Pulmonary Arterial Hypertension - Overview

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PAH Overview Outline

• Background and definition
• Clinical classification
• Epidemiology
• Pathophysiology/Natural history
• Signs and symptoms/diagnosis
• Importance of right heart catheterization
• PAH management trends and outcomes
• Treatment options
PAH Background

- Rare disease (orphan designation) of the pulmonary microvasculature affecting 15 to 50 people per million inhabitants in the Western world\(^1\)
  - Affects all races
  - Affects all ages; however, most prevalent in 4th and 5th decades of life
  - Higher prevalence in females


PAH Background

- Global burden of PAH may be underestimated because of:\(^1,2\)
  - Underdiagnosis (eg, nondescript symptoms)
  - Misdiagnosis (eg, asthma, left-heart disease)
  - Increasing risk factors (eg, HIV infection, schistosomiasis)

PAH Defined

- Mean PAP ≥ 25 mm Hg
- PCWP ≤ 15 mm Hg
- PVR > 3 Wood units

► Increased pressure load on RV
► Diagnosis of exclusion

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clincal group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥ 25 mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>PAPm ≥ 25 mmHg</td>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>PAWP ≤ 15 mmHg</td>
<td>3. PH due to lung diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Chronic thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>PAPm ≥ 25 mmHg</td>
<td>2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td></td>
<td>PAWP &gt; 15 mmHg</td>
<td></td>
</tr>
<tr>
<td>Isolated post-capillary PH</td>
<td>DPG &lt; 7 mmHg</td>
<td></td>
</tr>
<tr>
<td>(Ipc-PH)</td>
<td>and/or PVR &lt; 3 WU</td>
<td></td>
</tr>
<tr>
<td>Combined post-capillary PH</td>
<td>DPG &gt; 7 mmHg</td>
<td></td>
</tr>
<tr>
<td>and pre-capillary PH (Cpc-PH)</td>
<td>and/or PVR &gt; 3 WU</td>
<td></td>
</tr>
</tbody>
</table>

*European Heart Journal, Volume 37, Issue 1, 1 January 2016, Pages 67–119, https://doi.org/10.1093/eurheartj/ehv317*
### The 2013 Nice Classification of PAH

**5th WSPH**

- **Pulmonary Arterial Hypertension (1)**
  - Heritable PAH (FPAH)
  - Idiopathic PAH (IPAH)
  - Drug and toxin-induced
  - Associated PAH (APAH)
    - Connective tissue disease (CTD)
    - Human immunodeficiency virus (HIV)
    - Portal hypertension
    - Schistosomiasis
    - Congenital heart disease (CHD)
  - Persistent pulmonary hypertension of the newborn (PPHN)
    1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

- **Pulmonary Venous Hypertension (2)**
  - Heart failure (normal or low EF)
  - Valvular disease
  - Congenital Heart Disease
- **PH due to lung disease / hypoxemia**
  - Obstructive sleep apnea
  - Interstitial Lung disease
  - COPD/asthma
  - Mixed restrictive/obstructive
  - High altitude
  - Developmental disorders
- **CTEPH (4)**
- **Multifactorial (5)**
  - Metabolic - Thyroid disease
  - Hematological – splenomegaly
  - Systemic – sarcoidosis
WHO Classification: Group 1

<table>
<thead>
<tr>
<th>Group 1—PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PAH</td>
</tr>
<tr>
<td>Heritable</td>
</tr>
<tr>
<td>BMPR2</td>
</tr>
<tr>
<td>ALK-1, endoglin (with or without HHT)</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Drug and toxin-induced</td>
</tr>
<tr>
<td>PAH associated with:</td>
</tr>
<tr>
<td>Connective tissue diseases</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Congenital systemic to pulmonary shunts</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Chronic hemolytic anemia</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension of newborn</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis</td>
</tr>
</tbody>
</table>

Epidemiology of PAH (WHO Group 1)

- Prevalence of PAH in associated conditions:
  - CTD\textsuperscript{a}: 8%-12%\textsuperscript{2,3}
  - CHD: 15%-30%\textsuperscript{4}
  - PoPH: 2%-6%\textsuperscript{5,6}
  - HIV: 0.5%\textsuperscript{7}

PATHOPHYSIOLOGY/NATURAL HISTORY

Progression of Pulmonary Vascular Disease

- **Right Ventricle**
  - Normal
  - Compensated
  - Failure

- **Pulmonary Arteries**
  - Thin RV wall
  - Healthy PA endothelium
  - Thin-walled relaxed PAs
  - Large capillary network
  - Normal CO & PVR and perfusion

- **Hypertrophied RV**
  - Abnormal PA endothelium
  - Constricted stiff PAs
  - Loss of microvessels
  - Normal CO, mild ↑ PVR, moderate ↓ in perfusion

- **Dilated RV**
  - Cell proliferation in PA wall
  - Obliterative PA remodeling
  - Severe ↓ CO and perfusion, with severe ↑ PVR
Consequences of PAH

- ↑ PVR
- ↑ RV afterload
- ↓ RV ejection (CO) and PBF
- RV hypertrophy and dilation
- Death

Echocardiographic Characteristics of PAH

Parasternal view

Apical 4-chamber view

Echocardiography provides estimated RV systolic pressure and morphologic cardiac abnormalities
Tricuspid Regurgitation

Echocardiography in PAH

Tricuspid regurgitation (TR)

TR jet velocity (v)

Syst PAP = Right Ventricular Systolic Pressure
(in absence of pulmonary outflow obstruction)
RVSP = 4v² + RAP*

Estimation of RAP

<table>
<thead>
<tr>
<th>Findings</th>
<th>Estimated RAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small &amp; collapse</td>
<td>0–5 mmHg</td>
</tr>
<tr>
<td>Normal &amp; normal size</td>
<td>5–10 mmHg</td>
</tr>
<tr>
<td>Normal &amp; abnormal size</td>
<td>10–15 mmHg</td>
</tr>
<tr>
<td>Dilated &amp; abnormal size</td>
<td>15–20 mmHg</td>
</tr>
<tr>
<td>Dilated &amp; no change in size</td>
<td>&gt;20 mmHg</td>
</tr>
</tbody>
</table>

PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient.

Schematic Progression of PAH

Pre-symptomatic/Compensated

Symptom Threshold

CO=\frac{TPG}{PVR}

Time

PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient.

Courtesy of: Valerie V. McLaughlin, MD.
Schematic Progression of PAH

Pre-symptomatic/Compensated
Symptomatic/Decompensating

CO = \frac{TPG}{PVR}

Symptom Threshold

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; TPG = transpulmonary gradient.

Courtesy of: Vallerie V. McLaughlin, MD.
## PAH Determinants of Risk

<table>
<thead>
<tr>
<th>Determinants 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 VO₂ &gt;15 ml/min/kg (&gt;65% pred.) VE/VCO₂ slope &lt;36</td>
<td>Peak VO₂ 11–15 ml/min/kg (35–65% pred.) VE/VCO₂ slope 36–44.9</td>
<td>Peak VO₂ &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO₂ 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 cm² No pericardial effusion</td>
<td>RA area 18–26 cm² No or minimal pericardial effusion</td>
<td>RA area ≥26 cm² Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg CI ≥2.5 l/min/m² SvO₂ &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m² SvO₂ 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m² SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>

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**Survival by PAH Etiology**

![Survival by PAH Etiology graph](Chart.png)

SIGNS, SYMPTOMS & DIAGNOSIS

- Dizziness and/or fainting (syncope)
- Shortness of breath (dyspnea)
- Chest pain (angina)
- Rapid, hard, or irregular heartbeats (palpitations)
- Swollen abdomen (ascites)
- Feeling tired or worn out (fatigue)
- Swollen ankles or legs (edema)
REVEAL: Most Frequent PAH Presenting Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea at rest</td>
<td>11.5%</td>
</tr>
<tr>
<td>Cough</td>
<td>13.8%</td>
</tr>
<tr>
<td>Dizziness/confusion</td>
<td>15.0%</td>
</tr>
<tr>
<td>Presyncope/syncope</td>
<td>16.5%</td>
</tr>
<tr>
<td>Edema</td>
<td>21.9%</td>
</tr>
<tr>
<td>Chest pain/discomfort</td>
<td>22.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26.7%</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>26.2%</td>
</tr>
</tbody>
</table>

- Diagnosed ≤2 years after symptom onset (n=1,967)
- Diagnosed >2 years after symptom onset (n=526)

NYHA Functional Classification

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No symptoms with ordinary physical activity</td>
</tr>
<tr>
<td>Class II</td>
<td>Some symptoms with ordinary activity. Slight limitation of activity</td>
</tr>
<tr>
<td>Class III</td>
<td>Symptoms with less than ordinary activity. Marked limitation of activity</td>
</tr>
<tr>
<td>Class IV</td>
<td>Symptoms with any activity or even at rest</td>
</tr>
</tbody>
</table>
WHO Functional Classification

<table>
<thead>
<tr>
<th>WHO</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with PAH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with PAH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with PAH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea or fatigue may even be present at rest. Discomfort is increased by any physical activity</td>
</tr>
</tbody>
</table>

Diagnosis of PAH

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Evaluate signs and symptoms, family history, associated diseases, ANA</td>
</tr>
<tr>
<td>Chest x-ray&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Assess for RV enlargement, peripheral hypovascularity (pruning), and prominent pulmonary arteries</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Assess for RV and RA enlargement, RV dysfunction, TR velocity to measure RVSP</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Evaluate for right heart enlargement and strain, cardiac rhythm</td>
</tr>
<tr>
<td>Cardiac catheterization&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Evaluate for CHD; measure wedge pressure or LVEDP; establish severity and prognosis; test vasodilator therapy</td>
</tr>
<tr>
<td>PFTs with DLCO</td>
<td>Assess obstructive and restrictive airway disease</td>
</tr>
<tr>
<td>VQ scan</td>
<td>Rule out thromboembolic disease</td>
</tr>
</tbody>
</table>
PAH Diagnostic Testing

Pivotal Tests
- History
- Exam
- CXR
- ECG
- Echocardiogram
- VQ Scan
- PFTs
- Overnight Oximetry

Contingent Tests
- TEE
- Exercise Echo
- Pulmonary Angiography
- Chest CT Angiogram
- Coagulopathy Profile
- ABGs
- Polysomnography

Contribute to Assessment of:
- Index of Suspicion of PH
- RVE, RAE, ↑RVSP, RV Function
- Left Heart Disease
- VHD, CHD
- Chronic PE
- Ventilatory Function
- Gas Exchange
- Sleep Disorder
- HIV Infection
- Scleroderma, SLE, RA
- Portopulmonary Hypertension
- Establish Baseline
- Prognosis
- Confirmation of PH
- Hemodynamic Profile
- Vasodilator Response

Functional Test (6MWT, CPET)
- Vasodilator Test
- Exercise RH Cath
- Volume Loading
- Left Heart Cath

Right Heart Cath

Chest X-Ray Consistent With PH

RA enlargement, prominent PA
Loss of retrosternal airspace RV enlargement
CT-Chest: Pulmonary Dilation

Dilated Pulmonary Artery

PA Dilation 3.9cm

PA size and ratio vary by patient size and sex.
Sex-specific cutoff values:
- Men 29 mm
- Women 27 mm
Normal PA:aortic ratio = 0.9


CT-Chest: RA, RV, PA Enlargement

Enlarged PA, RV, RA, Pleural Effusions
Lack of Significant Parenchymal Disease
Ventilation Perfusion (V/Q) Scintigraphy in CTEPH

Case Example:
Perfusion is intact primarily to the right upper lobe
Hypo-perfused regions representing perfusion defects


Pulmonary Hypertension

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Right Heart Catheterization

- Confirm diagnosis
  - Gold standard
- Evaluate severity of PAH
- Assess congenital heart defects
- Exclude left-sided heart disease
- Assess response to vasodilator challenge
- Assess key hemodynamic parameters
Importance of Right Heart Catheterization

- Vast majority of PH cases are non–WHO group 1
- **PAH** characterized by
  - $↑$ PVR
  - $↑$ TPG
  - Normal left-sided filling pressures
- **PVH** characterized by
  - $↑$ PCWP
  - $↑$ LVEDP
  - $↑$ LAP

PAH Disease Pathways

↓ vasoconstriction
↓ proliferation
## PAH Disease Pathways

- **Soluble GC Stimulator**
  - Enhancing the sensitivity of sGC to nitric oxide NO
  - Direct sGC stimulator that will activate sGC to synthesize cGMP in the absence of NO

- **Nitric Oxide Deficiency**
  - PDE-5 inhibitors block the activity of PDE-5, restoring vasodilation through an increase in cGMP

- **Prostacyclin**
  - Supplement the deficiency in PGI2, resulting in vasodilation and inhibition of platelet aggregation.

- **Endothelin Receptor Antagonists**
  - Block the binding of ET-1 to its receptors, preventing a vasoconstriction effect

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## TREATMENT OF PULMONARY ARTERIAL HYPERTENSION
## PAH Treatment Goals

- Improve quality of life and survival
- Improve to FC I or II
- Improve 6MWD to $\geq 380$ m
- Improve hemodynamics
- Alleviate symptoms

## PAH Treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin Receptor Antagonists</td>
<td>Bosentan, Ambrisentan, Macitentan</td>
</tr>
<tr>
<td>Phosphodiesterase Inhibitors</td>
<td>Sildenafil, Tadalafil</td>
</tr>
<tr>
<td>Soluble GC Stimulator</td>
<td>Riociguat</td>
</tr>
<tr>
<td>Prostanoids</td>
<td>Epoprostenol (IV), Treprostinil (IV, SQ, inhaled, oral), Iloprost (inhaled), Selexipeg (oral)</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td></td>
</tr>
</tbody>
</table>
Prostanoids - Infused

- Treprostinil
  - The Crono Five
  - CADD MS-3® (microinfusion pump)
    - Subcutaneous or Intravenous infusion
  - Canò Crono Five
    - Expanded reservoir
    - Miniaturized pump
    - Intravenous infusion
  - CADD Legacy®
    - Intravenous infusion

- Epoprostenol
  - CADD Legacy®
    - Intravenous infusion

Prostanoids -- Inhaled

- Iloprost
  - I-neb® AAD®

- Treprostinil
  - Tyvaso Inhalation System
Calcium Channel Blocker Therapy

- Used for patients with IPAH who respond to acute vasodilator testing at the time of cardiac catheterization
  - Response defined by reduction in mPAP ≥10 mm Hg to a mPAP ≤40 mm Hg, with an unchanged or increased CO

- Approximately 13% of patients with IPAH respond to acute vasodilator testing
  - Only 6.8% had a favorable clinical response to chronic CCB therapy at 1 year

- Other PAH treatments should be evaluated if patient does not improve to FC I or II


PAH MANAGEMENT TRENDS & OUTCOMES
Treatment Algorithm for PAH

- **Treatment naive patient**
  - PAH confirmed by expert center
    - Acute vasoreactivity test (IPAH/HPAH/DPAH only)
      - CCB Therapy (Table 18)
        - Vasoreactive
          - Low or intermediate risk (WHO FC II–III)
            - Initial monotherapyb (Table 19)
            - Initial oral Combinationb (Table 20)
            - Consider referral for lung transplantation
          - High risk (WHO FC IV)
            - Initial combination including i.v. PCA c (Table 20)
            - Consider listing for lung transplantation² (Table 22)
        - Non-vasoreactive
          - Consider listing for lung transplantation² (Table 22)
    - General measures (Table 16)
      - Supportive therapy (Table 17)

- **Patient already on treatment**
  - Inadequate clinical response (Table 15)
  - Double or triple sequential combination (Table 21)


Ambition: upfront combination of Tadalafil + Letairis

- Combination therapy
- Pooled monotherapy

P < 0.001

MORTALITY IN PATIENTS WITH PAH IN THE MODERN ERA: DATA FROM THE QUALITY ENHANCEMENT RESEARCH INITIATIVE (QUERI)

QuERI Methods

- Despite advances in PAH therapy, patient mortality remains unacceptably high
- Although ACCP guidelines have been developed to assist clinicians in managing patients with PAH, the effectiveness of these guidelines is unclear
- Database was designed to collect information regarding medical management of patients with PAH initiated in 2005. Newly and previously diagnosed patients were enrolled (N=782)
  - Patients were enrolled from PAH centers and community centers
- Study determined whether ACCP guidelines were followed, including RHC for diagnosis
QuERI: Patient Demographics and Baseline Characteristics\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Disease subtype, %</th>
<th>All cases (N=782)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>38</td>
</tr>
<tr>
<td>Familial</td>
<td>3</td>
</tr>
<tr>
<td>Connective tissue diseases</td>
<td>30</td>
</tr>
<tr>
<td>Congenital heart diseases</td>
<td>7</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Drug exposure</td>
<td>7</td>
</tr>
<tr>
<td>HIV infection</td>
<td>4</td>
</tr>
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</table>

WHO functional class, %

<table>
<thead>
<tr>
<th>Class</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>39</td>
</tr>
<tr>
<td>III</td>
<td>48</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
</tr>
</tbody>
</table>


QuERI: Overall PAH Therapy Use in Enrolled Population\textsuperscript{1,2}

ERA, endothelin receptor antagonist; PDE-5i, phosphodiesterase type 5 inhibitor; QuERI, Quality Enhancement Research Initiative.

QuERI: 1-Year Mortality Remains High in FC IV Patients\textsuperscript{1,2}

![Bar chart showing 1-Year mortality in WHO FC classes: II (9%), III (29%), IV (46%), with note: <30% on prostanoid.]

FC, functional class; QuERI, Quality Enhancement Research Initiative; WHO, World Health Organization.


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QuERI: Current Use of CCB Therapy

![Bar chart showing 115 patients on CCB, with 87% not responding to acute vasoreactivity testing and 10% receiving PAH therapy without RHC-confirmed diagnosis.]

- 87% of patients receiving CCB did not respond to acute vasoreactivity testing
- ~10% were receiving PAH therapy without RHC-confirmed diagnosis

Has Survival Meaningfully Improved With Modern Therapies?

Conclusions

- PAH is a rare disease associated with very high mortality if untreated.
- PAH is a diagnosis of exclusion and diagnosis requires a comprehensive cardiopulmonary evaluation as well as a right heart catheterization.
- Current guidelines recommend use of upfront combination therapy, if tolerated.
- Patients with advanced PAH and right heart failure, should be treated with parental prostacyclins alone or in combination with other oral specific PAH vasodilators.
- Goals of care: functional capacity class I or II and normal right ventricular function.