Pulmonary hypertension due to left heart diseases

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PH-LHD: From Nice 2013…to Nice 2016

Key questions

• Size of the problem – prevalence and clinical relevance of PH-LHD?

• Haemodynamic definition – which variable for which purpose?

• Therapy for PH-LHD – hello from the other side
PH in left heart diseases: Some characteristics...

• Underlying condition as a trigger to the increase in PAP, through elevated left atrial pressure

• Wide range in prevalence (25 to 100%), as a ‘symptom’ of the underlying disorder (HF with or without preserved EF and valvular heart disease)

• Only a small subset of patients present with **significant pulmonary vascular disease** (< 15%)

• Has an impact on symptoms, including exercise limitations, and outcome (hospitalization and mortality)

• High prevalence of associated comorbidities (SAS, COPD…) also causes of PH

## Prevalence of PH-LHD in the community

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Design</th>
<th>RHC</th>
<th>HF definition</th>
<th>Ejection Fraction (EF)</th>
<th>% estimated PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damy 2010</td>
<td>1380</td>
<td>Consecutive referral to HF clinic</td>
<td>-</td>
<td>Clinical</td>
<td>&gt; 45% in 26%</td>
<td>26% with LVD</td>
</tr>
<tr>
<td>Adhyapak 2010</td>
<td>147</td>
<td>Consecutive echo series</td>
<td>-</td>
<td>Framingham criteria</td>
<td>Mean 39%</td>
<td>100%</td>
</tr>
<tr>
<td>Khush 2009</td>
<td>171</td>
<td>Substudy of ESCAPE trial</td>
<td>Yes</td>
<td>Clinical</td>
<td>Mean 30%</td>
<td>100%</td>
</tr>
<tr>
<td>Kjaergaard 2007</td>
<td>1,022</td>
<td>Substudy of ECHOS study</td>
<td>-</td>
<td>Clinical</td>
<td>&gt; 50% in 24%</td>
<td>38%</td>
</tr>
<tr>
<td>Grigioni 2006</td>
<td>196</td>
<td>Echocardiographic series</td>
<td>Yes</td>
<td>Clinical</td>
<td>Mean 27%</td>
<td>100%</td>
</tr>
<tr>
<td>Ghio 2001</td>
<td>377</td>
<td>Consecutive referral to HF clinic</td>
<td>Yes</td>
<td>Clinical</td>
<td>Only &lt; 35%</td>
<td>100%</td>
</tr>
<tr>
<td>Lam 2009</td>
<td>244</td>
<td>Community HF patients</td>
<td>-</td>
<td>Framingham criteria</td>
<td>Only &gt; 50%</td>
<td>83%</td>
</tr>
<tr>
<td>Shalaby 2008</td>
<td>270</td>
<td>Echocardiographic series</td>
<td>-</td>
<td>Clinical</td>
<td>NA (likely &lt; 35%)</td>
<td>79%</td>
</tr>
</tbody>
</table>

- > 3,000 patients studied, roughly 28% with preserved EF
- ADHF (Khush) to community (Lam) studies ➔ wide range
- Only 3 studies with RHC confirmation

Prevalence of PH (by RHC) in patients with aortic stenosis


17.8% 36.3% 8% 9%
Prevalence of PH-LHD in (single) PH centers

- Chicago: out of 622 patients, 16% of PH in HF pEF
- Vienna: n=3107 first RHC + 800 prospective cases, 34% all HF have PH (13% due to HF pEF)
- Ongoing initiative from the French Society of Cardiology to establish the true prevalence

2. Gerges M et al. Am J Respir Crit Care Med. 2015;192:1234-46
Clinical characteristics from population-based studies of HFpEF

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>244</td>
<td>2167</td>
<td>880</td>
<td>220</td>
<td>10072</td>
<td>26322</td>
<td>37</td>
<td>619</td>
<td>419</td>
<td>132</td>
</tr>
<tr>
<td>Age, y</td>
<td>76</td>
<td>74.4±14.4</td>
<td>75.4±11.5</td>
<td>80</td>
<td>75.6±13.1</td>
<td>73.9±13.2</td>
<td>65±10</td>
<td>71.7±14.1</td>
<td>65±13</td>
<td>72.3</td>
</tr>
<tr>
<td>Women, %</td>
<td>55</td>
<td>55.7</td>
<td>65.7</td>
<td>65</td>
<td>68</td>
<td>62</td>
<td>84</td>
<td>72.5</td>
<td>62</td>
<td>55.3</td>
</tr>
<tr>
<td>Black, %</td>
<td>15</td>
<td>15</td>
<td>17</td>
<td>76</td>
<td>30</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62±6</td>
<td>61±7</td>
<td>62.4</td>
<td>≥45</td>
<td>62±7</td>
<td>≥40</td>
<td>72±11</td>
<td>60</td>
<td>≥50³</td>
<td></td>
</tr>
<tr>
<td>% 1-y survival</td>
<td>71</td>
<td>78</td>
<td>80†</td>
<td>65†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88 (1.5 y)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>96</td>
<td>62.7</td>
<td>55.1</td>
<td>77</td>
<td>77</td>
<td>100</td>
<td>78.2</td>
<td>77</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>CAD, %</td>
<td>53</td>
<td>52.9</td>
<td>35.5</td>
<td>37</td>
<td>32</td>
<td>50</td>
<td>42</td>
<td>43.1</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>37</td>
<td>33.1</td>
<td>31.7</td>
<td>22</td>
<td>41</td>
<td>45</td>
<td>61</td>
<td>45.9</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Chronic kidney disease, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26</td>
<td>9.5</td>
<td>33</td>
<td>9 (end-stage renal disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>41.3</td>
<td>31.8</td>
<td>29</td>
<td>32</td>
<td>21</td>
<td></td>
<td>23.4</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132±23</td>
<td>156</td>
<td>145±24</td>
<td>150±33</td>
<td>153±33</td>
<td>143±25</td>
<td>160±36</td>
<td>125±20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>67±14</td>
<td></td>
<td>76±13</td>
<td>75±19</td>
<td>79±21</td>
<td>69±14</td>
<td>84±20</td>
<td>70±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32±21</td>
<td>30±8</td>
<td>27±5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8±2.1</td>
<td>12.4±2.2</td>
<td>1.2</td>
<td>1.7±1.5</td>
<td>1.4±0.7</td>
<td></td>
<td>11.8±2.2</td>
<td>11.9±1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.6±1.1</td>
<td>1.5±0.9</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Clinical characteristics of patients with PH in HF-pEF

- Single center study HF-pEF (n=45) vs PAH (n=522) vs PH HF-pEF (n=100)

- PH HF-pEF was more frequent in the presence of old age, hypertension, coronary artery disease and female gender

### Distinguishing clinical features between groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HFpEF</th>
<th>PH-HFpEF</th>
<th>PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Older</td>
<td>Older</td>
<td>Younger</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>Frequent</td>
<td>More frequent</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>RA enlargement</strong></td>
<td>Absent</td>
<td>Less frequent</td>
<td>More frequent</td>
</tr>
<tr>
<td><strong>LA enlargement</strong></td>
<td>Frequent</td>
<td>Frequent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Systolic aortic pressure</strong></td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normak</td>
</tr>
<tr>
<td><strong>RAP</strong></td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>CO</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>PVR</strong></td>
<td>Normal</td>
<td>↑</td>
<td>↑↑(↑↑)</td>
</tr>
</tbody>
</table>

Interim conclusion 1

• The true prevalence of PH in LHD is by large unknown, but likely high (>50%)

• PH-LHD is heterogeneous (population studied, definition of PH) and few studies report PH established by RHC.

• Patients with HF pEF and PH HF pEF have a similar profile, consistently different with PAH, although profiles may overlap.

• Differentiating PAH, PAH with comorbidities and from PH due to HF with preserved EF is challenging.

• PH complicating HF-pEF should be studied as a separate entity
PH-LHD: From Nice 2013…to Nice 2016
Key questions

• Size of the problem – prevalence and clinical relevance of PH-LHD?

• Haemodynamic definition – which variable for which purpose?

• Therapy for PH-LHD – hello from the other side
Haemodynamic definitions of pulmonary hypertension

Debate and controversy on which variable would be best
1. As a marker of pulmonary vascular disease and
2. To predict outcome

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥25 mmHg</td>
<td>All</td>
</tr>
</tbody>
</table>

Post-capillary PH
- Isolated post-capillary PH (lpc-PH)
- Combined post-capillary and pre-capillary PH (Cpc-PH)

|                              | PAPm ≥25 mmHg   | PAPm ≥25 mmHg   | 2. PH due to left heart disease
|                              | PAWP >15 mmHg  | DPG <7 mmHg and/or PVR ≤3 WUc |
|                              |                 | DPG ≥7 mmHg and/or PVR ≥3 WUc | 5. PH with unclear and/or multifactorial mechanisms |

How to define ‘out-of-proportion’ PH in LHD?

• Move towards a unified terminology for PH-LHD

• Define « pulmonary vascular disease » in LHD, i.e. the precapillary component, by an easily measurable HD criteria (similar to the definition of PH, based on mPAP)

• Candidates identified (alone or in combination?)

  1. Pulmonary vascular resistance
  2. Transpulmonary gradient (PAPm – PAWP)
  3. Diastolic pulmonary gradient (PAPd – PAWP)

  4. Compliance (SV/PP) ?

**Histology of PH-LHD**

<table>
<thead>
<tr>
<th>Vessel morphology (semi quantitative)</th>
<th>iPAH (n=10)</th>
<th>IpcPH (n=9)</th>
<th>CpcPH (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial hypertrophy</td>
<td>63 %</td>
<td>35 %</td>
<td>84 %</td>
</tr>
<tr>
<td>Intimal fibrosis</td>
<td>60 %</td>
<td>14 %</td>
<td>68 %</td>
</tr>
<tr>
<td>Adventitial fibrosis</td>
<td>64 %</td>
<td>13 %</td>
<td>25 %</td>
</tr>
<tr>
<td>Occluded</td>
<td>44 %</td>
<td>7 %</td>
<td>26 %</td>
</tr>
<tr>
<td>Plexiform lesions (%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

CPET: ventilatory efficiency in CpcPh in between PAH and IpcPH

![Graph showing ventilatory efficiency comparison between PAH, CpcPh, and IpcPh](image)

Caravita S et al. J Heart Lung Transplantation (under review)
Pulmonary hypertension in heart failure: epidemiology, right ventricular function and survival

- N=3107 stable patients with first diagnostic RHC + n=800 prospective
- 34% HF (21% HF-rEF and 13% HF-pEF)
- Cpc-PH in 14% (HF-rEF) and 12% (HF-pEF)

HF systolic dysfunction

HF diastolic dysfunction

Gerges M et al. Am J Respir Crit Care Med. 2015;192:1234-46
Retrospective analysis of outcome in 600 patients with aortic stenosis

Controversial issues: an abnormal DPG does not consistently predict outcome in PH-LHD

- No role in the UNOS database\(^1\) (22.6% had TPG > 12 mmHg) and a cardiomyopathy registry\(^2\) (37.9% had PH)
- Predictive in a large PH center\(^3\) (36% had TPG > 12 mmHg, 16% had a DPG ≥ 7 mmHg) and a valvular heart disease registry\(^4\)
- A PVR > 3 WU appears to be a better prognosis indicator than TPG in HF rEF
- Most studies focused on HF rEF \(^1,2,5\)
- A PVR > 3 WU appears to have prognostic value over TPG\(^2\)

- A marker of disease is not necessarily a prognostic indicator
- If a consistent definition is considered (DPG > 7 mmHg), ± 13% of patients with HF do have CpcPH\(^2,3,6\)
- Significant technical and methodological issues may explain why DPG may not always reflect prognosis

Forest plot predictors of mortality: role of severe PH

Vienna database revisited according to the new classification

<table>
<thead>
<tr>
<th>Patients with pulmonary hypertension (PH) due to left heart disease (n=1506, mean pulmonary artery pressure ≥25 mmHg, and mean pulmonary artery wedge pressure &gt;15 mmHg) stratified by diastolic pulmonary vascular pressure gradient (DPG) and pulmonary vascular resistance (PVR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TABLE 1</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>PVR ≤3 WU n (%)</strong></td>
</tr>
<tr>
<td><strong>PVR &gt;3 WU n (%)</strong></td>
</tr>
</tbody>
</table>

- **IpCpPH (DPG < 7 mmHg and/or PVR ≤ 3 WU)** = 57 %
- **CpcPH (DPG > 7 mmHg and/or PVR > 3 WU)** = 14.3 %
- **Other (unclassifiable) combination** = 28.7 %

Proposal: CpcPH could be defined by **DPG ≥ 7mmHg AND PVR > 3 WU**

Pros and cons in the choice of the determinant of „PVD“ in HF pEF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TPG</th>
<th>DPG</th>
<th>PVR</th>
<th>Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological rationale</td>
<td>-(+)</td>
<td>+++</td>
<td>+++</td>
<td>+(+)</td>
</tr>
<tr>
<td>Independance from flow and filling pressure</td>
<td>-</td>
<td>+</td>
<td>-(+)</td>
<td>-</td>
</tr>
<tr>
<td>Marker of disease</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Marker of prognosis</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>« Historical » variable</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Level of Comfort for clinical use</td>
<td>++</td>
<td>++(+)</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Level of controversy</td>
<td>++</td>
<td>++++</td>
<td>++</td>
<td>?</td>
</tr>
</tbody>
</table>

Level of controversy is proportionate to the strength of the physiological rationale and inversely correlated with history…

Vachiéry JL. Personal (strong) opinion, unpublished
PH-LHD: looking for different phenotypes, haemodynamic and clinical

"Left Ventricular Phenotype"

Right Ventricle "normal"  Left Ventricular Dysfunction

"Right Ventricular Phenotype"

Severe Right Ventricular Dysfunction  Left Ventricular Dysfunction

Spectrum of Right Ventricular Dysfunction and Presentation

Lower  Mortality  Higher

Treat myocardial / valve disease  Treatment  Clinical Trials & Registries

Post or Pre-capillary Pulmonary Hypertension  Resting Haemodynamics  Post or Pre-capillary Pulmonary Hypertension

The distinction between passive and active changes in the pulmonary circulation makes physiological and clinical sense.

The current terminology is appropriate to identify a distinct haemodynamic phenotype, to underscore the incremental role of PH on outcome.

However, the current controversies on outcome prediction should encourage the use of a combination of variables (i.e. DPG and PVR).

In addition, prognosis is highly likely linked to the degree of RV dysfunction and other factors independent from the degree of pulmonary vascular involvement. A clinical phenotype could complement HD characterization.
PH-LHD: From Nice 2013…to Nice 2016

Key questions

- Size of the problem – prevalence and clinical relevance of PH-LHD?

- Haemodynamic definition – which variable for which purpose?

- Therapy for PH-LHD – hello from the other side
Recommendations for treatment of patients with HF-pEF and HF-mrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>it is recommended to screen patients with HFPeF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in congested patients with HFPeF or HFmrEF in order to alleviate symptoms and signs.</td>
<td>I</td>
<td>B</td>
<td>178, 179</td>
</tr>
</tbody>
</table>

Why should we treat PH, a complication of an underlying condition with no evidence for therapy?

### Completed RCTs targeting the PDE5i/NO pathway in PH-LHD

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HF with reduced EF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Riociguat | 201   | 16 weeks       | Change in mPAP vs placebo              | AEs, PK, PVR, NT-proBNP               | • No change in mPAP  
• Decrease in PVR (CO)                                                |
| LEPHT    |       |                |                                       |                                       |                                                                         |
| Tadalafil| 2102  | Event-driven   | Time to CV death or 1st HF hospitalisation | Biomarkers, exercise, QoL          | • Study terminated in Feb 2014 (funding source)                           |
| PITCH2   | (23)  |                |                                       |                                       |                                                                         |
| (NCT01910389) |      |                |                                       |                                       |                                                                         |
| **HF with preserved EF**                                                                                                                                  |
| Riociguat| 48    | Acute (6 hours)| Change in mPAP vs placebo              | AEs, PK, PVR, NT-proBNP               | • No change in mPAP                                    |
| DILATE   |       |                |                                       |                                       |                                                                         |
| Sildenafil| 52    | 12 weeks       | Change in mPAP vs placebo              | AEs,, PVR, BNP, Peak VO₂              | • No change in mPAP  
• No change 2ary EP                                                   |
| Hoendermis |       |                |                                       |                                       |                                                                         |

- None of the above-mentionned studies met the primary endpoint
- < 300 patients included vs > 3,000 in recent RCTs in PAH

## Comparing the studies: Heterogeneity of patient demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LePHT Study (n = 201)</th>
<th>DILATE-1 Study (n = 36)</th>
<th>Dutch Study (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>86</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>58.1</td>
<td>71.0</td>
<td>74.0</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>27.8*</td>
<td>62.1</td>
<td>58.0</td>
</tr>
<tr>
<td>Atrial fibrillation at baseline, %</td>
<td>12.5*</td>
<td>44.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Origin of heart failure, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>45</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-ischaemic cardiomyopathy</td>
<td>54</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Data missing</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median NT-proBNP</td>
<td>-</td>
<td>1152.25 pg/L*</td>
<td>1087 ng/L</td>
</tr>
<tr>
<td>Mean 6MWD, m</td>
<td>395.4*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Calculated by taking the means of all treatment group mean values including placebo.

Comparing the studies: **RHC characteristics are typical of IpcPH**

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>LePHT Study(^1) ((n = 160)†)</th>
<th>DILATE-1 Study(^2) ((n = 36) )</th>
<th>Dutch Study(^3) ((n = 52) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP, mmHg</td>
<td>37.9</td>
<td>33.3</td>
<td>35.0</td>
</tr>
<tr>
<td>Mean PAWP, mmHg</td>
<td>23.9</td>
<td>20.2</td>
<td>20.4</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>9.6</td>
<td>11.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>-</td>
<td>4.8</td>
<td>5.4</td>
</tr>
<tr>
<td>Cardiac index, L/min/m(^2)</td>
<td>2.3</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>PVR, dynes/s/cm(^5)</td>
<td>273.6</td>
<td>243</td>
<td>205</td>
</tr>
<tr>
<td>TPG, mmHg</td>
<td>14.0</td>
<td>13.1</td>
<td>13</td>
</tr>
<tr>
<td>DPG, mmHg</td>
<td>-</td>
<td>2.0**</td>
<td>1</td>
</tr>
</tbody>
</table>

*Calculated by taking the mean or median of all treatment groups.
**Post-hoc analysis.
†Per-Protocol population.

# Ongoing RCTs in PH-LHD

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Start</th>
<th>End</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HF with reduced EF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>210</td>
<td>9/2012</td>
<td>6/2014</td>
<td>24 weeks</td>
<td>Patient Global Assessment and 6MWD</td>
<td>QoL, Kansas city questionnaire, AEs</td>
</tr>
<tr>
<td>Sil-HF (^1,(^2) (NCT01616381)</td>
<td></td>
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</tr>
<tr>
<td><strong>HF with EF &gt; 35%</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Macitentan</td>
<td>60</td>
<td></td>
<td></td>
<td>12 weeks</td>
<td>Safety and tolerability (fluid retention)</td>
<td>PVR, haemodynamics, changes in TPG and DPG, echo (RV function)</td>
</tr>
<tr>
<td>MELODY-1 (^2) (NCT02070991)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>HF with EF &gt; 50%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Riociguat</td>
<td>114</td>
<td>5/2015</td>
<td></td>
<td>26 weeks</td>
<td>Change in CO by RHC</td>
<td>PVR, haemodynamics, changes in TPG and DPG, echo (RV function)</td>
</tr>
<tr>
<td>DYNAMIC (^3) (NCT02744339)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Conclusions

- A small proportion of patients with PH-LHD present significant pulmonary vascular disease and a RV “phenotype”. The latter should be defined in complement of the haemodynamic characterization.

- The definition of CpcPH may be refined by the combination of DPG and PVR, pending validation in multicenter registries.

- Therapy should aim at treating the underlying condition and control confounding factors (OSAS, PE, COPD…).

- There is still no convincing evidence supporting the use of any PAH therapies in PH-LHD.
« The times they are a-changing »

1. Bob Dylan 1964
2. Bob Dylan 1063
3. Literature Nobel Price 2016

« The answer, my friend, is blowing in the wind »