2015 State-of-the-Art Management of Pulmonary Hypertension Based on an Understanding of the Various Etiologies

Vallerie V. McLaughlin, MD, FACC, FAHA
Kim A Eagle MD Endowed Professor of Cardiovascular Medicine
Director, Pulmonary Hypertension Program
University of Michigan Health System
Disclosures

• Has served as a consultant and/or advisor for Actelion Pharmaceuticals US, Inc., Bayer, Gilead Sciences, Inc., and United Therapeutics Corporation

• The University of Michigan has received research funding from Actelion Pharmaceuticals US, Inc., Bayer, and Gilead
Pulmonary Arterial Hypertension (PAH): Key Points

• Average 14-mo delay from initial presentation to diagnosis: need to diagnose early

• Evaluation must be methodical and include echocardiography and right heart catheterization

• To treat effectively and avoid harm, PAH must be differentiated from pulmonary venous hypertension

• Prognosis improves with therapy, but PAH remains a progressive fatal disease

• Therapies and management strategies continue to evolve
# 5th World Symposium on PH: Modified Classification of PH

## 1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
   1.2.1 BMPR2
   1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
   1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
   1.4.1 Connective tissue diseases
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart disease (update)

## 1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

## 1”. PPHN

## 2. PH due to LHD
2.1 LV systolic dysfunction
2.2 LV diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow obstruction

## 3. PH due to lung diseases and/or hypoxia
3.1 COPD
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (update)

## 4. CTEPH

## 5. PH with unclear multifactorial mechanisms
5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Echocardiogram
PFT’s
Polysomnography
VQ Scan
• Sleep Disorder
History
Exam
CXR
ECG
• Index of Suspicion of PH
Echocardiogram
VQ Scan
PFT’s
Overnight Oximetry
HIV
ANA
LFT’s
Functional Test (6MWT, CPET)
RH Cath
• Left Heart Disease
• VHD, CHD
HIV
Scleroderma, SLE, RA
Portopulmonary Htn
• Ventilatory Function
• Gas Exchange
• Chronic PE
• Confirmations of PH
• Hemodynamic Profile
• Vasodilator Response
TEE
Exercise Echo
Pulmonary Angiography
Chest CT Angiogram
Coagulopathy Profile
ABG’s
Polysomnography
Other CTD Serologies
• Establish Baseline
• Prognosis
Vasodilator Test
Exercise RH Cath
Volume Loading
Left Heart Cath
## Differentiating PAH and HFpEF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PAH more likely</th>
<th>HFpEF more likely</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>younger</td>
<td>older</td>
</tr>
<tr>
<td><strong>Comorbidities</strong>-DM, HTN, CAD, obesity (metabolic syndrome)</td>
<td>Often absent</td>
<td>Often multiple present</td>
</tr>
<tr>
<td><strong>Symptoms-PND, orthopnea</strong></td>
<td>Often absent</td>
<td>Often present</td>
</tr>
<tr>
<td><strong>Cardiac Examination</strong></td>
<td>RV heave, loud P2, TR murmur</td>
<td>Sustained LV impulse, RS4,</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>Clear lung fields</td>
<td>Pulmonary vascular congestion, pleural effusions, pulmonary edema</td>
</tr>
<tr>
<td><strong>Chest CT</strong></td>
<td>Often clear lungs</td>
<td>Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>RAD, RVE</td>
<td>LAE, LVE, Atrial Fibrillation, no RAD</td>
</tr>
<tr>
<td><strong>Naturetic peptides</strong></td>
<td>Often elevated</td>
<td>Often elevated</td>
</tr>
<tr>
<td><strong>Echo-LAE, LVH</strong></td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td><strong>Echo-diastolic dysfunction</strong></td>
<td>Grade 1 common</td>
<td>Grade 2, 3 common</td>
</tr>
<tr>
<td><strong>Echo-RV</strong></td>
<td>Often enlarged, may share the apex</td>
<td>Often normal, mildly enlarged</td>
</tr>
<tr>
<td><strong>Echo-pericardial effusion</strong></td>
<td>sometimes</td>
<td>rare</td>
</tr>
</tbody>
</table>
## Cardiopulmonary Circulation in Patients With Tight Mitral Stenosis With and Without Pulmonary Vascular Disease

<table>
<thead>
<tr>
<th>Normal</th>
<th>Tight mitral stenosis</th>
<th>Tight mitral stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVC</strong></td>
<td><strong>RA</strong></td>
<td><strong>RV</strong></td>
</tr>
<tr>
<td><strong>PA</strong></td>
<td><strong>PC</strong></td>
<td><strong>MVA=4.0 cm²</strong></td>
</tr>
<tr>
<td><strong>PV</strong></td>
<td><strong>LA</strong></td>
<td></td>
</tr>
<tr>
<td><strong>LV</strong></td>
<td><strong>Ao</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FLOW</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 5 20/5 20/8 (12) 6 6 6 120/6120/8</strong></td>
<td><strong>5 5 45/5 45/25 (32) 25 25 25 120/5</strong></td>
<td><strong>20 20 70/20 68/33(53) 24 24 24 110/5</strong></td>
</tr>
<tr>
<td><strong>MVA=1.0 cm²</strong></td>
<td></td>
<td><strong>FLOW 3L/min</strong></td>
</tr>
<tr>
<td><strong>FLOW 6L/min</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- SVC: Superior Vena Cava
- IVC: Inferior Vena Cava
- RA: Right Atrium
- RV: Right Ventricle
- PA: Pulmonary Artery
- PC: Pulmonary Capillary
- PV: Pulmonary Vein
- LA: Left Atrium
- LV: Left Ventricle
- Ao: Aorta
- FLOW: Flow
- MVA: Mitral Valve Area

**Notations:**
- **5**: Pressure in mmHg
- **20/5**: Systolic/Diastolic pressure in mmHg
- **68/33(53)**: Pressure in mmHg
- **45/25 (32)**: Pressure in mmHg
- **FLOW**: Flow rate in L/min
# PAH-Specific Therapies: Studies On PH-LV Dysfunction: Adverse Effects Trump Efficacy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Changes</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin</td>
<td>↑PVR, ↓SVR, ↓PAWP, ↑CO</td>
<td>↑Mortality</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>↓PVR, ↓PAWP, ↓MPAP, ↑CO</td>
<td>Lower PAP, Improved endothelial function and exercise tolerance</td>
</tr>
<tr>
<td>Bosentan</td>
<td>↓PVR</td>
<td>↑Transaminases, ↑Fluid Retention</td>
</tr>
<tr>
<td>Darusentan</td>
<td>↓SVR</td>
<td>No Benefits</td>
</tr>
<tr>
<td>Tezosentan</td>
<td>↓PVR, ↓SVR, ↓PAWP, ↑CI</td>
<td>No Benefits</td>
</tr>
</tbody>
</table>

No therapies that are approved for WHO Group 1 PAH are FDA approved for PH resulting from left heart failure.

<table>
<thead>
<tr>
<th>LOWER RISK</th>
<th>DETERMINANTS OF RISK</th>
<th>HIGHER RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression of symptoms</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6MWD</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak VO$_2$ &gt;10.4 mL/kg/min</td>
<td>CPET</td>
<td>Peak VO$_2$ &lt;10.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiography</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement</td>
</tr>
<tr>
<td>RAP &lt;10 mm Hg; CI &gt;2.5 L/min/m$^2$</td>
<td>Hemodynamics</td>
<td>RAP &gt;20 mm Hg; CI &lt;2.0 L/min/m$^2$</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

# Prostacyclin Analogues: Pivotal Trials for IV and SC Formulations

<table>
<thead>
<tr>
<th>Study Name / Drug</th>
<th>N / Etiol / Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRUST</td>
<td></td>
<td>Double-blind, placebo-controlled 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td>IV treprostinil vs placebo</td>
<td>44</td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td>IV epoprostenol vs conventional Rx</td>
<td>81</td>
<td>Open-label 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td>IPAH/FP A H III,IV</td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hemodynamics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>Survival</strong></td>
</tr>
<tr>
<td>IV epoprostenol vs conventional Rx</td>
<td>111</td>
<td>Open-label 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td>APAH S Sc III,IV</td>
<td></td>
<td>• Hemodynamics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td>SQ treprostinil vs SQ placebo</td>
<td>470</td>
<td>Double-blind 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td>PAH II-IV</td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hemodynamics</td>
</tr>
</tbody>
</table>

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**Prostacyclin Analogues: Pivotal Trials for Inhaled and Oral Formulations**

<table>
<thead>
<tr>
<th>Study Name / Drug</th>
<th>N / Etiol / Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| AIR               | 203 PH            | Double-blind 12-week | • Composite end point  
| Inhaled iloprost vs placebo | III-IV           |        | 6MWD             |
| TRIUMPH 1         | 235 PAH           | Double-blind 12-week on background oral Rx | • 6MWD  
| Inhaled treprostinil vs placebo § | III-IV*          |        |                  |
| FREEDOM-M         | 228 PAH           | Double-blind, placebo-controlled 12-week | • 6MWD  
| Oral treprostinil vs placebo | II-III          |        |                  |

*Approved for class III only. §Included background therapy with ERA or PDE5-I.

## Endothelin Receptor Antagonists: Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiology Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| **BREATHE-1**   | 213 PAH III, IV  | Double-blind 16-week | • 6MWD  
• Delay clinical worsening  
• Symptoms |
| Oral bosentan* vs placebo | | | |
| **EARLY**       | 185 PAH II       | Double-blind 6-month | • Delay clinical worsening  
• Hemodynamics |
| Oral bosentan vs placebo | | | |
| **ARIES-1&2**   | 394 PAH II, III  | Double-blind 12-week | • 6MWD  
• Delay clinical worsening |
| Oral ambrisentan§ vs placebo | | | |
| **SERAPHIN**    | 742 PAH II,III   | Morbidity and Mortality Endpoint Driven | • Delay disease progression  
• 6MWD  
• Symptoms |
| Oral macitentan† vs placebo | | | |

*Bosentan = Tracleer®. Approved for FC II-IV. 62.5-125 mg po bid.

§ Ambrisentan = Letairis®. Approved for FC II-III. 5-10 mg po qd

†Macitentan = Opsumit®. Approved for FC II-III. 10 mg po qd.

## PDE-5 Inhibitor Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiol Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| **SUPER-1** Oral sildenafil* vs placebo | 278 PAH I-IV | Double-blind 12-week | • 6MWD  
• Symptoms  
• Hemodynamics |
| **PHIRST-1** Oral tadalafil § vs placebo | 405 PAH I-IV | Double-blind 16-week | • 6MWD  
• Delay clinical worsening  
• Hemodynamics  
• HRQoL |

*Sildenafil = Revatio®. Approved for FC II-III. 20 mg po tid.
§ Tadalafil = Adcirca®. Approved for FC I-IV. 40 mg po qd.
# SGC Stimulator Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>N Etiol Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| PATENT-1 Oral riociguat* vs placebo | 443† PAH I-IV | Double-blind 12-week | • 6MWD  
• Symptoms  
• Hemodynamics  
• Delay clinical worsening |
| CHEST-1 Oral riociguat vs placebo | 261 CTEPH I-IV | Double-blind 16-week | • 6MWD  
• Symptoms  
• Hemodynamics |

*Riociguat = Adempas®. Approved for WHO Group 1; persistent CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH; titrated to maximum 2.5 mg po tid.

†63 patients on exploratory 1.5 mg tid were excluded from efficacy analysis.

GRIPHON primary endpoint: Time to first morbidity or mortality event up to EOT

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo</th>
<th>Selexipag</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>582</td>
<td>574</td>
</tr>
<tr>
<td>6</td>
<td>433</td>
<td>455</td>
</tr>
<tr>
<td>12</td>
<td>347</td>
<td>361</td>
</tr>
<tr>
<td>18</td>
<td>220</td>
<td>246</td>
</tr>
<tr>
<td>24</td>
<td>149</td>
<td>171</td>
</tr>
<tr>
<td>30</td>
<td>88</td>
<td>101</td>
</tr>
<tr>
<td>36</td>
<td>28</td>
<td>40</td>
</tr>
</tbody>
</table>

EOT: End of double-blind treatment; KM: Kaplan-Meier

Selexipag vs placebo: Risk reduction 40%
HR = 0.60; 99% CI 0.46–0.78; p < 0.0001
95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.
- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)

General measures and supportive therapy → Expert Referral (I-C) → Acute vasoreactivity test (I-C for IPAH) (IIb-C for APAH)

- Oral anticoagulants:
  - IPAH, heritable PAH, and PAH due to anorexigens (IIa-C)
  - APAH (IIb-C)
- Diuretics (I-C)
- Oxygen (I-C)
- Digoxin (IIb-C)

VASOREACTIVE → WHO-FC I-III → Sustained response (WHO-FC I-II) → Continue CCB

NONVASOREACTIVE → INITIAL THERAPY WITH PAH-APPROVED DRUGS

## 5th World Symposium on PH: 2013 Treatment Algorithm

### INITIAL THERAPY WITH PAH-APPROVED DRUGS

YELLOW: Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

Level of evidence is based on WHO-FC of majority of patients of studies

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
</table>
| I              | A or B   | • Ambrisentan, Bosentan  
• Macitentan  
• Riociguat  
• Sildenafil  
• Tadalafil | • Ambrisentan, Bosentan, Epoprostenol IV  
• Iloprost inh  
• Macitentan  
• Riociguat  
• Sildenafil  
• Tadalafil  
• Treprostinil SC, inh | • Epoprostenol IV |
| IIa            | C        | • Iloprost IV*, Treprostinil IV | | |
| IIb            | B        | • Beraprost* | | |
|                | C        | • Initial Combination Therapy | | |

*Not approved in US.
INITIAL THERAPY WITH PAH-APPROVED DRUGS

Sequential combination therapy (I-A)

- ERAs
  - Prostanoids
  - PDE-5 I or sGCS

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

Referral for Lung Transplantation (I-C)

Inadequate Clinical Response on Maximal Therapy

BAS (IIa-C)

5th World Symposium on PH Goals of Therapy: Setting the Bar Higher

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>• I or II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td>• Normalization of RV function (RAP &lt; 8 mm Hg and CI &gt; 2.5-3.0 L/min/m²)</td>
</tr>
<tr>
<td>Echocardiography/MRI</td>
<td>• Normal/near normal RV size and function</td>
</tr>
<tr>
<td>BNP level</td>
<td>• ‘Normal’</td>
</tr>
<tr>
<td>6-MWD</td>
<td>• 380-440 m, may not be aggressive enough</td>
</tr>
</tbody>
</table>
| CPET             | • Peak VO₂ > 15 mL/kg/min  
|                  | • VE/VCO₂ @ AT < 45 |