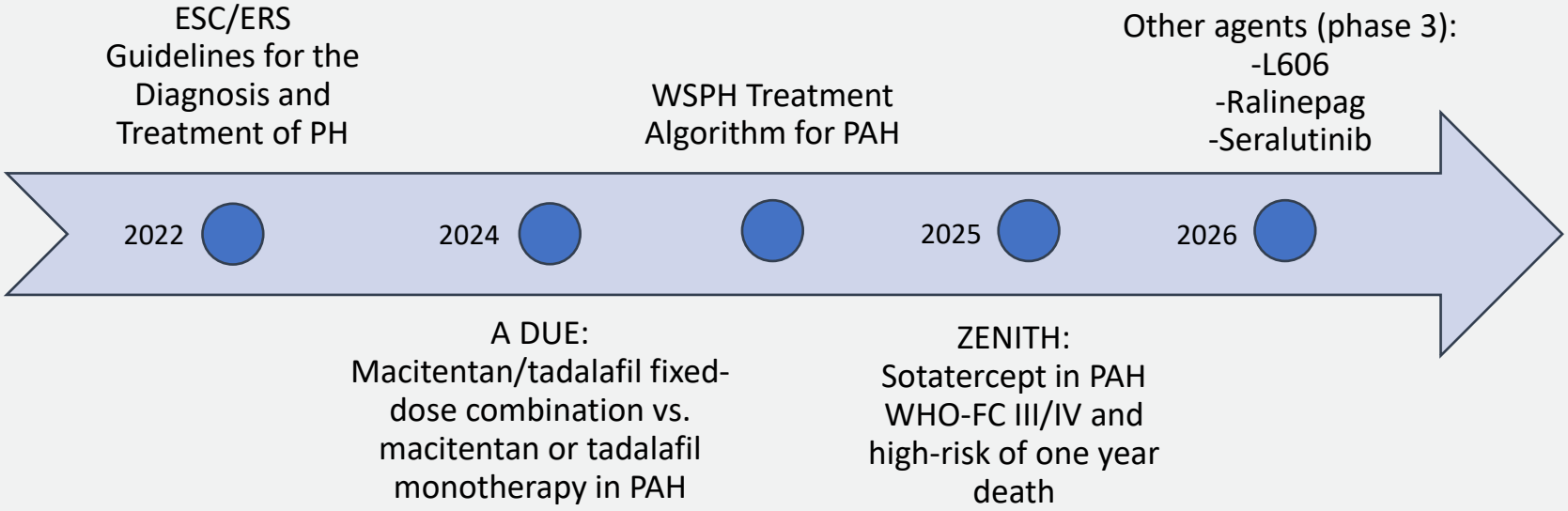

P A H
Subway

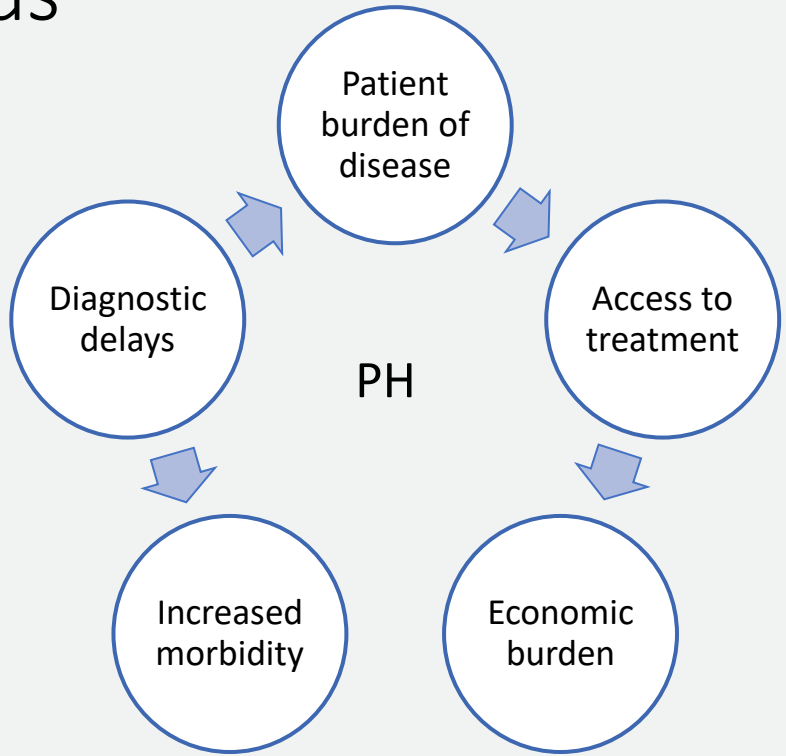
PAH Advances



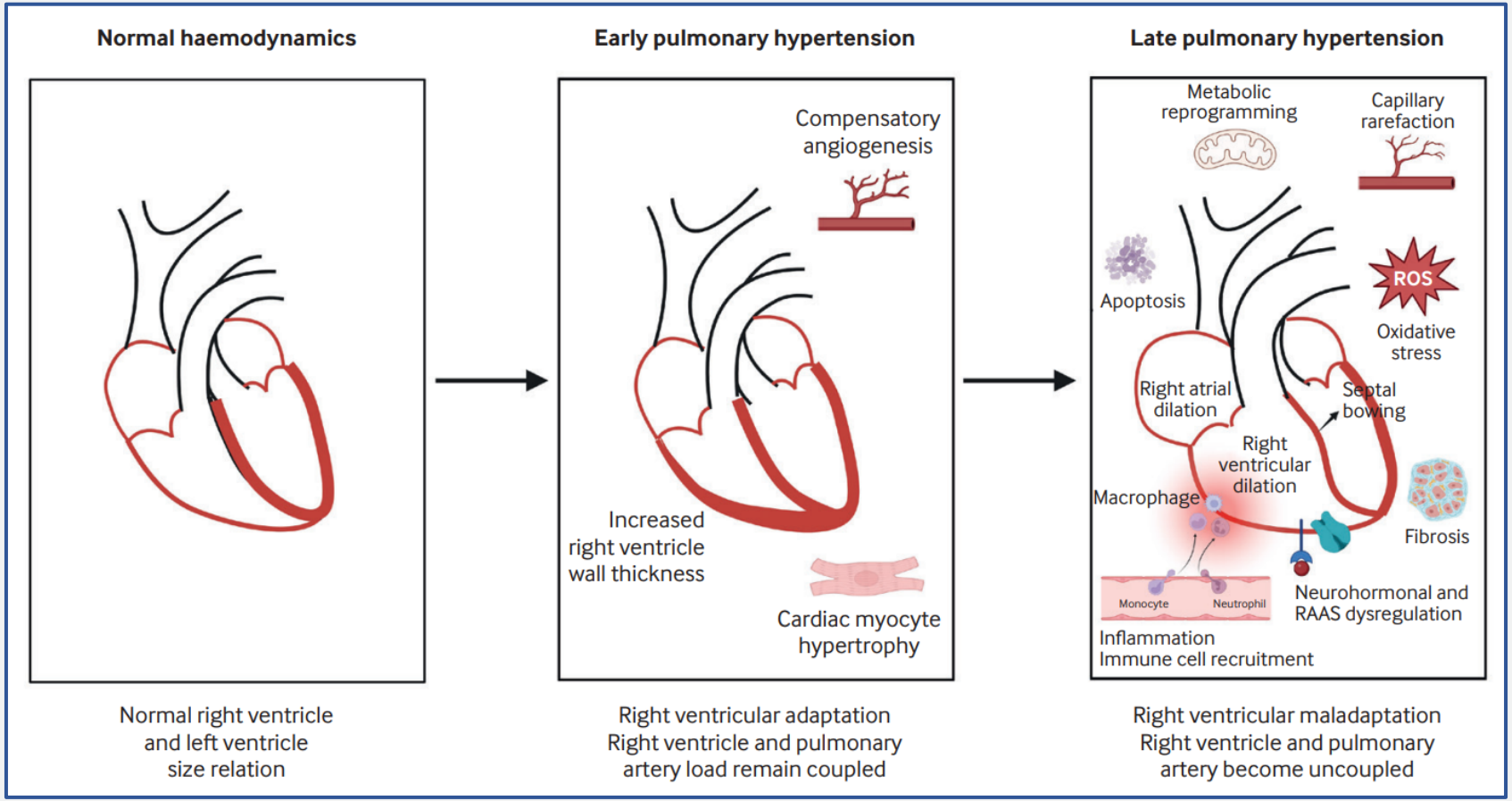
ESC, European Society of Cardiology; ERS, European Respiratory Society; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WHO-FC, World Health Organization Functional Class; WSPH, World Symposium on PH

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.
Grunig E, et al. *J Am Coll Cardiol.* 2024;83(4):473-484.
Chin KM, et al. *Eur Respir J.* 2024;64(4):2401325.
Humbert M, et al. *N Engl J Med.* 2025;392(20):1987-2000.
Preston IR, et al. *Eur Respir J.* 2025;66(1):2401435.

Unmet Needs



DuBrock HM, et al. *Pharmacoecon Open.* 2023;8(1):133-146.
Highland KB, et al. *Am J Manag Care.* 2019;25 (7 Suppl):S119-S127.
Khou V, et al. *Respirology.* 2020;25(8):863-871.
Kubota K, et al. *J Cardiol.* 2024;(83):365-370.



RAAS, renin-angiotensin-aldosterone system

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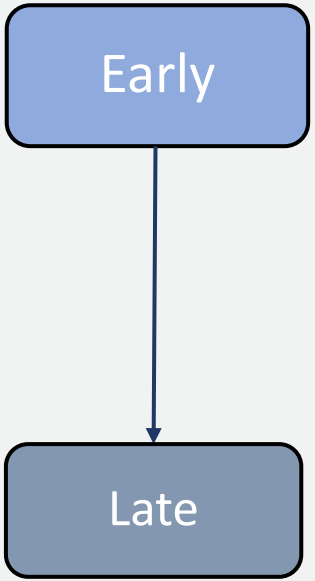
Symptoms



Key symptoms
- Dyspnea (non specific)
- Syncope (high risk)

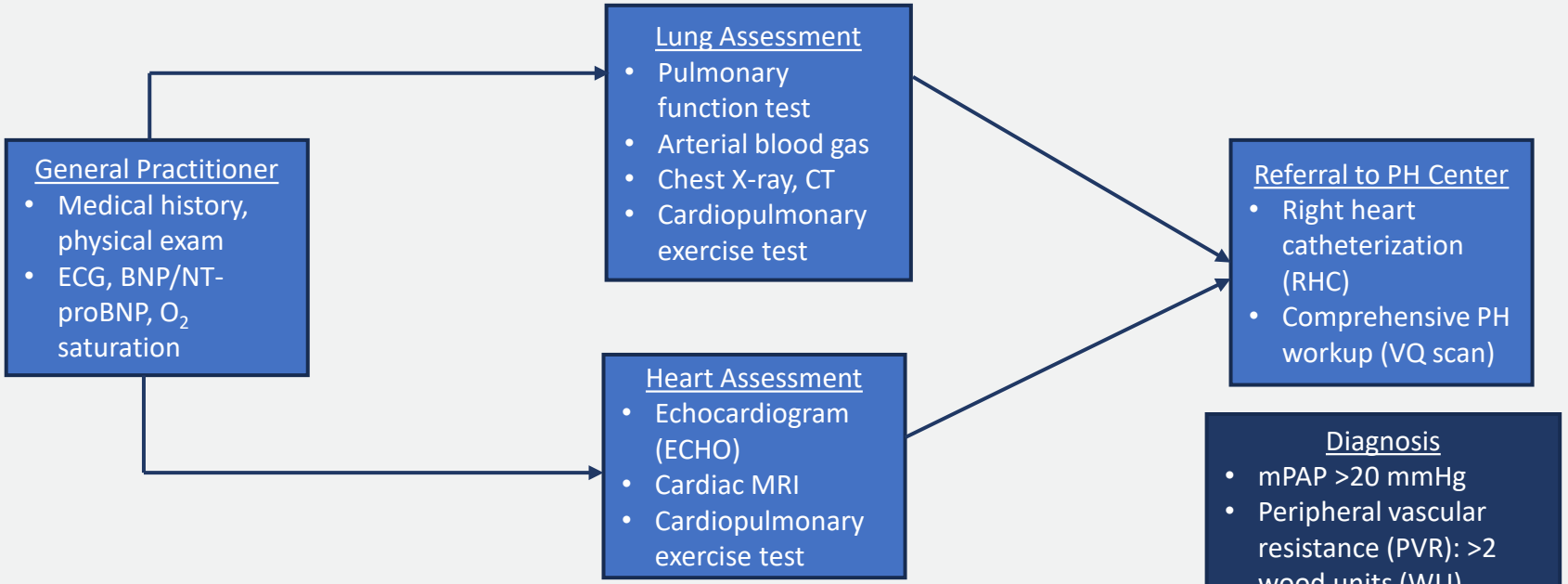
Other symptoms
- Abdominal distension
- Fatigue, rapid exhaustion
- Hemoptysis
- Palpitations
- Weight gain

Rare due to pulmonary artery dilation
- Exertional chest pain
- Hoarseness (dysphonia)
- Shortness of breath, wheezing, cough, LRTI, atelectasis

LRTI, lower respiratory tract infection

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.

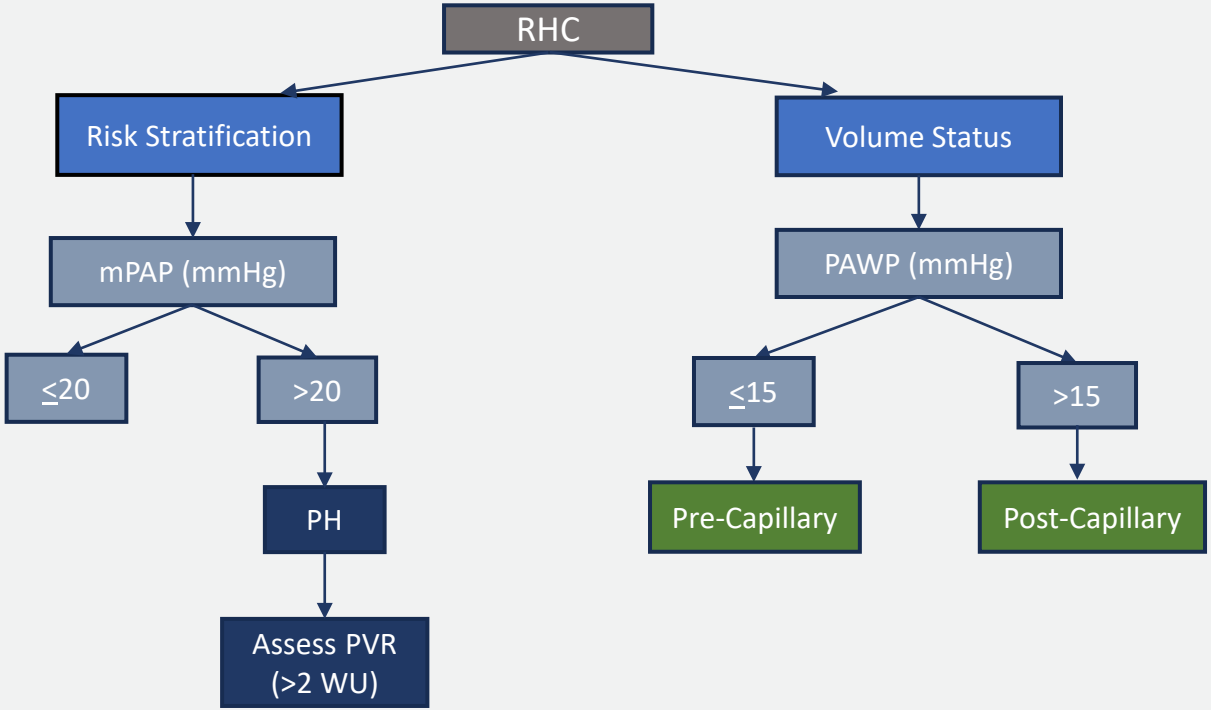
Diagnostic Assessment



BNP, B-type natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; mmHg, millimeters of mercury; mPAP, mean pulmonary artery pressure; MRI, magnetic resonance imaging; NT-proBNP, N-terminal proBNP; VQ, ventilation/perfusion

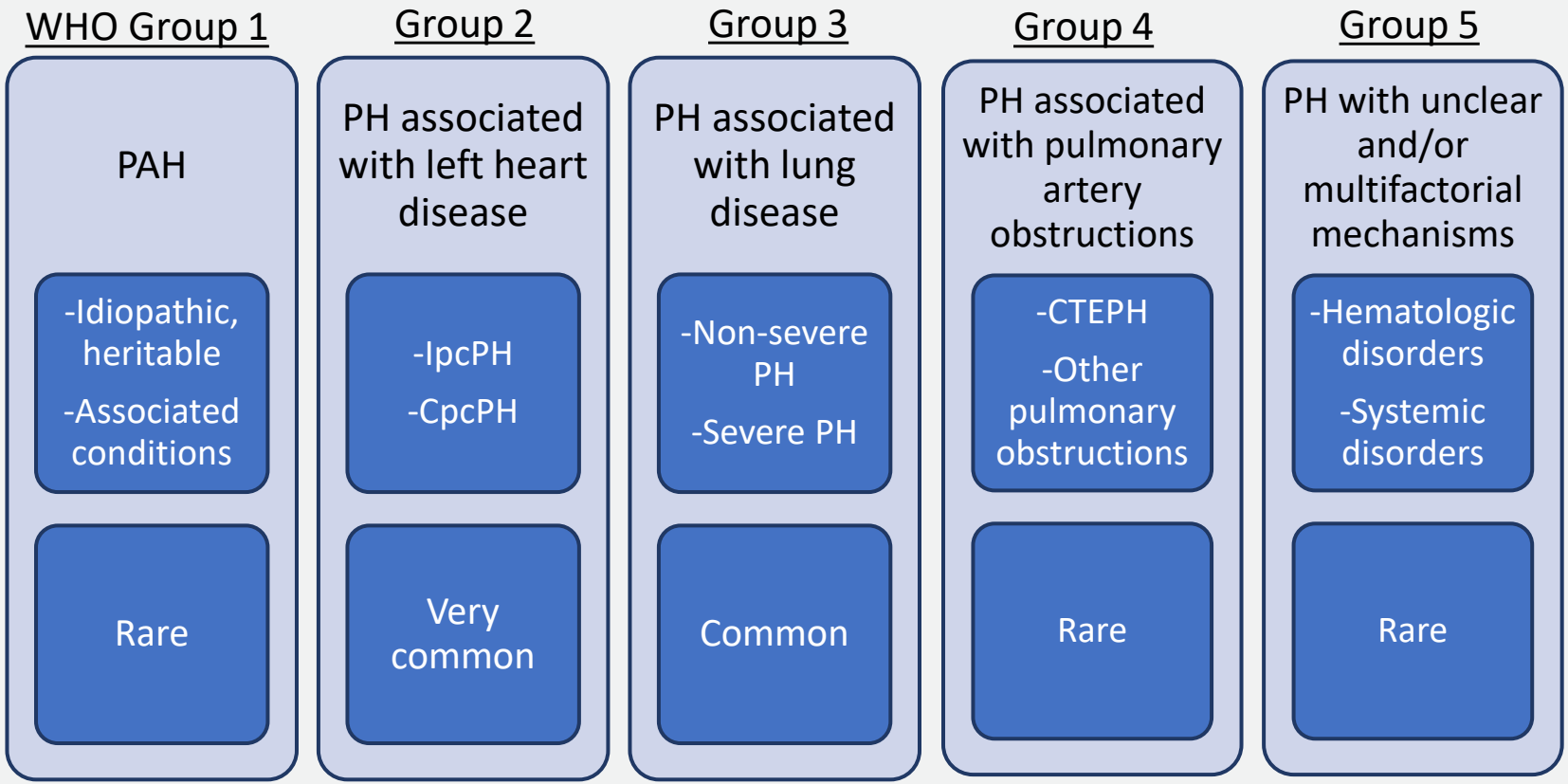
Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.
Mukherjee M, et al. *J Am Soc Echocardiogr.* 2025;38(3):141-186.
Klinger JR, et al. *Chest.* 2019;155(3):565-586.

Hemodynamic Assessment



PAWP, pulmonary arterial wedge pressure

Maron B, et al. *JACC.* 2020;76(22):2671-2681.
Kularatne M, et al. *J Cardiovasc Dev Dis.* 2024;11(3):78.



CpcPH, combined post- and pre-capillary pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.

Key Concept

- Presenting patient symptoms may vary based on disease severity
- RHC is essential for the diagnosis of PH
- Evaluation of disease severity includes heart and lung function assessments and laboratory and hemodynamic variables
  - 6-MWD for risk calculation
  - CPET with gas exchange better for tolerance and capacity

6-MWD, 6-minute walking distance; CPET, cardiopulmonary exercise test

Treatment Goals

- Improve patient survival
- Improve symptoms and quality of life
- Improve exercise capacity
- Prevent disease progression

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.
McLaughlin VV, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D73-81.

Risk Stratification – Three Strata Model

Variables*	
WHO Group 1 subgroup	6-MWD
Male age >60 years	BNP NT-proBNP
eGFR <60 mL/min/1.73m^2 or renal insufficiency	Pericardial effusion on ECHO
NYHA/WHO-FC	% predicted DL_{CO} <40
Systolic blood pressure, heart rate	mRAP >20 mmHg within 1 year
All-cause hospitalizations ≤6 mos	PVR <5 WU on RHC

Risk score, estimated one year mortality:	Low (0-6) (<5%)	Intermediate (7-8) (5-20%)	High (≥9) (>20%)

*REVEAL, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management, 2.0 Risk Calculator

DL_{CO} , diffusing capacity of carbon monoxide; eGFR, estimated glomerular filtration rate; mRAP, mean right atrial pressure; NYHA, New York Heart Association

Benza RL, et al. *Chest.* 2019;156(2):323-337.
Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.

Risk Stratification – Four Strata Model

Points Assigned				
	1	2	3	4
Four-strata model[†] WHO-FC 6MWD, m BNP, ng/L NT-proBNP, ng/L	 I or II >440 <50 <300	 -- 320-440 50-199 300-649	 III 165-319 200-800 650-1100	 IV <165 >800 >1100
Risk Status (one-year survival rate, %)	Low (98.5)	Intermediate-low (97.2)	Intermediate-high (91.3)	High (78)

[†]Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) 2.0 Risk Assessment Model

Hoeper MM, et al. *Eur Respir J.* 2022;60(1):2102311.

Key Concept

- Goal of PAH treatment is to improve patient morbidity and mortality
- Three strata model is recommended at the time of diagnosis
- Four strata model is recommended for risk stratification during follow-up

Guideline-Directed Treatment

General Measures

- To optimize outcomes by addressing systemic consequences of PH and right-sided heart failure

Pathway-Specific Therapy

- To achieve and maintain low-risk profile

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.

General Measures

- Physical activity, rehabilitation
- Anticoagulant therapy
  - Individualized decision on potential benefits/risks
  - Evidence with potential benefit in I/PAH and harm in PAH-SSc
- Diuretics
  - Right heart failure associated with systemic fluid retention, RAAS activation
  - Fluid intake restriction and/or use of loop diuretics, thiazides, MRAs

I/PAH, idiopathic PAH; MRA, mineralocorticoid receptor antagonist; PAH-SSc, PAH in systemic sclerosis

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.
Preston IR, et al. *Circulation.* 2015;132(25):2403-2411.
Khan MS, et al. *Cardiovasc Qual Outcomes.* 2018;11(9):e004757.
Wang P, et al. *Thromb Res.* 2020;196:251-256.

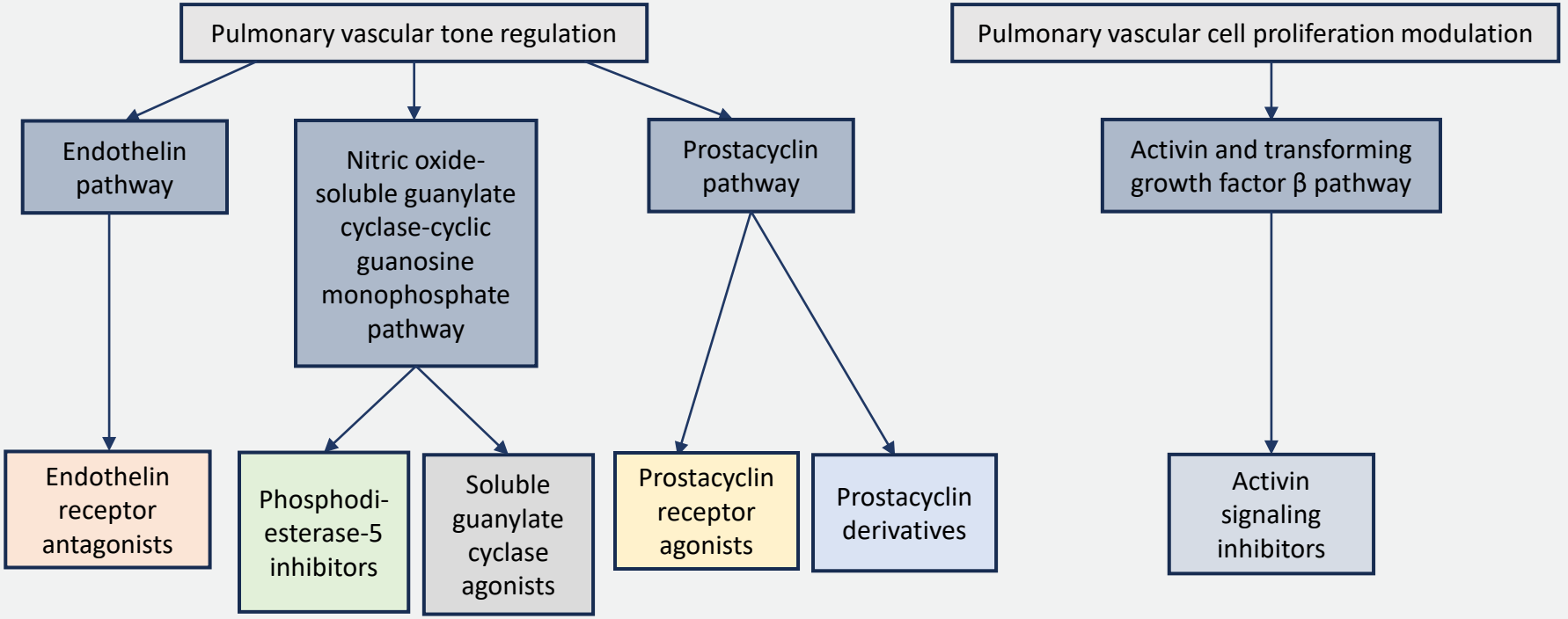
General Measures (cont)

- Select cardiovascular medications
  - Absent efficacy/safety data on the use of ARBs, ARNIs, SGLT-2i, beta-blockers, ivabradine in PAH
  - May cause hypotension and/or bradycardia
- Oxygen therapy
- Iron deficiency correction
- Vaccination
- Psychosocial support
- Counseling & contraception*

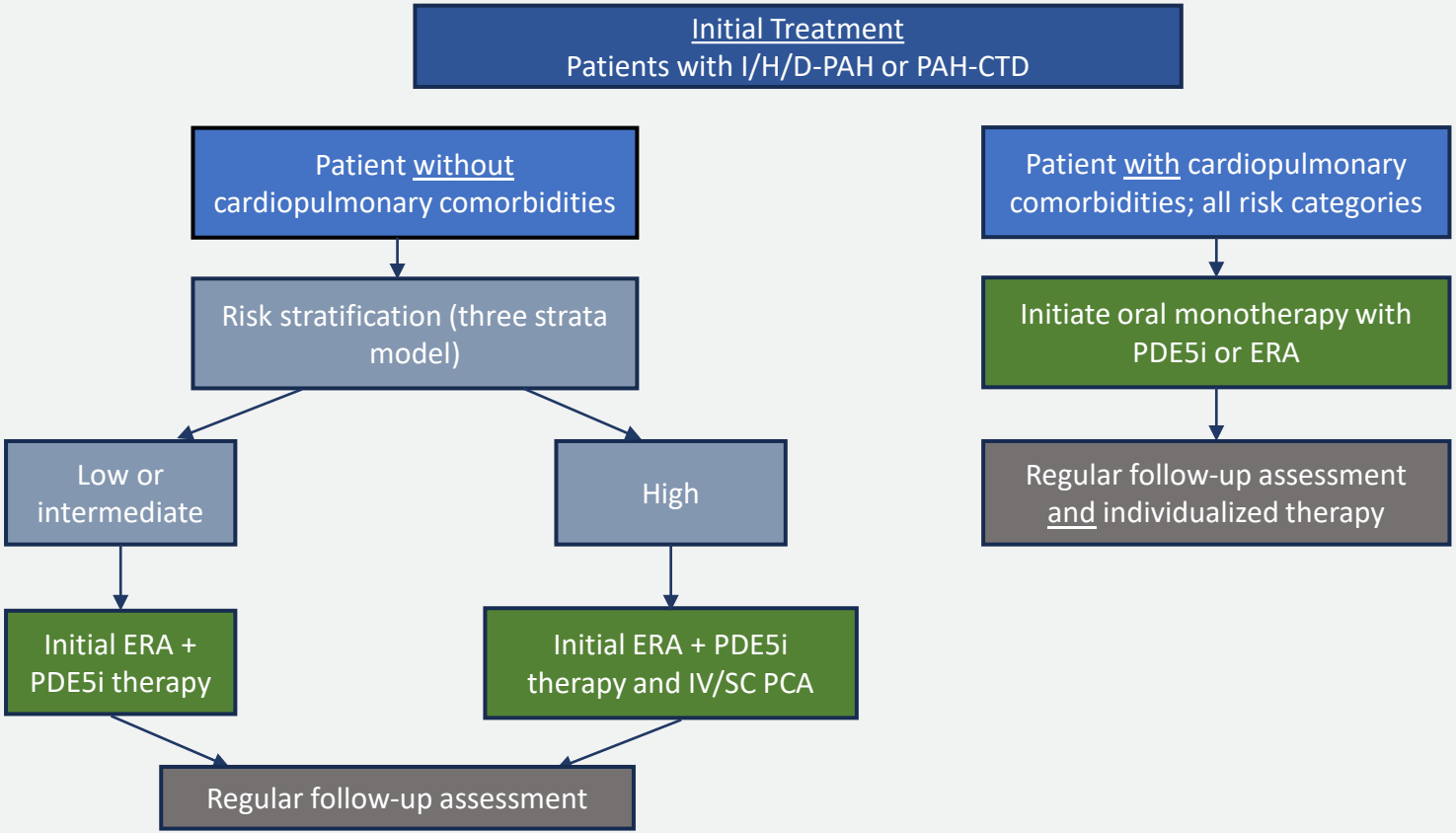
ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor-neprilysin inhibitors; I/PAH, idiopathic PAH; MRAs, aldosterone receptor antagonists; PAH-SSc, PAH in systemic sclerosis; SGLT2-i, sodium-glucose cotransporter-2 inhibitors

*Women of childbearing potential

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.
Preston IR, et al. *Circulation.* 2015;132(25):2403-2411.
Khan MS, et al. *Cardiovasc Qual Outcomes.* 2018;11(9):e004757.
Wang P, et al. *Thromb Res.* 2020;196:251-256.



Humbert M, et al. *Eur Respir J.* 2023;62(5):2301726.



ERA, endothelin receptor antagonist; I/H/D-PAH, idiopathic, heritable, or drug-associated PAH; IV, intravenous; PAH-CTD, PAH-connective tissue disease; PDE5i, phosphodiesterase-5 inhibitor; SC, subcutaneous

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.

Pathway-Specific Treatments

Approved for WHO Group 1

Medication Class	Agent(s)	Route(s) of Administration	Adverse Effects
Phosphodiasterase-5 Inhibitor (PDE5i)	Sildenafil	IV, oral	Diarrhea Flushing Headache
	Tadalafil	Oral	
Prostacyclin Analogue (PCA)	Epoprostenol	Inh, IV	Flushing Jaw pain Headache Nausea
	Treprostinil	Inh, IV, oral, SC	
Prostacyclin Receptor Agonist (PRA)	Selexipag	Oral	Flushing Headache Nausea
Soluble Guanylate Cyclase (sGC) Agonist	Riociguat	Oral	Headache Hypotension

Inh, inhaled; IV, intravenous; SC, subcutaneous

Pathway-Specific Treatments (cont)

Approved for WHO Group 1

Medication Class	Agent	Route(s) of Administration	Adverse Effects
Endothelin Receptor Antagonist (ERA)	Ambrisentan	Oral	Anemia Edema Hepatic transaminitis
	Bosentan		
	Macitentan		
Activin Signaling Inhibitor	Sotatercept	SC	Erythrocytosis Thrombocytopenia, bleeding Telangiectasias

Sotatercept: Pooled Analysis of PULSAR/STELLAR Trials

Objective	• Describe patient demographics, efficacy and safety of sotatercept vs. placebo

Design	• Exploratory, post hoc, pooled analysis from phase 2 (PULSAR) and phase 3 (STELLAR) trials
	  • RCTs with a 24-week placebo-controlled period
	  • PULSAR: Followed by 18-month OLE
	  • STELLAR: Followed by double-blinded 72-week extension period

Methods	• PAH patients WHO-FC II or III receiving approved background therapies in accordance with local treatment guidelines
	  • ERA, PDE5i, sGC, PCA and/or PRA
	• Randomized to add-on sotatercept or placebo
	  • PULSAR: Sotatercept 0.3 mg/kg or 0.7 mg/kg every 3 weeks
	  • STELLAR: Sotatercept 0.3 mg/kg (initial) escalated to target dose 0.7 mg/kg every 3 weeks

OLE, open-label extension; RCT, randomized controlled trial

Hoeper MM, et al. *Eur Respir J.* 2025;65(5):2401424.

Sotatercept: Pooled Analysis of PULSAR/STELLAR Trials (cont)

Outcomes/ Results	• Sotatercept (n = 237), placebo (n = 192)
	• Primary end point: Change from baseline at week 24 in 6MWD, PVR, and NT-proBNP level
	  • Multicompartment improvement[§]: sotatercept 100/236 (42.4%) patients vs. placebo 21/191 (11%) patients, *P*< 0.01
	• Safety: Incidence of TEAEs at week 24
	  • Sotatercept 85.2% vs. placebo 88%

Conclusion	• Pooled analysis demonstrates sotatercept delivers therapeutic benefit across a range of efficacy end-points with favorable safety profile in patients with PAH

[§]*Composite of 6MWD, PVR, and NT-proBNP level*

TEAEs, treatment-related adverse events

Hoeper MM, et al. *Eur Respir J.* 2025;65(5):2401424.

Sotatercept: SOTERIA Trial

SOTERIA (interim)	
Objective	• Evaluate the long-term efficacy, safety, and tolerability of sotatercept treatment in patients with PAH
Design	• Phase 3, open-label, interventional long-term follow-up study
Methods	• PAH patients on stable background therapy who completed a prior sotatercept study without early discontinuation • Monotherapy or combination therapy • Titration of sotatercept dose to 0.7 mg/kg every 21 days • Study to remain open for up to 7 years

Preston IR, et al. *Eur Respir J.* 2025:66(1):2401435.

Sotatercept: SOTERIA Trial (cont)

SOTERIA (interim)	

Outcomes	• Sotatercept (n = 426), median exposure/follow-up of 448.6 ± 172.9 days
	• Primary end point: Safety and tolerability (TEAEs, dose holds/reductions)
	  • TEAEs: 387/426 (90.8%) patients
	  • SAEs related to treatment: 11/426 (2.6%) patients
	  • Treatment discontinuation: 15/426 (3.8%) patients
	  • Dose holds: 115/426 (27%), dose reductions: 97/426 (22.8%) patients
	  • Severe decreased platelet count: 14/426 (3.3%) patients
	  • Moderate-to-severe increased hemoglobin: 59/426 (13.8%) patients

Conclusion	• Interim results support favorable benefit-risk of add-on sotatercept treatment in PAH patients

SAEs, serious adverse events

Preston IR, et al. *Eur Respir J.* 2025:66(1):2401435.

Clinical Development – Novel Targets

Satralizumab

IL-6 receptor modulation

- Phase 2 including I/H/D-PAH, PAH-CTD, WHO-FC I-III with IL-6 response phenotype
- Primary outcome: Evaluation of percent change in PVR from baseline to 24 weeks

Seralutinib

Platelet-derived growth factor receptor

- Phase III including I/H/D-PAH, PAH-CTD, WHO-FC II-III
- Primary outcome: Change in 6MWD from baseline to 24 weeks

IL-6, Interleukin-6

Clinicaltrials.gov. Updated July 8, 2024. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT05679570
Tamura Y, et al. *Pulm Circ.* 2023;13(2):e12251.
Clinicaltrials.gov. Updated June 4, 2025. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT05934526
Frantz RP, et al. *Lancet Respir Med.* 2024;12(7):523-534.

Clinical Development – Novel Agents

L606 — Liposomal treprostinil inhalation suspension (PCA)

- Phase 3 open-label study in PAH or PH-ILD receiving prior PCA or those likely to have clinical benefit
- Primary outcome: Incidence of treatment-emergent AEs/SAEs at 2, 12, and 48 weeks

Ralinepag — PRA

- Phase 3 RCT in PAH WHO Group 1
- Primary outcome: Time to the first adjudicated protocol-defined clinical worsening event

Frespaciguat — sGC

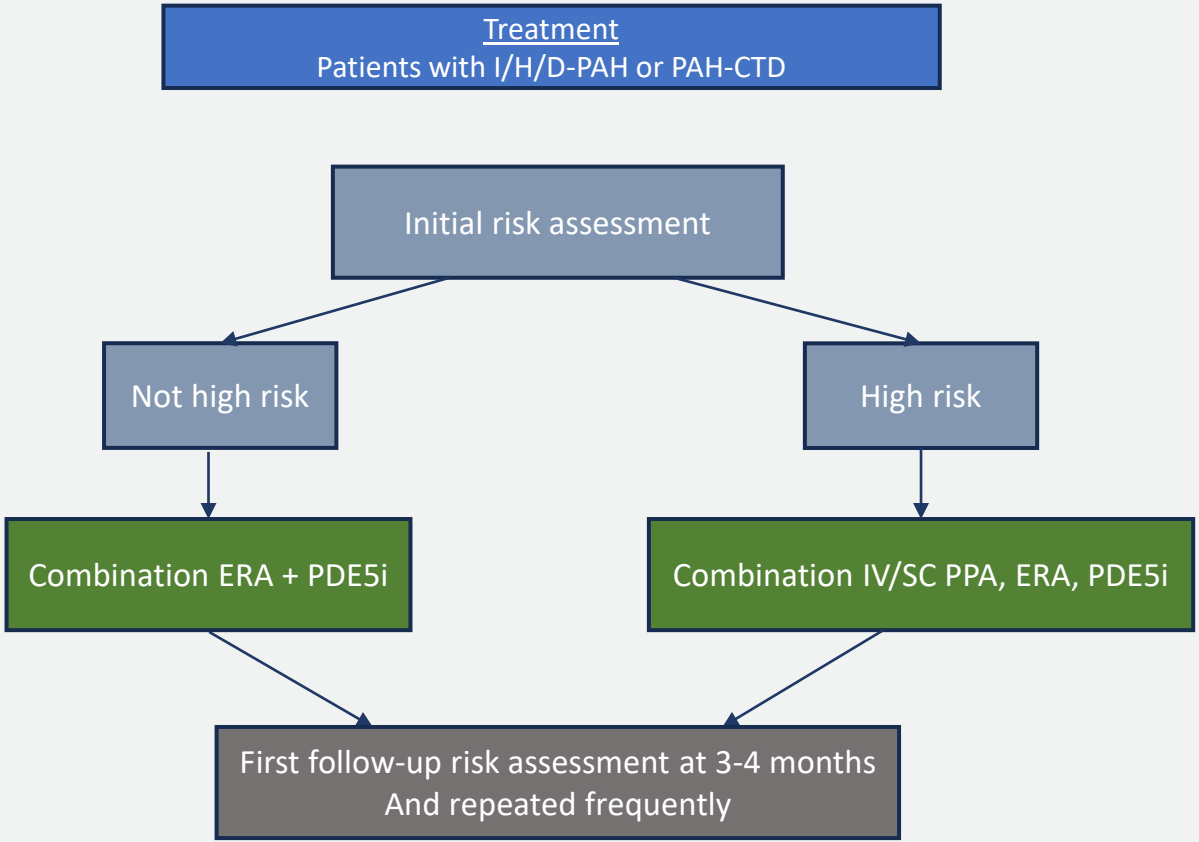
- Phase 2 RCT in patients with PAH-COPD WHO-FC II-IV on stable pharmacologic treatment and/or general measure(s)
- Primary outcome: Change in 6MWD from baseline to week 24

PAH-COPD, PAH-chronic obstructive pulmonary disease; PH-ILD, PH in interstitial lung disease

Clinicaltrials.gov. Updated October 9, 2024. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT04691154
Clinicaltrials.gov. Updated June 24, 2025. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT03626688
Barbera J, et al. *Adv Ther.* 2024;41(3):1062-1074.
Clinicaltrials.gov. Updated July 28, 2025. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT05612035
Humbert M, et al. *Eur Respir J.* 2024;64(5):2401110.

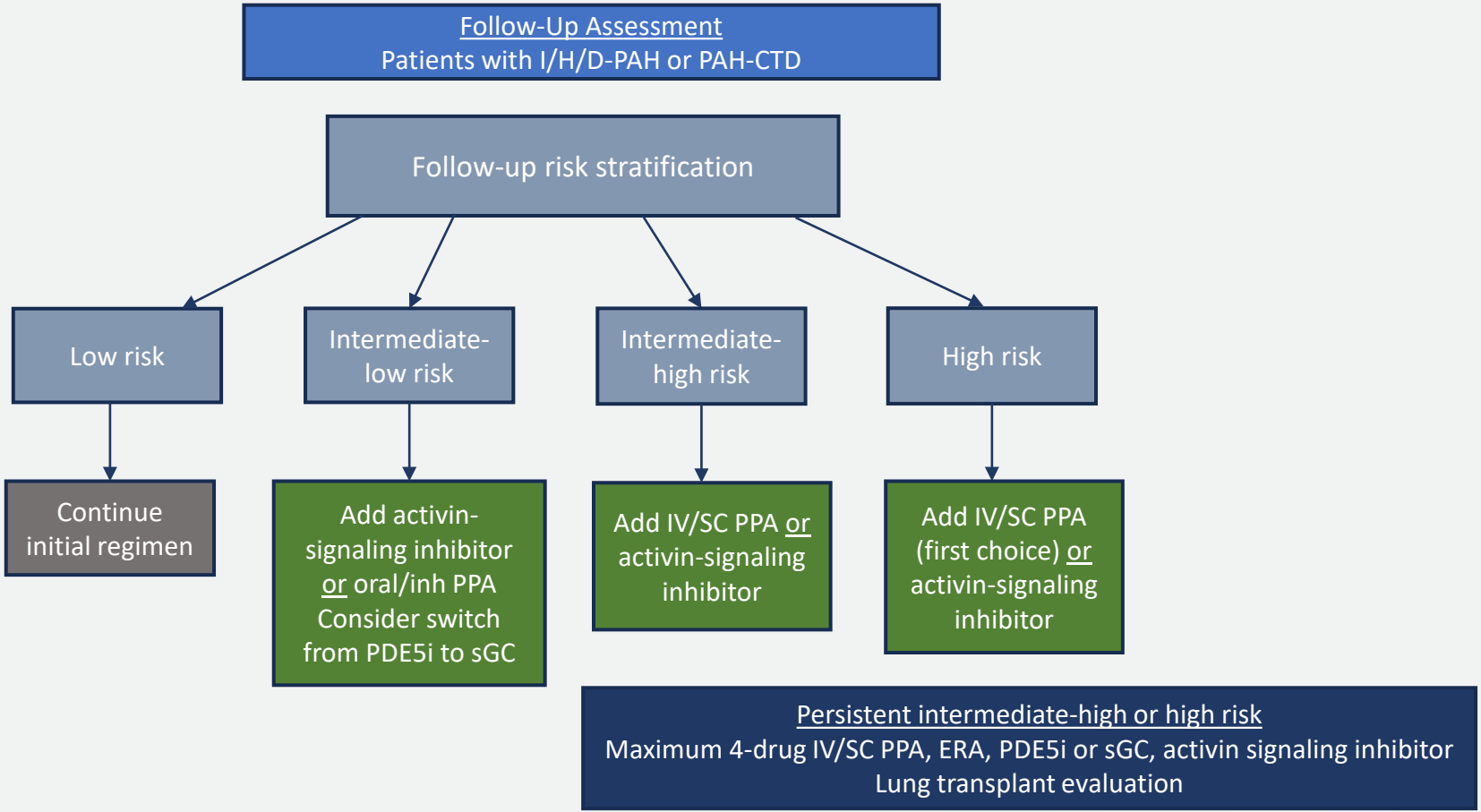
Key Concept

- Treatment goal is to achieve and maintain a low-risk profile on optimized medical therapy
- Consideration of general measures and patient-specific goals
- Selection of initial pathway-specific treatment based on cardiopulmonary comorbidities and risk stratification



PPA, prostacyclin pathway agent

Chin KM, et al. *Eur Respir J.* 2024;64(4):2401325.



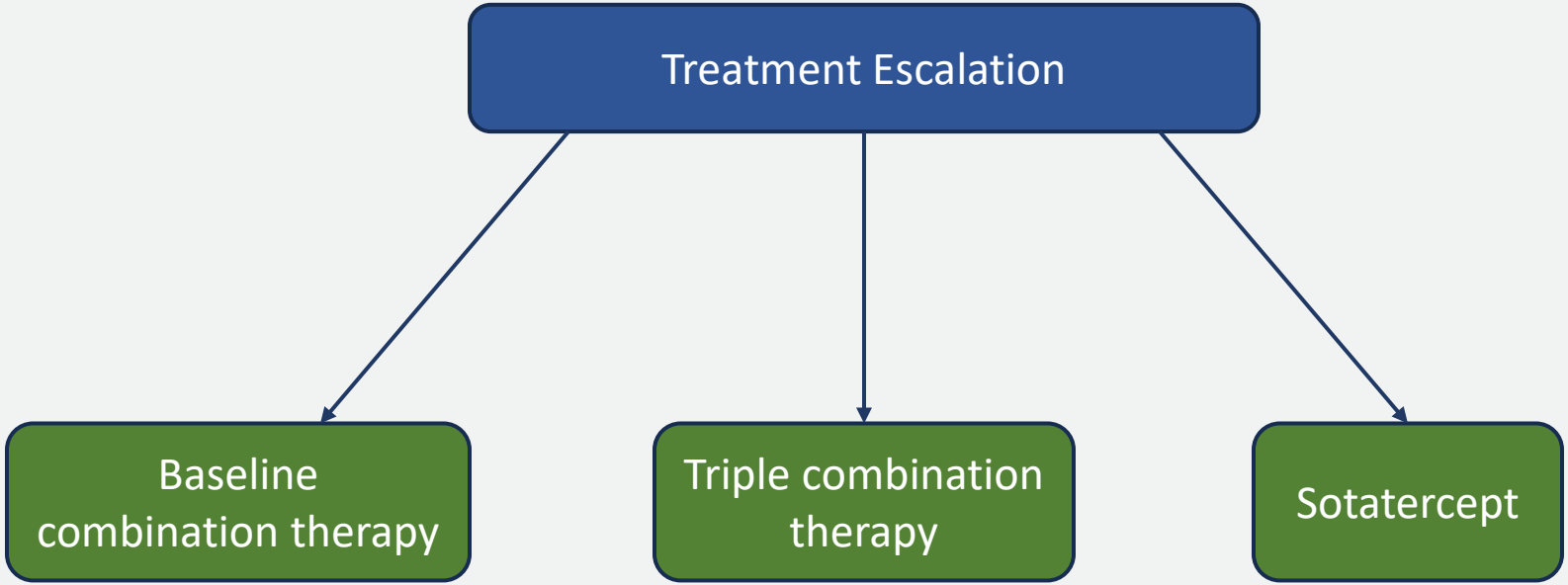
Chin KM, et al. *Eur Respir J.* 2024;64(4):2401325.

Combination vs. Monotherapy

Study	Methods	Treatment(s)	Outcomes
Galie 2015	RCT including Group 1 WHO-FC II-III patients not on treatment	Randomized 2:1:1 to ERA/PDE5i, ERA/placebo or PDE5i/placebo	First clinical failure reduced in combined therapy (18%) vs. pooled analysis of monotherapy (31%) (HR 0.5 [95% CI 0.35-0.72], *P*<0.01)
La Joie 2016	Meta-analysis of RCTs (Jan 1990-May 2015)	PAH-specific combination vs. monotherapy for at least 12 wks	Significant risk reduction for clinical worsening associated with combined therapy (17%) vs. monotherapy (28%) (RR 0.65 [95% CI 0.58-0.72], *P*<0.01)
Grunig 2024	RCT including Group 1 WHO-FC II-III patients naïve to treatment or receiving ERA or PDE5i therapy ≥3 mos	Randomized 2:1:1 to ERA/PDE5i, ERA/placebo, or PDE5i/placebo	Significant reduction in PVR at wk 16 greater in combined treatment vs. both monotherapies (TE 0.71 [95% CL 0.61-0.82], *P*<0.01)

HR, hazard ratio; RR, relative risk

Galie N, et al. *N Engl J Med.* 2015;373(9):834-844.
Lajoie AC, et al. *Lancet Respir Med.* 2016 Jun;4(6):e34.
Grunig E, et al. *J Am Coll Cardiol.* 2024;83(4):473-484



Optimization of Combination Therapy

- Treatment escalation based on risk assessment and patient discussion

Non-Vasoactive I/H/D-PAH	Class[a]	Level[b]
Initial Therapy High risk: PDE5i, ERA and IV/SC PCA	IIa	C
Follow-Up Intermediate-low risk: Selexipag added to ERA/PDE5i	IIa	B
Intermediate-high or high risk: IV/SC PCA added to ERA/PDE5i, referral for lung transplantation	IIa	C
Intermediate-low risk: Switch from PDE5i to riociguat, added to ERA	IIb	B

[a]Class of recommendation; [b]Level of evidence

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.

Optimization of Combination Therapy (cont)

- Treatment escalation based on risk assessment and patient discussion

Sequential Combination Therapy	Class[a]	Level[b]
Morbidity/mortality end point:		
Macitentan added to PDE5is or oral/inh PCAs	I	B
Selexipag added to ERAs and/or PDE5is	I	B
Oral treprostinil added to ERA or PDE5i/riociguat monotherapy	I	B
Exercise capacity end point:		
Sildenafil added to epoprostenol	I	B
Inh treprostinil added to sildenafil or bosentan monotherapy	IIa	B
Riociguat added to bosentan	IIa	B

[a]Class of recommendation; [b]Level of evidence

Humbert M, et al. *Eur Respir J.* 2023;61(1):2200879.

Real-World Outcomes

- Unmet need
  - Significant portion of patients with PAH-related hospitalizations receive prior treatment with monotherapy
- Recommendations
  - Add-on sequential therapy may significantly increase functional, echocardiographic, and hemodynamic parameters
  - Treatment escalation associated with lower rehospitalization rate

Combination therapy is now indicated for initial treatment

Deshwal H, et al *Ther Adv Respir Dis.* 2023;17:17534666231199693.
Mazurek JA, et al. *Sci Rep.* 2025;15(1):12235.

Sotatercept - Treatment Escalation

ZENITH	
Objective	• Evaluate the efficacy of sotatercept in patients with more advanced PAH on maximum tolerated background combination therapy
Design	• Phase 3, multicenter, double-blinded RCT

Methods	• Symptomatic WHO Group 1 PAH patients with WHO-FC III or IV and high one-year risk of death‡ who received maximum tolerated dose of background therapy
	  • PCA infusion, double or triple combination
	• Randomized to add-on sotatercept or placebo
	  • Sotatercept 0.3 mg/kg (initial) escalated to target dose 0.7 mg/kg every 3 wks

‡REVEAL Lite 2 risk score ≥9

PCA, prostacyclin analog

Humbert M, et al. *New Engl J Med.* 2025;392(20):1987-2000.

Sotatercept - Treatment Escalation (cont)

ZENITH	

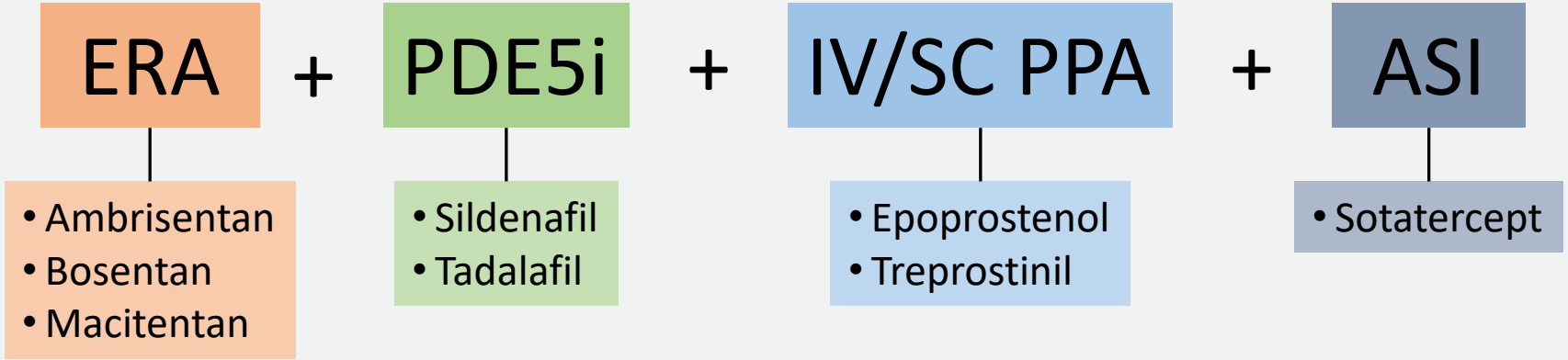
Outcomes/ Results	• Trial stopped early based on interim analysis of efficacy results
	• Sotatercept (n=86), placebo (n=86)
	• Primary end point: Composite of death from any cause, lung transplantation, or hospitalization for worsening PAH
	  • Sotatercept 17.4% vs. placebo 54.7% (HR 0.24, 95% CI 0.13 – 0.43; *P*<0.01)
	• Safety: Incidence of TEAEs
	  • Sotatercept 98.8% vs. placebo 96.5% (PE 2.3, 95% CI -3.2 – 8.8)

Conclusion	• Sotatercept resulted in a lower risk of death from any cause, lung transplantation, or PAH-related hospitalization among adult patients with PAH on maximum tolerated therapy

Humbert M, et al. *New Engl J Med.* 2025;392(20):1987-2000.

Persistent Intermediate-High or High-Risk I/H/D-PAH or PAH-CTD

- Evaluate for lung transplantation
- Intensify pharmacotherapy to 4-drug combination



ASI, activin-signaling inhibitor; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase-5 inhibitor; PPA, prostacyclin pathway agent

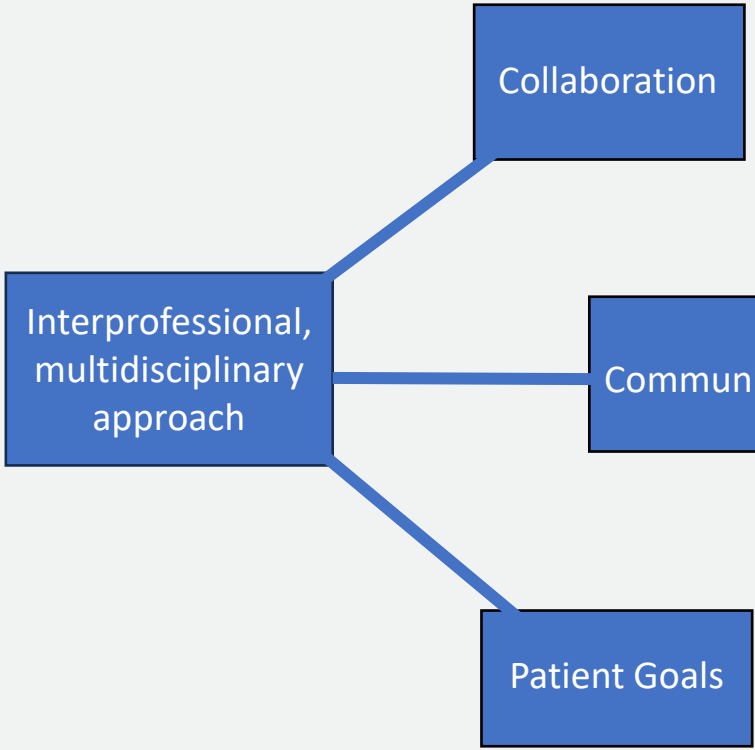
Chin KM, et al. *Eur Respir J.* 2024;64(4):2401325.

Key Concept

- Combination therapy associated with improved outcomes compared to monotherapy
- Treatment escalation based on guideline-directed risk assessment and general measures
- Sotatercept is an effective escalation therapy in patients receiving maximum tolerated background therapy

Personalizing Treatment Goals

- Clear short- and long-term goals of treatment
  - Establishment and maintenance
- Individualizing the approach to treatment
  - Role of phenotypes and genotypes
  - Symptom tolerance/management
  - Supportive therapy for general measures



- Approach between differing subspecialities in the diagnosis and management
- Role of team members to expedite and optimize care
- Referral to PH specialty center

- Care coordination between community and specialized center
- Education for non-expert care settings
- Transitions of care between inpatient and outpatient settings

- Integration into initial and subsequent selection(s) of therapy
- Ongoing assessment of disease burden and quality of life
- Support from organizations and resources

Strange G, et al. *J Multidiscip Healthc.* 2009;2:67-78.
Gillmeyer KR, et al. *Health Serv Res.* 2022;58(3):663-673.
Fernandes CJ, et al. *CHEST.* 2019;156(2):200-202.
Yang B, et al. *JTCVS Open.* 2025;24:147-155.

Key Concept

- Individualized treatment should include patient-specific goals
- Phenotype and genotype evaluation(s) may serve a role in the approach to personalized treatment
- An interprofessional, multidisciplinary approach is vital for the optimization and improvement of disease management in PH