Pulmonary arterial hypertension:
A practical roadmap from diagnosis to treatment

Practice aid for PAH

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Clinical classification of PH[1]

Group 1: PAH

1.1 Idiopathic
1.2 Heritable
1.3 Associated with drugs and toxins
1.4 Associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
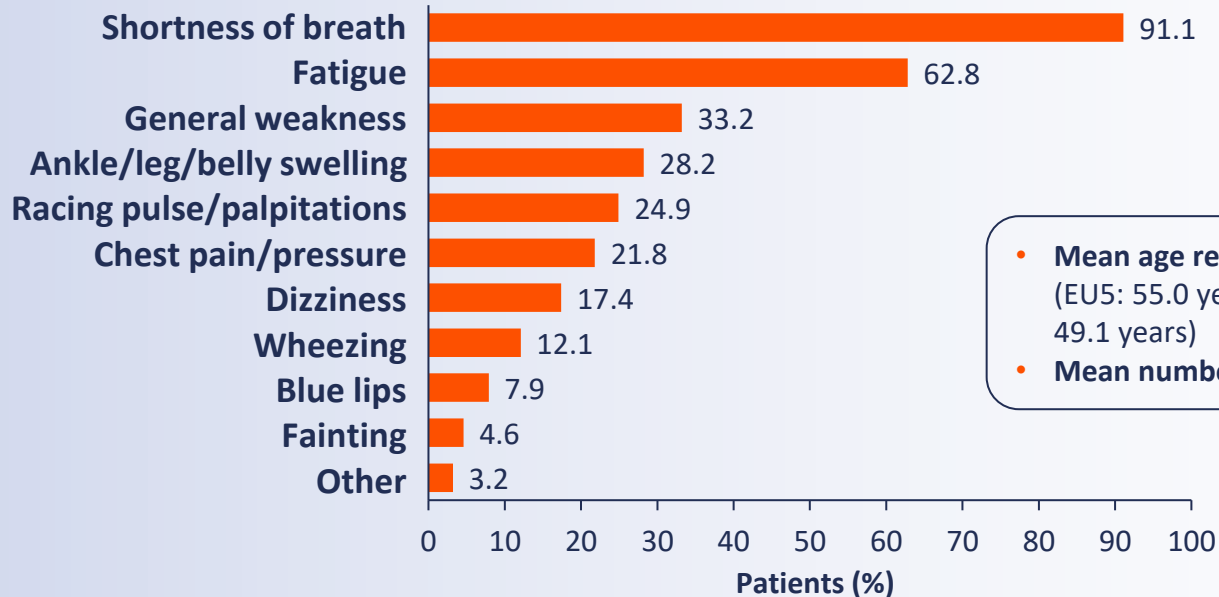1.6 Persistent PH of the newborn

Group 2: PH associated with left heart disease

Group 3: PH associated with lung diseases and/or hypoxia

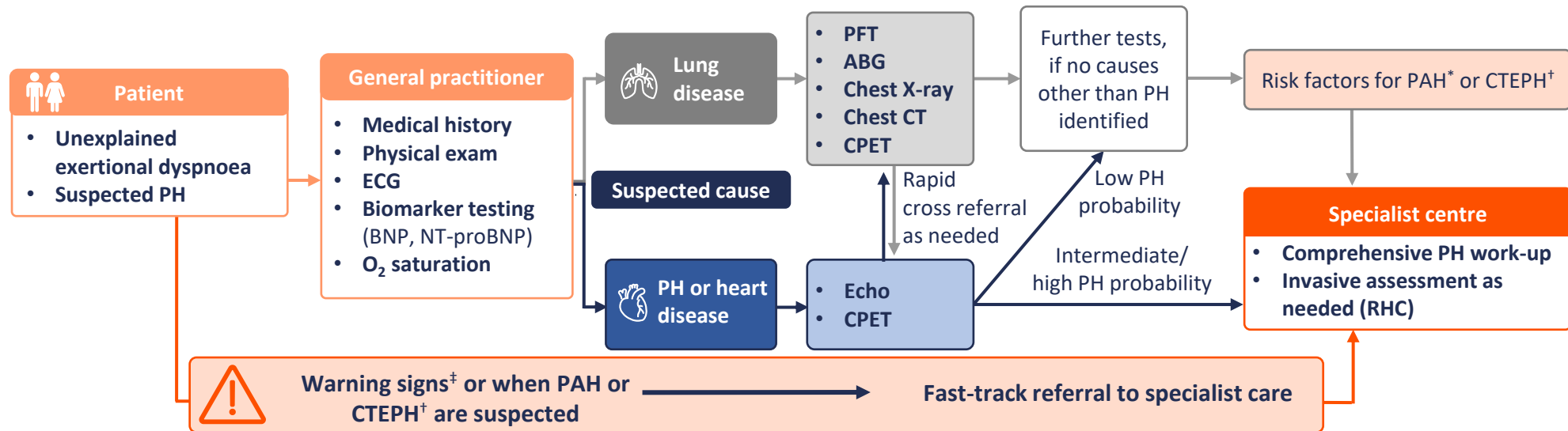**Group 4: PH associated with chronic pulmonary artery obstruction**

Group 5: PH with unclear and/or multifactorial mechanisms
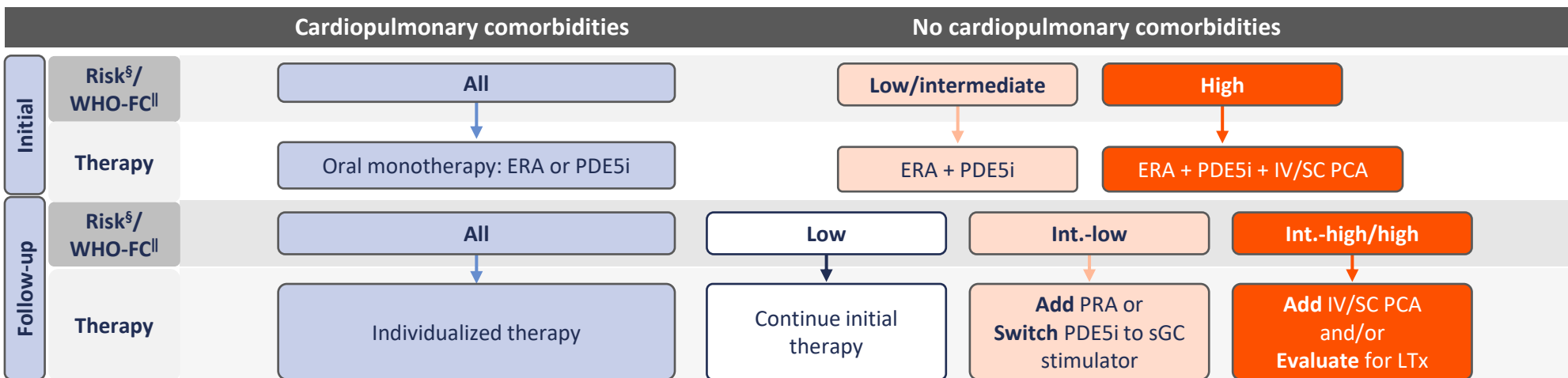
Symptoms of PAH first noticed by patients (N=572)[2]

Symptom	Patients (%)
Shortness of breath	91.1
Fatigue	62.8
General weakness	33.2
Ankle/leg/belly swelling	28.2
Racing pulse/palpitations	24.9
Chest pain/pressure	21.8
Dizziness	17.4
Wheezing	12.1
Blue lips	7.9
Fainting	4.6
Other	3.2

- **Mean age reporting: 53.3 years** (EU5: 55.0 years; Japan: 54.2 years; USA: 49.1 years)
- **Mean number of symptoms: 3.1**

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Diagnostic algorithm for PAH[1]

Patient
- Unexplained exertional dyspnoea
- Suspected PH

General practitioner
- Medical history
- Physical exam
- ECG
- Biomarker testing (BNP, NT-proBNP)
- O$_2$ saturation

Lung disease

Suspected cause

PH or heart disease

- PFT
- ABG
- Chest X-ray
- Chest CT
- CPET

Rapid cross referral as needed

Echo / CPET

Further tests, if no causes other than PH identified

Low PH probability

Intermediate/high PH probability

Risk factors for PAH* or CTEPH[†]

Specialist centre
- Comprehensive PH work-up
- Invasive assessment as needed (RHC)

⚠ Warning signs[‡] or when PAH or CTEPH[†] are suspected → Fast-track referral to specialist care

Treatment algorithm for PAH[1,3,4]

		Cardiopulmonary comorbidities	No cardiopulmonary comorbidities	
Initial	Risk[§]/WHO-FC[‖]	All	Low/intermediate	High
	Therapy	Oral monotherapy: ERA or PDE5i	ERA + PDE5i	ERA + PDE5i + IV/SC PCA

		Cardiopulmonary comorbidities	No cardiopulmonary comorbidities		
Follow-up	Risk[§]/WHO-FC[‖]	All	Low	Int.-low	Int.-high/high
	Therapy	Individualized therapy	Continue initial therapy	**Add** PRA or **Switch** PDE5i to sGC stimulator	**Add** IV/SC PCA and/or **Evaluate** for LTx

*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. [§]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.

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Agents for PAH: Newly approved or in phase III trials*

Agent	Approved (USA and Europe, 2024[5,6])		In phase III clinical trials		
	Sotatercept		**Ralinepag**	**MK-5475**	**Seralutinib**
MOA/Target	ACTRIIA ligand trap		PRA	sGC stimulator	TKI
Trial results/ Primary endpoint(s)	**Pivotal trial:** NCT04576988 (STELLAR): Change from BL in 6MWD vs placebo[7]	**Ongoing trials:** NCT04896008 (ZENITH): Time to first confirmed morbidity/mortality event[8] NCT04796337 (SOTERIA): Patients experiencing an AE[9] NCT04811092 (HYPERION): Time to clinical worsening[10]	NCT03683186 (ADVANCE EXTENSION): Patients with TEAEs[11] NCT03626688 (ADVANCE OUTCOMES): Time to first protocol-defined clinical worsening event[12]	NCT04732221 (INSIGNIA-PAH): Change from BL in 6MWD at 12 weeks[13]	NCT05934526 (PROSERA): Change from BL in 6MWD at 24 weeks[14] NCT06274801 (PROSERA-EXT): Incidence of TEAEs[15]
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

*Information up-to-date as of October 2024.

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Abbreviations and references

Abbreviations

6MWD, 6-minute walking distance; ABG, arterial blood gas analysis; ACTRIIA, activin receptor type IIA; AE, adverse event; BL, baseline; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thromboembolic PH; ECG, electrocardiogram; Echo, echocardiogram; ERA, endothelin receptor antagonist; ESC/ERS, European Society of Cardiology/European Respiratory Society; EU5, France, Germany, Italy, Spain, UK; IBD, inflammatory bowel disease; Int., intermediate; IV, intravenous; LTx, lung transplantation; MOA, mechanism of action; NT-proBNP, N-terminal pro-BNP; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PCH, pulmonary capillary haemangiomatosis; PDE5i, phosphodiesterase-5 inhibitor; PFT pulmonary function test; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; PVOD, pulmonary venoocclusive disease; RHC, right heart catheterization; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; SC, subcutaneous; sGC, soluble guanylate cyclase; TEAEs, treatment emergent AEs; TKI, tyrosine kinase inhibitor; WHO-FC, World Health Organization functional class.

References

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