Pulmonary Arterial Hypertension: Diagnosis of Treatment

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PAH

• Classification
• Diagnosis
• Current treatment
**Pulmonary Circulation**

- Originates from the RV
- Low Pressure, low resistance circuit
- Thin-walled vessels
- High compliance
- Receives entire CO from RV
- Accommodates wide range of CO without increase in PVR
Pulmonary Hypertension

- Mean PAP > 25 mmHg
- Not just one disease, but a large group of diverse diseases

Classification

1. Pulmonary arterial hypertension (PAH)
   - 1. Pulmonary arterial hypertension (PAH)
   - 1.1. Idiopathic (IPAH)
   - 1.2. Heritable
     - 1.2.1 BMPR2
     - 1.2.2 ALK1 Endoglin (with or without HHT)
     - 1.2.3 Unknown
   - 1.3. Drugs and Toxins
   - 1.4 Associated with (APAH):
     - 1.4.1. Collagen vascular disease
     - 1.4.2. HIV
     - 1.4.3. Portal hypertension
     - 1.4.4. Congenital Heart Disease
     - 1.4.5. Schistosomiasis
   - 1’1 Pulmonary veno-occlusive disease (PVOD)/Pulmonary capillary hemangiomatosis (PCH)
   - 1’2 Persistent pulmonary hypertension of the newborn
## Classification

### 2. Pulmonary hypertension with left heart disease
- 2.1. Left Ventricular Systolic Dysfunction
- 2.2. Left Ventricular Diastolic Dysfunction
- 2.3. Valvular Disease
- 2.4. Congenital /Aquired Left Heart inflow tract obstruction and congenital cardiomyopathies

### 3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
- 3.1. Chronic obstructive pulmonary Ds
- 3.2. Interstitial lung disease
- 3.3. Sleep-disordered breathing
- 3.4. Alveolar hypoventilation disorders
- 3.5. Chronic exposure to high altitude
- 3.6. Developmental abnormalities

### 4. Pulmonary hypertension due to chronic thromboembolic
Classification

- 5. Pulmonary Hypertension with unclear multifactorial mechanism
  - 5.1 Hematologic disorders, myeloproliferative disorders, splenectomy
  - 5.2 Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis
  - 5.3 Metabolic disorders, glycogen storage disease, Gaucher disease, thyroid
  - 5.4 Compression of pulmonary vessels tumor obstruction, fibrosing mediastinitis, Chronic renal failure

Pulmonary Arterial Hypertension

- Mean pulmonary artery pressure
  - > 25 mm Hg
  - Pulmonary artery wedge pressure <15
Incidence of PAH

- 187 patients followed over 7 years
- Mean age at diagnosis: 36 years
- Almost 2:1 female-to-male ratio
- Incidence: ~2 cases per 100,000
- Mean survival 2.8 yrs
- Mean duration of symptoms before diagnosis: 2 years

- 647 patients in 1 yr
- Prevalence increasing: 15 cases per million
  - IPAH = 5.9 per million
- Mean delay between enrollment and diagnosis: 6 ± 86 months

A Disease of Decline and Deterioration: IPAH Survival if Untreated

- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

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

% Patients NYHA Functional Class III-IV at Diagnosis
Is There a Reason to Suspect PAH?

Clinical Presentation

<table>
<thead>
<tr>
<th>Common Initial Symptoms (N=187)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>60</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
</tr>
<tr>
<td>Syncope or near syncope</td>
<td>13</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5</td>
</tr>
<tr>
<td>Leg edema</td>
<td>3</td>
</tr>
</tbody>
</table>


Physical Exam

Presence of PH
- Loud P2
- RV lift
- Systolic murmur (TR)
- Diastolic murmur (PR)
- RV S4

Presence of RV Failure
- JVD with V wave
- RV S3
- Hepatomegaly
- Edema
- Ascites
Chest X-Ray

Prominent Proximal Pulmonary Arteries

Chest X-Ray

Peripheral Hypovascularity (Pruning)
**Chest X-Ray**

RV Enlargement into Retrosternal Clear Space

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**Is There a Reason to Suspect PAH?**

**ECG**

Diagnostic Evaluation

- Pulmonary function tests
  - Mild restrictive defects
  - Decreased DLCO
- Arterial Blood gas
  - Hypoxemia
  - Increased A-a gradient

Chest X-Ray

- Peripheral Hypovascularity (Pruning)
- RV Enlargement into Retrosternal Clear Space
- Prominent Proximal Pulmonary Arteries
Cardiovascular Evaluation

Chamber size
LV and RV systolic function
LV diastolic function
Valvular function
TR
Bubble study

4.1 m/sec = 70 mmHg
+ RA Pressure = PA 80 mmHg
Diagnostic Approach

- RVE, RAE, ↑RVSP
- Left heart disease
- VHD
- CHD

Echocardiogram

- Emphysema
- ILD
- Thoracic abnl

- Exam
- CXR
- ECG

PFTs

- Sleep disorder
- Sleep study

- Ventilation-perfusion scan,
  Contrast CT,
  Angiography

- Autoantibody tests

- HIV test

- HIV

- BNP
- RH cath
- Vasodilator test

- LFTs and clinical evidence of cirrhosis and portal htn

- Portopulmonary hypertension

- Functional test
- Scleroderma
- SLE
- RA
- Vasculitis
- Chronic thromboembolism

Exercise testing

- Six – minute walk
- Cardiopulmonary exercise test
  - Assessment of functional status
  - Response to therapy

# Functional Assessment

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation of physical activity. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of physical activity. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to perform any physical activity without symptoms. Signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

* New York Heart Assoc./World Health Org. modification


http://www.who.int/ncd/cvd/pph.html

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# NYHA Staging / Survival in PPH

![NYHA Staging / Survival in PPH Diagram](image)
Right Heart Catheterization

- Invasive measurement of:
  - Right atrial Pressure
  - Right ventricular Pressures
  - PA Pressure
  - Pulmonary capillary wedge pressure
  - Mixed venous oxygen saturation
  - Cardiac output
  - Vasodilator challenge

Image from A.D.A.M.

Pivotal Tests

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>CXR</th>
<th>ECG</th>
<th>Echocardiogram</th>
<th>VQ Scan</th>
<th>PFT's</th>
<th>Overnight Oximetry</th>
<th>HIV</th>
<th>ANA</th>
<th>LFT's</th>
<th>Functional Test (6MWT, CPET)</th>
<th>RH Cath</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>Exercise Echo</td>
<td>Pulmonary Angiography</td>
<td>Chest CT Angiogram</td>
<td>Coagulopathy Profile</td>
<td>ABG's</td>
<td>Polysomnography</td>
<td>Other CTD Serologies</td>
<td>Vasodilator Test</td>
<td>Exercise RH Cath</td>
<td>Volume Loading</td>
<td>Left Heart Cath</td>
<td></td>
</tr>
</tbody>
</table>

Contingent Tests

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

ACCF/AHA Diagnostic Algorithm

### Mechanisms of Disease Pathology

<table>
<thead>
<tr>
<th>RISK FACTORS AND ASSOCIATED CONDITIONS</th>
<th>VASCULAR INJURY</th>
<th>DISEASE PROGRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen vascular disease</td>
<td>Endothelial Dysfunction</td>
<td>Loss of response to short-acting vasodilator trial</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Nitric oxide synthase</td>
<td></td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>Prostacyclin production</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>Thromboxane production</td>
<td></td>
</tr>
<tr>
<td>Drugs and toxins</td>
<td>Endothelin 1 production</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Vascular Smooth Muscle Dysfunction</td>
<td></td>
</tr>
<tr>
<td>Abnormal BMPR2 gene</td>
<td>Impaired voltage-gated potassium channel (K_V1.5)</td>
<td></td>
</tr>
<tr>
<td>Other genetic factors</td>
<td></td>
<td>susceptibility</td>
</tr>
</tbody>
</table>

**NORMAL**

**REVERSIBLE DISEASE**

**IRREVERSIBLE DISEASE**

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**Progression of PAH**

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

- CO: Symptom Threshold
- PAP
- PVR: Right Heart Dysfunction

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# Treatment

## General measures

- Supplemental oxygen
- Diuretics
- Digoxin
- Anticoagulation

## Anticoagulation

### Rationale:

- Fresh intrapulmonary clots
- High risk for thromboembolic event
- Improved survival

### Treatment

- Warfarin- goal INR 1.6-2.5
Digoxin

- Inotropic effect: variable
- Used in varying number of patients in major center trials of PAH
- Short-term administration associated with an increase in cardiac output and reduced circulating catecholamines
- No long-term data available


Diuretics

- Majority of patients require them
- Variable response
- Follow renal and electrolyte parameters
- Individual patient assessment
### Oxygen

- Hypoxemia is detrimental: results in vaso-constriction
- Altitude and sleep may result in hypoxemia
- In congenital heart disease, probably no benefit

### Other Management Issues

- Encourage exercise and activity within the limits of disease and ability to maintain $O_2$ levels
- Immunizations
- Contraception
Calcium Channel Blockers

Rationale:
• Rich et al NEJM 1992;327:76-81
• 64 patients with PPH
  • 17 Significant vasoreactivity
    • 13 treated with Nifedipine 172mg + 41 mg/day
    • 4 treated with Diltiazem 720 + 208 mg/day
  • 94% alive at 5 years

Treatment
• Diltiazem 360-900 mg/day
• Nifedipine 90-180 mg/day
• Amilodipine 20-40 mg/day

What Is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

Positive

Oral CCB

Sustained Response

No

Yes

Continue CCB

Negative

What Is the Optimal Treatment Strategy?

"Vasodilator Response"
- Fall in mPAP ≥ 10 mm Hg
- + PAPm (absolute) < 40 mm Hg
- + Normal CO

<table>
<thead>
<tr>
<th>II</th>
<th>WHO-class IV</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6MWD</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak VO₂ &lt;15.4 mL/kg/min</td>
<td>CPET</td>
<td>Peak VO₂ &lt;15.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiography</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement</td>
</tr>
<tr>
<td>RAP &lt;10 mm Hg; CI &gt;2.5 L/min/m²</td>
<td>Hemodynamics</td>
<td>RAP &gt;20 mm Hg; CI &lt;2.0 L/min/m²</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>


Survival in IPAH
Long-term CCB Responders

- Long-term CCB responders (~50% of acute responders or 56% of IPAH patients)
- Cumulative survival:
  - Long-term CCB responders
  - Long-term CCB failure
  - P=0.0007

<table>
<thead>
<tr>
<th>Subjects at risk, n</th>
<th>Long-term CCB responders</th>
<th>Long-term CCB failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 33 30 22 13 8 3 3 2 1</td>
<td>19 12 7 4 0</td>
<td></td>
</tr>
</tbody>
</table>

Approved Therapeutic Targets

Endothelin Pathway
- Pre-proendothelin
- Proendothelin
- Endothelial cells
- Endothelin-1

Nitric Oxide Pathway
- L-arginine
- L-citrulline
- Endothelial cells
- Arachidonic acid

Prostacyclin Pathway
- Prostacyclin (prostaglandin I₂)
- Endothelial cells

Pathway Diagram:
- Endothelin receptor A
- Endothelin receptor B
- Exogenous nitric oxide
- Phosphodiesterase type 5 inhibitor
- Prostacyclin derivatives

End points used in trials

- 6 minute walk distance
- VO2
- QOL
- Hemodynamics
- Time to clinical worsening

Approved Therapeutic Targets

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

**Nitric Oxide Pathway**
- L-arginine → L-citrulline
- Nitric oxide
- Exogenous nitric oxide
- Phosphodiesterase type 5 inhibitor

**Prostacyclin Pathway**
- Prostacyclin (prostaglandin I₂)
- Prostacyclin derivatives

**Endothelin-1**
- Arachidonic acid
- cGMP
- cAMP

**Endothelin-1 receptor**
- Endothelial cells
- Prostacyclin derivatives

**Endothelin receptor Blocker**

- **Ambrisentan**: selective (ETₐ) antagonist
  
  - Approved doses: 5 mg and 10 mg qd

- **Bosentan**: dual (ETₐ and ETₐ) antagonist
  
  - Approved doses: 62.5 mg bid starting dose for 4 weeks increased to 125 mg bid maintenance dose

- **Macitentan**: dual (ETₐ and ETₐ) antagonist

**Endothelin receptor blockers vs Placebo in PH**

- **Bosentan and Ambrisentan**
  - Increased exercise capacity
  - Delayed the time to clinical worsening
  - Improved dyspnea score
  - WHO Functional Class

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**Macitentan for PAH: Time To Clinical Worsening or Death**

Abstract

![Graph showing time to clinical worsening or death for Macitentan 10 mg, Macitentan 3 mg, and Placebo.](graph)

- Macitentan 10 mg: (n=242)
- Macitentan 3 mg: (n=250)
- Placebo (n=250)

Mean change from baseline in 6 MWD (m) vs Time from treatment start (months)

Macitentan 10 mg: Hazard ratio=0.55; log-rank p<0.0001
Macitentan 3 mg: Hazard ratio=0.70; log-rank p=0.0108

N=742. Double-blind, placebo-controlled Phase III study. Primary endpoint composite endpoint of death, atrial septostomy, lung transplantation, initiation of intravenous/subcutaneous prostanooids or 'other worsening' of PAH.

### Endothelin Receptor Antagonists: Side Effects

- Nasal congestion
- Abnormal hepatic function
  - reversible transaminase elevations >3X ULN
  - may require dose adjustments or discontinuations
  - monthly LFTs required
- Edema
  - lower extremity edema may require diuretic adjustment
- Use requires dual contraceptive methods (hormonal plus barrier)

### Approved Therapeutic Targets

![Diagram of Endothelin Pathway, Nitric Oxide Pathway, and Prostacyclin Pathway]

## Phosphodiesterase-5 Inhibitors

- **Sildenafil**
  - Approved dose: 20 mg tid
  - Approved for PAH (all classes)
- **Tadalafil**
  - Approved dose 40 mg once a day

## PDE-5 Inhibitor

- **Sildenafil Improved**
  - Exercise capacity
  - Functional class
  - Hemodynamics

- **Tadalafil Improved**
  - Exercise capacity
  - Quality of life measures
  - Delayed clinical worsening
**Riociguat**

- It is a stimulator of soluble guanylate cyclase (sGC)
- Stimulates NO production
- Does not require endogenous NO

- Initiate at 1 mg taken 3 times a day and titrate by 0.5 mg every 2 weeks as tolerated to 2.5 mg

**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)

N=445. Double-blind, placebo-controlled Phase III trial. 50% of patients were on stable background PAH therapy with ERAs (43%) or prostacyclin (7%).

Ghofrani H, et al.
Approved Therapeutic Targets


Prostacyclin Analogue: Intravenous Subcutaneous, Inhaled

Epoprostenol (Flolan®)
Treprostinil (Remodulin®)
Prostacyclin Analogues:
Intravenous, Subcutaneous, Inhaled

Epoprostenol (Flolan®)
Treprostinil (Remodulin®)

Prostacyclin Analogues:
Intravenous, Subcutaneous, Inhaled

Iloprost (Ventavis®)
Treprostinil (Tyvaso®)

Epoprostenol (Flolan®)
Treprostinil (Remodulin®)
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

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
- Initiate at low dose 2ng/kg/min

Flolan® (epoprostenol sodium) package insert. GlaxoSmithKline. Research Triangle Park, NC.
Continuous IV Epoprostenol vs conventional therapy in IPAH

- Improved
  - Exercise Capacity
  - Hemodynamics
  - NYHA Class
  - Survival

Treprostinil

- Longer-acting prostacyclin analogue
- Subcutaneous and IV infusion;
- Approved for Class II-IV
- Efficacy slower than epoprostenol, requires higher doses

Remodulin® (treprostinil sodium) package insert. United Therapeutics Corp. Research Triangle Park, NC.
**Inhalated Treprostinil**

1. Inhalation device assembled
2. Measuring cup
3. One inhaled treprostinil ampule
4. Carrying case provided

Dosage delivery of 6 µg per breath.
Start at 3 breaths QID to upto 9 breaths QID

**TYVASO (treprostinil) Improved Peak and Trough 6MWD at Week 12**

<table>
<thead>
<tr>
<th>Peak(^a)</th>
<th>Trough(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph of Peak change" /></td>
<td><img src="image" alt="Graph of Trough change" /></td>
</tr>
</tbody>
</table>

6MWD, 6-minute walk distance; PBO, placebo.

\(^a\) Peak defined as measure between 10 and 60 minutes after dose. \(^b\) Trough defined as measure ≥24 hours after dose.
### Iloprost

- Longer-acting prostacyclin analogue (20- to 30-min half-life)
- Aerosolized delivery system
- Approved for Class III and IV
- Requires frequent inhalations (6-9x/d)

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**I-neb® AAD® Once Daily Routine**

<table>
<thead>
<tr>
<th>At the beginning of each day, load Blue case with 6 CLEAN meshes</th>
<th>Administer therapy</th>
<th>After treatment, remove USED mesh and place it in Red case</th>
</tr>
</thead>
</table>

At the end of each day, remove the USED meshes from the Red case and wash along with the mouthpiece and drug chamber in distilled water with 1 drop of liquid detergent.
### PAH Determinants of Risk

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Determinants of Risk</th>
<th>Higher 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>Progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO class II, III</td>
<td>6MW distance</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Very elevated</td>
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<td>Minimal RV dysfunction</td>
<td>Echocardiographic findings</td>
<td>Pericardial effusion, significant RV dysfunction</td>
</tr>
<tr>
<td>Normal/near normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, low CI</td>
</tr>
</tbody>
</table>

McLaughlin VV and McGoon M. In press.

### PAH Evidence-based Treatment Algorithm

- Oral anticoagulants (E/B) – IVC/HRPH
- Diuretics (E/A)
- Oxygen (E/A)
- Digoxin (E/C)
- Supervised rehabilitation (E/B)
- **Expert referral (E/A)**
- **Supportive therapy and general measures**
- **Avoid excessive physical exertion (E/A)**
- **Birth control (E/A)**
- **Psychological and social support (E/C)**
- **Infection prevention (E/A)**

**ACUTE RESPONDER**

- WHO Class II
  - Ambienentan, Bosentan, Silidarelin (E)
  - **Sustained response (WHO I-II)**
  - **YES**
  - Ambienentan, Bosentan, Silidarelin, Epoprostenol (E)

**NON-RESPONDER**

- **WHO Class III**
  - Ambienentan, Bosentan, Epoprostenol IV (E)
  - **Strength of Recommendation**
  - A
  - Ambienentan, Bosentan, Epoprostenol IV (E)
  - **WHO Class III**
  - B
  - Sildenafil, Tadalafil (E)
  - **WHO Class IV**
  - C
  - Beraprost (E)
- **Sequential combination therapy**
  - Prostacyclins
  - **INADEQUATE CLINICAL RESPONSE**
  - **PDE-5 inhibitors**
  - **Atrial septectomy (E/B)**
  - **and/or lung transplant (E/A)**

**E/R**

- Not approved
- Epoprostenol IV, Tadalafil IV (E)
- Sequential combination therapy (E)

**Strength of Recommendation**

- A
- B
- C

**WHO Class IV**

- Epoprostenol IV (E)
- Tadalafil IV (E)
- Sequential combination therapy (E)
- Atrial septectomy (E/B)
- Lung transplant (E/A)
Treatment

Monitoring Response to Treatment

- 6 min walk
- Echocardiogram
- BNP
- Right heart Catheterization

On-therapy Prognostic Indicators

- Functional Class I or II
- 6MWD > 380 m
- Hemodynamics
  - Normal cardiac index (> 2.2 L/min/m²)
  - Normal RA pressure
- Positive response to CCB
- BNP <180 pg/mL
- Tricuspid Annular plane systolic excursion > 1.8 cm

### Goal oriented therapy

- Improve functional status
- RA pressure less than 10 mmHg
- BNP less than 100
- 6 minute walk > 350 m

### Goal Oriented Therapy

- If patient does not improve, what would you do?
  - Substitute therapy
  - Add therapies
Combination Therapy in PAH

- Endothelin receptor antagonists
- Prostanoids (IV, SC, PO, PI)
- Phosphodiesterase-5 inhibitors

PACES: Change From Baseline in 6MWD after adding Sildenafil to IV Epoprostenol

- Placebo (on the left)
- Sildenafil (on the right)

ATS, 2006

Goal Oriented Treatment and Combination Therapy for PAH

6MWD, 6-minute walk distance; NS, not significant.

Tadalafil Improved 6MWD in the Bosentan Treatment Subgroup

23-meter Improvement* after 16 weeks in background bosentan subgroup
p~NS

*Placebo-adjusted mean change.
Combination Therapy in PAH

Endothelin receptor antagonists

Prostanoids (IV, SC, PO, PI)

Phosphodiesterase-5 inhibitors

Atrial Septostomy

- Percutaneous catheter based technique
- Allows shunting from Right to left
- Shown to improve
  - clinical status
  - Long lasting benefit
- Carries a mortality of 5-6%
- Reserved for patients with refractory right heart failure or recurrent syncope despite maximal medical therapy
- Acceptable baseline oxygenation
- Poor outcome
  - mRA > 20mmHg
  - PVRI > 55u/m²
  - Not indicated in patients with hemodynamic instability
Transplantation

• Symptomatic, Progressive Ds

• NYHA class III or IV

• Hemodynamic parameters
  • Cardiac index < 2L/min/m2
  • RA pressures > 15 mmHg
  • mPA pressure > 55mmHg

1951

“Primary Pulmonary Hypertension”

• “Runs a malignant course, characterized by right heart failure, frequently ending in sudden death”

• “There is no effective treatment”