



Improving outcomes in pulmonary arterial hypertension: A multidisciplinary approach

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Best practice for early recognition and prompt diagnosis of PAH

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Clinical subtypes, associations and symptoms of PAH¹

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}

Suspected PAH at any point → **Fast track referral to specialist care^{1,3}**



- Rapid symptom progression
- Severely reduced exercise capacity
- Near syncope/syncope on mild exertion
- Signs of right heart failure

Family medicine

- Unexplained exertional dyspnoea
- Suspected PH

- Medical history
- Physical examination
- ECG
- Biomarker testing (BNP, NT-proBNP)
- O₂ saturation

PH or heart disease

- Echo
- CPET

Intermediate/high PH probability

Low PH probability

Lung disease

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

No causes other than PH identified

Specialist centre

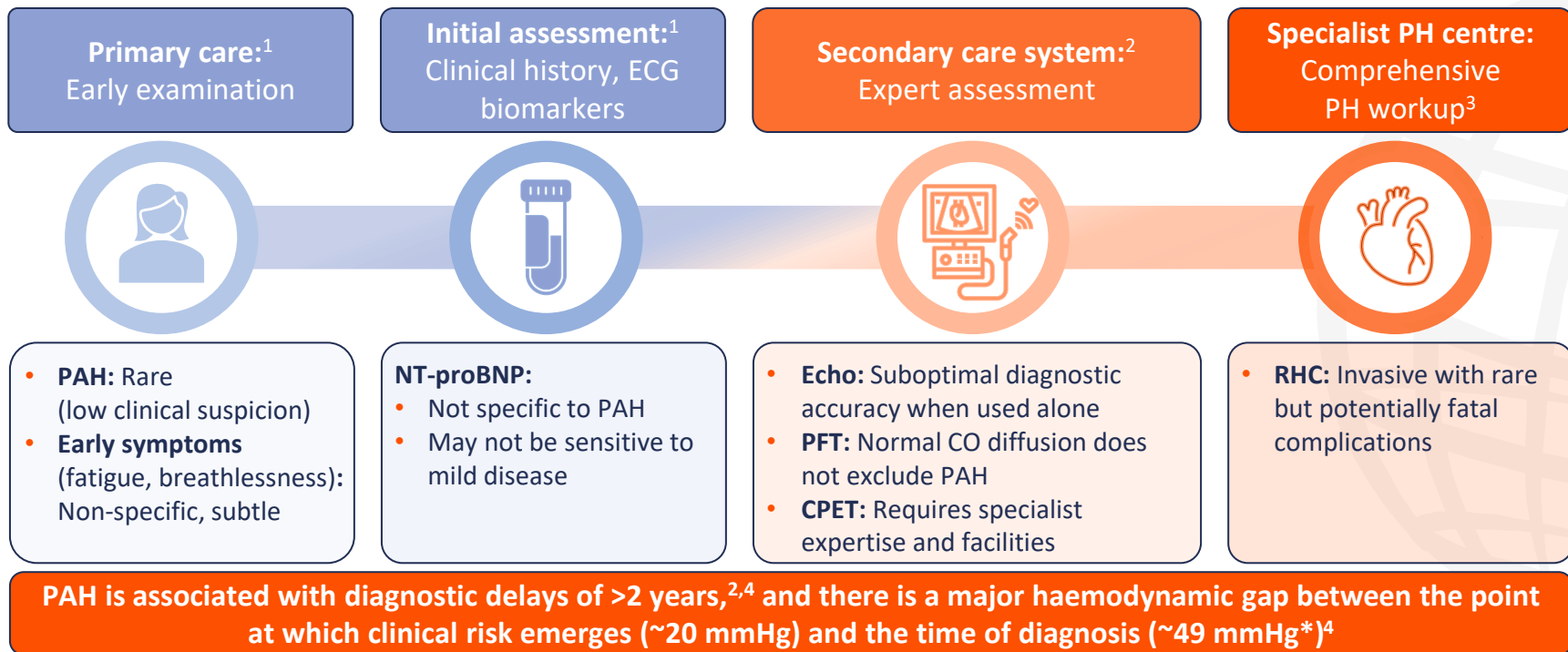
- Comprehensive PH workup
- Invasive assessment as needed (RHC)

Further tests, CTEPH assessment; PAH risk factors

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.

Challenges associated with diagnosing PAH



*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 Suppl.* 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.

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 groups²

*Between 2% and 6% of asymptomatic patients with portal hypertension will eventually 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 Suppl*. 2019;21(Suppl. K):K9–20.

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

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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.

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.

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
NT-proBNP, ng/L

<50

<300

50–199

300–649

200–800

650–1100

>800

>1100

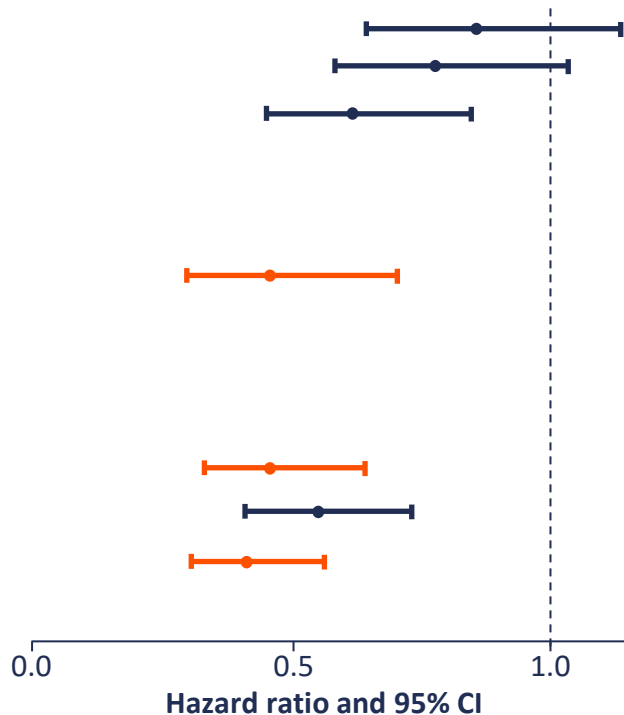
*Dependent on age, height and burden of comorbidities.

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; ERS, European Respiratory Society; ESC, European Society of Cardiology; 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.

Mortality risk associated with specific endpoints*

↑ 6MWD ≥30 m
 ↓ NT-proBNP by ≥30%[†]
REPLACE[‡]
 Two out of three criteria met:
 (↓ WHO FC: III to I/II; ↑ 6MWD by ≥30 m
 or ≥10%; ↓ NT-proBNP by ≥30%)
PULSAR[‡]
 All criteria met:
 (↓ WHO FC from III to I/II or maintained at I/II;
 ↑ 6MWD by ≥30 m; ↓ NT-proBNP by ≥30% or
 maintained at <300 ng/L)
ESC/ERS three strata
ESC/ERS four strata
French non-invasive model
 Number of variables meeting low-risk criteria:
 (WHO FC I/II, 6MWD >440 m, and NT-proBNP <300 ng/L)



*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. Hoepfer MM, et al. *J Heart Lung Transplant*. 2022;41:971–81.

Goals of therapy in PAH

Individualized approach to goal setting¹⁻³



- PAH risk category
- Age
- Comorbidities
- Tolerability

Alleviate symptoms²

Improve exercise capacity²

Improve QoL²

Preserve RV function²

Reduce mortality risk^{*2}



Composite treatment goals
provide a more meaningful
association with patient
outcomes compared with
simple goals³

- US guidelines note that **patient values and preferences, goals and HRQoL assessments** should inform treatment decisions⁴
- **Patient empowerment** is included in ESC/ERS 2022 guidelines and is central to the effective treatment and management of PAH¹
- Specialist **PH centres and patient advocacy groups** are essential for supporting **patient education**, facilitating **shared decision making** and ensuring effective **collaboration with patients**¹

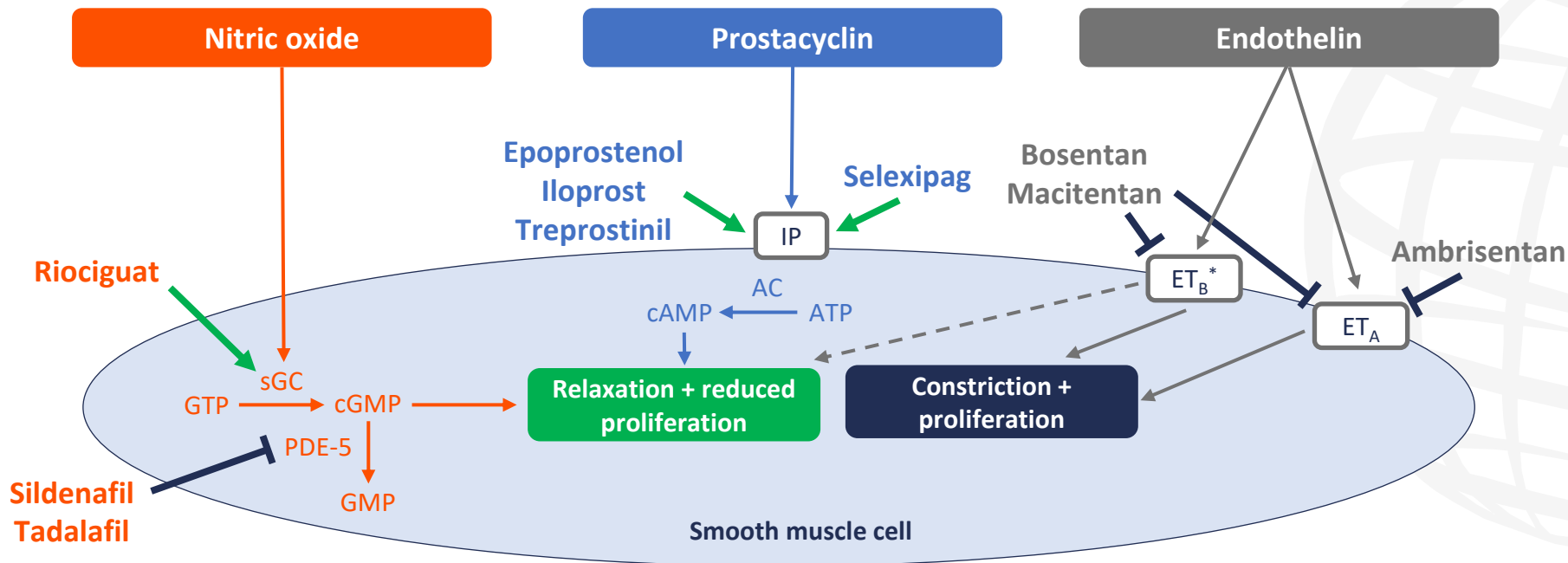
*Ideally, treatment will result in patients achieving and/or maintaining a low-risk status.

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.

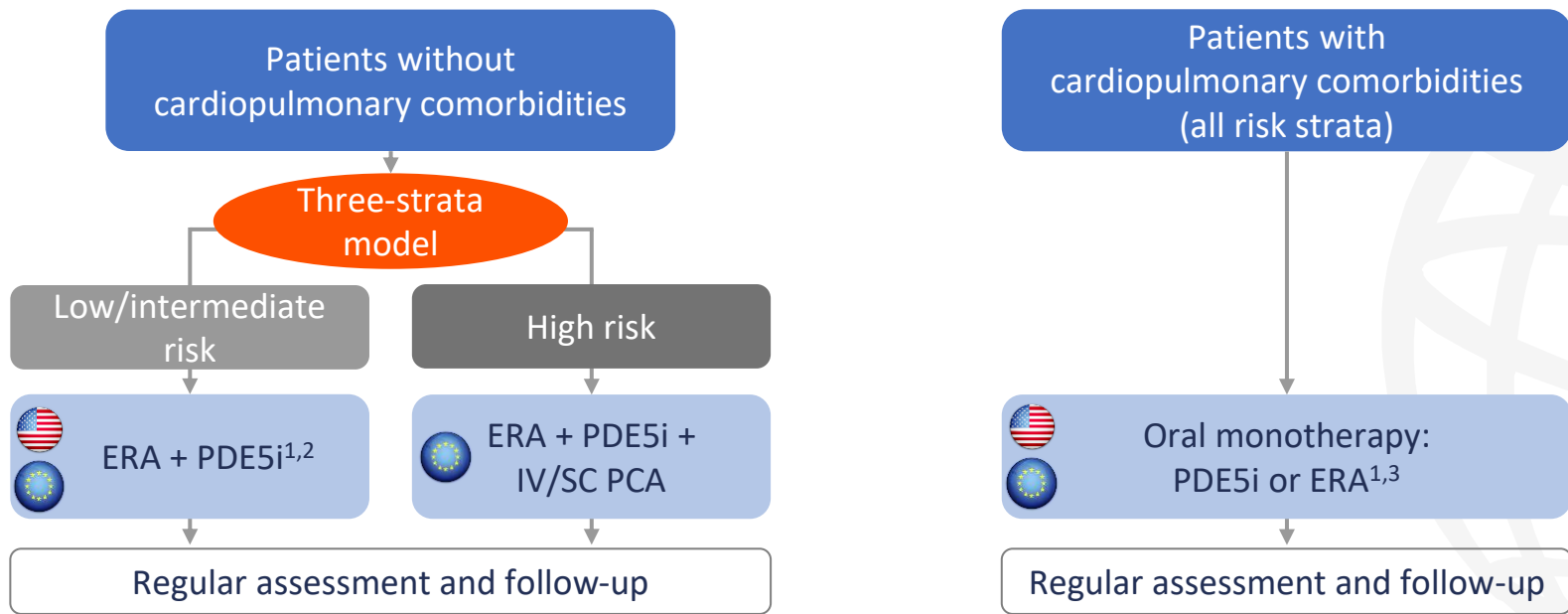
Key pathological pathways targeted in PAH and approved treatments



*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.

ESC/ERS treatment algorithm for PAH: Initial assessment

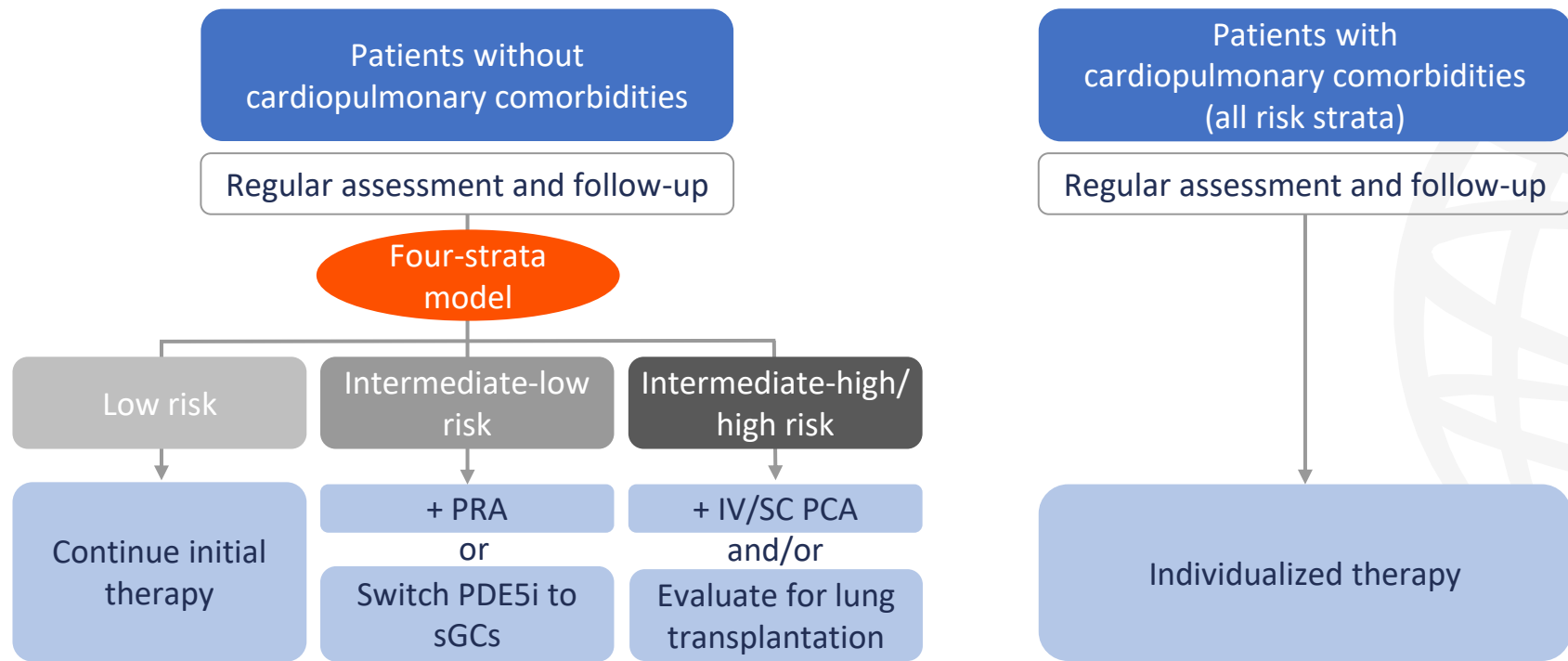


The 2019 US guidelines emphasize the role of monotherapy, but more recent US expert opinion suggests initial dual-combination therapy is now SoC in most low- and intermediate-risk patients with PAH^{1,2}

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.

ESC/ERS treatment algorithm for PAH: Reassessment



Optimizing pharmacotherapy in pulmonary arterial hypertension

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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

-  Anastrozole³
-  Fulvestrant⁴
-  Tamoxifen⁵
-  DHEA

Growth factor signalling

-  Seralutinib

Mitochondrial pathways and oxidative stress

-  Ifetroban


Epigenetic modulator

-  Apabetalone

Serotonin axis

-  Rodatristat ethyl

Immune modulators

-  Rituximab⁶
-  Tocilizumab

Metabolic pathways

-  Metformin⁷
-  Dapagliflozin⁸

BMPR2, bone morphogenetic protein receptor type 2; DHEA, dehydroepiandrosterone; PAH, pulmonary arterial hypertension; sGC, soluble guanylate cyclase;

TKI, tyrosine kinase inhibitor.




1. Cassidy 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/3TdIGsK (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).

Trial data: MK-5475, ralinepag and treprostinil

MK-5475 (phase I, NCT03744637)^{1,2}	Ralinepag (phase II, NCT02279160)^{1,3}	Treprostinil (INSPIRE; phase III, NCT03399604)^{1,4}
 <ul style="list-style-type: none"> • Pts 18–70 years • BMI ≤ 35 kg/m²; indication for RHC or prior RHC ≤ 3 years^{1,2} • Single-dose inhaled MK-5475 or PBO per period <p>N=25</p>	 <ul style="list-style-type: none"> • 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 <p>N=61</p>	 <ul style="list-style-type: none"> • Pts ≥ 18 years • WHO FC II–IV; 6MWD ≥ 150 m • Nebulized treprostinil for ≥ 90 days prior or prostacyclin naive • Inhaled treprostinil (all pts) <p>N=121</p>
<p>BL up to 185 days (part 2, open label)</p> <p>BL to ~32 weeks</p> <div> <p>PVR minimum change</p> <p>$\geq -20\%$ during RHC for 120, 240 and 360 μg MK-5475 doses</p> </div> <ul style="list-style-type: none"> • AEs: 52% all pts • Discontinuation due to AEs: 0% 	<p>Ralinepag vs PBO</p> <p>BL to 22 weeks</p> <div> <p>PVR median change</p> <p>-163.9 vs +0.7 dyn/s/cm⁻⁵ (p=0.02)</p> </div> <ul style="list-style-type: none"> • SAEs: 10% vs 29% pts • AEs more common in ralinepag vs PBO: Headache, nausea, diarrhoea, jaw pain, flushing 	<p>Transitioned vs prostacyclin naive pts</p> <ul style="list-style-type: none"> • TRAE: 73% vs 85% pts • SAEs: 11% vs 23% pts • Common AEs ($\geq 10\%$): Cough, headache, upper respiratory tract infection, dyspnoea, dizziness, throat irritation, diarrhoea, chest discomfort, fatigue, nasopharyngitis, nausea
<p>MK-5475 reduced PVR and had a favourable safety profile</p>	<p>Ralinepag significantly reduced PVR vs PBO in pts with moderately symptomatic PAH</p>	<p>Inhaled treprostinil had a favourable safety profile</p>

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.

Trial data: Imatinib, rodatristat ethyl and seralutinib

Imatinib (IMPAHCT; ph IIb/III; NCT05036135) ¹ (IMPAHCT-FUL; ph II/III; NCT05557942) ¹	Rodatrastat ethyl (ELEVATE 2 + OLE; ph IIb; NCT04712669) ^{1,2}	Seralutinib (TORREY + OLE; ph II; NCT04456998) ¹⁻³
 <ul style="list-style-type: none"> • Pts 18–75 years <ul style="list-style-type: none"> ◦ WHO FC II–IV; 6MWD 100–475 m ◦ Received ≥2 SoC drugs • Inhaled imatinib or PBO, randomized (ph IIb: three imatinib doses) <p>N=462</p>	 <ul style="list-style-type: none"> • Pts ≥18 years <ul style="list-style-type: none"> ◦ WHO FC II–III • Oral rodatristat ethyl (300 or 600 µg) or PBO, randomized 1:1:1 <p>N=90</p>	 <ul style="list-style-type: none"> • Pts 18–75 years <ul style="list-style-type: none"> ◦ WHO FC II/III; 6MWD 150–550 m ◦ On SoC for ≥4 weeks prior • Inhaled seralutinib BID or PBO, randomized 1:1 <p>N=80</p>
<p>Imatinib vs PBO</p> <div> <div> <p>IMPAHCT BL to 24 weeks</p> <p>PVR change (ph IIb)</p> <p>6MWD change (ph III)</p> </div> <div> <p>IMPAHCT-FUL BL to 3 years</p> <p>• Safety and tolerability</p> </div> </div>	<p>Rodatrastat ethyl vs PBO</p> <div> <div> <p>BL to 24 weeks</p> <p>PVR change</p> </div> <div> <p>• Safety up to 24 weeks</p> </div> </div>	<p>Seralutinib vs PBO</p> <div> <div> <p>BL to 24 weeks</p> <p>PVR change</p> </div> <div> <p>• Safety</p> </div> </div>
Ongoing (IMPAHCT and IMPAHCT-FUL); estimated completion Jan and Dec 2025	Ongoing; estimated completion was Feb 2023	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. Hoepfer MM, et al. *N Engl J Med.* 2023;10.1056/NEJMoa2213558.

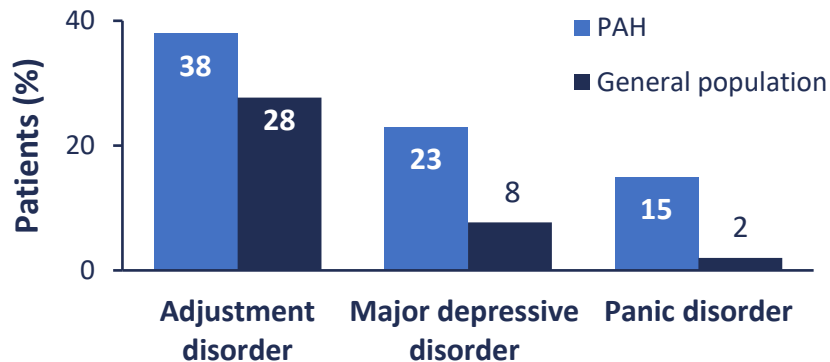
Factors that impact HRQoL of patients with PAH



*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.

Psychosocial burden and supportive strategies for patients with PAH

Proportion of psychological disorders in PAH vs the general German population¹



- PAH carries a psychosocial burden that can limit everyday activities²

Strategies to support PAH patients³



- 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**