Pulmonary Arterial Hypertension: The Cornucopia of New Drugs

Muhyaldeen Dia, MD, F.A.C.C.
Advocate Heart Institute
Pulmonary Hypertension

Definition

- Not a disease, but a collection of conditions characterized by an elevation in PAP
- Defined as a chronic increase in mPAP of ≥25 mmHg at rest as assessed by right heart catheterization
  - Normal arterial pressure is ~14 (±3) mm Hg
- Ultimately results in right heart failure and death
- Often undetected until it is quite advanced

- PAPm 25 mm Hg at rest by right-heart catheterization
- PVR > 3 Wood units remains part of definition
- PAPm levels between 21 and 24 mm Hg
  - Insufficient data to support use of the term “borderline PH”
  - Prognostic and therapeutic implications unknown
  - Patients should be carefully followed, particularly if at risk for developing PAH (eg, CTD, family with IPAH/heritable PAH)

PAH

- Rare disease with an incidence of 5-10 cases/million population/year
- Caused by progressive structural remodeling of the small pulmonary arteries due to pulmonary arterial endothelial cell dysfunction
- Treatable: 9 agents approved targeting 3 main pathways
  - Endothelin (block with endothelin receptor antagonists)
  - Nitric oxide (improve with PDE-5 inhibitors/sGC stimulators)
  - Prostacyclin (target with prostacyclin analogs or prostacyclin receptor agonists)
- Transplantation is a key treatment option in those who are refractory to drug therapy

Updated Classification of PH

- Group 1: PAH
  - Idiopathic PAH
  - Heritable PAH
    - Bone morphogenetic protein receptor type II
    - Activin receptor-like kinase 1, endoglin, SMAD9, caveolin 1, potassium channel subfamily K member 3
    - Unknown
  - Drug- and toxin-induced
  - Associated with
    - Connective tissue disease
    - HIV infection
    - Portal hypertension
    - Congenital heart diseases
    - Schistosomiasis

- Group 1’: Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis

- Group 1”’: Persistent PH of the newborn

- Group 2: PH caused by left heart disease
  - Left ventricular systolic dysfunction
  - Left ventricular diastolic dysfunction
  - Valvular disease
  - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Updated Classification of PH (Cont)

• Group 3: PH caused by lung diseases and/or hypoxia
  – 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
  – Developmental lung diseases

• Group 4: CTEPH

• Group 5: PH with unclear multifactorial mechanisms
  – Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
  – Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
  – Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
  – Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

PAH Challenges

High-Risk Populations

- Risk factors for PH include:
  - Connective tissue disease (e.g., scleroderma, lupus)
  - HIV infection
  - Congenital heart disease
  - Obesity
  - Sleep apnea
  - Chronic obstructive pulmonary disease and other lung disease
  - Left heart disease
  - Recreational drug (e.g., methamphetamines, cocaine) and appetite suppressant (e.g., fenfluramine) use
  - Recent acute pulmonary embolism
  - Sickle cell disease

Screening high-risk populations for PAH → population enrichment for diagnostic RHC
PAH Challenges

Diagnosis (cont)

- REVEAL Registry™
  - 2555 previously and 960 newly diagnosed patients with PAH from 55 centers; 2007 to 2011
  - Female-to-male ratio: 4.07:1
  - Mean age: 53 ± 14 years
  - Hemodynamic inclusion criteria (not accepted diagnostic criteria for PAH)
    - mPAP: 25 mm Hg at rest or 30 mm Hg with exercise
    - mean pulmonary capillary wedge pressure or left ventricular filling pressure: 18 mm Hg or less at rest
    - PVR: 3 or more Wood units
  - Interval from symptom onset to diagnosis
    - More than 1 year: more than 50%
    - More than 2 years: 21%
    - Median time to right heart catheterization: 13.6 months
  - Associated with delayed diagnosis: symptom onset at age younger than 36 years, history of obstructive airway disease or obstructive sleep apnea, 6MWD less than 250 m, mRAP less than 10 mm Hg, PVR less than 10 Wood units

Diagnostic Approach to PH

Patient's symptoms, signs, and history suggest PH

Is echocardiography compatible with PH?

No

PH is unlikely
- Other causes should be considered
- Recheck for PH

Yes

Consider most likely causes of PH
- Left heart disease
- Pulmonary disease

Evaluate history, signs, risk factors, cardiac/pulmonary function
- x-ray
- ECG
- PFT with DLCO
- Consider BGA, HR-CT

Do results confirm diagnosis of heart or lung disease?

Diagnostic Approach (cont)
Evaluation for CTEPH

Do results confirm diagnosis of heart or lung disease?

Yes

No signs of severe PH or RV dysfunction

Treatment for underlying disease

No

Excludes Groups 2, 3

Unmatched perfusion defects by V/Q scintigraphy?

Yes

Excludes Group 4

No

Right heart cath
- PAPm ≥ 25 mm Hg
- PAWP ≤ 15 mm Hg
- PVR > 3 WU

Group 5?

Likely CTEPH
- CT angiography
- Right heart cath + PA at pulmonary endarterectomy center

Diagnostic Approach (cont)
If Group 1 (PAH), Which Diagnosis?

- **Right heart cath**
  - PAPm ≥ 25 mm Hg
  - PAWP ≤ 15 mm Hg
  - PVR > 3 WU

- Yes
  - **PAH likely**
    - Determine specific diagnosis
      - HIV
      - Drugs or toxins
      - Connective tissue disease
      - PVOD/PCH
      - CHD
      - Portopulmonary
      - Schistosomiasis
      - Other (Group 5)

- No
  - Consider other causes

- **Group 1**

- **Idiopathic or heritable?**
  - Family history
  - Genetic testing (expert centers)

---

Diagnostic Workup: Electrocardiogram (ECG)

- ECG may suggest PAH by revealing:
  - Right ventricular hypertrophy (87% of patients with IPAH)
  - Right axis deviation (79% of patients with IPAH)
- However, ECG has inadequate sensitivity and specificity to be considered a reliable screening tool
- A patient may have severe PAH in the presence of a normal ECG

ECG in PAH demonstrating right-axis deviation, right ventricular hypertrophy, and anterior ST- and T-wave abnormalities consistent with a right ventricular strain pattern.

Echocardiography

- Echocardiography and other tests are useful for screening and evaluation
- Doppler echocardiography is the preferred screening tool

Echocardiographic Characteristics of PAH

- Echocardiography provides estimated RV systolic pressure and morphologic cardiac abnormalities

LA, left atrium; LV, left ventricle; PAH, pulmonary arterial hypertension; RA, right atrium; RV, right ventricle.

Pulmonary Arterial Hypertension (Compensated)

CO, cardiac output; PA, pulmonary arterial; PCW, pulmonary capillary wedge; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; TPG, transpulmonary pressure gradient; WU, Wood units.

Tracing courtesy of Michael A. Mathier, MD, FACC, University of Pittsburgh School of Medicine
Pulmonary Venous Hypertension

CO, cardiac output; PA, pulmonary arterial; PCW, pulmonary capillary wedge; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; TPG, transpulmonary pressure gradient; WU, Wood units.

Tracing courtesy of Michael A. Mathier, MD, FACC, University of Pittsburgh School of Medicine.

CO = 4 L/min
TPG = 7 mm Hg
PVR = 1.75 WU
Goals of Treatment:

- Improve symptoms
- Increase functional status
- Reduce risk of disease progression
- Improve quality of life
- Increase survival
- Reduce hospitalizations
REVEAL Registry™
Hospitalization Worsens Long-term Outcomes

3-Year Event Rates* in Patients With and Without First Hospitalization Within 1 Year After Enrollment

*3 years from discharge in patients with first hospitalization; 3 years from 1-year follow-up in patients without hospitalization.

Pathophysiologic Pathways Targeted by PAH Therapies

Pro-endothelin-1
Endothelin-1 (Vasoconstriction and Proliferation)
- Endothelin Receptor A
- Endothelin Receptor B
  + Selective ETA Receptor Antagonists
  - Dual ET Receptor Antagonists

L-arginine
Nitric Oxide (Vasodilatation and Antiproliferation)
- sGC Stimulation
  + PDE-5 Inhibitors
  - PDE5 Analogues
  + IP Receptor Agonists

Arachidonic Acid
Prostacyclin (Vasodilatation and Antiproliferation)
- GTP
- cGMP
- cAMP

# Medications Currently Available in the United States for Treating PAH

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERAs</strong></td>
<td>Ambrisentan</td>
<td>Oral</td>
<td>Once daily</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>Oral</td>
<td>2x daily</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Oral</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>PDE5 inhibitors</strong></td>
<td>Sildenafil</td>
<td>Oral</td>
<td>3x daily</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>Oral</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Guanylate cyclase stimulators</strong></td>
<td>Riociguat</td>
<td>Oral</td>
<td>3x daily</td>
</tr>
<tr>
<td></td>
<td>Epoprostenol</td>
<td>Intravenous</td>
<td>Continuous infusion</td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>Inhaled</td>
<td>6-9x daily, every 2 h</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>Continuous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treprostynil</td>
<td>Subcutaneous</td>
<td>Continuous infusion</td>
</tr>
<tr>
<td></td>
<td>Inhaled</td>
<td>4x daily, every 4 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>Continuous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>2x daily, every 12 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selexipag</td>
<td>Oral</td>
<td>2x daily</td>
</tr>
</tbody>
</table>
## Risk Stratification of Patients

**ESC/ERS Guidelines**

<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% predicted) VE/VCO₂ slope &lt;36</td>
<td>Peak VO₂ 11-15 mL/min/kg (&gt;35%-65% predicted) VE/VCO₂ slope &lt; 6-44.9</td>
<td>Peak VO₂ &lt;11 mL/min/kg (&lt;35% predicted) VE/VCO₂ slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/L NT-proBNP &lt;300 ng/mL</td>
<td>BNP 50-300 ng/L NT-proBNP 300-1400 ng/mL</td>
<td>BNP &gt;300 ng/L NT-proBNP &gt;1400 ng/mL</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 &gt;26 cm² Pericardial effusion</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;8 mm Hg Cl ≥ 2.5 L/min/m² SvO₂&gt;65%</td>
<td>RAP 8-14 mm Hg Cl 2.0-2.4 L/min/m² SvO₂ 60%-65%</td>
<td>RAP &gt;14 mm Hg Cl &lt; 2.0 L/min/m² SvO₂&lt;60%</td>
</tr>
</tbody>
</table>

### WHO Functional Class is a Symptom-Based Indicator of Disease Severity*

<table>
<thead>
<tr>
<th>Class</th>
<th>Functional Classification of Patients with PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or pre-syncpe</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity. No discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or pre-syncpe</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity. No discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or pre-syncpe</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to perform any physical activity and possible signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity</td>
</tr>
</tbody>
</table>

- 6-minute walk distance (6MWD) is a measure of exercise capacity and was the primary endpoint in most PAH pivotal trials

Treatment Algorithm for PAH

Treatment-Naïve Patient

PAH Confirmed by Expert Center

Acute Vasoreactivity Test (IPAH/HPAH/DPAH only)

Low or Intermediate Risk (WHO FC II-III)
- Initial Monotherapy
- Initial Oral Combination

Nonvasoreactive

High Risk (WHO FC IV)
- Initial Combination Including IV PCA

General Measures

Supportive Therapy

CCB Therapy

Adjuvant Therapies in PAH

- **Digoxin**
  - Variable inotropic effect and use
  - No long-term data; need to balance unproven benefits with known risks

- **Oxygen**
  - Use to prevent hypoxic vasoconstriction
  - Consider exercise, sleep, altitude
  - Aim for target saturation > 90%
  - May not correct hypoxia with shunt

- **Diuretics**
  - Most need; hypotension not a contraindication (may need BP support)
  - Renal function and electrolytes must be monitored closely

- **Anticoagulation**
  - Recommended in IPAH
  - Retrospective data only; need to balance unproven benefits with known risks
  - INR 1.5-2.5

Treatment Algorithm
ESC/ERS Guidelines

Low or intermediate risk (WHO FC II-III)
- Initial monotherapy
- Initial oral combination

High risk (WHO FC IV)
- Initial combination including IV PCA

Patient already on treatment
- Double or triple sequential combination

Inadequate clinical response
- Consider referral for lung transplantation

Inadequate clinical response
- Consider listing for lung transplantation

## Monotherapy Recommendations for PAH

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class - Level</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO-FC II</td>
<td>WHO-FC III</td>
<td>WHO-FC IV</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>I</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Bosentan</td>
<td>I</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Macitentan</td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>I</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>IIb</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td>Guanylate cyclase stimulators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riociguat</td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Prostacyclin analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostenol</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Inhale</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td>IIa</td>
</tr>
<tr>
<td>Iloprost</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Inhale</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td>Beraprost</td>
<td></td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td>IP receptor agonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selexipag (oral)</td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
</tbody>
</table>

FREEDOM-C and FREEDOM-C2

Study Design

Multicenter, double-blind, placebo-controlled study
Randomized: 670 patients (total of both studies)
Study duration: 16 weeks

Background Therapy: ERA or PDE-5i or both

Placebo (N=329, total of both studies)
Oral treprostinil twice daily (N=331, total of both studies)

Primary end point: Placebo-corrected change in 6MWD from baseline to week 16

RESULTS

- Background therapy
  - ~40% on ERA and PDE-5i
- Median dose achieved
  - 3 to 3.5 mg twice daily
- 6MWD
  - No significant improvement from baseline

The Rationale for Combination Therapy

- Several pathways involved in pathophysiology
- Potential for synergistic effect
- Severe nature of this disease
- Successfully used in heart failure, HIV infection...

Sequential (add-on) or Upfront (first-line)?
Recommendations for the Treatment of PAH

- Monotherapy
  - Works well, but the disease eventually progresses
- Combination therapy
  - Increasing evidence in support of its use
  - Includes sequential therapy or up-front combination therapy
  - Health economic barrier to up-front combination therapy, as many of the treatments are expensive
  - To justify up-front combination therapy, clear improvement in patient outcomes must be demonstrated

Humbert M. ERS 2015.
Sequential Combination Therapy

Supportive Evidence

- **PATENT-1**
  - Phase 3 study of riociguat as monotherapy or add-on therapy to ERA or non-IV prostanoid vs placebo
  - Riociguat improved 6MWD in both treatment-naive and pretreated patients

- **SERAPHIN**
  - Event-driven trial of macitentan as monotherapy or add-on therapy to PDE-5 inhibitor or prostanoid (oral or inhaled) versus placebo
  - Macitentan reduced morbidity and mortality in both treatment-naive and pretreated patients

COMPASS-2

- Patients with symptomatic PAH
  - Treated with sildenafil ≥ 12 weeks (N = 334)

  - Bosentan 125 mg twice daily (n = 159)
  - Placebo (n = 175)

Primary end point:
- Time to first morbidity/mortality event
  - Death
  - Hospitalization for PAH worsening
  - Intravenous prostanoid initiation
  - Atrial septoplasty
  - Lung transplantation
  - Worsening PAH

- Primary end point not met: risk reduction of 17% with bosentan vs placebo (P = .25)

- Liver enzyme elevations (more than three times the upper limit of normal)
  - Placebo: 6.4%
  - Bosentan: 21.8%

### Recommendations for Sequential Combination Therapy

<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>Macitentan added to sildenafil</td>
<td>I</td>
<td>B</td>
<td>Ia</td>
</tr>
<tr>
<td>Riociguat added to bosentan</td>
<td>I</td>
<td>B</td>
<td>Ia</td>
</tr>
<tr>
<td>Selexipag added to ERA and/or PDE-Si</td>
<td>I</td>
<td>B</td>
<td>Ia</td>
</tr>
<tr>
<td>Sildenafil added to epoprostenol</td>
<td>-</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>Treprostinil inhaled added to sildenafil or bosentan</td>
<td>Ila</td>
<td>B</td>
<td>Ia</td>
</tr>
<tr>
<td>Iloprost inhaled added to bosentan</td>
<td>IIb</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td>Tadalafil added to bosentan</td>
<td>Ila</td>
<td>C</td>
<td>Ila</td>
</tr>
<tr>
<td>Ambrisentan added to sildenafil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan added to epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan added to sildenafil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Sildenafil added to bosentan</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other double combinations</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other triple combinations</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Riociguat added to sildenafil or other PDE-Si</td>
<td>III</td>
<td>B</td>
<td>III</td>
</tr>
</tbody>
</table>

Up-Front Combination Therapy
Supportive Evidence

- AMBITION
  - Event-driven trial of up-front combination therapy with ambrisentan and tadalafil vs monotherapy with ambrisentan or tadalafil
  - Up-front combination therapy significantly reduced the risk of clinical failure by 50% compared with pooled monotherapy (HR = 0.50; \( P < .001 \))

Clinical failure = first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response

AMBITION

Patients with PAH Treatment naïve (N = 500)

- Ambrisentan (target dose: 10 mg) (n = 253)
- Tadalafil (target dose: 40 mg) (n = 126)
- Ambrisentan (target dose: 10 mg) (n = 126)
- Tadalafil (target dose: 40 mg) (n = 121)

24 weeks

Primary end point: Time to clinical failure
- Death
- Hospitalization for worsening PAH
- Disease progression
- Unsatisfactory long-term response

Ambrisentan/tadalafil reduced risk for clinical failure events (hospitalizations) by 63% vs ambrisentan or tadalafil alone (hazard ratio, 0.372; 95% confidence interval = 0.217-0.639; P = .0002)

## Initial Combination Therapy Therapy Recommendations for PAH

<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</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td>Other ERA + PDE-5i</td>
<td>IIa</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan + sildenafil + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
</tr>
<tr>
<td>Bosentan + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + s.c. treprostinil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + other i.v. prostacyclin analogues</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
</tbody>
</table>

Paradigm Shift in PAH Treatment

Short-term trials with goal-oriented outcomes (6MWD)

Long-term trials with event-driven outcomes (morbidity/mortality)
- SERAPHIN\textsuperscript{a}
- AMBITION\textsuperscript{b}
- GRIPHON\textsuperscript{c}

\textsuperscript{a} Pulido T, et al. \textit{N Engl J Med.} 2013;369:809-818\textsuperscript{[14]}; \textsuperscript{b} Galiè N. \textit{Eur Respir J.} 2014;44 Suppl 58:2916\textsuperscript{[18]}; \textsuperscript{c} McLaughlin VV, et al. \textit{J Am Coll Cardiol.} 2015;65(10_S).\textsuperscript{[20]}
GRIPHON
Study Design

Multicenter, double-blind, placebo-controlled, phase 3, event-driven study
Randomized: 1156 patients

Background Therapy: ERA or PDE-5i or both

Placebo (n=582)  Selexipag twice daily (n=574)

Primary end point: time from randomization to first morbidity/mortality event up to the end of treatment

Morbidity/mortality event = disease progression (15% decrease in 6MWD and either worsening of FC or need for additional PAH therapy), hospitalization for PAH worsening, PAH worsening (need for atrial septostomy or lung transplant, initiation of parenteral prostanoids, or chronic O₂ therapy), or all-cause death.

Selexipag

- Orally available prodrug
- Selective IP receptor agonist
- Chemically distinct from prostacyclin (PGI$_2$)
- Effects similar to prostacyclins
  - Induces vasodilation
  - Increases cAMP
  - Inhibits proliferation of vascular smooth muscle cells
GRIPHON

Results

• Background PAH therapy
  – 20% therapy naïve, 47% on ERA or PDE-5i, 33% on ERA and PDE-5i
• Primary end point
  – Selexipag reduced morbidity/mortality events by 40% vs placebo ($P<.0001$)
• Treatment effect consistent across
  – Age, gender, etiology, baseline FC, and background PAH therapy sub-groups
• Adverse events
  – Headache, diarrhea, nausea, jaw pain, myalgia, pain in extremity, flushing, and arthralgia

### SERAPHIN

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N = 250), N (%)</th>
<th>Macitentan 3 mg (N = 250), N (%)</th>
<th>Macitentan 10 mg (N = 242), N (%)</th>
<th>Macitentan 3 mg vs Placebo</th>
<th>Macitentan 10 mg vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event related to PAH or death as the first event (all events)</td>
<td>116 (46.4)</td>
<td>95 (38.0)</td>
<td>76 (31.4)</td>
<td>Hazard Ratio: 0.70</td>
<td>Hazard Ratio: 0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52-0.96</td>
<td>0.32-0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P Value: .01</td>
<td>P Value: &lt; .001</td>
</tr>
<tr>
<td>Death caused by PAH or hospitalization for PAH as the first event (all events)</td>
<td>84 (33.6)</td>
<td>65 (26.0)</td>
<td>50 (20.7)</td>
<td>Hazard Ratio: 0.67</td>
<td>Hazard Ratio: 0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46-0.97</td>
<td>0.34-0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P Value: .01</td>
<td>P Value: &lt; .001</td>
</tr>
</tbody>
</table>

**Macitentan reduces morbidity and mortality events in patients with PAH.**

SERAPHIN (cont)

- Rate reduction of PAH-related hospitalization per 100 patient-years (vs placebo)
  - Macitentan 3 mg: 44.5%; \(P = .0004\)
  - Macitentan 10 mg: 49.8%; \(P < .0001\)

- Reduction in number of PAH-related hospital days (vs placebo)
  - Macitentan 3 mg: 53.3%; \(P = .0001\)
  - Macitentan 10 mg: 52.3%; \(P = .0003\)

PAH Remains a Devastating Condition Despite Advances in Treatment

• Approximately 10% of patients with PAH die each year

• To improve outcomes it is important to:
  – Detect and manage PAH early
  – Provide goal-oriented therapy with sequential combination therapy
  – Consider initial combination therapy
  – Select treatments that target multiple pathophysiologic pathways

Humbert M. ERS 2015.
Progress in PAH Survival

Longitudinal Evaluation of PAH Patients
ACCF/AHA 2009 Expert Consensus

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Stable, no increase in symptoms or decompensation</th>
<th>Unstable, increase in symptoms or decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No evidence of RV failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FC I or II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 6MWD &gt;400 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• RAP and CI normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of evaluation</th>
<th>Every 3-6 months</th>
<th>Every 1-3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC assessment</td>
<td>Every clinic visit</td>
<td>Every clinic visit</td>
</tr>
<tr>
<td>6MWT</td>
<td>Every clinic visit</td>
<td>Every clinic visit</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Every 12 months or center dependent</td>
<td>Every 6-12 months or center dependent</td>
</tr>
<tr>
<td>BNP</td>
<td>Center dependent</td>
<td>Center dependent</td>
</tr>
<tr>
<td>RHC</td>
<td>Clinical deterioration and center dependent</td>
<td>Every 6-12 months or clinical deterioration</td>
</tr>
</tbody>
</table>

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; BNP, B-type natriuretic peptide; CI, cardiac index; FC, functional class; PAH, pulmonary arterial hypertension; RAP, right atrial pressure; RHC, right heart catheterization; RV, right ventricular. Reprinted from McLaughlin et al. J Am Coll Cardiol. 2009;53(17):1573-1619. With permission from Elsevier.
Value of Specialty Centers

- Equipped to treat patients in all WHO PAH group classifications
- Staffed with specialty nurses and specialty pharmacists
- Able to provide access to clinical trials
- Uses a coordinated care model that engages palliative care services earlier, not only for end-of-life care
Recommendations Looking Forward

• Earlier interface between community practices and specialty centers
  – Facilitate early diagnoses
  – Increase access to clinical trials and specialty nurses
  – Leverage more aggressive treatment options with oral combination therapy

• Increase connectivity between and among specialty centers
Future Targets for PAH Therapy

- Inflammation\textsuperscript{a}
- Genetics\textsuperscript{b,c,d}
  - \textit{BMPR2} mutation
- Epigenetics\textsuperscript{e}
  - DNA methylation\textsuperscript{e}
  - Histone modification\textsuperscript{e}
  - microRNAs\textsuperscript{e,f}

Novel Therapeutic Targets in PAH

• TGF-β/BMP imbalance
  – Involved in the development of PAH
  – Imbalance favors proliferation and apoptosis resistance
  – FK506 is a promising therapeutic candidate in phase 2 clinical development
  – FK506 activates BMPR2, rescues endothelial dysfunction, and reverses PH

• ZIP12 (a zinc transporter)
  – Upregulated in hypoxia-induced PH
  – PH development attenuated in ZIP12 gene knockout animals
  – ZIP12 presents a novel therapeutic target for pharmacologic management of PH

Summary

- PH diagnosis often delayed > 1 year after symptom onset\(^a,b\)
- Dyspnea on exertion is most common symptom\(^c\)
- A careful exam reveals clues
- Determine *cause* and *severity* of PH
- Echo is pivotal, usually suggesting PH
- Always do right-heart cath
- If PH present, always rule out CTEPH by V/Q scan
- 10+ drugs are now approved for PAH!
- Goals of therapy should be carefully realized