# PAH Clinical Research Highlights: CHEST 2024

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Accredited Continuing Education

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This program is supported by independent medical education grants from Merck and Mallinckrodt Pharmaceuticals.

# What is PAH?

- Pulmonary arterial hypertension (PAH) is rare condition that, as the name implies, involves hypertension in the pulmonary arteries.
- Symptoms include dyspnea during exercise and fainting spells, dizziness, swelling of the ankles or legs, chest pain, and a racing pulse.
- Some cases of PAH are due to genetic changes in the *BMPR2* gene and are inherited in an autosomal dominant pattern. Diagnosis is based on the symptoms, clinical examination, and specialized testing.
- There are a number of treatments approved to manage symptoms of PAH including phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostacyclin pathway agents including infusions, activin signaling inhibitors and combination therapies. Other therapies may also include blood thinners, anti-hypertensive agents, oxygen therapy, etc.
- Since it is a rare condition, data presented at large medical conferences, like CHEST 2024, can get overlooked.

Chin et al. Treatment algorithm for pulmonary arterial hypertension. *Eur Resp J.* 2024:64: 2401325.

# CHEST 2024

- American College of Chest Physicians Annual Meeting
- Held October 6-9, 2024, in Boston, Massachusetts
- One of the largest gatherings of clinicians and researchers focused on pulmonary medicine
- Abstracts published annually in supplement issue of *CHEST*

# Selected Clinical Trials Presented at CHEST 2024

# Self Reflective Question

“How do you stay updated on the latest clinical trial data, and what strategies do you use to effectively synthesize and apply that information to your clinical practice?”

# Long-Term Safety and Efficacy of Treprostinil Inhalation Powder – BREEZE Study

| Parameter | Baseline | Week 107 (N=19) | Week 131 (N=16) | Change from Baseline |
|---|---|---|---|---|
| 6MWD (meters) | 420 | 446 | 454 | +15 m (Week 107)<br>+14 m (Week 131) |
| PQ-ITD Satisfaction | - | 87% 'strongly agree' | - | N/A |
| Mean Dose | - | 72 ug QID | - | Max dose: 176 ug QID |
| Common Adverse Events (%) | - | - | - | 14% cough,<br>14% headache,<br>12% dizziness,<br>12% dyspnea<br>No serious Treatment-Related Adverse Events (TR-AEs) |

**Objective:** Assess long-term safety, tolerability, and clinical outcomes

**Design:** Pts transitioned to treprostinil inhalation powder (QID). Optional extension phase with dose titration

**Conclusion:** Treprostinil inhalation powder was well-tolerated, no serious AEs

Spikes LA et al. Long-term outcomes and dosing in the breeze study optional extension phase. *CHEST* 2024:166 (suppl): A6061–A6063.

# Real World Studies

# Self Reflective Question

“Are you familiar with Real-World Evidence (RWE) studies, and how do you incorporate their findings into your clinical practice?”

# Medication Up-Titration and Safety Using Midodrine

**Objective**: Assess effectiveness of midodrine in facilitating PAH medication up-titration

**Design**: Retrospective analysis of 433 PAH pts at Houston Methodist Lung Center (2005–2022)

- 57 pts prescribed midodrine; matched 1:1 with a control group

**Conclusion**: Midodrine was well tolerated and safe, showing no adverse hemodynamic effects

| Parameter | Midodrine Group (N=57) | Control Group (N=57) | P-Value |
|---|---|---|---|
| Pts w/ Medication Up-Titration | 30 | 17 | <0.05 |
| Selexipag Dose Increase | Yes | No | <0.05 |
| Epoprostenol Dose Increase | Yes | No | <0.001 |
| Treprostinil Dose Increase | Yes | No | <0.05 |
| Hemodynamic Compromise | None | None | N/A |
| Bradycardia | None | None | N/A |

Safdar Z et al. Hemodynamic effects of midodrine in pulmonary arterial hypertension. *CHEST* 2024:166 (suppl): A6522–A6523.

# Tolerability of Inhaled Treprostinil

| Group | FEV1/FVC Ratio | TAPSE (cm) | Cardiac Output (L/min) | Cardiac Index (L/min/m²) |
|---|---|---|---|---|
| Tolerant (N=34) | 81.2 | 2.1 | 4.5 | 2.4 |
| Intolerant (N=5) | 68.3 | 1.7 | 3.9 | 2.2 |
| Semi-Tolerant (N=4) | 66.8 | 1.6 | 3.3 | 1.9 |

**Objective:** Identify factors influencing tolerability of inhaled treprostinil in PAH and pulmonary hypertension associated with interstitial lung disease (PH-ILD)

**Design:** Retrospective analysis of 43 pts (21 PAH); stratified into groups based on tolerance

**Conclusion:** Obstructive lung disease and RV dysfunction may be linked to reduced tolerance of inhaled treprostinil. (Trends observed, but not statistically significant)

Diaz AL et al. Evaluating the tolerability of inhaled treprostinil in patients with PAH and PH-ILD: A comprehensive analysis of pulmonary function, echocardiogram, and hemodynamic testing. *CHEST* 2024:166 (suppl): A5892–A5893.

# Impact of SGLT2 Inhibitors (SGLT2i) on Mortality

**Objective**: Evaluate association between SGLT2i and all-cause mortality

**Design:** Retrospective analysis using TrinetX platform (2013-2023)

- Group A: 6,238 pts on SGLT2i
- Group B: 6,243 pts not on SGLT2i

**Conclusion:** SGLT2i use associated w/ reduced mortality at 1-, 3-, and 5-year follow-up

| Follow-up Period | Group A (SGLT2i) | Group B (Non-SGLT2i) | Risk Reduction | P-Value |
|---|---|---|---|---|
| **1 Year** | 8.1% mortality | 15.5% mortality | 7.4% | <0.0001 |
| **3 Years** | 13% mortality | 22.5% mortality | 9.2% | <0.0001 |
| **5 Years** | 14.6% mortality | 25% mortality | 10.4% | <0.0001 |

Lemonjava I et al. Impact of SGLT2 inhibitors on mortality in pulmonary arterial hypertension: Exploring the association. *CHEST* 2024:166 (suppl): A5793.

# Ethnic Differences in PAH Treatment Patterns and Outcomes with Macitentan

| Characteristic | HL Patients | nHL Patients |
|---|---|---|
| Median Age at Diagnosis | 53 years | 60 years |
| Congenital Heart Disease | 12.8% | 5.3% |
| Idiopathic/Heritable PAH | 49.5% | 57.0% |
| Obesity | 34.2% | 29.2% |
| 1-Year Survival Estimate | 93.8% | 89.9% |
| 1-Year Freedom from Hospitalization | 62.5% | 59.2% |
| Adverse Events | 74.5% | 81.5% |

**Objective:** Evaluate characteristics, treatment patterns, and outcomes for Hispanic/Latino (HL) vs non-Hispanic/Latino (nHL) pts w/ PAH using macitentan

**Design:** Combined dataset of 4626 PAH patients (517 HL, 3907 nHL)

**Conclusion:** HL pts were younger at diagnosis, more likely to have congenital heart disease, and had delayed therapy initiation compared to nHL pts

Melendres-Groves L et al. Characteristics, treatment patterns, and outcomes of pulmonary arterial hypertension patients by ethnicity: Real-world data from the combined OPUS/ORPHEUS studies. *CHEST* 2024:166 (suppl): A5777–A5780.

# Macitentan Outcomes in Black/African American vs. White Patients with PAH

**Objective**: Compare PAH treatment patterns and outcomes by race

**Design:** Descriptive analysis of 4626 pts w/ PAH from OPUS/OrPHeUS studies

**Conclusion:** Black/AA pts had more comorbidities and higher hospitalization rates, but overall treatment and survival were similar to White pts

| Metric | Black/AA | White |
|---|---|---|
| Median age (years) | 57 | 61 |
| Female (%) | 81.5% | 74.1% |
| Connective tissue PAH (%) | 33.0% | 25.1% |
| 1-year survival (%) | 89.6% | 90.3% |
| Freedom from hospitalization (%) | 52.5% | 61.2% |
| Persistence on macitentan (%) | 70.1% | 69.6% |

McLaughlin V et al. Characteristics, treatment patterns, and outcomes of patients with pulmonary arterial hypertension by race: Real-world data from the combined OPUS/ORPHEUS studies. *CHEST* 2024:166 (suppl): A5773–A5776.

# Real-World Treatment Approaches in PAH

**Objective**: Explore real-world PAH treatment approaches and how they differ by site of care and risk status

**Design:** Survey (Nov 2023–Feb 2024) w/ pulmonologists and cardiologists, providing data on 768 pts w/ PAH

**Conclusion:** Despite guideline recommendations, many pts remain on monotherapy, particularly lower-risk pts and in certain care settings

| Treatment Approach | Percentage of Pts |
|---|---|
| Monotherapy | 46% |
| Dual Combination Therapy | 42% |
| Triple Combination Therapy | 12% |

| Factors Influencing Treatment | Key Observations |
|---|---|
| Disease Severity (WHO FC) | Monotherapy decreases with increasing severity |
| Risk Status | Monotherapy higher in low-risk pts (81%) |
| Site of Care | Monotherapy more common in Private and Community settings |

Melendres-Groves et al. Current treatment patterns in pulmonary arterial hypertension (PAH): real-world data from a contemporary U.S. physician survey. *CHEST* 2024:166 (suppl): A5841–A5843.

# Surveys and Registry Data

# Symptom Burden and Health-Related Quality of Life in PAH

| Functional Class (FC) | Percentage of Pts |
|---|---|
| Class I | 16.5% |
| Class II | 41.5% |
| Class III | 35.5% |
| Class IV | 6.5% |

| Symptom Burden & HRQoL | Key Findings |
|---|---|
| EmPHasis-10 Score | Mean = 27.1 (moderate HRQoL impairment) |
| Most Bothersome Symptom | Tiredness (42.1%) |
| PAH Symptom Severity (>7 days) | 93% experienced some degree of symptoms |
| No Impact of PAH on Life | 7% reported no impact |

**Objective:** Explore symptom burden and HRQoL in pts w/ PAH through self-reported data

**Design:** Online survey conducted among 200 US adults w/ PAH, recruited via the Pulmonary Hypertension Association

**Conclusion:** Most pts experienced symptoms that impaired their HRQoL, highlighting need for patient reported outcomes (PROs) in clinical care

Ses DA et al. Patient-reported symptom burden and health-related quality of life in pulmonary arterial hypertension: Results from a patient's perspective on palliative care online survey. *CHEST* 2024:166 (suppl): A5835–A5836.

# Transitioning to Selexipag from Other PPAs

**Objective**: Describe outcomes of pts w/ PAH transitioning from one prostacyclin pathway agent (PPA) to selexipag

**Design:** Prospective, observational SPHERE registry study (2016–2021); data from 759 pts across US

**Conclusion:** Transitioning to selexipag from another PPA was well tolerated, with stable or improved disease in most pts after 18 months

| Outcomes | Findings |
|---|---|
| **18-Month Survival Rate** | 89% |
| **Stable/Improved WHO Functional Class (18-Month Follow-Up)** | 64% stable,<br>21% improved |
| **AEs Leading to Discontinuation (Selexipag-Related)** | <10% |
| **All-Cause Hospitalizations** | 40% of patients |
| **Discontinuation Due to Selexipag-Related AE** | 5 patients |

Chakinala MM et al. Characteristics and outcomes of patients with pulmonary arterial hypertension transitioning to selexipag from another prostacyclin pathway agent in the SPHERE registry. *CHEST* 2024:166 (suppl): A5806–A5811.

# Self-Reported Mental Health Comorbidities in Patients Receiving Selexipag

| Outcomes | With MH Comorbidities | Without MH Comorbidities |
|---|---|---|
| Dual Therapy (Endothelin Receptor Antagonist + PDE-5 Inhibitor) | 34% | 45% |
| Median Time to Selexipag Initiation from Diagnosis | 3.3 years | 2.6 years |
| WHO Functional Class (Stable/Improved at 18 Months) | 87% | N/A |
| REVEAL 2.0 Risk Status (Stable/Improved at 18 Months) | 40% | N/A |
| Median Time to First Hospitalization | 10.7 months | 15.6 months |
| 36-Month Survival | 77% | 84% |

**Objective:** Describe treatment and outcomes of pts with self-reported mental health comorbidities from the SPHERE registry

**Design:** US-based, multicenter, prospective, observational study of PAH patients (2016–2021)

**Conclusion:** Pts with mental health comorbidities have similar treatment patterns and outcomes to those without mental health comorbidities

McLaughlin V et al. Characteristics and outcomes of patients with pulmonary arterial hypertension and self-reported mental health comorbidities in SPHERE (selexipag: the users drug registry). *CHEST* 2024:166 (suppl): A6022–A6027.

# Comorbidities and Complicated Cases

# Self Reflective Question

“What are the most common comorbidities observed in PAH patients, and what strategies do you use to address these issues effectively?”

# Cardiopulmonary Hemodynamics and Outcomes in Pulmonary Hypertension Post-Kidney Transplant

**Objective**: Evaluate association of cardiopulmonary hemodynamics with adverse outcomes following kidney transplant (KT)

**Design:** Multicenter retrospective cohort study of KT pts who underwent right heart catheterization (RHC) for cardiopulmonary hemodynamic assessment ≤ 1 year prior to transplant

**Conclusion:** mPAP ≥30 mmHg and elevated cardiac output (CO) on RHC are strong predictors of mortality and MACE following KT

| Measure | Key Findings |
|---|---|
| **Pulmonary Hypertension (PH; mPAP >20 mmHg)** | Present in 79% |
| **Mortality** | 23% experienced post-KT |
| **Delayed Graft Function (DGF)** | Occurred in 25% of patients |
| **Major Adverse Cardiovascular Events (MACE)** | 34% experienced |
| **Predictor: mPAP ≥30 mmHg** | 2.77× risk of MACE (P=0.029)<br><br>Present in 63% of mortality cases (vs 32%, P=0.001) |
| **Predictor: Elevated CO** | 1.08× risk of mortality (P=0.033) |
| **Echocardiographic PH** | Not predictive of post-KT outcomes |

Jose A et al. Association of cardiopulmonary hemodynamics and outcomes in pulmonary hypertension following kidney transplant: A multicenter retrospective cohort study. *CHEST* 2024:166 (suppl): A6515-A6517.

# Efficacy and Safety of Inhaled Treprostinil in Connective Tissue Disease-Associated PAH (CTD-PAH): TRIUMPH Study Analysis

| Measure | CTD-PAH (iTRE) | CTD-PAH (PBO) | Non-CTD-PAH (iTRE) | Non-CTD-PAH (PBO) |
|---|---|---|---|---|
| 6MWD Change (m) | 24.8 (mean) | -3.4 (mean) | 37.0 (mean) | 8.0 (mean) |
| Improvement in 6MWD | 28.2 m | | 29.0 m | |
| NT-proBNP Change (pg/mL) | -90.0 (median) | | -36.0 (median) | |
| Functional Class Change | 13.5% improved | 0% worsened | 28.4% improved | 0% worsened |
| Adverse Events (%) | 97.5% | 97.3% | 98.7% | 92.8% |

**Objective:** Evaluate efficacy and safety of inhaled treprostinil in pts w/ CTD-PAH compared to non-CTD-PAH

**Design:** Post hoc analysis of the TRIUMPH study, a multicenter, double-blind, placebo-controlled study of inhaled TRE in pts w/ PAH

**Conclusion:** Inhaled treprostinil provides comparable improvements in 6MWD and NT-proBNP levels in CTD-PAH and non-CTD-PAH w/ similar safety profile

Highland KB et al. Inhaled treprostinil for the treatment of connective tissue-associated pulmonary arterial hypertension. *CHEST* 2024:166 (suppl): A5756–A5759.

# Iron Deficiency Anemia Treatment and Clinical Outcomes

| Outcomes | Post-Treatment |
|---|---|
| **Iron Levels** | Serum ferritin, iron level, and transferrin saturation significantly increased (P<0.05) |
| **Hemoglobin** | Significant increase (P<0.05) |
| **Pulmonary/Cardiac Indices** | Decrease in mean pulmonary artery pressure, improvement in cardiac index (P<0.05) |
| **Functional Outcomes** | Improved six-minute walk distance, WHO functional class, and REVEAL Lite 2.0 score (P<0.05) |

**Objective:** Evaluate the impact of iron deficiency anemia (IDA) treatment on clinical outcomes in pts w/ PAH

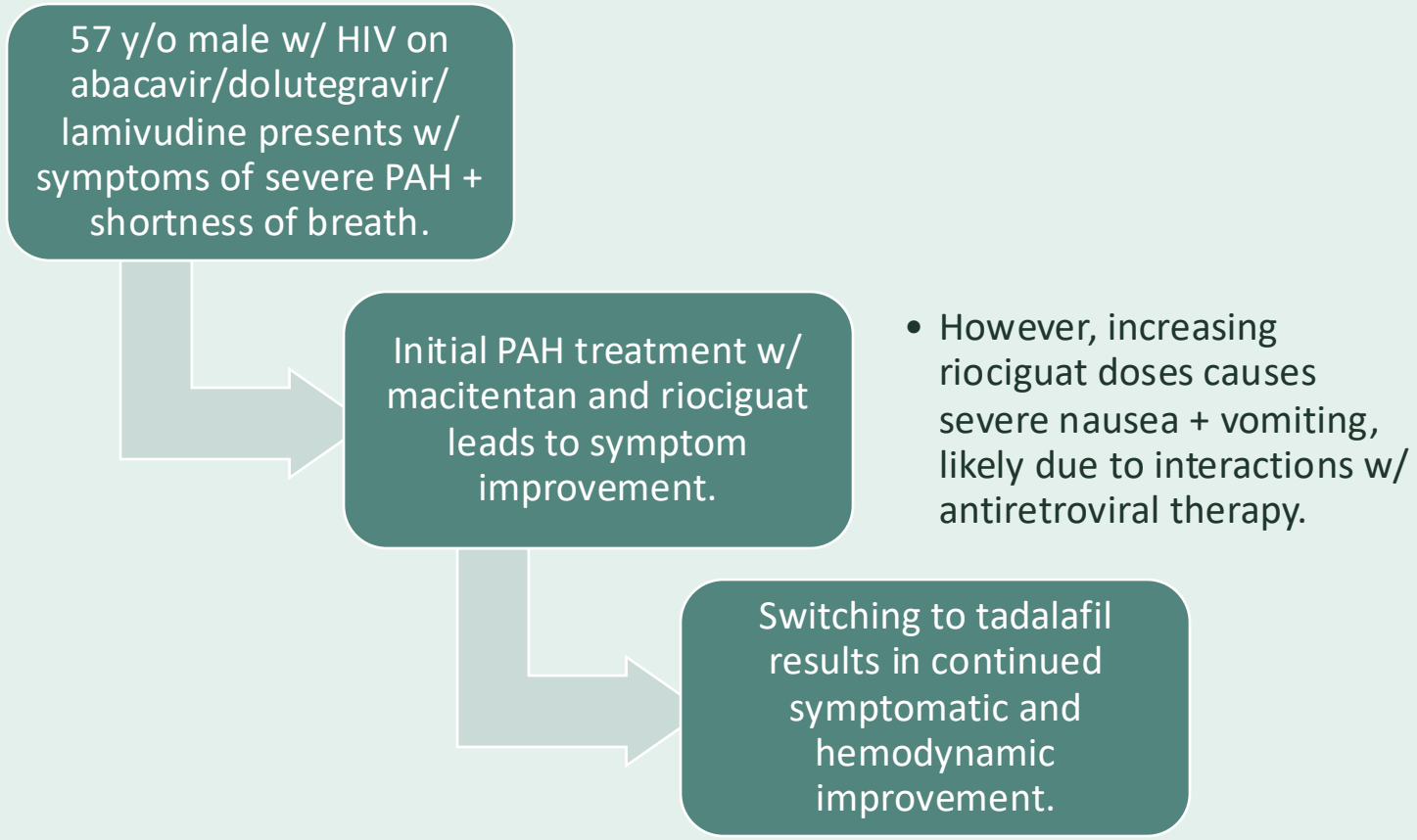
**Design:** Single-center, retrospective study; 53 pts w/ PAH and IDA, treated w/ oral (N=36) or intravenous (N=17) iron

**Conclusion:** Iron therapy in PAH w/ IDA significantly improved iron levels, pulmonary and cardiac indices, and functional outcomes

Singh S et al. Improved outcomes reveal(ed) with iron therapy in patients with pulmonary arterial hypertension and iron deficiency anemia. *CHEST* 2024:166 (suppl): A5794–A5795.

# Case Study: Managing HIV-Associated PAH with Drug-Drug Interactions (DDIs)

**Conclusion:** Clinicians must carefully assess and manage DDIs in HIV-PAH treatment to optimize outcomes and maintain viral suppression while minimizing adverse effects.




Abdullah M, Mwanga JK. Therapeutic challenges of HIV-associated pulmonary arterial hypertension in the current antiretroviral therapy era. *CHEST* 2024:166 (suppl): A6069.

# Efficacy of Parenteral Vasodilators in Treating Right Ventricular Failure with Elevated Pulmonary Capillary Wedge Pressure (PCWP)

| Parameter | Baseline | Post-Therapy | % Improvement |
|---|---|---|---|
| **Mean Pulmonary Artery Pressure (mPAP, mmHg)** | 53.6 | Reduced | Significant |
| **Pulmonary Vascular Resistance (PVR, Wood units)** | 11.5 | Reduced | Significant |
| **Cardiac Index (CI, L/min/m²)** | Low | Improved | Moderate |
| **Tricuspid Annular Plane Systolic Excursion (TAPSE, mm)** | Reduced | Improved | Moderate |
| **Right Ventricular Systolic Pressure (RVSP, mmHg)** | High | Reduced | Significant |

**Objective:** Evaluate efficacy and safety of parenteral vasodilators for RVF with elevated PCWP in pts w/ PAH.

**Design:** Retrospective case series; five PAH pts with RVF, treated with parenteral prostacyclin (IV epoprostenol or IV treprostinil)

- Pre- and post-therapy ECG and hemodynamic measurements analyzed.

**Conclusion:** Parenteral prostacyclin therapy safely improves RV function and reduces PCWP in PAH with RVF.

Jain TS et al. Pulmonary hypertension with right ventricular failure: Navigating an elevated (mechanical) wedge pressure. *CHEST* 2024:166 (suppl): A5926–A5927.

# Impact of PAH on Outcomes in First Myocardial Infarction Episodes

**Objective**: Assess impact of a first myocardial infarction (MI) on pts w/ PAH compared to general population

**Design:** Retrospective analysis using National Inpatient Sample Database (2016-2020)

**Conclusion:** PAH is associated w/ higher mortality, longer hospital stays, greater costs, and increased need for interventions in first MI episodes

| Outcome | First STEMI | First NSTEMI | Any First MI |
|---|---|---|---|
| Unadjusted Mortality OR | 2.36 (P<0.001) | 1.97 (P<0.001) | 1.74 (P<0.001) |
| Adjusted Mortality OR | 1.29 (P=0.002) | 1.23 (P<0.001) | 1.11 (P=0.006) |
| Length of Stay (days) | +1.7 | +1.3 | +1.35 |
| Cost Increase (USD) | +43,477.92 | +22,404.59 | +23,050.94 |
| Intubation Odds | 1.53 | 1.34 | 1.24 |
| Cardiac Assistance Odds | 1.88 | 1.73 | 1.52 |

Carvalhais RM et al. The burden of pulmonary artery hypertension on patients admitted due to first episode of myocardial infarction: A nationwide glance, 2016—2020. *CHEST* 2024:166 (suppl): A5819–A5820.

# Biomarkers

# Initial Validation of the Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR)

| Measure | PH-FC-SR | WHO-FC | Correlations (r) |
|---|---|---|---|
| Class Concordance ±1 | 93.1% | - | 0.52 (polychoric) |
| Class Concordance Exact | Class I: 68.8%, Class III: 56.3%, Class II: 36.8% | - | 0.44 (weighted kappa) |
| Shortness of Breath | - | r | = 0.75 |
| Fatigue | - | r | = 0.58 |
| Energy | - | r | = 0.61 |
| EmPHasis-10 | - | r | = 0.81 |
| SF-36 Physical Function | - | r | = 0.76 |

**Objective:** Validate PH-FC-SR in assessing disease severity from pt perspective

**Design:** Non-interventional, observational study using pt- and clinician-reported data collected via survey and clinical visit (Cleveland Clinic and Mayo Clinic)

**Conclusion:** PH-FC-SR demonstrates strong construct validity, aligning closely w/ WHO-FC while offering unique insights into pts' perception of PAH severity

Crawford R et al. Initial validation of the pulmonary hypertension functional classification self-report (PH-FC-SR): A patient focused measure for use in research and in the clinic. *CHEST* 2024:166 (suppl): A5830–A5832.

# Clinical Pearls

# Summary

- Treprostinil inhalation powder appears to be a safe, effective, and tolerable long-term treatment option for pts with PAH.
- Midodrine is well tolerated and safe, and may be used to safely facilitate medication adjustments in hospitalized pts.
- Pts with evidence of obstructive lung disease may be less tolerant of inhaled treprostinil.
- The use of SGLT2i is associated with mortality reduction in PAH.
- Both Hispanic/Latino, and Black/African American pts with PAH experience delayed PAH therapy initiation and more comorbidities compared to White pts; however, patterns of treatment safety and efficacy were similar.
- Despite recent guidelines recommending combination therapy for all pts with PAH, a substantial proportion remain on monotherapy.
- Most pts experience PAH symptoms that impair their health-related quality of life.
- Transitioning to selexipag from another PPA was well tolerated, w/ stable or improved disease in most pts after 18 months.

# Summary

- Pts w/ and w/out self-reported mental health comorbidities receive similar PAH-specific treatment and have similar outcomes.
- Inhaled treprostinil provides comparable improvements in 6MWD and NT-proBNP levels in CTD-PAH and non-CTD-PAH.
- Iron therapy in PAH pts w/ IDA improves iron levels, pulmonary and cardiac indices, and functional outcomes.
- Clinicians should carefully assess and manage DDIs in HIV-PAH treatment.
- Parenteral prostacyclin therapy safely improves RV function and reduces PCWP in PAH w/ RVF.
- The first MI episode in PAH significantly impacts patients.
- PH-FC-SR may serve as a valuable complementary tool to WHO-FC in patient-centered PH assessment.