

Snapshots On PH

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PAH Hemodynamic Definitions Have Changed Over Time

- The original definition of $mPAP \geq 25$ mmHg was a conservative cut-off value that allowed physicians to discriminate severe PH from other forms of PH

Arbitrary Definition (1973)

- Mean PAP ≥ 25 mmHg at rest measured by RHC

Evolving Definition (1998-2013)

- Mean PAP ≥ 25 mmHg or > 30 mmHg during exercise
- Normal left heart filling pressure (PAWP ≤ 15 mmHg)
- PVR ≥ 3 Wood units

New Definition (2018)

- Mean PAP ≥ 20 mmHg
- PAWP ≤ 15 mmHg
- PVR ≥ 2 Wood units (for all forms of pre-capillary PH)

How to differentiate between normal and abnormal mPAP?

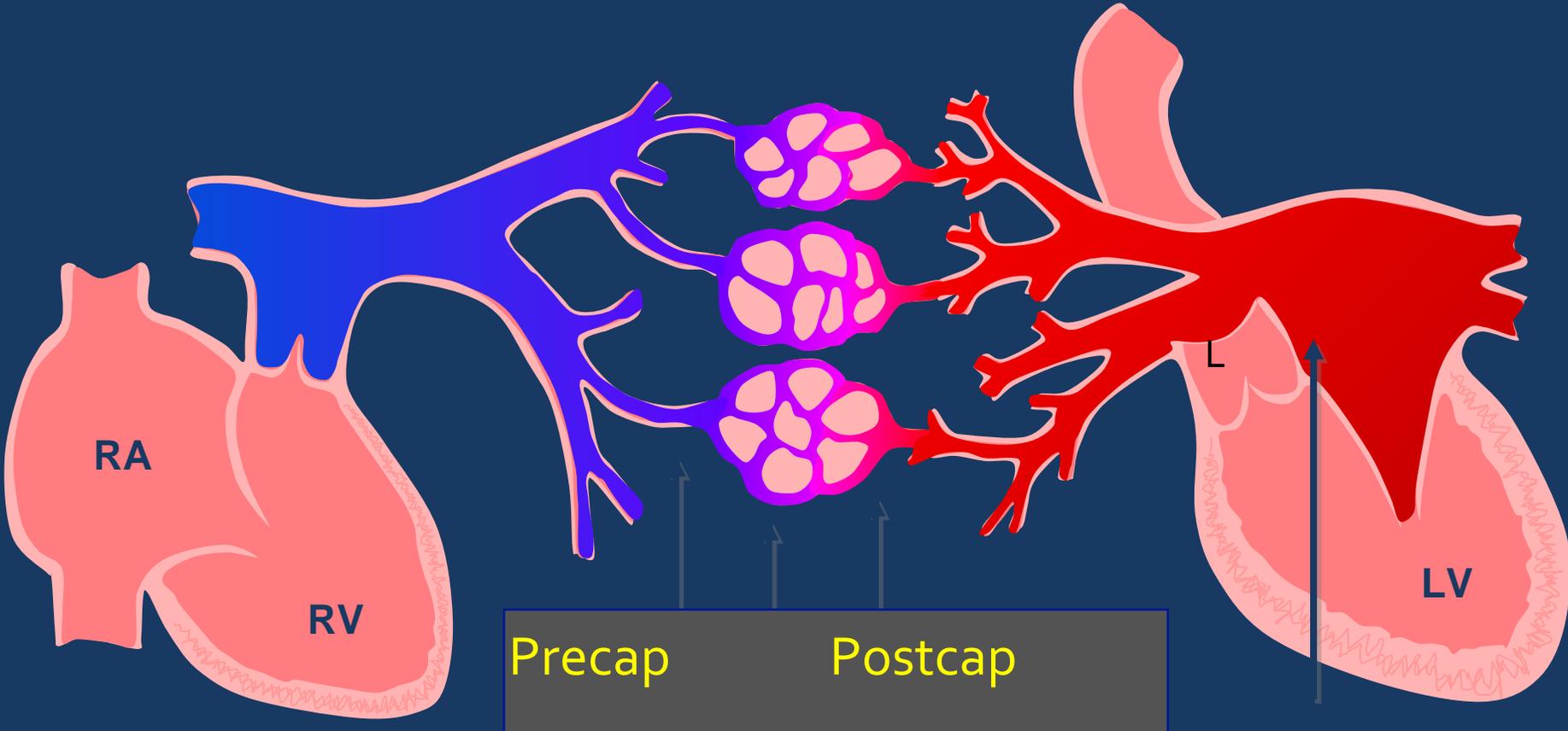
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Definitions

The definitions for PH are based on **haemodynamic** assessment by right heart catheterization (**RHC**).

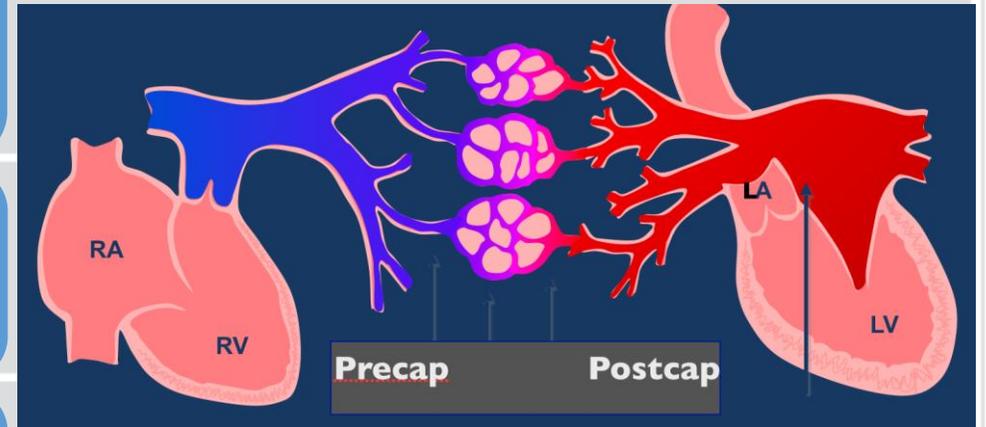
Although haemodynamics represent the central element of characterizing PH, the final diagnosis and classification should reflect the whole **clinical** context and consider the results of all investigations.

Pulmonary Hypertension (PH)



Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
Combined post- and pre-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min



Unclassified PH. !

- Elevated **mPAP** (>20 mmHg)
- Low **PAWP** (≤ 15 mmHg)
- Low **PVR** (≤ 2 WU).
- They do not fulfil the criteria of pre- or post-capillary PH.
- Patients with unclassified PH may present with :
 - Congenital heart disease (CHD),
 - Liver disease
 - Airway disease, lung disease
 - Hyperthyroidism
- Clinical **follow-up** of these patients is generally recommended.
- In the case of elevated pulmonary blood flow, its aetiology should be explored.

Exercise PH

- **mPAP/cardiac output (CO) slope $> 3\text{mmHg/L/min}$ between rest and exercise,**
(Associated with impaired prognosis in patients with exercise dyspnoea and in several cardiovascular conditions)
- **PAWP/ CO slope with a threshold $> 2\text{ mmHg/L/min}$ may best differentiate between pre- and post-capillary causes of exercise PH**

PH Classification

Pathophysiologic

Clinical

Haemodynamic

Therapeutic

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
 - 1.1.1 Non-responders at vasoreactivity testing
 - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable^a
- 1.3 Associated with drugs and toxins^a
- 1.4 Associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 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

- 2.1 Heart failure:
 - 2.1.1 with preserved ejection fraction
 - 2.1.2 with reduced or mildly reduced ejection fraction^b
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

GROUP 3 PH associated with lung diseases and/or hypoxia

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

GROUP 4 PH associated with pulmonary artery obstructions

- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions^c

GROUP 5 PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders^d
- 5.2 Systemic disorders^e
- 5.3 Metabolic disorders^f
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

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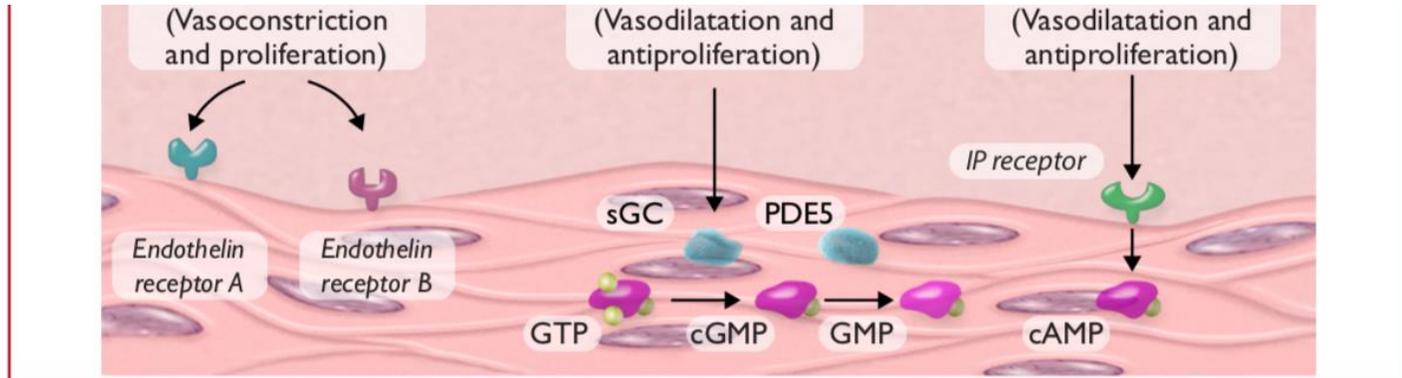
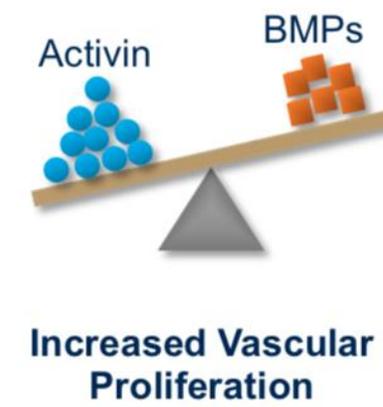
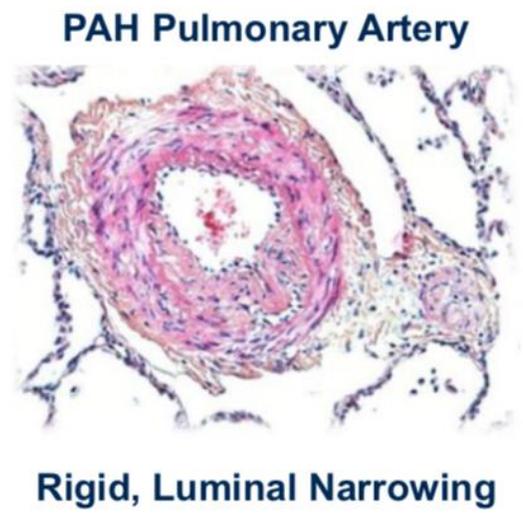
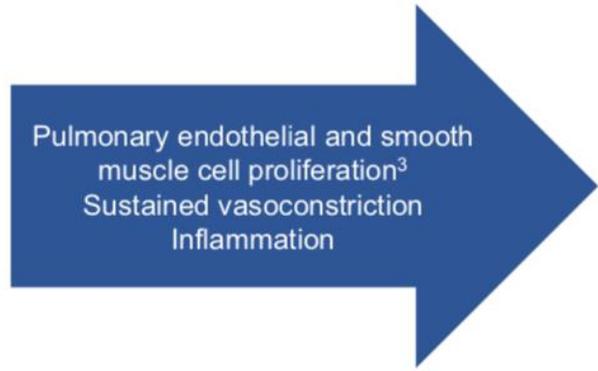
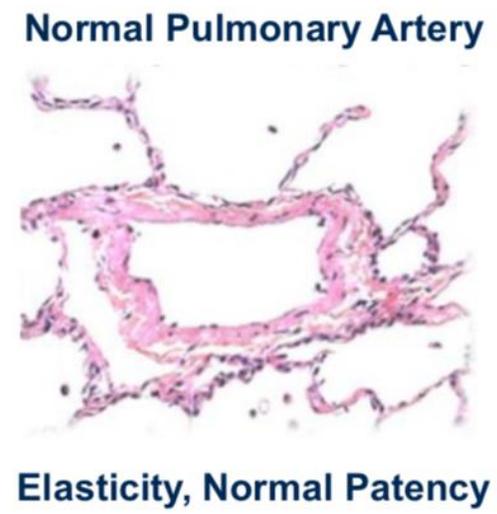
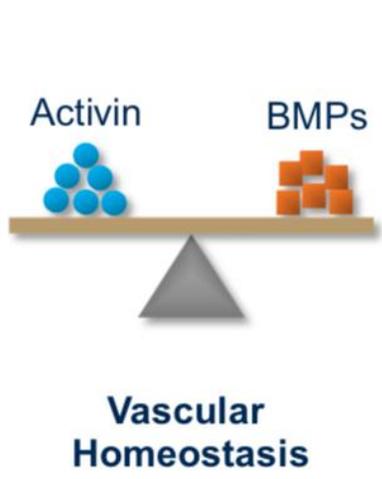
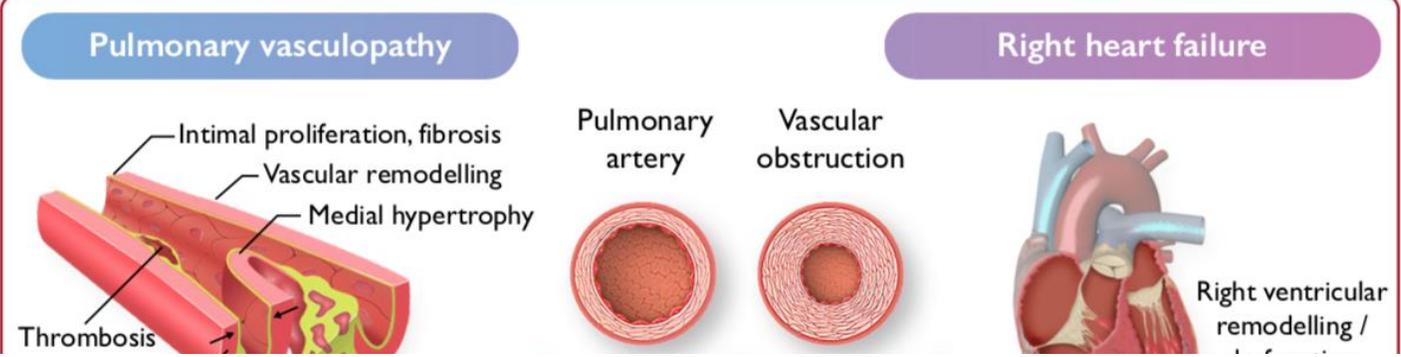
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1.4.4 Congenital heart disease

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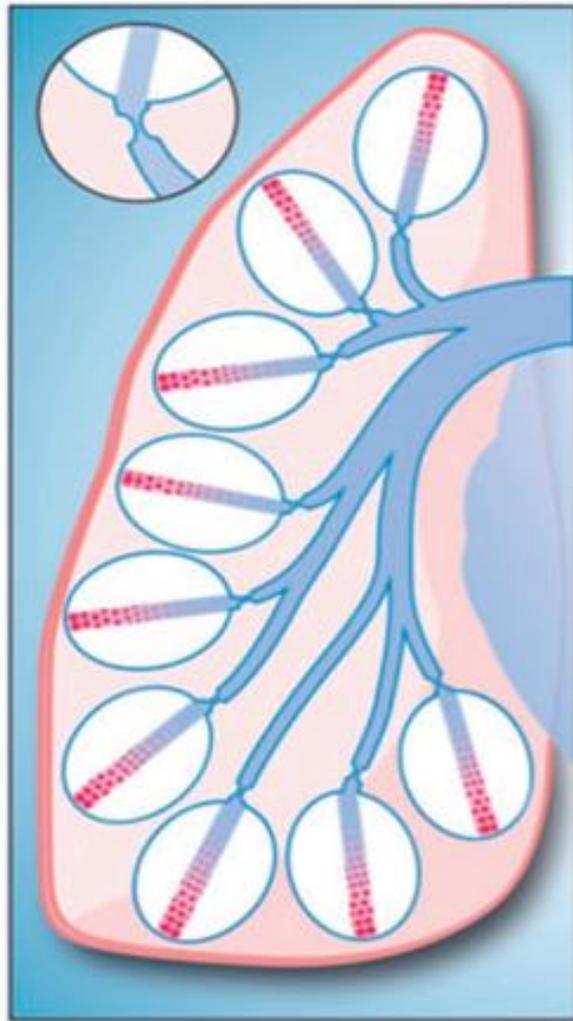
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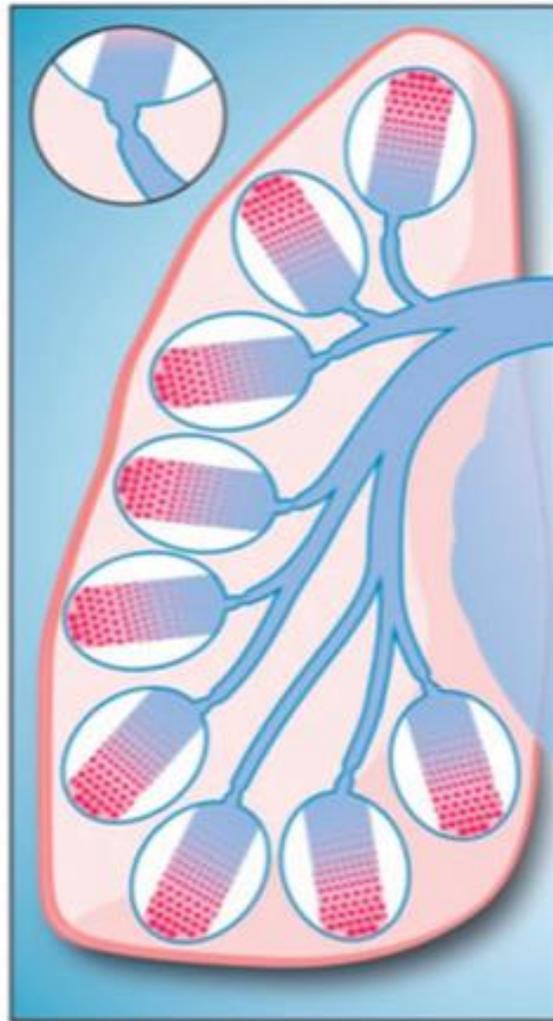
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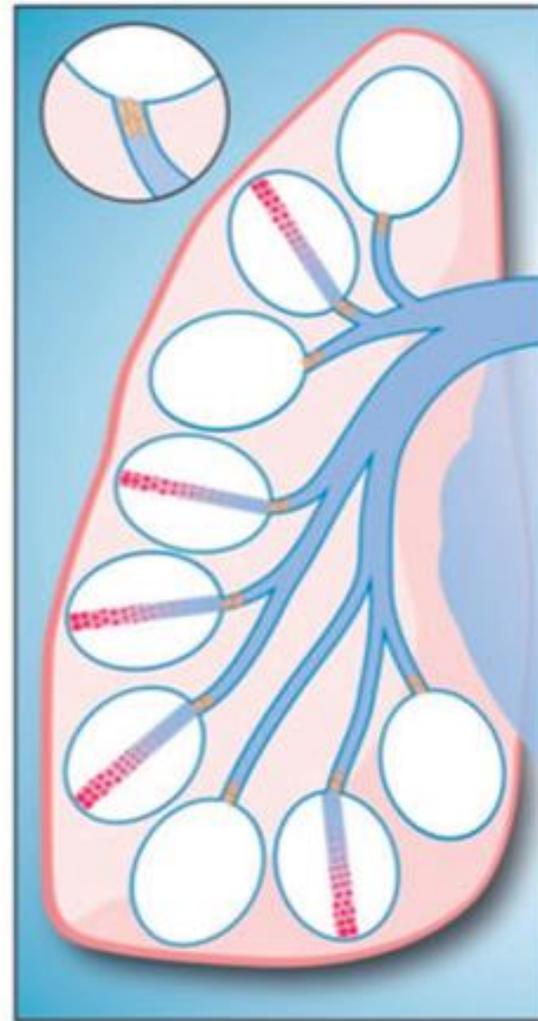
1.6 Persistent PH of the newborn



VR-PAH



VR-PAH After Vasodilation



VN-PAH

GROUP 1 Pulmonary arterial hypertension (PAH)

1.1 Idiopathic

1.1.1 Non-responders at 6 months of treatment

1.1.2 Acute responders at 6 months of treatment

1.2 Heritable

1.3 Associated with drugs

1.4 Associated with:

1.4.1 Connective tissue disease

1.4.2 HIV infection

1.4.3 Portal hypertension

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BMPR2

SOX17

CAV1

EIF2AK4

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**Definite
association**

Aminorex
Benfluorex
Dasatinib
Dexfenfluramin
Fenfluramine
Methamphetamine
Toxic rapeseed

drugs
**with data based on outbreaks,
epidemiological case-control
studies or large multicentre serie !!**

L-tryptophan
Phenylpropanolamine
Ponatinib
Selective proteasome inhibitors (carfilzomib)
Solvents (trichloroethylene)^a
St John's Wort

**Suggested by
multiple case series
or cases with drugs
with similar
mechanisms of
action.**

Possible association

Alkylating agents (cyclophosphamide, mitomycin C)^a
Amphetamines
Bosutinib
Cocaine
Diazoxide
Direct-acting antiviral agents against hepatitis C virus
(sofosbuvir)
Indirubin (Chinese herb Qing-Dai)
Interferon alpha and beta
Leflunomide
L-tryptophan
Phenylpropanolamine
Ponatinib
Selective proteasome inhibitors (carfilzomib)
Solvents (trichloroethylene)^a
St John's Wort

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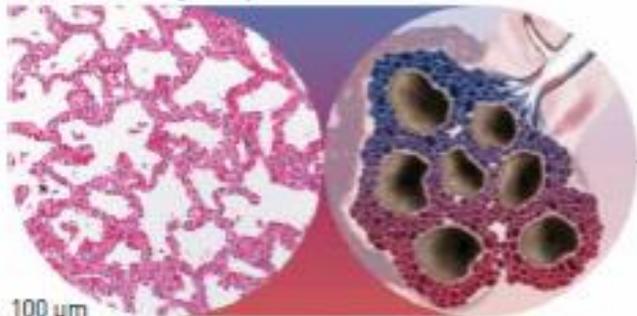
Lesions of PVOD

Pulmonary artery



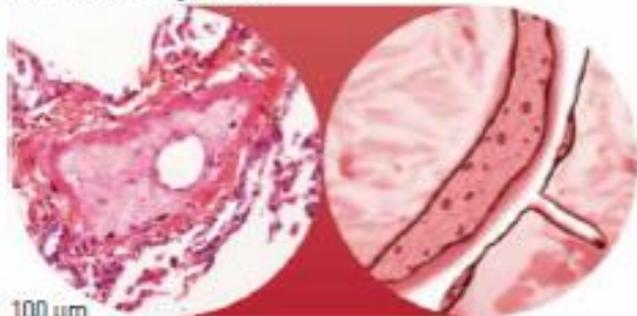
200 μm

Pulmonary capillaries



100 μm

Pulmonary vein



100 μm

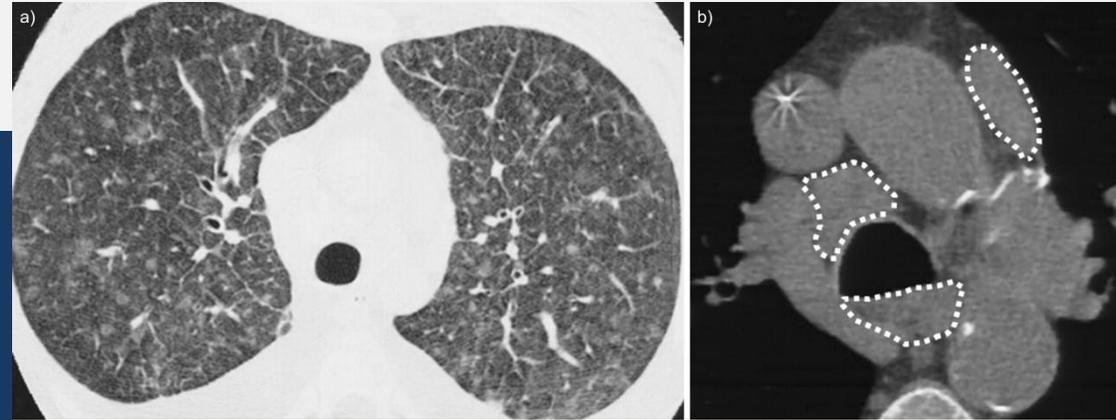
Pulmonary capillaries

Pulmonary artery

Bronchus

Pulmonary vein

PVOD - PCH



Signs evocative of venous and capillary (pulmonary veno-occlusive disease/pulmonary capillary haemangiomas) involvement

Pulmonary function tests

Decreased *DLCO* (frequently <50%)
Severe hypoxaemia

Chest HRCT

Septal lines
Centrilobular ground-glass opacities/nodules
Mediastinal lymph node enlargement

Response to PAH therapy

Possible pulmonary oedema

Genetic background

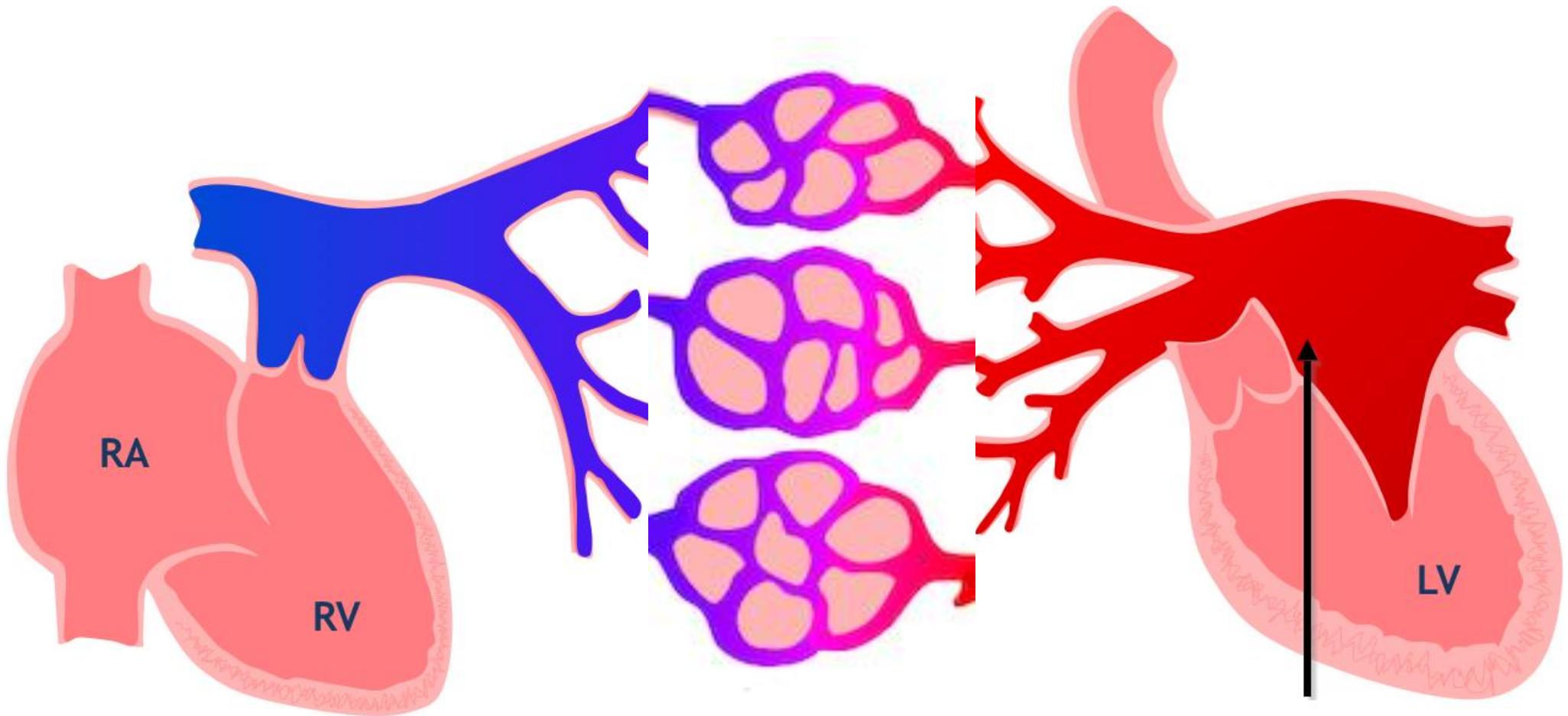
Biallelic *EIF2AK4* mutations

Occupational exposure

Organic solvent (trichloroethylene)

GROUP 2 PH associated with left heart disease

2.1 Heart failure:



2.

2.

GRO

3.

3.

3.

3.

3.

3.

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2.1 Heart failure:

2.1.1 with preserved ejection fraction

2.1.2 with reduced or mildly reduced ejection fraction

2.2 Valvular heart disease

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3.6 Developmental lung disorders

GROUP

2.1 H

2.

2.

2.2 V

2.3 C

GROUP

3.1 O

3.2 R

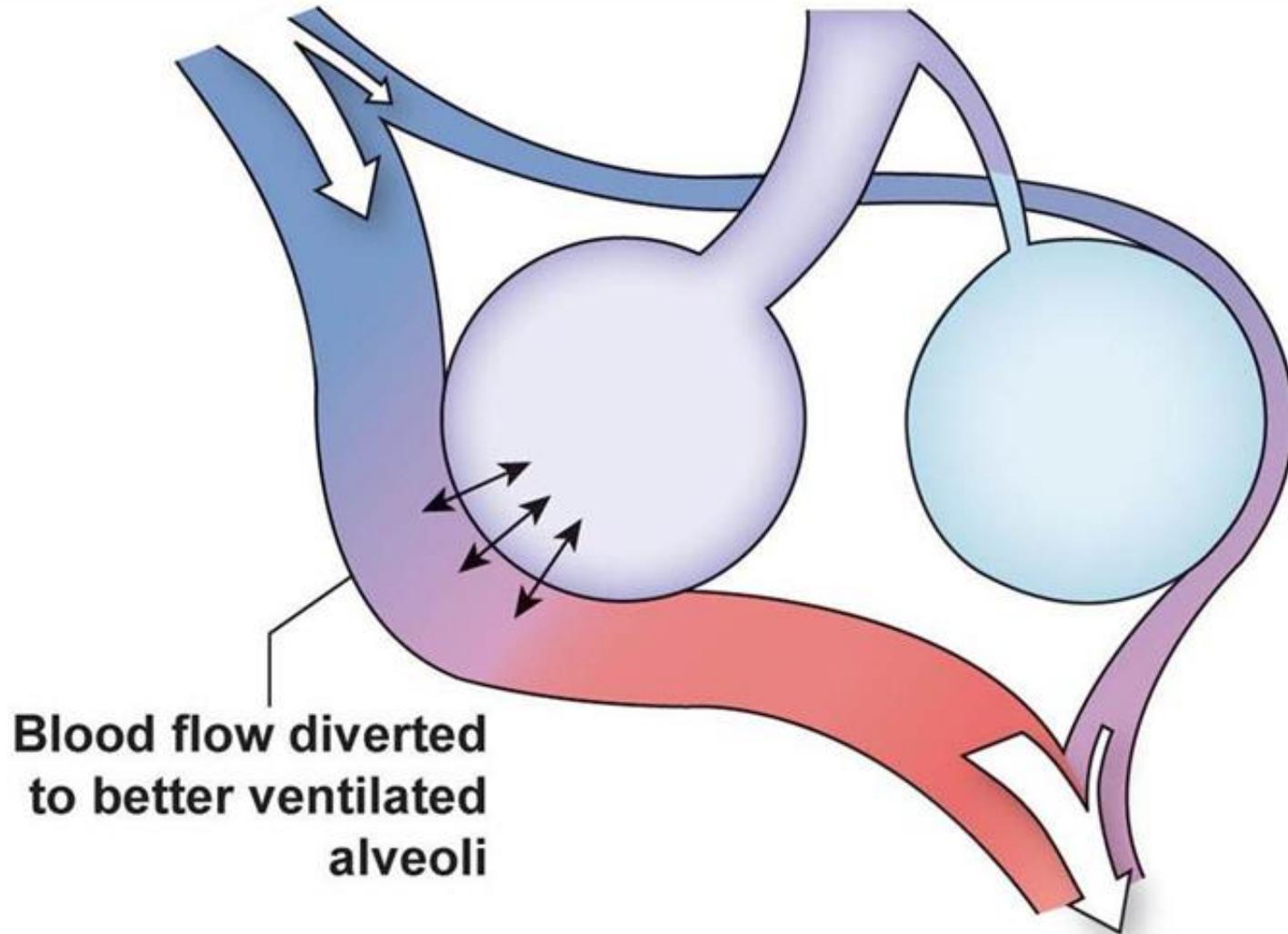
3.3 I

3.4 H

3.5 H

3.6 D

(c) Local control mechanisms try to keep ventilation and perfusion matched.



y PH

GROU

4.1

4.2

GROU

5.1

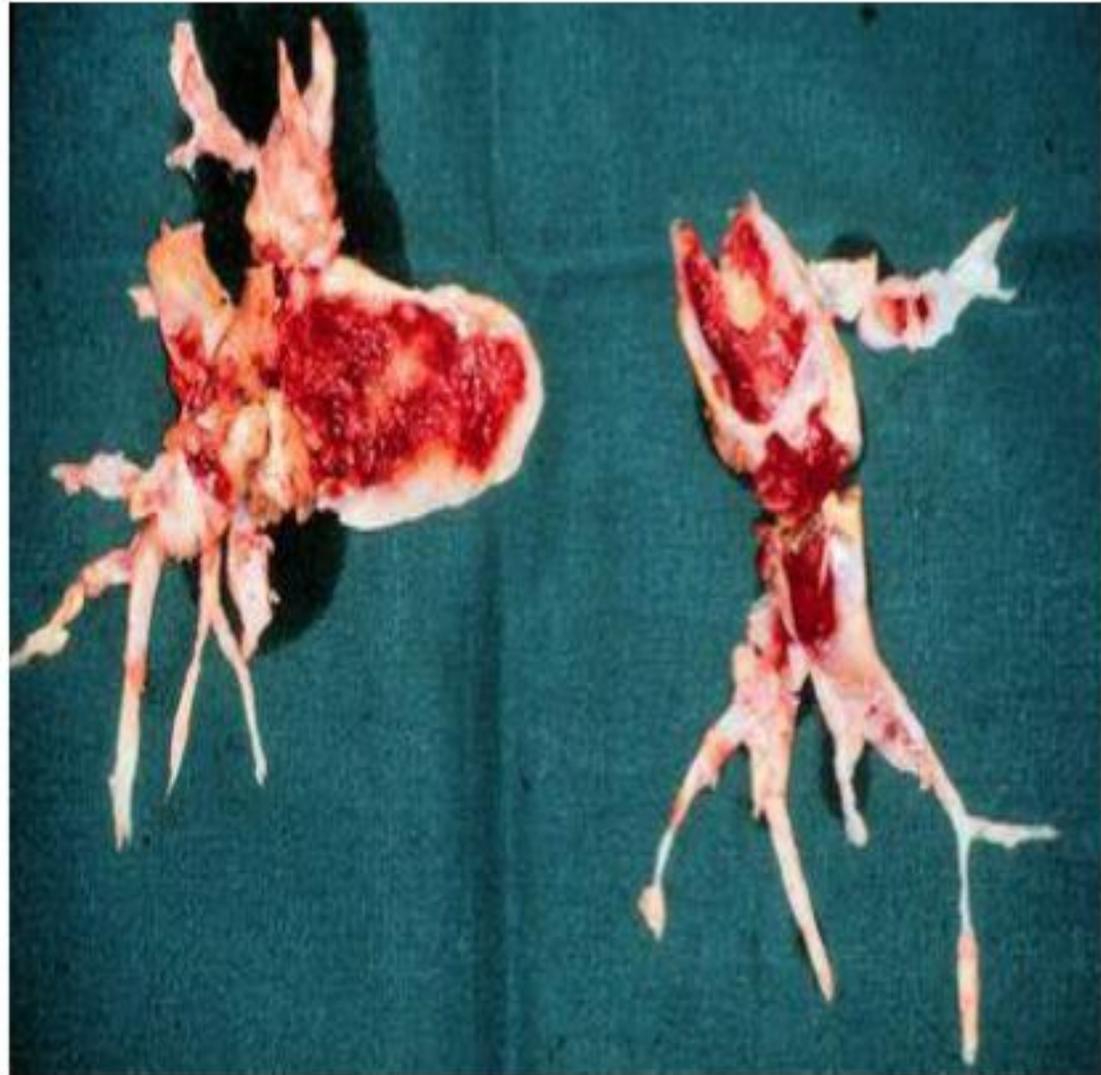
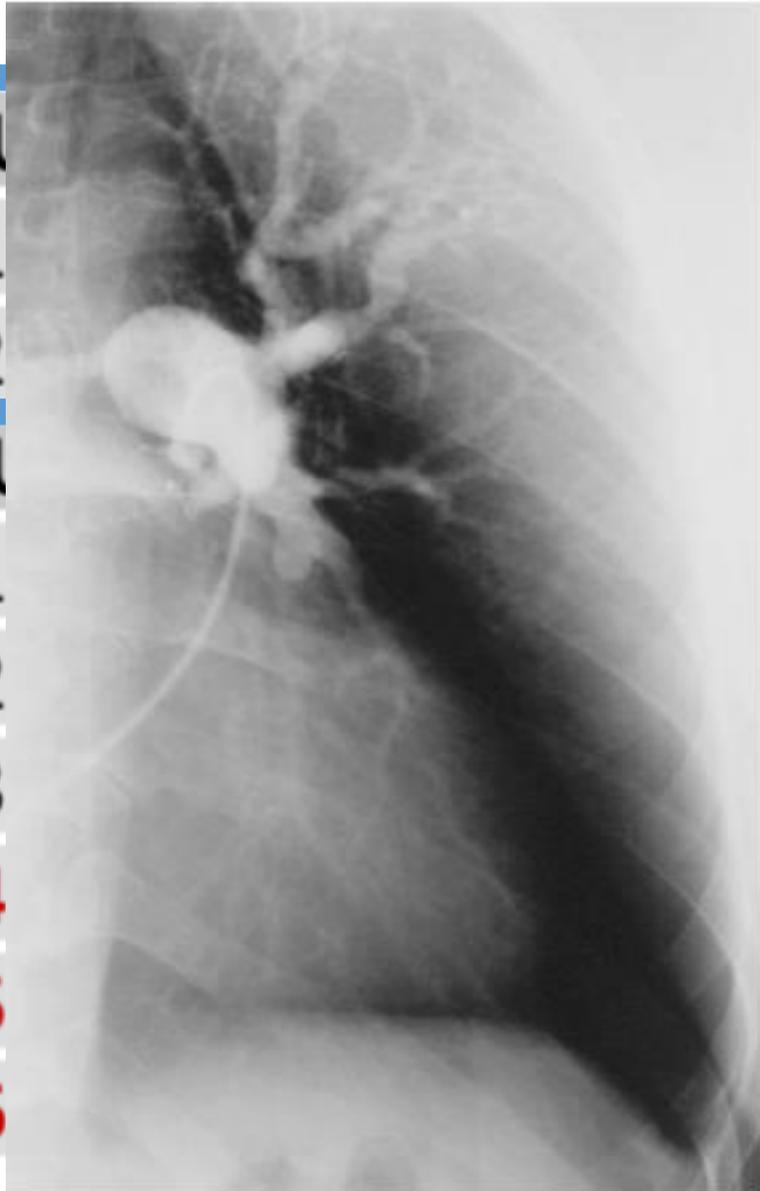
5.2

5.3

5.4

5.5

5.6



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Disorders associated with pulmonary hypertension

1 Haematological disorders

Inherited and acquired chronic haemolytic anaemia

- Sickle cell disease
- β -thalassaemia
- Spherocytosis
- Stomatocytosis
- Autoimmune disorders
- Chronic myeloproliferative disorders
- Chronic myelogenous leukaemia
- Polycythaemia vera
- Idiopathic myelofibrosis
- Essential thrombocytopenia
- Others

2 Systemic disorders

Sarcoidosis
Pulmonary Langerhans's cell histiocytosis
Neurofibromatosis type 1

3 Metabolic disorders

Glycogen storage disease
Gaucher disease

4 Chronic renal failure with/without haemodialysis

5 Pulmonary tumour thrombotic microangiopathy

6 Fibrosis mediastinitis

1 PAH

1.1 Idiopathic PAH

1.2 Heritable PAH

TABLE 7 Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders

Chronic haemolytic anaemia

Myeloproliferative disorders

5.2 Systemic and metabolic disorders

Pulmonary Langerhans cell histiocytosis

Gaucher disease

Glycogen storage disease

Neurofibromatosis

Sarcoidosis

5.3 Others

Chronic renal failure

Fibrosing mediastinitis

5.4 Complex congenital heart disease

See the Task Force on Diagnosis and Treatment of Pulmonary Hypertension

European Respiratory Society



SCD

It is clear that in this setting PH is frequently multifactorial, including :

- Elevated CO
- LHD
- Thromboembolic disease
- Altered blood viscosity and PVD due to endothelial dysfunction, mainly due to nitric oxide depletion .

- Restrictive cardiomyopathy has been better recognized and described in clinical and experimental studies

5 PH with unclear and/or multifactorial mechanisms

5.1 Haematological disorders

5.2 Systemic and metabolic disorders

5.3 Others

5.4 Complex congenital heart disease

1 PAH

1.1 Idiopathic PAH

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TABLE 7 Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders

β-thalassaemia

Chronic haemolytic anaemia

Myeloproliferative disorders

SCD

Better understanding about the risk factors for major complications of the disease, including PH.

In cohort of 1309 patients that underwent haemodynamic screening evaluation :

- pre-capillary PH in 2.1%
- post-capillary PH in 0.3% .

Older age and splenectomy were clear risk factors associated with PH.

Derchi G, et al Circulation 2014; 129: 338–345.

It is clear that in this setting PH is frequently multifactorial, including :

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*Fonseca G, et al . Ethn Dis 2016; 26: 545–552.
Mehari A, et al . Ethn Dis 2016; 26: 545–552.*

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
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3 PH due to lung diseases and/or hypoxia

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4 PH due to pulmonary artery obstructions (table 6)

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)

- 5.1 Haematological disorders
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3 PH due to lung diseases and/or hypoxia

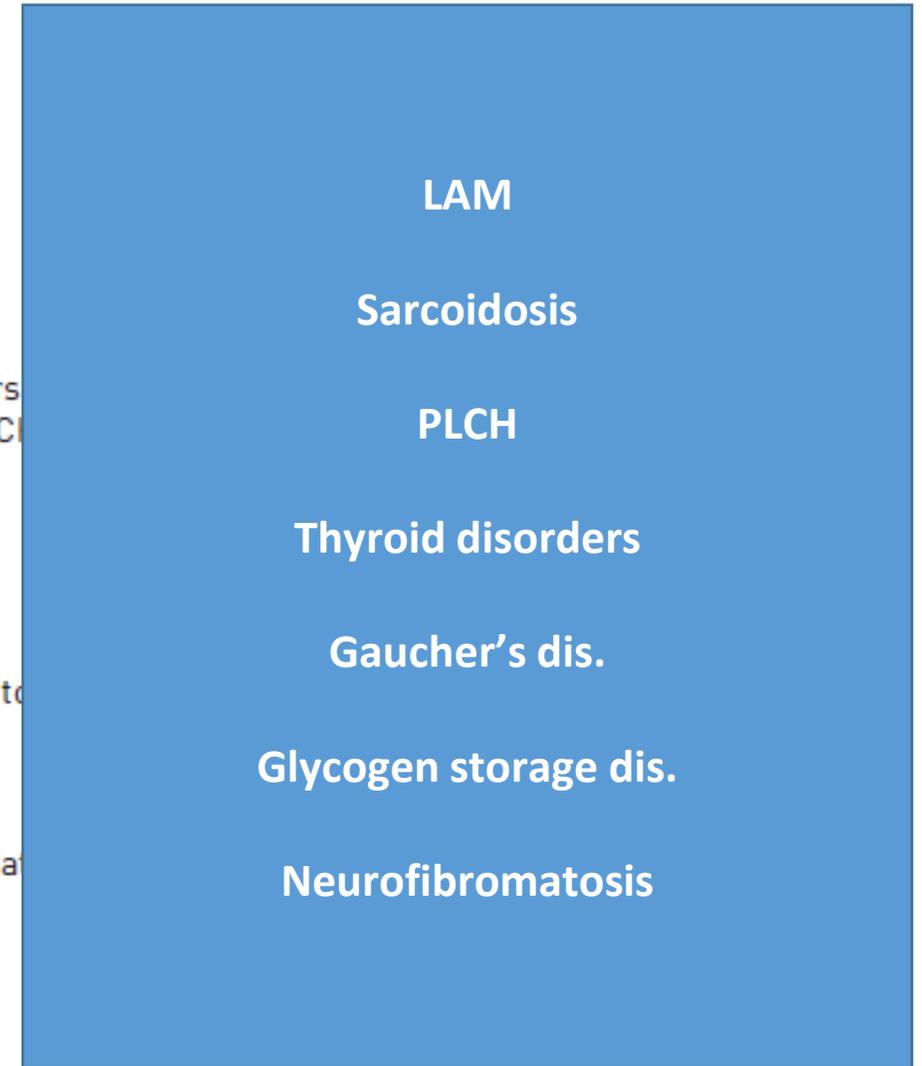
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)

- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease



1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 2)
- 1.4 PAH associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCPD)
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired vascular conditions leading to PH

3 PH due to lung disease and/or hypoxia

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LAM

Sarcoidosis

PLCH

Thyroid disorders

Gaucher's dis.

Glycogen storage dis.

Neurofibromatosis

Wu X, et al. Front Med 2018;

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
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 - 1.4.1 Connective tissue disease
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Neurofibromatosis

1 PAH

1.1 Idiopathic PAH

1.2 Heritable PAH

PH in sarcoidosis ranges from 5.7% to 74%

fibrosis-associated remodelling
obliteration of pulmonary vessels,
extrinsic compression of central pulmonary vessels by
lymphadenopathy or mediastinal fibrosis
pulmonary veno-occlusive-like lesions
granulomatous involvement of pulmonary vessels
left ventricular dysfunction
portopulmonary hypertension

Shorr AF, et al. Eur Respir J 2005; 25: 783–788.

Nunes H, et al. Thorax 2006; 61: 68–74.

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Neurofibromatosis

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with other diseases
 - 1.4.1 Connective tissue diseases
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH long-term response to treatment
- 1.6 PAH with overt features of right heart failure

Comorbidity , risk factor affecting prognosis

LAM

Sarcoidosis

PLCH

Thyroid disorders

Gaucher's dis.

Glycogen storage dis.

Neurofibromatosis

Richter MJ et al. J Heart Lung Transplant 2016; 35: 1427–1434.

of the new...
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 rt failure with preserved LVEF

- 2.2 PH due to heart failure with reduced LVEF
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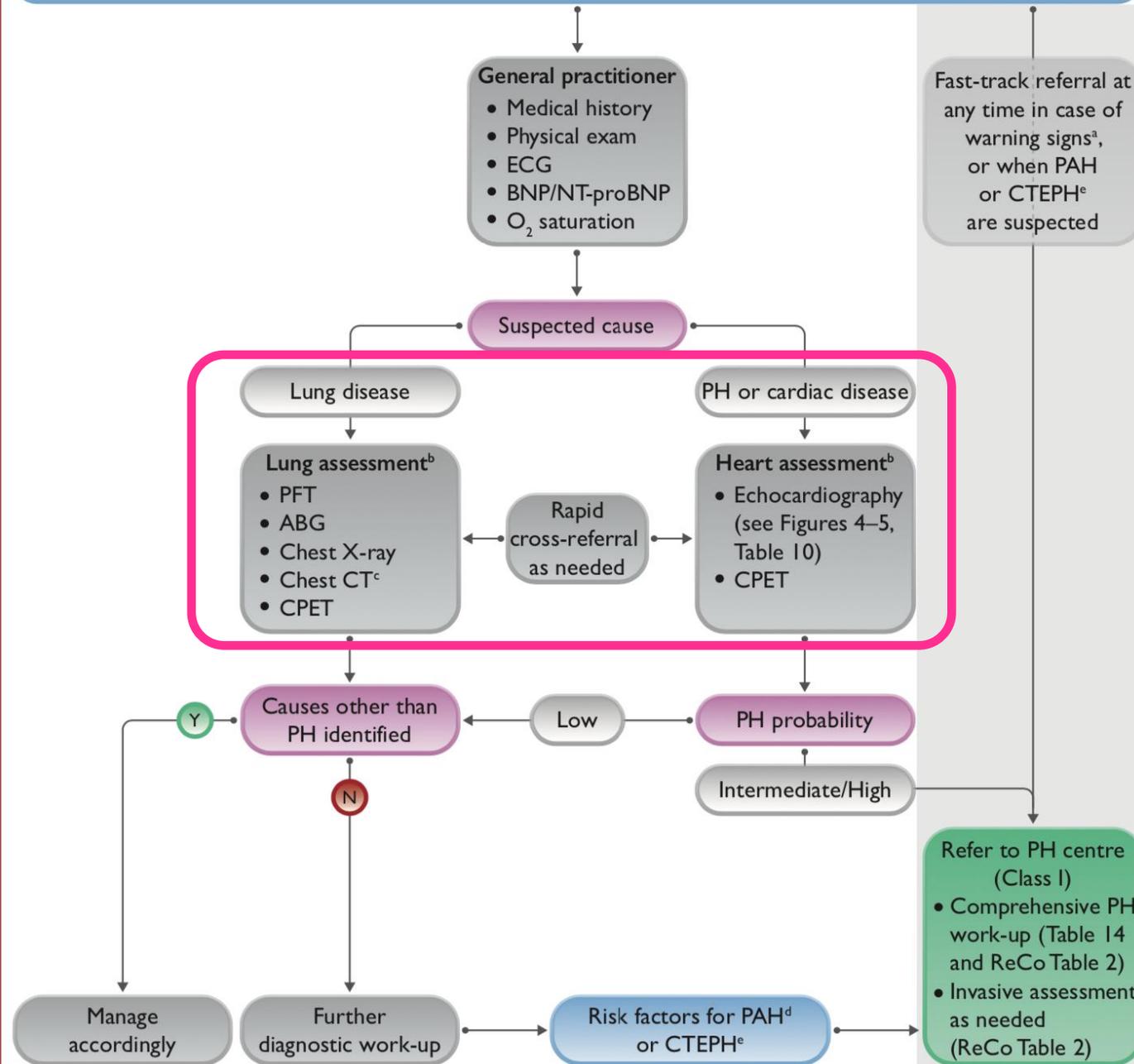
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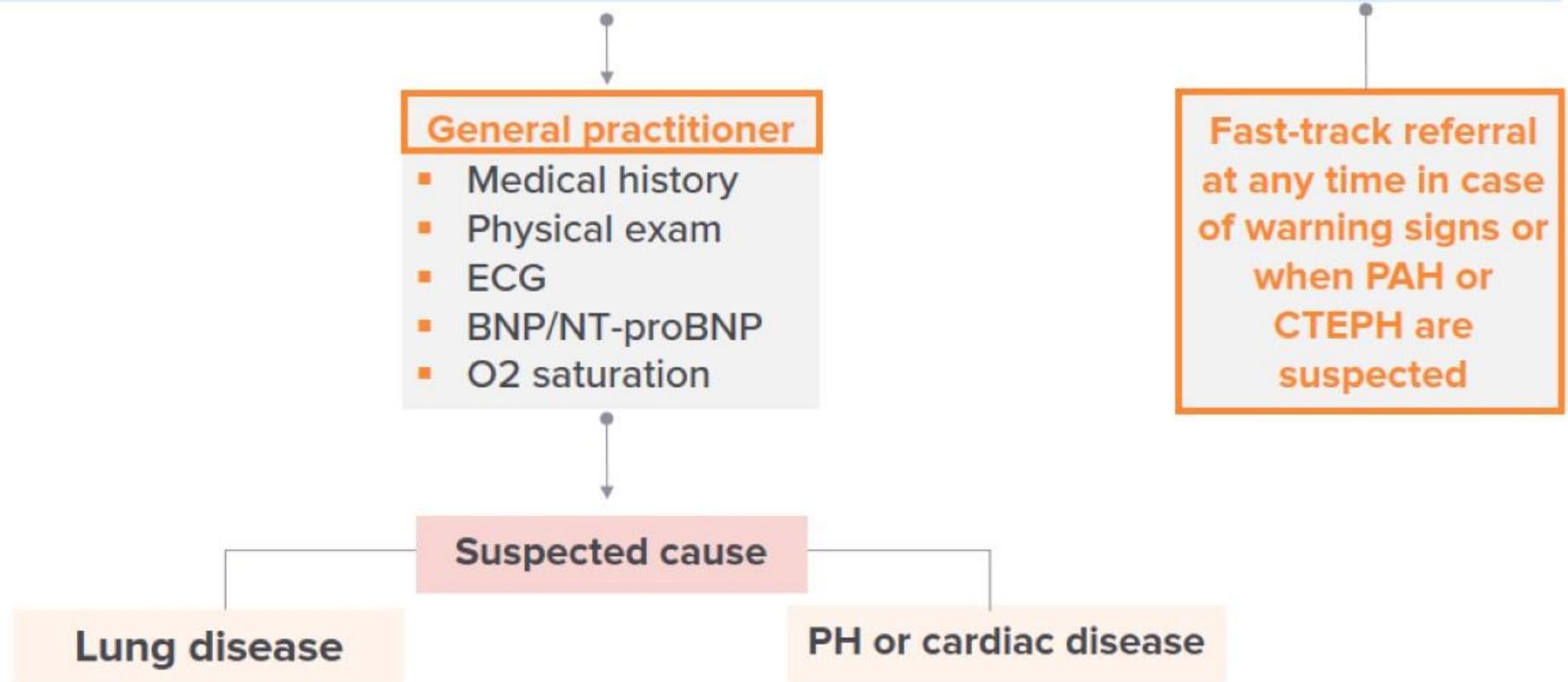
Diagnostic algorithm of patients with unexplained exertional dyspnoea and/or suspected PH



2022 ESC/ERS Guidelines for the Diagnosis and Treatment of PH

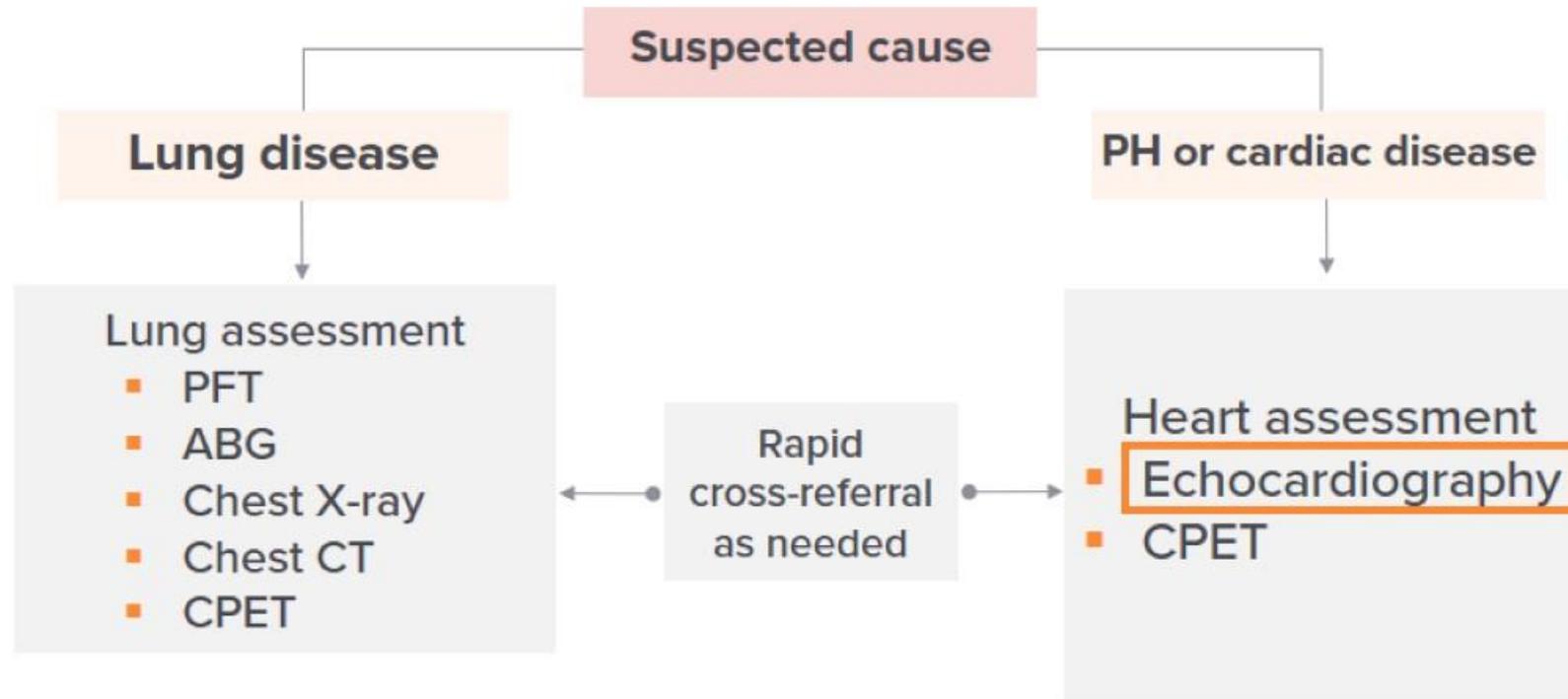
Changes to the Diagnostic Algorithm

Diagnostic algorithm of patients with **unexplained exertional dyspnea** and/or **suspected PH**



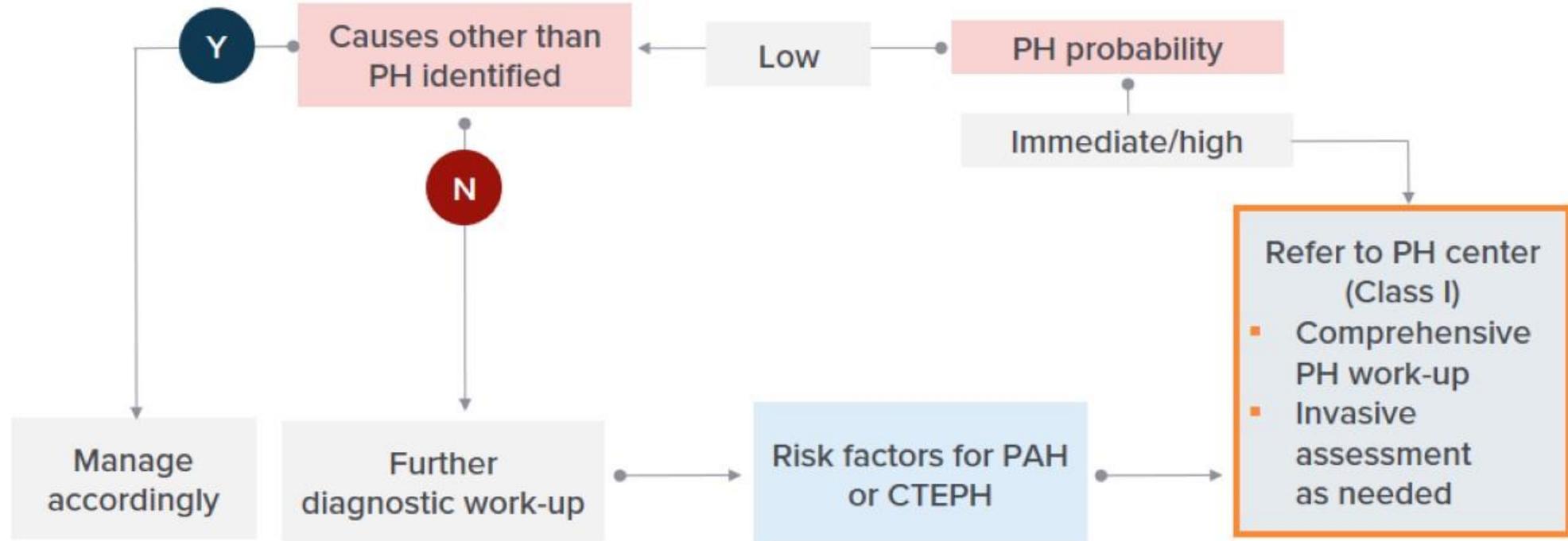
2022 ESC/ERS Guidelines for the Diagnosis and Treatment of PH

Changes to the Diagnostic Algorithm



2022 ESC/ERS Guidelines for the Diagnosis and Treatment of PH

Changes to the Diagnostic Algorithm



2022 ESC/ERS Guidelines for the Diagnosis and Treatment of PH

Class I Recommendations for Right Heart Catheterization



Perform RHC to confirm PH diagnosis and guide treatment decisions



RHC should be done in experienced centers in patients with suspected or known PH



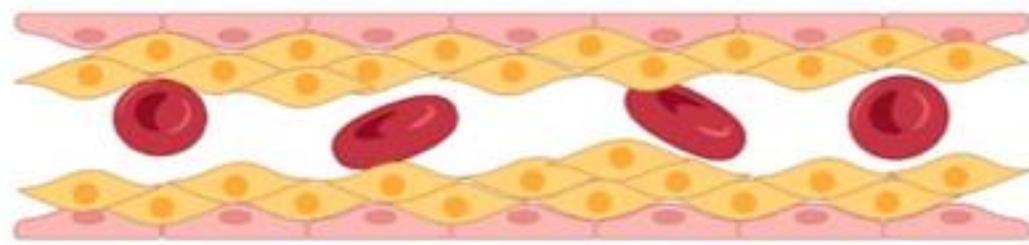
Include complete set of hemodynamic measures, following standardized protocols

Hemodynamic Measures Obtained During RHC

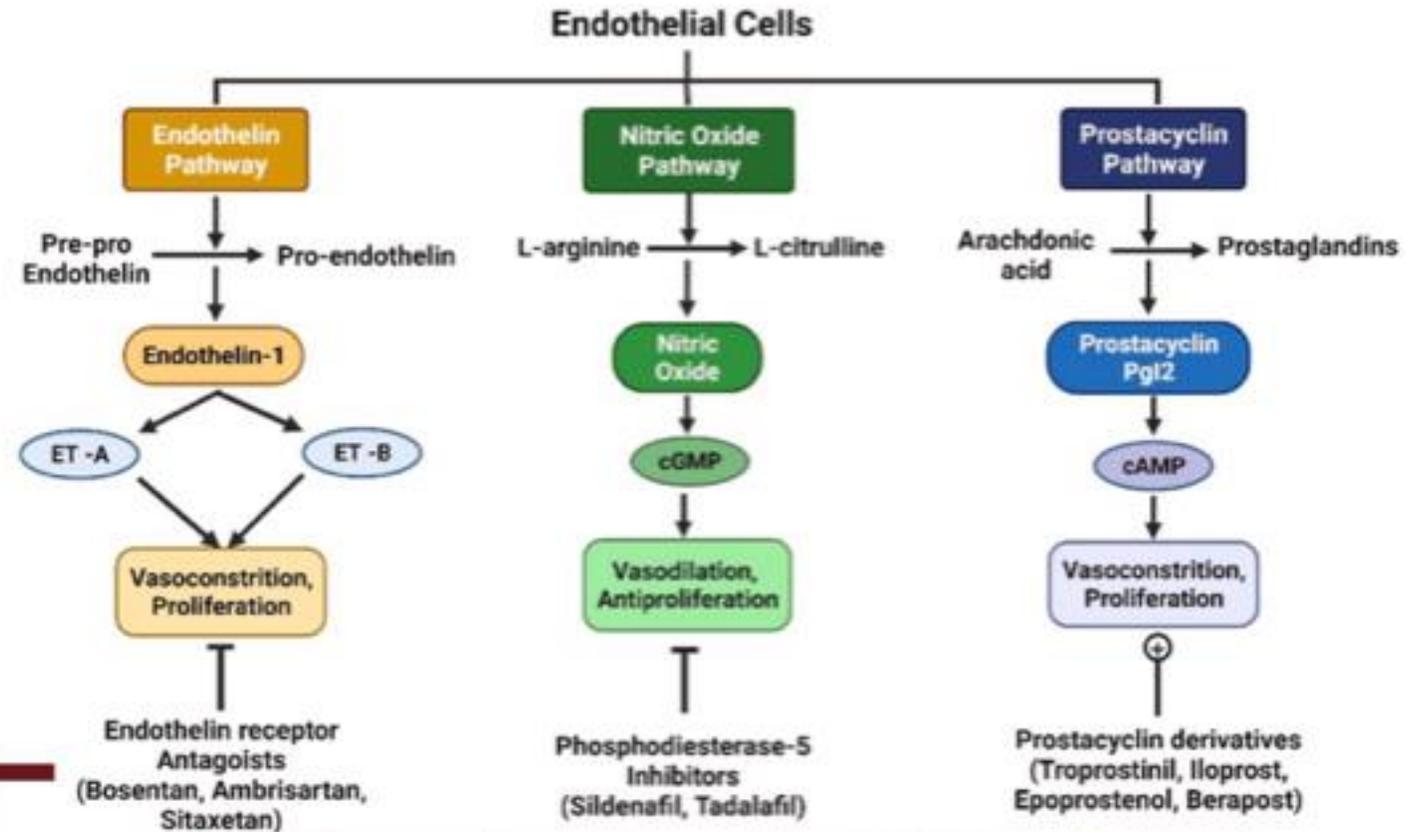
Measured variables	Normal value
Right atrial pressure, mean (RAP)	2-6 mm Hg
Pulmonary artery pressure, systolic (sPAP)	15-30 mm Hg
Pulmonary artery pressure, diastolic (dPAP)	4-12 mm Hg
Pulmonary artery pressure, mean (mPAP)	8-20 mm Hg
Pulmonary arterial wedge pressure, mean (PAWP)	≤ 15 mm Hg
Cardiac output (CO)	4-8 L/min
Mixed venous oxygen saturation (SvO ₂)	65% to 80%
Arterial oxygen saturation (SaO ₂)	95% to 100%
Systemic blood pressure	120/80 mm Hg
Calculated parameters	
Pulmonary vascular resistance (PVR)	0.3-2.0 WU
Pulmonary vascular resistance index (PVRI)	3-3.5 WU* m ²
Total pulmonary resistance (TPR)	< 3 WU
Cardiac index (CI)	2.5-4.0 L/min/m ²
Stroke volume (SV)	60-100 mL
Stroke volume index (SVI)	33-47 mL/m ²
Pulmonary arterial compliance (PAC)	> 2.3 mL/mm Hg

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope ^a	Repeated syncope ^b
WHO-FC	I, II	III	IV
6MWD ^c	>440 m	165–440 m	<165 m
CPET	Peak VO ₂ >15 mL/min/kg (>65% pred.) VE/VCO ₂ slope <36	Peak VO ₂ 11–15 mL/min/kg (35–65% pred.) VE/VCO ₂ slope 36–44	Peak VO ₂ <11 mL/min/kg (<35% pred.) VE/VCO ₂ slope >44
Biomarkers: BNP or NT-proBNP ^d	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm ² TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm ² TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm ² TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI ^e	RVEF >54% SVI >40 mL/m ² RVESVI <42 mL/m ²	RVEF 37–54% SVI 26–40 mL/m ² RVESVI 42–54 mL/m ²	RVEF <37% SVI <26 mL/m ² RVESVI >54 mL/m ²
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m ² SVI >38 mL/m ² SvO ₂ >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m ² SVI 31–38 mL/m ² SvO ₂ 60–65%	RAP >14 mmHg CI <2.0 L/min/m ² SVI <31 mL/m ² SvO ₂ <60%

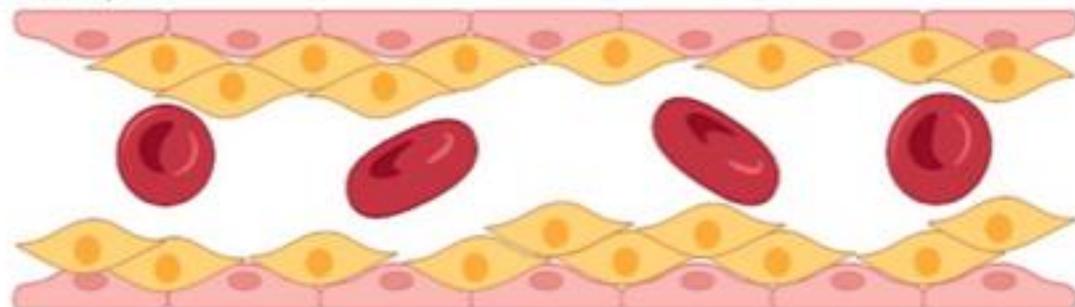
High resistance to blood flow due to vasoconstriction of pulmonary artery in PH



Currently available treatment modalities providing only symptomatic vasodilation without halting the underlying proliferative mechanisms.



Symptomatic vasodilation of pulmonary artery by currently available treatment modalities



Agents That Target Different Vasomotor Pathways in PAH

ET Pathway

- Bosentan (oral)
- Ambrisentan (oral)
- Macitentan (oral)

NO Pathway

- PDE-5 inhibitors
 - Sildenafil (oral, intravenous)
 - Tadalafil (oral)
- sGC stimulator
 - Riociguat (oral)

Prostacyclin Pathway

- Epoprostenol (continuous intravenous, inhalation)
- Treprostinil (SC, intravenous, inhalation, oral)
- Iloprost (inhalation)
- Selexipag (oral)

Figure 9

Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated pulmonary arterial hypertension

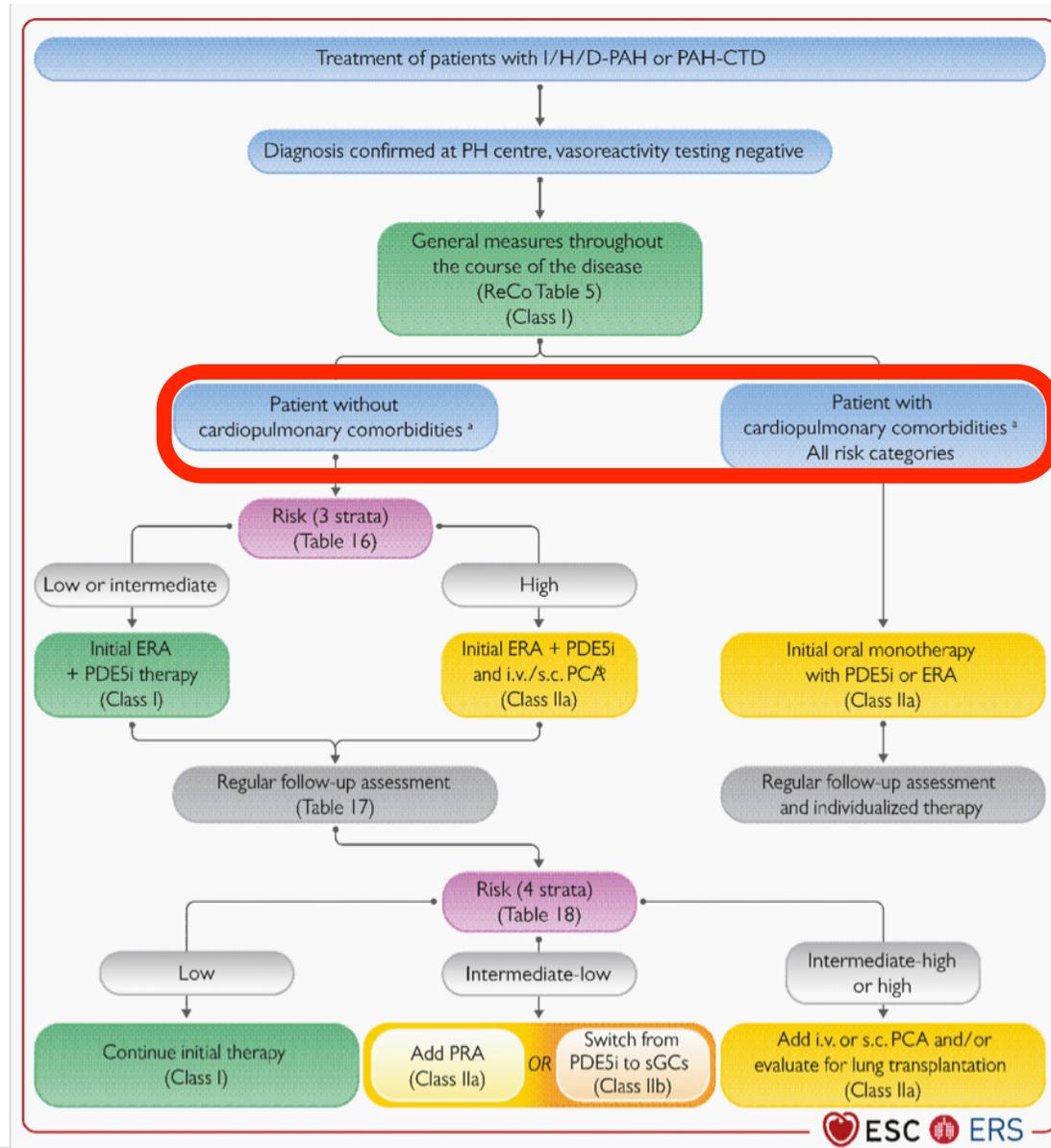


Figure 9

Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated pulmonary arterial hypertension

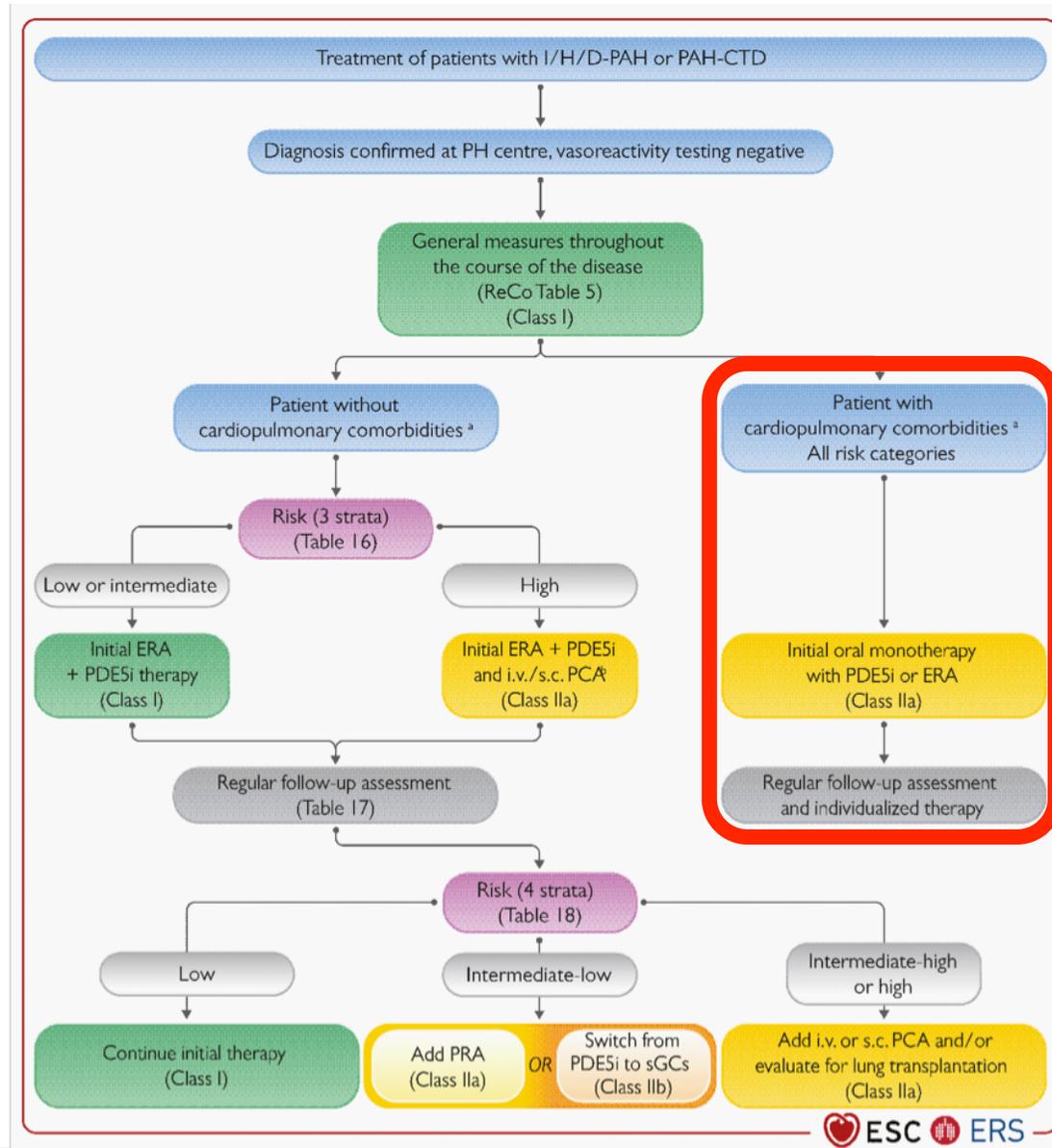
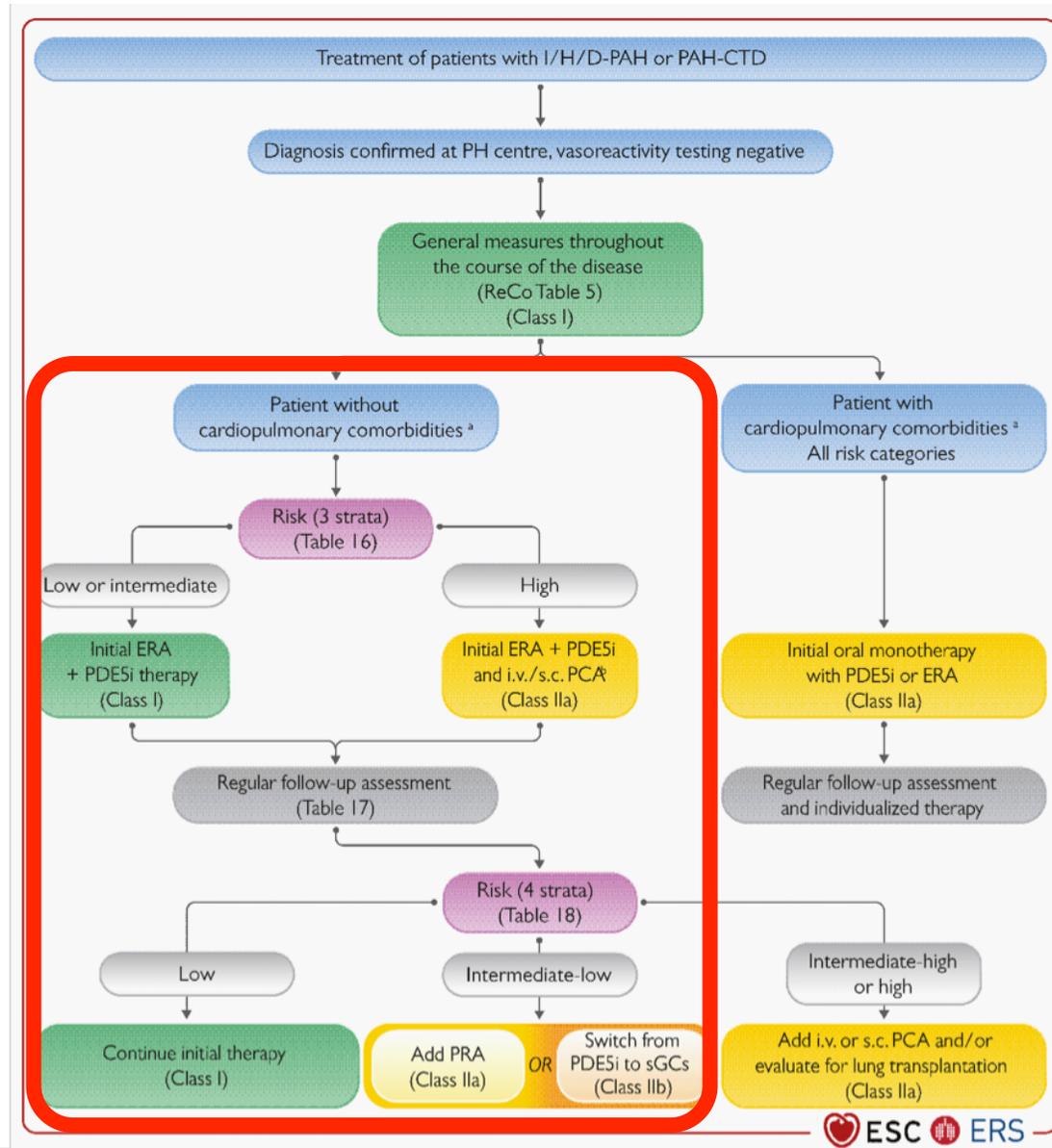


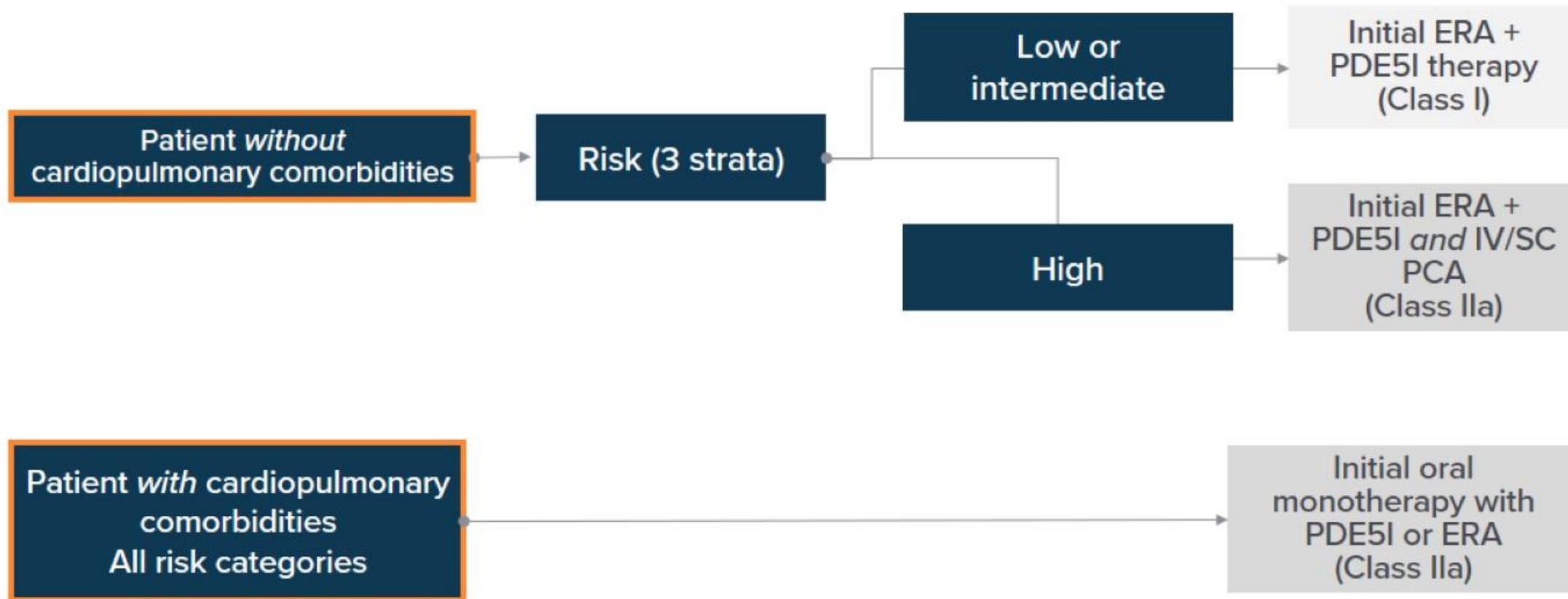
Figure 9

Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated pulmonary arterial hypertension



Treatment Algorithm for Patients With I/H/D-PAH or PAH-CTD

Initial Treatment Strategies



ERA, endothelin receptor agonist; IV, intravenous; I/H/D-PAH, Idiopathic, heritable, drug-associated pulmonary arterial hypertension; PAH-CTD, pulmonary arterial hypertension associated with connective tissue disease; PDE5I, phosphodiesterase 5 inhibitor; PCA, prostacyclin analogue; SC, subcutaneous.

Humbert M, et al. Eur Heart J. 2022;ehac237.

Follow Up Risk Assessment

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II ^a	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP, ^a ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

Treatment Algorithm for Patients With I/H/D-PAH or PAH-CTD

Follow-Up Treatment Strategies



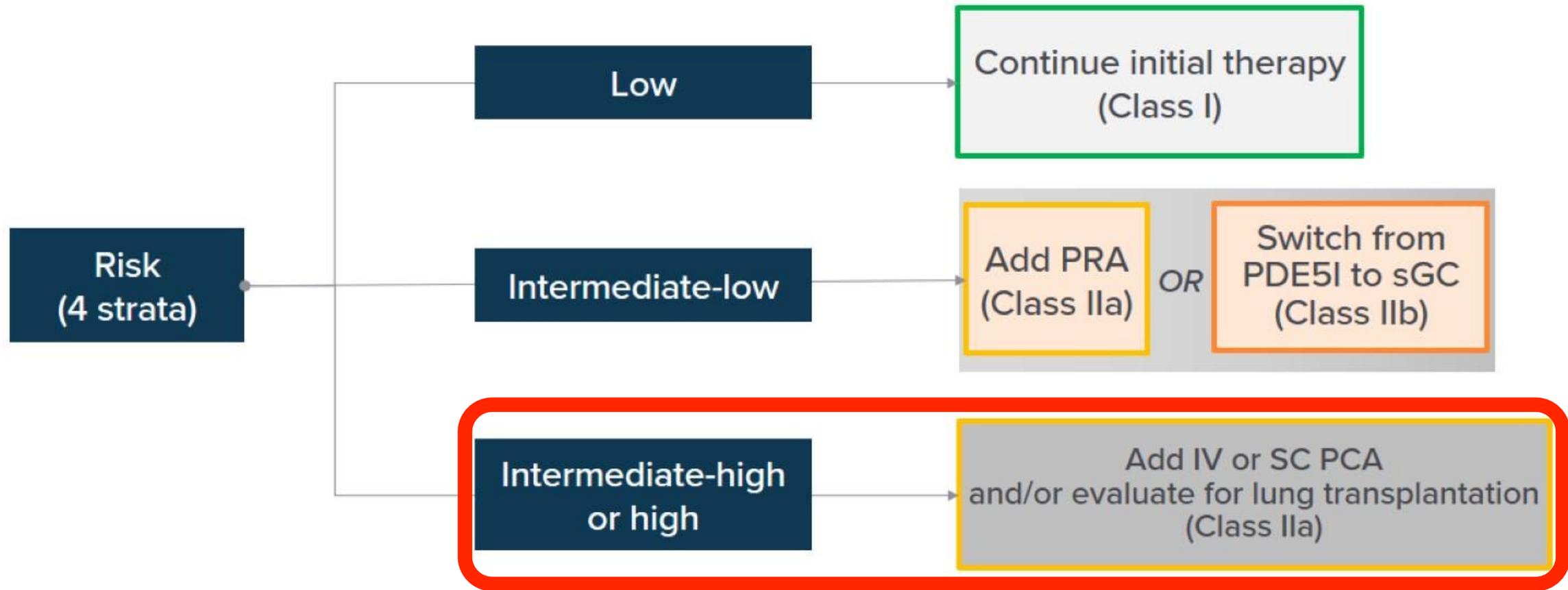
Treatment Algorithm for Patients With I/H/D-PAH or PAH-CTD

Follow-Up Treatment Strategies



Treatment Algorithm for Patients With I/H/D-PAH or PAH-CTD

Follow-Up Treatment Strategies



Take Home Message

- A new pressure level to define an abnormal elevation in the mPAP **>20 mmHg** and the need for PVR **2 WU** to define the presence of pre-capillary PH.
- **“PAH long-term responders to CCBs”** and **“PAH with overt features of venous/capillaries (PVOD/PCH) involvement”**, has been added.
- PH with **unclear and/or multifactorial** mechanisms was simplified with the removal of splenectomy and thyroid disorder.
- New insights for groups **2, 3 and 4** have been addressed.
- Treatment consideration for **comorbidities**, with **different risk-based treatment options** for naive and follow up cases were precised

Thank you

