The treatment of PAH has advanced dramatically in the last decade through the results of several well-designed clinical trials demonstrating the efficacy of several therapies that target specific abnormalities present in PAH. Currently, standard treatment including diet, oral anticoagulation, diuretic and digoxin, are part of the modern therapeutic approach.

**Standard treatment**

**Diet**

A low-salt diet and judicious use of diuretics can be helpful in reducing volume overload in patients with PAH and right ventricular failure. Because the right heart is dependent on preload, care should be taken to avoid excessive diuresis and further reduction of cardiac output.
Oral anticoagulation
Anticoagulation use is based on the improved survival data from two small retrospective studies as well as evidence of microscopic in situ thrombosis\textsuperscript{34}. In the absence of contraindications, anticoagulation is recommended to keep the target INR at 1.5 - 2.5. Anticoagulation use is controversial in scleroderma associated PAH and in CHD-PAH with hemoptysis, for high risk of bleeding complications\textsuperscript{35, 36}.

Diuretics
In the setting of PAH, three kinds of diuretics have been used: thiazide, loop, and potassium-sparing diuretics. These drugs are recommended for right ventricular failure. It is not known whether diuretics alter mortality or morbidity in PAH\textsuperscript{37, 38}. Loop diuretics are traditionally used and bumetanide, in addition to metolazone, could be another option\textsuperscript{39}.

Spironolactone
Sympathetic system stimulation, followed by activation of the renin, angiotensin, and aldosterone system, are important contributors to the vicious circle of chronic heart failure. Accounting for this excessive neurohormonal response resulted in major and highly effective changes in therapeutic approach to chronic heart failure, primarily due to left ventricular dysfunction. Right ventricular dysfunction due to severe PAH ultimately results in similar changes in systemic hemodynamic, trigger neurohormonal response, low cardiac index and hypotension. Spironolactone remains the only classical neurohormonal modulator, which found place in the treatment of isolated RV failure. It is used in PAH as an adjunct to loop diuretics, but also with the hope of limiting the aldosterone-induced myocardial fibrosis\textsuperscript{40}.

In addition, advances in the knowledge of the molecular mechanisms involved in PAH suggest that endothelial dysfunction with chronic impaired production of vasoactive mediators plays a key role. Reduced production of vasoactive mediators, such as NO and prostacyclin, along with prolonged overexpression of vasoconstrictors, such as endothelin-1 (ET-1), not only affect vascular tone but also promotes vascular remodeling. Thus, these substances represent
logical pharmacological targets. Experimental studies showed ET-1 could stimulate aldosterone secretion in different species, both in vivo and in vitro. Spironolactone should not be used in patients with serum creatinine > 2.5 mg/dl or potassium > 5.0 meq/L.

**Digoxin**
This drug has been used in right ventricular failure and flutter or atrial fibrillation patients, although it has not been studied extensively in PAH. If used as an inotropic agent, trough levels should be kept between 0.5 and 1.0 ng/ml to prevent its adverse effects. Considering that it has no activity of blood pressure, renal function and ejection fraction, it is an attractive option for PAH patients with flutter or atrial fibrillation. In addition, digoxin could induce favorable acute hemodynamic effects and decrease plasma norepinephrine in patients with right ventricular failure and IPAH. However, the long-term consequences of this treatment are unknown.

**Oxygen**
It is recommended in patients with proven hypoxemia, PaO2 < 55 mmHg or SaO2 < 89% at rest, during sleep or with ambulation to keep SaO2 > 90% at all times. Patients may require supplementation at night and during air travel even when during daytime the level of oxygenation is normal. Because hypoxia is a potent pulmonary vasoconstrictor, it is critical to identify and reverse hypoxemia. Low-flow supplemental oxygen therapy prolongs survival in hypoxemic patients. Failure to recognize and correct hypoxemia may be the error most frequently made in the treatment of PAH patients.

Maximizing supplemental oxygen therapy in a short-term period had beneficial effects as a selective pulmonary vasodilator in adult patients with PAH and was independent of baseline oximetry, hemodynamic, and echocardiographic right ventricular function. Improvement in pulmonary vascular resistance in response to maximum supplemental oxygen therapy may also serve as a marker of pulmonary vasoreactivity in adult and pediatric PAH and CHD populations. Supplementing arterial oxygen tension beyond the minimum target of 60 mm Hg may improve pulmonary vascular resistance and cardiac index. These short-
term effects are likely due at least partially to releasing hypoxic pulmonary vasoconstriction, but may also be due to additional mechanisms as yet unidentified. 47.

**Role of calcium channels blockers.**

Three kinds of calcium channels blockers (CCBs) are used in the treatment of patients with PAH: nifedipine, diltiazem and recently, amlodipine. Currently, we have strong evidence obtained through several clinical studies regarding nifedipine and diltiazem use. 48 - 52. There are no studies specifically evaluating the long-term effects of amlodipine in acute vasodilator responders. One small short-term study including only 6 patients with PAH (5 with chronic thromboembolic disease and one with IPAH) showed that amlodipine, up to a dose of 40 mg, was well-tolerated. 53. A mPAP and PVR > 20%, decreased with mild effects on systemic blood pressure in two patients was observed. The use of amlodipine in long-term treatments is based in part in the efficacy and safety shown in patients with congestive heart failure and perhaps on its long half-life, which may provide additional safety from hemodynamic deterioration that may occur after CCB withdrawal. 53 - 54. Despite a high average dose of CCBs, the doses of nifedipine and diltiazem ranged from 60 to 120mg daily and 180 to 720 mg respectively, indicating that some patients had long-term improvement with conventional doses of CCBs. 55. Whether these doses in Hispanics and Latin-Americans patients are safe is not known. No randomized clinical trials have been designed comparing treatment with low versus high doses of CCBs for chronic treatment based on the dose required for an acute vasodilator effect.

**Special recommendations**

Hot baths or showers are discouraged because the resultant peripheral vasodilatation can produce systemic hypotension and syncope. We discourage exposure to high altitudes (more than approximately 1800 m above sea level), as this may produce hypoxic pulmonary vasoconstriction and further compromise oxygen transport. Air travel can be problematic and traveling with oxygen is highly recommended. Nocturnal hypoxemia occurs in more than 75% of patients with IPAH without sleep apnea. The use of vasoconstricting sinus or cold medications or the use of serotonergic medications for migraine headaches
is not recommended. Immunization against influenza and pneumococcal pneumonia is suggested. Caution should be used with laparoscopic procedures in which carbon dioxide is used for abdominal insufflations, as its absorption can produce hypercarbia, which is a pulmonary vasoconstrictor.

**Optimal treatment Prostanoids**

Prostacyclins are endogenous substances that are produced by vascular endothelial cells and induce vasodilatation, inhibition of platelet activity, and antiproliferative effects. A dysregulation of prostacyclin metabolic pathways has been shown in patients with PAH and this represents the rationale for the exogenous therapeutic administration of this substance. The clinical use of prostacyclin in patients with PAH has been made possible by the synthesis of stable analogs that possess different pharmacokinetic properties but share similar pharmacodynamic effects. Experience in humans has been initially collected with epoprostenol, which is a synthetic salt of prostacyclin.

Epoprostenol has a short half-life in the circulation and requires continuous administration by the intravenous route by means of infusion pumps and permanent tunnelized catheters. For these reasons, alternatives to intravenous epoprostenol have been sought and this has led to the development of analogs that can be administered subcutaneously (treprostinil), orally (beraprost sodium) or by inhalation (iloprost). Three unblinded clinical trials and several uncontrolled trials have shown that treatment with epoprostenol improved symptoms and exercise capacity in NYHA class III patients, PAH patients, and also survival in patients with IPAH. Subcutaneous treprostinil improved symptoms, exercise, hemodynamics and clinical events in the largest clinical trial ever performed in PAH, but local infusion site reactions limited efficacy in a proportion of patients. Oral beraprost sodium improved exercise capacity only in patients with IPAH and is the only prostacyclin analog that has also been tested in NYHA class II patients.

Inhaled iloprost has improved symptoms, exercise capacity and clinical events in patients with PAH and inoperable CTPAH. The favorable effects of prostanoids observed in all studies coupled with different profiles of adverse
events and tolerability for each prostacyclin analog allow the unique opportunity to select the most appropriate compound for the individual patient with PAH.63 - 66.

**Phosphodiesterase - 5 inhibitors**

These drugs catalyse the hydrolysis of cyclic guanosine monophosphate (cGMP) to its inactive 5-nucleotide monophosphate. Inhibitors of PDE5 prevent the breakdown of cGMP, thereby enhancing NO; PDE 5 is expressed in lung tissue. Although the distribution of PDE in tissue is heterogeneous, there is a high deposition in the skeletal muscle, heart and vascular smooth muscle. Small preliminary studies have highlighted the potential for the PDE5 inhibitor sildenafil for the treatment of PAH, and its clinical profile has been evaluated in a larger, double-blind, placebo-controlled, dose ranging study.67 - 70. There has been no information of sildenafil interaction with warfarin.

**Endothelin-Receptor Antagonists**

Two endothelin-receptor isoforms, endothelin-A (ETA) and endothelin-B have been identified. The ETB receptors are thought to be principally involved in the clearance of endothelin, particularly in the vascular beds of the lung and kidney. Activation of ETB receptors may also cause vasodilatation and NO release.

**Bosentan**

It is an orally active, non-peptidic, non-selective, sulphonamide- class ETa/ETb antagonist with twice daily dosing. It was the first ERA to receive approval for the treatment of patients with PAH in NYHA functional class II. Significant benefits of bosentan treatment have been shown in separate studies.71 - 74.

The *Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients* (EARLY trial) was the first study specifically designed to evaluate effects of ERAs in PAH patients in functional class II. Primary results from this trial highlight a significant reduction in pulmonary vascular resistance while the other primary endpoint 6-MWT did not reach statistical significance. When CTEPH patients were considered, bosentan led to significant reductions in pulmonary vascular resistance and improved dyspnea score while the 6-MWT remained unchanged.
over the 6 month study period (BENEFIT trial). Bosentan partially induces the cytochrome P450 system, thereby increasing warfarin metabolism and the required dose.

**Sitaxsentan**
A highly selective ETa receptor antagonist of the sulphonamide class of ERA has received approval for the treatment of PAH patients with functional class III symptoms at an oral dose of 100 mg once daily (European Union, Canada, and Australia). In USA, sitaxsentan remains to be approved; currently STRIDE 5 is ongoing and at its end additional data will be obtained.

The safety and efficacy of sitaxsentan has been clinically tested in the sitaxsentan trials to relieve impaired exercise (STRIDE Program) \(^{75-76}\), three randomized placebo-controlled trials (STRIDE1 \(^{77}\), STRIDE 2 \(^{78}\), and STRIDE 4), two non-controlled studies (Study 211 and Stride 6) \(^{79}\) and three long-term studies (STRIDE 1X, STRIDE 2X, and STRIDE 3). Long-term data is available from a small group of patients, suggesting that efficacy and safety are maintained for up to 12 months \(^{80}\).

Data from a subgroup analysis did not exhibit a clinically relevant treatment effect; however, increase in 6-MWT in patients with PAH associated with connective tissue disease was observed \(^{80-81}\). Sitaxsentan inhibits the liver isoenzyme CYP2C9; therefore, combing sitaxsentan with warfarin can lead to a decrease dose of warfarin at initiation therapy to avoid bleeding complications.

**Ambrisentan**
It is an orally active ETa receptor antagonist belonging to the propanoic acid class. In the USA, ambrisentan has been approved at a dose of 5 – 10 mg once daily for the PAH patients (WHO functional class II or III) to improve exercise capacity and delay clinical worsening. Results are based on a 12-week, blinded dose (1, 2.5, 5 or 10mg daily) phase II study (improvements in 6-MWT, functional class, Borg score, quality of life and pulmonary hemodynamics) \(^{82-83}\). Long-term follow-ups of patients treated with ambrisentan in the two pivotal studies and the open label extension show that 95% were still receiving
ambrisentan monotherapy with sustained effects. Ambrisentan has no interaction with warfarin and has low profile to collateral effects.

**Combination therapies**

This therapeutic approach offers the possibility of enhanced efficacy and may permit individual agents to be used in lower doses, minimizing toxicity. The potentially complementary mechanisms of action among the three current pharmacologic approaches provide rationale for investigation of these agents in novel combination regimens. However, the impact of these strategy health systems needs to be analyzed (Table I).

*Acknowledgment:* to Alicia Sanchez - Ramirez for her editorial support
# Table I

<table>
<thead>
<tr>
<th>Combination Regimens.</th>
<th>Key finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERA plus Prostanoid.</strong></td>
<td></td>
</tr>
<tr>
<td>Bosentan plus Epoprostenol</td>
<td>36.3% decrease in pulmonary resistance versus 22.6% (placebo) (p=PS).</td>
</tr>
<tr>
<td>Iloprost plus Bosentan</td>
<td>58 m improvement in 6-MWT (p&lt;0.001).</td>
</tr>
<tr>
<td>Bosentan plus Iloprost</td>
<td>26 m placebo adjusted improvement in 6-MWT (p=0.051).</td>
</tr>
<tr>
<td><strong>PDE5 inhibitor plus prostanoid</strong></td>
<td></td>
</tr>
<tr>
<td>Sildenafil plus Iloprost</td>
<td>Maximun change in pulmonary vasodilatory potency seen with sildenafil 50mg plus inhaled iloprost. 44.2% decreased compared with -14.1% decreases with nitric oxide. Sildenafil and Iloprost act synergistically on pulmonary vasculature.</td>
</tr>
<tr>
<td>Iloprost plus Sildenafil</td>
<td>Combination Iloprost plus sildenafil reduced mPAP more than Iloprost alone (13.8 versus 9.4mm Hg; p&lt;0.009)</td>
</tr>
<tr>
<td>Sildenafil plus Beraprost</td>
<td>2.2 - fold greater reduction in mPAP on beraprost plus Sildenafil 1.6 - fold greater reduction in PVR.</td>
</tr>
<tr>
<td>Sildenafil plus Epoprostenol</td>
<td>Sildenafil decrease m PAP by 10% (p&lt;0.05) Sildenafil decrease PVR by 13% (p=NS)</td>
</tr>
<tr>
<td><strong>ERA plus PDE5 inhibitor</strong></td>
<td></td>
</tr>
<tr>
<td>Bosentan plus Sildenafil</td>
<td>84m improvement in 6MWD (p=0.04) Improvement in NYHA class (0% to 27.7% class I/II, p=0.02)</td>
</tr>
<tr>
<td>Bosentan plus Sildenafil</td>
<td>115m improvement in 6MWD at 3 months (p=0.007) 3.4ml/min/kg increase in peak oxygen consumption (p=0.006)</td>
</tr>
</tbody>
</table>
References


41. Hebei Medical University spironolactone combined with captopril and carvedilol for the treatment of pulmonary arterial hypertension ClinicalTrials.gov processed this record on May 19, 2009


80. Langleben D, Hirsch A, Shalite E et al. Sustained symptomatic, functional and hemodynamic benefit with the selective endothelin A receptor antagonist, sitaxsentan in patients with pulmonary arterial hypertension: a 1 year follow up study. CHEST 2004; 126:1377-1381


