Diagnosis and Treatment of Pulmonary Arterial Hypertension: The Role of the Primary Care Clinician

Emerging Challenges in Primary Care: Update 2013
Faculty

• **Charles D. Burger, MD**
  - Professor of Medicine, Pulmonary and Critical Care Medicine, Mayo Clinic Florida, Jacksonville, FL

• **Victor F. Tapson, MD**
  - Professor of Pulmonary and Critical Care Medicine, Director, Pulmonary Vascular Disease Center, Duke University Medical Center, Durham, NC

• **Arunabh Talwar, MD, FCCP**
  - Associate Professor of Medicine, Hofstra North Shore LIJ School of Medicine, Director Pulmonary Hypertension Program, North Shore University Hospital, Manhasset, NY
Faculty Disclosure

- **Charles D. Burger, MD FCCP**
  - Principal Investigator – Actelion, Gilead, United Therapeutics

- **Victor F. Tapson, MD**
  - Previous 3 years: Research funding - Actelion, Bayer, Novartis, United Therapeutics. Consulting- Actelion, Bayer, Gilead, Lung LLC, Novartis, United Therapeutics.

- **Arunabh Talwar, MD, FCCP**
  - Nothing to disclose
Faculty

• **Christine Archer-Chicko, MSN, CRNP**
  
  – Nurse Coordinator, Pulmonary Vascular Disease Program, Penn Presbyterian Medical Center, Philadelphia, PA

• **Charles D. Burger, MD**
  
  – Professor of Medicine, Pulmonary and Critical Care Medicine, Mayo Clinic Florida, Jacksonville, FL
  
  – Medical Director, Pulmonary Hypertension Clinic

• **Harold I. Palevsky, MD**
  
  – Professor of Medicine, Perelman School of Medicine of the University of Pennsylvania
  
  Chief, Pulmonary, Allergy and Critical Care
  
  Director, Pulmonary Vascular Disease Program
  
  Penn Presbyterian Medical Center, Penn Lung Center, Philadelphia, PA

• **Arunabh Talwar, MD**
  
  • Associate Professor of Medicine, Hofstra North Shore LIJ School of Medicine, Director Pulmonary Hypertension Program, North Shore University Hospital, Manhasset, NY
Faculty Disclosure

• Christine Archer-Chicko, MSN, CRNP
  – Consulting - United Therapeutics

• Charles D. Burger, MD
  – Consulting - Actelion, Gilead Sciences
  – Research - Actelion, Gilead, United Therapeutics

• Harold I. Palevsky, MD
  – Consulting - Actelion, Bayer Healthcare
  – Advisory Board - United Therapeutics
  – Serve on DSMB - Aires Pharm

• Arunabh Talwar, MD
  • No relationships to disclose.
Learning Objectives

• Explain the pathophysiology of pulmonary arterial hypertension (PAH)
• Determine when and how to screen for PAH
• Describe how to secure a firm diagnosis
• Describe current therapies for PAH
• Describe appropriate monitoring for patients receiving treatment for PAH
On a scale of 1 to 5, please rate how confident you would be in participating in the evaluation, management and referral of a patient with PAH?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Question 1

What is the recommended test to best determine the cause of pulmonary hypertension discovered on echocardiogram?

1. No test is needed, just treat with a calcium blocker and repeat echocardiogram in 1 year
2. Spirometry
3. Right heart catheterization
4. Cardiac stress test
Question 2

Which of the following scenarios would be most likely associated with pulmonary arterial hypertension?

1. Severe fatigue without dyspnea
2. Progressive dyspnea, clear lungs and ankle edema
3. Exertional chest pain in the absence of any other symptoms
4. Dyspnea, hypersomnolence and morning headache
Question 3

What do currently published practice guidelines recommend for Group 1 PAH treatment?

1. Calcium channel blockers are limited to patients vasoreactive by right heart catheterization
2. A repeat right-heart catheterization at approximately one year after diagnosis
3. A chest radiograph performed yearly
Question 4

Which is the most appropriate plan to determine clinical status and response to treatment in PAH patients?

1. 6 minute walk, BNP, each clinic visit with echocardiography every 6 to 12 months
2. 6 minute walk and cardiac MRI every 6 to 12 months
3. Cardiopulmonary exercise testing each clinic visit
4. Yearly chest CTA to follow pulmonary artery diameter and right ventricular size
5. 6 minute walk test and pulmonary function testing including diffusing capacity, every 6 to 12 months
Pulmonary Hypertension

High blood pressure within the pulmonary vascular bed

Key Issues:

1) Making the correct diagnosis
2) Assessing disease severity
3) Choosing an initial therapy
4) Reassessing the patient / response to therapy
Pulmonary Vascular Pressures

Normal

Pulmonary HTN

(8 mmHg)
15/4

(30 mmHg)
50/20

2
15/2

4

15

10

50/15
Definition of Pulmonary Arterial Hypertension (PAH)

Right Heart Catheterization Confirmed

Increased mean pulmonary arterial pressure (mPAP)* >25 mm Hg at rest

Normal pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg

Increased pulmonary vascular resistance (PVR)† >3 Wood units

* Normal resting mPAP = 8 – 20 mm Hg.
† In ACCF/AHA expert consensus; in 4th World Symposium on PH, increased PVR listed without a specific value.

# Clinical Classification of Pulmonary Hypertension (Dana Point)

## 1. PAH
- Idiopathic PAH
- Heritable
- Drug- and toxin-induced
- Persistent PH of newborn
  - Associated with:
    - CTD
    - HIV infection
    - portal hypertension
    - CHD
    - schistosomiasis
    - chronic hemolytic anemia

### 1’. PVOD and/or PCH

## 2. PH Owing to Left Heart Disease
- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

## 3. PH Owing to Lung Diseases and/or Hypoxia
- COPD
  - ILD
  - Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental abnormalities

## 4. Chronic Thromboembolic Pulm HTN (CTEPH)

## 5. PH With Unclear Multifactorial Mechanisms
- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Others

*Simonneau G et al. J Am Coll Cardiol. 2009;54;S43-S54.*
Common Case

• 76 yo AA woman with exertional dyspnea
• PMH: obesity, hypertension, CAD, and DM
• Echocardiogram reports “severe pulmonary hypertension”
• RVSP is 60 mmHg
• Other findings: EF 75%, LAE, LVH, normal RA size, and normal RV size and function
What is the significance of “pulmonary hypertension” on this patient’s echocardiogram?

Which of the following is NOT true?

1. The echocardiogram may overestimate pulmonary pressures
2. The patient likely has pulmonary arterial hypertension and should begin treatment immediately
3. The patient may have heart failure even with normal EF
4. Further evaluation is necessary to determine the correct diagnosis and treatment recommendation
Audience Response Question

How many different types of PH are there?

1. 2 types: Primary and secondary
2. 5 different groups: PAH, PVH, lung disease, Chronic thromboembolism, and miscellaneous
3. 3 types: Acute, subacute and chronic
4. 4 groups: the largest group is pulmonary “arterial” hypertension (PAH)
WHO DIAGNOSTIC GROUPS

• Group 1: Pulmonary arterial hypertension
• Group 2: Pulmonary venous hypertension
• Group 3: PH in association with hypoxemia
• Group 4: PH in association with CTEPH
• Group 5: Miscellaneous

Group 1 (PAH) Distributions in the US: REVEAL Registry

Overall

- Idiopathic (46.2%)
- Associated (50.7%)
- Heritable (2.7%)
- Pulmonary veno-occlusive (0.4%)

Based on Venice Clinical Classification (2003); 2967 patients.
At-Risk Populations for PAH

- Connective tissue disease (any etiology)
  - Up to 30% of scleroderma
- Congenital heart disease (R -> L shunts)
- HIV
- Liver disease with portal hypertension
- Drug and toxin exposure

HIV human immunodeficiency virus; IPAH=idiopathic pulmonary arterial hypertension; MCTD=mixed connective tissue disease; SSc=systemic sclerosis.

Symptoms of PAH

– Initial symptoms

  Dyspnea (on exertion)  Fatigue
  Pre-syncope  Edema
  Dizziness  Angina

  No Crackles

– Non-specific nature of complaints can lead to:
  Confusion with other conditions
  Delay in establishing a diagnosis
Evaluation of Suspected Pulmonary Hypertension

History

Physical Examination

Testing
- screening for PH
- confirming the diagnosis of PH
- establishing the etiology of the PH
ECG

Back to Our Case

- 76 yo AA woman with exertional dyspnea
- PMH: obesity, hypertension, CAD, and DM
- Echocardiogram reports “severe pulmonary hypertension”
- RVSP is 60 mmHg
- Other findings: EF 75%, LAE, LVH, normal RA size, and normal RV size and function
Is It Left Heart Disease (Group 2)?

- Paroxysmal nocturnal dyspnea
- Orthopnea
- Atrial fibrillation
- Absence of right axis deviation
- **Left atrial enlargement**, LV hypertrophy
- Limited right-sided involvement
- History of systemic hypertension, diabetes, coronary artery disease
- Obesity/OSA—
- Diastolic dysfunction
Echocardiogram: Four Chamber View
V=tricuspid jet velocity (m/s); RAP= right atrial pressure; RVSP=right ventricular systolic pressure; PASP=pulmonary artery systolic pressure.
ECHOCARDIOGRAM

• Pros
  – Readily available and non-invasive
  – Can detect evidence of left heart disease
  – Can estimate right heart pressures and size/fix
detecting PH (Not PAH)-SCR
  – SCREENING TEST

• Cons
  – Does not measure left heart pressures so does
    NOT diagnose PAH
  – Cannot eliminate left-to-right shunt
  – Estimated PA pressure is often NOT accurate
Diagnosis and Group Classification

Main Goals:
- Verify the existence of PH
- Determine which group
- Identify PAH patients for Rx
- Assess the severity of PH

Assess Severity of PAH

- Symptoms
- BNP
- Six-minute walk test
- ECHO assessment of RV
- RHC results
  - Right heart pressures
  - PVR
  - CO/CI
### Modified NYHA Functional Class for PAH

<table>
<thead>
<tr>
<th>WHO Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><strong>No</strong> limitation of usual activities</td>
</tr>
</tbody>
</table>
| II        | **Mild** limitation of usual activities  
Normal physical activity causes increased dyspnea, fatigue, chest pain, or near-syncope |
| III       | **Marked** limitation of physical activity  
Less than ordinary activity causes increased dyspnea, fatigue, chest pain, or near-syncope |
| IV        | **Unable** to perform most any physical activity  
Dyspnea and/or fatigue even at rest  
Syncope may be present  
May have signs of right ventricular failure |

6 Minute Walk Test (6MWT)

- Practical, simple test
- Measures distance walked on a flat, hard surface in 6 min
- Self-paced
- Assesses submaximal exercise capacity because most activities of daily living are performed at submaximal levels of exertion
- May better reflect the functional exercise level for daily physical activities
- Important results: distance, SpO2, dyspnea score, HR response to exercise and 1-minute post
PAH Diagnostic Workup

Echocardiography Suggests PH

Right Heart Catheterization to Confirm PH/PAH

Document hemodynamics, oxygen saturations, and acute response to vasodilator

Audience Response Question

Why is a right heart catheterization necessary for PH?

A. Pressures may have been over-estimated on echocardiogram and there may be no PH
B. To evaluate vascular responsiveness and reversibility
C. To diagnose ischemic heart disease
D. To measure hemodynamics for prognostic purposes

Please choose one of the following answers:

1. A, B,
2. A, B, C
3. A, B, D
4. A, B, C, D
Right Heart Catheterization

- Exclude congenital heart disease
- Measure wedge pressure or LVEDP
- Establish severity and prognosis
- Test vasodilator therapy (if PAH, especially IPAH)

*Catheterization is required when pulmonary hypertension is suspected*
ACCP Consensus: Definition of a Vasodilator Responder

-Only Responders get treated with CCBs-

Decrease in mean PAP by at least 10 mm Hg
Reduction in PA pressures to an absolute mean PAP <40 mm Hg
Unchanged or increased CO

It is essential to follow patients treated with CCBs closely to make sure the clinical response is as anticipated, to make sure there are no side effects of therapy, and very importantly, to make sure the response is sustained.
TREATMENT
PAH Treatment Goals

- Fewer/less severe symptoms
- Improved exercise capacity
- Improved hemodynamics
- Prevention of clinical worsening
- Improved quality of life
- Improved survival
Individual Audience Response

What general therapies and interventions should you provide in the care of the PAH patient?

Select best answer:

1. Supplemental oxygen for hypoxemia
2. Diuresis for fluid retention
3. Anticoagulation
4. Dietary advice
5. Exercise training
6. All of the above
Chronic Adjuvant Therapies in PAH

Oxygen
- Use to prevent hypoxic vasoconstriction
- Consider exercise, sleep, altitude
- Aim for target saturation of 92%

Diuretics
- Most patients need
- Low systemic BP and elevated Cr often not a contraindication

Anticoagulation
- Recommended in IPAH
- Warfarin with INR 1.5 – 2.5 range (can go off for procedures): other Rx not studied
- Newer agents such as dabigatran, rivaroxaban and apixaban not studied for IPAH

Dietary
- Sodium and fluid restriction often necessary for RV dysfunction and fluid retention

Exercise Training
- Supervised exercise training studied in PAH and useful to increase exercise capacity
Individual Audience Response

All patients deserve a trial of calcium channel blockers (cost effective/available).

1. True
2. False
ACCP Consensus: Definition of a Vasodilator Responder

-Only Responders get treated with CCBs-

Decrease in mean PAP by at least 10 mm Hg
Reduction in PA pressures to an absolute mean PAP <40 mm Hg
Unchanged or increased CO

It is essential to follow patients treated with CCBs closely to make sure the clinical response is as anticipated, to make sure there are no side effects of therapy, and very importantly, to make sure the response is sustained.
Survival in IPAH with CCB Therapy

Response / Warfarin

Response / No Warfarin

No Response / Warfarin

No Response / No Warfarin

Targets for Current Therapies in PAH

Prostacyclin Pathway
- Arachidonic Acid
- Prostacyclin Synthase
- Prostacyclin
- cAMP
- Prostacyclin Derivatives
- Vasodilatation and Antiproliferation

Endothelin Pathway
- Big Endothelin
- Endothelin-converting Enzyme
- Endothelin-1
- Endothelin Receptor Antagonists
  - Endothelin Receptor A
  - Endothelin Receptor B
- Vasoconstriction and Proliferation

Nitric Oxide Pathway
- Arginine
- Nitric Oxide Synthase
- Nitric Oxide
- Riociguat
- cGMP
- Exogenous Nitric Oxide
- Phosphodiesterase Type-5
- Phosphodiesterase Type-5 Inhibitors
- Vasodilatation and Antiproliferation

PAH Treatment Algorithm

Right Heart Catheterization With Acute Vasodilator Change

Positive Response
- Trial With Oral Calcium Channel Blocker Therapy
  - Sustained Response
    - No
    - Yes: Continue Therapy

Negative Response
- Lower risk
  - Oral therapies $\rightarrow$ Injectable therapies
- Higher Risk
  - Injectable therapies

Pharmacotherapy for PAH: Routes of Delivery

• **Oral therapy**
  - Endothelin receptor antagonists (ERAs)
  - PDE5 inhibitors
  - Soluble guanylate cyclase (sGC) stimulators to nitric oxide (NO)
  - Calcium channel blockers (only if documented to be vasoreactive)
# Endothelin Receptor Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Bosentan</th>
<th>Ambrisentan</th>
<th>Macitentan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice-daily</td>
<td>Once-daily</td>
<td>Once-daily</td>
</tr>
<tr>
<td><strong>Availability status</strong></td>
<td>FDA approved 2001 Group 1 PAH</td>
<td>FDA approved 2007 Group 1 PAH</td>
<td>FDA approved 2013 Group 1 PAH</td>
</tr>
</tbody>
</table>

- **Bosentan**: Initiate treatment at 62.5 mg bid for 4 weeks and then increase the maintenance dose of 125 mg bid.
- **Ambrisentan**: Initiate treatment at 5 mg once daily and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.
- **Macitentan**: Start 10 mg daily.
Macitentan

Endothelin-1 is predominantly secreted into tissue (e.g. stimulation by thrombin)

100 times more potent than bosentan
ETA/ETB
Directed towards tissues to avoid vascular effects

![Diagram showing the secretion of Endothelin-1 from basolateral to apical, with a bar graph comparing ET-1 levels under control and thrombin stimulation.](image-url)
## PDE-5 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Three times daily</td>
<td>Once-daily</td>
</tr>
<tr>
<td><strong>Availability status</strong></td>
<td>FDA approved 2006, Group 1 PAH</td>
<td>FDA approved 2009, Group 1 PAH</td>
</tr>
</tbody>
</table>

### Notes:

- a. Sildenafil full prescribing information. 2007. Approved dose 20 mg three times daily.

- b. Tadalafil full prescribing information. 2009. Initiate treatment with two 20 mg (total 40 mg) tablets once daily.
Riociguat directly stimulates the native soluble guanylate cyclase (sGC) independently of NO. Riociguat increases the sensitivity of native soluble guanylate cyclase (sGC) to NO. Both actions lead to vasodilatation (and anti-proliferation). Effect of riociguat is not limited by low NO levels (unlike PDE5-I).

Riociguat:

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Constricted</th>
<th>Pressure</th>
<th>Relaxed</th>
<th>Flow rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>↑</td>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Flow rate</td>
<td>↓</td>
<td></td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

NO

Riociguat → sGC* → cGMP

PDE5-I = phosphodiesterase-5-inhibitor
NO = nitric oxide

* native (intact)
PAH Treatment Algorithm

Right Heart Catheterization With Acute Vasodilator Change

Positive Response
- Trial With Oral Calcium Channel Blocker Therapy
  - Sustained Response
    - No
    - Yes: Continue Therapy

Negative Response
- Lower risk
  - Oral therapies → Injectable therapies
- Higher Risk
  - Injectable therapies
## Prognostic Factors for Risk of PAH Disease Progression

<table>
<thead>
<tr>
<th>Evidence of RV failure</th>
<th>Lower Risk</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO class</td>
<td>II, II</td>
<td>III, IV</td>
</tr>
<tr>
<td>6-minute walk distance</td>
<td>&gt;400 m</td>
<td>&lt;300 m</td>
</tr>
<tr>
<td>Brain natriuretic peptide</td>
<td>&lt;180 pg/mL</td>
<td>&gt;180 pg/mL</td>
</tr>
<tr>
<td>ECHO findings</td>
<td>Minimal right ventricular dysfunction</td>
<td>Pericardial effusion; significant right ventricular dysfunction</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Normal/near normal RAP (&lt;10 mm Hg) and CI (&gt;2.5 L/min/m²)</td>
<td>High RAP (15 -20), Low CI (&lt; 2.0)</td>
</tr>
</tbody>
</table>
Prostacyclins: Intravenous, Subcutaneous, or Inhaled

- Epoprostenol (Flolan® or Veletri®)
- Treprostinil (Remodulin®)
- Iloprost (Ventavis®)
- Treprostinil (Tyvaso®)
N=162 consecutive patients with IPAH in NYHA Class III or IV. 3-year survival with IV epoprostenol compared with expected survival from historical controls.

*P<0.001 at all time points.

Follow up

• Typically monthly to every 3-6 months by the PAH center/specialists
• Primary care clinicians partner to control CHF (diuresis/ weight/chemistry), anticoagulation, blood-work management
• Drug escalation by the PH center/ PAH specialists
• Tests at PH Center: FC, 6 minute walk, BNP, ECHO with RV assessment (pressures, size and function)
• Right heart cath: no preset schedule, usually at decision points for treatment or to confirm clinical suspicion
• May be different for patients in clinical research studies
Collaborative Care With PH Centers:

- Diagnostic dilemmas
- Diagnostic cath/ vasodilator trial
- Complex comorbidities
- Failure to achieve Rx goals
- Considering prostanoids
- Considering combination Rx
- Clinical trials
- Transplant referral
Take Home Message

• Be mindful of patient with typical cardiac symptoms (exertional dyspnea, chest pain or syncope) in atypical patient such as young woman: Get an echocardiogram.

• If the echocardiogram reports pulmonary hypertension, multiple questions need to be asked:
  – What kind of pulmonary hypertension?
    • It is left sided heart disease manifesting itself as elevated pulmonary pressures?
    • Which PH group does the patient belong to?
  – Is the elevated pressure truly elevated?

• All PH patients need a right heart catheterization to accurately assess hemodynamics and to help assign PH group
Take Home Message

• Pulmonary Hypertension (PH):
  – Increased mean pulmonary artery pressure mPAP ≥ 25

• Pulmonary Arterial Hypertension (PAH):
  – Normal pulmonary capillary wedge pressure PCWP≤ 15

• There are five groups of PH:
  – 1: In PAH, problem is in the pulmonary vasculature
  – 2: Cardiac dysfunction related
  – 3: Lung or sleep-disorder related
  – 4: CTEPH (related to pulmonary embolism)
  – 5: Miscellaneous
Take Home Message

• Therapy best started at PAH Centers
• No treatment with calcium channel blockers without evidence of vasoreactivity on right heart catheterization
• Patients require close follow-up, particularly with advanced/accelerated disease
• Therapy should be escalated aggressively.
• No patient should die with monotherapy or without trial of prostanoid therapy
Question 1
What is the recommended test to best determine the cause of pulmonary hypertension discovered on echocardiogram?

1. No test is needed, just treat with a calcium blocker and repeat echocardiogram in 1 year
2. Spirometry
3. Right heart catheterization
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Which of the following scenarios would be most likely associated with pulmonary arterial hypertension?

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What do currently published practice guidelines recommend for Group 1 PAH treatment?

1. Calcium channel blockers are limited to patients vasoreactive by right heart catheterization
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3. A chest radiograph performed yearly
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Which is the most appropriate plan to determine clinical status and response to treatment in PAH patients?

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2. 6 minute walk and cardiac MRI every 6 to 12 months
3. Cardiopulmonary exercise testing each clinic visit
4. Yearly chest CTA to follow pulmonary artery diameter and right ventricular size
5. 6 minute walk test and pulmonary function testing including diffusing capacity, every 6 to 12 months
On a scale of 1 to 5, please rate how confident you would be in participating in the evaluation, management and referral of a patient with PAH?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Which of the statements below describes your approach to participating in the evaluation, management and referral of patients with PAH?

1. I do not participate in the evaluation, management and referral of patients with PAH, nor do I plan to this year.

2. I did not participate in the evaluation, management and referral of patients with PAH before this course, but as a result of attending this course I’m thinking of doing this now.

3. I do participate in the evaluation, management and referral of patients with PAH and this course helped me change my methods.

4. I do participate in the evaluation, management and referral of patients with PAH and this course confirmed that I don’t need to change my methods.
Universe of PH

↑PVR
↑TPG
PAH (Group 1)
Hypoxic/Lung
CTEPH

↑CO
Fever
Thyrotoxicosis
Anemia
Pregnancy
Some PoPH

PH

↑PAWP
↑LVEDP
↑LAP

LH Disease
PV Obstruction
Diagnostic Subgroups for Group 1 PAH

- Idiopathic PAH
- PAH Related to:
  - Collagen vascular disease
  - Congenital heart disease
  - Portal hypertension
  - HIV
  - Drugs eg dietary suppressants

Progression of PAH

- Pre-symptomatic/Compensated
- Symptomatic/Decompensating
- Declining/Decompensated

CO
Symptom Threshold

PAP

PVR

WHO I
WHO II
WHO III
WHO IV

Right Heart Dysfunction
The Registry to EValuate Early And Long-term PAH Disease Management (REVEAL)

- Multicenter, observational, U.S.-based study of patients diagnosed with PAH.
- 55 sites in the United States.
- Demographic data gathered at the time of enrollment.

REVEAL DEMOGRAPHICS

N = 2,525

- Women 80%
- Mean age 53 years
- RACE
  - 73% Caucasian
  - 12% AA
  - 9% Hispanic
  - 3% Asian

PAH Registries: Functional Class at Diagnosis Indicates Delayed Diagnosis

% Patients NYHA Functional Class III-IV at Diagnosis

- More common in women
- Spans broad age range
- Delay in diagnosis persists
- Most patients diagnosed with late symptoms
- Poor prognosis if untreated

Frost AE et al. Chest 2011;139;128-137.
REVEAL Preliminary Analysis
(n = 2,967)

• Symptoms
  – Dyspnea 83%
  – Fatigue 27%
  – Chest pain or LE edema 20%
  – Syncope/near syncope 17%
  – Cough 14%
Modified NYHA Functional Class

• I  No limitation
• II Mild limitation: Symptoms (Sx) with ordinary activity
• III Moderate limitation: Sx with low level activity
• IV Severe limitation: Sx at rest, Syncope

Sx = symptoms: dyspnea, chest pain, near-syncope or syncope
REVEAL DEMOGRAPHICS

N = 2,525

- Functional Class I 7.5%
- Functional Class II 36.5%
- Functional Class III 50.0%
- Functional Class IV 5.5%

Technical Limitations of ECHO

- Cohort: 374 lung transplant candidates
- Echo 24–48 h prior to right heart catheterization.
- Prevalence of PH: 25%
- ECHO frequently inaccurate leading to over-diagnosis of PH in patients with advanced lung disease

### At-Risk Populations for PAH

<table>
<thead>
<tr>
<th>Populations</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPAH</td>
<td>6 cases/million population (1)</td>
</tr>
</tbody>
</table>
| Connective Tissue Disease            | ■ 8% to 27% in SSc (2)  
■ Up to 25% in MCTD (3)  
■ 0.5% to 14% in LUPUS (4)         |
| Congenital Heart Disease             | ■ 12% to 34% /o5  
■ 25% to 50% of patients with PAH will develop Eisenmenger syndromes |
| HIV Infection                        | 0.5% (2)                                                                  |
| Drugs/Toxins                         | 29% of IPAH patients reported prior amphetamine use in a retrospective study of 340 PAH and pulmonary hypertension patients (7) |

HIV human immunodeficiency virus; IPAH=idiopathic pulmonary arterial hypertension; MCTD=mixed connective tissue disease; SSc=systemic sclerosis.

Is It Lung Disease (Group 3)?

- HYPOXEMIA
- History of smoking and COPD with wheezing
- Exposure history for lung fibrosis with crackles
- Risk factors and history suggestive of sleep apnea
Chronic Pulmonary Embolism

Idiopathic Pulmonary Arterial Hypertension

Ventilation Perfusion Lung Scan

Chronic Pulmonary Embolism
CTEPH: A "Curable" Form of PH Not to Be Missed
Understanding The Right Side

ECHO:
EF=60%
Diastolic Dysfunction
Stage I
Mild LAE
RVSP 60

PA=54/25 (mean=34)

PCWP=25
CO=5L/min
PVR = (34-25) / 5
PVR=1.8 WU
Understanding The Right Side

ECHO:
EF=60
Mild RV Hypertrophy
RVSP 65

PA=77/30 (mean =45)

PCWP=8
CO=5L/min
PVR= 7.4 WU (45-8)/5
Approved Therapeutic Targets (More Coming!)

- Endothelin Pathway
  - Pre-proendothelin → Proendothelin
  - Endothelin-1
    - Endothelin receptor A
    - Endothelin receptor B
    - Endothelial cells
    - Vasoconstriction and proliferation
    - Endothelin-receptor antagonists
    - Phosphodiesterase type 5
    - Exogenous nitric oxide
    - Phosphodiesterase type 5 inhibitor

- Nitric Oxide Pathway
  - L-arginine → L-citrulline
  - Nitric Oxide
    - Endothelial cells
    - Vasodilation and antiproliferation
    - Prostacyclin (prostaglandin I2)
    - Prostacyclin derivatives

- Prostacyclin Pathway
  - Prostacyclin (prostaglandin I2)
    - Prostacyclin
    - Endothelial cells
    - Arachidonic acid

- Smooth muscle cells
  - Prostacyclin
  - Prostaglandin I2
  - Vasodilation and antiproliferation
  - Nitric Oxide Pathway
  - Endothelium

Bosentan*: 6-MWD (351 and BREATHE-1)

**Study 351**
Mean change from baseline (m).

- **Bosentan** (n=21)
- **Placebo** (n=11)

**BREATHE-1**
Mean change from baseline (m).

- **Bosentan** (n=144)
- **Placebo** (n=69)

*p=0.05 vs baseline; p=0.021 vs placebo. Values are mean±SEM.

Bosentan: Time to Clinical Worsening (BREATHE-1 and EARLY)

**BREATHE-1**
Event-free (%).

- **Bosentan** (n=144)
- **Placebo** (n=35)

*p=0.0038
89%

- **Bosentan** (n=89)
- **Placebo** (n=13)

*p=0.0015
63%

**EARLY**
Event-free (%).

- **Bosentan** (n=53)
- **Placebo** (n=27)

*p=0.0114


Ambrisentan* in PAH: 6MWD (ARIES)

**ARIES-1**
Δ6MWD (m).

- 10 mg ambrisentan
- 5 mg ambrisentan
- 2.5 mg ambrisentan
- Placebo

*p<0.001

**ARIES-2**
Δ6MWD (m).

- 5 mg ambrisentan
- 10 mg ambrisentan
- 2.5 mg ambrisentan
- Placebo

*p<0.01

*Letaire®. p-values are vs placebo.

Ambrisentan in PAH: Time to Clinical Worsening (ARIES)

**ARIES-1**
Event-free (%).

- 5 mg ambrisentan
- 10 mg ambrisentan
- 2.5 mg ambrisentan
- Placebo

**ARIES-2**
Event-free (%).

- 5 mg ambrisentan
- 10 mg ambrisentan
- 2.5 mg ambrisentan
- Placebo

Riociguat

• Soluble guanylate cyclase stimulator
• Indications
  – Group 1 PAH
  – Group 4 CTEPH (inoperable or persistent)
• Dosing
• CI: Use with PDE5 inhibitors because of risk of systemic hypotension
IV Epoprostenol in IPAH: Change From Baseline in 6MWD

Subcutaneous Treprostinil: Change From Baseline in 6MWD Overall and by Dose Quartile

Treprostinil IV: 6MWD (TRUST)

Inhaled Treprostinil: Median Change in 6MWD (TRIUMPH)

Hodges-Lehmmann estimate.
## Combination Therapy: Other Ongoing or Recently Completed Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Current therapy</th>
<th>Added therapy</th>
<th>Patients (n)</th>
<th>Study duration</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREEDOM-C</strong></td>
<td>Bosentan and/or sildenafil</td>
<td>Treprostinil oral</td>
<td>300</td>
<td>16 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td><strong>AMBITION</strong></td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>300</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>106</td>
<td>12 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td><strong>COMPASS-1</strong></td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>45</td>
<td>Single dose</td>
<td>PVR</td>
</tr>
<tr>
<td><strong>COMPASS-2</strong></td>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>250</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td><strong>COMPASS-3</strong></td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>100</td>
<td>16 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td><strong>ATHENA-1</strong></td>
<td>Sildenafil or tadalafil</td>
<td>Ambrisentan</td>
<td>40</td>
<td>24 weeks</td>
<td>PVR</td>
</tr>
<tr>
<td><strong>SERAPHIN</strong></td>
<td>Naïve/PDE-5/PGI/combo</td>
<td>Macitentan</td>
<td>742</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td><strong>PATENT</strong></td>
<td>Naïve/PGI/ERA</td>
<td>Riociguat</td>
<td>462</td>
<td>12 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td><strong>IMPRES</strong></td>
<td>≥2 current therapies</td>
<td>Imatinib</td>
<td>200</td>
<td>24 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td><strong>ATPAHSS</strong></td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>63</td>
<td>36 weeks</td>
<td>RV mass/PVR</td>
</tr>
<tr>
<td><strong>GRIPHON</strong></td>
<td>ERA, PDE5 or both</td>
<td>Selexipag</td>
<td>670</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>Novartis</td>
<td>Stable PAH therapy</td>
<td>Noilotinib</td>
<td>66</td>
<td>6 months</td>
<td>PVR</td>
</tr>
</tbody>
</table>
# PAH Determinants of Patient Risk

**ACC/AHA Expert Consensus**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Determinants of Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Disease progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO functional class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt; 400 meters)</td>
<td>6-MWD</td>
<td>Shorter (&lt; 300 meters)</td>
</tr>
<tr>
<td>Peak VO$_2$ &gt; 10.4 mL/kg/min</td>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO$_2$ &lt; 10.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimally elevated and stable</td>
<td>BNP/NT-proBNP</td>
<td>Significantly elevated</td>
</tr>
<tr>
<td>PaCO$_2$ &gt; 34 mm Hg</td>
<td>Blood gases</td>
<td>PaCO$_2$ &lt; 32 mm Hg</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>ECHO findings</td>
<td>Pericardial effusion, RV dysfunction, RA enlargement</td>
</tr>
<tr>
<td>RAP &lt; 10 mm Hg; CI &gt; 2.5 L/min/m$^2$</td>
<td>Hemodynamics</td>
<td>RAP &gt; 20 mm Hg; CI &lt; 2 L/min/m$^2$</td>
</tr>
</tbody>
</table>

ACCF/AHA Treatment Algorithm

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

Positive

Lower Risk

ERAs or PDE-5 Is (oral)
Epoprostenol or Treprostinil (IV)
Iloprost (inhaled)
Treprostinil (SC, inhaled)

Reassess: consider combo-therapy

Investigational Protocols

Negative

Higher Risk

Epoprostenol or Treprostinil (IV)
Iloprost (inhaled)
ERAs or PDE-5 Is (oral)
Treprostinil (SC)

Atrial septostomy
Lung transplant

Oral CCB
Sustained Response

Yes

No

Continue CCB

Definition of Pulmonary Hypertension (PH)

Right Heart Catheterization Confirmed

Increased mean pulmonary arterial pressure (mPAP) to $\geq 25$ mm Hg at rest

(upper limit of normal is age dependent, and is $<20$ mmHg)
REVEAL US REGISTRY - PAH

- 80% were women with mean age 53 years
- Most present with dyspnea (exertional), but chest discomfort, edema and near syncope/syncope occurred in about 20%.
- Most patients with functional class III at dx
- Diagnosis delayed – a mean of 2.8 years from symptom onset (median 1.13 years)

WHO Diagnostic Group 1

Patients in REVEAL Analytic Cohort
Who Met Traditional Hemodynamic Criteria

IPAH = Idiopathic pulmonary arterial hypertension (PAH)

APAH = Associated PAH e.g. with connective tissue disease

PH by Echo ≠ PAH

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

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung disease/sleep-related hypoventilation</td>
<td>9.7%</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1.9%</td>
</tr>
<tr>
<td>CTEPH</td>
<td>0.6%</td>
</tr>
<tr>
<td>PAH</td>
<td>2.3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.8%</td>
</tr>
<tr>
<td>Left heart disease</td>
<td>78.7%</td>
</tr>
</tbody>
</table>

N=483 of 4579 patients with echo PASP >40 mm Hg.

Gabby E. Am J Respir Crit Care Med. 2007;175:A113.
Clinical Presentation of PAH

- Symptoms are nonspecific
- Review risk factors: CVD, liver disease, etc.
- Typical cardiac symptoms or syncope in an atypical patient
- Diastolic dysfx: older age, AF, HTN, CKD, OSA, DM
- COPD: MPAP > 40 with FEV1 50% and hypoxemia
- ILD and OSA: generally mild
Is the PH Group 3?

• CXR and CT for ILD
• ABG to examine both PaO2 and PaCO2
• PFTs
  – Low TLC is restrictive disease
  – Low FEV1/FVC is obstructive
  – Low DLCO in isolation may indicate pulm vasc dis
• Overnight oximetry to screen for nocturnal hypoxemia and/or sleep-disordered breathing

Is It Thromboembolism (Group 4)?

- History of prior DVT and/or PE in ½ of patients
- Elevated PTT not on anticoagulation may suggest anti-cardiolipin antibody
- Lung bruits
- Abnormal V/Q
- CTA not as good for chronic PE and can be falsely negative

Exercise training significantly improves six-min walk distance in PAH.

PAH Treatment

• FDA-approved pulmonary vasodilator therapy is restricted to Group 1 PAH

• Beyond general therapies and use of CCB in vasoresponsive patients with preserved CO, the selection of the best therapy is complex

• Referral to a PH center for appropriate evaluation and treatment is recommended
# Hepatotoxicity with ERA’s

<table>
<thead>
<tr>
<th></th>
<th>Serum Aminotransferase &gt;3 x ULN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Week 12</td>
</tr>
<tr>
<td>Ambrisentan (all doses) (n=483)</td>
<td>2.3%</td>
</tr>
<tr>
<td>Bosentan 125 mg bid (n=165) PAH patients only</td>
<td>3%</td>
</tr>
</tbody>
</table>
Pharmacotherapy for PAH: Routes of Delivery

- **Inhaled therapy (prostanoids only)**
  - Iloprost
  - Treprostinil

- **Intravenous/subcutaneous therapy (prostanoids only)**
  - Epoprostenol
  - Treprostinil
Improvements on monotherapy do not restore normal 6MWD: Should we do more?

Randomized controlled trials

Patient Outcome on Oral Therapy

169 of 190 deaths (89%) on oral therapy only indicating that patients were dying without an attempt with aggressive therapy to improve survival.

PATENT-1: Riociguat for PAH

Change in 6MWD At Week 12

Six-minute Walk Distance

Placebo-corrected treatment effect = 36 m (95% CI: 20-52 m: p<0.0001)

50% of patients were on stable background PAH therapy with ERAs (43%) or prostacyclin (7%)/

# Endothelin Receptor Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Bosentan*</th>
<th>Ambrisentan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice-daily</td>
<td>Once-daily</td>
</tr>
<tr>
<td><strong>Availability status</strong></td>
<td>FDA approved 2001 Group 1 PAH</td>
<td>FDA approved 2007 Group 1 PAH</td>
</tr>
</tbody>
</table>

Bosentan: Start at 62.5 mg bid for 4 weeks and then increase to the maintenance dose of 125 mg bid.

Ambrisentan: Start at 5 mg once daily and consider increasing to 10 mg once daily if 5 mg is tolerated.

* Monitor monthly LFTs