# Pulmonary Arterial Hypertension in 2019: From death sentence to chronic disease

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Dr. Shah completed his fellowship training in pulmonary and critical care medicine at Rush University in Chicago, Illinois. He joined UT Southwestern's Pulmonary & Critical Care Medicine Division in 2016 and currently serves as Assistant Professor Of Internal Medicine. He attends on inpatient pulmonary hypertension service and Medical Intensive Care Unit at Clements University Hospital. Dr. Shah also is an integral part of the pulmonary hypertension program. He is actively involved in multiple multicenter clinical research trials in the field of pulmonary hypertension.

**Purpose and Overview:**

Pulmonary Arterial Hypertension (PAH) has been historically a disease associated with guarded prognosis and limited treatment options. Over the last two decades, multiple therapies for PAH have been approved and treatment landscape has evolved. The purpose of this session is to discuss improvement in long term prognosis of PAH with early diagnosis and treatment.

**Educational Objectives:**

At the end of this lecture, participants will be able to:

A. Define and Classify Pulmonary Hypertension
B. Describe the pathophysiology of Pulmonary Arterial Hypertension
C. Identify patients at risk for PAH and initiate diagnostic work-up for PAH.
D. Discuss commonly available treatment options for PAH
E. Review the prognosis of PAH patients in the era of modern therapy.

**Pulmonary Hypertension Definition**:

Since the first WHO World Symposium On Pulmonary Hypertension (WSPH) in 1973, Pulmonary Hypertension has been defined as mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg.[1] While this definition was used for several decades, it has been empiric and has not been based on a scientific approach. In 2009, Kovacs et. al. performed a systematic review on right heart catheterization (RHC) data on 1187 individuals and showed that in normal healthy population mean mPAP was 14 ± 3.3 mm Hg suggested that in healthy subjects mPAP rarely exceeds 20 mm Hg (97.5$^{th}$ percentile).[2] Based on the above evidence in 2018, during the 6$^{th}$ world symposium, the hemodynamic definition of PH was changed to mPAP > 20 mm Hg. Thus per 6$^{th}$ World Symposium on pulmonary hypertension, pulmonary hypertension is defined as mPAP > 20 mm Hg and its subgroup Pulmonary arterial hypertension (PAH) is defined as mPAP > 20 mm Hg, PCWP < 15 mm Hg and PVR > 3 Woods Units.

TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

| Definitions | Characteristics | Clinical groups[#] |
|---|---|---|
| **Pre-capillary PH** | mPAP >20 mmHg<br>PAWP ⩽15 mmHg<br>PVR ⩾3 WU | 1, 3, 4 and 5 |
| **Isolated post-capillary PH (IpcPH)** | mPAP >20 mmHg<br>PAWP >15 mmHg<br>PVR <3 WU | 2 and 5 |
| **Combined pre- and post-capillary PH (CpcPH)** | mPAP >20 mmHg<br>PAWP >15 mmHg<br>PVR ⩾3 WU | 2 and 5 |

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. [#]: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.

Table 1 : Haemodynamic definitions of pulmonary hypertension, 6$^{th}$ world symposium on pulmonary hypertension, Nice, France.

**Classification of Pulmonary Hypertension**:

The purpose of clinical classification is to categorize conditions associated with PH based on similar pathophysiological mechanisms, clinical presentations, hemodynamic characteristics and therapeutic management. Pulmonary hypertension is divided into 5 main subgroups.

1. **Pulmonary Arterial Hypertension (PAH):**
   Characterized by pulmonary arterial involvement with normal pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg and Pulmonary vascular resistance > 3.

2. **Pulmonary hypertension due to left heart disease:**
   Characterized by pulmonary venous hypertension with a pulmonary capillary wedge pressure (PCWP) > 15 mm Hg.

3. **Pulmonary hypertension due to lung disease and/or hypoxia:**
   Characterized by normal pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg and concomitant lung disease and/or hypoxia.

4. **Pulmonary hypertension due to pulmonary artery obstructions:**
   Characterized by normal pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg and an entity causing pulmonary artery obstruction. E.g. chronic thromboemboli.

5. **Pulmonary hypertension with unclear and/or multifactorial mechanisms:**
   Characterized by conditions causing pulmonary hypertension through multifactorial mechanisms that do not fit one particular group or have unclear underlying pathophysiological mechanisms.

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

**1 PAH**
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH 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 long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

**2 PH due to left heart disease**
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

**3 PH due to lung diseases and/or hypoxia**
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

**4 PH due to pulmonary artery obstructions (table 6)**
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

**5 PH with unclear and/or multifactorial mechanisms (table 7)**
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

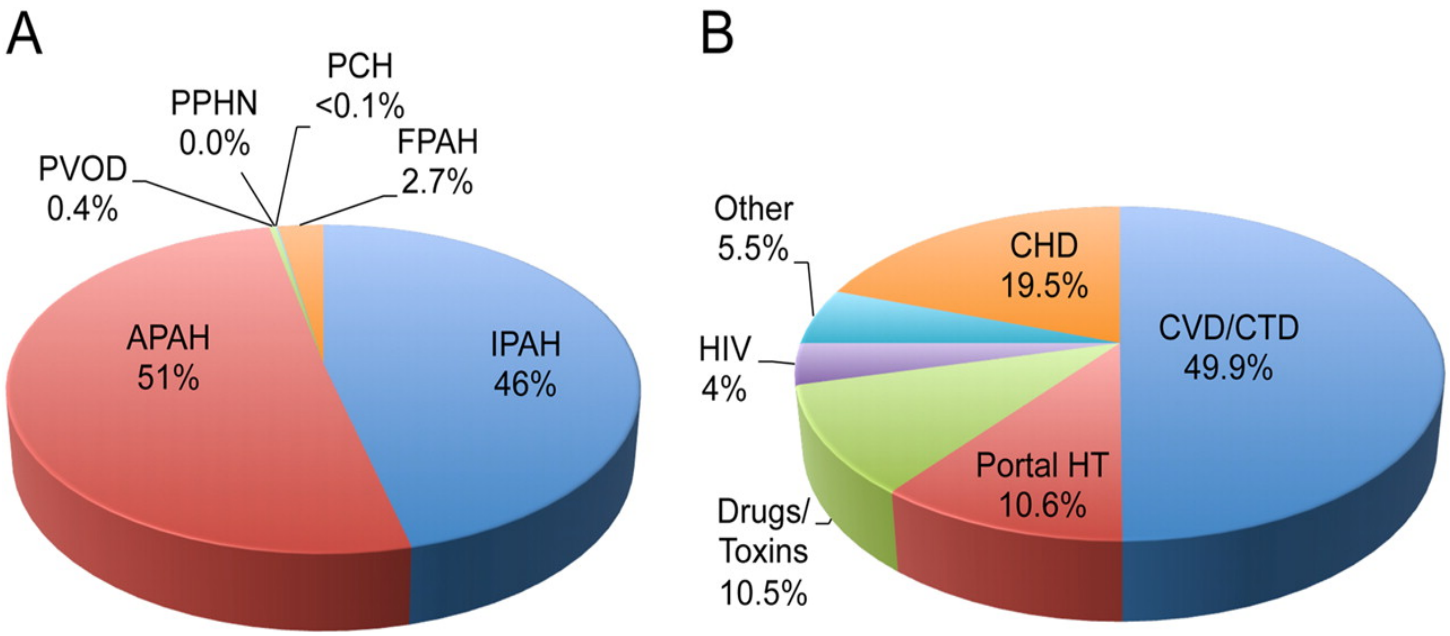
Table 2 : Updated classification of Pulmonary Hypertension, 6th world symposium on Pulmonary Hypertension, Nice, France.

## Epidemiology and causes of PAH:

Pulmonary hypertension, in general, is prevalent across all races, gender, and ages. The actual incidence and prevalence of pulmonary hypertension is unknown. Pulmonary arterial hypertension (PAH) is a rare disease in the general population with

an estimated 5 to 15 cases per million adults.[3] PAH has a female predominance which is variable across registries (65-80% of patients) and this decreases in the elderly.[3] Worldwide schistosomiasis appears to be the most common cause of pulmonary arterial hypertension and true estimates of the burden of PAH from schistosomiasis is unknown. Data from countries where schistosomiasis is not endemic shows that about 50 % of all patients with PAH are idiopathic and up to 10 % of which is attributable to Heritable PAH (HPAH).[3] The other 50 % is comprised of PAH attributable to associated causes like connective tissues diseases, congenital heart diseases, portopulmonary hypertension, Human immunodeficiency virus (HIV), Drugs/toxins, etc.[4] Connective tissue diseases are the most common cause of associated PAH with scleroderma being the most common.[4]

**Figure 1: World Health Organization (WHO) Group 1 PAH Classification of REVEAL (US Registry) Patients at Enrolment**




APAH, associated PAH; IPAH, idiopathic PAH; FPAH, familial PAH; PCH, pulmonary capillary hemangiomatosis; PPHN, persistent pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; CVD/CTD, collagen vascular disease/connective tissue disease; CHD, congenital heart disease; HT, hypertension.

Adapted from: Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, et al. (2010) Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 137:376–387.

**Pathophysiology of PAH:**

Despite multiple conditions associated with the development of PAH, the pathophysiology of PAH is similar. PAH is characterized by three pathological characteristics viz. in situ thrombosis, smooth muscle hypertrophy and intimal and adventitial proliferation.[5] Plexiform lesion which is frequently seen in PAH appears to be a dysfunctional response to vascular injury in these patients.[5]

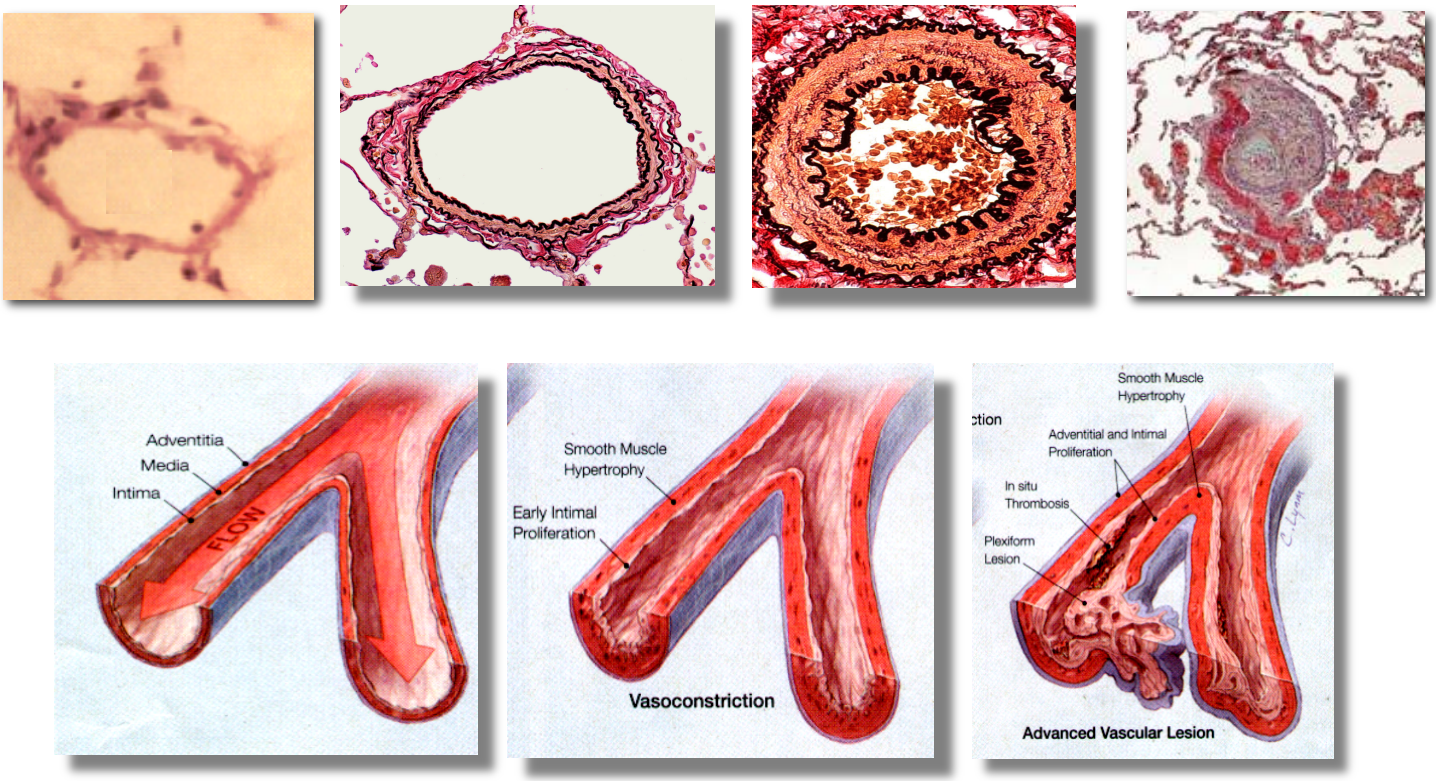



Figure 2: Progressive vasoconstriction, smooth muscle hypertrophy and proliferation of intima and adventitia in PAH.

Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.

Initially, in PAH the pulmonary vasculature is dynamically obstructed by vasoconstriction, in situ thrombosis, abnormal vascular remodeling, and proliferation. This leads to a progressive increase in right ventricular afterload which leads to right ventricular hypertrophy. This hypertrophy is initially adaptive and maintains normal

hemodynamics, but as further pulmonary vasculature is involved there is progressive right ventricular pressure and volume overload. This progressive increase in pulmonary vascular resistance leads to maladaptive right ventricular hypertrophy, rise in right atrial pressure and ultimately right heart failure and death.

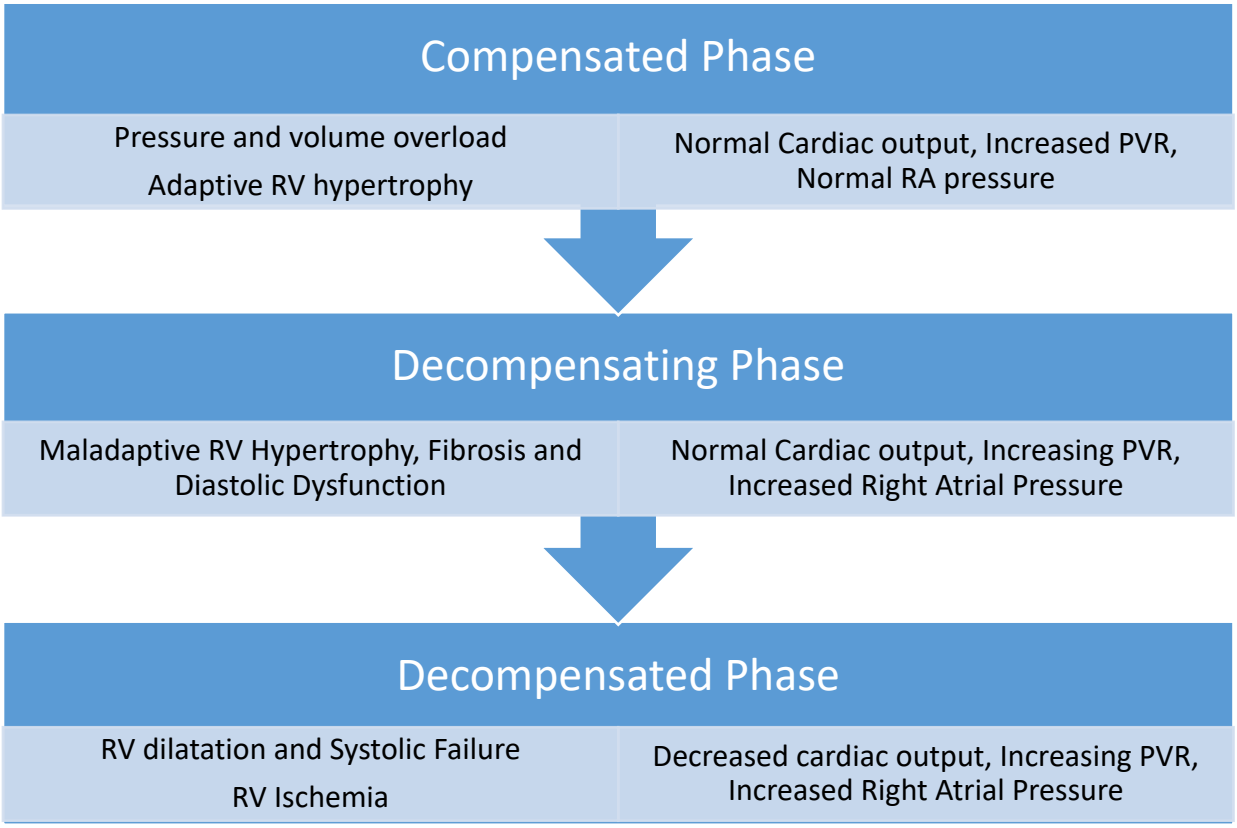



Figure 3: Physiology of PAH: Progressive occlusion and vasoconstriction of pulmonary vascular bed leads to progressive right ventricular hypertrophy and eventual right heart failure and death

**Clinical Features of PAH**:

Initial signs and symptoms of PAH are non-specific and mimic other cardiopulmonary diseases leading to a delay in diagnosis. Common symptoms are dyspnea on exertion, fatigue, pedal edema, chest pain, presyncope, syncope, dizziness, cough, palpitations and Raynaud's phenomenon.[6] Initially, the right ventricle is unable to increase cardiac output to demands of exertion and hence symptoms on exertion are common in earlier phases. As the disease progresses, overt signs of right heart failure like abdominal

distention, pedal edema, syncope and chest pain/dyspnea at rest occurs. The physical signs are characterized by signs of increased pulmonary vascular pressure and right heart failure. Signs of increased pulmonary vascular pressure include accentuated component of second heart sound, a holosystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation. Whereas signs of right heart failure include left parasternal lift (RV heave), elevated jugular venous pressure, hepatomegaly, ascites, peripheral edema and cool extremities.

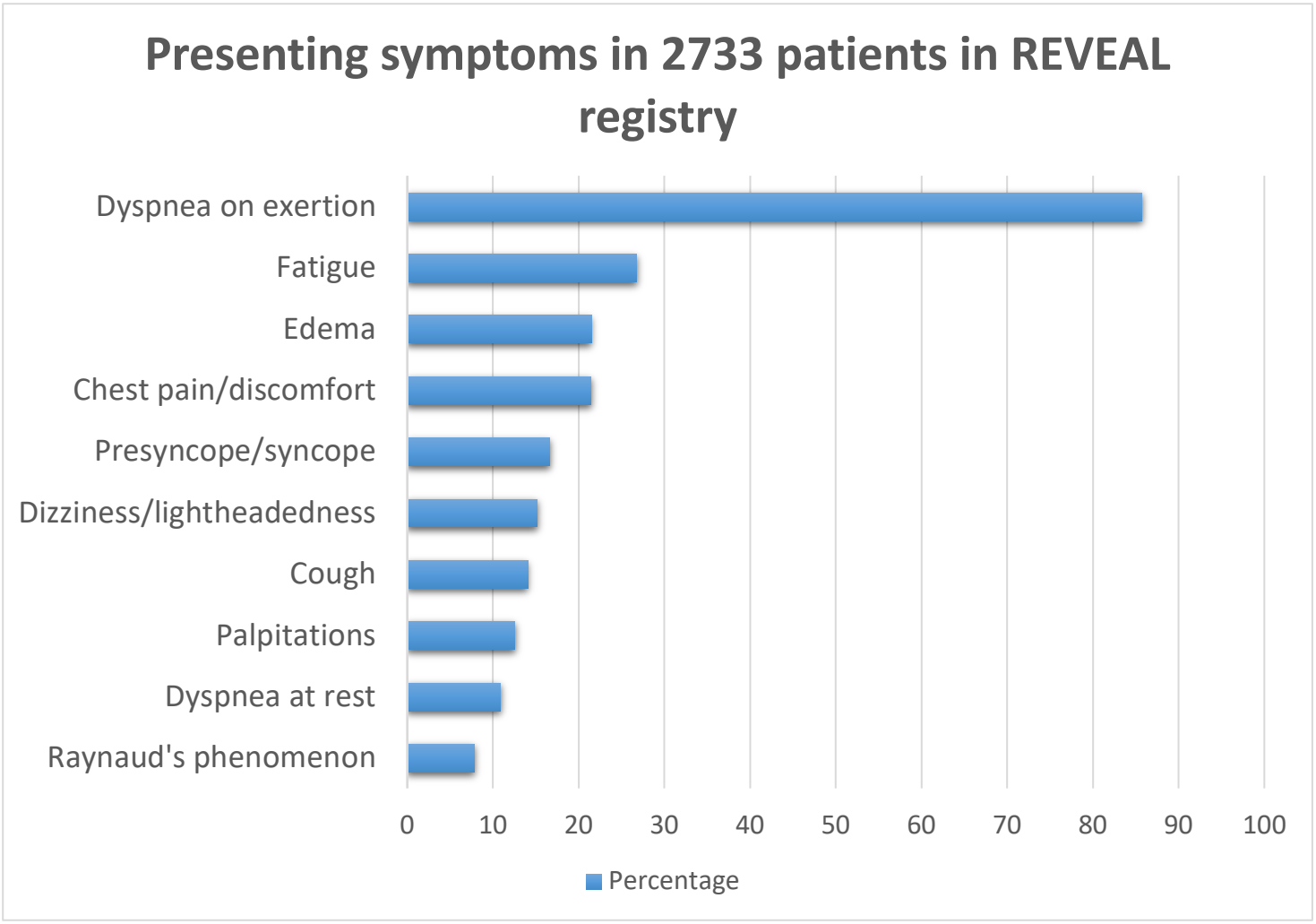



Figure 4: Presenting symptoms in PAH patients in REVEAL registry.

Adapted from Brown LM et. al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry, Chest. 2011;140:19-26.

**Diagnostic approach to PAH:**

As signs and symptoms of PAH are nonspecific, diagnostic approach is focused on ruling out more common group 2 (due to left heart disease) and group 3 PH (due to lung disease and/or hypoxia). Diagnosis of PAH needs high suspicion based on clinical features. An echocardiogram is the preferred screening test and provides an indirect assessment of pulmonary artery pressures as well as right ventricular size and function. More importantly, echocardiogram allows for assessment of more commonly encountered left heart disease. In fact, of all patients with suspected pulmonary hypertension presenting to outpatient cardiology clinic, 67.9 % were found to have PH secondary to left heart disease and 9.3% were found to have PH secondary to lung disease and/or hypoxia.[7]

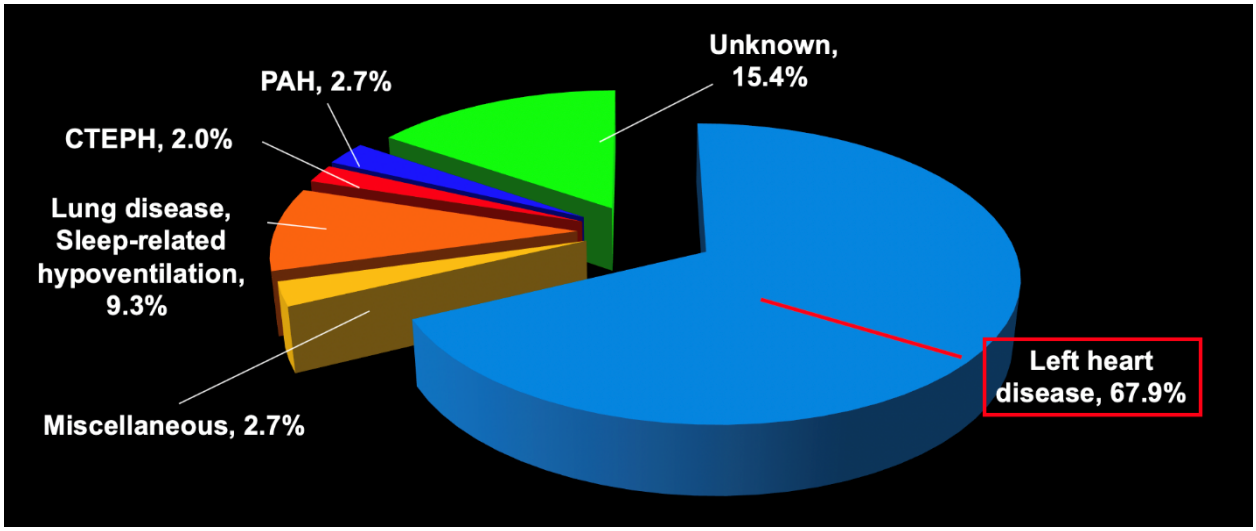



Figure 5: 67.9 % of patients with estimated pulmonary artery systolic pressure > 40 mm Hg on echocardiogram were found to have Group 2 PH.

Adapted from Strange G, et al. *Heart*. 2012;98:1805-11

In a patient with high suspicion of pulmonary hypertension, echocardiography allows for increasing pretest probability of pulmonary hypertension based on the estimated pulmonary arterial pressures and other markers of pulmonary hypertension as described in Table 3 and 4.[8]

| Estimated Right ventricular Systolic Pressure (RVSP) | Presence of other echo 'PH Signs' | Echocardiographic Probability of PH |
|---|---|---|
| ≤ 31 + RA pressure or not measurable | No | Low |
| ≤ 31 + RA pressure or not measurable | Yes | Intermediate |
| 31 to 46 + RA pressure | No | |
| 31 to 46 + RA pressure | Yes | High |
| > 46 + RA pressure | Not required | |

Table 3: Echocardiographic probability of PH.

Adapted from Galiè N, et al. *Eur Respir J*. 2016;37:67-119.

| A: The ventricles[a] | B: Pulmonary artery[a] | C: Inferior vena cava and right atrium[a] |
|---|---|---|
| Right ventricle/ left ventricle basal diameter ratio >1.0 | Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching | Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration) |
| Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole) | Early diastolic pulmonary regurgitation velocity >2.2 m/sec | Right atrial area (end-systole) >18 $cm^2$ |
| | PA diameter >25 mm. | |

PA = pulmonary artery.
[a]Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

Table 4: Echocardiographic Signs Used to Assess the Probability of PH (in Addition to Tricuspid Regurgitation Velocity).

Galiè N, et al. *Eur Respir J*. 2016;37:67-119.

To evaluate for lung disease and/or hypoxia, pulmonary function tests and overnight oximetry should be obtained and if these are suspicious for either cause then further tests should be obtained as suggested in figure 6.[9] All patients with suspected PAH in whom group 2 and group 3 PH are ruled out should undergo VQ scan to rule out chronic thromboembolic pulmonary hypertension, as this form of PH is commonly missed and is surgically treatable.[8, 9] A right heart catheterization (RHC) is mandatory for the diagnosis of PAH and should be obtained next to confirm the diagnosis and rule out left heart disease. [8, 9] In addition to confirmation of the diagnosis of PAH, right heart catheterization also helps determine severity and prognosis in patients with PAH. [8, 9]

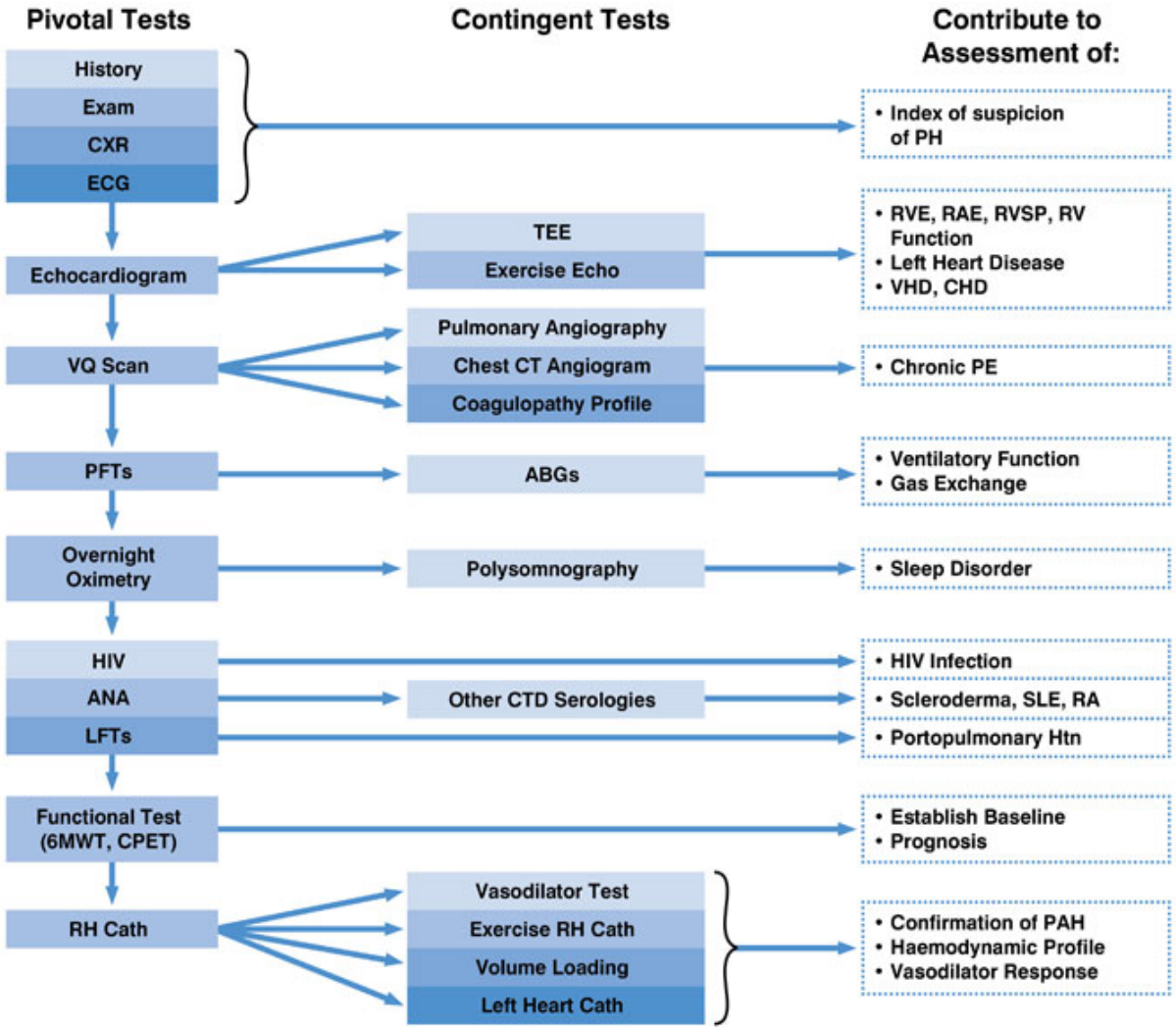



Figure 6: Suggested key tests for diagnostic work up of PAH

*Adapted from McLaughlin VV, Archer SL, Badesch DB, et al. Circulation 119:2250–94*

## Treatment options in PAH:

### Vasodilator testing and calcium channel blockers:

A small subset of patients with idiopathic PAH (IPAH), heritable PAH (HPAH) and drug/toxin induced PAH have a significant hemodynamic response to vasodilators like Inhaled nitric oxide (NO) at 10–20 parts per million (ppm) i.v. epoprostenol, i.v. adenosine or inhaled iloprost. A positive acute response is defined as a reduction of the mean pulmonary artery pressure ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged CO.[10] Only about 10% of patients with IPAH will meet these criteria. These patients can be treated with calcium channel blocker monotherapy but need to be followed closely and tested frequently to ensure that they continue to be long term responders. About 50 % of initial vasodilator responders fail to respond long term to calcium channel blocker therapy and need to be initiated on additional therapy.[11]

### Key pathways of PAH pathogenesis and approved targeted drug therapies:

Fourteen PAH therapies are currently available for PAH. These therapies target voltage-gated, L type calcium channels, nitric oxide/cyclic guanosine monophosphate (cGMP), endothelin and prostacyclin/cAMP pathways (Figure 7). Up until 1990s therapy of PAH was mainly supportive with diuretics, digoxin, and oxygen. The PPH study group in 1996, showed a significant improvement in survival with 12-week use of IV epoprostenol as compared to placebo.[12] Thereafter in the late 1990s to 2000's multiple drugs targeting the nitric oxide pathway, endothelin pathway and prostacyclin pathway were approved. These drugs were mainly approved based on 12-16-week placebo-controlled trials demonstrating improvements in six-minute walk distance, hemodynamic measures on right heart catheterization, WHO functional class and biomarkers like Nt-probnp.

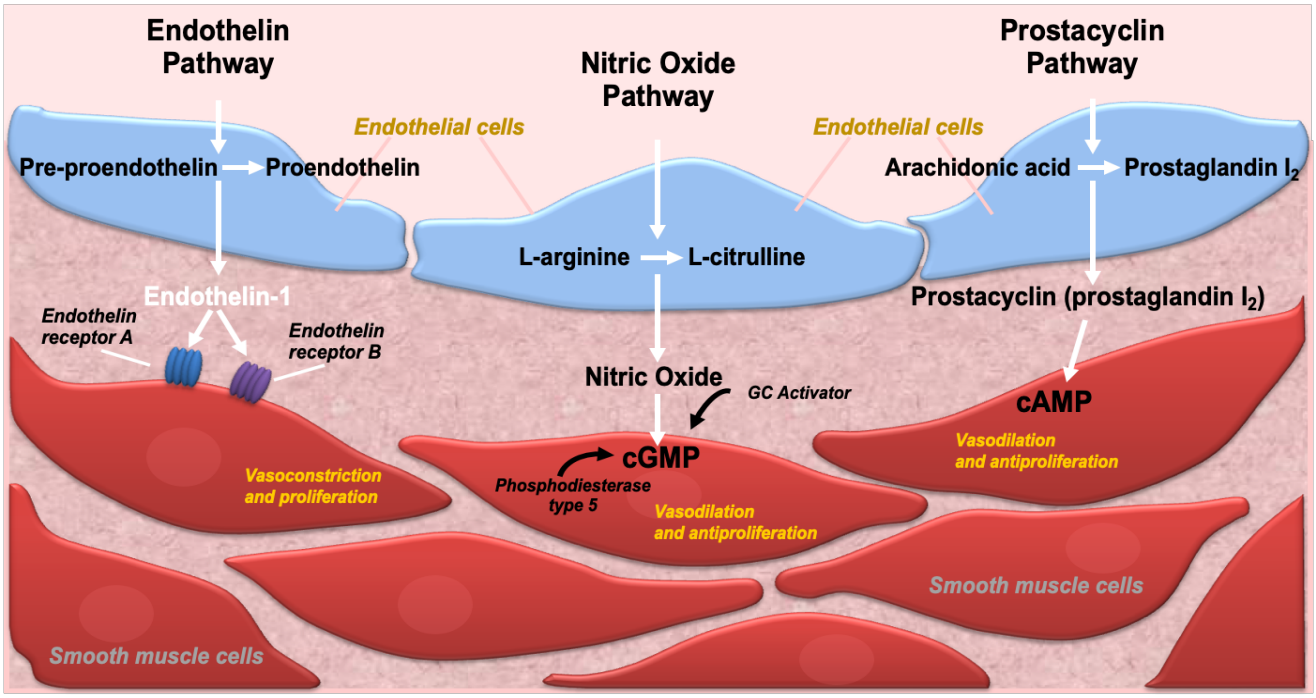



Figure 7: Key Pathways in PAH pathogenesis which are targeted for currently approved therapies. Humbert M et al. *N Engl J Med*. 2004;351:1425-1436

**Combination therapies in PAH:**

As more therapeutic options became available targeting different pathways, a combination of drugs targeting different pathways was explored. Multiple studies explored the sequential addition of combination therapy and showed the benefit of this approach.[13] In 2015, the AMBITION study was the first randomized control trial which studied upfront use of a combination of endothelin receptor agonist (ERA) Ambrisentan and phosphodiesterase 5 inhibitor (PDE 5i) tadalafil.[14] This study found that upfront combination of these two drugs was superior to either of single drug alone.[14] In addition, this study explored more clinically meaningful outcomes such as composite endpoint of worsening of PAH, hospitalization and death as the primary outcome and was a 69-79 week trial. [15, 16] Similarly other more recent large randomized control trials allowed for combination therapies to be used and assessed for more meaningful clinical endpoints and much longer follow up (69-104 weeks). [14-16] Currently ongoing randomized control trial (NCT02558231) will explore the use of triple upfront oral combination therapy (ERA + PDE 5i + IP receptor agonist) as compared to dual upfront oral combination therapy (ERA + PDE 5i).

| Nitric Oxide Pathway | Endothelin Pathway | Prostacyclin Pathway |
|---|---|---|
| • Phophosdiesterase 5 inhibitors<br>  • Sildenafil<br>  • Tadalafil | • Endothelin Receptor Antagonists<br>  • Nonselective : Bosentan<br>  • ETA Selective Antagonists<br>  • Ambrisentan<br>  • Macitentan | • Oral<br>  • IP receptor agonist : Selexipag<br>  • Prostacyclin<br>  • Treprostinil<br>  • Beraprost<br>• Inhaled<br>  • Treprostinil<br>  • Iloprost<br>  • epoprostenol<br>• Subcutaneous<br>  • Treprostinil<br>• Intravenous<br>  • Epoprostenol<br>  • Treprostinil |
| • Soluble Guanyl Cyclase Stimulators<br>  • Riociguat | | |

Table 5: Approved therapies for Pulmonary Arterial Hypertension

**Prognostic factors, risk assessment, and treatment approach in PAH:**

Several factors play an important role in the determination of prognosis in PAH patients. Several risk assessment tools are available to predict prognosis of PAH patients including the REVEAL 2.0 risk calculator and ERS/ESC risk assessment strategy.[8, 17] All risk assessment scores include a combination of clinical signs, symptoms, WHO functional class, six-minute walk distance, cardiopulmonary exercise testing, echocardiography, biomarkers, and hemodynamics. Table 6 demonstrates the most popular risk assessment tool based on the most recent guidelines from ERS/ESC in 2015.[8] Based on this risk assessment treatment can be tailored to patients with high risk vs low risk as suggested in figure 8.

| Determinants of prognosis[a] (estimated 1-year mortality) | Low risk <5% | Intermediate risk 5–10% | High risk >10% |
|---|---|---|---|
| Clinical signs of right heart failure | Absent | Absent | Present |
| Progression of symptoms | No | Slow | Rapid |
| Syncope | No | Occasional syncope[b] | Repeated syncope[c] |
| WHO functional class | I, II | III | IV |
| 6MWD | >440 m | 165–440 m | <165 m |
| Cardiopulmonary exercise testing | Peak $VO_2$ >15 ml/min/kg (>65% pred.) $VE/VCO_2$ slope <36 | Peak $VO_2$ 11–15 ml/min/kg (35–65% pred.) $VE/VCO_2$ slope 36–44.9 | Peak $VO_2$ <11 ml/min/kg (<35% pred.) $VE/VCO_2$ slope ≥45 |
| NT-proBNP plasma levels | BNP <50 ng/l NT-proBNP <300 ng/l | BNP 50–300 ng/l NT-proBNP 300–1400 ng/l | BNP >300 ng/l NT-proBNP >1400 ng/l |
| Imaging (echocardiography, CMR imaging) | RA area <18 $cm^2$ No pericardial effusion | RA area 18–26 $cm^2$ No or minimal, pericardial effusion | RA area >26 $cm^2$ Pericardial effusion |
| Haemodynamics | RAP <8 mmHg CI ≥2.5 l/min/$m^2$ $SvO_2$ >65% | RAP 8–14 mmHg CI 2.0–2.4 l/min/$m^2$ $SvO_2$ 60–65% | RAP >14 mmHg CI <2.0 l/min/$m^2$ $SvO_2$ <60% |

Table 6: ERS/ESC Risk based assessment strategy in PAH

Galiè N, et al. *Eur Respir J*. 2016;37:67-119

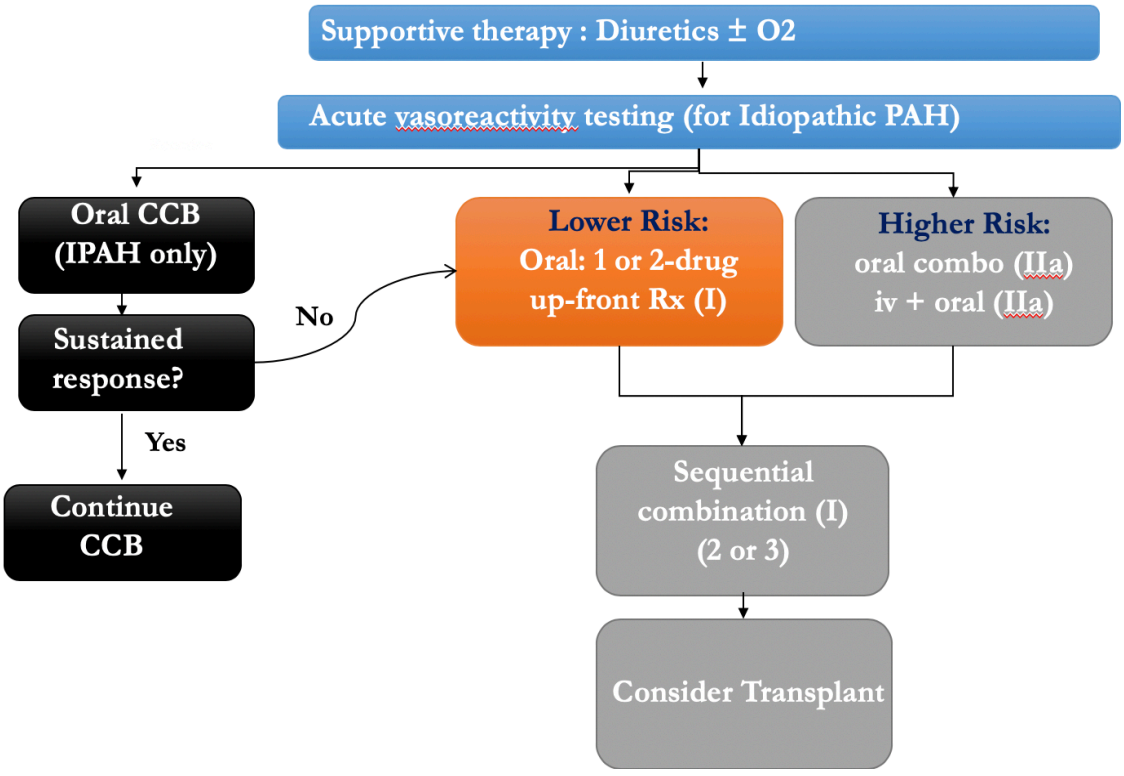



Figure 8: PAH Treatment algorithm in 2019

Adapted from Galiè N, et al. *Eur Respir J*. 2016;37:67-119

**Impact of Modern PAH therapy on survival:**

The NIH registry which enrolled 194 PAH patients from 1981 to 1988 i.e. prior to any available targeted treatments for PAH has been used as a predictor of survival in patients without treatment. As compared to the NIH registry, the French registry (2002-2003) and REVEAL (2006) registry which enrolled patients on PAH-specific therapy showed significant improvement in survival.[18] REVEAL registry showed improved 1 year, 3 year, 5 year and 7 year survival of 90.5 %, 74.5 %, 64.5 % and 58.9 % as opposed to predicted survival by NIH equation of 68.2 %, 46.9 %, 35.6 % and 32 % respectively.[18]

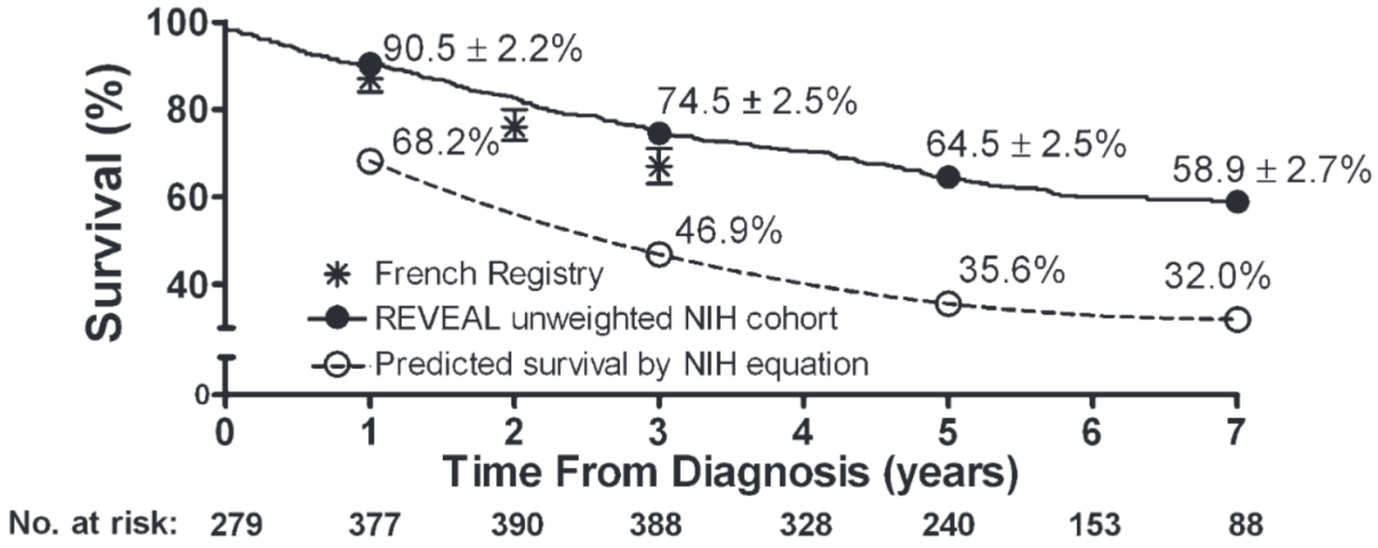



Figure 9: Comparison of survival in REVEAL registry, French registry and predicted survival by NIH equation

**Delay in the diagnosis of PAH:**

Based on NIH registry data, in 1980s time from symptom onset to diagnosis of PAH was 1.3 years. Reveal registry data show that average time to diagnosis of PAH from symptom onset is still 1.1 years. Moreover, one in five patients with PAH reported symptoms for greater than 2 years before their disease is recognized.[6] Obstructive airway disease, sleep apnea, age < 36 years, six-minute walk distance < 250 m, RAP < 10 mm Hg and PVR < 10 woods units are associated with a delayed diagnosis of PAH.[6] In the era of modern therapy for PAH this delay may add to significant morbidity and even

mortality. Improved disease awareness and a high index of suspicion will help decrease the gap between symptom onset and diagnosis of PAH.

**Emerging therapies and future directions in the treatment of PAH:**

Multiple therapeutic targets are currently evaluated for the treatment of PAH.[19] Some of the interest is as follows :

- **Sex hormones:** Estrogen and testosterone have been shown to worsen pulmonary vascular changes, RV function and hypertrophy in animal studies. Currently, federally funded trials are investigating the therapeutic potential of anastrozole, fulvestrant, tamoxifen and DHEA.

- **Genetics and epigenetics:** BMPR2 mutation is the most commonly associated cause of heritable PAH characterized by decreased BMPR2 signaling. FK 506 has been shown to increase BMPR2 signaling. Olaparib, an oral PARP-1 inhibitor is currently being studied in an open-label single arm study.

- **Elastase inhibition:** Fragmentation of vascular internal elastic lamina associated with smooth muscle cell hyperplasia and neointima formation is a major pathological finding in PAH. Elafin is endogenous elastase inhibitor which is currently being studied for clinical development.

- **Inflammation and immunity:** Tocilizumab (monoclonal antibody to IL-6 R) and Anakinra (blocks IL-1) are being studied in PAH patients. A double-blind placebo-controlled trial of rituximab (monoclonal antibody to CD-20) in systemic sclerosis-associated PAH just completed enrolment and results are awaited. Bardoxolone and Dimethyl fumarate (DMF) which target the NRF-2 pathway, are being investigated in scleroderma-associated PAH as well.

- **Mitochondrial dysfunction:** Dichloroacetate (DCA) activates pyruvate dehydrogenase and hence reverses the glycolytic shift in PAH. It has shown promise in 20 patient open-label study and further studies are needed to determine efficacy and safety.

- **Other metabolic pathways:** oral iron supplementation and metformin are being investigated for their therapeutic benefit as well.

- **Nervous system:** Sympathetic nervous system activation, parasympathetic downregulation, and renin-angiotensin system are implicated in the development of PAH. Low dose beta blocker, pulmonary artery denervation, and pulmonary rehabilitation are being investigated to restore the balance between sympathetic activation and parasympathetic down-regulation. Recombinant ACE2 and spironolactone are being investigated in PAH patients as well.

- **Cell-Based therapy:** Endothelial progenitor cells (EPCs) have the potential to help improve endothelial dysfunction and repair damage in pulmonary microvasculature. EPCs and eNOS enhanced EPCs are currently being investigated for their therapeutic potential in early clinical studies.

## Conclusion:

Pulmonary arterial hypertension is a progressive disease and in its natural course is associated with guarded prognosis and high mortality. Diagnosis of PAH is made by ruling out group 2, group 3 and group 4 PH and confirming hemodynamics by right heart catheterization. Therapeutic strategies and options in pulmonary arterial hypertension have evolved significantly over the last decade. Modern therapy of PAH improves overall survival in PAH patients. Diagnosis of PAH is often delayed even in the era of modern therapy and this delay may add to increased morbidity and mortality. Increased awareness is needed to diagnose and treat PAH early. Multiple ongoing early clinical studies on different therapeutic targets show promise towards possible development of new drugs for the treatment of PAH in the future.

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