Overview of randomized controlled trials in pulmonary arterial hypertension

Marc HUMBERT, MD, PhD

Centre de Référence de l’Hypertension Pulmonaire Sévère
Centre Hospitalier Universitaire de Bicêtre – INSERM U999
Université Paris-Sud – Le Kremlin-Bicêtre – France
Disclosures

– **Actelion**: consultancy (current), board or advisory committee (current), speaker (current)
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– **Novartis**: consultancy (current), board or advisory committee (current), speaker (current), research support (current)
– **Pfizer**: consultancy (current), board or advisory committee (current), speaker (current), research support (past)
Clinical classification of pulmonary hypertension (PH)

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic</td>
</tr>
<tr>
<td>1.2 Heritable</td>
</tr>
<tr>
<td>1.2.1 BMPR2 mutation</td>
</tr>
<tr>
<td>1.2.2 Other mutations</td>
</tr>
<tr>
<td>1.3 Drugs and toxins induced</td>
</tr>
<tr>
<td>1.4 Associated with:</td>
</tr>
<tr>
<td>1.4.1 Connective tissue disease</td>
</tr>
<tr>
<td>1.4.2 Human immunodeficiency virus (HIV) infection</td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
</tr>
<tr>
<td>1.4.4 Congenital heart disease (Table 6)</td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
</tr>
</tbody>
</table>

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension
PAH: A rare, but not an orphan disease

- Rare: prevalence 15–50/million (incidence 6/million/year)
- Pathophysiology: pulmonary artery endothelial cell dysfunction…
- Drugs: 10 agents approved in the last 15 years (orphan drug status)
- Lung/heart–lung transplantation: if refractory to medical therapy

5-HT, 5-hydroxytryptamine; ET-1, endothelin 1; FGF-2, fibroblast growth factor 2; SMC, smooth muscle cell.

**Treatment of Pulmonary Arterial Hypertension**

Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D.

**Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension**

Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jais, MD; Olivier Sitbon, MD, PhD; Gérald Simonneau, MD

*Circulation* 2014;130:2189–208.
Endothelial dysfunction in PAH

PAH-specific therapies target the 3 signaling pathways involved in PAH: “Drugs used in early trials”

**Endothelin pathway**
- Endothelin receptor antagonists (ERAs)
  - Ambrisentan
  - Bosentan

**NO–cGMP pathway**
- PDE5 inhibitors
  - Sildenafil
  - Tadalafil

**Prostacyclin pathway**
- Prostanoids
  - Beraprost
  - Epoprostenol iv
  - Iloprost iv, inhaled
  - Treprostinil iv, sc, inhaled, oral

**RCTs with monotherapy in PAH**

*Improvement in exercise capacity (3-4 months)*

![Graph showing changes in 6MWD (meters) with different treatments](image)

- **Epoprostenol (IPAH)**
  - Treatment effect: +47 m
  - P: < 0.003

- **Treprostinil (PAH-SSc)**
  - Treatment effect: +108 m*
  - P: < 0.001

- **Iloprost (AIR)**
  - Treatment effect: +18 m
  - P: 0.005

- **Bosentan (BREATHE-1)**
  - Treatment effect: +36 m
  - P: 0.004

- **Ambrisentan (AERIES)**
  - Treatment effect: +44 m
  - P: 0.0002

- **Sildenafil (SUPER-1)**
  - Treatment effect: +42 m
  - P: < 0.001

- **Tadalafil (PHIRST)**
  - Treatment effect: +44 m#
  - P: < 0.001

- **Barst, NEJM 1996.**
- **Simonneau, AJRCCM 2002.**
- **Rubin, NEJM 2002.**
- **Galiè, NEJM 2005.**
- **Badesch, Ann Int Med 2000.**
- **Olschewski, NEJM 2002.**
- **Galiè, Circulation 2009.**

*Control = placebo except for epoprostenol trials (‘Conventional therapy’)*

#: **monotherapy only**
**Effect of PAH-specific therapies on PVR after 3-6 months**


*Sildenafil:
-12% for 20 mg TID (approved dose)
-28% for 80 mg TID dose
A meta-analysis of randomized controlled trials in pulmonary arterial hypertension

Nazzareno Galiè*, Alessandra Manes, Luca Negro, Massimiliano Palazzini, Maria Letizia Bacchi-Reggiani, and Angelo Branzi

European Heart Journal (2009) 30, 394–403

- 23 RCTs
- Average duration 14.3 wks
- 3140 patients
- All-cause mortality rate in the control group = 3.8%
- Active treatments:
  - 43% reduction in mortality
  - RR 0.57 (95%CI 0.35–0.92)
  - \( P = 0.023 \)
Despite drug discovery and development PAH remains a devastating condition.

Current survival with PAH-targeted therapy (US REVEAL Registry):
- 90.5 ± 2.2%
- 74.5 ± 2.5%
- 64.5 ± 2.5%
- 58.9 ± 2.7%

Historical survival without any specific therapy:
- 68.2%
- 46.9%
- 35.6%
- 32.0%

How to do better?

- Do better with what we have
  - Prevention: Detect and treat “early”
  - Treat more aggressively and be ambitious!
    - Goal-oriented treatment strategy and sequential combination therapy
    - Changing strategy: Initial combination therapy

Strategies for combination therapy in PAH

1. **Sequential combination after clinical deterioration**
   - Slow sequential combo
   - Add drug B sometimes months/years after drug A
   - Likely the worst strategy…

2. **Sequential combination if treatment goals are not met**
   (goal-oriented treatment strategy)
   - Rapid (“aggressive”) sequential combo
   - Add drug B rapidly (3-6 months) after drug A

3. **Initial (“upfront”) combination therapy**
   - Treatment initiation with 2 or 3 drugs
   - Really different than option 2?
   - Some physicians are reluctant
     - “I prefer to keep a drug with me if my patient deteriorates…”
     - “I’m afraid by side effects…”
Goal-oriented therapy (risk assessment)

### Treatment Goals of Pulmonary Hypertension

Vallie V. McLaughlin, MD,* Sean Patrick Gaine, MD, PhD,† Luke S. Howard, DPhil,‡
Hanno H. Leuchte, MD,§ Michael A. Mathier, MD,∥ Sanjay Mehta, MD,¶
Massimillano Palazzini, MD,# Myung H. Park, MD,** Victor F. Tapson, MD,††
Olivier Sitbon, MD, PhD‡‡

<table>
<thead>
<tr>
<th>Functional class</th>
<th>I or II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography/CMR</td>
<td>Normal/near-normal RV size and function</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Normalization of RV function (RAP &lt; 8 mm Hg and CI &gt; 2.5 to 3.0 l/min/m²)</td>
</tr>
<tr>
<td>6-min walk distance</td>
<td>&gt;380 to 440 m; may not be aggressive enough in young individuals</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂ &gt; 15 ml/min/kg and EqCO₂ &lt; 45 l/min/l/min</td>
</tr>
<tr>
<td>B-type natriuretic peptide level</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Cl, cardiac index; CMR, cardiovascular magnetic resonance; EqCO₂, breathing equivalent for CO₂; RAP, right atrial pressure; RV, right ventricle; VO₂, oxygen consumption.

# ESC/ERS 2015 Guidelines for risk assessment in PAH

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

<sup>a</sup> Determinants of prognosis: clinical signs, progression of symptoms, syncope, WHO functional class, 6MWD, cardiopulmonary exercise testing, NT-proBNP plasma levels, imaging (echocardiography, CMR imaging), and haemodynamics.

<sup>b</sup> Occasional syncope: occurring occasionally, not affecting daily activities.

<sup>c</sup> Repeated syncope: occurring frequently, interfering with daily activities.

Suggested assessment and timing for the follow up of patients with PAH

<table>
<thead>
<tr>
<th></th>
<th>At baseline</th>
<th>Every 3–6 months</th>
<th>Every 6–12 months</th>
<th>3–6 months after changes in therapy</th>
<th>In case of clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical assessment and</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>determination of functional</td>
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<tr>
<td>class</td>
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<tr>
<td>ECG</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6MWT/Borg dyspnoea score</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CPET</td>
<td>+</td>
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<td></td>
<td>+</td>
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<tr>
<td>Echo</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Basic lab</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Extended lab</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Should be considered

Some centres perform RHCs at regular intervals during follow-up

Rationale for combination therapy

- Malignant nature of PAH requires a more aggressive approach
- Successfully used in chronic heart failure, HIV, cancer...
- PAH pathogenesis: several pathways are involved
- Potential for synergistic effects

Sequential or upfront?
Combination therapy: *What’s the evidence?*

- **Sequential combination therapy**
  - A lot of studies (RCTs) available
  - Results are not uniform

- **Initial combination therapy**
  - Only two RCTs: one negative (BREATHE-2), one positive (AMBITION)
  - Expanded experience in clinical practice (dual, triple)

- **Recent meta-analysis¹**: Combination therapy (all strategies, sequential and initial) is associated with significant risk reduction for clinical worsening compared with monotherapy:
  - *risk ratio [RR] 0.65 [95% CI 0.58–0.72], p<0.00001*

→ No comparison between sequential and initial combination therapy

Sequential combination therapy with “drugs used in early trials”: results are not uniform...

<table>
<thead>
<tr>
<th>Drug tested</th>
<th>Study</th>
<th>Background</th>
<th>N</th>
<th>Duration (weeks)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan¹</td>
<td>EARLY</td>
<td>None or sildenafil (16%)</td>
<td>185</td>
<td>24</td>
<td>PVR +, Δ6MWD (NS)</td>
</tr>
<tr>
<td>Bosentan²</td>
<td>COMPASS-2</td>
<td>Sildenafil</td>
<td>334</td>
<td>92</td>
<td>Morbi-mortality (NS)</td>
</tr>
<tr>
<td>Iloprost³</td>
<td>STEP</td>
<td>Bosentan</td>
<td>67</td>
<td>12</td>
<td>Δ6MWD (NS)</td>
</tr>
<tr>
<td>Iloprost⁴</td>
<td>COMBI</td>
<td>Bosentan</td>
<td>40</td>
<td>12</td>
<td>Δ6MWD (NS)</td>
</tr>
<tr>
<td>Sildenafil⁵</td>
<td>PACES</td>
<td>Epoprostenol</td>
<td>264</td>
<td>16</td>
<td>Δ6MWD (POS)</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>NCT00323297</td>
<td>Bosentan</td>
<td>104</td>
<td>12</td>
<td>Δ6MWD (NS)</td>
</tr>
<tr>
<td>Tadalafil⁶</td>
<td>PHIRST</td>
<td>None or bosentan (54%)</td>
<td>405</td>
<td>16</td>
<td>Δ6MWD (NS)</td>
</tr>
<tr>
<td>Treprostinil⁷</td>
<td>Inhaled- TRIUMPH</td>
<td>Bosentan or sildenafil</td>
<td>235</td>
<td>12</td>
<td>Δ6MWD (POS)</td>
</tr>
<tr>
<td>Treprostinil⁸</td>
<td>Oral- FREEDOM C1</td>
<td>Bosentan &amp;/or sildenafil</td>
<td>354</td>
<td>16</td>
<td>Δ6MWD (NS)</td>
</tr>
<tr>
<td>Treprostinil⁹</td>
<td>Oral- FREEDOM C2</td>
<td>Bosentan &amp;/or sildenafil</td>
<td>310</td>
<td>16</td>
<td>Δ6MWD (NS)</td>
</tr>
</tbody>
</table>

PAH-specific therapies target the 3 signaling pathways involved in PAH: drugs used in recent trials

Endothelin pathway

- Endothelin receptor antagonists (ERAs)
  - Ambrisentan
  - Bosentan

NO–cGMP pathway

- PDE5 inhibitors
  - Sildenafil
  - Tadalafil

Prostacyclin pathway

- Prostanoids
  - Beraprost
  - Epoprostenol iv
  - Iloprost iv, inhaled
  - Treprostinil iv, sc, inhaled, oral

- sGC stimulators
  - Riociguat

- Non prostanoids IP receptor agonist
  - Selexipag (oral)

## Sequential combination therapy: Recent studies

<table>
<thead>
<tr>
<th>Drug tested</th>
<th>Study</th>
<th>Background</th>
<th>N</th>
<th>Duration (weeks)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riociguat</td>
<td>PATENT</td>
<td>None (50%), bosentan or prostanoids</td>
<td>443</td>
<td>12</td>
<td>Δ6MWD (POS)</td>
</tr>
<tr>
<td>Macitentan</td>
<td>SERAPHIN</td>
<td>None (36%), PDE5i (61%) or oral/inhaled prostanoids</td>
<td>742</td>
<td>≈ 100</td>
<td>Time to first event of death or morbidity (POS)</td>
</tr>
<tr>
<td>Selexipag</td>
<td>GRIPHON</td>
<td>None (21%), ERA (13%), PDE5i (32%) or both (34%)</td>
<td>1156</td>
<td>≈ 70</td>
<td>Time to first event of death or morbidity (POS)</td>
</tr>
</tbody>
</table>

PATENT: Study Design

Primary endpoint (6MWD) at week 12

PATENT-1

- Titration 8 weeks
- Maintenance 4 weeks
- Riociguat up to 2.5 mg 3x/j
- Placebo
- Riociguat 1.5 mg 3x/j

20 weeks double blind

PATENT-2

- 8 weeks
- Fake titration
- Tiartion max 2.5 mg 3x/j
- Tiartion max 2.5 mg 3x/j

Open label extension phase d’extension up to 2.5 mg 3x/j

Primary endpoint: 6MWD

Total population (n=254/126)

+36 m
p<0.0001
(95% CI: 20–52 m)

Naïve population naïve (n=123/66)

+38 m
(95% CI: 15–62 m)

Pre-treated population (n=131/60)

+36 m
(95% CI: 15–56 m)

SERAPHIN: Primary endpoint

Time to 1st morbidity or mortality event

- Death
- Atrial septostomy
- Lung transplantation
- Initiation of i.v. or s.c. prostanoids
- Other worsening of PAH

A decrease in 6-MWD of at least 15%, confirmed by 2 tests on different days

AND

Worsening of PAH symptoms, which must include either:
- An increase in FC, or
- Appearance or worsening of symptoms of RHF

AND

Need for new PAH treatment(s):
- Oral or inhaled prostanoids
- Oral PDE-5 inhibitors
- ERA after study discontinuation
- Intravenous diuretics

All events adjudicated by a blinded clinical events committee

SERAPHIN: macitentan reduced the risk of the primary outcome composite of death or morbidity due to PAH

- Hazard ratio: 0.70 (3 mg); 0.55 (10 mg)
- Log-rank p-value: 0.01 (< 0.001)

Risk reduction of primary endpoint event vs placebo:
- Macitentan 10 mg: 45%
- Macitentan 3 mg: 30%

PAH worsening was the main component of the primary endpoint

SERAPHIN: macitentan reduced the risk of the primary outcome composite of death or morbidity due to PAH

**Treatment-naïve patients**
- Risk reduction 55%

**Patients on background therapy**
- Risk reduction 38%

**Graphs**
- Treatment-naïve patients: Hazard ratio (HR) 0.45, p (test Log-rank) < 0.001
- Patients on background therapy: Hazard ratio (HR) 0.62, p (test Log-rank) 0.009

**Table**
- Patients à risque: 88, 74, 68, 64, 58, 38, 17, 96, 66, 54, 45, 42, 24

GRIPHON study (phase III): ProstaGlandin I₂ Receptor agonist In Pulmonary arterial HypertensiON

- Multicenter, double-blind, placebo-controlled event-driven study
- 1156 PAH adult patients
- 80% on background treatment with ERA and/or PDE-5i
- Composite primary outcome measure: time to the first occurrence of death or morbidity event

NCT01106014: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Worsening of PAH resulting in need for lung transplantation or atrial septostomy

Initiation of parenteral prostanoids or chronic O\textsubscript{2} for worsening PAH

Hospitalization for worsening of PAH

Worsening of PAH resulting in need for lung transplantation or atrial septostomy

All-cause death

Patients with WHO FC II/III at baseline
Decrease in 6MWD of at least 15% and Worsening in WHO FC

Patients with WHO FC III/IV at baseline
Decrease in 6MWD of at least 15% and Need for additional PAH therapy

Morbidity or mortality events

Disease progression

All events adjudicated by a blinded critical events committee

EOT: End of double-blind treatment

Selexipag reduced the risk of the primary outcome composite of death or morbidity due to PH

Selexipag vs placebo: Risk reduction 40%
HR = 0.60; 99% CI 0.46–0.78; p < 0.0001

Hospitalisation for PAH worsening and disease progression were the main components of the primary endpoint

Consistent treatment effect of selexipag on primary composite endpoint according to background therapy

Selexipag vs placebo

All patients

PAH specific therapy at baseline
(interaction p value = 0.95)

- ERA + PDE-5i
- ERA monotherapy
- PDE-5i monotherapy
- No PAH-specific therapy

Hazard ratio (99% CI)

Favours selexipag  Favorse placebo

Selexipag  Placebo

No. of patients/ no. of events

574/155  582/242

179/47  197/80

94/23  76/29

189/54  185/84

112/31  124/49

Evolving paradigm: From sequential to initial combination therapy

- **Sequential Combination**
  - Drug 1
  - Drugs 1 + 2 + 3

- **Up-Front Combination**
  - 2 or 3 drugs (especially in patients who present with high-risk features)

Impact on Outcomes

BREATHE-2: Initial dual combination therapy with epoprostenol and bosentan

- **6-MWD (m)**
  - **Baseline (mean and 95% CI)**
    - Placebo + epo ($n=10$)
    - Bos + epo ($n=18$)
  - **Week 16 (median and 95% CI)**
    - Placebo + epo ($n=10$)
    - Bos + epo ($n=18$)

- **TPR change from baseline (%)**
  - Placebo + epo ($n=10$)
  - Bos + epo ($n=18$)

  - Week 16:
    - Placebo + epo
      - Median: $-60$
      - 95% CI: $-80$ to $-40$
    - Bos + epo
      - Median: $-100$
      - 95% CI: $-140$ to $-60$

  - Baseline:
    - Placebo + epo
      - Median: $0$
      - 95% CI: $-20$ to $20$
    - Bos + epo
      - Median: $0$
      - 95% CI: $-40$ to $40$

  - Change from Baseline:
    - Placebo + epo: $-20$
    - Bos + epo: $-60$

  - $P=0.08$

The AMBITION trial

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension


- Event-driven study
- Initial combo AMB+TADA vs monotherapy AMB or TADA
- N=500 treatment-naïve patients with PAH (31% FC II)
The AMBITION trial: Primary endpoint

Time to first clinical failure event

- **Death (all cause)**
- **Hospitalization for worsening PAH**
  - Any hospitalization for worsening PAH
  - Lung transplantation
  - Atrial septostomy
  - Initiation of parenteral prostanoid therapy
- **Disease progression**
  - Decrease in 6MWD > 15% vs baseline with FC III-IV (2 visits > 14 days)
- **Unsatisfactory long-term response**
  - 1 dose of IP and > 6 months in study
  - Decrease in 6MWD (any amount)
  - FC III at 2 visits separated by 6 months

All events were adjudicated

The AMBITION trial: main result

Hospitalisation for PAH worsening was the main component of the primary endpoint.

Initial combination is also efficacious in SSc-PAH

- 36 week prospective multicentre open-label uncontrolled study
- Initial combination of ambrisentan & tadalafil
  - 24 treatment-naïve patients with PAH-SSc
  - FC II / III: 35% / 65%

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>36 weeks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP (mmHg)</td>
<td>42 ± 12</td>
<td>30 ± 7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.6 ± 0.7</td>
<td>3.3 ± 1.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>8.4 ± 5.1</td>
<td>4.1 ± 3</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Percent decrease in PVR (after 3-6 months)

Initial therapy: effects on PVR

**Initial mono Rx with ETRA**
- Bosentan^1
- Ambrisentan^2
- Macitentan^3

**Initial mono RX with PDE5i**
- Sildenafil^4
- Tadalafil^5

**Initial mono RX with IV PGI2**
- Treproz^6
- Epoprostenol^7

**Initial combo with IV PGI2**
- Initial combo: epo + bosentan^8
- Initial combo: epo + bosentan + sildenafil^9

**Initial dual oral combo**

*Sildenafil:
- -12% for 20 mg TID (approved dose)
- -28% for 80 mg TID dose

Take-home messages

- Many PAH drugs are now available
- Strategy of sequential combination therapy with available medications has a positive impact on disease progression
- Sequential combination therapy may be more effective if part of a goal-oriented strategy
- Initial combination therapy is an appealing strategy:
  - Initial double/triple combination therapy incl. parenteral PGI$_2$ is notably effective in most severe patients (FC IV and some III)
  - Initial dual oral combination therapy with ERA and PDE5i is superior to monotherapy in FC II-III patients (AMBITION)
6th WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

NICE
February 27-28
March 1, 2018