# Recent Advances in Group 3 Pulmonary Hypertension - Focused on PH-ILD -

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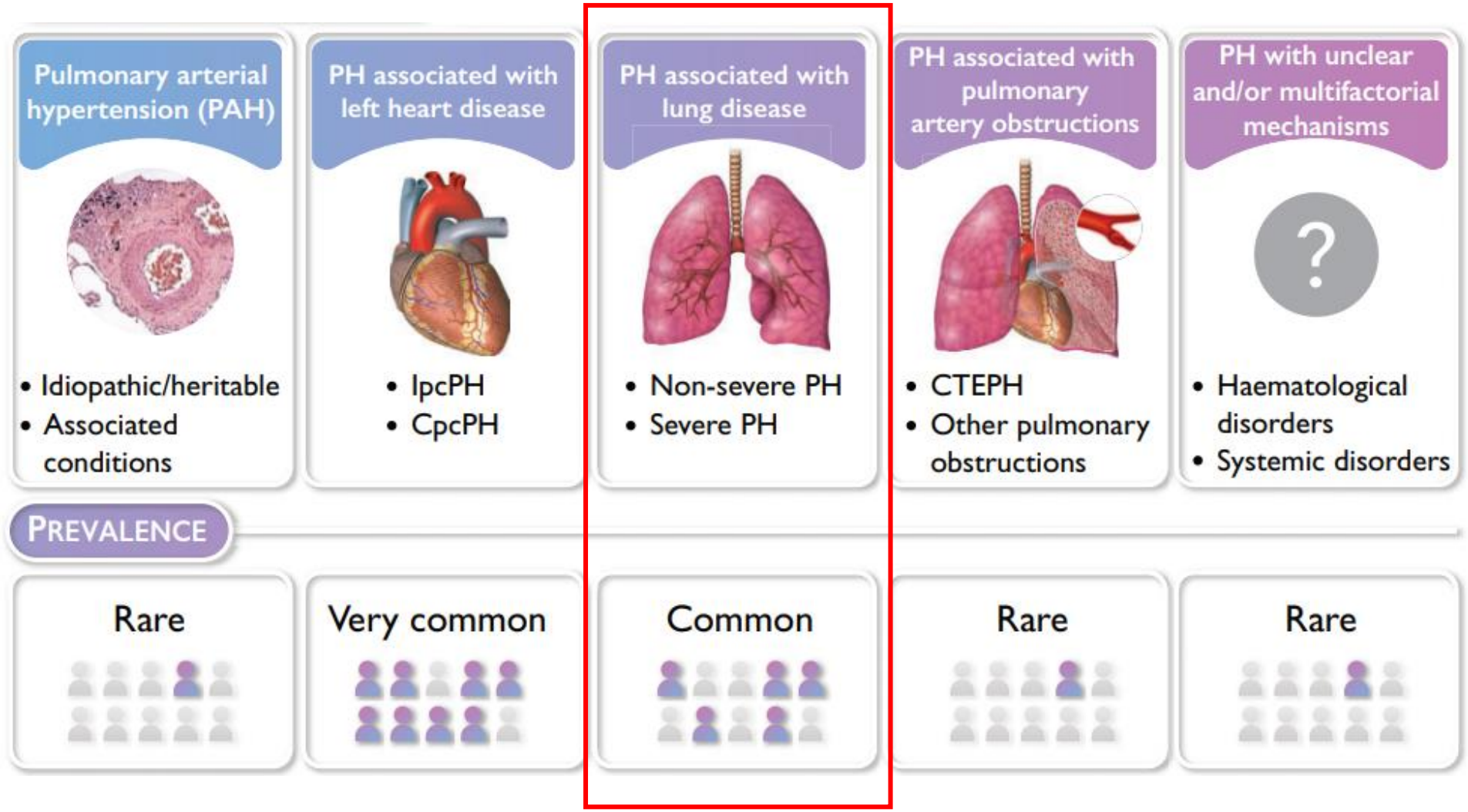
# Clinical classification of PH

- Group 3 PH – common type of PH




Eur Heart J. 2022;43(38):3618-3731

# Classification of group 3 PH

- Main disease category
  - COPD / Emphysema
  - ILD
  - CPFE

| 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 |

Eur Respir J. 2024;64(4):2401324

# Prevalence of group 3 PH

- COPD
  - Pooled prevalence 39% in recent meta-analysis
- ILD
  - Pooled prevalence 40% in recent meta-analysis

- Higher prevalence in lung transplantation cohorts
- Maybe still under-estimated
  - selection criteria for evaluation of PH
  - diagnostic method used for PH

Int J Chron Obstruct Pulmon Dis. 2022:17:1365-1379
Chest. 2024;166(4):778-792

# Impact of group 3 PH in chronic lung diseases

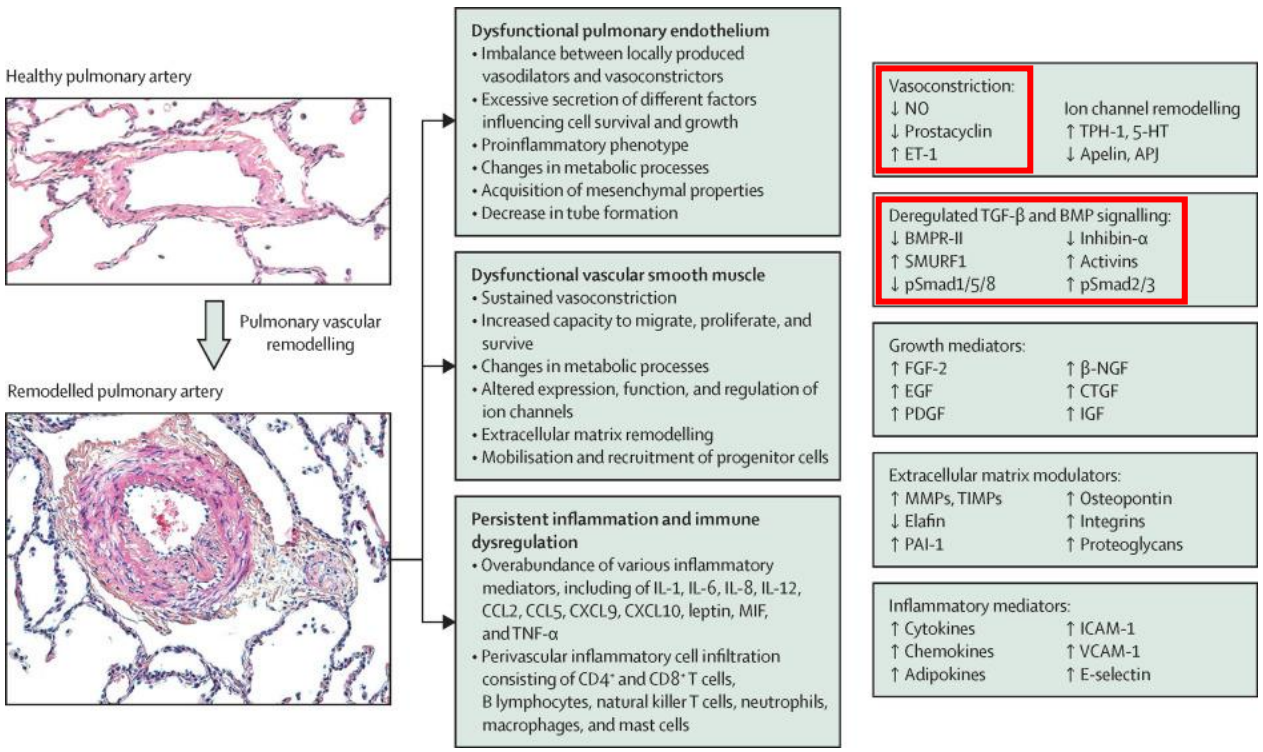
- Worse prognosis
  - Reduced exercise capacity
  - Greater need of oxygen supplementation
  - Decreased quality of life

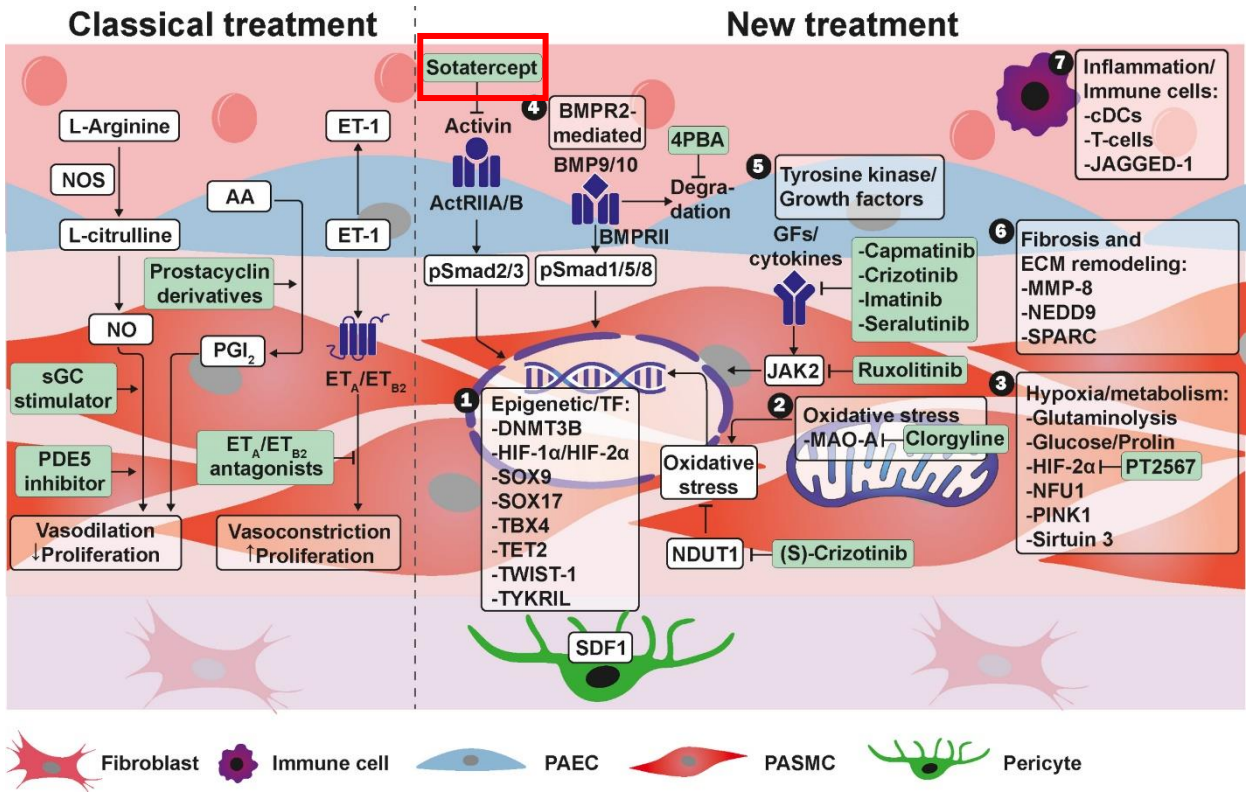
- Unmet need regarding optimal management
  - No standardized treatment strategy
  - Consideration for lung transplantation

J Clin Invest. 2023;133(16):e170502

# Pathogenesis of group 1 PAH

- Advance in understanding of PAH → Successful development of new drugs (ex. Sotatercept)




Lancet Respir Med. 2023;11(9):804-819
Am J Respir Crit Care Med. 2023;208(5):528-548

# Pathogenesis of group 3 PH

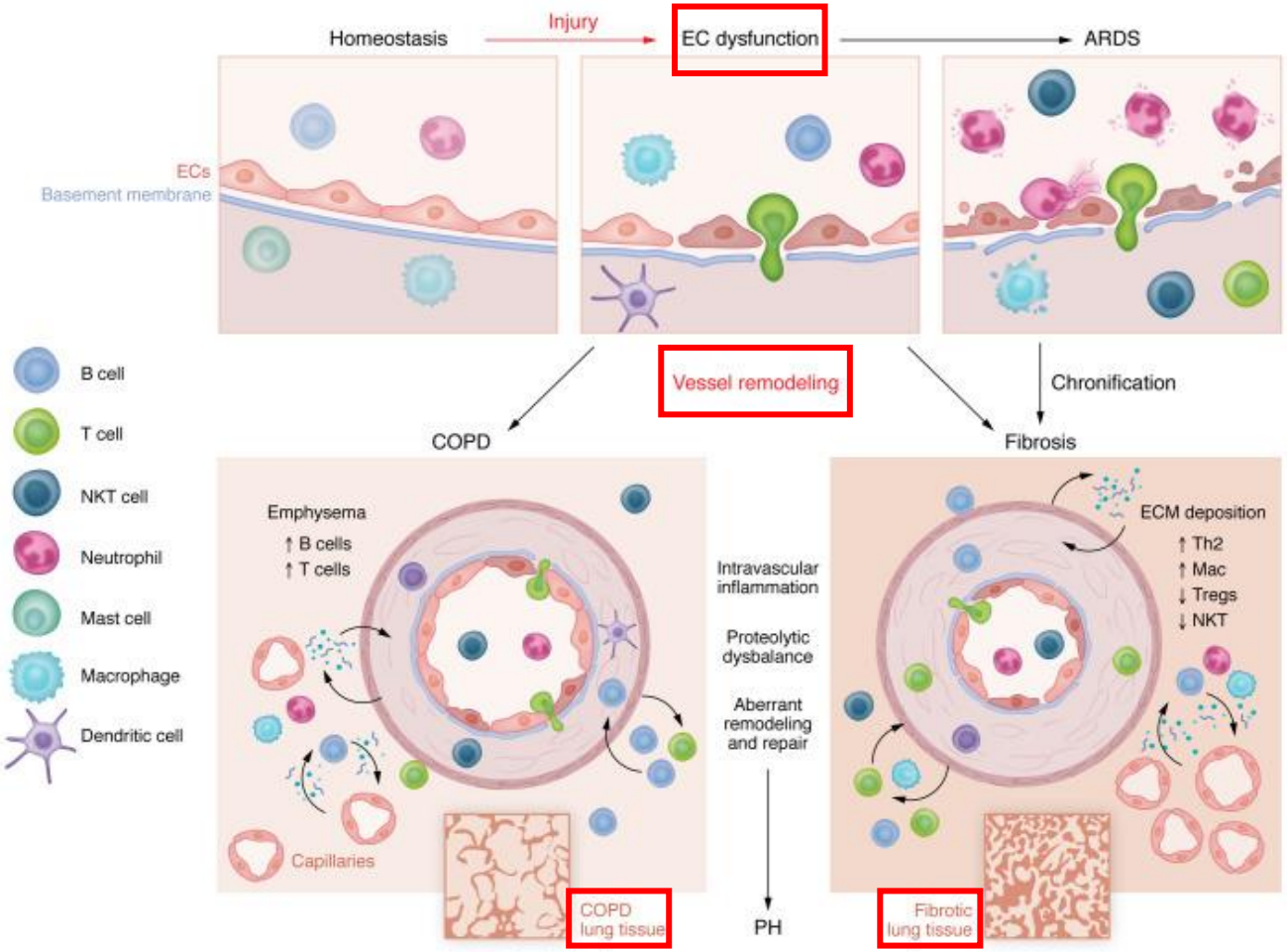
- Previous traditional concept
  - Consequence of hypoxia due to insufficient ventilation and diffusion

- Current concept
  - PH can develop independent of hypoxia
  - Vascular alteration & remodeling
  - Endothelial cell dysfunction

J Clin Invest. 2023;133(16):e170502

# Potential key role of endothelium

- Chronic endothelial cell dysfunction
  - vascular remodeling & development of PH
  - may participate in lung parenchymal damage




Parenchymal fibrosis

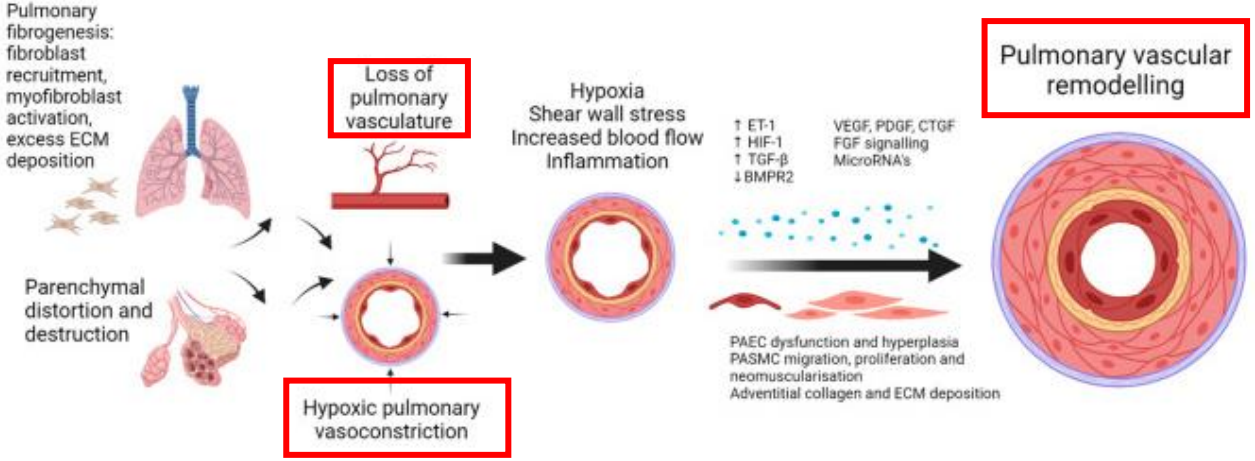
↕

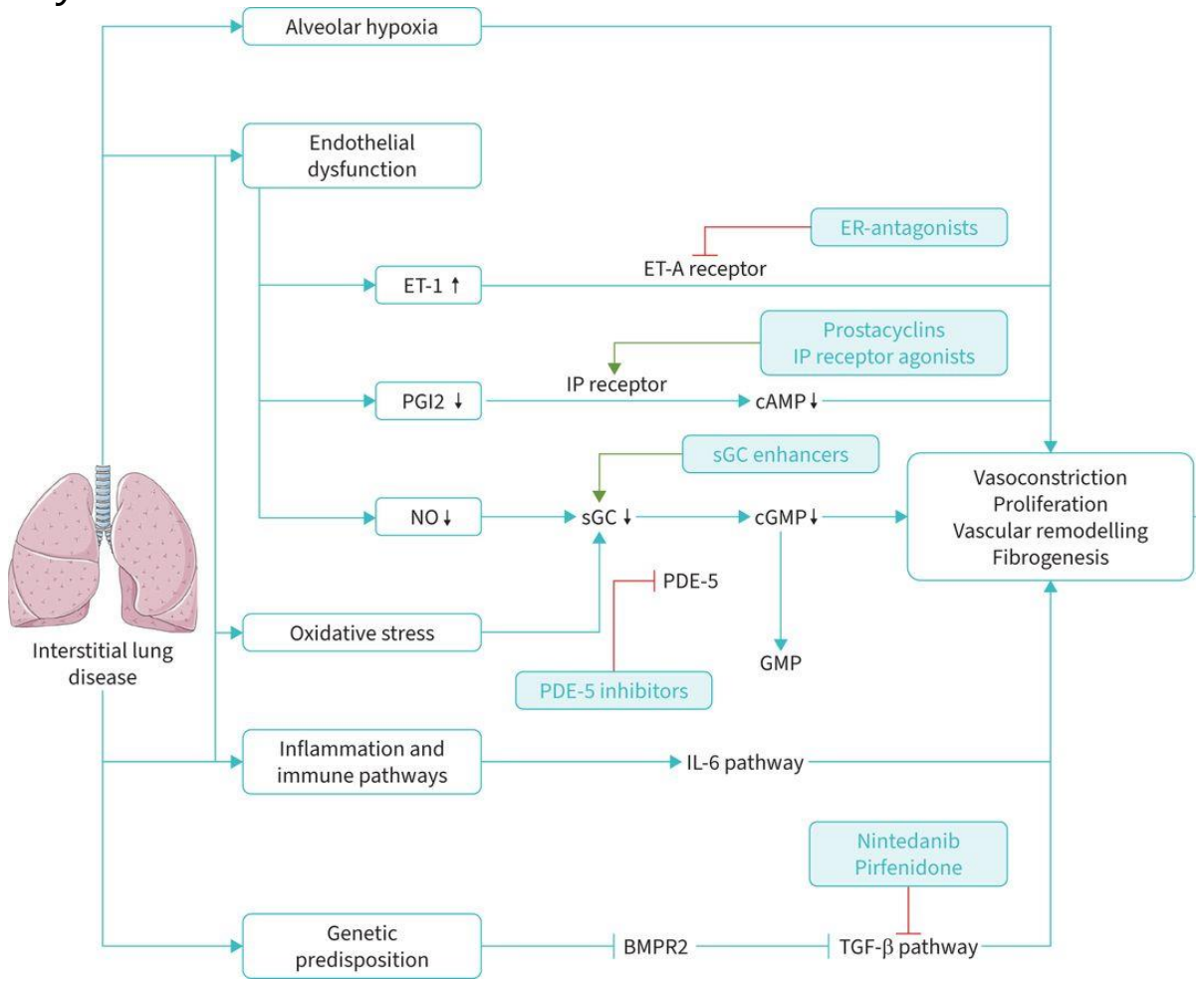
Vascular remodeling

J Clin Invest. 2023;133(16):e170502

# Pathogenesis of PH-ILD

- Detailed pathways associated with PH in ILD is still poorly understood
  - vasoconstriction
  - vascular remodeling
  - loss of microvasculature
- Lack of appropriate animal model

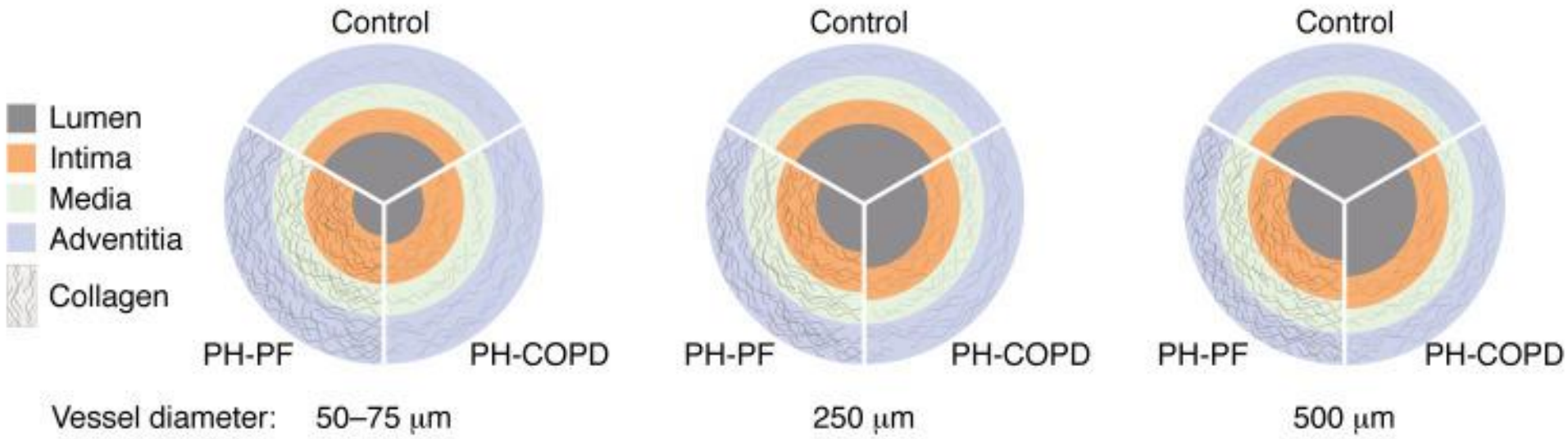



J Heart Lung Transplant. 2021;40(9):872-881
Life. 2024;14(9):1203
J ERJ Open Res. 2022;8(4):00272-2022

# PH-ILD vs. PH-COPD

- Similar in some ways, but different




Differentially regulated pathways (PH-PF vs PH-COPD):

- ECM receptor interaction
- Retinol metabolism
- Diverse immunoprofile

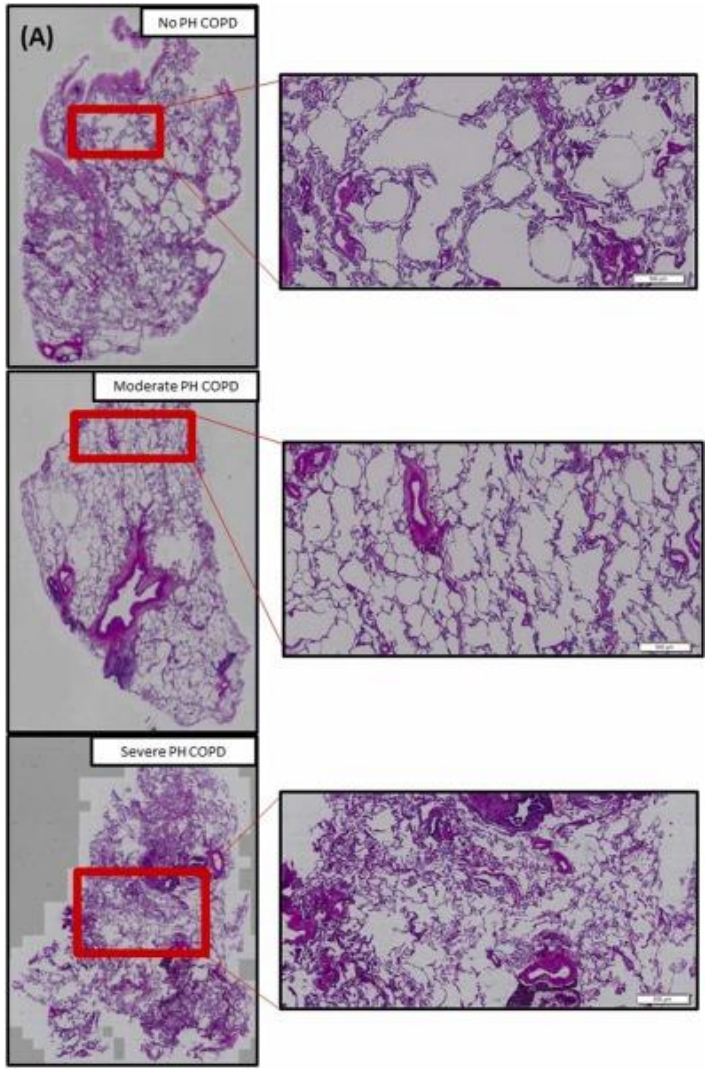
Putative common pathways:

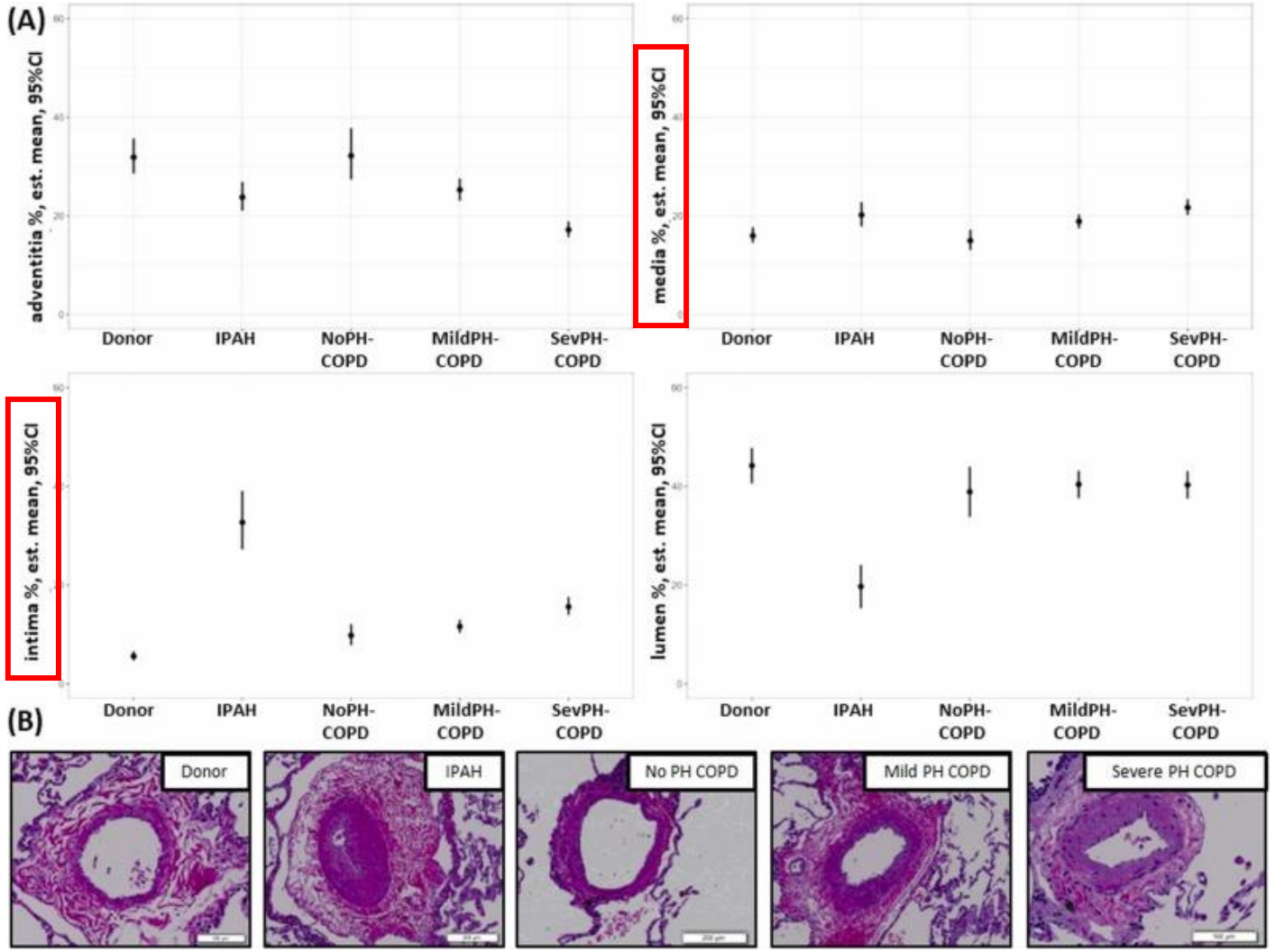
- Senescence
- Oxidative stress
- Disturbed EC homeostasis

J Clin Invest. 2023;133(16):e170502

# Histologic study in PH-COPD

- Idiopathic PAH vs. COPD with no PH vs. COPD with mild PH vs. COPD with severe PH



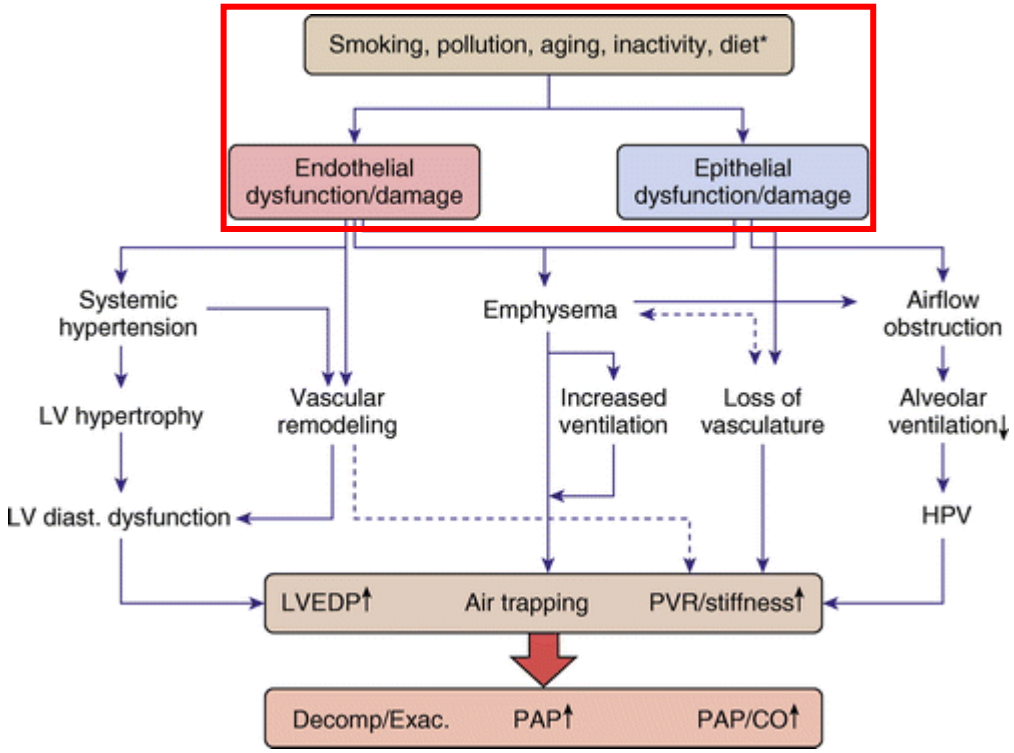

J Heart Lung Transplant. 2024;43(7):1090-1101

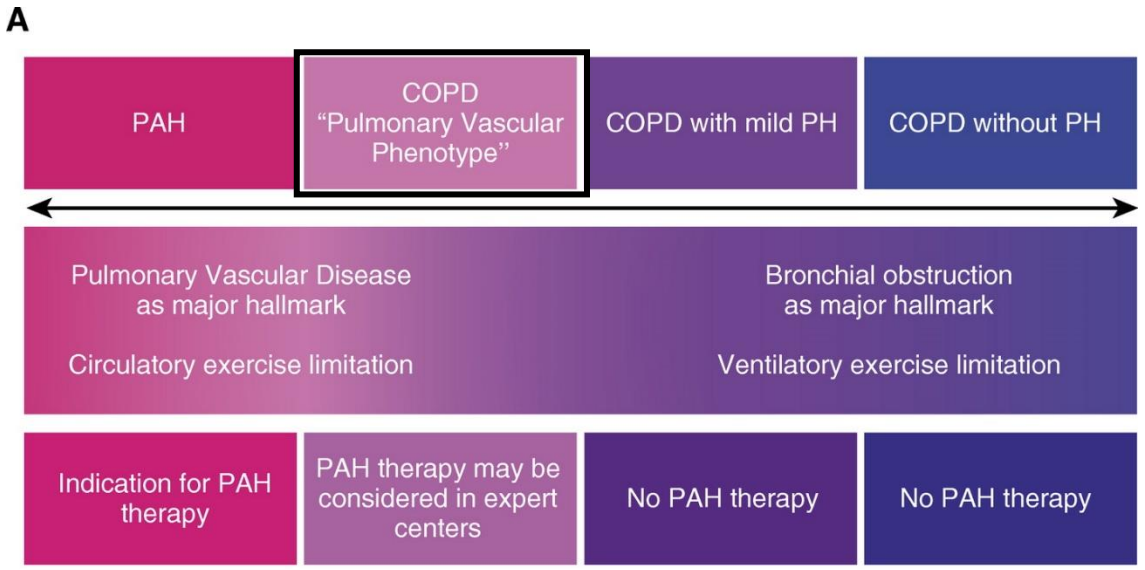
# COPD with vascular phenotype

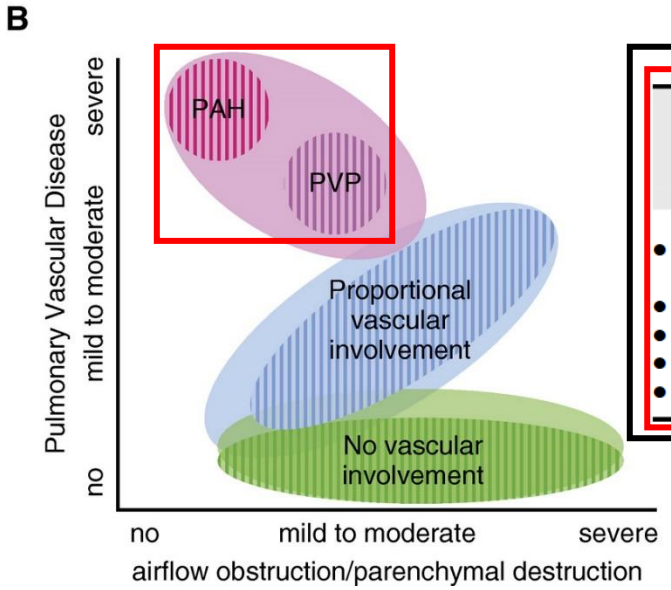
## PULMONARY PERSPECTIVE

### Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease

Is There a Pulmonary Vascular Phenotype?



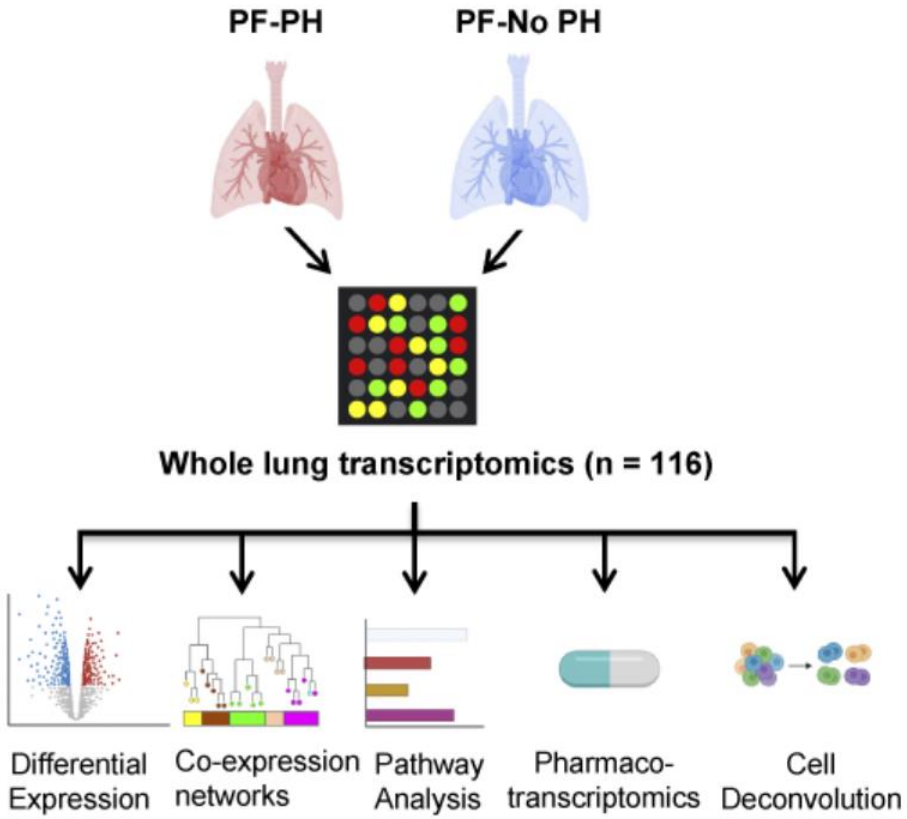

**Major Characteristics of Patients with COPD with the "Pulmonary Vascular Phenotype"**

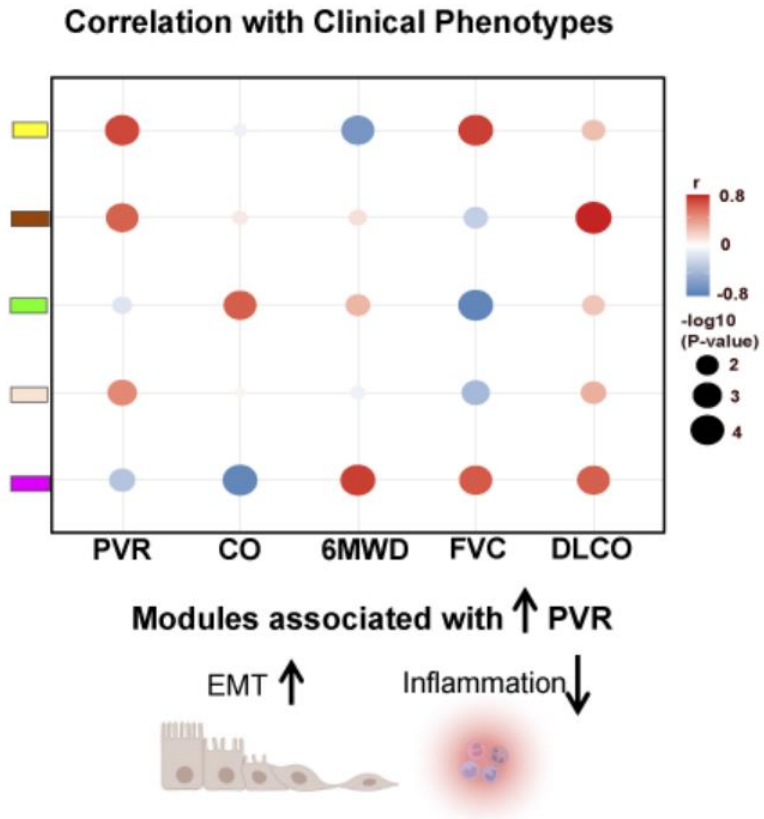
- Severe precapillary pulmonary hypertension*
- Moderate airflow limitation
- No or very mild hypercapnia
- Very low $D_{LCO}$ (<45% predicted)
- Circulatory exercise limitation

Am J Respir Crit Care Med. 2018;198(8):1000-1011

# Lack of basic research in PH-ILD

- Some results from transcriptome studies, but very limited data compared to IPF
- Most available studies are using explanted lung tissues
  - cannot properly address heterogeneity of disease, especially at early stage

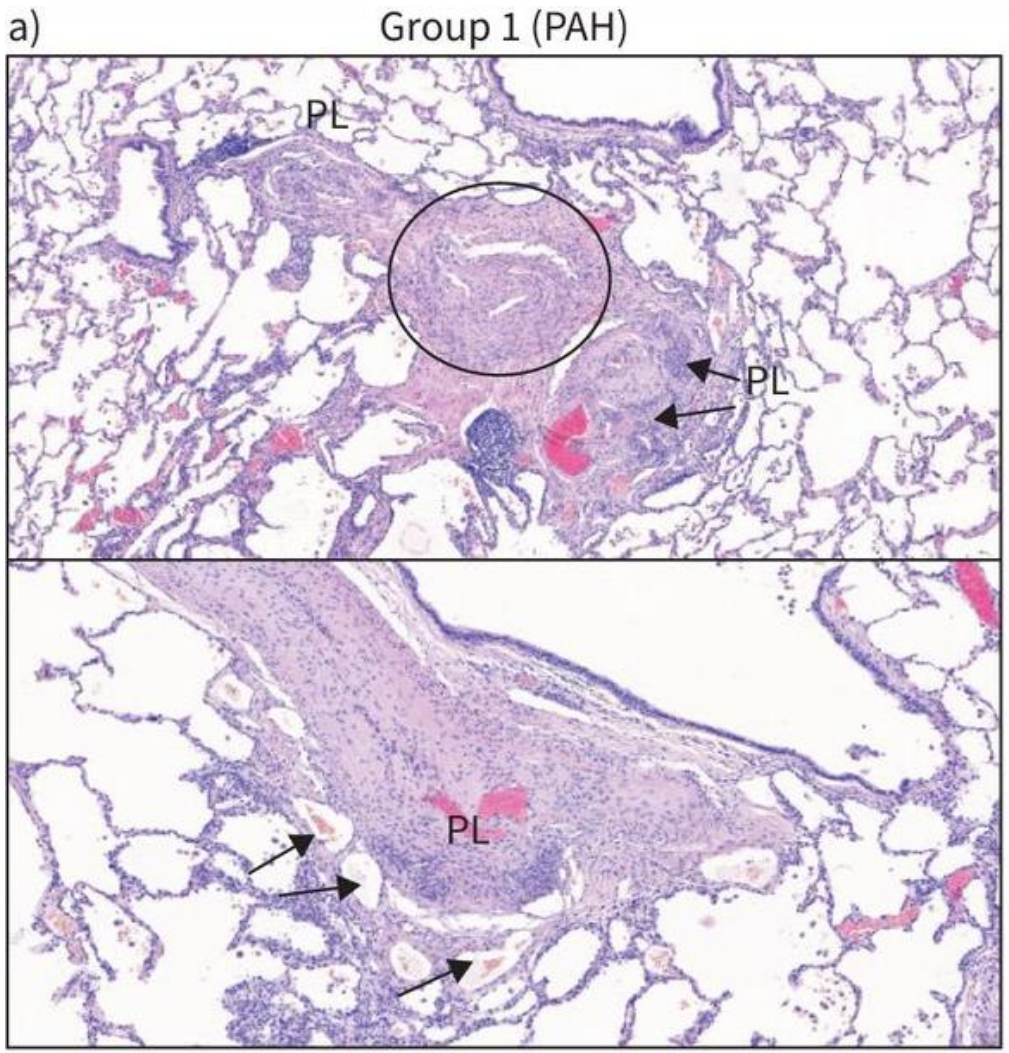


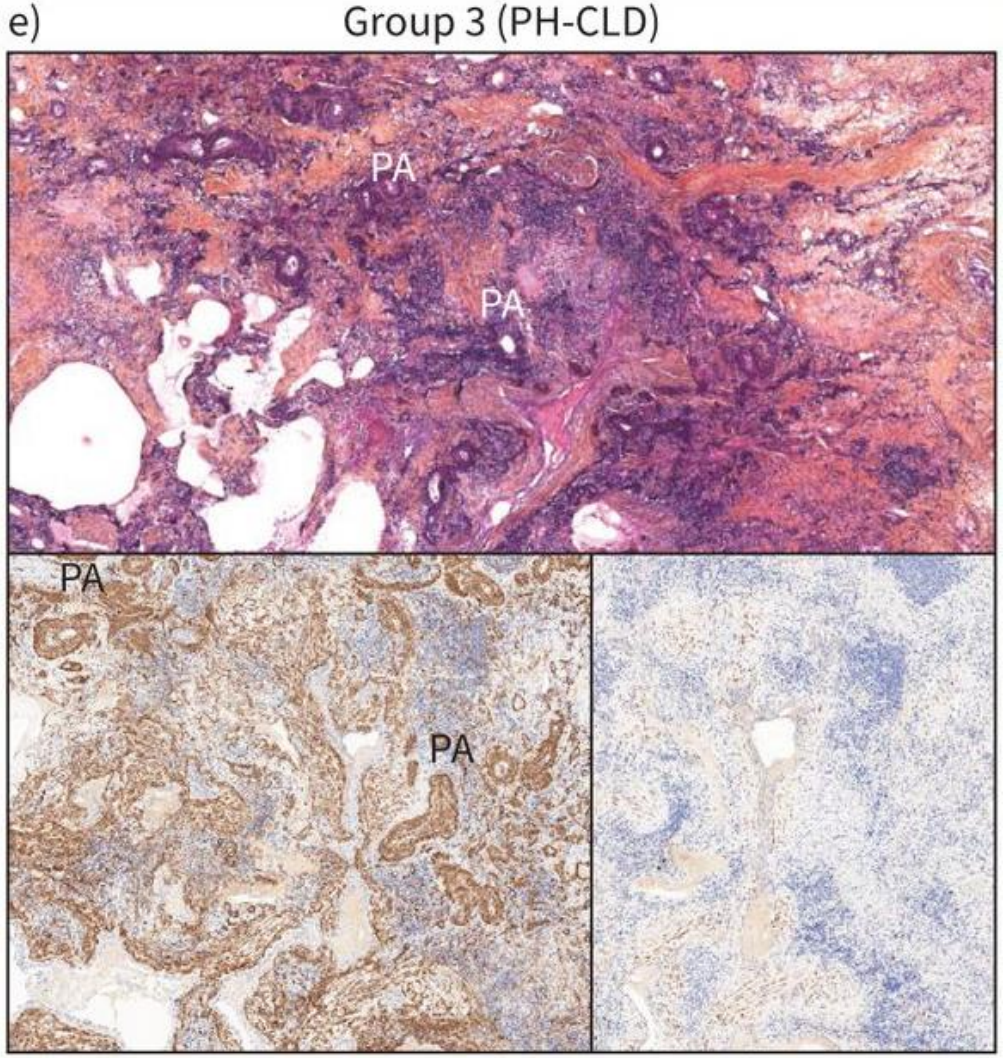




Am J Physiol Lung Cell Mol Physiol. 2024;327(4):L520-L534

# Difference between PAH and PH-ILD

- Different pathobiology → Different response to PAH targeted treatment

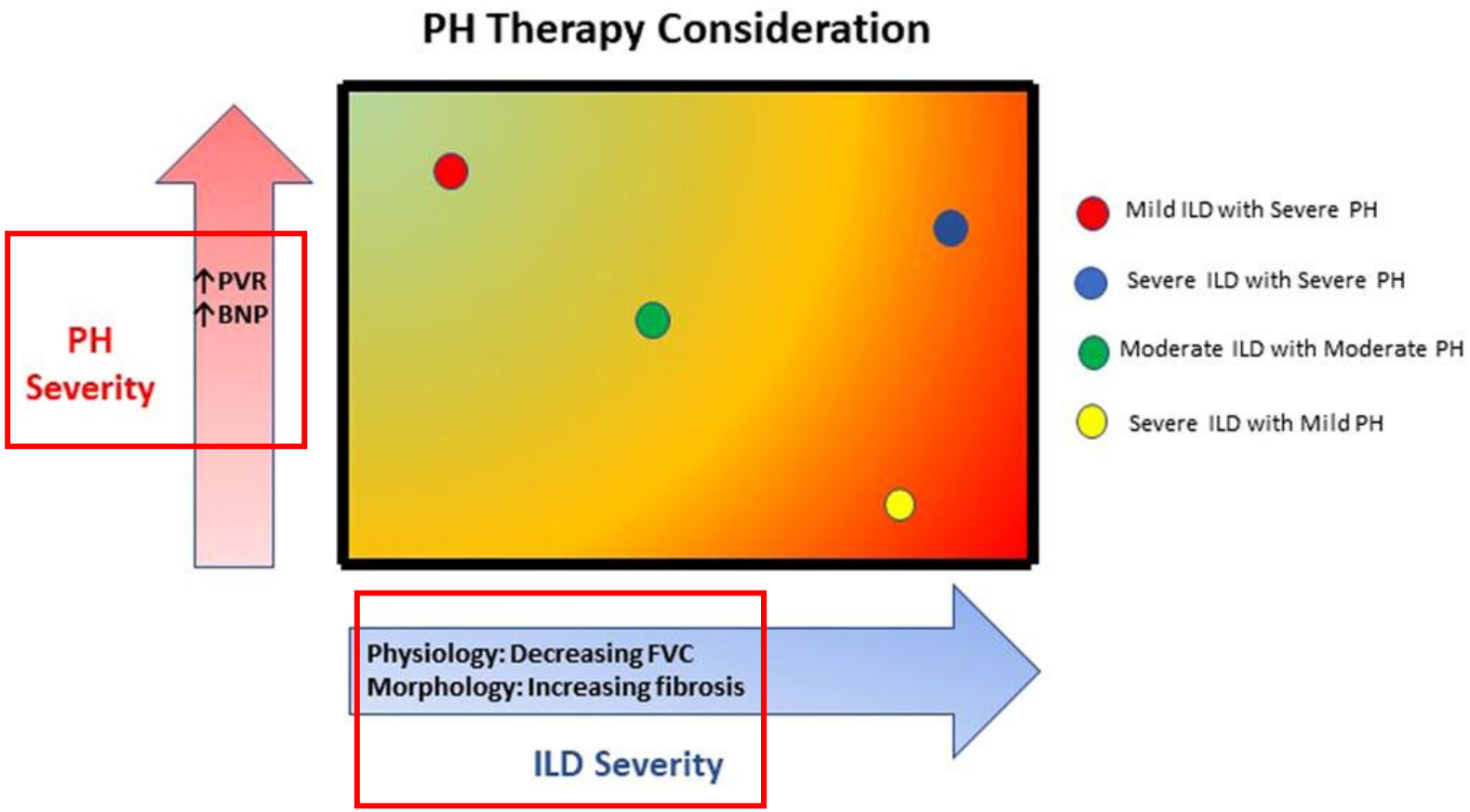



Eur Respir J. 2024;64(4):2401095

# Heterogeneity in PH-ILD

- Different phenotypes within PH-ILD
  - Severity of ILD
  - Severity of PH




Pulm Circ. 2024;14(1):e12310

# Ambiguity in differentiation between group 1 & 3

- Unclear threshold for defining group 3 PH
  - Multimodal assessment : PFT, DLCO, HRCT

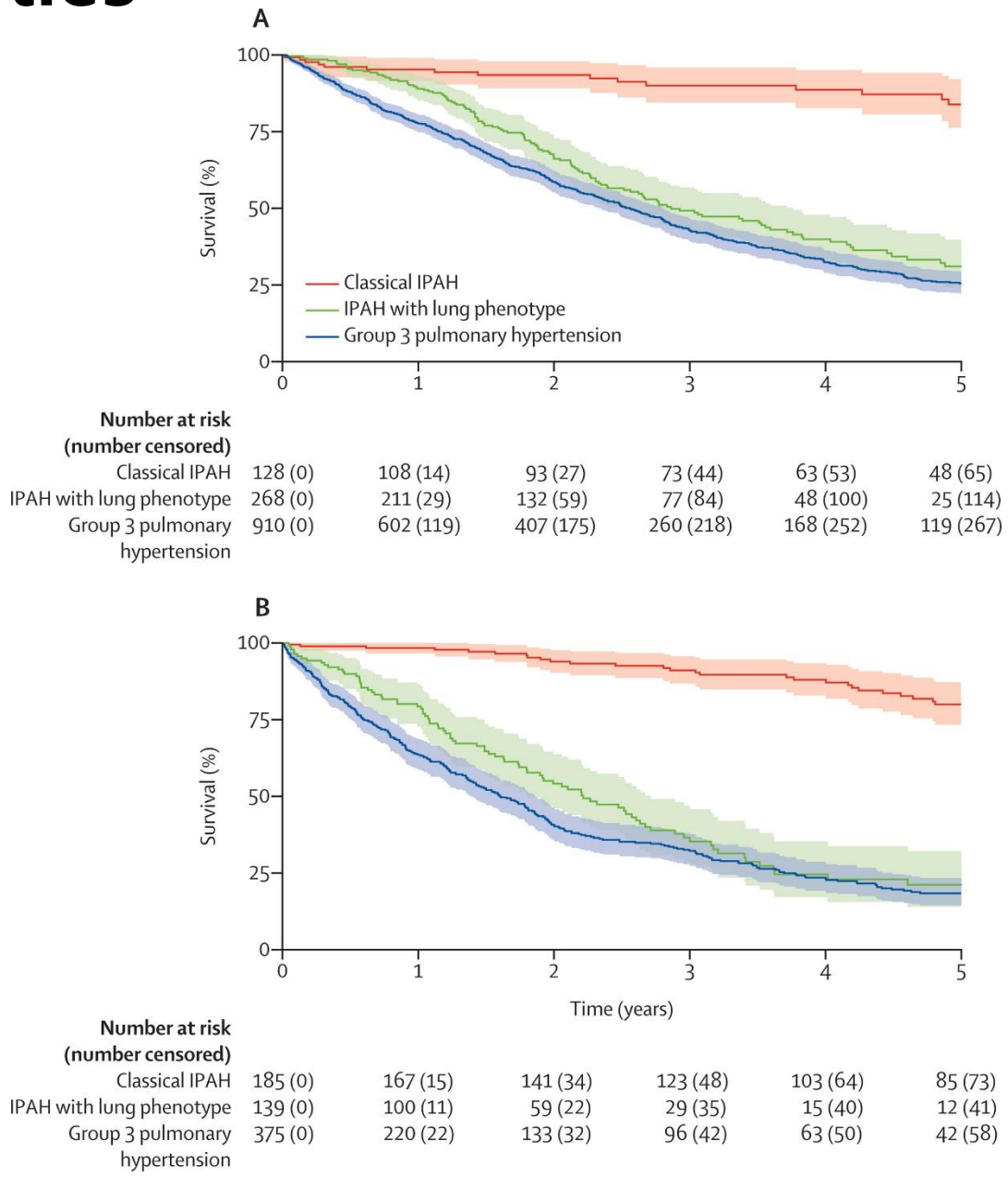
- Example of systemic sclerosis ILD
  - Mild parenchymal disease (limited SSc) → favor group 1
  - Extensive parenchymal disease (diffuse SSc) → favor group 3
  - Maybe combined with even group 2 (cardiac involvement)

Eur Respir J. 2024;64(4):2401324

# Concept of PAH with comorbidities

- COMPERA & ASPIRE cohort analysis
- PAH with lung phenotype vs. Group 3 PH
  - less severe lung parenchymal disease
  - however, similar survival outcomes

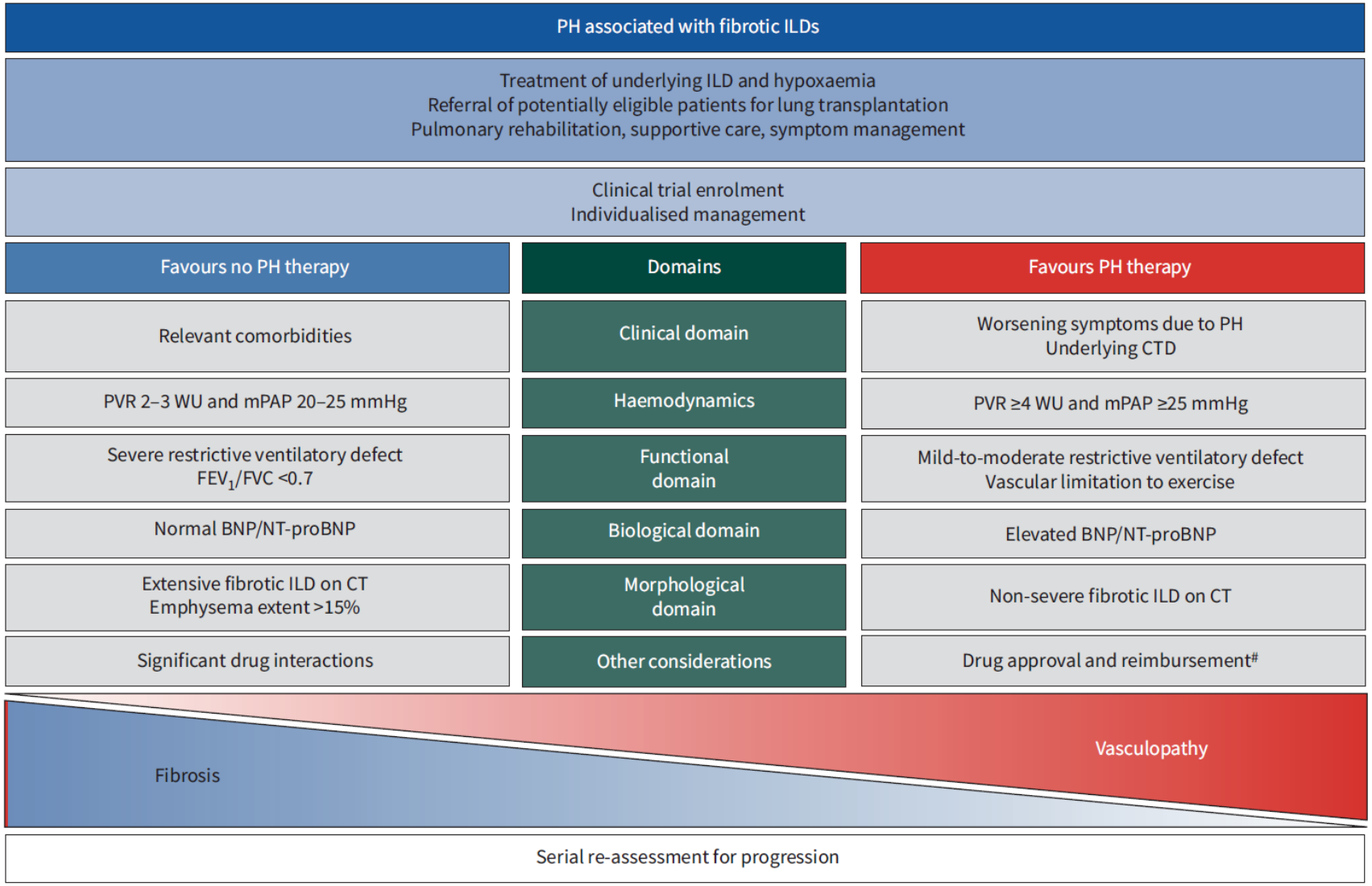
| | Classical IPAH | PAH with lung phenotype | Group 3 PH |
|---|---|---|---|
| CT fibrosis, any present | 9 (8%) | 26 (30%) | 102 (47%) |
| CT fibrosis by severity | | | |
| None | 100 (93%) | 60 (71%) | 117 (57%) |
| Mild | 6 (6%) | 21 (25%) | 21 (10%) |
| Moderate | 1 (1%) | 4 (5%) | 33 (16%) |
| Severe | 0 | 0 | 36 (17%) |
| CT emphysema, any present | 15 (14%) | 42 (49%) | 132 (60%) |
| CT emphysema by severity | | | |
| None | 94 (89%) | 44 (52%) | 87 (41%) |
| Mild | 11 (10%) | 22 (26%) | 21 (10%) |
| Moderate | 1 (1%) | 16 (19%) | 62 (30%) |
| Severe | 0 | 3 (4%) | 40 (19%) |




Lancet Respir Med. 2022;10(10):937-948

# What should we do in Group 3 PH-ILD?

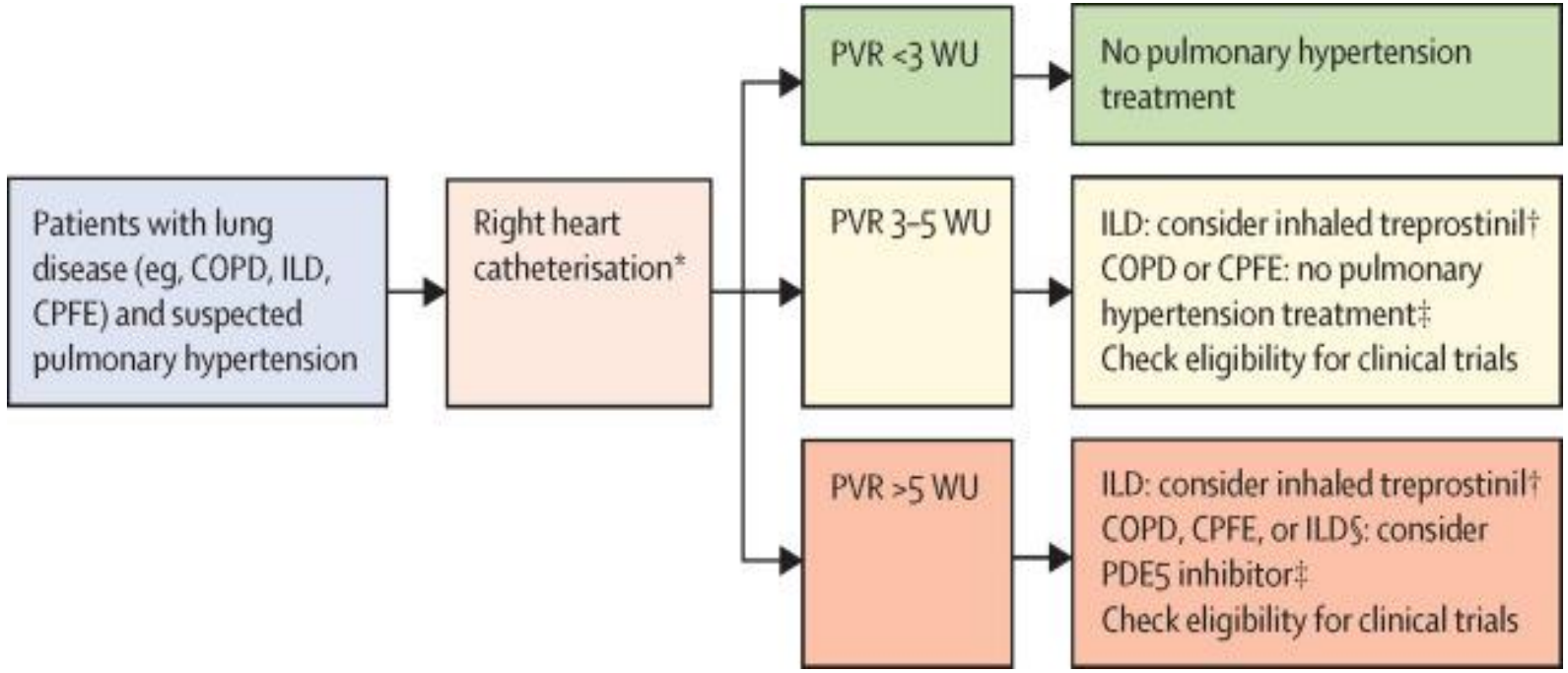
- Decide whether to try PAH therapy




Eur Respir J. 2024;64(4):2401200

# Which drugs should we consider?

- Potential options
  - PDE5 inhibitor (ex. sildenafil)
  - Inhaled treprostinil (if available)
  - Clinical trial




Lancet Respir Med. 2023;11(9):820-835

# Previous studies on PAH therapies in Group 3 PH

- PDE5 inhibitor maybe the most reasonable first choice

| Study/1st Author | Drug | Main inclusion criteria* | Primary outcome | Number of subjects | Results | Comments |
|---|---|---|---|---|---|---|
| **Endothelin Receptor Antagonists** | | | | | | |
| BUILD-1/King[73] | Bosentan | Mild to moderate IPF; absence of known PH | Change in 6-MW at 12 m | 158 | Negative | |
| BUILD-3/King[74] | Bosentan | Mild to moderate, SLB confirmed IPF < 3 yrs duration; < 5% honeycombing | Composite clinical worsening: event-driven | 616 (2:1 randomization) | Negative | |
| MUSIC/Raghu[75] | Macitentan | Same as BUILD-3 | Change in FVC at 12 m | 178 (2:1 randomization) | Negative | |
| ARTEMIS/Raghu[61] | Ambrisentan | IPF with < 5% honeycombing; RHC at baseline; PH allowed | Composite clinical worsening: event-driven | 494 (2:1 randomization) | More disease progression and mortality in treatment arm; study halted early | 10% with PH (mPAP ≥ 25 mm Hg); similar results in PH subset |
| †ARTEMIS-PH (NCT00879229) | Ambrisentan | IPF; RHC confirmed PH: mPAP ≥ 25 mm Hg | Change in 6-MWD at 16 wk | 40 (2:1 randomization) | Negative; halted early | 23% survival at 48 weeks |
| †BPHIT/Corte[62] | Bosentan | fIIP; RHC confirmed PH: mPAP ≥ 25 mm Hg | Fall in PVRi ≥ 20% at 16 wk | 60 (2:1 randomization) | Negative | Trend for greater $O_2$ requirement in bosentan group |
| **Phosphodiesterase type-5 Inhibitors and Soluble Guanylate Cyclase Stimulators** | | | | | | |
| STEP-IPF/IPF-Net[64] | Sildenafil | Advanced IPF, DLco < 35% | Improved 6-MWD ≥ 20% at 12 wk | 180 | Negative; trend for less fall in 6-MWD | Improved oxygenation, DLco, dyspnea and quality of life |
| Jackson[76] | Sildenafil | Mild to mod IPF; RVSP < 50 mm Hg | Change in 6-MWD at 6 m | 29 | Negative | |
| INSTAGE/Kolb[66] | Sildenafil with nintedanib initiation | Advanced IPF; DLco ≤ 35% | Change in quality of life (SGRQ) at 12 wk | 274 | Negative | Lower brain natriuretic peptide at 24 wk; Trend towards preservation of FVC |
| †Behr[68] | Sildenafil | IPF on stable pirfenidone; DLco ≤ 40%; At risk for PH (mPAP ≥ 20 mmHg by RHC or intermediate to high probability of PH on echo) | Composite clinical worsening at 52 wk | 177 | Negative; Disease progression in 73% of sildenafil group and 70% of placebo | Negative secondary end points of change in FVC, NT-proBNP and 6-MWD |
| †RISE-IIP/Nathan[63] | Riociguat | fIIP; FVC ≥ 45%; RHC confirmed PH: mPAP ≥ 25 mm Hg | Change in 6-MWD at 26 wk | 147 | Early termination due to increased serious adverse events | Mortality 11% in riociguat group vs. 4% in placebo |

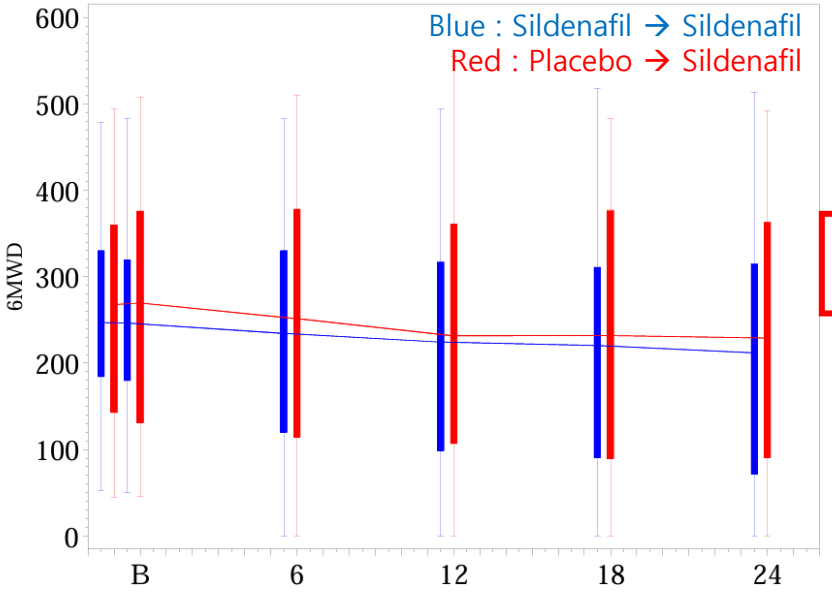
J Heart Lung Transplant. 2021;40(9):872-881

# Previous RCT – sildenafil

- Sildenafil in advanced IPF
  - inclusion criteria : DLCO < 35%
  - no thorough evaluation about PH
  - sildenafil vs. placebo for 12 weeks

  → open label sildenafil for 12 weeks

| Characteristic | Sildenafil (N=89) | Placebo (N=91) |
|---|---|---|
| Age — yr | 69.76±8.71 | 68.20±9.25 |
| Female sex — no. (%) | 14 (16) | 16 (18) |
| Supplemental use of oxygen during walk test — no. (%) | 28 (31) | 24 (26) |
| 6-Minute walk distance — m | | |
| First test | 246.93±99.11 | 267.71±127.75 |
| Second test | 246.39±103.40 | 269.55±129.83 |
| Forced vital capacity — % of predicted value | 54.89±14.00 | 58.73±14.12 |
| Carbon monoxide diffusion capacity — % of predicted value | 25.81±6.03 | 26.73±6.16 |




| 6MWD | Sildenafil → Sildenafil | Placebo → Sildenafil |
|---|---|---|
| Week 0 to 12 | -28.52 (-43.24, -13.80) | -45.22 (-59.65, -30.79) |
| Week 12 to 24 | -27.25 (-46.51, -8.00) | -16.95 (-36.35, 2.44) |

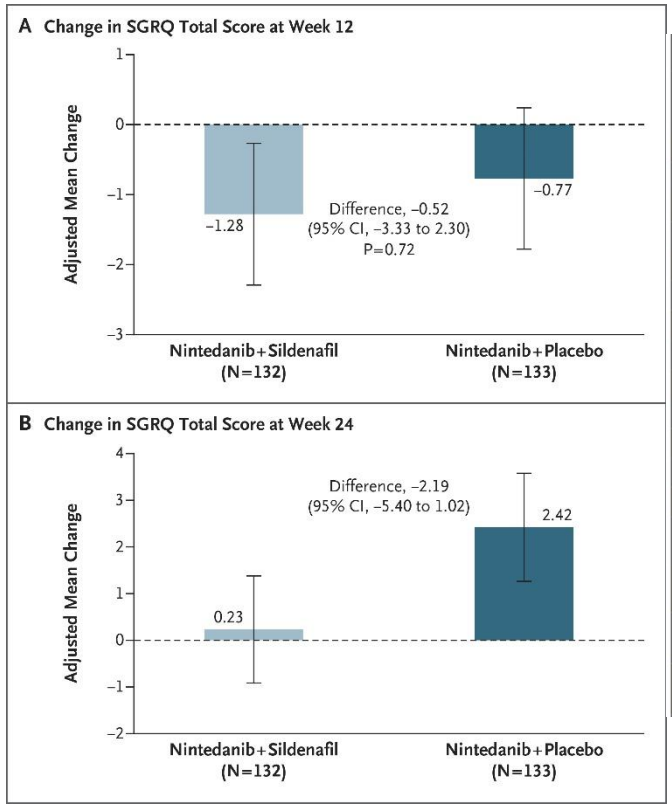
| Characteristic | Sildenafil (N=89) | Placebo (N=91) | Absolute Difference† | P Value |
|---|---|---|---|---|
| | *mean change (95% confidence interval)* | | | |
| **Dyspnea** | | | | |
| Score on Borg Dyspnea Index after walk test‡ | 0.04 (−0.30 to 0.37) | 0.37 (0.04 to 0.70) | −0.34 (−0.81 to 0.14) | 0.16 |
| Shortness of Breath Questionnaire‡ | 0.22 (−3.10 to 3.54) | 6.81 (3.53 to 10.08) | −6.58 (−11.25 to −1.92) | 0.006 |
| **Pulmonary function** | | | | |
| Forced vital capacity (% of predicted value) | −0.97 (−2.00 to 0.06) | −1.29 (−2.30 to −0.28) | 0.32 (−1.12 to 1.76) | 0.66 |
| Carbon monoxide diffusion capacity (% of predicted value) | −0.33 (−1.36 to 0.71) | −1.87 (−2.91 to −0.83) | 1.55 (0.08 to 3.01) | 0.04 |
| Partial pressure of oxygen (mm Hg) | −0.63 (−2.41 to 1.16) | −3.64 (−5.41 to −1.87) | 3.02 (0.50 to 5.53) | 0.02 |
| Partial pressure of carbon dioxide (mm Hg) | −0.01 (−0.75 to 0.73) | −0.02 (−0.75 to 0.71) | 0.01 (−1.03 to 1.05) | 0.98 |
| Alveolar–arterial gradient (mm Hg) | 0.41 (−1.54 to 2.37) | 2.95 (0.99 to 4.92) | −2.54 (−5.31 to 0.23) | 0.07 |
| Arterial oxygen saturation (%) | −0.17 (−1.02 to 0.69) | −1.38 (−2.23 to −0.52) | 1.21 (0.00 to 2.42) | 0.05 |

N Engl J Med. 2010;363(7):620-8

# Recent RCT – sildenafil + nintedanib

- INSTAGE trial – nintedanib + placebo vs. nintedanib + sildenafil in advanced IPF
  - inclusion criteria : DLCO < 35% (no thorough evaluation about PH)
  - stratified by echocardiography finding of RV dysfunction
  - primary outcome not met, but some improvements in secondary outcomes

| Characteristic | Nintedanib + Sildenafil (N=137) | Nintedanib + Placebo (N=136) |
|---|---|---|
| Age — yr | 70.3±8.6 | 70.0±7.9 |
| Male sex — no. (%) | 110 (80.3) | 106 (77.9) |
| Weight — kg | 73.7±17.7 | 74.2±15.5 |
| Time since diagnosis of IPF — yr | 2.2±1.9 | 2.1±1.8 |
| Emphysema — no. (%)† | 51 (37.2) | 45 (33.1) |
| Nintedanib treatment status — no. (%) | | |
| Not previously treated | 76 (55.5) | 87 (64.0) |
| Currently treated | 56 (40.9) | 46 (33.8) |
| Previously treated | 5 (3.6) | 3 (2.2) |
| Any echocardiographic sign indicative of right heart dysfunction — no. (%) | 61 (44.5) | 56 (41.2) |
| FVC | | |
| Mean — ml | 2246±749 | 2181±786 |
| Percentage of predicted value | 67.9±19.3 | 66.1±18.7 |
| $FEV_1$:FVC | 0.82±0.08 | 0.84±0.08 |
| $D_{LCO}$ — % of predicted value‡ | 25.8±6.8 | 25.6±7.0 |

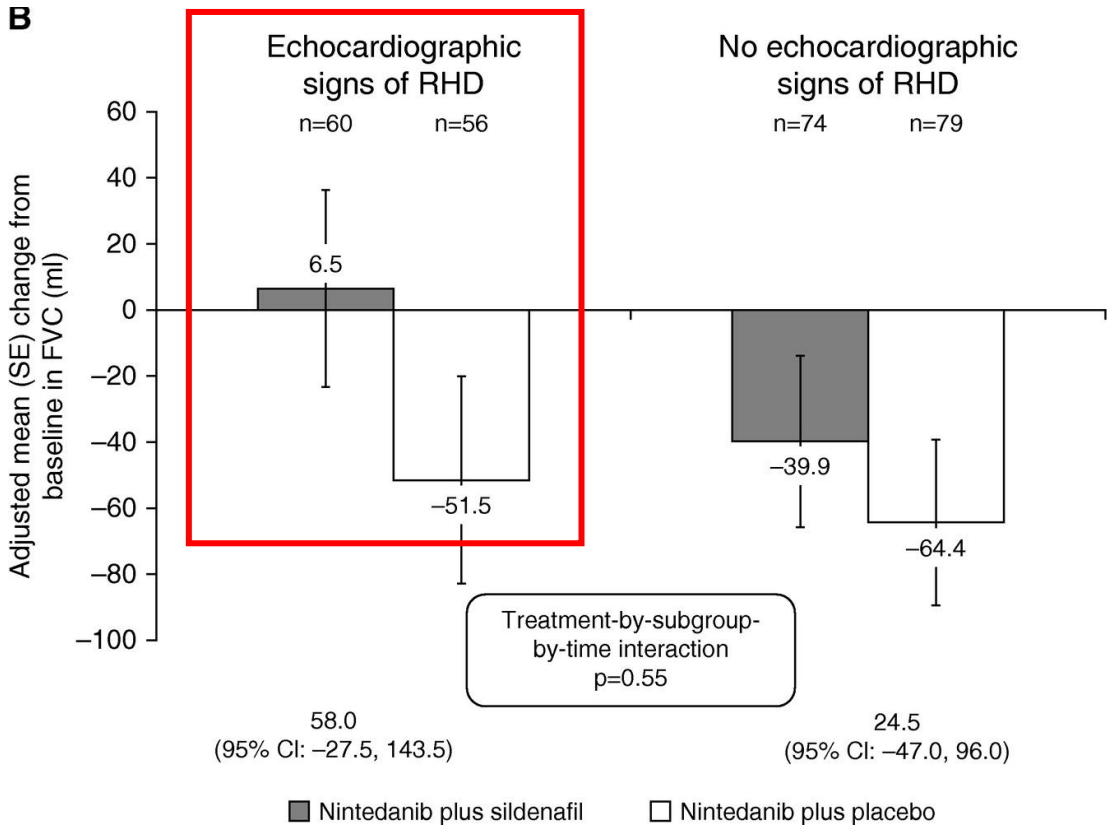


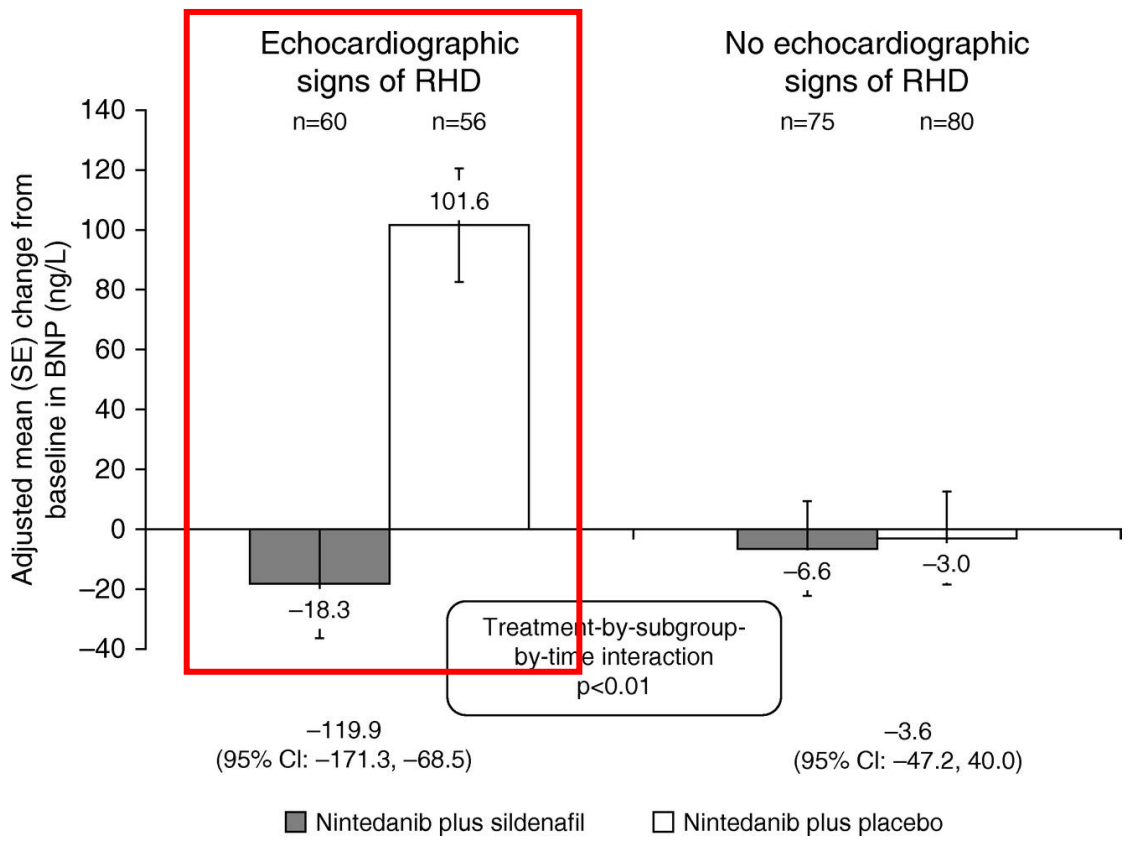

| End Point | Nintedanib + Sildenafil | | Nintedanib + Placebo | | Difference (95% CI) |
|---|---|---|---|---|---|
| | No. of Patients | Mean Change from Baseline | No. of Patients | Mean Change from Baseline | |
| FVC — ml | | | | | |
| At wk 12 | 119 | 7.0±15.9 | 124 | −25.5±15.7 | 32.5 (−11.6 to 76.6) |
| At wk 24 | 109 | −20.8±19.7 | 108 | −58.2±19.6 | 37.4 (−17.4 to 92.3) |
| Rate of FVC decline — ml/24 wk† | 137 | −20.4±19.7 | 136 | −66.7±19.5 | 46.3 (−8.3 to 100.9) |
| FVC — % of predicted value | | | | | |
| At wk 12 | 119 | 0.4±0.5 | 124 | −0.9±0.5 | 1.3 (−0.1 to 2.8) |
| At wk 24 | 109 | −0.5±0.6 | 108 | −1.9±0.6 | 1.4 (−0.3 to 3.1) |
| Oxygen saturation — % | | | | | |
| At wk 12 | 121 | 0.20±0.27 | 127 | 0.26±0.26 | −0.05 (−0.80 to 0.69) |
| At wk 24 | 113 | 0.03±0.32 | 111 | −0.32±0.32 | 0.35 (−0.55 to 1.25) |
| $D_{LCO}$ — % of predicted value | | | | | |
| At wk 12 | 114 | 1.3±0.7 | 120 | −0.4±0.7 | 1.7 (−0.3 to 3.7) |
| At wk 24 | 105 | −0.7±0.7 | 101 | −1.6±0.7 | 0.9 (−1.1 to 2.9) |
| Brain natriuretic peptide level at wk 24 — ng/liter | 108 | −11.6±12.1 | 106 | 39.7±12.0 | −51.3 (−85.1 to −17.6) |
| **Time-to-event analyses** | **No. of Patients** | **No. of Patients with Event (%)** | **No. of Patients** | **No. of Patients with Event (%)** | **Hazard Ratio (95% CI)** |
| Absolute decline of ≥5 percentage points in predicted FVC value or death | 137 | 43 (31.4) | 136 | 69 (50.7) | 0.56 (0.38 to 0.82) |
| Relative decline of ≥10% in predicted FVC value or death | 137 | 35 (25.5) | 136 | 50 (36.8) | 0.68 (0.44 to 1.05) |

N Engl J Med. 2018;379(18):1722-1731

# Recent RCT – sildenafil + nintedanib

- Post-hoc analysis regarding secondary outcomes
  - favorable response regarding FVC and BNP level
  - particularly for patients with RV dysfunction



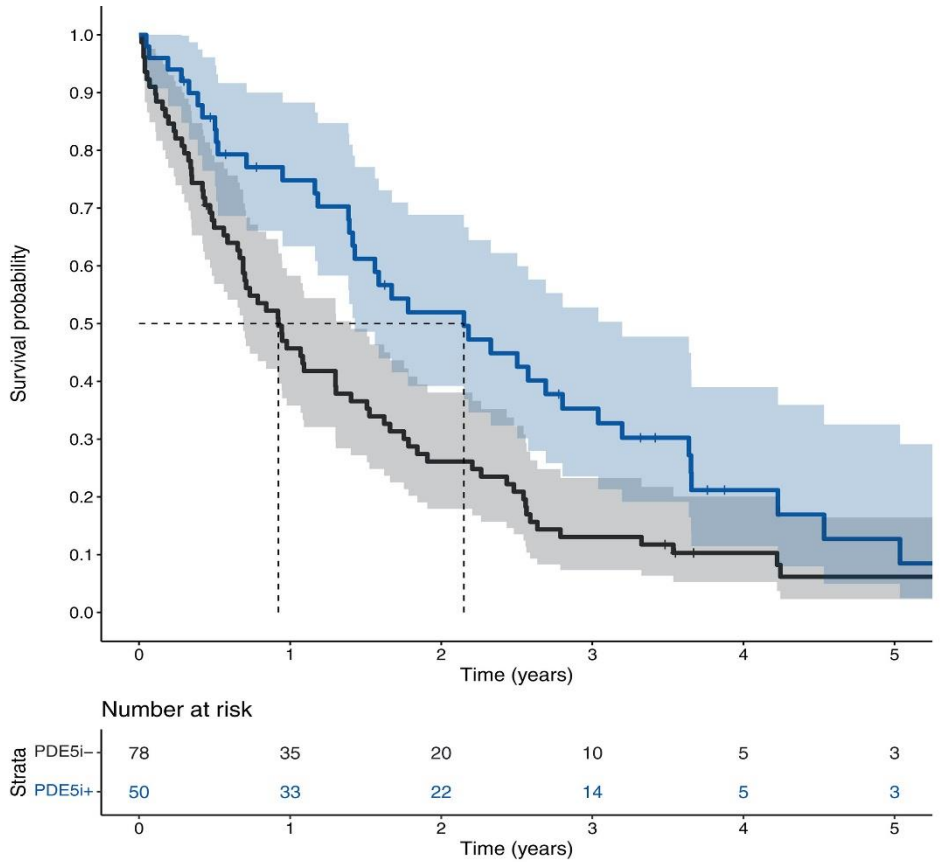




Am J Respir Crit Care Med. 2019;200(12):1505-1512

# Retrospective study of sildenafil in PH-ILD

- Single center study : PH referral center in UK)
  - Brompton Hospital National Pulmonary Hypertension Service at London
  - 128 patients : IPF 74, HP 17, NSIP 12, unclassifiable 8, others 17

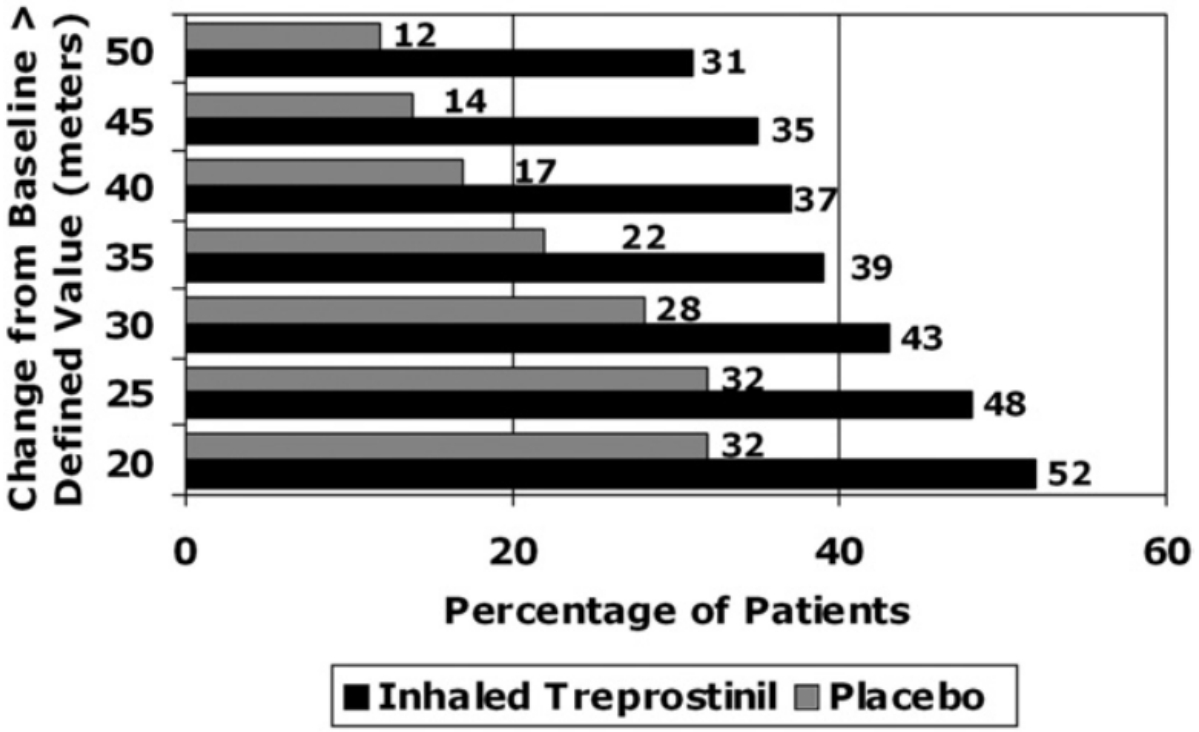
| | PDE5 inhibitor + | PDE5 inhibitor - |
|---|---|---|
| Number (%) | 50 (47) | 78 (53) |
| Demographics | | |
| Age, years | 64.8 ± 12.1 | 67.4 ± 10.3 |
| Gender, F/M | 29/21 | 58/20 |
| Spirometry | | |
| FVC, % predicted | 57 (51–73) | 52 (45–66) |
| DLCO, % predicted | 25 (19–34) | 26 (20–33) |
| Hemodynamics | | |
| mPAP, mmHg | 38 (34–43) | 35 (31–38) |
| PCWP, mmHg | 11 ± 5 | 10 ± 4 |
| CO, L/min | 4.1 (3.7–4.8) | 4.3 (3.8–4.9) |
| PVR, WU | 6.7 (5.7–8.5) | 6.0 (4.8–7.8) |
| Echocardiography | | |
| TAPSE, cm | 1.7 ± 0.4 | 1.9 ± 0.4 |
| Others | | |
| 6MWD, m | 258 ± 92 | 222 ± 93 |
| BNP, ng/L | 135 (48–281) | 72 (23–205) |

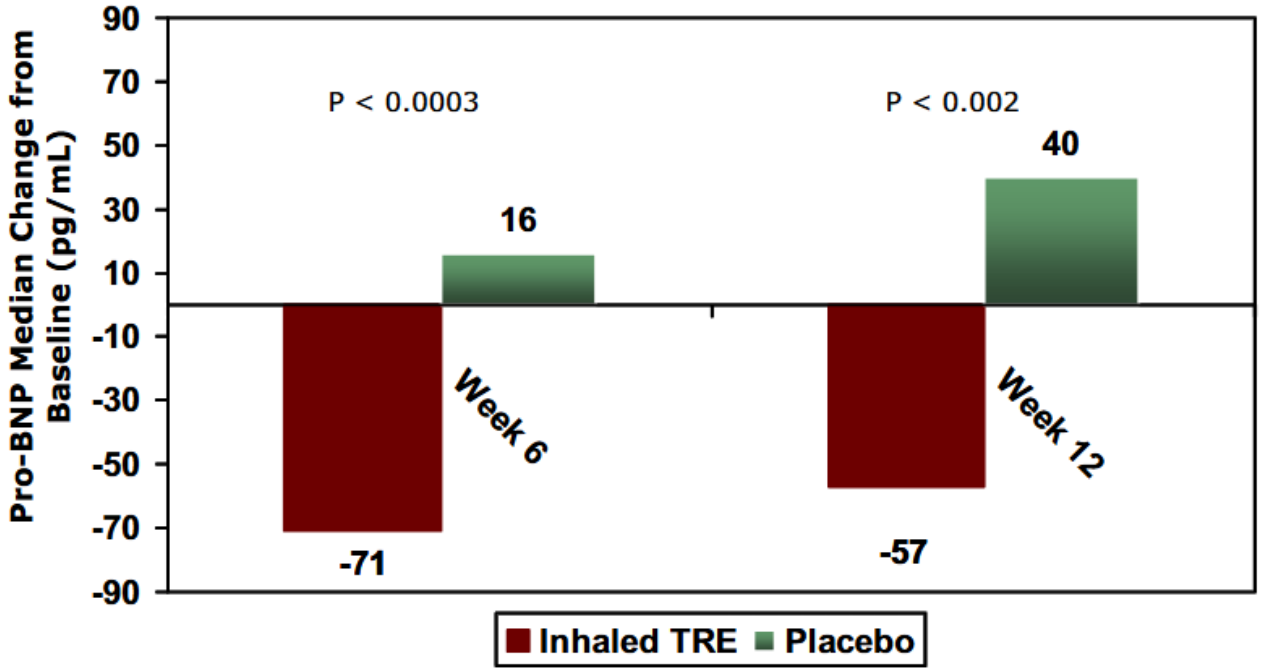



Respirology. 2023;28(3):262-272

# Inhaled treprostinil

- Previously approved for PAH
  - add-on treatment while on sildenafil or bosentan
- Inhaled iloprost & Inhaled treprostinil
  - an option for PAH patients who decline or cannot tolerate parenteral prostanoids




J Am Coll Cardiol. 2010;55(18):1915-22

# Success of inhaled treprostinil in PH-ILD

- INCREASE trial
- More sophisticated inclusion criteria (like trials of PAH)
  - right heart catheterization : mean PAP ≥ 25 mmHg, PCWP ≤ 15 mmHg, PVR > 3 WU
  - not restricted to IPF, but in case of CTD-ILD, FVC < 70%
- Used nebulizer : ultrasound, pulsed-delivery
  - 3 breaths 4 times/day → 9~12 breaths 4 times/day
- Primary endpoint : 6MWD



(Treatment Tracker example)

N Engl J Med. 2021 Jan 28;384(4):325-334

# INCREASE trial – main results

- Patient characteristics

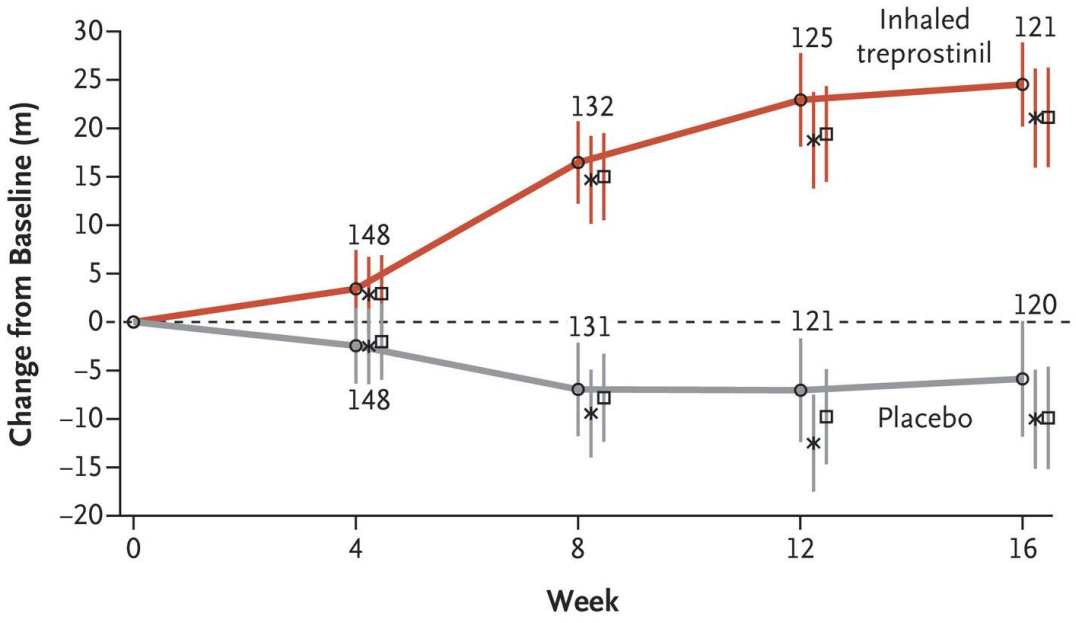
| Characteristic | Inhaled Treprostinil (N=163) | Placebo (N=163) | All Patients (N=326) |
|---|---|---|---|
| Female sex — no. (%) | 85 (52.1) | 68 (41.7) | 153 (46.9) |
| Mean age at randomization (range) — yr | 65.6 (26–90) | 67.4 (36–85) | 66.5 (26–90) |
| Age distribution — no. (%) | | | |
| <65 yr | 64 (39.3) | 48 (29.4) | 112 (34.4) |
| 65 to <80 yr | 83 (50.9) | 100 (61.3) | 183 (56.1) |
| ≥80 yr | 16 (9.8) | 15 (9.2) | 31 (9.5) |
| Cause of lung disease — no. (%) | | | |
| Idiopathic interstitial pneumonia | 65 (39.9) | 81 (49.7) | 146 (44.8) |
| Chronic hypersensitivity pneumonitis | 10 (6.1) | 9 (5.5) | 19 (5.8) |
| Occupational lung disease | 5 (3.1) | 1 (0.6) | 6 (1.8) |
| Combined pulmonary fibrosis and emphysema | 42 (25.8) | 40 (24.5) | 82 (25.2) |
| Connective tissue disease | 40 (24.5) | 32 (19.6) | 72 (22.1) |
| Other | 1 (0.6) | 0 | 1 (0.3) |
| Idiopathic interstitial pneumonia subcategory — no. (%) | | | |
| Idiopathic pulmonary fibrosis | 37 (22.7) | 55 (33.7) | 92 (28.2) |
| Idiopathic nonspecific interstitial pneumonia | 21 (12.9) | 16 (9.8) | 37 (11.3) |
| Respiratory bronchiolitis associated with interstitial lung disease | 2 (1.2) | 0 | 2 (0.6) |
| Desquamative interstitial pneumonia | 0 | 1 (0.6) | 1 (0.3) |
| Acute interstitial pneumonia | 0 | 1 (0.6) | 1 (0.3) |
| Unclassified idiopathic interstitial pneumonia | 5 (3.1) | 8 (4.9) | 13 (4.0) |
| Use of supplemental oxygen — no. (%) | 119 (73.0) | 114 (69.9) | 233 (71.5) |
| Background therapy — no. (%) | | | |
| None | 133 (81.6) | 119 (73.0) | 252 (77.3) |
| Pirfenidone only | 19 (11.7) | 25 (15.3) | 44 (13.5) |
| Nintedanib only | 11 (6.7) | 19 (11.7) | 30 (9.2) |

| | Inhaled Treprostinil (N=163) | Placebo (N=163) |
|---|---|---|
| 6-minute walk distance, meters; mean (range) | 254.1 (100-538) | 265.1 (30-505) |
| Median | 256.0 | 260.0 |
| Pulmonary vascular resistance, Woods units; mean (range) | 6.369 (3.11-18.05) | 6.013 (3.06-17.62) |
| Median | 5.570 | 5.060 |
| NT-proBNP, pg/mL; mean (range) | 1857.53 (10.2-21942.0) | 1808.86 (23.0-16297.0) |
| Median* | 550.50 | 420.80 |
| Pulmonary arterial pressure, mmHg; mean (range) | 37.2 (25-74) | 36.0 (25-61) |
| Median | 35.0 | 35.0 |
| Pulmonary capillary wedge pressure, mmHg; mean (range) | 10.1 (2-20) | 9.6 (0-15) |
| Median | 10.0 | 10.0 |
| Pulmonary function tests | | |
| $FEV_1$ % Predicted; mean (range) | 63.9 (23, 120) | 65.0 (22, 145) |
| Median | 63.0 | 63.0 |
| FVC % Predicted; mean (range) | 62.5 (24, 130) | 63.8 (20, 134) |
| Median | 60.0 | 61.0 |
| TLC % Predicted; mean (range) | 62.9 (25, 126) | 64.2 (30, 109) |
| Median | 62.0 | 62.5 |
| DLCO % Predicted; mean (range) | 30.0 (5, 86) | 28.1 (1, 86) |
| Median | 29.0 | 26.0 |

N Engl J Med. 2021 Jan 28;384(4):325-334

# INCREASE trial – main results

- Change in 6MWD

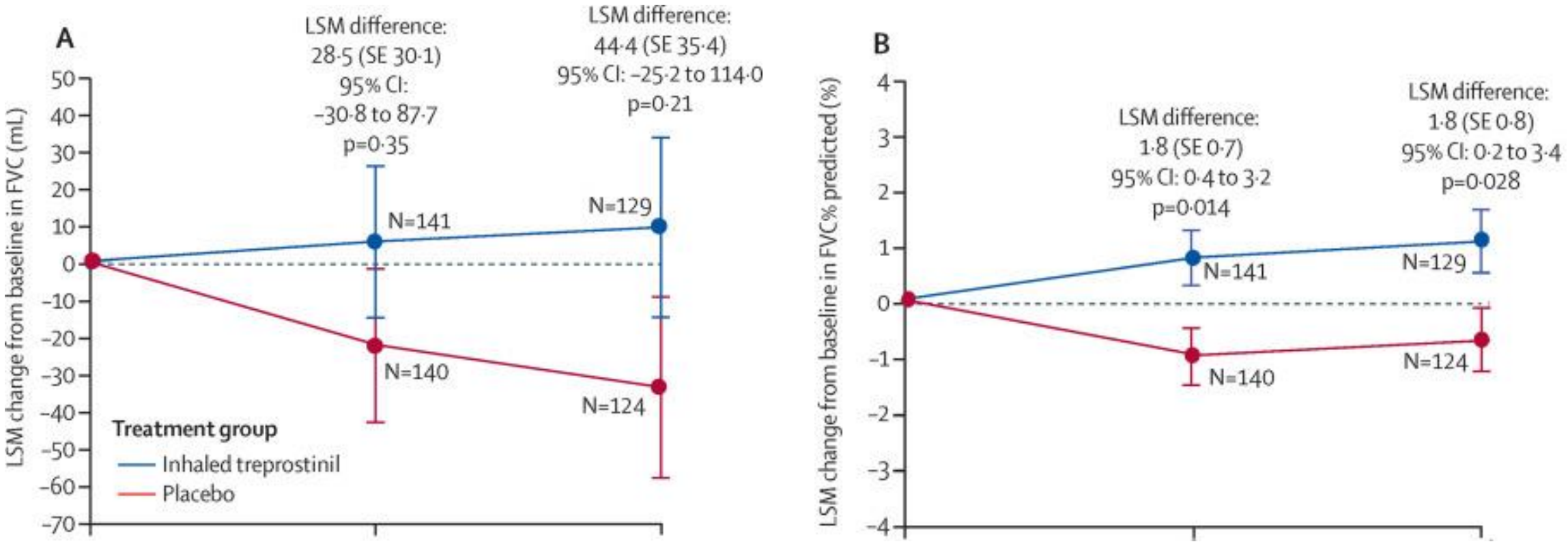



| Subgroup | Inhaled Treprostinil # Patients | Placebo # Patients | LS Mean Difference (95% CI) |
|---|---|---|---|
| Overall | 121 | 120 | 31.1 (16.9, 45.4) |
| Age Group | | | |
| <65 years | 48 | 32 | 27.0 (-2.2, 56.1) |
| 65 to 80 years | 63 | 78 | 32.9 (15.2, 50.5) |
| ≥80 years | 10 | 10 | 28.3 (-16.2, 72.9) |
| Sex | | | |
| Male | 55 | 68 | 24.3 (6.1, 42.5) |
| Female | 66 | 52 | 36.9 (13.7, 60.0) |
| Baseline 6MWD Category | | | |
| ≤350 meters | 99 | 100 | 33.8 (18.0, 49.6) |
| >350 meters | 22 | 20 | 14.6 (-19.5, 48.7) |
| Baseline DLCO (% Predicted) | | | |
| <40% | 90 | 98 | 33.0 (17.7, 48.3) |
| ≥40% | 23 | 18 | 10.7 (-23.5, 45.0) |
| PH-ILD Etiology | | | |
| Idiopathic Interstitial Pneumonia | 48 | 62 | 39.5 (18.3, 60.7) |
| Combined Pulmonary Fibrosis and Emphysema | 30 | 28 | 7.9 (-15.4, 31.3) |
| Connective Tissue Disease | 34 | 24 | 43.5 (9.6, 77.4) |
| Other | 9 | 6 | 22.4 (-61.4, 106.3) |
| Baseline PVR Category | | | |
| <4 Wood units | 27 | 25 | --7.6 (-30.9, 15.6) |
| ≥4 Wood units | 94 | 95 | 40.8 (24.1, 57.6) |
| Maximum Study Drug Dose | | | |
| 4-6 breaths | 6 | 2 | -9.5 (-52.2, 33.1) |
| 7-9 breaths | 37 | 24 | 17.7 (-10.9, 46.2) |
| 10-12 breaths | 77 | 92 | 33.7 (15.8, 51.7) |
| >12 breaths | 1 | 2 | |


N Engl J Med. 2021 Jan 28;384(4):325-334

# INCREASE trial – post-hoc results

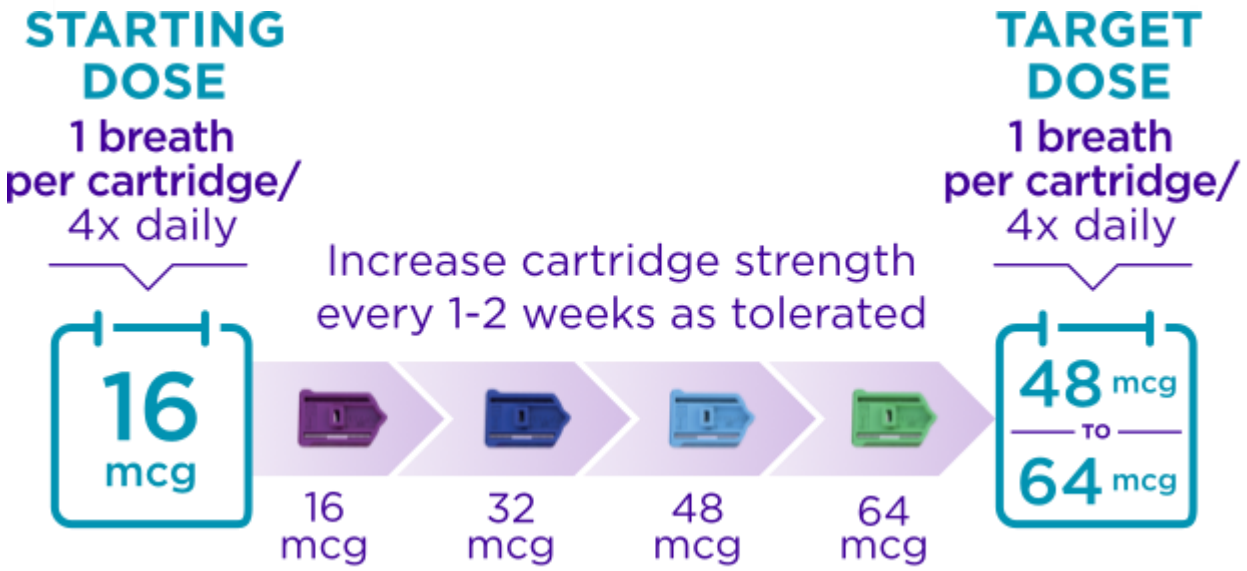
- Change in FVC




Lancet Respir Med. 2021;9(11):1266-1274

# DPI formulation of treprostinil

- Better compliance
  - conveniently portable
  - single-dose cartridges
  - 1 breath per cartridge
- Still 4 times / day



# Failure of inhaled treprostinil in COPD

- PERFECT trial – terminated d/t safety concern (increased risk of SAE)
- Premature data, but no change in 6MWD

| | Enrolled | Randomised | |
|---|---|---|---|
| | iTRE (run-in) (n=108) | iTRE[#] (blinded) (n=66) | Placebo (blinded) (n=58) |
| **Total TEAEs** | 165 | 178 | 122 |
| Subjects with ⩾1 TEAEs | 67 (62.0) | 47 (71.2) | 38 (65.5) |
| **SAEs** | 10 | 26 | 20 |
| Subjects with ⩾1 SAEs | 9 (8.3) | 17 (25.8) | 6 (10.3) |
| **TEAEs related to study treatment** | 115 | 77 | 32 |
| Subjects with ⩾1 TEAEs related to study treatment | 48 (44.4) | 29 (43.9) | 15 (25.9) |
| **TEAEs leading to treatment discontinuation** | 15 | 11 | 6 |
| Subjects with ⩾1 TEAEs leading to treatment discontinuation | 11 (10.2) | 8 (12.1) | 3 (5.2) |
| **TEAEs leading to study discontinuation** | 24 | 14 | 12 |
| Subjects with ⩾1 TEAEs leading to study discontinuation | 16 (14.8) | 10 (15.2) | 2 (3.4) |

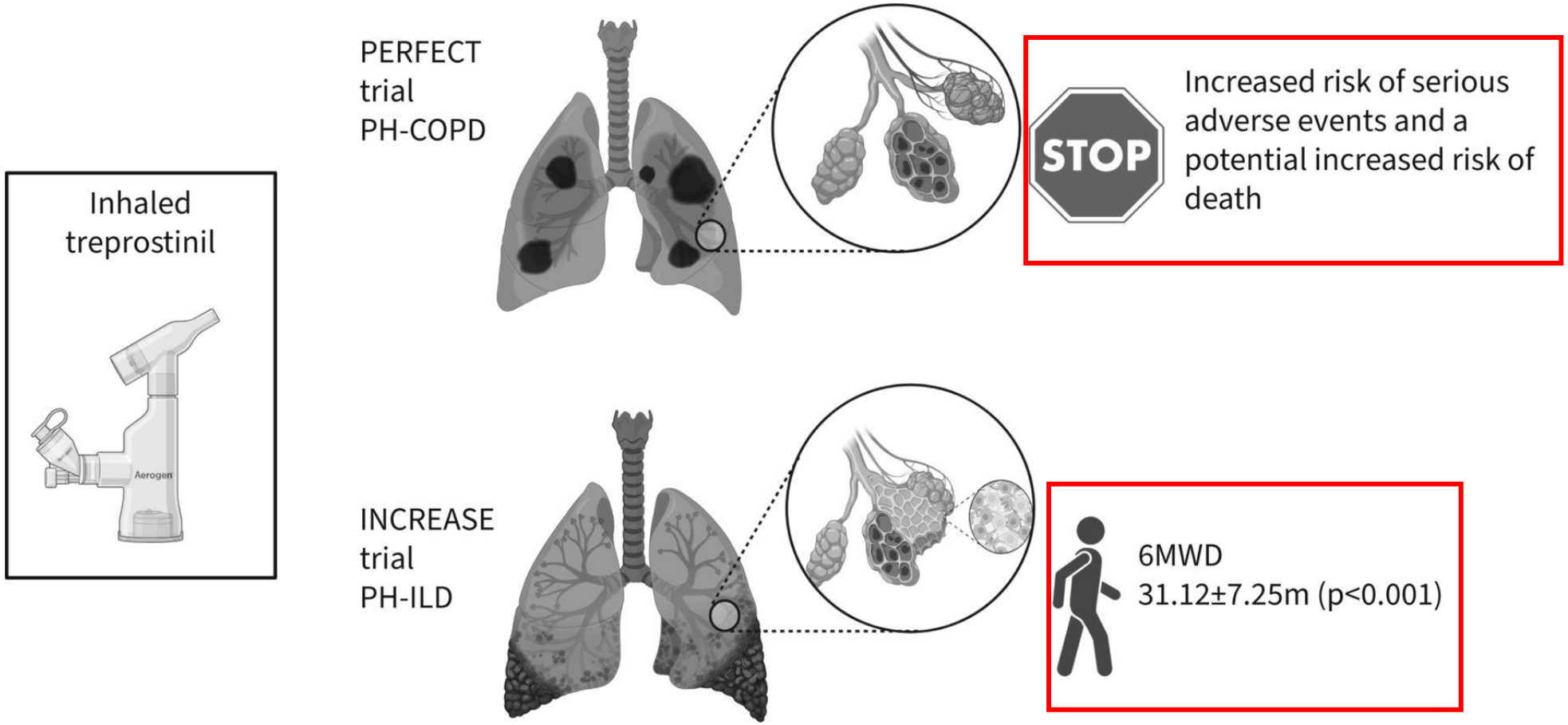
| | Enrolled | Randomised | |
|---|---|---|---|
| | iTRE (run-in) n=108 | iTRE[#] (blinded) n=66 | Placebo (blinded) n=58 |
| Respiratory, thoracic and mediastinal disorders | 46 (42.6) | 35 (53.0) | 22 (37.9) |
| Dyspnoea | 19 (17.6) | 19 (28.8) | 9 (15.5) |
| Cough | 16 (14.8) | 11 (16.7) | 3 (5.2) |
| Oropharyngeal pain | 9 (8.3) | 3 (4.5) | 2 (3.4) |
| Productive cough | 5 (4.6) | 4 (6.1) | 2 (3.4) |
| COPD | 5 (4.6) | 6 (9.1) | 4 (6.9) |
| Hypoxia | 4 (3.7) | 4 (6.1) | 3 (5.2) |
| Throat irritation | 5 (4.6) | 3 (4.5) | 0 |
| Acute respiratory failure | 3 (2.8) | 0 | 3 (5.2) |

| | Original crossover | |
|---|---|---|
| | iTRE (n=60) | Placebo (n=52) |
| **Baseline[#]** | | |
| Patients (n) | 38 | 42 |
| 6MWD (m) | | |
| Mean±SD | 222.71±77.80 | 228.60±75.21 |
| Median | 234.00 | 242.50 |
| Minimum[¶]–maximum | 64.0–396.0 | 78.0–358.0 |
| **Week 12[+]** | | |
| Patients (n) | 38 | 42 |
| 6MWD (m) | | |
| Mean±SD | 218.24±74.29 | 223.45±87.22 |
| Median | 224.00 | 233.50 |
| Minimum–maximum | 61.0–373.0 | 43.0–416.0 |
| **Change from baseline[§]** | | |
| Patients (n) | 38 | 42 |
| 6MWD (m) | | |
| Mean±SD | −4.47±39.01 | −5.14±50.71 |
| Median | 0.00 | 0.00 |
| Minimum–maximum | −85.0–78.0 | −176.0–124.0 |

Eur Respir J. 2024;63(6):2400172

# Inhaled treprostinil in PH-ILD vs. PH-COPD

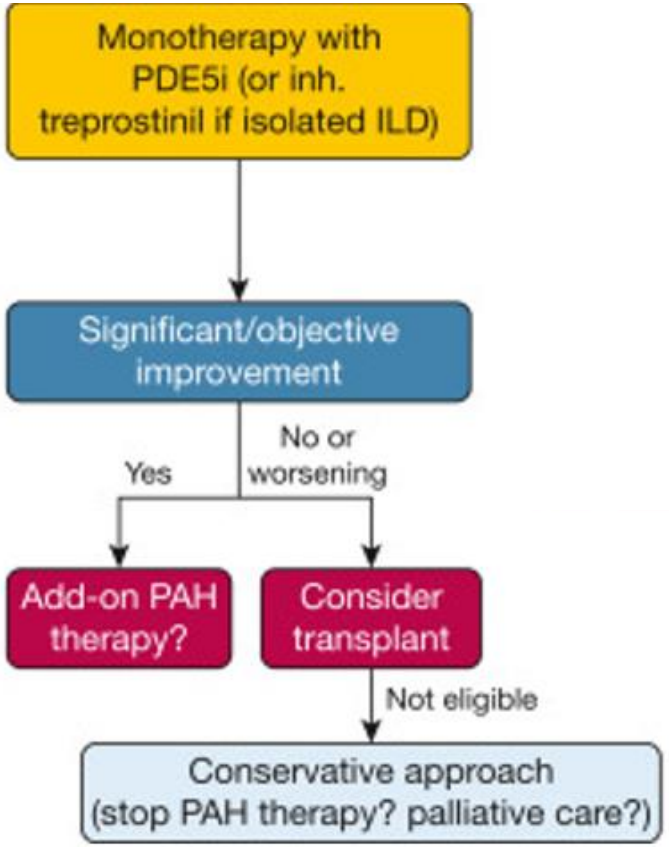
- PH-ILD may be quite different from PH-COPD
  - fibrotic disease vs. inflammatory disease




Breathe. 2025;21(1):240242

# Response monitoring after therapeutic trial

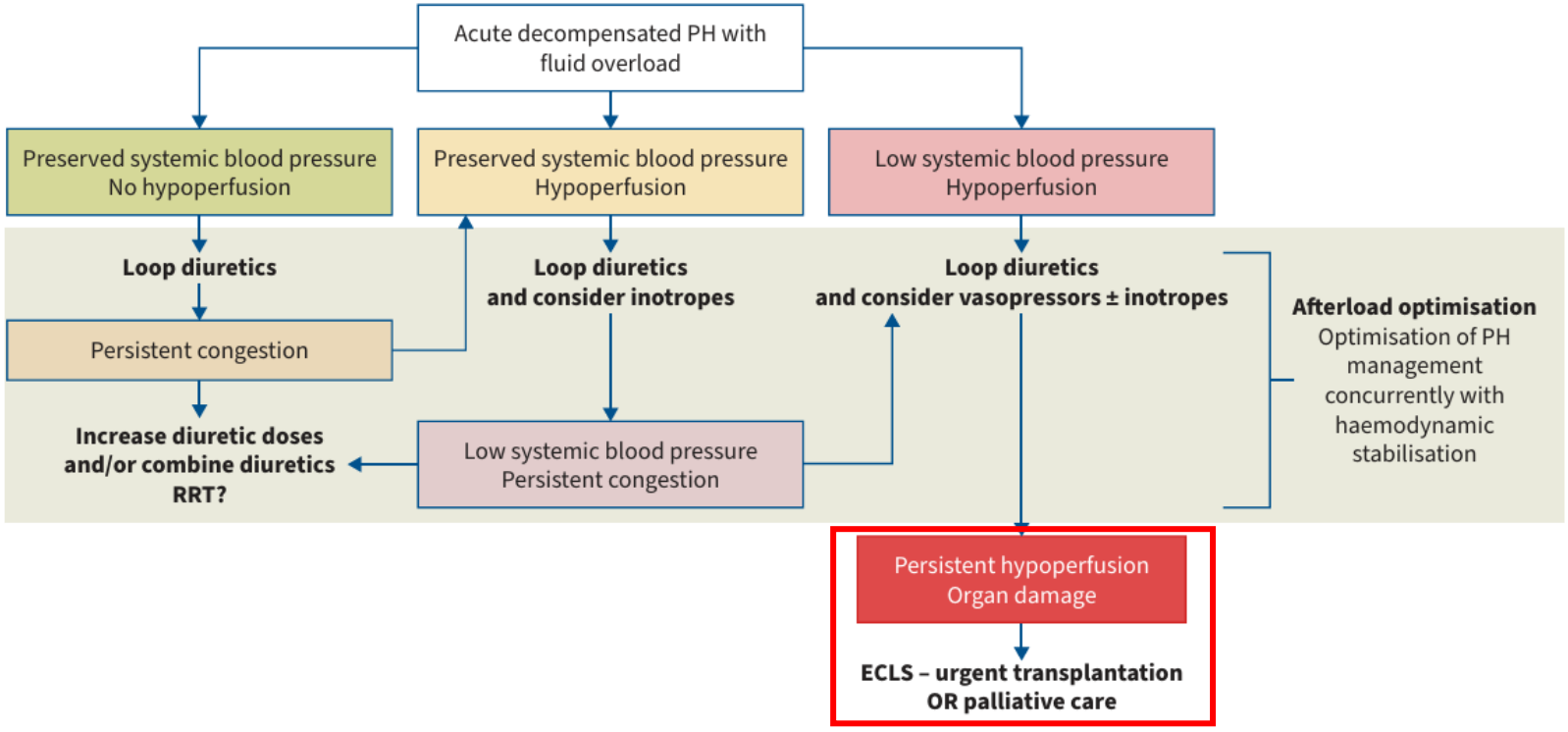
- Consider lung transplantation as soon as possible if not responsive to PAH therapy
- Consider combination of other PAH therapy if response to initial PAH therapy
- Clinical trial may be another option




Chest. 2024;165(3):682-691

# Acutely decompensated setting

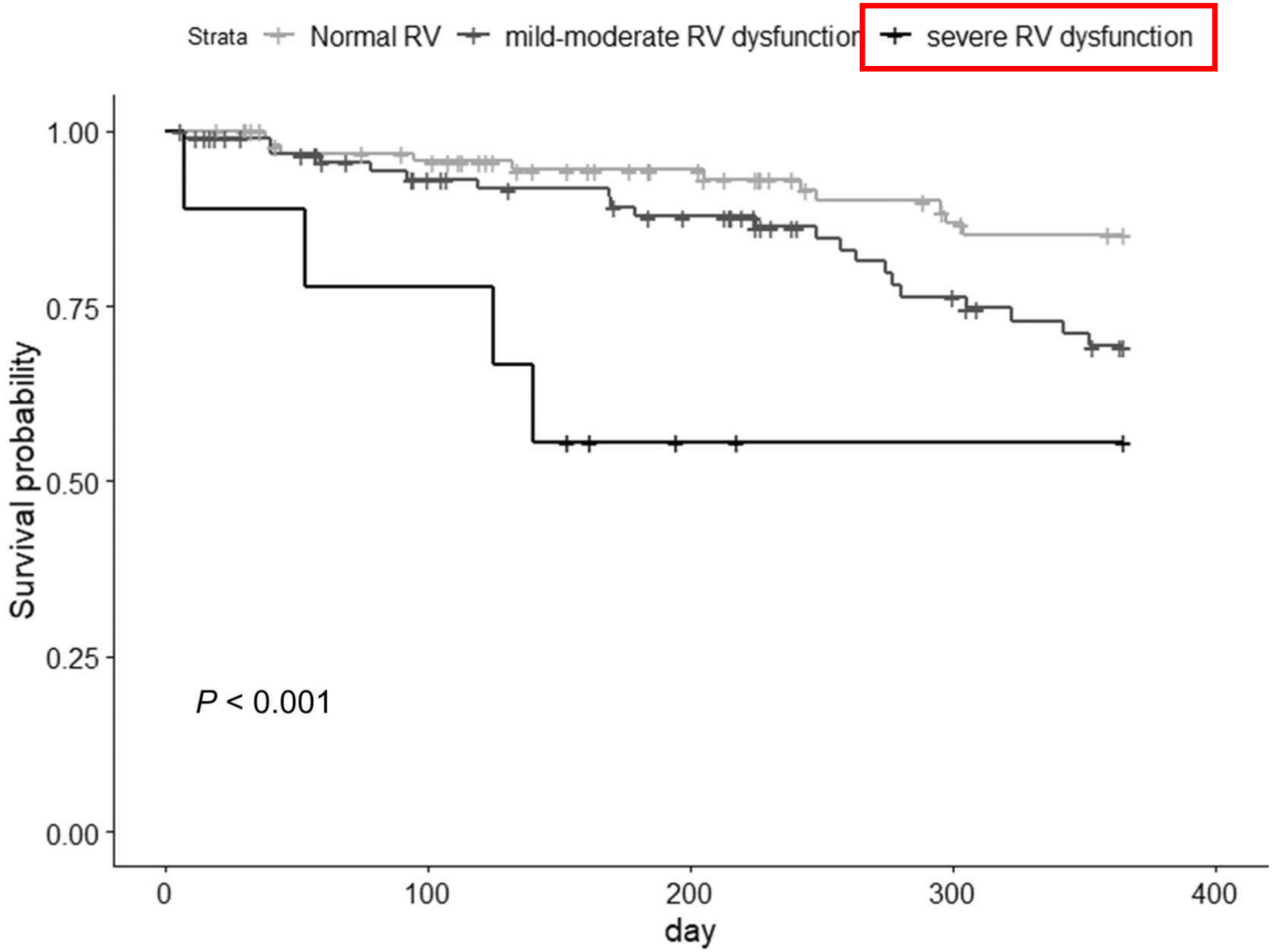
- Hemodynamic stabilization
  - Preload optimization : diuresis, renal replacement therapy
  - Afterload optimization : inhaled nitric oxide
  - Inotrope +/- vasopressor
- Bridge-to-transplantation




Eur Respir J. 2024;64(4):2401193

# Lung transplantation as a last resort

- Major consideration – Presence of RV dysfunction
- 203 patients on waiting list for lung transplantation at AMC




J Heart Lung Transplant. 2025 online ahead

# Thank you for your attention