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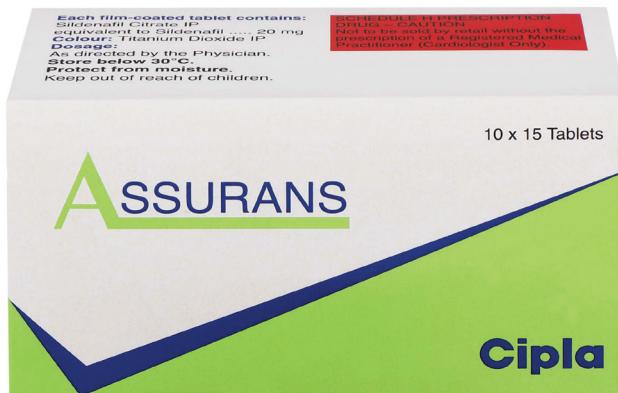


# PHencyclopedia

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# ASSURANS

Sildenafil 20 mg



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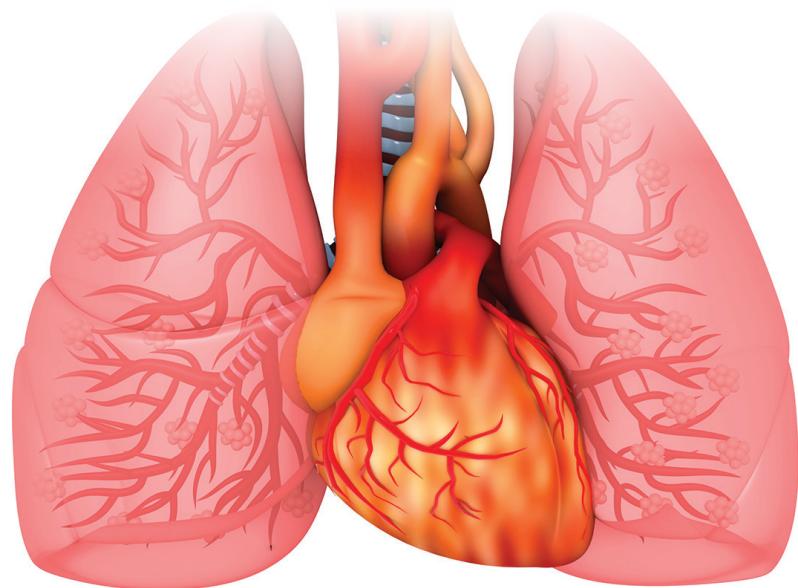
# Preface

PH Encyclopedia is an endeavor to provide comprehensive knowledge on pulmonary hypertension. Overall, this issue contains 3 sections which include thorough knowledge on pulmonary hypertension and pulmonary arterial hypertension. First two sections provides knowledge about definition, classification, epidemiology, pathology, factors involved in the pathogenesis, diagnosis and management of pulmonary hypertension.

However, the subsequent section highlights only pulmonary arterial hypertension which is categorized as Group I pulmonary hypertension according to the recent classification of 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines. This section further describe the sub-classification of pulmonary arterial hypertension, its prevalence, risk-assessment, pathophysiology, various biomarkers, diagnosis and assessment, and management of pulmonary arterial hypertension i.e., general measures, supportive treatment and pharmacological treatment. Lastly, this issue showcases the milestones of drug development in pulmonary arterial hypertension.

Each section aims to provide unbiased and evidence-based knowledge acquired from the clinical expertise of outstanding practicing doctors. The current issue is expected to be an invaluable addition to the clinical library of readers!!

# Pulmonary hypertension

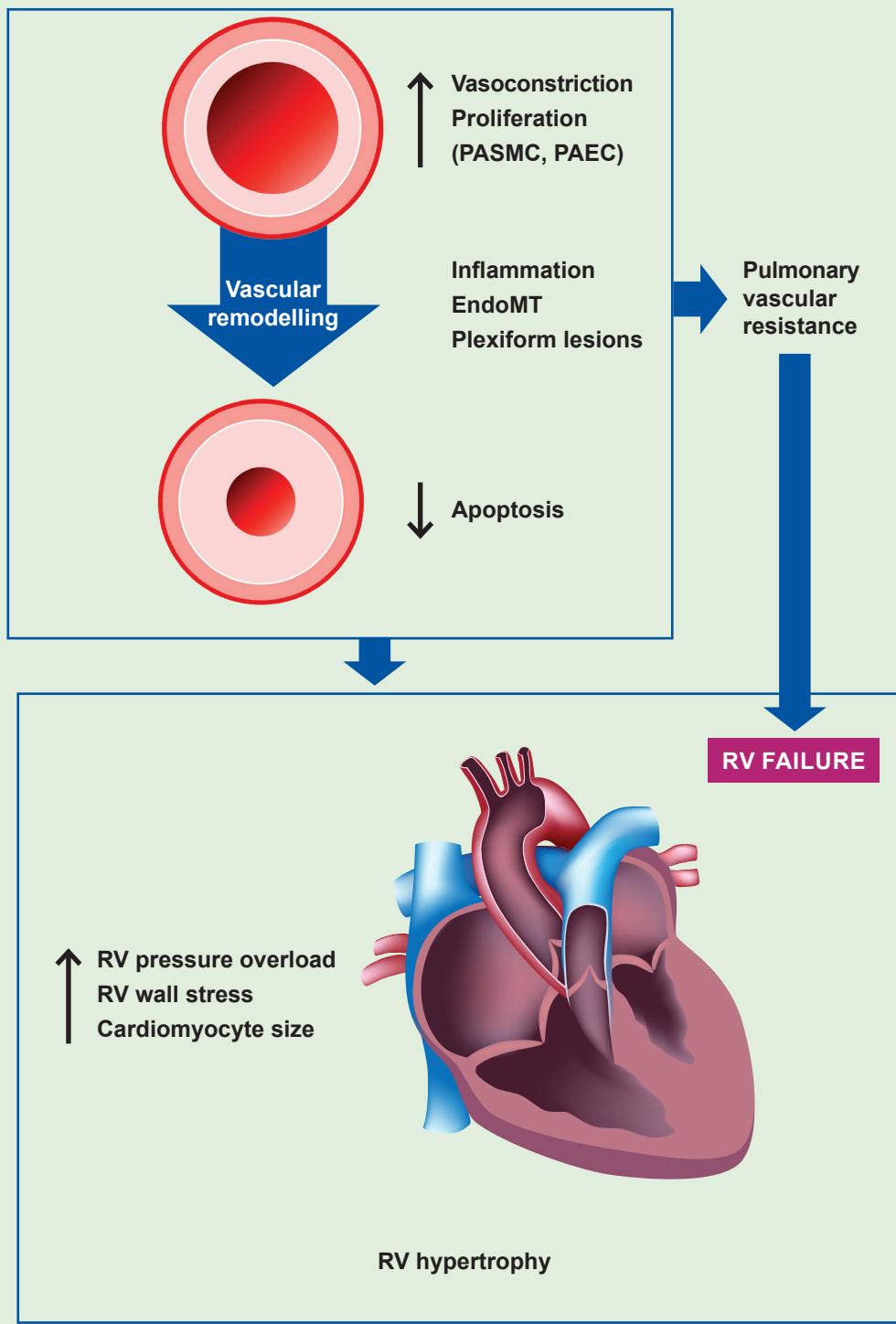


“  
Pulmonary hypertension is a progressive disease that can arise from several etiologies and ultimately leads to right heart failure as the main cause of morbidity and mortality  
”

## Pulmonary hypertension

- Pulmonary hypertension (PH) is a progressive disease that can arise from several etiologies and ultimately leads to right heart failure as the main cause of morbidity and mortality.<sup>1,2</sup>
- The umbrella term – PH – comprises a group of diseases in which the mean pulmonary artery pressure (mPAP) exceeds 25 mmHg at rest.<sup>1</sup> Recently, however, the 6<sup>th</sup> World Symposium on PH has recommended to lower this cut-off further to 20 mmHg.<sup>1,3</sup>
- PH is therefore now defined as a mPAP  $\geq 20$  mmHg as measured by right heart catheterization.<sup>4</sup>
- It may develop as a disease process specific to pulmonary arteries with no identifiable cause or may occur in relation to other cardiopulmonary and systemic illnesses.<sup>4</sup>
- Right ventricle (RV) hypertrophy and dysfunction are the main cause of morbidity and mortality in PH (Figure 1).<sup>2</sup>

Figure 1: Right ventricle (RV) hypertrophy and dysfunction: The main cause of morbidity and mortality in PH<sup>2</sup>



## Hemodynamic indices & definitions of PH

- The traditional hemodynamic definition of precapillary PAH was updated at the 6<sup>th</sup> World Symposium on Pulmonary Hypertension in 2018 to include: a) mean PA pressure >20 mmHg, b) pulmonary capillary wedge pressure ≤15 mmHg, and c) pulmonary vascular resistance (PVR) ≥3 Wood Units (WU).<sup>4</sup>
- The new 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of PH however, further modify this hemodynamic definition by lowering the PVR criterion to any value >2 WU.<sup>4</sup>

## Hemodynamic definitions of PH<sup>4</sup>

Table 1 describes the hemodynamic definitions of PH.

## Classification of Pulmonary hypertension

- Pulmonary hypertensive diseases were first classified by the World Health Organization (WHO) according to pathological and clinical features in 1973 during the 1<sup>st</sup> World Symposium on Pulmonary Hypertension in Geneva, Switzerland.<sup>4</sup>
- Overtime, this classification system has been further refined, with the most recent updates coming from the 6<sup>th</sup> World Symposium in 2018 and the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines for the Diagnosis and Treatment of PH.<sup>4</sup>
- The WHO now classifies PH into five groups based on identifiable cause (the primary mechanisms causing increased pulmonary vascular resistance) and risk factors.<sup>1,4</sup>

The WHO now classifies PH into five groups based on identifiable cause (the primary mechanisms causing increased pulmonary vascular resistance) and risk factors

**Table 1: Hemodynamic definitions of PH<sup>4</sup>**

Pre-capillary PH	mPAP >20 mmHg PAWP <15 mmHg PVR >2 WU
Post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR <2 WU
Combined pre- and post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU

## General characteristics of WHO PH classification groups

Table 2 enumerates the characteristics of WHO PH classification groups.

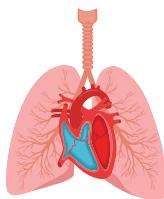
**Table 2: General characteristics of WHO PH classification groups<sup>3,4</sup>**

WHO Groups	Characteristic features
Group 1 (PAH)	<ul style="list-style-type: none"> <li>Distinct arteriopathy characterized by excessive proliferation of the cellular components of the vascular wall, smooth muscle hypertrophy, <i>in situ</i> thrombosis and formation of plexiform lesions occluding the vessel lumen.</li> <li>Hyperproliferative changes may also develop in pulmonary venous structures.</li> </ul>
Group 2 (PH-LHD) LHD-Left heart disease Most common cause of PH	<ul style="list-style-type: none"> <li>Includes left ventricular systolic and diastolic dysfunction and valvular heart disease.</li> <li>Results mainly from rising post-capillary pressures as seen in diseases affecting the left side of the heart (e.g., cardiomyopathies or valvular heart disease).</li> <li>Another mechanism causing PH is mediated by hypoxia and associated vasoconstriction.</li> </ul>
Group 3 (PH-CLD) Caused by chronic lung disease (CLD) and/or hypoxia Second most common cause of PH	<ul style="list-style-type: none"> <li>Hypoxic vasoconstriction may be associated with high altitude, sleep apnea and other lung diseases, such as pulmonary fibrosis or emphysema.</li> <li>Guidelines proposed complex lung function testing cut-offs of forced expiratory volume in the first second (FEV1) &lt;60% (obstructive pathologies) and forced vital capacity (FVC) &lt;70% (restrictive pathologies) in conjunction with moderate to severe computed tomography (CT) parenchymal abnormality designating as CLD-PH.</li> </ul>
Group 4 [Chronic thromboembolic PH (CTEPH)]	<ul style="list-style-type: none"> <li>Comprises of conditions where obstructive lesions of the pulmonary artery lead to PH, with CTEPH being the most common.</li> <li>Can occur due to circulatory flow obstruction, resulting from thromboembolic or other embolic events.</li> <li>CTEPH is described as PH in the setting of unresolved pulmonary emboli despite 3 months of anticoagulation and is estimated to complicate 3% to 4% of pulmonary embolism (PE) cases.</li> </ul>
Group 5 (PH with unclear and/or multifactorial mechanisms)	<ul style="list-style-type: none"> <li>Consists of disorders that are associated with pulmonary hypertension, without any unifying mechanistic features.</li> <li>This group included PH associated with myeloproliferative disorders, chronic renal failure, sarcoidosis, and thyroid disease.</li> </ul>

## Sub-classification of WHO PH groups<sup>4</sup>

### WHO Group 1 (PAH)

#### Pulmonary Arterial Hypertension



##### 1.1 Idiopathic

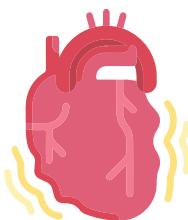
- 1.1.1 Non-responders at vasoreactivity testing
- 1.1.2 Acute responders at vasoreactivity testing



##### 1.2 Heritable<sup>a</sup>

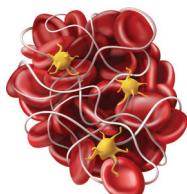


##### 1.3 Associated with drugs or toxins<sup>a</sup>



##### 1.4 Associated with:

- 1.4.1 Connective tissue disease
- 1.4.2 Human immunodeficiency virus (HIV) infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease
- 1.4.5 Schistosomiasis



##### 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement



##### 1.6 Persistant PH of the newborn

<sup>a</sup>Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders.

## Sub-classification of WHO PH groups<sup>4</sup>

### WHO Group 2

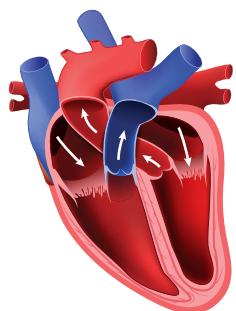
#### Pulmonary Hypertension Associated With Left Heart Disease



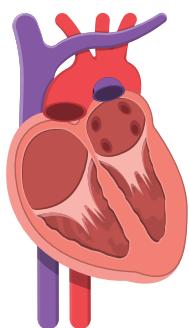
##### 2.1 Heart failure

2.1.1 With preserved ejection fraction

2.1.2 With reduced or mildly reduced ejection fraction<sup>b</sup>



##### 2.2 Valvular heart disease



##### 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

<sup>b</sup>Left ventricular ejection fraction (LVEF) for heart failure (HF) with reduced ejection fraction: <40%; for HF with mildly reduced ejection fraction: 41–49%.

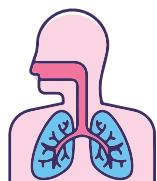
## Sub-classification of WHO PH groups<sup>4</sup>

### WHO Group 3

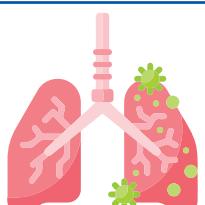
#### Pulmonary Hypertension Associated With Lung Diseases and/or Hypoxia



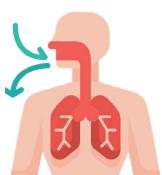
3.1 Obstructive lung disease or emphysema



3.2 Restrictive lung disease



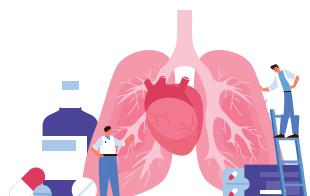
3.3 Lung disease with mixed obstructive and restrictive components



3.4 Hypoventilation syndrome



3.5 Hypoxia without lung disease (e.g. high altitude)

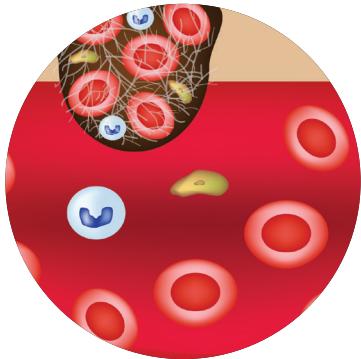


3.6 Developmental lung diseases

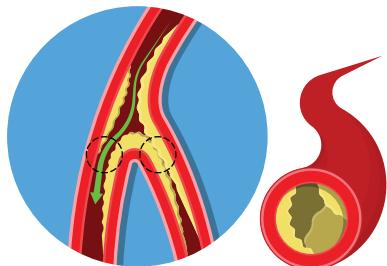
## Sub-classification of WHO PH groups<sup>4</sup>

### WHO Group 4

#### PH Associated With Pulmonary Artery Obstructions



4.1 Chronic thromboembolic pulmonary hypertension



4.2 Other pulmonary artery obstructions<sup>c</sup>

<sup>c</sup>Other causes of pulmonary artery obstructions might include: sarcoma (high or intermediate grade or angiosarcoma), other malignant tumors (eg, renal carcinoma, uterine carcinoma, germ-cell tumors of the testes), non-malignant tumors (eg, uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis.

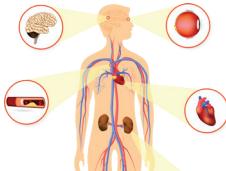
## Sub-classification of WHO PH groups<sup>4</sup>

### WHO Group 5

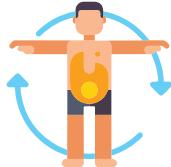
#### Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms



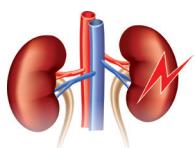
5.1 Hematologic disorders<sup>d</sup>



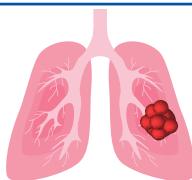
5.2 Systemic disorders<sup>e</sup>



5.3 Metabolic disorders<sup>f</sup>



5.4 Chronic renal failure with or without hemodialysis



5.5 Pulmonary tumour thrombotic microangiopathy



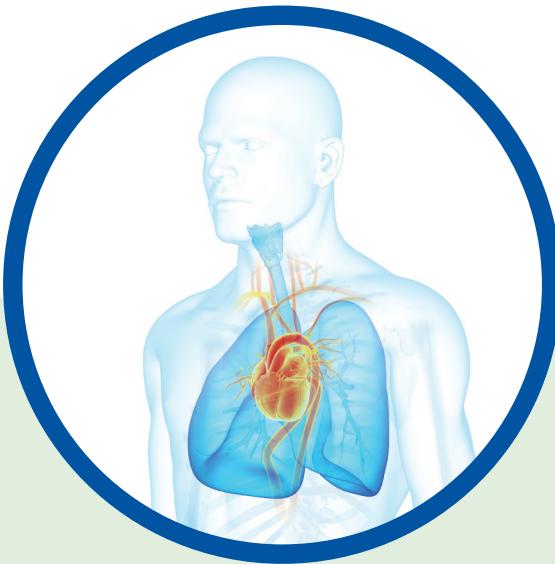
5.6 Fibrosing mediastinitis

<sup>d</sup>Including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders.

<sup>e</sup>Including sarcoidosis, pulmonary Langerhan's cell histiocytosis, and neurofibromatosis type 1.

<sup>f</sup>Including glycogen storage diseases and Gaucher disease.

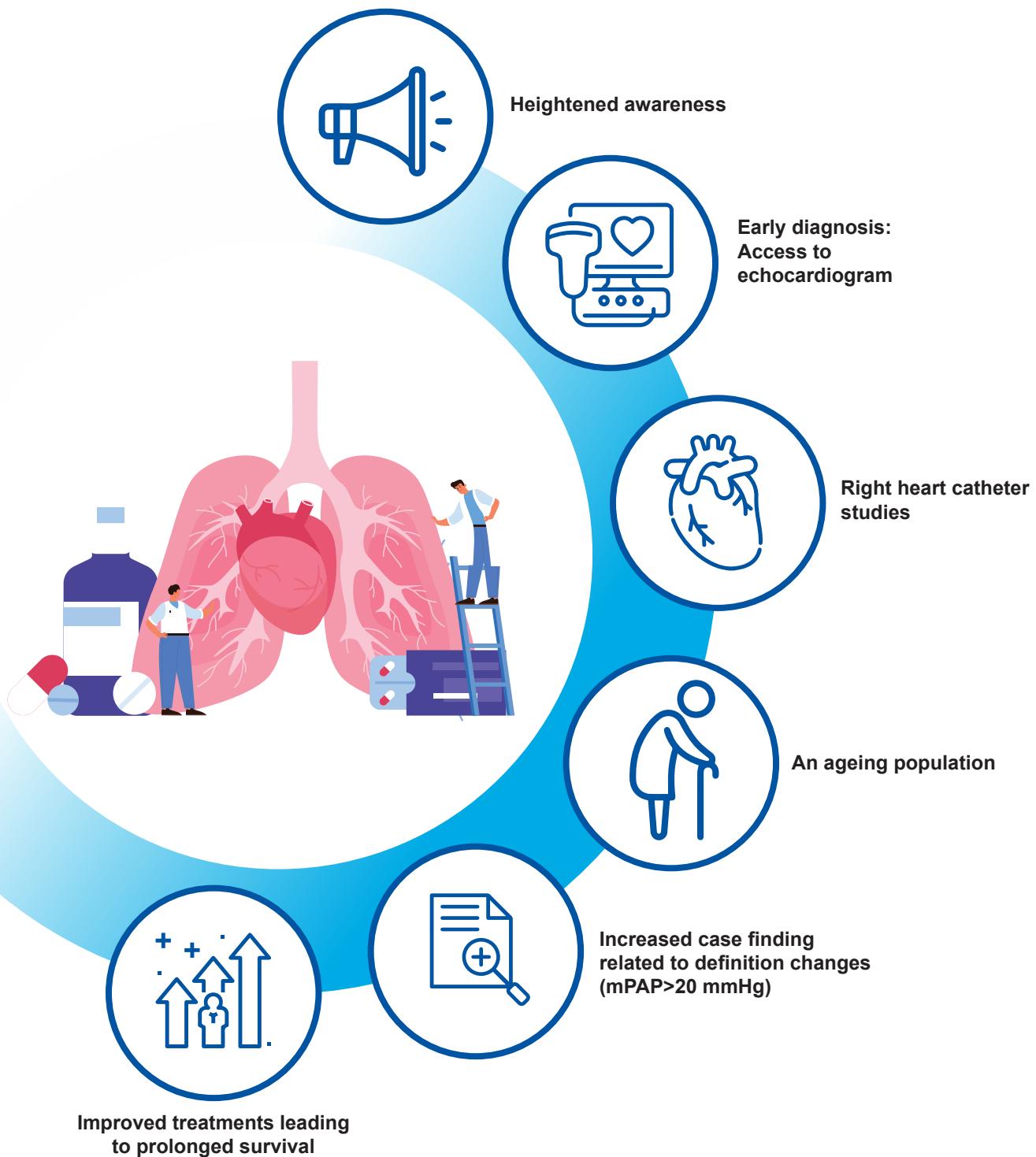
**Abbreviations:** HF, heart failure; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary venoocclusive disease



## Epidemiology of PH

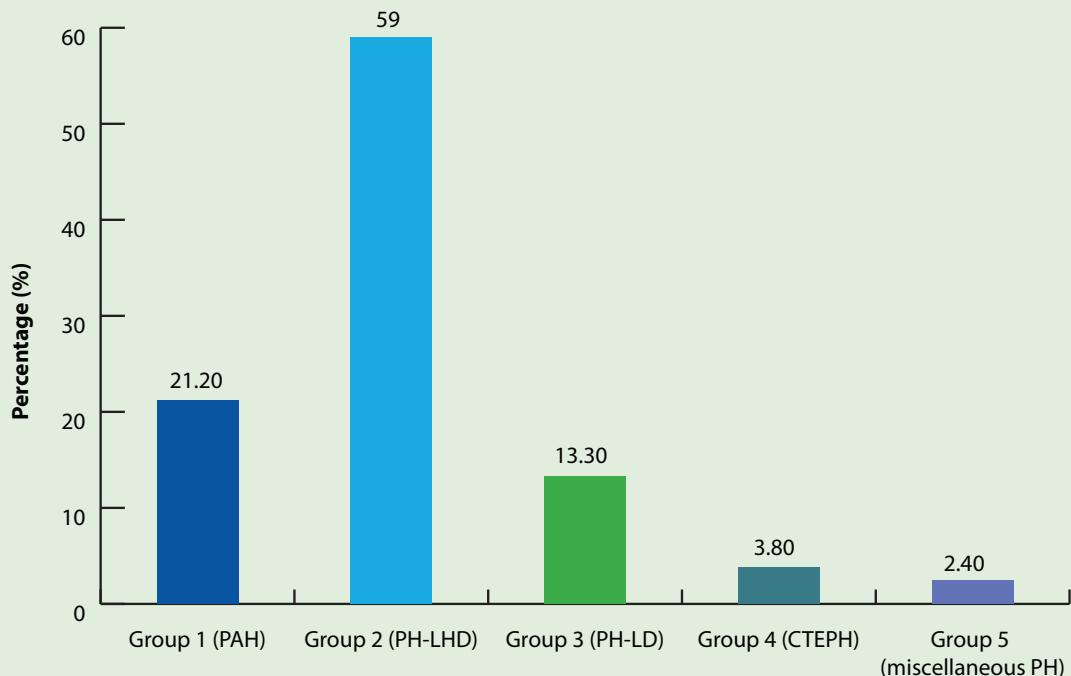
- The prevalence of specific PH etiologies may differ depending on the geographic region.<sup>3</sup>
- An estimated prevalence of PH at the population level is approximately 1% to 3%, though both incidence and prevalence of the disease is increasing, likely for multifactorial reasons.<sup>3</sup>
- Worldwide, PH caused by left heart disease (PH-LHD) is the most common cause of PH.<sup>3</sup>
- Asian registry data also suggests that PH-LHD is the most common PH subtype, as is the case in the West.<sup>3</sup>
- In Asia, rates of PH caused by chronic lung disease may be higher than that observed in West due to high rates of smoking and tuberculosis.<sup>3</sup>
- Furthermore, there is likely increased prevalence of PH related to infections in socioeconomically disadvantaged Asian regions, mirroring middle- and low-income countries globally compared to Western countries.<sup>3</sup>
- Finally, high altitude pulmonary hypertension occurs in persons living above 2,500 m sea level, and the Asian Himalayas are home to >50 million people.<sup>3</sup>
- The largest Asian registry describing all PH subtypes is the PRO-KERALA registry based in the state of Kerala (Figure 2).<sup>3,5</sup>
- In terms of group 1 PAH, Asian registry data suggest a similar mean age of diagnosis of PAH as mentioned in western registry, with a greater proportion of connective tissue disease-PAH (CTD-PAH) and congenital heart disease-associated PAH (CHD-PHA) relative to idiopathic PAH.<sup>3</sup>
- Nonetheless, utilization rates of PH specific drug therapies are remarkably lower in Asian countries like India than the Western population.<sup>5</sup>

## Factors contributing to increasing incidence and prevalence of pulmonary hypertension<sup>3</sup>



## Prevalence of WHO PH subtypes seen in PRO-KERALA registry:<sup>3,5</sup>

**Figure 2: Prevalence of WHO PH subtypes seen in PRO-KERALA registry among 2,003 patients across 50 centres**



**Abbreviations:** PAH: Pulmonary arterial hypertension; PH-LHD: PH caused by left heart disease; PH-LD: PH caused by lung disease; CTEPH: chronic thromboembolic PH

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1. Liu SF, Veetil NN, Li Q, et al. Pulmonary hypertension: Linking inflammation and pulmonary arterial stiffening. *Front Immunol.* 2022;13:959209.
2. Bisserier M, Pradhan N, Hadri L, et al. Current and emerging therapeutic approaches to pulmonary hypertension. *Rev Cardiovasc Med.* 2020;21(2):163–179.
3. Anderson JJ, Lau EM. Pulmonary Hypertension Definition, Classification, and Epidemiology in Asia. *JACC Asia.* 2022;2:538–546.
4. Swisher JW, Weaver E, et al. The Evolving Management and Treatment Options for Patients with Pulmonary Hypertension: Current Evidence and Challenges. *Vasc Health Risk Manag.* 2023;19:103–126.
5. Harikrishnan S, Sanjay G, Ashish kumar M, et al. Pulmonary hypertension registry of Kerala, India (PRO-KERALA) — Clinical characteristics and practice patterns. *International Journal of Cardiology.* 2018;265:212–217.

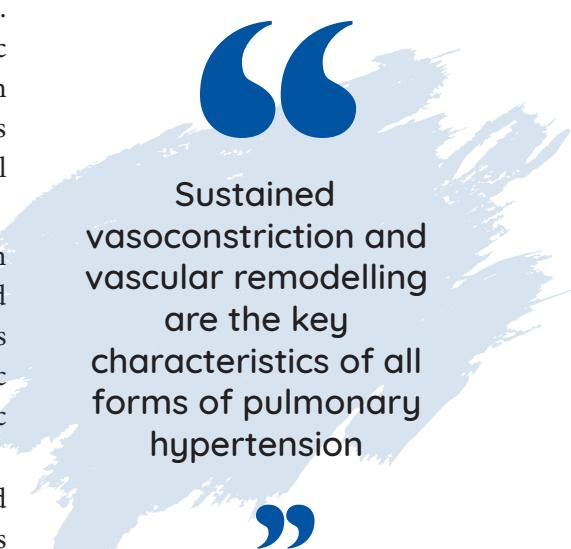
# Pulmonary vascular remodelling in PH pathogenesis

## Overview

Though the causes of PH are not known, it has been known that sustained vasoconstriction and vascular remodelling are the key characteristics of all forms of PH. Thickening of intimal or medial layer of muscular vessels marks the associated feature of remodeling of pulmonary blood vessels. Moreover, there is appearance of cells expressing smooth muscle specific markers in pre-capillary arterioles (distal muscularization), resulting from proliferation and migration of pulmonary arterial smooth muscle cells (PASMCs) and cellular trans-differentiation (i.e., endothelial-mesenchymal transformation).<sup>1</sup>

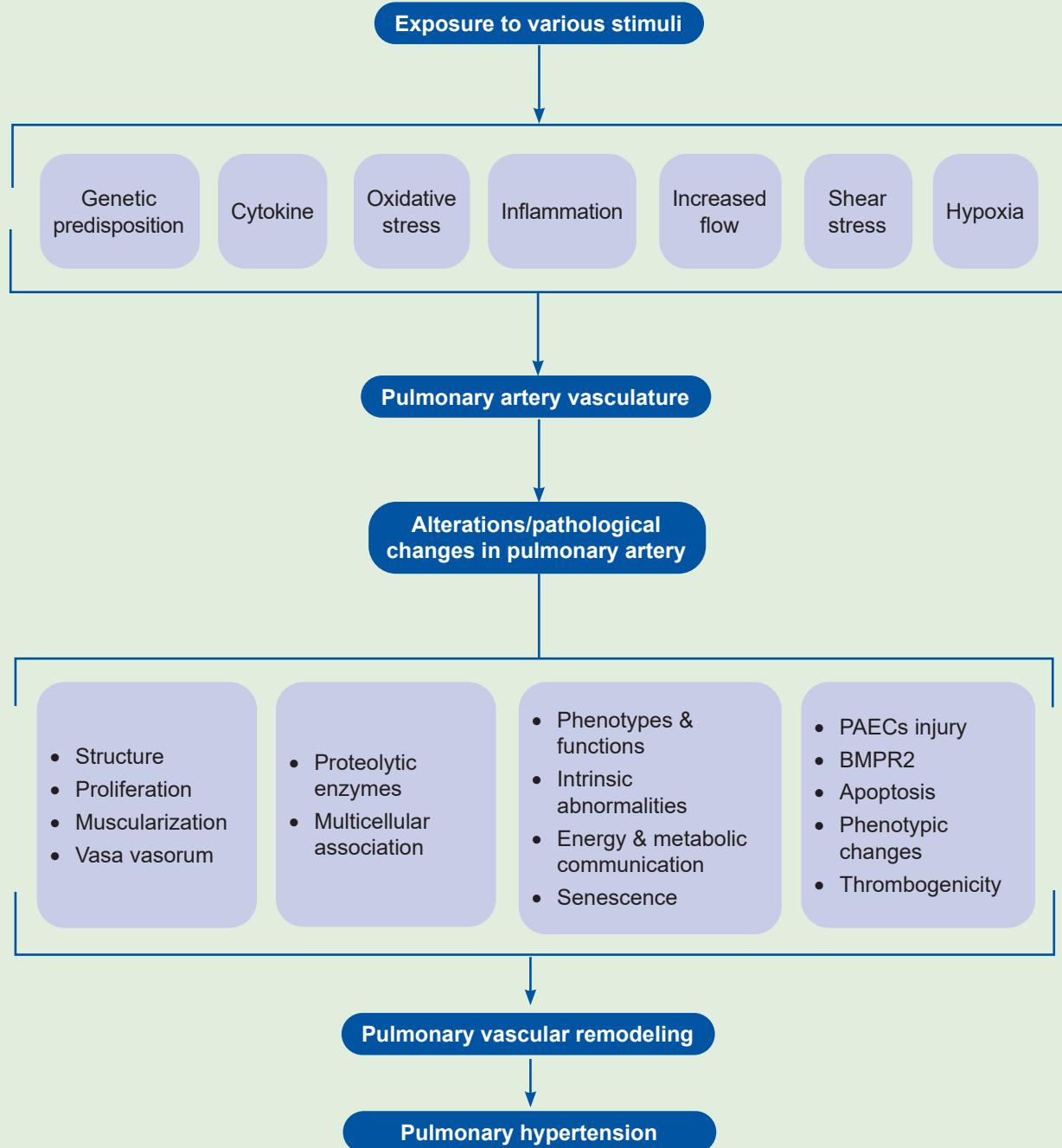
Furthermore, alterations in pulmonary vascular structure and function often give rise to blood flow resistance and development of right-sided heart failure, leading to severe morbidity and mortality. In PH, all layers of the vascular wall are involved, because of interaction between genetic and environmental factors and have essential genetic and epigenetic mechanisms.

In pulmonary vascular remodelling, there is proliferation and phenotypic transformation of pulmonary artery endothelial cells (PAECs) and PASMCs of the middle membranous pulmonary artery, as well as complex interactions involving external layer pulmonary artery fibroblasts (PAFs) and extracellular matrix (ECM).<sup>2</sup> Figure 1 showcases pulmonary vascular remodeling in PH pathogenesis, and table 1 highlights characteristics of pulmonary vascular remodeling in humans.<sup>1,2</sup>



Sustained vasoconstriction and vascular remodelling are the key characteristics of all forms of pulmonary hypertension

**Figure 1: Pulmonary Vascular Remodelling in PH Pathogenesis<sup>2</sup>**



**Abbreviations:** PAECs: Pulmonary artery endothelial cells, BMPR2: Bone morphogenic type 2 receptor

**Table 1: Characteristics of pulmonary vascular remodeling in humans<sup>1</sup>**

Species	Medial Hypertrophy	Intimal Proliferation	Alveolar Muscularity	Occlusive Lesions	Proximal Stiffening	Acute Reduction of Ppa by ROCK inhibitor
Human Class 1 PH	++	++	++	Yes	Yes	+
Class 3: Lung disease and/or hypoxia	+	+	+	NO		

## Intima remodeling in pulmonary vascular remodeling

Intima exhibits an endothelial cell-thick interface between the muscular media and the flowing blood. Endothelial cells in the intima are associated with an unobstructed flow surface area that accounts for relatively low perfusion pressures, hallmark of the pulmonary circulation. In patients with severe PH, there is threefold increase in the thickness of intima, which gives rise to 40-fold increase in resistance of the pulmonary vascular.<sup>2</sup>

Factors such as shear stress, hypoxia, inflammation, PAECs phenotypes, the bone morphogenic type 2 receptor (BMPR2), and cilia length precipitate PAECs dysfunction in pulmonary hypertension (Figure 2).<sup>2</sup>

## Media remodelling

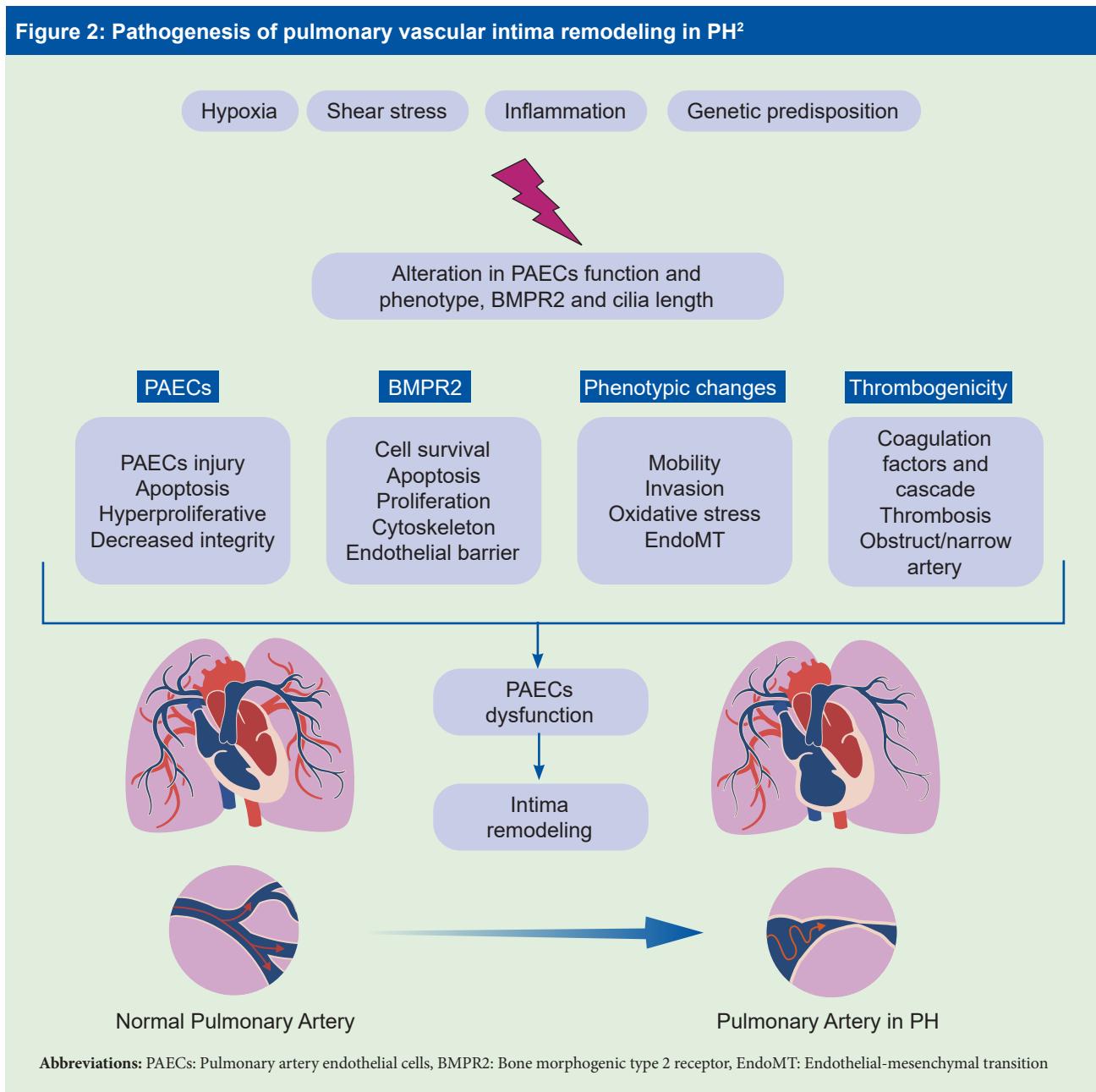
Since media, composed primarily of PASMCs, regulates hypoxic pulmonary vasoconstriction, it is the main focus of PH. Combined intima and media thickness are significantly associated with pulmonary artery pressures and pulmonary resistance; and an increase in pulmonary artery pressures and pulmonary vascular resistance is associated with heightened media (and intima) remodeling. In contrast to this, above finding also supports the fact that combined remodeling of both the intima and the media plays a vital role in the pathogenesis of pulmonary hypertension.<sup>3</sup>

## Factors involved in PH

Though the causes of pulmonary hypertension are not known, medical conditions as depicted in Table 2 can damage, change, or block the blood vessels of the pulmonary arteries, leading to pulmonary hypertension.<sup>4</sup>

“  
Combined remodeling of both the intima and the media plays a vital role in the pathogenesis of pulmonary hypertension  
”

**Figure 2: Pathogenesis of pulmonary vascular intima remodeling in PH<sup>2</sup>**



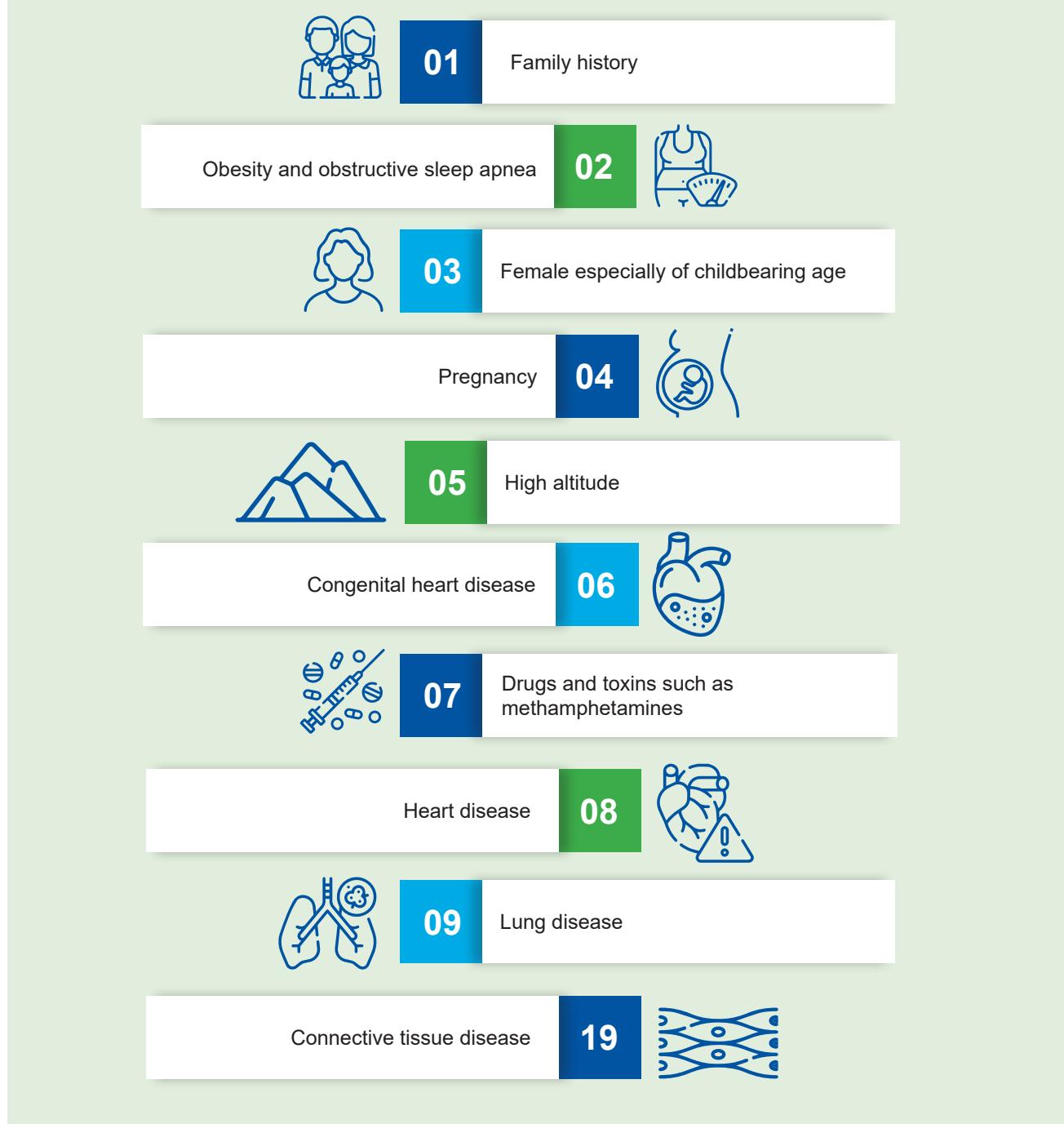
**Table 2: Causes of pulmonary hypertension<sup>4</sup>**

- Left heart diseases
- Congenital heart defects
- Lung diseases that include COPD, interstitial lung diseases
- Liver disease
- Sickle cell disease
- Blood clots in the lungs

## Risk factors associated with pulmonary hypertension

Though pulmonary hypertension can be diagnosed in any individual, there are certain risk factors that predispose an individual to a greater risk of developing pulmonary hypertension (Figure 3).<sup>4,5</sup>

**Figure 3: Risk factors for pulmonary hypertension<sup>4,5</sup>**



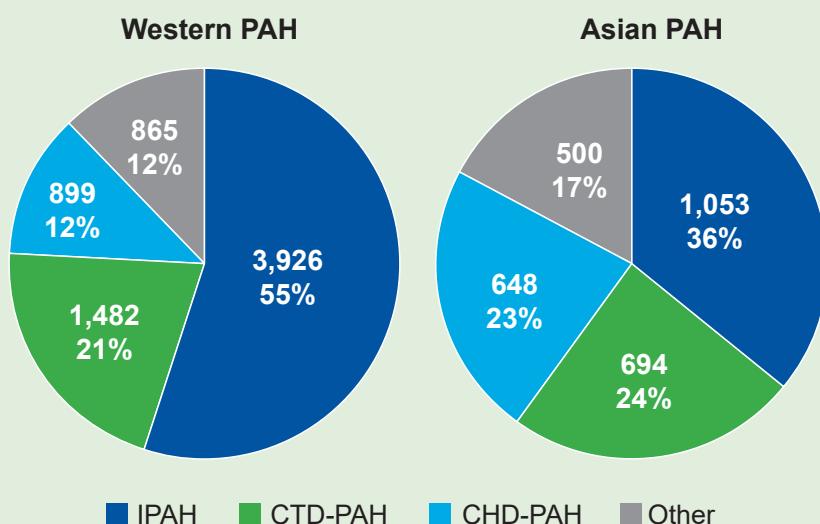
“  
 Registries are a set of useful cohort studies to illuminate epidemiological traits, natural history, survival, and treatment data in rare diseases such as pulmonary arterial hypertension  
 ”

## Etiological differences between Western and Asian PAH registries

Registries are a set of useful cohort studies to illuminate epidemiological traits, natural history, survival, and treatment data in rare diseases such as pulmonary arterial hypertension. Unlike Asian registries, idiopathic PAH is the most common etiology, accounting for 30% to 50% of all PAH cases, followed by connective tissue disorder (CTD)-PAH and congenital heart disease (CHD)-PAH in western countries (Figure 4). Survival rates at 1, 3, and 5 years in the REVEAL registry from diagnostic right heart catheter were 85%, 68%, and 57%, respectively.<sup>6</sup>

The largest Asian registry describing all PH subtypes is PRO-KERALA registry based in Kerala, India. In the data collected from 50 hospitals across the state for consecutive PH patients, it was found that mean age of patients included was  $56 \pm 16.1$  years, with a female predominance (52%), and etiologies PH-LHD (59%), group 1 PAH (42%), PH-LD (13.3%), CTEPH (3.8%), and group 5 miscellaneous PH (2.4%; Figure 4). Survival rates at 1, 5, and 10 years were 85.8%, 66.9%, and 55.4%.<sup>6</sup>

**Figure 4: Etiological differences between Western and Asian PAH registries<sup>6</sup>**

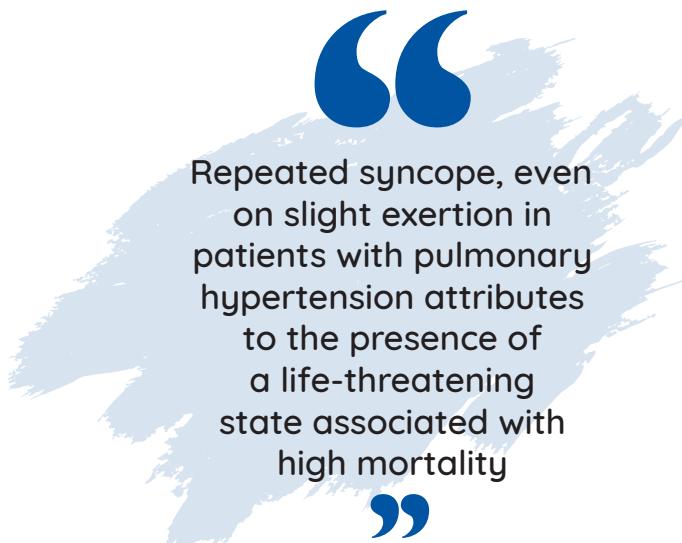


**Abbreviations:** CTD-PAH: Connective tissue disease–PAH, CHD-PAH: Congenital heart disease–associated PAH, IPAH: Idiopathic pulmonary arterial hypertension

## Signs and symptoms of pulmonary hypertension

Progressive exercise induced dyspnea accompanied by fatigue and exhaustion are the key clinical presentations of pulmonary hypertension (Figure 5). It is the non-specific nature of associated symptoms that causes a delay of months or even years between onset of symptoms and diagnosis. As the disease progresses, there is worsening of symptoms and occurrence of new symptoms such as dyspnea on bending down (bendopnea) and syncope; latter being pronounced during or immediately after physical exertion. Repeated syncope, even on slight exertion, in patients with pulmonary hypertension attests to the presence of a life-threatening state associated with high mortality. A typical triad of cervical venous congestion, ascites, and edema develops in cases of cardiac decompensation when the right cardiac filling pressures rise.<sup>7</sup>

Left parasternal lift or retraction, augmented second heart sound, right ventricular third heart sound, elevated jugular venous pressure with abnormal waveform, low volume arterial pulses, hepatomegaly, ascites, peripheral edema, and a tricuspid regurgitant murmur are the associated physical findings.<sup>8</sup>

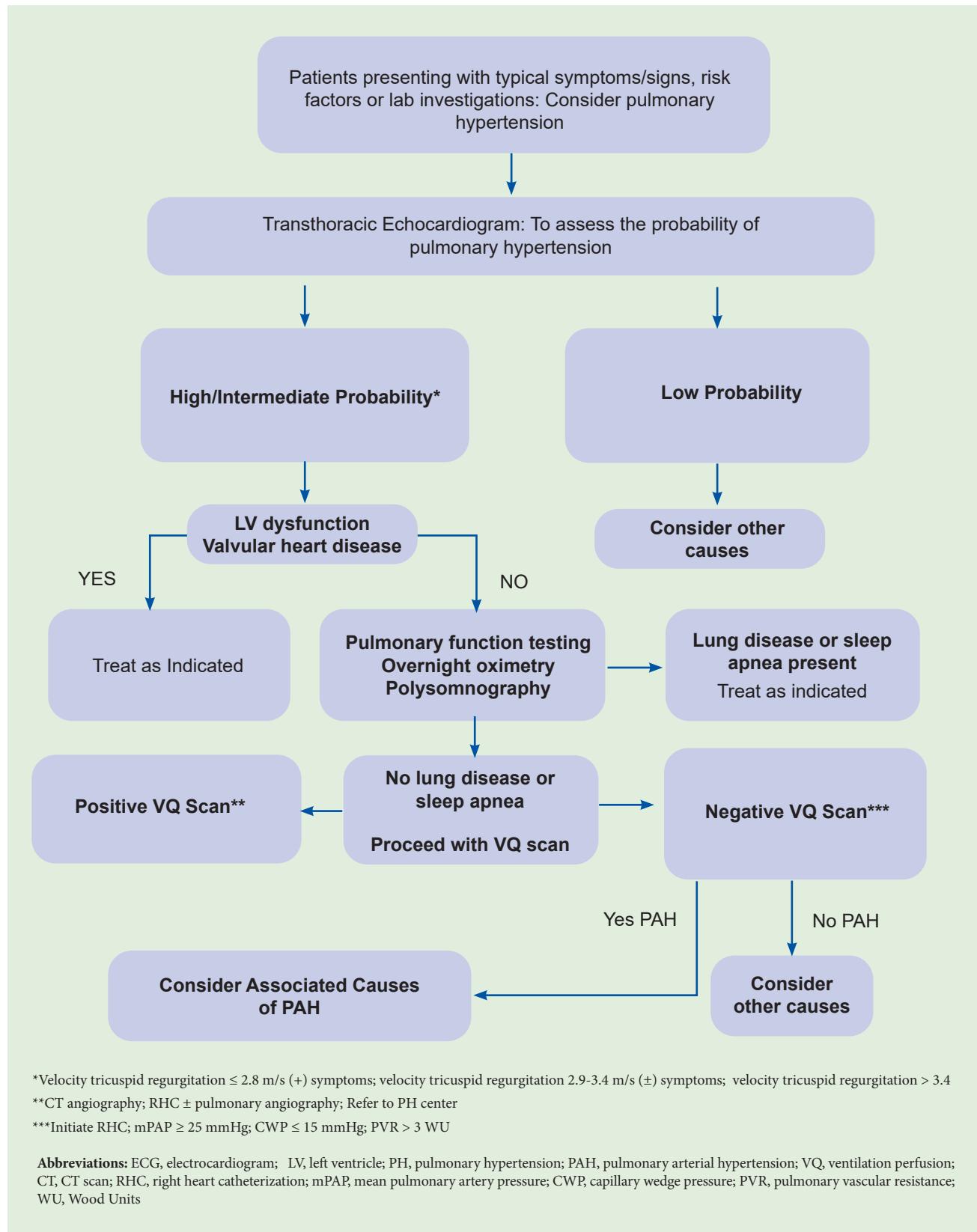


Repeated syncope, even on slight exertion in patients with pulmonary hypertension attributes to the presence of a life-threatening state associated with high mortality

Figure 5: Cardinal symptoms of pulmonary hypertension<sup>7</sup>



## Algorithm for diagnosis of pulmonary hypertension<sup>9</sup>



## Treatment modalities in pulmonary hypertension (all types)

In patients with pulmonary hypertension, an integrative approach has been recommended while treating them because, if inappropriately selected, the therapy can be harmful to such patients. Integrative approach considers the mechanism of pulmonary hypertension development, response to vasoreactivity testing, and the patients' risk of disease progression and death. Various medications have been used for the treatment. Table 3 summarizes various FDA-approved drugs used in pulmonary hypertension management.<sup>10</sup> Table 4 summarizes groupwise treatment approach of PH.<sup>13</sup>

**Table 3: List of approved drug class for pulmonary hypertension<sup>10-12</sup>**

Class of drug	Drug	Indications
Prostacyclin analog	<ul style="list-style-type: none"> <li>• Treprostinil (oral, inhaled, subcutaneous, intravenous)</li> <li>• Iloprost (inhaled)</li> </ul>	<ul style="list-style-type: none"> <li>• To improve exercise tolerance</li> <li>• To improve exercise tolerance, NYHA functional class</li> </ul>
Synthetic prostacyclin	• Epoprostenol	• To improve exercise capacity
Non-prostanoid prostaglandin receptor agonist	• Selexipag (Oral)	• To improve composite endpoint including lack of clinical deterioration
Endothelin receptor antagonist	<ul style="list-style-type: none"> <li>• Bosentan (Oral)</li> <li>• Macitentan (Oral)</li> <li>• Ambrisentan (Oral)</li> </ul>	• Improvement of exercise capacity and to decrease clinical worsening
Phosphodiesterase 5 inhibitor	<ul style="list-style-type: none"> <li>• Sildenafil (Oral)</li> <li>• Tadalafil (Oral)</li> </ul>	<ul style="list-style-type: none"> <li>• Improvement of exercise capacity and to decrease clinical worsening</li> <li>• To improve exercise ability</li> </ul>
Guanylate cyclase stimulator	• Riociguat (Oral)	• To improve exercise ability
Combination therapy	<ul style="list-style-type: none"> <li>• Ambrisentan plus tadalafil</li> <li>• Macitentan plus tadalafil</li> </ul>	<ul style="list-style-type: none"> <li>• Reduces risk of clinical failure in treatment-naive patients with PAH</li> <li>• Improves cardiopulmonary hemodynamics and functional capacity</li> </ul>

Integrative approach considers the mechanism of pulmonary hypertension development, response to vasoreactivity testing, and the patients' risk of disease progression and death

**Table 4: Group wise treatment of pulmonary hypertension<sup>13</sup>**

Type of PH	Treatment modalities
<b>Pulmonary arterial hypertension (Group 1)</b>	<ul style="list-style-type: none"> <li>• Physical activity and supervised rehabilitation</li> <li>• Anticoagulation</li> <li>• Diuretics: Loop diuretics, thiazides, and mineralocorticoid receptor antagonists— used as monotherapy or in combination</li> <li>• Cardiovascular drugs</li> <li>• Pulmonary arterial hypertension therapies <ul style="list-style-type: none"> <li>» Calcium channel blockers</li> <li>» Endothelin receptor antagonists (oral administration)</li> <li>» Phosphodiesterase 5 inhibitors (PDE5i) (oral administration)</li> <li>» Prostacyclin (oral, inhaled, iv or sc administration)</li> <li>» Prostacyclin agonist (oral administration)</li> </ul> </li> </ul>
<b>Pulmonary hypertension associated with left heart failure (Group 2)</b>	<p><b>Pulmonary hypertension associated with left-sided heart failure</b></p> <p>Heart failure with reduced ejection fraction</p> <ul style="list-style-type: none"> <li>• Implanting an LVAD</li> </ul> <p>Heart failure with preserved ejection fraction</p> <ul style="list-style-type: none"> <li>• SGLT-2i empagliflozin</li> </ul> <p>Interatrial shunt devices</p> <p><b>Pulmonary hypertension associated with valvular heart disease</b></p> <p>Surgical or interventional approaches for valvular repair improve cardiopulmonary hemodynamics by reducing PAWP and PAP and improving forward SV</p>
<b>Pulmonary hypertension associated with lung diseases and/or hypoxia (Group 3)</b>	<ul style="list-style-type: none"> <li>• Treatment of the underlying lung disease, including supplementary oxygen and non-invasive ventilation, pulmonary rehabilitation programmes</li> <li>• Inhaled treprostinil for PH in ILD</li> <li>• Oral sildenafil may be considered for PH due to severe lung disease</li> </ul>
<b>Chronic thrombo-embolic pulmonary hypertension (Group 4)</b>	<ul style="list-style-type: none"> <li>• Combinations of pulmonary endarterectomy (PEA), balloon pulmonary angioplasty, and medical therapies</li> <li>• Lifelong therapeutic anticoagulation is recommended</li> </ul>
<b>Pulmonary hypertension with unclear and/or multifactorial mechanisms (Group 5)</b>	Systemic disorders: Corticosteroids or immunosuppressive therapy may improve hemodynamics

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# Pulmonary arterial hypertension

**P**ulmonary arterial hypertension (PAH) is defined as a mean pulmonary arterial pressure (mPAP)  $\geq 20$  mmHg, pulmonary artery wedge pressure (PAWP)  $\leq 15$  mmHg and pulmonary vascular resistance (PVR)  $>3$  Wood units. It is a chronic and progressive disorder distinguished by angio-proliferative vasculopathy in the pulmonary arterioles, which leads to endothelial and smooth muscle proliferation and dysfunction, inflammation, and thrombosis.<sup>1</sup>

## Sub-classification of PAH

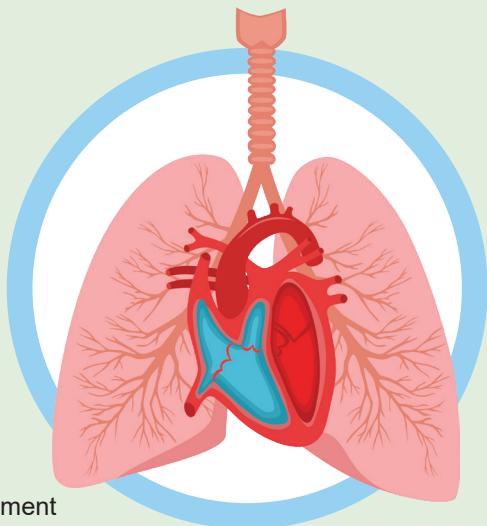
Pulmonary arterial hypertension is classified as Group 1 pulmonary hypertension, according to the updated 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines (Box 1). It is further classified based on its cause, with idiopathic PAH (iPAH) accounting for the majority of cases, followed by PAH linked with

Pulmonary arterial hypertension is a chronic and progressive disorder distinguished by angio-proliferative vasculopathy in the pulmonary arterioles

### Box 1: Sub-classification of PAH<sup>2</sup>

#### GROUP 1: PAH

- 1.1 Idiopathic
  - » 1.1.1 Non-responders at vasoreactivity testing
  - » 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable
- 1.3 Associated with drugs and toxins
- 1.4 Associated with:
  - » 1.4.1 Connective tissue disease
  - » 1.4.2 HIV infection
  - » 1.4.3 Portal hypertension
  - » 1.4.4 Congenital heart disease
  - » 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn



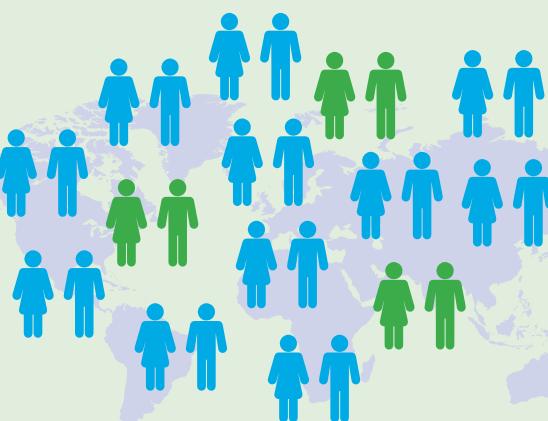
connective tissue diseases (CTD) and congenital heart disease. In PAH, angio-proliferative vasculopathy damages the pre-capillary arterioles, increasing pulmonary vascular resistance leads to an increase in right ventricular afterload, and right heart failure is the eventual cause of death. Evidences show that PAH has the good prognosis when properly treated in comparison to other PH categories.<sup>1</sup>

## Prevalence of PAH

The incidence of PAH (i.e., group 1 PH) is about five cases per million people per year, with a frequency of about 25 cases per million people. The initial definition of the demographic profile, which emphasized younger women of reproductive age as the prototype patients with idiopathic PAH, has now evolved. In clinical trials and registries nowadays, individuals with a new diagnosis are on average 53 years old. This epidemiological change is partly due to a broader understanding of the risk factors for PAH, such as the relation of PAH with liver disease, connective tissue disease, and other age-related comorbidities. Moreover, variations in the epidemiology of PAH now compared to an earlier age are likely due to increasing awareness among clinicians.<sup>3</sup>

The gender ratio in older patients is equal, despite the fact that in general PAH is still more common in women. Generally, males with more severe hemodynamic derangements respond less to modern medical care than women. Additionally, methamphetamine use is a unique risk factor for PAH, with estimates indicating that 50 million users globally are affected.<sup>3</sup>

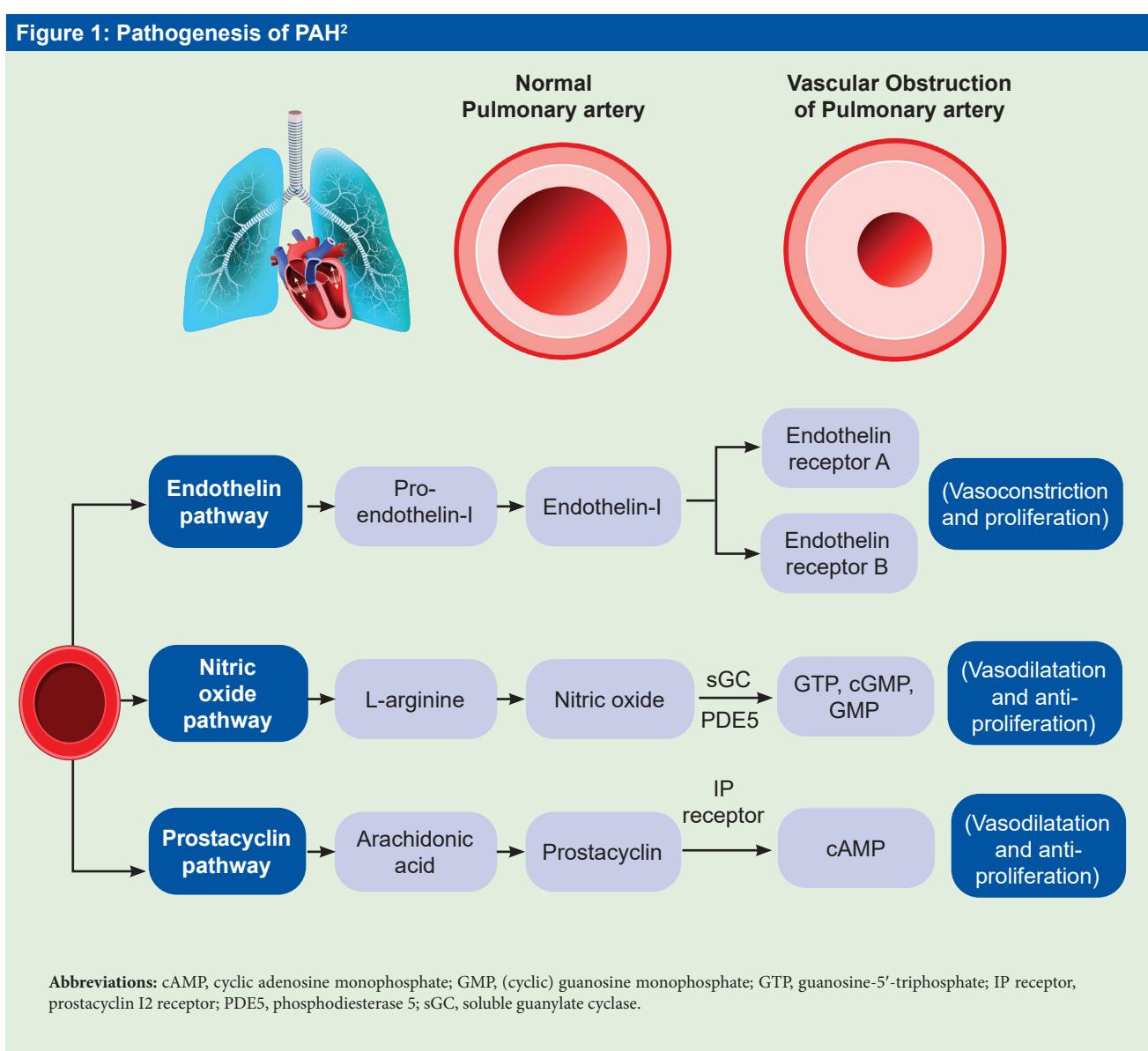
The incidence of PAH is about five cases per million people per year, with a frequency of about 25 cases per million people



**ABOUT 25 CASES PER MILLION PATIENTS OF PAH**

At the population level, the prevalence of PH is thought to range between 1% and 3%. However, with an estimated frequency of 15 to 30 per million, PAH is an uncommon disease. According to Asian registries, connective tissue disease-associated (CTD-PAH) and congenital heart disease-associated PAH (CHD-PHD) are more prevalent. Other PAH includes PAH related to schistosomiasis, HIV infection, and portal hypertension. The incidence and prevalence of PH are rising, most likely due to multifactorial reasons. The main factors responsible for the prevalence of PAH are likely increased awareness, accessibility to right heart catheter investigations, echocardiograms, and an ageing population. More case discovery owing to definition revisions ( $\text{mPAP} > 20 \text{ mmHg}$ ) and improved therapies that extend survival are less important aspects of prolonged survival.<sup>4</sup>

**Figure 1: Pathogenesis of PAH<sup>2</sup>**



## Pathophysiology of PAH

PAH can be idiopathic or related to a variety of diseases, but patients demonstrate comparable pathological changes, including increased pulmonary arteriole contractility, endothelial dysfunction, remodeling and proliferation of endothelial and smooth muscle cells, and *in situ* thrombi. The physiological result of these changes is the partial obstruction of tiny pulmonary arteries, which results in increased PVR, right ventricular failure, and mortality.<sup>1</sup>

The breakdown of three important signaling pathways, nitric oxide (NO), prostacyclin (PGI<sub>2</sub>), thromboxane A<sub>2</sub> (TXA<sub>2</sub>), and endothelin-1 (ET-1), is at the core of these progressive pulmonary vascular abnormalities. In general, PAH is caused by diminished PGI<sub>2</sub> synthesis (cyclooxygenase-2 dysregulation) and NO synthase (eNOS) activity, with concomitant vasoconstrictive and mitogenic consequences of an elevated ET-1 signaling pathway (Figure 1).<sup>1,2</sup>

## Biomarkers of PAH

A biomarker is defined as “an objectively measured and analyzed characteristic that serves as an indication of normal biological processes,

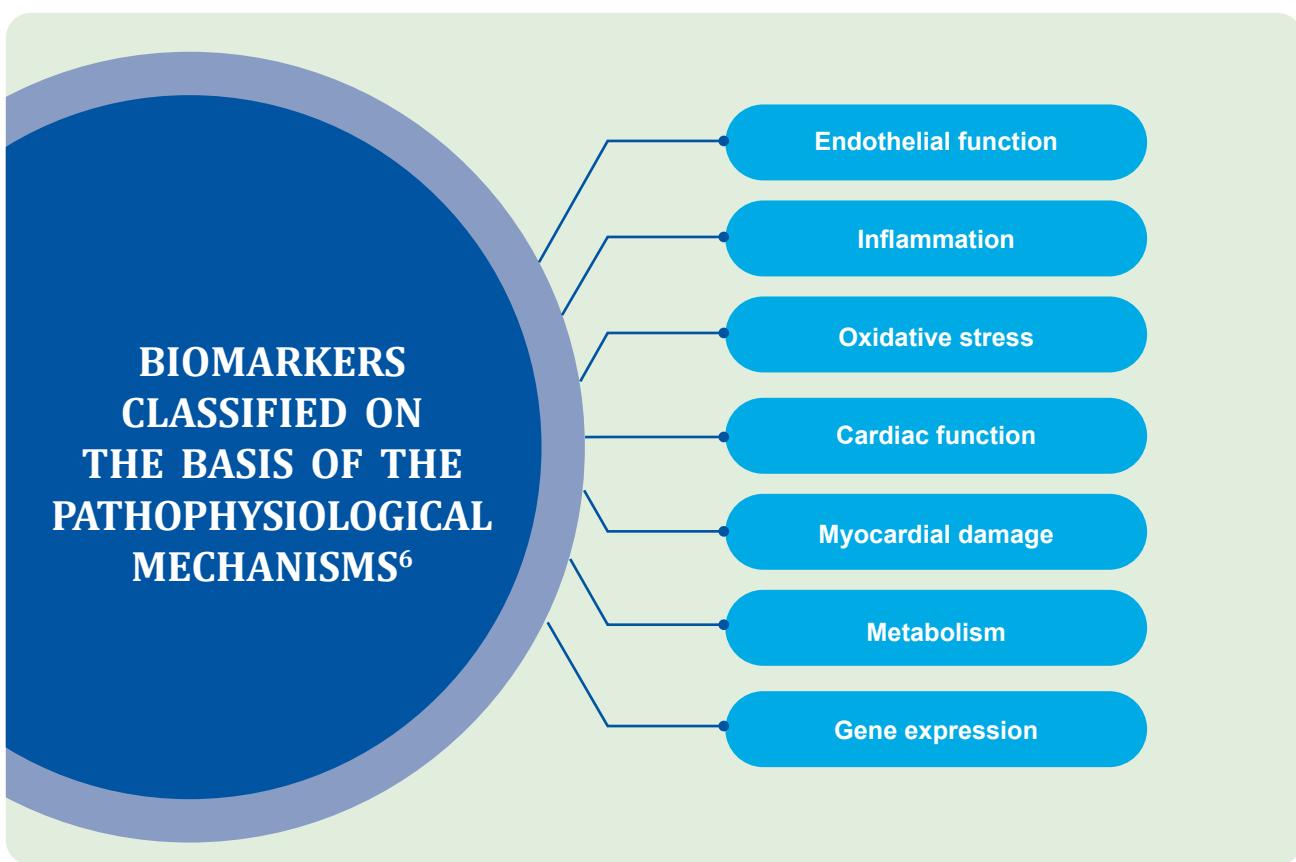


Figure 2: Various biomarkers of the PAH<sup>6</sup>



### CARDIAC FUNCTION/DAMAGE

- Natriuretic peptides
- Troponins
- Cystatin C



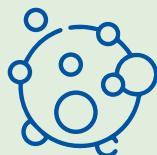
### ANGIOGENESIS

- Angiopoietins
- Endoglin
- Endostatin
- Bone morphogenic protein 9
- Vascular endothelial growth factor



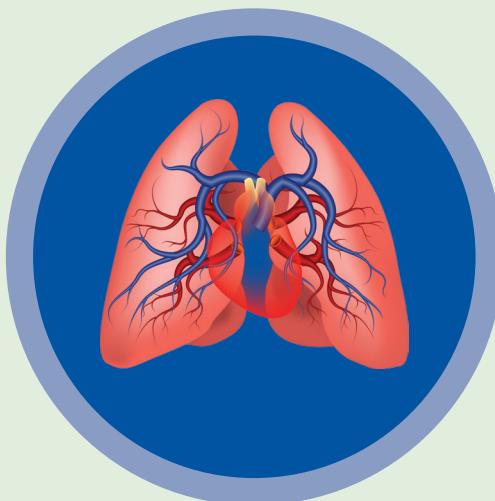
### TRANSCRIPTION REGULATORS/ONCOGENES

- PIM-1



### METABOLISM

- Tryptophan metabolites
- Ghrelin



### HEMATOPOIESIS

- Homocysteine
- Red cell distribution width



### ENDOTHELIAL DYSFUNCTION/VASCULAR REMODELLING AND DAMAGE

- Endothelin-1
- Adrenomedulin
- Copeptin
- Nitric oxide
- Asymmetric dimethylarginine
- D-dimers
- Cyclic guanosine monophosphate
- Serotonin
- Osteopontin
- von Willebrand factor
- Microparticles

### INFLAMMATION/OXIDATIVE STRESS

- C-reactive protein
- Growth differentiation factor-15
- Uric acid
- Galectin-3
- Interleukins
- Monocyte chemoattracting protein-1
- Isoprostanes
- Oxidized lipids
- CD40/CD49L

pathogenic processes, or pharmacological reactions to a therapeutic intervention” or “a biomarker is a molecular alteration in tissues and/or bodily fluids caused by a disease process”. A biomarker should ideally indicate clinical outcomes, which are how the patient feels and what stage of disease he or she is in; it should also act as a diagnostic and prognostic tool, as well as a therapeutic marker, providing information on the response of patient to a certain treatment.<sup>6</sup>

Although there is no known PAH biomarker that can be identified by a single, easy test, there are numerous well-known and well-defined biomarkers that may potentially prove to be powerful diagnostic and prognostic indicators in the future. These biomarkers are classified on the basis of the pathophysiological mechanisms with which they are connected, which reflects the complexity of the syndrome (Figure 2).<sup>6</sup>

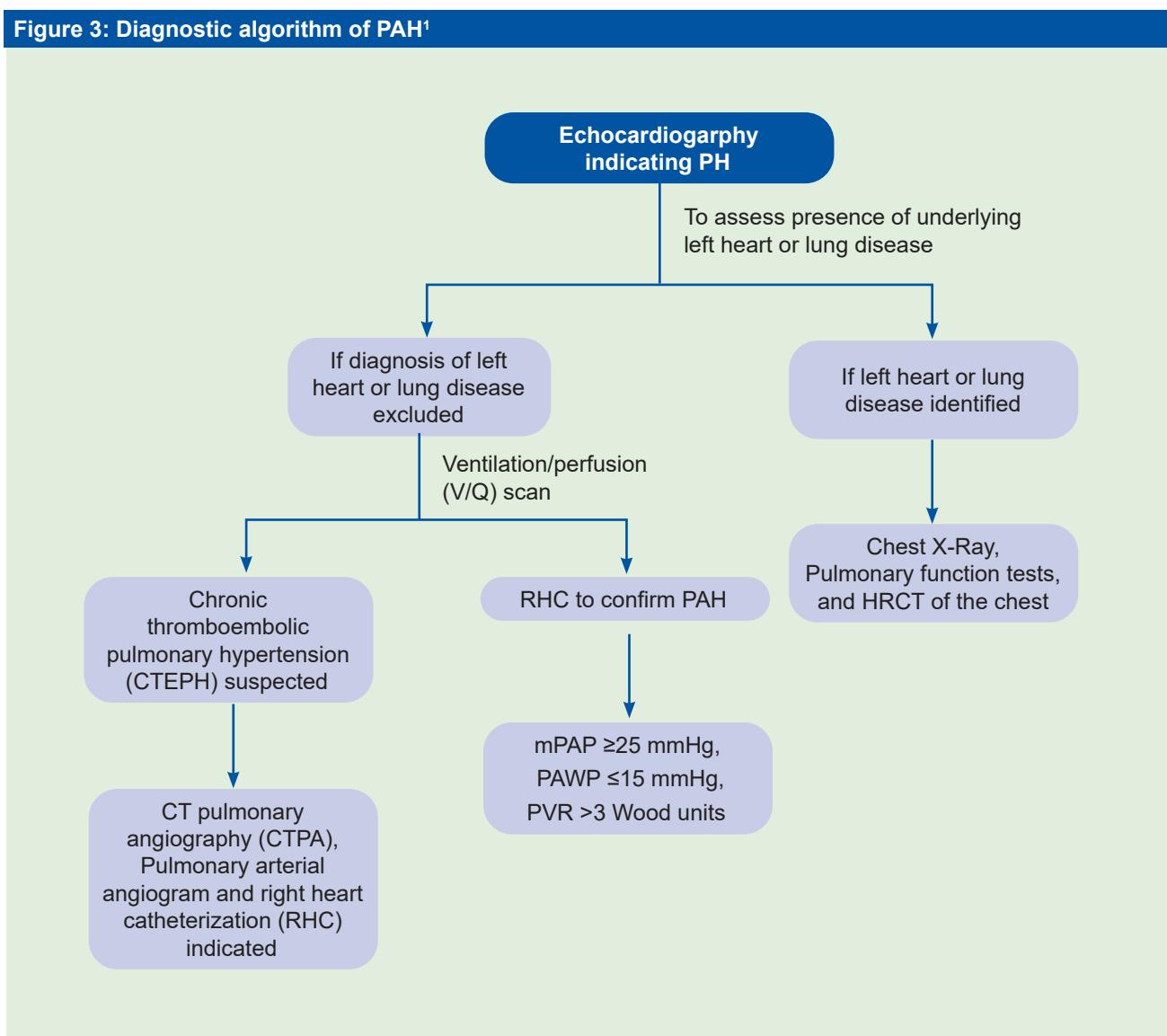
## Diagnosis and assessment of PAH

Further clinical examinations, such as a chest radiograph, pulmonary function tests, and high-resolution computed tomography (HRCT) of the chest, are requested when echocardiographic findings indicate a high or intermediate probability of PH in order to determine the presence of Group 2 or Group 3 PH (Figure 3). A ventilation/perfusion (V/Q) lung scan should be done to differentiate between CTEPH and PAH if the diagnosis of left heart or lung parenchymal disorders has been ruled out. In order to confirm the diagnosis and determine if pulmonary endarterectomy is feasible for patients with suspected Group 4 PH, right heart catheterization (RHC) should be combined with CT pulmonary angiography (CTPA) and a selective pulmonary arterial angiogram (PEA). Consideration should be given to group 1 (PAH) or uncommon instances of group 5 PH when the V/Q scan reveals normal or a mild perfusion deficit.<sup>1,7</sup>

“

Main factors responsible for the prevalence of PAH are likely increased awareness, accessibility to right heart catheter investigations, echocardiograms, and an ageing population

”

**Figure 3: Diagnostic algorithm of PAH<sup>1</sup>**

## Management of PAH

### General measures for the management of PAH

Patients with PAH require interdisciplinary care and a thorough treatment plan. In addition to using PAH medications, general precautions and attention in special circumstances are essential parts for optimized patient care. In this situation, it is important to control the systemic effects of PH and right-sided HF, which frequently increase the burden of the condition.<sup>2</sup>

## Risk assessment of PAH

- Risk stratification of PAH patients to determine prognosis and guide to treatment is achieved by combining several parameters to predict outcome (Table 1 and 2).
- Currently discovered medications focus on one of the three pathways ie prostacyclin, endothelin, or nitric oxide pathways which are implicated in the pathogenesis of PAH and contribute to endothelial dysfunction.
- The choice of the most effective first and successive treatment approaches has advanced.
- Multiple clinical parameters are integrated into risk stratification based on projected mortality, and therapeutic decisions are now made based on the severity of the disease at the time of diagnosis and assessment of response to treatment.<sup>2,5</sup>

**Table 1: Risk assessment of PAH (three-strata model) at time of diagnosis<sup>2</sup>**

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
<b>Clinical observations and modifiable variables</b>			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO-FC	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
CPET	<ul style="list-style-type: none"> <li>Peak VO<sub>2</sub> &gt;15 mL/min/kg (&gt;65% pred.)</li> <li>VE/VCO<sub>2</sub> slope &lt;36</li> </ul>	<ul style="list-style-type: none"> <li>Peak VO<sub>2</sub> 11–15 mL/min/kg (35–65% pred.)</li> <li>VE/VCO<sub>2</sub> slope 36–44</li> </ul>	<ul style="list-style-type: none"> <li>Peak VO<sub>2</sub> &lt;11 mL/min/kg (&lt;35% pred.)</li> <li>VE/VCO<sub>2</sub> slope &gt;44</li> </ul>
Biomarkers: BNP or NT-proBNP	<ul style="list-style-type: none"> <li>BNP &lt;50 ng/L</li> <li>NT-proBNP &lt;300 ng/L</li> </ul>	<ul style="list-style-type: none"> <li>BNP 50–800 ng/L</li> <li>NT-proBNP 300–1100 ng/L</li> </ul>	<ul style="list-style-type: none"> <li>BNP &gt;800 ng/L</li> <li>NT-proBNP &gt;1100 ng/L</li> </ul>
Echocardiography	<ul style="list-style-type: none"> <li>RA area &lt;18 cm<sup>2</sup></li> <li>TAPSE/sPAP &gt;0.32 mm/mmHg</li> <li>No pericardial effusion</li> </ul>	<ul style="list-style-type: none"> <li>RA area 18–26 cm<sup>2</sup></li> <li>TAPSE/sPAP 0.19–0.32 mm/mmHg</li> <li>Minimal pericardial effusion</li> </ul>	<ul style="list-style-type: none"> <li>RA area &gt;26 cm<sup>2</sup></li> <li>TAPSE/sPAP &lt;0.19 mm/mmHg</li> <li>Moderate or large pericardial effusion</li> </ul>
cMRI	<ul style="list-style-type: none"> <li>RVEF &gt;54%</li> <li>SVI &gt;40 mL/m<sup>2</sup></li> <li>RVESVI &lt;42 mL/m<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>RVEF 37–54%</li> <li>SVI 26–40 mL/m<sup>2</sup></li> <li>RVESVI 42–54 mL/m<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>RVEF &lt;37%</li> <li>SVI &lt;26 mL/m<sup>2</sup></li> <li>RVESVI &gt;54 mL/m<sup>2</sup></li> </ul>
Hemodynamics	<ul style="list-style-type: none"> <li>RAP &lt;8 mmHg</li> <li>CI ≥2.5 L/min/m<sup>2</sup></li> <li>SVI &gt;38 mL/m<sup>2</sup></li> <li>SvO<sub>2</sub> &gt;65%</li> </ul>	<ul style="list-style-type: none"> <li>RAP 8–14 mmHg</li> <li>CI 2.0–2.4 L/min/m<sup>2</sup></li> <li>SVI 31–38 mL/m<sup>2</sup></li> <li>SvO<sub>2</sub> 60–65%</li> </ul>	<ul style="list-style-type: none"> <li>RAP &gt;14 mmHg</li> <li>CI &lt;2.0 L/min/m<sup>2</sup></li> <li>SVI &lt;31 mL/m<sup>2</sup></li> <li>SvO<sub>2</sub> &lt;60%</li> </ul>

**Abbreviations:** 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO<sub>2</sub>, 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<sub>2</sub>, ventilatory equivalents for carbon dioxide; VO<sub>2</sub>, oxygen uptake; WHO-FC, World Health Organization functional class.

**Table 2: Risk stratification of PAH on follow up (4 strata model)<sup>2</sup>**

Determinants of prognosis	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP	<50	50–199	200–800	>800
NT-proBNP, ng/L	<300	300–649	650–1100	>1100

**Abbreviations:** 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.

## General measures

- Under medical therapy, the following recommendations are made:
  - » **Supervised exercise training**
  - » **Psychosocial support**
  - » **Immunization** against SARS-CoV-2, influenza, and *Streptococcus pneumoniae*
  - » **Diuretic medication** with indicators of right ventricular failure and fluid retention
  - » **Correction of iron status** in the presence of iron-deficiency anemia
  - » When arterial blood oxygen pressure of a patient is below 8 kPa (60 mmHg), **long-term oxygen therapy** is recommended.
- **Anticoagulation may be considered** on case-by-case basis
- Unless necessary due to comorbidities, using ACE inhibitors, ARBs, ARNIs, SGLT-2 inhibitors, beta-blockers, or ivabradine is not recommended.<sup>2</sup>





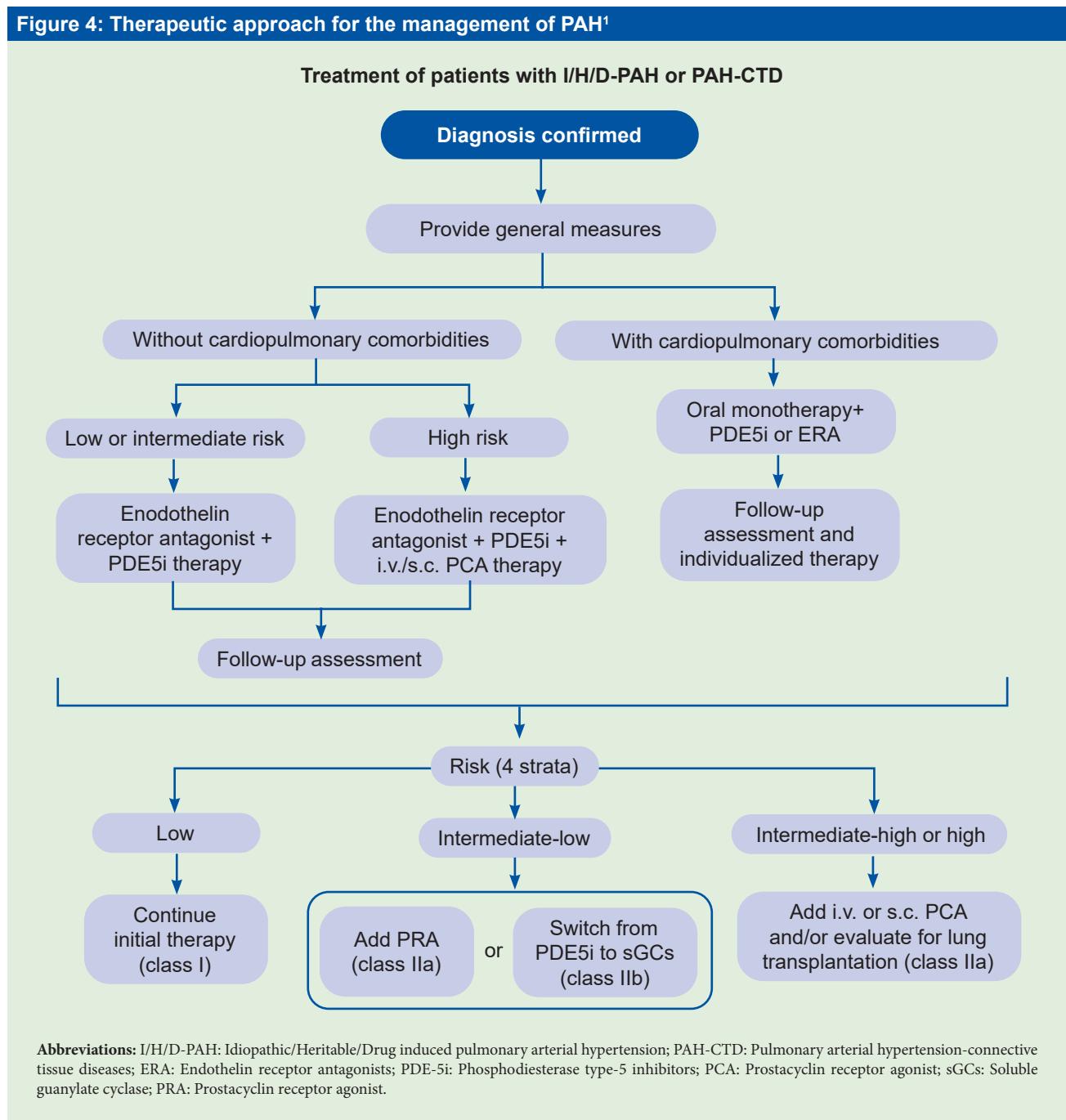
## Supportive treatment

- The following supportive therapies are recommended:
  - » For patients who **require oxygen** or whose arterial blood oxygen pressure is **<8 kPa (60 mmHg)** at sea level
  - » **Women of childbearing potential** with PAH receive **clear contraceptive advice**, taking into account the individual needs of the woman but recognising that the implications of contraceptive failure are significant in PAH
  - » **Women with PAH who consider becoming pregnant** or who become pregnant receive **prompt counselling in an experienced PH centre**, to facilitate genetic counselling and shared decision-making, and to provide psychological support
  - » **Women with PAH who have abortions performed in PH centres**, with psychological support provided to the patients and their families.
- For interventions **requiring anaesthesia, multidisciplinary consultation at a PH centre** to assess risk and benefit should be taken into consideration
- **Adoption and surrogacy with preconception genetic counselling may be considered** for women with PAH who want to have children
- Since **endothelin receptor antagonists and riociguat** have been shown to be teratogenic in pre-clinical studies, these drugs are **not recommended during pregnancy.<sup>2</sup>**

## Pharmacological treatment

Pulmonary arterial hypertension treatment approach recommended by the ESC/ERS guidelines is depicted in Figure 4. Discovery of targeted treatments have changed the outlook of PAH managed and have significantly improved the overall survival. Therapies available for the management of PAH are phosphodiesterase type 5 inhibitors, guanylate

**Figure 4: Therapeutic approach for the management of PAH<sup>1</sup>**



**Table 3: Commonly used medications for the pharmacological treatment of adults patients with pulmonary arterial hypertension<sup>2</sup>**

Medications	Target dose
<b>Calcium channel blockers (oral administration)</b>	
Amlodipine	15–30 mg o.d.
Diltiazem	120–360 mg b.i.d.
Felodipine	15–30 mg o.d.
Nifedipine	20–60 mg b.i.d. or t.i.d.
<b>Endothelin receptor antagonists (oral administration)</b>	
Ambrisentan	10 mg o.d.
Bosentan	125 mg b.i.d.
Macitentan	10 mg o.d.
<b>Phosphodiesterase 5 inhibitors (oral administration)</b>	
Sildenafil	20 mg t.i.d.
Tadalafil	40 mg o.d.
<b>Prostacyclin receptor agonist (oral administration)</b>	
Selexipag	Maximum tolerated dose up to 1600 µg b.i.d.
<b>Prostacyclin analogues (inhaled administration)</b>	
Iloprost	5.0 µg 6–9 times per day
Treprostinil	54–72 µg 4 times per day
<b>Prostacyclin analogues (i.v. or s.c. administration)</b>	
Epoprostenol i.v	16–30 ng/kg/min
Treprostinil s.c. or i.v.	25–60 ng/kg/min

**Abbreviations:** b.i.d., twice daily; i.v., intravenous; o.d., once daily; s.c., subcutaneous; t.i.d., three times daily.

In addition to using PAH medications, general precautions and attention in special circumstances are essential parts for optimized patient care

**Figure 5: Milestones for drug development in PAH<sup>8,9</sup>**

## Approval of targeted PAH drugs

- Epoprostenol (1995)
- Treprostinil (2001)
- Bosentan (2002)
- Iloprost (2003)
- Sildenafil (2005)
- Ambrisentan (2008)
- Tadalafil (2010)
- Macitentan (2013)
- Riociguat (2014)
- Selexipag (2016)

**Treatment has improved from past to present in terms of:**

- Treatment strategies (e.g, combination therapies)
- Novel targets/disease modifying therapies
- Interventional therapies (e.g, pulmonary artery denervation)
- General/supportive therapies

## New potential targets

- Epigenetic alterations
- Growth factors
- Vasoactive factors
- Inflammatory mediators
- Oxidative stress modulator
- Stem cell therapy



cyclase stimulators, prostacyclin analogues, prostacyclin receptor agonists, and dual or selective endothelin receptor antagonists (Table 3). Since more than ten years ago, drugs that target all three pathways of pathophysiology have been used to treat PAH; however, recent progress has been made in the development of methods for combining these drugs and scaling up the dosage in response to the reactions of patients (Figure 5).<sup>1,7-9</sup>

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# Opsutan



## Macitentan 10 mg





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