Pulmonary Arterial Hypertension: Contemporary Approach to Treatment

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Lecture Outline
- What is PAH?- Definitions/diagnosis
- PAH severity and risk-assessment- How bad is it, Doc?
- Treatment options for PAH- which one(s), when, how?
- What do the Guidelines say about PAH treatment?
- When/How to follow-up
Pulmonary Hypertension (PH) - Definition

mPAP >25 mm Hg at rest

Pulmonary Hypertension (PAH) - Definition

mPAP >25 mm Hg at rest
+ PCWP (or LVEDP) ≤15 mm Hg
+ PVR >3 Wood units

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      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 diseases
      1.4.5. Schistosomiasis
   1.5. Portal hypertension
   1.6. Congenital heart diseases
   1.7. Schistosomiasis
   1" Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   1" Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   3.1. Chronic obstructive pulmonary disease
   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 abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
PAH Determinants of Patient Risk

ACC/AHA Expert Consensus

<table>
<thead>
<tr>
<th>Determinants of prognosis</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
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<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope</td>
<td>Repeated syncope</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>I–II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;460 m</td>
<td>166–440 m</td>
<td>&lt;165 m</td>
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<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂ &gt;50 m/min/kg</td>
<td>Peak VO₂ &gt;45 m/min/kg</td>
<td>Peak VO₂ &gt;35 m/min/kg</td>
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<tr>
<td></td>
<td>VE/VO₂ slope &gt;45</td>
<td>VE/VO₂ slope &gt;40</td>
<td>VE/VO₂ slope &gt;35</td>
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<tr>
<td>NT-proBNP plasma levels</td>
<td>NT-proBNP &lt;50 ng/l</td>
<td>NT-proBNP 50–500 ng/l</td>
<td>NT-proBNP &gt;500 ng/l</td>
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<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm²</td>
<td>RA area 18–26 cm²</td>
<td>RA area &gt;26 cm²</td>
</tr>
<tr>
<td></td>
<td>No pericardial effusion</td>
<td>Pericardial effusion</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;14 mm Hg</td>
<td>RAP 14–20 mm Hg</td>
<td>RAP &gt;20 mm Hg</td>
</tr>
<tr>
<td></td>
<td>CVP 2–4 mm Hg</td>
<td>CVP 4–8 mm Hg</td>
<td>CVP &gt;8 mm Hg</td>
</tr>
<tr>
<td></td>
<td>SVO₂ 76–85%</td>
<td>SVO₂ 60–75%</td>
<td>SVO₂ &lt;60%</td>
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Galie N, et al. Eur Heart J 2015 a
### PAH Treatments: US Approved

#### Specific PAH agents

<table>
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<tr>
<th>Prostacyclin analogues</th>
<th>Endothelin antagonists</th>
<th>PDE-5 inhibitors</th>
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<tbody>
<tr>
<td>Epoprostenol (IV)</td>
<td>Bosentan (po)</td>
<td>Sildenafil (po)</td>
</tr>
<tr>
<td>Iloprost (inh)</td>
<td>Ambrisentan (po)</td>
<td>Tadalafil (po)</td>
</tr>
<tr>
<td>Treprostinil (IV, SQ, inh, po)</td>
<td>Macitentan (po)</td>
<td>Soluble guanylate cyclase agonist</td>
</tr>
<tr>
<td>Selexipag (po)</td>
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<td>Riociguat (po)</td>
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- **There are now >10 FDA-approved PAH drugs**
- **In 1995, there were none**

**PAH Treatments: Efficacy**

**Primary Endpoint: Time To Clinical Worsening or Death**

Mean change from baseline in 6MWD (m)

- **Macitentan 10 mg**: Hazard ratio=0.55; log rank \( P<0.001 \)
- **Macitentan 3 mg**: Hazard ratio=0.70; log-rank \( P=0.01 \)

N=742. Double-blind, placebo-controlled Phase III study. Primary endpoint composite endpoint of death, atrial septostomy, lung transplantation, initiation of intravenous/subcutaneous prostanoids or other worsening of PAH.


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**PAH Treatments: Efficacy**

**A Combination Therapy vs. Pooled Monotherapy**

Hazard ratio, 0.50 (95% CI, 0.35–0.72) \( P<0.001 \)

No. at Risk
- Combination therapy: 253, 229, 186, 145, 106, 71, 36, 4

References:
4. Ambrisentan (Letairis) and tadalafil (Adcirca) for pulmonary arterial hypertension. Med Lett Drugs Ther 2016;58:2-4.
**Brief Biosketch**

Ronald J. Oudiz, MD, Professor of Medicine, David Geffen School of Medicine at UCLA is Director of the Pulmonary Hypertension Center and is a Faculty Cardiologist at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. He is a past holder of scientific research awards from the American Heart Association and the National Institutes of Health. Dr. Oudiz received the Pulmonary Hypertension Association (PHA) Award of Excellence in Pulmonary Arterial Hypertension (PAH) Care in 2011, the PHA Legacy Award in 2015, and in 2015 her was named a PHA Periwinkle Pioneer for his contributions to the pulmonary hypertension field. He has authored several papers in field of pulmonary hypertension and has presented his research at national and international seminars. Dr. Oudiz has been on task forces for the past four World Symposia on Pulmonary Hypertension, covering clinical endpoints, diagnostic testing, and right ventricular function & physiology. He is the immediate past Chair of the American College of Physicians CHEST Pulmonary Vascular NetWork, and is Chair-Elect of the PHA's Scientific Leadership Council (SLC). Dr. Oudiz is also a past Editor-in-Chief of the journal Advances in Pulmonary Hypertension. He has participated in several trials of innovative medical treatments for pulmonary hypertension, many of which are still ongoing. His research focus has been to describe the physiologic abnormalities that are caused by PH using measurements of lung gas exchange during exercise, and to study exercise rehabilitation as a treatment modality for patients with pulmonary hypertension.