Pulmonary Hypertension: Classification and Treatment Options

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### PAH Survival

**Median Survival 2.8 years**

#### IPAH Survival
- 1 yr - 68%
- 3 yr - 47%
- 5 yr - 36%
- 7 yr - 32%

D’Alonzo, 1991 Annals of Internal Medicine

#### IPAH/Familial PAH Survival
- 1 yr - 91%
- 3 yr - 74%
- 5 yr - 65%
- 7 yr - 59%

Benza, 2012 CHEST
Timeline: FDA Approval of PAH Therapy

- Epoprostenol (1995)
- Bosentan
- Iloprost
- Intravenous Treprostinil
- Sildenafil
- Tadalafil
- Inhaled Treprostinil
- Ambrisentan
- Temperature-stable Epoprostenol
- Riociguat
- Macitentan
- Extended-release Treprostinil
- Selexipag (2015)
The key to appropriate management is appropriate diagnosis.
Nice 5th World Symposium
Classification of Pulmonary Hypertension

1. Pulmonary Arterial Hypertension
2. Pulmonary Venous Hypertension
3. PH Secondary to Chronic Hypoxia
4. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
5. Pulmonary hypertension with unclear, multifactorial mechanisms

Simonneau et al., JACC 2013;62:D34-41
Hemodynamic Definition

- **Pulmonary Hypertension (PH)**
  - mPAP $\geq$ 25 mmHg  (Normal 8 -20 mmHg)

- **Pulmonary Arterial Hypertension (PAH)**
  - mPAP $\geq$ 25 mm Hg
  - and
  - PAWP $\leq$ 15 mm Hg
  - and
  - PVR $\geq$ 3 WU ($\geq$240 dyne•sec•cm$^{-5}$)

**Trans pulmonary Gradient (TPG) $>$ 12 mmHg**
Nice 5th World Symposium
Classification of Pulmonary Hypertension

1. Pulmonary Arterial Hypertension
   - Collagen Vascular Disease
   - Congenital Heart Disease (L→R Shunt)
   - HIV
   - Drug and Toxin: Anorexigens (i.e. Fen-Phen) and amphetamines
   - Porto-pulmonary HTN
   - Familial/Heritable PAH (BMPR2, ALK-1, ENG, SMAD, CAV1)
   - Idiopathic PAH
   - Schistosomiasis

1’. Pulmonary veno-occlusive disease
1”. Persistent pulmonary hypertension of the newborn

Simonneau et al., JACC 2013;62:D34-41
Less Is More

Referral of Patients With Pulmonary Hypertension Diagnoses to Tertiary Pulmonary Hypertension Centers

The Multicenter RePherral Study

Roderick C. De Sanctis, MD, MPH; Cherylanne Glassner-Kolmin, BS; Melvyn Rubenstein, MD; Adaani Frost, MD; Scott Viscoetti, MD; Valerie V. McLaughlin, MD; Mardit Gomberg-Maitland, MD, MSc


Table 2. Prereferal Diagnosis Compared With Postreferal Diagnosis

<table>
<thead>
<tr>
<th>Prereferal diagnosis</th>
<th>Group 1 (n = 56)</th>
<th>Group 2 (n = 27)</th>
<th>Group 3 (n = 19)</th>
<th>Group 4 (n = 3)</th>
<th>Group 5 (n = 1)</th>
<th>No PH (n = 29)</th>
<th>Unknown (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 56)</td>
<td>41 (73)</td>
<td>3 (5)</td>
<td>4 (7)</td>
<td>0</td>
<td>0</td>
<td>7 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Group 2 (n = 13)</td>
<td>0</td>
<td>8 (62)</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>4 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Group 3 (n = 22)</td>
<td>4 (18)</td>
<td>3 (14)</td>
<td>13 (59)</td>
<td>0</td>
<td>0</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Group 4 (n = 4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (75)</td>
<td>0</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Group 5 (n = 2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0</td>
</tr>
<tr>
<td>No PH (n = 1)</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown (n = 42)</td>
<td>12 (29)</td>
<td>13 (31)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>14 (33)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>
Referral of Patients With Pulmonary Hypertension Diagnoses to Tertiary Pulmonary Hypertension Centers

The Multicenter RePHerral Study

Roderick C. Deleo, MD, MPH; Cherylanne Glossner-Kolwin, BS; Melvin Rubenfire, MD; Adaani Frest, MD; Scott Visovatti, MD; Vealere V. McLaughlin, MD; Mardi Gomberg-Maitland, MD, MSc


Table 4. Patients Receiving PAH-Specific Medications Prior to Referral Stratified by Postreferral Diagnosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Postreferral Diagnoses, No. a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>0</td>
</tr>
<tr>
<td>ERA</td>
<td>4</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>10</td>
</tr>
<tr>
<td>PG12/ERA</td>
<td>0</td>
</tr>
<tr>
<td>PG12/PDE5 inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>ERA/PDE5 inhibitor</td>
<td>7</td>
</tr>
<tr>
<td>PG12/ERA/PDE5 inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviations: ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PH, pulmonary hypertension.

a Group 1, pulmonary arterial hypertension; group 2, PH left-sided heart disease; group 3, PH lung disease; group 4, chronic thromboembolic PH; group 5, miscellaneous PH.

45% inappropriate PAH targeted therapy

=19
1. Screen with an echocardiogram
2. Rule out CTEPH
3. Confirm with right heart catheterization
• Estimation of the PA pressure by tricuspid jet
  • $RVSP = (RA\ pressure) + 4(\text{TR velocity})^2$
VQ Scan

WASH IN  EQUIL  WASHOUT1  WASHOUT2

ANT Q  POST Q  LPO Q  RPO Q

LLAT Q  RLAT Q  LAC Q  RAO Q
CTEPH: Curable with a Pulmonary Thromboendarterectomy
# Vasoreactivity Testing

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Route</th>
<th>Half-life</th>
<th>Dose</th>
<th>2 ng/kg/min</th>
<th>10 min/per</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoporostenol</td>
<td>IV</td>
<td>6 min</td>
<td>2-12ng/kg/min</td>
<td>2 ng/kg/min</td>
<td>10 min/per</td>
</tr>
<tr>
<td>Adenosine</td>
<td>IV</td>
<td>5-10 min</td>
<td>50-350 mcg/min</td>
<td>50 mcg</td>
<td>2 min/per</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>Inhaled</td>
<td>51-30 sec</td>
<td>10-20 ppm</td>
<td>---</td>
<td>5 min</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Inhaled</td>
<td>20-30 min</td>
<td>5 mcg</td>
<td>---</td>
<td>15 min</td>
</tr>
</tbody>
</table>

**Figure 2.** Kaplan-Meier estimates in the 57 of 70 acute responder patients who survived after 1 year onward on CCB. The number of patients included in the long-term CCB failure subgroup was only 19 of 32, with the 13 remaining patients being dead (n=6), transplanted (n=4), or lost to follow-up (n=3, considered “dead” in the analysis) within the first year. The difference between the group of long-term CCB responders (solid line) and that of patients who failed on CCB (dashed line) was highly significant (P=0.0007 by Cox-Mantel log-rank test).
Current Therapeutic Targets in PAH

- CCB
- Anticoagulation
- Digoxin
- Diuretics
- IV Epoprostenol
- Bosentan
- SC Treprostinil
- Sildenafil
- Ambrisentan
- Tadalafil
- Inhaled Iloprost
- Inhaled Tresprostinil
- Macitentan
- Riociguat
- Oral Treprostinil

Composite End-Point

Selexipag

In case of inadequate clinical response to initial combination therapy or initial monotherapy (Table 15), sequential double or triple combination therapy is recommended according to Table 21. The combination of riociguat and PDE-5i is contraindicated. In case of inadequate clinical response with sequential double combination therapy, triple combination therapy should be attempted (Tables 20 and 21).

It seems reasonable to consider eligibility for lung transplantation after an inadequate clinical response to the initial monotherapy or initial combination therapy and to refer the patient for lung transplantation soon after the inadequate clinical response is confirmed on maximal combination therapy. BAS should be regarded as a palliative or bridging procedure in patients deteriorating despite maximal medical therapy.

**Functional Class Driver of Therapeutic Choice**

**Combination therapy**

Which combination?

- Class vs. Molecule Specific?
Goals of Treatment

- **NHYA Functional Class is an important predictor of survival**
- Improvement in NHYA FC from FC III/IV to FC I/II improves PAH prognosis

### Table 13 Risk assessment in pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Determinants of prognosis* (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope*</td>
<td>Repeated syncope*</td>
</tr>
<tr>
<td>WHO Functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165–440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂ &gt;15 ml/min/kg (&gt;65% pred.) VE/VO₂ slope &lt;36</td>
<td>Peak VO₂ 11–15 ml/min/kg (35–65% pred.) VE/VO₂ slope 36–44.9</td>
<td>Peak VO₂ &lt;11 ml/min/kg (&lt;35% pred.) VE/VO₂ slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l</td>
<td>NT-proBNP &lt;300 ng/l</td>
<td>BNP &gt;300 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm² No pericardial effusion</td>
<td>RA area 18–26 cm² No or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm² Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg CI ≥2.5 l/min/m² SvO₂ &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m² SvO₂ 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m² SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>
Macitentan (Opsimut)

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

Tomás Pulido, M.D., Igor Adzerikh, M.D., Richard N. Channick, M.D., Marion Delcroix, M.D., Nazzareno Galì, M.D., Hossein-Ardeshir Ghofrani, M.D., Pavel Jansa, M.D., Zhi-Cheng Jing, M.D., Franck-Olivier Le Brun, M.Sc., Sanjay Mehta, M.D., Camilla M. Mittelholzer, Ph.D., Loic Perchenet, Ph.D., B.K.S. Sastry, M.D., Olivier Sitbon, M.D., Rogério Souza, M.D., Adam Torbicki, M.D., Xiaofeng Zeng, M.D., Lewis J. Rubin, M.D., and Gérald Simonneau, M.D., for the SERAPHIN Investigators*

Aug, 2013 ORIGINAL ARTICLE

*Primary End-Point - Composite

• Death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH.
• Worsening PAH – All 3
  • 6MD 15%, ↓PAH symptoms, need more PAH therapy

• 10 mg arm --- Hazard Ratio 0.55 (97.5% CI, 0.39 to 0.76; P<0.001)
• 63% on background therapy with PDE5i, inhaled/oral PCA
Selexipag for the Treatment of Pulmonary Arterial Hypertension

Olivier Sitbon, M.D., Richard Channick, M.D., Kelly M. Chin, M.D., Aline Frey, Pharm.D., Sean Gaine, M.D., Nazzareno Galié, M.D., Hossein-Ardeschir Ghofrani, M.D., Marius M. Hoeper, M.D., Irene M. Lang, M.D., Ralph Preiss, M.D., Lewis J. Rubin, M.D., Lilla Di Scala, Ph.D., Victor Tapson, M.D., Igor Adzerikho, M.D., Jinming Liu, M.D., Olga Moiseeva, M.D., Xiaofeng Zeng, M.D., Gérald Simonneau, M.D., and Vallerie V. McLaughlin, M.D., for the GRIPHON Investigators*

ABSTRACT

• Oral Prostacyclin (PGI2) Receptor agonist
• N=1,156  - Largest RCT in PAH patients to date
• 14% were on ERA, 32% on PDE5i, 32% on ERA/PDE5i
• Up to 4.3 years of follow up
• Composite morbidity/mortality primary endpoint
• Decreased the risk of event by 40%  (p<0.0001)
Primary Endpoint Composite Event

<table>
<thead>
<tr>
<th>Component</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>Existence of death certificate</td>
</tr>
<tr>
<td>Hospitalization for worsening pulmonary arterial hypertension</td>
<td>Any hospitalization for worsening pulmonary arterial hypertension, lung or heart and lung transplantation, atrial septostomy, or initiation of parenteral prostanooid therapy</td>
</tr>
<tr>
<td>Disease progression</td>
<td>A decrease of more than 15% from baseline in the 6-minute walk distance combined with World Health Organization (WHO) functional class III or IV symptoms at two consecutive visits separated by at least 14 days</td>
</tr>
<tr>
<td>Unsatisfactory long-term clinical response</td>
<td>Any decrease from baseline in 6-minute walk distance at two consecutive clinic visits after baseline separated by at least 14 days, and WHO functional class III symptoms assessed at two clinic visits separated by at least 6 months; assessed only among participants who were in the study for at least 6 months</td>
</tr>
</tbody>
</table>

* A clinical end-point committee, whose members were unaware of the study-group assignments and of the identity of the investigator, adjudicated all reported clinical events.
Primary Endpoint Composite Event

Hazard ratio 0.50 P <0.001

Secondary Endpoints:

• + Change in Nt Pro BNP
• + Change in 6MW (49 m vs 24 m)

• NO Difference in WHO Functional Class improvement between groups
Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

Olivier Sitbon\textsuperscript{1,2,3}, Xavier Jais\textsuperscript{1,2,3}, Laurent Savale\textsuperscript{1,2,3}, Vincent Cottin\textsuperscript{4}, Emmanuel Bergot\textsuperscript{5}, Elise Artaud Macari\textsuperscript{1,2,3}, Hélène Bouvaist\textsuperscript{6}, Claire Dauphin\textsuperscript{7}, François Picard\textsuperscript{8}, Sophie Bulifon\textsuperscript{1,2,3}, David Montani\textsuperscript{1,2,3}, Marc Humbert\textsuperscript{1,2,3} and Gérald Simonneau\textsuperscript{1,2,3}

ERJ March, 2014

• Retrospective study of 19 consecutive incident cases PAH
• 19 WHO Class III (n=8)/IV(n= 11)

AND

• Severe HD impairment
  \begin{itemize}
  \item CI < 2.0 L/min/m2
  \item mRA >20 mmHg
  \item PVR > 1000 dyn.s.cm-5
  \end{itemize}

Triple Combintaion

• IV Epoprostenol
• Bosentan
• Sildenafil
Long term Follow Up
32.3±19.4 mos (8.5–73.3 mos)

Transplant free
Survival
1yr – 94%
2yr – 94%
3yr – 94%