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

Definition, classification and diagnosis of pulmonary hypertension

Marion Delcroix, University Hospitals of Leuven, Belgium

ESC European Society of Cardiology
ERS EUROPEAN RESPIRATORY SOCIETY

Disclosures

- **Institutional speaker, consultant, or steering committee member:**
  - Acceleron, AOP, Bayer, Daiichi Sankyo, Ferrer, Inari, Janssen, MSD, Pfizer

- **Institutional research grants:**
  - Janssen

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(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

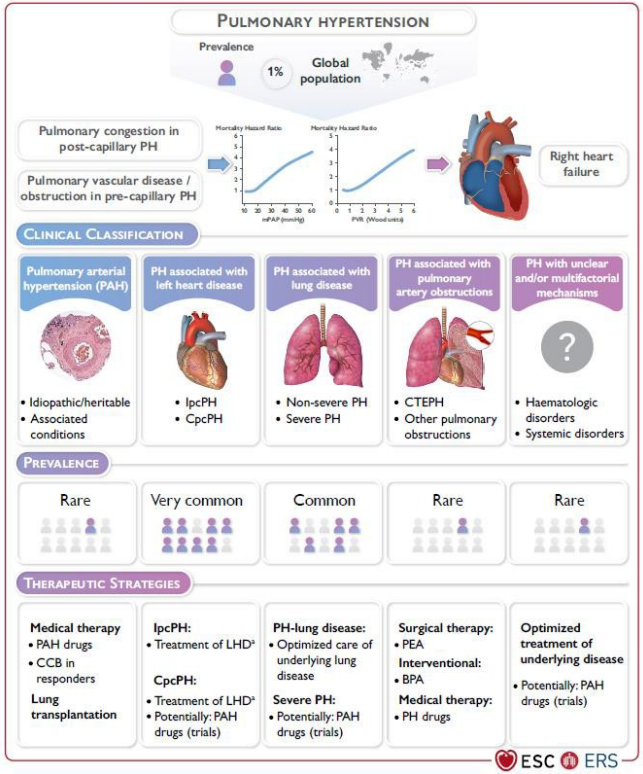
2022 ESC/ERS Guidelines for the diagnosis and treatment of Pulmonary Hypertension

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

Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS).

Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG).

Authors/Task Force Members: Marc Humbert (France), Gabor Kovacs (Austria), Marius M. Hoeper (Germany), Roberto Badagliacca (Italy), Rolf M.F. Berger (Netherlands), Margarita Brida (Croatia), Jørn Carlsen (Denmark), Andrew J.S. Coats (United Kingdom), Pilar Escribano-Subias (Spain), Pisana Ferrari (Italy), Diogenes S. Ferreira (Brazil), Hossein Ardeschir Ghofrani (Germany), George Giannakoulas (Greece), David G. Kiely (United Kingdom), Eckhard Mayer (Germany), Gergely Meszaros (Hungary), Blin Nagavci (Germany), Karen M. Olsson (Germany), Joanna Pepke-Zaba (United Kingdom), Jennifer K. Quint (United Kingdom), Göran Rådegran (Sweden), Gerald Simonneau (France), Olivier Sitbon (France), Thomy Tonia (Switzerland), Mark Toshner (United Kingdom), Jean-Luc Vachiery (Belgium), Anton Vonk Noordegraaf (Netherlands), Marion Delcroix *† (ERS Chairperson) (Belgium), Stephan Rosenkranz *† (ESC Chairperson) (Germany), and ESC/ERS Scientific Document Group



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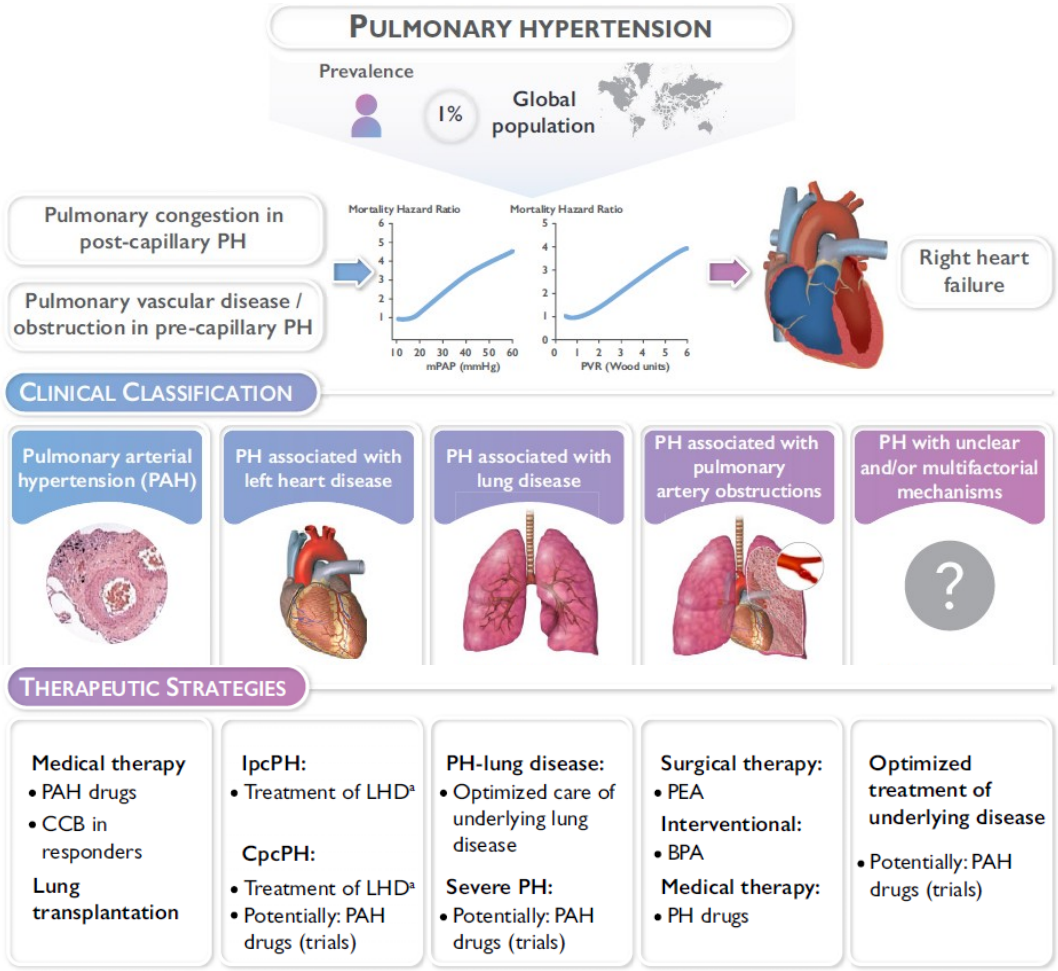
Minor adjustments in the clinical classification

Central illustrati



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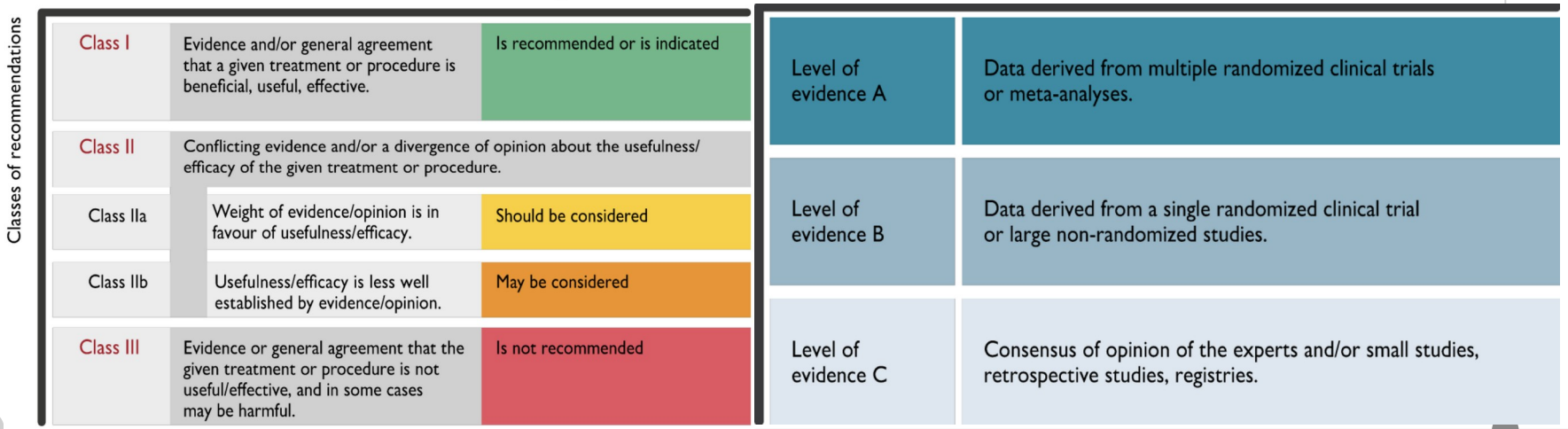
Methods

- **4 PICO questions were assessed with full systematic reviews and application of the GRADE approach and the Evidence to Decision framework**
  - Recommendation strength (strong/conditional)
  - Quality of evidence (high/moderate/low/very low)
- **8 additional, more global, key questions were assessed similarly but graded using the usual ESC approach, as were the remaining topics**



Classes of recommendations

Definition		Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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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**

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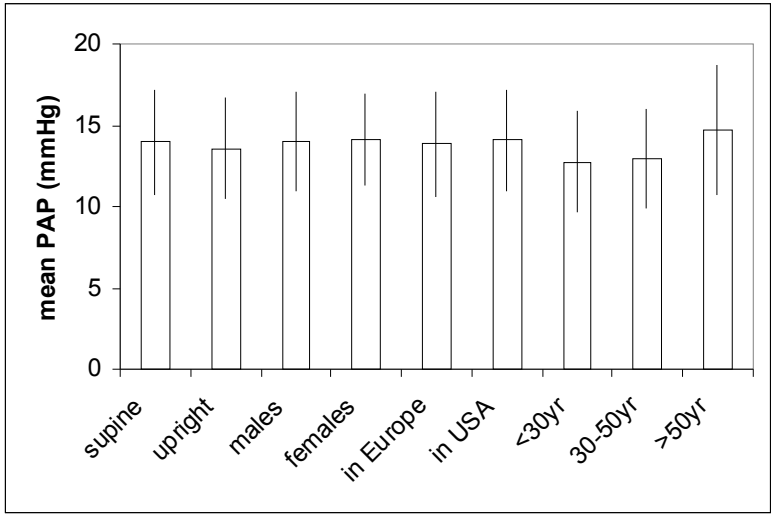
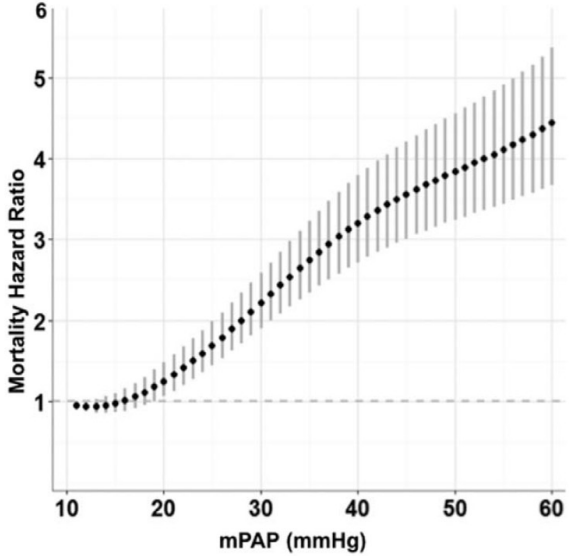
Haemodynamic definitions of pulmonary hypertension
mPAP





normal mPAP = 14.0 ± 3.3 mmHg

Kovacs et al. ERJ 2009; Maron et al. Circulation 2016

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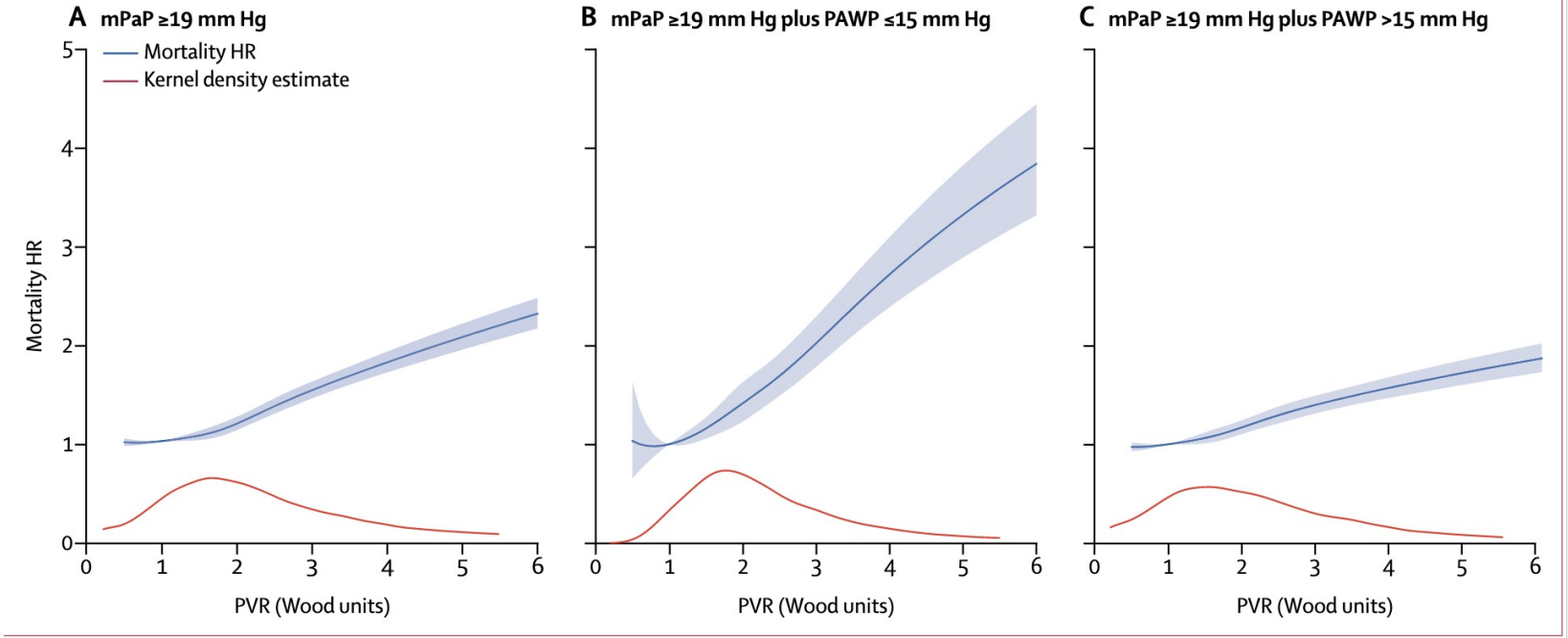
Haemodynamic definitions of pulmonary hypertension
PVR



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Maron et al. Lancer Respir Med 2020

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Clinical classification of pulmonary hypertension (1)

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

1.3 Associated with drugs and toxins

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

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Clinical classification of pulmonary hypertension (2)

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

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

p-disordered breathing is removed from the classification

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Clinical classification of pulmonary hypertension (3)

GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thrombo-embolic PH
4.2 Other pulmonary artery obstructions
GROUP 5 PH with unclear and/or multi-factorial mechanisms
5.1 Haematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

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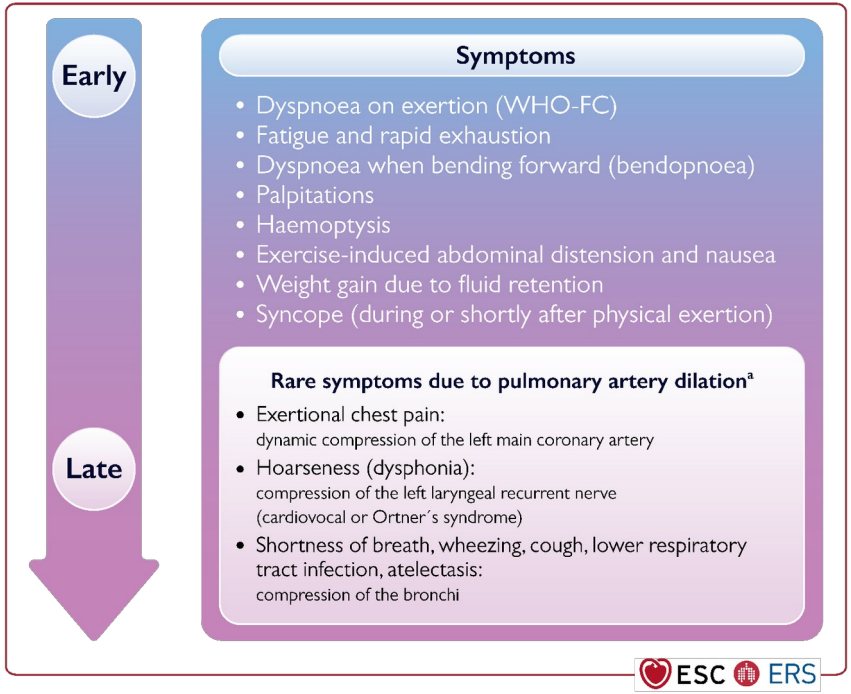
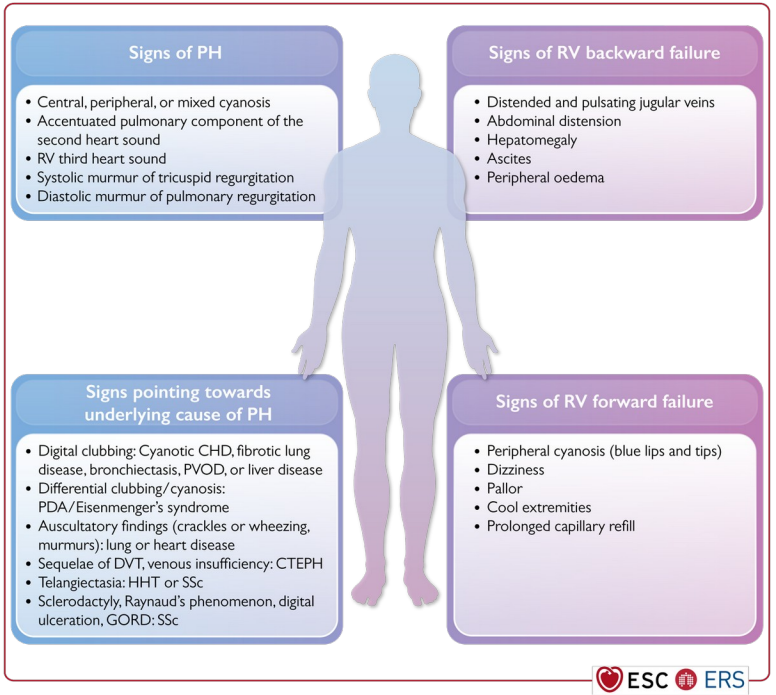
Symptoms and signs of Pulmonary Hypertension





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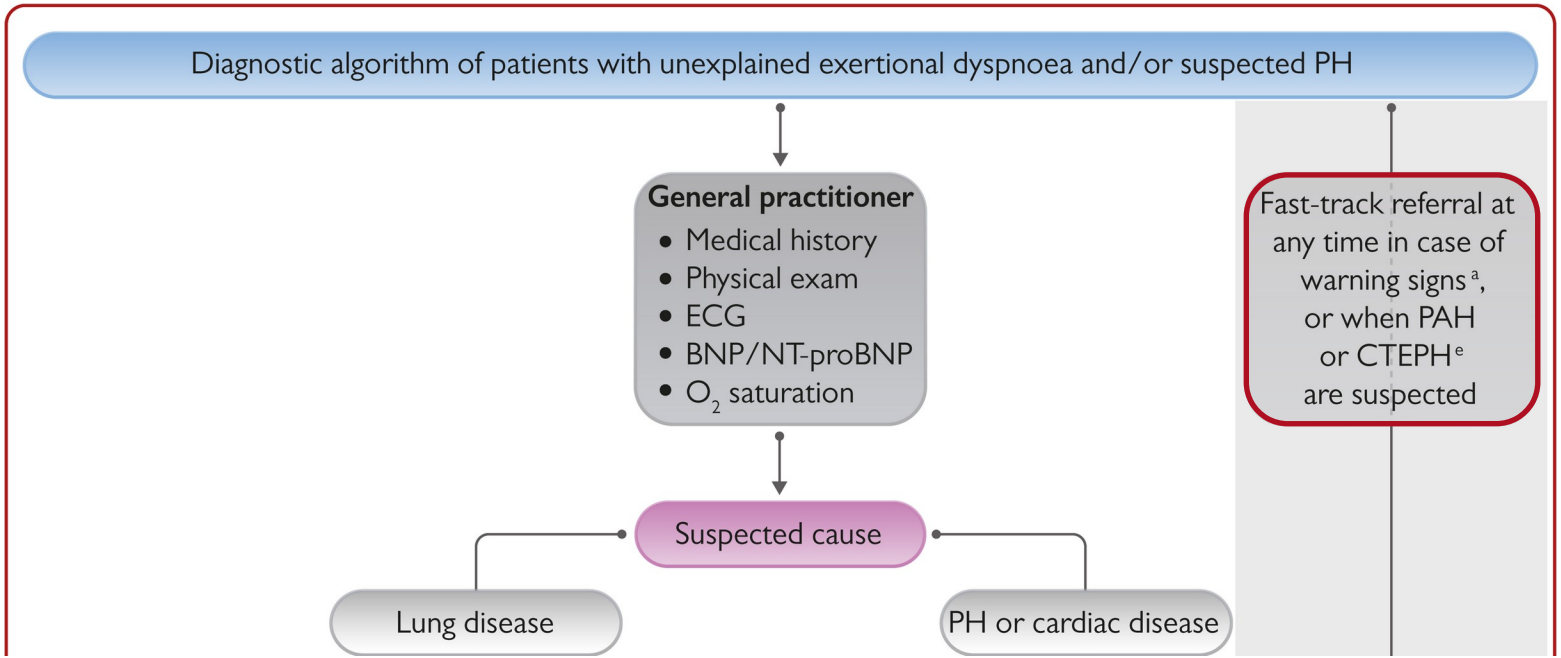
New diagnostic algorithm: unexplained dyspnoea and/or suspicion of PH

1 = SUSPICION: general practitioner + seeking for a common (respiratory or ca

track referral in “warning” clinical scenario



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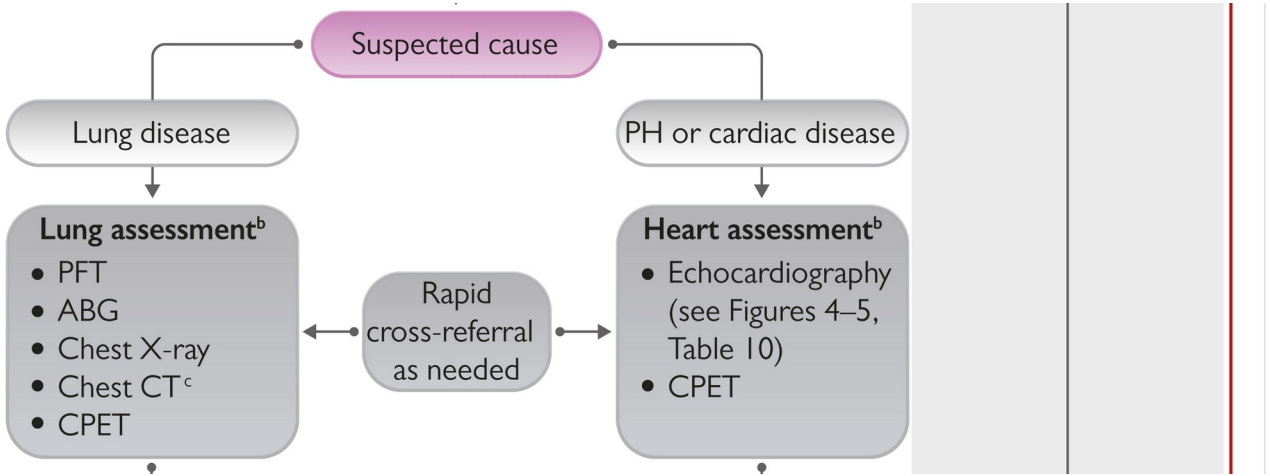
Diagnostic algorithm of patients with unexplained dyspnoea and/or suspected pulmonary hypertension

ep 2 = DETECTION: heart (with echocardiography) and lung assessment
oss-talk pneumo/cardio



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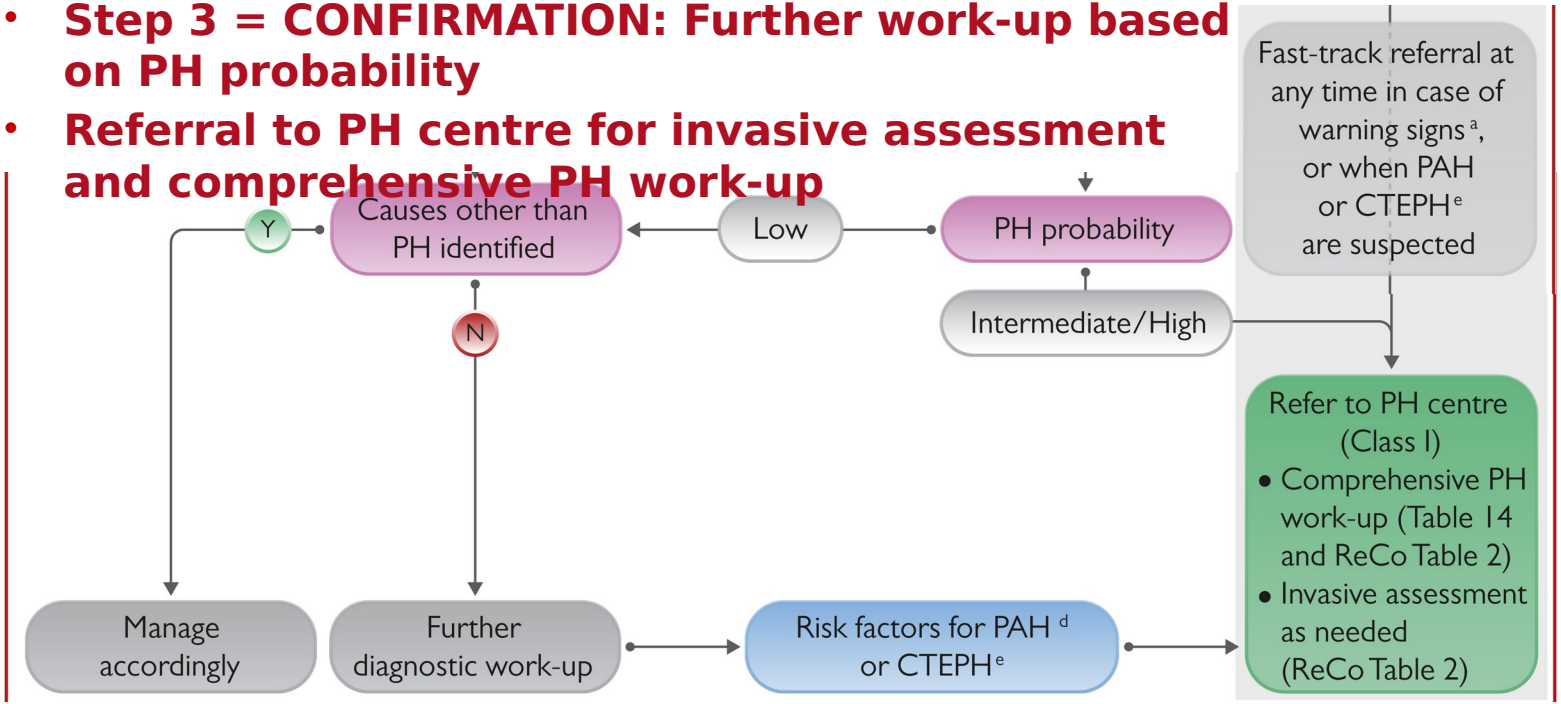
Diagnostic algorithm of patients with unexplained dyspnoea and/or suspected pulmonary hypertension

- **Step 3 = CONFIRMATION: Further work-up based on PH probability**
- **Referral to PH centre for invasive assessment and comprehensive PH work-up**



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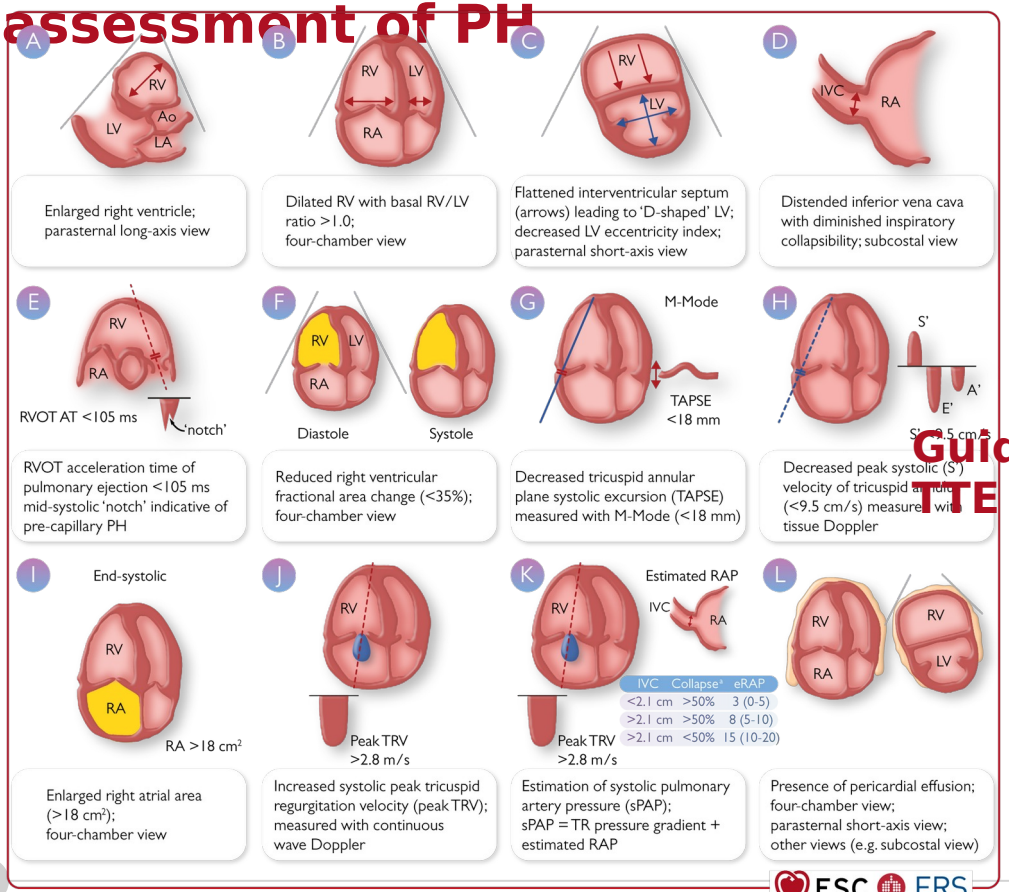
Transthoracic echocardiographic parameters in the assessment of PH



Guidance for right heart imaging by TTE for all patients with suspected PH

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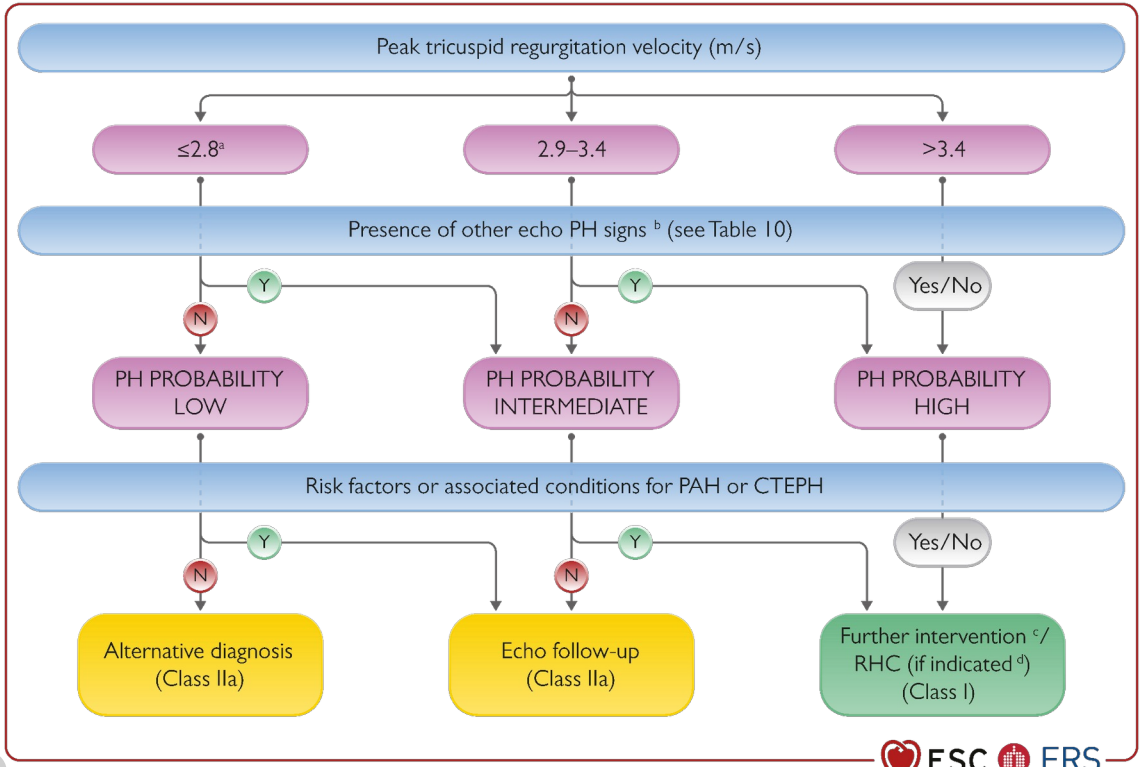
Echocardiographic probability of PH and recommendations for further assessment



Same threshold for TRV

I C m/s, 2.9 – 3.4, > 3.4 m/s)

Presence of other PH signs

I B PAPs for coupling)

Presence of risk factors

(echo follow-up)

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Additional echocardiographic signs suggestive of pulmonary hypertension

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and RA
RV/LV basal diameter/area ratio >1.0	RVOT AT <105 ms and/or mid-systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LVEI >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm^2
TAPSE/sPAP ratio <0.55 mm/mmHg	PA diameter > AR diameter PA diameter >25 mm	

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Recommendations for screening and improved detection of PAH in CTD (systemic sclerosis)

Recommendations	Class	Level
Systemic sclerosis		
In patients with SSc, an **annual** evaluation of the risk of having PAH is recommended	I	B
In adult patients with SSc with >3 years' disease duration, an FVC ≥40%, and a DLCO <60%, the DETECT algorithm is recommended to identify asymptomatic patients with PAH	I	B
In patients with SSc, where breathlessness remains unexplained following non-invasive assessment, RHC is recommended to exclude PAH	I	C

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Recommendations for right heart catheterization and vasoreactivity testing

Recommendations	Class	Level
Right heart cathete		
RHC is recommended	ially	I B
PAH or CTEPH), and to		
In patients with suspe	to	I C
perform RHC in experi		
It is recommended tha		
of haemodynamics, ar	d	I C
protocols		

Table 11 Haemodynamic measures obtained during right heart catheterization

Measured variables	Normal value
Right atrial pressure, mean (RAP)	2–6 mmHg
Pulmonary artery pressure, systolic (sPAP)	15–30 mmHg
Pulmonary artery pressure, diastolic (dPAP)	4–12 mmHg
Pulmonary artery pressure, mean (mPAP)	8–20 mmHg
Pulmonary arterial wedge pressure, mean (PAWP)	≤15 mmHg
Cardiac output (CO)	4–8 L/min
Mixed venous oxygen saturation (SvO_2)[a]	65–80%
Arterial oxygen saturation (SaO_2)	95–100%
Systemic blood pressure	120/80 mmHg
Calculated parameters	
Pulmonary vascular resistance (PVR)[b]	0.3–2.0 WU
Pulmonary vascular resistance index (PVRI)	3–3.5 WU·m^2
Total pulmonary resistance (TPR)[c]	<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)[d]	>2.3 mL/mmHg

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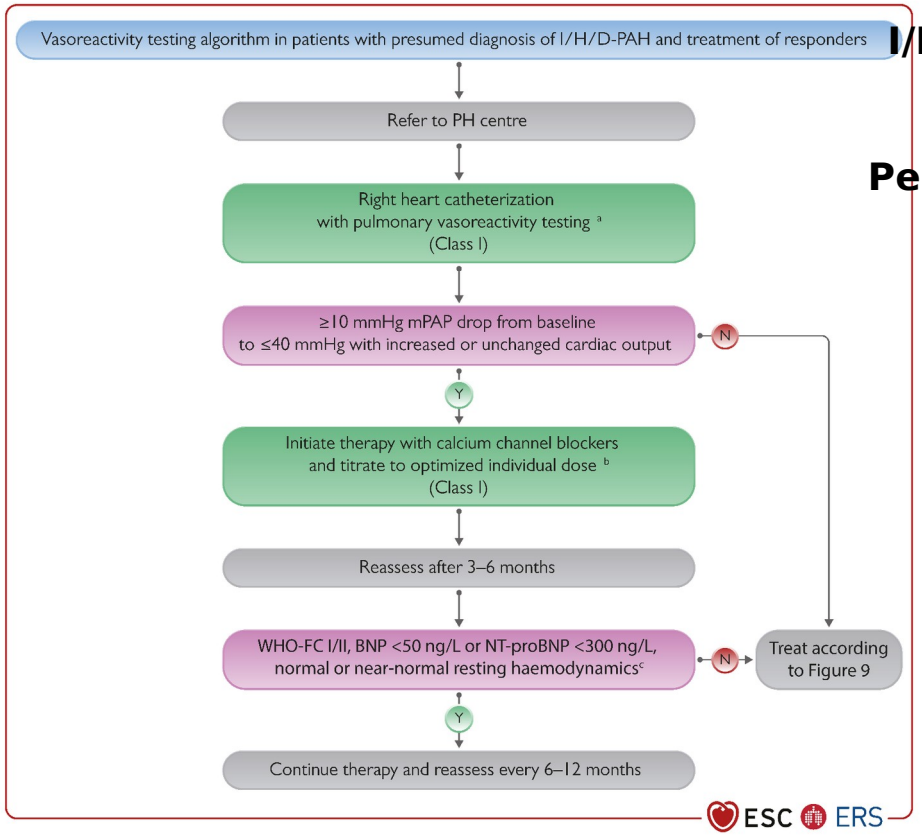
Vasoreactivity testing



I/H/D-PAH I B **others** III C

Performed at PH centres I C

NO, inh iloprost, i.v. stenol I C

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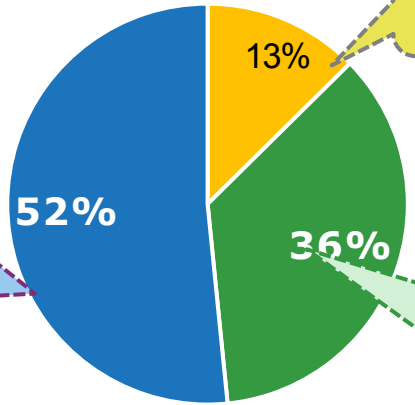
Majority of patients with PAH present with cardiovascular comorbidities

COMPERA (enrolment June 2007 – Nov 2019) cluster analysis

679 (81%) of all patients had ≥ 1 comorbidity, and distinct phenotypical clusters were identified



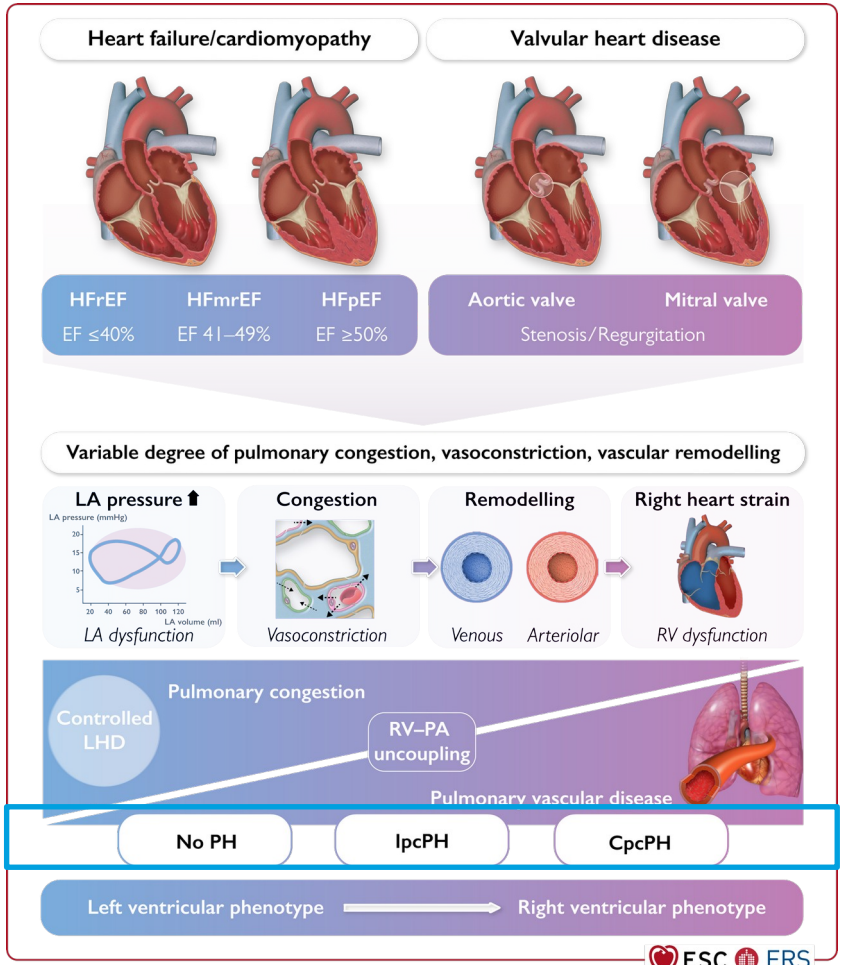
Cluster 1 (n = 106):
- No comorbidities
- Median age 45 years

Cluster 3 (n = 434):
- 94% with ≥ 1 CV comorbidity
  - 25% with 3-4 comorbidities
- Median age 72 years, 72% male
- 79% with a smoking history and half with a DLCO <45% of the predicted value

Cluster 2 (n = 301):
- 91% with ≥ 1 CV comorbidity
  - 28% with 3-4 comorbidities
- Median age 75 years, 98% female
- 94% had ≥1 of the prespecified risk factors for left heart disease

Hoeper MM, *et al. J Heart Lung Transplant* 2020; 39:1435-44.

Pulmonary hypertension associated with left heart disease (group 2)



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Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

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Patient phenotyping and likelihood for left heart disease as cause of pulmonary hypertension (1)

Feature	PH-LHD unlikely	Intermediate probability	PH-LHD likely
Age	<60 years	60–70 years	>70 years
Obesity, hypertension, dyslipidaemia, glucose intolerance/diabetes	No factors	1–2 factors	>2 factors
Presence of known LHD	No	Yes	Yes
Previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Permanent/ persistent
Structural LHD	No	No	Present
ECG	Normal or signs of RV strain	Mild LVH	LBBB or LVH

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Patient phenotyping and likelihood for left heart disease as cause of pulmonary hypertension (2)

Feature	PH-LHD unlikely	Intermediate probability	PH-LHD likely
Echocardiography	No LA dilation E/e' <13	No LA dilation Grade <2 mitral flow	LA dilation (LAVI > 34 mL/m^2) LVH Grade >2 mitral flow
CPET	High VE/VCO_2 slope No EOV	Elevated VE/VCO_2 slope EOV	Mildly elevated VE/VCO_2 slope EOV
cMRI	No left-heart abnormalities		LVH LA dilation (strain or LA/RA >1)

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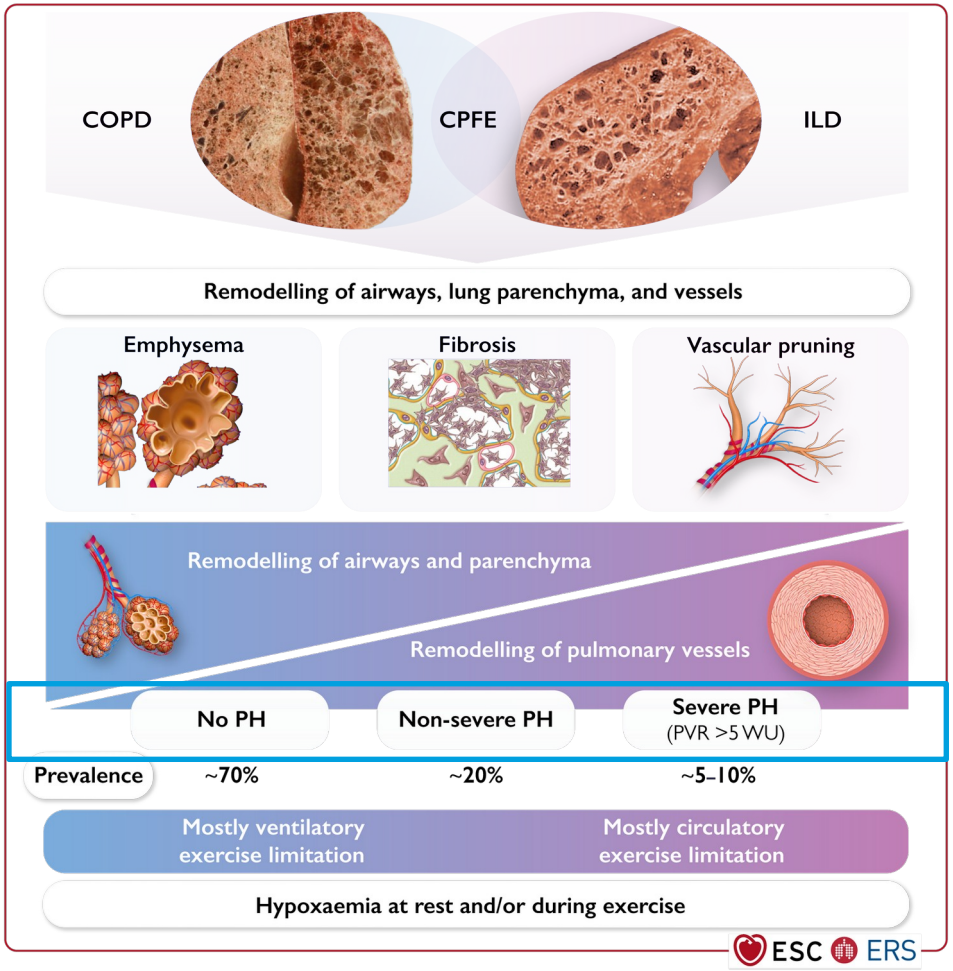
Pulmonary hypertension associated with lung disease (group 3)



PVR >5 WU

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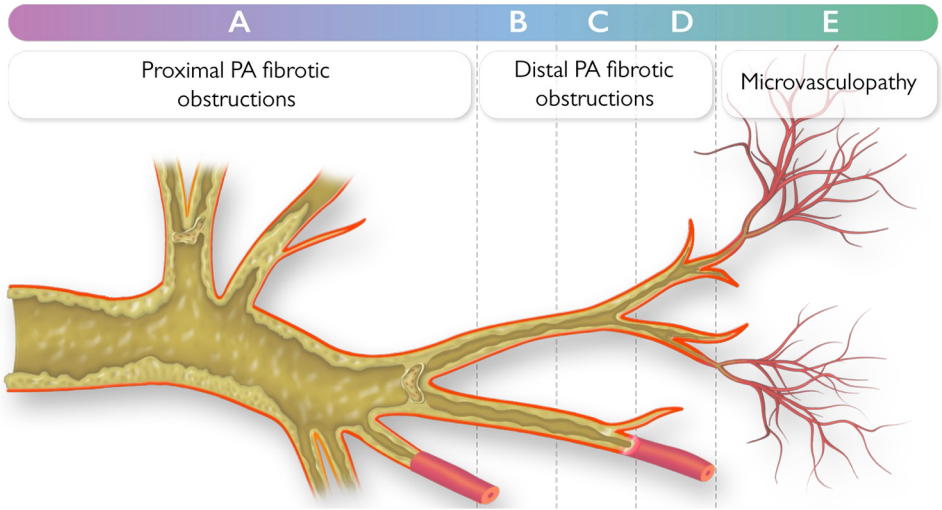
Chronic thrombo-embolic pulmonary hypertension



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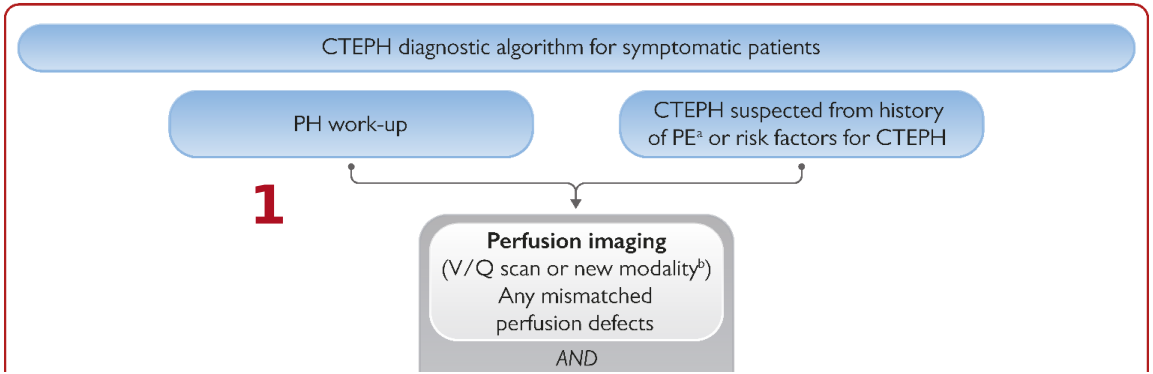
Diagnostic strategy in CTEPH



Recommendations	Class	Level
Imaging		
Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to assess for CTEPH	I	C

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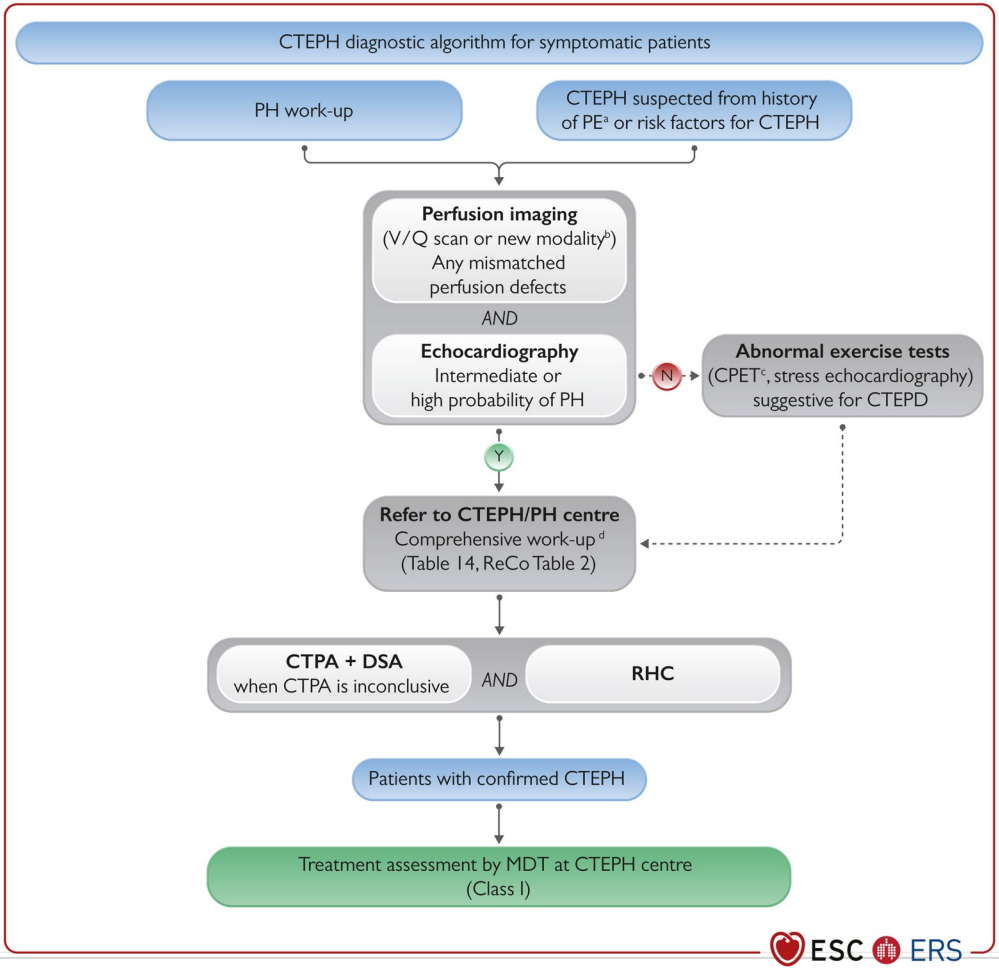
Diagnostic strategy in chronic thrombo-embolic pulmonary hypertension



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ESC/ERS Guidelines – take home messages

- **PH is defined by a mPAP >20 mmHg, measured during right heart catheterization (mandatory for the diagnosis of PH)**
  - **A PVR >2 WU identifies the presence of a precapillary component**
- **The term “associated with” applies to group 1 – 4**
- **Precise diagnostic work-up and DD is crucial because therapeutic strategies are fundamentally different**
  - **Echocardiography plays a key role in the detection of PH (and its underlying cause) –The threshold for TRV to estimate sysPAP is maintained at >2.8 m/s**
  - **Invasive assessment of haemodynamics by RHC must be precise and complete**
  - **Idiopathic PAH is sub-stratified according to the response to acute vasoreactivity testing**

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Authors/Task Force Members:

Marc Humbert (France), Gabor Kovacs (Austria), Marius M. Hoeper (Germany), Roberto Badagliacca (Italy), Rolf M. F. Berger (Netherlands), Margarita Brida (Croatia), Jørn Carlsen (Denmark), Andrew J. S. Coats (United Kingdom), Pilar Escribano-Subias (Spain), Pisana Ferrari (Italy), Diogenes S. Ferreira (Brazil), Hossein Ardeschir Ghofrani (Germany), George Giannakoulas (Greece), David G. Kiely (United Kingdom), Eckhard Mayer (Germany), Gergely Meszaros (Hungary), Blin Nagavci (Germany), Karen M. Olsson (Germany), Joanna Pepke-Zaba (United Kingdom), Jennifer K. Quint (United Kingdom), Göran Rådegran (Sweden), Gerald Simonneau (France), Olivier Sitbon (France), Thomy Tonia (Switzerland), Mark Toshner (United Kingdom), Jean-Luc Vachiery (Belgium), Anton Vonk Noordegraaf (Netherlands), **Marion Delcroix (ERS Chairperson) (Belgium), Stephan Rosenkranz (ESC Chairperson) (Germany)**.

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Patient representatives were actively involved in developing these guidelines.