State-of-the-Art Management of Pulmonary Hypertension
Monitoring and Approach of the Three Main Etiopathogenesis
L-Sided Failure, Pulmonary Arterial Hypertension, Thromboembolic

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Co-Director of the Clinical Trials Unit
Inova Heart and Vascular Institute
Professor of Medicine
VCU School of Medicine
PA, pulmonary artery; WHO, World Health Organization.
Group 1: Pulmonary Arterial Hypertension
Timeline of medical therapies in PAH

My PH timeline


- No Rx
- \(O_2\)
- diuretics
- digoxin
- Epoprostenol
- Epoprostenol
- CCBs
- Epoprostenol
- CCBs
- Bosentan
- Treprostinil
- Sildenafil
- Ambrisentan
- Tadalafil
- Iloprost
- Macitentan
- Riociguat
- Selexipag
Improvements on Monotherapy Do Not Restore Normal PAP:
PAH Patient who lived 20 yrs on epoprostenol

ESC/ERS 2015: Evidence-based Treatment Algorithm for PAH Patients (Group 1 Patients)

Treatment-Naïve Patient
- CCB Therapy

Patient Already On Treatment
- Acute Vasoreactivity Test (IPAH/hPAH/DPAH Only)
  - Vasoreactive
    - PAH Confirmed by Expert Center
      - General Measures
      - Supportive Therapy
  - Non-Vasoreactive
    - Low or Intermediate Risk (WHO FC II-III)
      - Initial Monotherapy
    - High Risk (WHO FC IV)
      - Initial Combination Including IV PCA
        - Consider Referral For Lung Transplantation

Inadequate Clinical Response
- Double or Triple Combination
  - Inadequate Clinical Response
    - Consider Listing for Lung Transplantation

Courtesy of Dr I Preston
Initial Combination is better than monotherapy

- **Aimed to answer the question:**
  - Is initial treatment with combination therapy superior to initial treatment with monotherapy?

- **Novel clinical endpoint: Time to Clinical Failure:**
  - TTCF= death, hospitalization for worsening PAH or disease progression, or unsatisfactory clinical response at 6 months (drop 6mwd from BL, remained FC III)

**Combination vs pooled monotherapy**

- Combination decreased clinical failure event rate vs. monotherapy by 50% \((p=0.00002)\)

**Secondary endpoints ALL in favor of combination:**
- \(\Delta NT\)-proBNP
- % achieving satisfactory clinical response,
- 6MWD

95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.

Upfront triple therapy in sick patients
“Hit them hard and early”: Phase 3 study enrolling

- Small cohort all given aggressive therapy
- Class III/IV, CI<2.0 L/min/m², +/- or mRAP>20 mmHg, +/- or PVR≥12.5 Units
- No CTD, HIV, CHD, portal HTN
- Epo 1ng/kg/min q12h up to 10ng/kg/min + bosentan 62.5mg bid + sildenafil 20 mg tid day 5
- Max Epo 16ng/kg/min, bosentan 125mg bid, sildenafil 20 mg tid

Sitbon O. *Eur Respir J* 2014; 43: 1691-1697/
Combination Therapy: The answer or the question?

Are all combinations the same? Is it a class effect?

The ideal combination of agents is still unknown

- It is unclear if there are “class” effects
- More drugs available = more uncertainty
- Costs/expenditures; third-party hurdles, approvals, country specific regulations
- More questions than answers

McLaughlin V. Eur Respir J 2015;46: 405-13
New treatment Approaches and Endpoints: Event Driven Trials

<table>
<thead>
<tr>
<th>Drug tested</th>
<th>Study</th>
<th>Background</th>
<th>Primary endpoint</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan</td>
<td>SERAPHIN</td>
<td>None, PDE5i or inhaled iloprost</td>
<td>Morbidity and mortality</td>
<td>742</td>
</tr>
<tr>
<td>Selexipag</td>
<td>GRIPHON</td>
<td>1 or 2 background therapies not PG</td>
<td>Morbidity and mortality</td>
<td>1156</td>
</tr>
</tbody>
</table>

95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.

ERS 2015: Evidence-based Treatment Algorithm for PAH Patients (Group 1 Patients)

- **Treatment-Naïve Patient**
  - CCB Therapy
  - **PAH Confirmed by Expert Center**
    - Acute Vasoreactivity Test (IPAH/hPAH/DPAH Only)
      - **Vasoreactive**
      - **Non-Vasoreactive**
        - Low or Intermediate Risk (WHO FC II-III)
        - High Risk (WHO FC IV)
          - Initial Oral Combination
            - Inadequate Clinical Response
              - Double or Triple Combination
                - Inadequate Clinical Response
                  - Consider Listing for Lung Transplantation
              - Initial Combination Including IV PCA
                - Consider Referral for Lung Transplantation
          - Supportive Therapy
        - General Measures
      - **Initial Monotherapy**
        - Inadequate Clinical Response
          - Double or Triple Combination
            - Inadequate Clinical Response
              - Consider Listing for Lung Transplantation
      - **Non-Vasoreactive**
        - Supportive Therapy
      - **Low or Intermediate Risk (WHO FC II-III)**
        - Initial Oral Combination
          - Inadequate Clinical Response
            - Double or Triple Combination
              - Inadequate Clinical Response
                - Consider Listing for Lung Transplantation
        - **Initial Combination Including IV PCA**
          - Consider Referral for Lung Transplantation

Patient on therapy presents to clinic on Friday 4PM

HELP!
NO NO NO!!!!!!
LET’S RETHINK THIS.........
Goal-Oriented Therapeutic approach is not new in 2017


- We want the best results for each patient to translate to better:
  - QoL physical
  - QoL emotional
  - Survival

<table>
<thead>
<tr>
<th>Subjects at Risk (n)</th>
<th>Treatment Group</th>
<th>Historic Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89   83   69   61   46   43</td>
<td>67   64   47   38   31   23</td>
</tr>
<tr>
<td>6  12  18  24  30  36</td>
<td>37</td>
<td>20</td>
</tr>
</tbody>
</table>

Treatment Group vs Historic Control Group, p=0.011
Treatment Group vs Expected Survival, p<0.001 for all time points
Risk assessment is a composite

<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 &lt;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) slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l NT-proBNP &lt;300 ng/l</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 &lt;8 mmHg CI ≥2.5 l/min/m(^2) Sv(_O_2) &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m(^2) Sv(_O_2) 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m(^2) Sv(_O_2) &lt;60%</td>
</tr>
</tbody>
</table>

Multiple risk assessment tools:

**CUBE**

- Modifiable prognostic variables
  - Low (<50%)
  - Intermediate (5-10%)
  - High (>10%)

- Symptoms/functional class
- Exercise capacity
- Right ventricular function

**Initial Risk Assessment**

- Contributions
- Treatment burden

**Initial Treatment Response**

- Clinical worsening & disease progression

**Clinical decision making**

- Younger
  - No/few comorbidities
  - Low treatment burden

- Older
  - More comorbidities
  - High treatment burden

**PAH RISK SCORE**

- WHO Group 1 Subgroup
- Demographics & comorbidities
- NYHA/WHO functional class
- Vital signs
- 6-Minute Walk Test
- N-terminal pro-B-type natriuretic peptide (NT-proBNP)
- Echocardiogram
  - Pulmonary function test
  - Right heart cath <1 yr

**SUM OF ABOVE**

- +6

**RISK SCORE**

**CUBE** vs. **CALCULATOR**

New Targets:
Target signaling linked to genetic mutations

- **FK506- tacrolimus**
  - BMPR2 mutations associated with heritable PAH known nearly 20 years
  - Powerful modulator of the immune system enhances BMPR2 activity in animal PAH models improving PAH
  - Small case series- 3 patients, low dose FK506
  - 16 week trial, mixed PAH population, short (16 weeks), not at high dosing, BMPR2 mRNA expression attenuated but not related to clinical “responders”.
  - Still potential target, needs well-designed proof of concept clinical study

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Group 2 PH: Histopathology & Definitions of PH-LHD

- Medial hyperterophy and intimal/adventitial proliferation small PA

- Medial hyperterophy and intimal/adventitial proliferation small PV

- Re-canalized fibrotic thrombus in arterioles

**Diastolic Pulmonary Gradient: PAPd-PAWP**

- Normal value: 1 – 2 mmHg
- Abnormal level: > 5 mmHg
- Prognostic marker: ≥ 7 mmHg
- Pre-capillary PH: > 10 mmHg

**Terminology**

<table>
<thead>
<tr>
<th>PH Type</th>
<th>PAWP</th>
<th>DPG PAPd-PAWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated post capillary PH</td>
<td>&gt; 15 mmHg</td>
<td>&lt; 7 mmHg</td>
</tr>
<tr>
<td>Combined post capillary &amp; pre-capillary PH</td>
<td>&gt; 15 mmHg Normalized</td>
<td>≥ 7 mmHg</td>
</tr>
</tbody>
</table>

Group 2 PH: Phenotypes using DPG

Naeije R. Circ Heart Fail 2017; Sep; Gorges M. Am J Respir Crit Care Med. 2015;192:1234-1246 (survival derived from)
Sildenafil for Improving Outcomes after Valvular Correction (SIOVAC) Trial 200 patients

Corrected Valvular Heart Disease > 1 yr; RHC < 1 mo mPAP ≥ 30 mmHg/ echo PASP > 50 mmHg and cath = mPAP ≥ 30 mmHg

- **Sildenafil should NOT be given to these patients**

Clinical Outcome

HF Hospitalizations

OR = 0.43 (0.20-0.94); P = 0.035

Bermejo, J on behalf of SIOVAC investigators; ESC 2017, Milan, Italy.
## Current Recommendations for PHTN-LHD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease).</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>It is recommended to identify other causes of PH (i.e. COPD, SAS, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>It is recommended to perform invasive assessment of PH in patients on optimized volume status.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH center for a complete diagnostic work-up and an individual treatment decision.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>The use of PAH approved therapies is not recommended in PH-LHD.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

*Eur Heart J, 2015*
*Eur Respir J, 2015*
Novel studies of PAH therapies in PH-HFpEF

Southpaw Study:
Oral Treprostinil in Subjects with pulmonary hypertension and HFpEF

Adaptive Study Design:
- Interim safety reviews at N=10, 30, 60, 100, + 200 pts
- Start with low dose with increased max dose following each review
- Initiate trial at select centers to allow for highest likelihood of success

Target RV:
- Echo: RV dysfunction
- LVEF<50%
- PVR<4U (TD)
- PCWP>15 but <30 mmHg
- mPAP>25 mmHg
- 6MWD>200 m

Primary endpoint: placebo-corrected change in 6MWD at week 24

Key Secondary endpoints:
- N-terminal pro-BNP
- QoL
- Clinical worsening
- Safety

N=314
Randomize 1:1
24-week treatment period
75 PH clinical sites

Serenade Study:
Oral Macitentan in Subjects HFpEF and pulmonary vascular disease

Multicenter Phase 2b
- Stratified by NTproBNP <1000 and ≥1000 pg/ml
- Screening up to 30 days
- Single blind placebo run-in 4 weeks followed by single blind macitentan run-in

Targeting RV
- Cath within 6 mo, Echo: (1) LAV, LAVI, LA area, LA diameter, LV septal thickness, NTproBNP/BNP ≥ 250/75 pg/ml in NSR, or ≥ 1000/300 pg/ml in AF
- RV disease: (1), DPG>5mmHg, PVR<3U, mPAP<40mmHg, peak TR>2.8 m/s/TAPSE<17, RVFAC<35% RV tissue doppler s' <9.5 cm/s

N=300
Randomize 1:1
24-week treatment period
100 clinical sites
15 countries

Primary endpoint: reduces NTproBNP vs. placebo

Key Secondary endpoints:
- Daily physical activity
- QoL
- Worsening of HF
Goal/Premise: Monitoring catches change early

Continuous Physiologic Monitoring Designed to Detect Early Decompensated HF

Slide adapted from Dr. RL. Benza
Monitoring in PH-LHD: So what? Why?

**Individual Benefit:**
- Monitoring may detect early decompensation ✔
- Monitoring may help personalize response to therapy ✔

**Society Benefit:**
- Monitoring can increase access to care ✔
- Monitoring might decrease
  - MD visit ✔
  - hospitalizations ✔
- and overall medical cost ✔✔
**PH Cohort in CHAMPION:**

**HF Hospitalization Rates Improved with Monitoring (Treatment vs. Control)**

<table>
<thead>
<tr>
<th>HF hosp rates</th>
<th>Treatment</th>
<th>Control</th>
<th>RRR</th>
<th>Andersen-Gill model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HF hosp</td>
<td>HF hosp rate (annualized)</td>
<td>n</td>
</tr>
<tr>
<td>Mean PAP &gt; 25 mm Hg</td>
<td>151</td>
<td>113</td>
<td>0.60</td>
<td>163</td>
</tr>
<tr>
<td>PVR ≥ 3</td>
<td>75</td>
<td>63</td>
<td><strong>0.74</strong></td>
<td>76</td>
</tr>
<tr>
<td>PVR &lt; 3</td>
<td>76</td>
<td>50</td>
<td>0.48</td>
<td>87</td>
</tr>
<tr>
<td>Transpulmonary gradient &gt; 15</td>
<td>56</td>
<td>49</td>
<td><strong>0.69</strong></td>
<td>45</td>
</tr>
<tr>
<td>Transpulmonary gradient ≤ 15</td>
<td>95</td>
<td>64</td>
<td>0.54</td>
<td>118</td>
</tr>
</tbody>
</table>
Cardiomems: General use trends are better than trial cohort with greater drop in mPAP

Analysis of first **2000 patients** in US implanted with cardiomems - de-identified data from Merlin.net remote monitoring with 6 mo f/u:

- **PA trends compared with historic CHAMPION trial**
  - General use patients **higher mPAP** vs CHAMPION pts (active + control groups): 34.9 ± 10.2 mmHg

- Pressure information transmitted with a median 1.27 days between transmissions

- **Monitoring lowered PAP over time more than CHAMPION**

- **PAP dropped most in patients with higher mPAP; similar HFrEF-PH and HFpEF-PH**
CTEPH Pathophysiology: Known as Dual Vascular Disease

Group 4: Chronic Thromboembolic Pulmonary Hypertension

OCCLUDED

Organized thromboemboli

Changes are similar to those seen in PAH

Angiogram and PEA specimen images are speaker's own.
Group 4 PH: Chronic thromboembolic disease
Long-term outcome from International Registry

- 27 centers: operated vs non-operated CTEPH patients
- 629 patients prospectively enrolled over 24 months: Operated > survival
- Bridging with PAH therapy increased risk of death in operated patients; PAH therapy given to sicker patients in non-operated group, unclear benefit
- IVC filter did not improve mortality

Delcroix M. *Circulation* 2016;133:859-71.
Group 4 PH: Chronic thromboembolic disease
Long-term outcome From UK National Cohort

- 880 patients prospectively enrolled: RHC and non-invasive tests 3-6, +12 months after OR (1997-2012)
- Higher center experience = higher overall survival
- Worse mPAP ≥ 38 mmHg
- 51% mPAP > 25 mmHg at 3-6 mo. Irrespective of immediate post-op HD

Cannon JE. Circulation 2016;133:1761-1771.
MERIT-1: Macitentan in CTEPH Phase 2

Balloon pulmonary angioplasty (BPA) for CTEPH

Balloon Pulmonary Angioplasty for Treatment of Chronic Thromboembolic Pulmonary Hypertension

Jeffrey A. Feinstein, MD, MPH; Samuel Z. Goldhaber, MD; James E. Lock, MD; Susan M. Fernandez, PA-C; Michael J. Landzberg, MD

Background—Although pulmonary thromboendarterectomy is the gold standard for the treatment of CTEPH, balloon pulmonary angioplasty (BPA) is an alternative to surgery for selected patients. We report our experience with BPA as a strategy of pulmonary angioplasty (BPA).

Methods and Results—Eighteen patients (mean age, 51.8 years; range, 14 to 75 years) with CTEPH underwent BPA; they averaged 2.6 procedures (range, 1 to 5) and 6 dilations (range, 1 to 12). Selection of pulmonary artery segments for dilation required (1) complete occlusion, (2) filling defects, or (3) signs of intravascular webs. After an average of 36 months of follow-up (range, 0.5 to 60 months), the average New York Heart Association class improved from 3.3 to 1.8 (P<0.001), and 6-minute walking distances increased from 209 to 497 yards (P<0.001). Pulmonary artery mean pressures decreased from 43.0 to 18.8 mm Hg (P<0.001). One patient developed pulmonary edema; 3 required mechanical ventilation, and 2 required hospitalization for good medical therapy.

Conclusions—BPA reduces pulmonary hypertension and improves functional capacity. Significant improvement in New York Heart Association class and 6-minute walking distances. BPA is a promising interventional technique that warrants randomized comparison with medical therapy in CTEPH patients who are not surgical candidates. (Circulation. 2001;103:10-13.)

Key Words: balloon angioplasty • embolism • thrombus • pulmonary heart disease

Baseline  Follow-up

6WMD  209 =>497 yards

Reperfusion edema, n=11
(Mechanical ventilation, n=3)

BPA German Experience

- 56 pts 266 BPA (median 5/pt), cath baseline and 24 weeks post BPA
- BPA improved 6mwd (+33m) RV function, hemodynamics (mPAP 18%, PVR 26%)
- Most common complication: pulmonary vascular injury & pulmonary bleeding- why?
- Undersize balloon, longer prevalence disease

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Total</th>
<th>Hannover</th>
<th>Bad Nauheim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>266</td>
<td>155</td>
<td>111</td>
</tr>
<tr>
<td>Pulmonary arterial dissection without bleeding</td>
<td>2 (0.8)</td>
<td>1 (0.6)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Vascular lesions with pulmonary bleeding but without haemoptysis</td>
<td>3 (1.1)</td>
<td>1 (0.6)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Vascular lesions with haemoptysis</td>
<td>15 (5.6)</td>
<td>5 (3.2)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Reperfusion oedema</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (1.1)</td>
<td>2 (1.3)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Total</td>
<td>25 (9.4)</td>
<td>9 (5.8)</td>
<td>16 (14.4)</td>
</tr>
</tbody>
</table>

Data are presented as n (%), unless otherwise stated. #: others were groyne haematoma (n=1), peripheral arteriovenous fistula (n=1), induction of atrial fibrillation, self-limiting (n=1); †: one event was fatal, see text for details; ‡: both patients recovered after noninvasive ventilation.


FIGURE 1 a) Digital subtraction angiography of the middle lobe arteries in a 63-year-old man with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) showing a pulmonary artery dissection (arrow) after manipulation with the guiding catheter. b) Digital subtraction angiography of the right upper lobe arteries in a 72-year-old woman with inoperable CTEPH showing pulmonary haemorrhage (arrow) after guidewire perforation.
**In summary:**

- **Group 1 PAH:** New treatments, approaches, and risk assessment

- **Group 2 PH-LHD:** Better phenotyping, monitoring and targeted treatment trials

- **Group IV CTEPH:** Improved understanding of the epidemiology, surgical, medical, and interventional care