OPEN ACCESS

# Advances in the management of pulmonary arterial hypertension

Himanshu Deshwal, Tatiana Weinstein, Roxana Sulica

Pulmonary, Sleep and Critical Care Medicine, New York University Grossman School of Medicine, New York, New York, USA

**Correspondence to**
Dr Roxana Sulica, Pulmonary, Sleep and Critical Care Medicine, New York University Grossman School of Medicine, New York, New York, USA; rsulica@yahoo.com

Accepted 8 September 2021

## ABSTRACT

The management of pulmonary arterial hypertension (PAH) has significantly evolved over the last decades in the wake of more sensitive diagnostics and specialized clinical programs that can provide focused medical care. In the current era of PAH care, 1-year survival rates have increased to 86%–90% from 65% in the 1980s, and average long-term survival has increased to 6 years from 2.8 years. The heterogeneity in the etiology and disease course has opened doors to focusing research in phenotyping the disease and understanding the pathophysiology at a cellular and genetic level. This may eventually lead to precision medicine and the development of medications that may prevent or reverse pulmonary vascular remodeling. With more insight, clinical trial designs and primary end-points may change to identify the true survival benefit of pharmacotherapy. Identifying responders from non-responders to therapy may help provide individualized patient-centered care rather than an algorithm-based approach. The purpose of this review is to highlight the latest advances in screening, diagnosis, and management of PAH.

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular endothelial dysfunction, smooth muscle proliferation, fibrosis, and in situ thrombosis, eventually leading to right ventricular (RV) failure and death. The first case of PAH was discovered on autopsy in 1891 when thickening of the pulmonary artery was noted in the absence of lung or heart disease in a deceased patient. However, PAH remained unrecognized until 1951, when Dr Dresdale identified three cases and termed it primary pulmonary hypertension.[1 2] Since then, significant research has shed light on its pathophysiology, disease course, and various targetable pathways for pharmacotherapy. Despite improvement in screening techniques, the diagnosis of PAH is often delayed leading to increased morbidity and mortality. While several drugs targeting different pathways associated with PAH may lead to significant improvement in functional status, hemodynamics, and quality of life, the data on survival is still minimal. The heterogeneity in the etiology and disease course has opened doors to focusing research in phenotyping the disease and understanding the pathophysiology at a cellular and genetic level.[3] This may eventually lead to precision medicine and the development of medications that may prevent or reverse pulmonary vascular remodeling. With more insight, the clinical trial designs and primary end-points may change to identify the true survival benefit of pharmacotherapy. Identifying responders from non-responders to therapy may help provide individualized patient-centered care rather than an algorithm-based approach.

Newer screening methodologies are being validated for clinical use for early detection. Modern imaging and exercise testing have revolutionized the assessment of PAH patients to objectively characterize RV function and pulmonary vascular remodeling and to assess the precise etiology of a patient's exertional symptoms. Medical management has also changed due to improved diagnostic and prognostic techniques with a multidisciplinary approach, early initiation of combination therapies, and referral for lung transplantation. The purpose of this review is to highlight the current advances in the understanding and management of PAH and its impact on clinical practice and outcomes for our patients.

### Changes in definitions: clinical impact

The sixth World Symposium on Pulmonary Hypertension (WSPH) revised the hemodynamic definitions of pulmonary hypertension (table 1).[4] The mean pulmonary artery pressure (mPAP) was lowered from ≥25 mm Hg to >20 mm Hg based on scientific evidence suggesting normal mPAP at rest to be 14.0±3.3 mm Hg and upper limit of normal defined as 20 mm Hg, which is 2 SD above the mean.[5] The definition for precapillary PH for all five groups of PH includes pulmonary artery wedge pressure (PAWP) <15 mm Hg and pulmonary vascular resistance (PVR) of ≥3 woods unit. PVR helps determine the presence of vasculopathy even in patients with co-existing left ventricular dysfunction and elevated PAWP. While it has its own limitations, it is a useful marker to differentiate isolated postcapillary pulmonary hypertension without pulmonary vasculopathy from co-existing precapillary pulmonary hypertension with pulmonary vasculopathy. The utility of the new guidelines may pave way for appropriate phenotyping of group

Linked

► http://dx.doi.org/10.1136/jim-2021-002152

Check for updates



**To cite:** Deshwal H, Weinstein T, Sulica R. *J Investig Med* 2021;**69**:1270–1280.

**Table 1** Revised hemodynamic definitions of pulmonary hypertension[4]

| Phenotype | Hemodynamic definition |
|---|---|
| Precapillary pulmonary hypertension | mPAP >20 mm Hg + PAWP <15 mm Hg + PVR ≥3 woods units |
| Isolated postcapillary pulmonary hypertension | mPAP >20 mm Hg + PAWP ≥15 mm Hg + PVR <3 woods units |
| Combined precapillary and postcapillary pulmonary hypertension | mPAP >20 mm Hg + PAWP ≥15 mm Hg + PVR ≥3 woods units |

mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

2 PH and assess hemodynamic response to vasodilator therapies in future clinical trials. It also guides the clinicians to optimize the left heart dysfunction before repeating right heart catheterization or trialing vasodilator therapy for underlying precapillary pulmonary hypertension.

While an ideal hemodynamic marker for pulmonary vascular disease should be independent of stroke volume and left atrial pressures, and take into account the pulsatile nature of pulmonary blood flow, PVR has most commonly been utilized in clinical practice.

The newer definition will potentially have a significant clinical impact on management and mortality in patients with pulmonary hypertension. Previous studies have demonstrated increased mortality and morbidity in patients with mPAP ranging between 21 and 24 mm Hg comparable with patients with mPAP >25 mm Hg. In patients with systemic sclerosis, initial abnormal mPAP (21–24 mm Hg) has been found to predict disease progression with mPAP greater than 25 mm Hg. This highlights a potential gap in clinical practice where early initiation of vasodilator therapy may be beneficial. If combined with improved screening techniques such as the DETECT algorithm (a systematic approach to screen for pulmonary hypertension in systemic sclerosis detailed below), novel biomarkers and non-invasive testing, the new definition may help identify many high-risk patients early in the disease course and lead to early initiation of therapy.[6 7]

The EARLY study had demonstrated the benefit of treating mild symptomatic PH (mPAP ≥25 mm Hg).[8] It can be anticipated that aggressive pharmacotherapy early in the disease (mPAP >20 mm Hg) course may prevent pulmonary vascular remodeling and disease progression using the newer definitions. This may eventually lead to improved morbidity and mortality; however, longitudinal studies are needed to demonstrate the true benefit.

The newer definitions may also impact future clinical trials and research design to include patients with mPAP >20 mm Hg. The inclusion of these patients may provide an insight into the natural history of early disease and assist with investigating different treatment modalities for these patients. While studies have demonstrated the safety and efficacy of pharmacotherapy in patients with mPAP 21–24 mm Hg in systemic sclerosis, more extensive clinical trials are underway to assess the benefits and outcomes of these therapies in group 1 PAH[9] (NCT02290613, NCT01725763).

## DIAGNOSTIC ADVANCES

The current diagnostic approach includes an extensive workup to assess various causes of pulmonary hypertension (table 2). A transthoracic echocardiogram is the most common screening tool to identify RV function and signs of pulmonary hypertension based on the clinical picture. Laboratory and serologic testing are conducted to identify underlying connective tissue disease, HIV infection, and indirect biomarkers of RV dysfunction such as brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP). This is often followed by ECG, pulmonary function testing (PFT), and chest imaging to evaluate for underlying lung disease (obstructive or restrictive) (group 3 PH). PFTs should include spirometry, lung volumes, and diffusion capacity (DLCO). A contrast-enhanced CT of the chest or CT angiography and ventilation–perfusion scan are performed to screen for chronic thromboembolic pulmonary hypertension (CTEPH) (group 4 PH).

Current guidelines recommend all patients undergo nocturnal oximetry to assess for nocturnal hypoxemia, sleep disordered breathing, and sleep apnea as these disorders are highly prevalent and may worsen pulmonary hypertension.[10] Right heart catheterization is the gold standard for diagnosis. Still, it is usually the last step in diagnosis as alternate causes of RV failure or pulmonary hypertension are first excluded using non-invasive testing. Once the diagnosis is made, prognostic exercise testing such as a 6 min walk test (6-MWT) or a cardiopulmonary exercise test (CPET) are often required to assess objective data to characterize functional status.

### Advances in screening and diagnosis for PAH

In recent years, various non-invasive modalities have gained interest in screening for PAH. A clinical approach using the DETECT algorithm has been recommended in patients with systemic sclerosis since the fifth WSPH.[10] This approach includes an initial clinical assessment including features of telangiectasias, positive anticentromere antibody, elevated serum urate, and NT-proBNP, right axis deviation on ECG, and FVC%/DLCO% <1.6 on PFT. An echocardiographic assessment of the right atrial area and tricuspid regurgitation jet velocity is recommended in patients with high clinical scores. Patients with a higher pretest probability of PAH based on echocardiographic parameters are recommended to undergo right heart catheterization for confirming the diagnosis.[7 11]

More recently, genetic analysis and serum biomarkers have been associated with various phenotypes of pulmonary hypertension. Patients with a family history of heritable PAH are recommended to undergo genetic counseling and testing to screen for mutations commonly associated with PAH. A bone morphogenetic protein receptor 2 (BMPR2) mutation is frequently associated with heritable PAH. Montani *et al*[12] reported a high risk of developing PAH in carriers of BMPR2 mutations with an annual incidence of 2.3%/year. BMPR2 mutation is also associated with early and more aggressive disease courses with less response to acute vasodilator testing and increased risk of death than those without the mutation.[13] A mutation in the Eukaryotic translation Initiation Factor 2 Alpha Kinase 4 (EIF2AK4) gene is classically associated with pulmonary veno-occlusive disease and worse outcomes.[14]

**Table 2** Clinical classification of pulmonary hypertension[4]

| | |
|---|---|
| Group 1: PAH | Idiopathic PAH<br>Heritable PAH<br>Drug and toxin-induced PAH<br>PAH associated with:<br>► Connective tissue disease<br>► HIV infection<br>► Portal hypertension<br>► Congenital Heart disease<br>► Schistosomiasis<br>PAH long-term responders to calcium channel blockers<br>PAH with over features of venous/capillary (PVOD/PCH) involvement<br>Persistent PH of the newborn syndrome |
| Group 2: PH due to left heart disease | PH due to heart failure with preserved left ventricular ejection fraction<br>PH due to heart failure with reduced left ventricular ejection fraction<br>Valvular heart disease<br>Congenital/acquired cardiovascular conditions leading to postcapillary PH |
| Group 3: PH due to lung diseases and/or hypoxia | Obstructive lung disease<br>Restrictive lung disease<br>Other lung disease with mixed restrictive/obstructive pattern<br>Hypoxia without lung disease<br>Developmental lung disorders |
| Group 4: PH due to pulmonary artery obstruction | Chronic thromboembolic PH<br>Other pulmonary artery obstructions: sarcoma or angiosarcoma, other malignant tumors (renal carcinoma, uterine carcinoma, germ cell tumors), non-malignant tumors (uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary artery stenosis, parasites (hydatidosis) |
| Group 5: PH with unclear and/or multifactorial mechanisms | Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders<br>Systemic and metabolic disorders: pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis<br>Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis<br>Complex congenital heart disease |

PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

## Biomarkers

Serum biomarkers have increasingly been used in clinical practice to screen, monitor, and prognosticate patients with PAH. NT-proBNP and BNP have commonly been used in routine clinical practice to classify the severity of the patient and estimate prognosis.[15 16] Several novel biomarkers are being studied in PAH, focusing on different aspects of the pathophysiology, such as inflammation, oxidative stress, pulmonary vascular endothelial dysfunction, and markers of RV dysfunction. The current interest lies in finding biomarkers that can screen for PAH, distinguish PH due to left heart disease from pulmonary vascular disease, predict severity, mortality, and response to therapy. Rhodes *et al*[17] studied nearly 1129 plasma proteins and found 20 proteins that could differentiate survivors from non-survivors with idiopathic pulmonary arterial hypertension (IPAH). Out of the 20 proteins, they found nine replicable and prognostic proteins for IPAH independent of NT-proBNP levels. These nine proteins included interleukin-1 receptor-like protein, erythropoietin, complement factors D and H, insulin-like growth factor binding protein-1, tissue inhibitors of metalloproteinases 1 and 2 (TIMP-1, TIMP-2), plasminogen, and apolipoprotein E (Apo E). The authors also found that adding these biomarkers to risk stratification strategies such as the REVEAL equation significantly improved the predictive ability of the scores.[17] Benza *et al*[18] assessed genetic differences in patients that may predict response to endothelin-1 receptor antagonists (ERAs). They found that a single nucleotide polymorphism (rs11157866) in the G-protein α and γ subunits was associated with a significant response to ERA therapy in the form of improved functional class and 6 min walk distance at 12 and 18 months.[18]

## Cardiac magnetic resonance imaging

While echocardiogram is a readily available and good screening test, cardiac magnetic resonance imaging (CMR) is gaining frequent clinical use due to its accuracy in assessing RV morphology and function at baseline and follow-up visits.[19] The accuracy of an echocardiogram depends on the operator and quality of the acoustic windows. It has inherent inaccuracies in assessing RV function, while CMR is reproducible and accurate and allows for RV assessment in a standardized manner.[19 20] CMR can be used for diagnosing intracardiac shunts, aberrant pulmonary vascular morphology, left-sided disease, and other congenital anomalies.[21]

Interestingly, despite their seemingly similar pathophysiology, in IPAH and systemic sclerosis-related PAH, identical treatment modalities targeting RV afterload reduction result in vastly different outcomes. This divergent response to therapy in systemic sclerosis-related PAH may be partially attributed to a more nuanced interaction of the RV and pulmonary vasculature in systemic sclerosis.[22] Therefore, a thorough assessment of RV function, morphology, and PA vasculature with CMR becomes critical to devise an appropriate treatment strategy. CMR can also monitor the success of pulmonary endarterectomy (PEA) in CTEPH patients.[23 24] Volumetric assessment of the RV using CMR can improve risk stratification of PAH patients when added

to current stratification strategies.[25] In addition, CMR can identify the impaired longitudinal right atrial strain that can predict decompensated hemodynamics in PAH and predict poor outcomes.[26]

### Exercise testing

The most common and often the first symptom in PAH patients is exertional dyspnea. An exercise stress test can accurately assess the severity of exertional symptoms. A 6-MWT assesses exercise capacity in clinical practice and has been included as a prognostic parameter in PAH.[27] However, it may be a suboptimal test in younger patients who have severe PAH and RV dysfunction but can still walk more than 500 m. This may lead to a false sense of reassurance about the severity of their disease and a less aggressive or delayed medical therapeutic approach. CPET has recently become a useful clinical tool to reliably assess patients' functional status and RV function during exercise. It provides valuable clinical information that can be utilized to monitor response to therapy and predict clinical worsening.[28]

Exertional dyspnea in PAH patients may occur due to two predominantly pathophysiologic mechanisms. On exertion, the oxygen delivery cannot match the oxygen demand due to the inability to increase stroke volume. This occurs due to increased venous return and worsening RV dysfunction leading to low stroke volume. Cardiac output is maintained mainly via an increase in heart rate and unable to match the $O_2$ demand, leading to early transition to anaerobic metabolism and lactic acidosis in peripheral tissues, observed as a low anaerobic threshold. The low cardiac output and anaerobic metabolism are characterized by low $O_2$ pulse and peak oxygen consumption ($VO_2$), respectively. The buildup of lactic acidosis may stimulate the carotid bodies and increase ventilator drive, as observed by increased V'E on CPET. In addition, there is low mixed venous oxygen saturation and low alveolar-arterial diffusion of oxygen in PAH, leading to arterial hypoxemia. The combined effect of increased V'E and poor perfusion leads to increased V/Q mismatch causing an increase in physiologic dead space. This is reflected as a high ratio of V'E/V'$CO_2$ or increased slope of the V'E/V'$CO_2$ slope.[29] The increase in physiologic dead space is often associated with reduced end-tidal $CO_2$ tension ($PetCO_2$).[30] Peak $VO_2$, peak $VO_2$% predicted, and VE/V'$CO_2$ slope and arterial oxygen saturation are better prognostic markers for risk stratification in PAH.[29] Clinical variables obtained by CPET also serve as an attractive end-point target for clinical trials and monitor response to therapy.[31 32]

### Invasive cardiopulmonary exercise testing (iCPET)

Invasive hemodynamic monitoring with right heart catheterization during CPET (also known as invasive CPET or iCPET) is gaining significant clinical interest in understanding the etiology of symptoms in complex patients who may have PAH and underlying lung, muscular, or cardiac disease. Walkey *et al*[33] studied iCPET in systemic sclerosis patients. They successfully distinguished the etiology of exertional limitation when routine studies such as the echocardiogram, PFTs, and imaging were unreliable.[33] The use of iCPET has led to the development of a 'Dyspnea clinic' in several PAH centers to address the multifactorial etiology of dyspnea in patients whose preliminary workup is unrevealing.[34] Invasive CPET is particularly useful in patients with a suspected component of exertional post-capillary PH due to left heart disease, exercise-induced PAH, and patients who have preload limitation to exercise. In exertional post-capillary PH, the mPAP is often elevated along with normal PVR and elevated PCWP on exertion. In patients with preload limitation to exercise, the maximum right atrial pressure is less than 8 mm Hg on exertion, and $VO_2$ max is less than 80% of predicted with otherwise normal central hemodynamics.[35 36] Guth *et al*[37] conducted a prospective study on chronic thromboembolic disease patients to assess the impact of PEA on exercise hemodynamics. They found a significant reduction in mPAP, PVR, mPAP/cardiac output slop, and increase in peak $VO_2$ after PEA. They also observed a significant improvement in WHO functional classification and quality of life based on the Cambridge Pulmonary Hypertension Outcome Review Questionnaire after 1 year of PEA.[37]

## ADVANCES IN MANAGEMENT: EARLY AGGRESSIVE TREATMENT

### Current Medical Therapy (200)

Once the diagnosis is made, several risk stratifying tools and WHO functional classification can be used clinically to determine the choice of pharmacotherapy in each individual patient (table 3).

More recently, an updated REVEAL 2.0 risk score has been validated for risk stratification of patients (figure 1). Benza *et al*[38] identified REVEAL 2.0 score as an excellent predictor of clinical deterioration and mortality and performed better than COMPERA, and the French Pulmonary Hypertension Registry (FPHR) scores in patients followed up for greater than 1 year. Pharmacotherapy is targeted at various pathways involved in the development of PAH (figure 2). Currently, the FDA has approved five classes of drugs to treat PAH[39] (table 4). While only intravenous epoprostenol has demonstrated direct survival benefit

**Table 3** WHO functional classification of pulmonary hypertension[10]

| NYHA/WHO functional class | |
|---|---|
| **Classifications** | **Symptoms** |
| Class I | No symptoms and no limitation in ordinary physical activity. |
| Class II | Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. |
| Class III | Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest. |
| Class IV | Severe limitations. Experiences symptoms even while at rest. |

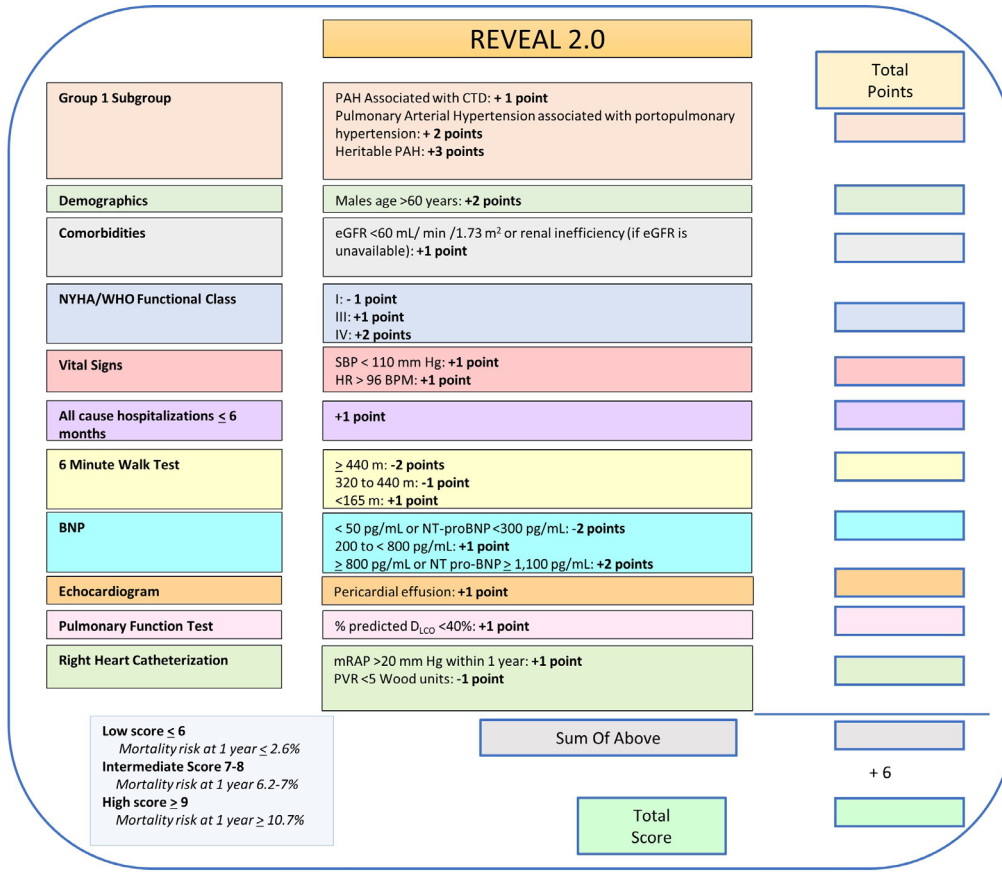


**Figure 1** REVEAL 2.0 Risk score calculator for pulmonary arterial hypertension.[38] BNP, brain natriuretic peptide; CTD, connective tissue disease; eGFR, estimated glomerular filtration rate; HR, heart rate; mRAP, mean right atrial pressure; NT-proBNP, N-terminal proBNP; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SBP, systolic blood pressure.

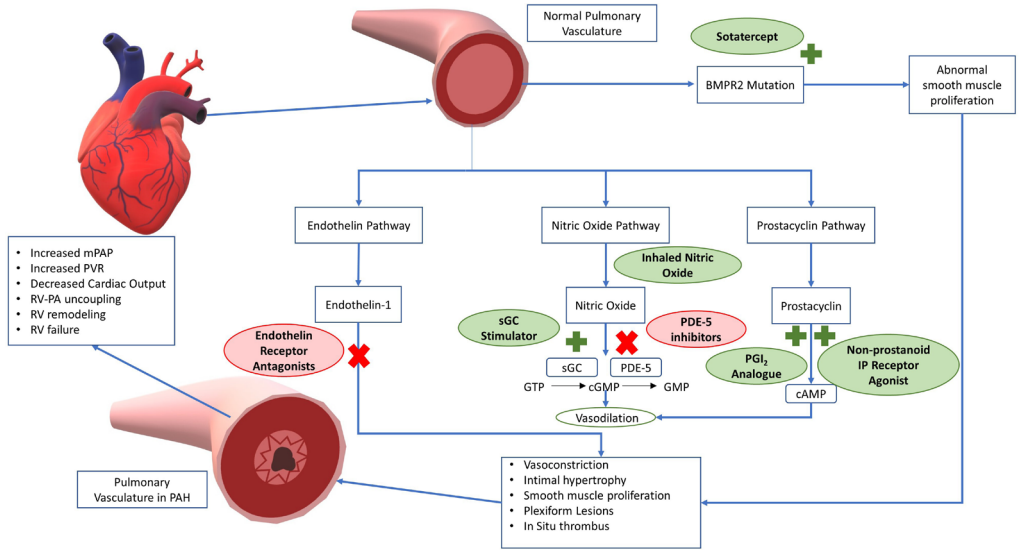


**Figure 2** Pathogenic pathways and drug targets in pulmonary arterial hypertension. BMPR-2, bone morphogenetic protein receptor 2; cAMP, cyclic AMP; GMP, guanosine monophosphate; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PDE-5, phosphodiesterase-5; PGI2, prostaglandin I2; PVR, pulmonary vascular resistance; RV, right ventricle; sGC, soluble guanylate cyclase.

Table 4 Conventional pharmacotherapy for pulmonary hypertension

| PDE-5 inhibitors | sGC stimulators | Prostaglandin analogue | Prostacyclin receptor agonists | Endothelin receptor agonist |
|---|---|---|---|---|
| Sildenafil | Riociguat | Epoprostenol | Selexipag | Ambrisentan |
| Tadalafil | | Treprostinil | | Macitentan |
| | | Iloprost | | Bosentan |

PDE-5, phosphodiesterase-5; sGC, soluble guanylate cyclase.

in a 3-month controlled study of IPAH patients, other classes of drugs are associated with significant improvement in functional status, symptoms, and hemodynamics, including RV function.[10 40] The primary goal of pharmacotherapy is to decrease a patient's risk to ultimately achieve and maintain a low-risk category and improve functional and hemodynamic status. It has been demonstrated that lowering the risk category can improve overall survival and functional status in PAH.[10 41]

Patients with mild disease or lower risk category can be initiated on monotherapy with close follow-up and risk assessment. It is recommended for patients who are intermediate to the high-risk category to initiate combination therapy, including a parenteral pulmonary vasodilator with intravenous prostacyclin reserved for severe disease.[10 42] A 3-month to 6-month follow-up is recommended with a re-assessment of risk status. If the patient is not at goal on current medical therapy, sequential combination therapy is recommended with a different class of drug.[10 42] For aggressive and severe disease non-responsive to pharmacotherapy, early lung transplant referral is recommended.[43] In addition, treatment of hypoxia, exercise, rehabilitation, psychosocial support, nutrition, and appropriate vaccination and age-based cancer screening is recommended to optimize the patient's overall health.

Historically, anticoagulation was recommended for patients with IPAH. This guidance was largely based on the notion that, in addition to pulmonary vascular remodeling, in situ thrombosis of the small pulmonary arteries contributed significantly to the clinical course of disease. Early clinical studies in favor of this in IPAH were largely limited to observational data, retrospective studies, and single-center experiences. Additionally, they were largely conducted prior to the introduction of many of the vasodilator therapies currently on the market. More recent randomized trials and data utilizing the REVEAL registry, however, have suggested no survival advantage in IPAH patients and in fact, according to the REVEAL registry data poorer survival in systemic sclerosis-related PAH taking warfarin.[44] Thus, the most recent guidelines note that the potential benefit of anticoagulation is less clear in IPAH and lowered it to a class IIb recommendation (may be considered, usefulness is less well established by evidence/opinion).[10] One notable exception is IPAH patients receiving long-term therapy intravenous therapy with prostaglandins. Anticoagulation may be of benefit in this setting due to the risk of catheter-associated thrombosis. There is a paucity of data regarding the role of the new oral anticoagulants in PAH.

## Identifying super responders

During diagnostic RHC, vasodilator testing is a standard practice to identify patients who may respond to calcium channel blocker (CCB) therapy. Inhaled nitric oxide is the preferred vasodilator challenge. Adenosine and intravenous epoprostenol have also been used to assess acute vasoreactivity in the cardiac catheterization laboratory. Reduction in mPAP of >10 mm Hg to less than 40 mm Hg with preserved cardiac output and blood pressure is considered a positive vasodilator test.[10 45] Patients with positive vasodilator tests often have an overall better survival and can initiate CCB monotherapy.[45 46] Interestingly, these findings are specific to idiopathic PAH and do not predict better survival in patients with HIV, connective tissue disease, or portopulmonary hypertension.[45 47] Raffy *et al*[48] demonstrated that a decrease in the total PVR index greater than 50% in response to short-term infusion of prostacyclin at the time of diagnosis predicted slow progression of the disease and better prognosis.

However, due to the heterogeneous nature of PAH, many patients who have a negative vasodilator test may respond to a different class of medication more than the others and are termed as 'super responders'.[49] Identifying super responders is challenging and is an area of significant clinical interest. Various patient factors can often determine responsiveness to different classes of drugs. For example, female sex tends to be more responsive to bosentan, while GNG2 polymorphism has been associated with an excellent hemodynamic response to macitentan.[18 50 51] Younger age and male sex are associated with a better response to phosphodiesterase-5 (PDE-5) inhibitors.[52] With the advent of genomics and transcriptomics in translational research, genetic phenotyping may highlight the predominant pathway of disease progression and guide the titration of therapy accordingly. Hemnes *et al*[53] performed a quantitative PCR on peripheral blood samples from PAH patients to identify RNA expression patterns that could predict vasodilator response to CCBs. They identified 13 genes that were significantly different between vasodilator responsive PAH patients and vasodilator non-responsive PAH patients.[53] Allen *et al*[54] used morphometric and hemodynamic measurements of the pulmonary vasculature to identify high pulmonary arteriolar shear stress load from low shear stress load that may differentiate reversible from non-reversible disease early in the disease course. They also found that treprostinil could stall progression when administered in the early phase compared with later stages, suggesting that prostacyclin therapy may delay pulmonary vascular remodeling if initiated in the early disease course.[54]

With more evidence to predict responsiveness to therapy and differentiate phenotypes of PAH, it may be possible to tailor therapy in a patient-centered manner in the future. This may allow shifting from an algorithmic treatment approach to individualized care in evidence-based practice.

## Newer drugs in PAH

### Riociguat

Riociguat is a soluble guanylate cyclase stimulator (sGC) that increases intracellular cyclic guanosine monophosphate by directly activating sGC, leading to pulmonary vasodilation and platelet inhibition. It was initially approved for CTEPH based on CHEST-1 trial that demonstrated significant improvement in PVR and 6MWD in CTEPH patients receiving riociguat.[55] However, follow-up studies PATENT-1 and PATENT-2 by the same authors assessed the role of riociguat in iPAH and connective tissue disease-PAH patients and found an increase in 6MWD by 30 m compared with the placebo group (6 m), time to clinical worsening, increase in cardiac output, decrease in PVR and NT-proBNP, and improvement in WHO functional class.[56] Following these results, riociguat was approved for group 1 PAH patients. Smoking generally reduces the bioavailability of riociguat by 50%–60%, and the patient is thus recommended to quit smoking or dose adjustment may become necessary.[57] Riociguat is generally contraindicated in patients on PDE-5 inhibitors due to increased risk of hypotension. In patients with suboptimal response to PDE-5 inhibitors, riociguat is a good alternative. The RESPITE trial showed an increase in 6MWD by 31 m, a decrease in NT-proBNP, and improvement in WHO functional class in patients transitioned to riociguat from PDE-5 inhibitors.[58] However, up to 52% of patients had experienced drug-related adverse events, with 16% being serious adverse events (although only 3% of serious events were felt to be study drug related). The recently concluded REPLACE trial confirmed these findings of delay in clinical worsening and disease progression in intermediate-risk PAH patients switched to riociguat from PDE-5 inhibitors.[59]

### Selexipag

Selexipag is a non-prostanoid oral drug that is highly selective to prostacyclin receptors in the pulmonary vasculature. Selexipag promotes pulmonary vasodilation, inhibits platelet aggregation, and has antiproliferative effects on pulmonary artery smooth muscle cells. The FDA has recently approved it for the treatment of PAH FC II–III patients. The dose is generally started at 200 µg twice a day and titrated up weekly to a maximum dose of 1600 µg twice a day. Selexipag was studied in the double-blinded, placebo-controlled, phase 3 RCT, the GRIPHON trial, which demonstrated a reduced risk of hospitalization and death compared with placebo.[60] The trial included selexipag monotherapy or as an add-on therapy to ERA or PDE-5i or both compared with placebo and demonstrated a reduction in clinical worsening (HR 0.6, 99% CI 0.46 to 0.78, $p<0.001$).[60] Often, patients may need to be transitioned from one drug to another based on tolerability and adverse effects. TRANSIT-1 study found that slow down titration of inhaled treprostinil and up-titration of selexipag was well tolerated and safe in PAH patients with FC II/III.[61]

### Ralinepag

Ralinepag a selective, non-prostanoid prostacyclin receptor (IP) agonist is an immediate-release oral drug that is currently being studied in PAH. A phase 2 RCT investigating 61 patients found a significant reduction in PVR by 163.9 Dyn.sec/cm$^5$ and an increase in 6MWD by 36.2 m in patients receiving ralinepag monotherapy or combination therapy compared with placebo.[62] Currently, ADVANCE CAPACITY, ADVANCE OUTCOMES, and ADVANCE ENDURANCE are three major phase 3 trials studying the safety, efficacy, clinical outcomes, and survival benefit of extended-release ralinepag in symptomatic PAH patients[63] (NCT03626688, NCT04084678).

### Sotatercept

Sotatercept is a selective ligand trap for transformic growth factor beta (TGF-β) superfamily members such as activins and growth differentiation factors that can improve BMPR2 signaling and decrease pulmonary vascular smooth muscle proliferation and remodeling. It is administered by subcutaneous route every 3 weeks. The recently published PULSAR trial demonstrated improved 6MWD by 29 m and decreased NT-proBNP in the sotatercept group compared with placebo.[64] Thrombocytopenia and increased hemoglobin were the most commonly identified adverse events.[64] A phase 2 multicenter, open-label exploratory study, the SPECTRA trial, is also investigating the efficacy of sotatercept in PAH, with the primary outcome being the change in peak oxygen uptake ($VO_2$ max) from baseline (NCT03738150). Being the first in its class drug, sotatercept has been designated a breakthrough therapy by the FDA. A phase 3 double-blinded RCT (STELLAR) is ongoing to evaluate the efficacy of sotatercept plus background therapy compared with placebo, with preliminary results expected in early 2023 (NCT04576988).

### Other drugs

Several other drugs working via various mechanisms such as anti-inflammatory pathway (bardoxolone methyl), tyrosine kinase inhibitor (imatinib), vasoactive intestinal peptide, endothelial nitric oxide synthase couplers (sapropterin dihydrochloride), Rho kinase inhibitor (fasudil), serotonin recept antagonist (terguride), and apelin are currently being studied for feasibility in pulmonary hypertension.[65] With significant advancement in the understanding of several pathophysiologic pathways associated with PAH development, newer drugs are being developed and studied and offer a ray of hope for this debilitating disease.

## Upfront triple combination therapy for patients not at goal

Sequential combination therapy has been shown to reduce clinical worsening compared with monotherapy.[66] The BREATHE-2 trial was a proof-of-concept study that showed the feasibility of upfront dual combination therapy in PAH but was underpowered to assess a significant effect on hemodynamics and functional status.[67] The landmark AMBITION trial demonstrated a significant reduction in clinical failure and improvement in 6 min walk distance with upfront combination therapy of ambrisentan and tadalafil for patients not at goal.[68] A post hoc analysis of the AMBITION trial found a survival advantage in the combination therapy group compared with the monotherapy group.[69] An observational study also demonstrated a significant reduction in PVR, pulmonary artery pressures, and NT-proBNP in patients treated with upfront combination

therapy of ERA and PDE-5 inhibitors compared with patients in the monotherapy group.[70] They also found a reduction in calculated RV wall stress and volumes in the combination therapy group.[70] Several other observational studies and meta-analysis have been able to replicate these results in severe PAH patients[71 72]

The primary goal of therapy in PAH is to improve patient's risk category and inhibit remodeling in the pulmonary vasculature and the RV. An early aggressive approach for intermediate-risk and high-risk groups appears a feasible option to normalize hemodynamics and delay clinical worsening. An upfront triple combination therapy for intermediate-risk and high-risk patients seems logical and needs longitudinal study to assess actual benefits. A pilot study evaluated the feasibility of triple combination therapy of intravenous epoprostenol, bosentan, and sildenafil in 19 PAH patients with NYHA functional class III/IV.[73] They found sustained clinical and hemodynamic improvement with lower NYHA functional class I/II and 100% survival at 1, 2, and 3 years of follow-up.[73] A retrospective observational study demonstrated a reduced risk of death in patients treated with subcutaneous prostacyclin and two oral drugs compared with dual combination therapy or monotherapy.[74]

D'Alto *et al*[75] studied the hemodynamic impact of a combination of subcutaneous treprostinil, ambrisentan, and tadalafil in newly diagnosed severe PAH patients. In addition to improved hemodynamics, 6MWD, and functional class, they demonstrated reversal in RV remodeling observed on follow-up echocardiogram. Early addition of selexipag to initial dual combination therapy has also been observed to have a significant clinical, functional, and hemodynamic improvement in severe PAH and CTEPH patients.[76] A recent multicenter, placebo-controlled, double-blinded randomized control trial, the TRITON study, compared the effect of upfront triple (selexipag, macitentan, tadalafil) versus double (macitentan and tadalafil) therapy in PAH. The study demonstrated sustained improvement in hemodynamics, NT-proBNP, and a reduction in disease progression with triple therapy and double combination therapy, but no statistically significant difference between the two groups. However, exploratory analysis indicated a signal for improved long-term outcome with initial triple versus initial double therapy (odds raio 0.59;p=0.08)[77] (NCT02558231). These findings highlight the need to consider an aggressive approach early on in treatment-naive PAH patients who are in an intermediate or high-risk group at diagnosis.

### Monitoring and follow-up

There is a structured follow-up schedule recommended during the management of PAH patients. Risk stratification scoring, ECG, 6MWD, basic laboratory workup including metabolic panel, NT-proBNP, and complete blood count are recommended every follow-up visit. Transthoracic echocardiogram, CPET, blood gas analysis, and right heart catheterization are recommended at baseline and after that yearly, unless there is a change in pharmacotherapy or clinical worsening, in which case they can be repeated earlier.[10 42]

Implantable hemodynamic sensors known as CardioMEMS HF system have been increasingly used in patients with congestive heart failure for monitoring and predicting clinical worsening.[78] Benza *et al*[79] studied the feasibility and safety of the CardioMEMS HF system as a monitoring tool for PAH. They found the device to be safe, and it could predict clinical worsening or medication non-adherence weeks in advance.[79] They also found that implantation of the device was associated with a significant reduction in mPAP and improvement in cardiac output as treating physicians could guide therapy based on the data obtained from the device.[79] The device offers excellent potential in safely predicting and preventing clinical decompensation; however, more extensive trials and longitudinal studies are currently needed to identify such implantable wireless devices' true potential in monitoring and managing PAH patients.

## MULTIDISCIPLINARY APPROACH

The management of PAH has significantly evolved over the last 4–5 decades in the wake of more sensitive diagnostics and specialized clinicians who can provide focused medical care. In the current era of PAH care, 1-year survival rates have increased to 86%–90% from 65% in the 1980s, and average long-term survival has increased to 6 years from 2.8 years.[80] These clinical advances have resulted in considerable economic and social burdens for patients and their caretakers who are now faced with the day-to-day management of a complicated, chronic illness. Thus, a team-based, multidisciplinary approach to care is paramount in the patient with PAH to optimize outcomes. A team often includes a range of specialist physicians and extends to include nutritionists, pharmacists, and social workers whose goal is to provide a well-rounded approach to patient care.

The first line of management in systemic hypertension includes dietary and lifestyle changes. Although there is a paucity of data regarding dietary changes in pulmonary hypertension, some preliminary studies and hypotheses have compelling results. For example, some suggest that PAH patients have a larger proportion of vitamin D deficiency, vitamin C deficiency, and iron deficiency than the general population and that this may play a role in disease severity and progression. Correcting these relative deficiencies may involve a simple modification that could potentially have a meaningful clinical impact. Involving a nutritional expert in a patient care team can be beneficial, especially as data is evolving in the field.[81]

The mainstay of treatment in PAH is pharmacologic therapy. However, due to the complicated delivery system and frequent dosing, patient education and adherence to the dosing schedule become challenging in clinical practice. Epoprostenol, for example, requires a continuous intravenous infusion through central access. Therapeutic success requires a dynamic conversation between the patient and their healthcare professionals. Pharmacist-driven discussions have shown to be quite helpful for patients navigating issues that arise in this domain. The Pharmacist Collaborative Care Program (PCCP) in Grenoble, France, has successfully implemented interventions in patient education, psychosocial barriers to adherence, and technical support to foster therapeutic success.[82] This success has been underscored in data regarding the role of the PCCP in lung transplant teams. A retrospective analysis assessing more than

1400 patients over 7 years revealed that involving a clinical pharmacist prevented major or lethal outcomes in 7.1% of cases and moderate drug-related effects in almost 60% of cases. More importantly, the study showed that, when accepted, a clinical pharmacist presented a positive clinical impact for 98.9% of patients, and none had a negative clinical impact.[83] The role of a pharmacist in patient-care teams can be an invaluable asset.

In addition to more conventional communication approaches, there is significant potential for digital and virtual healthcare support systems. Many patients already use home-based, mobile, and wearable technologies to take ownership of their health. Medical technology has not been formally studied in the realm of health literacy. Nevertheless, it provides a compelling opportunity for future directions in adverse event monitoring, therapeutic compliance, and patient engagement.[84] Not only are current PAH therapies riddled with administration issues and side effects that act as patient compliance barriers, but they are also expensive. This can create significant financial stress for patients and their loved ones. Social workers are often an essential part of healthcare teams and can help navigate and counsel patients through complicated financial barriers.[85]

Although PAH medications have shown tremendous success in preventing clinical worsening, none are curative. Patients should be referred for a lung transplant as early as possible. Generally, the decision to list is made when the patient's status declines to the point that survival without transplant is unlikely. Transplant is recommended for patients with PAH who fall into WHO functional class III or IV on maximal medical therapy and patients with rapidly progressive disease, as evidenced by worsening 6 min walk distance, rising NT-proBNP, and worsening RV function and hemodynamics. Patients with an estimated 1-year mortality >10% based on a comprehensive assessment should also be considered for lung transplant.[85–87] Certain procedures can act as a bridge to transplant or as destination palliative therapy in severe symptomatic PAH.[87] Atrial septostomy is one such intervention, allowing for right heart decompression through creating an iatrogenic shunt. This procedure has been shown to improve functional class, exercise tolerance, symptoms, and even survival. RV assist devices and pulmonary artery denervation have also shown promising results in symptomatic and functional improvement. However, there is a paucity of data in general in terms of mortality benefits for any of these procedures. Veno-arterial extracorporeal membrane oxygenators have also been successfully utilized as a bridge to transplant.[80] In general, the transplant listing process is a long and trying course for patients and their loved ones. An experienced multidisciplinary team is necessary to steer through the challenging road patients face.

Despite all the advances made over the last few decades with treatment modalities, PAH is still a devastating, rapidly progressive disease with a mortality of at least 50% at 7 years.[88] PAH patients bear a sizeable psychological burden as they navigate a debilitating illness requiring cumbersome and expensive care. The disease itself inevitably has an enormous impact on a patients' day-to-day functioning. Frequently, patients are unable to even keep their employment due to disease burden. The emotional stress of disease has led to high rates of anxiety and depression in the PAH population, with some studies citing depression rates as high as 55%.[89] Palliative care referral which focuses on symptomatic relief and quality of life should be implemented early in the diagnosis. Patients can benefit from various therapeutic avenues within the palliative care team ranging from support groups and educational tools to financial assistance and health insurance coverage support. Palliative care specialists can assist with medical management of dyspnea, anxiety, pain, and anorexia. Even some more invasive procedures such as atrial septostomy, RV assist devices, and pulmonary artery denervation can act as palliative destination therapy and improve patient's quality of life. A palliative specialist can support patients and their families through these types of procedures. Finally, as patients progress in their disease course, palliative care specialists can help guide advanced directives, end-of-life care, and even spiritual support.[85]

Improving outcomes in the PAH patient extends beyond just managing disease and its progression. A multidisciplinary, holistic approach is imperative to meet the needs of patients and their families. However, equally as crucial in therapeutic success is the act of patient engagement and ownership over their care. This can help tailor support and management to meet the individual patient's needs.[84]

## CONCLUSION

Medical management of PAH has made significant strides with encouraging results from clinical trials and studies. Early referral to PH expert center, close follow-up, and using advanced technologies to accurately characterize patient's functional and risk status is of foremost importance in patient care for PAH. Current studies have demonstrated improved functional outcomes and reverse RV and pulmonary vascular remodeling in patients started on combination therapies early in the disease course. Newer therapies targeting novel receptors involved in the pathogenesis of PAH are currently understudying and offer a ray of hope for the future. A multidisciplinary approach including PH experts, transplant physicians, nursing, nutritionist, pharmacist, physical therapist, and social workers is paramount in managing PAH patients.

**Contributors** All authors contributed to the manuscript in a substantial manner. HD, TW, and RS reviewed the relevant literature and made necessary edits to the final manuscript and drafted the manuscript. RS gave final approval for submission for publication of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** RS has received research support from Bayer, United Therapeutics, Reata and Complexa, and served on advisory boards for Actelion, Altavant, Bayer, Gossamer, and United Therapeutics.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Commissioned; externally peer reviewed.



**ORCID iD**

Himanshu Deshwal http://orcid.org/0000-0003-2086-1281

## REFERENCES


1 Dresdale DT, Schultz M, MICHTOM RJ. Primary pulmonary hypertension. I. Clinical and hemodynamic study. *Am J Med* 1951;11:686–705.
2 Dresdale DT, Michtom RJ, SCHULTZ M. Recent studies in primary pulmonary hypertension, including pharmacodynamic observations on pulmonary vascular resistance. *Bull N Y Acad Med* 1954;30:195–207.
3 Dweik RA, Rounds S, Erzurum SC, *et al*. An official American thoracic Society statement: pulmonary hypertension phenotypes. *Am J Respir Crit Care Med* 2014;189:345–55.
4 Simonneau G, Montani D, Celermajer DS, *et al*. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53:1801913.
5 Kovacs G, Berghold A, Scheidl S, *et al*. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009;34:888–94.
6 Kiely DG, Lawrie A, Humbert M. Screening strategies for pulmonary arterial hypertension. *Eur Heart J Suppl* 2019;21:K9–20.
7 Coghlan JG, Denton CP, Grünig E, *et al*. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014;73:1340–9.
8 Galiè N, Rubin L, Hoeper M, *et al*. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093–100.
9 Kovacs G, Maier R, Aberer E, *et al*. Pulmonary arterial hypertension therapy may be safe and effective in patients with systemic sclerosis and borderline pulmonary artery pressure. *Arthritis Rheum* 2012;64:1257–62.
10 Galiè N, Humbert M, Vachiery J-L, *et al*. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint Task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:67–119.
11 Young A, Moles VM, Jaafar S, *et al*. Performance of the DETECT algorithm for pulmonary hypertension screening in a systemic sclerosis cohort. *Arthritis Rheumatol* 2021;73:1731–7.
12 Montani D, Girerd B, Jaïs X, *et al*. Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation. *Eur Respir J* 2021;58. doi:10.1183/13993003.04229-2020. [Epub ahead of print: 22 07 2021].
13 Evans JDW, Girerd B, Montani D, *et al*. BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. *Lancet Respir Med* 2016;4:129–37.
14 Eyries M, Montani D, Girerd B, *et al*. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet* 2014;46:65–9.
15 Fijalkowska A, Kurzyna M, Torbicki A, *et al*. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. *Chest* 2006;129:1313–21.
16 Nagaya N, Nishikimi T, Uematsu M, *et al*. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000;102:865–70.
17 Rhodes CJ, Wharton J, Ghataorhe P, *et al*. Plasma proteome analysis in patients with pulmonary arterial hypertension: an observational cohort study. *Lancet Respir Med* 2017;5:717–26.
18 Benza RL, Gomberg-Maitland M, Demarco T, *et al*. Endothelin-1 pathway polymorphisms and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2015;192:1345–54.
19 Aryal SR, Sharifov OF, Lloyd SG. Emerging role of cardiovascular magnetic resonance imaging in the management of pulmonary hypertension. *Eur Respir Rev* 2020;29. doi:10.1183/16000617.0138-2019. [Epub ahead of print: 30 Jun 2020].
20 Finkelhor RS, Lewis SA, Pillai D. Limitations and strengths of doppler/echo pulmonary artery systolic pressure-right heart catheterization correlations: a systematic literature review. *Echocardiography* 2015;32:10–18.
21 Wessels JN, de Man FS, Vonk Noordegraaf A. The use of magnetic resonance imaging in pulmonary hypertension: why are we still waiting? *Eur Respir Rev* 2020;29. doi:10.1183/16000617.0139-2020. [Epub ahead of print: 30 Jun 2020].
22 Mathai SC, Hassoun PM. Therapy for pulmonary arterial hypertension associated with systemic sclerosis. *Curr Opin Rheumatol* 2009;21:642–8.
23 Schoenfeld C, Hinrichs JB, Olsson KM, *et al*. Cardio-Pulmonary MRI for detection of treatment response after a single BPA treatment session in CTEPH patients. *Eur Radiol* 2019;29:1693–702.
24 Schoenfeld C, Cebotari S, Hinrichs J, *et al*. Mr Imaging-derived regional pulmonary parenchymal perfusion and cardiac function for monitoring patients with chronic thromboembolic pulmonary hypertension before and after pulmonary endarterectomy. *Radiology* 2016;279:925–34.
25 Lewis RA, Johns CS, Cogliano M, *et al*. Identification of cardiac magnetic resonance imaging thresholds for risk stratification in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2020;201:458–68.
26 Leng S, Dong Y, Wu Y, *et al*. Impaired cardiovascular magnetic Resonance-Derived rapid semiautomated right atrial longitudinal strain is associated with decompensated hemodynamics in pulmonary arterial hypertension. *Circ Cardiovasc Imaging* 2019;12:e008582.
27 Fritz JS, Blair C, Oudiz RJ, *et al*. Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension. *Chest* 2013;143:315–23.
28 Farina S, Correale M, Bruno N, *et al*. The role of cardiopulmonary exercise tests in pulmonary arterial hypertension. *Eur Respir Rev* 2018;27. doi:10.1183/16000617.0134-2017. [Epub ahead of print: 30 Jun 2018].
29 Ferrazza AM, Martolini D, Valli G, *et al*. Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. *Respiration* 2009;77:3–17.
30 Yasunobu Y, Oudiz RJ, Sun X-G, *et al*. End-Tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest* 2005;127:1637–46.
31 Trip P, Vonk-Noordegraaf A, Bogaard HJ. Cardiopulmonary exercise testing reveals onset of disease and response to treatment in a case of heritable pulmonary arterial hypertension. *Pulm Circ* 2012;2:387–9.
32 Waxman AB, Farber HW. Using clinical trial end points to risk stratify patients with pulmonary arterial hypertension. *Circulation* 2015;132:2152–61.
33 Walkey AJ, Ieong M, Alikhan M, *et al*. Cardiopulmonary exercise testing with right-heart catheterization in patients with systemic sclerosis. *J Rheumatol* 2010;37:1871–7.
34 Ryan JJ, Waxman AB. The dyspnea clinic. *Circulation* 2018;137:1994–6.
35 Maron BA, Cockrill BA, Waxman AB, *et al*. The invasive cardiopulmonary exercise test. *Circulation* 2013;127:1157–64.
36 Gao Y, Wang T, Liu C, *et al*. Clinical application of invasive cardiopulmonary exercise test for dyspnea diagnosis in Chinese people. *J Thorac Dis* 2018;10:S4176–8.
37 Guth S, Wiedenroth CB, Rieth A, *et al*. Exercise right heart catheterisation before and after pulmonary endarterectomy in patients with chronic thromboembolic disease. *Eur Respir J* 2018;52. doi:10.1183/13993003.00458-2018. [Epub ahead of print: 17 09 2018].
38 Benza RL, Gomberg-Maitland M, Elliott CG, *et al*. Predicting survival in patients with pulmonary arterial hypertension: the reveal risk score calculator 2.0 and comparison with ESC/ERS-Based risk assessment strategies. *Chest* 2019;156:323–37.
39 Galiè N, Corris PA, Frost A, *et al*. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013;62:D60–72.
40 McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002;106:1477–82.
41 Weatherald J, Boucly A, Sahay S, *et al*. Sitbon O: the low-risk profile in pulmonary arterial hypertension. *Time for a Paradigm Shift to Goal-oriented Clinical Trial Endpoints? American journal of respiratory and critical care medicine* 2018;197:860–8.
42 Klinger JR, Elliott CG, Levine DJ, *et al*. Therapy for pulmonary arterial hypertension in adults: update of the chest guideline and expert panel report. *Chest* 2019;155:565–86.
43 George MP, Champion HC, Pilewski JM. Lung transplantation for pulmonary hypertension. *Pulm Circ* 2011;1:182–91.
44 Preston IR, Roberts KE, Miller DP, *et al*. Effect of warfarin treatment on survival of patients with pulmonary arterial hypertension (PAH) in the registry to evaluate early and long-term PAH disease management (REVEAL). *Circulation* 2015;132:2403–11.
45 Sitbon O, Humbert M, Jaïs X, *et al*. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005;111:3105–11.
46 Halliday SJ, Hemnes AR, Robbins IM, *et al*. Prognostic value of acute vasodilator response in pulmonary arterial hypertension: beyond the "classic" responders. *J Heart Lung Transplant* 2015;34:312–8.
47 Mukerjee D, St George D, Coleiro B, *et al*. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;62:1088–93.
48 Raffy O, Azarian R, Brenot F, *et al*. Clinical significance of the pulmonary vasodilator response during short-term infusion of prostacyclin in primary pulmonary hypertension. *Circulation* 1996;93:484–8.
49 Halliday SJ, Hemnes AR. Identifying "super responders" in pulmonary arterial hypertension. *Pulm Circ* 2017;7:300–11.

50 Gabler NB, French B, Strom BL, *et al*. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. *Chest* 2012;141:20–6.
51 Helman DL, Brown AW, Jackson JL, *et al*. Analyzing the short-term effect of placebo therapy in pulmonary arterial hypertension: potential implications for the design of future clinical trials. *Chest* 2007;132:764–72.
52 Mathai SC, Hassoun PM, Puhan MA, *et al*. Sex differences in response to tadalafil in pulmonary arterial hypertension. *Chest* 2015;147:188–97.
53 Hemnes AR, Trammell AW, Archer SL, *et al*. Peripheral blood signature of vasodilator-responsive pulmonary arterial hypertension. *Circulation* 2015;131:401–9. discussion 409.
54 Allen RP, Schelegle ES, Bennett SH. Diverse forms of pulmonary hypertension remodel the arterial tree to a high shear phenotype. *Am J Physiol Heart Circ Physiol* 2014;307:H405–17.
55 Ghofrani H-A, D'Armini AM, Grimminger F, *et al*. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013;369:319–29.
56 Ghofrani H-A, Galiè N, Grimminger F, *et al*. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013;369:330–40.
57 Frey R. Mück W: clinical implications of riociguat pharmacokinetics and pharmacodynamics: introduction to the riociguat clinical pharmacology supplement. *Pulmonary Circulation* 2016;6:S1–4.
58 Hoeper MM, Simonneau G, Corris PA, *et al*. RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors. *Eur Respir J* 2017;50. doi:10.1183/13993003.02425-2016. [Epub ahead of print: 09 09 2017].
59 Hoeper MM, Al-Hiti H, Benza RL, *et al*. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (replace): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med* 2021;9:573-584.
60 Sitbon O, Channick R, Chin KM, *et al*. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015;373:2522–33.
61 Frost A, Janmohamed M, Fritz JS, *et al*. Safety and tolerability of transition from inhaled treprostinil to oral selexipag in pulmonary arterial hypertension: results from the TRANSIT-1 study. *J Heart Lung Transplant* 2019;38:43–50.
62 Torres F, Farber H, Ristic A, *et al*. Efficacy and safety of ralinepag, a novel oral IP agonist, in PAH patients on mono or dual background therapy: results from a phase 2 randomised, parallel group, placebo-controlled trial. *Eur Respir J* 2019;54. doi:10.1183/13993003.01030-2019. [Epub ahead of print: 10 10 2019].
63 McLaughlin VV, Channick R, *et al*, on behalf of the Advance Program Global Steering C. Study design of the phase 3 advance program evaluating Time-to-Clinical events and exercise capacity in patients with pulmonary arterial hypertension treated with Ralinepag. *American Thoracic Society* 2019:A5074.
64 Humbert M, McLaughlin V, Gibbs JSR, *et al*. Sotatercept for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2021;384:1204–15.
65 Galiè N, Ghofrani A-H. New horizons in pulmonary arterial hypertension therapies. *Eur Respir Rev* 2013;22:503–14.
66 Lajoie AC, Lauzière G, Lega J-C, *et al*. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. *Lancet Respir Med* 2016;4:291–305.
67 Humbert M, Barst RJ, Robbins IM, *et al*. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004;24:353–9.
68 Galiè N, Barberà JA, Frost AE, *et al*. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;373:834–44.
69 Hoeper MM, McLaughlin VV, Barberá JA, *et al*. Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled ambition study. *Lancet Respir Med* 2016;4:894–901.
70 van de Veerdonk MC, Huis In T Veld AE, Marcus JT, *et al*. Upfront combination therapy reduces right ventricular volumes in pulmonary arterial hypertension. *Eur Respir J* 2017;49. doi:10.1183/13993003.00007-2017. [Epub ahead of print: 29 06 2017].
71 D'Alto M, Romeo E, Argiento P, *et al*. Initial tadalafil and ambrisentan combination therapy in pulmonary arterial hypertension: cLinical and haemodYnamic long-term efficacy (ITALY study). *J Cardiovasc Med* 2018;19:12–17.
72 Kirtania L, Maiti R, Srinivasan A, *et al*. Effect of combination therapy of endothelin receptor antagonist and phosphodiesterase-5 inhibitor on clinical outcome and pulmonary haemodynamics in patients with pulmonary arterial hypertension: a meta-analysis. *Clin Drug Investig* 2019;39:1031–44.
73 Sitbon O, Jaïs X, Savale L, *et al*. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J* 2014;43:1691–7.
74 Boucly A, Savale L, Weatherald JC. Impact of initial triple combination therapy on long-term survival in pulmonary arterial hypertension (PAH). *American Thoracic Society* 2019:A5585.
75 D'Alto M, Badagliacca R, Argiento P, *et al*. Risk Reduction and Right Heart Reverse Remodeling by Upfront Triple Combination Therapy in Pulmonary Arterial Hypertension. *Chest* 2020;157:376–83.
76 Berlier C, Schwarz EI, Saxer S, *et al*. Real-life experience with selexipag as an add-on therapy to oral combination therapy in patients with pulmonary arterial or distal chronic thromboembolic pulmonary hypertension: a retrospective analysis. *Lung* 2019;197:353–60.
77 Chin KM, Sitbon O, Doelberg M. Efficacy and safety of initial triple oral versus initial double oral combination therapy in patients with newly diagnosed pulmonary arterial hypertension (PAH): results of the randomized controlled Triton study. *American Thoracic Society* 2020:A2928.
78 Adamson PB, Abraham WT, Bourge RC, *et al*. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail* 2014;7:935–44.
79 Benza RL, Doyle M, Lasorda D, *et al*. Monitoring pulmonary arterial hypertension using an implantable hemodynamic sensor. *Chest* 2019;156:1176–86.
80 Thenappan T, Ormiston ML, Ryan JJ, *et al*. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ* 2018;360:j5492.
81 Callejo M, Barberá JA, Duarte J, *et al*. Impact of nutrition on pulmonary arterial hypertension. *Nutrients* 2020;12. doi:10.3390/nu12010169. [Epub ahead of print: 07 Jan 2020].
82 Bedouch P, Roustit M, Quetant S, *et al*. Development of a pharmacist collaborative care program for pulmonary arterial hypertension. *Int J Clin Pharm* 2011;33:898–901.
83 Duwez M, Chanoine S, Lepelley M, *et al*. Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study. *BMJ Open* 2020;10:e041563.
84 Graarup J, Ferrari P, Howard LS. Patient engagement and self-management in pulmonary arterial hypertension. *Eur Respir Rev* 2016;25:399–407.
85 Khirfan G, Tonelli AR, Ramsey J, *et al*. Palliative care in pulmonary arterial hypertension: an underutilised treatment. *Eur Respir Rev* 2018;27. doi:10.1183/16000617.0069-2018. [Epub ahead of print: 31 Dec 2018].
86 Orens JB, Estenne M, Arcasoy S, *et al*. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006;25:745–55.
87 Baillie TJ, Granton JT. Lung transplantation for pulmonary hypertension and strategies to bridge to transplant. *Semin Respir Crit Care Med* 2017;38:701–10.
88 Gall H, Felix JF, Schneck FK, *et al*. The Giessen pulmonary hypertension registry: survival in pulmonary hypertension subgroups. *J Heart Lung Transplant* 2017;36:957–67.
89 Verma S, Sahni S, Vijayan VK, *et al*. Depression in pulmonary arterial hypertension: an undertreated comorbidity. *Lung India* 2016;33:58–63.