Pulmonary Hypertension in Left Heart Disease (PH-LHD): Is There a Role for Pulmonary Arterial Hypertension (PAH) Specific Therapy? and Who May Benefit?

Antoine Hage, M.D

Director, Solid Organ Transplant Cardiology
Co-Director, Pulmonary Hypertension Program
Cedars Sinai Heart Institute
Clinical Professor of Medicine/ Cardiology
Disclosures

• Research grants:
  • Actelion Pharmaceuticals
  • Bayer
  • United Therapeutics Corporation/ Lung RX LLC
  • REATA
  • Arena
### Hemodynamic Definitions of Pulmonary Hypertension (PH)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension (PH)</td>
<td>Mean PAP &gt; 25 mm Hg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>Mean PAP ≥ 25 mm Hg</td>
<td>1. Pulmonary arterial hypertension (PAH)</td>
</tr>
<tr>
<td></td>
<td>PWP ≤ 15 mm Hg</td>
<td>3. PH due to lung disease</td>
</tr>
<tr>
<td></td>
<td>CO normal or reduced</td>
<td>4. CTEPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>Mean PAP ≥ 25 mm Hg</td>
<td>2. PH due to left heart disease (PH-LHD)</td>
</tr>
<tr>
<td></td>
<td>PWP &gt; 15 mm Hg</td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Isolated post-capillary PH (Ipc-PH)</td>
<td>TPG ≤ 12 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DPAP - PCWP &lt; 7 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR &lt; 3 WU</td>
<td></td>
</tr>
<tr>
<td>Combined post-capillary and pre-capillary PH</td>
<td>TPG &gt; 12 mm Hg</td>
<td>TARGET FOR Rx: Patients with severe aspect of this abnormality/ RV dysfunction</td>
</tr>
<tr>
<td>(Cpc-PH)</td>
<td>DPAP - PCWP &gt; 7 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR &gt; 3 WU</td>
<td></td>
</tr>
</tbody>
</table>

Modified from 2015 ESC/ERS Guidelines on PH
Is There a Role for PAH Specific Therapies in PH-LHD?

Exploratory Studies

- **MELODY-1**: The primary endpoint/ (safety) outcome was the proportion of patients experiencing significant fluid retention or a worsening of WHO functional class from baseline. In this exploratory study, macitentan was well tolerated in the Group 2 pulmonary hypertension patient population with heart failure. In addition, encouraging hemodynamic effects were observed.

- **LEPH**: Riociguat in Patients with Pulmonary Hypertension due to Systolic Left Ventricular Dysfunction: A Phase IIb Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Hemodynamic Study: the primary endpoint of the study, change in mPAP was not met (PAP -3 mm Hg; p=0.1), because of increase in CI and SVI, but riociguat was well tolerated in patients with PH-sLVD and improved cardiac index, decrease in pulmonary (-16%) and systemic vascular resistance ( -15%) and improved Minnesota living with heart failure score.

- **DILATE-1**: Effect of Single dose riociguat on PAP in HFP EF
No requirement for high PAP or PVR
RELAX should be considered a trial of sildenafil in HFP EF, not PH-LHD
### Table 3.1 Management of pulmonary hypertension in left heart disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease)</td>
<td>I</td>
<td>B</td>
<td>396</td>
</tr>
<tr>
<td>It is recommended to identify other causes of PH (i.e. COPD, sleep apnoea syndrome, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD</td>
<td>I</td>
<td>C</td>
<td>396</td>
</tr>
<tr>
<td>It is recommended to perform invasive assessment of PH in patients on optimized volume status</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH centre for a complete diagnostic workup and an individual treatment decision</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation</td>
<td>III</td>
<td>C</td>
<td>396</td>
</tr>
<tr>
<td>The use of PAH-approved therapies is not recommended in PH-LHD</td>
<td>III</td>
<td>C</td>
<td>396</td>
</tr>
</tbody>
</table>

Why is Cpc-PH a target for Rx?

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
Cardiopulmonary Interaction and Pathobiology of Pulmonary Hypertension (PH) in Left Ventricular Heart Failure: Similarities with PAH.

PULMONARY CIRCULATION

Superimposed components:
- Vasoconstriction
- NO availability
- Desensitisation to NP-induced vasodilation
- Arteriolar remodeling
- Venous congestion
- Metabolic factors
- Inflammatory cells

Pulmonary vascular disease (i.e. remodeling)

Passive backward transmission of left-sided filling pressures

RIGHT HEART

RV failure

LEFT HEART

Loss of LA compliance
(exercise increased)
Mitral regurgitation
Systolic/diastolic LV dysfunction

RV-PA coupling needs to be the focus of intervention, rather than direct pulmonary vasodilatation.

Stephan Rosenkranz et al. Eur Heart J 2015;eurheartj.ehv512
Pulmonary Vascular Remodeling in PH-LHD

100 cases of MVR for severe MS in India
PA pressure correlated with degree of medial thickness

Linear correlation between medial thickness and:
- Transpulmonary gradient (TPG)
- Pulmonary vascular resistance (PVR)

*Tandon HD and Kasturi J. British Heart Journal 1975

* Tandon HD and Kasturi J. British Heart Journal 1975
5-Year Survival Without Treatment in IPAH (NIH National Registry) vs PAH Patients in REVEAL

Of 2967 adult patients enrolled, 239 (8%) had an elevated PAWP (16-18 mm Hg)

1 yr: 85%
3 yr: 68%
5 yr: 57%
7 yr: 49%

1 yr: 68%
3 yr: 48%

Median survival NIH: 2.8 yrs

5 yr: 34%
Sildenafil improves exercise capacity (6MWT) and QOL in HFrEF+PH
HFpEF, n=44
12 months of sildenafil 50mg TID vs placebo
RAP=23, PCWP=22, PVR=3.3, TAPSE=11.2.
DPG 9 mmHg (Pts with CpcPH)

Improvement also in:
- Pulmonary vascular resistance
- Right ventricular (RV) end-diastolic pressure–stroke volume relationship
- Pulmonary arterial elastance
- Tricuspid annular plane systolic excursion (TAPSE)
- Right ventricular (RV) mean systolic ejection rate (MSEJ)
- Mean RA and PCWP
- Beneficial changes in alveolar-capillary membrane conductance
- QOL

PDE5i improved hemodynamics (PVR, RA and PCWP), RV function (TAPSE), gaz exchange, QOL and multiple other cardio-pulmonary parameters.

138 consecutive LVAD patients.
58 pts had persistent PH post LVAD (PVR= 5.4 WU)
Sildenafil group (n=26) improved (2-4 weeks post sildenafil)
Persisted through 12-15 weeks post
24/26 of sildenafil group reduced PVR <3
- 19 became Tx eligible
- 10 transplanted
- 1 had post-tx RV dysfunction
Control group (n=32)
- 18 transplanted without complication
- 5 post op RV dysfunction
A Comparison of Characteristics and Outcomes of Patients with Atypical and Classical Pulmonary Arterial Hypertension from the AMBITION Trial

VV McLaughlin, N Galiè, JA Barbera, A Frost, HA Ghofrani, M Hoeper, A Peacock, G Simonneau, JL Vachiery, C Blair, H Gillies, K Miller, J Harris, J Langley, LJ Rubin

American Thoracic Society International Conference
May 17, 2015
Denver, CO
Oral Abstract #A2196
Time to First Clinical Failure Event (Ex-PAS)

Excluded:
3 or > risks factors:
- BMI > 30
- HTN
- DM
- CAD

COMPERA Registry:
Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension:
A Pathophysiological Continuum

COMPERA cohort
N= 5935

Excluded (N 5149)
• Non IPAH-PAH
• Non HFpEF PH
• Children
• Prevalent cases
• Inconsistent hemodynamics,
  etc

PH-HFpEF (N=226)
mPAP > 25
PCWP > 15

Total N=786

IPAH (N=560)
mPAP > 25 PCWP < 15

Typical IPAH
(N=421)
< 3 risk factors

Atypical IPAH
(N=139)
> 3 risk factors

Hemodynamics:
mPAP 46 mm Hg
CI 2.2
TPG 26

Comparison of typical IPAH, Atypical IPAH (> 3 Risk Factors) and HF-pEF

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Characteristics</th>
<th>≥ 3 Cardiac RF</th>
<th>Typical vs. Atypical</th>
<th>Typical vs. PH-HFpEF</th>
<th>Atypical vs. PH-HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (N = 786)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>66.6 ± 15.0</td>
<td>61.5 ± 17.3</td>
<td>71.3 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>467 (59.4)</td>
<td>250 (59.4)</td>
<td>77 (55.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 (24.5-32.6)</td>
<td>26.0 (23.3-29.8)</td>
<td>32.2 (28.3-36.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHO-FC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>91 (11.8)</td>
<td>71 (17.4)</td>
<td>12 (8.8)</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>III</td>
<td>540 (70.3)</td>
<td>275 (67.6)</td>
<td>96 (70.6)</td>
<td>169 (75.1)</td>
</tr>
<tr>
<td>IV</td>
<td>137 (17.8)</td>
<td>61 (15.0)</td>
<td>28 (20.6)</td>
<td>48 (21.3)</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>289.5 ± 121.8</td>
<td>319.0 ± 123.5</td>
<td>250.5 ± 104.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>9.8 ± 5.4</td>
<td>8.5 ± 5.2</td>
<td>8.9 ± 4.8</td>
<td>0.615</td>
</tr>
<tr>
<td>PAPm, mm Hg</td>
<td>46.0 ± 11.9</td>
<td>46.9 ± 13.3</td>
<td>43.9 ± 10.7</td>
<td>0.025</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>12.5 ± 6.0</td>
<td>9.3 ± 3.4</td>
<td>10.0 ± 3.6</td>
<td>0.186</td>
</tr>
<tr>
<td>TPG, mm Hg</td>
<td>33.5 ± 13.1</td>
<td>37.6 ± 13.6</td>
<td>33.9 ± 11.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiac index, l/min/m²</td>
<td>2.2 ± 0.8</td>
<td>2.3 ± 0.8</td>
<td>2.2 ± 0.8</td>
<td>0.629</td>
</tr>
<tr>
<td>PVR, Wood Units</td>
<td>9.6 ± 6.7</td>
<td>10.8 ± 6.0</td>
<td>9.8 ± 10.6</td>
<td>0.309</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>62.2 ± 9.0</td>
<td>62.1 ± 9.9</td>
<td>62.7 ± 9.0</td>
<td>0.804</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>269 (127-541)</td>
<td>287 (199-543)</td>
<td>200 (115-469)</td>
<td>1.000</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml</td>
<td>1,738 (621-3,891)</td>
<td>1,435 (541-3,888)</td>
<td>1,683 (478-2,815)</td>
<td>1.000</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>66.5</td>
<td>43.2</td>
<td>98.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>32.0</td>
<td>15.7</td>
<td>59.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30.6</td>
<td>10.7</td>
<td>74.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF</td>
<td>28.9</td>
<td>10.7</td>
<td>42.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>37.6</td>
<td>23.5</td>
<td>65.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

5-Year Overall Survival
There was no significant difference in survival among patients with PH who were studied. $p_1 = p$ value for typical IPAH versus atypical IPAH; $p_2 = p$ value for typical IPAH versus PH-HFpEF; $p_3 = p$ value for atypical IPAH versus PH-HFpEF; other abbreviations as in Figure 1.
Various factors and comorbidities appear more or less frequently in patients with typical idiopathic pulmonary arterial hypertension (IPAH), defined as <3 risk factors for left heart disease; in patients with atypical IPAH (≥3 risk factors); and in patients with PH–heart failure with preserved ejection fraction (HFpEF). Given the patterns and tendencies seen, is there a disease continuum ranging from typical IPAH through atypical IPAH to PH-HFpEF? AF = atrial fibrillation; CAD = coronary artery disease; DPG = diastolic pressure gradient; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; TPG = transpulmonary pressure gradient.
Cologne Consensus Conference 2010:
Specific Recommendations of The Working Group Regarding treatment of PH Associated with Left Heart Disease (Cpc-PH)

• **Potential Use of Targeted PAH Therapies in PH-LHD (PCWP > 15 mm Hg):**
  – Requirement: Complete diagnostics including RHC and LHC
  – Pronounced precapillary component foregrounded to the disease
  – Persistent High PVR/TPG/DPG despite optimization of LHD (remodeling of PA/RV dysfunction)

• **Patients must fulfill the following criteria:**
  – No treatable cause of heart failure (CAD, valvular disease)
  – Guideline-based, evidence-based treatment for heart failure for a reasonable time (>3-6 months), and at the anticipated target doses
  – Exclusion of other causes of PH and CTEPH

• **Primary Goal:** Inclusion in clinical trials/ careful Phenotyping (e.g., VICTORIA, SOPRANO, SERENADE, MELODY, SOCRATES, DILATE-1, LEPHT)

Modified from Rosenkranz et al, DMW 2010, 135 (suppl 3: S102-S114)