What Surgeons Need to Know About Pulmonary Arterial Hypertension

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Disclosure of Commercial Interest

Dr. Badesch has received grant/research support from Glaxo Wellcome, United Therapeutics / Lung Rx, Actelion / CoTherix, Encysive, Myogen / Gilead, Pfizer, and Lilly / ICOS.

He has served as a consultant to Glaxo Wellcome / GlaxoSmithKline, Actelion / CoTherix, Berlex, Gilead / Myogen, Encysive, Pfizer, United Therapeutics / Lung Rx, MondoBiotech / Biogen IDEC, and PR Pharmaceuticals.
The Hemodynamic *Definition* of Pulmonary Arterial Hypertension (PAH)

- Systolic PA pressure >35 to 40 mm Hg
- Mean PA pressure ≥25 mm Hg
- PCWP, LAP, LVEDP ≤15 mm Hg
- Pulmonary vascular resistance >3U

Normal Circulation:

PCWP=Pulmonary capillary wedge pressure.
LAP=Left arterial pressure.
LVEDP=Left ventricular end-diastolic pressure.
Venice Classification of Pulmonary Hypertension

- Group 1: Pulmonary Arterial Hypertension
- Group 2: Pulmonary Venous Hypertension
- Group 3: Associated with Hypoxemia
- Group 4: Chronic thrombotic or embolic disease
- Group 5: Miscellaneous
Classification: The 2003 Venice Classification of PAH

• Sporadic (IPAH)
• Familial (FPAH)
• Related to:
  – Connective tissue disease
  – Congenital heart disease
  – Portal hypertension
  – HIV infection
  – Drugs and toxins
  – Other
• PAH with significant venule and/or capillary involvement
  – Pulmonary veno-occlusive disease
  – Pulmonary capillary hemangiomatosis
• Persistent fetal circulation

PAH: Pathogenesis

**RISK FACTORS AND ASSOCIATED CONDITIONS**
- Collagen Vascular Disease
- Congenital Heart Disease
- Portal Hypertension
- HIV Infection
- Drugs and Toxins
- Pregnancy

**SUSCEPTIBILITY**
- Abnormal BMPR2 Gene
- Other Genetic Factors

**VASCULAR INJURY**
- Endothelial Dysfunction
  - ↑ Nitric Oxide Synthase
  - ↑ Prostacyclin Production
  - ↑ Thromboxane Production
  - ↑ Endothelin 1 Production
- Vascular Smooth Muscle Dysfunction
  - Impaired Voltage-Gated Potassium Channel (K_{V_{1.5}})

**DISEASE PROGRESSION**
- Loss of Response to Short-Acting Vasodilator Trial

**NORMAL**

**REVERSIBLE DISEASE**
- Adventitia
- Media
- Intima
- Smooth Muscle Hypertrophy
- Early Intimal Proliferation
- Vasoconstriction

**IRREVERSIBLE DISEASE**
- Adventitial and Intimal Proliferation
- In situ Thrombosis
- Plexilorn Lesion
- Advanced Vascular Lesion

Pulmonary Arterial Hypertension

Pathology

• A disease of the small arteries and arterioles of the pulmonary circulation

• Characteristic changes include:
  – Medial hypertrophy
  – Intimal proliferation
  – In situ thrombosis
  – Plexiform lesions

Plexiform Lesion
IPAH (PPH) NIH Registry
The Natural History of IPAH

Adapted from D’Alonzo GE. Ann Int Med. 1991;115:343-349.
Is There A Reason to Suspect PAH?

Clinical History (Symptoms, Risk Factors), Exam, CXR, ECG

- Dyspnea
- Chest pain
- Syncope
- Edema
- Raynaud’s phenomenon
Is There A Reason to Suspect PAH?

Clinical History (Symptoms, Risk Factors), Exam, CXR, ECG

- Family history
- Connective tissue disease
- Congenital heart disease
- Liver disease / portal hypertension
- DVT/PE history
- Appetite suppressant use/drug use
- HIV
Is There A Reason to Suspect PAH?

Clinical History (Symptoms, Risk Factors),
Exam, CXR, ECG

- Presence of PH
  - Loud P2
  - RV lift
  - Systolic murmur (TR)
  - Diastolic murmur (PR)

- Presence of RV failure
  - JVD with V wave
  - Hepatomegaly
  - Edema
  - Ascites

TR=Tricuspid valve regurgitation.
PR=Pulmonary regurgitation.
JVD=Jugular venous distension.
Is There A Reason to Suspect PAH?

Clinical History (Symptoms, Risk Factors), Exam, CXR, ECG

Peripheral Hypovascularity (Pruning)

Prominent Hilar Pulmonary Arteries

RV Enlargement into Retrosternal Clear Space
Is There A Reason to Suspect PAH?

Clinical History (Symptoms, Risk Factors), Exam, CXR, ECG

ECHO: Parasternal Short Axis

Normal

PAH
ECHO: Apical Four Chamber

Normal

PAH
ECHO: Tricuspid Regurgitation
Pulmonary Venous Hypertension:

- Valvular heart disease (MS, MR)
- Hypertensive heart disease
- Cardiomyopathies
- Transmitted back pressure results in reactive vasoconstriction
- Treat primary problem
Ventilation Perfusion Lung Scan

- **Primary / Idiopathic Pulmonary Hypertension**
- **Chronic Pulmonary Embolism**
Contrast-Enhanced CT
Is Chronic PE Confirmed and Operable?
Pulmonary Angiogram
Cardiac Catheterization

• To exclude congenital heart disease
• To measure wedge pressure or LVEDP
• To establish severity and prognosis
• To test vasodilator therapy

Catheterization is required for nearly every patient with suspected pulmonary hypertension.

LVEDP=Left ventricular end-diastolic pressure.
Schematic Progression of PAH

Presymptomatic/Compensated

Symptomatic/Decompensating

Declining/Decompensated

CO = \frac{TPG}{PVR}

TPG = Transpulmonary gradient.
Symptomatic Pulmonary Arterial Hypertension

General Treatment Measures:
Oral anticoagulants \([B \text{ for IPAH, } E/C \text{ for other PAH}] +\) diuretics + oxygen \([E/A]\)

Acute Vasoreactivity Testing \([A \text{ for IPAH, } E/C \text{ for other PAH}]\)

Positive

Oral CCB \([B \text{ for IPAH, } E/B \text{ for other PAH}]\)

Sustained Response?

Yes

Continue CCB

No

FC II

- Sildenafil \([A]\)
- Treprostinil SC \([C]\)
- Treprostinil IV \([C]\)

FC III

- Bosentan \([A]\)
- Sildenafil \([A]\)
- Epoprostenol \([A]\)
- Iloprost inh \([A]\)
- Treprostinil SC \([B]\)
- Treprostinil IV \([C]\)

FC IV

- Epoprostenol IV \([A]\)
- Bosentan \([B]\)
- Iloprost inh \([B]\)
- Sildenafil \([C]\)
- Treprostinil SC \([C]\)
- Treprostinil IV \([C]\)

Combination Therapy?

- Prostanoid
- Boesentan
- Sildenafil

No Improvement or deterioration

Combination Therapy?

Atrioseptostomy ± Lung Transplantation

ACCP Guidelines Statement
Quality of Evidence, Net Benefit, and Strength of Recommendation

• Quality of the Evidence
  – Good: based on RCTs or metaanalyses.
  – Fair: based on controlled trials or RCTs with minor flaws.
  – Low: based on nonrandomized, case-control, or other observational studies.
  – Expert opinion: no studies meet the criteria for inclusion in the literature review.

• Net Benefit:
  – Substantial
  – Intermediate
  – Small/weak
  – None
  – Conflicting
  – Negative

• Strength of Recommendation:
  – A: Strong recommendation
  – B: Moderate recommendation
  – C: Weak recommendation
  – D: Negative recommendation
  – I: No recommendation possible
  – E/A: Strong recommendation based on expert opinion only
  – E/B: Moderate recommendation based on expert opinion only
# ACNP Guidelines Statement

## Relationship of Strength of the Recommendation Scale to Quality of Evidence and Net Benefits

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Substantial</th>
<th>Intermediate</th>
<th>Small/Weak</th>
<th>None</th>
<th>Conflicting</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>D</td>
<td>I</td>
<td>D</td>
</tr>
<tr>
<td>Fair</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>I</td>
<td>D</td>
</tr>
<tr>
<td>Low</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>I</td>
<td>I</td>
<td>D</td>
</tr>
<tr>
<td>Expert Opinion</td>
<td>E/A</td>
<td>E/B</td>
<td>E/C</td>
<td>I</td>
<td>I</td>
<td>E/D</td>
</tr>
</tbody>
</table>
Criteria for "Responders"
Criteria for long-term beneficial effect of CCB

- 557 consecutive IPAH
  - 70 acute responders (12.6%)
  - 487 non responders (87.4%)
  - 38 long-term CCB responders (6.8%)
  - 32 long-term CCB failures

93.2% “non-responders”

• Acute vasodilator testing with Pgl2 (n = 150) or NO (n = 407)
• Acute response = Fall in mPAP and PVR > 20%
  → Initiation of chronic CCB
• Long-term CCB responders = NYHA FC I / II after at least one year on oral CCB without need for prostanoids and/or ERA

Survival in IPAH
Long-term CCB responders

Cumulative Survival

Long-term CCB responders

subjects at risk, n

Long-term CCB failure

ACCP Consensus Definition of A Responder

- Fall in mean PAP by at least 10 mm Hg, to an absolute PAP mean of \( \leq 35-40 \) mm Hg
- Unchanged or increased CO

It is important to follow patients treated with CCBs for both safety and efficacy of the therapy.
**Medical Therapy: Vasoreactivity Testing**

1. **Patients with IPAH** should undergo acute vasoreactivity testing using a short acting agent such as intravenous epoprostenol, adenosine, or inhaled nitric oxide.  
   *Level of Evidence: Fair; Benefit: Substantial; Grade of Recommendation: A.*

2. **Patients with PAH associated with underlying processes,** such as scleroderma or congenital heart disease, should undergo acute vasoreactivity testing.  
   *Level of Evidence: Expert Opinion; Benefit: Small/Weak; Grade of Recommendation: E/C.*

3. **Patients with PAH** should undergo vasoreactivity testing by a physician experienced in the management of pulmonary vascular disease.  
   *Level of Evidence: Expert Opinion; Benefit: Substantial; Grade of Recommendation: E/A.*
4. **Patients with IPAH**, in the absence of right heart failure, demonstrating a favorable acute response to vasodilator (defined as a fall in mean pulmonary artery pressure of at least 10 mmHg to less than or equal to 40 mmHg, with an increase or unchanged cardiac output), should be considered candidates for a trial of therapy with an oral calcium channel antagonist. *Level of Evidence: Low; Benefit: Substantial; Grade of Recommendation: B.*

5. **Patients with PAH associated with underlying processes such as scleroderma or congenital heart disease**, in the absence of right heart failure, demonstrating a favorable acute response to vasodilator (defined as a fall in mean pulmonary artery pressure of at least 10 mmHg to less than or equal to 40 mmHg, with an increase or unchanged cardiac output), should be considered candidates for a trial of therapy with an oral calcium channel antagonist. *Level of Evidence: Expert Opinion; Benefit: Intermediate; Grade of Recommendation: E/B.*
6. In patients with PAH, calcium channel blockers should not be used empirically to treat pulmonary hypertension in the absence of demonstrated acute vasoreactivity. Level of Evidence: Expert Opinion; Benefit: Substantial; Grade of Recommendation: E/A.
Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]

Positive

Oral CCB [B for IPAH, E/B for other PAH]

Sustained Response?

Yes

No

Continue CCB

Grade of Recommendation Noted in

7. **Patients with IPAH** should be anticoagulated with **warfarin**. *Level of evidence: Fair; Benefit: Intermediate; Grade of Recommendation: B.*

8. **In patients with PAH occurring in association with other underlying processes, such as scleroderma or congenital heart disease,** anticoagulation should be considered. *Level of Evidence: Expert opinion; Benefit: Small/Weak; Recommendation: E/C.*

9. **In patients with PAH,** supplemental oxygen should be used as necessary to maintain oxygen saturations at > 90% at all times. *Level of Evidence: Expert Opinion; Benefit: Substantial; Recommendation: E/A.*
Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]

General Treatment Measures:
Oral anticoagulants [B for IPAH, E/C for other PAH] ± diuretics ± oxygen [E/A]

Sustained Response?
Positive
Oral CCB [B for IPAH, E/B for other PAH]

Sustained Response?
Yes
Continue CCB

Grade of Recommendation Noted in [ ]
**PAH: Advanced Therapy**

**A) PGI$_2$**

- EC
- Arach. a. $\rightarrow$ PGI$_2$
- PGI$_2$ $\rightarrow$ SMC $\rightarrow$ cAMP
- Prostanoids
- Epoprostenol
- Treprostinil
- Beraprost
- Iloprost
- TxA$_2$ $\rightarrow$ SMC

**B) NO**

- EC
- L-arginine $\rightarrow$ L-citrulline
- NO $\rightarrow$ SMC $\rightarrow$ cGMP
- PDE$_5$
- Vasodilation
- Antiproliferative
- Vasoconstriction
- Proliferation

**C) ET-1**

- EC
- Pre-pro-ET $\rightarrow$ pro-ET
- ET$_A$
- ET$_B$
- $G_i$
- ET-1

Adapted from Omar Manai.
Epoprostenol in PPH/IPAH Study
Median Change from Baseline in 6-Minute Walk Exercise Test at Week 12

<table>
<thead>
<tr>
<th>Median Change (meters)</th>
<th>Treatment:</th>
<th>Baseline = 315</th>
<th>Treatment:</th>
<th>Baseline = 270</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epoprostenol</td>
<td></td>
<td>Conventional</td>
<td></td>
</tr>
<tr>
<td>-50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-40</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>-30</td>
<td></td>
<td></td>
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<tr>
<td>-20</td>
<td></td>
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</tr>
<tr>
<td>-10</td>
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</tr>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td></td>
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<tr>
<td>20</td>
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<tr>
<td>30</td>
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</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.002

# Cardiopulmonary Hemodynamic Measurements (PPH/IPAH)

## Epoprostenol vs. Conventional Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Change from Baseline</th>
<th>Baseline</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>$PAP_m$</td>
<td>61 ± 2</td>
<td>-4.8 ± 1.3*</td>
<td>59 ± 2</td>
<td>1.9 ± 1.6</td>
</tr>
<tr>
<td>PVR</td>
<td>16 ± 1</td>
<td>-3.4 ± 0.7*</td>
<td>16 ± 1</td>
<td>1.5 ± 1.2</td>
</tr>
<tr>
<td>$RAP_m$</td>
<td>13 ± 1</td>
<td>-2.2 ± 1.1*</td>
<td>12 ± 1</td>
<td>0.1 ± 0.9</td>
</tr>
<tr>
<td>CI</td>
<td>2.0 ± 0.1</td>
<td>0.3 ± 0.1*</td>
<td>2.1 ± 0.2</td>
<td>-0.2 ± 0.2</td>
</tr>
</tbody>
</table>

Mean change ± standard error

*Significantly different from conventional therapy

Survival Among Patients with PPH/IPAH

Epoprostenol vs. Conventional Therapy

Barst et al. NEJM 1996;334:296-301.
Long-term Outcome in IPAH With Epoprostenol

PAH Associated with Scleroderma: Median Change from Baseline in 6-Minute Walk Test

<table>
<thead>
<tr>
<th>Week</th>
<th>Treatment</th>
<th>Median Change (meters)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epoprostenol</td>
<td>Baseline = 271.5m</td>
</tr>
<tr>
<td>Week 1</td>
<td></td>
<td>-7.0</td>
</tr>
<tr>
<td>Week 6</td>
<td></td>
<td>-14.0</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td>-36.0</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>Baseline = 240.0m</td>
</tr>
</tbody>
</table>

*B p < 0.003

### PAH Associated with Scleroderma: Cardiopulmonary Hemodynamic Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Epoprostenol</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td>PAP&lt;sub&gt;m&lt;/sub&gt;</td>
<td>50.9 ± 1.41</td>
<td>-5.03 ± 1.09*</td>
</tr>
<tr>
<td>PVR</td>
<td>14.2 ± 0.95</td>
<td>-4.58 ± 0.76*</td>
</tr>
<tr>
<td>RAP&lt;sub&gt;m&lt;/sub&gt;</td>
<td>13.1 ± 0.67</td>
<td>-1.26 ± 0.82*</td>
</tr>
<tr>
<td>CI</td>
<td>1.9 ± 0.08</td>
<td>0.50 ± 0.08*</td>
</tr>
</tbody>
</table>

†Mean change ± standard error
*Significantly different from conventional therapy

## Treprostinil in PAH

### Exercise Capacity: Six Minute Walk

<table>
<thead>
<tr>
<th>Exercise (meters)</th>
<th>UT-15</th>
<th>Placebo</th>
<th>Effect*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>+10</td>
<td>0</td>
<td>+16</td>
<td>0.0064</td>
</tr>
<tr>
<td>Week 6</td>
<td>+13</td>
<td>+4</td>
<td>+11</td>
<td>0.032</td>
</tr>
<tr>
<td>Week 1</td>
<td>+11</td>
<td>+8</td>
<td>+5</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Non-parametric Analysis of Covariance (Hodges-Lehmann estimate)

Last Rank Carried Forward for AE
Lowest Rank for Death/Deterioration

Treprostinil in PAH
Change in Exercise Versus Dose (Week 12)

Mean ± SE Change from Baseline (meters)

1st Quartile < 5.0
(2.5 ± 0.2)

2nd Quartile 5 to <8.1
(5.6 ± 0.1)

3rd Quartile 8.1 to 13.8
(9.4 ± 0.2)

4th Quartile >13.8
(16.2 ± 0.4)

+3.3 ± 10
(N=45)

+1.4 ± 9
(N=55)

+20 ± 8
(N=49)

+36.1 ± 31
(N=58)

p-value 0.03

Effect of Inhaled Iloprost and Placebo on Mean Change in 6-Minute Walk

PAH: Advanced Therapy

A) PGI$_2$

EC $\rightarrow$ PGI$_2$  
Arach. a. $\rightarrow$ PGI$_2$  
PGI$_2$ $\rightarrow$ PGI$_2$  

B) NO

EC $\rightarrow$ L-citrulline  
L-arginine $\rightarrow$ L-citrulline  

C) ET-1

EC $\rightarrow$ pro-ET  
Pre-pro-ET $\rightarrow$ pro-ET  

Adapted from Omar Manai.
Pilot Study of Bosentan in PAH: 6-Minute Walk Test
Change From Baseline Over Time

Pilot Study of Bosentan in PH: Change in Hemodynamics From Baseline to Week 12

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 10)</th>
<th>Bosentan (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean Pulmonary Arterial Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary Vascular Resistance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 12</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>L/min/m²</strong></td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>mm Hg</strong></td>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Dyn.sec.cm⁻⁵</strong></td>
<td>200</td>
<td>400</td>
</tr>
</tbody>
</table>

*P* < 0.0001  
*P* = 0.0001

BREATHE-1: Walk Test ITT
Change From Baseline to Week 16

Δ Walk Distance (meters)

Baseline  Week 4  Week 8  Week 16

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

62.5 mg/bid  125 or 250 mg/bid

P = 0.0002

Mean ± SEM

BREATHE-1
Time to Clinical Worsening
Up to 28 Weeks

Event-Free (%) vs Time (weeks)

- Bosentan: n = 144, n = 103, n = 20
- Placebo: n = 69, n = 51, n = 17

P = 0.0015

## BREATHE-1
### Summary of Adverse Events During Study Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 69) %</th>
<th>Bosentan (n = 144) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>7.2</td>
<td>11.8</td>
</tr>
<tr>
<td>Headache</td>
<td>18.8</td>
<td>20.8</td>
</tr>
<tr>
<td>Flushing</td>
<td>4.3</td>
<td>9.0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Syncope</td>
<td>5.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Hepatic Funct. Abnormal</td>
<td>2.9</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Incidence of events: bosentan > placebo

Bosentan as Initial Therapy*
Observed and Predicted Survival

Kaplan-Meier survival estimates with 99.9% CI

Event Rate / year (exponential): 5.5%

*As first-line treatment for PPH. Some patients may have been switched to alternative therapies.

McLaughlin V. Eur Respir J 25:244-9; 2005
Ambrisentan in PAH: 6-Minute Walk Distance
Change from Baseline at Week 12

Ambrisentan in PAH:
Hemodynamics
Week 0 (n=34) and Week 12 (n=29)

Mean Pulmonary Artery Pressure

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmHg</td>
<td>54</td>
<td>46.6</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>48.7</td>
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<td></td>
<td>46</td>
<td>42.4</td>
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<td></td>
<td>42</td>
<td>38.2</td>
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<td>38</td>
<td>35.6</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>33.0</td>
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Cardiac Index

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/min/m²</td>
<td>3.0</td>
<td>3.33</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.67</td>
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<tr>
<td></td>
<td>2.6</td>
<td>2.52</td>
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<tr>
<td></td>
<td>2.4</td>
<td>2.35</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>2.18</td>
</tr>
</tbody>
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Pulmonary Vascular Resistance

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>dynes/cm²-sec</td>
<td>1500</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td>1200</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>600</td>
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<tr>
<td></td>
<td>600</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>0</td>
</tr>
</tbody>
</table>

Mean Right Atrial Pressure

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmHg</td>
<td>8.5</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>6.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>

\( \Delta = -5.2 \) p<0.001
\( \Delta = +0.33 \) p<0.001
\( \Delta = -226 \) p<0.001
\( \Delta = -0.45 \) p=ns
Ambrisentan in PAH: Adverse Events
12-Week Blinded Treatment Period

- Peripheral Edema
- Upper Respiratory Tract Infection
- Nasal Congestion
- Headache
- Nausea
- Flushing
- LFTs >3X
- LFTs >8X

Percent of Subjects with AE (%)
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.
Ambrisentan ARIES-2 Primary Endpoint: Change in 6MWD at Week 12

N=192.
Placebo-adjusted changes: 2.5 mg = 32.3 m ($P=0.022$)
5 mg = 59.4 m ($P<0.001$)

ARIES-2: Time to Clinical Worsening With Ambrisentan

Time to clinical worsening = Combined endpoint of death, lung transplantation, atrial septostomy, hospitalization for PAH, addition of other drugs for PAH, or early escape from clinical trial.

PAH: Advanced Therapy

A) PGI₂

- EC
  - Arach. a. → PGI₂
  - PGI₂-S
- SMC
  - cAMP

B) NO

- EC
  - L-arginine → L-citrulline
- SMC
  - cGMP
  - PDE₅
  - NO

C) ET-1

- EC
  - Pre-pro-ET → pro-ET
  - G₁
  - ETₐ, ETᵇ
  - ET-1

Adapted from Omar Manai.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Medication</th>
<th>Duration</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Weeks</td>
<td>Placebo tid</td>
<td>4 weeks</td>
<td>6-min-walk BORG, Hemodynamics, BORG 6-min-walk, Clinical Worsening</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>20 mg tid</td>
<td>8 weeks</td>
<td>6-min-walk BORG, Hemodynamics, BORG 6-min-walk, Clinical Worsening</td>
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<tr>
<td>12 Weeks</td>
<td>40 mg tid</td>
<td>12 weeks</td>
<td>6-min-walk BORG, Hemodynamics, BORG 6-min-walk, Clinical Worsening</td>
</tr>
<tr>
<td>16 Weeks</td>
<td>80 mg tid</td>
<td>16 weeks</td>
<td>6-min-walk BORG, Hemodynamics, BORG 6-min-walk, Clinical Worsening</td>
</tr>
</tbody>
</table>

Sildenafil in PAH – SUPER-1: Improvements in 6-MWD

**Sildenafil in PAH – SUPER-1: Hemodynamics**

**mPAP (mm Hg)**

- Placebo: -2.7
- Sildenafil 20 mg: -3.0
- Sildenafil 40 mg: -5.1

**Cardiac Output (L/min)**

- Placebo: 0.5
- Sildenafil 20 mg: 0.5
- Sildenafil 40 mg: 0.8

**PVR (dyne.s/cm²)**

- Placebo: -171
- Sildenafil 20 mg: -192
- Sildenafil 40 mg: -310

# Sildenafil in PAH – SUPER-1: AEs ≥3% and Sildenafil > Placebo

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Percentage of patients reporting event</th>
<th>Sildenafil (N=207)</th>
<th>Placebo (N=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>Flushing</td>
<td></td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Back Pain</td>
<td></td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Limb pain</td>
<td></td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Gastritis</td>
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<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo</td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

10. PAH patients in functional class II who are not candidates for, or who have failed, CCB therapy, may benefit from treatment with:
   a. Sildenafil (Level of Evidence: Good; Benefit: Substantial; Grade of Recommendation: A).
   b. Subcutaneous treprostinil (Level of Evidence: Low; Benefit: Small/Weak; Grade of Recommendation: C).
   c. IV treprostinil (Level of Evidence: Low; Benefit: Small/Weak; Grade of Recommendation: C).

- Although treprostinil is FDA approved for use in patients in FC II, it would seldom be recommended in such patients due to the complexity of administration, side effects, and cost.
- Data pertaining to the treatment of FC II patients remain limited, and enrollment in clinical trials is encouraged.
Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]

General Treatment Measures:
Oral anticoagulants [B for IPAH, E/C for other PAH] + diuretics + oxygen [E/A]

Positive
Oral CCB [B for IPAH, E/B for other PAH]
Sustained Response?
Yes
Continue CCB
No

Negative

FC II

• Sildenafil [A]
• Treprostinil SC [C]
• Treprostinil IV [C]

Symptomatic Pulmonary Arterial Hypertension

ACCP 2007

Grade of Recommendation Noted in [ ]
11. **PAH patients in functional class III** who are not candidates for, or who have failed, calcium channel blocker therapy, are candidates for long-term therapy with:

- **a. Endothelin receptor antagonists (bosentan), or sildenafil, in no order of preference.** *Level of Evidence: Good; Benefit: Substantial; Grade of Recommendation: A.*

- **b. IV epoprostenol.** *Level of Evidence: Good; Benefit: Substantial; Grade of Recommendation: A.*

- **c. Inhaled iloprost.** *Level of Evidence: Good; Benefit: Intermediate; Grade of Recommendation: A.*

- **d. Subcutaneous treprostinil.** *Level of Evidence: Fair; Benefit: Intermediate; Grade of Recommendation: B.*

- **e. IV trepostinil.** *Level of Evidence: Low; Benefit: Intermediate; Grade of Recommendation: C.*

*With the approval of ambrisentan by the FDA, the recommendations for FC II and III patients will need to be updated again.*
Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]

General Treatment Measures:
Oral anticoagulants [B for IPAH, E/C for other PAH] + diuretics + oxygen [E/A]

Symptomatic Pulmonary Arterial Hypertension

Positive
Oral CCB [B for IPAH, E/B for other PAH]

Sustained Response?
Yes
Continue CCB

No
Sildenafil [A]
Treprostinil SC [C]
Treprostinil IV [C]

Negative
FC II
Bosentan [A]
Sildenafil [A]
Epoprostenol [A]
Iloprost inh [A]
Treprostinil SC [B]
Treprostinil IV [C]

Grade of Recommendation Noted in
12. PAH patients in functional class IV who are not candidates for, or who have failed, calcium channel blocker therapy, are candidates for long-term therapy with intravenous epoprostenol (treatment of choice). Level of Evidence: Good; Benefit: Substantial; Grade of Recommendation: A.

13. Other treatments available for the treatment of functional class IV PAH patients include, in no hierarchal order:
   a. Endothelin receptor antagonists (bosentan). Level of Evidence: Fair; Benefit: Intermediate; Grade of Recommendation: B.
   b. Inhaled iloprost. Level of Evidence: Fair; Benefit: Intermediate; Grade of Recommendation: B.
   c. Subcutaneous treprostinil. Level of Evidence: Fair; Benefit: Intermediate; Grade of Recommendation: B.
   d. Sildenafil. Level of Evidence: Low; Benefit: Intermediate; Grade of Recommendation: C.
   e. IV treprostinil. Level of Evidence: Low; Benefit: Intermediate; Grade of Recommendation: C.
Symptomatic Pulmonary Arterial Hypertension

General Treatment Measures:
Oral anticoagulants [B for IPAH, E/C for other PAH] + diuretics + oxygen [E/A]

Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]

Positive

Oral CCB [B for IPAH, E/B for other PAH]

Sustained Response?

Yes  No

Continue CCB

FC II

- Sildenafil [A]
- Treprostinil SC [C]
- Treprostinil IV [C]

FC III

- Bosentan [A]
- Sildenafil [A]
- Epoprostenol [A]
- Iloprost inh [A]
- Treprostinil SC [B]
- Treprostinil IV [C]

FC IV

Epoprostenol IV [A]
Bosentan [B]
Iloprost inh [B]
Sildenafil [C]
Treprostinil SC [C]
Treprostinil IV [C]

Grade of Recommendation Noted in [ ]
## STEP Study of Inhaled Iloprost in Patients Already Receiving Bosentan:
Post-inhalation change in 6-MWD (Week 12)

<table>
<thead>
<tr>
<th></th>
<th>Iloprost</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Meters Walked</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td>Baseline (m)</td>
<td>336 ± 61</td>
<td></td>
</tr>
<tr>
<td>Week 12 (m)</td>
<td>367 ± 84</td>
<td>30 m</td>
</tr>
<tr>
<td>p-value (vs. baseline)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Placebo-adjusted Difference: +26 m (p = 0.051)

McLaughlin et al: AJRCCM.
PAH Study of Sildenafil added to Background Epoprostenol Therapy

Change from Baseline in 6-MWD

Symptomatic Pulmonary Arterial Hypertension

General Treatment Measures:
Oral anticoagulants [B for IPAH, E/C for other PAH] ± diuretics ± oxygen [E/A]

Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]

- Positive
  - Oral CCB [B for IPAH, E/B for other PAH]
  - Sustained Response?
    - Yes: Continue CCB
    - No: FC II

  FC II
  - Sildenafil [A]
  - Treprostinil SC [C]
  - Treprostinil IV [C]

  FC III
  - Bosentan [A]
  - Sildenafil [A]
  - Epoprostenol [A]
  - Iloprost inh [A]
  - Treprostinil SC [B]
  - Treprostinil IV [C]

  FC IV
  - Epoprostenol IV [A]
  - Bosentan [B]
  - Iloprost inh [B]
  - Sildenafil [C]
  - Treprostinil SC [C]
  - Treprostinil IV [C]

Combination Therapy?

- Prostanoid
  - Bosentan
  - Sildenafil

No Improvement or deterioration

- Atrioseptostomy ± Lung Transplantation

Summary

Current therapies

• Improve:
  – Exercise capacity, as assessed by 6MWD
    • 6MWD test is predictive of survival
  – Functional class
  – Time to clinical worsening
  – Survival (epoprostenol / Flolan only)
• Have associated toxicities and adverse effects
• Are expensive
Current Knowledge Deficits:

• Controlled long-term survival data are unavailable for most (all) agents

• Insufficient data are available for:
  – Quality of life
  – Cost-effectiveness
  – Combination therapy

• The potential impact of new classes agents is unknown:
  – Antiproliferative therapies
  – Immunomodulatory therapies
  – Statins
Future Directions:
PAH is Not Simply a Vasoconstrictive Process

While advances have occurred in treating the functional/hemodynamic manifestations of PAH, continued progress will likely require new strategies more directly addressing the proliferative component of the disease.
Future Directions: Newer Endpoints

- Imaging
  - MRI
    - RV mass and volume
    - Measurement of absolute flow and volume
    - May be more reproducible than ECHO
    - Challenges include:
      - Time
      - Cost
      - Pumps/magnet issues
  - Spiral / multi-detector CT
    - High resolution
  - ECHO
    - 3D echocardiography
    - Tissue Doppler imaging
      - Assessment of indices of RV function
Future Directions: Newer Endpoints

- Hemodynamics
  - Measurement with exercise, as well as at rest
  - Recognizing the possibility that single-point measurements at rest may under- or over-estimate changes in functional state
    - Obtaining measurements at multiple levels of flow (CO) may allow definition of resistance from a multipoint pressure/flow line
    - Could be done with exercise or low-dose dobutamine
  - Continuous 24-hour monitoring of PAP may show the effects of therapy on hemodynamics during activities of daily living
    - Exercise
    - Sleep
    - Postural changes
Future Directions: Newer Endpoints

• Quality of Life
  – Until recently, generic instruments were utilized:
    • SF-36
    • Nottingham Health Profile
    • European Quality of Life
    • Living with Heart Failure Minnesota questionnaire
  
  – More recently, a disease-specific QOL questionnaire has been developed:
    • CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review)
      – Validated in a number of countries and languages
      – May be more responsive than generic questionnaires
Future Directions:
Venice / WHO Classification of Pulmonary Hypertension

• Group 3: Associated with Hypoxemia
  – COPD
  – ILD
  – Sleep-disordered breathing
  – Alveolar hypoventilation disorders
  – Altitude exposure
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