Improving outcomes in pulmonary arterial hypertension: A multidisciplinary approach

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Best practice for early recognition and prompt diagnosis of PAH

Prof. Harrison Farber

Pulmonologist
Tufts Medical Center
Boston, MA, USA

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Clinical subtypes, associations and symptoms of PAH[1]

Underlying causes

- Idiopathic
- Heritable*

Conditions associated with PAH

- CHD
- CTD
- HIV
- Portal hypertension
- PVOD
- Schistosomiasis

Drug/toxin induced

- Aminorex
- Benfluorex
- Dasatinib
- Dexfenfluramine
- Fenfluramine
- Methamphetamines
- Toxic rapeseed oil

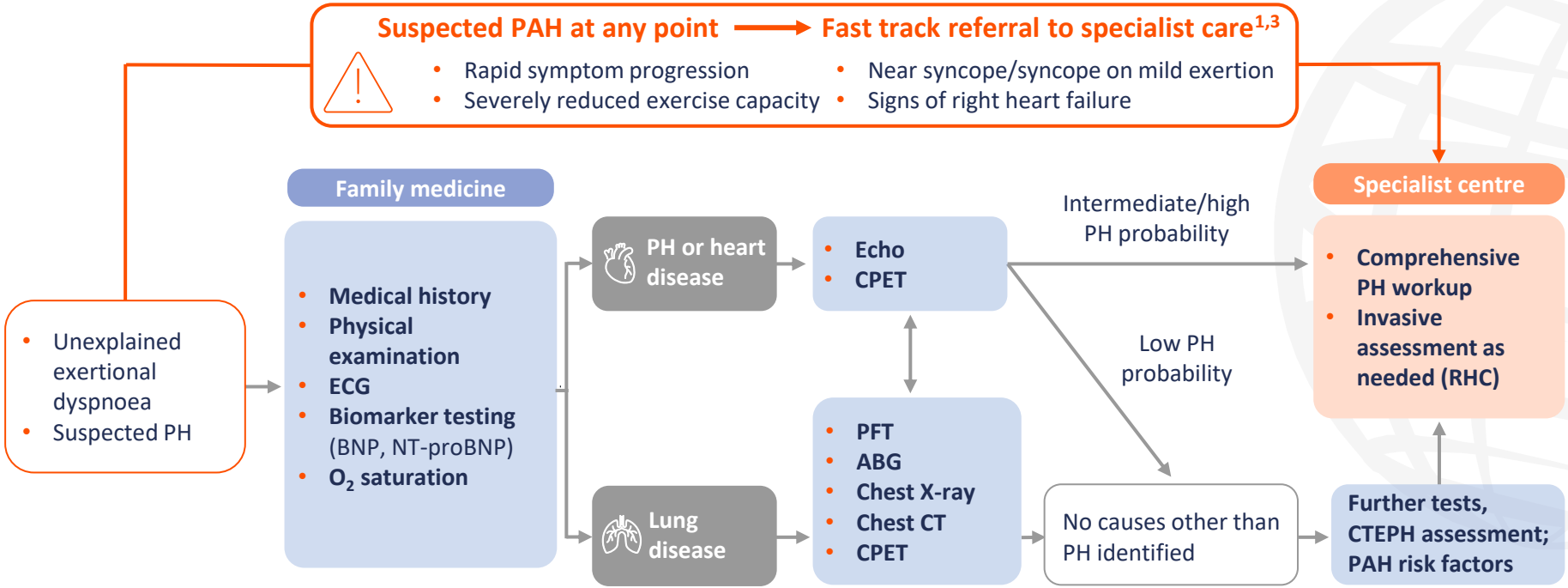
Early symptoms of PAH

- Dyspnoea on exertion (WHO FC)
- Fatigue and rapid exhaustion
- Dyspnoea when bending forward (bendopnoea)
- Palpitations
- Haemoptysis
- Exercise-induced abdominal distension and nausea
- Weight gain due to fluid retention
- Syncope/near syncope (during or shortly after physical exertion)

*Most commonly due to heterozygous mutations of the *BMPR2* gene, which carry a lifetime risk of 20% of developing PAH.[1,2]
BMPR2, bone morphogenetic protein receptor type 2; CHD, congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; WHO FC, World Health Organization functional class.

1. Humbert M, et al. *Eur Heart J.* 2022;43:3618–731; 2. Larkin EK, et al. *Am J Respir Crit Care Med*. 2012;186:892–6.

Diagnostic algorithm for patients with unexplained exertional dyspnoea and/or suspected PH[1,2]



ABG, arterial blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thromboembolic PH; ECG, electrocardiogram; echo, echocardiogram; NT-proBNP, N-terminal pro-BNP; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterization.

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

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Challenges associated with diagnosing PAH

Primary care:[1]
Early examination

Initial assessment:[1]
Clinical history, ECG biomarkers

Secondary care system:[2]
Expert assessment

Specialist PH centre:
Comprehensive PH workup[3]

- **PAH:** Rare (low clinical suspicion)
- **Early symptoms** (fatigue, breathlessness): Non-specific, subtle

NT-proBNP:
- Not specific to PAH
- May not be sensitive to mild disease

- **Echo:** Suboptimal diagnostic accuracy when used alone
- **PFT:** Normal CO diffusion does not exclude PAH
- **CPET:** Requires specialist expertise and facilities

- **RHC:** Invasive with rare but potentially fatal complications

PAH is associated with diagnostic delays of >2 years,[2,4] and there is a major haemodynamic gap between the point at which clinical risk emerges (~20 mmHg) and the time of diagnosis (~49 mmHg*)[4]

*49 mmHg was the average mPAP at baseline in the AMBITION trial (NCT01178073), which is the largest randomized clinical trial on patients with incident PAH.[4]
CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; echo, echocardiogram; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterization.

1. Kiely DG, et al. *Eur Heart J Supp.* 2019;21(Suppl. K):K9–20; 2. Humbert M, et al. *Eur Heart J.* 2022;43:3618–731; 3. Chen Y, et al. *Cardiol Rev.* 2020;28:36–41;
4. Maron BA, et al. *Am J Respir Crit Care Med.* 2021;203:1472–87.

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Targeting patient screening to reduce diagnostic delays in PAH

At-risk populations likely to benefit from targeted screening for PAH[1–3]

Asymptomatic

- *BMPR2* mutation carriers
- First-degree relatives of patients with HPAH
- Patients with SSc, mixed CTDs or other CTDs with scleroderma features
- Patients with portal hypertension referred for liver transplant*

Symptomatic

- Portal hypertension
- HIV infection
- Non-SSc CTD

Serial surveillance of clinical symptoms and the use of non-invasive screening may be a practical approach for early detection of PAH in some patient groups[2]

*Between 2% and 6% of asymptomatic patients with portal hypertension will eventualy develop PAH. Assessment should be offered as a precautionary measure if patients with portal hypertension are referred for liver transplantation because of the risks associated with surgery.

BMPR2, bone morphogenetic protein receptor type 2; CTD, connective tissue disease; HIV, human immunodeficiency virus; HPAH, heritable PAH; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

1. Humbert M, et al. *Eur Heart J.* 2022;43:3618–731; 2. Maron BA, et al. *Am J Respir Crit Care Med*. 2021;203:1472–87; 3. Kiely DG, et al. *Eur Heart J Supp*. 2019;21(Suppl. K):K9–20.

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Practical management with pharmacotherapy in pulmonary arterial hypertension: A patient-centric approach

Prof. Marion Delcroix

Pulmonologist
University Hospitals Leuven
Leuven, Belgium

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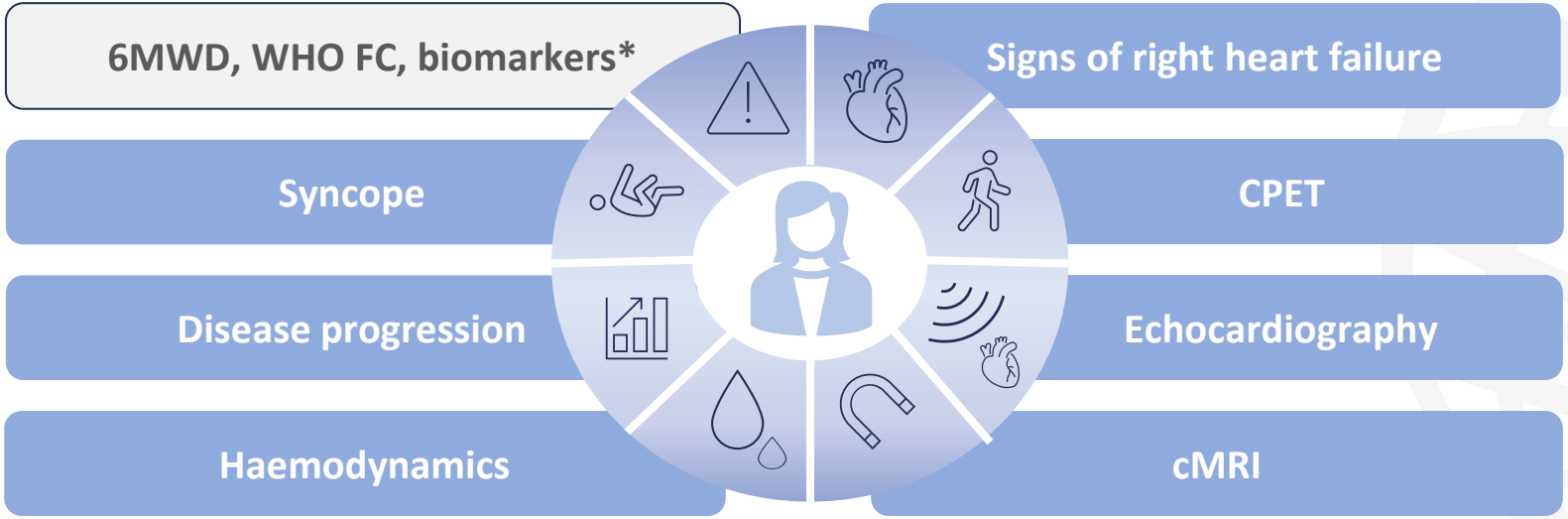
Risk stratification in PAH should incorporate multiple factors[1,2]



Individual factors should also be considered: age, sex, disease type, comorbidities and kidney function

*BNP or NT-proBNP.
6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; cMRI, cardiac magnetic resonance imaging; NT-proBNP, N-terminal pro-BNP; PAH, pulmonary arterial hypertension; 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.

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The ESC/ERS three-strata model for initial assessment

Estimated 1-year mortality risk based on highest prognostic predictors	Low <5%	Intermediate 5–20%	High >20%
6MWD,* m	>440	165–440	<165
WHO FC, class	I, II	III	IV
BNP, ng/L NT-proBNP, ng/L	<50 <300	50–800 300–1100	>800 >1100

*Dependent on age, height and burden of comorbidities.
6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; ERS, European Respiratory Society; ESC, European Society of Cardiology; NT-proBNP, N-terminal pro-BNP; WHO FC, World Health Organization functional class.
Humbert M, et al. *Eur Heart J.* 2022;43:3618–731.

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The ESC/ERS four-strata model for follow-up

Estimated 1-year mortality risk based on highest prognostic predictors	Low 0–3%	Intermed-low 2–7%	Intermed-high 9–19%	High >20%
6MWD,* m	>440	320–440	165–319	<165
WHO FC, class	I, II	–	III	IV
BNP, ng/L	<50	50–199	200–800	>800
NT-proBNP, ng/L	<300	300–649	650–1100	>1100

*Dependent on age, height and burden of comorbidities.
6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; ERS, European Respiratory Society; ESC, European Society of Cardiology; intermed, intermediate; NT-proBNP, N-terminal pro-BNP; WHO FC, World Health Organization functional class.
Humbert M, et al. *Eur Heart J.* 2022;43:3618–731.

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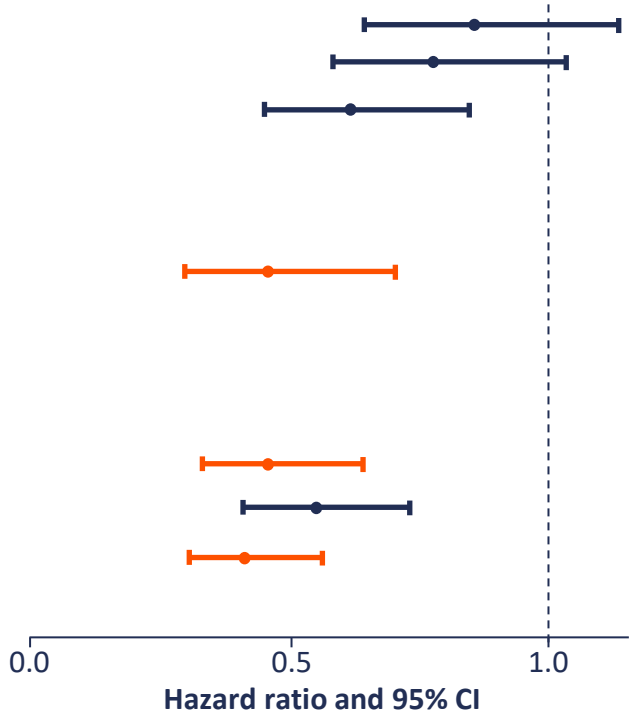
Mortality risk associated with specific endpoints*



*Cox proportional hazard analysis depicting the relative risk of death depending on improvement versus no improvement in the respective endpoints from baseline to first follow-up. Data from the COMPERA database (N=596); †NCT02891850; ‡NCT03496207.
6MWD, 6-minute walking distance; CI, confidence interval; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; ERS, European Respiratory Society; ESC, European Society of Cardiology; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO FC, World Health Organization functional class.
Hoeper MM, et al. *J Heart Lung Transplant.* 2022;41:971–81.

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Goals of therapy in PAH

Individualized approach to goal setting[1–3]

- PAH risk category
- Age
- Comorbidities
- Tolerability

- **Alleviate symptoms**[2]
- **Improve exercise capacity**[2]
- **Improve QoL**[2]
- **Preserve RV function**[2]
- **Reduce mortality risk***[2]

Composite treatment goals provide a more meaningful association with patient outcomes compared with simple goals[3]

- US guidelines note that **patient values and preferences, goals and HRQoL assessments** should inform treatment decisions[4]
- **Patient empowerment** is included in ESC/ERS 2022 guidelines and is central to the effective treatment and management of PAH[1]
- Specialist **PH centres and patient advocacy groups** are essential for supporting **patient education**, facilitating **shared decision making** and ensuring effective **collaboration with patients**[1]

*Ideally, treatment will result in patients achieving and/or maintaining a low-risk status.
ERS, European Respiratory Society; ESC, European Society of Cardiology; HRQoL, health-related QoL; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; QoL, quality of life; RV, right ventricular.
1. Humbert M, et al. *Eur Heart J.* 2022;43:3618–731; 2. Gale S. *Am J Manag Care.* 2021;27(Suppl. 3):S42–52; 3. McLaughlin V, et al. *J Am Coll Cardiol.* 2013;62(Suppl. D):D73–81; 4. Klinger JR, et al. *Chest.* 2019;155:565–86.

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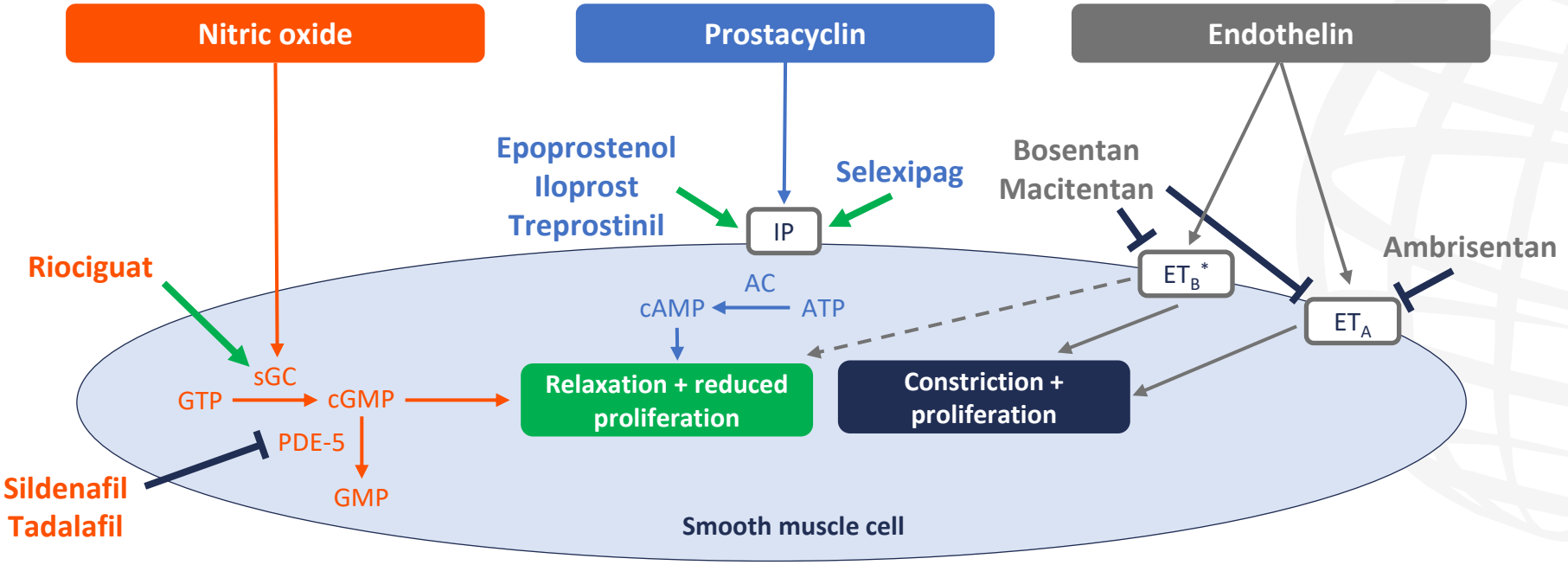
Key pathological pathways targeted in PAH and approved treatments



*The dashed line from ET_B denotes action of endothelial ET_B activation via nitric oxide and prostacyclin production.
AC, adenylyl cyclase; AMP, adenosine monophosphate; ATP, adenosine triphosphate; c, cyclic; ET, endothelin; GMP, guanosine monophosphate; GTP, guanosine triphosphate; IP, I-prostanoid; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase 5; sGC, soluble guanylate cyclase.
Lan NSH, et al. *Diseases.* 2018;6:38.

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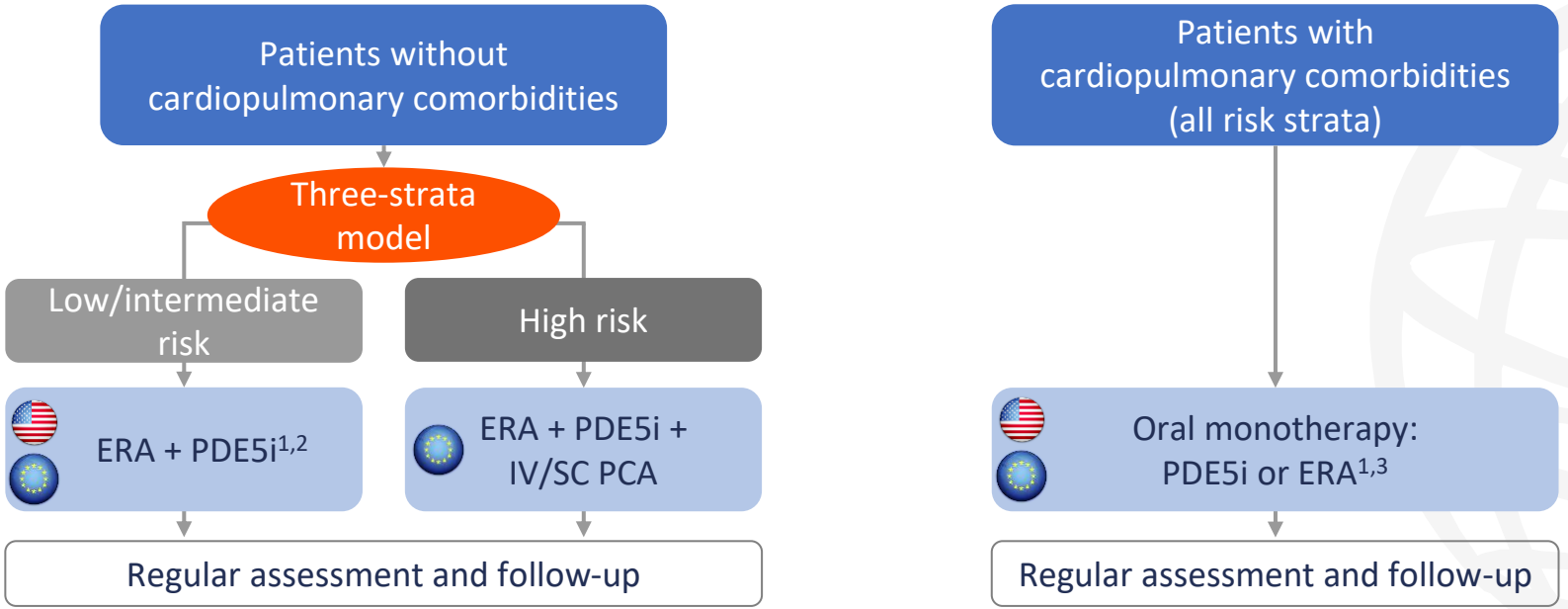
ESC/ERS treatment algorithm for PAH: Initial assessment



The 2019 US guidelines emphasize the role of monotherapy, but more recent US expert opinion suggests initial dual-combination therapy is now SoC in most low- and intermediate-risk patients with PAH[1,2]

ERA, endothelin receptor antagonist; ERS, European Respiratory Society; ESC, European Society of Cardiology; IV, intravenous; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE5i, phosphodiesterase 5 inhibitor; SC, subcutaneous; SoC, standard of care.

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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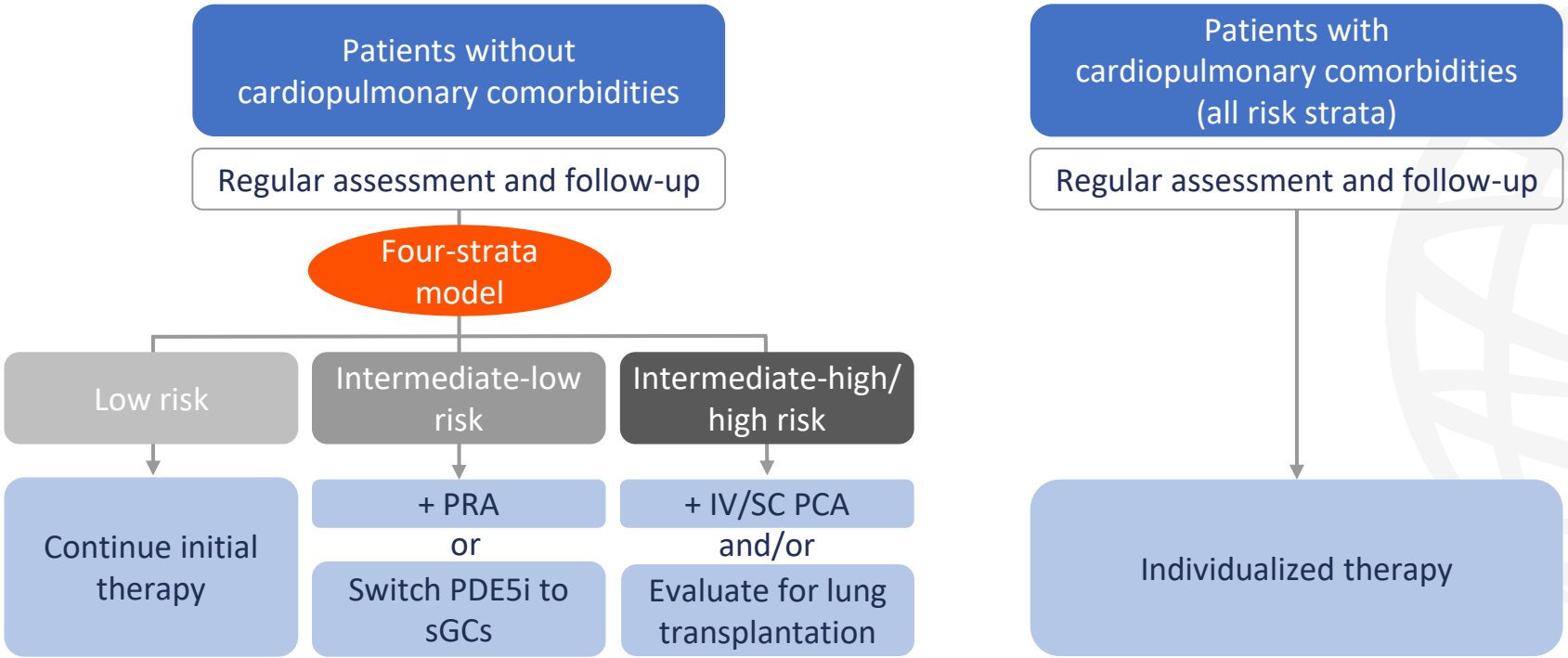
ESC/ERS treatment algorithm for PAH: Reassessment



ERS, European Respiratory Society; ESC, European Society of Cardiology; IV, intravenous; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE5i, phosphodiesterase 5 inhibitor; PRA, prostacyclin receptor agonist; SC, subcutaneous; sGCs, soluble guanylate cyclase stimulator.

Humbert M, et al. *Eur Heart J.* 2022;43:3618–731.

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Optimizing pharmacotherapy in pulmonary arterial hypertension

Prof. Stephan Rosenkranz

Cardiologist
University of Cologne
Germany

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Emerging pharmacotherapies for PAH in phase II/III development

Emerging treatments using established pathways

Prostacyclin pathway
- Ralinepag
- Treprostinil

sGC pathway
- MK-5475

Emerging treatments using novel pathways[1,2]

BMPR2 pathway
- Sotatercept

TKIs and related agents
- Imatinib

Sex hormones
- Anastrozole[3]
- Fulvestrant[4]
- Tamoxifen[5]
- DHEA

Growth factor signalling
- Seralutinib

Mitochondrial pathways and oxidative stress
- Ifetroban

Epigenetic modulator
- Apabetalone

Serotonin axis
- Rodatristat ethyl

Immune modulators
- Rituximab[6]
- Tocilizumab

Metabolic pathways
- Metformin[7]
- Dapagliflozin[8]

BMPR2, bone morphogenetic protein receptor type 2; DHEA, dehydroepiandrosterone; PAH, pulmonary arterial hypertension; sGC, soluble guanylate cyclase; TKI, tyrosine kinase inhibitor.

1. Cassady SJ, et al. *Front Drug Discov*. 2022;2:1022971; 2. Zolty R. *J Exp Pharmacol*. 2021;13:817–57; 3. ClinicalTrials.gov. NCT03229499. Available at: bitly.ws/BGuP (accessed April 2023); 4. Kawut SM, et al. *Ann Am Thorac Soc*. 2019;16:1456–9; 5. ClinicalTrials.gov. NCT03528902. Available at: bit.ly/3TdlGsK (accessed April 2023); 6. ClinicalTrials.gov. NCT01086540. Available at: bit.ly/3JCjEPQ (accessed April 2023); 7. ClinicalTrials.gov. NCT03617458. Available at: bit.ly/3ZTQ2Tg (accessed April 2023); 8. ClinicalTrials.gov. NCT05179356. Available at: bit.ly/3JzCqHh (accessed April 2023).

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Trial data: MK-5475, ralinepag and treprostinil

MK-5475 (phase I, NCT03744637)[1,2]

N=25

- Pts 18–70 years
  - BMI ≤35 kg/m^2; indication for RHC or prior RHC ≤3 years[1,2]
- Single-dose inhaled MK-5475 or PBO per period

BL up to 185 days (part 2, open label)

PVR minimum change

≥-20% during RHC for 120, 240 and 360 µg MK-5475 doses

BL to ~32 weeks

- **AEs:** 52% all pts
- **Discontinuation due to AEs:** 0%

MK-5475 reduced PVR and had a favourable safety profile

Ralinepag (phase II, NCT02279160)[1,3]

N=61

- Pts 18–75 years
  - WHO FC II–IV; 6MWD 100–500 m
  - SoC for ≥90 days prior
- Oral BID ralinepag or PBO, randomized 2:1

Ralinepag vs PBO

BL to 22 weeks

PVR median change

-163.9 vs +0.7 dyn/s/cm^{-5} (p=0.02)

- **SAEs:** 10% vs 29% pts
- **AEs more common in ralinepag vs PBO:** Headache, nausea, diarrhoea, jaw pain, flushing

Ralinepag significantly reduced PVR vs PBO in pts with moderately symptomatic PAH

Treprostinil (INSPIRE; phase III, NCT03399604)[1,4]

N=121

- Pts ≥18 years
  - WHO FC II–IV; 6MWD ≥150 m
  - Nebulized treprostinil for ≥90 days prior or prostacyclin naive
- Inhaled treprostinil (all pts)

Transitioned vs prostacyclin naive pts

- **TRAE:** 73% vs 85% pts
- **SAEs:** 11% vs 23% pts
- **Common AEs (≥10%):** Cough, headache, upper respiratory tract infection, dyspnoea, dizziness, throat irritation, diarrhoea, chest discomfort, fatigue, nasopharyngitis, nausea

Inhaled treprostinil had a favourable safety profile

6MWD, 6-minute walking distance; AE, adverse event; BID, twice daily; BL, baseline; BMI, body mass index; PAH, pulmonary arterial hypertension; PBO, placebo; pts, patients; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SAE, serious AE; SoC, standard of care; TRAE, treatment-related AE;
WHO FC, World Health Organization functional class. 1. ClinicalTrials.gov. Available at: https://beta.clinicaltrials.gov/, search according to trial number (accessed April 2023);
2. Bajwa EK, et al. *Resp Med.* 2023;206:107065; 3. Torres F, et al. *Eur Respir J.* 2019;54:1901030; 4. Hill NS, et al. *Pulm Circ.* 2022;12:e12119.

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Trial data: Imatinib, rodatristat ethyl and seralutinib

Imatinib
(IMPAHCT; ph IIb/III; NCT05036135)[1]
(IMPAHCT-FUL; ph II/III; NCT05557942)[1]

N=462

- Pts 18–75 years
  - WHO FC II–IV; 6MWD 100–475 m
  - Received ≥2 SoC drugs
- Inhaled imatinib or PBO, randomized (ph IIb: three imatinib doses)

Imatinib vs PBO

IMPAHCT BL to 24 weeks	IMPAHCT-FUL BL to 3 years
PVR change (ph IIb) 6MWD change (ph III)	• Safety and tolerability

Ongoing (IMPAHCT and IMPAHCT-FUL); estimated completion Jan and Dec 2025

Rodatristat ethyl
(ELEVATE 2 + OLE; ph IIb; NCT04712669)[1,2]

N=90

- Pts ≥18 years
  - WHO FC II–III
- Oral rodatristat ethyl (300 or 600 µg) or PBO, randomized 1:1:1

Rodatristat ethyl vs PBO

BL to 24 weeks

PVR change

- Safety up to 24 weeks

Ongoing; estimated completion was Feb 2023

Seralutinib
(TORREY + OLE; ph II; NCT04456998)[1–3]

N=80

- Pts 18–75 years
  - WHO FC II/III; 6MWD 150–550 m
  - On SoC for ≥4 weeks prior
- Inhaled seralutinib BID or PBO, randomized 1:1

Seralutinib vs PBO

BL to 24 weeks

PVR change

- Safety

Primary endpoint met; awaiting published data[4]

6MWD, 6-minute walking distance; BID, twice daily; BL, baseline; PBO, placebo; ph, phase; pts, patients; PVR, pulmonary vascular resistance; SoC, standard of care; WHO FC, World Health Organization functional class.

1. ClinicalTrials.gov. Available at: https://beta.clinicaltrials.gov/, search according to trial number (accessed April 2023); 2. Lazarus HM, et al. *Pulm Circ.* 2022;12:e12088; 3. Frantz RP, et al. *Pulm Circ*. 2021;11:20458940211057071; 4. *Pulmonary Hypertension News*. Available at: bit.ly/3ZMMimp (accessed April 2023).

Trial data: Sotatercept

PULSAR (NCT03496207; phase II + OLE)[1–3]

N=106

- Pts ≥18 years
  - WHO FC II/III
  - On SoC for ≥90 days prior
- SC sotatercept (0.3 or 0.7 mg/kg) or PBO Q3W, randomized 3:3:4

Sotatercept vs PBO

BL to 24 weeks

PVR LSM difference

0.3 mg/kg sotatercept vs PBO: -145.8 dyn/sec/cm^{-5} (p=0.003)

0.7 mg/kg sotatercept vs PBO: -239.5 dyn/sec/cm^{-5} (p<0.001)

- **SAEs**: 6% vs 24% vs 9% pts;[2] OLE: 31% TRAEs (serious)[3]
- **AE of special interest**:[2]* Leukopenia, neutropenia, thrombocytopenia
- **Deaths:** n=3 (sotatercept groups; not treatment related)[3]
- **AEs more common in sotatercept vs PBO**:[2] Headache, diarrhoea and dizziness

Sotatercept reduced PVR vs PBO and demonstrated a favourable long-term safety profile[2,3]

STELLAR (NCT04576988; phase III)[1,4]

N=323

- Pts ≥18 years
  - WHO FC II/III
  - On SoC for ≥90 days prior
- SC sotatercept + SoC or PBO + SoC Q3W, randomized 1:1

Sotatercept vs PBO

BL to 24 weeks

6MWD median change

Hodges–Lehmann location shift: 40.8 m (p<0.001)

- **SAEs**: 14% vs 23% pts
- **AEs of special interest:*** Bleeding events, thrombocytopenia
- **TR-SAEs**: 1% pts in both groups
- **AEs more common in sotatercept vs PBO**: Epistaxis, telangiectasia and dizziness

Risk of death or nonfatal clinical worsening events: 84% lower in sotatercept vs PBO

Sotatercept improved 6MWD vs PBO with a favourable benefit–risk ratio

*Haemoglobin increase: PULSAR, sotatercept 0.3 mg=1 pt (3%) vs sotatercept 0.7 mg=7 pts (17%) vs PBO=0 pts; STELLAR, sotatercept=9 pts (6%) vs PBO=0 pts.
6MWD, 6-minute walking distance; AE, adverse event; BL, baseline; LSM, least-squares mean; OLE, open-label extension; PBO, placebo; pt, patient; PVR, pulmonary vascular resistance; Q3W, every 3 weeks; SAE, serious AE; SC, subcutaneous; SoC, standard of care; TR, treatment related; WHO FC, World Health Organization functional class.

1. ClinicalTrials.gov. Available at: https://beta.clinicaltrials.gov/, search according to trial number (accessed April 2023); 2. Humbert M, et al. *N Engl J Med*. 2021;384:1204–15; 3. Humbert M, et al. *Eur Respir J*. 2023;61:2201347; 4. Hoeper MM, et al. *N Engl J Med*. 2023:10.1056/NEJMoa2213558.

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Factors that impact HRQoL of patients with PAH

Disease-related factors

- Fatigue
- Shortness of breath
- Light headedness

Social factors

- Highest education level
- Employment status
- Income
- PH centre care rating

*Data from the US Pulmonary Hypertension Association Registry and based on the e10 score that measures HRQoL in patients with PAH.
e10, emPHasis-10; HRQoL, health-related quality of life; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.
Borgese M, et al. *Eur Respir J.* 2021;57:2000414.

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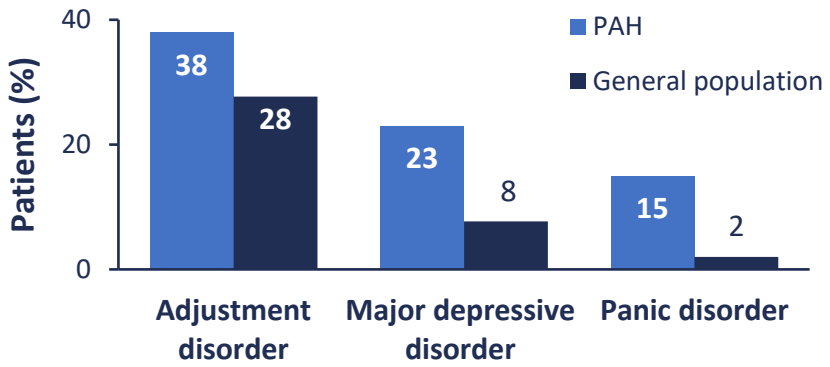
Psychosocial burden and supportive strategies for patients with PAH

Proportion of psychological disorders in PAH vs the general German population[1]



- PAH carries a psychosocial burden that can limit everyday activities[2]

Strategies to support PAH patients[3]

- Establish collaboration between PH centres and **patient advocacy groups**
- Provide empathic and hopeful **communication**
- Enhance **disease-specific knowledge**
- Empower through **shared decision making**
- Identify patients who may benefit from **psychopharmacological medication**
- Discuss access to **social support**

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

1. Olsson KM, et al. *Front Psychiatry.* 2021;12:667602; 2. Guillevin L, et al. *Eur Respir Rev.* 2013;22:535–42; 3. Humbert M, et al. *Eur Heart J.* 2022;43:3618–731.

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