Exeter
South West Peninsula
Interstitial Lung Disease Service

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Interstitial Lung Disease Interdisciplinary Network
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REFRAMING PULMONARY HYPERTENSION IN ILD: INNOVATIONS AND FUTURE DIRECTIONS

Dr Pilar Rivera Ortega

Respiratory Consultant with sub-specialty in ILD

ILD Research Lead of Academic Department of Respiratory Medicine

Senior Consultant – Joint Pulmonary Hypertension & ILD Clinic/MDT

Clinical and Research Lead of the Familial Interstitial Pneumonia (FIP) Service

Associate Director of Research and Development

p.riveraortega@nhs.net

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

Humbert M, et al. Eur Respir J 2023;61(1):2200879

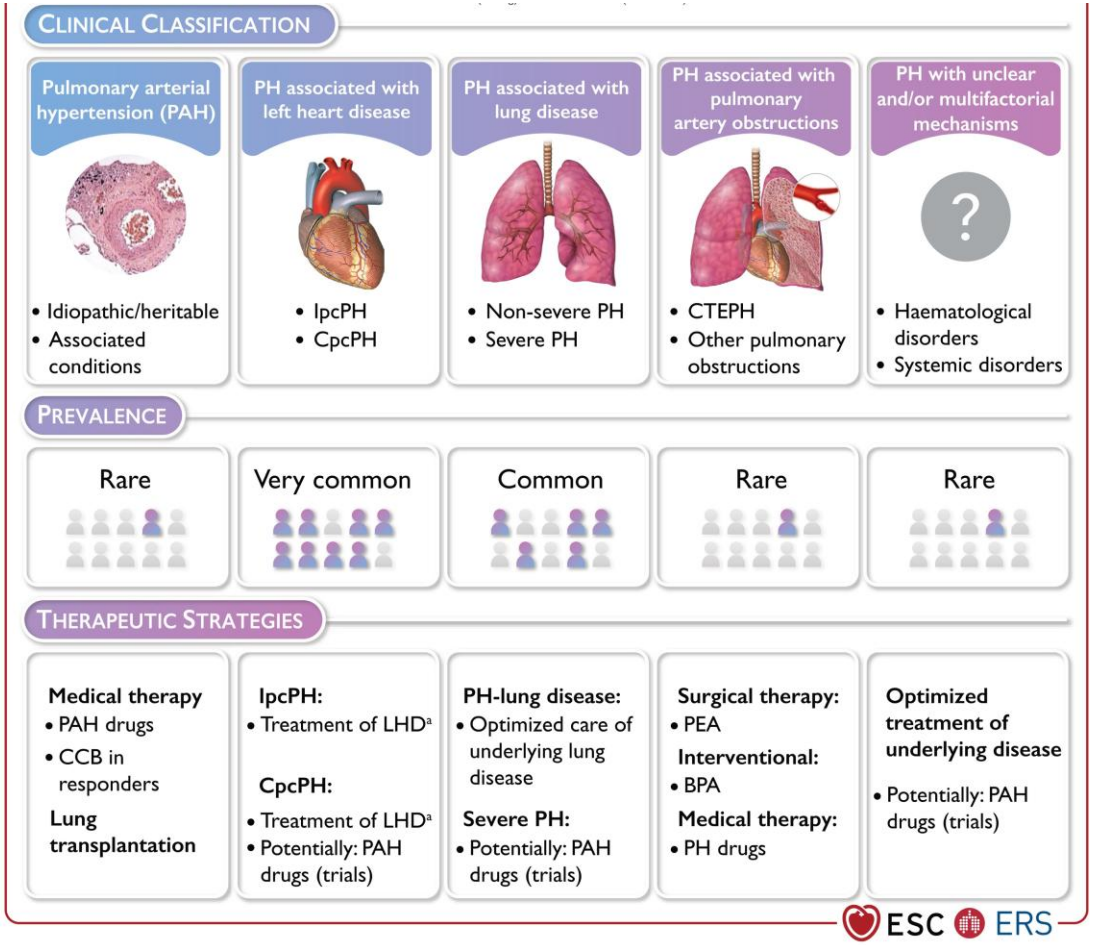


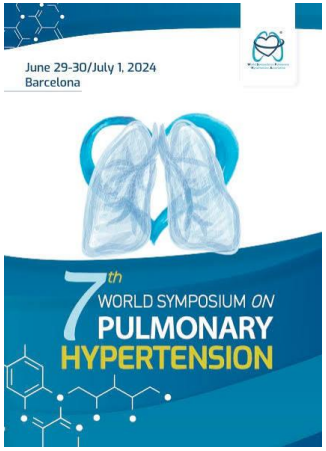
FIGURE 1 Central illustration. BPA, balloon pulmonary angioplasty; CCB, calcium channel blocker; CTEPH, chronic thrombo-embolic pulmonary hypertension; CpCPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; LHD, left heart disease; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension. [a]Treatment of heart failure according to the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [27]. Treatment of left-sided valvular heart disease according to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease [28].

Definition, classification and diagnosis of pulmonary hypertension

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

Group 1: PAH
1.1 Idiopathic
1.1.1 Long-term responders to calcium channel blockers
1.2 Heritable[#]
1.3 Associated with drugs and toxins[#]
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
2.1.3 cardiomyopathies with specific aetiologies[¶]
2.2 Valvular heart disease:
2.2.1 aortic valve disease
2.2.2 mitral valve disease
2.2.3 mixed valvular disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
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
Group 4: PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions[§]
Group 5: PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders[f]
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1
5.3 Metabolic disorders[##]
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis
5.7 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis. [#]: patients with heritable PAH or PAH associated with drugs and toxins might be long-term responders to calcium channel blockers; [¶]: hypertrophic, amyloid, Fabry disease and Chagas disease; [+]: parenchymal lung diseases not included in group 5; [§]: other causes of pulmonary artery obstructions include sarcomas (high- or intermediate-grade or angiosarcoma), other malignant tumours (*e.g.* renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), nonmalignant tumours (*e.g.* uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses and hydatidosis; [f]: including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders; [##]: including glycogen storage diseases and Gaucher disease.



Kovacs G, et al. Eur Respir J 2024; 64:2401324

Definition, classification and diagnosis of pulmonary hypertension

TABLE 1 Haemodynamic criteria of pulmonary hypertension (PH)

	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
Isolated post-capillary PH (ipcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
Combined post- and pre-capillary PH (cpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope >3 mmHg/L/min between rest and exercise

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units; CO: cardiac output.

Kovacs G, et al. Eur Respir J 2024; 64:2401324

Definition, classification and diagnosis of pulmonary hypertension

TABLE 3 Drugs and toxins associated with pulmonary arterial hypertension (PAH)

Definite association	Possible association
Aminorex	Alkylating agents
Benfluorex	Amphetamines
Carfilzomib	Bevacizumab
Dasatinib	Bortezomib
Dexfenfluramine	Bosutinib
Fenfluramine	Cocaine
Methamphetamines	Diazoxide
Mitomycin C[#]	Direct-acting antiviral agents against hepatitis C virus (sofosbuvir)
Toxic rapeseed oil	Indigo naturalis (Chinese herb Qing-Dai)
	Interferon-α and -β
	Leflunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Solvents (trichloroethylene)[#]
	St John's wort

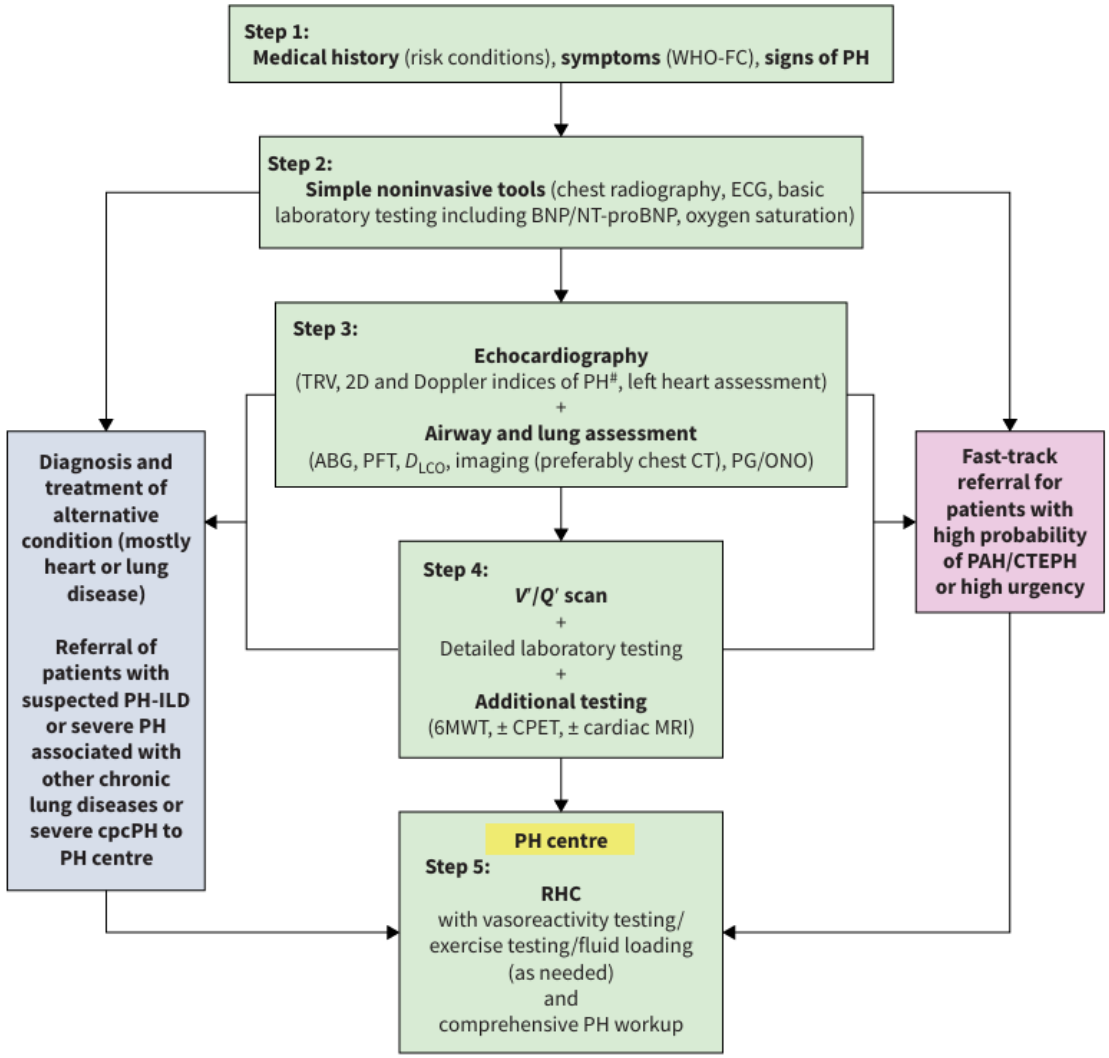
[#]: PAH with features of venous (pulmonary veno-occlusive disease)/capillary (pulmonary capillary haemangiomatosis) involvement.

Kovacs G, et al. Eur Respir J 2024; 64:2401324

Definition, classification and diagnosis of pulmonary hypertension

FIGURE 1 Suggested diagnostic approach to pulmonary hypertension (PH). Steps 1–5 represent the most important diagnostic steps of PH from the first presentation of the patient with symptoms or an existing risk condition towards final diagnosis with invasive assessment. WHO-FC: World Health Organization functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; TRV: tricuspid regurgitation velocity; 2D: two-dimensional; ABG: arterial blood gases; PFT: pulmonary function testing; D_{LCO}: diffusion capacity of the lung for carbon monoxide; CT: computed tomography; PG: polygraphy; ONO: overnight oximetry; V'/Q' scan: ventilation/perfusion scan of the lung; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; MRI: magnetic resonance imaging; RHC: right heart catheterisation; PH-ILD: pulmonary hypertension associated with interstitial lung disease; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; cpcPH: combined post- and pre-capillary PH. #: refer to figure 2.

Kovacs G, et al. Eur Respir J 2024; 64:2401324



Pulmonary hypertension associated with lung diseases

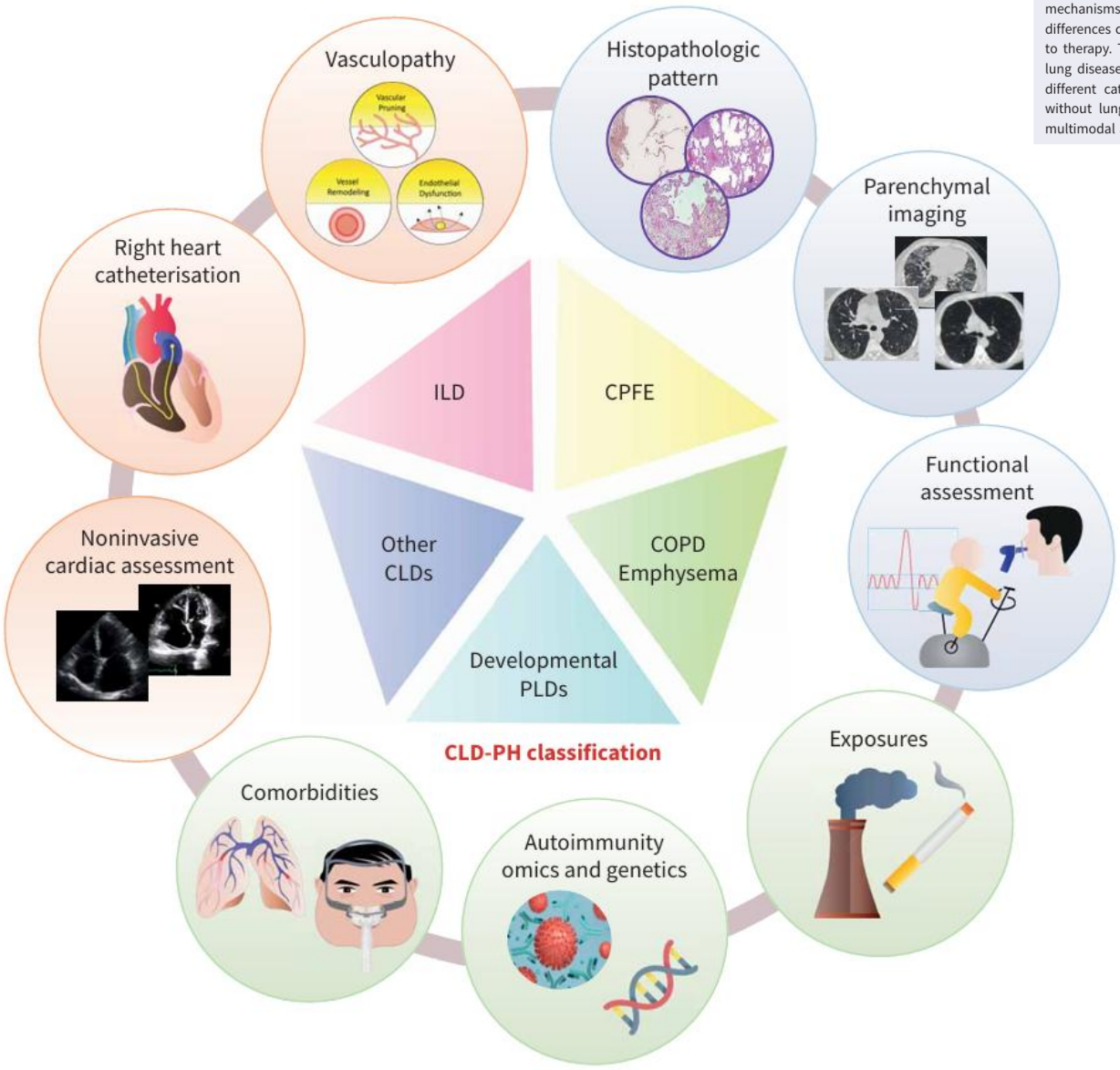


FIGURE 1 Major components of the updated classification of group 3 pulmonary hypertension (PH). Chronic lung diseases (CLDs) encompass a wide range of parenchymal processes which often have unique pathogenetic mechanisms and clinical presentations. Recent literature demonstrates that there are important pathogenic differences contributing to PH complicating different CLDs, which is likely to impact how these entities respond to therapy. These considerations led to a change in classification of group 3 PH that placed COPD, interstitial lung disease (ILD), combined pulmonary fibrosis emphysema (CPFE) and other parenchymal lung diseases in different categories, in addition to developmental lung diseases, nonparenchymal restriction and hypoxia without lung disease (which are not represented on the figure). Making a diagnosis of CLD-PH requires a multimodal approach, with particular emphasis on a high-quality radiographic assessment.

Shlobin OA, et al. Eur Respir J 2024; 64:2401200

Pulmonary hypertension associated with lung diseases

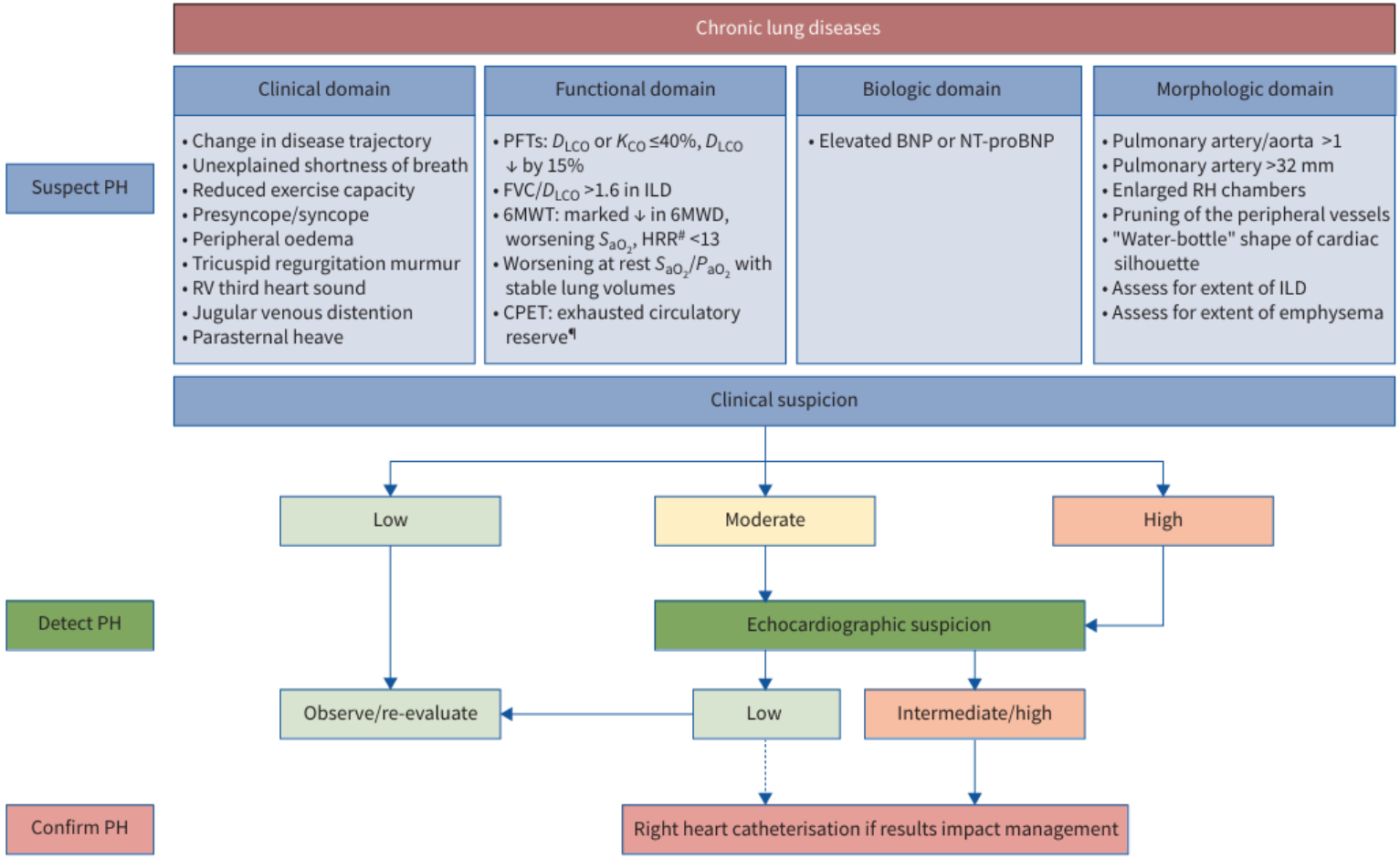


FIGURE 2 Diagnostic algorithm for pulmonary hypertension (PH) in the setting of COPD and interstitial lung disease (ILD). The decision to perform a right heart catheterisation should be predicated by a clinical or research need that would impact management and/or provide prognostic information, such as considerations of disease phenotyping and therapeutic interventions, clinical trial enrolment, pre-operative clearance/assistance with perioperative management, evaluation for lung transplantation and, in COPD, assessment for lung volume reduction therapy. A multimodal assessment, including lung function, functional, radiographic and echocardiographic data is recommended to determine when to proceed with haemodynamic assessment. 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). RV: right ventricular; PFTs: pulmonary function tests; D_{LCO}: diffusion capacity of the lung for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; FVC: forced vital capacity; 6MWT: 6-min walk test; 6MWD: 6-min walk distance; S_{aO_2}: arterial haemoglobin oxygen saturation; HRR: heart rate recovery; P_{aO_2}: arterial partial pressure of oxygen; CPET: cardiopulmonary exercise testing; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RH: right heart. #: in idiopathic pulmonary fibrosis; ¶: especially in severe PH.

Shlobin OA, et al. Eur Respir J 2024; 64:2401200

Pulmonary hypertension associated with lung diseases

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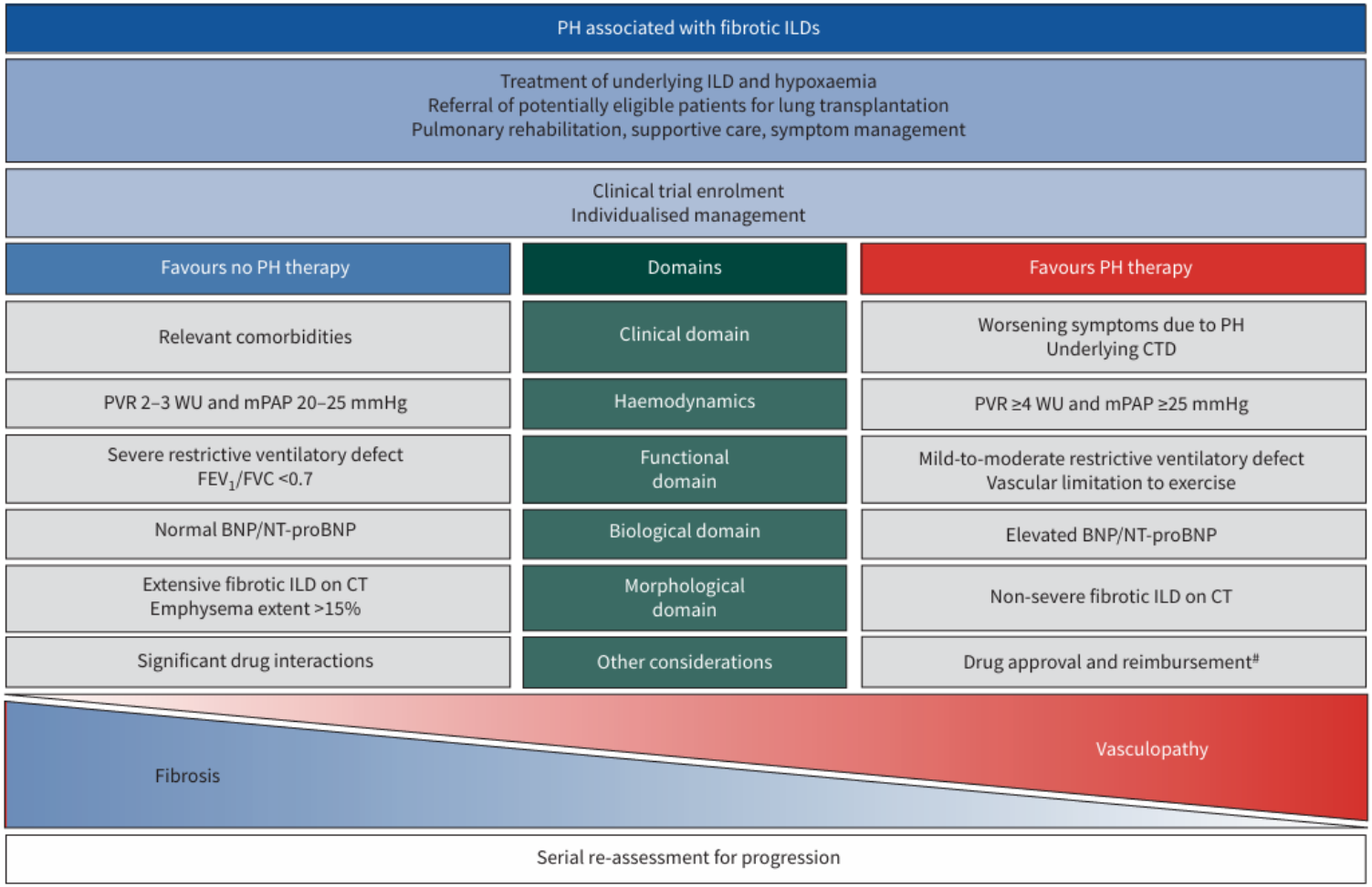
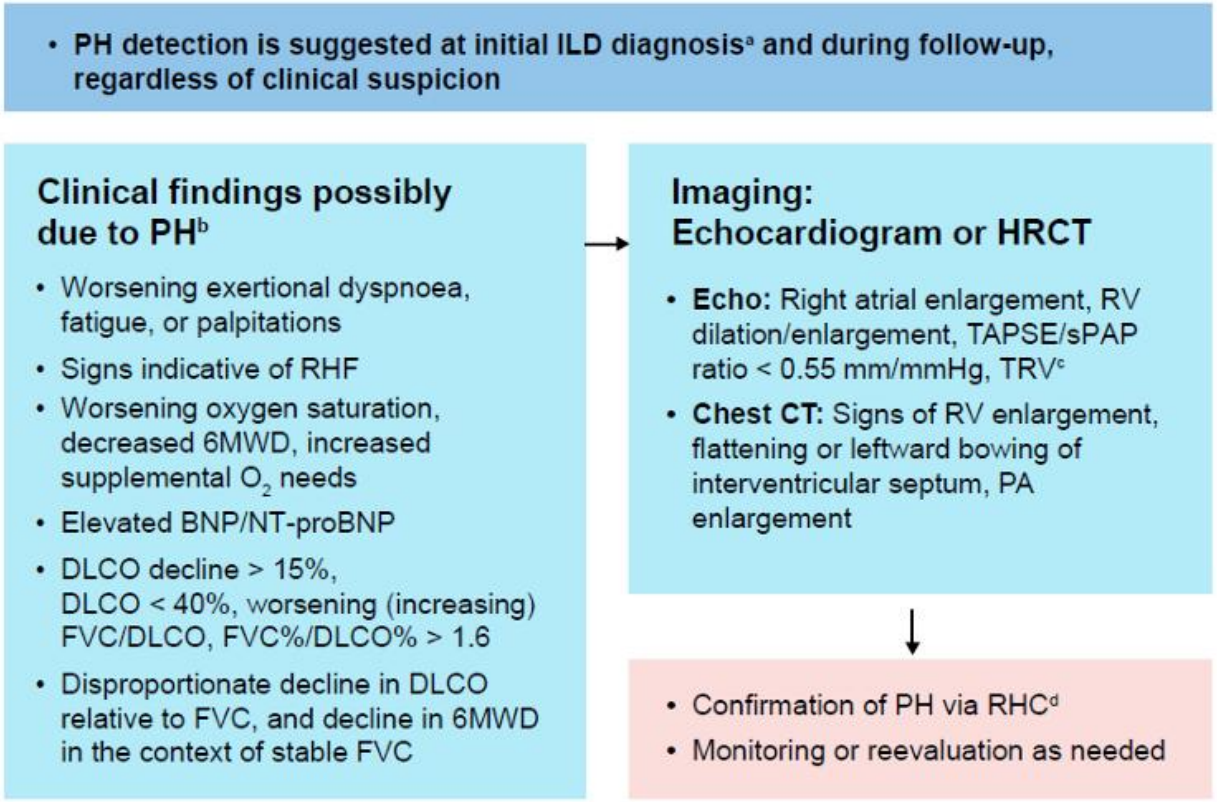


FIGURE 3 Framework for management of patients with interstitial lung disease (ILD)-associated pulmonary hypertension (PH). This figure represents a framework for management of PH in patients with ILD. The columns "Favours PH therapy" and "Does not favour PH therapy" are not prescriptive and are meant to guide providers in selecting appropriate patients for treatment. Each patient needs to be evaluated in the context of their disease and their treatment needs to be individualised. Please refer to the text for further details. PVR: pulmonary vascular resistance; WU: Wood units; mPAP: mean pulmonary arterial pressure; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; CT: computed tomography; CTD: connective tissue disease. #: inhaled treprostinil where approved; off-label use of other PH drugs such as phosphodiesterase-5 inhibitors in an individualised manner (ambrisentan is contraindicated in idiopathic pulmonary fibrosis and riociguat is contraindicated in idiopathic interstitial pneumonia-PH).

Pulmonary Hypertension Associated With Interstitial Lung Disease: State-of-the-Art Review

Figure 1. Early Detection of Pulmonary Hypertension in Patients with Underlying Interstitial Lung Disease



6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CT = computed tomography; DLCO = diffusion capacity for carbon monoxide; FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; ILD-PH = PH associated with ILD; JVD = jugular vein distention; mPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal prohormone of BNP; O_2 = oxygen; PA = pulmonary artery; PAWP = pulmonary arterial wedge pressure; PFT = pulmonary function testing; PH = pulmonary hypertension; PVR = pulmonary vascular pressure; RHC = right heart catheterisation. RHF = right heart failure; RV = right ventricle; RVSP = right ventricular systolic pressure; sPAP = Systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitant velocity; WU = Wood units.

[a]Initiation of discussions of lung transplant considerations at initial diagnosis of ILD-PH is suggested.

[b]In addition to clinical worsening, at least 1 objectively measurable finding may be necessary along with absence of alternative causes.

[c]TRV to evaluate the probability of PH was recommended by the 2022 European Society of Cardiology/European Respiratory Society guidelines and is recently endorsed by the 7th World Symposium on Pulmonary Hypertension, where TRV >3.4 m/s is considered as an independent high risk finding regardless of the additional signs on echocardiography. TRVs of 2.9-3.4 m/s and ≤2.8 m/s are considered intermediate and low risk, respectively, and may indicate PH in the presence of additional echocardiographic signs.

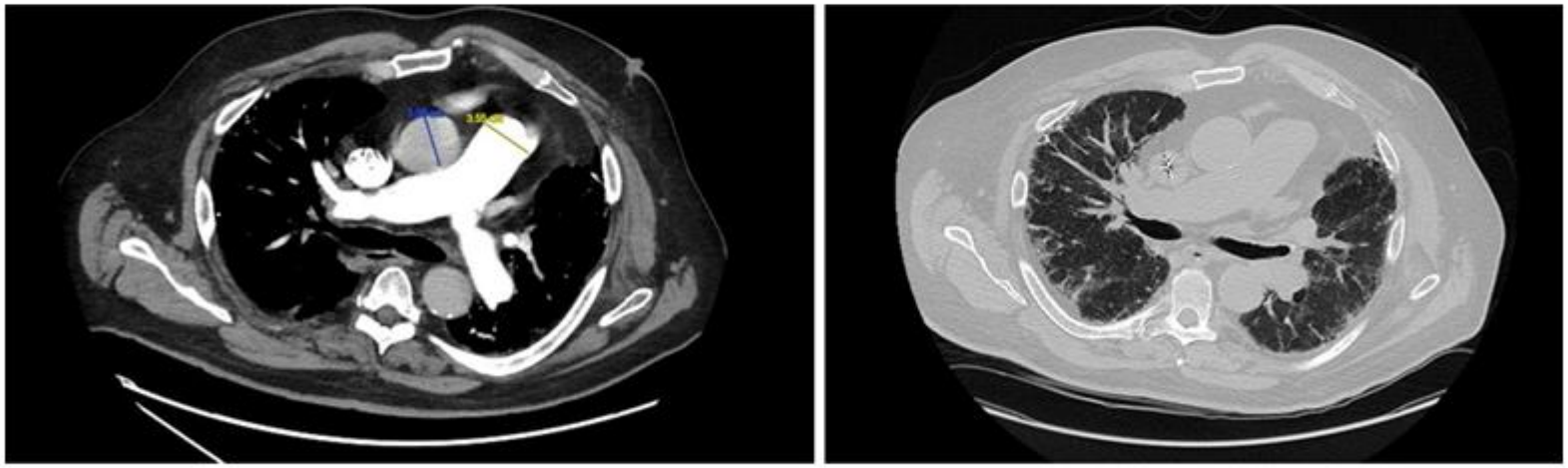
[d]The haemodynamic definition of PH is mPAP >20 mm Hg, and precapillary PH is further defined by elevation of PVR >2 WU and PAWP ≤15 mm Hg. Severe ILD-PH is defined as a PVR exceeding 5 WU; nonsevere ILD-PH is mPAP >20 mm Hg with PVR≤5 WU.

Raghu G, et al. Eur Respir J 2026; 68(1):2502651

Pulmonary Hypertension Associated With Interstitial Lung Disease: State-of-the-Art Review

Figure 2. Computed Tomographic Images From a Patient with Pulmonary Hypertension Associated With Interstitial Lung Disease

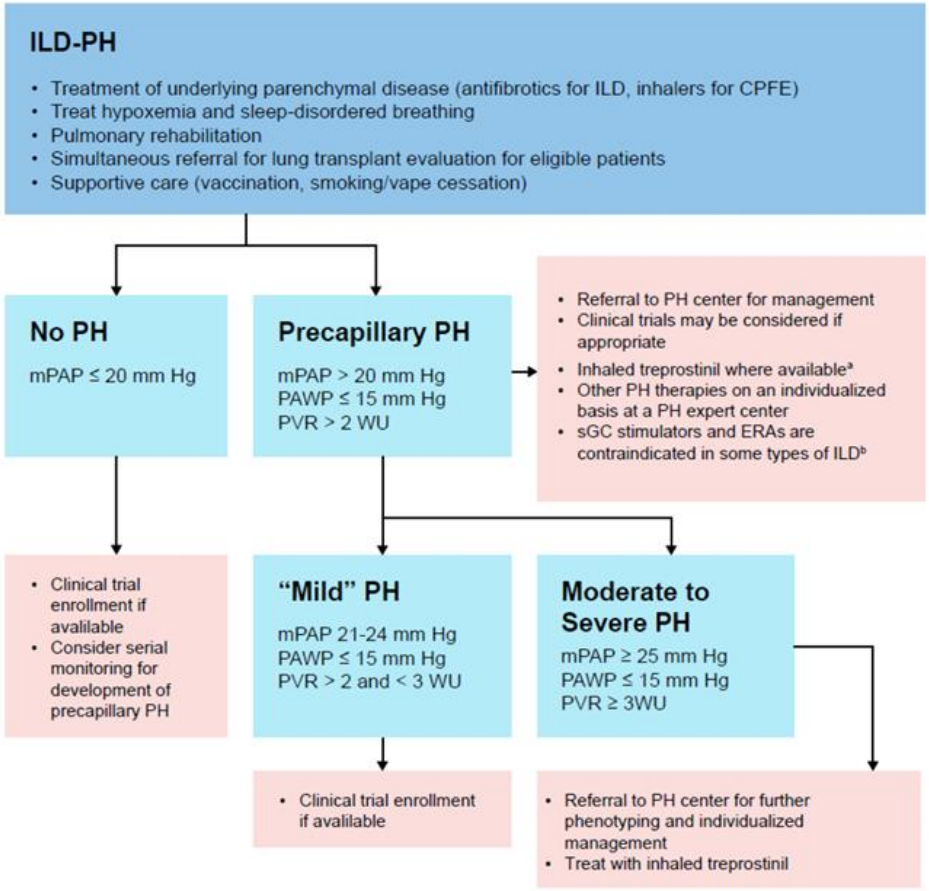
A) B)



Computed tomography from a patient with idiopathic pulmonary fibrosis and hemodynamically confirmed pulmonary hypertension showing: (A) a pulmonary artery–to–aorta (PA:A) ratio >1, and (B) fibrotic interstitial changes.

Pulmonary Hypertension Associated With Interstitial Lung Disease: State-of-the-Art Review

Figure 5. Proposed Approach to Pulmonary Hypertension Associated With Interstitial Lung Disease Management



CPFE = combined pulmonary fibrosis and emphysema; ERA = endothelin receptor antagonist; ILD = interstitial lung disease; ILD-PH = PH associated with ILD; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PDE5i = phosphodiesterase-5 inhibitors; PH = pulmonary hypertension; PH-CPFE = PH associated with CPFE; PVR = pulmonary vascular pressure; sGC = soluble guanylate cyclase; WU = Wood units. Note: The 2022 ESC/ERS guidelines use PVR >5 WU to define severe PH. More recently, based on the evolving evidence regarding predictive role of haemodynamics in ILD-PH, the 7th WSPH proposes that severity of PH is better assessed as a continuum.

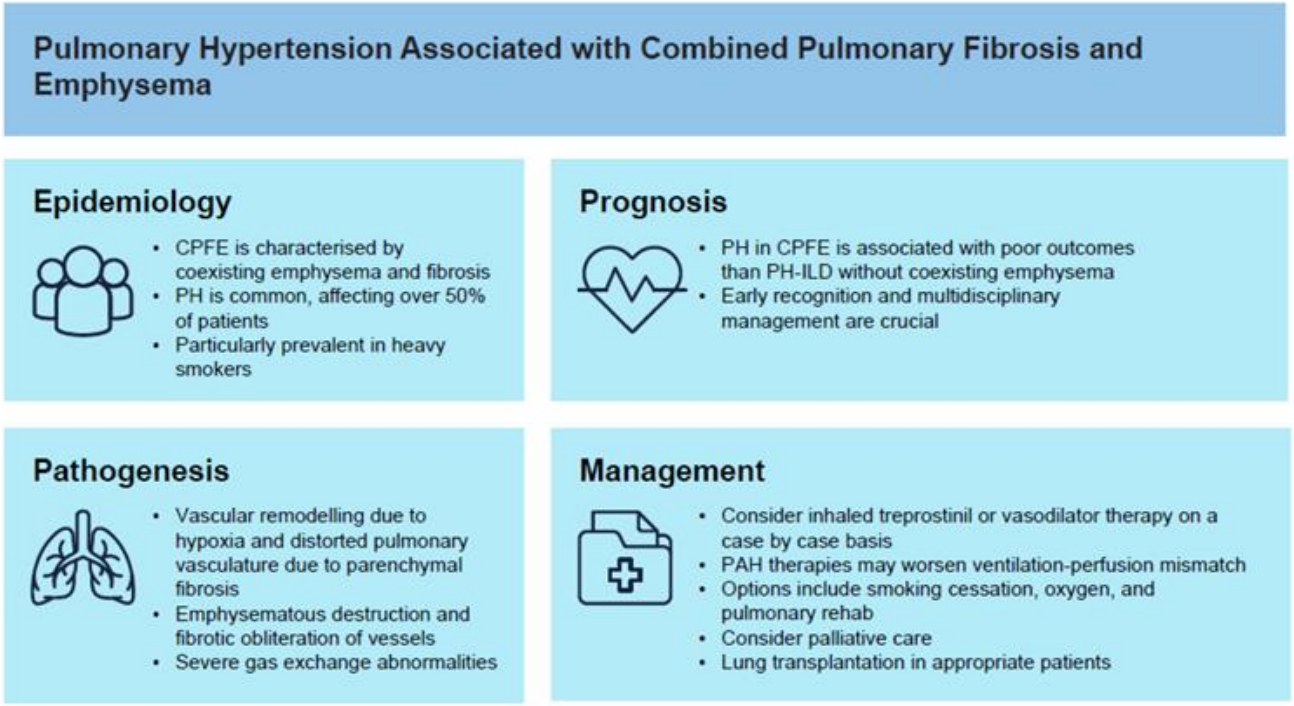
[a] Caution in patients with PH associated with CPFE with predominant emphysema.

[b] ERA ambrisentan and sGC riociguat were associated with negative outcomes in trials of PH associated with idiopathic pulmonary fibrosis and PH associated with idiopathic pulmonary fibrosis, respectively.

Raghu G, et al. Eur Respir J 2026; 68(1):2502651

Pulmonary Hypertension Associated With Interstitial Lung Disease: State-of-the-Art Review

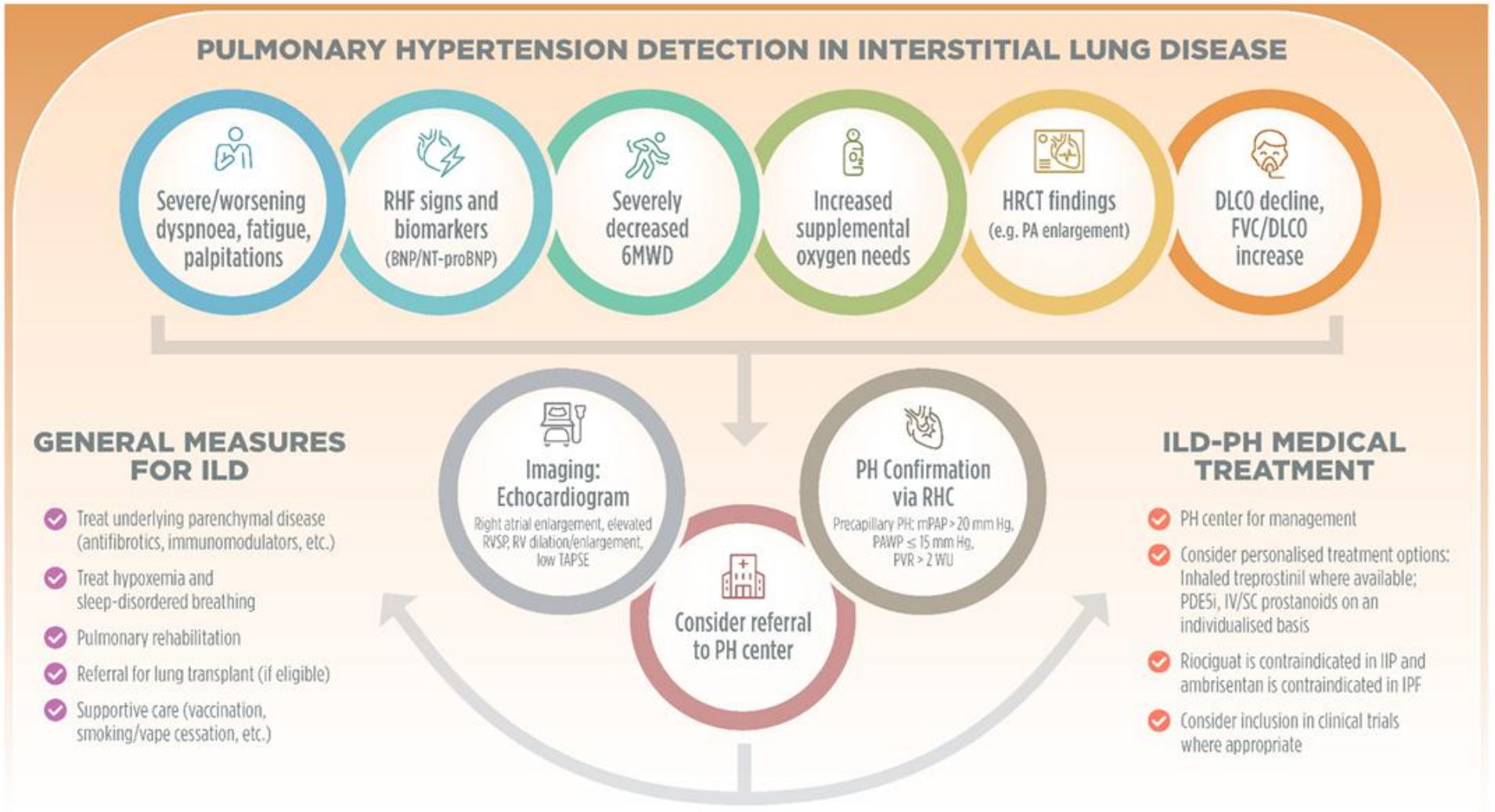
Figure 6. Pulmonary Hypertension Associated with Combined Pulmonary Fibrosis and Emphysema: Overview and Management



PAH = pulmonary arterial hypertension; PH-CPFE = pulmonary hypertension associated with combined pulmonary fibrosis and emphysema.

Raghu G, et al. Eur Respir J 2026; 68(1):2502651

Pulmonary Hypertension Associated With Interstitial Lung Disease: State-of-the-Art Review



Raghu G, et al. Eur Respir J 2026; 68(1):2502651

Clinical studies- INCREASE trial

INCREASE

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Interstitial Lung Disease

Waxman et al., N Engl J Med . 2021;384(4):325-334.

INCREASE I trial- Objectives & Design

Objective of the study

- Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension.
- The objective of the INCREASE trial **was to evaluate the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease**

Design of the study

- *A multicenter, randomized, double-blind, placebo-controlled trial*
- *Randomization stratified by 6MWD(≤350 m vs. >350 m)*
- *The primary efficacy end point change in 6MWD at week 16.*
- *Secondary end points included the change in NT-proBNP and the time to clinical worsening.*
- *Follow up 16 weeks*

Waxman et al., N Engl J Med . 2021;384(4):325-334.

PVR: Pulmonary vascular resistance. PCWP : Pulmonary capillary wedge pressure. mPAP: mean pulmonary arterial pressure. 6MWD: 6-minute walking distance

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INCREASE I trial- Patients & Treatment

Key inclusion Criteria

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

Key Exclusion Criteria

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

Waxman et al., N Engl J Med . 2021;384(4):325-334.

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INCREASE I trial- Study assessment

Primary Endpoint

- **Change in 6MWD measured at peak exposure from Baseline to Week 16**
  – 6-minute walk test (6MWT) performed at peak plasma treprostinil exposure
- Between 10 to 60 minutes after most recent dose of study drug

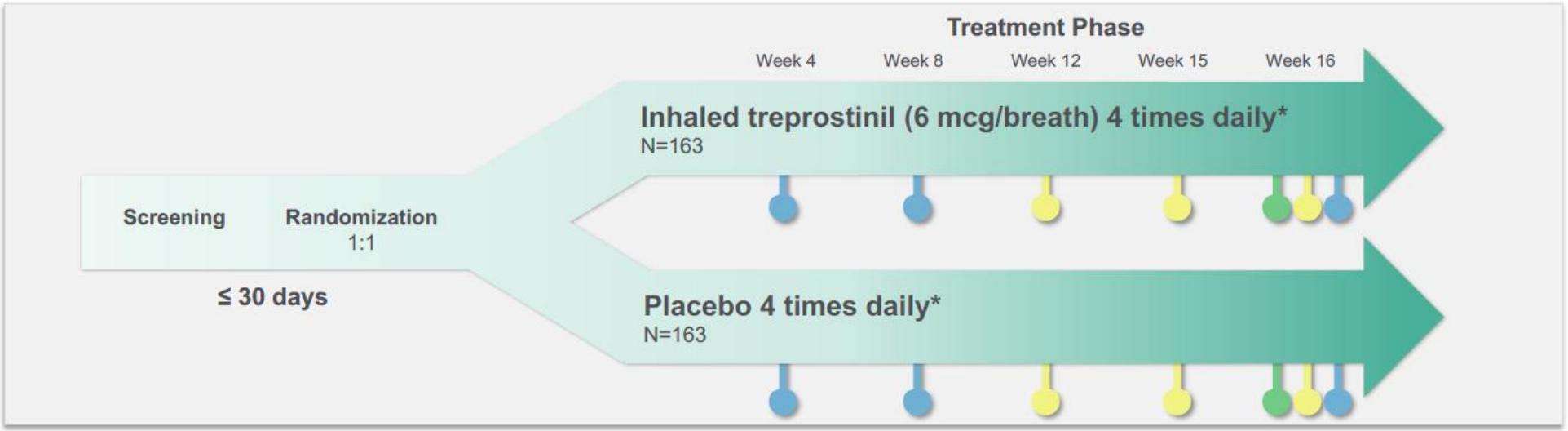
Secondary Endpoints

- Change in NT-proBNP from Baseline to Week 16
- Time to clinical worsening - time of randomization until study discontinuation
  – Hospitalization due to a cardiopulmonary indication,
  – Decrease in 6MWD >15% from Baseline directly related to disease under study at 2 consecutive visits and at least 24 hours apart
  – Death (all causes),
  – Or lung transplantation
- Change in Peak 6MWD at Week 12
- Change in Trough 6MWD at Week 15
  – ≥4 hours after the most recent study drug dose and 24h prior to Week 16 6MWT

Waxman et al., N Engl J Med . 2021;384(4):325-334.

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INCREASE I trial- Study procedure



* 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

Waxman et al., N Engl J Med . 2021;384(4):325-334.

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INCREASE I trial- Baseline characteristics

The majority of patients had **Idiophatic Interstitial Pneumonia** (39.9%), mainly **Idiophatic Pulmonary Fibrosis** (IPF, 22.7%)

	Inhaled Treprostinil N=163	Placebo N=163
Age		
Mean (SD)	65.6 (12.7)	67.4 (11.2)
Sex, n (%)		
Male	78 (47.9%)	95 (58.3%)
Female	85 (52.1%)	68 (41.7%)
Time since PH-ILD Diagnosis, years		
Mean (SD)	0.54 (1.16)	0.54 (1.31)
Etiology of PH-ILD, n (%)		
Idiopathic interstitial pneumonia (IIP)	65 (39.9%)	81 (49.7%)
Idiopathic pulmonary fibrosis subtype of IIP	*37 (22.7%)*	*55 (33.7%)*
Combined pulmonary fibrosis and emphysema	42 (25.8%)	40 (24.5%)
Connective tissue disease	40 (24.5%)	32 (19.6%)
Chronic hypersensitivity pneumonitis	10 (6.1%)	9 (5.5%)
Occupational lung disease	5 (3.1%)	1 (0.6%)
Other	1 (0.6%)	0
Use of Supplemental Oxygen, n (%)	119 (73.0%)	114 (69.9%)
Use of Background Therapy, n (%)		
None	133 (81.6%)	119 (73%)
Pirfenidone only	19 (11.7%)	25 (15.3%)
Nintedanib only	11 (6.7%)	19 (11.7%)

Waxman et al., N Engl J Med . 2021;384(4):325-334.

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INCREASE I trial- Baseline assessments

Pulmonary Function Tests	Inhaled Treprostinil N=163	Placebo N=163
FEV_1 % Predicted		
Mean (range)	63.9 (23, 120)	65 (22, 145)
Median	63	63
FVC % Predicted		
Mean (range)	62.5 (24, 130)	63.8 (20, 134)
Median	60	61
TLC % Predicted		
Mean (range)	62.9 (25, 126)	64.2 (30, 109)
Median	62	62.5
DLCO % Predicted		
Mean (range)	30 (5, 86)	28.1 (1, 86)
Median	29	26

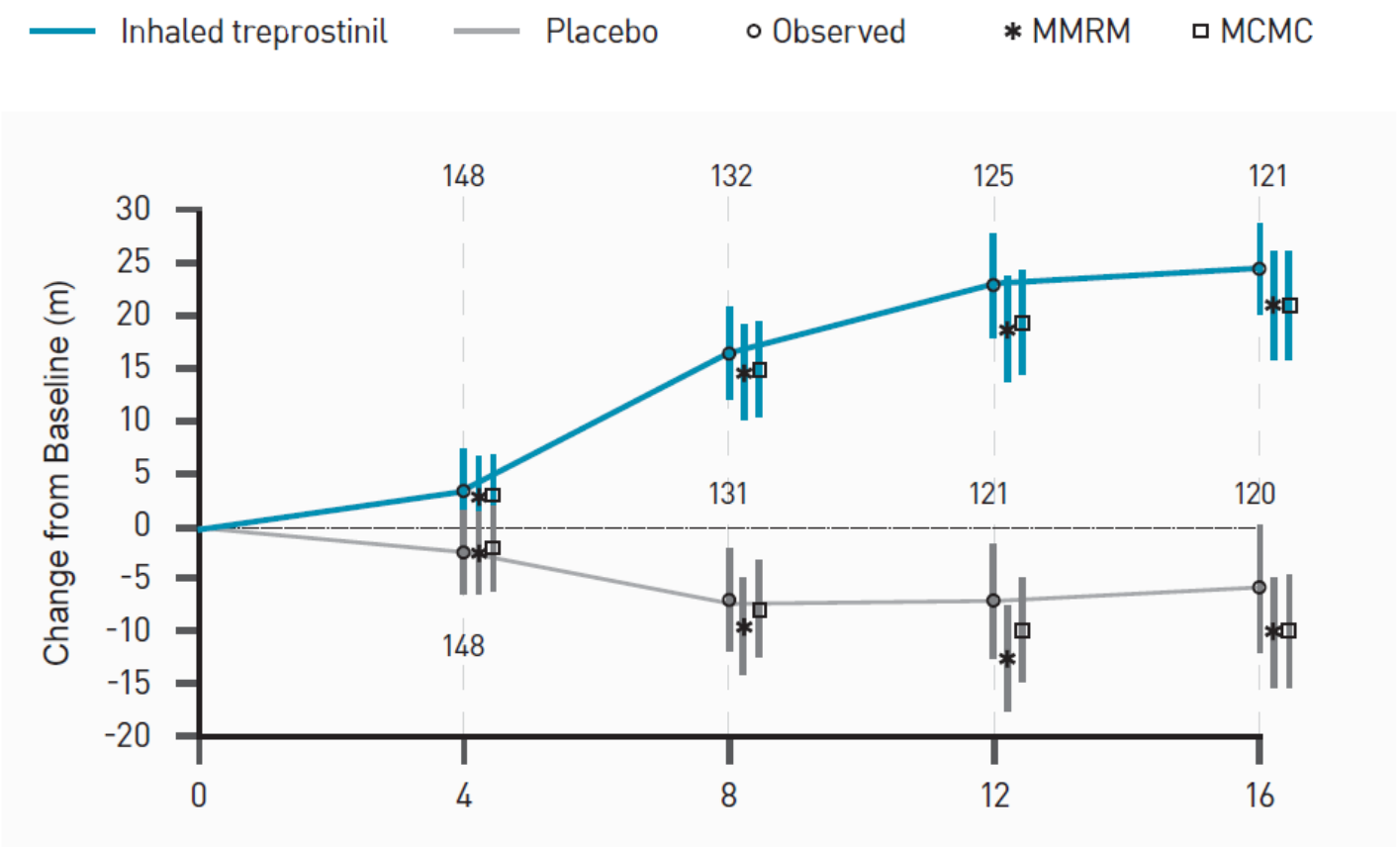
DLCO: lung diffusion capacity; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity

Waxman et al., N Engl J Med . 2021;384(4):325-334.

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INCREASE I trial- Primary endpoint

At Week 16, inhaled treprostinil patients had a placebo corrected difference from Baseline in peak 6MWD of **31.12 m** (95% CI: 16.85, 45.39; P<0.001).



Waxman et al., N Engl J Med . 2021;384(4):325-334.

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INCREASE I trial- Secondary and exploratory endpoints

Significant differences were observed with inhaled treprostinil, including:

– Improvements in NT-proBNP

– Reduction in time to clinical worsening

– Improvements in peak 6MWD at Week 12

– Improvements in trough 6MWD at Week 15

No significant differences in patient-reported SGRQ or DSP at Week 16).

6MWD: six-minute walk distance; DSP: distance saturation product; NT-proBNP: N-terminal pro-brain natriuretic peptide; SGRQ: The St. George's Respiratory Questionnaire

Waxman et al., N Engl J Med . 2021;384(4):325-334.

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INCREASE I trial- Safety analysis

- Treatment was well tolerated
- Safety profile was consistent with previous studies of inhaled treprostinil
- Most treatment-related AEs were mild to moderate in intensity

- 10% of oral treprostinil and 8% of placebo patients prematurely discontinued treatment due to an AE
- Serious AEs occurred in 23.3% of patients receiving inhaled treprostinil and 25.8% of placebo patients

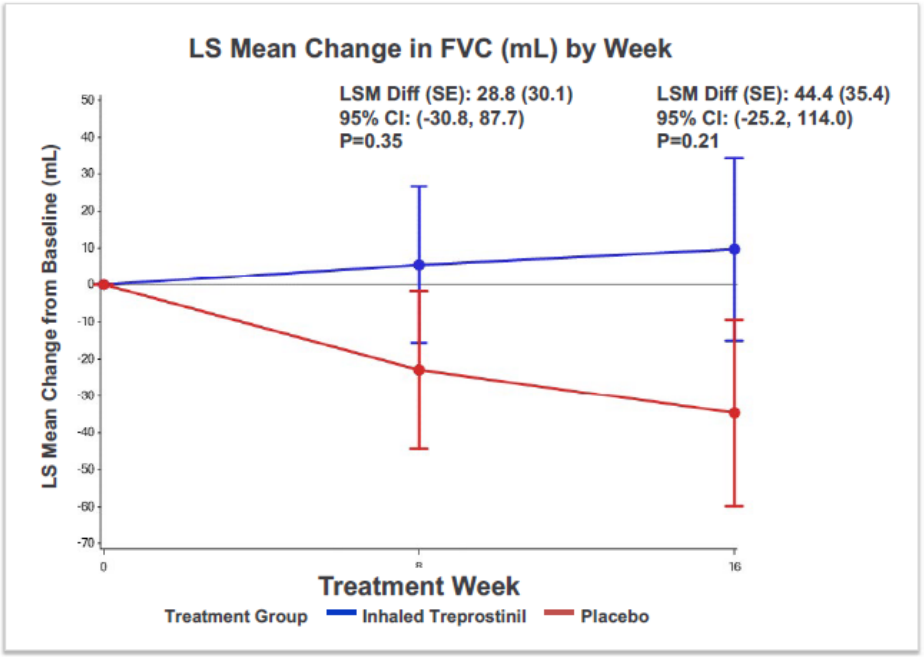
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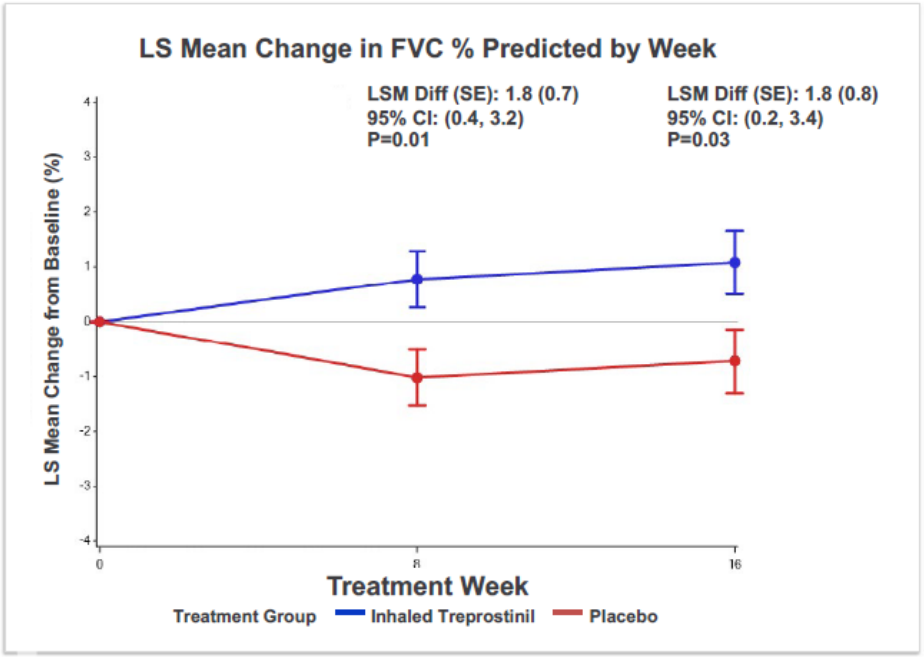
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INCREASE I trial- FVC Results by Study Visit

Inhaled treprostinil resulted in placebo-corrected improvements in FVC of 28.47 mL and 44.40 mL at Weeks 8 and 16, respectively.

Percent predicted FVC at Week 8 (1.79%; P=0.01) and Week 16 (1.80%; P=0.03).





FVC: forced vital capacity; LS Mean: least squares mean; SE: standard error. LS Mean (SE), P-values, estimated difference (SE), and associated 95% CIs are from the mixed model repeated measurement with the change from Baseline in FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; Baseline FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Waxman et al., N Engl J Med . 2021;384(4):325-334.

INCREASE

Clinical studies- INCREASE I trial- Secondary endpoint

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

NT-ProBNP

- Decrease 15% with Treprostinil
- Increase 46% with Placebo

Clinical worsening

- 22.7% Treprostinil
- 33.1% placebo
- HR: **0.61** (IC95% 0.4-0.92, P=0.04)

Waxman et al., N Engl J Med . 2021;384(4):325-334.

INCREASE

Clinical studies- INCREASE I trial- Safety

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

* P values were calculated with the use of Fisher's exact test.
† A list of serious adverse events is shown in Table S5.
‡ Shown are the most frequently occurring adverse events occurring in more than 10% of patients in either group in the safety population, which comprised all patients who underwent randomization and received at least one dose of treprostinil or placebo.

Waxman et al., N Engl J Med . 2021;384(4):325-334.

INCREASE

UK PH Specialist Centres



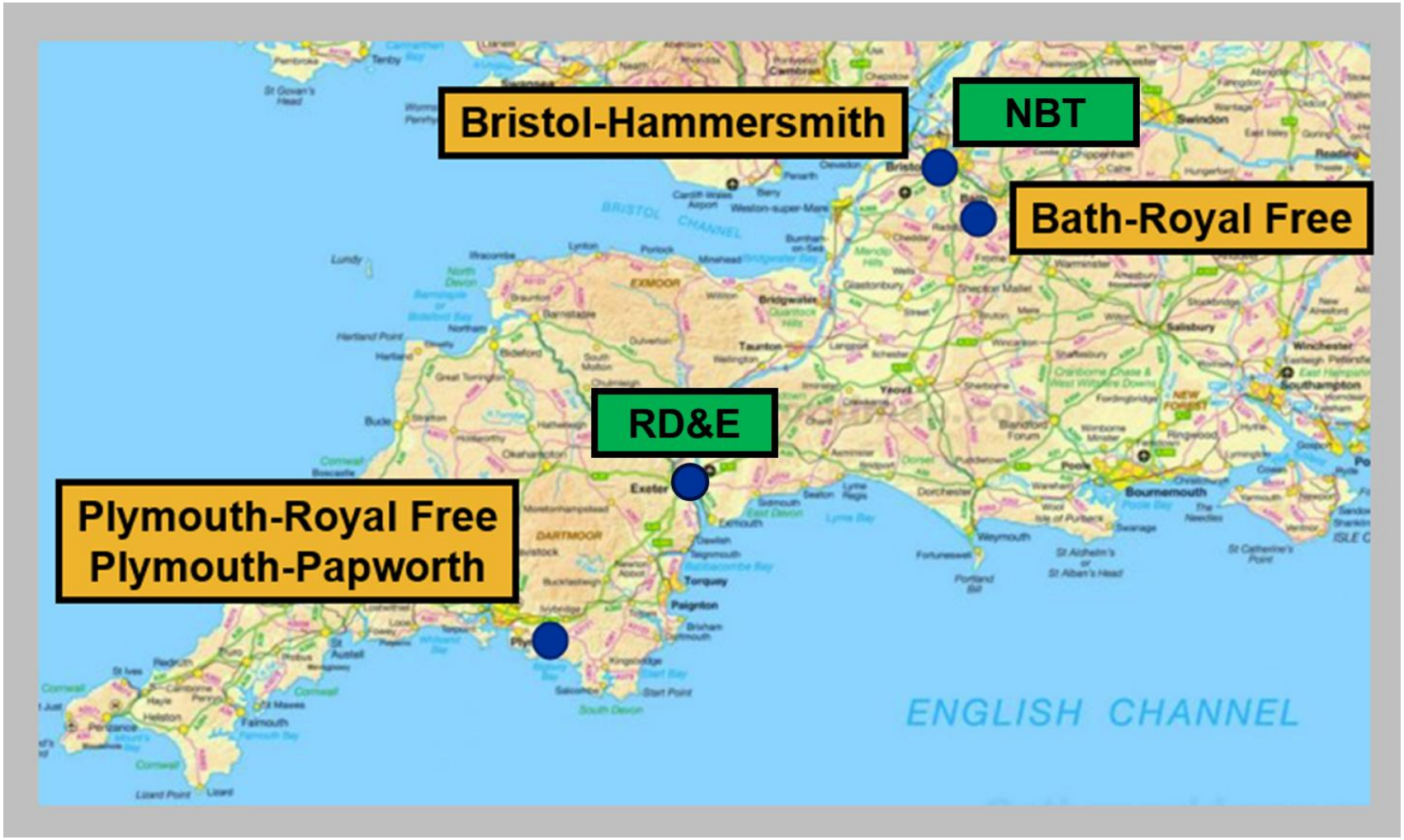
https://www.phauk.org/about-ph-2/treatment-for-pulmonary-hypertension/pulmonary-hypertension-specialist-centres/

Exeter
South West Peninsula
Interstitial Lung Disease Service

NHS
Royal Devon
University Healthcare
NHS Foundation Trust

Satellite PH Centre

ILD Specialist Centre (Tier 3)



CONFERENCE AWARD

Action for Pulmonary Fibrosis

Interstitial lung disease with pulmonary hypertension – considerations after 2024 World Symposium for Pulmonary Hypertension (WSPH) guidance: a single Interstitial Lung Disease centre perspective

NHS Manchester University NHS Foundation Trust

Jonathon Shaw[1], Trishala Raj[1], Saniya Rizwan[2], Harshana Bandara[1], Pilar Rivera-Ortega[1]

Interstitial lung disease unit, Wythenshawe hospital, Manchester, UK [1] ; Cardiology department, Wythenshawe hospital, Manchester, UK [2]

Introduction

- Pulmonary hypertension (PH) is a common complication of interstitial lung disease (ILD) and is associated with increased mortality.
- Management options are often limited with limited evidence base for targeted PH treatment in ILD patients.
- The WSPH[1] has recently published guidance describing the diagnostic pathway for patients suspected of having PH associated with chronic lung diseases, including ILD.
- In patients with intermediate or high likelihood of PH on echocardiogram, WSPH suggests right heart catheterisation (RHC) to confirm PH, if the results will impact patient management. We sought to assess our performance against the WSPH guideline.

Aims

- To retrospectively assess adherence to the 2024 WSPH guidance in diagnosing and managing pulmonary hypertension (PH) in patients with interstitial lung disease (ILD) at a tertiary ILD specialist centre, and to evaluate the impact of this adherence in access to PH-specific therapies.

Methods

- Patients at a tertiary ILD specialist centre in Manchester (UK) under a single ILD follow-up clinic were screened retrospectively over a 2-year period between September 2022–September 2024.
- Those with echocardiogram demonstrating intermediate or high probability of PH were included for analysis.
- Data on ILD diagnosis, baseline characteristics, echocardiographic evidence of pulmonary hypertension and PH referral and management were collected.

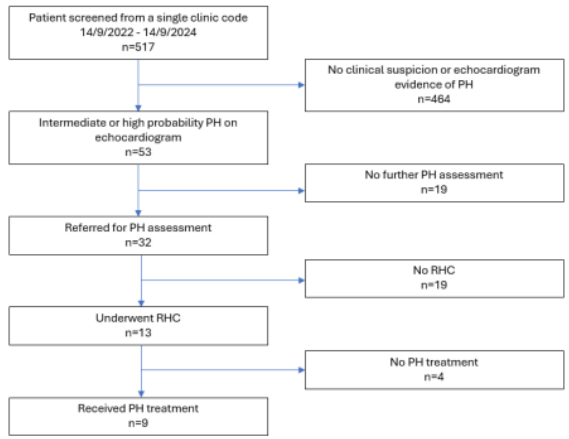
Results

Table 1 – baseline demographics and relevant investigations/ treatments received for pulmonary hypertension

Characteristics	N=53
Age (mean, ±S.D.)	72.2 (±11.9)
Sex	
Male	26 (49.1%)
Female	27 (51.9%)
ILD diagnosis	
IPF	23 (43.4%)
CTD-ILD	8 (15.1%)
fHP	6 (11.3%)
iNSIP	5 (9.4%)
Other	11 (20.8%)
Baseline lung function (mean, ±S.D.)	
FVC (L)	2.20 (±0.66)
DLCO (mmol/min/kPa)	2.64 (±0.86)
MRC dyspnoea scale (median, IQR)	3 (3-3)
Baseline serum NT-proBNP (mean, ±S.D.) *(ng/L)*	1711.9 (±2392.5) (n=16)
Echocardiogram characteristics (mean, ±S.D.)	
TRV (m/sec)	3.34 (±0.6)
sPAP (mmHg)	37.5 (±14.30)
TAPSE (cm)	1.92 (±0.43)
TAPSE/sPAP (mm/mmHg)	0.48 (±0.23)
PH specific therapy received	
Phosphodiesterase-5 inhibitor	8 (15.1%)
Endothelin receptor antagonist	3 (5.7%)
Selective prostacyclin receptor agonist	1 (1.9%)
Death during follow-up period	11 (20.8%)

Legend: ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis; CTD-ILD=connective tissue disease associated with interstitial lung disease; fHP=fibrotic hypersensitivity pneumonitis; iNSIP=idiopathic non-specific interstitial pneumonia; FVC=forced vital capacity; DLCO=diffusing capacity of the lungs for carbon monoxide; MRC=modified medical research council; NT-proBNP=N-terminal pro B-type natriuretic peptide; TRV=tricuspid regurgitation velocity; sPAP=systolic pulmonary artery pressure; TAPSE=tricuspid annular plane systolic excursion; SD=standard deviation; IQR=interquartile range.

Figure 1– proportion of ILD patients undergoing PH assessment



Discussion and Conclusions

- Pulmonary hypertension is common in this patient cohort.
- The majority underwent specific pulmonary hypertension assessment although <25% of patients underwent right heart catheterisation.
- WSPH guidance suggests that patients with intermediate to high probability of PH on echocardiogram should undergo RHC if impacting on patient management.
- The results reflect the limited available treatment in PH-ILD in the UK and suggest an urgent need for treatment identification in this group with high symptom burden and mortality.

References

1. Shlobin OA, et al. Pulmonary hypertension associated with lung diseases. Eur Respir J. 2024 Oct 31;64(4):2401200.

ATS 2025

https://orcid.org/0000-0002-7960-8822

p.riveraortega@nhs.net

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Pulmonary Hypertension In Interstitial Lung Disease – Is It Just Group 3 Pulmonary Hypertension?

NHS Manchester University NHS Foundation Trust

S. Rizwan[1], J. Shaw[2], T. Raj[2], H. Bandara[2] and P. Rivera-Ortega[2]

Cardiology Department, Wythenshawe Hospital, Manchester, UK[1], Interstitial Lung Disease Unit, Respiratory Medicine Department, Wythenshawe Hospital, Manchester, UK[2]

Introduction

Pulmonary Hypertension (PH) in patients with Interstitial Lung Disease (ILD) is mostly classified/treated as Group 3–PH (secondary to chronic lung disease). Cardiovascular comorbidity is frequently encountered in ILD patients.

Aim

To determine the presence of underlying cardiac dysfunction in ILD patients as a possible contributing factor to Pulmonary Hypertension (PH) i.e. Group 2-PH overlap.

Methods

Patients were screened retrospectively between September 2022 to September 2024 in a single ILD follow-up clinic at a tertiary ILD specialist centre in Manchester (UK). Those with echocardiogram demonstrating intermediate or high probability of Pulmonary Hypertension were included for analysis.

Results

517 ILD patients were screened of which 51 (9.86%) had echocardiographic evidence of PH.

Key clinical, radiological, functional and echocardiographic characteristics of ILD patients with PH are shown in **Table 1**.

Echocardiographic parameters of significance for PH screening were reviewed as shown in **Table 1**. We also reviewed echocardiographic parameters related to left heart disease. 4 (7.8%) patients showed impaired left ventricular ejection fraction.

Results

However, 17 (33.3%) patients had enlarged Left Atrial size (LA>20cm^2), which is a marker of heart failure with preserved ejection fraction (HFpEF).

19 (37.25%) of them were on diuretic therapy. No patients were referred for Cardiology consultation from ILD clinic, however interestingly 23 (45.09%) were under the care of a Cardiologist for other cardiovascular conditions.

13 (25.49%) of them had Right Heart Catheterisation , with an average Mean Pulmonary Artery Pressure of 33mmHg. 25 (49%) patients were on oxygen therapy. 9 of these patients received treatment for PH (8 were on PDE5 inhibitor).

Conclusions

In our cohort, a significant number of ILD patients had echocardiographic evidence suggestive of HFpEF, which may have a contributory factor in the development of PH. In the absence of a standard of care therapy for Group 3-PH in the UK, where the mainstay of treatment is optimising underlying lung disease, identifying evidence of Left Heart Disease gives an avenue to initiate evidence-based therapies. Our data suggests that the contribution of Left Heart Disease in PH-ILD patients is often overlooked, which could benefit from active Cardiology review and heart failure management.

Table 1: Clinical, Radiological, Functional and Echocardiographic Characteristics of ILD Patients with Pulmonary Hypertension.

Characteristics	N=51
Demographic & Clinical	
Age in years, mean (±SD)	72.2 (12.0)
Male, n (%)	26 (51.0)
White race, n (%)	40 (88.9)
Weight in Kg, mean (±SD)	71.5 (15.4)
Smoking history, n (%)	23 (45.1)
ILD diagnosis	
-Idiopathic Pulmonary Fibrosis (IPF), n (%)	23 (45.1)
-Connective tissue disease associated with ILD, n (%)	9 (17.6)
-Idiopathic non-specific interstitial pneumonia (NSIP), n (%)	5 (9.8)
-Fibrotic hypersensitivity pneumonitis (HP), n (%)	6 (11.8)
-Other, n (%)	8 (15.7)
Cardiovascular comorbidities	
-Ischaemic heart disease (IHD), n (%)	10 (19.6)
-Arterial hypertension, n (%)	25 (49.0)
-Atrial fibrillation (AF), n (%)	12 (23.5)
WHO functional class III or IV, n (%)	41 (80.4)
Pro B-type natriuretic peptide (pro BNP), mean (±SD)	1712 (2392)
Seen by Cardiologist for other cardiovascular conditions, n (%)	23 (45.1)
Follow-up in months, mean (±SD)	38.2 (25.5)
Deceased, n (%)*	11 (21.6)
Radiological	
Definite UIP pattern, n (%)	9 (17.7)
Probable UIP pattern, n (%)	14 (27.5)
Indeterminate for UIP pattern, n (%)	5 (9.8)
Inconsistent for UIP pattern/alternative diagnosis, n (%)	23 (45.1)
Pulmonary artery diameter, mean (±SD)	32.5 (6.3)
Baseline lung function	
FVC - percent predicted, mean (±SD)	80.6 (20.9)
DLCO - percent predicted, mean (±SD)	49.7 (16.6)
FVC/DLCO ratio, mean (±SD)	1.74 (0.56)
Follow up lung function*	
FVC - percent predicted, mean (±SD)	69.1 (20.4)
DLCO - percent predicted, mean (±SD)	36.9 (14.1)
FVC/DLCO ratio, mean (±SD)	2.14 (0.80)
Echocardiographic	
Tricuspid regurgitation velocity (TRV) in cm/s, mean (±SD)	333.8 (60.0)
Right ventricular outflow tract acceleration time (RVOT AT) in ms, mean (±SD)	82.1 (15.4)
Dilated end systolic right atrial area (≥18cm^2), n (%)	20 (39.2)
Increased basal right ventricle/left ventricle ratio (>1.0), n (%)	16 (31.4)
Tricuspid annular plane systolic excursion (TAPSE) in mm, mean (±SD)	19.3 (4.3)
Systolic pulmonary artery pressure (sPAP), mean (±SD)	42.29 (13.78)
TAPSE/sPAP, mean (±SD)	0.48 (0.23)
Dilated inferior vena cava diameter (≥2.1cm), n (%)	7 (13.7)
Parameters related to heart failure	
-Impaired left ventricular ejection fraction (LVEF <50%), **n (%)**	4 (7.8)
-Enlarged left atrial size (>20cm^2), n (%)	17 (33.3)

ILD=interstitial lung disease; FVC=forced vital capacity; DLCO=diffusing capacity of the lungs for carbon monoxide; UIP=usual interstitial pneumonia; SD= standard deviation. *Cut-off data in September 2024.

https://orcid.org/0000-0002-7960-8822

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p.riveraortega@nhs.net

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Prevalence and Clinical Management of Patients with ILD Associated with PH – A UK Regional ILD Centre Perspective

CS Crook[1], J Francesqui[2], SC Stanel[1], P Hughes[3], J Lentaigne[3], S Lines[1], C Young[3], MA Gibbons[1,4,5], P Rivera-Ortega[1]

[1]Exeter South West Peninsula Interstitial Lung Disease Service, Academic Department of Respiratory Medicine, Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK, [2]Department of Respiratory Medicine and Allergy, Hospital de la Santa Creu i Sant Pau. Institut de Recerca Sant Pau (IR SANT PAU). Barcelona, Spain , [3]Pulmonary Hypertension Centre, University Hospital Plymouth NHS Trust, Plymouth, UK, [4]Department of Clinical & Biomedical Sciences, University of Exeter, Exeter, UK, [5]NIHR Exeter Biomedical Research Centre, University of Exeter, Exeter, UK

Rationale

Pulmonary hypertension (PH) is a common, serious comorbidity of interstitial lung disease (ILD), associated with increased mortality. Early recognition can support more timely, targeted care.

Methods

Retrospective data from a UK regional centre (Nov 2024–Nov 2025) were screened; cases with intermediate or high echocardiographic likelihood of pulmonary hypertension were analysed for key clinical, radiological, and echocardiographic features (Figure 1).

777 patients were screened for PH

7% received intermediate to high probability of PH on echocardiogram

7% were referred to a PH centre

National Audit of Pulmonary Hypertension Dashboard Great Britain 2024-25

All PH groups:

The number of new referrals to PH centres has increased year-on-year, except in 2020-21 (during the COVID-19 pandemic)

The number of new referrals rose from 1,868 in 2009-10 (the first year of the Audit) to 4,469 in 2024-25.

Active Patients on 31/Mar/25:

Total PH=9140 patients

PH-lung disease=787 patients (8.6% of all patients diagnosed with PH)

https://digital.nhs.uk/data-and-information/publications/statistical/national-pulmonary-hypertension-audit/16th-annual-report#

Table 1: Clinical, Radiological, Functional and Echocardiographic Characteristics of ILD Patients with Pulmonary Hypertension: Regional ILD Service from November 2024 to November 2025.

Characteristics	N=54
Demographic & Clinical	
Age in years, mean (±SD)	78.2 (8.6)
Male, n (%)	38 (70.0)
Smoking history, n (%)	34 (63.0)
ILD diagnosis	
-Idiopathic Pulmonary Fibrosis (IPF), n (%)	26 (48.2)
-Systemic Autoimmune and Rheumatic Disease associated with ILD, n (%)	4 (7.4)
-Idiopathic non-specific interstitial pneumonia (NSIP), n (%)	4 (7.4)
-Hypersensitivity pneumonitis (HP), n (%)	8 (14.8)
-Other, n (%)	12 (22.2)
Respiratory comorbidities	
-Chronic obstructive pulmonary disease (COPD), n (%)	9 (16.7%)
-Asthma, n (%)	4 (7.4%)
-Emphysema[§], n (%)	19 (35.2)
Cardiovascular comorbidities	
-Ischaemic heart disease (IHD), n (%)	5 (9.3)
-Arterial hypertension, n (%)	21 (38.9)
-Atrial fibrillation (AF), n (%)	21 (38.9)
Pro B-type natriuretic peptide (pro BNP)[¥], median (±IQR)	515.5 (1173.0)
Antifibrotic treatment, n (%)	19 (35.2)
Oxygen therapy, n (%)	17 (31.5)
Deceased*, n (%)	12 (22.2)
Radiological	
Pulmonary artery diameter in mm, median (±IQR)	32.5 (7.0)
Pulmonary Artery diameter/Aorta diameter ratio (PA:Ao), mean (±SD)	0.95 (0.14)
Baseline lung function	
FVC - percent predicted, mean (±SD)	75.6 (22.3)
DLCO - percent predicted, mean (±SD)	42.8 (15.8)
FVC/ DLCO ratio, mean (±SD)	1.91 (0.71)
FVC/DLCO ratio >1.60, n (%)	31 (59.6)
Echocardiographic	
Tricuspid regurgitation velocity (TRV) in cm/s, mean (±SD)	325.6 (55.6)
Dilated end systolic right atrial area (≥18cm²), n (%)	29 (56.9)
Increased basal right ventricle/left ventricle ratio (>1.0), n (%)	23 (44.2)
Tricuspid annular plane systolic excursion (TAPSE) in mm, mean (±SD)	19.5 (5.4)
Systolic pulmonary artery pressure (sPAP), mean (±SD)	43.4 (14.8)
TAPSE/sPAP, mean (±SD)	0.50 (0.23)
Dilated inferior vena cava diameter (≥2.1cm), n (%)	11 (29.0)
Parameters related to heart failure	
-Impaired left ventricular ejection fraction (LVEF <50%), n (%)	15 (27.8)
-Enlarged left atrial size (>20cm²), n (%)	29 (72.5)

ILD=interstitial lung disease; FVC=forced vital capacity; DLCO=diffusing capacity of the lungs for carbon monoxide; SD= standard deviation; IQR=interquartile range. [§]Confirmed by CT-based visual assessment.
[¥]Pro BNP reference range: 0 – 399ng/L.
*Cut-off data in January 2026. *Overall mortality among patients with IPF in our Regional ILD Service was 22% between October 2020 and October 2024, approximately 5.5% annually. Comparison: in our cohort of patients with ILD and PH, mortality was four times higher.*

Results

Of 777 patients screened, 54 (7%) had intermediate or high echocardiographic probability of PH. Mean maximum tricuspid regurgitation velocity (TRVmax) was 3.25 m/s and mean systolic pulmonary artery pressure (sPAP) 43.4 mmHg.

Pro-BNP was measured in 70%, median of 515.5 pg/mL. Mean FVC/DLCO ratio was 1.9, above the >1.6 PH-risk threshold in ILD. Oxygen therapy was used by 31.5% (17/54): 22% ambulatory oxygen and 9% ambulatory and long-term oxygen.

Cardiovascular comorbidities were present in 87% (38/54), most commonly arterial hypertension (38.9%), atrial fibrillation (38.9%), and ischemic heart disease (9.3%). Emphysema was identified on CT scan in 35.2%.

By mid-January 2026, 22.2% (12/54) had died during follow-up. Only 7% (4/54) were referred to a PH centre, with one patient receiving phosphodiesterase-5 inhibitor therapy.

Conclusion

Our data show frequent echocardiographic likelihood of PH in the ILD cohort, underscoring the need for a carefully defined PH-ILD care pathway to ensure accurate diagnosis and timely access to targeted treatment.

Charlotte S. Crook ORCID ID: 0009-0009-8497-6564
Pilar Rivera-Ortega ORCID ID: 0000-0002-7960-8822

ERS CONGRESS 2026
PA6326

c.crook1@nhs.net
p.riveraortega@nhs.net

Take-home messages

- Pulmonary hypertension (PH) is associated with poor prognosis and reduced quality of life.
- Early diagnosis is essential.
- A multidisciplinary approach and personalised care strategies for PH-ILD are strongly recommended.
- National Care Pathway for PH-ILD, working in partnership with Patient Associations/Organisations.
- Research/Real-world Evidence (RWE): National Service Evaluation for PH-ILD, protocol under development (Exeter ILD Team).
- Support groups for patients and carers.





Thank you!!





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