PAH: Standard of Care

Nazzareno Galiè
Istituto di Cardiologia
Università di Bologna

nazzareno.galie@unibo.it
A. Do we have additional information on the role of rehabilitation in PAH patients?

B. Should first-line combination therapy be the gold standard of severe WHO FC IV PAH (and what about other FC)?

C. How can we modify the current treatment algorithm including the new approved drugs?

D. Should we adapt the treatment algorithm to the different PAH types and to different countries (country organization)?
1st WHO PH
Geneva
1973
PH Classification 1950-1998

(1st WHO PH Geneva 1973)

1. Primary Pulmonary Hypertension
2. Secondary Pulmonary Hypertension
3. Associated Pulmonary Hypertension
PAH time course of Treatments

Tolazoline, Hydralazine, Acetylcholine, Phentolamine, Isoproterenol, Diazoxide, Nitrates,…

Calcium Channel Blockers in vasoreactive pts
Calcium Channel Blockers

Vasoreactivity – NO test

Definition

\[ \downarrow \text{mPAP} > 10, < 40 \text{ mmHg abs; CO } =/\uparrow \]

\[ \sim 10\% \]

Treatment Algorithm before 1998

Pulmonary Arterial Hypertension

Supportive Therapy and General Measures

Vasoreactive

Non-vasoreactive

Oral anticoagulants
Diuretics
Oxygen (Iia)
Digoxin

Exercise Limitation
Birth Control
Psychological Assistance
Infections Prevention

Acute Vasoreactivity Test

NYHA Class I-IV

Oral CCB (I C)

???????
A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION


FOR THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP*

Published RCTs in PAH

1. Rubin, **Epoprostenol** in PPH. Ann Intern Med 1990
**Treatment Algorithm ...1998 - 2003**

Pulmonary Arterial Hypertension

- Supportive Therapy and General Measures
  - Oral anticoagulants
  - Diuretics
  - Oxygen (Ia)
  - Digoxin

- Exercise Limitation
- Birth Control
- Psychological Assistance
- Infections Prevention

Acute Vasoreactivity Test

- Vasoreactive
- Non-vasoreactive

- NYHA Class I-IV
  - Oral CCB (I C)

- NYHA Class III-IV
  - Epoprostenol
Published RCTs in PAH

5. Langleben, Terbogrel in PPH. Am J Cardiol 2002
6. Simonneau, Treprostinil in PAH. Am J Respir Crit Care Med 2002
7. Galié, Beraprost in PAH. J Am Coll Cardiol 2002
11. Sastry, Sildenafil in IPAH. J Am Coll Cardiol 2004
3rd WSPAH
Venice
2003
Approved Drugs for PAH

Bosentan
Epoprostenol iv
Iloprost inhal
Sildenafil
Treprostinil sc

Bosentan
Epoprostenol iv
Iloprost inhal
Sildenafil
Treprostinil sc
Monotherapy

Monotherapy and/or Sequential Combination

Upfront Combination

N. Galiè, M. Palazzini, A. Manes, Eur Heart J 2010
Approved Drugs for PAH

Ambrisentan  
Bosentan  
Epoprostenol iv  
Iloprost inhal  
Sildenafil

Sitaxentan
Tadalafil
Treprostinil sc

Ambrisentan  
Bosentan  
Epoprostenol iv  
Iloprost inhal  
Sildenafil

Tadalafil
Treprostinil sc, iv, inhal
Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses

Nazzareno Galiè*, M Palazzini, A Manes

Institute of Cardiology, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy

Received 9 December 2008; revised 18 December 2008; accepted 9 January 2009

• Medline search from January 1990 to April 2010
• 25 RCTs, 3839 patients
**All Cause Mortality**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin Analogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubin-1990</td>
<td>0.36 (0.04, 3.00)</td>
<td>4.90</td>
</tr>
<tr>
<td>Barst-1996</td>
<td>0.06 (0.00, 0.96)</td>
<td>2.74</td>
</tr>
<tr>
<td>Badesch-2000</td>
<td>0.79 (0.22, 2.77)</td>
<td>13.72</td>
</tr>
<tr>
<td>Simmoneau-2002</td>
<td>0.92 (0.38, 2.21)</td>
<td>28.03</td>
</tr>
<tr>
<td>Galiè-2002</td>
<td>1.00 (0.06, 15.65)</td>
<td>2.88</td>
</tr>
<tr>
<td>Olschewski-2002</td>
<td>0.25 (0.03, 2.22)</td>
<td>4.62</td>
</tr>
<tr>
<td>Barst-2003</td>
<td>0.47 (0.04, 5.01)</td>
<td>3.88</td>
</tr>
<tr>
<td>McLaughlin-2010</td>
<td>0.35 (0.01, 8.45)</td>
<td>2.14</td>
</tr>
<tr>
<td>McLaughlin-2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Hoepner-2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.682)</td>
<td>0.62 (0.34, 1.12)</td>
<td>62.91</td>
</tr>
<tr>
<td>Endothelin Receptor Antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubin-2002</td>
<td>0.24 (0.02, 2.60)</td>
<td>3.84</td>
</tr>
<tr>
<td>Barst-2004</td>
<td>1.54 (0.06, 37.19)</td>
<td>2.15</td>
</tr>
<tr>
<td>Galiè-2008</td>
<td>0.99 (0.08, 15.58)</td>
<td>2.87</td>
</tr>
<tr>
<td>Channick-2001</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Galiè-2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Barst-2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.597)</td>
<td>0.60 (0.12, 2.86)</td>
<td>8.86</td>
</tr>
<tr>
<td>Phosphodiesterase Type 5 Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sastry-2004</td>
<td>0.39 (0.02, 8.73)</td>
<td>2.27</td>
</tr>
<tr>
<td>Galiè-2005</td>
<td>1.01 (0.11, 9.55)</td>
<td>4.32</td>
</tr>
<tr>
<td>Galiè-2008</td>
<td>0.41 (0.11, 1.49)</td>
<td>12.95</td>
</tr>
<tr>
<td>Simmoneau-2008</td>
<td>0.07 (0.00, 1.15)</td>
<td>2.68</td>
</tr>
<tr>
<td>Galiè-2009</td>
<td>0.51 (0.05, 5.53)</td>
<td>3.83</td>
</tr>
<tr>
<td>Singh-2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.696)</td>
<td>0.40 (0.16, 1.01)</td>
<td>26.05</td>
</tr>
<tr>
<td>Thromboxane synthase inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Langleben-2002</td>
<td>1.66 (0.07, 39.30)</td>
<td>2.18</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td>1.66 (0.07, 39.30)</td>
<td>2.18</td>
</tr>
</tbody>
</table>

Heterogeneity between groups: p = 0.788

Overall (I-squared = 0.0%, p = 0.908) | 0.56 (0.35, 0.90) | 100.00 |

**RR = -44%  P = 0.016**
Areas of Algorithm Improvement

• Upfront combination therapy
• Place for new drugs (Imatinib, Macitentan, Riociguat, Selexipag)
• Transplantation indication
• RV assistance
• Indications for complications
• Definition of expert center/Country organization
Areas of Algorithm Improvement

- Upfront combination therapy
- Place for new drugs (Imatinib, Macitentan, Riociguat, Selexipag)
- Transplantation indication
- BAS indication
- RV assistance
- Indications for complications
- Definition of expert center/Country organization
Areas of Algorithm Improvement

- Upfront combination therapy
- Place for new drugs (Imatinib, Macitentan, Riociguat, Selexipag)
- Transplantation indication
- BAS indication
- RV assistance
- Indications for complications
- Definition of expert center/Country organization
Combination Strategies

Drug A

Inadequate response

Drug B

Sequential Combination

Drug A+B

Upfront Combination
BREATHE-2
Epoprostenol + bosentan

29 of 32 patients completed at week 16

Effect of up-front combination therapy

Epo + bosentan combination therapy 
(n = 23)

Epoprostrenol monotherapy 
(n = 46)

\[ p = 0.0001 \]

-48 ± 17%

-29 ± 17%

Up-front triple combination therapy in PAH

Epoprostenol monotherapy (n=46)
-29 ± 17%

Epoprostenol + bosentan combination therapy (n=23)
-48 ± 17%

Epo + bosentan + sildenafil combination therapy (n=11)
-69 ± 8%
Ambition Study

A randomized, double-blind, placebo-controlled, multicenter study of first-line combination therapy with Ambrisentan and Tadalafil vs. monotherapy in subjects with pulmonary arterial hypertension.

- Phase III randomised controlled study comparing upfront combination therapy (Ambrisentan + Tadalafil) to initial monotherapy (Ambrisentan or Tadalafil).
- Time to treatment failure as primary end-point.
- Event driven sample size and duration starting with 510 patients and a minimum F-U of 10 months.
Efficacy of up-front combination

Naive Patients

- Ambrisentan 10 mg
- Tadalafil 40 mg

- Ambrisentan 10mg + Tadalafil 40mg

Phase III: AMBITION
Primary End Point “Time to Clinical Failure”

Time to clinical failure is defined as the time from randomization to the first occurrence of:

- **Death (all-cause)**
- **Hospitalization for worsening PAH (adjudicated)**
  - Non-elective hospitalization for worsening PAH
  - Lung or heart/lung transplant
  - Atrial septostomy
  - Initiation of parenteral prostanoid therapy
- **Disease progression (adjudicated)**
  - >15% decrease from baseline in 6MWD combined with WHO class III or IV symptoms (at two consecutive post-baseline clinic visits separated by ≥14 days)
- **Unsatisfactory long-term clinical response (adjudicated, all criteria required)**
  - Receiving randomized treatment for at least 6 months
  - Any decrease from baseline in 6MWD at two consecutive post-baseline clinic visits separated by ≥14 days
  - Sustained WHO class III symptoms for ≥6 months (WHO class III symptoms assessed at two clinic visits separated by ≥6
Areas of Algorithm Improvement

- Upfront combination therapy
- Place for new drugs (Imatinib, Macitentan, Riociguat, Selexipag)
- Transplantation indication
- RV assistance
- Indications for complications
- Definition of expert center/Country organization
**ADVENTITIA**
- Inflammatory Cells †‡
- Fibrosis ↑
- Cyto/Chemokines †‡
- MMP and tenascin †‡
- B-FGF †

**MEDIA**
- SMC Hyperplasia *†
- K⁺ch dysfunction and related ↑[Ca ++ ]*↓BMPRs †
- Angiopoietin †

**ENDOTELIUM**
- Endothelin *†
- Prostacyclin †
- Nitric Oxide/cGMP †
- TxA₂ *§↑VEGF †
- BMPRs †

**INTIMA**
- MFB Hyperplasia †
- Fibrosis †
- PDGF receptors †
- Cyto/Chemokines †‡

**BLOOD**
- Hypercoagulability §
- Platelets Dysfunction §
- Serotonin †
- PDGF †
- VIP †

**Treatments**
- Ca ++ -Channel blockers (Vasoreactivity responders)
- PDE-5 inhibitors
- Prostanoids

**Pathobiology**
- *Vasoconstriction;
- †Proliferation/migration;
- ‡Inflammation;
- §Thrombosis

**Tissue ERAs**
- Direct Stimulator of GC
- Oral IP Receptor Agonist

**Anticoagulants**
- Serotonin Antagonists
- Vasoactive Intestinal Peptide

---

N. Galiè, M. Palazzini, A. Manes, Eur Heart J 2010
### RCTs in PAH with new oral therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPRES (imatinib)</td>
<td>TK inhibitor PDGF-R inhibitor</td>
</tr>
<tr>
<td>SERAPHIN (macitentan)</td>
<td>Endothelin Tissue-specific ERA</td>
</tr>
<tr>
<td>PATENT (riociguat)</td>
<td>Nitric oxide GC stimulator</td>
</tr>
<tr>
<td>FREEDOM (treprostinil)</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>GRIPHON (selexipag)</td>
<td>Prostacyclin P-R agonist</td>
</tr>
</tbody>
</table>
## RCTs in PAH with new oral therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPRES (imatinib-TKI)</td>
<td>6-MWD</td>
</tr>
<tr>
<td>SERAPHIN (macitentan-ERA)</td>
<td>M/M</td>
</tr>
<tr>
<td>PATENT (riociguat-GS)</td>
<td>6-MWD</td>
</tr>
<tr>
<td>FREEDOM (treprostinil-P)</td>
<td>6-MWD</td>
</tr>
<tr>
<td>GRIPHON (selexipag-PRS)</td>
<td>M/M</td>
</tr>
</tbody>
</table>
Enrolment of patients and completion of the study

Screened
n=326

Randomized
n=202

Imatinib
n=103

Discontinued: n=34 (33.0%)
• AEs: 27 (26.2%)
• Unsatisfactory therapeutic effect: 1 (1.0%)
• Death: 2 (1.9%)
• Withdrew consent: 2 (1.9%)
• Abnormal laboratory value: 1 (1.0%)
• Protocol deviation: 1 (1.0%)
• Administrative problems: 0 (0.0%)

Completed 24 weeks
n=69 (67.0%)

Placebo
n=99

Discontinued: n=18 (18.2%)
• AEs: 7 (7.1%)
• Unsatisfactory therapeutic effect: 5 (5.1%)
• Death: 2 (2%)
• Withdrew consent: 1 (1%)
• Abnormal laboratory value: 1 (1%)
• Protocol deviation: 1 (1%)
• Administrative problems: 1 (1%)

Completed 24 weeks
n=81 (81.8%)
LS mean 6MWD was significantly higher at Week 24 in patients receiving imatinib (383±9.8 m) than in those receiving placebo (351±9.8 m) – between-group difference: \(31.8\pm10.1\) m (\(p=0.002\))

Values are means and standard errors. \(p\)-values are for between-group comparisons.
The primary variable was analyzed using the full analysis set and a mixed effects model for repeated measures. Missing values imputed with plausible values. \(LS = \text{least squares}\)
Change in haemodynamic parameters at Week 24

- **Pulmonary arterial pressure**
  \[\Delta -5.18\, \text{mmHg}, \, p<0.001\]
  - Imatinib: \(-3.54\, \text{mmHg}\)
  - Placebo: \(1.63\, \text{mmHg}\)

- **Cardiac Output**
  \[\Delta +0.88\, \text{L/min}, \, p<0.001\]
  - Imatinib: \(+1.17\, \text{L/min}\)
  - Placebo: \(+0.29\, \text{L/min}\)

- **Pulmonary Vascular Resistance**
  \[\Delta -378.6\, \text{dynes.sec.cm}^{-5}, \, p<0.001\]
  - Imatinib: \(-366.5\, \text{dynes.sec.cm}^{-5}\)
  - Placebo: \(+12.1\, \text{dynes.sec.cm}^{-5}\)

Data is least squares (LS) means, full analysis set.
Time to clinical worsening

Hazard ratio: 1.16 (95% CI, 0.71–1.90)  
p=0.563 (Cox regression)
Subdural Hematomas in the QTI Clinical Program

- There have been 11 cases of subdural hematoma (SDH)s:
  - 9 in the QTI571 clinical trials
    - 8 Phase III trial: core and extension (n=181)
    - 1 Phase II trials core (n= 45)
    - 0 Drug-drug interaction trial (n=18)
  - 1 spontaneous report in Patient Supply Programs (requests from physicians for drug)
    - 0 Japan Named Patient Program (n=9)
    - 0 Individual Patient Supply Program UK (n=4)
    - 1 Individual Patient Supply Program Switzerland (n=23)
  - 1 spontaneous report from off label use in patient with prior h/o SDH

- 7 females and 2 males between the ages of 47-66 years old

- Time to event ranges from 12 days to 18 months

- All SDH cases were also anticoagulated; no SDH cases have occurred in non-anticoagulated patients
# Macitentan in the SERAPHIN trial

## Study objectives

<table>
<thead>
<tr>
<th>Primary objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>To demonstrate that macitentan prolongs the time to the first morbidity or mortality event in patients with symptomatic PAH</td>
</tr>
</tbody>
</table>

www.clinicaltrials.gov, NCT00660179.
Primary efficacy endpoint

Macitentan reduced the risk of a morbidity and mortality event

<table>
<thead>
<tr>
<th>Dose of macitentan (mg)</th>
<th>Observed risk reduction (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30</td>
<td>0.0108</td>
</tr>
</tbody>
</table>

Actelion. Press release 2012
Primary efficacy endpoint

A dose-related effect has been observed

<table>
<thead>
<tr>
<th>Dose of macitentan (mg)</th>
<th>Observed risk reduction (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>45</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>0.0108</td>
</tr>
</tbody>
</table>

Actelion. Press release 2012
Secondary efficacy endpoints

Both doses of macitentan demonstrated a statistically significant effect on secondary objectives:

- Change from baseline to month 6 in 6-MWD
- Change from baseline to month 6 in WHO functional class
- Time to either death due to PAH or hospitalisation due to PAH*

*Over the whole treatment period.
### Macitentan: Aminotransferase elevations

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Macitentan 3 mg</th>
<th>Macitentan 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT or AST &gt; 3 x upper limit of normal</td>
<td>4.5%</td>
<td>3.6%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

ALT: alanine transaminase  
AST: aspartate transaminase  

Actelion. *Press release 2012*
Riociguat for chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension: a phase II study.

N=75 patients with PAH or CTEPH
No PDE5i or PGI2 – 6 on bosentan
Most tolerated a dose of 2.5 mg tid

Bars show 95% confidence intervals

***p <0.001

<table>
<thead>
<tr>
<th>Author</th>
<th>Acronym</th>
<th>Study drug</th>
<th>Patients</th>
<th>N</th>
<th>Duration (wks)</th>
<th>1 EP</th>
<th>Efficacy 1EP</th>
<th>TtCW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapson V CHEST 2012</td>
<td>FREEDOM C</td>
<td>UT 15 C</td>
<td>PAH</td>
<td>354</td>
<td>16</td>
<td>6MWD</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tapson V ATS 2012</td>
<td>Freedom M</td>
<td>UT 15 C</td>
<td>PAH</td>
<td>300</td>
<td>16</td>
<td>6MWD</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Tapson V ATS 2012 A2493</td>
<td>FREEDOM C²</td>
<td>UT 15 C</td>
<td>PAH</td>
<td>310</td>
<td>16</td>
<td>6MWD</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Unpublished data.
6mwt, 6-minute walk test; CHD, congenital heart disease; CTD, connective-tissue disease; I EP, initial endpoint; IPAH, idiopathic PAH; ND, no significant difference; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TPR, total pulmonary resistance; TtCW, time to clinical worsening.
Effects of Beraprost Sodium, an Oral Prostacyclin Analogue, in Patients With Pulmonary Arterial Hypertension: A Randomized, Double-Blind, Placebo-Controlled Trial

Nazzareno Galié, MD,* Marc Humbert, MD,† Jean-Luc Vachiéry, MD,‡ Carmine Dario Vizza, MD,§ Meinhard Kneussl, MD,|| Alessandra Manes, MD,* Olivier Sitbon, MD,† Adam Torbicki, MD,¶ Marion Delcroix, MD,# Robert Nacije, MD,‡ Marius Hoeper, MD,** Ari Chaouat, MD,†† Sophie Morand, MD,‡‡ Bruno Besse, MD,‡‡ Gerald Simonneau, MD,† for the Arterial Pulmonary Hypertension and Beraprost European Trial (ALPHABET) Study Group

JACC Vol. 39, No. 9, 2002
May 1, 2002:1496–502
Selexipag Phase II study

N=43 patients with PAH on ERA, PDE5i or both
3:1 randomization selexipag (200-800 µg bid) vs pbo
Final optimized dose at day 35 – assessment at 17 weeks

ITT analysis: Treatment effect: −33.0% (95% CL: −47.0, −15.2; p=0.0022*)

*Wilcoxon rank-sum test
Question C: How can we modify the current treatment algorithm including the new approved drugs?
(Nazzareno Galiè)

- First line therapy, if any
- Place for newly approved drugs (inhaled remodulin, iv sildenafil)
- Place for new drugs with available phase III data (imatinib, macitentan, oral treprostinil, riociguat)
- Place for upfront combination therapy
Question C: How can we modify the current treatment algorithm including the new approved drugs?

*First line therapy* should be based on the following principles:

- Benefit to risk ratio (first more safe drugs, last drugs with more side effects)
- Specific labeling (exercise capacity vs outcome)
- Experience of the treating physician
- Pharmacoeconomy (drug costs, hospitalizations costs, etc)
- Country approvals
- Head to head comparison?
Question C: How can we modify the current treatment algorithm including the new approved drugs?

The place of new drugs in the algorithm should be based on:

- Grade of recommendation (I, IIa, IIb, III) and level of evidence (A, B, C)
- Characteristics of the pivotal(s) RCT(s) (primary end-point, secondary end-points, patients population, background therapy, ...)
- Innovation as compared to already existing drugs in the same (class or group)
### Table 1  Classes of recommendations

<table>
<thead>
<tr>
<th>Classes of Recommendations</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
</tr>
</tbody>
</table>

### Table 2  Levels of evidence

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Evidence A</td>
<td>Data derived from multiple randomized clinical trials(^a) or meta-analyses.</td>
</tr>
<tr>
<td>Level of Evidence B</td>
<td>Data derived from a single randomized clinical trial(^a) or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of Evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>

\(^a\)Or large accuracy or outcome trial(s) in the case of diagnostic tests or strategies.
Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)
Supervised rehabilitation (IIa-B)
Psycho-social support (IIa-C)
Avoid excessive physical activity (III-C)

**General measures and supportive therapy**

Diuretics (I-C)
Oxygen* (I-C)
Oral anticoagulants: IPAH, heritable PAH and PAH due to anorexigen (IIa-C)
APAH (IIb-C)
Digoxin (IIb-C)

**Acute vasoreactivity test**
(I-C for IPAH)
(IIb-C for APAH)

**VASOREACTIVE**

**NON VASOREACTIVE**

**WHO-FC I-III**
CCB (I-C)

**Sustained response** (WHO-FC I-II)

**YES**
Continue CCB

**NO**

<table>
<thead>
<tr>
<th>Recommendation-Evidence</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-A</td>
<td>Ambrisentan, Bosentan, Sitaxentan, Sildenafil</td>
<td>Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Epoprostenol i.v., Iloprost inhalated</td>
<td>Epoprostenol i.v.</td>
</tr>
<tr>
<td>I-B</td>
<td>Tadalafil†</td>
<td>Tadalafil†</td>
<td>Treprostinil s.c., inhalad†</td>
</tr>
<tr>
<td>IIa-C</td>
<td>Sitaxentan</td>
<td>Iloprost i.v., Treprostinil i.v.</td>
<td>Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Tadalafil†, Iloprost inhalad, and i.v. Treprostinil s.c., i.v., Inhalad† Initial Combination Therapy</td>
</tr>
<tr>
<td>IIb-B</td>
<td>Beraprost</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INADEQUATE CLINICAL RESPONSE**

Sequential combination therapy (IIa-B) §

- Prostanoïds
- ERA
- PDE-5 I

**BAS (I-C) and/or Lung transplantation (I-C)**

Galiè.N et al
Eur Heart J and Eur Respir J, 2009
Question C: How can we modify the current treatment algorithm including the new approved drugs?

Some uncertainties

- Is it appropriate an algorithm based on the primary end-point (exercise capacity vs outcome/effect on mortality)?
- Are PDE-5 inhibitors & GC stimulators in the same group of drugs?
- Place of imatinib if approved (issue of transplantation?)
- Can we include iv sildenafil in the treatment algorithm without clinical data on PAH patients for the theoretical indication (forced fasting in patients already treated with the oral form due to surgery etc.)?
- BAS? Still to be included??? Survey?
- If oral treprostinil is approved (1 RCT positive in monotherapy and 2 RCTs negative in combo) should be indicated only in naïve patients? Should then we re-evaluate oral beraprost?
Areas of Algorithm Improvement

- Upfront combination therapy
- Place for new drugs (Imatinib, Macitentan, Riociguat, Selexipag)
- Transplantation indication
- RV assistance
- Indications for complications
- Definition of expert center/Country organization
PAH complications

- PA aneurisms/Rupture/Dissection
- PA thrombosis
- Left main CA compression
- Emophysis
- Supraventricular arrhythmias
Areas of Algorithm Improvement

• Upfront combination therapy
• Place for new drugs (Imatinib, Macitentan, Riociguat, Selexipag)
• Transplantation indication
• RV assistance
• Indications for complications
• Definition of expert center/Country organization
Definitions of PH Expert Center

Background-1

- Pulmonary hypertension is a rare chronic progressive condition which is lethal, disabling, costly and treatable.
- Diagnosis and treatment options are complex.
- Patients often look well, even when they are deteriorating, and in inexperienced hands this may result in missed opportunities for treatment.
- Current therapies slow disease progression and are not curative.
- There are many novel drugs which may be effective but require testing in clinical trials.
Definitions of PH Expert Center

Background-2

• High volume units have been recurrently shown in medicine to obtain best outcomes for patients while maintaining greatest patient satisfaction, lowest complication rates, shortest length of hospital stay and best value for healthcare payors
Definitions of PH Expert Center

Proposal

1. Each country should have at least two adult expert centres.
2. Each country should have at least one paediatric expert centre.
3. The ideal number of patients seen by an adult or paediatric centre per annum should be no less than 200 (either PAH or CTEPH)
4. In countries with a population >10 million, adult centres should ideally expand to >300 patients seen per annum