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REVIEW

Recent Advances in the Diagnosis and Management of Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a rare, progressive, debilitating and life shortening condition characterized by raised pulmonary arterial pressures. PAH includes a group of conditions sharing similar pathophysiology, clinical features and response to therapy. The commonest sub-groups of PAH include idiopathic pulmonary arterial hypertension (IPAH), and PAH associated with connective tissue disease. Recently published international guidelines emphasize the need for disease awareness and early referral to expert centres in suspected cases. Following diagnosis and careful risk stratification, combination therapy is recommended using drugs targeting the nitric oxide, endothelin and prostacyclin signaling pathways. Promising new therapies are on the horizon, however, the survival remains disappointing with a median survival of 7 years. In this review, we focus on the diagnostic evaluation, risk stratification, available treatment options and future directions in PAH.

Key words: pulmonary arterial hypertension; diagnosis; treatment

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Introduction

Pulmonary hypertension (PH) is a relatively uncommon, progressive, debilitating, and life limiting condition that is defined by a resting mean pulmonary artery pressure above 20 mmHg at right heart catheterization (Humbert et al, 2022; Kovacs et al, 2024). PH has a prevalence of ~1% of the global population and is much higher in the population above 65 years of age (Humbert et al, 2023).

PH is categorized into 5 groups based on similarities in pathophysiology, clinical features and response to treatment (Table 1). This includes Group 1, pulmonary arterial hypertension (PAH), Group 2, PH associated with left heart disease, Group 3, PH associated with lung disease and/or hypoxia, Group 4, PH associated with pulmonary artery obstructions and Group 5, PH associated with unclear and/or multifactorial mechanisms. Group 2 and Group 3 PH are the most common forms of PH and account for 70% and 25% of PH cases respectively. Group 1 and 4 PH, while less common, have unique treatment approaches (Humbert et al, 2022; Kovacs et al, 2024).

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Table 1. Classification of pulmonary hypertension (Humbert et al, 2022).

Group 1	Group 2	Group 3	Group 4	Group 5
Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease and/or hypoxia	PH associated with pulmonary artery obstruction	PH associated with unclear and/or multifactorial mechanisms
Idiopathic PAH	Heart Failure	Obstructive lung disease or emphysema	Chronic thromboembolic PH	Haematologic disorders (inherited/acquired, chronic haemolytic anaemia & chronic myeloproliferative disorders)
- Non-responders at vaso-reactivity testing	- Preserved ejection fraction	Restrictive lung disease	Other pulmonary artery obstructions	Systemic disorders
- Acute responders at vasoreactivity testing	- Reduced (<40%) or mildly reduced (41–49%) ejection fraction	Lung disease with mixed restrictive/obstructive pattern	- sarcomas	(sarcoidosis, pulmonary Langerhan's cell histiocytosis and neurofibromatosis type 1)
Heritable	Valvular heart disease	Hypoventilation syndromes	- malignant/non-malignant tumours	Metabolic disorders
Associated with drugs/toxins	Congenital/acquired cardiovascular conditions leading to postcapillary PH	Hypoxia without lung disease (e.g., high altitude)	- Arteritis without CTD	(glycogen storage diseases and Gaucher's disease)
Associated with: - CTD - HIV - Portal hypertension - Congenital heart disease - Schistosomiasis		Developmental lung disorders	- Congenital pulmonary artery stenosis - Hydatidosis	Chronic renal failure with or without haemodialysis Pulmonary tumour thrombotic microangiopathy Fibrosing mediastinitis
PAH with features of venous/capillary (PVOD/PCH)				
Persistent PH of the newborn				

PAH, pulmonary arterial hypertension; CTD, connective tissue disease; HIV, human immunodeficiency virus; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary haemangiomatosis; PH, pulmonary hypertension.

Table 2. Haemodynamic classification by right heart catheterization (Humbert et al, 2022).

Haemodynamic properties	mPAP (mmHg)	PAWP (mmHg)	PVR (WU)	Clinical group
Pre-capillary PH	>20	≤15	>2	1, 3, 4, 5
IpcPH	>20	>15	≤2	2, 5
CpcPH	>20	>15	>2	2, 5

CpcPH, combined post and pre-capillary pulmonary hypertension; IpcPH, isolated postcapillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance.

PH can be classified haemodynamically into three groups, pre-capillary, post-capillary and combined post and pre-capillary PH (Table 2) (Humbert et al, 2022). PH Groups 1, 3 and 4 are pre-capillary, and Group 2 is post-capillary while 5 may be pre- or post-capillary PH (Humbert et al, 2022).

Over the past 40 years the treatment of PAH has evolved significantly and the median life expectancy has increased from under 3 years if untreated, to over 7 years based on registry data (Humbert et al, 2023). Indeed, a new therapeutic option has more recently emerged, providing further hope of progress (Hoeper et al, 2023). In this review, we focus on the diagnostic evaluation, risk stratification, available treatment options and future directions in PAH.

Definition and Classification of PAH

PAH includes a group of conditions sharing similarities in the underlying disease process, presentation and treatment response with an annual incidence of approximately 6 cases per million and a prevalence of 48–55 cases per million (Humbert et al, 2022).

A detailed classification of PAH based on the latest guidelines is presented in Table 1 (Humbert et al, 2022). Idiopathic pulmonary arterial hypertension (IPAH) is the commonest form of PAH and accounts for up to 70% of patients with PAH (Austin et al, 2024). Connective tissue disease is the second most common cause accounting for up to 25% of patients. The common connective tissue diseases that are associated with PAH include systemic sclerosis, systemic lupus erythematosus and mixed connective tissue disease. Congenital heart diseases, such as atrial septal defect, ventricular septal defect and patent ductus arteriosus, are also associated with the development of PAH. Porto-pulmonary hypertension is a less common cause of PAH and is usually associated with cirrhosis of the liver but can also occur in the setting of non-cirrhotic portal hypertension (Humbert et al, 2022).

Pathophysiology of PAH

The pathophysiology of PAH is diverse and multifaceted including genetic, inflammatory and drug-related causes. PAH is characterized by pulmonary vascular remodeling with the cellular proliferation of all layers of the pulmonary artery including the endothelial cells of the tunica intima, the smooth muscle cells of the tunica media and the fibroblasts of the tunica externa (Fig. 1) (Guignabert et al,

2024; Humbert et al, 2022). This vasculopathy leads to vasoconstriction, *in situ* thrombosis and plexiform lesions which increases pulmonary vascular resistance ultimately resulting in right heart failure (Hemnes et al, 2024).

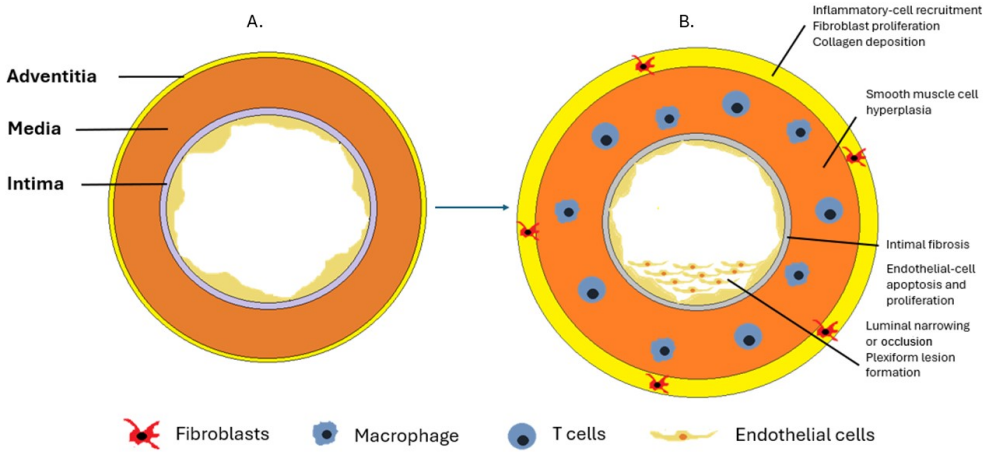

Fig. 1. Remodeling of three vessel-wall layers. (A) Normal pulmonary artery. (B) Pulmonary arterial hypertension (PAH). Drawings made using Microsoft Paint 11.2408.30.0 (Microsoft Corporation, Redmond, WA, USA).

Diagnostic Evaluation in PAH

The signs and symptoms of PAH are non-specific in nature resulting in a delay in diagnosis.

The detailed diagnostic evaluation of patients presenting with symptoms and signs suspicious of PAH is outlined in Fig. 2. Annual screening is recommended for patients with an increased risk of developing PAH including systemic sclerosis, BMPR2 mutation carriers and those with portal hypertension awaiting liver transplant (Humbert et al, 2022).

Risk Stratification in PAH

At baseline a 3-strata, multiparametric risk model, stratifies patients into a low, intermediate, and high-risk group on the basis of combined clinical, functional and haemodynamic measures (Fig. 3). Cardiac magnetic resonance imaging (MRI) and cardiopulmonary exercise test (CPET) are additional investigations that have been recommended in the new guidelines and are performed in selected centres. The estimated one-year mortality is less than 5%, 5–20% and >20% in low, intermediate and high-risk groups respectively (Humbert et al, 2022). The most recent international consensus statement in PAH recommends classifying patients into 'high risk' and 'not high risk' groups and is in keeping with the initial treatment strategies (Dardi et al, 2024).

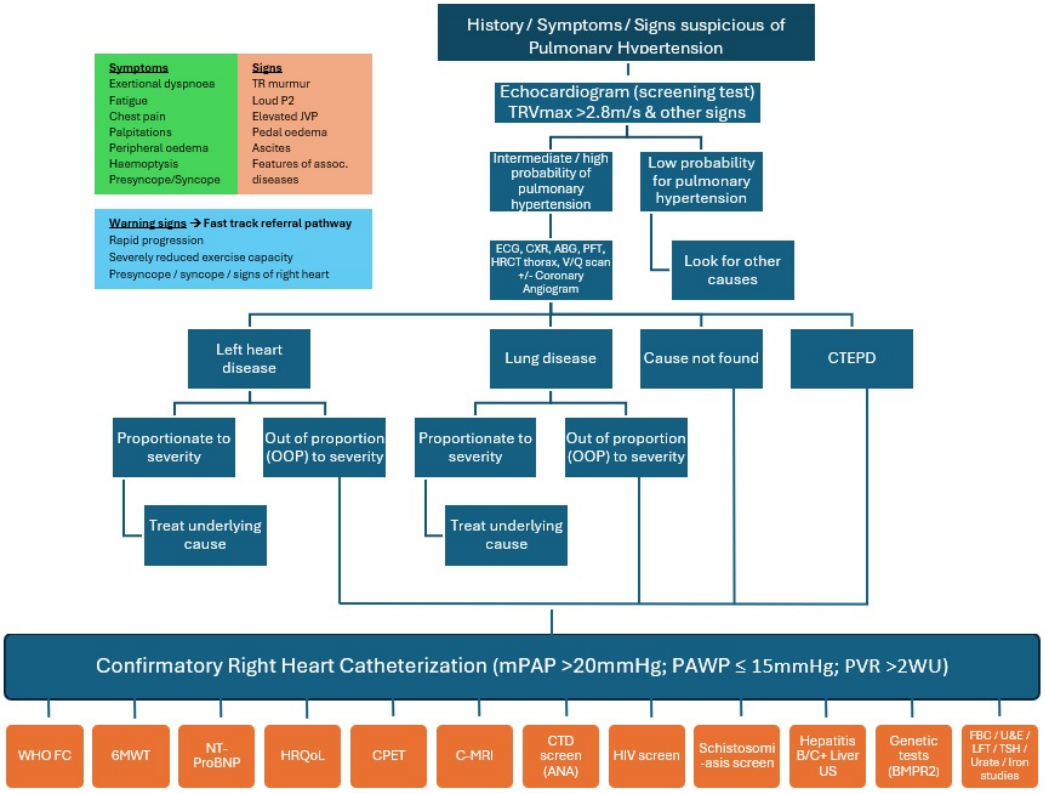

Fig. 2. Diagnostic evaluation in PAH. The flowchart was made with Microsoft Word for Microsoft 365 MSO (Version 2408, Microsoft Corporation, Redmond, WA, USA). TR, tricuspid regurgitation; TRVmax, tricuspid regurgitant maximal velocity; JVP, jugular venous pressure; ECG, electrocardiogram; CXR, chest x-ray; ABG, arterial blood gas; PFT, pulmonary function test; HRCT thorax, high resolution computed tomography thorax; V/Q scan, ventilation/perfusion scintigraphy; CTEPD, chronic thromboembolic pulmonary disease; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization functional classification; 6MWT, 6-minute walk test; NT-ProBNP, N-terminal pro-brain natriuretic peptide; HRQoL, health related quality of life questionnaire; CPET, cardiopulmonary exercise test; C-MRI, cardiac magnetic resonance imaging; CTD screen, connective tissue disease screen; ANA, anti-nuclear antibody; Liver US, Liver ultrasound; BMPR2, bone morphogenic protein receptor type 2; FBC, full blood count; U&E, urea and electrolytes; LFT, liver function tests; TSH, thyroid stimulating hormone.

At the first follow-up at around three months, and each subsequent follow-up visit a 4-strata risk assessment model is recommended. Patients are assessed based on non-invasive testing using refined cut-off levels of World Health Organization (WHO) functional class, 6-minute walking distance and N-terminal pro-brain natriuretic peptide (NT-proBNP) allowing categorization of patients into low, intermediate-low, intermediate-high and high-risk groups (Fig. 4). The 1-year mortality is estimated at 0–3%, 2–7%, 9–19% and >20% for low, intermediate-low, intermediate-high, and high-risk groups respectively (Humbert et al, 2022). Other parameters such as right heart catheter haemodynamic data can be added to the 4-Strata model if necessary for greater clarity on a patient's prognosis and response to treatment (Humbert et al, 2022).

Three-strata model			
Determinants of prognosis (Estimated 1- year mortality)	Low risk (<5%)	Intermediate risk (5-20%)	High risk (>20%)
Signs of RHF	Absent	Absent	Present
Symptom progression	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO-FC	I, II	III	IV
6MWD	>440m	165-440m	<165m
CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 36–44	Peak VO_2 <11mL/min/kg (<35% pred.) VE/VCO_2 > 44
Biomarkers: BNP / NT-proBNP (ng/L)	BNP <50 NT-proBNP <300	BNP 50-800 NT-proBNP 300-1100	BNP >800 NT-proBNP >1100
Echocardiography	RA area <18cm^2 TAPSE/sPAP > 0.32 mm/mmHg No pericardial effusion	RA area 18-26cm^2 TAPSE/sPAP 0.19-0.32 mm/mmHg Minimal pericardial effusion	RA area >26cm^2 TAPSE/sPAP<0.19 mm/mmHg Moderate or large pericardial effusion
cMRI	RVEF > 54% SVI > 40mL/m^2 RVESVI < 42mL/m^2	RVEF 37-54% SVI 26-40mL/m^2 RVESI 42-54mL/m^2	RVEF <37% SVI<26 mL/m^2 RVESI > 54mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥ 2.5 L/min/m^2 SVI > 38mL/m^2 SvO_2 > 65%	RAP 8-14 mmHg CI 2.0 – 2.4 L/min/m^2 SVI 31 – 38 mL/m^2 SvO_2 60 - 65%	RAP >14mmHg CI <2.0 L/min/m^2 SVI <31 mL/m^2 SvO_2 <60%

Fig. 3. Three strata model (Humbert et al, 2022). Reproduced with permission of the © European Society of Cardiology & European Respiratory Society 2024: European Respiratory Journal 61 (1) 2200879; DOI: 10.1183/13993003.00879-2022 Published 6 January 2023. 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; RHF, right heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, ventilatory equivalent of carbon dioxide; VO_2, oxygen uptake; WHO-FC, World Health Organization functional class.

Four-strata Model				
Determinants of prognosis (Estimated 1-year mortality)	Low risk 0-3%	Intermediate – low risk 2-7%	Intermediate – high risk 9-19%	High risk >20%
Points assigned	1	2	3	4
WHO-FC	I or II	-	III	IV
6MWD (m)	>440m	320-440m	165-319m	<165m
BNP NT-proBNP (ng/L)	<50 <300	50-199 300-649	200-800 650-1100	>800 >1100

Fig. 4. Four-strata model (Humbert et al, 2022). Reproduced with permission of the © European Society of Cardiology & European Respiratory Society 2024: European Respiratory Journal 61 (1) 2200879; DOI: 10.1183/13993003.00879-2022 Published 6 January 2023. 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.

Treatment of PAH

General measures in the treatment of PAH include diuretics, oxygen therapy, vaccinations, supervised exercise programmes, psychological support, iron supplementation when required and avoidance of pregnancy (Humbert et al, 2022). Fe-

males of childbearing age should be informed about the serious risks involved during pregnancy and contraceptive advice with at least two forms of contraception should be recommended (Preston et al, 2024). The guidelines recommend that anticoagulation is reserved on a case-by-case basis and the use of beta-blockers is generally not recommended in patients with PAH (Humbert et al, 2022).

PAH Specific Treatment Options

Acute Responders at Vasoreactivity Testing

Pulmonary vasoreactivity testing is performed in patients with IPAH, HPAH or drug-associated pulmonary arterial hypertension (DPAP) at the time of the initial right heart catheterization. Vasoreactivity is defined as a reduction in mean pulmonary arterial pressure of $\geq$10 mmHg, to an absolute value of $\leq$40 mmHg, accompanied by an increase or no change in cardiac output in response to inhalation of 10–20 parts per million of nitric oxide (NO) for 5–10 minutes. A positive result is seen in less than 10% of patients with IPAH. These individuals are treated with calcium channel blockade often at high doses (e.g., Diltiazem 120–360 mg twice a day (BD), Amlodipine 15–30 mg once a day (OD), Nifedipine 20–60 mg BD), with favourable long-term outcomes in approximately two-thirds of responders (Humbert et al, 2022; Kovacs et al, 2024).

Non-Responders at Vasoreactivity Testing

Although the haemodynamic definition of pre-capillary PH is a resting mean pulmonary artery pressure (mPAP) $>$20 mmHg, pulmonary arterial wedge pressure (PAWP) $\leq$15 and pulmonary vascular resistance (PVR) $>$2 Wood Units, treatment is only initiated in newly diagnosed patients with PAH with a resting mPAP $\geq$25 mmHg, a PAWP $\leq$15 mmHg and a PVR $>$3 Wood Units at right heart catheterization based on results from randomized controlled trials (Humbert et al, 2022; Kovacs et al, 2024).

Initial Treatment

For patients without significant comorbidity (see PAH with comorbidities below) who are low and intermediate risk at presentation, the standard of care is initial combination therapy upfront with a phosphodiesterase-5 inhibitor targeting the nitric oxide signaling pathway (e.g., phosphodiesterase-5 inhibitors (PDE5i)—sildenafil 20 mg three times a day or tadalafil 40 mg once daily) and an endothelin receptor antagonist (e.g., bosentan 125 mg twice daily, ambrisentan 10 mg once daily and macitentan 10 mg once daily) (Humbert et al, 2022). If a patient is deemed high risk at presentation, continuous infusion of parenteral prostacyclin analogue, including subcutaneous treprostinil or intravenous epoprostenol should be considered in addition to the dual therapy (Humbert et al, 2022). Initial triple-combination therapy with parenteral prostacyclin may also be indicated in patients presenting in the intermediate-risk category with severe pulmonary haemodynamics (Humbert et al, 2022).

PAH with Comorbidities

Two distinct patterns of cardiopulmonary comorbidities have been described in PAH. The *left heart phenotype*—usually elderly females with risk factors for heart failure with preserved ejection fraction such as obesity, hypertension, hypercholesterolemia, coronary artery disease, structural heart disease, atrial fibrillation. The *cardiorespiratory phenotype*—this typically includes elderly males usually hypoxemic with a significant history of smoking and low gas transfer with risk factors for left heart disease. Careful, closely monitored, initial monotherapy with a PDE5i or an endothelin receptor antagonist (ERA) is recommended for those with PAH and cardiopulmonary comorbidities (Fig. 5) (Humbert et al, 2022).

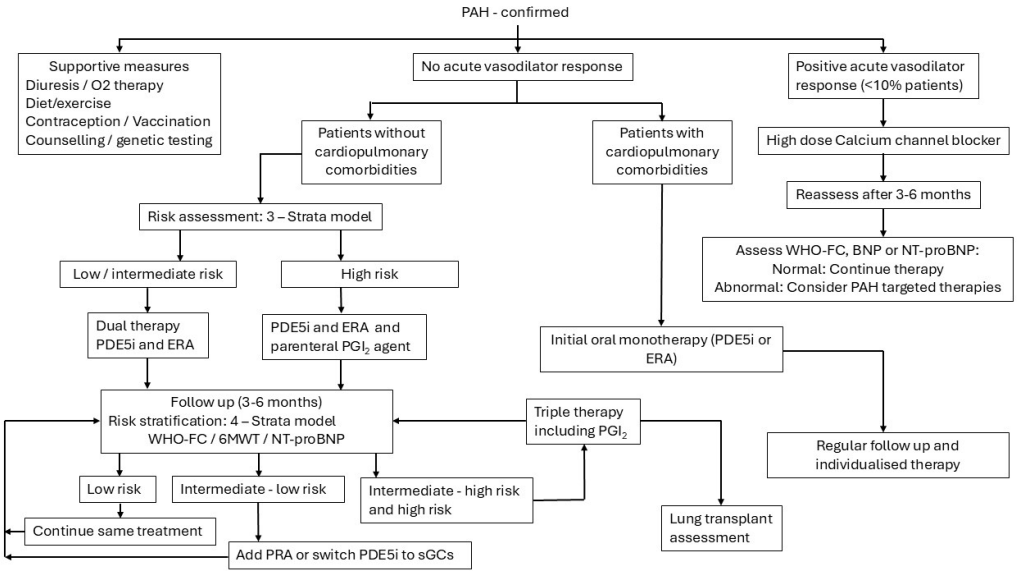

Fig. 5. Treatment algorithm. Drawn in Microsoft Word for Microsoft 365 MSO (Version 2408, Microsoft Corporation, Redmond, WA, USA). PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; ERA, endothelin receptor antagonist; PGI_2, prostaglandin I_2; WHO-FC, World Health Organization functional class; 6MWT, 6-minute walk test; NT-proBNP, N-terminal pro-brain natriuretic peptide; PRA, prostacyclin receptor agonist; sGCs, soluble guanylate cyclase stimulator.

Follow Up

At follow-up, for patients with an intermediate-low risk profile after initial PH therapy, the addition of selexipag (an oral prostacyclin receptor agonist) or replacing PDE5i with riociguat (a soluble guanylate cyclase stimulator also targeting the nitric oxide pathway), is recommended (Humbert et al, 2022). For patients with an intermediate-high risk or high-risk profile, despite PDE5i/ERA therapy, the addition of parenteral prostacyclin analogues and referral for lung transplantation assessment should be considered (Humbert et al, 2022).

An exciting new therapy that has demonstrated promising results is sotatercept, a fusion protein that acts as a ligand trap by binding activins, helping to restore the balance between pro- and anti-proliferative pathways. It is believed to work in

PAH by blocking the Activin receptor 2 A/B-SMAD 2/3 signaling pathway and it is administered subcutaneously every three weeks at a dose of 0.7 mg/kg and has demonstrated significant efficacy in the STELLAR trial, where it improved six-minute walk distance by 41 meters compared to placebo. However, side effects observed in the study included thrombocytopenia, polycythemia, bleeding, epistaxis, and telangiectasia (Hoeper et al, 2023). Sotatercept has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of PAH and is awaiting broader global approval. A recent consensus statement recommends considering sotatercept as an alternative to selexipag in intermediate low-risk cases, and as a potential alternative to parenteral prostacyclin analogues in intermediate high-risk cases. Additionally, it is recommended in high-risk cases where there are contraindications or intolerance to parenteral prostacyclin or persistent high-risk features despite parenteral prostacyclin as a four-drug combination (Chin et al, 2024). Other interventional treatment options may include atrial septostomy and Potts shunt for symptom management in centres experienced in these techniques (Humbert et al, 2023).

Bilateral Lung Transplantation

Lung transplantation referral for evaluation should be considered when candidates have an inadequate response to oral therapy, indicated by an intermediate-high or high-risk stratification at follow-up. Lung transplantation has a one-year survival of up to ninety percent and a median survival of ten years in high-volume centres (Humbert et al, 2022; Savale et al, 2024). The rationale for lung transplant referral assessment in patients with intermediate-high and high-risk groups at follow-up is their greater than 10% one-year mortality. Recent recommendations suggest considering the referral of selected high-risk group patients for lung transplant evaluation at the time of diagnosis. Additionally, it is advised to discuss lung transplantation as a potential future treatment option with the patient at diagnosis (Chin et al, 2024).

Prognosis of PAH

The prognosis in PAH will vary depending on many factors including the subgroup of PAH involved. Compared to patients with IPAH, PAH associated with congenital heart disease (PAH-CHD) has a better long-term survival, with reported 5-year survival estimates of 54% and 76% respectively (Kaemmerer et al, 2020). PAH associated with connective tissue disease particularly systemic sclerosis has a poorer estimated 5-year survival at 37% (Humbert et al, 2023; Xanthouli, 2023). Amongst the rarer forms of PAH, pulmonary veno-occlusive disease (PVOD) has the worst prognosis, with a 27% estimated 5-year survival, and should be referred for lung transplant assessment at diagnosis (Boucly et al, 2024). Patients with IPAH who are acute vasoreactivity responders at initial NO testing and are considered calcium channel blocker responders generally have an excellent prognosis of 100% estimated at 5 years (Hirakawa et al, 2024; Humbert et al, 2022).

Future Directions

The Unisus study, a phase 3 randomized controlled trial (RCT) comparing the efficacy, safety, and tolerability of macitentan at a dose of 75 mg and 10 mg in patients with PAH, to determine if higher doses of the drug have added benefits, is due to be reported in 2025 (UNISUS; clinicaltrial.gov identifier NCT04273945, https://clinicaltrials.gov/study/NCT04273945?id=NCT04273945&rank=1) (McLaughlin et al, 2022). Additionally, a phase 2 RCT is underway investigating a once-daily dry powder inhaler formulation of Treprostinil Palmitil in PAH patients (clinicaltrials.gov identifier NCT05147805, https://clinicaltrials.gov/study/NCT05147805). Treprostinil Palmitil, a pro-drug of Treprostinil with a longer half-life, could offer significant convenience if proven effective, particularly for those currently using Treprostinil via dry powder inhaler or nebulization (Ismat et al, 2022). Moreover, a phase 1/2 RCT is currently looking at the best-tolerated dose of once-daily oral imatinib (100–400 mg) at 4 weeks followed by comparing their efficacy at 24 weeks is underway (Wilkins et al, 2021).

Furthermore, the PROSERA trial, a phase 3 RCT of the inhaled tyrosine kinase inhibitor Seralutinib, is ongoing (PROSPERA; clinicaltrials.gov identifier NCT05934526, https://clinicaltrials.gov/study/NCT05934526). This drug is hypothesized to act as an anti-proliferative and anti-inflammatory agent with favorable effects on haemodynamics demonstrated in the phase 2 trial (PROSPERA; clinicaltrials.gov identifier NCT05934526). Another promising development is Ker-012, a modified activin receptor type IIB (Act RIIB) ligand trap being studied for PAH treatment. It was found to be safe and well-tolerated in a phase 1 study (Natarajan et al, 2023). Ker-012 is currently in phase 2 RCT recruitment (TROPOS study) (TROPOS; clinicaltrials.gov identifier NCT05975905, https://clinicaltrials.gov/study/NCT05975905). Ker-012 may offer a better side effect profile, particularly concerning increased haemoglobin, levels, bleeding and telangiectasia, compared to sotatercept.

Finally, other biological agents targeting the proliferative and apoptotic pathways are in the early stages of development. These include bone morphogenic protein 9/10 (BMP9/BMP10), anti-Gremlin-1 antibody, anti-BMP9 antibody, and anti-Osteoprotegerin (OPG) antibody, which has shown promising preclinical results (Hye et al, 2023).

Conclusion

Advances in therapy have improved prognosis in PAH. Referral to Pulmonary Hypertension centres and early treatment to achieve a low-risk status is a core principle of the current guidelines. New agents, such as sotatercept, and drugs in development, are hoped to add further improvements in survival and quality of life.

Key Points

- Increased disease awareness and early referral to expert PH centres are recommended.
- Combination therapy is recommended to reduce mortality following careful risk stratification.
- Sotatercept, a novel activin ligand trap, has recently been approved for the treatment of PAH.
- Lung transplantation remains the only treatment option in patients with refractory PAH that potentially improves survival.

Availability of Data and Materials

Not applicable.

Author Contributions

EM and SRQ performed the literature search. All authors interpreted the data. EM and SRQ drafted the manuscript. EM, SRQ, BM and SG revised the content critically for important intellectual content and all authors have approved the final manuscript, participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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