Nuovi approcci terapeutici nel trattamento dell’ipertensione arteriosa polmonare in pediatria

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L'obiettivo di questa lettura è la trattazione di temi scientifici per lo scambio didattico e scientifico tra medici che trattano pazienti affetti da Ipertensione Arteriosa Polmonare.

The aim of this symposium is to debate actual key scientific issues and provide a forum for educational and scientific exchange between clinicians treating patients with PAH.

I dati presentati durante la lettura riflettono quanto sostenuto dalla letteratura scientifica in merito pubblicata e esprimono le opinioni degli esperti in materia di Ipertensione Arteriosa Polmonare e non sono necessariamente supportati o condivisi da Pfizer.

The data presented during the lecture are scientific data published and expressed opinions of experts about Pulmonary Arterial Hypertension and they are not necessarily endorsed or shared by Pfizer.
PAH is a chronic proliferative vasculopathy, regardless of aetiology and age, characterised by a progressive increase in pulmonary vascular resistance (PVR) leading to right heart failure and death.
7.4.1 Paediatric pulmonary arterial hypertension

**Paediatric PH is similar to adult disease** even if the lungs are still developing in a growing child. The **worse prognosis in children** with a median survival estimated at 10 months compared with 2.8 years in the adult **has not been confirmed**. The exact **incidence and prevalence** of PH in children **is not known**. All forms of PH included in the clinical classification have been described **in children**, but **the majority of patients present with PH associated with CHD or idiopathic/heritable forms**. In contrast, the prevalence of PH associated with CTD, portal hypertension, HIV infection, and drugs and toxins is lower. **Patients with chronic lung disease of prematurity are a growing population**. Persistent PH of the neonate is also classified under PAH. Its natural history, treatment, and outcome are sufficiently different to justify its exclusion from this discussion. **No clear differences** have been identified **among the mechanisms** involved in the development of PAH in children and adults.

The most common forms in children are those associated with CHD or IPAH/HPAH

PAH aetiology varies in children and adults

**Adults**¹

- 9.5
- 3.9
- 15.3
- 11.3
- 10.4
- 6.2
- 4.3

**IPAH**
**Two co-existing risk factors**
**HIV**
**Portal hypertension**
**CHD**
**CTD**
**Anorexigenic agents**
**FPAH**

**Children**²

- 6.5
- 27.8
- 48.1

- 13.4
- 4.2
- 4.2

**IPAH**
**CHD**
**CTD**
**Lung disease**
**Other***

*including HIV, bone marrow transplantation and metabolic disorders

Pathogenesis of PAH is the same in children and adults.

**RISK FACTORS AND ASSOCIATED CONDITIONS**
- CTD
- CHD
- Portal hypertension
- HIV
- Drugs and toxins
- Pregnancy

**SUSCEPTIBILITY**
- BMPR2 mutation
- Other genetic factors

**VASCULAR INJURY**
- Endothelial dysfunction
  - ↓ NO synthase
  - ↓ PGI₂ production
  - ↑ Thromboxane production
  - ↑ ET-1 production

**DISEASE PROGRESSION**
- Smooth muscle hypertrophy
- Adventitial and intimal proliferation
- In situ thrombosis
- Plexiform lesion
- Advanced vascular lesion

**Normal**
- Adventitia
- Media
- Intima

**Reversible disease**
- Early intimal proliferation
- Smooth muscle hypertrophy
- Vasoconstriction

**Irreversible disease**
- Adventitia
- Smooth muscle hypertrophy

CHD = congenital heart disease; CTD = connective tissue disease; ET-1 = endothelin-1; HIV = human immunodeficiency disease; NO = nitric oxide; PAH = pulmonary arterial hypertension; PGI₂ = prostacyclin; BMPR2 = bone morphogenetic protein receptor 2

PAH may present at any age from infancy to adulthood

In the last decade, treatments that target disease specific abnormalities have been developed that improve exercise capacity, haemodynamic parameters, WHO- functional class, overall quality of life and survival in adults

The efficacy of these therapies in adults and the poor prognosis in the absence of treatment have led to the inclusion of these new agents in the current recommendations by the paediatric pulmonary hypertension community for treating paediatric PAH

However, there is currently limited information from published randomised controlled trials in children evaluating the safety and/or efficacy of these medications
Epoprostenol (…1995) still considered the “gold-standard” for treatment of severe PAH, the delivery system is not without risk.

Thus, the focus of PAH research in the past decade has been to develop alternative treatments that are less invasive and with fewer side effects.

There are currently three major drug classes available for the long-term treatment of PAH: prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors.

There is evidence that each can benefit the appropriate PAH child.
Complex multifactorial pathobiology similar in children and adults

PAH diagnostic algorithm is the same for children and adults\textsuperscript{1}

RHC + vasoreactive testing are vital diagnostic steps in children as well as adults\textsuperscript{1}


ALK-1, activin-receptor-like kinase
ANA, anti-nuclear antibodies
BMPR2, bone morphogenetic protein receptor 2
CMR, cardiac magnetic resonance
Group, clinical group
HHT, hereditary haemorrhagic telangiectasia
HRCT, high-resolution computed tomography
LFT, liver function tests
PCH, pulmonary capillary haemangiomatosis
PFT, pulmonary function test
PVOD, pulmonary veno-occlusive disease
PWP, pulmonary wedge pressure
RHC, right heart catheterisation
TEE, transoesophageal echocardiography
TTE, transthoracic echocardiography
US, ultrasonography
V/Q scan, ventilation/perfusion lung scan

\textsuperscript{1} Gali\textsuperscript{é} et al. Eur Heart J 2009; 30: 2493–537.
Definition of paediatric and adult PAH is the same

- In both children and adults, PAH is defined as:

  - **mPAP** \(\geq 25\) mm Hg at rest
  - **mPCWP or left atrial pressure** \(\leq 15\) mm Hg
  - **CO** Normal or reduced

  Right heart catheterisation (RHC) is essential to:
  - confirm the diagnosis of PAH
  - assess the severity of haemodynamic impairment
  - test the vasoreactivity of the pulmonary circulation

In clinical practice, echo often used instead card-CAT

- **PH if syst. PAP > 50% of systolic systemic pressure**

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### Symptoms at diagnosis of IPAH/HPAH in children and adults

Taken from the US REVEAL registry

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Children n=99</th>
<th>Adults n=1287</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea on exertion</td>
<td>43%</td>
<td>85%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>32%</td>
<td>19%</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25%</td>
<td>24%</td>
<td>0.84</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12%</td>
<td>15%</td>
<td>0.40</td>
</tr>
<tr>
<td>Palpitations</td>
<td>6%</td>
<td>12%</td>
<td>0.065</td>
</tr>
<tr>
<td>Oedema</td>
<td>4%</td>
<td>22%</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*P-value obtained from Fisher’s exact test.

**Barst et al. J Heart Lung Transplant 2009; 28: S146 (Poster)**
### Haemodynamics at diagnosis in children and adults

Haemodynamic variables (mean±SD) at diagnosis of IPAH/HPAH taken from the US REVEAL registry

<table>
<thead>
<tr>
<th>Normal values</th>
<th>Haemodynamic variable</th>
<th>Children/Adults (n)</th>
<th>Children</th>
<th>Adults</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-5</td>
<td>mPAP, mmHg</td>
<td>99/1287</td>
<td>58 ± 20</td>
<td>52 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.5–4</td>
<td>CI, L/min/m²</td>
<td>74/929</td>
<td>3.6 ± 1.7</td>
<td>2.2 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-5</td>
<td>mRAP, mmHg</td>
<td>95/1158</td>
<td>7 ± 3</td>
<td>10 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;160</td>
<td>PVRI, dynes·s·m²·cm⁻⁵</td>
<td>77/23</td>
<td>1,520 ± 1,440</td>
<td>1,840 ± 960</td>
<td>0.013</td>
</tr>
</tbody>
</table>

HPAH, hereditary pulmonary arterial hypertension; mRAP, mean right arterial pressure; CI, cardiac index; PVRI, pulmonary vascular resistance index.

Barst et al. *J Heart Lung Transplant* 2009; **28**: S146 (Poster)
Survival of children with PAH

... 5-year survival still only 75%, with a freedom from death or transplantation of only 57%, ... far from ideal...

Outcome with transplantation is also far from ideal, ie, 5-year survival of approximately 45%
Treatment of pediatric pulmonary hypertension

Treatment of acute disease

Children presenting with syncope, right heart failure or post-operative PAH must be diagnosed and treated promptly and safely

This may be

Good ventilation in ICU – Oxygen
inhaled form (Nitric oxide), orally
with sildenafil, intravenously
(epoprostenol) or with hemodynamic
support (ECMO)

Treatment of acute disease

Nitric oxide (inhalation - reduces PA pressure rapidly)

- among the first line treatments for post-op paediatric PAH
- severe new presentation of PAH in ICU

- Current European guidance suggests that there is insufficient evidence at present to recommend the use of prophylactic post-operative inhaled NO in patients with CHD at risk of PAH

- However, there is sufficient evidence to support a trial of NO therapy in patients with significant peri-operative PAH

Evidence-based treatment algorithm for group 1 PAH patients.

*To maintain arterial blood O\textsubscript{2} pressure $\geq$8kPa (60 mmHg).

§IIa-C for WHO-FC II.

†Under regulatory review in the European Union

BAS, balloon atrial septostomy; ERA, endothelin receptor antagonist; PDE5 I, phosphodiesterase type-5 inhibitor; WHO-FC, World Health Organization functional class

Sitaxentan has been withdrawn (December 2010)

Few paediatric trials have investigated non-specific therapies

Prior to development of PAH-specific therapies, many treatments were routinely used to treat PAH in adults and children although their efficacy had not been fully assessed.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Use in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulants</td>
<td>No studies are available in children, and the risk–benefit profile is a problem in small children. Consensus is to anti-coagulate children with overt right heart failure indwelling central venous lines or with a hypercoagulable state</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Used in vasoresponders, but close follow-up is essential as patients may fail long-term therapy (recommended for these patients to start PAH disease specific targeted therapy)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>High doses are commonly needed but must be initiated cautiously as paediatric patients are often dependent on preload to maintain cardiac output</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>Indicated if there is nocturnal systemic arterial oxygen desaturation, upper respiratory tract infections, severe right ventricular failure and resting hypoxaemia, polycythaemia resulting from right-to-left shunting via a patent foramen ovale</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Use in children is controversial, but may be beneficial in children with right-sided heart failure</td>
</tr>
</tbody>
</table>
Adult treatment algorithm is used in children.
## PAH-specific therapy in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paediatric use</th>
<th>Paediatric formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Revatio</strong>&lt;sup&gt;®&lt;/sup&gt;&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension (see section 4.1). Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease (See section 5.1).</td>
<td>May 2011</td>
</tr>
<tr>
<td><strong>Adcirca</strong>&lt;sup&gt;®&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Adcirca (tadalafil) should not be used in individuals below 18 years of age</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Tracleer</strong>&lt;sup&gt;®&lt;/sup&gt;&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Tracleer (bosentan) labelling based on 2 studies BREATHE 3 (n=19) &amp; FUTURE (n=36). BREATHE 3 supports paediatric labelling in Section 5.1 Pharmacodynamic properties; 5.2 Pharmacokinetic properties</td>
<td>Quadrisect, dispersible 32 mg tablet formulation</td>
</tr>
<tr>
<td><strong>Volibris</strong>&lt;sup&gt;®&lt;/sup&gt;&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Volibris (ambrisentan) is not recommended for use in patients below 18 years of age due to a lack of data on safety and efficacy</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Flolan</strong>&lt;sup&gt;®&lt;/sup&gt;&lt;sup&gt;5&lt;/sup&gt;</td>
<td>There (epoprostenol) is limited information on the use of Flolan for PAH in children</td>
<td>n/a</td>
</tr>
<tr>
<td>Therapy</td>
<td>Design</td>
<td>Patients</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10–80 mg TID sildenafil</td>
<td>16-week randomised, double-blind, placebo-controlled</td>
<td>n=234 (1–17 years); IPAH/HPAH/CHD-PAH</td>
</tr>
<tr>
<td>4 weeks bosentan 2mg/kg b.i.d.</td>
<td>FUTURE-1 was a prospective, open-label, single-arm study consisting of</td>
<td>n=36 children aged 2–11 years, IPAH/HPAH in WHO FC II/III. Concomitant</td>
</tr>
<tr>
<td>and then 8 weeks 4mg/kg b.i.d.</td>
<td>a screening period, a 12-week treatment period, and a 28-day post-treatment follow-up period.</td>
<td>medications: epoprostenol, iloprost and CCB</td>
</tr>
<tr>
<td>SC treprostinil.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>al.</td>
<td></td>
</tr>
</tbody>
</table>
Uncontrolled epoprostenol study in children

- Single UK centre, open-label, retrospective study, from 1997 to 2005
- Children (4 months to 17 years) with PAH (n=39) treated with IV epoprostenol
- 28 children had additional oral specific therapy (bosentan)

- Epoprostenol therapy improved survival, WHO functional class, exercise tolerance and ability to thrive in children with severe PAH

Lammers et al. Heart 2007; 93: 739-43
Bosentan has been evaluated in three paediatric trials

- **BREATHE-3**: Bosentan Randomised trial of Endothelin Antagonist THerapy for pulmonary hypertension (open label study, evaluate the PK, efficacy and safety of bosentan in paediatric PAH pts)

- **FUTURE-1**: Paediatric FormUlation of bosenTan in pUlmmary arterial hypeRtEnsion (non-controlled open-label study, evaluate PK - safety of a new ped formulation of Tracleer)

- **FUTURE-2**: an open-label safety extension study is ongoing to assess long-term safety and outcome data

Bosentan

Bosentan is an oral, dual ERA that has been demonstrated to improve haemodynamics, exercise capacity, time to clinical worsening and WHO-FC in adults with PAH and haemodynamics, exercise capacity and WHO-FC in those with Eisenmenger’s physiology.

Although no randomised, controlled trial has yet been performed in children with PAH, open-label controlled and uncontrolled studies in children demonstrate improvements in haemodynamic measurements, exercise capacity or WHO-FC with bosentan therapy, either as monotherapy or in combination with other PAH therapies.

A specific pediatric formulation has been recently approved in Europe.

Dose: age ≥ 2 yrs 2mg/kg BID

Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children

A.A. Hislop*, S. Moledina*†‡, H. Foster*, I. Schulze-Neick† and S.G. Haworth*†‡

ABSTRACT: The aim of the present study was to evaluate a 5-yr experience of bosentan in children with pulmonary arterial hypertension (PAH). A retrospective, observational study was made of children in the UK Pulmonary Hypertension Service for Children (Great Ormond Street Hospital for Children, London, UK) who were given bosentan as monotherapy or in combination, from February 2002 to May 2008 and followed up for ≥ 6 months.

Detailed studies were made of 101 children with idiopathic PAH (IPAH) (n=42) and PAH associated with congenital heart disease (n=59). Before treatment, World Health Organization (WHO) functional class, 6-min walk distance (6MWD), height, weight and haemodynamic data were determined. Evaluations were analysed after 6 months and annually to a maximum of 5 yrs.

Median duration of treatment was 31.5 months. Initial improvement in WHO functional class and 6MWD was maintained for up to 3 yrs. Height and weight increased but the z-scores did not improve. After 3 yrs, bosentan was continued as monotherapy in only 21% of children with IPAH, but in 69% of repaired cases and 56% of those with Eisenmenger syndrome. The Kaplan–Meier survival estimates for the 101 patients were 96, 89, 83 and 60% at 1, 2, 3 and 5 yrs, respectively.

A treatment regime that includes bosentan is safe and appears to be effective in slowing disease progression in children with PAH.
Inhibition of phosphodiesterase type 5 (PDE5) induces vasodilation and also exerts antiproliferative effects (prevent the breakdown of cGMP)

... are acute pulmonary vasodilators as efficient as inhaled NO
... potentiate pulmonary vasodilation with NO
... they may be particularly beneficial in conjunction with NO, when

withdrawal of NO may lead to rebound PAH (potential cost of systemic hypotension, increased pulmonary shunting and impaired oxygenation)

Recently Sildenafil ev form. has been approved for adults by FDA - EMA
Examination of the current literature reveals limited data concerning the effect of treatments in paediatric PAH, for both general therapies and those specific to the disease. However, those data that are available suggest that, in the short- to medium-term at least, treatment effects in children are comparable to those observed in adults.

In order to provide clinicians with more robust recommendations based on firm experimental evidence, randomised, controlled clinical trials of PAH treatments in the paediatric setting are necessary.
### Study

<table>
<thead>
<tr>
<th>Study design</th>
<th>16-week randomised, double-blind, placebo-controlled, dose-ranging, parallel group study of oral Sildenafil in Treatment naïve children (Aged 1-17 years) with Pulmonary Arterial Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>10–80 mg TID SIL, PBO</td>
</tr>
<tr>
<td><strong>Patient</strong></td>
<td>characteristics</td>
</tr>
<tr>
<td></td>
<td>n=234 (1–17 years); IPAH/HPAH/CHD-PAH</td>
</tr>
<tr>
<td><strong>1° efficacy</strong></td>
<td>end-point</td>
</tr>
<tr>
<td></td>
<td>% change in peak VO$_2$ improved 7.7% in the combined SIL group vs PBO (p=0.056): 3.8%, 11.3%, and 8.0%, for the low, medium, and high SIL vs PBO</td>
</tr>
<tr>
<td><strong>2° efficacy</strong></td>
<td>end point</td>
</tr>
<tr>
<td></td>
<td>The SIL medium and high dose groups improved over PBO in mPAP (−3.5 and −7.3 mmHg) and PVRI (−4.5 and −7.2 units $\cdot m^{-2}$). Improvements in FC and global assessments were also observed with SIL vs PBO</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Six pts discontinued treatment (2 SIL pts due to AEs). Serious AEs were reported for 11 pts (1, 1, 7, and 2 in the low, medium, high, and PBO groups); 2 were treatment related in SIL pts. There were no treatment-emergent deaths</td>
</tr>
</tbody>
</table>

STARTS-1: Sildenafil study design in children

Screening (Can occur up to 3 weeks before randomisation [-21 to -1 days])

Randomisation Day 1

Double-blind Treatment Phase (16 weeks; Day 1 – Day 112)

Placebo

Sildenafil Low Dose

Sildenafil Low Dose

Sildenafil Low Dose

Sildenafil Med Dose

Sildenafil High Dose

Weeks 2–16

Follow-up (30–40 days)

Forced Titration (1 week; Day 1–Day 7)

Main Objective: Assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in paediatric subjects aged 1–17 years with PAH.

- Primary endpoint:
  - Exercise capacity (Peak VO$_2$, assessed by cycle ergometry)
    Increase in oxygen consumption at peak exercise (% change in Peak VO$_2$) at week 16 for combined sildenafil doses

- Secondary endpoints:
  - Change in haemodynamics (placebo corrected change in mPAP, PVRI, PVR, CI and RAP) as assessed by RHC
  - Time to Peak VO$_2$
  - Physical and psychological scales from the Child Health Questionnaire – Parent Form (CHQ-PF28)
  - Change in WHO functional class

PAH = pulmonary arterial hypertension; WHO = World Health Organization; CTD = connective tissue disease; IPAH = idiopathic PAH; CI = cardiac index
Subjects were randomised to one of three treatment groups (low, medium or high dose) or placebo.

Actual doses depended on body weight.

Target plasma concentrations of sildenafil were selected based on *in vitro* PDE5 inhibition data:

- Sildenafil dose levels were then selected based on body weight to achieve target plasma concentrations at steady state.

**Sildenafil doses (TID) to achieve target sildenafil steady-state maximum concentrations of 47, 140 and 373 ng/mL at the low, medium and high doses, respectively**

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8–20</td>
<td>NA†</td>
<td>10†</td>
<td>20</td>
</tr>
<tr>
<td>&gt;20–45</td>
<td>10</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>&gt;45</td>
<td>10</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

†Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8–20 kg patients (i.e., patients would receive the same dose because of the available tablet strengths); consequently there was no low dose for this group.
Inclusion and exclusion criteria

- **Inclusion criteria:**
  - Age 1–17 years
  - Weight ≥8 kg
  - IPAH, HPAH, or PAH associated with CHD or CTD

- **Exclusion criteria:**
  - PH secondary to other diseases, left-sided heart disease and other similar heart-related disease
  - Off-label treatment with sildenafil, endothelin receptor antagonists or prostacyclin/prostacyclin analogues within 30 days prior to randomisation
  - Other medications e.g. parenteral inotropic medication, parenteral vasodilators within 3 months of screening, alpha-blockers or cytochrome p450 (CYP) 3A4 inhibitors
# Baseline demographics

<table>
<thead>
<tr>
<th>Overall n (%) (n=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>1-4</td>
</tr>
<tr>
<td>5-12</td>
</tr>
<tr>
<td>13-17</td>
</tr>
<tr>
<td>≥18</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Region</strong></td>
</tr>
<tr>
<td>Asia</td>
</tr>
<tr>
<td>America</td>
</tr>
<tr>
<td>Europe</td>
</tr>
<tr>
<td>South America</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aetiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PAH</td>
</tr>
<tr>
<td>Shunts</td>
</tr>
<tr>
<td>Surgical repair</td>
</tr>
</tbody>
</table>
## Baseline Peak VO\(_2\) haemodynamics and functional class

<table>
<thead>
<tr>
<th></th>
<th>Normal Values</th>
<th>Placebo Means (SD)</th>
<th>Sildenafil (combined) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO(_2) ml/kg/min*</td>
<td>30–35</td>
<td>20.02 (3.8)</td>
<td>17.61 (4.22)</td>
</tr>
<tr>
<td>(exercising subpopulation)</td>
<td></td>
<td>n=29</td>
<td>n=77</td>
</tr>
<tr>
<td>mPAP, mmHg*</td>
<td>12–15</td>
<td>59.4 (22)</td>
<td>62.8 (22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=56</td>
<td>n=165</td>
</tr>
<tr>
<td>PVRI, Wood units/m(^2)*</td>
<td>2</td>
<td>20.9 (16.6)</td>
<td>16.1 (12.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=50</td>
<td>n=152</td>
</tr>
<tr>
<td>CI, litres/min/m(^2)*</td>
<td></td>
<td>4.08 (2.31)</td>
<td>3.44 (1.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=52</td>
<td>n=154</td>
</tr>
<tr>
<td>WHO FC, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25 (42)</td>
<td>50 (29)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>29 (48)</td>
<td>91 (52)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>6 (10)</td>
<td>29 (17)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

* Intention to treat cohort

mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; CI: cardiac index FC = functional class; WHO = World Health Organization
Primary endpoint: improvement in exercise capacity

Peak VO₂ (% change from baseline to week 16) vs placebo (n=29) with 95% CIs

- Low (n=24): 3.81
- Medium (n=26): 11.33
- High (n=27): 7.98
- Low/Med/High (n=77): 7.71

p=0.056

Revatio EU SmPC May 2011;
Effects of sildenafil on PVRI in children: Proportional Comparison

Ratio Comparison to Placebo (n=52) with 95% CIs

Low (n=37)  Medium (n=51)  High (n=68)  L/M/H (n=156)

0.836  0.727  0.819  0.982

Effects of sildenafil on mPAP in children

(Change from baseline to week 16) comparison to placebo (n=56) with 95% CIs (mmHg)

Low (n=39)  Medium (n=55)  High (n=71)  L/M/H (n=165)

-7.3  -3.5  -3.1  1.6
WHO functional class comparisons to placebo

Odds Ratio Comparison to Placebo (n=60) with 95% CIs

- Low (n=40): 0.60
- Medium (n=54): 2.25
- High (n=76): 4.52

Baseline FC I
either stayed the same or worsened

Baseline FC II - IV
either improved or remained stable

% of Subjects

- Placebo
- Low
- Medium
- High

Improvement
No Change
Worsened
Medium and high dose **sildenafil** achieves a **meaningful Peak VO\textsubscript{2} response** in children.

A **dose response** was demonstrated with the secondary endpoints **mPAP and PVRI**.

Treatment with medium and high dose sildenafil is associated with **improvement or stabilisation of WHO FC**.
4.1 Indicazioni terapeutiche

Trattamento di pazienti adulti con ipertensione arteriosa polmonare di classe funzionale II e III dell’OMS, al fine di migliorare la capacità di fare esercizio fisico. L’efficacia è stata dimostrata nell’ipertensione polmonare primaria e nell’ipertensione polmonare associata a malattia del tessuto connettivo.

**Popolazione pediatrica**
Trattamento di pazienti pediatrici di età compresa tra 1 e 17 anni con ipertensione arteriosa polmonare. L’efficacia in termini di miglioramento della capacità di fare esercizio fisico o di emodinamica polmonare è stata dimostrata nell’ipertensione polmonare primaria e nell’ipertensione polmonare associata a malattia cardiaca congenita (vedere paragrafo 5.1).
INDICAZIONI PEDIATRICHE

4.1 Indicazioni terapeutiche

Popolazione pediatrica
Trattamento di pazienti pediatrici di età compresa tra 1 e 17 anni con ipertensione arteriosa polmonare
efficacia in termini di miglioramento della capacità di fare esercizio fisico o di emodinamica polmonare è stata dimostrata nell’ipertensione polmonare primaria e nell’ipertensione polmonare associata a malattia cardiaca congenita (vedere paragrafo 5.1).

4.2 Posologia e modo di somministrazione

Popolazione pediatrica
La sicurezza e l’efficacia di Revatio nei bambini di età inferiore a 1 anno non sono state stabilite. Non ci sono dati disponibili.

Per i pazienti pediatrici di età compresa tra 1 e 17 anni, la dose raccomandata nei pazienti ≤ 20 kg è 10 mg (1 ml di sospensione ricostituita) tre volte al giorno, e per i pazienti > 20 kg è 20 mg (2 ml di sospensione ricostituita o 1 compressa) tre volte al giorno. Dosi più elevate non sono raccomandate nei pazienti pediatrici (vedere paragrafo 5.1).

Per le istruzioni sulla preparazione del medicinale prima della somministrazione, vedere paragrafo 6.6.
Currently, its role in PAH therapy may be for patients who do not improve or who deteriorate.

Potential treatment combinations include combining ERAs with prostanoids, prostanoids with PDE inhibitors, PDE inhibitors with ERAs.

With results from ongoing randomized trials the question of whether combination therapy offers therapeutic advantages over monotherapy may finally be answered.

However, despite the lack of clear guidance, experts agree that initial results are encouraging.

Moledina et al, Heart 2010;96:1401-1406
- Atrial septostomy (mortality 5-15%) has been shown to improve symptoms,\(^1,2\) haemodynamics\(^1\) and survival\(^2\) in children with PAH with recurrent syncope and/or RH failure

- Potts shunt has also been shown to help improve symptoms and haemodynamics\(^3\)

- As in adults, the only way to cure PAH in children is through lung transplantation\(^4\)
  - Lack of suitable donors is a major problem\(^4\)

As in adults, the only way to cure PAH in children is through lung transplantation
- Lack of suitable donors is a major problem
- The timing of listing (probability of surviving 2 years without transplant is ≤50%)

Median survival in children is 4.3 yrs, with a tendency toward improved outcome in younger children (0–10 yrs). 3 and 5-yr survival rates in children with heart–lung transplantation are 69% and 45%, respectively.

Due to its progressive and devastating nature, the prognosis of paediatric PAH remains a serious concern.

Various pharmaceutical treatments options are on the horizon, which may offer increased hope in the future; but until then, timely treatment and early combination therapy may be the best courses of action to improve survival in childhood PAH.
Grazie per l'attenzione
Schematic diagram showing the ideal approach to pulmonary arterial hypertension management, which involves regular monitoring and early intervention.

Sitbon, Galiè Eur Respir Rev 2010; 19: 118, 272-278