

Pulmonary arterial hypertension: A practical roadmap from diagnosis to treatment

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Clinical diagnosis of PAH: Signs and steps to diagnosis

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Clinical classification of PH and symptoms of PAH



Clinical classification of PH¹

Group 1

- PAH

Group 2

- PH associated with left heart disease

Group 3

- PH associated with lung diseases and/or hypoxia

Group 4

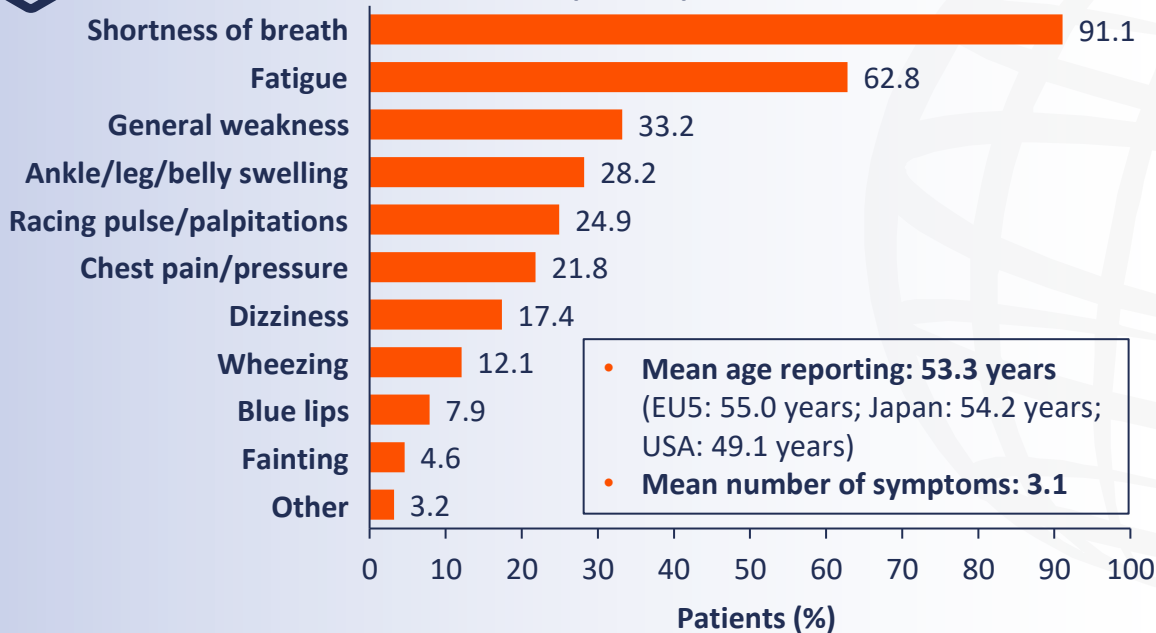
- PH associated with chronic pulmonary artery obstruction

Group 5

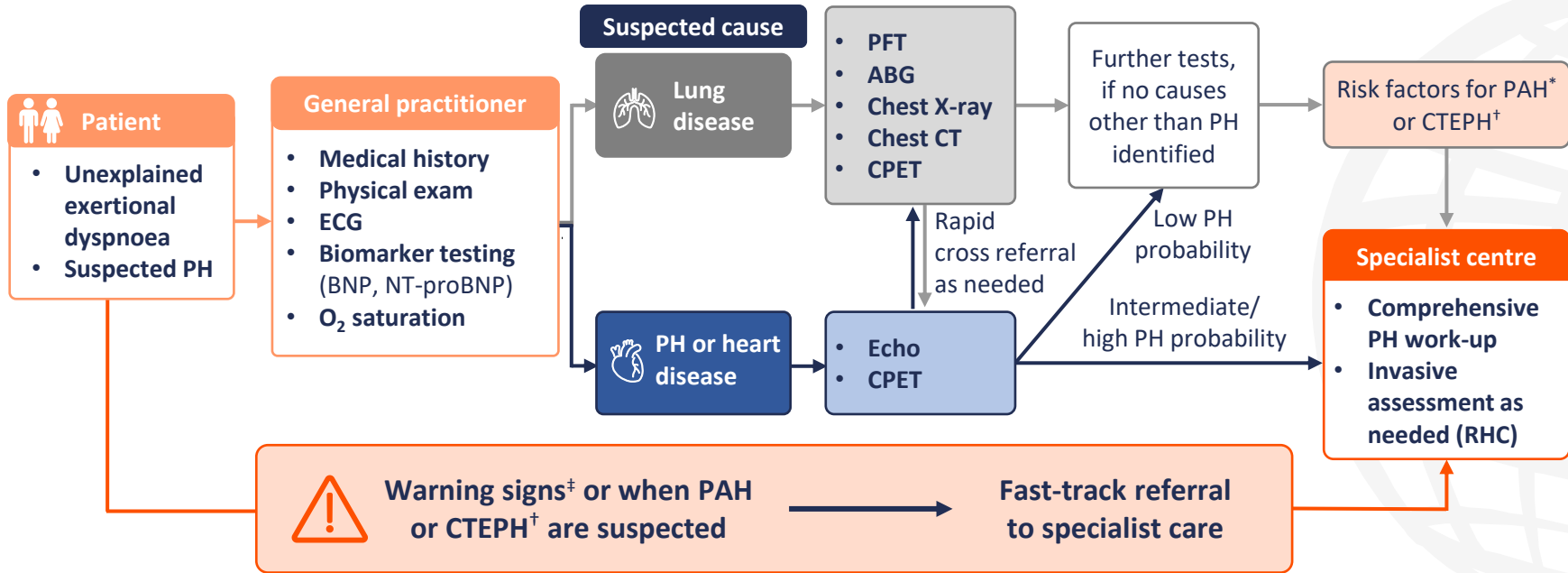
- PH with unclear and/or multifactorial mechanisms



Symptoms of PAH first noticed by patients (N=572)²



Diagnostic algorithm for PAH



*Includes connective tissue disease (especially systemic sclerosis), portal hypertension, HIV infection, and family history of PAH. †A range of factors including a history of pulmonary embolism, IBD and essential thrombocythaemia. ‡Warning signs include rapid progression of symptoms, severely reduced exercise capacity, pre-syncope or syncope on mild exertion, signs of right heart failure. ABG, arterial blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thromboembolic PH; ECG, electrocardiogram; Echo, echocardiogram; IBD, inflammatory bowel disease; NT-proBNP, N-terminal pro-BNP; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterization. Humbert M, et al. *Eur Heart J.* 2022;43:3618–731.



Risk stratification of PAH: Working towards individualized treatment

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Approaches for risk stratification in PAH

Multiple models

2022 ESC/ERS risk score^{1,2}

COMPERA 2.0^{2,3}

Comparative, Prospective Registry of Newly Initiated Therapies for PH*

FPHR⁴

French PH Registry

REVEAL⁵

Registry to Evaluate Early and Long-Term PAH Disease Management

SPAHR⁶

Swedish PAH Registry

Multiple variables within the different models⁷

Commonly included

WHO-FC

6MWD

NT-proBNP/BNP

Right atrial pressure

SvO₂

Cardiac index

Model specific

Clinical signs of RHF

Symptom progression

Syncope

Right atrial area

Pericardial effusion

Parameters

Risk categories (ESC/ERS guidelines[†])

Low

Intermediate

High

*A four-strata model that is recommended for patients for follow-up when on treatment.¹ †The ESC/ERS guidelines apply a three-strata model for initial assessment and a four-strata model (Low, Intermediate-low, Intermediate-high, and High) for follow-up. 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; ESC/ERS, European Society of Cardiology/European Respiratory Society; NT-proBNP, N-terminal pro-BNP; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHF, right heart failure; SvO₂, mixed venous oxygen saturation; WHO-FC, World Health Organization functional class.

1. Humbert M, et al. *Eur Heart J*. 2022;43:3618–731; 2. 2022 3-Strata Risk Score Calculator. Available at: <https://bit.ly/4dIoTKg> (accessed 9 September 2024);

3. Hoepfer MM, et al. *Eur Respir J*. 2017;50:1700740; 4. Boucly A, et al. *Eur Respir J*. 2017;50:1700889; 5. Benza RL, et al. *Chest*. 2012;141:354–62;

6. Kylhammar D, et al. *Eur Heart J*. 2018;39:4175–81; 7. Ahmed A, et al. *Eur Heart J Open*. 2023;3:oead012.

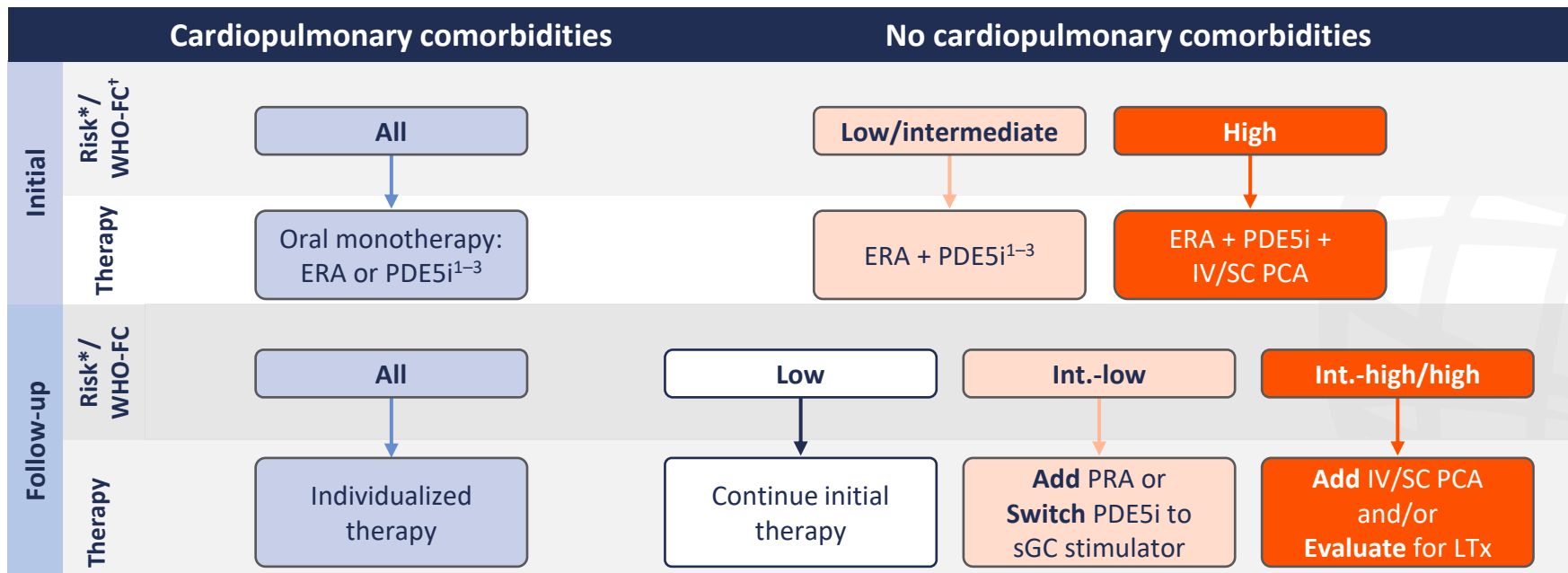
Treatment algorithms for PAH: An evolving landscape

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Treatment algorithm for PAH¹⁻³



A principal goal of treatment is to achieve minimal symptom burden. Up-front dual-combination therapy is now the standard of care for most low- and intermediate-risk patients with PAH after diagnosis with careful reassessment at 3 months.³

*ESC/ERS guidelines recommend using a 3-strata risk model pre-treatment and a 4-strata risk model when on treatment.

[†]US guidelines either emphasize WHO-FC class² or REVEAL 2.0³ to guide treatment selection.

ERA, endothelin receptor antagonist; ESC/ERS, European Society of Cardiology/European Respiratory Society; Int., intermediate; IV, intravenous; LTx, lung transplantation; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE5i, phosphodiesterase-5 inhibitor; PRA, prostacyclin receptor agonist; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; SC, subcutaneous; sGC, soluble guanylate cyclase; WHO-FC, World Health Organization functional class.

1. Humbert M, et al. *Eur Heart J*. 2022;43:3618–731; 2. Klinger JR, et al. *Chest*. 2019;155:565–86; 3. Maron BA, et al. *Am J Respir Crit Care Med*. 2021;203:1472–87.

Agents for PAH: Newly approved or in phase III trials

	Approved (USA and Europe, 2024 ^{1,2})		In phase III clinical trials		
Agent	Sotatercept 		Ralinepag 	MK-5475 	Seralutinib 
MOA/Target	ACTRIIA ligand trap		PRA	sGC stimulator	TKI
Trial results/ Primary endpoint(s)	Pivotal trial	Ongoing trials	NCT03683186 (ADVANCE EXTENSION): Patients with TEAEs ⁷ NCT03626688 (ADVANCE OUTCOMES): Time to first protocol-defined clinical worsening event ⁸	NCT04732221 (INSIGNIA-PAH): Change from BL in 6MWD at 12 wks ⁹	NCT05934526 (PROSERA): Change from BL in 6MWD at 24 wks ¹⁰ NCT06274801 (PROSERA-EXT): Incidence of TEAEs ¹¹
	NCT04576988 (STELLAR): ³ Change from BL in 6MWD vs placebo	NCT04896008 (ZENITH): Time to first confirmed morbidity or mortality event ⁴ NCT04796337 (SOTERIA): Patients experiencing an AE ⁵ NCT04811092 (HYPERION): Time to clinical worsening ⁶			
Completion date	Completed	NCT04896008: Nov 2025 NCT04796337: Nov 2027 NCT04811092: Dec 2029	NCT03683186: Sept 2024 NCT03626688: Dec 2024	Completed	NCT05934526: Oct 2025 NCT06274801: Dec 2026

6MWD, 6-minute walking distance; ACTRIIA, activin receptor type IIA; AE, adverse event; BL, baseline; MOA, mode of action; PAH, pulmonary arterial hypertension; PRA, prostacyclin receptor agonist; sGC, soluble guanylate cyclase; TEAEs, treatment emergent AEs; TKI, tyrosine kinase inhibitor.

1. FDA. Sotatercept PI. Available at: <https://bit.ly/4fv6coc> (accessed 9 September 2024); 2. EMA. Summary of opinion. Sotatercept. Available at: <https://bit.ly/3Xzlg2z> (accessed 10 September 2024); 3. Hoepfer MM, et al. *N Engl J Med.* 2023;388:1478–90; 4. ClinicalTrials.gov. NCT04896008; 5. ClinicalTrials.gov. NCT04796337; 6. ClinicalTrials.gov. NCT04811092; 7. ClinicalTrials.gov. NCT03683186; 8. ClinicalTrials.gov. NCT03626688; 9. ClinicalTrials.gov. NCT04732221; 10. ClinicalTrials.gov. NCT05934526; 11. ClinicalTrials.gov. NCT06274801. Clinical trials are available at: <https://bit.ly/4dvfpkS> using the study identifier (accessed 10 September 2024).