Pulmonary hypertension new aspects

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Conflict of interest

I have received fees for serving as a speaker, consultant and advisory board member from the following:

• Actelion,
• Bayer
• Dompè,
• GSK,
• Italfarmaco,
• Lilly,
• Mochida
• Pfizer,
• United Therapeutics.
Pulmonary Hypertension: definition

PAPm > 25 mmHg at rest
> 30 mmHg during exercise (?)
Pulmonary Hypertension: Hemodynamic Classification

**Normal**
- Pulm. Artery: 16 mmHg
- Left Atrium: 8 mmHg

**PostCapillary PH**
- Pulm. Artery: 26 mmHg
- Left Atrium: 18 mmHg

**Precapillary PH**
- Pulm. Artery: 35 mmHg
- Left Atrium: 8 mmHg
# Hemodynamic definitions of PH

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>mPAP ≥25 mmHg</td>
<td>All</td>
</tr>
</tbody>
</table>
| Pre-capillary PH | mPAP ≥25 mmHg, PAWP ≤15 mmHg | 1. Pulmonary arterial hypertension  
2. PH due to left heart disease  
3. PH due to lung diseases  
4. Chronic thromboembolic PH  
5. PH with unclear and/or multifactorial mechanisms |
| Post-capillary PH | mPAP ≥25 mmHg, PAWP >15 mmHg | 2. PH due to left heart disease  
5. PH with unclear and/or multifactorial mechanisms |
| Isolated post-capillary PH (lpc-PH) | DPG <7 mmHg and/or PVR ≤3 WU |               |
| Combined post-capillary and pre-capillary PH (Cpc-PH) | DPG ≥7 mmHg and/or PVR>3 WU<sup>b</sup> |               |

<sup>a</sup> Characteristics may vary depending on the presence or absence of clinical symptoms and signs.

<sup>b</sup> PVR: Pulmonary Vascular Resistance.

Pulmonary Hypertension Unit
La Sapienza University of Rome

1. Pulmonary Arterial Hypertension (PAH)
   - Idiopathic
   - Hereditary (BMPR-II; ALK-1)
   - Drug and Toxin induced
   - Associated with:
     - Connective Tissue Disease
     - HIV infection
     - Portal hypertension
     - Congenital heart disease
     - Schistosomiasis
   - Persistent PH in the newborn

2. PH due to left heart disease
   - Systolic/Diastolic dysfunction
   - Valvulopaties

3. PH due to lung disease or hypoxia
   - COPD
   - Interstitial lung disease
   - Breathing sleep disorders
   - Chronic exposure to high altitude
   - Developmental lung disorders

4. Chronic Thromboembolic PH (CTEPH)

5. PH with multifactorial mechanisms
   - Hematologic disorders, Vasculitis, Sarcoidosis, Metabolic disorders (glicogenosisi)
Hemodynamic findings in precapillary PH

<table>
<thead>
<tr>
<th></th>
<th>PAH</th>
<th>COPD</th>
<th>ILD</th>
<th>CTEPH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=44</td>
<td>n=141</td>
<td>n=32</td>
<td>n=12</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>11±6</td>
<td>8±4</td>
<td>8±5</td>
<td>10±5</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>62±21</td>
<td>31±6</td>
<td>34±9</td>
<td>54±14</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>24±11</td>
<td>5.5±2</td>
<td>8±5</td>
<td>21±9</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.4±0.8</td>
<td>3.4±0.7</td>
<td>3±0.6</td>
<td>2.7±0.6</td>
</tr>
<tr>
<td>RV EF (%)</td>
<td>26±13</td>
<td>42±11</td>
<td>40±10</td>
<td>28±10</td>
</tr>
</tbody>
</table>

‡ p=0.001 PAH & CTEPH vs COPD e ILD

Vizza CD, Chest 1998
Pulmonary Hypertension: natural history

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

- **CO**
- **PAP**
- **PVR**

Right heart dysfunction

Time (months to years)
PH: Clinical Picture

Vessels disease
Right ventricular dysfunction
Heart Failure
Differential Diagnosis ...
Diagnostic algorithm

Clinical suspicion
History, Chest XR, ECG

Echo 2D-Doppler
Pulmonary Hypertension

Referral to PH Center

Differential Diagnosis

Chronic Thromboembolic PH

Pulmonary Arterial Hypertension

PH Associated Lung Disease
Pulmonary Hypertension Unit
La Sapienza University of Rome

PH findings
ECHO Doppler

Left Ventricle

Perfusion Scan

Echo Bubble

ASD-VSD

Perfusioan Scan

Segmental Defects

Auto-antibody
Capillaroscopy
HIV
Portal Vein Echo

PAH

Post-Capillary PH

Pulm. Funct Test

Deficit

Mod-severe

HR CT

PH-Lung Dis

Polisonnography

Normal

Mild

OSAS

Left Ventricle

Normal

Abnormal

Hemodynamic Evaluation
Vasodilator challenge

CTEPH

Botallo
1. Pulmonary Arterial Hypertension
   - Idiopathic
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   - Drug and Toxin induced
   - Associated with:
     - Connective Tissue Disease
     - HIV infection
     - Portal hypertension
     - Congenital heart disease
     - Schistosomiasis
   - Persistent PH in the new born
   1^A Veno-occlusive disease

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   - Systolic/Diastolic dysfunction
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4. Chronic Thromboembolic PH

5. PH with multifactorial mechanisms
   Hematologic disorders, Vasculitis, Sarcoidosis, Metabolic disorders (glicogenosisi)
PAH: prevalence

900-3000 patients in Italy

Adapted from Peacock et al. *Eur Respir J.* 2007;30:104-109
PAH incidence

120-450 new cases every year

Adapted from Peacock et al. Eur Respir J. 2007;30:104-109
A progressive and debilitating disease

- **BMPR2**, bone morphogenetic protein receptor, type 2, gene
- **HIV**, human immunodeficiency virus

Therapeutic approach in PAH
PAH: therapy

Until 1995

Medical Treatment
- Anticoagulation
- Diuretics
- Vasodilators

Good clinical response in 10% of patients

Surgery
- Ballon Atrial Septostomy
- Lung Transplantation

1995-2018

- Prostanoids – IP agonists
- ET1 receptor antagonist
- PDE5 inhibitors – sGC Stimulators
Which results with monotherapy?
Short-term Efficacy on 6-min walk distance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control</th>
<th>Active Tx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPH 81 pts</td>
<td>+ 47 m</td>
<td>+ 108 m</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>SSC 111 pts</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Beraprost</td>
<td>+ 25 m</td>
<td>+ 44 m</td>
<td>0.036</td>
</tr>
<tr>
<td>130 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treprostinil</td>
<td>+ 18 m</td>
<td>+ 37 m</td>
<td>0.005</td>
</tr>
<tr>
<td>470 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iloprost</td>
<td>+ 36 m</td>
<td>+ 47 m</td>
<td>0.004</td>
</tr>
<tr>
<td>203 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>+ 44 m</td>
<td>+ 46 m</td>
<td>0.0002</td>
</tr>
<tr>
<td>231 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitaxentan</td>
<td>+ 37 m</td>
<td>+ 46 m</td>
<td>0.001</td>
</tr>
<tr>
<td>178 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>+ 47 m</td>
<td>+ 33 m</td>
<td>0.001</td>
</tr>
<tr>
<td>398 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>+ 46 m</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>278 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>+ 33 m</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>79 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Short-term Efficacy on Pulmonary Vascular Resistance

**Epoprostenol (PPH)** (Scl)

- **Beraprost**: Mean change in PVR (mmHg/L) = -1.6, **P value**: <0.001
- **Treprostinil**: Mean change in PVR (mmHg/L) = -4.7, **P value**: 0.001
- **Iloprost**: Mean change in PVR (mmHg/L) = -4/-1.1, **P value**: 0.01 / ns <0.001
- **Bosentan 30 pts**.
- **Sitaxentan**.
- **Ambrisentan 2g pts**.
- **Sildenafil**.
- **Tadalafil**.
- **Control**.

**Active Tx**

- **Epoprostenol**.
  - Mean change in PVR (mmHg/L) = -4.9, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -5.5, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -1.6, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -4.7, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -4/-1.1, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -5.1, **P value**: 0.01 / ns <0.001
  - Mean change in PVR (mmHg/L) = -3.3, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -2.6, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -1.5, **P value**: <0.001
  - Mean change in PVR (mmHg/L) = -2, **P value**: 0.01
  - Mean change in PVR (mmHg/L) = -3.2, **P value**: 0.001
  - Mean change in PVR (mmHg/L) = -2.6, **P value**: 0.05

**Open trials**

- Tx effect- 4.9 - 5.5
- P value <0.001 < 0.001

**Double-blind trials**

- #
Short-term Efficacy on Cardiac Index

<table>
<thead>
<tr>
<th>Tx</th>
<th>Mean change in Cardiac Index (L/min/m²)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol (PPH)</td>
<td>+0.5 ns</td>
<td>0.01</td>
</tr>
<tr>
<td>Epoprostenol (ScI)</td>
<td>+0.6 ns</td>
<td>0.01</td>
</tr>
<tr>
<td>Beraprost</td>
<td>+0.18 (CO)</td>
<td>0.003</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>+0.2</td>
<td>ns</td>
</tr>
<tr>
<td>Iloprost</td>
<td>+0.75/0.25</td>
<td>0.001</td>
</tr>
<tr>
<td>Bosentan</td>
<td>+1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Sitaxentan</td>
<td>+0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>+0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>+0.23/0.26/0.4</td>
<td>ns/0.03/0.001</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>+0.36</td>
<td></td>
</tr>
</tbody>
</table>
Monotherapy: Reduction in short-term mortality

Mortality Reduction 43% (p=0.023) after 12-16 wks of active treatment
Therapeutic strategies 2009
Kaplan-Meier estimation of survival with combination therapy

First-line bosentan
Addition of sildenafil/iloprost
2002-2004

Historical control group
1999-2001

Expected survival

Treatment group vs historical control group, \( p=0.011 \)
Treatment group vs expected survival, \( p<0.001 \) for all time points

Subjects at risk (n)

<table>
<thead>
<tr>
<th>Months</th>
<th>Treatment group</th>
<th>Historical control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>89</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>69</td>
<td>47</td>
</tr>
<tr>
<td>18</td>
<td>61</td>
<td>38</td>
</tr>
<tr>
<td>24</td>
<td>46</td>
<td>31</td>
</tr>
<tr>
<td>30</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>36</td>
<td>37</td>
<td>20</td>
</tr>
</tbody>
</table>

Progress in PAH Survival

D'Alonzo GE, Ann Intern Med 1991
Thenappan T, Eur Resp J 2010
Humbert M, Eur Respir J 2010
Benza RL, Chest 2012
Upfront combination therapy in PAH (Ambrisentan+Tadalafil)

Treatment algorithm 2015

- Treatment naïve patient
  - PAH confirmed by expert center
    - Acute vasoreactivity test (IPAH/HPAH/DPAH only)
      - Vasoreactive
        - Non-vasoreactive
          - Low or intermediate risk (WHO FC II-III)
            - Initial monotherapy (Table 19)
          - High risk (WHO FC IV)
            - Initial oral combination (Table 20)
            - Initial combination including i.v. PCA (Table 20)
    - Supportive therapy (Table 17)
  - CCB Therapy (Table 18)

- Patient already on treatment
  - Inadequate clinical response (Table 15)
    - Double or triple sequential combination (Table 21)
      - Inadequate clinical response (Table 15)
        - Consider listing for lung transplantation (Table 22)
      - General measures (Table 16)

Galie N et al, Eur Heart J 2015
### Risk strata …..

<table>
<thead>
<tr>
<th>Determinants of prognosis(^a) (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(^b)</td>
<td>Repeated syncope(^c)</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 VO(_2) &gt;15 ml/min/kg (&gt;65% pred.) VE/VCO(_2) slope ≤36</td>
<td>Peak VO(_2) 11–15 ml/min/kg (35–65% pred.) VE/VCO(_2) slope 36–44.9</td>
<td>Peak VO(_2) &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO(_2) ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l NT-proBNP &lt;300 ng/ml</td>
<td>BNP 50–300 ng/l NT-proBNP 300–1400 ng/l</td>
<td>BNP &gt;300 ng/l NT-proBNP &gt;1400 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm(^2) No pericardial effusion</td>
<td>RA area 18–26 cm(^2) No or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm(^2) Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP ≤8 mmHg CI ≥2.5 l/min/m(^2) SvO(_2) &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m(^2) SvO(_2) 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m(^2) SvO(_2) &lt;60%</td>
</tr>
</tbody>
</table>

This table was not validated! Just an Expert Consensus

Galie N et al, Eur Heart J 2015
A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension

David Kylhammar¹*, Barbro Kjellström², Clara Hjalmarsson³, Kjell Jansson⁴, Magnus Nisell⁵, Stefan Söderberg⁶, Gerhard Wikström⁷, and Göran Rådegran¹, on behalf of SveFPH and SPAHR
How was calculated the risk

<table>
<thead>
<tr>
<th>Determinants of prognosis</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO functional class</td>
<td>II, III</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>NT-proBNP levels</td>
<td>&lt;300 ng/L</td>
<td>300-1400 ng/L</td>
<td>&gt;1400 ng/L</td>
</tr>
<tr>
<td>Imaging (echocardiography)</td>
<td>RA area &lt;18 cm²</td>
<td>RA area 18-26 cm²</td>
<td>RA area &gt;26 cm²</td>
</tr>
<tr>
<td>No pericardial effusion</td>
<td></td>
<td>No or minimal pericardial effusion</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt; 8 mmHg</td>
<td>RAP 8-14 mmHg</td>
<td>RAP &gt; 14 mmHg</td>
</tr>
<tr>
<td></td>
<td>CI &gt; 2.5 L/min/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SvO₂ &gt; 65%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Points
1 point 2 points 3 points

Score = 9/5 = 1.8 rounded to 2

Patient
FC II, 6MWT 400 m, Pericardial effusion, CI 2.7 L/min/m², RAP 10 mmHg

Kylhammar D. and Coll. ERJ 2017
Survival per subgroups at entry

Log rank, p<0.001

Number at risk
- "Low risk": 120, 100, 86, 73, 58, 42
- "Intermediate risk": 355, 246, 176, 124, 80, 51
- "High risk": 55, 35, 22, 13, 5, 4
Survival per subgroups at FU evaluation
How aggressive should be the strategy?
Back to pathophysiology ...

- Pulmonary arterial hypertension is characterized by a marked increase in PVR that leads to right ventricular dysfunction.

- The pathophysiology of RV dysfunction is a type of afterload mismatch: RV contractility is increased, but can not meet the increase in afterload.

- The main effect of current PAH therapies is to decrease PVR and, hopefully, improve RV function...
Impact of RV EF and PVR changes after therapy on survival

- Significant PVR reduction in order to obtain RVEF improvement
- In a subgroup RVEF drops despite PVR reduction (myocardial damage)
What impact do current treatments have on PVR?

Effect of treatment on PVR

<table>
<thead>
<tr>
<th>Change in PVR (%)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>Bosentan 1</td>
</tr>
<tr>
<td>-10%</td>
<td>Ambrisentan</td>
</tr>
<tr>
<td>-20%</td>
<td>Macitentan</td>
</tr>
<tr>
<td>-30%</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>-40%</td>
<td>Tadalafil</td>
</tr>
<tr>
<td>-50%</td>
<td>Riociguat</td>
</tr>
<tr>
<td>-60%</td>
<td>Selexipag</td>
</tr>
<tr>
<td>-70%</td>
<td>Iloprost</td>
</tr>
<tr>
<td>-80%</td>
<td>Epoprostenol high dose</td>
</tr>
<tr>
<td>-90%</td>
<td>Treprostinil</td>
</tr>
<tr>
<td>-100%</td>
<td>Prost-Oral</td>
</tr>
<tr>
<td>-110%</td>
<td>Epoprostenol + bosentan</td>
</tr>
<tr>
<td>-120%</td>
<td>Epoprostenol + tadalafil</td>
</tr>
<tr>
<td>-130%</td>
<td>Epoprostenol + sildenafil</td>
</tr>
</tbody>
</table>

Adapted from the references listed below.

Influence of various therapeutic strategies on right ventricular morphology, function and hemodynamics in pulmonary arterial hypertension

Roberto Badagliacca, MD, PhD, Amresh Raina, MD, Stefano Ghio, MD, Michele D’Alto, MD, Marco Confalonieri, MD, Michele Correale, MD, Marco Corda, MD, Giuseppe Paciocco, MD, Carlo Lombardi, MD, Massimiliano Mulè, MD, Roberto Poscia, MD, Laura Scelsi, MD, Paola Argiento, MD, Susanna Sciomer, MD, Raymond L. Benza, MD, and Carmine Dario Vizza, MD
Impact of different therapeutic strategies: RV function
Impact of different therapeutic strategies: risk strata
From pathophysiology to imaging
Reverse Remodelling in IPAH

IPAH NO-responder: mPAP 53mmHg

mPAP 30mmHg
Key points

- PAH is a group of diseases characterized by severe pulmonary vasculopathy with diffuse obstruction of small vessels (mainly arterioles)
- Diagnosis is complex and requires the exclusion of all the most frequent type of pulmonary hypertension
- Until recently the approach was sequential combination therapy in case of lack of efficacy with monotherapy
- With this strategy registries suggest an improved survival (+ 10-15% yearly)
- Up-front combination therapy is emerging as an effective approach
- The use of parenteral prostanoids should not be delayed
1. **Pulmonary Arterial Hypertension**
   - Idiopathic
   - Hereditary (BMPR-II; ALK-1)
   - Drug and Toxin induced
   - Associated with:
     - Connective Tissue Disease
     - HIV infection
     - Portal hypertension
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   - Chronic exposure to high altitude
   - Developmental lung disorders

4. **Chronic Thromboembolic PH**

5. **PH with multifactorial mechanisms**
   - Hematologic disorders, Vasculitis, Sarcoidosis, Metabolic disorders (glicogenosisi)
Pulmonary endoarterectomy (PEA)

- Median sternotomy
- Cardio Pulmonary Bypass
- Deep hypothermia (16-18°C)
- Circulatory arrest (<25 min)
- Reperfusion period (≥10 min)
- Bilateral


A. D’ Armini – Policlinico S. Matteo Pavia
P.A. – 66 yrs M – Jun 2001 – PEA #60

Baseline

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPm</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>CI</td>
<td>1.4</td>
<td>2.2</td>
</tr>
<tr>
<td>PVR</td>
<td>1385</td>
<td>293</td>
</tr>
</tbody>
</table>
Riociguat in CTEPH: study CHEST

Adverse event  1 (0.2%)
Death        4 (0.9%)
Not eligible 165 (37%)
  Withdrawal of consent 15 (3.4%)  

Completed treatment n=261

Adverse event  2 (2.3%)
Death          2 (1.2%)
Lack of efficacy 1 (1.2%)
Non-compliance 1 (0.6%)
Protocol violation 2 (1.2%)
Withdrawal of consent 2 (1.2%)

Completed treatment n=160 (92%)

Randomized and treated n=173

Riociguat individual titration

Adverse event  4 (2.3%)
Death          2 (1.2%)
Lack of efficacy 2 (1.2%)
Non-compliance 1 (0.6%)
Protocol violation 2 (1.2%)
Withdrawal of consent 2 (1.2%)

Completed treatment n=83 (94%)

Placebo n=88

Adverse event  2 (2.3%)
Death          2 (2.3%)
Lack of efficacy 1 (1.1%)

Completed treatment n=83 (94%)

Screened n=446

Not completed n=13 (8%)

1 death during follow-up

Not completed n=5 (6%)

Withdrawal of consent  15
Primary endpoint (6MWD)

Placebo-corrected treatment effect = 46 m (95% CI: 25–67 m; p<0.0001)

- 6MWD, 6-minute walking distance.
- Last visit = last observed value (not including follow-up) for patients who completed the study or withdrew, except imputed worst value (zero) in case of death or clinical worsening without a termination visit or a measurement at that termination visit.

Primary end-point: 6MW distance

Primary endpoint: entire population (n=173/88)

+46 m  
*p<0.0001  
(95% CI: 25–67 m)

Population with persistent/recurrent PH after PEA (n=52/20)

+27 m  
(95% CI: -10–63 m)

Inoperable population (n=121/68)

+54 m  
(95% CI: 29–79 m)

6MWD, 6-minute walking distance; PEA, pulmonary endarterectomy.

Secondary End points

Secondary endpoints
- Pulmonary vascular resistance (PVR) (p<0.0001),
- N-terminal prohormone brain natriuretic peptide (NT-pro BNP) (p<0.0001),
- WHO functional class (FC) (p=0.0026),
- Borg dyspnea score (p=0.0035)

- A trend in Time to clinical worsening (TTCW) (p=0.17)
Balloon Pulmonary Angioplasty
Clinical Case - Angiography

courtesy from I. Lang
Clinical Case - 1st BPA session: right A10
## Clinical case - Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Before BPA</th>
<th>After BPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO FC</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>mPAP – mmHg</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>PVR – WU</td>
<td>5.4</td>
<td>2.3</td>
</tr>
<tr>
<td>6-MWD – m</td>
<td>500</td>
<td>697</td>
</tr>
<tr>
<td>Nt-proBNP – pg/mL</td>
<td>763.1</td>
<td>78.5</td>
</tr>
</tbody>
</table>

*courtesy from I. Lang*
Thank you for your attention!
Conclusion

• PAH and CTEPH are the only PH forms that have an effective medical and surgical therapy
• Negative randomized controlled trial in PH related to left heart disease
• Controversial results of small proof-of-concept trial in PH related to COPD or ILD
PH Unit
La Sapienza, University of Rome
Coordinator Carmine Dario Vizza

PH clinicians (Cardiology ward, CCU, consultation & outpatients management):
- Senior Cardiologists: Dr Vizza, Dr Badagliacca Dr. Poscia
- Fellows: Dr Gambardella, Dr. Pezzuto, Dr Papa,
- In Training: Dr Mezzapesa, Dr Nocioni

Echo Lab
Dr. Sciomer
Dr. Badagliacca

PFTs-CPX Lab
Prof. Palange
Dott. Valli

CT & RNM Lab
Dott. Carbone
Dott. Francone

Right Cath Lab
Dott. Mancone
Dott. Stio

Reumathologists
Prof Valesini
Prof. Riccieri

Liver Transplant Unit
Prof. Rossi
Prof. Corradini

HIV clinic
Prof. Vullo

Pulmonologists
Prof. Parola

Lung Transplant Program
Prof. Venuta

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