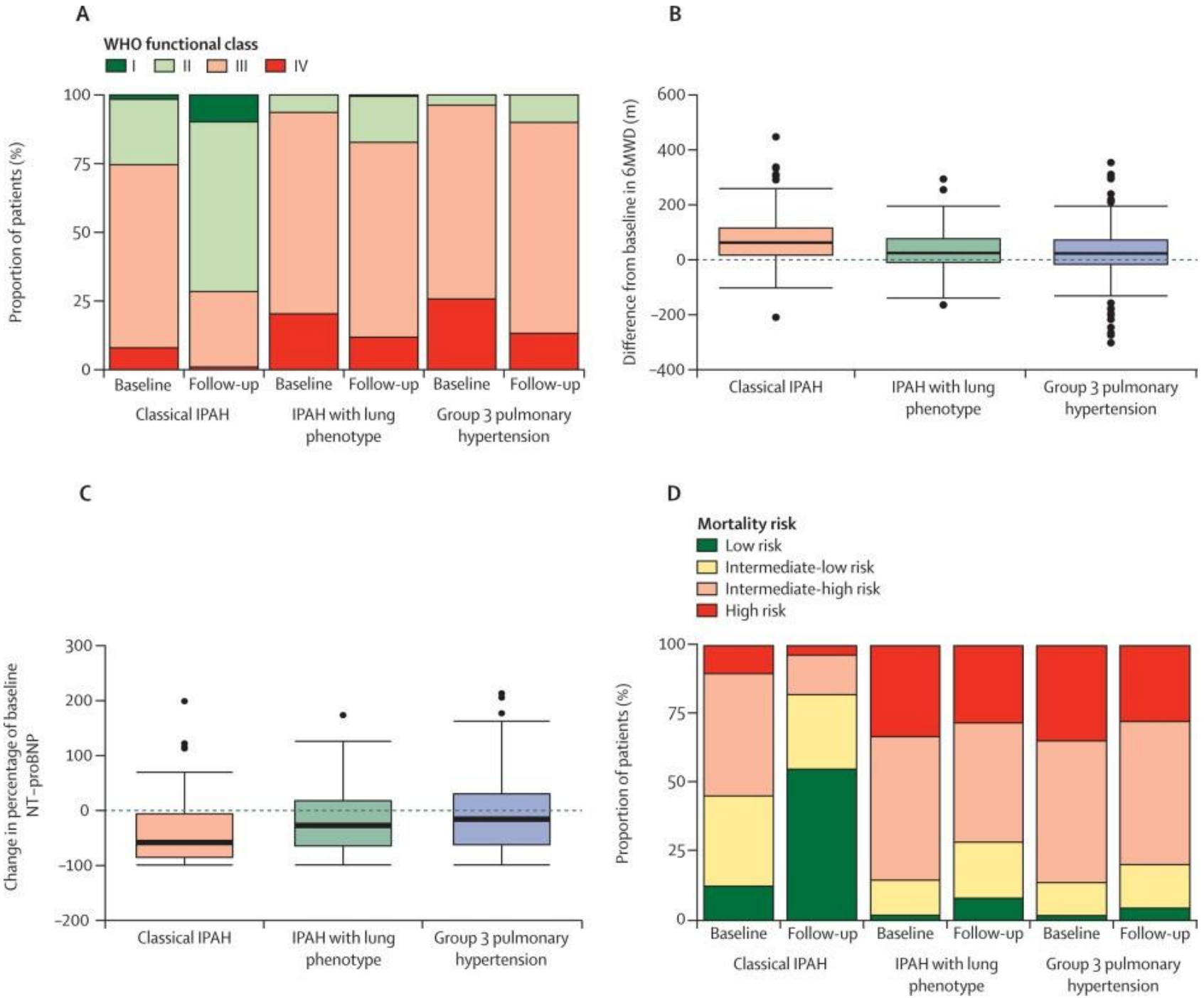



The analysis included 128 (COMPERA) and 185 (ASPIRE) patients with classical IPAH, 268 (COMPERA) and 139 (ASPIRE) patients with IPAH and a lung phenotype, and 910 (COMPERA) and 375 (ASPIRE) patients with pulmonary hypertension due to lung disease.

# Grouped bar plots showing age distribution of patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 pulmonary hypertension in COMPERA (A) and ASPIRE (B)

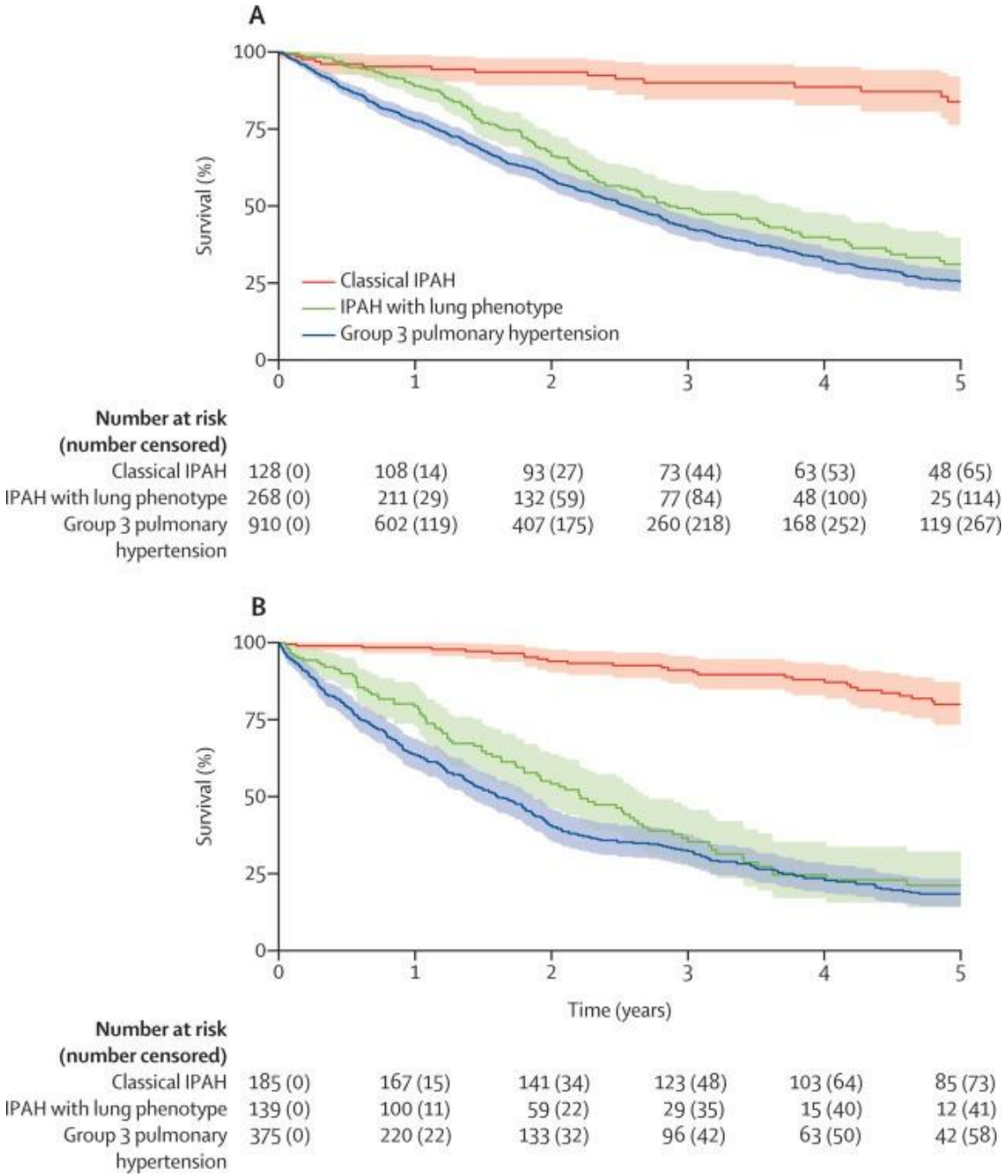



Hoeper M, et al. Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. The Lancet Respiratory Medicine, 2022; 10, 937-948




**Baseline and first follow-up measurement for functional class (A), 6MWD (B), NT-proBNP (C), and mortality risk (D) in COMPERA in patients with classical IPAH, IPAH with a lung phenotype, and patients with group 3 pulmonary hypertension**

Hoeper M, et al. Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. The Lancet Respiratory Medicine, 2022; 10, 937-948




**Kaplan-Meier survival estimates for patients classified as classical IPAH, IPAH with a lung phenotype, and group 3 pulmonary hypertension in COMPERA (A) and ASPIRE (B)**

Hoeper M, et al. Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. The Lancet Respiratory Medicine, 2022; 10, 937-948

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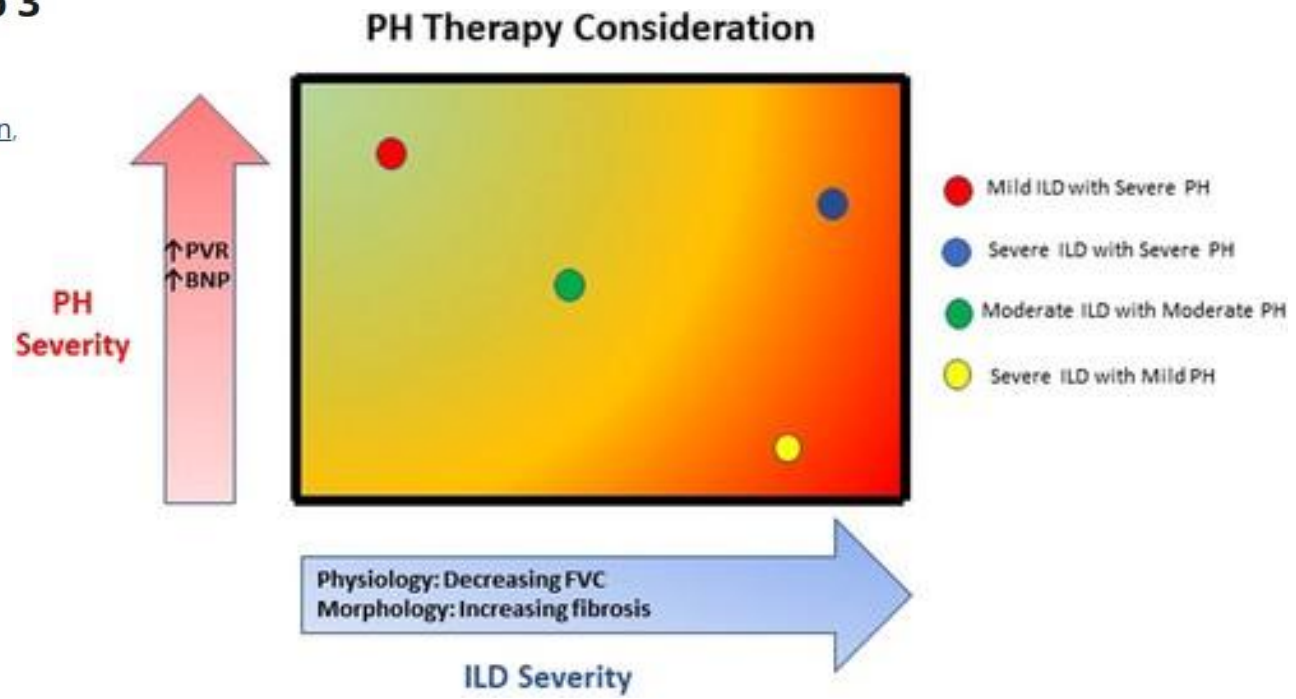
# Pulmonary hypertension in the setting of interstitial lung disease: Approach to management and treatment. A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative—Group 3 Pulmonary Hypertension

Oksana A. Shlobin, Eric Shen, Stephen J. Wort, Lucilla Piccari, John A. Scandurra, Paul M. Hassoun, Sylvia M. Nikkho, Steven D. Nathan

Pulmonary hypertension (PH) in interstitial lung disease (ILD) treatment according to disease phenotype.

Patients with ILD and PH might present different phenotypes according to the severity of both ILD and PH.

These phenotypes sit across a spectrum for both conditions; the phenotype should be taken into account when therapeutic strategies are considered for PH-ILD patients.



# Group 3 PH or PAH with a lung phenotype?

A vascular-predominant phenotype does not establish Group 1 PAH. Classification requires a multidisciplinary assessment of the lung, pulmonary circulation and comorbidities.

| | Fibrosis-predominant PH-ILD | Vascular-predominant presentation |
|---|---|---|
| **HRCT** | Extensive or clearly clinically relevant fibrotic ILD | Limited parenchymal abnormalities may coexist with severe vascular disease |
| **Physiology** | Restriction and reduced DLCO, often reflecting the extent of ILD | DLCO may be severely impaired despite relatively preserved lung volumes |
| **Haemodynamics** | PH severity is variable; severe PH can occur (PVR >5 WU) | Elevated PVR and RV dysfunction may be disproportionate to the extent of ILD |
| **Clinical interpretation** | Recognise and treat clinically significant ILD; evaluate the impact and severity of PH | Reassess HRCT, PFTs, RHC, left-heart disease and PAH risk factors before classification |

Humbert M et al. Eur Heart J. 2022 (ESC/ERS); Shlobin OA et al. Eur Respir J. 2024 (WSPH); Hoeper MM et al. Lancet Respir Med. 2022.

# When mild CT abnormalities change the PH phenotype

Classification is not determined by PVR or a mild CT abnormality alone: adjudicate the dominant phenotype in an expert multidisciplinary setting.

| | **CLASSICAL IPAH**<br>Predominantly vascular disease | **IPAH WITH LUNG PHENOTYPE**<br>Vasculopathy + subtle lung injury | **FIBROTIC ILD–PH (GROUP 3)**<br>Clinically significant lung disease |
|---|---|---|---|
| **HRCT / parenchyma** | No clinically relevant parenchymal abnormalities | Mild emphysema or limited interstitial abnormalities | Definite fibrotic ILD or CPFE; extent varies |
| **Physiology / gas transfer** | Relatively preserved lung volumes; DLCO variably reduced | DLCO often markedly reduced despite relatively preserved volumes | DLCO frequently very low; restriction and/or hypoxaemia may coexist |
| **Clinical profile** | Typical PAH phenotype; less smoking-associated | Often older; substantial tobacco exposure is common | Exercise limitation reflects both parenchymal and vascular disease |
| **Haemodynamics** | Pre-capillary PH; vascular disease dominates | Often substantial pulmonary vascular impairment | Severe PH is defined by PVR >5 WU; possible even with limited fibrosis |
| **Treatment evidence** | Established PAH treatment algorithms | Registry data suggest attenuated response to PAH therapy | Optimise ILD care; consider PH-directed therapy according to ILD-specific evidence |

Hoeper MM et al. Lancet Respir Med 2022;10:937–948 | Shlobin OA et al. Eur Respir J 2024;64:2401200 | Raghu G et al. Eur Respir J 2026;68:2502651

# Why CPFE matters: discordance between spirometry and pulmonary vascular burden

Relatively preserved lung volumes may coexist with profound impairment of gas transfer and clinically important PH.

İnterpret HRCT, DLCO, oxygenation and haemodynamics together—not FVC in isolation.

| | CPFE–PH: CLINICAL PATTERN | INTERPRETATION / EVIDENCE |
|---|---|---|
| **HRCT / structural burden** | Coexistent emphysema and fibrosis; the relative extent of each component varies. | Characterise both processes on HRCT; neither FVC nor fibrosis extent alone defines the phenotype. |
| **Physiology / gas transfer** | FVC and TLC may be relatively preserved despite a markedly reduced DLCO. | Disproportionate DLCO impairment should prompt assessment of vascular involvement and emphysema burden. |
| **Gas exchange / exercise** | Exertional desaturation, hypoxaemia and exercise limitation are common. | Integrate 6MWT, oxygen requirement and functional trajectory with imaging and haemodynamics. |
| **Pulmonary circulation** | PH is frequent and may be severe despite modest spirometric impairment. | Evaluate RV function and haemodynamics; consider RHC when results will alter management. |
| **Therapeutic evidence** | CPFE represented 25.2% of INCREASE; no clear 6MWD benefit emerged in the CPFE subgroup. | Subgroup findings are not definitive. Do not assume either efficacy or inefficacy from the overall PH-ILD result. |

Cottin V et al. Am J Respir Crit Care Med 2022;206:e7–e41
Shlobin OA et al. Eur Respir J 2024;64:2401200
Lichtblau M et al. Breathe 2025;21:240242

# The FORD Index

| Predictor | Category | Points[a] |
|---|---|---|
| **FVC%/DLCO%** | <2 | 0 |
| | 2-3 | 2 |
| | >3 | 34 |
| **Oxygenation** Oxygen saturation (%) nadir during 6MWT | >88 | 0 |
| | 83-88 | 19 |
| | ≤82 | 33 |
| **Race** | White | 0 |
| | Non-White | 20 |
| **Distance** Distance ambulated during 6MWT (m) | >350 | 0 |
| | 250-350 | 9 |
| | <250 | 13 |

## FORD Index Cutpoints and Their Performance Characteristics in Predicting Pulmonary Hypertension in the Derivation Cohort

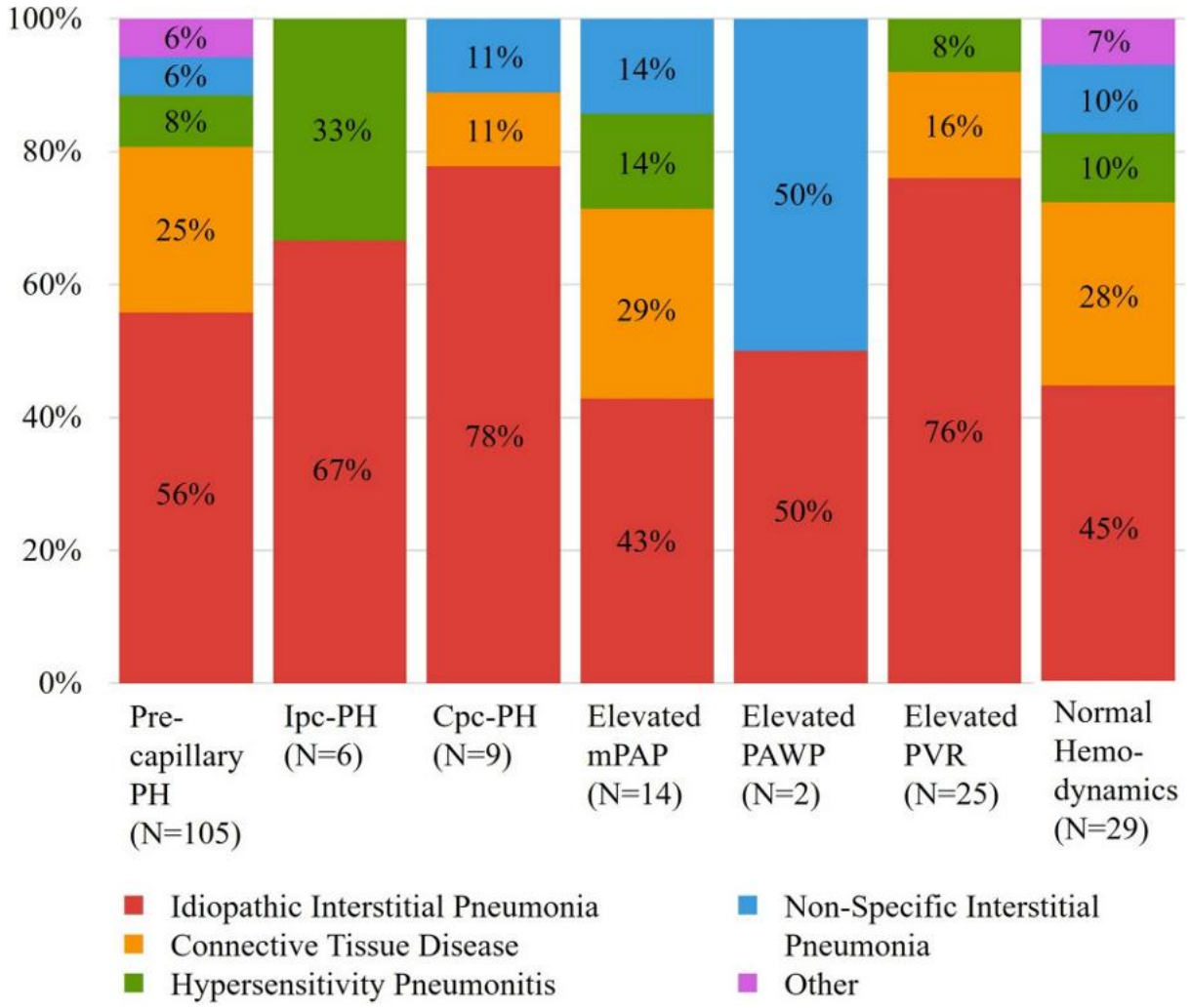
| Cutpoint | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| Score ≥ 3 | 87.2 | 37.9 | 13.4 | 96.4 |
| Score ≥ 20 | 74.5 | 65.2 | 19.1 | 95.8 |
| Score ≥ 25 | 61.7 | 73.6 | 20.6 | 94.6 |
| Score ≥ 30 | 59.6 | 77.6 | 22.8 | 96.6 |
| Score ≥ 40 | 42.6 | 92.5 | 38.5 | 93.6 |
| Score ≥ 60 | 12.8 | 99.3 | 66.7 | 91.1 |
| Score ≥ 21 (optimal via Youden's index) | 72.3 | 69.4 | 20.7 | 95.8 |
| Score ≥ 53 (optimal via CART) | 23.4 | 98.1 | 57.9 | 92.1 |

**Prediction models can support, but not replace RHC**

Nathan et al., JHLT 2024 – FORD Model

# Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study

## ILD subtypes among predefined hemodynamic subgroups of interes




### Key Summary Points

Despite the significant morbidity and mortality associated with pulmonary hypertension (PH) in interstitial lung disease (ILD), evidence-based PH screening guidelines are lacking in this population; to address this, the ongoing PHINDER study will enroll approximately 300 patients with ILD who undergo noninvasive assessments followed by right heart catheterization (RHC), to identify predictors of PH in ILD.

Preliminary findings from 190 patients, 55% with RHC-confirmed precapillary PH, suggest that supplemental oxygen use, low DLCO, TAPSE/RVSP ratio, TRV, RV/LV diameter ratio, and PA/aorta ratio may be predictive of PH.

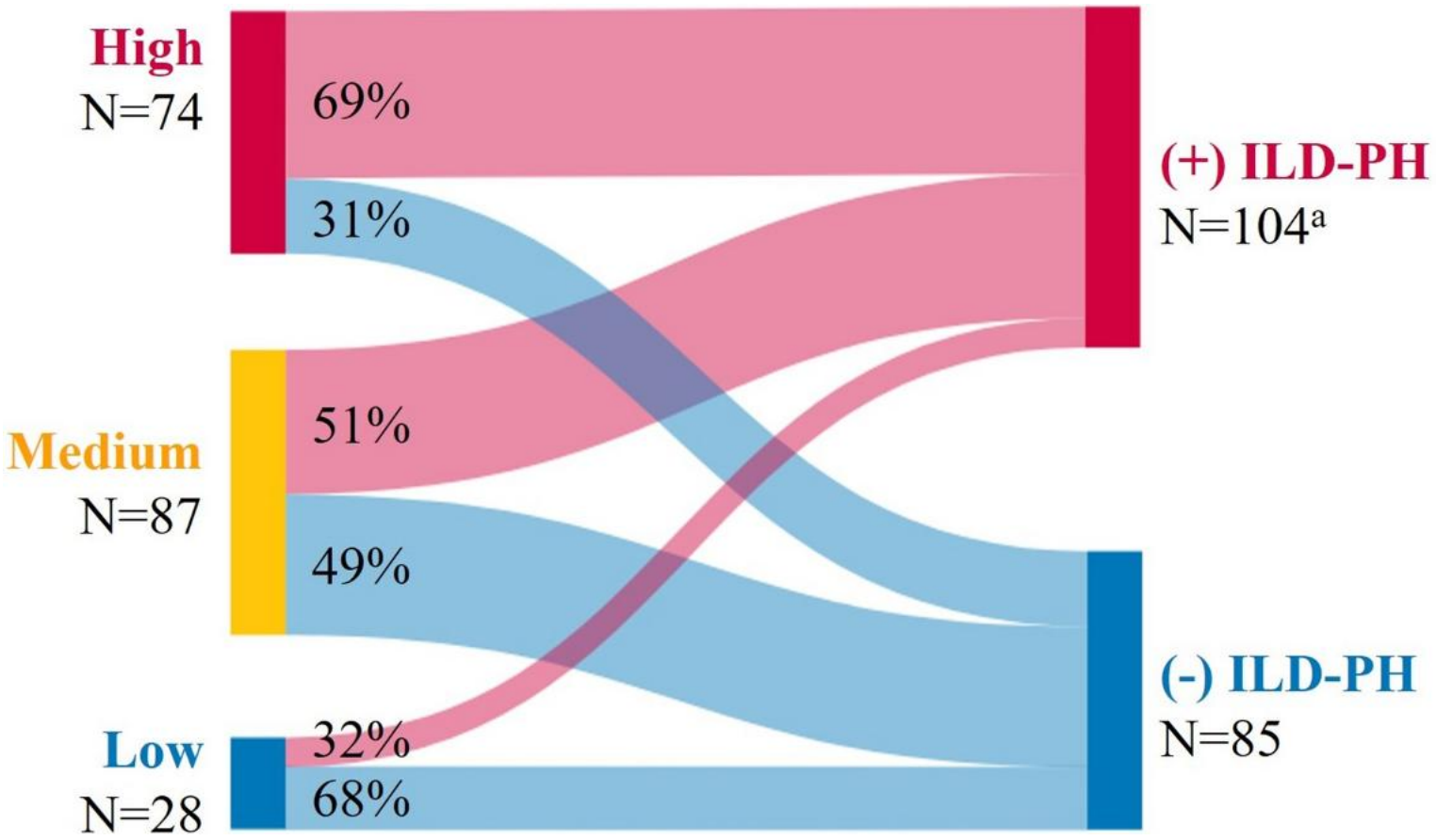
Clinician suspicion of PH was largely inaccurate, with precapillary PH confirmed in a third of patients who were deemed low likelihood for PH prior to RHC, underscoring the need for a more objective screening approach.

These preliminary results support a combination of pulmonary function tests, echocardiography, and CT imaging to improve early detection of PH in ILD, rather than relying solely on clinical judgment or echocardiography.

The final dataset from PHINDER will be used to establish prognostic thresholds for noninvasive measurements and to develop a validated PH screening tool to apply in ILD care.

Zisman et al., Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study, Advances in Therapy 2026 – PHINDER

# Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study




A high level of discrepancy was observed between gestalt-based assessments and RHC-confirmed diagnoses of precapillary PH

Having medium or high suspicion of precapillary PH resulted in a positive predictive value of 59%, while having a low suspicion resulted in a negative predictive value of 68%; overall, clinician suspicion had a sensitivity of 91%, specificity of 22%, and accuracy of 60%.

Clinical suspicion alone, or lack thereof, was insufficient for accurately identifying and ruling out precapil- lary PH, as substantial discordance was observed between clinician-assessed suspicion levels and RHC-confirmed diagnoses.

Zisman et al., Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study, Advances in Therapy 2026 – PHINDER

## Regression analysis results for parameters significantly associated with precapillary PH, performed against patients with normal mPAP, PVR, and PAWP, and against all patients without precapillary PH.

| | Precapillary PH vs normal RHC | | | Precapillary PH vs all other patients | | |
|---|---|---|---|---|---|---|
| | OR | CI | *P* value | OR | CI | *P* value |
| Medical history | | | | | | |
| Supplemental $O_2$ use | 3.65 | 1.51–8.81 | 0.0040 | 2.19 | 1.22–3.94 | 0.0090 |
| 6MWD, meters | 0.995 | 0.992–0.999 | 0.0141 | 1.00 | 1.00–1.00 | 0.3644 |
| Pulmonary function | | | | | | |
| DLCO, % predicted | 0.96 | 0.93–0.98 | 0.0006 | 0.97 | 0.95–0.99 | 0.0018 |
| DLCO, mL/min/mmHg | 0.89 | 0.82–0.97 | 0.0045 | 0.90 | 0.84–0.96 | 0.0016 |
| %FVC/%DLCO ratio | 1.13 | 1.03–1.24 | 0.0080 | 1.08 | 1.02–1.14 | 0.0047 |
| Echocardiography | | | | | | |
| RVSP, mmHg | 1.09 | 1.03–1.15 | 0.0023 | 1.03 | 1.004–1.06 | 0.0247 |
| TAPSE/RVSP ratio | 0.82 | 0.70–0.97 | 0.0198 | 0.88 | 0.78–0.998 | 0.0466 |
| TRV, m/s | 4.42 | 1.53–12.83 | 0.0062 | 2.12 | 1.13–4.00 | 0.0200 |
| RAP, mmHg | 1.32 | 0.91–1.92 | 0.1410 | 1.17 | 1.002–1.36 | 0.0470 |
| Computed tomography | | | | | | |
| RV/LV diameter ratio | 1.53 | 1.07–2.20 | 0.0207 | 1.30 | 1.03–1.62 | 0.0246 |
| RV/LV ratio > 1 | 3.55 | 1.13–11.16 | 0.0299 | 2.74 | 1.33–5.63 | 0.0062 |
| PA/aorta ratio | 1.66 | 1.18–2.34 | 0.0038 | 1.42 | 1.14–1.78 | 0.0020 |
| PA/aorta ratio > 1 | 2.06 | 0.80–5.36 | 0.1368 | 2.09 | 1.09–4.03 | 0.0268 |
| PA enlargement[a] | 10.6 | 2.98–37.69 | 0.0003 | 2.98 | 1.58–5.61 | 0.0007 |

Patients with ILD who are found to have decreased DLCO on PFTs, elevated RVSP or TRV on echocardiography, and/or elevated PA/aorta diameter ratio or RV/ LV diameter on CT may benefit from undergoing RHC to determine if PH is present.

Zisman et al., Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study, Advances in Therapy 2026 – PHINDER

# Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study

## Enrichment criteria for study eligibility

| Category 1<br>PFTs and/or HRCT | Category 2<br>Exercise capacity, oxygenation, biomarkers, and/or physical exam | Category 3<br>Echocardiography |
|---|---|---|
| *Pulmonary function testing* | *Exercise testing and oxygenation* | • TAPSE < 2 cm |
| • DLCO < 40% | • Decline in 6MWD ≥ 15% | • RVSP > 35 mmHg |
| • DLCO decline ≥ 15% based on 2 most recent assessments | • Desaturation on 6MWT disproportionate to ILD severity | • RV dilation or enlargement |
| • DLCO decline > 10% with FVC decline < 5% (i.e., worsening FVC/DLCO ratio) based on 2 most recent assessments | • Recent worsening desaturation | • RV abnormality |
| *HRCT* | *Biomarkers* | |
| • RV/LV ratio > 1 | • BNP > 200 pg/mL | |
| • PA/aorta ratio > 1 | • NT-proBNP > 395 pg/mL | |
| • Enlarged PA | *Symptoms and physical exam* | |
| • Enlarged PAs in lung periphery | • Symptoms disproportionate to ILD severity or changes in symptoms not explained by ILD progression | |
| • Ventricular septal flattening | • ≥ 1 of syncope, JVD, peripheral edema, ascites, loud P2 or S2 heart sound, or hepatomegaly | |

*BNP* B-type natriuretic peptide, *DLCO* diffusing capacity of the lung for carbon monoxide, *FVC* forced vital capacity, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *JVD* jugular venous distention, *LV* left ventricle, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *PA* pulmonary artery, *PFT* pulmonary function test, *RV* right ventricle, *RVSP* right ventricular systolic pressure, *TAPSE* tricuspid annular plane systolic excursion, *6MWD* 6-min walk distance, *6MWT* 6-min walk test

**Preliminary Results from the PHINDER Study**

These findings support the need for structured screening protocols that integrate objective imaging and functional assessments alongside clinical judgment to improve diagnostic accuracy, as commonly used screening approaches such as gestalt, echocardiography, and natriuretic peptide levels should not be relied upon.

These results also suggest that the current threshold for performing RHC in this population may warrant reconsideration; specifically, the data suggest that relying solely on echocardiographic findings and/or the absence of clinical suspicion may be insufficient to rule out PH.

# Treatment

**Prostacyclin analogues**

Prostacyclin analogues have drawn interest for their ability to regulate fibrotic pathways and increase blood flow by stimulating the production of cAMP. While the pharmacological profile of prostacyclin class therapies such as iloprost and treprostinil differs considerably depending on the receptor being targeted, they can lead to vasodilation and reduced vascular remodelling, antifibrotic effects *via* reduced fibroblast activity and proliferation and deposition of collagens, and reduced lung inflammation

**Phosphodiesterase 5 inhibitors**

Clinical trials of several phosphodiesterase 5 inhibitors (PDE5i), including sildenafil, have been performed in ILD and ILD-PH. Observational studies have shown that PDE5i may improve survival outcomes, particularly if started early in ILD-PH disease progression, before the onset of RV dysfunction.

**Endothelin receptor antagonists**

**Endothelin-1**, a potent vasoconstrictor and growth factor, has been implicated in the pathogenesis of pulmonary fibrosis.
Endothelins have been implicated in fibrosis, particularly in the stimulation of myofibroblast differentiation and ECM production. Biological samples from patients with ILD have indicated that endothelins are overexpressed in fibrotic lung tissue and may be associated with ILD severity.
As such, endothelin receptor antagonists (ERA) were considered promising for the treatment of IPF and ILD-PH because they targeted both vasodilation and antifibrotic pathways.

**Nitric oxide**

Nitric oxide (NO) is a well-documented vasodilator due to its role as a stimulator of the cyclisation of guanosine triphosphate to cGMP; cGMP production also stimulates the relaxation and dedifferentiation of myofibroblasts, thereby reducing fibrosis. Inhaled NO has been shown to protect against the development of PH in rats. Lower levels of exhaled NO have been associated with PH and ILD

**Soluble guanylate cyclase stimulators**

An alternative method to increase cGMP levels for the treatment of ILD-PH is the use of soluble guanylate cyclase (sGC) stimulators, such as riociguat.

Treatment

Review | State Of The Art  Open access

# Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review

Ganesh Raghu | Sandeep Sahay | Laura C. Price  Show More

European Respiratory Journal 2026 68(1): 2502651; DOI: https://doi.org/10.1183/13993003.02651-2025

**TABLE 2** Studies evaluating pulmonary hypertension (PH) therapies in interstitial lung disease (ILD) and ILD-PH, 2000–2025

| | Study population | Study drug | Comparator | Study type | Study identifier | Study setting and size (n) | Primary end-point | Study outcome |
|---|---|---|---|---|---|---|---|---|
| **NO and sGC stimulators** | | | | | | | | |
| Hoeper *et al.* [208] | IPF, non-specific ILD, scleroderma or sarcoidosis | Riociguat | Baseline | Proof of concept | NA | Multicentre (22) | Safety and tolerability throughout initial 12-week study period and at 12 months | Primary end-point reached; riociguat was well tolerated; improved PVR and 6MWD but not mPAP |
| Nathan *et al.* [114] | IIP-PH | Riociguat | Placebo | RCT | RISE-IIP, NCT02138825 | Multicentre (147) | Change in 6MWD | Primary end-point not reached; terminated early for unfavourable risk/benefit profile |
| Nathan *et al.* [209] | fILD and FVC >40% predicted | Inhaled NO | Placebo | RCT | NCT03267108 | Single centre (41) | Physical activity parameters, 6MWD and oxygen saturation | Primary end-point reached; improved overall and vigorous activity |
| **PDE5i** | | | | | | | | |
| Collard *et al.* [148] | IPF-PH | Sildenafil | Baseline | Prospective | NCT00352482 | Single centre (14) | Change in 6MWD | Primary end-point reached; improvement in 6MWD |
| Corte *et al.* [149] | ILD-PH | Sildenafil | Baseline | Prospective | NA | Single centre (15) | Proportion of patients with increase in 6MWD ⩾20% at 12 weeks | Primary end-point reached; improved 6MWD and BNP levels, but no improvement in haemodynamics |
| Dawes *et al.* [150] | ILD-PH | PDE5i (various) | Baseline | Retrospective | NA | Single centre (128) | All-cause mortality | Primary end-point reached; longer survival observed in patients treated with PDE5i, with improved survival in those with preserved right heart function on baseline echocardiography |
| Ghofrani *et al.* [151] | PH secondary to lung fibrosis | Sildenafil | Intravenous epoprostenol (mean 8.0 ng·kg$^{-1}$·min$^{-1}$) +inhaled NO | RCT | NA | Single centre (16) | Decrease in PVRi | Primary end-point reached; sildenafil improved haemodynamics and oxygenation |
| Zimmermann *et al.* [108] | ILD-PH | Sildenafil, tadalafil | Baseline | Prospective | NA | Single centre (10) | Improvement in pulmonary haemodynamics, 6MWD and BNP from baseline to follow-up | Primary end-point partially reached; improved haemodynamic measures, but no significant improvement in 6MWD and BNP |
| **ERA** | | | | | | | | |
| Corte *et al.* [210] | fIIP-PH | Bosentan | Placebo | RCT | NA | Multicentre (60) | Fall from baseline PVRi of ⩾20% over 16 weeks | Primary end-point not reached; no improvement in haemodynamics or functionality |
| Gilead Sciences [159] | IPF-PH | Ambrisentan | Placebo | RCT | ARTEMIS-PH, [illegible] | Multicentre (40) | hange from baseline in 6MWD | Primary end-point not reached; study terminated due to safety and efficacy concerns |
| Tanaka *et al.* [211] | IPF-PAH and IPF-PH | Bosentan | No treatment | RCT | UMIN000004749 | Single centre (32) | Changes in prognosis and respiratory failure from baseline to month 12 | Primary end-point reached; improved activities of daily living, pulmonary circulation and $D_{LCO}$ |

**TABLE 2** Continued

| | Study population | Study drug | Comparator | Study type | Study identifier | Study setting and size (n) | Primary end-point | Study outcome |
|---|---|---|---|---|---|---|---|---|
| **Prostacyclin analogues** | | | | | | | | |
| Baughman *et al.* [212] | SAPH | Inhaled iloprost | Baseline | Prospective | NCT00403650 | Multicentre (22) | Change in 6MWD | Improvement in haemodynamics and quality of life |
| Nathan *et al.* [213] | ILD-PH | Inhaled treprostinil | Placebo | *Post hoc* analysis | INCREASE, NCT02630316 (*post hoc*) | Single centre (326) | Number of patients who experienced a clinical worsening event or who demonstrated clinical improvement between weeks 4 and 16 | Primary end-point reached; improvements in FVC |
| Nathan *et al.* [116] | ILD-PH | Inhaled treprostinil | Placebo | *Post hoc* analysis | INCREASE, NCT02630316 (*post hoc*) | Multicentre (326) | Pulmonary function testing at baseline, week 8 and week 16 | Primary end-point reached; reduction in clinical worsening |
| Saggar *et al.* [134] | IPF-PH | Parenteral treprostinil | Baseline | Prospective | NCT00705133 | Single centre (15) | Change in haemodynamic parameters, DE, oxygenation, dyspnoea, and quality of life indices and 6MWD before and 12 weeks after parenteral treprostinil | Primary end-point reached; improved haemodynamics and echocardiographic function |
| Waxman *et al.* [136] | ILD-PH | Inhaled treprostinil | Prior placebo arm of INCREASE trial | Prospective | INCREASE OLE, NCT02633293 | Multicentre (242) | No prespecified end-point; data captured includes change in 6MWD, NT-proBNP, SGRQ and DSP from baseline to week 64 | Reduced clinical worsening |
| Waxman *et al.* [115] | ILD-PH | Inhaled treprostinil | Placebo | RCT | INCREASE, NCT02630316 | Multicentre (326) | Change in peak 6MWD from baseline to week 16 | Primary end-point reached; improved outcomes of interest (6MWD, FVC and NT-proBNP levels) and reduced clinical worsening |
| **Combination/ mixed class and other** | | | | | | | | |
| Czepiel *et al.* [214] | ILD-PH | Hymecromone (hyaluronan synthesis inhibitor) | Placebo | Phase 2 RCT | SATURN, NCT05128929 | Single centre (16) | Change in PVR and 6MWD from baseline to week 24 | No significant difference in PVR, but some improvements in 6MWD and quality of life |
| Keir *et al.* [215] | SAPH | PDE5i, ERA or combination | Baseline | Retrospective | NA | Single centre (33) | Change from baseline to 6-month follow-up in 6MWD, BNP, TAPSE and WHO FC | Primary end-point reached; 6MWD, BNP levels, TAPSE, and WHO FC improved with treatment (no controls) |
| Le Pavec *et al.* [216] | PLCH-PH | Various | Baseline | Retrospective | NA | Multicentre (29) | Improvements in WHO FC, 6MWD, haemodynamic parameters and pulmonary [illegible] | Primary end-point partially reached; improved haemodynamics and WHO FC [illegible] |

**TABLE 2** Continued

| | Study population | Study drug | Comparator | Study type | Study identifier | Study setting and size (n) | Primary end-point | Study outcome |
|---|---|---|---|---|---|---|---|---|
| Le Pavec *et al.* [217] | SSc-PH | Various | Baseline | Retrospective | NA | Multicentre (70) | Change from baseline to follow-up in WHO FC, 6MWD and haemodynamic parameters | Primary end-point not reached; no improvements to clinical outcomes |
| Mina *et al.* [218] | fILD-PH | Epoprostenol or bosentan (prostacyclin analogue or ERA) | Baseline | Retrospective | NA | Single centre (19) | Improvement in 6MWD >50 m at 3- or 6-month follow-ups and WHO FC | Primary end-point partially reached; short-term functional improvements (6MWD and WHO FC) |
| Mittoo *et al.* [219] | CTD-ILD-PH | Bosentan, sildenafil or bosentan plus sildenafil (ERA and/or PDE5i) | Baseline | Retrospective | NA | Single centre (13) | Death or lung transplantation | Primary end-point reached; treatments were well tolerated; efficacy not measured |
| Selvan *et al.* [220] | ILD-PH | Vasodilators (various) | Baseline | Abstract | NA | Single centre (42) | Change in NT-proBNP, pulmonary haemodynamics, 6MWD and WHO FC from [illegible] | Primary end-point reached; improvements in pulmonary haemodynamics and NT-proBNP [illegible] |
| [illegible]hara *et al.* [221] | IPF-PH | Nintedanib (receptor TKI) | Historical control | Retrospective-prospective | NA | Single centre (16 in prospective study; 15 in historical control study) | Change in PASP | Primary end-point reached; increased PASP |
| Tanabe *et al.* [222] | PH associated with respiratory disease | Various, primarily PDE5i | Treatment-naïve patients | Prospective | NA | Multicentre (281) | Survival (time from baseline to death or lung transplantation) | Patients had better outcomes when treated with PAH-targeted therapies compared with no treatment |

# Treatment: Key negative or harmful evidence

THE LANCET
Respiratory Medicine



ARTICLES · Volume 7, Issue 9, P780-790, September 2019 Download Full Issue

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

Prof. Steven [a] · Prof. Jürgen Behr, MD [b,c] · Prof. Harold R. Collard, MD [d] · Prof. Vincent Cottin, MD [e] · Prof. Marius M. Hoeper, MD [f] · Prof. Fernando J. Martinez, MD [g] · et al. Show more

Affiliations & Notes · Article Info · İlgili Makaleler (2)

Trial stopped early: higher serious adverse events and mortality with no 6MWD efficacy.

Avoid riociguat in PH associated with idiopathic interstitial pneumonia.

### Findings

Between Ju
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6–203]) at t
participant
absence of
placebo group), and nine died in the extension phase (one in the riociguat group, eight in the former placebo group; all received riociguat). In the main study, the most common adverse events were peripheral oedema (16 [22%] of 73 in the riociguat group *vs* seven [9%] of 74 in the placebo group) and diarrhoea (11 [15%] *vs* seven [9%]). The most common serious adverse events were worsening of interstitial lung disease (main study: six [8%] of 73 in the riociguat group *vs* five [7%] of 74 in the placebo group) and pneumonia (four [5%] *vs* one [1%]). Riociguat did not improve 6MWD versus placebo at 26 weeks (least-squares mean difference 21 m; 95% CI −9 to 52).

### Interpretation

In patients with PH-IIP, riociguat was associated with increased serious adverse events and mortality, and an unfavourable risk–benefit profile. Riociguat should not be used in patients with PH-IIP.

**Negative trials are an argument for phenotype-specific, not class-wide therapy.**

Annals of Internal Medicine®



Original Research | 7 May 2013

## Treatment of Idiopathic Pulmonary Fibrosis With Ambrisentan: A Parallel, Randomized Trial

**Authors**: Ganesh Raghu, MD, Juergen Behr, MD, Kevin K. Brown, MD, Jim J. Egan, MD, Steven M. Kawut, MD, Kevin R. Flaherty, MD, Fernando J. Martinez, MD, ... SHOW ALL ... the ARTEMIS-IPF Investigators AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

**ARTEMIS-IPF • ambrisentan**

IPF trial showed increased risk of disease progression / respiratory hospitalization.

### Results:

The study wa
mean duration of exposure to study medication, 34.7 weeks) because an interim analysis indicated a low likelihood of showing efficacy for the end point by the scheduled end of the study. Ambrisentan-treated patients were more likely to meet the prespecified criteria for disease progression (90 [27.4%] vs. 28 [17.2%] patients; $P = 0.010$; hazard ratio, 1.74 [95% CI, 1.14 to 2.66]). Lung function decline was seen in 55 (16.7%) ambrisentan-treated patients and 19 (11.7%) placebo-treated patients ($P = 0.109$). Respiratory hospitalizations were seen in 44 (13.4%) and 9 (5.5%) patients in the ambrisentan and placebo groups, respectively ($P = 0.007$). Twenty-six (7.9%) patients who received ambrisentan and 6 (3.7%) who received placebo died ($P = 0.100$). Thirty-two (10%) ambrisentan-treated patients and 16 (10%) placebo-treated patients had pulmonary hypertension at baseline, and analysis stratified by the presen
primary end point.

ERA did not demonstrate significant clinical improvements in IPF or in ILD-PH and may even be harmful, and as such ambrisentan is contraindicated in patients with IPF

### Conclusion:

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

# INCREASE: a landmark in haemodynamically confirmed PH-ILD

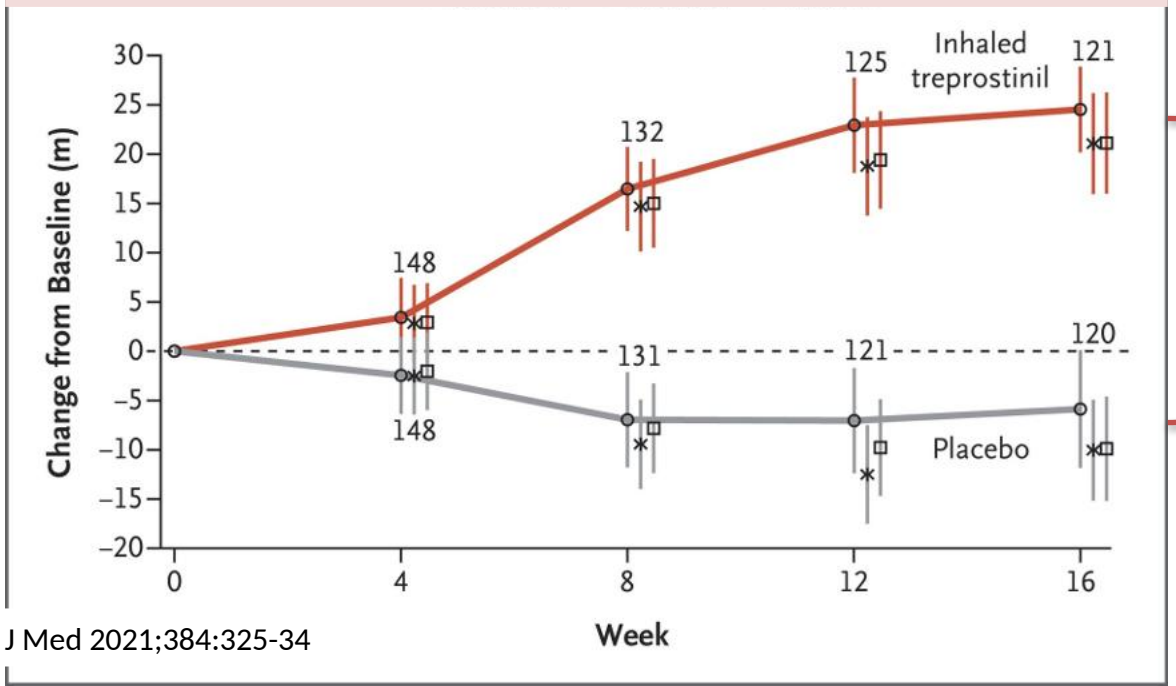
The NEW ENGLAND JOURNAL of MEDICINE

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.

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




31.12 m

ABSTRACT

**BACKGROUND**

No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. The safety and efficacy of inhaled treprostinil for patients with this condition are unclear.

**METHODS**

We enrolled patients with interstitial lung disease and pulmonary hypertension (documented by right heart catheterization) in a multicenter, randomized, double-blind, placebo-controlled, 16-week trial. Patients were assigned in a 1:1 ratio to receive inhaled treprostinil, administered by means of an ultrasonic, pulsed-delivery nebulizer in up to 12 breaths (total, 72 μg) four times daily, or placebo. The primary efficacy end point was the difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary end points included the change in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level at week 16 and the time to clinical worsening.

**RESULTS**

A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

**CONCLUSIONS**

In patients with pulmonary hypertension due to interstitial lung disease, inhaled treprostinil improved exercise capacity from baseline, assessed with the use of a 6-minute walk test, as compared with placebo. (Funded by United Therapeutics; INCREASE ClinicalTrials.gov number, NCT02630316.)

N Engl J Med 2021;384:325-34

# INCREASE: boundary conditions and generalizability

**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 | −11,423.0 to 5272.1 | −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†† |

**Table 3. Summary of Adverse Events.**

| Variable | Inhaled Treprostinil (N=163) | Placebo (N=163) | P Value* |
|---|---|---|---|
| Total no. of adverse events | 890 | 793 | |
| Patients with ≥1 adverse event — no. (%) | 152 (93.3) | 149 (91.4) | 0.68 |
| Total no. of serious adverse events† | 53 | 89 | |
| Patients with ≥1 serious adverse event — no. (%) | 38 (23.3) | 42 (25.8) | 0.70 |
| Total no. of adverse events leading to withdrawal of treprostinil or placebo | 47 | 38 | |
| Most frequently occurring adverse events — no. of patients (%)† | | | |
| Cough | 71 (43.6) | 54 (33.1) | 0.07 |
| Headache | 45 (27.6) | 32 (19.6) | 0.12 |
| Dyspnea | 41 (25.2) | 51 (31.3) | 0.27 |
| Dizziness | 30 (18.4) | 23 (14.1) | 0.37 |
| Nausea | 25 (15.3) | 26 (16.0) | >0.99 |
| Fatigue | 23 (14.1) | 23 (14.1) | >0.99 |
| Diarrhea | 22 (13.5) | 19 (11.7) | 0.74 |
| Throat irritation | 20 (12.3) | 6 (3.7) | 0.007 |
| Oropharyngeal pain | 18 (11.0) | 4 (2.5) | 0.003 |
| NT-proBNP increased | 9 (5.5) | 25 (15.3) | 0.006 |

| Strengths | What remains uncertain |
|---|---|
| Randomization with objective RHC inclusion | Variable treatment effect by ILD subtype / CPFE |
| Clinically relevant functional endpoint | Long-term survival or RV remodeling effect |
| Biomarker and clinical-worsening support | Generalisation to patients without documented PH |
| Inhaled route plausibly limits systemic vasodilation | Optimal position with antifibrotic and newer agents |

# INCREASE → TETON: a hypothesis became an IPF trial

**Crucial distinction: the same drug does not imply the same indication, phenotype or endpoint.**

Review | State Of The Art  Open access

**Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review**

Ganesh Raghu | Sandeep Sahay | Laura C. Price  Show More

European Respiratory Journal 2026 68(1): 2502651; DOI: https://doi.org/10.1183/13993003.02651-2025

## TETON-2: direct antifibrotic effects in IPF

Prior to the 2021 INCREASE trial discussed below, data for prostacyclin analogues in ILD-PH were mixed. In an early physiological study, inhaled iloprost at the time of RHC was shown to acutely reduce mPAP and PVR in a small cohort of patients with pulmonary fibrosis [132]. However, a subsequent randomised double-blind, placebo-controlled trial of inhaled iloprost in 51 patients with IPF and PH did not show benefit in 6-min walk distance (6MWD), New York Heart Association Functional Class, dyspnoea scores or exertional oxygenation when compared with placebo [133]. A small 2014 open-label study assessed the impact of parenteral treprostinil in pulmonary fibrosis patients with an advanced PH phenotype, and found improvements in right heart haemodynamics and echocardiographic function, although robust randomised trial data on parenteral prostacyclins in ILD-PH are lacking [134]. A randomised trial of inhaled treprostinil in ILD-PH (INCREASE) met its primary end-point, demonstrating a significant improvement in 6MWD, with findings published in 2021 [115]. Regarding secondary end-points for efficacy, a lower risk of clinical worsening, as well as NT-proBNP reduction, were seen with inhaled treprostinil during the 16-week randomised study period. Further, in a *post hoc* analysis of the INCREASE study, patients who received inhaled treprostinil had fewer ILD exacerbations and clinical worsening events and decreases in NT-proBNP levels [115, 135]. Along with continued safety, reduction in risk of underlying lung disease exacerbation was also found in the phase 3 open-label extension over 52 weeks [136]. A Japanese single-arm trial of inhaled treprostinil at the same dose and duration as that in the INCREASE trial demonstrated improvements in haemodynamics and a safety profile consistent with prior studies [137]. The INCREASE trial showed a placebo-corrected improvement in FVC, which suggested inhaled treprostinil has the potential of being an antifibrotic drug, a concept being pursued in the TETON studies in patients with IPF and progressive pulmonary fibrosis (PPF) [138, 139]. Positive results of the TETON-2 trial were recently reported, suggesting possible direct antifibrotic effects in IPF [140].

# Proposed approach to PH associated with ILD management.

Review | State Of The Art Open access

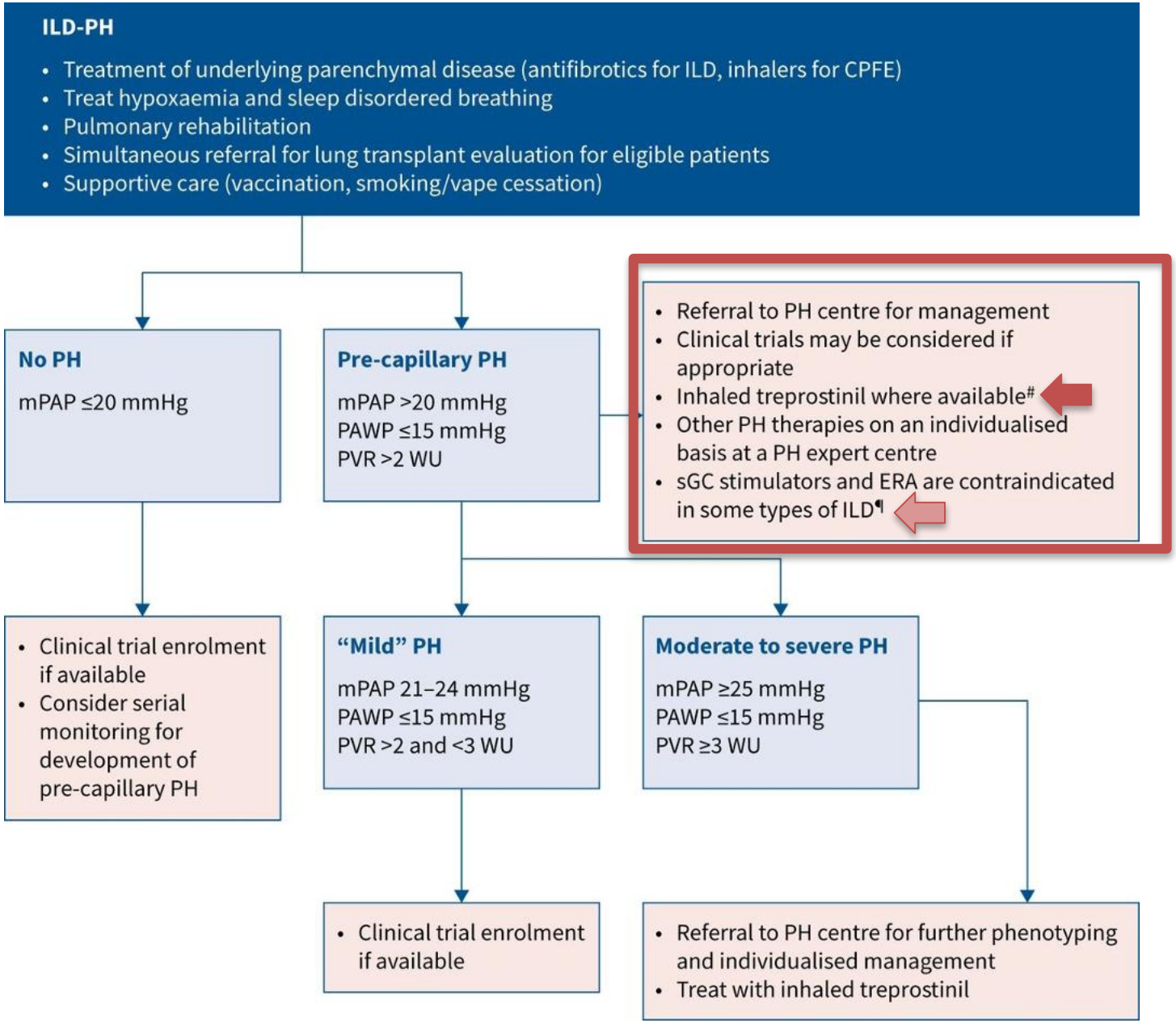
**Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review**

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#: caution in patients with PH associated with CPFE with predominant emphysema

¶: the ERA ambrisentan and the sGC stimulator riociguat were associated with negative outcomes in trials of PH associated with idiopathic pulmonary fibrosis and PH associated with idiopathic interstitial pneumonia, respectively.



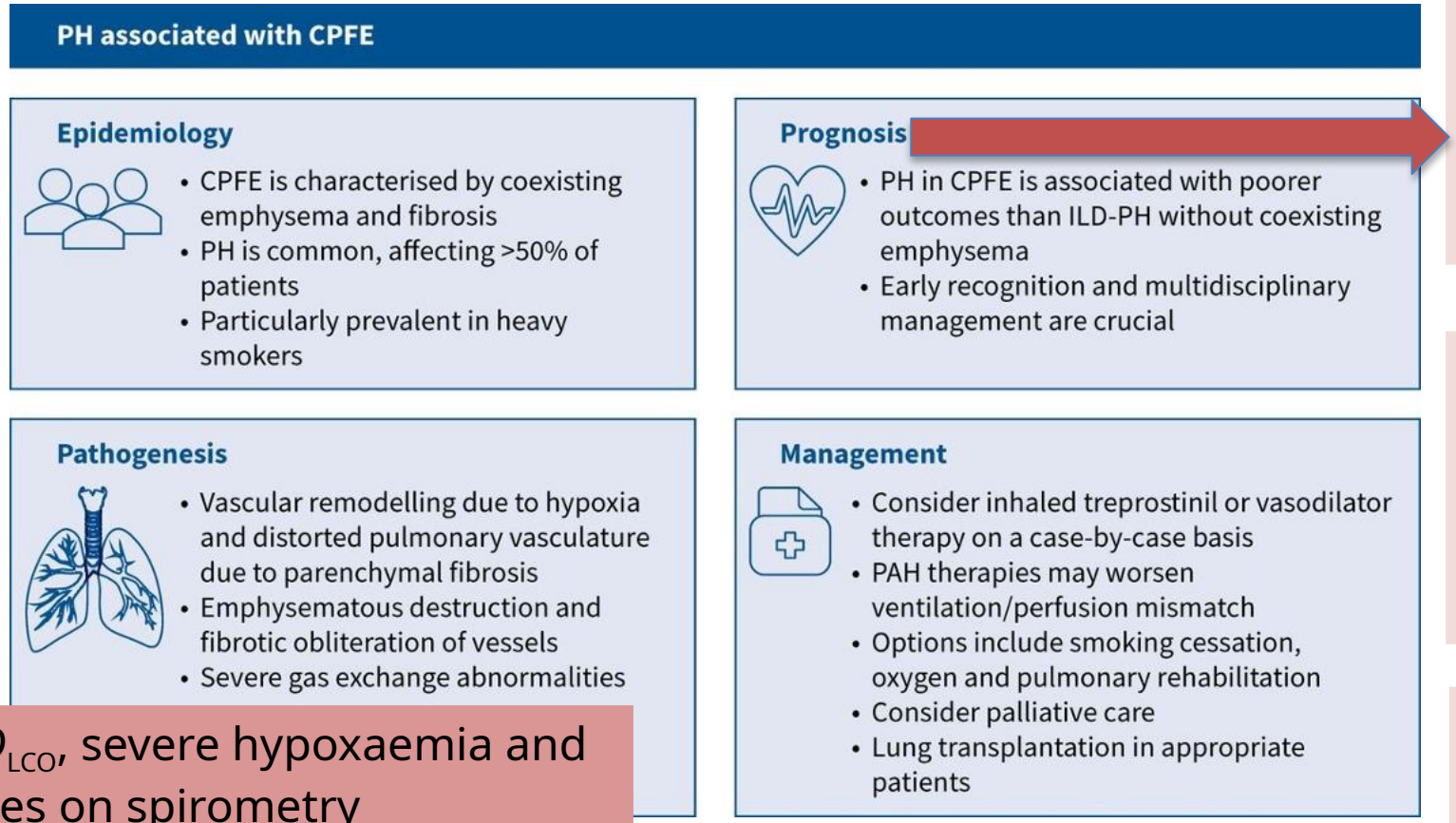
# Pulmonary hypertension (PH) associated with combined pulmonary fibrosis and emphysema (CPFE): overview and management.

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**Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review**

Ganesh Raghu | Sandeep Sahay | Laura C. Price Show More

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Marked reduction in $D_{LCO}$, severe hypoxaemia and preserved lung volumes on spirometry

A *post hoc* analysis of the RISE-IIP study suggested that patients whose HRCT of the chest had more emphysema than fibrosis may have contributed to the negative outcomes of the trial

This is consistent with the PERFECT study testing inhaled treprostinil in patients with PH, which was terminated early due to suggestive evidence of increased risk of serious adverse events and mortality in COPD-PH

In the INCREASE trial, there appeared to be attenuated efficacy of inhaled treprostinil in the subgroup with CPFE with respect to 6MWD and disease progression events, although such subgroup analyses are underpowered and must be interpreted with caution

Therefore, given the data from **RISE-IIP, INCREASE and PERFECT trials**, future studies on CPFE-PH should target patients with predominantly fibrotic and less emphysematous phenotypes. In addition, future registries should collect high-quality HRCT data to better understand whether there is a difference in response to treatment based on a particular CPFE phenotype. Lung transplantation remains a definitive option in eligible patients with progressive disease despite optimal therapy. Ongoing research is focused on better characterising the pulmonary vascular phenotype not only in CPFE but in smokers who present with PH for evaluation.

# Therapies under investigation for the treatment of pulmonary hypertension associated with interstitial lung disease (ILD-PH)

Review | State Of The Art Open access

**Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review**

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European Respiratory Journal 2026 68(1): 2502651; DOI: https://doi.org/10.1183/13993003.02651-2025

## Antifibrotic therapies

There is a lack of information about the potential effect of currently approved antifibrotic therapies on the development of PH.

Nintedanib, a tyrosine kinase inhibitor (TKI), is currently approved for the treatment of various forms of ILD. Limited data suggest that nintedanib does not have direct benefits on pulmonary vascular disease

Given the positive results of TETON-2, a novel question is whether prostacyclin therapies might reduce the risk of incident PH in patients with fibrotic ILDs such as IPF.

# Therapies under investigation for the treatment of pulmonary hypertension associated with interstitial lung disease (ILD-PH)

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**Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review**

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Since inhaled medications have fewer systemic side-effects and decreased probability of potential ventilation/perfusion mismatches, inhaled therapeutics are an attractive option for ILD-PH.
Inhaled treprostinil has demonstrated efficacy in ILD-PH.

## İnhaled therapeutics

Recently, positive results from the phase 1B ATMOS trial investigating the inhaled sGC activator mosliciguat in ILD-PH were announced, and the phase 2 PHocus trial (NCT06635850) has recently completed enrolment

Additionally, a new, inhaled liposomal formulation of treprostinil (L606) as well as treprostinil palmitil (a long-lasting formulation for once-daily inhalation) are being evaluated in phase 2B/3 trials (NCT04691154).

**TABLE 3** Therapies under investigation for the treatment of pulmonary hypertension associated with interstitial lung disease (ILD-PH)

| Study drug and identifier | Mechanism of action | Study population | Comparator | Study type | Study size (n) | Primary end-point |
|---|---|---|---|---|---|---|
| Inhaled treprostinil palmitil (DPI) NCT05176951 | PCA | ILD-PH | Placebo | Phase 2 extension | 39 | Proportion of participants with adverse events |
| Inhaled treprostinil (DPI) NCT06129240 | PCA | ILD-PH | NA | Phase 3 ASCENT extension | 80 | Proportion of participants with adverse events |
| Inhaled liposomal treprostinil NCT04691154 | PCA | ILD-PH and PAH | NA | Phase 3 OLE | 28 | Proportion of participants with adverse events |
| Inhaled mosliciguat (DPI) NCT06635850 | sGC activator | ILD-PH | Placebo | Phase 2 PHocus study | 135 | Changes in PVR over 16 weeks |
| Inhaled seralutinib (DPI) NCT07181382 | TKI | ILD-PH | Placebo | Phase 3 SERANATA | 480 | Change in 6MWD from baseline over 24 weeks |
| Oral pioglitazone NCT06336798 | PPAR-γ agonist | CLD-PH | Placebo | Phase 2 | 20 | Change in mitochondrial metabolism parameters over 70 days |
| Oral hymecromone NCT05128929 | Hyaluronan synthesis inhibitor | ILD-PH and PAH | Placebo | Phase 2 | 17 | Change in PVR measured by RHC |

DPI: dry powder inhaler; PCA: prostacyclin analogue; NA: not applicable; PAH: pulmonary arterial hypertension; OLE: open-label extension; sGC: soluble guanylate cyclase; PVR: pulmonary vascular resistance; TKI: tyrosine kinase inhibitor; 6MWD: 6-min walk distance; PPAR-γ: peroxisome proliferator-activated receptor-γ; CLD: chronic lung disease; RHC: right heart catheterisation.

# Mosliciguat: Promising Phase 2 PHocus Results

## Key Highlights: Mosliciguat PHocus Trial in PH-ILD

All results achieved with convenient, one breath-per-day dosing

| Key Clinical Endpoints | Week 24 Exploratory Analyses | Cardiac Measures | Safety & Tolerability |
|---|---|---|---|
| **Primary Endpoint**: **-56.3%** Placebo-adjusted PVR reduction at Week 16 (p<0.0001) | **-75.9%** Placebo-adjusted reduction in **NT-proBNP at Week 24** (p<0.0001) | **-22.8%** Reduction in **mean pulmonary arterial pressure** (p<0.0001) | **98%**[1] Of patients reached highest (4 mg) dose and remained on 4 mg through Week 24 |
| **Key Secondary Endpoint**: **+35.2m** Placebo-adjusted increase in **6MWD at Week 16** (p=0.0027) | **+52.7m** Placebo-adjusted increase in **6MWD at Week 24** (p<0.0001) | **+26.2%** Increase in **cardiac output** (p<0.0001) | Well-tolerated with **cough rates lower than placebo (12.1% mosliciguat vs. 18.2% placebo)** |

**Phase 3 PHrontier program in PH-ILD initiated**

roivant

Mosliciguat is an investigational drug and subject to regulatory approval

Note: P-values except primary and key secondary endpoints are nominal given they are exploratory endpoints.
1. Excludes patients who discontinued during treatment period; 87% with discontinuations not linked

PVR: Pulmonary Vascular Resistance; 6MWD: 6-minute walk distance; PH: Pulmonary Hypertension; ILD: Interstitial Lung Disease

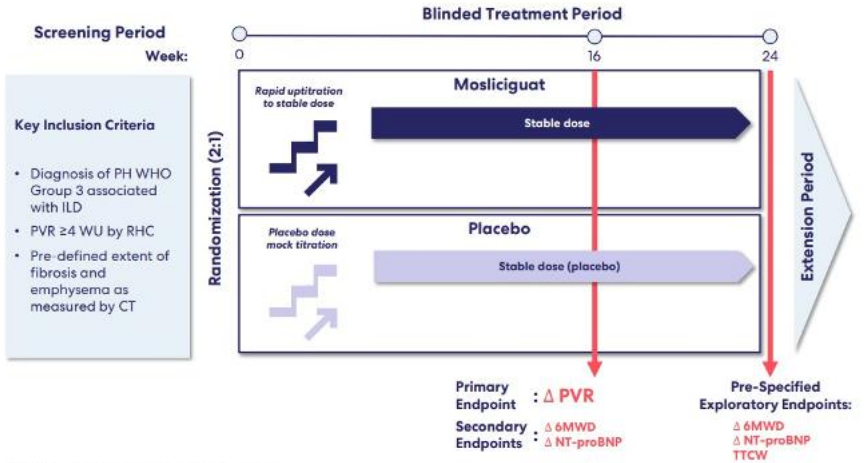


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## PHocus Study of Mosliciguat in Adult Patients With PH-ILD

phocus

Double-blinded, multi-center, global trial in N=135 PH-ILD patients across 87 sites in 20 countries




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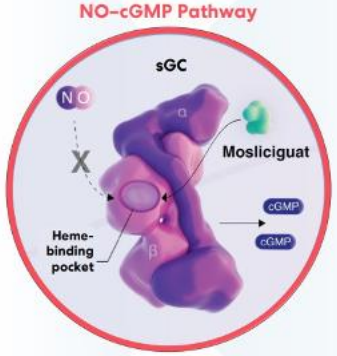
Mosliciguat is an investigational drug and subject to regulatory approval

Notes: Not all pre-specified endpoints listed. Abbreviations: PH: pulmonary hypertension; ILD: interstitial lung disease; PVR: pulmonary vascular resistance; 6MWD: six-minute walk distance; NT-proBNP: N-terminal pro-B type natriuretic peptide; WHO: World Health Organization; RHC: Right Heart Catheterization; CT: computed tomography; TTCW: Time to clinical worsening



For investor audiences only

## Mosliciguat is Delivered Directly to the Lungs to Activate Impaired sGC – Potentially the First Non-Treprostinil Treatment Option




- **sGC is a key enzyme in the NO-cGMP pathway** and its activity is essential for vascular homeostasis[1]
- **Oxidative stress** in pulmonary disease reduces NO production and impairs the sGC binding site, **resulting in sGC dysfunction**[2]
- **Mosliciguat activates** impaired sGC, as well as native sGC, **restoring cGMP production,** resulting in vasodilation and potential reduction of fibrosis and inflammation[1,3]
- Optimized particle size ensures **distal lung deposition** for targeted delivery[4]

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Mosliciguat is an investigational drug and subject to regulatory approval

Abbreviations: sGC: soluble guanylate cyclase; cGMP: cyclic guanosine 3',5'-monophosphate; NO: nitric oxide

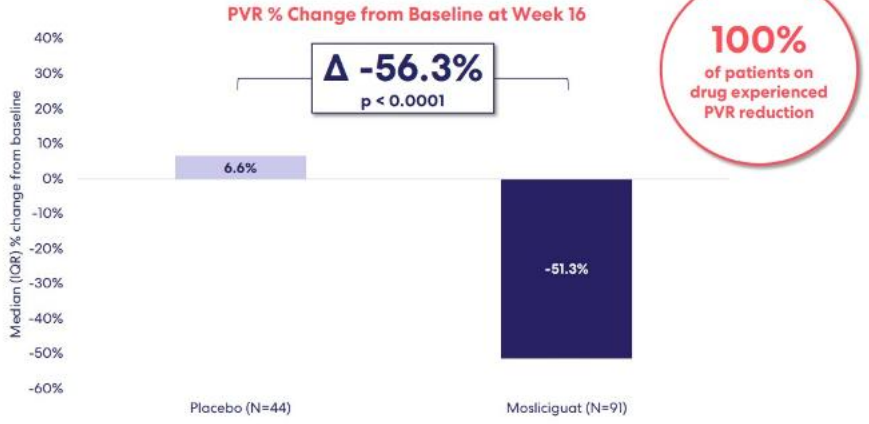
Sources: 1. Sandner et al., Respir Med (2017); 2. Thoonen et al., Nat Commun (2015); 3. Becker-Pelster et al., Respir Res (2022); 4. Saleh et al., Clin Pharmacokinet (2025)



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## Mosliciguat Met the Primary Endpoint Of Pulmonary Vascular Resistance % Change From Baseline at Week 16 With a 56.3% Placebo-Adjusted Reduction

Highest-ever reported PVR % reduction in any randomized, controlled trial in PH




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Mosliciguat is an investigational drug and subject to regulatory approval

PVR percent change from baseline at Week 16 was analyzed using a nonparametric ANCOVA model (stratified Wilcoxon test)

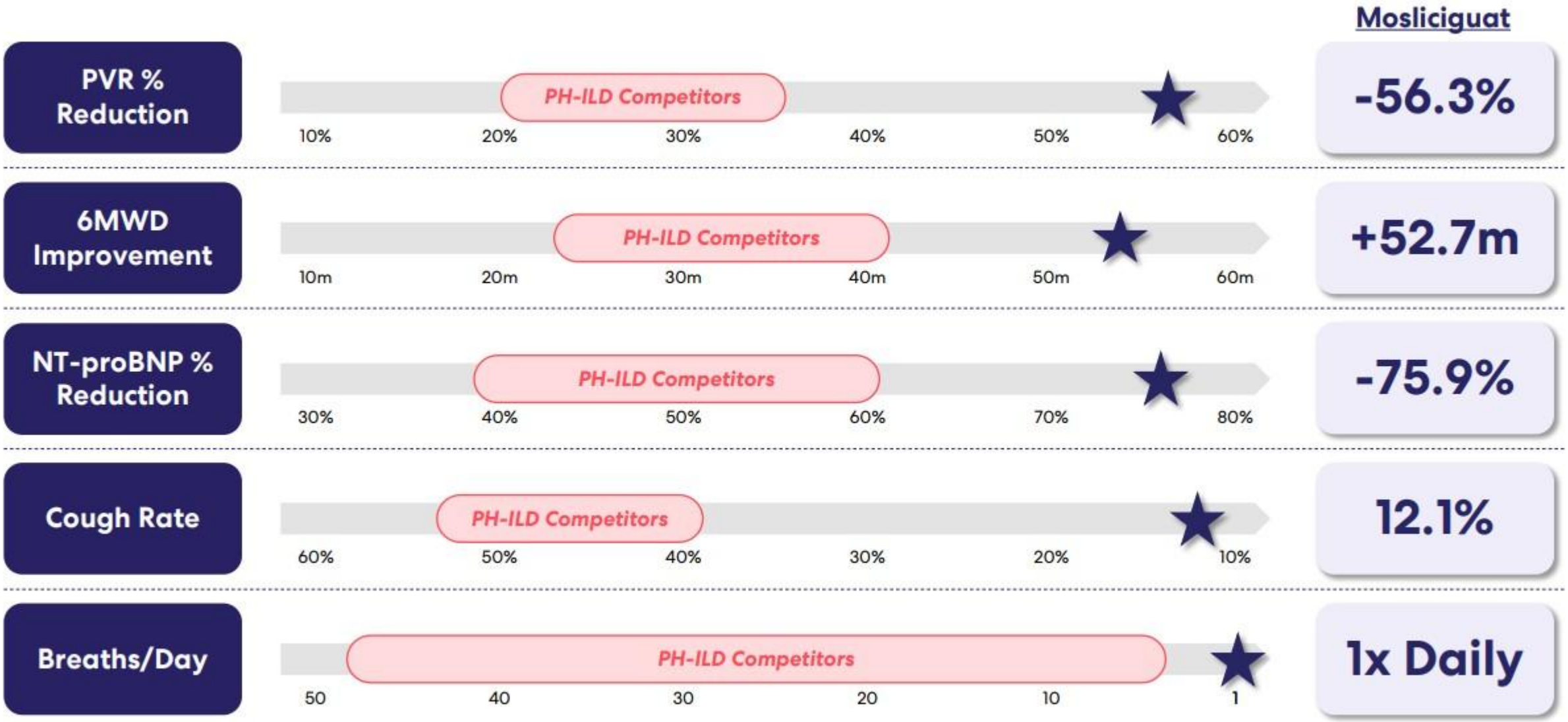
Abbreviations: IQR: interquartile range; PVR: pulmonary vascular resistance; Source data on file.



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# Mosliciguat: In A League Of Its Own

★ Mosliciguat




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Mosliciguat is an investigational drug and subject to regulatory approval; PVR: Pulmonary Vascular Resistance; 6MWD: 6-minute walk distance; m = Meters; NT-proBNP: N-terminal pro b-type natriuretic peptide. Notes: Mosliciguat and competitor efficacy data represent placebo-adjusted improvements on efficacy measures at Week 16 for PVR and at Week 24 for 6MWD and NT-proBNP. Competitor data is approximate – ranges represented by data from Tyvaso, Yutrepia, TPIP, L606.



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Figure represents a cross-study comparison and not a head-to-head study. Differences exist between study designs and subject characteristics, and caution should be exercised when comparing data across studies.

# Mosliciguat: a 2026 signal worth watching- PHOCUS PHASE 2

**−56.3%**

**Placebo-adjusted PVR**

**+35.2 m**

**Placebo-adjusted 6MWD**

**−53.2%**

**Placebo-adjusted NT-proBNP**

**Not yet equivalent to a peer-reviewed phase 3 clinical outcome trial.**
**Phase 3 PHrontier has started.**

With International Participation

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