A review of therapeutic agents for the management of pulmonary arterial hypertension

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Abstract: Pulmonary arterial hypertension (PAH) is an uncommon, progressive and life threatening disease characterized by a proliferative vasculopathy of the small muscular pulmonary arterioles resulting in elevated pulmonary vascular resistance and eventually right ventricular failure. An increasing understanding of the pathobiology of PAH and its natural history has led to the development of numerous targeted therapies. Despite these advances there is significant progression of disease and the survival rate remains low. This article reviews the agents currently available for the medical management of PAH.

Keyword: pulmonary arterial hypertension, prostanoid, endothelin receptor antagonist, phosphodiesterase inhibitor, soluble guanylate cyclase stimulator

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Introduction

Pulmonary arterial hypertension (PAH) is a proliferative vasculopathy affecting the small muscular arteries and arterioles characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, and thrombosis *in situ* of the small pulmonary arteries and arterioles. The World Health Organization (WHO) classified pulmonary hypertension (PH) into five groups based upon etiology and mechanism (Table 1). This review will focus on the therapeutic agents available for the management of group 1 PAH.

Presentation

Patients with PH have a varied spectrum of presentation. A small percentage of patients are asymptomatic on presentation, but may have exertional dyspnea, fatigue, weakness, or dizziness early in the disease process. With disease progression, dyspnea at rest, exertional angina, and palpitations may develop [Udeoji and Schwarz, 2013; McGoon *et al.* 2004].

Physical exam findings including an accentuated pulmonary component of the second heart sound, early systolic ejection click, a midsystolic ejection murmur, palpable parasternal lift, right ventricular S4 gallop, and a prominent jugular 'a' wave are often subtle, but when present can suggest the diagnosis [McGoon *et al.* 2004]. Signs of more advanced disease can include a diastolic murmur of pulmonary regurgitation and a holosystolic murmur of tricuspid regurgitation. With disease progression, findings indicative of right heart failure can be seen including distended jugular veins, hepatojugular reflex, a pulsatile liver, and peripheral edema. Cyanosis, if present, suggests right-to-left shunting, severely reduced cardiac output, or impairment in intrapulmonary gas transfer [McGoon *et al.* 2004]. Clubbing is a rare finding, and if present, congenital heart disease or pulmonary veno-occlusive disease should be considered [Holcomb *et al.* 2000].

Diagnostic testing

EKG

EKG findings can suggest a diagnosis of PH but is not sensitive enough to use as a screening test. Many patients with PH can have a normal EKG [Ahearn *et al.* 2002]. EKG findings can include right axis deviation, right ventricular (RV) hypertrophy, RV strain, right bundle branch block, or QTc prolongation [Rich *et al.* 1987; Galie *et al.* 2015b]. An abnormal EKG is more likely to be seen in severe disease and a normal EKG does not exclude PH [Galie *et al.* 2016].

Table 1. WHO classification of pulmonary hypertension.

Group 1 Pulmonary arterial hypertension (PAH)	Idiopathic Heritable Drug and toxin induced Associated with: - Connective tissue diseases - HIV infection - Portal hypertension - Congenital heart disease - Schistosomiasis Pulmonary veno-occlusive disease Persistent pulmonary hypertension of the newborn
Group 2 Pulmonary hypertension due to left heart diseases	Systolic dysfunction Diastolic dysfunction Valvular disease Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group 3 Pulmonary hypertension due to lung diseases and/or hypoxemia	Chronic obstructive pulmonary disease Interstitial lung disease Other pulmonary diseases with mixed obstructive/restrictive pattern Sleep disordered breathing Alveolar hypoventilation Chronic exposure to high altitude Developmental abnormalities
Group 4 Chronic thromboembolic pulmonary hypertension (CTEPH)	CTEPH Other pulmonary artery obstructions: - Angiosarcoma - Other intravascular tumors - Arteritis - Congenital pulmonary arteries stenosis - Parasites (hydatidosis)
Group 5 Unclear multifactorial mechanisms	Hematologic disorders - Myeloproliferative disorders - Splenectomy - Chronic hemolytic anemia Systemic disorders - Sarcoidosis - Pulmonary Langerhans cell histiocytosis - Lymphangioleiomyomatosis - Neurofibromatosis - Vasculitis Metabolic disorders - Glycogen storage disease - Gaucher disease - Thyroid disorders Other - Tumoral obstruction - Fibrosing mediastinitis - Chronic renal failure

Echocardiography

Echocardiography is essential for screening and initial noninvasive assessment of PH. This allows estimation of the pulmonary artery systolic pressure (PASP), assessment of the atrial and ventricular thickness, systolic and diastolic function, valve function, detection of pericardial effusions and intracardiac shunts [Rudski *et al.* 2010]. If estimated RVSP is greater than 40 mmHg, further evaluation is warranted if there are no other conditions that can cause elevated pressures, such as left heart disease or advanced lung disease, are present [McLaughlin *et al.* 2009].

Cardiac catheterization

Cardiac catheterization is an essential in the diagnosis of PH and should be performed prior

to the initiation of PAH-specific therapy. A right heart catheterization provides direct measurements of right atrial pressures (RAP), pulmonary venous pressure [pulmonary artery wedge pressure (PAWP)], pulmonary blood flow. It also allows for calculation of mixed venous oxygen saturation and pulmonary vascular resistance (PVR) [McGoon *et al.* 2004].

On right heart catheterization, PAH is defined as a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest with a PAWP of 15 mmHg or less and a PVR greater than 3 Wood units [Hoeper *et al.* 2013]. Vasodilator testing should be performed in all patients with idiopathic PAH (IPAH) without contraindications to test the presence of pulmonary vasoreactivity for possible long-term calcium channel blocker (CCB) therapy. An acute responder is defined as a reduction in mPAP of at least 10 mmHg to an absolute mPAP of less than 40 mmHg without a decrease in cardiac output [McLaughlin *et al.* 2009]. At some centers vasoreactivity testing is only performed in patients with IPAH but many centers perform this on all WHO group 1 patients and treat accordingly [Taichman *et al.* 2014; Hunt *et al.* 2014].

Assessment of severity

Once a diagnosis of PAH is made, evaluation to determine the severity of disease should be performed to assess risk and to guide treatment. WHO functional class is a predictor of survival and can also be used during follow-up as an indicator of disease progression [Humbert *et al.* 2010; Galie *et al.* 2016]. The 6-minute walk distance (6MWD) is easy to perform and widely available, and correlates with functional class and survival in patients with PAH [Miyamoto *et al.* 2000]. Cardiopulmonary exercise testing (CPET) provides information on exercise capacity as well as on gas exchange and cardiac function during exercise [Galie *et al.* 2016]. Low peak $\dot{V}O_2$ and peak systolic blood pressure are strong predictors of impaired survival [Wensel *et al.* 2002]. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels correlate with myocardial dysfunction and is associated with prognosis [Galie *et al.* 2009b].

General management

Goals of therapy include improving quality of life and chances for survival. Patients should be counseled on appropriate diet and low-level aerobic exercise. Heavy physical exertion or isometric exercise should be avoided [McLaughlin *et al.* 2009]. Immunizations against influenza and pneumococcal pneumonia should be up to date. Nonessential surgery should be avoided and when necessary, should be performed at a PH center. Diuretics are indicated to manage RV volume overload [Taichman *et al.* 2014; Galie *et al.* 2016]. Digoxin can be considered in patients with right heart failure as it has been shown to improve cardiac output [Rich *et al.* 1998].

Oxygen supplementation should be considered for all patients with hypoxemia to maintain oxygen saturation above 90% at rest and, if possible, with exercise and sleep. High altitudes should be avoided as it may cause hypoxic vasoconstriction and compromise oxygen delivery [Roubinian *et al.* 2012].

Although controlled data is limited, a survival benefit has been noted in patients on anticoagulation with warfarin in observational studies [Frank *et al.* 1997]. The recommendation has been to titrate international normalized ratio (INR) to 1.5–2.5 [McLaughlin *et al.* 2009], however, other studies failed to show a significant survival advantage with warfarin use and the role of anticoagulation in all patients with PAH has been questioned [Preston *et al.* 2015; Roldan *et al.* 2016].

High-dose CCBs, most commonly nifedipine and diltiazem, may have sustained hemodynamic benefits in select patients with PAH. Acute vasodilator testing with CCB to identify potential responders may have severe side effects, therefore inhaled nitric oxide (NO) is used for this purpose. An acute responder to NO testing is defined above (see the section on cardiac catheterization). One study showed 10 out of 33 patients acutely had response to NO. Of these, nine patients subsequently had response to CCB and were initiated on long-term treatment with oral CCB. Sustained improvements in hemodynamics were observed in only six of these patients [Sitbon *et al.* 1998].

Although maternal mortality has significantly improved, pregnancy still remains a considerable risk [Weiss *et al.* 1998; Jais *et al.* 2012]. Current expert consensus recommends the use of effective contraception and avoidance of pregnancy. Bosentan may decrease the effectiveness of

hormonal contraception and should be used with caution. If pregnancy occurs, early termination is recommended, but if the patient elects to continue with pregnancy, the patient should be treated at a PH center. Bosentan, ambrisentan, macitentan, and riociguat are category X drugs and are contraindicated in pregnancy. Dual contraceptives should be used by patients of childbearing age who are taking these medications [Taichman *et al.* 2014].

Specific management

Pathobiologic basis for therapy

An imbalance between vasoconstriction and vasodilation, thrombosis, cell proliferation, and remodeling of the pulmonary arterial walls contribute to PAH. The discovery of three main pathobiologic pathways (NO, endothelin, and prostacyclin) have revolutionized the approach to the treatment of PAH, allowing the development of effective therapies which will be reviewed.

Prostacyclin and thromboxane A2

The endothelium metabolizes arachidonic acids to produce prostacyclin and thromboxane A2. Prostacyclin acts as a potent vasodilator, has antiproliferative properties and inhibits platelet activation. The IP receptor is the main target of prostacyclin and is expressed in the vascular smooth muscle cell layer found in the pulmonary vasculature. Once activated, conversion of ATP to cyclic AMP (cAMP) results thereby increasing protein kinase A (PKA) activity subsequently leading to vasodilation [Humbert and Ghofrani, 2016]. Thromboxane A2 is a potent vasoconstrictor and platelet agonist [Gerber *et al.* 1980]. In PAH, the imbalance between prostacyclin and thromboxane A2 is shifted toward the latter and the production of prostacyclin synthase is decreased in the small and medium-sized pulmonary arteries [Christman *et al.* 1992; Tuder *et al.* 1999]. Prostanoids are synthetic analogues of prostacyclin that act as a substitution for the decreased endogenous prostacyclin in patients with PAH [Humbert and Ghofrani, 2016]. Table 2 reviews the major trials of prostanoids that are discussed in detail in the following section.

Prostanoids.

Epoprostenol. Epoprostenol is an intravenous prostanoid administered via continuous infusion. It is started at a low dose and titrated up based on symptoms and side effects of the drug as determined by a physician expert in PAH.

A 12-week, prospective, multicenter, randomized, controlled, open-label trial in 81 patients with New York Heart Association (NYHA) functional class III or IV, showed significant improvement in the primary endpoint of 6MWD in patients with epoprostenol (362 m at week 12 *versus* 315 m at baseline) compared with conventional therapy alone (204 m at week 12 *versus* 270 m at baseline). Improvements in secondary endpoints, including hemodynamics and quality of life, were also seen. A survival benefit was noted in patients receiving epoprostenol ($p = 0.003$). This was the only randomized control trial in PAH in which a survival advantage was seen; however, the study was small and not blinded [Barst *et al.* 1996].

In a 12-week, multicenter, open-label, randomized study in 111 patients with scleroderma spectrum of disease, exercise capacity, the primary outcome, improved in the epoprostenol group (316 m *versus* 270 m at baseline), but decreased in the conventional therapy group (192 m *versus* 240 m at baseline). Improvements in hemodynamics ($p < 0.001$) and WHO functional class were observed, but no survival benefit was seen [Badesch *et al.* 2000].

Common side effects include headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Chronic overdose can result in high cardiac output failure. Catheter-related blood stream infections are well-documented risks of therapy. Guidelines were published on prevention of central venous catheter-related blood stream infections while on prostanoid therapy [Doran *et al.* 2008; Rich and McLaughlin, 1999; Barst *et al.* 1996].

Treprostinil. Treprostinil, an analogue of prostacyclin sharing similar pharmacological actions to epoprostenol, is chemically stable with an elimination half-life of about 4.5 hours compared with 6 minutes for epoprostenol. It was first evaluated using subcutaneous administration in a 12-week, placebo-controlled, multicenter, randomized trial of 470 patients with NYHA functional class II, III, or IV PAH. A dose-related median difference in the primary endpoint of 6MWD of 16 m was seen between the treprostinil and placebo groups. Most common adverse effects included pain or injection site reaction, as well as headache, diarrhea, rash, and nausea [Simonneau *et al.* 2002].

Table 2. Major trials for prostanoids.

Authors	Study	Study Size	Duration	Primary Endpoint	Secondary Endpoints
Epoprostenol					
Barst *et al.* [1996]	A Comparison of Continuous Intravenous Epoprostenol (Prostacyclin) with Conventional Therapy for Primary Pulmonary Hypertension	81	12 weeks	6MWD	QoL, hemodynamics, survival
Badesch *et al.* [2000]	Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial	111	12 weeks	6MWD	Hemodynamic, signs and symptoms of PH and scleroderma, survival
Treprostinil					
Simonneau *et al.* [2002]	Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial	470	12 weeks	6MWD	Principal efficacy endpoints: Signs and symptoms of PH, Dyspnea Fatigue Rating, Number of deaths, lung transplantations or discontinuations for clinical deterioration. Borg Dyspnea Scale, Hemodynamics, Minnesota Living with Heart Failure Questionnaire
Tapson *et al.* [2006]	Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial	16	12 weeks	6MWD	Naughton–Balke treadmill time, Borg dyspnea score, hemodynamics
McLaughlin *et al.* [2010]	Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial	235	12 weeks	6MWD	Time to clinical worsening, Borg Dyspnea Score, NYHA functional class, 12-week trough 6MWD, 6-week peak 6MWD, quality of life, PAH signs and symptoms
Tapson *et al.* [2012]	Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial	350	16 weeks	6MWD	Time to clinical worsening, clinical deterioration, combined ranking of 6MWD and Borg dyspnea score, Dyspnea fatigue index score
Tapson *et al.* [2013]	Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial	310	16 weeks	6MWD	Clinical worsening, Borg dyspnea score, combined walk distance and Borg score, NT-proBNP, WHO functional classification, the Cambridge Pulmonary Hypertension Outcome Review, signs and symptoms of PAH, and safety
Jing *et al.* [2013]	Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial	349	12 weeks	6MWD	Trough 6MWD, Time to clinical worsening, combined 6MWD and Borg, WHO functional class, Dyspnea-fatigue index, symptoms of PAH, 6MWD at week 4 and 8
Iloprost					
Olschewski *et al.* [2002]	Inhaled iloprost for severe pulmonary hypertension	203	12 weeks	increase in 6MWD by at least 10% and improvement in NYHA functional class	6MWD, NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, QoL, clinical deterioration, death, need for transplantation
Hoeper *et al.* [2000]	Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue	24	12 months		6MWD, hemodynamics
Selexipag					
Simonneau *et al.* [2012]	Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension	43	17 weeks	PVR	Additional hemodynamics, 6MWD, aggravation of PAH, Borg dyspnea score, WHO functional class, NT-proBNP
Sitbon *et al.* [2015]	Selexipag for the Treatment of Pulmonary Arterial Hypertension	1156	36 months	Composite of death or complication related to PAH	6MWD, WHO functional class, death or hospitalization

6MWD, 6-minute walk distance; IV, intravenous; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; WHO, World Health Organization.

Subcutaneous treprostinil was approved by the FDA in 2002 for use in functional class II, III, and IV PAH [McLaughlin *et al.* 2009].

A subsequent study evaluating the bioequivalency and pharmacokinetics of intravenously administered treprostinil showed comparative results [Laliberte *et al.* 2004]. In 2004, intravenous treprostinil was approved by the FDA for use in functional class II, III and IV PAH patients not tolerating subcutaneous infusion [McLaughlin *et al.* 2009].

Intravenous treprostinil as monotherapy was studied in 16 patients (14 in WHO functional class III, 2 in WHO functional class IV) in a 12-week, open-label, multicenter trial. An improvement of 82 m in the primary efficacy endpoint of 6MWD was seen in 14 patients (13 in WHO functional class III, 1 in WHO functional class IV) who completed the study [Tapson *et al.* 2006]. The side-effect profile of intravenous treprostinil is similar to epoprostenol. There has been a reported increase in incidence of bloodstream infections, particularly with Gram-negative organisms, in patients receiving intravenous treprostinil. The overall infection rate was higher with intravenous treprostinil as compared to epoprostenol [Doran *et al.* 2008].

TRIUMPH evaluated the efficacy and safety of inhaled treprostinil in patients with PAH receiving therapy with either bosentan or sildenafil. 235 patients with NYHA functional class III or IV and 6MWD of 200 to 250 m while on treatment with bosentan or sildenafil were randomized to inhaled treprostinil or inhaled placebo four times daily. Treatment was safe and well-tolerated and significant improvements in the primary endpoint of 6MWD as well as quality of life measures were seen [McLaughlin *et al.* 2010].

The FREEDOM-C Study was a 16-week, multicenter, double-blind, placebo-controlled trial in 350 patients with stable PAH on background ETRA, PDE-5 inhibitor, or both randomized to placebo or oral treprostinil. Initial dosing was 1 mg twice daily with increases of 1 mg increments but due to tolerability issues, doses of 0.5 and 0.25 mg were made available later in the study. There was no statistically significant difference in the primary endpoint of 6MWD, but results suggested there may be a dose-related response. In addition, high discontinuation rates suggested a lower dose may be better tolerated [Tapson *et al.* 2012].

FREEDOM-C2 was a 16-week, multicenter, randomized, double-blind, placebo-controlled trial in which 310 patients on background ETRA, PDE-5 inhibitor, or both were randomized to oral treprostinil or placebo. Dosing was initiated at 0.25 mg bid with escalation of dosing by 0.25 mg bid every 3 days if clinically indicated. No statistically significant changes were seen in the primary endpoint of 6MWD or secondary endpoints [Tapson *et al.* 2013].

FREEDOM-M [Jing *et al.* 2013], a 12-week, randomized, double-blind, placebo-controlled trial, studied the effect of oral treprostinil in 349 treatment-naïve PAH patients. Dosing was originally initiated at 1 mg bid, but due to tolerability issues noted in FREEDOM-C [Tapson *et al.* 2012], the study protocol was amended to lower the starting dose to 0.5 mg and later 0.25 mg bid. The 6MWD was improved making oral treprostinil the first oral prostacyclin analogue meeting the primary endpoint in a randomized, controlled trial. Most common adverse effects of oral treprostinil included headache, nausea, diarrhea, jaw pain, and vomiting [Jing *et al.* 2013].

Iloprost. Iloprost is a stable analogue of prostacyclin delivered by an adaptive aerosol device. Inhaled iloprost was studied in a 12-week, multicenter, placebo-controlled, randomized trial of 203 functional class III and IV patients with either IPAH, PAH associated with scleroderma spectrum of diseases or appetite suppressants, or PH related to inoperable chronic thromboembolic disease. The combined primary endpoint of improvement in functional class by at least 1 level and improvement in 6MWD by at least 10% in the absence of clinical deterioration was met by 16.8% of those receiving inhaled iloprost compared with 4.9% receiving placebo. There was a mean increase of 36 m in the overall population in favor of iloprost [Olschewski *et al.* 2002]. An observational study evaluating 24 IPAH patients treated with iloprost showed there was a sustained benefit in exercise capacity and hemodynamics at 1 year [Hoeper *et al.* 2000]. Common side effects of inhaled iloprost include cough, headache, flushing, and jaw pain. Iloprost was approved by the FDA in 2004 for functional class III and IV PAH [McLaughlin *et al.* 2009].

Selexipag. Selexipag, an oral, selective prostacyclin receptor agonist, was evaluated in a proof-of-concept, phase II, randomized, double-blind, placebo-controlled trial of 43 patients which

showed a decrease in mean PVR at 17 weeks [Simonneau *et al.* 2012]. Subsequently, GRIPHON, a phase III, event-driven, randomized, double-blind, placebo controlled trial, enrolled 1156 patients with WHO functional class II or III. A primary endpoint event (death or complication of PAH) occurred in 347 patients (41.6% in placebo group, 27% in selexipag group). Patients on selexipag had reduction in hospitalizations and disease progression, but mortality benefits were not seen [Sitbon *et al.* 2015]. It was approved by the FDA for treatment of PAH in December 2015.

Endothelin-1

Endothelin-1 (ET-1) exerts its effects by binding to two distinct receptor isoforms in pulmonary vascular smooth muscle cells; endothelin receptor type A (ET_A) and B (ET_B) [Davie *et al.* 2002]. Both ET_A and ET_B receptors facilitate vasoconstriction and proliferation of vascular smooth muscle cells. In addition to expression in vascular smooth muscle cells, ET_B is also found in endothelial cells, fibroblasts, and neuronal cells [Boss *et al.* 2016]. ET_B has a dual role and mediates vasodilation via NO, as well as facilitate the clearance of endothelin [Giaid *et al.* 1993; Benigni and Remuzzi, 1999]. Under normal physiologic conditions, the predominant effect of ET-1 is vasodilation via ET_B receptors. In PAH, there is a shift in ET-1 activity due to unclear mechanisms and induces potent vasoconstriction and cell proliferation [Aversa *et al.* 2015]. ET-1 is a smooth muscle mitogen that contributes to the development of PAH [Stelzner *et al.* 1992]. Endothelin receptor antagonists (ETRA) attempt to reverse the vasoconstriction that occurs in PAH. Both selective and nonselective antagonists are available. Selective antagonism of the ET_A receptor has greater benefit in PAH than mixed or selective ET_B antagonism due to the potential vasoconstriction that can result from blockade of the ET_B receptor [Davenport *et al.* 2016]. Table 3 reviews the major trials of ETRA that are discussed.

Endothelin Receptor Antagonists (ETRA)

Bosentan. Bosentan is an orally active dual ETRA that competitively binds the ET_A receptor with 20 times greater affinity than the ET_B receptor. It has been shown to improve exercise capacity, hemodynamics, and slow the clinical progression of disease [Davie *et al.* 2002]. It was initially evaluated in a double-blind, placebo-controlled study of 32 patients with WHO functional class III or IV disease due to IPAH or PAH associated with systemic sclerosis. After 12 weeks of treatment, bosentan improved all endpoints studied including 6MWD, PVR, Borg dyspnea index, and WHO functional class.

A second double-blind, randomized, placebo-controlled trial across 27 centers evaluated 213 patients with severe WHO functional class III or IV PAH, despite general treatment. After 16 weeks of treatment, the primary endpoint of 6MWD was increased by 36 m in the bosentan group *versus* a deterioration of 8 m in the placebo group. Both 125 mg twice daily and 250 mg daily dosing showed a significant treatment effect, though the placebo-corrected improvement was more pronounced for the higher dosing (54 m *versus* 35m). There was no dose response relation for efficacy [Rubin *et al.* 2002].

The efficacy and safety of adding bosentan in those already receiving stable doses of either inhaled iloprost or oral beraprost was studied in 20 patients. Results showed improvement in 6MWD as well as increases in maximum work rate, VO_2 max, anaerobic threshold, oxygen pulse, and peak systolic blood pressure during maximal exercise on CPET. The therapy was tolerated well, though elevations in liver enzymes were observed in two patients, one was transient and the other was related to alcohol intake. INR decreased in 17 of 20 patients requiring dose adjustments of anticoagulants [Hoeper *et al.* 2003]. Subsequently, the COMBI study evaluated the efficacy and safety of combination therapy of bosentan and aerosolized iloprost in 40 patients with IPAH. The trial terminated early after interim analysis revealed a low-likelihood of reaching the primary end-point of 6MWD [Hoeper *et al.* 2006].

BREATHE-2 evaluated the efficacy and safety of the combination of bosentan with epoprostenol. A total of 33 patients with severe primary PAH or PAH related to connective tissue disease with NYHA functional classes III or IV received epoprostenol therapy (2 ng/kg/min) and 2 days later were randomized to receive bosentan or placebo. Another 2 days later the epoprostenol dose was increased to 4 ng/kg/min. Both groups showed improvement in total pulmonary resistance, the primary outcome, as well as all other hemodynamic variables, and the trend was higher in the combination group but did not reach statistical significance [Humbert *et al.* 2004].

Table 3. Major trials for endothelin receptor antagonists.

Authors	Study	Study Size	Duration	Primary Endpoint	Secondary Endpoints
Bosentan					
Rubin *et al.* [2002]	Bosentan therapy for pulmonary arterial hypertension	213	16 weeks	6MWD	Borg dyspnea index, WHO functional class, time to clinical worsening
Humbert *et al.* [2004]	Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2	33	16 weeks	Total pulmonary resistance	Hemodynamics, 6MWD, Dyspnea-fatigue rating, NYHA functional class
Galie *et al.* [2006]	Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study	54	16 weeks	Change in SpO_2	Hemodynamics, 6MWD, WHO functional class
Galie *et al.* [2008b]	Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial	185	6 months	PVR, 6MWD	Time to clinical worsening, WHO functional class, Borg dyspnea index, hemodynamics
McLaughlin *et al.* [2015]	Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension	334	16 weeks	Composite of first morbidity/mortality event	6MWD, functional class, NT-proBNP, all-cause death
Ambrisentan					
Galie *et al.* [2008a]	Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2	Aries-1 202, Aries-2 192	12 weeks	6MWD	Time to clinical worsening, WHO functional class, QoL, Borg dyspnea score, NT-proBNP
Macitentan					
Pulido *et al.* [2013]	Macitentan and morbidity and mortality in pulmonary arterial hypertension	742	Event driven (median 115 weeks)	Composite of time to clinical worsening and death from all causes	6MWD, WHO functional class, death or hospitalization from PAH

6MWD, 6-minute walk distance; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; WHO, World Health Organization.

BREATHE-5, was a 16-week, multicenter, randomized, double-blind, placebo-controlled study in 54 patients with WHO functional class III Eisenmenger syndrome randomized in a 2:1 fashion to bosentan or placebo. Primary safety endpoint was systemic pulse oximetry and primary efficacy endpoint was PVR. Bosentan did not worsen oxygen saturation, and compared to placebo, reduced the pulmonary vascular index (–472 dyne·s·cm^{-5}), decreased the mPAP (–5.5 mmHg), and increased 6MWD (53.1 m) [Galie *et al.* 2006].

The EARLY study was a prospective, randomized, double-blind, multicenter trial evaluating 185 patients with WHO functional class II PAH. Primary endpoints were change in PVR and 6MWD at month 6. The mean PVR was 83.2% [95% confidence interval (CI) 73.8–93.7%] of the baseline value in the bosentan group and 107.5% (95% CI 97.6–118.4%) in the placebo group. The mean 6MWD increased in the bosentan group by 11.2 m (95% CI −4.6 to 27 m) and decreased in the placebo group by −7.9 m (95% CI −24.3 to 8.5 m) but did not achieve statistical significance. There was a delay in time to clinical worsening with bosentan compared with placebo, and treatment was associated with lower incidence of worsening functional class [Galie *et al.* 2008b].

COMPASS-2 was a prospective, double-blind, event-driven trial evaluating 334 symptomatic PAH patients receiving stable sildenafil for greater than 3 months randomized to placebo and bosentan. The study did not demonstrate adding bosentan to stable sildenafil therapy was superior to sildenafil monotherapy in delaying the time to first morbidity/mortality event, the composite primary endpoint [McLaughlin *et al.* 2015].

Bosentan can potentially be hepatotoxic, and the FDA requires liver function tests be checked monthly in addition to hematocrit checks every 3 months for anemia. Abnormal hepatic function was more frequently reported in the high-dosage bosentan group [Rubin *et al.* 2002]. Other side effects include the development of edema, syncope, and flushing. [McLaughlin *et al.* 2009]. ETRA as a class may cause testicular atrophy and male infertility, and male patients should be counseled prior to starting these drugs.

Ambrisentan. Ambrisentan is a selective antagonist that competitively binds the ET_A receptor with 260 times more affinity than the ET_B receptor, with a bioavailability and half-life that allows for a once-daily oral regimen. ARIES-1 and ARIES-2 were concurrent, double-blind, placebo-controlled studies that evaluated ambrisentan in 202 patients and 192 patients with PAH, respectively. Patients in all WHO functional classes, majority in functional class II (38%) or III (58%), were randomized to receive placebo or ambrisentan orally once daily for 12 weeks. The primary outcome measure, 6MWD, improved from baseline with ambrisentan at each dose group at the end of 12 weeks. ARIES-1 showed an improvement in 6MWD in both 5 and 10 mg groups by 31 and 51 m, respectively, as compared with placebo. ARIES-2 showed improvement in 6MWD in the 2.5 and 5 mg groups by 32 and 59 m, respectively, as compared with placebo.

Both ARIES-1 and ARIES-2 showed improvements in time to clinical worsening but only ARIES-2 showed statistical significance. There was a statistically significant improvement in time to clinical worsening for the combined 5 mg groups compared with combined placebo groups from both studies. Both studies showed improvement in WHO functional class, but did not achieve statistical significance in ARIES-2.

Peripheral edema, headache, and nasal congestion were more common in the ambrisentan groups. No clinically significant elevation in serum aminotransferase was noted, and the mean alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase did not increase from baseline. No clinically significant changes in prothrombin time, INR, or oral anticoagulant dose were observed. A decrease in mean hemoglobin concentration by −0.84 (± 1.2) g/dl was noted in patients on ambrisentan compared with placebo 0.2 (± 1.0) g/dl, so periodic hemoglobin measurements may be required [Galie *et al.* 2008a].

Macitentan. Macitentan is a dual ETRA developed by modifying the structure of bosentan to increase efficacy and safety [Bolli *et al.* 2012]. Though it is classified as a mixed antagonist, macitentan tends to be more selective for the ET_A receptor [Davenport *et al.* 2016]. The SERAPHIN study was a multicenter, double-blind, randomized, placebo-controlled, phase III trial designed to evaluate morbidity and mortality with macitentan. A total of 742 patients were randomly assigned to receive placebo,

macitentan 3 or 10 mg. The composite primary endpoint was the time from the initiation of treatment to the first event related to PAH or death from any cause. A total of 287 patients had a primary endpoint event over median treatment period of 115 weeks: placebo (46.4%), macitentan 3 mg (38%), and macitentan 10 mg (31.4%). Worsening of PAH was the most frequent primary endpoint. The hazard ratio (HR) for the primary endpoint with the macitentan 3 mg dose *versus* placebo was 0.70 (97.5% CI 0.52–0.96; $p = 0.01$), and with the 10 mg dose *versus* placebo was 0.55 (97.5% CI 0.39–0.76; $p < 0.001$). At 6 months, the placebo group had a decrease in 6MWD by 9.4 m *versus* an increase in both macitentan 3 and 10 mg groups, 7.4 and 12.5 m, respectively.

The incidence of peripheral edema and of alanine aminotransferase or aspartate aminotransferase levels more than three times the upper limit of normal were similar across all three groups. Higher percentage of patients in both macitentan groups had nasopharyngitis, headache, and anemia [Pulido *et al.* 2013].

NO

The NO–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) signal-transduction pathway plays an important role in the regulation of pulmonary vascular tone and resistance in PAH [Lang *et al.* 2012]. Endogenous NO, a potent pulmonary vasodilator, is produced from L-arginine in endothelial cells by endothelial nitric oxide synthase (eNOs). It is also an inhibitor of platelet activation and vascular smooth-muscle cell proliferation and has been shown to play a major role in the pathobiology of IPAH. Reduced levels of eNOs have been seen in the pulmonary vascular tissue of PH patients, particularly those with IPAH [Giaid and Saleh, 1995; McQuillan *et al.* 1994]. However, in IPAH cases with plexiform lesions eNOs is increased and probably promotes pulmonary endothelial-cell proliferation [Mason *et al.* 1998]. The enzyme phosphodiesterase type 5 (PDE5) is the predominant phosphodiesterase isoform in the lung that metabolizes cGMP. By selectively inhibiting this enzyme, the PDE5 inhibitors cause an accumulation of intracellular cGMP, resulting in enhanced NO-mediated vasodilation as well as antiproliferative effects on pulmonary vascular smooth muscle cells. Soluble guanylate cyclase stimulators are a newer class of medication that have a dual mode of action. It stimulates sGC directly and increases the enzyme's activity independently of NO, while also increasing sensitivity to levels of NO [Grimminger *et al.* 2009]. Tables 4 and 5 review the major trials of PDE5 inhibitors and the soluble guanylate cyclase stimulator that are discussed below.

Phosphodiesterase type 5 inhibitors

Sildenafil. Sildenafil was approved for PAH by the FDA in 2005. The first randomized, placebo-controlled, double-blind crossover study evaluating the efficacy of sildenafil in PAH was in 2004 [Sastry *et al.* 2004]. A total of 22 patients with WHO functional class II or III were evaluated after 6 weeks of placebo or sildenafil (dose range 25–100 mg three times daily). Patients were then crossed over to alternate therapy and evaluated after another 6 weeks of treatment. Exercise time was found to have significantly increased by 44% from 475 ± 168 s at the end of placebo phase to 686 ± 224 s at the end of sildenafil phase ($p < 0.0001$). Cardiac index also improved from 2.8 ± 0.9 to 3.45 ± 1.1 l/m^2 ($p < 0.0001$). PASP as measured by transthoracic echocardiography decreased from 105 ± 17 to 98 ± 24 mmHg, but was not statistically significant ($p = 0.09$).

The SUPER study, a 12-week, double-blind, placebo-controlled trial evaluated 278 patients with symptomatic PAH associated with connective tissue disease were randomized to receive placebo or sildenafil (20, 40, or 80 mg) orally three times daily [Galie *et al.* 2005]. The primary endpoint of placebo-corrected change from baseline in 6MWD improved by 45, 46, and 50 m in the 20, 40, and 80 mg groups, respectively. The mPAP and PVR also significantly decreased and cardiac index significantly increased in the sildenafil groups. In a *post hoc* subgroup analysis of the 84 patients with PAH due to connective tissue disease, sildenafil-treated patients had mean increases in 6MWD at week 12 while placebo-treated patients had a mean decrease [Badesch *et al.* 2007].

The SERAPH study compared the addition of sildenafil to conventional therapy *versus* bosentan, the standard practice at the time of the study. A total of 26 patients were randomized in a double-blind fashion to receive either drug in incrementally higher doses over a period of 16 weeks. Patients who received sildenafil showed a significant reduction in the primary efficacy measure of RV mass ($p = 0.015$) but the change from

Table 4. Major studies for phosphodiesterase type 5 inhibitors.

Authors	Study	Study Size	Duration	Primary Endpoint	Secondary Endpoints
Sildenafil					
Galie *et al.* [2005]	Sildenafil citrate therapy for pulmonary arterial hypertension	278	12 weeks	6MWD	mPAP, Borg dyspnea scale, WHO functional class, time to clinical worsening
Badesch *et al.* [2007]	Sildenafil for pulmonary arterial hypertension associated with connective tissue disease	278	12 weeks	6MWD	WHO functional class, hemodynamics
Wilkins *et al.* [2005]	Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study	26	16 weeks	RV mass	Hemodynamics, 6MWD, plasma BNP levels, QoL
Simonneau *et al.* [2008]	Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial	265	16 weeks	6MWD	Hemodynamics, time to clinical worsening, Borg dyspnea score, QoL
Simonneau *et al.* [2014]	Long-term sildenafil added to intravenous epoprostenol in patients with pulmonary arterial hypertension	242	3 years	6MWD	WHO functional class, survival status, hemodynamics
Tadalafil					
Galie et al. [2009a]	Tadalafil therapy for pulmonary arterial hypertension	406	16 weeks	6MWD	WHO functional class, time to clinical worsening, Borg dyspnea score, QoL, hemodynamics
Oudiz et al. [2012]	Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study	294	52 weeks	6MWD	WHO functional class, time to clinical worsening, safety, death and survival
Galie et al. [2015a]	Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension	605	mean 609 days	First event of clinical failure	NT-proBNP, 6MWD, WHO functional class, Borg dyspnea index

6MWD, 6-minute walk distance; BNP, pro-brain natriuretic peptide; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; QoL, quality of life; RV, right ventricular; WHO, World Health Organization.

Table 5. Major studies for soluble guanylate cyclase stimulator.

Authors	Study	Study Size	Duration	Primary Endpoint	Secondary Endpoints
Riociguat					
Ghofrani et al. [2013]	Riociguat for the treatment of chronic thromboembolic pulmonary hypertension	261	16 weeks	6MWD	PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg dyspnea score, QoL
Simonneau *et al.* [2015]	Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2)	237	1 year	Adverse events	6MWD, NT-proBNP, WHO functional class, time to clinical worsening, Borg dyspnea score, QoL
Galie et al. [2015c]	PATENT PLUS: a blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension	18	12 weeks	Maximum change in supine SBP from baseline within 4 hours of dosing	Maximum standing SBP, supine and standing DBP, and supine and standing heart rate, safety

6MWD, 6-minute walk distance; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; QoL, quality of life; SBP, systolic blood pressure; WHO, World Health Organization.

baseline was not significant in the bosentan group ($p = 0.172$). Similarly, changes in plasma brain natriuretic peptide (BNP) levels were significantly decreased in the sildenafil group ($p = 0.014$). Improvements in 6MWD and cardiac index were seen in both groups [Wilkins *et al.* 2005].

The safety and effectiveness of oral sildenafil in combination with inhaled iloprost was studied in a randomized, controlled, open-label trial in 30 patients with severe PH. All patients received inhaled NO and aerosolized iloprost and were then randomized to receive sildenafil 12.5 mg, sildenafil 50 mg, sildenafil 12.5 mg plus inhaled iloprost, or sildenafil 50 mg plus inhaled iloprost. Patients who received sildenafil 50 mg plus iloprost had a maximum change in pulmonary vasodilatory potency of −44.2% (95% CI −49.5% to −38.8%) compared with −14.1% (95% CI −19.1% to −9.2%) in response to NO. The study showed that oral sildenafil acts synergistically with inhaled iloprost to cause strong pulmonary vasodilation without serious adverse events [Ghofrani *et al.* 2002].

Sildenafil has also been used as an adjunct therapy in patients who experienced deterioration while receiving inhaled iloprost [Ghofrani *et al.* 2003]. A total of 73 patients had baseline 6MWD of 217 ± 31 m that improved to 305 ± 28 m within the first 3 months of iloprost therapy. When 6MWD subsequently declined, in 14 of these patients, to 256 ± 30 m after 18 ± 4 months of therapy, sildenafil was added. 6MWD increased to 346 ± 26 m after 3 months of combined therapy, an improvement that was sustained at 12 months.

The addition of sildenafil to bosentan monotherapy was evaluated in 82 patients with IPAH and PAH due to scleroderma experiencing bosentan failure due to worsening symptoms, decline in functional class, or drop in 6MWD by more than 30 m [Mathai *et al.* 2007]. After addition of sildenafil, functional class improved in 5 of 13 patients with IPAH *versus* 2 of 12 patients with PAH due to scleroderma. Also, patients with IPAH walked further. It is important to note that bosentan significantly decreases the plasma concentration of sildenafil in patients receiving combination therapy [Paul *et al.* 2005].

The PACES-1 study was a multinational, 16-week, randomized, placebo-controlled trial of 267 patients which showed that adding oral sildenafil to intravenous epoprostenol improved 6MWD, particularly in the group with baseline distances of 325 m or more, improved hemodynamics, and delayed time to clinical worsening [Simonneau *et al.* 2008]. Patients completing PACES-1 could receive sildenafil titrated to 80 mg three times daily, as tolerated, in an open-label extension study, PACES-2 [Simonneau *et al.* 2014]. 6MWD improved or was maintained in 59%, 44%, and 33% of patients at 1, 2, and 3 years, respectively. WHO FC improved or was maintained in 74%, 59%, and 46% of patients at 1, 2, and 3 years, respectively. A total of 66% of patients were known to be alive, 24% were known to have died, and 10% were lost to

follow up at 3 years. Patients with 6MWD less than 325 m in PACES-1 who did not improve in 6MWD during the initial 20 weeks of sildenafil treatment had poorer survival.

Common side effects include epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis. At higher doses, incidence of adverse reactions are greater including diarrhea, myalgia, retinal hemorrhage, and visual disturbances with sensitivity to light.

Tadalafil. Tadalafil is a PDE-5 inhibitor with once-daily dosing. The PHIRST study, a 16-week, double-blind, placebo-controlled trial of 405 patients with PAH who were either treatment-naïve or on background bosentan therapy were randomized to receive placebo or tadalafil at 2.5, 10, 20, or 40 mg. Only patients who received tadalafil 40 mg had a statistically significant increase in the primary outcome of 6MWD by 33 m (95% CI 15–50 m) with a greater increase in the bosentan-naïve group. Tadalafil also significantly improved the time to clinical worsening, health-related quality of life, without a statistically significant change in WHO functional class [Galie *et al.* 2009a].

PHIRST-2 evaluated the long-term safety and efficacy of tadalafil (20 or 40 mg) [Oudiz *et al.* 2012]. This 52-week, double-blind, uncontrolled, extension study showed improvements in 6MWD achieved in PHIRST were maintained for the duration of the study.

The AMBITION trial studied the effect of initial combination therapy with ambrisentan and tadalafil in 605 patients with WHO functional class II or III. The combination group received ambrisentan 10 mg and tadalafil 40 mg, the ambrisentan group received ambrisentan 10 mg and placebo, and the tadalafil group received 40 mg and placebo once daily. The primary endpoint in a time-to-event analysis was the first event of clinical failure, which was 50% lower among the initial combination therapy group than those who received monotherapy with either drug. Earlier trials compared the addition of a therapy with placebo in patients already receiving treatment and this trial supports that early combination therapy can be beneficial [Galie *et al.* 2015a].

The most common adverse effects were headaches, myalgia, and flushing. Several case reports have suggested the safety and efficacy of tadalafil use in conjunction with prostacyclins, such as treprostinil or epoprostenol, and other ETRA [Faruqi *et al.* 2010; Bendayan *et al.* 2008].

Soluble guanylate cyclase stimulator

Riociguat. Riociguat increases the level of cGMP resulting in vasorelaxation and is thought to prevent progression of vascular remodeling [Lang *et al.* 2012]. CHEST-1, a phase III, 16-week, double-blind, randomized, placebo-controlled study at 89 centers in 26 countries evaluated patients with inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy, with a 6MWD of 150–450 m, PVR more than 300 dyn·sec·cm^{-5}, and a mPAP of at least 25 mmHg. A total of 261 patients, most in WHO functional class II or III, underwent randomization to receive riociguat or placebo. At week 16, the primary endpoint of 6MWD increased from baseline by a mean of 39 m in the riociguat group *versus* 6 m in the placebo group. PVR decreased by 226 dyn·sec·cm^{-5} in the riociguat group compared with an increase of 23 dyn·sec·cm^{-5} in the placebo group. Riociguat also showed improved mPAP, NT-proBNP levels, WHO functional class, and Borg dyspnea score. No significant difference in the incidence of clinical worsening events was noted between the riociguat and placebo groups [Ghofrani *et al.* 2013].

Ninety-eight percent of the patients who completed the study entered the long-term extension (LTE) study, CHEST-2, evaluating the long-term safety and efficacy. The study assignments were concealed for the first 8 weeks, and afterwards the treatment was open-label. The first 12 weeks of CHEST-2 showed further increase in 6MWD in the group that received riociguat in CHEST-1, with a mean increase of 63 ± 64 m over baseline with a favorable risk–benefit profile [Simonneau *et al.* 2015].

The most frequent serious adverse effects were right ventricular failure, syncope, and hemoptysis. Drug-related serious adverse events included syncope and gastritis. Others included acute renal failure and hypotension.

Riociguat added to sildenafil. The PATENT PLUS, a randomized, double-blind, placebo-controller, multicenter study evaluated the safety and efficacy of riociguat added to sildenafil. Eighteen patients with symptomatic PAH on sildenafil 20 mg three times daily were randomized to placebo or riociguat

for 12 weeks. Primary outcome was maximum change in supine systolic blood pressure (SBP) from baseline within 4 hours of dosing and secondary outcomes were maximum standing SBP, supine and standing diastolic blood pressure (DBP), supine and standing heart rate, and safety. There were no differences in primary and secondary outcomes between the riociguat and placebo groups. In the LTE study in which all patients received riociguat, all patients reported adverse effects and there were high rates of discontinuation due to hypotension. There were three (18%) deaths reported in the LTE but not considered drug related by the investigator. In conclusion, the addition of riociguat to sildenafil therapy provided no clear benefit with increased risk of adverse effects. Consequently, concomitant use of riociguat with PDE-5 inhibitors is contraindicated [Galie *et al.* 2015c].

Conclusion

PAH is a progressive and fatal disease if left untreated. Historically the treatment of PAH had been restricted by a limited number of therapeutic options. However, recent advances in our understanding of the pathophysiological and molecular mechanisms underlying PAH have led to the development of a large number of targeted pharmacologic therapies which improve hemodynamic measures, WHO functional class, and 6MWD. Avoiding a delay in diagnosis, referring early or collaborating care with specialized PAH centers, and instituting appropriately tailored drug therapy remain the top priorities for patient care. Furthermore, combination therapy focused on targeting the multiple pathways leading to PAH is being increasingly used and has led to an overall increase in PAH survival. As a result of this paradigm shift, studies are now evaluating morbidity and mortality as primary endpoints of treatment as opposed to just the 6MWD. Ongoing research with new outcome measures remains essential and continues to provide hope to both the physicians and the patients suffering from this debilitating disease.

Conflict of interest statement

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