Clinical Advances in Pulmonary Arterial Hypertension
Faculty

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Franck Rahaghi, MD, MHS, FCCP serves as a consultant, lecturer and researcher for Actelion, Bayer, Gilead, United Therapeutics and Lung Biotech.
Learning Objectives

1. Discuss the pathophysiology of pulmonary arterial hypertension (PAH)

2. Recognize signs and symptoms suggestive of PAH and the appropriate diagnostic strategy

3. Describe how to monitor patients with PAH for disease progression

4. Review current and emerging treatments for patients with PAH
Pulmonary Hypertension

- Is an imprecise term!
- One interpretation can be Increased Pulmonary Pressure which happens in multiple conditions and is not a disease but a manifestation of disease: An echo cardiogram shows Pulmonary Hypertension
- A Set of diseases which manifest with increased pulmonary pressure
- Incorrectly and interchangeably used as Pulmonary Arterial Hypertension
What Is Pulmonary Arterial Hypertension?

Chronic, progressive, cardiopulmonary condition associated with:

- Progressive exertional shortness of breath
- Decreased endurance related to physical activity
- Syncope, chest pain or fatigue

Hemodynamically defined as:

- Abnormal increase in pulmonary artery pressure
- Normal pulmonary capillary wedge pressure
- Increased pulmonary vascular resistance

Pulmonary hypertension results in right ventricular pressure/volume overload leading to right heart failure and death.
An estimated RVSP ≥35 mm Hg should raise concern, especially when accompanied by evidence of right heart pressure overload:
- Right atrial enlargement
- Right ventricular enlargement, hypertrophy or dysfunction
- Significant tricuspid regurgitation

American College of Cardiology / American Heart Association expert consensus recommends further evaluation of patient with dyspnea and an estimated RVSP >40 mm Hg.

Fifth World Symposium on Pulmonary Hypertension: Diagnostic Definition of PAH

### Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery pressure (mPAP)</td>
<td>$\geq 25$ mm Hg</td>
</tr>
<tr>
<td>And</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery wedge pressure (PAWP)</td>
<td>$\leq 15$ mm Hg</td>
</tr>
<tr>
<td>With</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>$&gt;3$ Wood units</td>
</tr>
</tbody>
</table>

As measured by right-heart catheterization.

Pathophysiology of PAH Includes:
Vasoconstriction, Vasoproliferation, and Eventual Right Heart Failure

Schematic Progression of PAH

Adapted from: Hill NS. *Pulmonary Hypertension Therapy*. Summit Communications, LLC; 2006:9.
Presentations of Dyspnea

Sudden onset

- Pulmonary embolism, pneumonia, myocardial infarction

Slowly progressive conditions

- COPD, interstitial lung disease, cardiomyopathy, pulmonary vascular disease

Dyspnea with chronic cough

- Airway disease, interstitial lung disease, GERD

Nocturnal symptoms

- Asthma, COPD, GERD, cardiomyopathy, neuromuscular conditions
REVEAL: Most Frequent PAH Presenting Symptoms

- Dyspnea at rest: 11.5% (Diagnosed ≤2 years after symptom onset), 8.4% (Diagnosed >2 years after symptom onset)
- Cough: 13.8% (Diagnosed ≤2 years after symptom onset), 14.8% (Diagnosed >2 years after symptom onset)
- Dizzy/lightheaded: 15.0% (Diagnosed ≤2 years after symptom onset), 1.60% (Diagnosed >2 years after symptom onset)
- Presyncope/syncope: 16.5% (Diagnosed ≤2 years after symptom onset), 18.3% (Diagnosed >2 years after symptom onset)
- Edema: 21.9% (Diagnosed ≤2 years after symptom onset), 1.71% (Diagnosed >2 years after symptom onset)
- Chest pain/discomfort: 22.2% (Diagnosed ≤2 years after symptom onset), 21.1% (Diagnosed >2 years after symptom onset)
- Fatigue: 26.7% (Diagnosed ≤2 years after symptom onset), 26.2% (Diagnosed >2 years after symptom onset)
- Dyspnea on exertion: 86.1% (Diagnosed ≤2 years after symptom onset), 85.4% (Diagnosed >2 years after symptom onset)

NYHA/WHO Functional Classification for PAH (Disease Severity)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation of physical activity; no discomfort at rest. Ordinary activity causes undue dyspnea, fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of physical activity; no discomfort at rest. Less than ordinary physical activity causes undue dyspnea, fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to perform any physical activity without symptoms; signs of right ventricular failure or syncope; dyspnea and/or fatigue may be present at rest; discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

Examination Findings Suggestive of PH/PAH

- **Lungs:** CTA w/o wheeze / crackles
- **Liver:** Hepatomegaly, Pulsatile liver
- **Abdomen:** Ascites
- **Joint:** Changes c/w CTD
- **Digits:** Cool, Cyanotic
- **Neck:** HJR, JVD
- **Skin:** Changes c/w CTD
- **Heart:** Heave, RRR, Increased P2, TR SM
- **Extremities:** Edema

Classification: 5 Groups

1. PAH
   - Idiopathic
   - Heritable
   - Drug and toxin induced
   - Persistent PH of newborn
   - Associated with
     - CTD
     - HIV
     - Portal HTN
     - Congenital HD
     - Schistosomiasis
     1’ PVOD and PCH
     1” PPH of the newborn

2. PH due to Left Heart Disease
   - Systolic Dysfunction
   - Diastolic Dysfunction
   - Valvular Disease

3. PH owing to Lung Disease and/or Hypoxia
   - COPD
   - ILD
   - Sleep disordered breathing
   - Alveolar hypoventilation syndromes
   - Chronic exposure to high altitude
   - Developmental abnormalities

4. Chronic ThromboEmbolic PH
   - Other pulmonary artery obstruction

5. PH with unclear mechanisms
   - Chronic hemolytic anemias / Splenectomy
   - Sarcoidosis
   - Pulm LCH / LAM
   - Metabolic disorders
   - Others – Chronic renal failure, tumoral obstruction, fibrosing mediastinitis
Classification of Pulmonary Arterial Hypertension by Etiology

Group 1-- Pulmonary Arterial Hypertension (PAH):
- Idiopathic (IPAH)
- Heritable (HPAH)
  - BMPR2
  - ALK-1, endoglin, SMAD9, CAV1, KCNK3
  - Unknown
- Drugs and toxins induced
- Associated with:
  - Connective Tissue Diseases
  - HIV Infection
  - Portal Hypertension
  - Congenital Heart Diseases
  - Schistosomiasis
  - Group 1’ Pulmonary Veno Occlusive Disease (PVOD) and/or Pulmonary Capillary Hemangiomatosis (PCH)
  - Group 1” Persistent pulmonary hypertension of the newborn (PPHN)

Clinical Classification of Other Forms of Pulmonary Hypertension

Group 2 -- Pulmonary Hypertension Due to Left Heart Disease  *(Most common)*

- Left ventricular systolic dysfunction
- Left ventricular diastolic dysfunction
- Valvular disease
- Congenital / acquired left heart inflow / outflow tract obstruction
Clinical Classification of Other Forms of Pulmonary Hypertension

Group 3 -- Pulmonary Hypertension Due to Lung Diseases and/or Hypoxemia *(Common)*

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
Clinical Classification of Other Forms of Pulmonary Hypertension

Group 4 -- Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Clinical Classification of Other Forms of Pulmonary Hypertension

Group 5 -- Pulmonary Hypertension with Unclear Multifactorial Mechanisms

- **Hematologic disorders**: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
- **Systemic disorders**: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- **Metabolic disorders**: glycogen storage disease, Gaucher disease, thyroid disorders
- **Others**: tumor obstruction, fibrosing mediastinitis, chronic renal failure

Elevated Pulmonary Artery Pressures Are Seen in Wide Range of Conditions

Image courtesy of Jean Elwing, MD
## Prevalence of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced EF heart failure</td>
<td>12 - 14 % of pts with HF</td>
</tr>
<tr>
<td>Preserved EF heart failure</td>
<td>12 % of pts with HF</td>
</tr>
<tr>
<td>COPD</td>
<td>20 - 50 % of pts with advanced lung disease</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>20 %</td>
</tr>
<tr>
<td>Chronic thromboembolic</td>
<td>0.5 - 3.8 % pts with acute pulmonary embolism</td>
</tr>
</tbody>
</table>
Prevalence of PAH in associated conditions

<table>
<thead>
<tr>
<th>Associated condition</th>
<th>Prevalence of PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic sclerosis</td>
<td>7 - 12 %</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>2 - 6 %</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Eisenmenger’s syndrome</td>
<td>1 - 12 % with systemic to pulmonary shunts 25 - 50 %</td>
</tr>
<tr>
<td>HIV infection</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>4.6 % with hepatic involvement</td>
</tr>
</tbody>
</table>
Diagnosing PAH: Assessment of Patients Presenting With Unexplained Dyspnea

- History including risk factors
- Physical examination
- Chest X-ray
- ECG
- PFT including DLCO
- Echocardiogram
- Chest CT
- Serology: HIV, Hepatitis B & C, ANA
- Ventilation-perfusion scan
- Right heart catheterization

Echocardiogram: Apical Four Chamber

Normal structure and function

Abnormal structure and function

Image courtesy of Vallerie McLaughlin, MD
Echocardiography: Tricuspid Regurgitation

Modified Bernoulli’s Equation:

\[ 4 \times (V)^2 + \text{RAP} = \text{RVSP} (\text{PASP}) \]

\( V = \) tricuspid jet velocity (m/s); \( \text{RAP} = \) right atrial pressure; \( \text{RVSP} = \) right ventricular systolic pressure; \( \text{PASP} = \) pulmonary artery systolic pressure.
Tricuspid Annular Plane Systolic Excursion (TAPSE)

Forfia et al. AJRCCM 2006; 174:1034-1041
Echocardiogram in Pulmonary Hypertension

Echocardiogram findings in pulmonary hypertension (PH)

- **RA/RV**
  - Right atrial enlargement (RAE), RV dilation
  - RV dysfunction
  - Decreased tricuspid annular plane excursion (TAPSE)
  - Elevated pulmonary artery pressure (PAP)

Echocardiogram findings in PH associated with left heart disease

- Left atrial enlargement (LAE), LVH, LV dilation
- LV systolic dysfunction
- Grade II/III diastolic dysfunction
- Mitral/aortic valvular disease
Echocardiographic Estimation of Pulmonary Hypertension in Clinical Practice

- In the echo lab a commonly measured and reported value is systolic pulmonary artery pressure or RVSP.

Normal resting values defined as peak systolic pressure of 35 or 36 mmHg.

- American College of Cardiology / American Heart Association expert consensus recommends further evaluation of patient with dyspnea and an estimated RVSP >40 mm Hg.

- Echo-derived reports of PH are not considered diagnostic.

- **Further work-up is required**

PH by Echo ≠ PAH

- Single echo lab/Australian community of 160,000
- Etiology of PH noted on echocardiogram

N=483 of 4579 patients with echo PASP >40 mm Hg.
Gabby E. Am J Respir Crit Care Med. 2007;175:A713.
Diagnostic Testing Results Frequently Found with PAH

Pulmonary function testing
- Preserved pulmonary mechanics
- Isolated low DLco
- Example: FEV1 88%, FVC 86%, DLco 42%

V/Q
- No evidence of acute or chronic PE

CT chest
- Lack of significant parenchymal disease
- Enlarged PA/RA/RV

Overnight pulse oximetry
- Normal or mild hypoxemia

Polysomnogram
- Normal or controlled OSA
Ventilation Perfusion (V/Q) Scintigraphy in CTEPH

Case Example:
Perfusion is intact primarily to the right upper lobe

Blue Arrows:
Hypo-perfused regions representing perfusion defects

CT Findings Suggestive of PH

- Ratio of diameters of main pulmonary artery to ascending aorta (PA/Ao) ≥1.0 should prompt investigation for PH
  - Sensitivity 75%, specificity 92%, positive predictive value 95%, negative predictive value 64%

- RV/LV ratio ≥1.20 measured on the axial view or PA/Ao ≥1.0
  - Sensitivity 94%, specificity 80%, positive predictive value 91%, negative predictive value 87%

CT-Chest: RA, RV, PA Enlargement

Enlarged PA, RV, RA, Pleural Effusions
Lack of Significant Parenchymal Disease

Image courtesy of Jean Elwing, MD
V/Q Scan More Sensitive Than CTA

<table>
<thead>
<tr>
<th></th>
<th>V/Q High-Probability Scans</th>
<th>CTPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.2%</td>
<td>51.3%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.6%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>95.2%</td>
<td>82.8%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>97.9%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>90.3%</td>
<td>97.6%</td>
</tr>
</tbody>
</table>

N=227 single center.

6MWT

Baseline 6MWD and survival at 1 year

REVEAL Registry data - Farber HW: 2015 JHLT 34
6MWT

Percent Change in 6MWD and survival at 1 year

REVEAL Registry data - Farber HW: 2015 JHLT 34
Right heart catheterization is necessary to establish cause of pulmonary hypertension.
Low Use of Right Heart Catheterization Prior to Initiation of PAH-specific Medications

N=1,159 patients receiving PAH-specific medications from national (US) private insurance database. Patients were enrolled continuously for 27 months (12 months prior and 15 months after initial office visit for PH).

PAH (Group 1)
Hypoxic/Lung
CTEPH

†PVR
†TPG

PH

PAH

PVH

†PAOP
†LVEDP
†LAP

LH Disease
PV Obstruction

†CO
Thyrotoxicosis
Anemia
Pregnancy
Some PoPH

†PBF
Right Heart Catheterization

Which hemodynamic profile is associated with PAH?

1. RAP 13, PAP 70/25 (40), wedge 25, CO 5, PVR 3
2. RAP 15, PAP 80/42 (55), wedge 10, CO 3.5, PVR 13
3. RAP 11, PAP 60/18 (32), wedge 15, CO 10, PVR 1.7
4. None of the above

RAP - Right atrial pressure (mmHg)
PAP – Pulmonary artery pressure (mmHg)
Wedge – pulmonary capillary wedge pressure (mmHg)
CO – Cardiac output L/min
CI – Cardiac index L/min/m²
PVR = mPAP – wedge / CO
What RHC’s Will and Will Not Show Us

- If there is Group II disease through elevated Wedge pressure
- Show severity of disease through PVR and CO and RA and pressures
- If PH is present and NOT group II,
  - The RHC will NOT tell us if the PH is PAH, Group III or Group IV (CTEPH)
Facts About Pulmonary Hypertension

- Pulmonary Hypertension represents a group of diseases that manifest themselves in increased pressures in the pulmonary arteries.

- The group that has been subject of the most attention has been Pulmonary Arterial Hypertension (disease in the vasculature of the lungs).

- It is of outmost importance to ask these questions face with the statement: “Patient has Pulmonary Hypertension”
  - Verify if the patient truly has PH and What kind of pulmonary hypertension?
  - Why does the patient have it?
  - How severe is the disease?
Survival in PAH phenotypes is decreased and similar to metastatic breast cancer

Long-term Survival From Time of Diagnosis of PAH in the REVEAL Registry


Survival in REVEAL Patients With PAH Matched to NIH Cohort

- Predicted survival by NIH equation
- REVEAL weighted to match NIH cohort

At Risk:
- Matched REVEAL: 279, 377, 390, 388, 328, 240, 153, 88

Survival (%) vs. Time From Diagnosis (years)
# 2015 ESC/ERS Guidelines: Disease Progression Risk Factors in PAH

<table>
<thead>
<tr>
<th>Determination of prognosis (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5-10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<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>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165-440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; &gt; 15 ml/min/kg (&gt;65% pred.) VE/VCO&lt;sub&gt;2&lt;/sub&gt; slope &lt;36</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; 11-15 ml/min/kg (35-65% pred.) VE/VCO&lt;sub&gt;2&lt;/sub&gt; slope 36-44.9</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO&lt;sub&gt;2&lt;/sub&gt; slope 45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt; 50 ng/l NT-proBNP &lt;300 ng/l</td>
<td>BNP 50-300 ng/l NT-proBNP 300-1400 ng/l</td>
<td>BNP &gt;300 ng/l NT-proBNP &gt;1400 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm&lt;sup&gt;2&lt;/sup&gt; No pericardial effusion</td>
<td>RA area 18-26 cm&lt;sup&gt;2&lt;/sup&gt; No or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm&lt;sup&gt;2&lt;/sup&gt; Pericardial effusion</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;8 mmHg CI 2.5 l/min/m&lt;sup&gt;2&lt;/sup&gt; SvO&lt;sub&gt;2&lt;/sub&gt; &gt;65%</td>
<td>RAP 8-14 mmHg CI 2.0-2.4 l/min/m&lt;sup&gt;2&lt;/sup&gt; SvO&lt;sub&gt;2&lt;/sub&gt; 60-65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m&lt;sup&gt;2&lt;/sup&gt; SvO&lt;sub&gt;2&lt;/sub&gt; &lt;60%</td>
</tr>
</tbody>
</table>

Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk). If N-terminal proBNP is available and BNP is not, listed cut points are replaced with < 300 pg/mL and > 1500 pg/mL.

Survival Based on Reveal Score

B

Risk calculator

Risks strata

- Score = 1–7 (n = 159)
- Score = 8 (n = 98)
- Score = 9 (n = 86)
- Score = 10–11 (n = 115)
- Score ≥ 12 (n = 46)

No. at risk:

<table>
<thead>
<tr>
<th>Score = 1–7</th>
<th>159</th>
<th>156</th>
<th>155</th>
<th>151</th>
<th>150</th>
<th>150</th>
<th>141</th>
<th>140</th>
<th>139</th>
<th>120</th>
<th>120</th>
<th>119</th>
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<tbody>
<tr>
<td>Score = 8</td>
<td>98</td>
<td>93</td>
<td>91</td>
<td>89</td>
<td>87</td>
<td>86</td>
<td>84</td>
<td>81</td>
<td>81</td>
<td>71</td>
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<tr>
<td>Score = 9</td>
<td>86</td>
<td>84</td>
<td>84</td>
<td>81</td>
<td>80</td>
<td>78</td>
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<td>73</td>
<td>72</td>
<td>65</td>
<td>64</td>
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<tr>
<td>Score = 10–11</td>
<td>115</td>
<td>107</td>
<td>102</td>
<td>99</td>
<td>96</td>
<td>95</td>
<td>95</td>
<td>85</td>
<td>85</td>
<td>82</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>Score ≥ 12</td>
<td>46</td>
<td>42</td>
<td>40</td>
<td>38</td>
<td>38</td>
<td>36</td>
<td>35</td>
<td>31</td>
<td>29</td>
<td>28</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

Survival (%) over Months from enrollment.
(A) Patients with pulmonary vascular resistance (PVR) 650 dyne·s·cm\(^{-5}\) showed better survival rates than patients with PVR 650 (p < 0.04).

(B) Patients with right ventricular ejection fraction (RVEF) 35% showed better survival rates compared with RVEF 35% (p < 0.001).

(C) Survival rates based on the coupling of PVR and RVEF. PAH pulmonary arterial hypertension.

van de Veerdonk et al. J Am Coll Cardiol 2011;58:2511–9
Treatment Goals

Sitbon O & Galie N: 2010 Eur Res Rev 19: 118
# PAH-specific FDA-approved Therapies for Use in the US

<table>
<thead>
<tr>
<th>Endothelin Receptor Antagonists</th>
<th>NO-cGMP Pathway</th>
<th>Prostanoids – Prostacyclin Analogs</th>
<th>Prostacyclin Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bosentan (PO)</strong>&lt;br&gt;FDA Approved: 2001</td>
<td><strong>Sildenafil (PO)</strong>&lt;br&gt;FDA Approved: June 2005</td>
<td><strong>Epoprostenol (IV)</strong>&lt;br&gt;FDA Approved: September 1995&lt;br&gt;FDA Approved: June 2008</td>
<td><strong>Selexipag (PO)</strong>&lt;br&gt;FDA Approved: December 2015</td>
</tr>
<tr>
<td><strong>Ambrisentan (PO)</strong>&lt;br&gt;FDA Approved: June 2007</td>
<td><strong>Tadalafil (PO)</strong>&lt;br&gt;FDA Approved: May 2009</td>
<td><strong>Treprostinil (IV, SC, PO, and inhaled)</strong>&lt;br&gt;First (SC formulation)&lt;br&gt;FDA Approved: July 2002</td>
<td></td>
</tr>
<tr>
<td><strong>Macitentan (PO)</strong>&lt;br&gt;FDA Approved: October 2013</td>
<td><strong>Riociguat (PO)</strong>&lt;br&gt;FDA Approved: October 2013</td>
<td><strong>Iloprost (inhaled)</strong>&lt;br&gt;FDA Approved: December 2004</td>
<td></td>
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</tbody>
</table>

# Initial Therapy with Approved PAH Drugs—Recommendations

## Initial Therapy with Approved PAH Drugs

**RED**: Clinical trials supporting approval utilized mortality and morbidity endpoints in randomized controlled studies or reduced all-cause mortality. Level of evidence is based on the WHO FC and the majority of patients in supportive trials.

<table>
<thead>
<tr>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan</td>
<td>Ambrisentan</td>
<td>Epoprostenol (IV)</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Bosentan</td>
<td>Ambrisentan</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Macitentan</td>
<td>Bosentan</td>
</tr>
<tr>
<td>Riociguat</td>
<td>Riociguat</td>
<td>Macitentan</td>
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<tr>
<td>Sildenafil</td>
<td>Sildenafil</td>
<td>Riociguat</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Tadalafil</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Selexipag**</td>
<td>Treprostinil (SC or inhaled)</td>
<td>Tadalafil</td>
</tr>
<tr>
<td></td>
<td>Iloprost (inhaled)</td>
<td>Treprostinil (SC, IV, inhaled) (oral*)</td>
</tr>
<tr>
<td></td>
<td>Epoprostenol Selexipag**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iloprost (IV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treprostinil (IV) (oral*)</td>
<td></td>
</tr>
</tbody>
</table>

**Beraprost***

*Oral treprostinil was approved by the FDA in December 2013, for treatment of WHO Group I patients to improve exercise capacity.

**Selexipag was approved by the US FDA in December 2015.

***Beraprost approved in Japan, not in the US.

---

Calcium Channel Blockers:

-only to be used on a patients that had a right heart catheterization and had a response to vasodilators;

AND NO ONE ELSE!

---

Both groups showed acute vasoreactivity to either epoprostenol or NO.

Acute vasoreactivity (iNO / iloprost / adenosine)
- Decrease in mPAP by > 10 and to < 40 mm Hg with an unchanged / improved CO.
Combination Therapy

Sequential / Add on

1

1+2+3

1+2

Upfront

1+2+3
Combination Therapy Reduces Risk of Events Compared to Ambrisentan or Tadalafil Monotherapy

SERAPHIN: Macitentan, Monotherapy or Sequential Combination Therapy

61% of patient population were on background PDE-5 inhibitor therapy at study enrollment. 5% were receiving oral/inhaled prostanoids.

N=742. Double-blind, placebo-controlled Phase III study. Primary endpoint was time to first event related to PAH [worsening of PAH, initiation of IV or SC prostanoids, lung transplantation, or atrial septostomy] or all-cause death.

## Guidelines

### 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan + tadalafil</td>
<td>I, B, I, B</td>
</tr>
<tr>
<td>Other ERA + PDE-5i</td>
<td>IIa, C, IIa, C</td>
</tr>
<tr>
<td>Bosentan + sildenafil + i.v. epoprostenol</td>
<td>IIa, C, IIa, C</td>
</tr>
<tr>
<td>Bosentan + i.v. epoprostenol</td>
<td>IIa, C, IIa, C</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + s.c. treprostinil</td>
<td>IIb, C, IIb, C</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + other i.v. prostacyclin analogues</td>
<td>IIb, C, IIb, C</td>
</tr>
</tbody>
</table>

### Measure/ Treatment

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan + tadalafil</td>
<td>I, B, I, B</td>
<td>IIb, C</td>
<td></td>
</tr>
<tr>
<td>Other ERA + PDE-5i</td>
<td>IIa, C</td>
<td>IIa, C</td>
<td>IIb, C</td>
</tr>
<tr>
<td>Bosentan + sildenafil + i.v. epoprostenol</td>
<td>IIa, C</td>
<td>IIa, C</td>
<td>IIa, C</td>
</tr>
<tr>
<td>Bosentan + i.v. epoprostenol</td>
<td>IIa, C</td>
<td>IIa, C</td>
<td>IIa, C</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + s.c. treprostinil</td>
<td>IIb, C</td>
<td>IIb, C</td>
<td>IIb, C</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + other i.v. prostacyclin analogues</td>
<td>IIb, C</td>
<td>IIb, C</td>
<td>IIb, C</td>
</tr>
</tbody>
</table>

### Classes of Recommendations

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Suggested wording to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
<td>Is recommended/indicated</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
<td></td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
<td>Should be considered</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
<td>May be considered</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
<td>Is not recommended</td>
</tr>
</tbody>
</table>

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Cleveland Clinic Florida
# General PAH Care

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>In general, IPAH patients receive anticoagulant therapy. Anticoagulation therapy should be considered for patients with secondary PAH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Hypoxia is a potent vasoconstrictor and can elevate PA pressure.</td>
</tr>
</tbody>
</table>
| Fluid/volume control | Diuretics  
|                 | Fluid restriction  
|                 | Low salt diet |

IPAH=idiopathic pulmonary arterial hypertension; PA=pulmonary artery; PAH=pulmonary arterial hypertension.
A Problem

- 15 to 30% of patients self-discontinue medications, with adverse effects and lack of perceived benefits being the most common reasons.

BJU Int. 2010;105(9):1276-82
Personal Communication with Marketing and sales of Advanced Lung Disease related Pharmaceutical Companies
The “Side Effect” Problem

- Lack of Communication Regarding Adverse Events
  - Lack of understanding by the patients
  - Lack of clear/contextual vocabulary
  - Lack of adequate explanation/contextualization by providers

- Lack of Guidance on prevention and management of adverse events
Adverse Events (AE)

- An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality or relationship to the drug.

- An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.
The FDA recommends classifying adverse events on the basis of “seriousness, severity, frequency, and strength of causal relationship.” Serious adverse effects, such as those resulting in hospitalization or death, are classified as ‘boxed warnings’ and receive detailed description.

Common adverse effects are defined as those “occurring at a rate of 10 percent or greater.”

The FDA further recommends avoiding “exhaustive lists of every reported adverse event, including those that are infrequent or minor” claiming that such lists are “not informative and tend to obscure the more clinically meaningful information.”
AE Management Interventions

Example: Nausea with Orenitram

- Non Pharmacological
  - Take meds with Caloric Food

- Pharmacological
  - First Line
    - Ondansetron (Zofran™)
    - PPI’s
  - Second Line
    - Prochlorperazine (Compazine™-Oral/ Suppository)
    - Oral Promethazine (Phenergan™)

- Dose Down Titration/ Holiday/ (followed by possible Re-Uptitration)

Suggested Follow-up

<table>
<thead>
<tr>
<th>Test</th>
<th>At baseline</th>
<th>Every 3–6 months(^a)</th>
<th>Every 6–12 months(^a)</th>
<th>3–6 months after changes in therapy(^a)</th>
<th>In case of clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical assessment and determination of functional class</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ECG</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6MWT/Borg dyspnoea score</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CPET</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Echo</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Basic lab(^b)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Extended lab(^c)</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Blood gas analysis(^d)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>+</td>
<td>+(^f)</td>
<td>+(^e)</td>
<td>+(^e)</td>
<td>+(^e)</td>
</tr>
</tbody>
</table>