Pulmonary Hypertension Update and Case Studies 2020

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Disclosures

Speakers Bureau – Actelion Pharmaceuticals/ Johnson & Johnson
Case Study

Paul is a 66 year old male who presented to his primary care physician’s office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and osteoarthritis. He had a recent Cardiolite stress test which was negative. BP in office is 160/90. An echocardiogram was ordered.

Height 64 inches. Weight 275 lbs.
Physical Exam- III/VI SEM, 1+ lower extremity edema
Britney is a 26 year old female who presented to her primary care physician’s office with complaints of cough, increased fatigue and dyspnea which has been worsening over the past 1 year. She now c/o SOB at rest. No previous significant past medical history. Was seen by her PCP and placed on an inhaler and steroids. BP in office is 110/70. An echocardiogram was ordered.

Height 64 inches. Weight 145 lbs.
Physical Exam- III/VI SEM
1+ lower extremity edema
Case Study

Denise is a 46 year old female who presented to her primary care physicians office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and scleroderma. She had a recent Cardiolite stress test which was negative. BP in office is 130/80. An echocardiogram was ordered.

Height 64 inches. Weight 195 lbs.
Physical Exam- III/VI SEM
1+ lower extremity edema
Case Study

Agnes is a 96 year old female smoker who presented to her primary care physician’s office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking x 70 years and osteoarthritis. She had a recent Cardiolite stress test which was negative. BP in the office is 140/800. An echocardiogram was ordered.

Height 64 inches. Weight 175 lbs.

Physical Exam- III/VI SEM, 1+ lower extremity edema
2D Echo results:

LVEF: 65%
Reduced RV function
Severe right atrial and ventricular size
Severe tricuspid regurgitation
Small pericardial effusion
RVSP 60 mmHg
Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath
What is PAH?

- PAH is a syndrome characterised by a progressive increase in pulmonary vascular resistance (PVR)
  - leads to right ventricular overload
  - eventually leads to right ventricular failure and premature death\(^1\)
  - If untreated, the median survival is 2.8 years\(^2\) which is comparable with some malignancies

- Increased PVR is related to progressive changes in the pulmonary arterioles
  - vasoconstriction
  - obstructive remodelling of the pulmonary vessel wall
  - inflammation
  - in-situ thrombosis

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Clinical Classification of Pulmonary Hypertension (2018)

1. PAH
   - Idiopathic PAH
   - Heritable
   - Drug- and toxin-induced
   - Associated with:
     - CTD
     - HIV infection
     - portal hypertension
     - Systemic to pulmonary shunts
     - Chronic hemolytic anemia
     - Schistosomiasis
     - PVOD

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

3. PH Owing to Lung Diseases and/or Hypoxia
   - COPD
   - ILD
   - Sleep-disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities
   - Broncho pulmonary dysplasia (BPD)

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms
   - Hematologic disorders
   - Systemic disorders
   - Metabolic disorders
   - Congenital heart Disease- Other than systemic to pulmonary shunt
   - Others chronic hemolytic anemia

BMJ 2018.
Pulmonary Arterial Hypertension (PAH)
PAH: why does it develop?

- Exact cause of PAH remains unknown

- Endothelial dysfunction occurs early on in the disease process

- Endothelial dysfunction results in
  - reduced production of vasodilators
  - over production of vasoconstrictors
  - endothelial and smooth muscle cell proliferation
  - remodelling of the pulmonary vascular bed and increased vascular resistance
Approved Therapeutic Targets

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

**Nitric Oxide Pathway**
- L-arginine
- L-citrulline
- Nitric Oxide
  - Phosphodiesterase type 5
  - Exogenous nitric oxide
  - Vasodilation and antiproliferation

**Prostacyclin Pathway**
- Arachidonic acid
- Prostaglandin I
- Prostacyclin (prostaglandin I)
- Prostacyclin (prostaglandin I)
- Prostacyclin derivatives
- cAMP
  - Vasodilation and antiproliferation

Smooth muscle cells

PAH: why does it develop?

- Reduced production of vasodilators
  - Prostacyclin
    - potent vasodilator
    - potent inhibitor of platelet activation
    - therapy with synthetic forms of prostacyclin may help to correct this deficiency
  - Nitric oxide
    - potent vasodilator
    - possesses anti-proliferative properties
    - vasodilatory effect is mediated by cGMP
      - rapidly degraded by phosphodiesterases
PAH: why does it develop?

• Increased production of vasoactive compounds
  – Endothelin (ET)
    • elevated levels are seen in PAH patients\(^1\)–\(^3\)
    • levels correlate with disease severity\(^4\)
    • deleterious effects mediated through endothelin receptors\(^5\)
      – fibrosis
      – hypertrophy and cell proliferation
      – inflammation
      – vasoconstriction
  • endothelin receptor antagonists can block these effects
• Endothelin, nitric oxide and prostacyclin have been the principal focus of research into treatments for PAH

Pathophysiology of PAH: An Integrated View

- Genetic Predisposition
- Other Risk Factors
- Altered Pathways and Mediators

Vascular Remodeling

- Proliferation
- Thrombosis
- Vasoconstriction
Pathogenesis of Pulmonary Arterial Hypertension

PAH: how common is it?

• PAH is rare
  – an estimated prevalence of 30–50 cases per million\(^1\)
  – most common in young women

• Mean age of diagnosis 36 years\(^2\)

• The prevalence in certain at-risk groups is higher
  – HIV-infected patients (0.50%)\(^3\)
  – sickle cell disease (20–40%)\(^4\)
  – systemic sclerosis (16%)\(^5\)

• True prevalence may be higher

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1. Peacock AJ. *BMJ* 2003
PAH Related to Connective Tissue Disease

• Connective tissue diseases
  – scleroderma (most common)
  – systemic lupus erythematosus
  – Sjogren’s syndrome
  – rheumatoid arthritis
  – MCTD

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

Survival in Pulmonary Arterial Hypertension

- Survival rates (patients with IPAH) at 1, 3 and 5 years were 68%, 48% and 34% respectively

- PAH mortality contributed to
  - Right heart failure 47%
  - Sudden Death 26%
  - Other (pneumonia) 27%

- Although new treatments have improved mortality rates, there is little evidence to support reversal of aberrant remodeling

Schematic Progression of PAH

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

**Equations:**
- PVR = PAP - PCW
- CO = PAP - PCW

**Right Heart Dysfunction**
Diagnosis of Pulmonary Arterial Hypertension (PAH)
Pivotal Tests

- History
- Exam
  - CXR
  - ECG

Echocardiogram

Contingent Tests

- Loud P2
  - listen at apex
- RV lift
  - left parasternal - fingertips
- Systolic murmur (TR)
  - inspiratory augmentation
- Diastolic murmur (PR)
- RV S4
- JVD with V wave, A wave, hepatojugular reflux
- RV S3
- Hepatomegaly
- Edema
- Ascites
- Pulsatile liver
- Low BP, low PP, cool extremities
- Early systolic click; midsystolic ejection murmur

Pivotal Tests

- CXR
- ECG

Contingent Tests

- Echocardiogram
- PFT's
- Polysomnography
- VQ Scan
- Sleep Disorder
- Chronic PE
- Functional Test (6MWT, CPET)
- Overnight Oximetry
- HIV
- ANA
- LFT's
- RH Cath
- TEE
- Exercise Echo
- Pulmonary Angiography
- Chest CT Angiogram
- Coagulopathy Profile
- Vasodilator Test
- Exercise RH Cath
- Volume Loading
- ABG's

Other CTD Serologies

- Index of Suspicion of PH
  - RVE, RAE, RVSP, RV Function
  - Left Heart Disease
    - VHD, CHD
  - Ventilatory Function
  - Gas Exchange

- Contingent Tests Contribute to Assessment of:

**Pivotal Tests**

- Echocardiogram

**Contingent Tests**

- VQ Scan
- Polysomnography
- Sleep Disorder
- Chronic PE
- Functional Test (6MWT, CPET)
- Overnight Oximetry
- HIV
- ANA
- LFT's
- RH Cath
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- Coagulopathy Profile
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- Volume Loading
- ABG's
- Index of Suspicion of PH
- RVE, RAE, RVSP, RV Function
- Left Heart Disease
- VHD, CHD
- Ventilatory Function
- Gas Exchange
- Other CTD Serologies
- HIV Infection
- Scleroderma, SLE, RA
- Portopulmonary Htn
- Establish Baseline
- Prognosis
- Confirmation of PH
- Hemodynamic Profile
- Vasodilator Response

Contingent Tests Contribute to Assessment of:

- Left Heart Cath

**Echocardiogram**

- RA, RV enlargement, IVS straightening
- RV systolic dysfunction
- TAPSE
- IVC diameter and inspiratory collapse
- TR severity
- Estimated PVR, MPAP, DPAP

**RVSP= 4(V_{TR})^2 + RAP**

Echo estimate of PAP often inaccurate in advanced lung disease

- Cohort: 374 lung txp pts
- Echo 24–48 h prior to RHC
- Prevalence of PH: 25%
- Echo frequently leads to over-diagnosis of PH in patients with advanced lung disease
Arbitrary criteria for detecting the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest*

• Echocardiographic diagnosis: PH unlikely
  • Tricuspid regurgitation velocity \( \leq 2.8 \text{ m/sec} \), PA systolic pressure \( \leq 36 \text{ mmHg} \) and no additional echocardiographic variables suggestive of PH

• Echocardiographic Diagnosis PH possible
  • Tricuspid regurgitation velocity \( \leq 2.8 \text{ m/sec} \), PA systolic pressure \( \leq 36 \text{ mmHg} \) but presence of additional echocardiographic variables suggestive of PH.
  • Tricuspid regurgitation velocity 2.8-3.4 m/sec, PA systolic pressure 36-50 mmHg with or without additional echocardiographic variables suggestive of PH

• Echocardiographic diagnosis: PH likely
  • Tricuspid regurgitation velocity \( > 3.4 \text{ m/sec} \), PA systolic pressure \( > 50 \text{ mmHg} \) with/without additional echocardiographic variables suggestive of PH

Arcasoy SM et al. Am J Respir Crit Care Med. 2003;167:735-740. General Overview of Pulmonary Hypertension Tashirul Islam MD,FCCP,MRCP(UK) Indiana University Hospital Arnett Lafayette, IN

European Heart Journal 2009;30:2493-2537
- 3-4% of acute PE do not entirely resolve
- ½ of those with CTEPH do not have an apparent history of acute PE
- Normal or very low probability VQ essentially excludes chronic PE
- CTEPH should be excluded, even when another explanation for PH is present

• 17% (37/220) of patients with OSA have daytime mPAP >20 mm Hg *Chaouat A et al. Chest. 1996;109:380-386.*
  - 16 had mPAP >25 mm Hg; only 2 had mPAP >35 mm Hg
  - Marked ↑ with sub-max exercise (mean mPAP 47 mm Hg) – in part due to ↑ PCWP
  - Contributing factors: obesity, hypoxemia, COPD

• In patients with OSA, ↓PAP reported in response to CPAP therapy

• Untreated – response to other treatment likely less effective
<table>
<thead>
<tr>
<th>Pivotal Tests</th>
<th>Contingent Tests</th>
<th>Contribute to Assessment of</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oxygen saturations (SVC, IVC, PA, SA)</td>
<td>• Right atrial pressure</td>
<td>Index of Suspicion of PH</td>
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<tr>
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<td>• Pulmonary vascular resistance</td>
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<tr>
<td>• Thermodilution or Fick CO, CI</td>
<td>• Systemic systolic, diastolic, and mean pressure</td>
<td>• Gas Exchange</td>
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<td>• Pulmonary vascular resistance</td>
<td>• Heart rate</td>
<td></td>
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<td>• Heart rate</td>
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</tbody>
</table>

**RH Cath**

Proposed Hemodynamic Definition of PH/PAH - Updated 2019 6th World Symposium

**PH**  
Mean PAP $\geq 20$ mm Hg

**PAH**  
Mean PAP $\geq 20$ mm Hg plus  
PCWP/LVEDP $\leq 15$ mm Hg,  
PVR $> 3$ Woods Units

[Link](https://www.acc.org/latest-in-cardiology/articles/2019/10/30/08/08/the-6th-world-symposium-on-ph-part-1)
## Proposed Hemodynamic Definition of PH/PAH- Updated 2019 6th World Symposium

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Characteristics</th>
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<tr>
<td>Pre-Capillary PH</td>
<td>mPAP &gt;20 mmHg</td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery wedge pressure ≤15 mmHg</td>
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<tr>
<td></td>
<td>PVR ≥3 Wood units</td>
</tr>
<tr>
<td>Isolated Post-Capillary PH</td>
<td>mPAP &gt;20 mmHg</td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery wedge pressure &gt;15 mmHg</td>
</tr>
<tr>
<td></td>
<td>PVR &lt;3 Wood units</td>
</tr>
<tr>
<td>Combined Pre- and Post-Capillary PH</td>
<td>mPAP &gt;20 mmHg</td>
</tr>
<tr>
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<td>Pulmonary artery wedge pressure &gt;15 mmHg</td>
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[Link to source](https://www.acc.org/latest-in-cardiology/articles/2019/10/30/08/08/the-6th-world-symposium-on-ph-part-1)
• **Vasodilator response**
  - iNO recommended
  - Decrease in mPAP by ≥10 mm Hg
  - Decrease of mPAP to ≤40 mm Hg
  - rare in scleroderma, hereditary, diet-pill-induced
  - risk of pulmonary edema with left heart disease or PVOD

• **RHC is safe (1.1% serious events)**
  - hematoma, pneumothorax, arrhythmias, hypotension
  (Hoeper M et al. JACC. 2006;48:2546-2552.)

• **Minimize spontaneous variability**
  - take measurements over 2-3 respiratory cycles at end-expiration

Treating PAH
PAH: How is it treated?

• There is currently no cure for PAH

• Prognosis is influenced by the status of WHO FC when treatment is started – those who start therapy in WHO FC I or II demonstrate a better prognosis than those whose therapy is started in the more severe stages\(^1\)

• By recognizing and treating patients as early as possible, disease progression may be delayed

• Without treatment, patients in WHO FC II can rapidly deteriorate within 6 months to more advanced PAH as evidenced by progression of symptoms.\(^2\)

Early Recognition and Treatment of PAH is Essential

Prognosis of untreated PAH is poor, even when mildly symptomatic (WHO FC II)

FC=functional class; PAH=pulmonary arterial hypertension; WHO=World Health Organization.
PAH Treatments—a Historical Overview

CCB, anticoagulation, digitalis, diuretics

Epoprostenol

SC treprostinil

Iloprost

IV treprostinil

Sildenafil

Ambrisentan


CCB = calcium channel blocker.
PAH Treatments—a Historical Overview

- Veletri (Epoprostenol)
- Adcirca
- Oral treprostinil (Orenitram)
- Oral macitentan (Opsmit)
- Oral adempas (Riociguat)
- Oral selexipag (Uptravi)

Timeline:
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2020
When to use a Calcium Antagonist?
CCB Therapy is Effective in Only a Small Percent of PAH Patients

A retrospective study of 557 patients who were tested for acute vasoreactivity:

- 70 (12.6%) patients responded and were put on CCB therapy
- Of those 70 patients, only 38 improved
- Therefore only 6.8% of the total number of patients benefited from long-term CCB therapy
- For the 32 patients who responded positively to acute vasoreactivity testing but who failed to respond to CCB therapy, the 5-year survival rate was 48%

*Long-term CCB responders represent <10% of iPAH patients*
**What is the Optimal Treatment Strategy?**

### Vasodilator Study

- **Anticoagulate ± Diuretics ± Oxygen ± Digoxin**
  
  **Positive**
  - **Oral CCB**
    - **Sustained Response**
      - **Yes**
        - **Continue CCB**
  
  **Negative**
  - Determinants of Risk
    - **Lower Risk**
      - No
      - Gradual
      - II, III
      - Longer (>400 m)
      - Minimally elevated
      - Minimal RV Dysfunction
      - Normal/Near normal RAP and CI
    - **Determinants of Risk**
      - Clinical Evidence of RV Failure
      - Progression
      - NYHA Class IV
      - 6 Minute Walk Distance
      - BNP
      - Echocardiographic Findings
      - Hemodynamics
    - **Higher Risk**
      - Yes
      - Rapid
      - IV
      - Shorter (<300 m)
      - Very elevated
      - Pericardial Effusion
      - Significant RV Dysfunction
      - High RAP, Low CI

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Goal-Oriented Therapy

Diagnosis of PAH
Vasoreactivity test negative
NYHA II or IV

Baseline examination and 3-to-6-month reevaluation to assess treatment goals
(6MWD >380 m, peak VO₂ >10.4 mL/min/kg,
peak systolic BP >120 mm Hg during exercise)

First-line treatment PDE-5 Inhibitor

Addition of an ERA (within 1 month)

Addition of an inhaled or oral prostacyclin

Transition from inhaled to intravenous prostacyclin

Highly urgent lung transplantation

Treatment goals not met

Treatment continued

Treatment Targets for Pulmonary Arterial Hypertension Patients (WHO Group I)
Phosphodiesterase 5 Inhibitors

• Oral
  – Sildenafil (Viagra)
  – Tadalafil (Adcirca)

*FDA approved
Soluble Guanylate Cyclase (sGC) Stimulator

- Oral
  - Riociguat (Adempas)

*FDA approved
Phosphodiesterase 5 Inhibitors

- Prevent breakdown of cGMP the downstream mediator of nitric oxide
- Major side effects
  - Vasodilatory- headaches, flushing, sinus congestion
  - Visual color changes and blurriness
Sildenafil (Revatio)

- 278 patients\(^1\)
  - 65% IPAH
  - 40% Class II and 56% Class III

- Treatment effect
  \(~45\) meters

- No difference in 6 MWD between doses

Effect of Tadalafil on 6MWD (PHIRST)


![Graph showing the effect of Tadalafil on 6MWD over 16 weeks. The graph compares Placebo, Tadalafil 2.5 mg, Tadalafil 10 mg, Tadalafil 20 mg, and Tadalafil 40 mg. Significant improvements are noted at various time points with p-values less than 0.05 and 0.001.](image-url)
SUPER-1: improvements in 6MWD with sildenafil in PAH-CTD patients

![Graph showing mean (95% CI) change from baseline (m) for different treatment groups.]

- **Placebo (n=21†):** -13
- **20 mg sildenafil TID (n=20):** 42
- **40 mg sildenafil TID (n=18†):** 36
- **80 mg sildenafil TID (n=19§):** 15

* *p<0.003

† Patients without baseline 6MWD: 1 in placebo group and 2 in 40 mg group; § 2 patients discontinued due to adverse events after 4-week evaluation.

Endothelin Antagonists (ERAs)

• Oral
  – Bosentan (Tracleer)
  – Ambrisentan (Letairis)
  – Macitentan (Opsumit)

*FDA approved
Significant Change in 6MWD*
Study 351

*Data are mean ± SEM.

TRACLEER® (bosentan)
(n=21)

Treatment Effect: 76 m
(P=0.02)

Placebo (n=11)

62.5 mg bid 125 mg bid
BREATHE-1: Impact of Bosentan on 6-Minute Walk Distance in WHO Classes III and IV


*P<0.001 vs placebo. †P<0.01 vs placebo.

Ambrisentan ARIES-1 Primary Endpoint: Change in 6MWD at Week 12

N=202.
Placebo-adjusted changes:
10 mg = +51.4 m (P=0.0001)
5 mg = +30.6 m (P=0.0084)

Oudiz RJ, et al. Chest. 2006;130:Abstract 121S.
# SERAPHIN: A landmark study in PAH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>Bosentan</td>
<td>Study-351¹,²</td>
<td>12 wks</td>
<td>6-MWD</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>BREATHE-1³</td>
<td>16 wks</td>
<td>6-MWD</td>
<td>213</td>
</tr>
<tr>
<td></td>
<td>EARLY⁴</td>
<td>26 wks</td>
<td>PVR, 6-MWD</td>
<td>185</td>
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<tr>
<td>Ambrisentan</td>
<td>ARIES-1⁵,⁶</td>
<td>12 wks</td>
<td>6-MWD</td>
<td>202</td>
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<tr>
<td></td>
<td>ARIES-2⁵,⁷</td>
<td>12 wks</td>
<td>6-MWD</td>
<td>192</td>
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<tr>
<td>Sildenafil</td>
<td>SUPER-1⁸</td>
<td>12 wks</td>
<td>6-MWD</td>
<td>277</td>
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<tr>
<td>Tadalafil</td>
<td>PHIRST⁹</td>
<td>16 wks</td>
<td>6-MWD</td>
<td>405</td>
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<tr>
<td>Macitentan</td>
<td>SERAPHIN¹⁰</td>
<td>96 wks*</td>
<td>Time to first morbidity/mortality event</td>
<td>742</td>
</tr>
</tbody>
</table>

*Mean study drug exposure

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SERAPHIN morbidity and/or mortality primary endpoint

Robust nature of the primary endpoint = only clinically relevant events are captured
Morbidity/mortality as primary endpoint is considered more clinically relevant as it reflects the true progression of PAH

All events adjudicated by a blinded clinical events committee

- All-cause death
- Atrial septostomy
- Lung transplantation
- Initiation of i.v. or s.c. prostanoids
- Other worsening of PAH

Pulido T et al. NEJM 2013; 369:809-18
SERAPHIN primary endpoint: Other worsening of PAH

- A decrease in 6-MWD of at least 15%, confirmed by 2 tests on different days
- Worsening of PAH symptoms, which must include either:
  - An increase in FC, or
  - Appearance or worsening of symptoms of RHF
- Need for new PAH treatment(s):
  - Oral or inhaled prostanoids
  - Oral PDE-5 inhibitors
  - ERA after study discontinuation
  - Intravenous diuretics

All events adjudicated by a blinded clinical events committee

Pulido T et al. NEJM 2013; 369:809-18
Summary

• Macitentan also significantly improved clinically important secondary endpoints including 6-MWD, WHO FC and hospitalization

• There was no mortality benefit.
Combination therapy with a PDE-5 and a Endothelin Receptor Antagonist

- Oral
  - Tadalafil (Adcirca)
  - Ambrisentan (Letairis)

Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial

*FDA approved
Prostacyclins

- Intravenous (epoprostenol, treprostinil)
- Subcutaneous (treprostinil)
- Inhaled (iloprost, treprostinil)
- Oral (selexipag, treprostinil)

*FDA approved
Ventavis® (iloprost) Inhalation Solution: Dosage and Administration

- Indicated for inhalation via the Prodose® AAD® system only
- 2.5 mcg initial dose
  - increase to 5 mcg if 2.5 mcg dose is tolerated
  - maintain at maximum tolerable dose (2.5 mcg or 5 mcg)
- 6-9 inhalations daily during waking hours; 8-10 minutes each
Inhaled Iloprost: Change in 6MWD in PAH Patients

Mean (± SEM) absolute change vs baseline (m) 30 minutes postinhalation

Placebo-corrected difference at 12 weeks = 40 m (P<0.01)

Inhaled Treprostinil (Tyvaso)

- Inhaled prostacyclin
- Administered 4 times daily
- Proprietary nebulizer
- TRIUMPH study showed improvements in 6MWD
Inhaled Treprostinil
Distribution of Changes in 6MWD

6MWD, 6-minute walk distance.
Uptravi® - Selexipag
Clinical Application

• Indications:
  • Treatment of pulmonary arterial hypertension (PAH), WHO Group I, to delay disease progression and reduce risk of hospitalization for PAH

• Place in therapy:
  • As monotherapy or in combination with other classes of PAH medications
Uptravi® - Selexipag Literature Review

• Conclusions:
  • Selexipag lowers complication related to PAH vs. placebo (Hospitalization or disease progression)
  • No difference in mortality between groups
  • Addition of selexipag to baseline regimen of two meds gave benefits consistent with overall treatment effect
  • Similar efficacy regardless of dose range

SC Treprostinil

- Requires capable patient
- Site pain is major impediment
  - Affects 85%
  - Local measures: ice, heat, lidocaine, capsaicin, collagenase ± effective
  - NSAIDs, narcotics, gabapentin ± effective

- pain
- erythema
- induration
Treprostinil (Remodulin)

SQ Treprostinil - 6MW distance

Mean ± SE Change from Baseline (meters)

1st Quartile < 5.0 ng/kg/min
(2.5 ± 0.2)

-4 ± 12
(N=34)

2nd Quartile 5 to <8.2 ng/kg/min
(5.6 ± 0.1)

+7 ± 10
(N=52)

3rd Quartile 8.2 to <13.8 ng/kg/min
(9.4 ± 0.2)

+15 ± 7
(N=58)

4th Quartile >13.8 ng/kg/min
(16.2 ± 0.4)

+36 ± 9
(N=58)

1Adapted from Simonneau G et al. Am J Respir Crit Care Med 2002;165:800-04

Adapted from Hill, N. NJ Fellows Conf in PAH 12/2/06
Epoprostenol

- Synthetic salt of prostacyclin
- Rapid efficacy; short, 3- to 5-min half-life
- Approved for Class III and IV
- Invasive: requires continuous IV infusion
- Individualized dosing regimen required
- Two RCTs showing efficacy
Long-term Outcome in IPAH With Epoprostenol

Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain

- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery site complications

Vary according to drug and route of delivery
Emerging Therapies
Reducing Hospitalizations

Impact of Current and Emerging Therapies

- Macitentan (ERA): SERAPHIN trial\textsuperscript{a,b}
  - Included pts on macitentan mono- and combination therapy (PDE-5 inhibitors, oral or inhaled prostanoids, CCBs, l-arginine)
  - Macitentan reduced primary end point (composite of death, atrial septostomy, lung transplantation, initiation of treatment with IV or SC prostanoids, worsening PAH) by 30%-45% (dose dependent; \(P = .01; P < .001\))
  - Reduced all-cause hospitalization by 32% (HR, 0.677; \(P = .0051\))

- Ambrisentan (ERA) ± tadalafil (PDE-5 inhibitor) vs monotherapy: AMBITION Trial\textsuperscript{c}
  - Reduced clinical failure events by 50% (HR, 0.502; \(P = .0002\)); superior to each individual monotherapy (\(P < .01\)) → main treatment effect driven by hospitalizations

- Selexipag (selective IP receptor agonist): GRIPHON top-line data\textsuperscript{d}
  - 80% of pts receiving oral PAH therapy at onset
  - Reduced morbidity/mortality event vs placebo by 39% (\(P < .0001\))

\textsuperscript{a} Pulido T, et al. \textit{N Engl J Med.} 2013;369:809-818\textsuperscript{[8]}; \textsuperscript{b} Mehta S, et al. ATS 2014. Abstract B17\textsuperscript{[9]}; \textsuperscript{c} Galiè N, et al. ERS 2014. Abstract 2916\textsuperscript{[6]}; \textsuperscript{d} Actelion press release.\textsuperscript{[10]}
The Real Cost of PAH Drugs

• History of expensive PAH drugs
  • IV epoprostenol/SC treprostinil: ~ $90,000/year
  • Bosentan: ~ $80,000/year
  • Ambrisentan: ~ $80,000/year
  • Oral treprostinil
    – ~ $500,000/year [12 mg, three times daily → patients transitioning from parenteral treprostinil (ongoing trial)c]
    – Compared with placebo: improved 6MWD, Borg dyspnea score (intent-to-treat population → 26.0 m; \( P = .0001 \))d

## Longitudinal Evaluation

<table>
<thead>
<tr>
<th>Stable; no increase in symptoms and/or decompensation</th>
<th>Clinical course</th>
<th>Unstable; increase in symptoms and/or decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3-6 months</td>
<td>Frequency of evaluation</td>
<td>Every 1-3 months</td>
</tr>
<tr>
<td>Every clinic visit</td>
<td>Functional class assessment</td>
<td>Every clinic visit</td>
</tr>
<tr>
<td>Every clinic visit</td>
<td>6MW distance</td>
<td>Every clinic visit</td>
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<tr>
<td>Every 12 months or center dependent</td>
<td>Echocardiography</td>
<td>Every 6-12 months or center dependent</td>
</tr>
<tr>
<td>Center dependent</td>
<td>BNP</td>
<td>Center dependent</td>
</tr>
<tr>
<td>Clinical deterioration and center dependent</td>
<td>Right heart catheterization</td>
<td>Every 6-12 months or clinical deterioration</td>
</tr>
</tbody>
</table>

Case Studies
Case Study

Paul is a 66 year old male who presented to his primary care physicians office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and osteoarthritis. He had a recent Cardiolite stress test which was negative. BP in office is 160/90. An echocardiogram was ordered.

Height 64 inches. Weight 275 lbs.
Physical Exam- III/VI SEM, 1+ lower extremity edema
Case Study

2D Echo results:

LVEF: 65%
Normal RV function
Stage I diastolic dysfunction
Mild LVH
Mild biatrial chamber size enlargement
Normal left and right ventricular size
Severe tricuspid regurgitation
RVSP 60 mmHg
Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath
Case Study

You decided to place Paul on HCTZ 25 mg and lisinopril 5 mg daily. He returns one month later with continued dyspnea. BP in office is improved at 138/80.

Given RVSP of 60 mmHg a sleep study, PFT was performed, both of which were severely abnormal. Patient was treated with a CPAP and treatments for COPD. Symptoms improving.

An Echocardiogram was performed in 12 months demonstrating an RVSP of 48 mmHg with normal LV/RV function.

Patient continued medical therapy.
Case Study

Britney is a 26 year old female who presented to her primary care physician’s office with complaints of cough, increased fatigue and dyspnea on exertion which has been worsening over the past 1 year. She now c/o SOB at rest. No previous significant past medical history. Was seen by her PCP and placed on an inhaler and steroids. BP in office is 110/70. An echocardiogram was ordered.

Height 64 inches. Weight 145 lbs.

Physical Exam- III/VI SEM
1+ lower extremity edema
Case Study

2D Echo results:

LVEF: 65%
Reduced RV function
Severe right atrial and ventricular size
Severe tricuspid regurgitation
Small pericardial effusion
RVSP 60 mmHg
Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath
Case Study

You decided to set up patient with a right heart cath.

Findings:

mPAP- 56, PAOP- 6. CO 2 L/m, negative NO vasodilator study

You diagnose patient with severe pulmonary hypertension.
What is the Optimal Treatment Strategy?

- **Anticoagulate ± Diuretics ± Oxygen ± Digoxin**

  - **Vasodilator Study**
    - Positive
      - Oral CCB
        - Sustained Response
          - Yes
            - Continue CCB
    - Negative
      - Determinants of Risk
        - Higher Risk
          - Clinical Evidence of RV Failure
            - Yes
          - Progression
            - Rapid
          - NYHA Class
            - IV
          - 6 Minute Walk Distance
            - Shorter (<300 m)
          - BNP
            - Very elevated
          - Echocardiographic Findings
            - Pericardial Effusion
          - Minimal RV Dysfunction
            - Significant RV Dysfunction
          - Normal/Near normal RAP and CI
            - Hemodynamics
            - High RAP, Low CI
          - Minimally elevated

Case Study

You perform a 6 MWT in the office and she is able to walk 250 meters.

Based on her echo, RHC and clinical findings you refer her for IV epoprostenol therapy.

In the meantime, laboratory studies are ordered to exclude CTD, HIV, liver disease, etc.
Case Study

Agnes is a 96 year old female smoker who presented to her primary care physician’s office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking x 70 years and osteoarthritis. She had a recent Cardiolite stress test which was negative. BP in the office is 140/800. An echocardiogram was ordered.

Height 64 inches. Weight 175 lbs.
Physical Exam- III/VI SEM, 1+ lower extremity edema
Case Study

2D Echo results:

- LVEF: 65%
- Reduced RV function
- Stage I diastolic dysfunction
- Mild LVH
- Mild biatrial chamber size enlargement
- Mild right ventricular enlargement
- Severe tricuspid regurgitation
- RVSP 60 mmHg
Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath
Case Study

No further workup for her pulmonary hypertension is warranted given her age and unlikely nature it would be from PAH.
COPD and PH

- Retrospective study of 215 COPD patients
- 13% had a PA mean >35 mm Hg
- Correlated best (inversely) with PaO2
- A small number had only moderate obstruction: treatable sub-group?

Case Study

Denise is a 46 year old female who presented to her primary care physicians office with complaints of cough, increased fatigue and dyspnea on exertion. Past medical history includes hypertension, smoking and scleroderma. She had a recent Cardiolite stress test which was negative. BP in office is 130/80. An echocardiogram was ordered.

Height 64 inches. Weight 195 lbs.
Physical Exam- III/VI SEM
1+ lower extremity edema
Case Study

2D Echo results:

LVEF: 65%
Normal RV function
Stage I diastolic dysfunction
Mild LVH
Mild biatrial chamber size enlargement
Normal left and right ventricular size
Severe tricuspid regurgitation
RVSP 60 mmHg
Case Study

Based on the initial presentation and echocardiogram your next step would be as follows?

A. No further testing or treatment is indicated
B. Start on oral diuretics
C. Set up for a PFT, VQ Scan and Sleep Study
D. Place on anti-hypertensive medications
E. Set up for a Right Heart Cath
Given her symptoms and history of scleroderma a comprehensive evaluation is performed including:

- PFT with DLCO
- Sleep Study
- VQ Scan

PFT was normal with abnormal DLCO. Moderate obstructive sleep apnea, normal VQ Scan

Patient continues to have SOB. Given this you decide to proceed with a RHC.

Findings: mPAP 42 mmHg, PAOP 19 mmHg, Normal CO/CI
• 17% (37/220) of patients with OSA have daytime mPAP >20 mm Hg  
  • 16 had mPAP >25 mm Hg; only 2 had mPAP >35 mm Hg
  • Marked ↑ with sub-max exercise (mean mPAP 47 mm Hg) – in part due to ↑ PCWP
  • Contributing factors: obesity, hypoxemia, COPD

In patients with OSA, ↓ PAP reported in response to CPAP therapy


• Untreated – response to other treatment likely less effective
Case Study

Findings: mPAP 42 mmHg, PAOP 19 mmHg, Normal CO/CI

Given moderate sleep apnea and hypervolemia you decide to place on low dose Lasix and recommend CPAP with plans to repeat a RHC.

Treatment with CPAP and Lasix 3 months, feeling better but still SOB. RHC mPAP 35 mmHg, PAOP 15 mmHg, Normal CO/CI

Patient diagnosed with PAH WHO Group I out of proportion to underlying medical conditions and you place patient on a PDE-5 inhibitor followed by a ERA one month later.
Final Thoughts

• Comprehensive history and physical is foundation for diagnosis

• Noninvasive screening as indicated

• Treat any identified factor(s) that could contribute to or exacerbate pulmonary hypertension

• Invasive hemodynamics are crucial

• Refer early
References


References (cont)


