New Evidence for Upfront Combination Therapy in Pulmonary Arterial Hypertension

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Pulmonary Hypertension Service
Royal Prince Alfred Hospital
Speaker Disclosure

• In accordance with the policy of the Thoracic Society of Australia and New Zealand the following presenter has indicated that they have a relationship which in the context of their presentation, could be perceived as a real or apparent conflict of interest but do not consider that it will influence their presentation. The nature of the conflict is listed:

• Actelion Pharmaceuticals – speaker fees and travel support
• Menarini Pharmaceuticals – speaker fees
Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.3 Drugs and Toxins
   1.4 Associated with:
      - Connective tissue diseases
      - HIV infection
      - Portal hypertension
      - Congenital Heart Diseases
      - Schistosomiasis

1’. Pulmonary veno-occlusive disease

1”. Persistent pulmonary hypertension of newborn

2. PH due to left heart disease
   2.1 Left heart systolic dysfunction
   2.2 Left heart diastolic dysfunction
   2.3 Valvular heart disease
   2.4 Congenital/acquired left heart disease

3. PH due to lung disease and/or hypoxia
   3.1 COPD
   3.2 Interstitial lung disease
   3.3 Other disease with mixed restriction/obstruction
   3.4 Sleep disordered breathing
   3.5 Alveolar hypoventilation syndrome
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung disease

4. Chronic thromboembolic disease

5. PH with unclear/multifactorial mechanisms
   5.1 Haematological disorders: sickle cell,
   5.2 Sarcoïd, histiocytosis, LAM
   5.3 Metabolic disorders
   5.4 Others: tumours, mediastinal fibrosis, renal failure

Simonneau et al. JACC 2013
Group 1 Pulmonary Arterial Hypertension (PAH)

1. Pulmonary arterial hypertension (PAH)
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.3 Drugs and Toxins
   1.4 Associated with:
       - Connective tissue diseases
       - HIV infection
       - Portal hypertension
       - Congenital Heart Diseases
       - Schistosomiasis

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   3.5 Alveolar hypoventilation syndrome
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung disease
Pathogenesis of PAH – 3 Key Pathways

**Endothelin pathway**
- Pro-endothelin-1
  - ET-1
  - ET<sub>A</sub>, ET<sub>B</sub>
- Selective ERA
  - Ambrisentan
- Dual ERA
  - Bosentan
  - Macitentan

**(Vasoconstriction & proliferation)**

**Nitric oxide pathway**
- L-arginine
  - NO
- sGC stimulator
- PDE-5 inhibitors
- Sildenafil
- Tadalafil
- Riociguat
- cGMP

**(Vasodilation & anti-proliferation)**

**Prostacyclin pathway**
- Arachidonic acid
  - PGI<sub>2</sub>
- Non-prostanoid IP receptor agonist
  - Selexipag
- PGI<sub>2</sub> analogues
  - Epoprostenol
  - Treprostinil
  - Iloprost

**(Vasodilation & anti-proliferation)**

*Adapted from Humbert et al. Circulation 2014*
### Increasing Use of Combination Therapy

<table>
<thead>
<tr>
<th>Registry</th>
<th>Period</th>
<th>Incident or prevalent cases</th>
<th>N</th>
<th>% on combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>French</td>
<td>2002-2003</td>
<td>Both</td>
<td>354</td>
<td>12.6%</td>
</tr>
<tr>
<td>US Reveal</td>
<td>2006-2007</td>
<td>Both</td>
<td>2525</td>
<td>52.4%</td>
</tr>
<tr>
<td>COMPERA European</td>
<td>2007-2011</td>
<td>Incident</td>
<td>587</td>
<td>55.6% (age 18-65) 31.6% (age &gt;65)</td>
</tr>
</tbody>
</table>

Humbert M et al. Circulation 2010  
Badesch DB et al. Chest 2010  
Hoepel M et al. Int J Cardiol 2013
How best to approach combination therapy?

Humbert, Lau....Circulation 2014
AMBITION Study

A Randomised, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension
AMBITION Study

• Randomised, double-blind, multicentre study comparing the safety and efficacy of first-line combination therapy (ambrisentan and tadalafil) with first-line monotherapy (ambrisentan or tadalafil) in subjects with FC II and III PAH.

• Primary comparison between *initial combination* and *pooled monotherapy*.
Upfront Combination Therapy: AMBITION STUDY

N = 610

Randomized 2:1:1 to Combination arm or Monotherapy arm

Combination arm: AMB + TAD

Monotherapy arm: AMB + PBO Group

OR

Monotherapy arm: TAD + PBO Group

105 events: primary endpoint

Following first event, subjects could receive Blinded Combination Therapy, and remained in the study

AMB: ambrisentan
TAD: tadalafil
PBO: placebo
AMBITION STUDY: Primary Endpoint

- **Death from any cause**
- **Hospitalisation for worsening PAH**
  - Hospitalization for worsening PAH, lung or heart and lung transplantation, atrial septostomy, initiation of parenteral prostanoid therapy
- **Disease progression**
  - Decrease >15% in 6MWD combined and WHO FC III or IV symptoms at two consecutive visits separated by at least 14 days
- **Unsatisfactory long-term clinical response**
  - Any decrease from baseline in 6MWD at two consecutive clinic visits after baseline separated by at least 14 days, and WHO FC 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

All events adjudicated by a clinical end-point committee
## AMBITION Study: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Pooled monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>253</td>
<td>247</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>188 (74)</td>
<td>200 (81)</td>
</tr>
<tr>
<td>Aetiology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>127 (50)</td>
<td>138 (56)</td>
</tr>
<tr>
<td>APAH-CTD</td>
<td>103 (41)</td>
<td>84 (34)</td>
</tr>
<tr>
<td>Time from diagnosis (days, median)</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>FC II/III (%)</td>
<td>30/70</td>
<td>32/68</td>
</tr>
<tr>
<td>Baseline 6MWD, mean, m</td>
<td>353.5 ± 87.9</td>
<td>351.7 ± 91.8</td>
</tr>
<tr>
<td>PVR, dyne/sec/cm(^5)</td>
<td>824.1 ± 467.0</td>
<td>825.7 ± 402.1</td>
</tr>
</tbody>
</table>
AMBITION STUDY: Primary Endpoint

Combination vs pooled monotherapy

Hazard ratio 0.50 (95% CI, 0.35 - 0.72)
\( p < 0.001 \)

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
<th>144</th>
<th>168</th>
<th>192</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>253</td>
<td>229</td>
<td>186</td>
<td>145</td>
<td>106</td>
<td>71</td>
<td>36</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pooled monotherapy</td>
<td>247</td>
<td>209</td>
<td>155</td>
<td>108</td>
<td>77</td>
<td>49</td>
<td>25</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Galie et al. NEJM 2015
AMBITION STUDY: Primary Endpoint

Galie et al. NEJM 2015
### AMBITION STUDY: Secondary Endpoints

<table>
<thead>
<tr>
<th>Secondary Endpoints [change from baseline to week 24]</th>
<th>Combo</th>
<th>Pooled Mono</th>
<th>Difference and Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTproBNP (% reduction)</td>
<td>-67.4</td>
<td>-49.7</td>
<td>% difference-35.3; 95% CI:-46.2, -22.2</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>% subjects achieving a satisfactory clinical response at week 24</td>
<td>39</td>
<td>29</td>
<td>odds ratio 1.56; 95% CI: 1.05, 2.32</td>
<td>p=0.026</td>
</tr>
<tr>
<td>6 Minute Walk Distance (meters, median change)</td>
<td>49.0</td>
<td>23.8</td>
<td>22.75m; 95% CI: 12.00, 33.50</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>WHO Functional Class (median change)</td>
<td>0</td>
<td>0</td>
<td>0; 95% CI 0, 0</td>
<td>P=NS</td>
</tr>
<tr>
<td>Borg Dyspnoea Scale (median change)</td>
<td>-1.0</td>
<td>-0.5</td>
<td>-0.38; 95% CI: -0.75, 0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Galie et al. NEJM 2015*
## AMBITION STUDY: Main Subgroups

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Class</td>
<td></td>
</tr>
<tr>
<td>FC II</td>
<td>0.211 (95% CI: 0.071, 0.629)</td>
</tr>
<tr>
<td>FC III</td>
<td>0.576 (95% CI: 0.388, 0.855)</td>
</tr>
<tr>
<td>Disease Aetiology</td>
<td></td>
</tr>
<tr>
<td>I/HPAH</td>
<td>0.535 (95% CI: 0.329, 0.871)</td>
</tr>
<tr>
<td>APAH</td>
<td>0.453 (95% CI: 0.259, 0.790)</td>
</tr>
<tr>
<td>Geographical Region</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>0.505 (95% CI: 0.295, 0.866)</td>
</tr>
<tr>
<td>ROW</td>
<td>0.506 (95% CI: 0.307, 0.834)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>0.454 (95% CI: 0.260, 0.792)</td>
</tr>
<tr>
<td>&lt; 65</td>
<td>0.524 (95% CI: 0.322, 0.852)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.473 (95% CI: 0.308, 0.726)</td>
</tr>
<tr>
<td>Male</td>
<td>0.581 (95% CI: 0.283, 1.194)</td>
</tr>
<tr>
<td>Baseline 6MWD</td>
<td></td>
</tr>
<tr>
<td>Baseline 6MWD ≥ 364m</td>
<td>0.380 (95% CI: 0.187, 0.769)</td>
</tr>
<tr>
<td>Baseline 6MWD &lt; 364m</td>
<td>0.537 (95% CI: 0.349, 0.827)</td>
</tr>
</tbody>
</table>
Safety and Side Effects

- Peripheral oedema (combination: 46%; ambrisentan: 33%; tadalafil: 28%)

- Headache (combination: 42%; ambrisentan: 33%; tadalafil: 35%)

- Nasal congestion (combination: 21%; ambrisentan: 15%; tadalafil: 12%)

- Anaemia (combination: 15%; ambrisentan: 6%; tadalafil: 12%).
Key Messages from AMBITION Study

• Upfront combination with ambrisentan and tadalafil is superior to monotherapy alone in FC II/III.

• Clinically relevant morbidity and mortality driven primary endpoint.

• Benefit seen even in patients with milder disease (FC II) suggesting that early aggressive use of combination therapy should be considered in PAH.
Real world experience with upfront combination therapy

Initial dual oral combination therapy in pulmonary arterial hypertension

Olivier Sitbon¹,²,³, Caroline Sattler¹,²,³, Laurent Bertolletti⁴,⁵, Laurent Savale¹,²,³, Vincent Cottin⁶, Xavier Jais¹,²,³, Pascal De Groote⁷, Ari Chaouat⁸,⁹, Céline Chabannes¹⁰, Emmanuel Bergot¹¹, Hélène Bouvaist¹², Claire Dauphin¹³, Arnaud Bourdin¹⁴, Fabrice Bauer¹⁵, David Montani¹,²,³, Marc Humbert¹,²,³ and Gérald Simonneau¹,²,³

• Observational study from the French PH Network
• 97 PAH initiated on initial dual oral combination therapy
• Mainly idiopathic/heritable/anorexigen induced PAH
• FC II/III/IV: 15/72/12
• Bos/Sild = 61/; Bos/Tad = 17; Amb/Sild = 8; Amb/Tad = 11
Real world experience with upfront combination therapy

<table>
<thead>
<tr>
<th>NYHA FC I/II/III/IV n</th>
<th>Baseline</th>
<th>First follow-up visit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0/15/70/12</td>
<td>4/57/31/5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical signs of RHF n (%)</td>
<td>49 [51]</td>
<td>25 [26]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-min walk distance m</td>
<td>324±132</td>
<td>395±114</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Borg dyspnoea index</td>
<td>4.3±2.0</td>
<td>3.1±1.9</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>BNP\textsuperscript{II} ng·L\textsuperscript{−1} median (IQR)</td>
<td>372 [115–710]</td>
<td>62 [34–274]</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

**Haemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First follow-up visit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP mmHg</td>
<td>9.5±5.7</td>
<td>6.7±4.5</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>mPAP mmHg</td>
<td>53.9±10.4</td>
<td>45.1±10.9</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>PAWP mmHg</td>
<td>8.8±3.5</td>
<td>8.7±3.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Cardiac output L·min\textsuperscript{−1}</td>
<td>3.94±1.17</td>
<td>5.65±1.62</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Cardiac index L·min\textsuperscript{−1}·m\textsuperscript{−2}</td>
<td>2.14±0.51</td>
<td>3.13±0.79</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>PVR dyn·s·cm\textsuperscript{−5}</td>
<td>1021±357</td>
<td>565±252</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Mean BP mmHg</td>
<td>97±18</td>
<td>87±13</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Heart rate beats per min</td>
<td>85±15</td>
<td>81±12</td>
<td>&lt;0.011</td>
</tr>
<tr>
<td>Sv\textsubscript{o}₂ %</td>
<td>59±8</td>
<td>67±8</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

*Sitbon et al. Eur Resp J (in press)*
## Real world experience with upfront combination therapy

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Patients n</th>
<th>Visit</th>
<th>PVR $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$</th>
<th>Change in PVR from baseline $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-2}$</th>
<th>p-value $^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan+PDE5 inhibitor</td>
<td>78</td>
<td>Baseline</td>
<td>1040±736</td>
<td>−452±23 (−498−−407)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>First follow-up</td>
<td>579±273</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrisentan+PDE5 inhibitor</td>
<td>19</td>
<td>Baseline</td>
<td>913±258</td>
<td>−470±46 (−561−−379)</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First follow-up</td>
<td>504±143</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil+ERA</td>
<td>69</td>
<td>Baseline</td>
<td>1044±371</td>
<td>−427±24 (−474−−380)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>First follow-up</td>
<td>605±267</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadalafil+ERA</td>
<td>28</td>
<td>Baseline</td>
<td>945±323</td>
<td>−524±37 (−596−−451)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First follow-up</td>
<td>465±188</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Sitbon et al. Eur Resp J (in press)*
Real world experience with upfront combination therapy

Aggressive Upfront Triple Combination Therapy in Severe Idiopathic PAH

Idiopathic, heritable or anorexigen induced PAH (n=19)

• NYHA FC III or IV
• CI < 2.0 and/or RAP > 20 and/or PVR > 12 WU

Sitbon et al. ERJ 2014
2016 Treatment Algorithm in PAH

- **Treatment naive patient**
  - CCB therapy (table 18)
  - Vasoreactive
    - Acute vasoreactivity test (IPAH/HPAH/DPAH only)
    - PAH confirmed by expert centre
      - General measures (table 16)
      - Supportive therapy (table 17)
      - 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)
# First Step is Comprehensive Risk Assessment

<table>
<thead>
<tr>
<th>Determinants of prognosisa (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 syncopec</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/VCO₂ slope &lt;36</td>
<td>Peak VO₂ 11–15 ml/min/kg (35–65% pred.) VE/VCO₂ slope 36–44.9</td>
<td>Peak VO₂ &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO₂ slope &gt;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 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 &gt;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>

Also our treatment goal!!
2015 Treatment Algorithm in PAH

- Treatment naive patient
  - PAH confirmed by expert centre
    - General measures (table 16)
    - Supportive therapy (table 17)
  - CCB therapy (table 18)
    - Acute vasoreactivity test (IPAH/HPAH/DPAH only)
      - Vasoreactive
        - Low or intermediate risk (WHO FC II–III)
          - Initial monotherapy (table 19)
          - Initial oral combination (table 20)
      - Non-vasoreactive
        - High risk (WHO FC IV)
          - Initial combination including i.v. PCA (table 20)
2016 Treatment Algorithm in PAH

Galie et al. Eur Heart J 2015
Patient already on treatment

Inadequate clinical response (table 15)

Consider referral for lung transplantation

Double or triple sequential combination (table 21)

Inadequate clinical response (table 15)

Consider listing for lung transplantation (table 22)

Galie et al. Eur Heart J 2015
Is Upfront Monotherapy Still Satisfactory in 2016?

CAVEATS AND UNANSWERED QUESTIONS

1. Upfront combination therapy has never been compared to an aggressive (or early) sequential combination therapy head-to-head.

2. Some (probably minority) do maintain long-term excellent response to oral monotherapy.

3. Applicability of trial population into real-life population (AMBITION Study)

4. Economic considerations
Ex-PAS (n=105)

AMBITION STUDY PATIENT FLOW CHART
AMBITION Protocol Amendment: Classical PAH vs. Non-Classic PAH

Original inclusion criteria

PAH confirmed by:
• \( \text{mPAP} \geq 25 \text{ mmHg} \)
• \( \text{PAWP} \leq 15 \text{ mmHg} \)
• \( \text{PVR} > 240 \text{ dyne.sec.cm}^{-5} \)

Amended inclusion criteria (PAS)

PAH confirmed by:
• \( \text{mPAP} \geq 25 \text{ mmHg} \)
• If \( \text{PAWP} \leq 12 \text{ mmHg} \)
  • \( \text{PVR} > 300 \text{ dyne.sec.cm}^{-5} \)
• If \( \text{PAWP} 13-15 \text{ mmHg} \)
  • \( \text{PVR} > 500 \text{ dyne.sec.cm}^{-5} \)

Must not have >2 of:
• \( \text{BMI} \geq 30 \text{ kg/m}^2 \)
• Systemic hypertension
• Diabetes
• History of CAD

“All-comers” including non-classic PAH

“More classical PAH”
• We now have high-quality evidence to support the use of upfront combination therapy in PAH.

• This should probably be offered to the majority of patients, particularly if they present in FC III/IV or severe haemodynamic derangement.

• If initial monotherapy is pursued, treatment should be escalated early if treatment goals are not reached.

• No head-to-head data to compare different combinations of therapy.