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 PH[1]

Group 1
- PAH

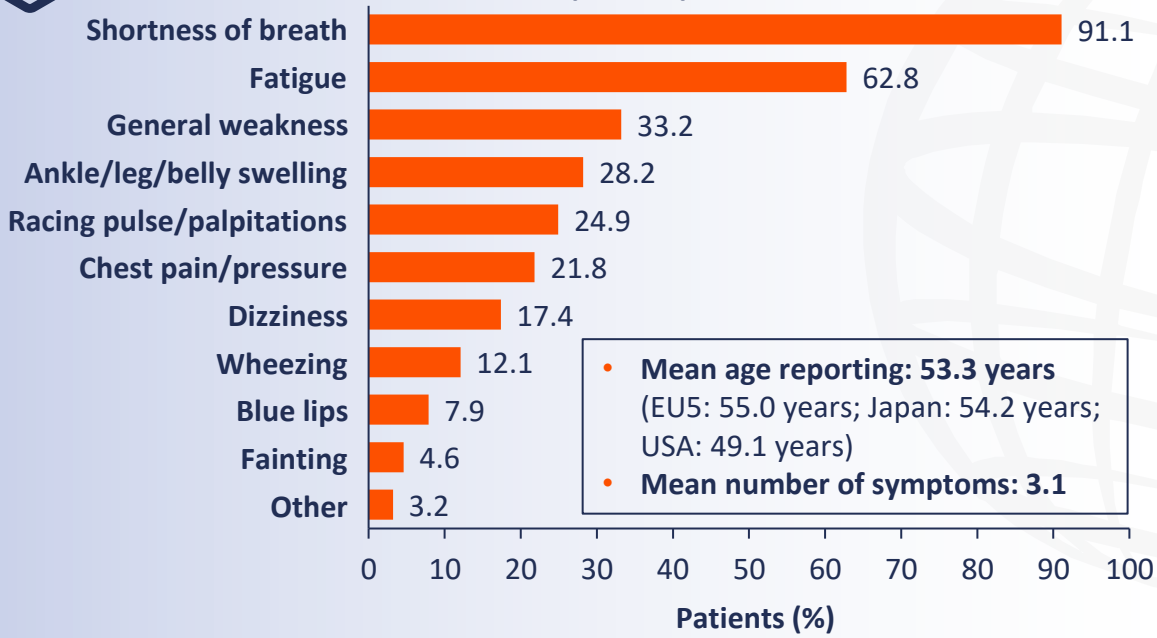
Group 2
- PH associated with left heart disease

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

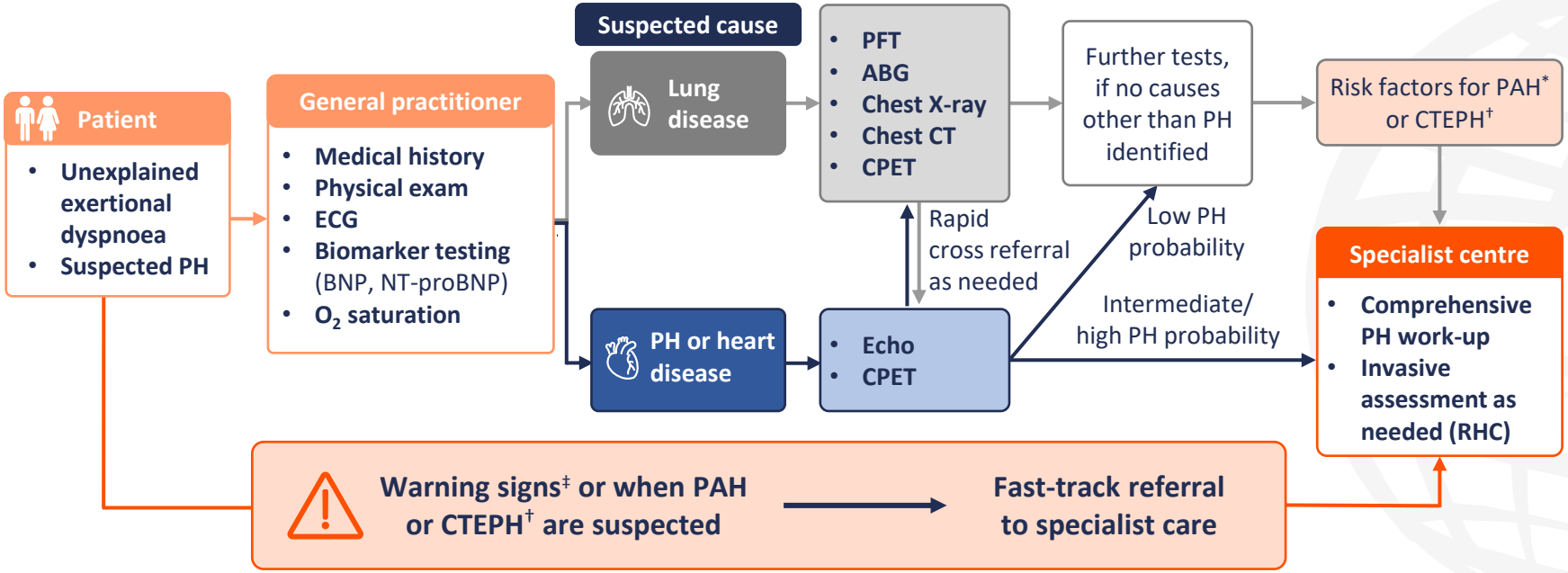
Symptoms of PAH first noticed by patients (N=572)[2]



EU5, France, Germany, Italy, Spain, UK; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

1. Humbert M, et al. *Eur Heart J.* 2022;43:3618–731; 2. Small M, et al. *Ther Adv Respir Dis.* 2024;18:17534666231218886.

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.

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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]

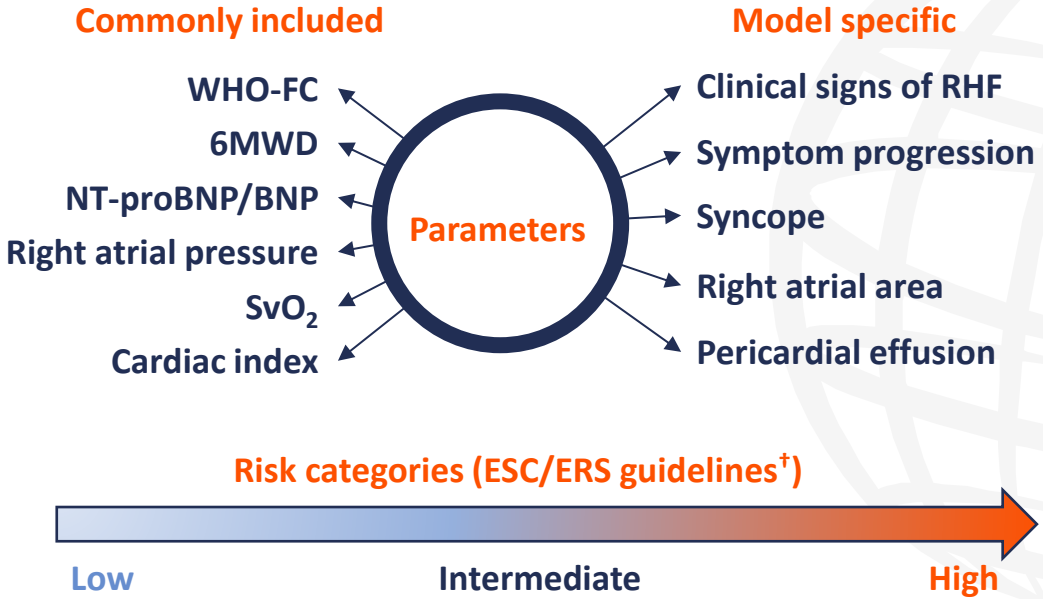
COMPERA 2.0[2,3]
Comparative, Prospective Registry of Newly Initiated Therapies for PH*

FPHR[4]
French PH Registry

REVEAL[5]
Registry to Evaluate Early and Long-Term PAH Disease Management

SPAHR[6]
Swedish PAH Registry

Multiple variables within the different models[7]



*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; SvO_2, 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. Hoeper 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.

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Treatment algorithms for PAH: An evolving landscape

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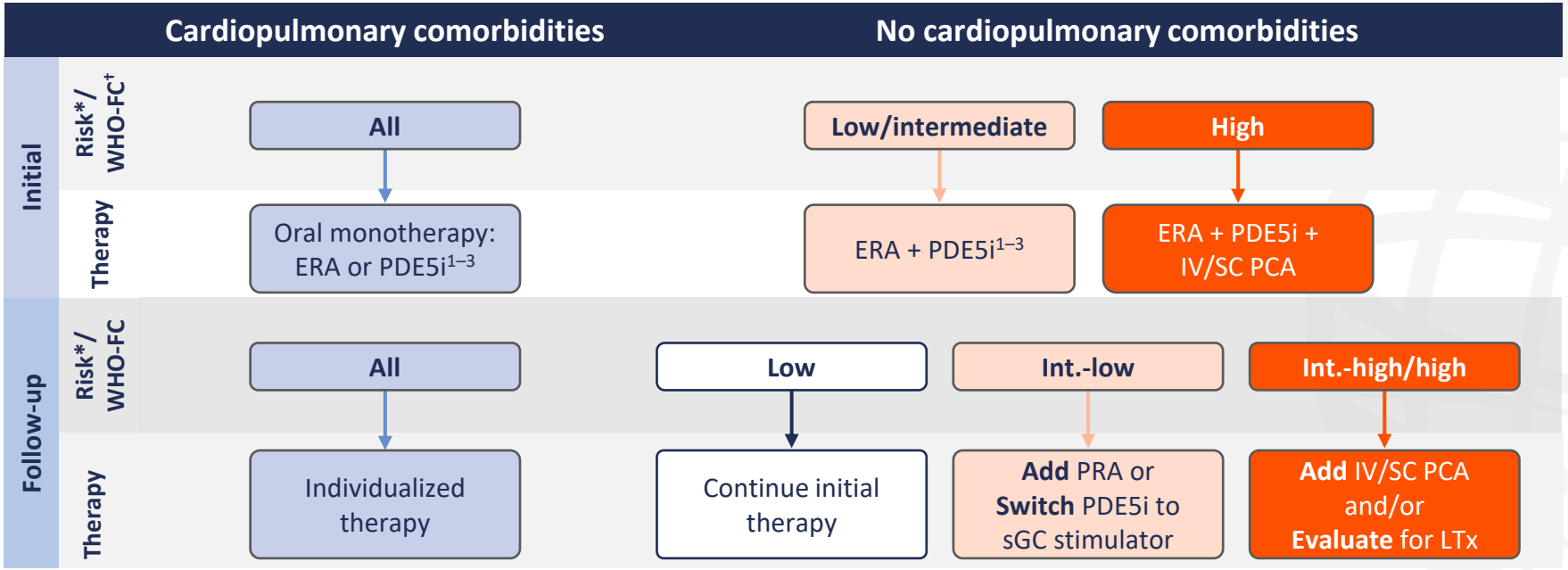
Treatment algorithm for PAH[1–3]



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 class[2] or REVEAL 2.0[3] 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.

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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** **NCT04576988 (STELLAR):**[3] Change from BL in 6MWD vs placebo	**Ongoing trials** **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]	**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]
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/3XzIg2z (accessed 10 September 2024); 3. Hoeper 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).