# Treatment Options for World Health Organization Groups 2 and 3 Pulmonary Hypertension: Using Pulmonary Arterial Hypertension Medication

**Austin Makadia[1], Jorge Garza[2], Arjun Kamath[2], Ahsan Syed[2], Vishesh Persaud[1], Abhay Vakil[1]**

1 Department of Pulmonary Medicine, HCA Corpus Christi Medical Center, Corpus Christi, Texas; 2 Department of Internal Medicine,, HCA Corpus Christi Medical Center, Corpus Christi, Texas

CORPUS CHRISTI MEDICAL CENTER

*An HCA Affiliated Hospital*

## Background

Pulmonary hypertension (PH) is defined as a pulmonary artery pressure of greater than 25 mmhg at rest. PH can lead to decreased quality of life and even death. PH has a multitude of different etiologies and, for most of them, treating underlying causes is the mainstay of treatment for PH. Certain medications, such as phosphodiesterase-5-inhibitor (PDE5-I), endothelin receptor antagonists, and prostacyclin analogs have been shown to be effective in treating idiopathic PH. We wanted to see if there was a role for using these drugs in treating other forms of pulmonary hypertension.

## Clinical/Pathophysiological differences

While pulmonary hypertension may be due to a variety of underlying etiologies, everyone exhibits a number of similar pathophysiologic changes. These include increased arteriolar contractility in the pulmonary circulation, endothelial dysfunction, remodeling and proliferation of endothelial and smooth muscle cells. These pathologic changes eventually lead to decreased blood flow in the small pulmonary arteries, which leads to increased pulmonary vascular resistance, and eventual right sided heart failure. In idiopathic pulmonary arterial hypertension, increased pulmonary vascular resistance is caused, not only to impaired vasodilation of pulmonary vessels, but also from increased vasoconstriction. There is dysregulation in cyclooxygenase 2 and nitric oxide (NO) synthase which are normally responsible for vasodilation as well as upregulated endothelin-1 system which leads to increased vasoconstriction [5].

Group 2 pulmonary hypertension is secondary to left heart disease. Impaired cardiac function causes increased pressure in the pulmonary circulation due to increased left atrial pressures. Eventually, chronically increased pressures in the pulmonary circulation lead to retrograde transmission of left atrial pressure into the pulmonary circulation. Chronic venous hypertension leads to medial hypertrophy and intimal proliferation of pulmonary arteries and arterioles that increase pulmonary vascular resistance [6].

Group 3 pulmonary hypertension is due to chronic hypoxemia, therefore, is largely the result of pulmonary hypoxic vasoconstriction. In response to hypoxia, intrapulmonary arteries constrict. Chronic hypoxia will eventually lead to vascular remodeling caused by upregulation of mediators that reinforce vasoconstriction [7].

Classic symptoms of pulmonary hypertension include fatigue, lethargy, dyspnea, exertional syncope/presyncope. Physical examination findings may include a loud p2, tricuspid regurgitation murmur, third or fourth heart sound [8].

## Established group treatments

World Health Organization (WHO) group 1 pulmonary arterial hypertension (PAH) is commonly treated with a combination of Ambristan, an endothelin-receptor-antagonist (ERA) and tadalafil an PDE5-I [11]. It has been shown that combination therapy results in lower rates of treatment failure compared to treatment with Ambristan and tadalafil alone. Typically group 2 and group 3 PH is treated by treating the underlying conditions that result in increased pulmonary pressures. In WHO group 2 PH established treatment targets the pathophysiologic mechanisms that lead to worsening heart function such as reducing blood pressure, volume control, reversing valvular disease, or reducing sympathetic and renin-angiotensin-aldosterone-system (RAAS) activation [9]. Similarly group 3 PH treatment targets the underlying lung disease with anti-inflammatory therapies, bronchodilators, supplemental oxygen and CPAP [9].

## Potential Group 2-3 treatments

Treatment of patients with group 2 and group 3 PH has traditionally focused on treating the underlying cause of PH. However, there is evidence that suggests that these patients may benefit from treatments traditionally used for group 1 PAH. Exercise tolerance is associated with improved quality of life as well as decreased mortality in heart failure. Patients with heart-failure-with-reduced-ejection-fraction (HFrEF) and combined postcapillary and precapillary pulmonary hypertension treated with sildenafil showed improvements in exercise capacity as measured by six-minute-walk-test (6MWT), peak VO2, and ventilatory efficiency as well as significant improvements in new-york-heart-association (NYHA) functional class [15, 21, 26]. Findings from echocardiogram and cardiac catheterization also reflected improvements in hemodynamic parameters and right ventricular function suggesting improvements in pulmonary vasculopathy [15, 21]. In addition to objective measures, self reported quality of life questionnaires were also higher in HFrEF patients treated with sildenafil compared to those who were not further supporting the clinical applicability of sildenafil in this subset of patients. In addition, sildenafil combined with beraprost sodium also led to significantly lower pulmonary arterial hypertension associated biochemical indicators, mean pulmonary arterial pressures, left-ventricular-ejection-fraction (LVEF), stroke-volume (SV), and cardiac-output (CO). This suggests that combination therapy with sildenafil and beraprost sodium may be more effective than sildenafil alone at improving pulmonary arterial hypertension and improving left heart failure [18].

Furthermore, fewer hospitalizations and deaths have been observed with HFrEF being treated with PDE5-Is. While this suggests that treatment with PDE5-I may potentially reduce death and hospitalizations in patients with HFrEF, data on these outcomes was limited. However, this raises the possibility of PDE5-I as a potential new addition to the treatment regimen for a subset of patients with HFrEF. In patients with heart-failure-with-preserved-ejection-fraction (HFpEF), treatment with PDE5-I has failed to show significant improvements in exercise capacity, cardiac performance, or reductions in pulmonary pressures [21, 22, 24]. In fact, treatment with PDE5-I may lead to acute pulmonary edema in patients with pulmonary hypertension due to HFpEF [14].

In pulmonary hypertension secondary to lung disease/hypoxia, data is more varied. Goudie et al. found no difference in exercise capacity or quality of life in patients with chronic obstructive pulmonary disease (COPD) treated with tadalafil despite causing pulmonary vasodilation [27]. Some studies have shown improvements in 6MWT as well as improvement in the body-mass-index-airflow-obstruction-dyspnea-exercise index (BODE) index in patients treated with sildenafil compared to placebo [16, 19, 25]. Tanabe et al. did find significant differences in survival in patients receiving PDE5-I therapy, but these differences were more pronounced in those patients with pulmonary fibrosis with emphysema and interstitial pneumonia [28]. In japanese patients with pulmonary hypertension associated with respiratory diseases, patients initially treated with PH targeted therapies (mostly PDE5-I) had better survival although these were predominantly patients with mild ventilatory impairment. Patients with chronic thromboembolic pulmonary embolism, treatment with sildenafil did not improve exercise capacity, but it did have a significant effect on WHO class and pulmonary vascular resistance [29].

## Conclusion

Pulmonary hypertension can be debilitating and deadly for those affected by it. Only WHO group 1 PAH has proven and widely accepted medical therapies that target pulmonary hypertension. While treatment for WHO group 2 and group 3 PH has traditionally focused on treating the underlying cause, PH targeted therapies may offer potential treatment options that may benefit these patients. There is a growing body of evidence that suggests that PAH specific treatments may improve the quality of life and clinical outcome of patients with WHO group 2 pulmonary hypertension. The evidence for WHO group 3 pulmonary hypertension is less conclusive, however studies have shown that certain PAH specific treatments may have a beneficial effect on certain subgroups within this patient population. The research into this topic is still limited and more research is needed to understand the clinical utility of these therapies for patients with WHO group 2 or 3 PH.

## References

1. A Global view of pulmonary hypertension. The Lancet. Prof Marius M Hoeper
2. Definitions and diagnosis of pulmonary hypertension. Journal of the American College of Cardiology. Marius M Hoeper et al.
3. 3. Increasing Incidence and Prevalence of World Health Organization Groups 1 to 4 Pulmonary Hypertension. D Thiwanka Wijeratne et al.
4. Pulmonary arterial hypertension: classification, diagnosis, and contemporary management. Postgraduate medical journal. D J Fox and R S Khattar
5. Pulmonary arterial hypertension: Pathophysiology and treatment. Diseases. Norris S. H. Lan et al.
6. The biologic basis of group 2 pulmonary hypertension. Ana L Fernandez et el. International journal of molecular sciences
7. Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. Chest. Kimberly J Dunham-Snary et al.
8. Pulmonary arterial hypertension: the clinical syndrome. Circulation Research. Yen-Chun Lai et al.
9. Pulmonary Hypertension: Types and treatments. Cardiology Reviews. Lisa J Rose-Jones
10. Five year outcomes of patients enrolled in the REVEAL registry. Chest. Harrison W Farber et al.
11. Clinical and hemodynamic improvements after adding ambrisentan to background pde5i therapy in patients with pulmonary arterial hypertension exhibiting a suboptimal therapeutic response (ATHENA-1). Respiratory Medicine. Shelly Shapiro et al.
12. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. New England Journal of Medicine. Nazzareno Galie et al.
13. ARIES-3:ambrisentan therapy in a diverse population of patients.
14. Differential effects of the phosphodiesterase inhibition in chronic heart failure depending on the echocardiographic phenotype (HFREF or HFpEF): a meta-analysis
15. Phosphodiesterase 5 inhibitor sildenafil in patients with heart failure with preserved ejection fraction and combined pre- and postcapillary pulmonary hypertension: a randomized open-label pilot study. BMC Cardiovascular disorders. Evgeny Belyavskiv.
16. Phosphodiesterase 5 inhibitors for pulmonary hypertension. Chochrane review. Haley Barnes
17. Therapeutic benefits of PDE-5 inhibition on chronic heart failure: A Meta-analysis. Renato De Vecchis. (retracted)
18. Efficacy of Beraprost Sodium Combined with Sildenafil and Its Effects on Vascular Endothelial Function and Inflammation in Patients Experiencing Left Heart Failure Complicated with Pulmonary Arterial Hypertension. Medical Science Monitor. Daoyuan Sun
19. Efficacy and safety of Sildenafil treatment in pulmonary hypertension caused by chronic obstructive pulmonary disease: A meta-analysis. Life Sciences. Yingying Hao.
20. Acute effect of sildenafil on central hemodynamics in mechanically ventilated patients with WHO group III pulmonary hypertension and right ventricular failure necessitating administration of dobutamine. International journal of cardiology. Dimitrios Karakitsos.
21. Pulmonary hemodynamics and effects of phosphodiesterase type 5 inhibition in heart failure: a meta-analysis of randomized trials. BMC Cardiovascular disorders. In-Chang Hwan.
22. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. European Heart Journal. Elke S Hoendermis.
23. Multi-Institutional Prospective Cohort Study of Patients With Pulmonary Hypertension Associated With Respiratory Diseases. Circulation Journal. Nobuhiro Tanabe.
24. Phosphodiesterase-5 Inhibitors Improve Clinical Outcomes, Exercise Capacity and Pulmonary Hemodynamics in Patients With Heart Failure With Reduced Left Ventricular Ejection Fraction: A Meta-Analysis. Journal of Clinical Medicine Research. Renato De Veccis.
25. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial. Journal of Heart and Lung Transplantation. Patrizio Vitulo.
26. Comparative effectiveness of sildenafil for pulmonary hypertension due to left heart disease with HFrEF. Hypertension Research. Rong Jiang.
27. Tadalafil in patients with chronic obstructive pulmonary disease: a randomized, double-blind, parallel-group, placebo-controlled trial. Lancet Respiratory Medicine. Andrew R Goudie.
28. Multi-institutional retrospective cohort study of patients with severe pulmonary hypertension associated with respiratory diseases. Respirology. Nobuhiro Tanabe.
29. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. Chest. Jay Suntharalimgam

*This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.*

HCA Healthcare®