Updates in Diagnosis and Management of Pulmonary Hypertension

19TH ANNUAL PULMONARY, CRITICAL CARE AND SLEEP MEDICINE UPDATE

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Overview:

GUIDELINES UPDATE

CURRENT PRACTICE PATTERNS

UPCOMMING CLINICAL TRIALS AND TREATMENTS

Most Recent Guidelines

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)

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DEFINITIONS

TABLE 5 Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units. Some patients present with elevated mPAP (>20 mmHg) but low PVR (⩽2 WU) and low PAWP (⩽15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH' (see text for further details).

CLASSIFICATION

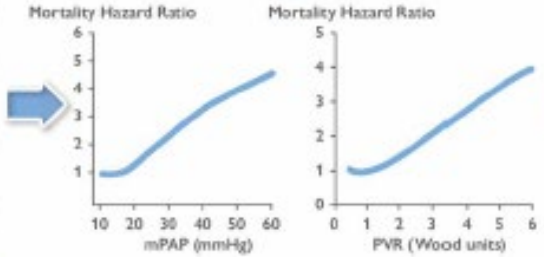
PULMONARY HYPERTENSION

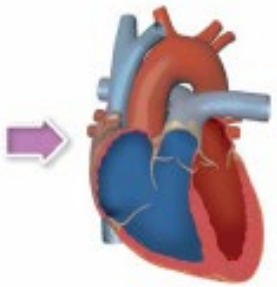
Prevalence

1% Global population

Pulmonary congestion in post-capillary PH

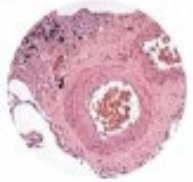
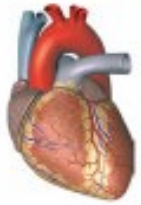
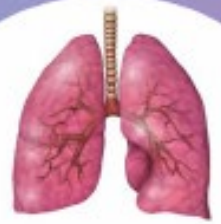
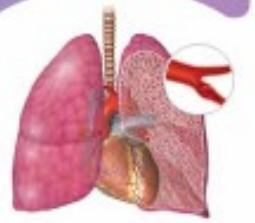
Pulmonary vascular disease / obstruction in pre-capillary PH





Right heart failure

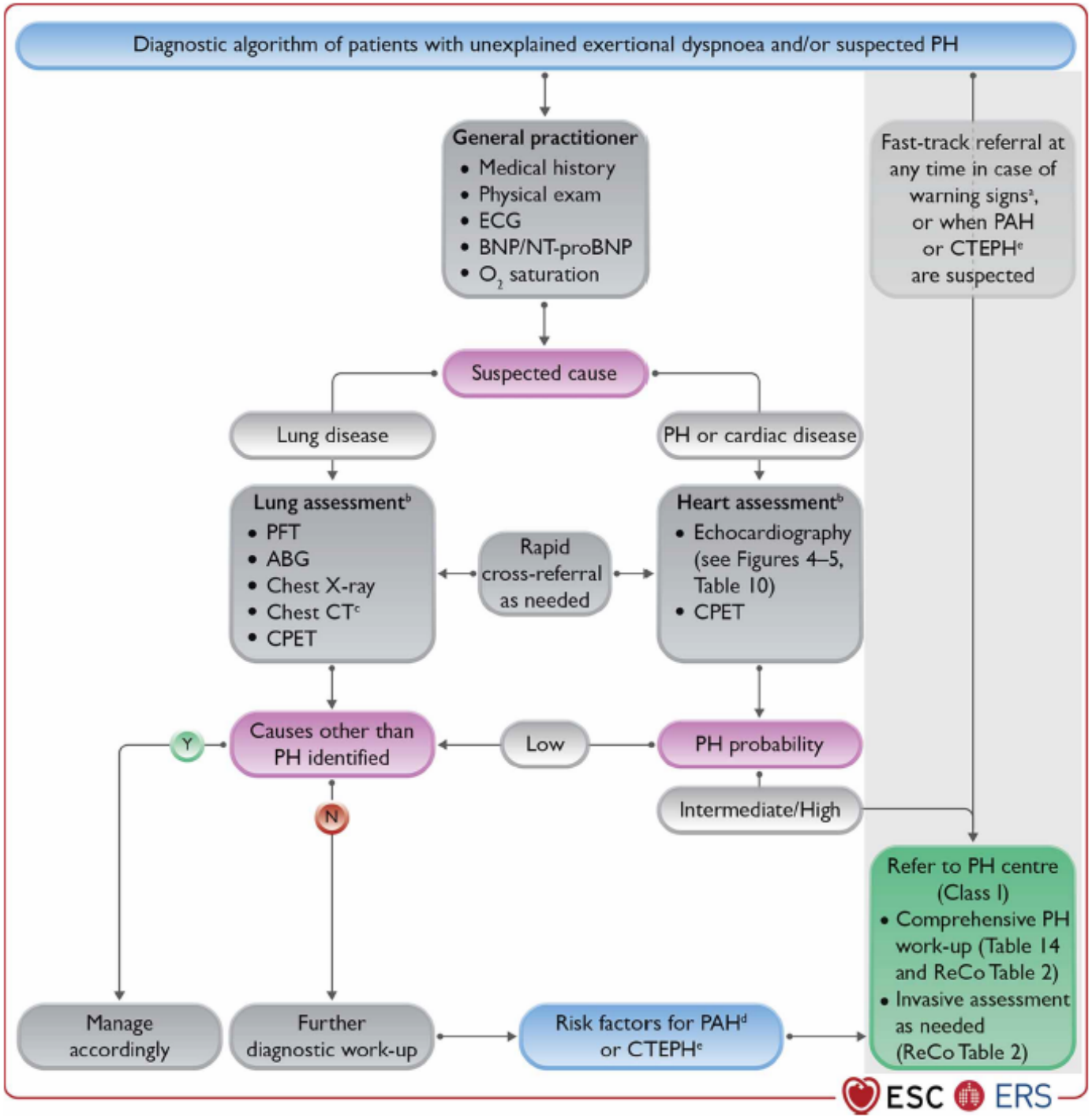
CLINICAL CLASSIFICATION

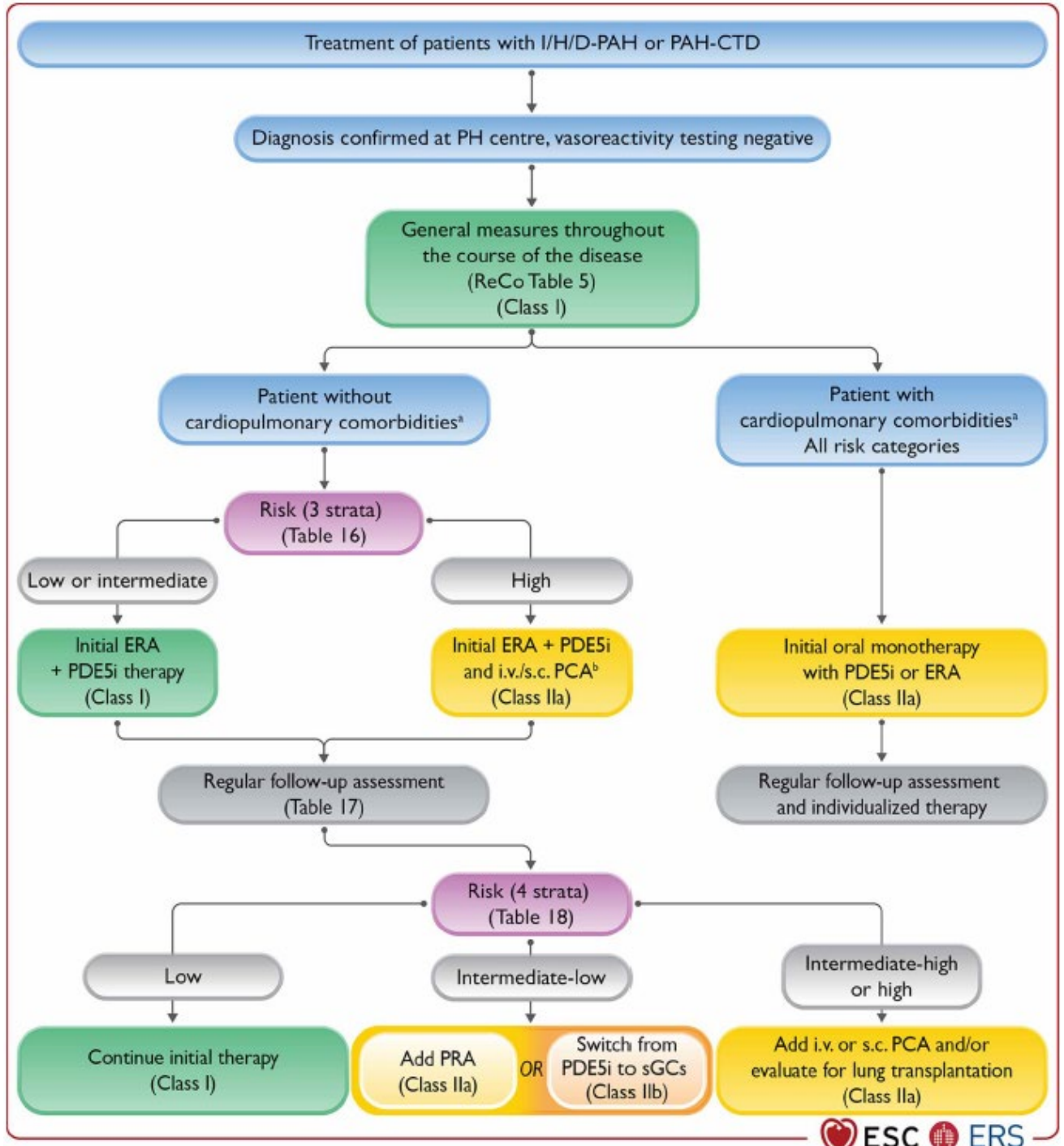
Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				?
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders

PREVALENCE

Rare	Very common	Common	Rare	Rare
				

DIAGNOSIS


Diagnostic algorithm of patients with unexplained exertional dyspnoea and/or suspected PH
General practitioner
• Medical history
• Physical exam
• ECG
• BNP/NT-proBNP
• O_2 saturation
Fast-track referral at any time in case of warning signs[a], or when PAH or CTEPH[e] are suspected
Suspected cause
Lung disease
PH or cardiac disease
Lung assessment[b]
• PFT
• ABG
• Chest X-ray
• Chest CT[c]
• CPET
Rapid cross-referral as needed
Heart assessment[b]
• Echocardiography (see Figures 4–5, Table 10)
• CPET
Causes other than PH identified
Y
N
Low
PH probability
Intermediate/High
Refer to PH centre (Class I)
• Comprehensive PH work-up (Table 14 and ReCo Table 2)
• Invasive assessment as needed (ReCo Table 2)
Manage accordingly
Further diagnostic work-up
Risk factors for PAH[d] or CTEPH[e]
ESC ERS


Treatment of patients with I/H/D-PAH or PAH-CTD
Diagnosis confirmed at PH centre, vasoreactivity testing negative
General measures throughout the course of the disease (ReCo Table 5) (Class I)
Patient without cardiopulmonary comorbidities[a]
Patient with cardiopulmonary comorbidities[a] All risk categories
Risk (3 strata) (Table 16)
Low or intermediate
High
Initial ERA + PDE5i therapy (Class I)
Initial ERA + PDE5i and i.v./s.c. PCA[b] (Class IIa)
Initial oral monotherapy with PDE5i or ERA (Class IIa)
Regular follow-up assessment (Table 17)
Regular follow-up assessment and individualized therapy
Risk (4 strata) (Table 18)
Low
Intermediate-low
Intermediate-high or high
Continue initial therapy (Class I)
Add PRA (Class IIa)
OR
Switch from PDE5i to sGCs (Class IIb)
Add i.v. or s.c. PCA and/or evaluate for lung transplantation (Class IIa)
ESC
ERS

RISK – BASELINE

TABLE 16 Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model)

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%

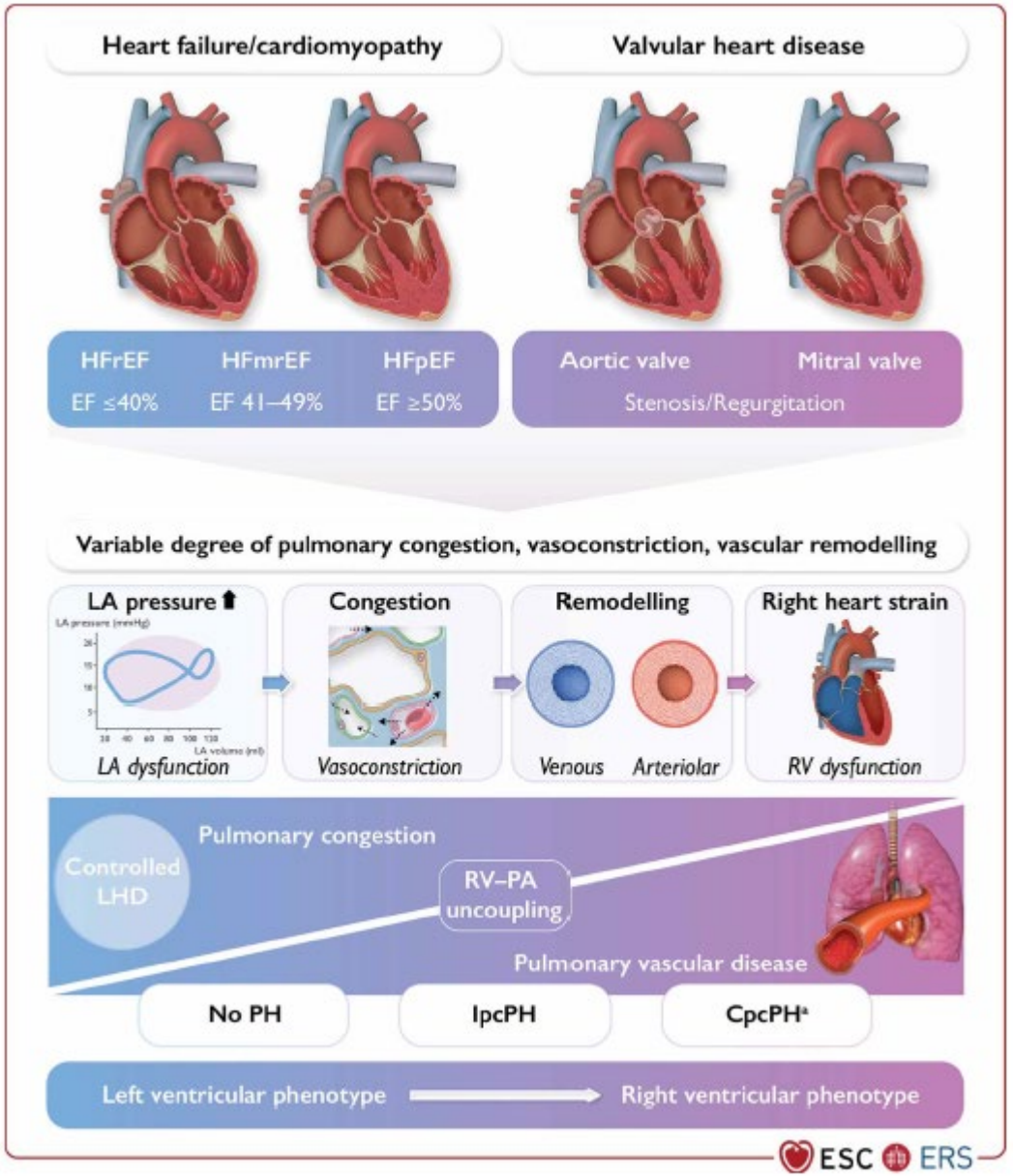
PHENOTYPING

TABLE 13 Phenotypic features associated with pulmonary arterial hypertension mutations

Gene	Pulmonary hypertension phenotypic association	Putative molecular mechanism	Inheritance pattern	Potential distinguishing clinical and examination features	Investigations	Populations	Reference
BMPR2	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Paediatric and adult	[152]
ATP13A3		Unknown	Autosomal dominant			Adult	[149]
AQP1		Unknown	Autosomal dominant			Adult	[149]
ABCC8		Haploinsufficiency	Autosomal dominant			Adult	[153]
KCNK3		Haploinsufficiency	Autosomal dominant			Adult	[154]
SMAD9		Haploinsufficiency	Autosomal dominant			Adult	[155]
Sox17	Heritable and idiopathic PAH Congenital heart disease	Unknown	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Paediatric and adult	[149]
CAV1	Heritable and idiopathic PAH Lipodystrophy	Gain of function; dominant negative	Autosomal dominant	Deficiency of subcutaneous adipose tissue	Fasting triglyceride and leptin levels	Paediatric and adult	[156]
TBX4	Heritable and idiopathic PAH Small patella syndrome (ischiopatellar dysplasia) Parenchymal lung disease Bronchopulmonary dysplasia Persistent pulmonary hypertension of the neonate	Unknown	Autosomal dominant	Patellar aplasia Skeletal abnormalities, in particular pelvis, knees, and feet	Skeletal X-rays: pelvis, knees, and feet CT chest: diffuse parenchymal lung disease	Paediatric and (less commonly) adult	[149, 157]
EIF2AK4	Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis	Loss of function	Autosomal recessive	Distal phalangeal clubbing	Reduced DLCO CT chest: interlobular septal thickening and mediastinal lymphadenopathy, and centrilobular ground-glass nodular opacities	Adult	[158]
KDR	Heritable and idiopathic PAH	Loss of function	Autosomal dominant	No specific or diagnostic clinical features described	Possible reduced DLCO	Older-onset adult	[159]
ENG	Heritable and idiopathic PAH; hereditary haemorrhagic telangiectasia	Unknown	Autosomal dominant	Telangiectasia	Iron-deficiency anaemia	Adult and paediatric	[160]
ACVRL1		Haploinsufficiency	Autosomal dominant	Abnormal blood vessel formation	Presence on imaging of pulmonary, hepatic, cerebral, or spinal arteriovenous malformations	Adult and paediatric	[160]
GDF2		Haploinsufficiency	Autosomal dominant	Visceral arteriovenous malformations Bleeding diathesis	Invasive endoscopic assessment of gastrointestinal telangiectasia	Adult and paediatric	[149]

CT, computed tomography; DLCO, lung diffusion capacity for carbon monoxide; PAH, pulmonary arterial hypertension.

PH – LEFT HEART DISEASE



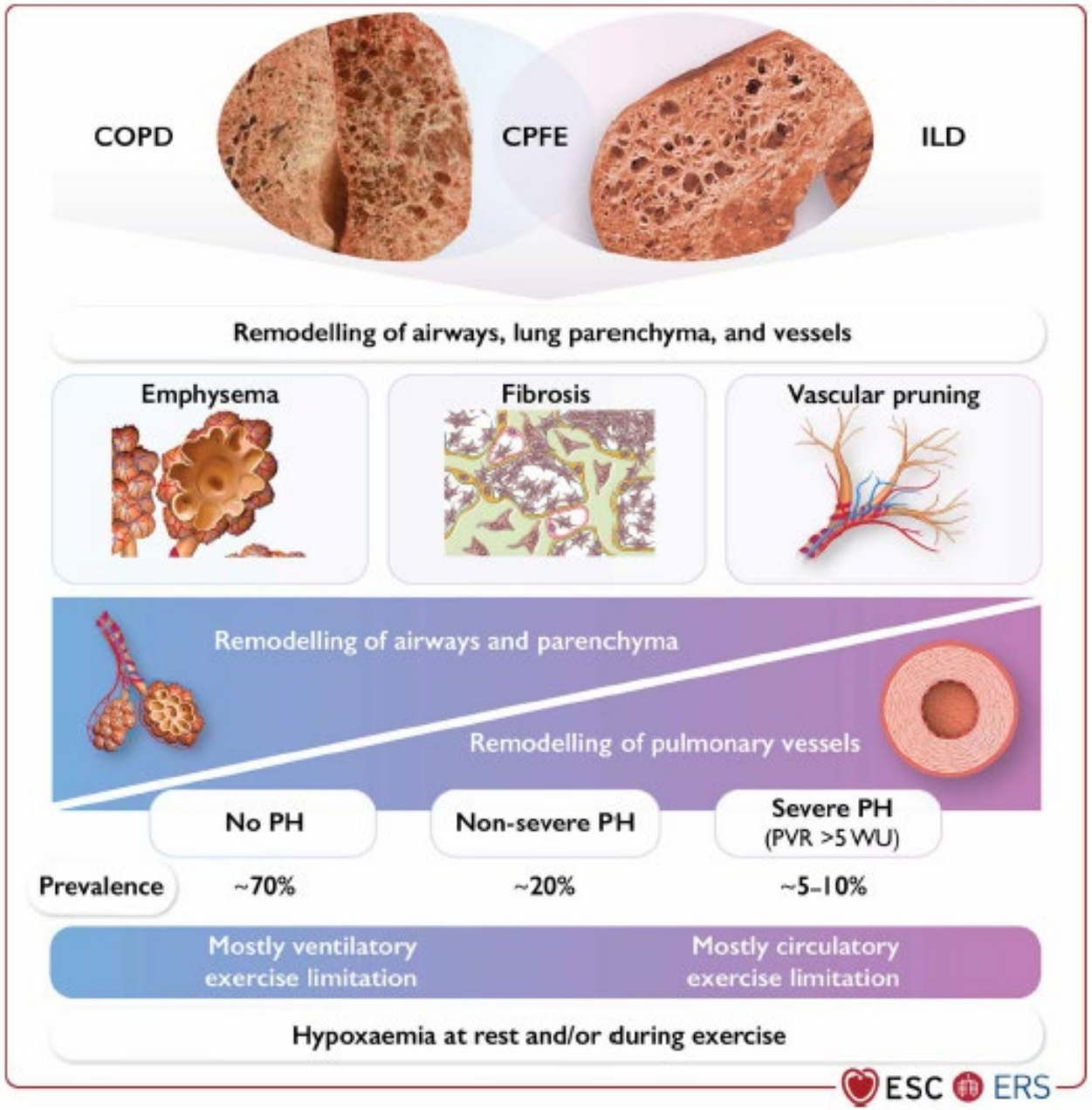
RECOMMENDATION TABLE 22A Recommendations for pulmonary hypertension associated with left heart disease

Recommendation	Class[a]	Level[b]
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH [27, 28]	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended [29, 47, 142]	I	C
In patients with LHD and CpcPH with a severe pre-capillary component (*e.g.* PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH [133, 143]	IIb	C
Drugs approved for PAH are not recommended in PH-LHD[c] [631, 678, 683, 684, 701, 706]	III	A

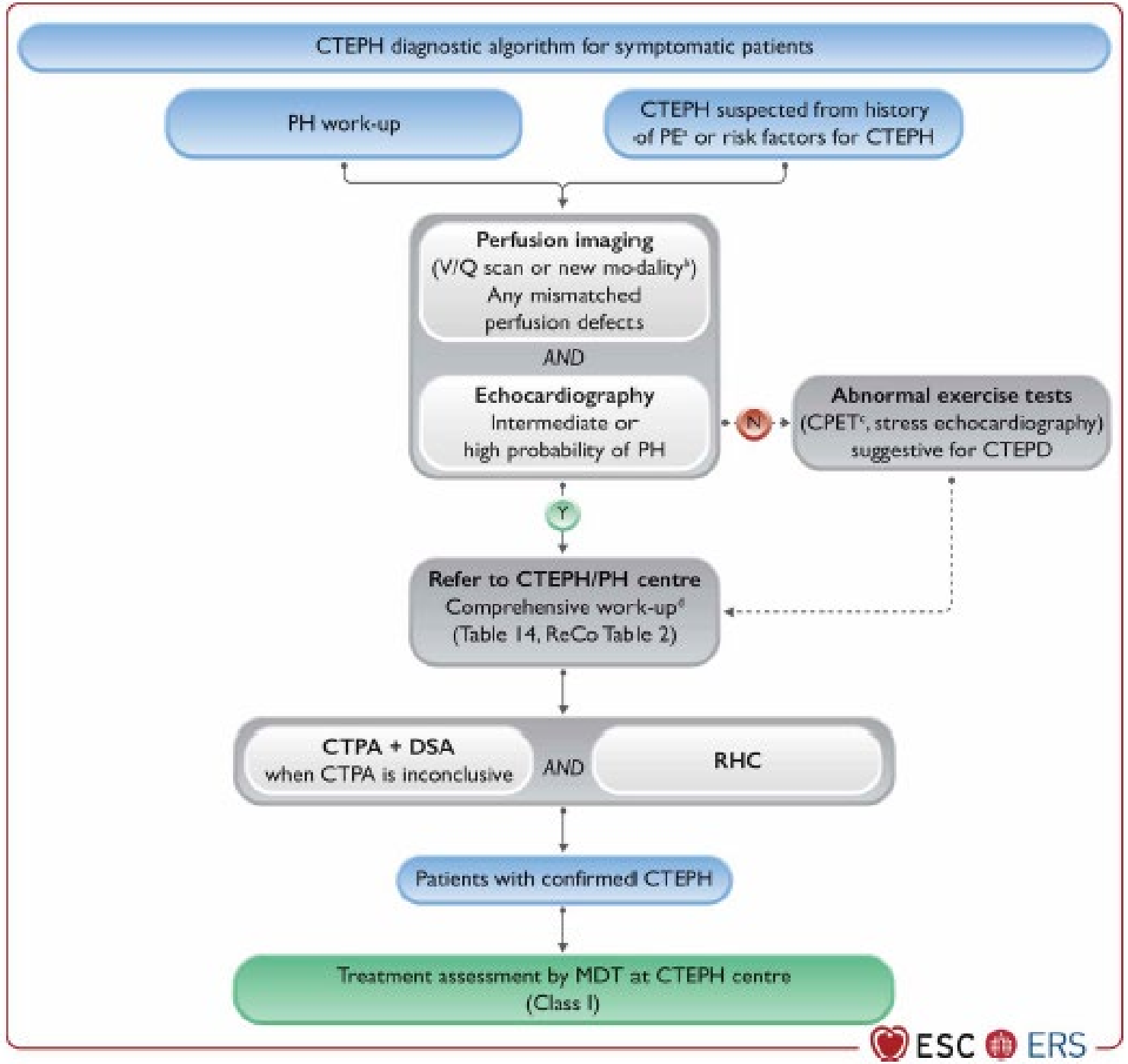
RECOMMENDATION TABLE 22B Recommendations for pulmonary hypertension associated with left heart disease

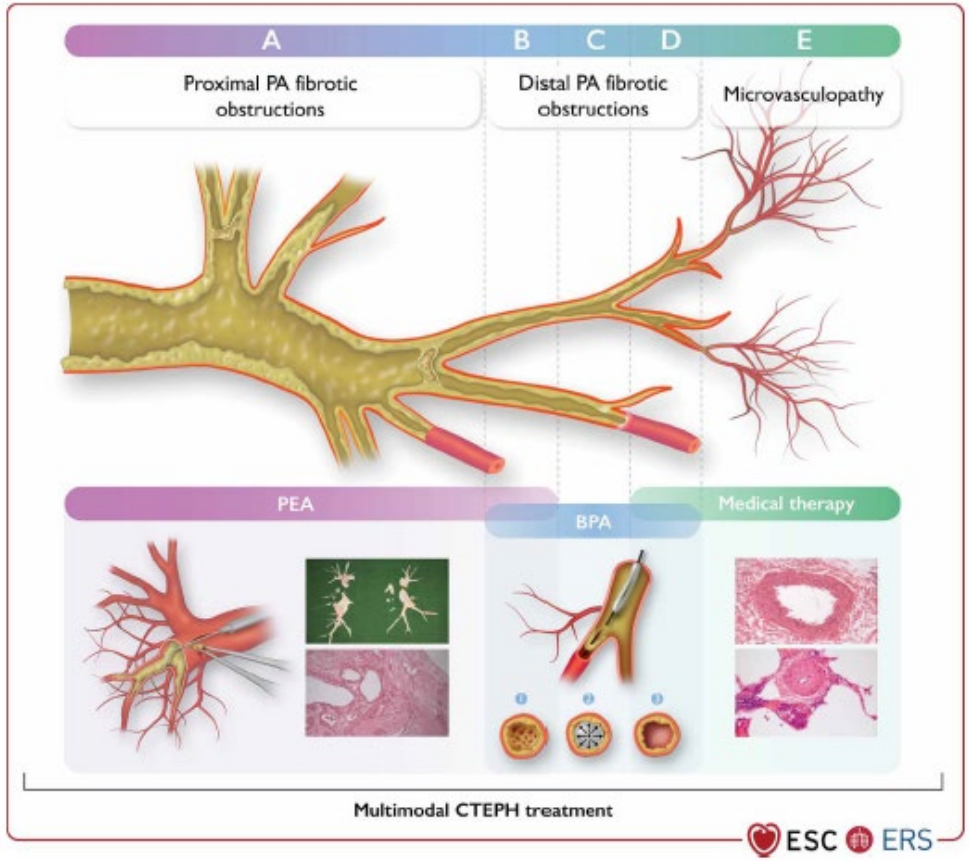
Recommendations	GRADE		Class[a]	Level[b]
	Quality of evidence	Strength of recommendation		
No recommendation can be given for or against the use of PDE5is in patients with HFpEF and combined post- and pre-capillary PH	Low	None		
The use of PDE5is in patients with HFpEF and isolated post-capillary PH is not recommended	Low	Conditional	III	C

LUNG DISEASE



CTEPH


CTEPH diagnostic algorithm for symptomatic patients
PH work-up
CTEPH suspected from history of PE[a] or risk factors for CTEPH
Perfusion imaging
(V/Q scan or new modality[b])
Any mismatched perfusion defects
AND
Echocardiography
Intermediate or high probability of PH
N
Abnormal exercise tests
(CPET[c], stress echocardiography[d])
suggestive for CTEPD
Y
Refer to CTEPH/PH centre
Comprehensive work-up[e]
(Table 14, ReCo Table 2)
CTPA + DSA
when CTPA is inconclusive
AND
RHC
Patients with confirmed CTEPH
Treatment assessment by MDT at CTEPH centre
(Class I)
ESC ERS


A
B
C
D
E
Proximal PA fibrotic obstructions
Distal PA fibrotic obstructions
Microvasculopathy
PEA
BPA
Medical therapy
Multimodal CTEPH treatment
ESC ERS

1. The new definition of PH is meant to lead to early recognition of pulmonary vascular disease with a goal of implementing preventive measures when feasible, and not necessarily a recommendation to treat with PH-targeted therapies.

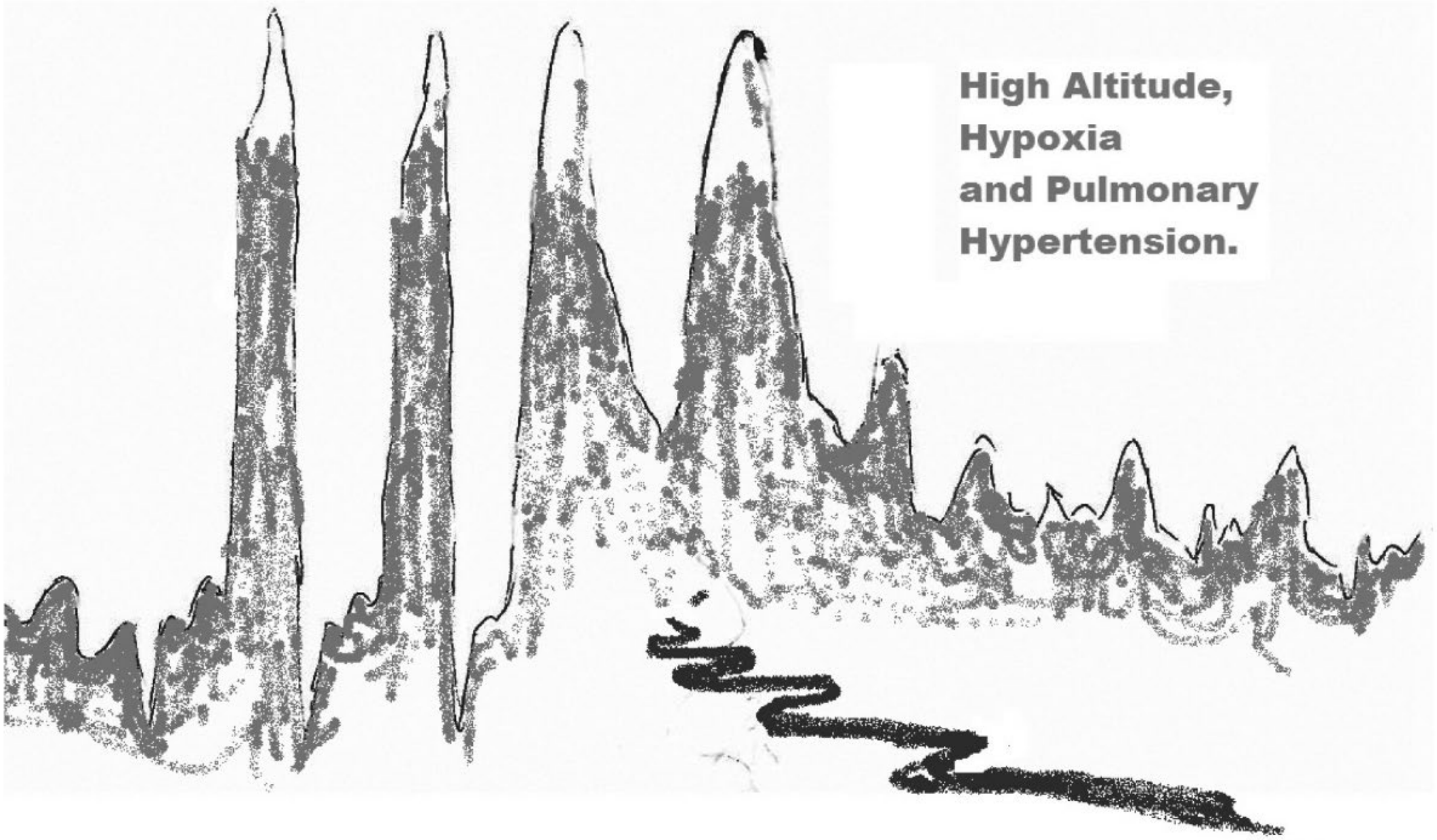
2. It remains to be determined the impact of these updated hemodynamic thresholds on the burden of PH, proper use of PH-targeted therapies, and the socio-economic impact on patients and health care systems.

3. Patients at intermediate-high risk using the 4-strata risk assessment during follow up are viewed as high-risk patients in need of escalation of therapy or referral to lung transplantation.

4. Patients with group 1 PH and multiple comorbidities should be treated initially with oral monotherapy.

5. A PVR > 5 Wood units is associated with worse outcomes, defines “severe PH” associated with left heart or lung disease, and requires an individualized treatment approach, which can include inhaled treprostinil for PH associated with interstitial lung disease.

General Management



Bussotti Maurizio*, Marchese Giovanni, High Altitude Pulmonary Hypertension, Cardiovascular & Hematological Disorders-Drug Targets 2018; 18(3) . https://dx.doi.org/10.2174/1871529X18666180518085245

Review Article on Pediatric Pulmonary Hypertension

Altitude exposure in pediatric pulmonary hypertension—are we ready for (flight) recommendations?

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Contributions: (I) Conception and design: U Herberg, J Breuer; (II) Administrative support: U Herberg, J Breuer; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: U Herberg; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

CONSENSUS STATEMENT

ISHLT consensus statement: Perioperative management of patients with pulmonary hypertension and right heart failure undergoing surgery

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Access to Medically Necessary Reproductive Care for Individuals with Pulmonary Hypertension

Elizabeth Sonntag[1], Kathleen M. Akgün[2,3], Remzi Bag[4], Erika B. Rosensweig[5], Roberto J. Bernardo[6], Colleen Burnetti[7], Amy Chybowski[8], Vinicio A. de Jesus Perez[9], Johnell Diwan[10], Kate M. Guthrie[11], Torre Halscott[12], Tim Lahm[13], Jason Vaught[12], Corey E. Ventetuolo[14,*], and Anna R. Hemnes[15,*]

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Reviews in Cardiovascular Medicine

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Original Research

Maternal and Neonatal Outcomes in Pregnancy Complicated with Pulmonary Hypertension

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1. Hypobaric hypoxia may induce arterial hypoxemia, additional hypoxic pulmonary vasoconstriction, and increased RV load in PAH. Patients should travel with written information about their disease, including a medication list, bring extra doses of their medication, and be informed about local PH centres near their travel destination.

2. Surgical procedures in patients with PH are associated with an elevated risk of right HF and death

3. Women with PH of childbearing potential should be provided with clear contraceptive advice, considering the individual needs of the woman but recognizing that the implications of contraceptive failure are significant in PH. With appropriate use, many forms of contraception, including oral contraceptives, are highly effective. In patients treated with bosentan, reduced efficacy of hormonal contraceptives should be carefully considered. Using hormonal implants or an intrauterine device are alternative options with low failure rates. Surgical sterilization may be considered but is associated with peri-operative risks. Emergency post-coital hormonal contraception is safe in PH.

Updates in Hemodynamics

Impact of Esophageal Pressure Measurement on Pulmonary Hypertension Diagnosis in Patients With Obesity

Ghaleb Khirfan MD, Celia A. Melillo BS, Sami Al Abdi MD, James E. Lane BSN, RN, Raed A. Dweik MD, Robert L. Chatburn MHHS, RRT-NPS, Umur Hatipoğlu MD and Adriano R. Tonelli MD

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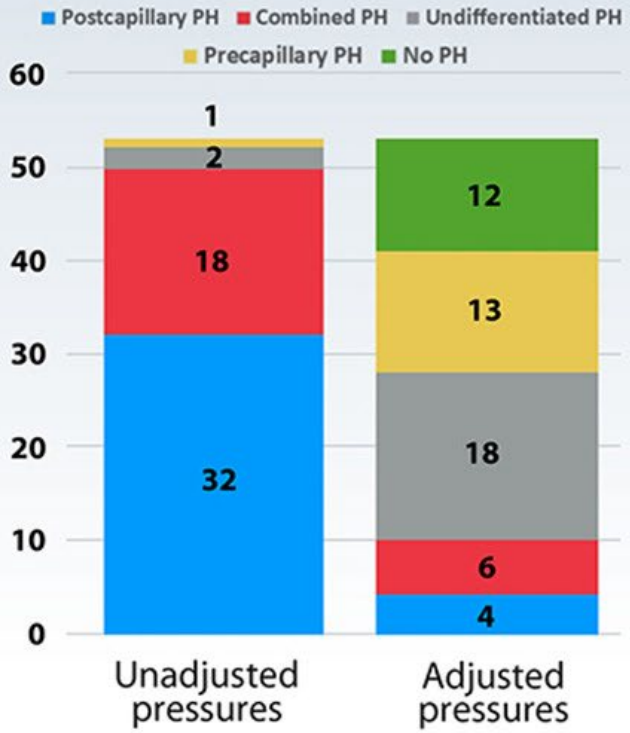
In Obese Individuals, How Does Adjusting for Esophageal Pressure Impact Pulmonary Hypertension Diagnosis?

STUDY DESIGN

- **Prospective cohort study** of **53** patients with obesity who underwent right heart catheterization and had elevated pulmonary artery wedge pressure (≥12 mm Hg)
- **End-expiratory pressures adjusted for esophageal pressure (P_{es})** and pulmonary hypertension (PH) diagnosed and classified using adjusted and unadjusted measurements

RESULTS



P_{es} adjustment led to:

- **decrease in postcapillary** PH (60% to 8%)
- **decrease in combined** PH (34% to 11%)
- **increase in no** PH (0% to 23%)
- **increase in precapillary** PH (2% to 25%)
- **increase in undifferentiated** PH (4% to 34%)

Adjusting pulmonary hemodynamics for P_{es} in obese individuals leads to a pronounced reduction in the number of patients diagnosed with postcapillary PH.

Khirfan G, et al. *CHEST* September 2022 | @journal_CHEST | https://doi.org/10.1016/j.chest.2022.04.002

1. Interpretation of right heart catheterization in the clinical setting is important, and an individualized approach to medical management by an experienced provider is necessary

Emerging Therapies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotatercept for the Treatment of Pulmonary Arterial Hypertension

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Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

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1. Sotatercept is a first-in-class drug that for the first time shows efficacy in a phase 3 trial modulating a biological pathway highly relevant to PAH not targeted by currently available PAH therapies, and importantly, in a heavily pre-treated PAH
population.

2. Consistent with effects observed in the phase 2 trial, sotatercet reduced PVR by decreasing pulmonary artery pressure without changing the cardiac output, suggesting that regression of pulmonary vascular remodeling might be the underlying mechanism behind its clinical benefits, but this and other potential mechanisms warrant further study

3. Ongoing and future studies should determine if the clinical benefits are also observed in other PH populations such us children, newly diagnosed PAH, high-risk or unstable PAH, and combined pre- and post-capillary PH due to heart failure with preserved ejection fraction.

4. Further study is warranted to determine the clinical benefits of sotatercept in PAH populations not well represented in the STELLAR trial, such as connective tissue disease, older age, and non-white individuals.

5. While sotatercept appears to be well tolerated, vascular side effects, particularly bleeding and telangiectasia, need to be monitored in longer-term studies.

Honorable Mention

EUROPEAN RESPIRATORY REVIEW
REVIEW
A.B. WAXMAN ET AL.

Recent advances in the management of pulmonary hypertension with interstitial lung disease

Aaron B. Waxman [1], Davide Elia [2], Yochai Adir [3,4], Marc Humbert [5] and Sergio Harari [2,6]

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Thank you.

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