What is new in pulmonary hypertension?

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World Pulmonary Hypertension Symposia

The aim of WSPHA is to foster constructive scientific interactions and collaborations among the top worldwide experts on pulmonary hypertension.

Traditionally the World Pulmonary Hypertension Symposia series, started in Geneva in 1973 and held every 5 years, has marked the progresses in PH science and has anticipated future developments.

WSPHA, World Symposia on Pulmonary Hypertension Association.
Humbert M, et al. *Eur Respir J.* 2024 Sep 2:2401222.

Timeline

1960

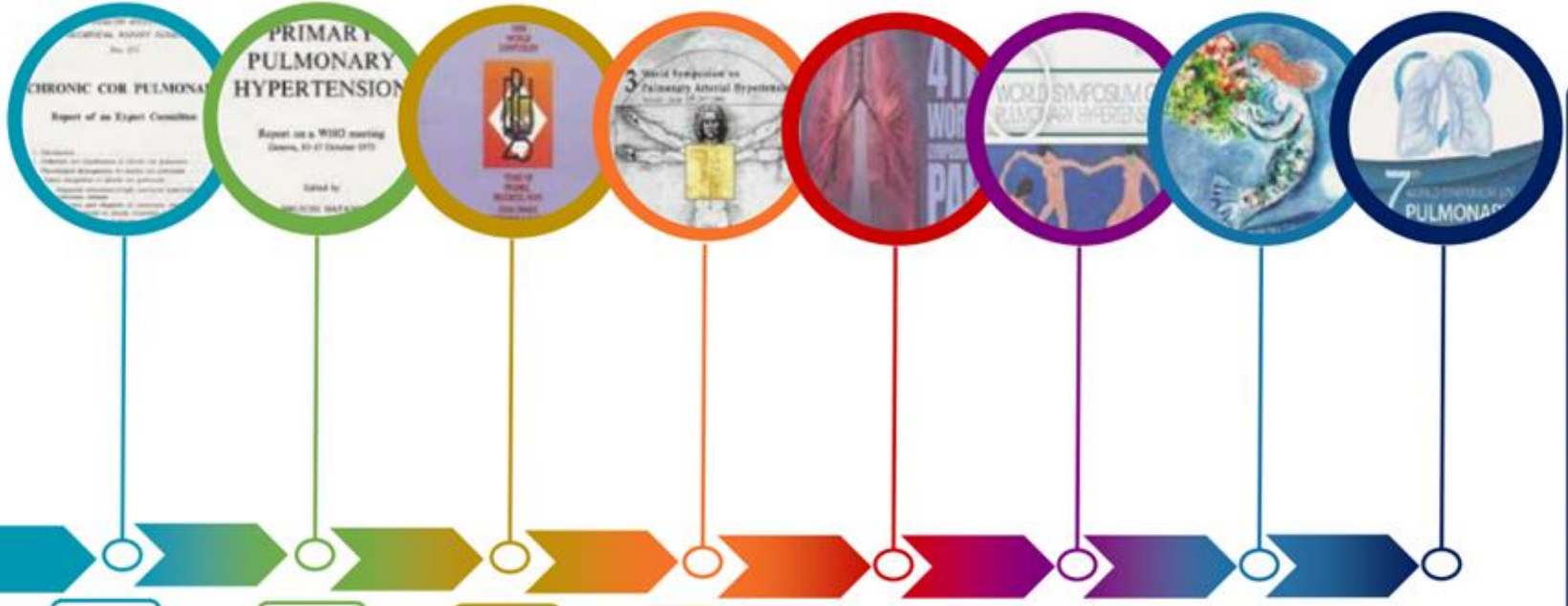
Geneva

1960: WHO Committee on Chronic Cor Pulmonale (Geneva, Switzerland)

- **Focus**: Chronic cor pulmonale (right heart disease caused by lung conditions).
- **Key Outcomes**: Provided the first definition and classification of diseases leading to right ventricular hypertrophy and pulmonary vascular disease. Identified three major disease categories affecting the right ventricle: lung diseases, pulmonary vessel diseases, and primary cardiac diseases.
- **Significance**: This report laid the foundation for modern understanding of PH and emphasized the need for research on the interaction between lung disease and the heart.

WHO, World Health Organization.
Humbert M, et al. *Eur Respir J.* 2024 Sep 2:2401222.

Timeline



1960 Geneva

1973 Geneva

1998 Evian

2003 Venice

2008 Dana Point

2013 Nice

2018 Nice

2024 Barcelona

2024: Seventh WSPH (Barcelona, Spain)
Focus: Innovations in treatment, risk stratification, and patient involvement.

Who Attended?

Global Collaboration:

- The 7th WSPH took place between June 29 and July 1, 2024, in Barcelona, Spain, and emphasized **multidisciplinary and international collaboration**.
- The symposium was endorsed by major **global organizations** such as the European Respiratory Society (ERS), the International Society for Heart and Lung Transplantation (ISHLT), and patient organizations like **PHA Europe, PHA USA,** and others from Japan, Korea, and Latin America.

7th WSPH included:

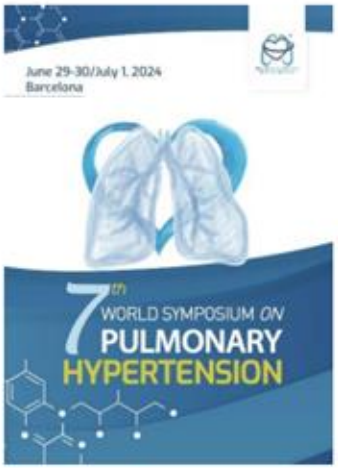
- **129** task force members
- **15** working groups
- **1700** attendees from around the world, including specialists, researchers, and healthcare professionals, contributed to the symposium's open sessions.
- This collaboration further cemented the global commitment to tackling PH through innovative research, education, and care initiatives.

Humbert M, et al. *Eur Respir J.* 2024 Sep 2:2401222.

What Was Discussed?

Symposium Goals:

- To advance global knowledge of PH through research, clinical guidelines, and emerging therapies.



The symposium aimed to:

Refine diagnostic criteria and classifications of PH, improving the accuracy of early detection.

- Specifically in Group 2 and 3 PH where sub-classification changed to disease specific

Explore emerging treatment strategies, focusing on personalized medicine and new therapeutic interventions.

Promote **collaborative efforts** between clinicians, researchers, and patient groups to optimize PH management and improve patient outcomes.

Emphasize the **integration of the patient perspective** in clinical research and care approaches to address quality of life issues.

Promote education and awareness of PH in both high- and low-resource settings.

The definitions of PH have been expanded[1]

Hemodynamic definitions of PH

- PH is now defined by a mPAP >20 mmHg at rest
- PAH would also include a PVR >2 WU and PAWP ≤15 mmHg

Definitions and hemodynamic characteristics of PH and PA

PH

- mPAP >20 mmHg

PAH

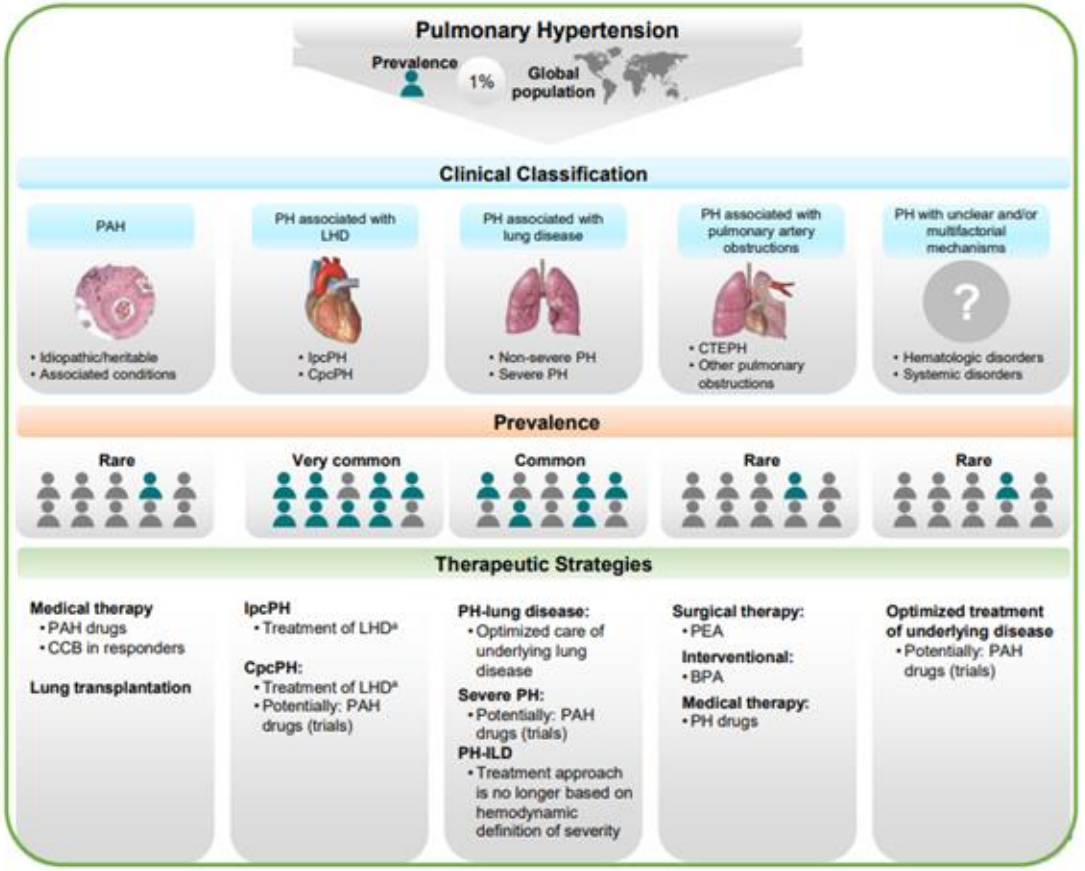
- mPAP >20 mmHg
- PAWP ≤15 mmHg
- PVR >2 WU

Classification, Prevalence, and Treatment of PH[1,2]

Definition	Hemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg **PVR >2 WU**
IpcPH	mPAP >20 mmHg PAWP >15 mmHg **PVR ≤2 WU**
CpcPH	mPAP >20 mmHg PAWP >15 mmHg **PVR >2 WU**
Exercise PH	**mPAP/CO slope between rest and exercise >3 mmHg/L/min**

Footnotes captured in speaker notes.

1. Humbert M, et al. *Eur Respir J.* 2022 Aug 30:2200879.
2. Humbert M, et al. *Eur Heart J.* 2022;43(38):3618-3731.
3. McDonagh TA, et al. *Eur Heart J.* 2021; 42: 3599-3726.
4. Vahanian A, et al. *Eur Heart J.* 2022;43:561-632.



PAH PREVALENCE AND CHARACTERISTICS

PREVALENCE

15-~60

PEOPLE PER 1 MILLION INHABITANTS IN COUNTRIES WHERE STUDIES HAVE BEEN CONDUCTED[11,2]

INCIDENCE (US)

~1000 NEW CASES

ARE DIAGNOSED IN THE UNITED STATES EVERY YEAR[13]

DEMOGRAPHICS

MORE COMMON IN WOMEN

70%-80%

OF CASES[4]

OLDER PATIENTS

50-65 YEARS

OF AGE[1*]

DIAGNOSIS & PROGNOSIS

TIME TO DIAGNOSIS FROM SYMPTOMS ONSET TO DIAGNOSTIC CATHETERIZATION[7]

5-YEAR SURVIVAL AVERAGE: 61%[8]

*In the first US National Institutes of Health registry (started 1981), the mean age of patients was 36 years.[1]

Updated Classification of PH – Group 1

7th WSPH

1. Pulmonary Arterial Hypertension

- 1.1 Idiopathic PAH
  - 1.1.1 Long-term responders to calcium channel blockers
- 1.2 Heritable PAH[a]
- 1.3 Associated with Drugs and Toxins[a] – refer to next slide
- 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

Red items are changed from previous 6th WSPH classification, and crossed out items are no longer included.

[a]Patients with heritable PAH or PAH associated with drugs and toxins might be long-term responders to calcium channel blockers, HIV, human immunodeficiency virus; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease; WSPH, World Symposium on Pulmonary Hypertension.

Kovacs G, et al. *Eur Respir J*. 2024 Aug 29:2401324. Simonneau G, et al. *Eur Respir J*. 2019 Jan 24;53(1). pii: 1801913.

Updated Classification of PH – Group 2

7th WSPH

2. PH associated with Left Heart Disease (LHD)

2.1 Heart failure:
- 2.1.1 with preserved ejection fraction
- 2.1.2 with reduced or mildly reduced ejection fraction
- 2.1.3 cardiomyopathies with specific etiologies[a]

2.2 Valvular heart disease:
- 2.2.1 aortic valve disease
- 2.2.2 mitral valve disease
- 2.2.3 mixed valvular disease

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

Red items are changed from previous 6th WSPH classification; and crossed out items are no longer included.

[a]Hypertrophic, amyloid, Fabry disease and Chagas disease.

Kovacs G, et al. *Eur Respir J.* 2024 Aug 29:2401324. Simonneau G, et al. *Eur Respir J.* 2019 Jan 24;53(1), pii: 1801913.

Updated Classification of PH – Group 3

7th WSPH

3. PH associated with lung disease and/or hypoxia

Parenchymal & Nonparenchymal Diseases

- 3.1 COPD and/or emphysema
- 3.2 Interstitial lung disease
- 3.3 Combined pulmonary fibrosis and emphysema
- 3.4 Other parenchymal lung diseases[a]
- 3.5 Nonparenchymal restrictive diseases:
  - 3.5.1 hypoventilation syndromes
  - 3.5.2 pneumonectomy

Other Causes

- 3.6 Hypoxia without lung disease (eg, high altitude)
- 3.7 Developmental lung diseases

Red items are changed from previous 6th WSPH classification; and crossed out items are no longer included.
[a]Parenchymal lung diseases not included in group 5.
COPD, chronic obstructive pulmonary disease.
Kovacs G, et al. *Eur Respir J*. 2024 Aug 29:2401324. Simonneau G, et al. *Eur Respir J*. 2019 Jan 24;33(1), pii: 1801913.

Updated Classification of PH – Groups 4 and 5

7th WSPH

4. PH associated with pulmonary artery obstructions

PH associated with obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions[a]

5. PH with unclear and/or multifactorial mechanisms

- 5.1 Hematological disorders[b]
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1
- 5.3 Metabolic disorders[c]
- 5.4 Chronic renal failure with or without hemodialysis
- 5.5 Pulmonary tumor thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis
- 5.7 Complex congenital heart disease

Red items are changed from previous 6th WSPH classification; and crossed out items are no longer included.

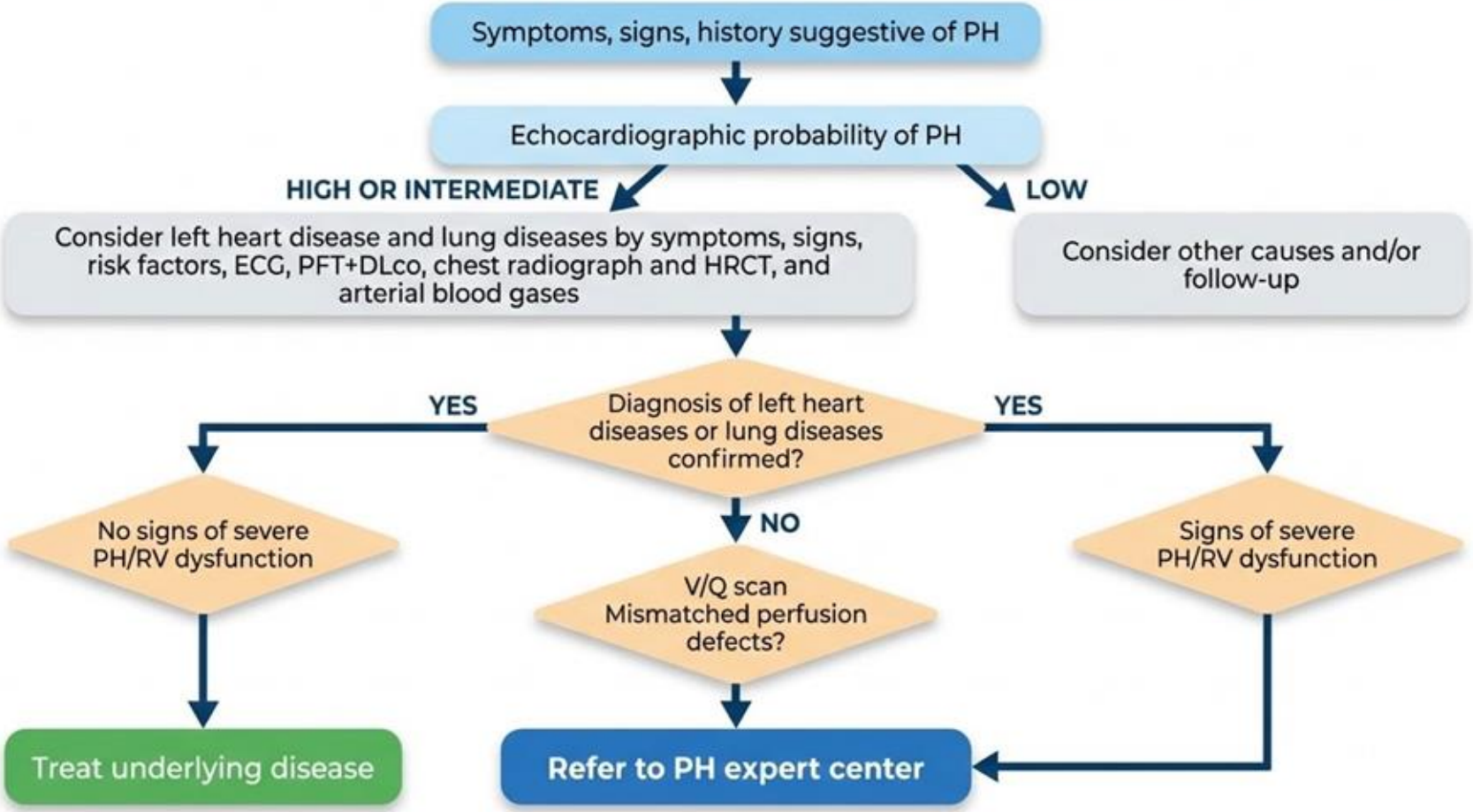
[a]Other causes of pulmonary artery obstructions include sarcomas (high- or intermediate-grade or angiosarcoma), other malignant tumors (eg, renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), nonmalignant tumors (eg, uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses and hydatidosis.

[b]Including inherited and acquired chronic hemolytic anemia and chronic myeloproliferative disorders.

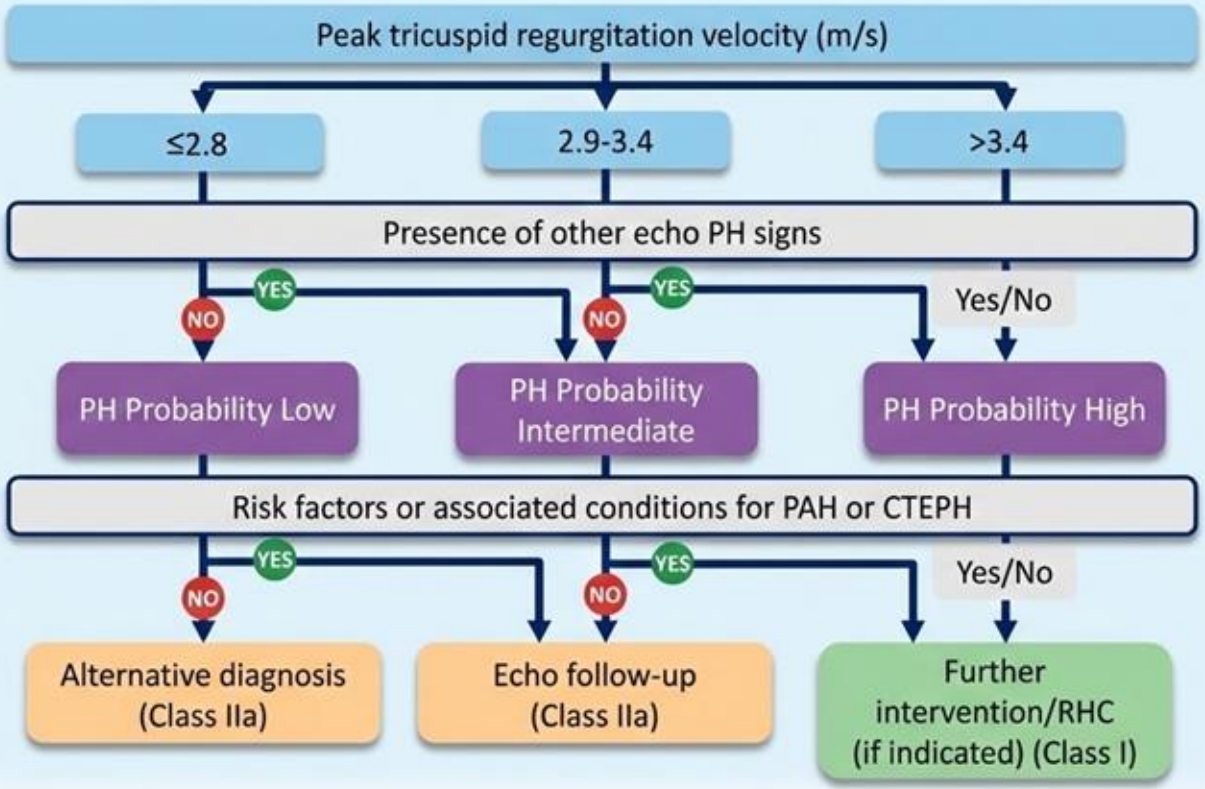
[c]Including glycogen storage diseases and Gaucher disease.

Kovacs G, et al. *Eur Respir J*. 2024 Aug 29:2401324. Simonneau G, et al. *Eur Respir J*. 2019 Jan 24;53(1), pii: 1801913.

Diagnostic Algorithm for Suspected PH



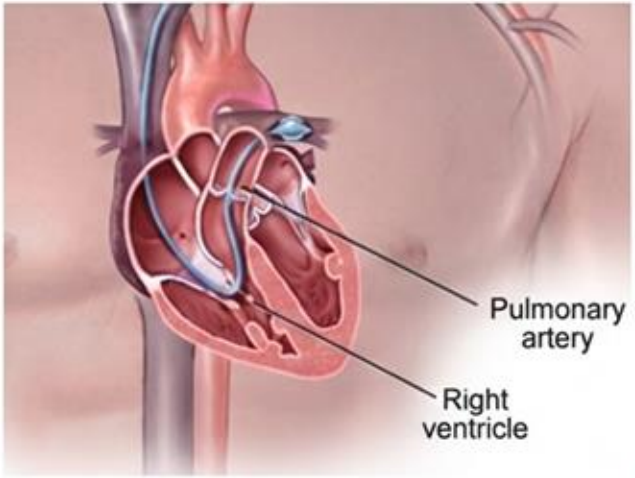
Echocardiographic Probability of PH and Recommendations for Further Assessment



Humbert. Eur Heart J. 2022;43:3618. Humbert. Eur Resp J. 2023;61:2200879. Simonneau. Eur Resp J. 2019;53:1801913.

Credit: clinicaloptions.com

RIGHT HEART CATHETERIZATION



PH

- mPAP >20 mmHg

PAH

- mPAP >20 mmHg
- PAWP ≤15 mmHg
- PVR >2 WU

Vasodilator Challenge

Procedure:
iNO (most commonly) at 40 ppm

Positive Criteria:

- Drop in mPAP ≥10 mm Hg to a mean ≤40 mm Hg
- No decline in CO/CI
- No rise in PCWP

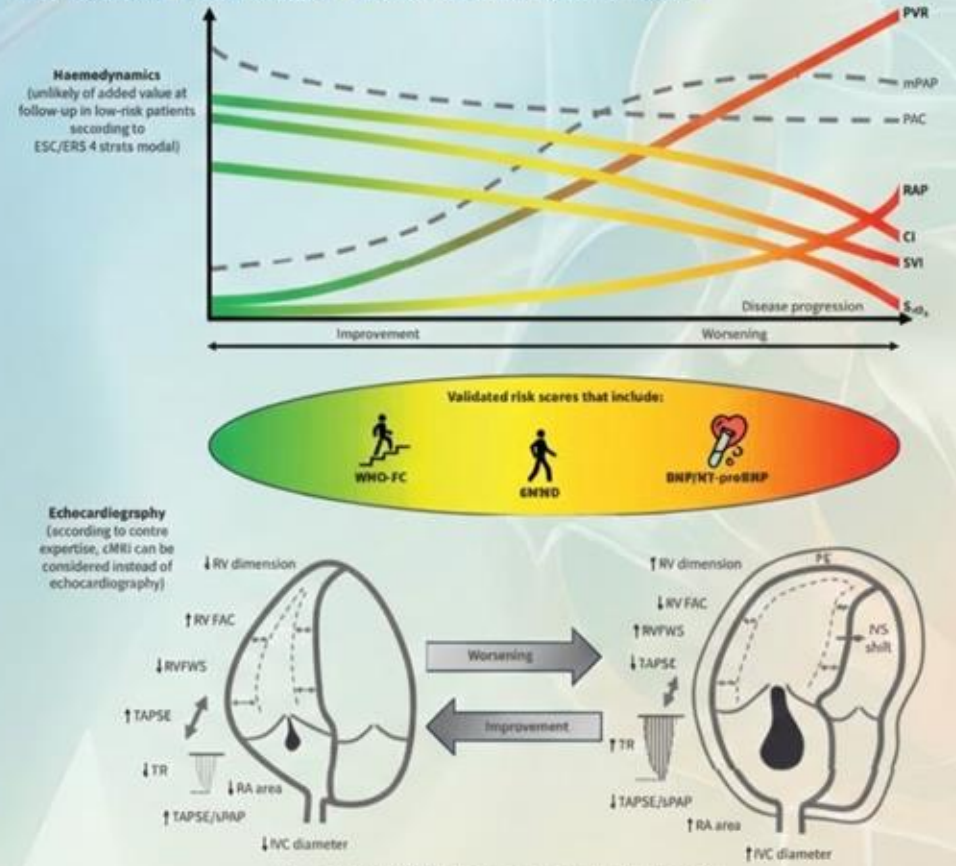
Implication: Suggests response to calcium channel blocker

Caveat:

- Only indicated for patients with IPAH

Risk stratification and treatment goals in pulmonary arterial hypertension

Fabio Dardi, Athénais Boucly, Raymond Benza, Robert Frantz, Valentina Mercurio, Horst Olschewski, Göran Rådegran, Lewis J. Rubin and Marius M. Hoeper



In grey: risk determinants with a less well-defined role as treatment goals

REVEAL risk scoring

	-2	-1	0	1	2	3
WHO group 1 subgroup			Other	CTD	Heritable	PoPH
Male >60 years			No		Yes	
All cause hospitalisation ≤6 months			No	Yes		
eGFR <60 mL/min/1.73m² or renal insufficiency			No	Yes		
Systolic BP (mmHg)			≥110	<110		
Heart rate (bpm)			>95	>95		
WHO-FC		I	II	III	IV	
6MWD (m)	≥440	320–440	165–240	<165		
BNP (ng·L⁻¹) or NT-proBNP (ng·L⁻¹)	<50 <300		50–200 300–1100	200–800	≥800 ≥1100	
PE on echocardiogram			No	Yes		
D_{LCO} <40 % pred			No	Yes		
RAP >20 mmHg within 1 year			No	Yes		
PVR >5 WU		Yes	No			

Overall risk = sum of the points +6 = 0–6 Low risk; 7–8 Intermediate risk; ≥9 High risk

REVEAL Lite 2

	-2	-1	0	1	2
eGFR <60 mL/min/1.73m² or renal insufficiency			No	Yes	
Systolic BP (mmHg)			≥110	<110	
Heart rate (bpm)			>95	>95	
WHO-FC		I	II	III	IV
6MWD (m)	≥440	320–440	165–220	<165	
BNP (ng·L⁻¹) or NT proBNP (ng·L⁻¹)	<50 <300		50–200 300–1100	200–800	≥800 ≥1100

Overall risk = sum of the points +6 = 0–5 Low risk; 6–8 Intermediate risk; ≥9 High risk

FIGURE 1 Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) risk tools. WHO: World Health Organization; eGFR: estimated glomerular filtration rate; BP: blood pressure; WHO-FC: WHO functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; PE: pericardial effusion; D_{LCO}: diffusing capacity of the lung for carbon monoxide; RAP: right atrial pressure; PVR: pulmonary vascular resistance; WU: Wood Units; CTD: connective tissue disease; PoPH: portopulmonary hypertension.

ECS/ERS 3 risk-strata

Determinants of prognosis (according to 1 year estimated mortality)		Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical parameters	Signs of right HF	Absent	Absent	Present
	Symptom progression	No	Slow	Rapid
	Syncope	No	Occasional	Repeated
	WHO-FC	I, II	III	IV
Exercise tests	6MWD	>440 m	165–440 m	<165 m
	CPET			
	Peak V'_{O_2}	>15 mL kg^{-1} min^{-1}	11–15 mL kg^{-1} min^{-1}	<11 mL kg^{-1} min^{-1}
	V'_E/V'_{CO_2}	<36	36–44	>44
Biomarkers	BNP	<50 ng L^{-1}	50–800 ng L^{-1}	>800 ng L^{-1}
	NT-proBNP	<300 ng L^{-1}	300–1100 ng L^{-1}	>1100 ng L^{-1}
Imaging	Echocardiography			
	RA area	<18 cm^2	18–26 cm^2	>26 cm^2
	TAPSE/sPAP	>0.32 mm/mmHg	0.19–0.32 mm/mmHg	<0.19 mm/mmHg
	PE	No	Minimal	Moderate or large
	cMRI			
	RVEF	>54%	37–54%	<37%
	SVI	>45 mL/m^2	26–45 mL/m^2	<26 mL/m^2
	RVESVI	<42 mL/m^2	42–54 mL/m^2	>54 mL/m^2
RHC	Haemodynamics			
	RAP	<8 mmHg	8–14 mmHg	>14 mmHg
	CI	≥2.5 L/min^{-1}/m^{-2}	2.5–2.4 L/min^{-1}/m^{-2}	<2.0 L/min^{-1}/m^{-2}
	SVI	>38 mL/m^2	31–38 mL/m^2	<31 mL/m^2
	S_{vO_2}	>65%	60–65%	<60%

ECS/ERS 4 risk-strata

Determinants of prognosis	Low	Intermediate-low	Intermediate-high	High
WHO-FC	I, II		III	IV
6MWD	>440 m	320–440 m	165–319 m	<165 m
BNP NT-proBNP	<50 ng L^{-1} <300 ng L^{-1}	50–199 ng L^{-1} 300–649 ng L^{-1}	200–800 ng L^{-1} 650–1100 ng L^{-1}	>800 ng L^{-1} >1100 ng L^{-1}

ESC/ERS risk calculation

SPAHR/COMPERA 1.0

Parameters		
Low risk 1 point	Intermediate risk 2 points	High risk 3 points

Overall risk = sum of the points / n of parameters

- 1.0–1.49 = Low risk
- 1.5–2.49 = Intermediate risk
- ≥2.5 = High risk

FPHR invasive

Low risk parameters	
WHO-FC 6MWD BNP CI	I–II >440 m <50 ng L^{-1} ≥2.5 L/min/m^2

Low risk = 4 low risk parameters

FPHR noninvasive

Low risk parameters	
WHO FC 6MWD BNP/NT-proBNP	I–II >440 m <50/300 ng L^{-1}

Low risk = 3 low risk parameters

COMPERA 2.0

Parameters			
Low risk 1 point	Intermediate-low risk 2 points	Intermediate-high risk 3 points	High risk 4 points

Overall risk = sum of the points / n of parameters

- 1.0–1.49 = Low risk
- 1.5–2.49 = Intermediate-low risk
- 2.5–3.49 = Intermediate-high risk
- ≥3.5 = High risk

FIGURE 2 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk tools. RHC: right heart catheterisation; HF: heart failure; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; CPET: cardiopulmonary exercise testing; V'_{O_2}: oxygen uptake; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RA: right atrium; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; PE: pericardial effusion; cMRI: cardiac magnetic resonance imaging; RVEF: right ventricular ejection fraction; SVI: stroke volume index; RVESVI: right ventricular end-systolic volume index; RAP: right atrial pressure; CI: cardiac index; S_{vO_2}: mixed venous oxygen saturation; SPAHR: Swedish Pulmonary Arterial Hypertension Registry; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry.

GOALS:

Domain	Treatment goals	Comments	Limitations
Exercise tolerance 	**6MWD >440 m** **WHO-FC I or II**	Not disease-specific, potentially affected by conditions other than PAH	Goals may not be achievable in patients with other conditions limiting exercise capacity
RV function and strain 	**BNP <50 ng·L^{-1}** **NT-proBNP <300 ng·L^{-1}**	Not disease-specific, potentially affected by conditions other than PAH	Goals may not be achievable in patients with interfering conditions
	Need for research prioritisation: RA area <18 cm^2 TR, none or trace TAPSE/sPAP >0.32 mm·mmHg^{-1}	Other imaging parameters from echocardiography and MRI are emerging	TAPSE/sPAP threshold requires further validation
Haemodynamics 	**RAP <8 mmHg** **CI ≥2.5 L·min^{-1}·m^{-2}** **SVI >37 mL·m^{-2}** **S_{vO_2} >65%** **PVR <5 WU**	Uncertain added value in low-risk patients according to ESC/ERS 4 strata model PVR <5 WU treatment goal may not apply to patients with congenital heart disease	Established prognostic value; however, not necessarily independent of noninvasive parameters
	Need for research prioritisation: mPAP <30–35 mmHg PAC ≥2.5 mL·mmHg^{-1}	With emerging therapies and effective combination treatment strategies, comprehensive haemodynamic assessment of treatment response is expected to play a prominent role in the management of patients with PAH	The proposed thresholds may be associated with long-term survival; however, this is not evidence-based and requires further validation

FIGURE 3 Comprehensive treatment goals in pulmonary arterial hypertension (PAH). RV: right ventricle; 6MWD: 6-min walk distance; WHO-FC: World Health Organization functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RA: right atrium; TR: tricuspid regurgitation; TAPSE/sPAP: tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio (estimated by echocardiography); RAP: right atrial pressure; CI: cardiac index; SVI: stroke volume index; S_{vO_2}: mixed venous oxygen saturation; PVR: pulmonary vascular resistance; WU: Wood Units; mPAP: mean pulmonary artery pressure; PAC: pulmonary arterial compliance; ESC: European Society of Cardiology; ERS: European Respiratory Society.

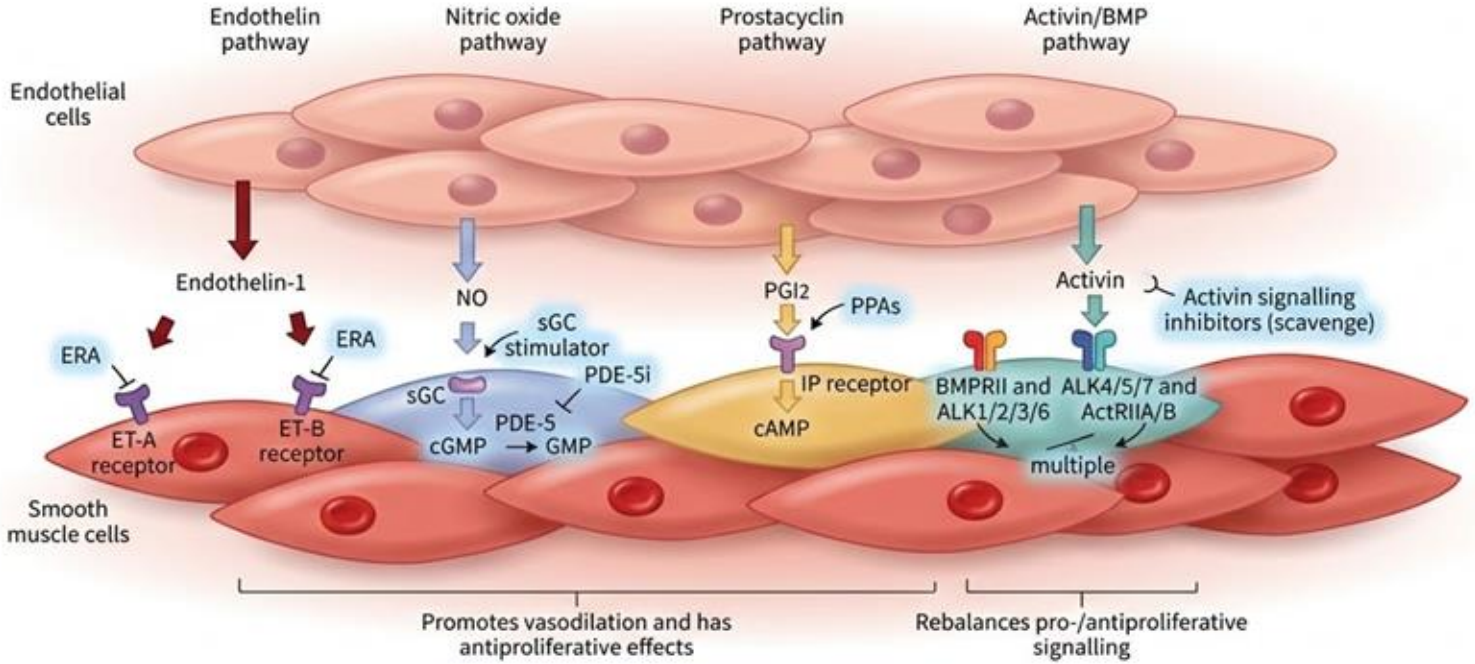


FIGURE 2 Pulmonary arterial hypertension (PAH) therapies work through four major pathways: endothelin-1 receptor antagonists (ERAs) block the endothelin (ET)-1 receptor. Phosphodiesterase-5 inhibitors (PDE-5i) and soluble guanylyl cyclase (sGC) stimulators increase signalling in the nitric oxide (NO) and cyclic GMP (cGMP) pathway, resulting in increased cGMP levels, and prostacyclin (PGI2) and other prostacyclin pathway agents (PPAs) bind the prostacyclin receptor (IP receptor), promoting the production of cAMP, leading to vasodilation and inhibiting vascular cell growth. Sotatercept, a novel biologic agent targeting the transforming growth factor-β superfamily, acts as a ligand trap for activins and related growth factors. This helps rebalance growth-promoting and growth-inhibiting signalling pathways, with multiple downstream effects. Signalling is shown as proceeding from endothelial cell to smooth muscle call for simplicity, but is bidirectional. BMPR: bone morphogenetic protein receptor; ALK: anaplastic lymphocyte kinase; ActR: activin receptor. [#]: In addition, signalling mediators also originate from multiple other cell types, particularly for activin.

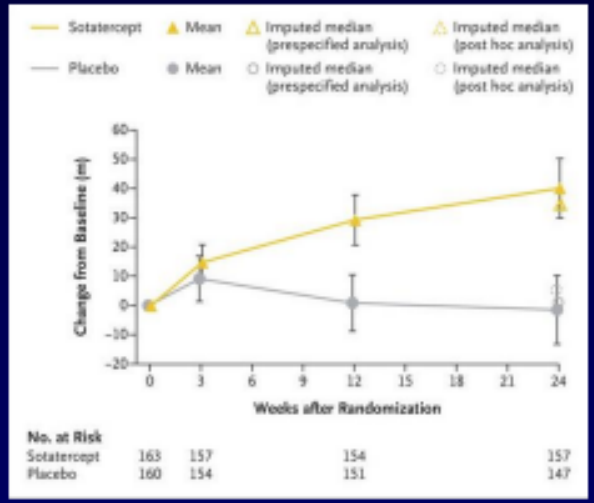
TABLE 2 Medications for pulmonary arterial hypertension

	Medications	Common adverse reactions	Other important information
Oral medications			
PDE-Si [18–21]	Sildenafil, tadalafil	Headache Flushing Dyspepsia Epistasis	Rare loss of vision or hearing Avoid with nitrates, riociguat
Guanylyl cyclase stimulators [22]	Riociguat	Headache Dysppesia Dizziness Hypotension	Avoid in pregnancy[b], avoid with nitrates, PDE-Si Monitor for hypotension; may require dove adjustment based on systemic SBP
Endothelin-1 receptor antagonists [21, 23–27]	Ambrisentan, bosentan, macitentan	Peripheral oedema Nasal congestion Anaemia[a]	Avoid in pregnancy[a], monitor haemoglobin (all), liver function (monthly for bosentan, as clinically indicated for others)
Prostacyclin receptor agonists [28]	Selexipag	Prostanoid-type AEs[c]	Data on selesipag in pregnancy are not available
Prastanolds, p.o. [11, 29–32]	Treprostinil, beraprost	Prostanoid-type AEs[c]	
Inhaled medications			
Prostanolds, inhaled [33, 34]	Iloprost, treprostinil	Cough Prostanoid-type AEs[c]	
Parenteral medications			
Prostanolds, parenteral [35, 36]	Epoprostenal (*i.v.*), treprostinil (*i.v.*, s.c.)	Prostanoid-type AEs[c]	Sudden discontinuation of parenteral prostanolds can be life-threatening
Activin-signalling inhibitor [7, 8]	Sotatercept (s.c.)	Headache Dlarrhoes Nosebleed Bleeding events Telangiectasia	Avoid in pregnancy[a]; potential risk of reduced future fertility based on animal studies; monitor for thrombocytopenia and increased haemoglobin for first five doses and periodically

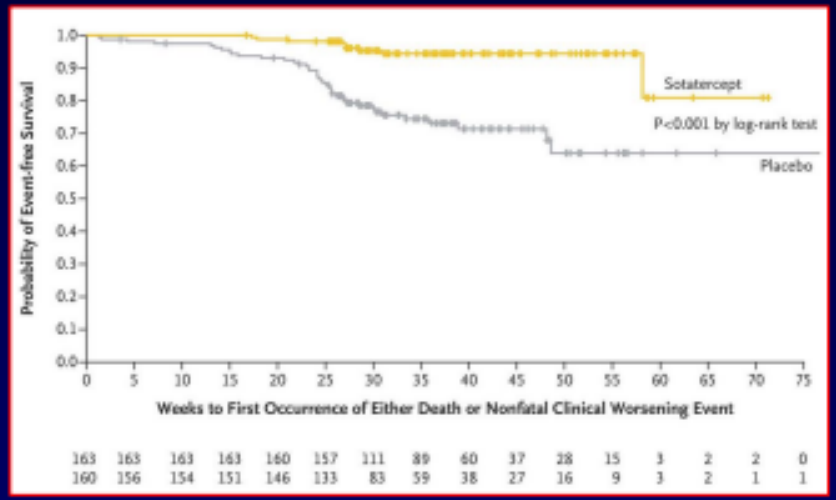
PDE-SI: phosphodiesterase-5 inhibitor; SBP: systalic blood pressure; AE: adverse events; *i.v.*: intravenous; s.c.: subcutaneous. [a]: highly reliable contraception and monthly pregnancy testing required for all individuals of childbearing potential due to risk of teratogenicity; [b]: while adverse reactions to endothelin-1 receptor antagonists tend to be class effects, there is some variabiiity and switching within the same class can be considered; [c]: prostanoid type AEs include flushing, headache, jaw pain, nausea/vomiting, diarrhoea.

STELLAR: Effect of Sotatercept in PAH

6MWD



Time to Death/ Clinical Worsening



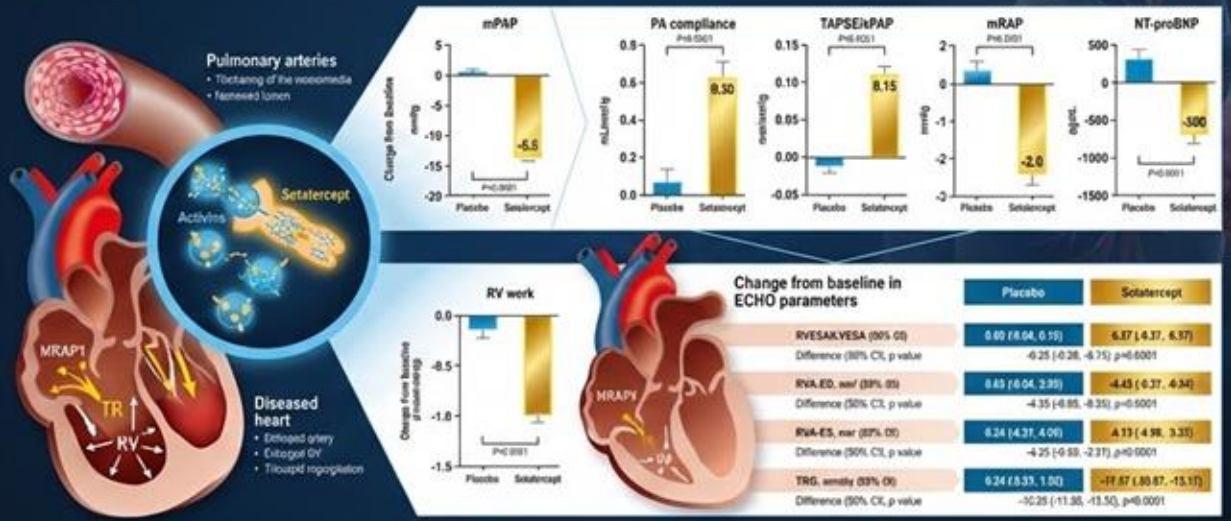
100% on background therapy:
-13% on monotherapy
-35% on double therapy
-61% on triple therapy

Hoeper MM et al. *N Engl J Med*. 2023. DOI: 10.1056/NEJMoa2213558

Treatment With Sotatercept for 24 Weeks

Significantly Reduced Right Heart Size and Improved RV Function and Haemodynamic Status in Patients With PAH

- Pathologic remodeling in PAH



Error bars in graph represent standard error.

CI, confidence interval: ECHO, echocardiography; LVESA, left ventricle end-systolic area; mmHg, millimeters of mercury, mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure measured by right heart catheterieation;

NT-proBNP, N-terminal pro B-type natriuretic peptide; PA, pulmonary artery; PAH, pulmonary arterial hypertension; RA, right atrium; RHC, right heart catheterization; RV, right ventricle; RVA-ED, right ventricular area in end-diastole;

RVA-ES, right ventricular area in end-systole; RVESA, right ventricle and systolic area; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TRG, TR gradient.

Souza R, et al. *Eur Resp J*. 2023.

HYPERION: Sotatercept Delays Worsening of PAH Diagnosed Within First Year

Patient Population & Study Design

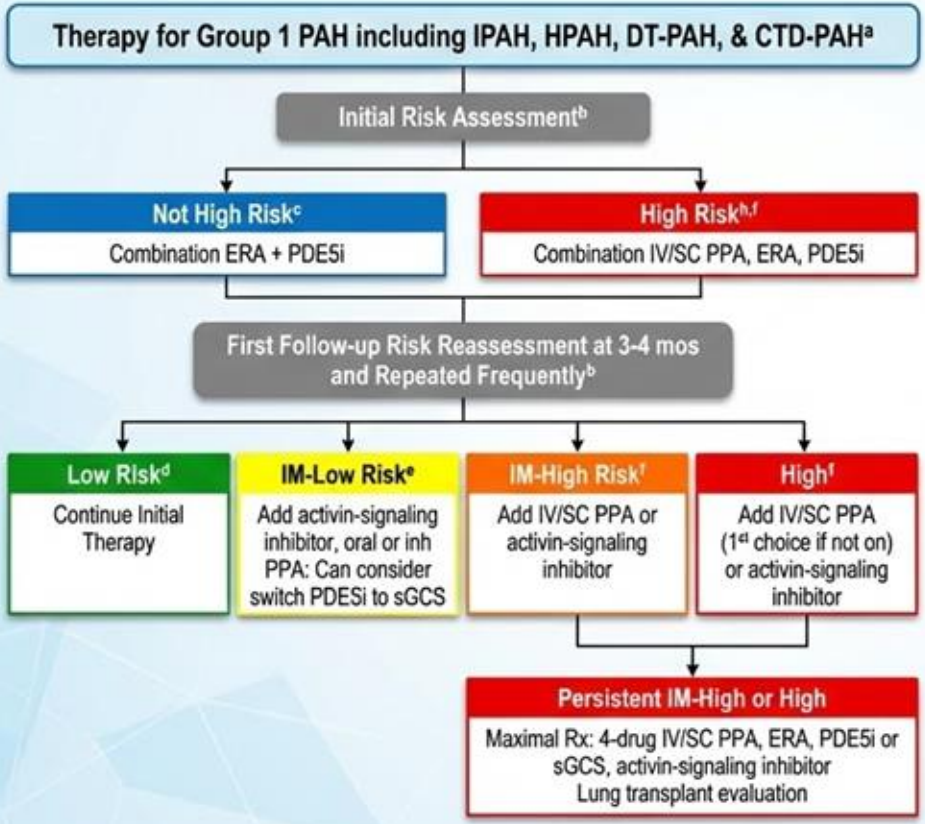
- 320 adults (mean age, 56 years; 73% women)
- WHO functional class II or III PAH
- Diagnosed less than one year earlier
- Intermediate or high risk of death
- Receiving double or triple background therapy
- Assigned to add-on therapy with subcutaneous sotatercept (0.3-0.7 mg/kg) or placebo every 21 days (n=160 each group)

Primary Endpoint: Clinical Worsening

RESULTS
at a median of 13.2 months:

One or more primary endpoint events occurred.
Hazard ratio, 0.24; p<0.001.

7th WSPH Treatment Algorithm: First Follow-up Risk Assessment at 3-4 Months and Repeat Frequently



Treatment Algorithm Key Points

a. Treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-out, ***mPAP ≥25 and PVR >3*** and no significant response on acute vasoreactivity testing). Treatment nuances in PAH with complex phenotypes.

b. ***Risk Assessment*** should be performed at baseline, within 3-4 months and periodically thereafter, and using FC, 6MWD and natriuretic peptides as a part of a validated risk calculator. Hemodynamics, RV imaging and other measures should be used to supplement risk assessment.

c. ***Initial triple therapy*** with an IV/SC PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and or poor RV function.

d. Most ***low risk*** at follow-up patients should continue initial therapy.

e. Clinical trials with oral and inhaled trepostinil included ***only patients on monotherapy***, while studies of selexipag and sotarcept included patients on combination therapy.

f. ***Transplant referral*** should be considered for select high risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

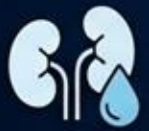
Chin KM et al. *Eur Respir J.* 2024. in press: 2401225 [DOI: 10.1183/13993003.01325-2024].

7th WSPH: Recommended Supportive Measures

Supervised exercise training

Psychological support

Immunization against SARS-CoV-2, influenza, Streptococcus pneumoniae and consider vaccination against RSV



Diuretic treatment in patients with fluid retention

Continuous long-term oxygen therapy when arterial blood O_2 pressure is consistently <8 kPa (60 mm Hg)

Correction of iron status in patients with iron-deficiency anemia

Advise against pregnancy

Clear contraceptive advice

Pre-transplant counseling

Chin KM et al. *Eur Respir J*. 2024. in press: 2401225 [DOI: 10.1183/13993003.01325-2024].

Mild PAH with mPAP of 21-24 mmHg and PVR <3 WU

Therapeutic Gap

NO approved therapies for patients with mPAP between 21 and 24 mmHg.

Initiation Consensus

Consensus on initiating PAH therapies is lacking.

Clinical Guidance

- Clinical trial enrollment recommended.
- Closely monitor for progression.
- If starting therapy, **initial monotherapy** is recommended.

Vasoreactivity and Calcium channel blockers

Only for IPAH, HPAH and DT-PAH

Acute vasoreactivity is defined by:
1) a decrease of the mPAP by ≥10 mmHg,
2) to reach an absolute mPAP <40 mmHg, and
3) **without** a decrease in cardiac output.

CCB used at high doses

No longer responsive to CCB?
→ use standart (non-vasodilator) PAH algorithm and continue CCB (this is not well studied)

TABLE 1 Ongoing or recently completed phase 2 and phase 3 clinical trials in pulmonary arterial hypertension (PAH)

	Mechanism of action	Trial name and registration	Phase	Sample size	Primary outcome	Status[#]
Ambrisentan	Endothelin receptor antagonist	TAPE (NCT04972550)	3	420	Incidence of PAH (mPAP ≥25 mmHg) at 1 year[a] Change in PVR at 1 year	Recruiting
Dapagliflozin	Sodium glucose co-transporter-2 inhibitor	DAPAH (NCT05179395)	2	52	Change in V_{O_2}max at 3 months	Recruiting
DHEA	Activation of NO synthase, suppresses ET-1, cardiac remodelling	EDIPHY (NCT03643385)	2 crossover	24	RV longhudinal strain on CMR	Active, not recruiting
Empagliflozin	Sodium glucose co-transporter-2 inhibitor	Emphower PoC (NCT05493371)	2a	8	Tolerability, feasibility, safety at 12 weeks	Recruiting
eNOS-enhanced endothelial progenitor cells	Anglogenic stem cells	SAPPHIRE (NCT03031414)	2 crossover	12	Change in 6MWD at 6 months	Active, not recruiting
Famoditine	Antihistamine	REHAB-PH (NCT03554291)	2	20	Change in 6MWD at week 24	Completed
FK506	Activation of GMPRII signalling	TransformPAH (NCT01647945)	2a	23	Safety	Completed
KER-012	Activin signalling inhibitor	TROPOS (NCT05979905)	2	90	Change in PVR at week 24	Recruiting
Ifetrohan	Selective thrombexane receptor antagonist	NCT02682511	2	94	Adverse events and serious adverse events up to week 56	Recruiting
Imatinib	Oral tyrosine binase inhibitor	PIPAH (NCT44416750)	2	43	Highest telerated does; PVR at week 24	Active, not recruiting
Imatinib DPI (AV-101)	Inhaled tyrosine binase inhibitor	IMPAHCT (NCT05036135)	2b/3	462	Phase 2b: PVR at week 24 Phase 3: change in 6MWD at week 24	Terminated 17 June 2024
LAM-001	Inhaled mTOR inhibitor	NCT05799923	2a	15	Change in V'_{O_2} at 24 weeks	Recruiting
LTP001	SMURF1 Inhibitor	NCT05135000	2	47	PVR at week 25	Active, not recruiting
Macitentan (75 mg)	Endothelin receptor antagonist	UNISUS (NCT04273945)	3	900	Morbidity or mortality events (up to 4 years)	Recruiting
Metformin	Decreases gluconeogenesis, increases fatty acid oxidation, and reduces oxidative strass	NCT03617458	2	82	Change in 6MWD at week 2 Change in WHO-FC at week 12	Active, not recruiting
MK-5475	Inhaled soluble guanylate cyclase stimulator	INSIGNIA-PAH (NCT04732221)	2/3	450	Phase 2: PVR at week 12 Phase 3: change in 6MWD at week 12	Active, not recruiting

TABLE 1 Ongoing or recently completed phase 2 and phase 3 clinical trials in pulmonary arterial hypertension (PAH) (continued)

	Mechanism of action	Trial name and registration	Phase	Sample size	Primary outcome	Status*
Olaparib	Poly(ADP-ribose) polymerase inhibitor	OPTION (NCT03782818)	2	20	Treatment-emergent adverse events at week 24	Recruiting
Ralinepag	Prostacyclin receptor agonist	ADVANCE (NCT03626688)	3	1000	TTCW	Recruiting
		ADVANCE CAPACITY (NCT04084670)	3	10	Change in peak V'_O, at week 28	Terminated
Satralizumab	IL-6 receptor antagonist	SATISFY-JP (NCT05679570)	2	24	Change in PVR at week 24	Active, not recruiting
Seralutinib (GB002)	Inhaled PDGF-&, CSF1R and c-KIT inhibitor	PROSERA (NCT05934526)	3	350	Change in 6MWD at week 24	Recruiting
Sodium valproate (CS1)	Histone deacetylase inhibition	NCT05224531 (NCT05331414)	2	30	Patient-reported adverse events	Recruiting
Sotatercept	Activin-signalling inhibitor	HYPERION (NCT04811092)	3	444	TTCW	Active, not recruiting
		MOONBEAM – paediatric PAH (NCT05587712)	2	42	Time to first morbidity or mortality event	Active, not recruiting
Spironolactone	Mineralocorticoid receptor antagonist	MK-7962-020 (NCT05818137)	3	46	Change in PVR at week 24 6 months	Terminated
Tamoxifen	Selective oestrogen receptor modulator	T3PAH (NCT03528902)	2	18	TAPSE on echo at week 24	Completed
Treprostinil liposomal	Inhaled prostacyclin analogue	NCT04691154	3	60	Adverse events after switching from inhaled	Recruiting
suspension (L606)	-	NCT04691154	3	60	treprostinil (Tyvaso)	Recruiting
Treprostinil palmitil DPI	Inhaled prostacyclin analogue	NCT05147805	2b	99	PVR at week 24	Recruiting
Vardenefil DPI (RT234)	Inhaled phosphodiesterase type-5 inhibitor	VIPAH-PRN (NCT04266197)	2b	60	Adverse events, change in ms:	Recruiting

(treprostinil) inhalation powder

An **inhaled medication** used to treat:

- Pulmonary arterial hypertension (Group 1 PH)
- Pulmonary hypertension associated with interstitial lung disease (Group 3 PH)

Works to improve the ability to exercise.

2002 (inhaled treprostinil)

2022 (dry inhalation powder)

May 2025 (FDA Approved)

Each treprostinil formulation has its own unique inhalation device, not interchangeable.

Cohort A: Open-label, Multicenter Study to Evaluate Safety and Tolerability of LIQ861 in Patients with Newly Diagnosed PH-ILD

Inclusion Criteria

WHO Group 3 PH-ILD, including CPFE

- Prostacyclin naïve
- Stable dose of ILD medications
- **18-75 years** of age: conditional 76-80
- **6MWD ≥125m**
- **FEV_1/FVC ≥70%**

		OR	ILD LIMITED SUBSET (NO CPFE):
PVR	≥3 WU		≥3 WU
PCWP	≤15 mmHg		≤15 mmHg
mPAP	≥30 mmHg		≥21 - ≤29 mmHg

ASCENT LIQ861 – Summary

1. The treatment-related TEAs observed are consistent with the known safety profile of inhaled treprostinil
2. The median dose at Week 8 was 132.5mcg QID (15 nebulized breath equivalent), increasing to 159mcg QID (18 nebulized breath equivalent) by Week 16
3. 92.3% of treatment related cough was mild. No worsening in patient-perceived cough score was observed despite higher LIQ861 dosing
4. By Week 16, median improvement in 6MWD was +31.5 meters above boseline. 29.3% improved by +50 meters or more.

Seralutinib

Seralutinib is an investigational, inhaled, small molecule inhibitor of:

PDGFR CSF1R c-KIT

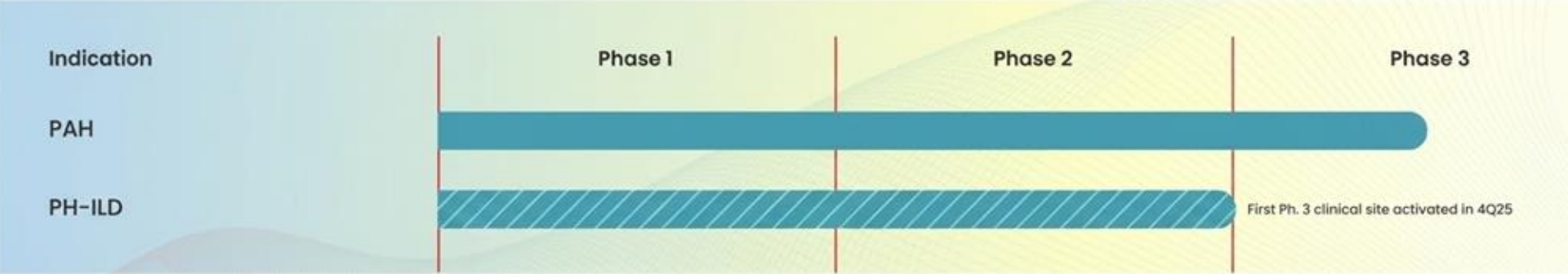
Designed to target underlying mechanisms of pulmonary hypertension

Delivered via dry powder inhaler to disease site

In pre-clinical models, seralutinib:

- ✓ Reversed pulmonary vascular remodelling
- ✓ Decreased right ventricular systolic pressure
- ✓ Improved pulmonary hemodynamics
- ✓ Increased BMPR2 expression

Seralutinib Clinical Development



Sotatercept for WHO group II PH.

A Study of Sotatercept for the Treatment of Cpc-PH Due to HFpEF (MK-7962-007/A011-16) (CADENCE)

Study Overview

This is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of sotatercept versus placebo in adults with Cpc-PH due to HFpEF.

Adults with Cpc-PH due to HFpEF

Phase 2, Double-blind, Randomized, Placebo-controlled Study

Sotatercept

Placebo

The objective of this study is to evaluate the efficacy, safety and tolerability of sotatercept versus placebo in adults with Cpc-PH due to HFpEF. Efficacy is measured by change from baseline in pulmonary vascular resistance (PVR, primary endpoint) and 6-minute walk distance (6MWD, key secondary endpoint).

Study Objectives & Endpoints

Primary Endpoint
Change from baseline in Pulmonary Vascular Resistance (PVR)

Key Secondary Endpoint
Change from baseline in **6-Minute Walk Distance** (6MWD)

CADENCE


Thank you!
For your attention and interest.