CARDIAC DRUGS
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Second Edition

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Preface to the Second Edition

Globally, cardiovascular disease is a major cause of morbidity and mortality and the burden of disease is expected to grow even further. Management of cardiovascular disease has been a rapidly evolving field with the ever increasing armamentarium of pharmacological agents for treating these disorders. As new research moves ahead, newer and newer agents with novel mechanisms are being developed. However, this has led to a unique situation where, in many clinical circumstances, the physician faces the dilemma of choosing the most appropriate available drug therapy for the patient. It was our goal to help the care providers identify the best-available drug options when the first edition of ‘Cardiac Drugs’ was planned.

The first edition was very well appreciated and it is the conviction of the readers that has given us the strength and direction to come out with the second edition in its present shape and form. The chapters have once again been written by experts, amalgamating evidence-based research with years of experience in treating the patients. Like the first edition, this edition is replete with diagrams and illustrations and elaborate tables which help readers understand the concepts clearly and easily. Latest references and guidelines have been incorporated to keep the information current and relevant and some of the chapters have been extensively re-written.

We thank all those who have been associated with us in this exciting journey and once again implore our readers to keep sending in their suggestions and feedback so that we have the opportunity to evolve and live up to their expectations. We thank all the contributors for their efforts and time and for making this book, a reference title, suitable both for clinicians and trainees in cardiovascular medicine.

Kanu Chatterjee
Eric J Topol
Preface to the First Edition

The book *Cardiac Drugs* presents an evidence-based approach towards the pharmacologic agents that are used in various clinical conditions in cardiovascular medicine.

The classes of drugs, such as renin-angiotensin-aldosterone blocking drugs, positive inotropic drugs, diuretics, and anti-hypertensive drugs are discussed in great details with their pharmacokinetics, pharmacodynamics, indications, contraindications, and doses. Drugs for heart failure, acute coronary syndromes, and pulmonary hypertension are also discussed similarly. Pharmacologic agents, which are in development for various clinical syndromes are also discussed. The unique feature of this book is the detailed discussion on the guidelines of the American College of Cardiology/American Heart Association for the use of pharmacologic agents in various clinical conditions.

Kanu Chatterjee
Eric J Topol
Drugs for Pulmonary Hypertension

Introduction

The pulmonary vasculature under normal conditions is a low-pressure and low-resistance system. Pulmonary hypertension (PH) is a hemodynamic state characterized by elevated pressure in the pulmonary vascular bed. The pressure in the pulmonary artery is considered elevated when the resting mean pulmonary arterial pressure (mPAP) is above or equal to 25 mmHg, measured during right heart catheterization (RHC). Many clinical conditions can lead to PH and an extensive evaluation focused on elucidating underlying etiology is the key to successful management. This chapter provides an overview of the classification of PH and reviews in detail the therapies currently available for the management of pulmonary arterial hypertension (PAH). Since the publication of the first edition of this book, several new drugs have been approved by the US Food and Drug Administration (US FDA) and added to the armamentarium of medical therapy available to treat PAH.

Nomenclature and Classification

Clinically, the World Health Organization (WHO) classifies PH into five major categories on the basis of pathological, physiological and therapeutic characteristics (Table 1). Recent modifications and updates in the classification, proposed during the 5th World Symposium held in 2013 in Nice, have been incorporated in this chapter. The nomenclature can be quite confusing and is worth reviewing. The term PH encompasses all WHO categories. WHO group 1 PAH includes idiopathic PAH (iPAH), hereditary PAH (hPAH) and PH associated with several clinical conditions. The clinical conditions are detailed in Table 1 and have similar pathophysiology and treatment response as iPAH. Idiopathic PAH was previously referred to as “primary PH”, but this term has been abandoned. WHO group 2 PH is PH owing to elevated left heart pressures that result from...
TABLE 1: Updated WHO classification of pulmonary hypertension

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH (previously primary pulmonary hypertension)
   1.2 Heritable PAH
      1.2.1 Bone morphogenic protein receptor type 2 (BMPR2)
      1.2.2 Activin receptor-like kinase type 1 (ALK1), endoglin, caveolin-1, SMAD9
      1.2.3 Unknown
   1.3 Drug and toxin induced
   1.4 Associated with:
      1.4.1 Connective tissue disease
      1.4.2 Human immunodeficiency virus (HIV) infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart disease
      1.4.5 Schistosomiasis

1ª Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1º Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   2.1 Left ventricular systolic dysfunction
   2.2 Left ventricular diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanism
   5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

either left-sided valvular disease or heart failure. This group is also referred to as pulmonary venous hypertension (PVH) or postcapillary PH. The other two major categories of PH are WHO group 3 PH due to lung disease or sleep-disordered breathing and WHO group 4 PH from chronic thrombotic and/or embolic disease. Lastly, WHO group 5 PH consists of various miscellaneous conditions that have been found to be risk factors for PH, but the pathophysiology is unclear.
The hemodynamic classification of PH has two major components—mPAP and left heart pressures. The 5th World Symposium recommends that mPAP above or equal to 25 mmHg at rest by RHC should be considered elevated. Based on left heart pressures, i.e., left atrial pressure as estimated by pulmonary artery wedge pressure (PAWP) or the more directly measured left ventricular end-diastolic pressure (LVEDP), PH can be further categorized as precapillary (PAWP or LVEDP ≤15 mmHg) and postcapillary (PAWP or LVEDP >15 mmHg). WHO group 1 PAH, WHO group 3 PH due to lung disease and/or hypoxia, WHO group 4 chronic thromboembolic PH (CTEPH) and WHO group 5 PH with unclear or multifactorial mechanism all result in precapillary PH and cannot be distinguished based on hemodynamics alone. Patients with PAH are characterized by precapillary PH with mPAP above or equal to 25 mmHg, PAWP below or equal to 15 mmHg and elevated pulmonary vascular resistance (PVR) more than 3 Wood units.

WHO Group 1 Pulmonary Arterial Hypertension

World Health Organization group 1 PAH has been the focus of intense research over the last 20 years and major advances have been made in the understanding of pathophysiology and treatment of this condition. The clinical conditions that fall into this category (Table 1) have been found to have similar pathology, clinical presentation, hemodynamics and response to treatment. The exact prevalence of PAH is unclear but ranges between 15 and 50 cases per million in Western countries. PAH is a progressive and often fatal disease and the pathophysiology is characterized by vasoconstriction, excessive cellular proliferation, inflammation and in situ thrombosis. Patients with PAH have an imbalance between endothelial production of vasodilatory and antiproliferative agents like nitric oxide and prostacyclin, and vasoconstrictive and proliferative substances like endothelin-1. The outcome is obstructive remodeling of the pulmonary vessels and an increase in pulmonary arterial pressure (PAP) and PVR. The progressive increase in PVR ultimately leads to right ventricular (RV) hypertrophy and dilatation and, eventually, RV failure.

Better understanding of the pathophysiology of PAH has resulted in the availability of multiple medical treatment options that target one of three pathways, i.e., the prostacyclin, nitric oxide or endothelin pathways (Fig. 1). Prior to 1995, there was no specific treatment for PAH, and patients were treated empirically with calcium-channel blockers (CCBs), digoxin, diuretics and anticoagulation. The first PAH-specific treatment, epoprostenol, was approved by the US FDA in 1995. Since then, the number of US FDA-approved therapeutic options has increased steadily with 12 PAH-specific therapies available at the end of the year of 2014 (Fig. 2).
This chapter focuses on the treatment of WHO group 1 PAH, starting with general treatment measures, followed by supportive therapies and the role of CCBs and lastly disease-specific therapies. These therapeutic options are generally not applicable to non-WHO group 1 PH.
Goals of Treatment in Pulmonary Arterial Hypertension

With advances in our understanding of the pathophysiology of PH and availability of increasing number of therapeutic options there has been a shift in therapeutic goals from short-term functional changes to improvements in long-term outcomes. Variables used in clinical practice to determine response to therapy and prognosis include improvement in functional class to I or II, normal or near normal RV size and function based on echocardiographic or magnetic resonance imaging (MRI) evaluation, normalization of right atrial pressure (RAP) (<8 mmHg) and CI (>2.5–3.9 L/minute/m²), 6-minute walk distance (MWD) more than 380–440 m, peak oxygen uptake (VO₂) more than 15 mL/minute/kg and normal B-type natriuretic peptide level.5

General Treatment Measures

Diet

Limiting fluid and sodium intake (<2.4 g/day) is advised and is particularly important in patients with symptomatic right heart failure for managing the volume status.

Rehabilitation and Exercise Training

Results from three randomized controlled trials suggest that supervised exercise training improves functional capacity, quality of life and functional class.6-8 Exercise training programs should be implemented by centers experienced in management of patients with PAH.

Immunizations

Routine immunizations against influenza and pneumococcal pneumonia are advised.
Pregnancy

According to current guidelines, pregnancy should be avoided or terminated as early as possible in women with PAH. The hemodynamic fluctuations during pregnancy, labor, delivery and the postpartum period are potentially devastating. In fact, maternal mortality rate as high as 30–50% has been observed in some series.9 It is important to discuss effective birth control with women of childbearing age. Use of estrogen-containing contraceptives may increase the risk of venous thromboembolism, but preparations with a lower dose can be used with concurrent warfarin anticoagulation. Use of barrier methods or surgical sterilization can also be used as alternatives.

Supportive Therapies for Pulmonary Arterial Hypertension

Supportive therapies are treatments that are directed at the consequences of PAH. Supportive therapies have only been studied in retrospective and/or nonrandomized trials. Recommendations regarding their use are thus based on expert opinion.10

Oxygen

Oxygen supplementation is recommended to maintain arterial blood oxygen pressure above or equal to 60 mmHg to avoid hypoxia-mediated pulmonary vasoconstriction. Patients with hypoxemia should be evaluated for pulmonary embolism and right-to-left shunt. Exposure to high altitudes may worsen hypoxia and result in hypoxic pulmonary vasoconstriction. Similarly, some patients may require oxygen during air travel. Although there is no data from controlled trials, it is recommended that if the patient's pre-flight oxygen saturation as determined by pulse oximetry is less than 92%, he or she should receive supplemental oxygen.11

Anticoagulation

The pathologic evidence of in situ thrombosis and abnormal platelet function provides a rationale for anticoagulation in patients with PAH.12 Anticoagulants have been studied in three noncontrolled observational series in patients with mainly iPAH.13-15 An improvement in survival with warfarin anticoagulation has been observed. Anticoagulation is recommended in patients with iPAH and those with advanced disease requiring intravenous therapy (International Randomized Ratio goal of 1.5–2.5).10 The role of newer anticoagulants, such as thrombin and factor Xa inhibitors, has not been studied in PAH.
Diuretics

Diuretics are used to manage RV volume overload, which manifests as elevated jugular venous pressure, lower extremity edema and abdominal distention. Loop diuretics including furosemide, bumetanide and torsemide are frequently used in clinical practice. Goals of therapy are to reduce the central venous pressure and eliminate renal and hepatic congestion without causing hypotension. Aldosterone antagonists, such as spironolactone can be used in patients to help conserve K⁺ and may also have beneficial effects on RV remodeling. Renal function and electrolytes should be closely monitored in patients receiving diuretics.

Digoxin

Digoxin is sometimes used in patients with RV failure and low cardiac output or in patients with atrial arrhythmias. One study demonstrated that giving intravenous digoxin to iPAH patients produced a modest increase in cardiac output and a reduction in circulating norepinephrine levels after 2 hours. Longer-term data are not available.¹⁶ There is a narrow therapeutic window and the goal serum digoxin level, as with any other heart failure patient being treated with digoxin, is 0.5–0.8 ng/mL. Levels should be closely monitored in elderly and patients with renal dysfunction.

Calcium-Channel Blockers

Acute vasodilator testing and the use of CCBs in PAH have mainly been studied in patients with iPAH. The rationale for vasodilator testing in diagnostic evaluation of PAH is based on two factors: (1) acute vasodilator responsiveness identifies patients with a better prognosis and (2) responders are more likely to have a sustained response to oral CCBs than nonresponders and can be treated with these less expensive drugs.¹⁷ Acute vasodilator testing should be done only in referral centers and preferably using inhaled nitric oxide (iNO); although, intravenous epoprostenol or intravenous adenosine may be used as an alternative. A positive response is defined as a decrease in mPAP by at least 10 mmHg to an absolute level of mPAP below 40 mmHg without a decrease in cardiac output.

Calcium-channel blockers have been used in iPAH since 1992 when a study demonstrated 95%, 5-year survival in patients who exhibited an acute vasodilator response.¹³ The typical agents used in PAH are dihydropyridines, including amlodipine or nifedipine, or the non-dihydropyridine diltiazem. The choice of CCB is based upon the patient’s heart rate with relative bradycardia favoring the dihydropyridines and tachycardia favoring diltiazem. Verapamil is not used because of its potential negative inotropic effects. If a patient
who meets the definition of an acute responder does not improve to WHO functional class I or II on CCB, the patient should no longer be considered a responder, and alternative or additional PAH-specific therapy should be instituted. Only approximately 8% of iPAH will continue to respond to CCB therapy over the following year. In order to achieve the maximum benefit, patients generally need high doses of CCBs that are higher than those conventionally used to treat systemic hypertension, 20–30 mg/day of amlodipine, 180–240 mg/day of nifedipine and 720–960 mg/day of diltiazem.

Acute vasoreactivity testing is recommended in patients with idiopathic pulmonary PAH to identify patients that are likely to favorably respond to long-term treatment with high doses of CCBs. Vasoreactivity testing is not recommended in non-WHO group 1 PH. Lastly, testing should be done with caution in patients with concomitant left ventricular disease as pulmonary edema has been reported in patients with stable left-sided heart failure.

Pulmonary Arterial Hypertension—Approved Drugs

Prior to 1995, there was no specific treatment for PAH. Extensive research over the last two decades has resulted in the development of several new treatment options. Currently, there are four classes of PAH approved drugs: (1) prostacyclin analogues, (2) endothelin receptor antagonists (ERAs), (3) phosphodiesterase-5 inhibitors (PDE-5is) and (4) soluble guanylate cyclase stimulators. Historically, approval of drug therapies in PAH has been largely supported by data from relatively small, randomized, placebo-controlled studies of 12–16 weeks duration demonstrating modest improvements in functional class, exercise capacity and hemodynamics. However, several more recent studies have been designed to prospectively assess long-term morbidity and mortality. Evidence supporting survival benefits of current PAH therapies is mostly surmised from observational post hoc analyses, referencing historical control data and meta-analysis. It should be noted that PAH-specific therapies have mainly been evaluated in patients with iPAH, hPAH, PAH associated with connective tissue disease (CTD) and in patients with PAH from anorexigen use. Extrapolation of findings to other PAH subgroups should be done with caution and this data does not apply to other categories of PH (Table 2).

Prostacyclins or Its Analogues

Prostacyclins are generated through the breakdown of arachidonic acid using prostacyclin synthase, an enzyme that is reduced in PAH patients (Fig. 1). The arachidonic acid
### TABLE 2: Disease-specific therapies for pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostacyclin analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostenol (IV)</td>
<td>Started at low dose of 1–2 ng/kg/min and increased by 1–2 ng/kg/minute weekly or biweekly, as tolerated to an optimal dose of 20–45 ng/kg/minute</td>
<td>Headache, flushing, jaw pain, nausea, diarrhea, hypotension, dizziness, thrombocytopenia, leg pain, cough (inhaled) and site pain (subcutaneous)</td>
<td>Interruption of IV therapy can cause life-threatening worsening of pulmonary hypertension</td>
</tr>
<tr>
<td>Treprostinil (SC, IV, inhaled and oral)</td>
<td>Treprostinil (SC and IV) started at low dose of 1–2 ng/kg/minute and increased to 20–80 ng/kg/minute</td>
<td>Treprostinil (inhaled) 3–9 breaths 4 times daily while awake</td>
<td>Treprostinil oral is started at a dose of 0.25 mg every 12 hours, increased every 3–4 days by 0.25–0.5 mg BID to a maximum dose of 21 mg every 12 hours</td>
</tr>
<tr>
<td>Iloprost (inhaled)</td>
<td>Iloprost (inhaled), every 2 hours 6–9 times a day</td>
<td></td>
<td>Line infections and thrombosis can occur in patients with indwelling catheters</td>
</tr>
<tr>
<td><strong>Endothelin receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>Started at 62.5 mg BID and titrated to 125 mg BID after 4 weeks</td>
<td>Peripheral edema, liver toxicity, anemia, teratogenicity, reduced hormonal contraceptive efficacy, reduced sperm count, and drug-drug interactions with strong inducers or inhibitors of CYP450 enzymes</td>
<td>Monthly LFTs with bosentan (US FDA recently removed the monthly monitoring requirement for ambrisentan)</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Ambrisentan is started at a dose of 5 mg daily and is up titrated to 10 mg daily</td>
<td></td>
<td>Monthly pregnancy test for women of childbearing potential</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Macitentan is started at 10 mg daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Table 2 (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phosphodiesterase-5 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>USFDA approved dose—20 mg TID</td>
<td>Headache, dizziness, nausea, priapism, epistaxis, hearing loss, AION and optic atrophy</td>
<td>Nitrates contraindicated due to potential life-threatening hypotension</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>USFDA approved dose—40 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Soluble guanylate cyclase stimulator</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riociguat</td>
<td>USFDA approved initial dose is 1 mg TID. Consider 0.5 mg TID if patient becomes hypotensive. If systolic BP &gt;95 mmHg and no symptoms of hypotension, up-titrate dose by 0.5 mg PO TID with dose increase no sooner than 2 weeks apart to highest tolerated dose (not to exceed 2.5 mg PO TID)</td>
<td>Nausea, vomiting, diarrhea, dyspepsia, gastritis, constipation, dizziness, headache, hypotension, anemia, serious bleeding, hemoptysis</td>
<td>Contraindicated in combination with PDE-5is because of hypotension</td>
</tr>
</tbody>
</table>

AION, anterior ischemic optic neuropathy; BID, twice a day; LFT, liver function test; TID, three times a day; PDE-5i, phosphodiesterase-5-inhibitors.
metabolism is shifted toward production of thromboxane (a vasoconstrictor and promoter of platelet aggregation), which contributes to the pathogenesis of PAH. The vasodilator and antiproliferative effects of prostacyclin \( I_2 \) are mediated through the production of cyclic adenosine monophosphate (cAMP) (Fig. 3).\(^{18}\) Prostacyclin and its analogues also inhibit platelet aggregation.

Prostacyclins are US FDA approved for use in patients with PAH. Their use has been associated with reduced survival in patients with systolic heart failure (WHO group 2 PH) and increased pulmonary shunt flow and hypoxemia in patients with lung disease (WHO group 3 PH).\(^{19-21}\)

There are three approved prostacyclins and four different modes of delivery:

1. Intravenous epoprostenol
2. Intravenous treprostinil, subcutaneous treprostinil, inhaled treprostinil, oral treprostinil
3. Inhaled iloprost.

The choice of prostacyclin and the route of administration are determined by a combination of severity of illness and patient factors. Severity of illness is based mainly on WHO functional class, but other risk factors should also be taken into consideration (Table 3). Patient factors include patient’s preference of route, social support, manual dexterity and

![FIG. 3: Prostacyclins: Mechanism of action in pulmonary arterial hypertension.](image)
Epoprostenol has a very short half-life of 3–6 minutes and is administered as a continuous intravenous infusion through a central venous catheter.

Epoprostenol was found to be beneficial in three unblinded randomized controlled trial in patients with iPAH and in those with PAH associated with scleroderma spectrum of diseases. Epoprostenol improves symptoms, exercise capacity and hemodynamics in both clinical conditions. Up until recently it was the only treatment shown to improve survival in iPAH. Macitentan, as discussed later in this chapter, has also been shown to improve morbidity and mortality in patient with PAH (composite endpoint).

Epoprostenol is US FDA-approved therapy for PAH. It is unstable at room temperature and needs to be maintained on ice after reconstitution. In 2010, a room temperature stable form of epoprostenol was approved for usage in PAH. Epoprostenol is started at a low dose of 1–2 ng/kg/minute and increased slowly by 1–2 ng/kg/minute weekly or biweekly, depending on tolerability and side effects to an optimal dose of 20–45 ng/kg/minute. A more rapid up-titration can be done under close monitoring in an intensive care unit. Because epoprostenol has a very short half-life, interruption of the infusion can result in rebound worsening of PH, which can be life-threatening. Likewise, inadvertent bolus administration can lead to life-threatening systemic vasodilation and hypotension.

### TABLE 3: Determinants of prognosis in pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Determinants of risk</th>
<th>Lower</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence of RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO class</td>
<td>II and III</td>
<td>IV</td>
</tr>
<tr>
<td>6-MWD</td>
<td>Longer (&gt;400 m)</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO₂ &gt; 10.4 mL/kg/minute</td>
<td>Peak VO₂ &lt; 10.4 mL/kg/minute</td>
</tr>
<tr>
<td>BNP</td>
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<td>Pericardial effusion and significant RV dysfunction</td>
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<td>RAP &gt; 20 mmHg Cl &lt; 2.0 L/minute/m²</td>
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6-MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; CPET, cardiopulmonary exercise testing; RAP, right atrial pressure; RV, right ventricular; CI, confidence interval.
Treprostinil

Treprostinil is a more stable prostanoid with an elimination half-life of about 4.5 hours. Treprostinil was initially studied as a subcutaneous infusion but is now also available as an intravenous infusion and as an inhaled formulation.

The following studies led to US FDA approval of various delivery forms of treprostinil. In a 12-week, double-blind, placebo-controlled, multicentre trial of 470 patients with functional classes II, III or IV PAH, subcutaneous treprostinil resulted in a modest but statistically significant median increase of 16 m of the 6-MWD, which was dose-related.26,27

The TRUST trial (Treprostinil for Untreated Symptomatic PAH Trial) was a 12-week placebo-controlled study of intravenous treprostinil in 44 patients with New York Heart Association (NYHA) class III symptoms due to iPAH and hPAH. Six-MWD improved by a placebo corrected median of 83 m in patients treated with treprostinil (p = 0.0008).28 Treprostinil patients also had a reduction in Borg scale of dyspnea by a median of 2 units (p = 0.02) and improved NYHA functional class by a median of class 1 (p = 0.051). The TRIUMPH trial (inhaled TReprostinil sodiUM in Patients with severe Pulmonary arterial Hypertension) showed that inhaled treprostinil improved exercise capacity, N-terminal pro-brain natriuretic peptide (NT-proBNP) and quality of life in PAH patients on background therapy with either bosentan or sildenafil.29

Lastly, oral treprostinil at peak dose improved 6-MWD by 26 m in a randomized controlled trial of patients with de novo PAH not on any background therapy.30


Treprostinil (subcutaneous and intravenous) is started at a low dose of 1–2 ng/kg/minute and is increased gradually to a dose of 20–80 ng/kg/minute. If a rapid up-titration is needed, it should be done with close monitoring of the hemodynamic status. Inhaled treprostinil is administered via an ultrasonic nebulizer and the total dose is administered in less than a minute with 3–9 breaths four times a day. Oral treprostinil is started at a dose of 0.25 mg every 12 hours, increased every 3–4 days by 0.25–0.5 mg BID to a maximum dose of 21 mg every 12 hours.

Iloprost

Iloprost is a synthetic analogue of prostacyclin PGl2. In the AIR trial (Aerosolized Randomized Iloprost Study) inhaled iloprost
was compared to placebo inhalation in patients with PAH and CTEPH. The study showed improvement in exercise capacity, symptoms, PVR and clinical events.31

The US FDA approved inhaled iloprost in 2004 for functional class III and IV PAH. Iloprost is administered via the hand-held portable I-neb Adaptive Aerosol Delivery System every 2 hours while the patient is awake for a total of 6–9 treatments daily. The device also contains a computer microchip, which can be analyzed with software that provides useful information, such as patient compliance and treatment times.

**Selexipag**

Selexipag is an oral, selective prostacyclin receptor agonist. A large multicenter, double-blind, placebo-controlled, phase III study (GRIPHON) to demonstrate the efficacy and safety of selexipag was completed in 2014. This study is the largest study that has been completed in PAH and enrolled 1,156 patients. This was an event-driven study and the primary endpoint was time to first clinical worsening. Patients were treated for up to 4.3 years with selexipag 200–1600 μg or placebo twice a day. The results of this study have not been published but based on information provided by the company selexipag decreased the morbidity/mortality by 39% compared to placebo (p < 0.0001). Selexipag has been submitted to the US FDA for approval for treatment of PAH.

**Prostacyclin Side Effects**

Common side effects of prostacyclin and prostacyclin analogues include headache, flushing, jaw pain, nausea, diarrhea, hypotension, dizziness and leg pain. Patients with intravenous catheters are at risk of infection and thrombosis as well as interruption of therapy. When given as a subcutaneous infusion (treprostinil), approximately 85% of patients experience infusion pain and/or infusion site reactions, which can be mitigated by rotating the infusion site. However, 5–23% of patients discontinue the subcutaneous infusion due to this complication. The inhaled agents are commonly associated with cough.

**Endothelin Receptor Antagonists**

Endothelin-1 is a vasoconstrictor and smooth muscle mitogen that may contribute to the development of PAH. The actions of endothelin-1 are mediated via two endothelin receptors, ET-A and ET-B (Fig. 1). Although activation of ET-A leads to vasoconstriction and ET-B tends to lead to vasodilatation and release of antiproliferative factors, selective versus nonselective blockade of receptors does not appear to affect clinical outcome (Fig. 4).
Rugs for Pulmonary Hypertension

Like prostacyclins, ERAs are only approved for use in WHO group 1 PAH. Benefits of therapy have not been shown in other types of PH and inappropriate use may result in harm. In patients with chronic left heart failure and PVH (WHO group 2), bosentan did not improve hemodynamic parameters. More patients, however, stopped therapy due to adverse effects including worsening of heart failure and death. In patients with chronic left heart failure and PVH (WHO group 2), bosentan did not improve hemodynamic parameters. More patients, however, stopped therapy due to adverse effects including worsening of heart failure and death.32 Similarly, studies on patients with WHO group 3 PH due to lung disease have not found ERAs to be beneficial and some have shown a decrease in exercise capacity and worsening of hypoxemia.33,34

Bosentan

Bosentan is a dual endothelin receptor antagonist. Five randomized controlled trials (Study-351, BREATH (Bosentan Randomized trial of Endothelin Antagonist Therapy)-1, BREATH-2, BREATH-5 and EARLY (Endothelin Antagonist Trial in Mildly symptomatic pulmonary arterial hypertension patients)] showed improvement in exercise capacity, functional class, hemodynamic parameters, echocardiographic and Doppler variables, and time to clinical worsening.35-39

**FIG. 4:** Endothelin receptor antagonists: Mechanism of action in pulmonary arterial hypertension.
Most studies on PAH-specific therapies have been performed on patients with advanced functional class (III or IV). In the EARLY study, bosentan therapy was evaluated in mildly symptomatic (WHO functional II) PAH. Patients were randomized to receive bosentan or placebo for 26 weeks. There was a significant improvement in PVR, but not in 6-MWD. There was a significant improvement in time to clinical worsening.38 In patients with Eisenmenger syndrome, bosentan reduced PVR index, decreased mPAP and increased exercise capacity.

Bosentan was the first oral agent approved by the US FDA in 2001. The recommended starting dose is 62.5 mg twice a day with up-titration to 125 mg twice a day after 4 weeks.

**Ambrisentan**

Ambrisentan is a relatively selective endothelin-A receptor antagonist. The efficacy of ambrisentan was evaluated in a pilot study40 and two large randomized controlled trials [AIRES (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, double-blind, placebo-controlled, multicentre, Efficacy Study)-1 and AIRES-2).41 Subjects who received ambrisentan had improvement in symptoms, exercise capacity, hemodynamics and time to clinical worsening when compared to placebo.

Use of ambrisentan has been studied in a small cohort of patients with portopulmonary hypertension (POPH). In this small study, 13 patients with POPH were given ambrisentan. The investigators found that ambrisentan decreased mPAP and PVR but no change in liver function tests (LFTs).42

The US FDA approved ambrisentan for use in PAH in 2007. It is given orally and the recommended starting dose is 5 mg daily, and it can be up-titrated to 10 mg daily.

**Macitentan**

Macitentan is a dual ERA that was developed by modifying the structure of bosentan to increase safety and efficacy. Macitentan is characterized by sustained receptor binding and enhanced tissue penetration. In the event-driven SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome), Macitentan significantly reduced morbidity and mortality among patients with PAH and also increased exercise capacity. The primary endpoint of this study was the time from the initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids or worsening of PAH. The benefits were observed regardless of whether the patient was receiving therapy for PAH.25
Macitentan was approved by US FDA in 2013 for treatment of PAH to delay disease progression. It is started at a dose of 10 mg/day.

**Side Effects of Endothelin Receptor Antagonists**

Side effects of the ERAs include peripheral edema, potential for liver toxicity, anemia, teratogenicity and drug-drug interactions with strong inducers or inhibitors of cytochrome P450 enzymes.

Bosentan leads to dose-related increases in liver transaminases in 10–15% patients,\(^{36,43}\) For this reason, the US FDA mandates that LFTs be monitored monthly in all patients on bosentan. Monthly LFTs are not required in patients on ambrisentan and macitentan but periodic liver function testing is still recommended as part of the routine management of all patients with PAH, who may develop right heart failure and associated liver dysfunction.

Lower extremity edema can develop in up to 28% of patients treated with ambrisentan but may be less frequent with bosentan.\(^{36,41}\) Although the etiology of edema has not been established, it is likely related to fluid retention rather than peripheral vasodilation. The side effect can usually be anticipated and controlled with diuretic adjustment without the need for drug discontinuation in most patients. It may be better to avoid initiating these therapies in patients with acutely decompensated right heart failure until the congestion has been adequately treated.

**Nitric Oxide Pathway**

The vasodilatory effects of nitric oxide depend upon its ability to augment and sustain cyclic guanosine monophosphate (cGMP) content in vascular smooth muscle. Nitric oxide activates guanylate cyclase, which increases cGMP production. This cGMP in turn causes vasorelaxation, but the effects are short-lived, as cGMP undergoes rapid degradation to GMP, and this is mediated by PDEs. PDE-5 hydrolyzes cAMP and cGMP, limiting their intracellular signaling (Fig. 1). Two classes of PAH-approved drugs affect the NO pathway, phosphodiesterase-5 inhibitors and soluble guanylate cyclase stimulators.

Sildenafil and tadalafil are PDE-5is and enhance the effects of vasodilating (and perhaps antiproliferative) cyclic nucleotides (Fig. 5). Like prostacyclins and ERAs, PDE-5is are currently only approved for use in PAH. Several small studies have looked at the role of PDE-5is in the treatment of WHO group 2 PH secondary to congestive heart failure.\(^{44-46}\) These studies indicate that PDE-5is may improve exercise capacity in patients with PH due to heart failure, but further studies are needed. PDE-5is have also been studied in patients with PAH to delay disease progression.
with WHO group 3 PH due to lung disease. A small study of patients with chronic obstructive lung disease found that sildenafil acutely improved hemodynamics but inhibited hypoxic vasoconstriction resulting in impairment of arterial oxygenation. A study of 180 patients with idiopathic pulmonary fibrosis found no improvement in 6-MWD after 12 weeks of sildenafil therapy. At this time, there is no clear role for PDE-5is in the setting of PH due to lung disease.

**Sildenafil**

Sildenafil was the first PDE-5i that was approved for use in patients with PAH. It has a short half-life of 3–4 hours and needs to be administered three times a day. Sildenafil is mostly used orally but is also available intravenously.

In the landmark SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) study, sildenafil improved 6-MWD in patients with PAH. Sildenafil reduced the mPAP and improved functional class. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil versus placebo.
The US FDA approved sildenafil in patients with PAH in 2005 and the recommended dose is 20 mg orally three times a day.

**Tadalafil**

Tadalafil is a longer acting PDE-5i with a half-life of 17.5 hours and can be dosed once a day. Tadalafil at a dose of 40 mg/day, in the PHIRST trial (Pulmonary Arterial Hypertension and Response to Tadalafil) significantly improved 6-MWD and time to clinical worsening. There was no difference in change in functional class or Borg dyspnea score between tadalafil and placebo.50

The US FDA approved tadalafil for use in patients with PAH in 2009, and the recommended dose is 40 mg/day.

**Side Effects of Phosphodiesterase-5 Inhibitors**

Side effects of PDE-5is include headache, dizziness, nausea, epistaxis and priapism. There have been rare reports of patients treated with PDE-5is developing anterior ischemic optic neuropathy and optic atrophy, but causal association has not been clearly defined. Patients who develop visual changes while taking these medications should seek medical attention and discontinue use in the event of sudden vision loss. Hearing loss has been reported, but causality and mechanism remain unclear.

Use of nitrates is contraindicated in patients on PDE-5is because of the potential for life-threatening hypotension. Patients on PDE-5is should be advised to avoid all nitrates, including nitroglycerin and isosorbide mononitrate and isosorbide dinitrate. In patients who develop acute coronary syndrome, nitrates can be administered with close hemodynamic monitoring, 24 hours after the last dose of sildenafil and 48 hours after the last dose of tadalafil. Caution should be exercised when using β-blockers with PDE-5is because of the potential for orthostatic hypotension.

**Riociguat (Soluble Guanylate Cyclase Stimulator)**

Riociguat is a direct stimulator of the soluble guanylate cyclase independent of NO availability. It enhances the production of cGMP and is potentially effective also in conditions in which endogenous NO is depleted. In the PATENT (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial)-1 riociguat showed favorable results on exercise capacity, hemodynamics, WHO functional class and time to clinical worsening in PAH patients.51

Riociguat was approved by US FDA for PAH in 2013. The initial dose is 1 mg TID. Consider 0.5 mg TID if patient becomes hypotensive. If systolic BP is above 95 mmHg and no symptoms
of hypotension, up-titrate dose by 0.5 mg PO TID with dose increase no sooner than 2 weeks apart to highest tolerated dose (not to exceed 2.5 mg PO TID).

The adverse effects of riociguat include nausea, vomiting, diarrhea, dyspepsia, gastritis, constipation, dizziness, headache, hypotension, anemia, serious bleeding and hemoptysis.

The combination of riociguat and PDE-5is is contraindicated because of hypotension.

Combination of Currently Approved Disease-specific Therapies for Pulmonary Arterial Hypertension

The management of PAH has been extensively studied over the last two decades, resulting in the development of many new treatment options. However, many questions remain; for example, is one drug therapy better than another, should more than one therapy be started simultaneously upon diagnosis, should a second drug be added later in the course of the disease, and if so, when. Given the availability of medications that target different pathologic processes, combination therapy is an attractive theoretical option. The fact that PAH is an orphan disease makes it difficult to conduct studies that have enough power to answer questions like this. However, several small studies have been performed on combination therapies, and more studies are underway. A recent meta-analysis on six randomized controlled trials showed that combination therapy reduced the risk of clinical worsening, increased 6-MWD and reduced mPAP, RAP and PVR.

The approaches to institute combination therapy may be sequential or initial (upfront). Sequential combination therapy is the most widely utilized strategy. Drugs are added to monotherapy if there is inadequate clinical response or clinical deterioration. The PACES trial (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil) studied the effects of the addition of sildenafil or placebo in PAH patients who remained symptomatic while on stable dose of intravenous epoprostenol for at least 3 months. Patients treated with sildenafil experienced a placebo-adjusted improvement in 6-MWD at 16 weeks, as well as improvement in mPAP, cardiac output and time to clinical worsening. The TRIUMPH-1 study showed improvement in 6-MWD when inhaled treprostinil was added to either bosentan or sildenafil. The COMPASS-1 study (The Effects of Combination of Bosentan and Sildenafil vs. Sildenafil Monotherapy on Morbidity and Mortality in Symptomatic Patients with Pulmonary Arterial Hypertension) investigated the acute pharmacodynamic effects of addition of sildenafil to bosentan in patients with PAH. Mean PVR was significantly
reduced from baseline to 60 minutes following sildenafil administration. The reduction in PVR following sildenafil was comparable to that resulting from iNO. Sequential combination therapy has been allocated a grade of recommendation I and level of evidence A in PAH patients with inadequate clinical response to initial monotherapy. Initial combination therapy has been allocated a grade of recommendation IIb and level of evidence C in WHO-FC IV PAH patients in case of nonavailability of IV prostanoids. The experience on randomized controlled trials with upfront combination therapy is limited to the small BREATH-2 study, which failed to demonstrate any significant difference between patients treated initially with the combination epoprostenol and bosentan as compared to epoprostenol alone. In a more recent study, 23 treatment naive PAH patients were treated with initial combination of epoprostenol and bosentan and compared with matched historical control group treated with epoprostenol. There was a statistically significant decrease in PVR in the initial combination therapy group but this hemodynamic benefit did not translate into statistically significant difference in survival, or in transplant-free survival. The results of the AMBITION (A randomized, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension) were recently presented at the European Respiratory Society International Congress 2014 in Munich, Germany. This study compared first-line monotherapy with tadalafil, monotherapy with ambrisentan and combination therapy with tadalafil and ambrisentan in de novo WHO-FC II and III PAH patients. Combination therapy reduced the risk of clinical failure compared to pooled ambrisentan and tadalafil monotherapy arms. This was mainly driven by reduction in hospitalization. There was also significant decrease in NT-proBNP and improvement in 6-MWD.

Invasive Therapies

Lung and Combined Heart and Lung Transplantation

None of the current medical therapies for PAH are curative. Patients who have continued progression of the disease on medical therapies and patients with advanced disease (WHO-FCs III-IV) should be referred to a center that specializes in lung transplantation. Delayed referral in combination with the length of the waiting time, due to the shortage of organ donors, may increase the mortality on the waiting list and clinical severity at the time of transplantation. Patients who undergo lung transplantation for PAH have higher perioperative mortality, reflecting the hemodynamic severity of the disease;
however, the long-term post-transplant outcomes among those who survive the first year are similar to lung transplant recipients with other indications. The survival post-transplant is 52–75% at 5 years and 45–66% at 10 years. The etiology of PAH may help the decision making because the prognosis varies according to the underlying condition. PAH associated with CTD has a worse prognosis than iPAH even when treated with prostanoids, while patients with PAH associated with congenital heart disease have a better survival. The worst prognosis is seen in patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis because of the lack of effective medical treatments and these patients should be listed for transplantation at diagnosis.

**Atrial Septostomy**

As the right heart function worsens in response to ongoing severe PAH, patients experience progressive dyspnea, ascites, lower extremity edema and may have presyncope or syncope. Atrial septostomy creates a right-to-left interatrial shunt, decreasing RV filling pressure and improving RV function and LV filling. While the created shunt decreases systemic arterial oxygen saturation, it is anticipated that improved cardiac output will result in overall augmentation of systemic oxygen delivery.

The procedure can be performed either surgically or in the cardiac catheterization laboratory with balloon septostomy. A percutaneous approach is preferred in most patients because of the very high risk of surgery. The procedure can be considered for patients with recurrent syncope despite optimization of medical therapies as a bridge to lung transplantation or palliation in patients who are not transplant candidates. The procedure-related mortality is high (around 16%). Several recommendations have been made to minimize the risk. Atrial septostomy should be performed in centers with experience in its use and management of potential complications. A mean RAP above 20 mmHg, PVR index more than 55 Wood units/m² and a predicted 1-year survival less than 40% are significant predictors of a procedure-related death. Before cardiac catheterization, patients should have systemic oxygen saturation more than 90% in room air and optimized cardiac function.

**Pulmonary Thromboendarterectomy**

Patients with suspected PAH should undergo evaluation for WHO-group 4 PH, i.e., CTEPH. The screening tool of choice for CTEPH is a ventilation perfusion scan. If indicative of CTEPH, a pulmonary angiogram should be performed. Patients are considered to be candidate for pulmonary thromboendarterectomy (PTE) if they have surgically accessible
disease and present acceptable surgical risk. The goal of PTE is to remove sufficient material from the pulmonary arteries to substantially lower PVR and improve cardiac output. This complex and life-saving procedure is best performed at high volume centers.

Patients who have no surgical targets and thus have inoperable CTEPH and patients who have persistent PH after PTE have been shown to benefit from the guanylate cyclase stimulator riociguat. The CHEST (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial)-1 trial showed that riociguat improved exercise capacity and PVR in this group of patients.59

Riociguat was approved by the US FDA in 2013 for use in patients with CTEPH. For dosing and side effects see section on guanylate cyclase stimulators.

PROGNOSIS

Pulmonary arterial hypertension is a progressive disease, and the overall prognosis is poor. Estimated median survival of patients with iPAH before available therapy was 2.8 years after diagnosis.60 With the advent of new therapies over the last two decades, however, contemporary survival and quality of life of patients with PAH have improved substantially compared with prior survival estimates.60,62 A meta-analysis of all the randomized, controlled trials performed from 1990 to 2008 demonstrated a reduction in mortality of 43%. Number of patients to be treated to prevent one death was 61.6 and 16.2 deaths were prevented in each 1,000 patients treated.63 Predictors of a poor outcome include clinical evidence of RV failure, rapid progression of disease and advanced functional class, poor exercise capacity as measured by 6-MWD or cardiopulmonary exercise test, elevated brain natriuretic peptide, RV dysfunction or pericardial effusion by echocardiogram and high RA pressure, high PVR and low cardiac index by RHC (Table 3). Information from two large present-day registries of patients with PAH gives us the opportunity to better understand the prognosis of PAH, its determinants and outcomes in the current treatment era. These registries are the French National Registry and the REVEAL Registry (the Registry to Evaluate Early and Long-Term PAH Disease Management). French National Registry enrolled 354 consecutive idiopathic, heritable and anorexigen-associated patients from October 2002 to October 2003. The 1-year, 2-year and 3-year survival rates per this registry are 82.9%, 67.1% and 58.2%, respectively. Univariate analysis suggested that the factors associated with better prognosis were female sex, functional class I or II symptoms, greater 6-MWD, lower RAP and higher cardiac output. The multivariate analysis reduced
this list to three independent factors, namely, sex, 6-MWD and cardiac output at diagnosis. The REVEAL Registry analyzed 2,716 patients with PAH and found 1-year survival to be 91% from the date of enrollment and the 1-year and 3-year survival rates from the time of PAH diagnosis of 87.7% and 72.1%, respectively. Sex, functional class, 6-MWD, origin of PAH, age, PVR, RAP, renal insufficiency, resting systolic blood pressure and heart rate, BNP, presence of a pericardial effusion and diffusing capacity of the lung for carbon monoxide were predictive of outcome.

TREATMENT ALGORITHM AND EVALUATING RESPONSE TO THERAPY

There is emerging evidence that earlier initiation of therapy when patients are mildly symptomatic improves functional and clinical status. The decision to initiate vasodilator therapy and the specific agents used depend on the patients’ WHO-FC, risk profile and preference. PAH patients with symptoms that result in slight limitation of physical activity (WHO-FC II) should be started on oral agents, either ERAs or PDE-5is. Patients that are unable to carry out any physical activity without symptoms (WHO functional class IV) need more aggressive therapy and prostacyclin therapy should be considered. The guidelines propose a wide range of treatment options for patients who are asymptomatic at rest but have marked limitation of physical activity (WHO-FC III). Patients with WHO-FC III symptoms and poor prognostic factors should be considered for prostacyclin therapy, while patients with good prognostic profile can be started on oral therapy.

Close follow-up is crucial in all patients started on PAH-specific therapy. Stable patients on oral therapy can be followed every 4–6 months. Patients with more advanced and/or progressive symptoms, right heart failure and patients on intravenous therapy need to be seen at least every 3 months. With each clinic visit, WHO-FC, BNP/NT-proBNP and exercise capacity (6-MWD or graded treadmill) is checked to help determine response to therapy. A repeat echocardiogram is done at least 6 months after commencing PAH-specific therapy. The timing of repeat RHC varies between PH centers. RHC should be considered in patients with progressive symptoms in spite of therapy, prior to addition of a new PAH specific agent, and many experts routinely repeat RHC after 1 year on therapy, particularly in patients on prostacyclin therapy (Fig. 6).

Patients who have inadequate clinical response on monotherapy, i.e., symptoms progress or do not improve...
to WHO-FC I or II may benefit from switching PAH-specific agents or from a combination of agents. As discussed above, combining PAH-specific therapies that affect different pathways make therapeutic sense and are currently under intense investigation. Lastly, invasive therapies like lung transplantation or atrial septostomy may be an option for patients who have progressive symptoms in spite of optimization of medical therapies.

**FIG. 6:** Evidence-based treatment algorithm for the management of pulmonary arterial hypertension. Drugs within the same grade of evidence are listed in alphabetical order and not order of preference.10

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Inadequate clinical response:
- Consider eligibility for lung transplantation

Sequential combination therapy (I-A)
- ERAs
- Prostanooids
- PDE-5i or sGCS
- Bas (Ia-C)

Inadequate clinical response on maximal therapy:
- Referral for lung transplantation (II-C)
CONCLUSION

Over the last two decades, remarkable progress has been made in the understanding of the pathophysiology and pathogenesis of PAH. Improvement in knowledge has resulted in many new treatment options. PAH has evolved from a rare, untreatable and fatal entity to that of an effectively managed disease with improvement in quality of life and survival. There is still much to learn and accomplish in managing this complex disease.

REFERENCES


