Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension (PAH): An Overview

Kansas Association of Osteopathic Medicine
Mid-Year Conference
Wichita, Kansas

November 9, 2019
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Integris Baptist Medical Center
Oklahoma City, Oklahoma
Housekeeping Notes

- Please **mute your cellphones/pagers now**

- **Syllabus folder** contains slides, agenda, and faculty disclosure information.

- **PHA material and website** contain valuable professional and patient resource information.
Faculty Disclosure

- Has served as a consultant and/or on advisory committees for Bayer AG; and served on speakers' bureaus for and/or received honoraria from Actelion Pharmaceuticals US, Inc., Bayer, and United Therapeutics Corporation.
The **Pulmonary Hypertension Association (PHA)** is the leading non-profit organization for PH research, public awareness, and services. The organization has over 16,000 members, including patients, family members, and medical professionals.

[www.PHAssociation.org](http://www.PHAssociation.org)
Let’s get started...
Vascular Pressure in Systemic and Pulmonary Circulations (mm Hg)

**Systemic Circulation**
- **Arteries**: 120/80, mean 93
- **Veins**: 25/8, mean 14
- **Mean**: 30

**Pulmonary Circulation**
- **Arteries**: 25/8, mean 14
- **Veins**: 120/5, mean 30
- **Mean**: 12

5th World Symposium on PH: Hemodynamic Definition of PH/PAH

**PH**
Mean PAP \( \geq 25 \text{ mm Hg} \)
at rest during RHC

**PAH**
Mean PAP \( \geq 25 \text{ mm Hg} \) *plus*
PAWP \( \leq 15 \text{ mm Hg} \) *plus*
PVR \( >3 \text{ Wood units} \)

6th World Symposium Proceedings Recently Released
Could Affect This Definition

### 6th World Symposium on PH: Proposed Hemodynamic Definition of PH/PAH

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Characteristics</th>
<th>Clinical Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-capillary PH</td>
<td>mPAP &gt;20 mmHg PAWP ≤15 mmHg PVR ≥3WU</td>
<td>1, 3, 4, 5</td>
</tr>
<tr>
<td>Isolated post-capillary PH</td>
<td>mPAP &gt;20 mmHg PAWP &gt;15 mmHg PVR &lt;3 WU</td>
<td>2, 5</td>
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<td>Combined pre- and post-capillary PH</td>
<td>mPAP &gt;20 mmHg PAWP &gt;15 mmHg PVR ≥3WU</td>
<td>2, 5</td>
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6th World Symposium Classification of PH

1. Pulmonary Arterial Hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.3 Drug- and toxin-induced PAH
   1.4 PAH associated with:
      1.4.1 Connective tissue disease
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases
      1.4.5 Schistosomiasis
   1.5 PAH long-term responders to CCBs
   1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
   1.7 Persistent PH of the newborn syndrome

2. PH Due to Left Heart Disease
   2.1 PH due to HF with preserved LVEF
   2.2 PH due to HF with reduced LVEF
   2.3 Valvular heart disease
   2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH Due to Lung Diseases and/or Hypoxia
   3.1 Obstructive lung disease
   3.2 Restrictive lung disease
   3.3 Other lung disease with mixed restrictive/obstructive pattern
   3.4 Hypoxia without lung disease
   3.5 Developmental lung disorders

4. PH Due to Pulmonary Artery Obstructions
   4.1 Chronic thromboembolic PH
   4.2 Other pulmonary artery obstructions

5. PH With Unclear and/or Multifactorial Mechanisms
   5.1 Hematological disorders
   5.2 Systemic and metabolic disorders
   5.3 Others
   5.4 Complex congenital heart disease

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5.2 Systemic and metabolic disorders
5.3 Others
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6. World Symposium Classification of PH Considerations – Group 1

- PVOD/PCH (BMPR2 vs EIF2AK4)
- Persistent PH of the newborn?
- What about PAH with vasoreactivity?
- Updates on drugs- and toxins-induced?

Heritable PAH

• Autosomal dominant
• BMPR2 (bone morphogenetic protein receptor type 2) is the major predisposing gene
• Mutation detection rate for known genes is ≈75% in familial PAH
• Major predisposing gene has a highly variable penetrance between families
• Genetic anticipation
• ALK1 (ACVRL1; activin A receptor type-III-like kinase 1) is major gene when PAH is associated with hereditary hemorrhagic telangiectasia (HHT)

PAH Related to Connective Tissue Disease

- Connective tissue diseases
  - limited scleroderma (most common)
  - diffuse scleroderma
  - mixed connective tissue disease
  - systemic lupus erythematosus
  - rheumatoid arthritis
  - Sjogren’s syndrome

- PH is one of the leading causes of death in scleroderma
- Similar to IPAH pathology
- Medical treatment same as for IPAH, but benefits less than for IPAH

Prevalence of PAH in Scleroderma

- Prevalence 7.9% in large prospective study (N=599) with confirmatory catheterizations
  - excluded severe PFT abnormalities
  - all underwent Doppler echocardiography
  - catheterization if VTR > 3 m/sec or 2.5–3 m/sec + unexplained dyspnea

- Prevalence of PAH: found in 47 of 599 scleroderma patients
  - 29 had known PAH at study entry
  - 18 patients were newly diagnosed with PAH

Portopulmonary Hypertension

- Prevalence overall: 2-5% by RHC; liver transplant candidate: 4% to 17%
- Dependent on portal HTN, not hepatocellular dysfunction
- Poor prognosis: higher risk of death than IPAH pts
- Liver transplant
  - may improve survival with mild to moderate PAH (28-56%, 5 yr)
  - significant PAH (mPAP >35 mm Hg) predicts unacceptably high perioperative mortality

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6th World Symposium Classification of PH

6th World Symposium Considerations – Group 2 Refinements
• Congenital post-capillary obstructive lesions?

Most Common Cause of Elevated PAPs by Echo: Left Heart Disease

**Symptoms**
- paroxysmal nocturnal dyspnea
- orthopnea

**History**
- diabetes
- hypertension
- obesity
- coronary artery disease
- metabolic syndrome

**ECG**
- atrial fibrillation
- absence of right axis deviation

**Echo**
- left atrial enlargement
- left ventricular hypertrophy
- normal RA, RV
- abnormal diastolic filling
- mitral or aortic disease
Percentage of PAH and PVH Patients With All 4 Metabolic Syndrome Factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>13.7</td>
<td>(1.6-113.0)</td>
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<tr>
<td>Obesity</td>
<td>7.1</td>
<td>(1.9-26.8)</td>
</tr>
<tr>
<td>DM</td>
<td>5.7</td>
<td>(1.6-20.4)</td>
</tr>
<tr>
<td>HL</td>
<td>4.2</td>
<td>(1.2-15.7)</td>
</tr>
</tbody>
</table>

*p ≤ 0.005; **p = 0.023.

6th World Symposium Classification of PH

6th World Symposium Considerations – Group 3 Refinements

- Developmental lung disorders?
- LAM-associated PH now grouped with other parenchymal lung diseases

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Chronic Obstructive Pulmonary Disease (COPD) and PH

- Retrospective study of 215 COPD patients
- 13.5% had a PA mean >35 mm Hg
- Correlated best (inversely) with PaO2
- A small number had only moderate obstruction: treatable sub-group?

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6th World Symposium Considerations – Group 4 Refinements

- PH due to pulmonary artery obstruction?
- “CTEPH” and “Other PAO”?

Incidence of CTEPH

- Approximately 3% to 4% 1-2 yr after acute PE
- USA: 600,000 cases of acute PE each year
- Only 40% to 50% of CTEPH patients have a history of previous episodes of acute PE
- VQ scan identifies old PE better than CTA

Pathology of PAH

WHO Group I: Characterized by progressive growth and vasoconstriction of small pulmonary arteries

PAH: Hemodynamic and Clinical Course

Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.
PAH: Hemodynamic and Clinical Course

Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.
PAH: Hemodynamic and Clinical Course

Adventitia
Media
Intima

Smooth Muscle Hypertrophy
Early Intimal Thickening

Reversible Disease

Irreversible Disease

Adventitial, Intimal Proliferation
Thrombosis
Plexiform Lesions

CO
PAP
PVR

NYHA I II III IV

Time

Adapted from Gaine S. JAMA. 2000;284:3160-3168.
Survival in PAH

McLaughlin VV et al. *Chest.* 2004;126:78S-92S.
Idiopathic PAH: Survival If Untreated

- Incidence: 2-6 cases per million in US
- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

![Graph showing survival rates over years of follow-up](image)

French Registry: Kaplan-Meier Survival Estimates in Combined PAH Population vs NIH-predicted

REVEAL: Observed 1-year Survival From Time of Enrollment According to Predicted Risk Strata

Survival (%)

No. at risk:

- Low: 1374, 1368, 1364, 1359, 1356, 1352, 1351, 1346, 1341, 1336, 1311, 1304, 1303
- Average: 665, 659, 657, 653, 648, 647, 640, 628, 625, 618, 604, 602, 596
- Mod. high: 280, 277, 274, 269, 264, 263, 260, 259, 255, 254, 249, 244, 243
- Very high: 102, 100, 96, 89, 81, 74, 72, 69, 61, 59, 55, 52, 49

Key Pathways Implicated in PAH Pathogenesis

**Endothelin Pathway**
- Pre-proendothelin → Proendothelin
- Endothelin-1
  - Endothelin receptor A
  - Endothelin receptor B
- Vasoconstriction and proliferation

**Nitric Oxide Pathway**
- L-arginine → L-citrulline
- Nitric Oxide
  - Phosphodiesterase type 5
  - Vasodilation and antiproliferation
- cGMP

**Prostacyclin Pathway**
- Arachidonic acid → Prostaglandin I₂
- Prostacyclin
  - Prostaglandin I₂
- cAMP
  - Vasodilation and antiproliferation

**Endothelial cells**
- Smooth muscle cells
- Preproendothelin
- Proendothelin

Case: Jane

- 37-yr-old woman, previously healthy
- Delivered second child 14 mo previously
- Limited exercise tolerance since delivery, attributed to weight gain
- Dyspnea while playing with older child; syncope while walking up an incline
Jane: Initial Symptoms

- Currently has dyspnea with mild exertion, walks slowly in store
- Exertional light-headedness
- Atypical chest pain
- Occasional palpitations
- Lower extremity edema
Multiple Guidelines, Consistent Message: Comprehensive Diagnostic Evaluation/Robust PH Specialty Center Collaboration Are Necessary
Follow Basic Steps of American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Consensus Algorithm, With Some Updates

• To identify:
  
  – the presence of PH
  
  – which group of PH (WHO I-V)

Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc; and the Pulmonary Hypertension Association
Echocardiogram
PFT's
Polysomnography
V/Q Scan
• Sleep Disorder
• Chronic PE
• Ventilatory Function
• Gas Exchange

Overnight Oximetry
Polysomnography
• Sleep Disorder

Functional Test
(6MWT, CPET)
Vasodilator Test
Exercise RH Cath
Volume Loading
Left Heart Cath
• Confirmation of PH
• Hemodynamic Profile
• Vasodilator Response

Exercise Echo
TEE
Pulmonary Angiography
Chest CT Angiogram
Coagulopathy Profile
• Index of Suspicion of PH
• RVE, RAE, ↑RVSP, RV Function
• Left Heart Disease
• VHD, CHD

ECG
HIV
ANA
LFT's
HIV Infection
Scleroderma, SLE, RA
Portopulmonary Htn
• Establish Baseline
• Prognosis

Other CTD Serologies

HIV
ANA
LFT's

Histoy
Exam
CXR
ECG

Echocardiogram

**History and Physical Exam Findings Are Insensitive Unless Advanced Disease/RV Failure Present**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam (PH)</th>
<th>Exam (RV Failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dyspnea (86%)</td>
<td>• Loud P2</td>
<td>• JVD; increased A wave, V wave; hepatojugular reflex</td>
</tr>
<tr>
<td>• Fatigue (27%)</td>
<td>• RV lift</td>
<td>• RV S3, S4</td>
</tr>
<tr>
<td>• Chest pain (22%)</td>
<td>• Systolic murmur (TR; inspiratory augmentation)</td>
<td>• Pulsatile liver</td>
</tr>
<tr>
<td>• Edema (22%)</td>
<td>• Early systolic click</td>
<td>• Hepatomegaly</td>
</tr>
<tr>
<td>• Syncope (17%)</td>
<td>• Midsystolic ejection murmur</td>
<td>• Edema</td>
</tr>
<tr>
<td>• Dizziness (15%)</td>
<td>• Diastolic murmur (PR)</td>
<td>• Ascites</td>
</tr>
<tr>
<td>• Cough (14%)</td>
<td></td>
<td>• Low BP, low PP, cool extremities</td>
</tr>
<tr>
<td>• Palpitations (13%)</td>
<td></td>
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Jane: Physical Exam

- HR 90 bpm; BP 130/68 mm Hg; Ht 5'4”; Wt 190 lb
- JVP ~15 cm, reduced carotid upstrokes
- Clear lungs
- Palpable RV heave, RRR, normal S, loud P2, III/VI holosystolic murmur, consistent with TR
- 2+ LE edema
Jane: Additional History

- PMH: 2 children, 4 yr and 14 mo
  - IBS: diet-controlled
- Meds: none
- Allergies: contrast dye
- FH: PAH in a paternal aunt, CAD, DM, Htn
- SH: rare ETOH, otherwise unremarkable
Chest Radiograph May Show Right Heart and Vascular Abnormalities in Advanced Disease

Healthy

PH

Prominent central pulmonary artery

Peripheral hypo-vascularity (pruning)

Chest Radiograph May Show Right Heart and Vascular Abnormalities in Advanced Disease

Healthy

PH

Electrocardiogram May Show Right Heart Abnormalities in Advanced Disease

- Right Axis Deviation
- Right Atrial Enlargement
- Right Ventricular Strain
- Right Ventricular Hypertrophy

Image courtesy Christopher F. Barnett, MD, MPH
Jane’s ECG

Normal sinus rhythm
Incomplete right bundle branch block
Right ventricular hypertrophy
Prolonged QT
Abnormal ECG
Pivotal Tests

- History
- Exam
- CXR
- ECG

Echocardiogram

Contingent Tests

- TEE
- Exercise Echo
- Pulmonary Angiography
- Chest CT Angiogram
- Coagulopathy Profile
- Polysomnography
- ABG’s
- Overnight Oximetry
- HIV
- ANA
- LFT’s
- Functional Test (6MWT, CPET)
- RH Cath

Contribute to Assessment of:

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

Checklist for Echocardiographic Assessments When PH Is Suspected

- Estimate pulmonary artery systolic pressure
- Evaluate severity of TR
- Evaluate right heart size and function
- Exclude left heart valvular disease and systolic dysfunction
- Exclude congenital heart disease
- Differentiate PAH from PH due LHD
- Estimate RA pressure
- Evaluate for pericardial effusion

PASP is estimated using tricuspid regurgitant jet velocity.

Modified Bernoulli equation:

\[ RVSP = 4(V_{TR})^2 + RAP \]

PASP = RVSP in the absence of pulmonic outflow obstruction.

TR Jet Signal Quality Affects Reliability of Estimated PASP

Poor signal quality

Good signal quality

Images courtesy Christopher F. Barnett, MD, MPH
Structural Echocardiographic Findings in Patients With PH

- RV enlargement
- RA enlargement
- Septal flattening
- Pericardial effusion

Pivotal Tests
- History
- Exam
- CXR
- ECG

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Other CTD Serologies
- HIV
- ANA
- LFT's

Functional Test (6MWT, CPET)
- RH Cath

Exercise RH Cath
- Volume Loading
- Left Heart Cath

Ventilation Perfusion Scan (V/Q): Best Screening Test to Exclude CTEPH

- Should never be missed
- Is potentially curable with pulmonary endarterectomy (PEA)
- 3% to 4% of acute PE will develop CTEPH
- Half of those with CTEPH do not have an apparent history of thromboembolism
- Normal V/Q scan excludes CTEPH
- CTEPH may be diagnosed on CT pulmonary angiogram, however, reported sensitivity varies from 50-98%

Ventilation Perfusion Scan (V/Q) to Exclude CTEPH

Image courtesy Kelly Chin, MD
High-Quality Conventional Pulmonary Angiography: Gold Standard Test for CTEPH Diagnosis

CTEPH: A Surgical Disease
Survival Without Surgery Is Poor

Image courtesy Christopher F. Barnett, MD, MPH
Echocardiogram
- PFT's
- Overnight Oximetry
- Functional Test (6MWT, CPET)
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ACCF/AHA Diagnostic Algorithm

Presence and Severity of Lung Disease Must Be Assessed

- Underlying lung disease (diagnostic group III)
- Abnormalities consistent with PH

**IPAH and CTEPH**
- 20% have isolated reduction in DLCO
- DLCO mildly reduced (60%-80% predicted NIH registry)
- PVR correlates with reduction in DLCO

**Systemic Sclerosis**
- 20% have isolated reduction in DLCO
- Severity predicts future PAH
- DLCO correlates inversely with PASP

DLCO = diffusing capacity of the lungs for carbon monoxide

Overnight Pulse Oximetry Is a Useful Screening Test for Sleep Disordered Breathing

- Hypoxia may signal underlying sleep apnea
- In patients with obstructive sleep apnea (OSA), PAPs reported to decrease in response to CPAP therapy
- Untreated—response to other treatment likely to be less effective

If there is a suspicion of OSA, or an abnormal overnight test, refer patient for a formal study

Pivotal Tests
- History
- Exam
- CXR
- ECG

Echocardiogram
- TEE
  - Exercise Echo

V/Q Scan
- Pulmonary Angiography
- Chest CT Angiogram
- Coagulopathy Profile

PFT’s
- ABG’s

Overnight Oximetry
- Polysomnography

HIV
- Other CTD Serologies

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LFT’s
- Functional Test (6MWT, CPET)

RH Cath
- Vasodilator Test
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Chronic Thromboembolic PH
- Ventilatory Function
- Gas Exchange

Sleep Disorder
- HIV Infection
- Scleroderma, SLE, RA
- Portopulmonary Htn

Establish Baseline
- Prognosis

Confirmation of PH
- Hemodynamic Profile
- Vasodilator Response

## Functional Assessment: WHO Functional Class

*Modified From NYHA Classification*

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

Rubin LJ. *Chest.* 2004;126:7S-10S.
Jane: Laboratory Studies

- ANA: negative
- Echo: normal LV function, RAE, RVE, RVSP 60 mm Hg, TEE—no shunt found after agitated saline injection
- VQ: normal
- PFTs: normal volumes and flows, DLCO 81%
- 6MWD: 222 m, 99-96%
Cardiac Catheterization

Required when PAH is suspected

- Confirm echo findings
- Survey for left heart disease
  - measure wedge pressure or LVEDP
- Measure CO; calculate PVR
- Exclude systemic to pulmonary shunts
- Establish severity and prognosis
- Acute vasodilator challenge
PH: The Importance of Hemodynamics

Pulmonary venous hypertension

*Elevated PCWP, normal PVR*

PAH

PH with respiratory disease

CTEPH

*Normal PCWP, elevated PVR*

Other: high CO
Vasodilator Testing Identifies Patients Who Respond Well Long Term to Treatment With Calcium Channel Blockers

- Vasodilator testing
  - Nitric Oxide Inh or epoprostenol IV
  - Positive test defined by:
    - Drop in mPAP ≥10 mm Hg to a mPAP≤40 mmHg
    + normal CO

---

Jane: Right Heart Cath

<table>
<thead>
<tr>
<th></th>
<th>1/29/07 Baseline</th>
<th>Nitric Oxide 20 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mm Hg)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>93/40, mean 63</td>
<td>93/46, mean 64</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>52.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Femoral artery</td>
<td>91.4</td>
<td>91.7</td>
</tr>
<tr>
<td>Cardiac output / Cardiac index (L/min) Fick</td>
<td>2.5/1.3</td>
<td>2.88/1.52</td>
</tr>
<tr>
<td>PVR (Wood units) Fick</td>
<td>21.2</td>
<td>15.2</td>
</tr>
</tbody>
</table>
Screening and Diagnosis Summary

- High index of suspicion
- Thorough diagnostic evaluation
- Exclude thromboembolic disease
- Evaluate potential causes/contributing issues
- RHC required prior to initiating PAH therapy
- Baseline functional evaluation
PAH Treatment Goals

- Improve survival
- Improve quality of life
- Improve exercise capacity
  - 6MWD
  - WHO functional classification
- Improve hemodynamics
- Fewer/less severe symptoms
- Prevent clinical worsening
  - escalation of therapy
  - hospitalization
  - lung transplantation
  - death
**6th World Symposium Proposed Algorithm for PAH Treatment**

- **Treatment-naive Patient**
- **PAH Confirmed by Expert Center**
- **General measures Supportive measures**
- **Vasoreactive**
  - **Acute Vasoreactivity Test** (IPAH/HPAH/DPAH only)
- **Non-Vasoreactive**
- **CCB Therapy*”

*Treated with high doses (progressively titrated) of CCB, with adequate response confirmed after 6-12 mo of treatment (WHO-FC I-II with near normalization of hemodynamics).

Adapted from Galiè N et al. *Eur Respir J.* 2019; 53 1801889 [https://doi.org/10.1183/13993003.01889-2018].
Chronic 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
- No longer recommended in PAH

Other Management Issues

• Encourage exercise and activity within the limits of disease and ability to maintain O₂ levels

• Consider enrollment in a pulmonary rehabilitation program

• Immunizations

• Contraception (council patient on avoiding pregnancy and using contraception correctly)

• Psycho-social support; role of support groups
6th World Symposium Proposed Algorithm for PAH Treatment

![Algorithm Diagram]

- **Treatment-naive Patient**
  - Vasoreactive
    - **CCB Therapy** *
  - Non-Vasoreactive
- **PAH Confirmed by Expert Center**
  - Acute vasoreactivity test (IPAH/HPAH/DPAH only)
- **General measures**
  - Supportive measures

*Treated with high doses (progressively titrated) of CCB, with adequate response confirmed after 6-12 mo of treatment (WHO-FC I-II with near normalization of hemodynamics).

Adapted from Galiè N et al. *Eur Respir J.* 2019; 53 1801889 [https://doi.org/10.1183/13993003.01889-2018].
Survival in IPAH: Long-term CCB Responders

Long-term CCB responders (~50% of acute responders or ≤7% of IPAH patients)

$\text{Cumulative survival}$

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>33</td>
<td>30</td>
<td>22</td>
<td>13</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>12</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p=0.0007$

Some specific PAH subsets in which efficacy-to-safety ratio of initial combination therapy is not established may be treated with initial monotherapy.

## Risk Assessment in PAH

<table>
<thead>
<tr>
<th>Prognostic Determinants (est. 1-yr 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 HF</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</td>
<td>Repeated</td>
</tr>
<tr>
<td>WHO FC</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>CPET Peak VO₂ (% predicted)</td>
<td>&gt;15 mL/min/kg (&gt;65%)</td>
<td>11-15 mL/min/kg (35%-65%)</td>
<td>&lt;11 mL/min/kg (&lt;35%) ≥45</td>
</tr>
<tr>
<td></td>
<td>&lt;36</td>
<td>36-44.9</td>
<td></td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP NT-proBNP</td>
<td>&lt;50 ng/L &lt;300 ng/mL</td>
<td>50-300 ng/L 300-1400 ng/L</td>
<td>&gt;300 ng/L &gt;1400 ng/L</td>
</tr>
<tr>
<td>Imaging (echo, CMR) RA area Pericardial effusion</td>
<td>&lt;18 cm² No</td>
<td>18-26 cm² No or minimal</td>
<td>&gt;26 cm² Yes</td>
</tr>
<tr>
<td>Hemodynamics RAP CI</td>
<td>≤8 mmHg, ≥2.5 L/min/m² &gt;65%</td>
<td>8-14 mm Hg, CI 2.0-2.4 L/min/m² 60-65%</td>
<td>&gt;14 mmHg &lt;2.0 L/min/m² &lt;60%</td>
</tr>
</tbody>
</table>

## What Does Risk Assessment in PAH Tell Us? Four Registry Scores

<table>
<thead>
<tr>
<th></th>
<th>REVEAL</th>
<th>Swedish PAH Register</th>
<th>COMPERA</th>
<th>French PH Network</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. required variables</strong></td>
<td>12-14</td>
<td>8</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><strong>No. patients at baseline</strong></td>
<td>2716</td>
<td>530</td>
<td>1588</td>
<td>1017</td>
</tr>
<tr>
<td><strong>No. patients at follow-up</strong></td>
<td>2529</td>
<td>383</td>
<td>1094</td>
<td>1017</td>
</tr>
<tr>
<td><strong>Associated PAH included</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Definition of low risk</strong></td>
<td>≤6 REVEAL score</td>
<td>&lt;1.5 average score</td>
<td>&lt;1.5 average score</td>
<td>3-4 (of 4) low-risk criteria</td>
</tr>
<tr>
<td><strong>1-y mortality by risk (low, intermediate, high, %)</strong></td>
<td>≤2.6</td>
<td>1.0</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>7.0</td>
<td>9.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>≥10.7</td>
<td>26.0</td>
<td>21.2</td>
<td>13.0-30.0</td>
</tr>
</tbody>
</table>

Importance of Risk Assessment at Baseline

Swedish PAH Register

<table>
<thead>
<tr>
<th>Years</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>97.2</td>
<td>90.1</td>
<td>78.8</td>
</tr>
<tr>
<td>2</td>
<td>91.5</td>
<td>80.3</td>
<td>66.0</td>
</tr>
<tr>
<td>3</td>
<td>84.2</td>
<td>68.1</td>
<td>53.2</td>
</tr>
<tr>
<td>4</td>
<td>80.2</td>
<td>60.1</td>
<td>44.7</td>
</tr>
<tr>
<td>5</td>
<td>75.9</td>
<td>51.9</td>
<td>32.4</td>
</tr>
</tbody>
</table>

COMPERA

<table>
<thead>
<tr>
<th>Years (years)</th>
<th>Survival (%)</th>
<th>Cases left (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>97.2</td>
<td>90.1</td>
</tr>
<tr>
<td>2</td>
<td>91.5</td>
<td>80.3</td>
</tr>
<tr>
<td>3</td>
<td>84.2</td>
<td>68.1</td>
</tr>
<tr>
<td>4</td>
<td>80.2</td>
<td>60.1</td>
</tr>
<tr>
<td>5</td>
<td>75.9</td>
<td>51.9</td>
</tr>
</tbody>
</table>

No. at risk:
- Low risk: 120, 355, 55
- Intermediate risk: 100, 246, 35
- High risk: 86, 176, 22

Importance of Risk Assessment at Follow-up

Swedish PAH Register

- Log rank, $P < 0.001$
- No. at risk:
  - Low risk: 111, 96, 80, 65, 48, 33
  - Intermediate risk: 229, 180, 127, 85, 54, 36
  - High risk: 43, 24, 9, 5, 2, 1

<table>
<thead>
<tr>
<th>Years after enrollment</th>
<th>Survival (%)</th>
<th>Cases left (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low risk</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>96.5</td>
<td>91.8</td>
</tr>
<tr>
<td>2</td>
<td>91.4</td>
<td>78.0</td>
</tr>
<tr>
<td>3</td>
<td>86.8</td>
<td>66.8</td>
</tr>
<tr>
<td>4</td>
<td>79.8</td>
<td>59.3</td>
</tr>
<tr>
<td>5</td>
<td>68.1</td>
<td>51.1</td>
</tr>
</tbody>
</table>


Importance of Achieving Low-Risk Status at Follow-up

Swedish PAH Register

- Stable "Low risk"
- Improved to "Low risk"
- Stable "Intermediate risk" or "high risk"
- Worsened to "Intermediate risk or "high risk"

Log rank, p<0.001

<table>
<thead>
<tr>
<th>Years After enrollment</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>57 50 44 37 28 21</td>
</tr>
<tr>
<td>1</td>
<td>54 46 36 28 20 12</td>
</tr>
<tr>
<td>2</td>
<td>213 163 108 69 41 26</td>
</tr>
<tr>
<td>3</td>
<td>59 41 28 21 15 11</td>
</tr>
</tbody>
</table>

No. at risk:

- Stable Low risk
- Improved to Low risk
- Stable Intermediate risk or high risk
- Worsened to Intermediate risk or high risk

Survival (%)

- 100% for Stable Low risk
- 98%, 96% for Improved to Low risk
- 68%, 50% for Stable Intermediate risk
- 43% for Worsened to Intermediate risk or high risk

Log rank, p<0.001

COMPERA

Survival (%)

- Stable Low risk
- Worsened from low to intermediate risk
- Improved from intermediate to low risk
- Stable Intermediate risk
- Worsened from intermediate to high risk
- Improved from high to intermediate risk
- Stable high risk

Survival (%)

- 100% for Stable Low risk
- 98% for Improved to Low risk
- 68% for Stable Intermediate risk
- 43% for Worsened to Intermediate risk or high risk

Time since follow-up risk assessment (yrs)

Survival (%)

Patients at risk (n)

Survival (%)
Importance of Risk Assessment at Baseline and Over Time: French Registry

Baseline

Transplant-free survival (%)

0 1 2 3 4 5

Years

No. at risk:

- 59
- 112
- 217
- 371
- 258

No. low-risk criteria

- 4
- 3
- 2
- 1
- 0

Follow-up

Transplant-free survival (%)

0 1 2 3 4 5

Years

No. at risk:

- 175
- 247
- 275
- 225
- 95

No. low-risk criteria

- 4
- 3
- 2
- 1
- 0

Low-risk Status at Noninvasive Follow-up

Transplant-free survival (%)

0 1 2 3 4 5

Years

No. at risk:

- 115
- 145
- 175
- 168

No. low-risk criteria

- 3
- 2
- 1
- 0

Some specific PAH subsets in which efficacy-to-safety ratio of initial combination therapy is not established may be treated with initial monotherapy.

Adapted from Galiè N et al. Eur Respir J. 2019; 53 1801889 [https://doi.org/10.1183/13993003.01889-2018].
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6th World Symposium Proposed Algorithm for PAH Treatment

Patient Already on Treatment

After 3-6 months of treatment

Low Risk
Structured Follow-up

Intermediate or High Risk

Maximal Medical Therapy Combination and Listing for Lung Tx

Intermediate or High Risk

Treatment Escalation*

After 3-6 months of treatment

Consider referral for lung Tx

*For example, escalate to triple therapy, switch from oral to parenteral PCA, etc.
Adapted from Galiè N et al. Eur Respir J. 2019; 53 1801889 [https://doi.org/10.1183/13993003.01889-2018].
Combination Therapy

sGC Stimulators

Prostanoids

Endothelin Receptor Antagonists

Phosphodiesterase Inhibitors

*53% on background ERA for PHIRST, 50% on background ERA or prostanoid for PATENT-1
†64% on background PDE-5I or prostanoid in SERAPHIN. 84% on background ERA and/or PDE-5I in GRIPHON

PATENT-1*  TRIUMPH STEP SERAPHIN†  GRIPHONγ

PHIRST*  SERAPHIN†  AMBITION

TRIUMPH PACES GRIPHON
Jane: Initial Management

- Admitted to hospital following cath
- IV diuresis
- IV epoprostenol initiation +/- upfront ERA, PDE5-I so long as not limiting up-titration of epo
On-therapy Prognostic Indicators

- Functional class I or II
- 6MWD >380 m
  - limiting supporting data; do not use in isolation
- Hemodynamics
  - normal cardiac index (>2.2 L/min/m$^2$)
  - normal RA pressure
- Positive response to CCB
- BNP <180 pg/mL

## Important Prognostic Variables

<table>
<thead>
<tr>
<th>French Registry</th>
<th>REVEAL Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Functional class</td>
<td>• Functional class</td>
</tr>
<tr>
<td>• 6-minute walk</td>
<td>• 6-minute walk</td>
</tr>
<tr>
<td>• RAP</td>
<td>• PVR, RAP</td>
</tr>
<tr>
<td>• CO</td>
<td>• Vitals</td>
</tr>
<tr>
<td>• Age</td>
<td>• BNP</td>
</tr>
<tr>
<td>• Gender</td>
<td>• Pericardial effusion</td>
</tr>
<tr>
<td>• Etiology</td>
<td>• DLCO</td>
</tr>
</tbody>
</table>

Jane: Return Visits in May & September

- Significantly improved
- No limitations
- Functional class I
- Meds
  - IV Epoprostenol +/- ERA+PDE5-I
  - Furosemide 20 mg
  - KCl 10 mEq qd
Jane: Follow-up Physical Exam

- HR 80 bpm; BP 103/59 mm Hg; Wt 144.8 lb
- JVP 6, carotid upstrokes normal
- Clear lungs
- Palpable RV heave, normal S, loud P2, II/VI TR murmur
- No LE edema
Jane: 6MWD

- 222 m: 99-96% in January
- 486 m: 99-97% in May
- 556 m: 99-97% in September
Collaborative Care With PH Centers:

- Diagnostic dilemmas
- Diagnostic cath/vasodilator trial
- Fluid management
- Acute issues
- PAH-specific therapies
- Side effects
- Hospitalizations
- Transplant
- Clinical trials
Thank you for your participation!

For more information on upcoming PHA Medical Education Programs, please visit:

www.PHAssociation.org