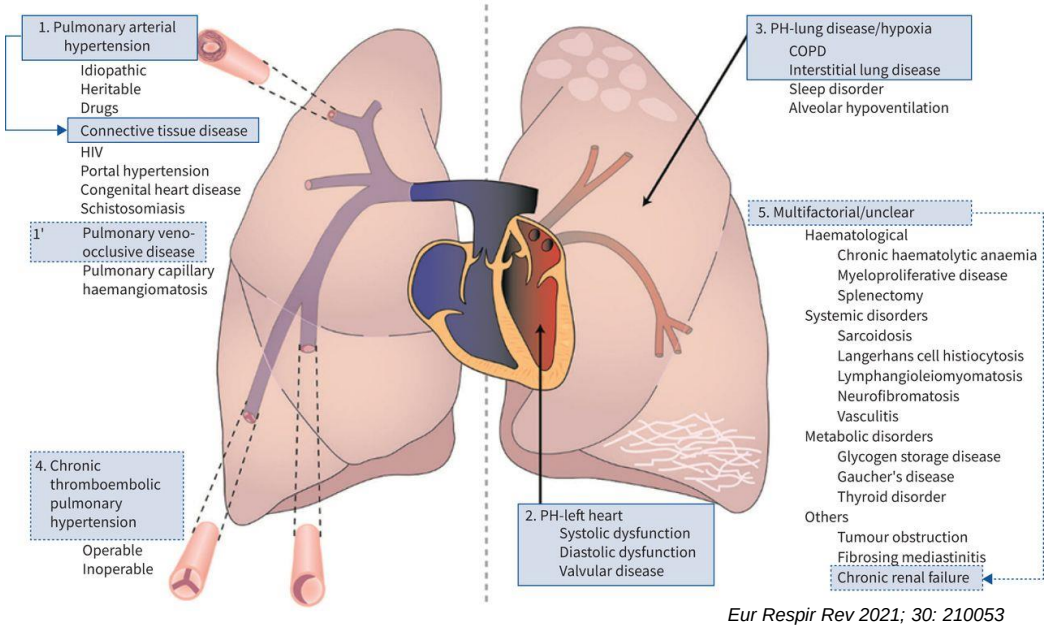
Overview of 2022 ESC/ERS PH Guideline



Eur Respir Rev 2021; 30: 210053

Seoul Metropolitan Seoul Medical Center

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Suhyun Kim

Evolution of the ESC/ERS Guidelines

Table 2 *Changes in the haemodynamic definitions of PH*

WSPH/guideline document	PH	PAH	Pre-capillary PH	Post-capillary PH	Exercise PH
First WSPH (Geneva 1973)	mPAP >25 mmHg	Not defined	Not defined	Not defined	mPAP >30 mmHg
Second WSPH (Evian 1998)	No change	No change	No change	No change	No change
Third WSPH (Venice 2003)	No change	mPAP >25 mmHg + PAWP ≤15 mmHg + PVR >3 WU	No change	No change	No change
ESC PAH Guidelines 2004 [6]	No change	No change	No change	No change	No change
Fourth WSPH (Dana Point 2008)	mPAP ≥25 mmHg	mPAP ≥25 mmHg + PAWP ≤15 mmHg	No change	No change	Not defined
ESC/ERS PH Guidelines 2009 [9]	No change	No change	mPAP ≥25 mmHg + PAWP ≤15 mmHg	mPAP ≥25 mmHg + PAWP >15 mmHg (passive: TPG ≤12 mmHg, reactive: TPG >12 mmHg)	No change
Fifth WSPH (Nice 2013)	No change	mPAP ≥25 mmHg + PAWP ≤15 mmHg + PVR >3 WU	mPAP >25 mmHg + PAWP ≤15 mmHg + PVR >3 WU	mPAP ≥25 mmHg + PAWP >15 mmHg (isolated: DPG <7 mmHg, combined: DPG ≥7 mmHg)	No change
ESC/ERS PH Guidelines 2015 [15]	No change	No change	mPAP ≥25 mmHg + PAWP ≤15 mmHg	mPAP ≥25 mmHg + PAWP >15 mmHg (isolated: DPG <7 mmHg and/or PVR ≤3 WU, combined: DPG ≥7 mmHg and/or PVR >3 WU)	No change
Sixth WSPH (Nice 2018)	mPAP >20 mmHg	mPAP >20 mmHg + PAWP ≤15 mmHg + PVR ≥3 WU	mPAP >20 mmHg + PAWP ≤15 mmHg + PVR ≥3 WU	mPAP >20 mmHg + PAWP >15 mmHg (isolated: PVR <3 WU, combined: PVR ≥3 WU)	No change

Kovacs G et al. Breathe 2021; 17: 210076

ESC European Society of Cardiology
European Heart Journal (2022) **00**, 1–114
https://doi.org/10.1093/eurheartj/ehac237

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).

Table 3 **Classes of recommendations**

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

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Table 4 **Levels of evidence**

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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2022 4th edition of ESC/ERS Guidelines for PH : What is new

1. **New definitions of PH** including a revised cut-off level for mPAP, pulmonary vascular resistance (PVR) and a definition of exercise PH.
2. **The classification of PH** has been updated, including repositioning of vasoreactive patients with IPAH and a revision of group 5 PH.
3. **A new diagnostic algorithm** aiming at earlier detection of PH in the community with expedited referral for high-risk or complex patients.
4. **The PAH treatment algorithm modification** highlighting risk assessment both at diagnosis and follow-up, and the importance of **combination therapies**.
   - Treatment strategies during follow-up based on the **four strata model.**
   - The recommendations for **managing PH-LHD and lung** including a new hemodynamic definition of **severe PH in patients with lung disease.**
5. **In group 4 PH,**
   - **the term CTEPD** with or without PH has been introduced
   - Interventional treatment by BPA in **combination** with medical therapy in the **therapeutic algorithm of CTEPH.**

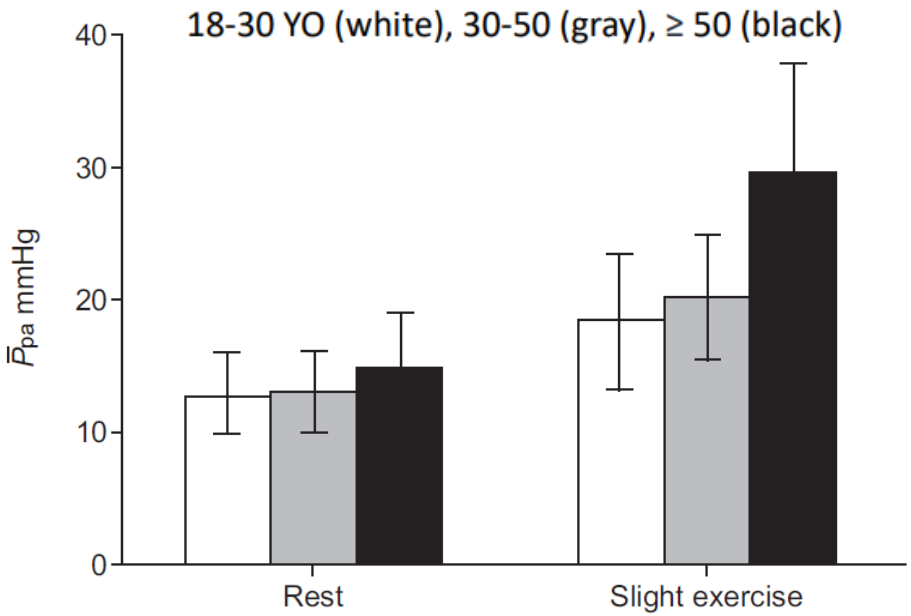
Definition of Pulmonary Hypertension (PH)

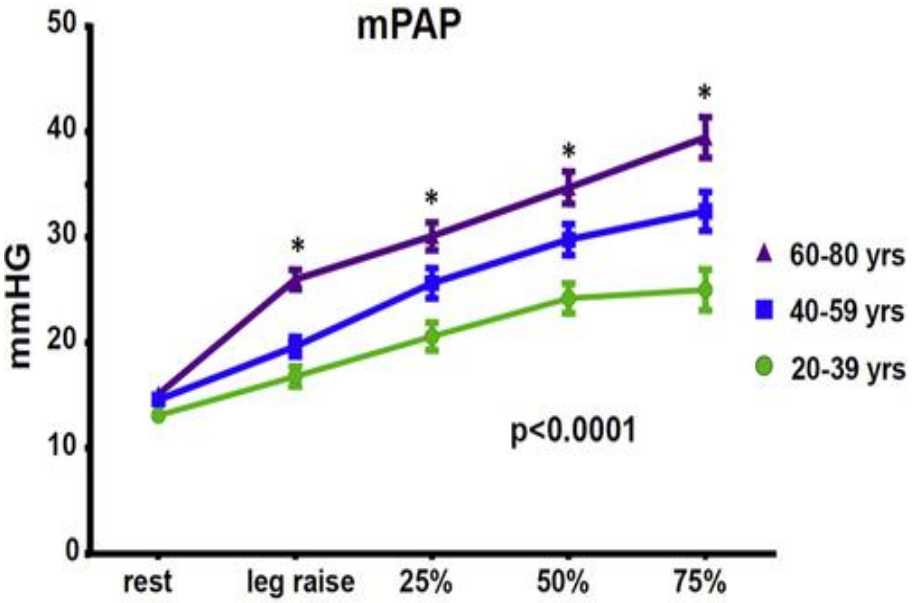
- The definitions for PH are based on hemodynamic assessment by right heart catheterization (RHC).
  - an increase in pressure in the pulmonary vessels, as denoted by an elevation in mean pulmonary arterial pressure **(mPAP) > 20 mmHg at rest.**

2022 Updated

European Heart Journal (2022) 00, 1–114

Normal mPAP in healthy subjects



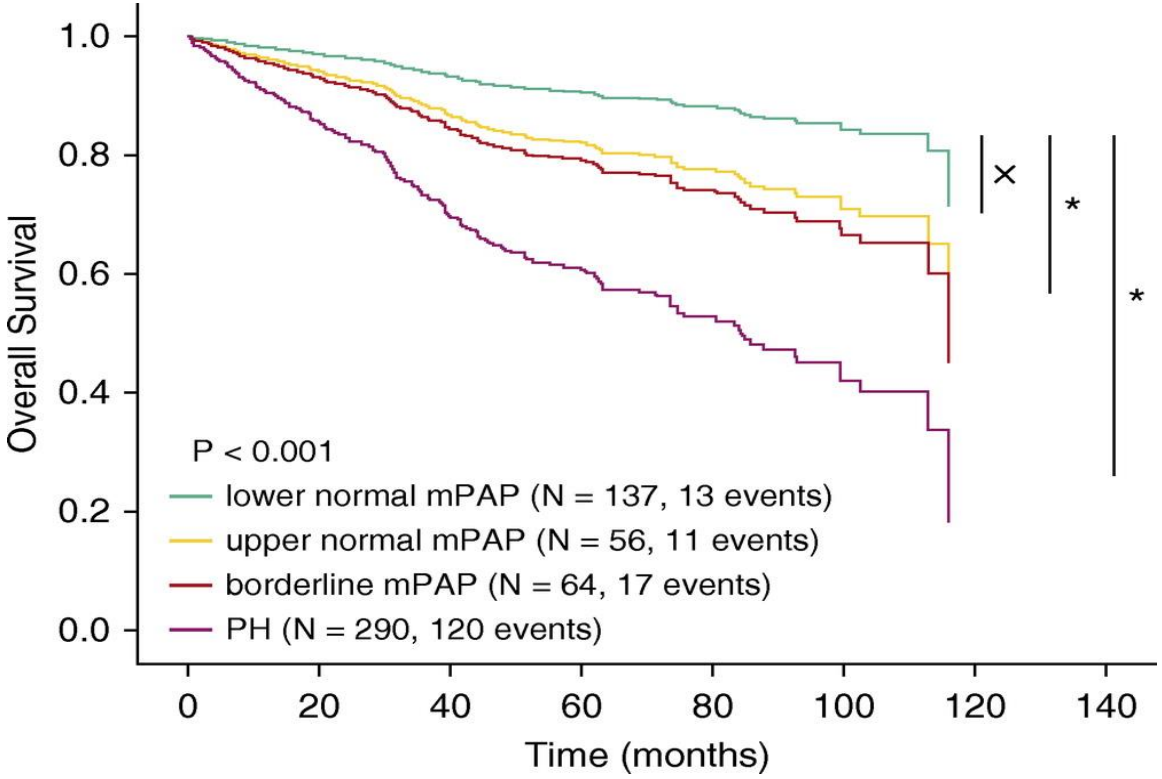


- 1187 normal subjects from 47 studies by RHC
- **mPAP = 14.0 ± 3.3 mmHg**

- 62 Caucasians (32 women, 30 men)
- No patients exceeded 21 mmHg of mPAP during rest.

J Am Coll Cardiol HF 2016; 5:337-346
Eur Respir J 2009:34:888

Mild elevation of PAP as a predictor of mortality



lower normal (≤ 17.3 mmHg)
upper normal (17.4~20.6 mmHg)
borderline (20.6~24.9 mmHg)
manifest (≥ 25mmHg)

- A total of 547 patients undergoing RHC.
- Values between 20 mmHg and 25 mmHg represent an **independent predictor of poor survival.**

Am J Respir Crit Care Med 2018:197(4):509–516

Hemodynamic definitions of PH

Pulmonary Hypertension

Mean PAP > 20 mmHg at rest by right heart catheterization (RHC)

Pre-capillary PH

Mean PAP
> 20 mmHg
at rest by RHC

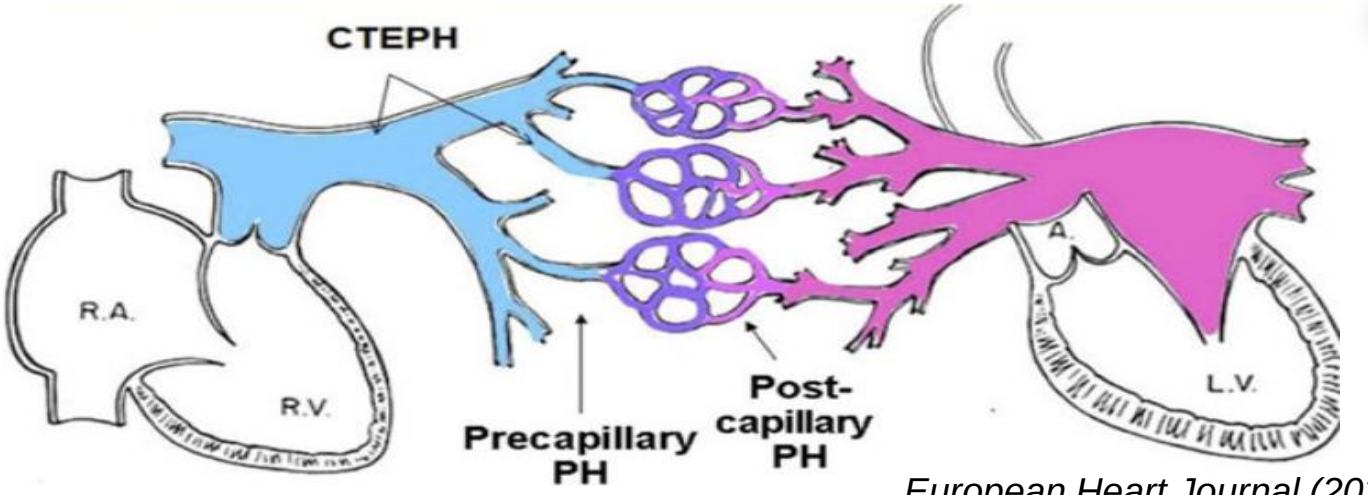
+

PAWP
≤ 15 mmHg

+

Pulmonary vascular
Resistance **(PVR)**
> 2 Wood units (WU)

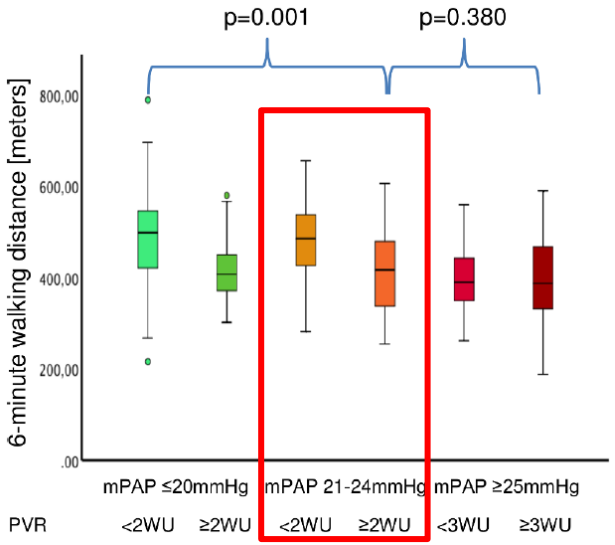
2022 Updated

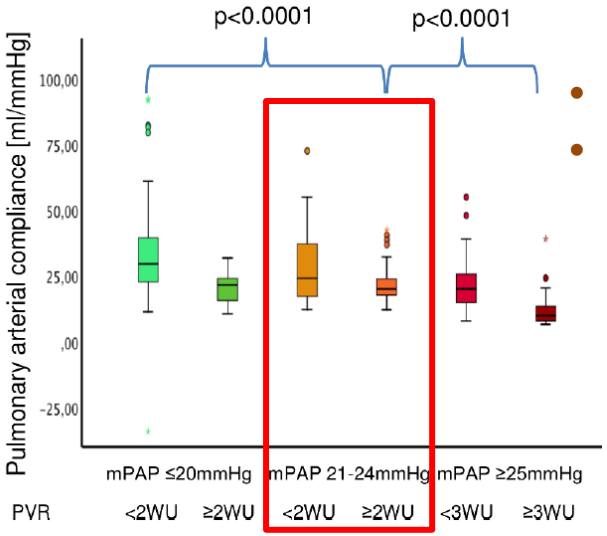


PAWP, pulmonary arterial wedge pressure

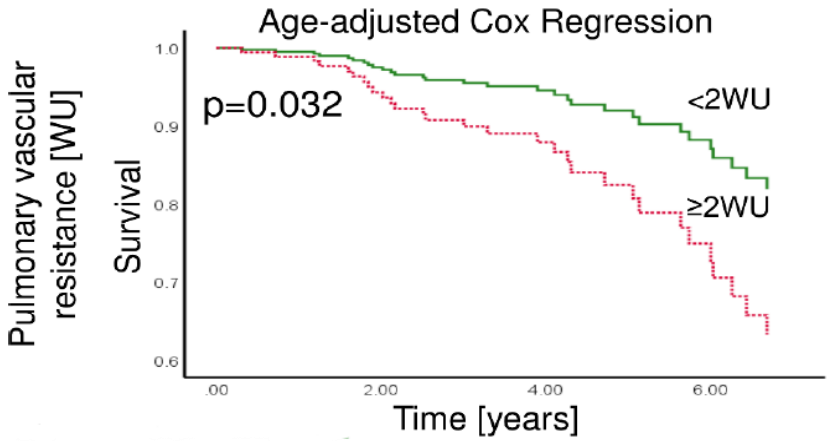
European Heart Journal (2022) 00, 1–114
Continuing Cardiology Education, 2018; 4(1)

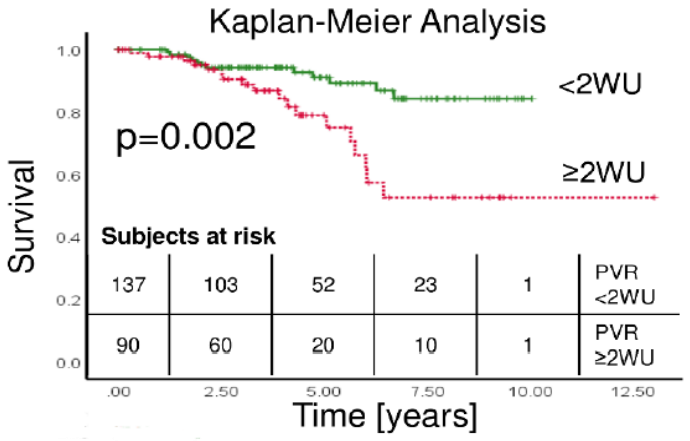
too high PVR (PVR=(mPAP−PAWP)/CO) threshold ≥3 WU to enable an early diagnosis of PAH





- 284 SSc patients
- 28(9.8%) patients with **mPAP of 21–24 mm Hg & PVR ≥2 WU** already presented with early pulmonary vascular disease.



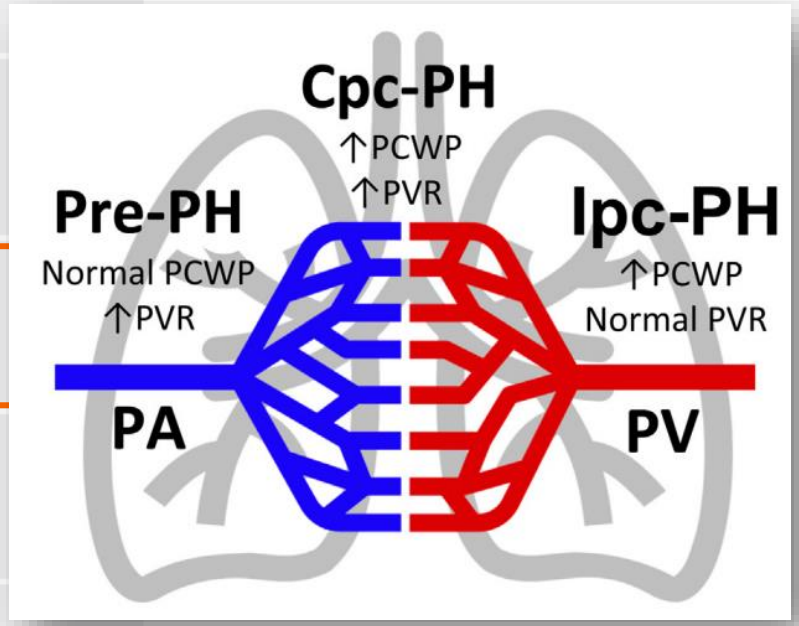


- **Patients with PVR <2 WU showed a significantly better survival than with PVR ≥2 WU.**

*Ann Rheum Dis 2020;**79**:370–378.*

2022 ESC/ERS Guidelines
Hemodynamic definitions of PH

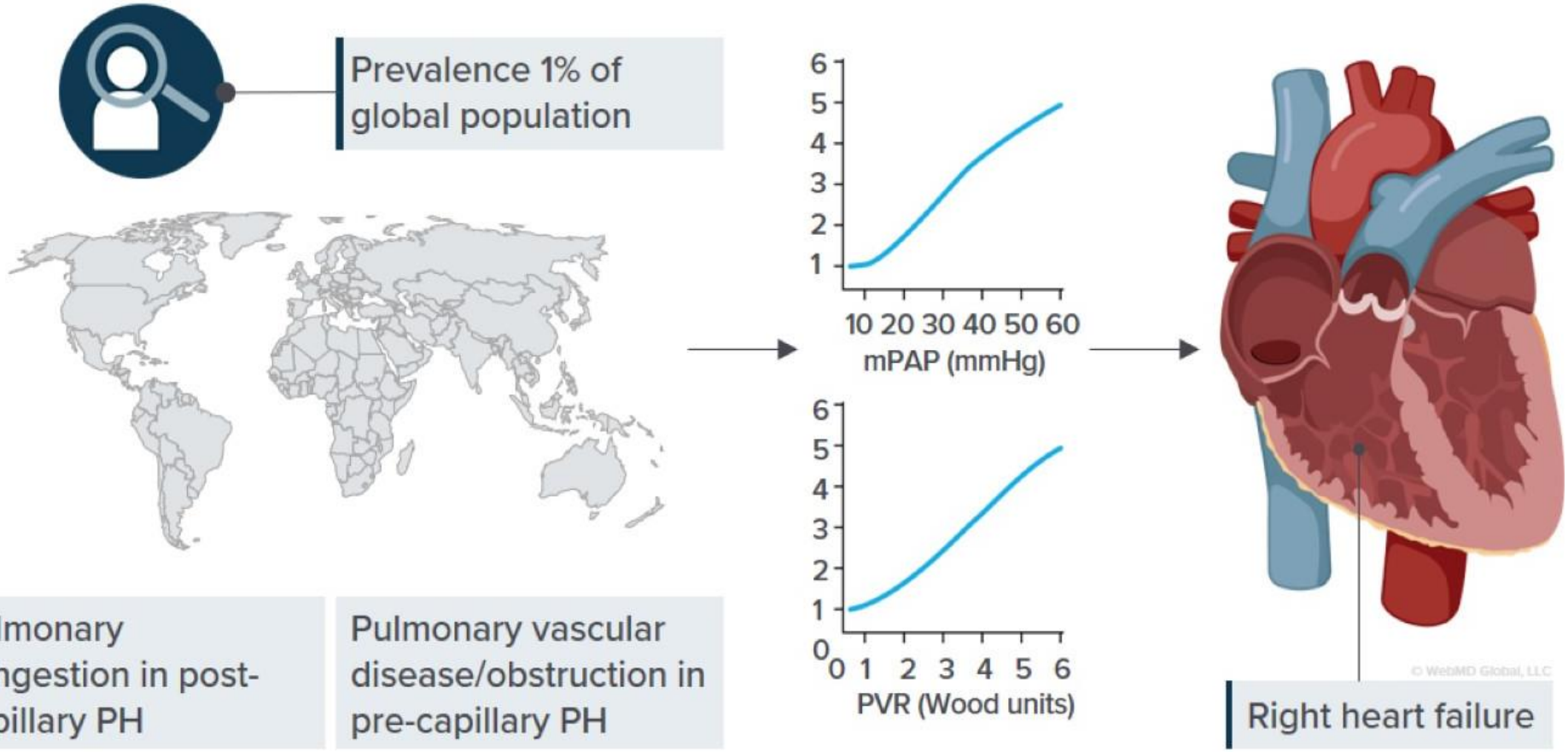
Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
Unclassified PH 2022 Updated	mPAP >20 mmHg PAWP ≤15 mmHg PVR ≤2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH 2022 Updated	mPAP/CO slope between rest and exercise >3 mmHg/L/min



Am J Kidney Dis. 2020:75(5);713-724.

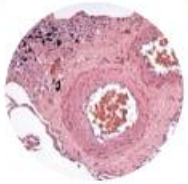
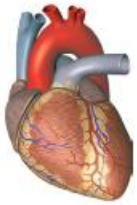
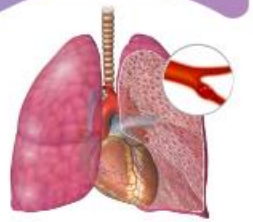
IpcPH, Isolated post-capillary pulmonary hypertension;
CpcPH, Combined post- and pre-capillary pulmonary hypertension

Epidemiology of PH



European Heart Journal (2022) 00, 1–114

Clinical Classification

GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
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
				

Therapeutic Strategies

Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

European Heart Journal (2022) 00, 1–114

Clinical classification of PH

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

[d]Including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders.
[e]Including sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1.
[f]Including glycogen storage diseases and Gaucher disease.

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Group 1. Pulmonary arterial hypertension (PAH)

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

PVOD, pulmonary veno-occlusive disease;
PCH, pulmonary capillary haemangiomatosis

Epidemiology of PAH

- 건강보험심사평가원 자료에 기반한 후향적 연구 (2008~2016년) :
  - 연간 인구 100만 명당 4.84명 (평균연령 44±13세, 여성 69.3%)

PLoS ONE 2018:13(12): e0209148

- 국내의 4개 학회가 참여한 전향적 등록연구 (KORPAH) :
  - 인구 100만 명당 1.9명으로 추정 (평균연령 48±16세, 여성호발)

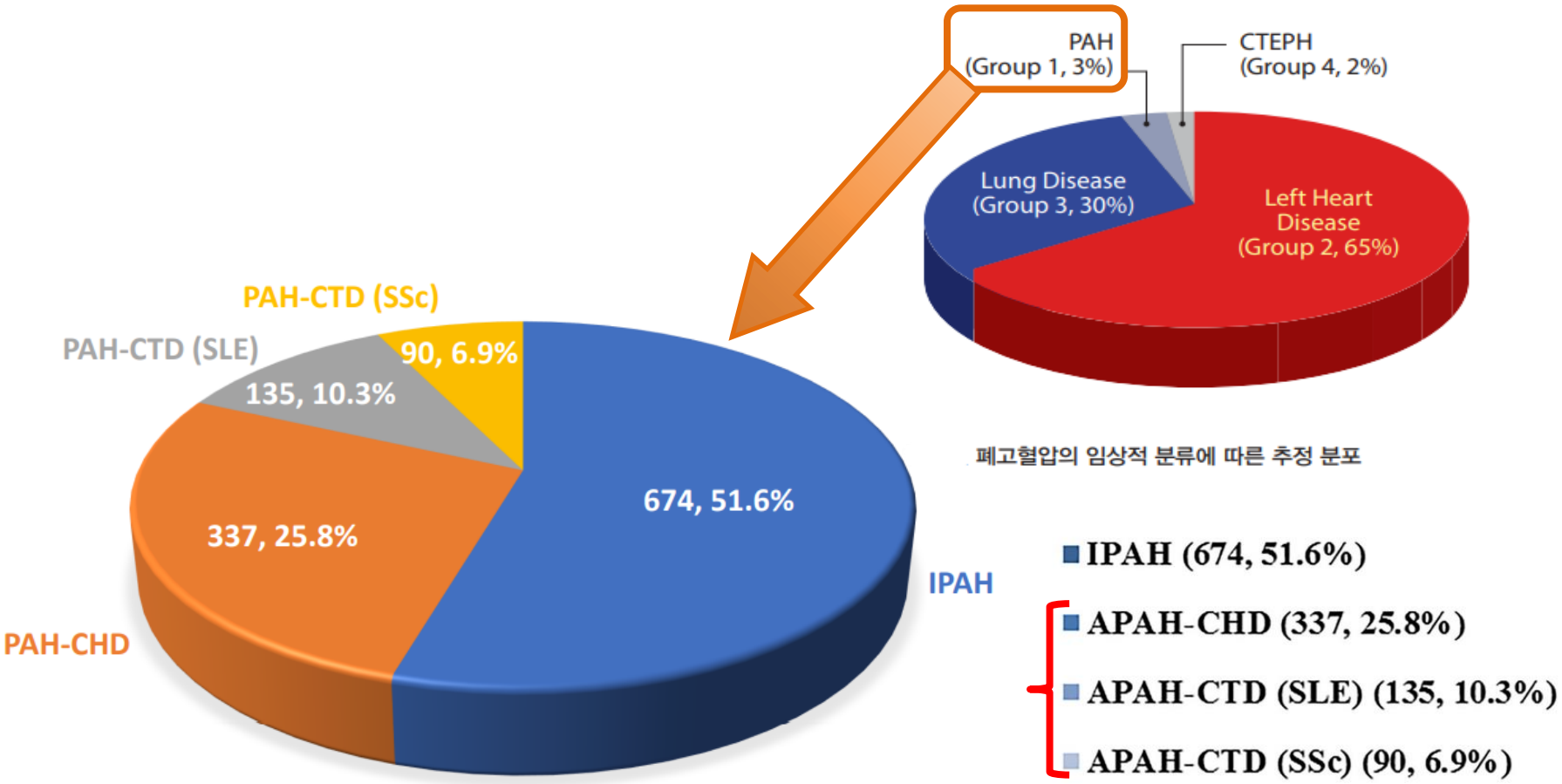
J Korean Med Sci 2015; 30: 1429-1438

- Recent data from the USA and Europe
  - 평균 연령 36세 → 50-65세
  - often present with cardiovascular comorbidities
  - 여성 호발 → 고령 환자에서 발병 시 more equal distribution

European Heart Journal (2022) 00, 1–114

Etiology of PAH in Korea

: derived from HIRA claim database 2008–2016



- January 2008 to December 2016, mean age (44±13 years), female (69.3%)
- 3-year survival rate = 54%
- annual incidence = 4.84 patients/1 million/year

PLoS ONE 2018:13(12): e0209148

Associated with Drugs and Toxins

Definite association	Possible association
Aminorex	Alkylating agents (cyclophosphamide, mitomycin C)[a]
Benfluorex	Amphetamines
Dasatinib	Bosutinib
Dexfenfluramine	Cocaine
Fenfluramine	Diazoxide
Methamphetamines	Direct-acting antiviral agents against hepatitis C virus (sofosbuvir)
Toxic rapeseed oil	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

[a]Pulmonary veno-occlusive disease.

Recommendations	Class[a]	Level[b]
It is recommended to make a diagnosis of drug- or toxin-associated PAH in patients who had relevant exposure and in whom other causes of PH have been excluded	I	C
In patients with suspected drug- or toxin-associated PAH, it is recommended to immediately discontinue the causative agent whenever possible	I	C
Immediate PAH therapy should be considered in patients who present with intermediate-/high-risk PAH at diagnosis	IIa	C
Patients with low-risk PAH should be re-evaluated 3–4 months after discontinuing the suspected drug or toxin, and PAH therapy may be considered when the haemodynamics have not normalized	IIb	C

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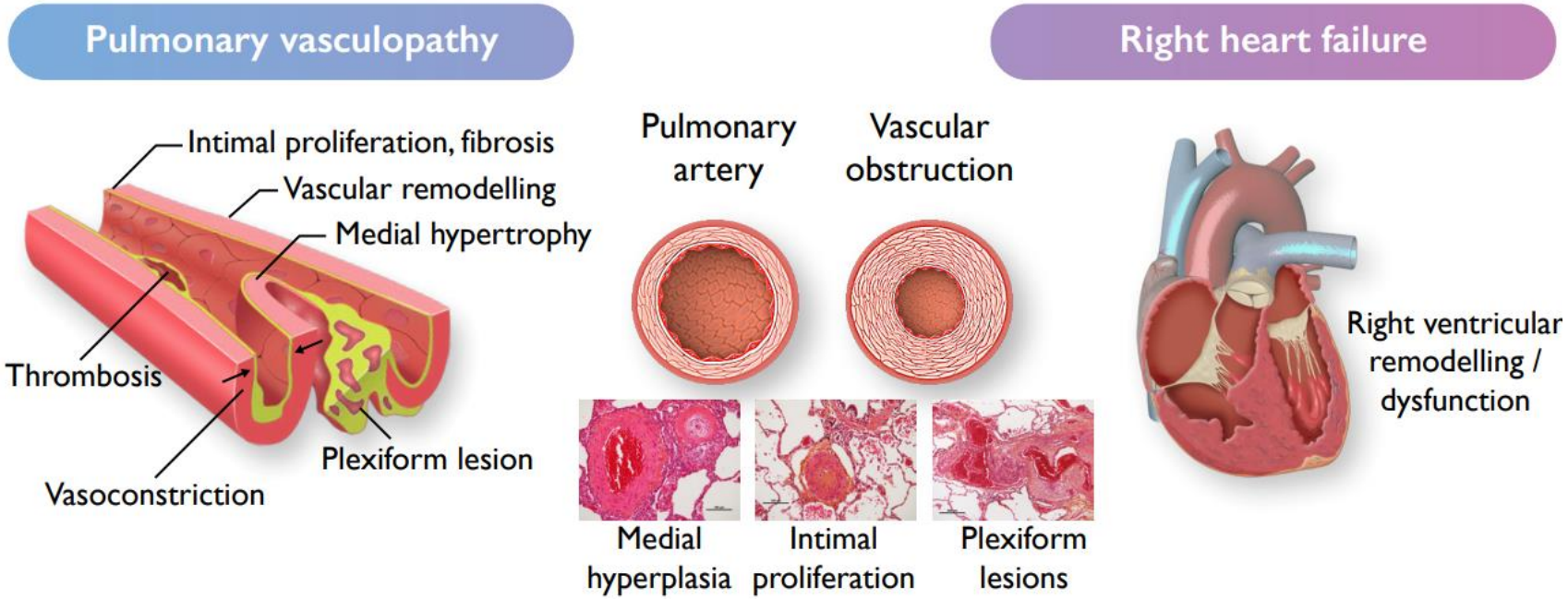
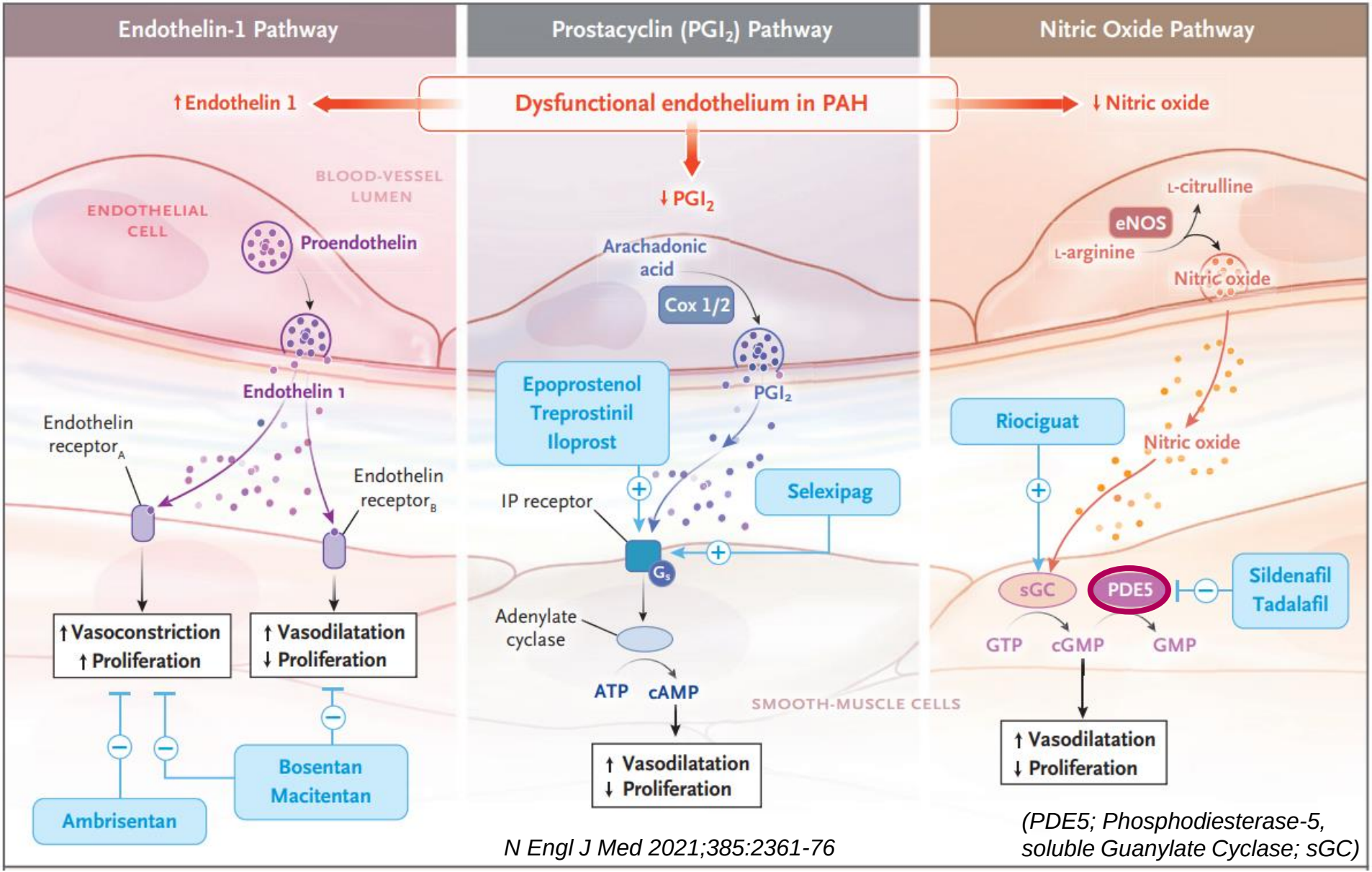
Pathology of PAH



작은 폐동맥에 병변이 발생하여 혈관 내부 공간이 줄어들고 점차적으로 폐혈관 저항이 증가하고, 결과적으로 우심실 후부하가 증가되어 우심실 부전 발생

European Heart Journal (2022) 00, 1–114

Three Classic Pathways of Targeted Therapy for PAH



N Engl J Med 2021;385:2361-76

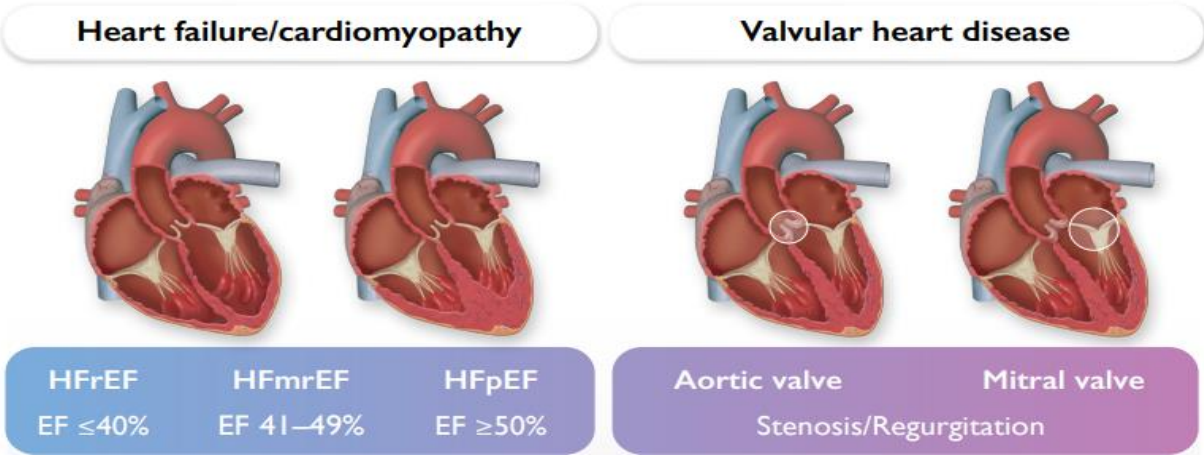
(PDE5; Phosphodiesterase-5, soluble Guanylate Cyclase; sGC)

Group 2. PH associated with left heart disease (PH-LHD)

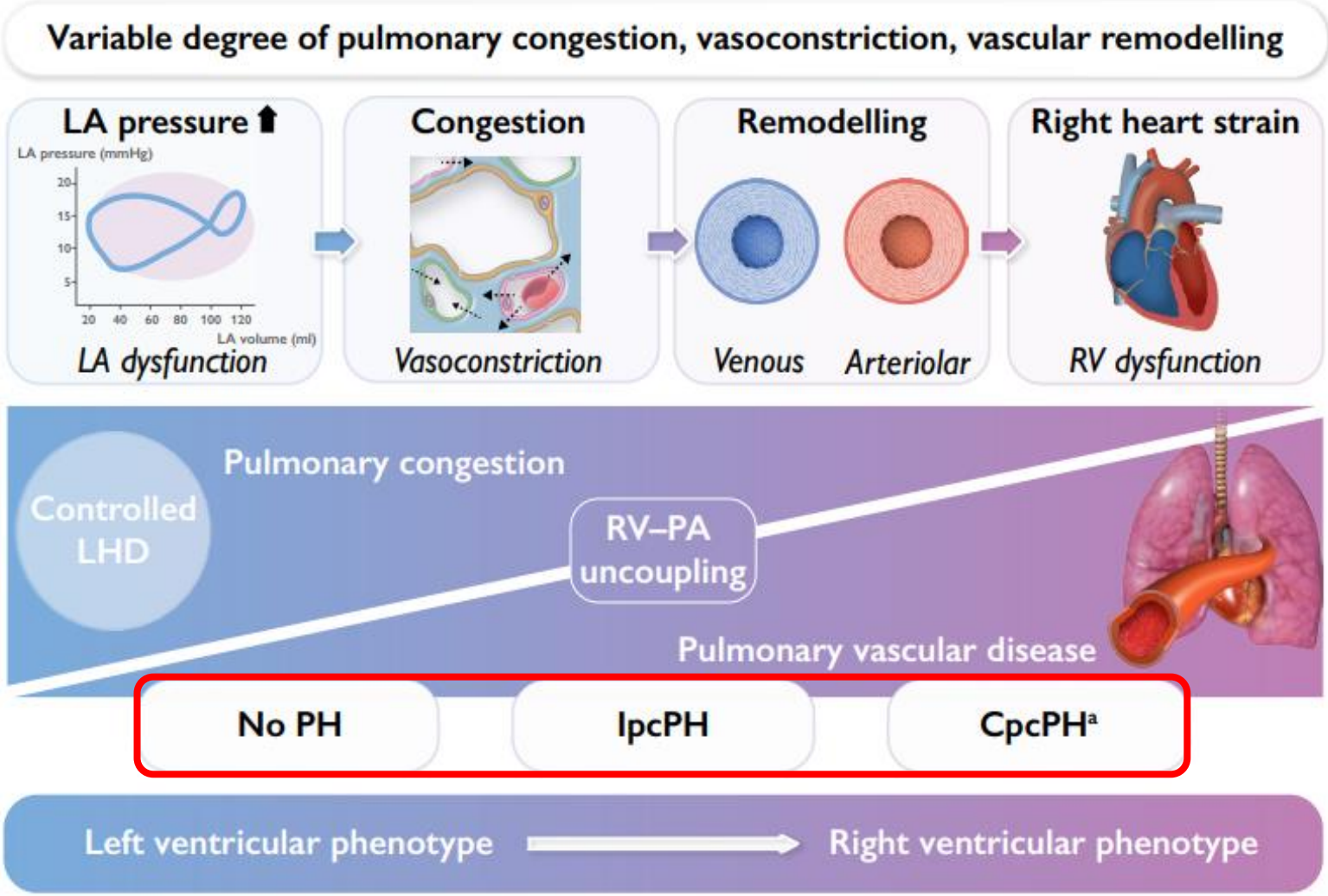
GROUP 2 PH associated with left heart disease

- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction **(HFpEF)**
  - 2.1.2 with reduced or mildly reduced ejection fraction[b] **(HFrEF, HFmrEF)**
- 2.2 Valvular heart disease **(Left-sided VHD)**
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

[b]Left ve
with m



- PH-LHD represents the most prevalent form of PH : 65–80% of PH.
- 20–30% of patients are categorized as having CpcPH.



Patient phenotyping and likelihood for Left Heart Disease as cause of PH

Table 23 **Patient phenotyping and likelihood for left heart disease as cause of pulmonary hypertension**

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	Mild LVH	LBBB or LVH

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)

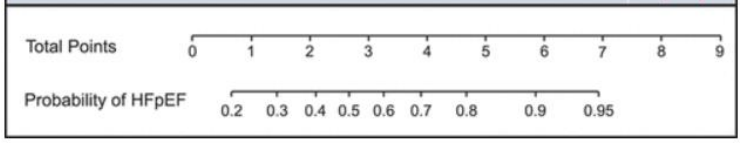
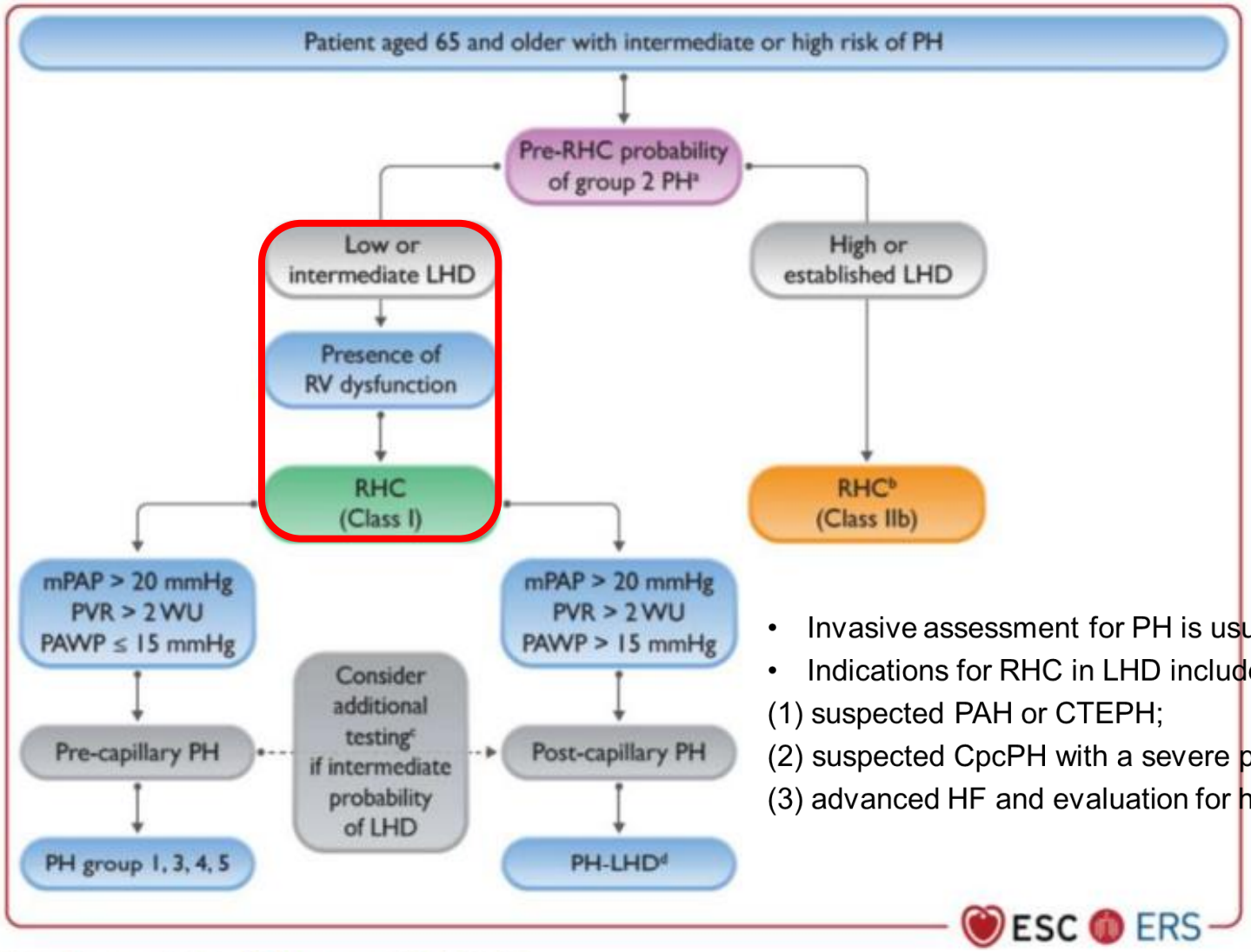


Figure 1. H2FPEF Score proposed by Reddy et al.
https://doi.org/10.1161/CIRCULATIONAHA.118.034646

Supplementary Table 1. Calculation of HFA-PEFF score

Parameter	HFA-PEFF score			
	Major		Minor	
	Value	Point	Value	Point
Functional	Septal e' < 7 cm/sec or lateral e' < 10 cm/sec or average E/e' ≥ 15 or TR Vmax > 2.8 m/sec (PASP > 35 mmHg)	2	Average E/e' 9–14 or GLS < 16%	1
Morphological	LAVI > 34 mL/m² or LVMI ≥ 149/122 g/m² (M/W) + RWT > 0.42	2	LAVI 29–34 mL/m² or LVMI ≥ 115/95 g/m² (M/W) or RWT > 0.42 or LV wall thickness ≥ 12 mm	1
Biomarker				
SR	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	2	NT-proBNP 125–220 pg/mL or BNP 35–80 pg/mL	1
AF	NT-proBNP > 660 pg/mL or BNP > 240 pg/mL	2	NT-proBNP 365–660 pg/mL or BNP 105–240 pg/mL	1

Invasive assessment in PH-LHD



- Invasive assessment for PH is usually not indicated.
- Indications for RHC in LHD include:

(1) suspected PAH or CTEPH;
(2) suspected CpcPH with a severe pre-capillary component;
(3) advanced HF and evaluation for heart transplantation.

[a]According to probability of LHD as cause of PH (*Table 24*).

[b]RHC may be considered and indicated for prognosis or specific treatment decision purposes, according to the appropriate guidelines.

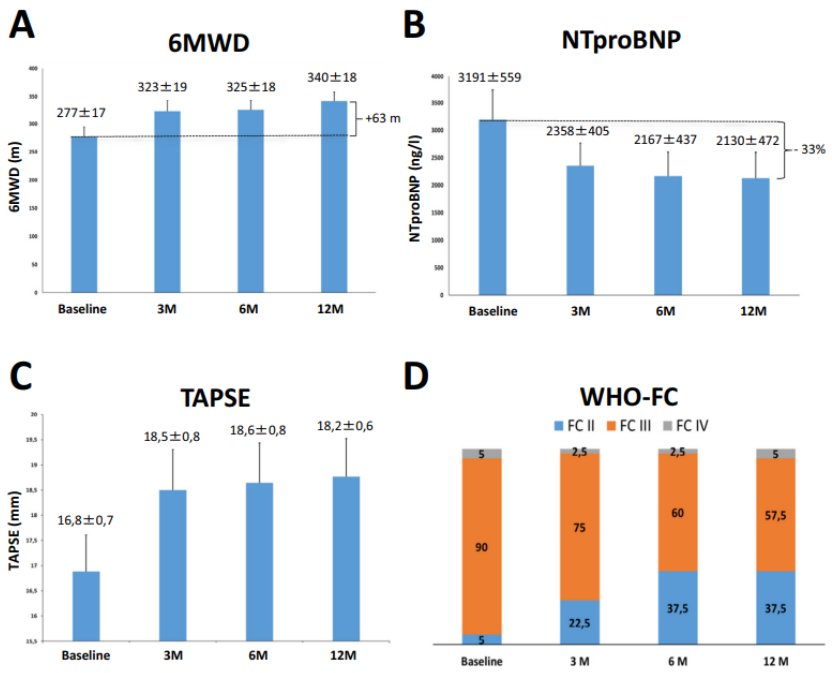
Use of drugs approved for PAH in PH-LHD

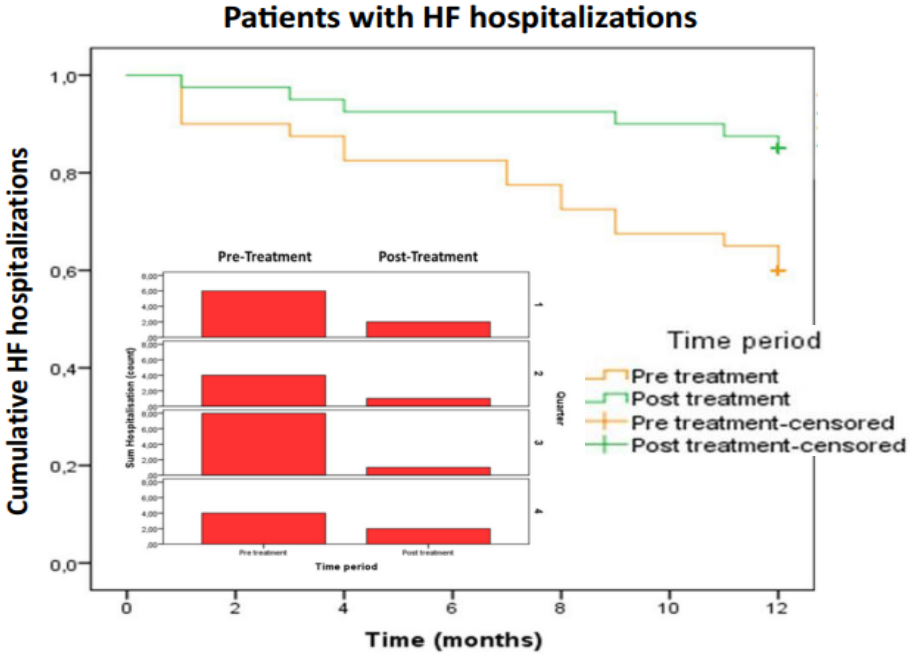
Recommendations	Class[a]	Level[b]
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH[27,28]	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients 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

[c]Safety concerns have been identified when ERAs are used in patients with HF (HFpEF and HFrEF, with or without PH) and when sildenafil is used in patients with persistent PH after correction of valvular heart disease.

	Macitentan	Placebo	Treatment effect % (95% CI)[#]	p-value[¶]
Subjects n	31	32		
Significant fluid retention or worsening in NYHA functional class from baseline[+]	7 (22.6)	4 (12.5)	10.08 (−15.07 to 33.26)	0.34
Significant fluid retention	7 (22.6)	3 (9.4)	13.21 (−11.96 to 36.21)	0.18
Increased body weight from baseline by ⩾5% or ⩾5 kg due to fluid overload	3 (9.7)	0 (0)		
Parenteral administration of diuretics	5 (16.1)	3 (9.4)		
Worsening in NYHA functional class from baseline[§]	1 (3.2)	2 (6.3)		

Eur Respir J 2018; 51: 1702589.





International Journal of Cardiology 283 (2019) 152–158

- In 40 hemodynamically precisely characterized patients with HFpEF and Cpc-PH who were treated with a PDE5i for at least 12 months
- A subset with HFpEF and CpcPH who tolerate PDE5i may benefit from targeted therapy.

	GRADE			
Recommendations	**Quality of evidence**	**Strength of recommendation**	**Class[a]**	**Level[b]**
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

Group 3. PH associated with lung diseases and/or hypoxia

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

2022 ESC/ERS guidelines for PH

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- ~~3.4 Sleep-disordered breathing~~
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

2015 ESC/ERS guidelines for PH

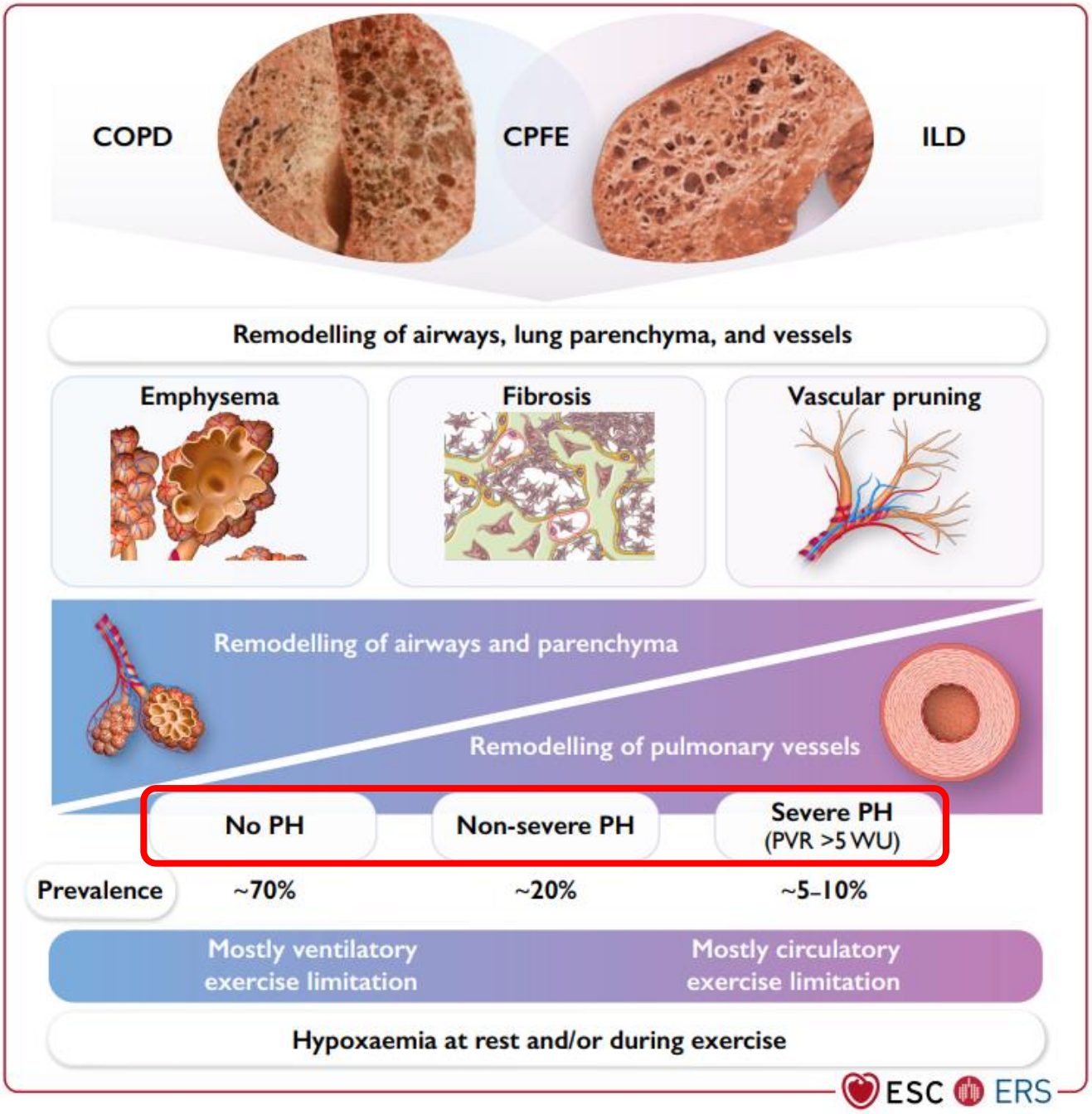


Figure 12 Pathophysiology of pulmonary hypertension associated with lung disease (group 3).

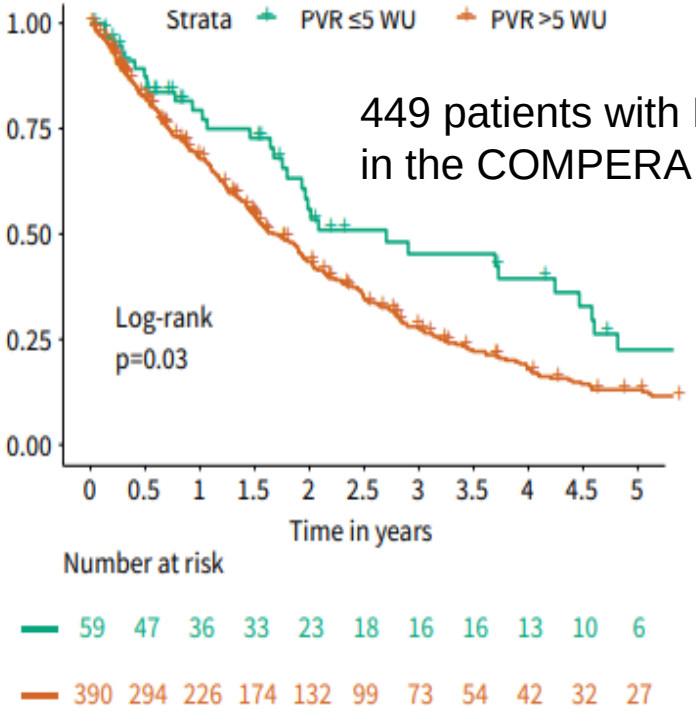
Definition of severe PH-Lung disease

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

2015 ESC/ERS guidelines for PH

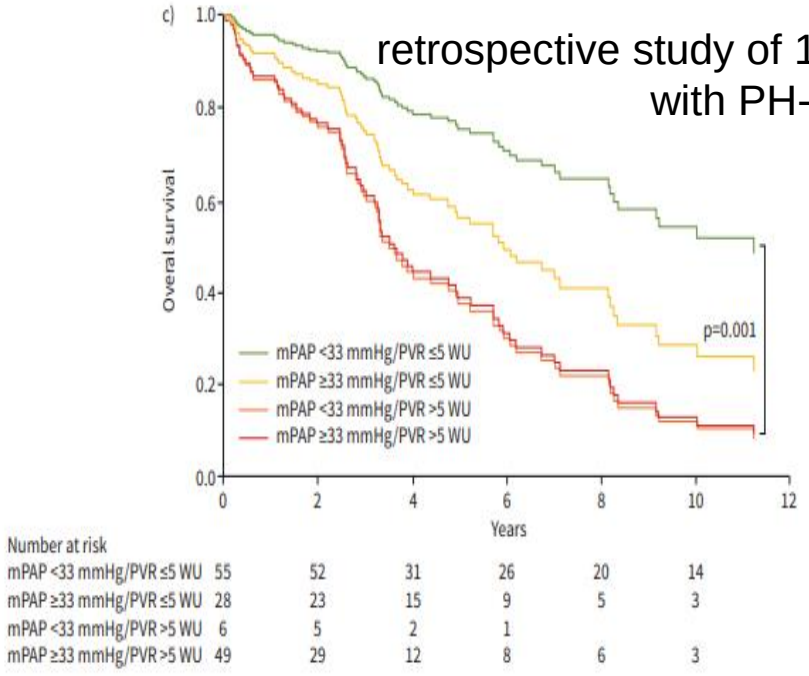
In COPD/ILD	Threshold
non-severe PH	PVR ≤5 WU
severe PH	PVR >5 WU

2022 ESC/ERS guidelines for PH



449 patients with PH-ILD
in the COMPERA registry

Olsson KM, et l. Eur Respir J 2021; 58: 2101483



retrospective study of 139 pts
with PH-COPD

Zeder K, et al. Eur Respir J. 2021;58: 210094

Recommendations	Class[a]	Level[b]
If PH is suspected in patients with lung disease, it is recommended that echocardiography[c] be performed and the results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging	I	C
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I	C
In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[d]	I	C
In patients with lung disease and severe PH, an individualized approach to treatment is recommended	I	C
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation	I	C
In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I	C
Inhaled treprostinil may be considered in patients with PH associated with ILD[734] 2022 Updated	IIb	B
The use of ambrisentan is not recommended in patients with PH associated with IPF[740]	III	B
The use of riociguat is not recommended in patients with PH associated with IIP[181]	III	B
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]	III	C

	GRADE			
Recommendations	Quality of evidence	Strength of recommendation	Class[a]	Level[b]
PDE5is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	IIb	C
The use of PDE5is in patients with ILD and non-severe PH is not recommended	Very low	Conditional	III	C

The NEW ENGLAND JOURNAL of MEDICINE

WHO Group 3

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

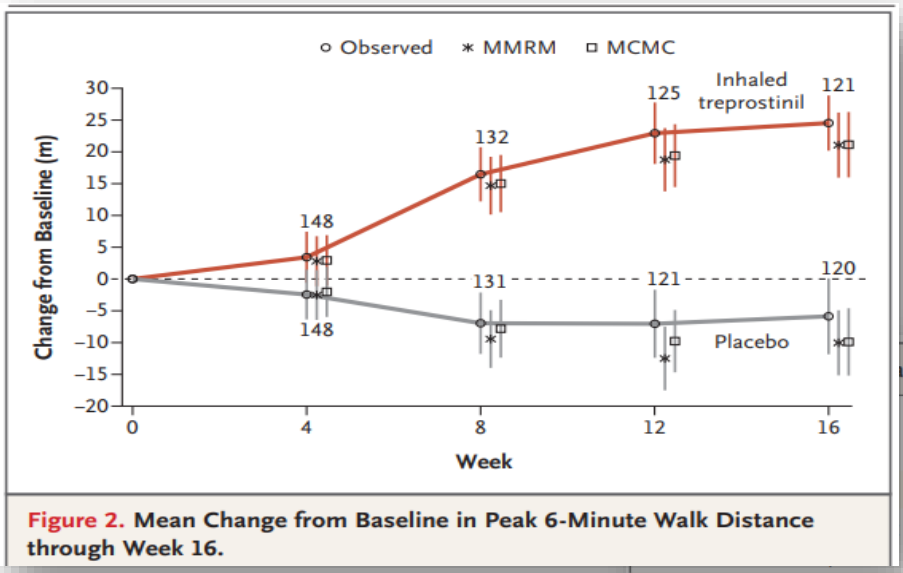


Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

N Engl J Med 2021;384:325-34 INCREASE study

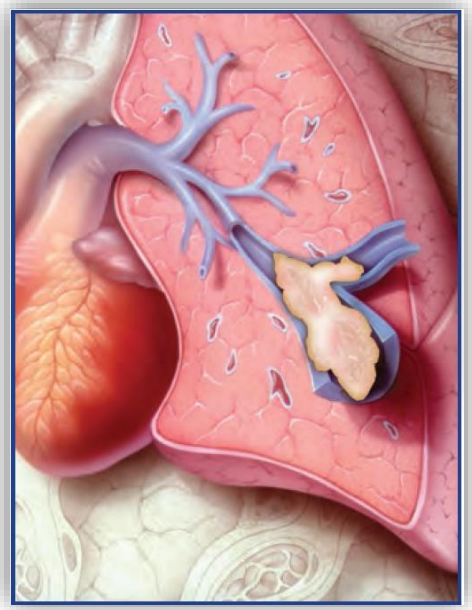
…nd Secondary End Points.*	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
…distance from baseline	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		

Group 4. PH associated with pulmonary artery obstructions

GROUP 4 PH associated with pulmonary artery obstructions

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

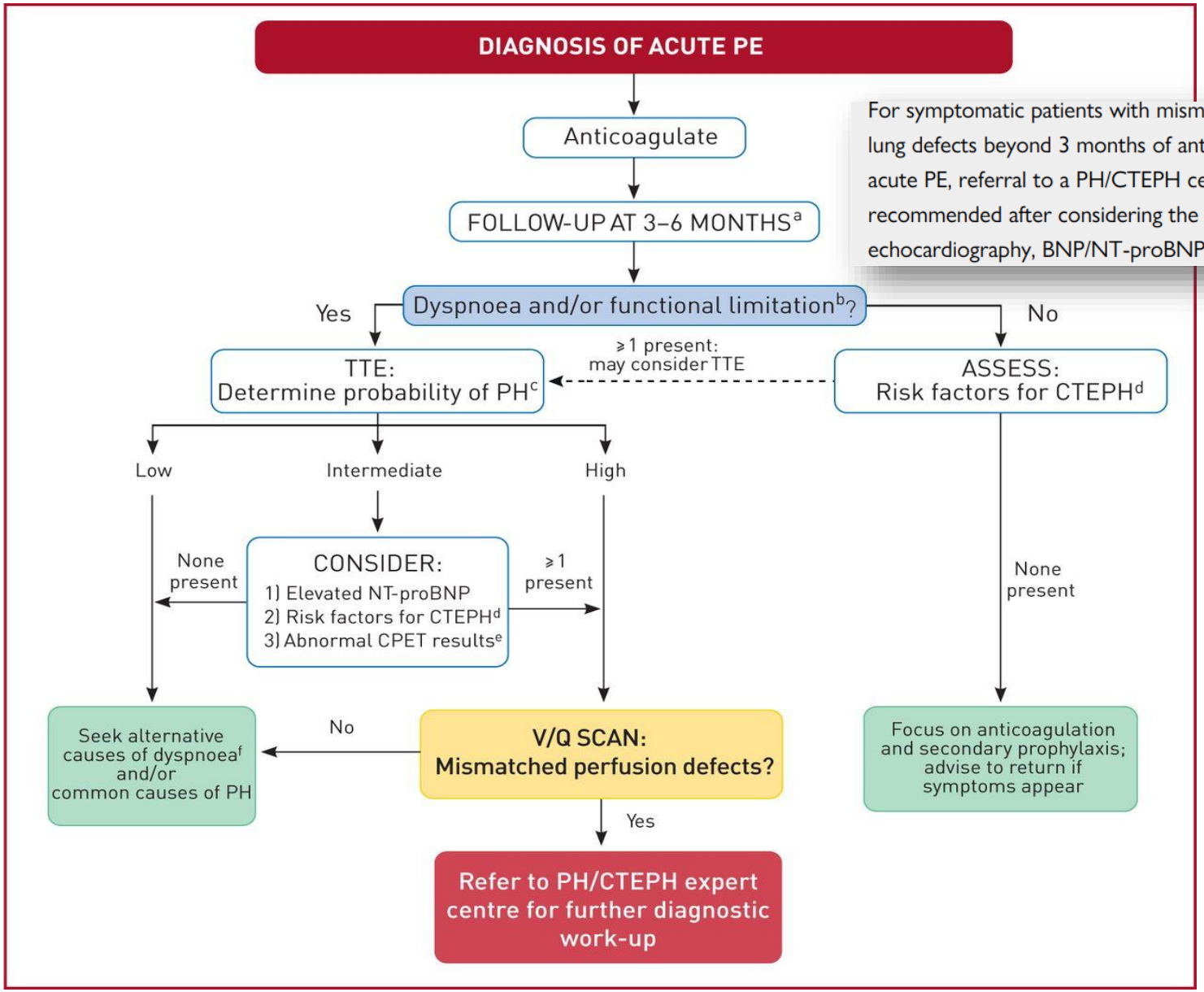
Chronic Thrombo-embolic Pulmonary Hypertension (CTEPH)



- **Defining CTEPH**
  → PH after 3 months of therapeutic anticoagulation
  - Persistent perfusion defect(s) on V/Q scan with chronic, organized, fibrotic clots in CTPA/DSA.
  - not only a consequence of PA obstruction by organized fibrotic clots but can also be related to the associated microvasculopathy.
- CTEPH is thought to develop following a pulmonary embolism (PE) that fails to resolve in between 0.1% and 11.8% of patients.

In patients with persistent or new-onset dyspnoea or exercise limitation following PE, further diagnostic evaluation to assess for CTEPH/CTEPD is recommended	I

Eur Heart J 2022:ehac206
European Heart Journal 2022:00, 1–114

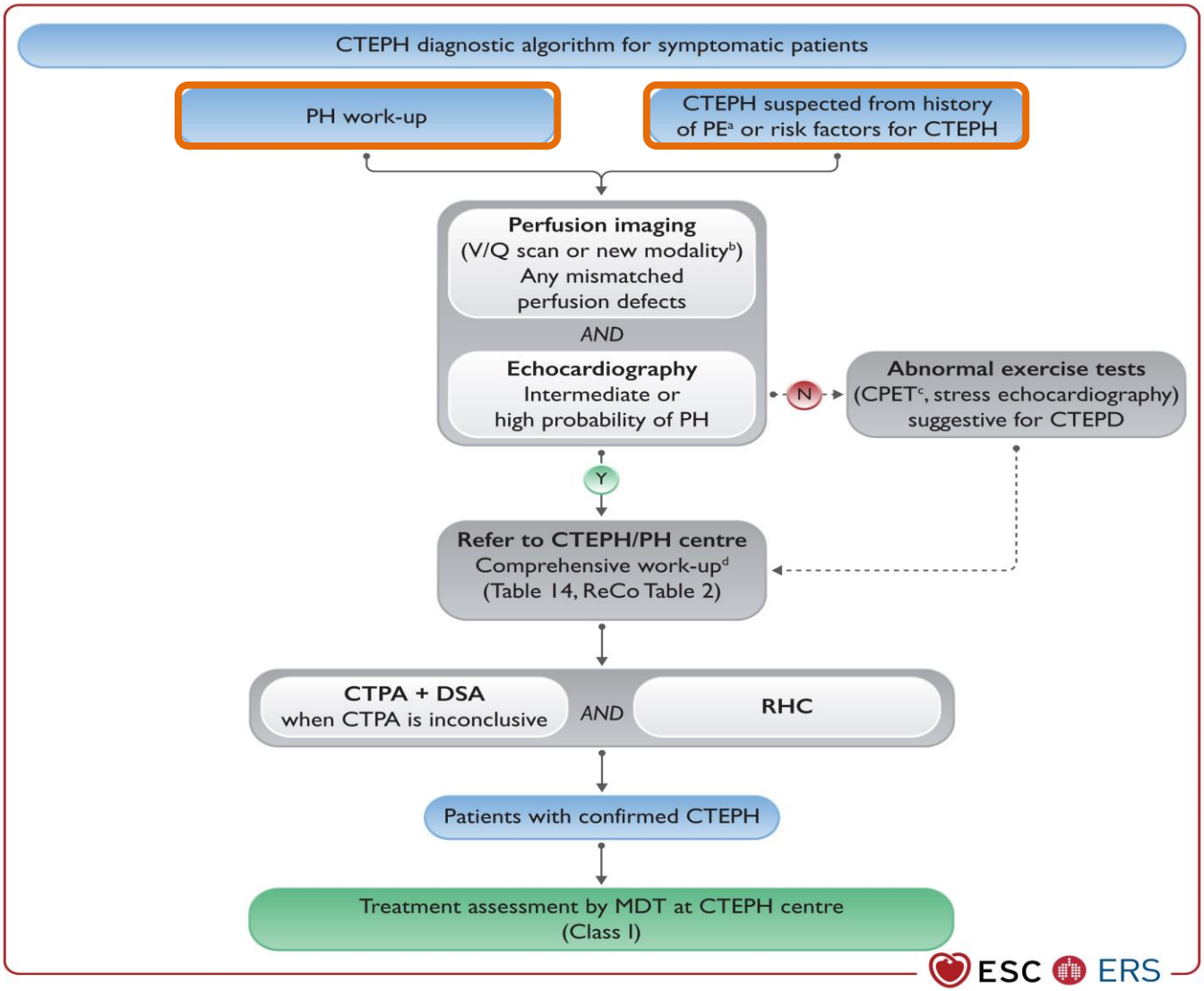


For symptomatic patients with mismatched perfusion lung defects beyond 3 months of anticoagulation for acute PE, referral to a PH/CTEPH centre is recommended after considering the results of echocardiography, BNP/NT-proBNP, and/or CPET

I

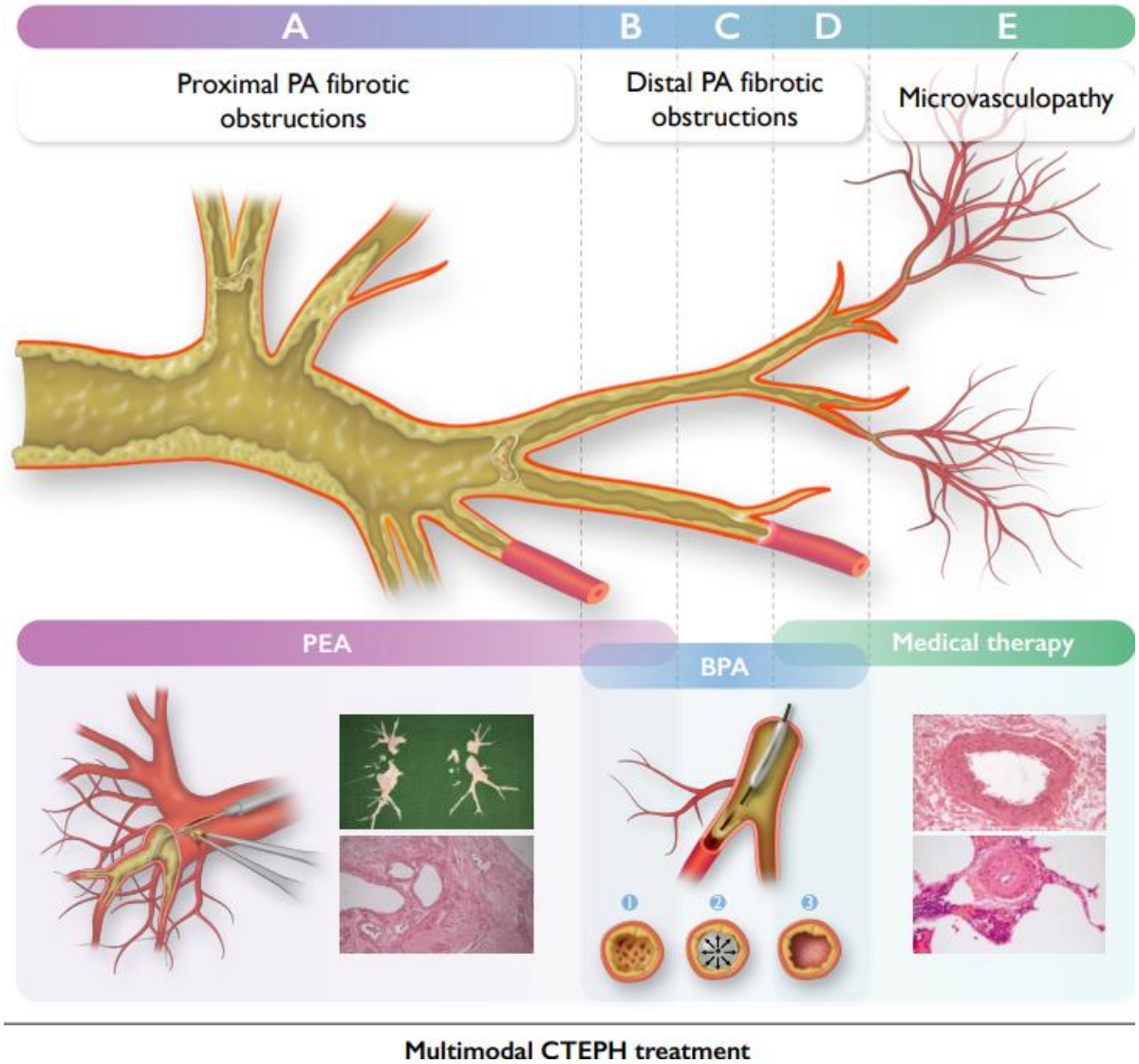
Eur Respir J 2019; 54: 1901647

Diagnostic strategy in CTEPH



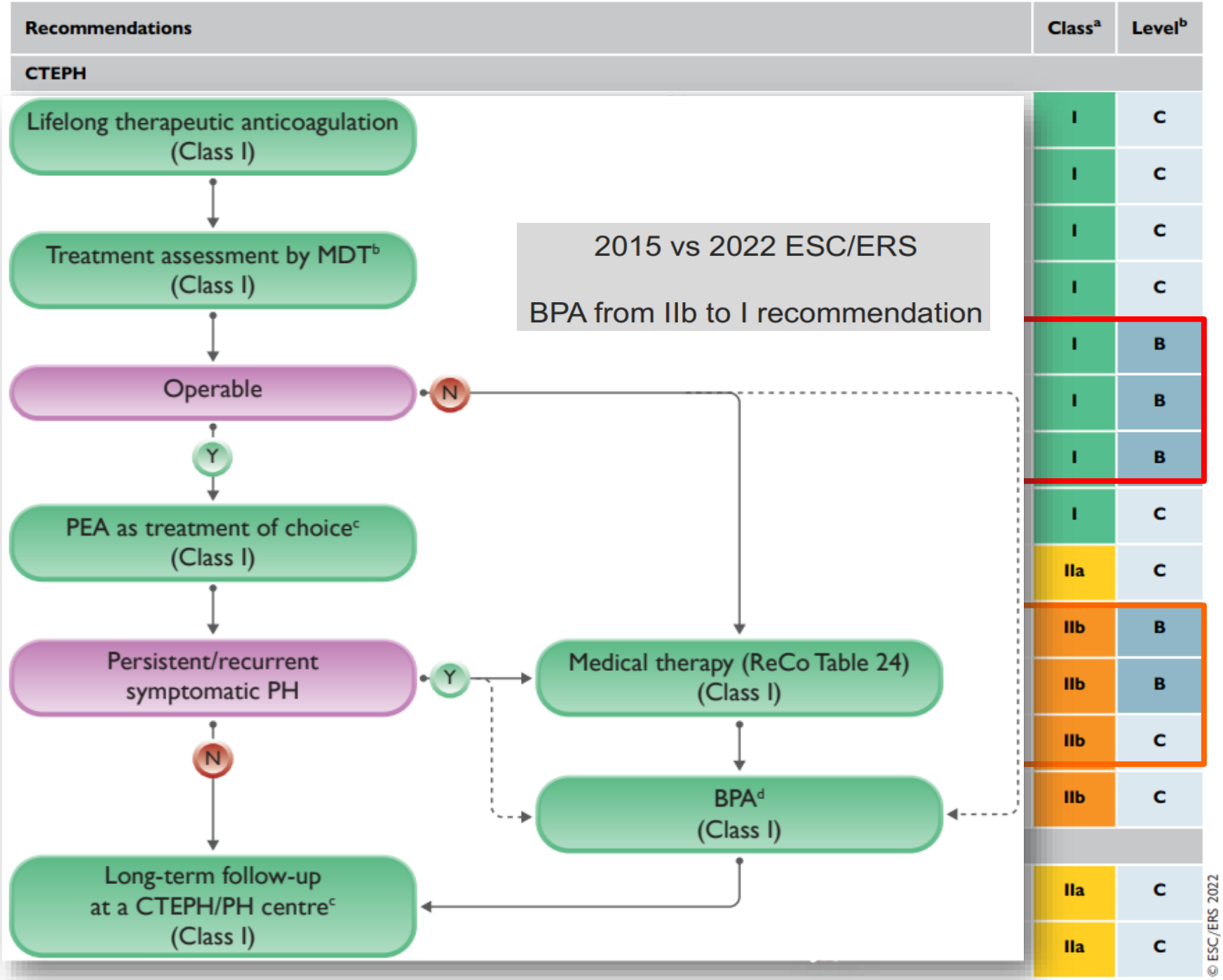
[b]Alternative perfusion imaging techniques—such as iodine subtraction mapping, DECT, and MRI perfusion
CTPA, computed tomography pulmonary angiography; DSA, digital subtraction angiography;

Management strategy in CTEPH



PEA, Pulmonary endarterectomy;
BPA, Balloon pulmonary angioplasty

European Heart Journal (2022) 00, 1–114


Recommendations
Class[a]
Level[b]
CTEPH
Lifelong therapeutic anticoagulation (Class I)
Treatment assessment by MDT[b] (Class I)
Operable
N
Y
PEA as treatment of choice[c] (Class I)
Persistent/recurrent symptomatic PH
Y
N
Medical therapy (ReCo Table 24) (Class I)
BPA[d] (Class I)
Long-term follow-up at a CTEPH/PH centre[c] (Class I)
2015 vs 2022 ESC/ERS
BPA from IIb to I recommendation
I C
I C
I C
I C
I B
I B
I B
I C
IIa C
IIb B
IIb B
IIb C
IIb C
IIa C
IIa C
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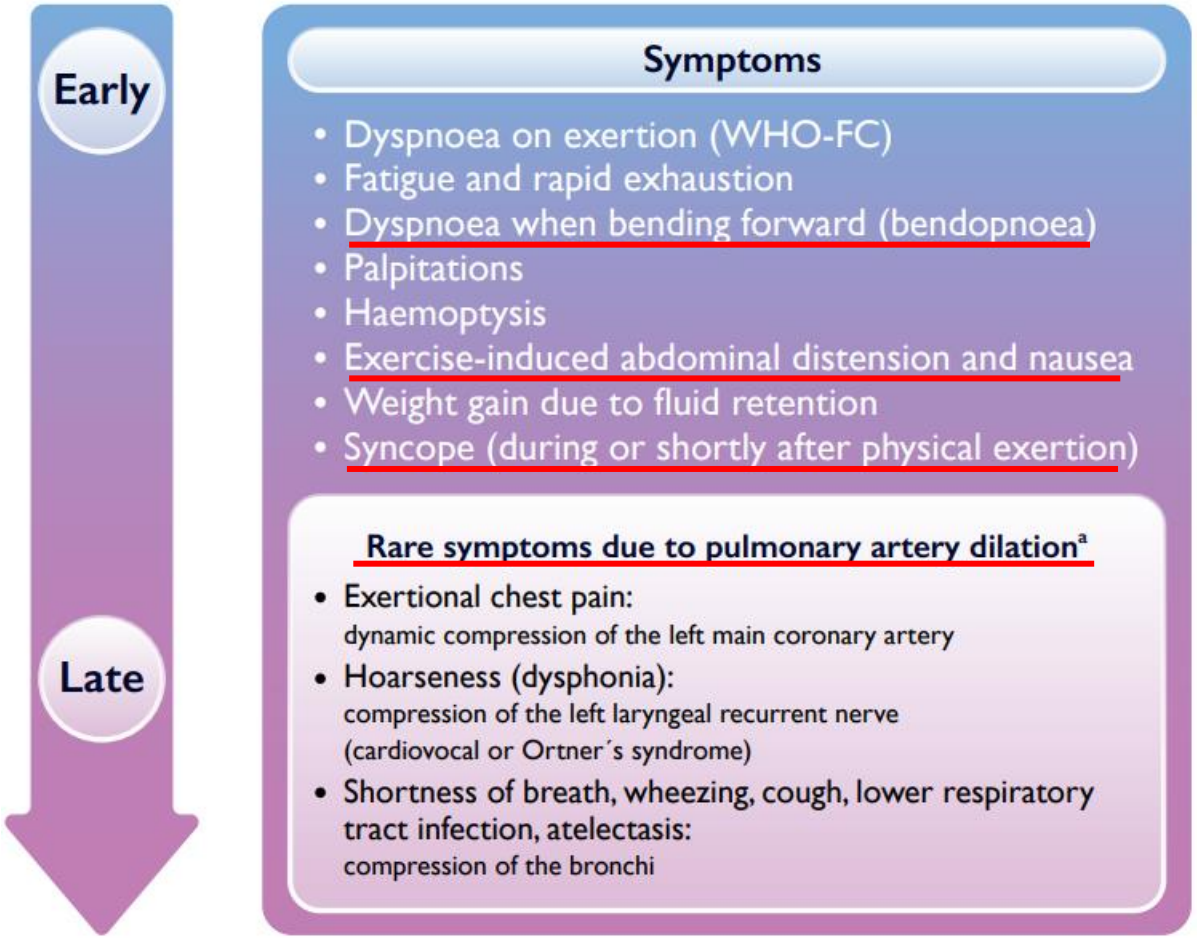
Diagnosis and Assessment of PH/PAH

New ESC Pulmonary Hypertension Guidelines Urge Earlier Diagnosis

1. To raise early suspicion of PH
→ fast-track referral to PH centers in patients with a high likelihood of PAH, CTEPH, or other forms of severe PH.
2. To identify underlying diseases (LHD, lung disease, comorbidities)
→ proper classification, risk assessment, and treatment

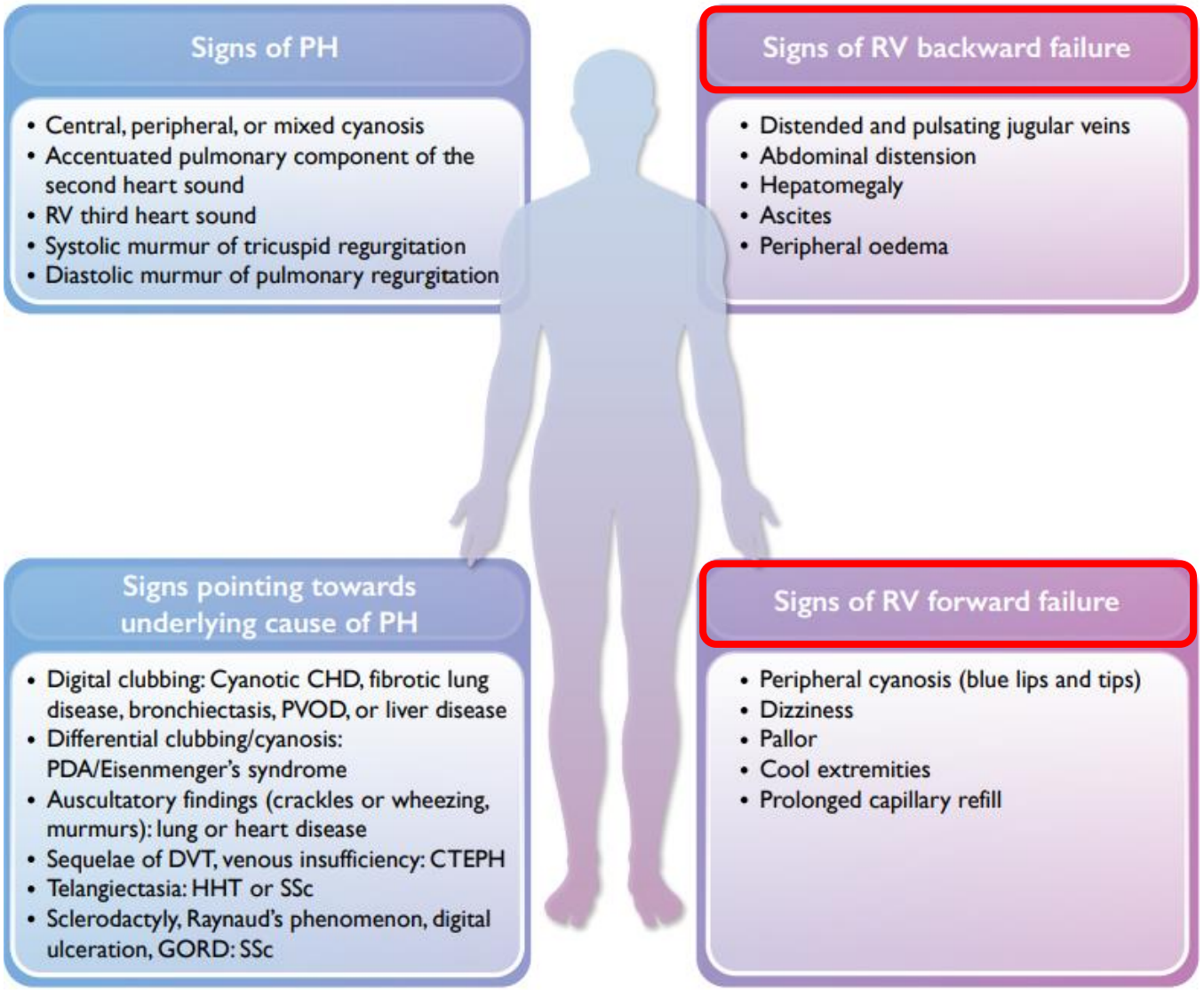
Symptoms in patients with PH



[a]*Thoracic compression syndromes are found in a minority of patients with PAH with pronounced dilation of the pulmonary artery, and may occur at any disease stage and even in patients with otherwise mild functional impairment.*

European Heart Journal (2022) 00, 1–114

Clinical signs in patients with PH



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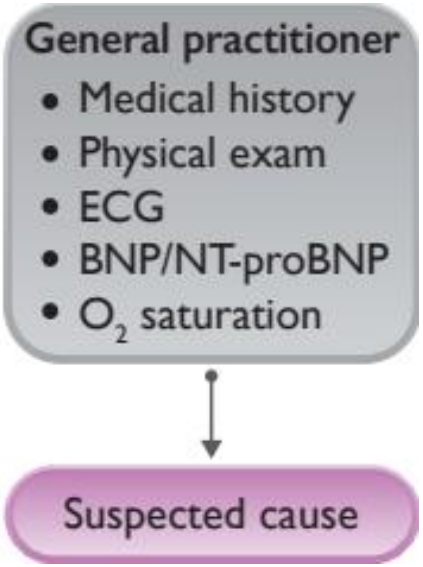
Diagnostic algorithm

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

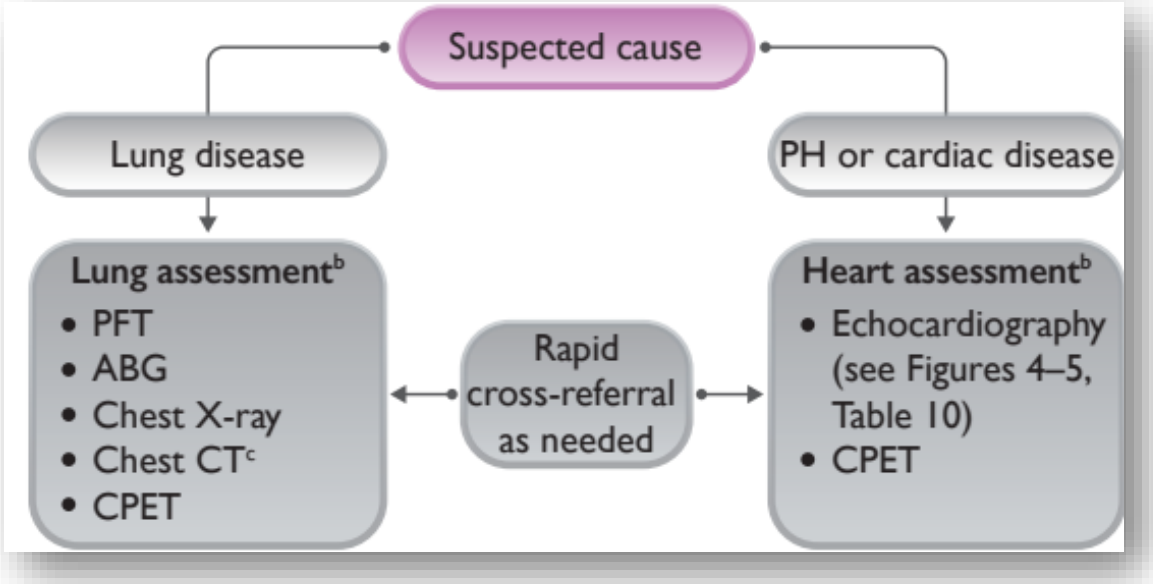
- **Step 1 (suspicion) : initial evaluation**
- raise a suspicion of a cardiac or respiratory disorder causing the symptom

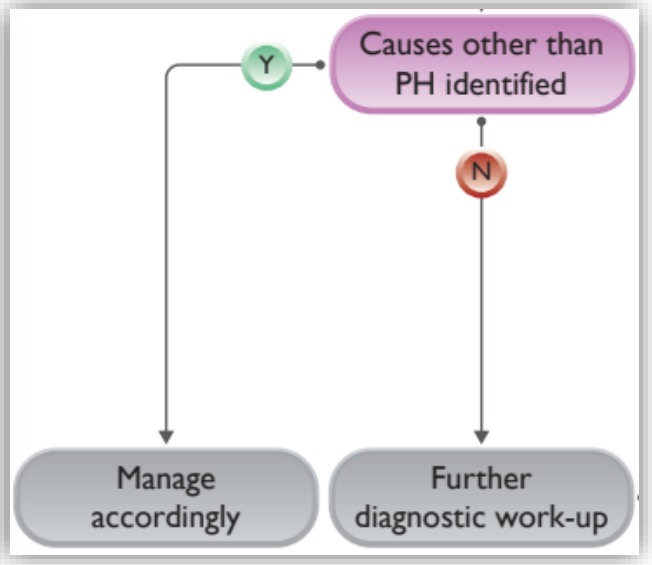
– a comprehensive medical/familial history
– thorough physical examination
(including BP, HR,SpO_2)
– blood test to determine BNP/NT-proBNP
– resting ECG



Diagnostic algorithm

- **Step 2 (detection)** : non-invasive lung & cardiac testing
- **Screening of PH with cardiac echo** is important.
- Patients should be managed accordingly based on this initial assessment.





Diagnostic algorithm

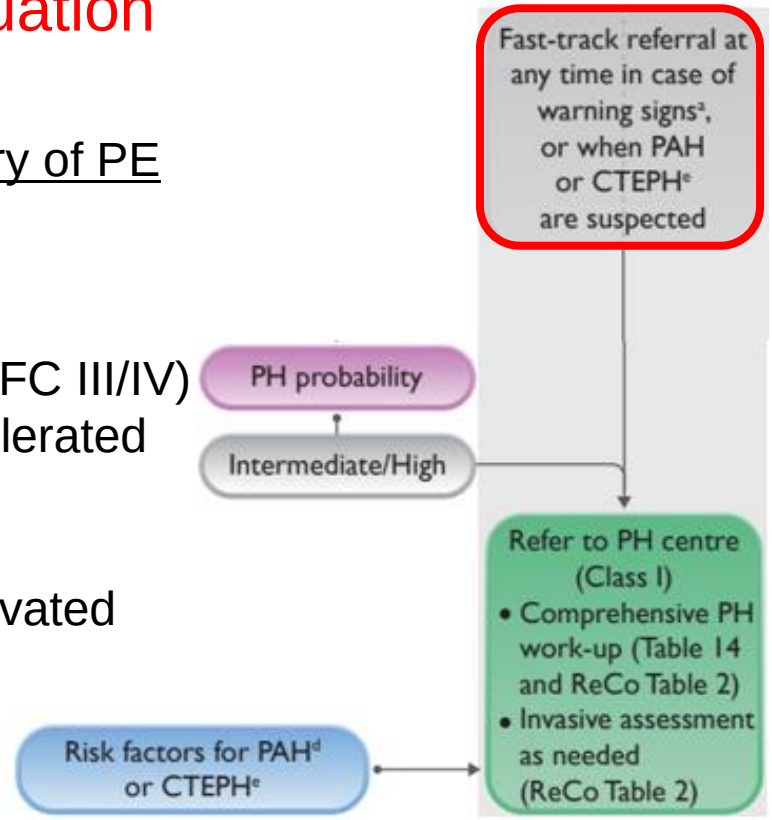
- **Step 3 (confirmation)** : comprehensive & invasive w-up
- distinguishing between the various causes of PH according to the current clinical classification

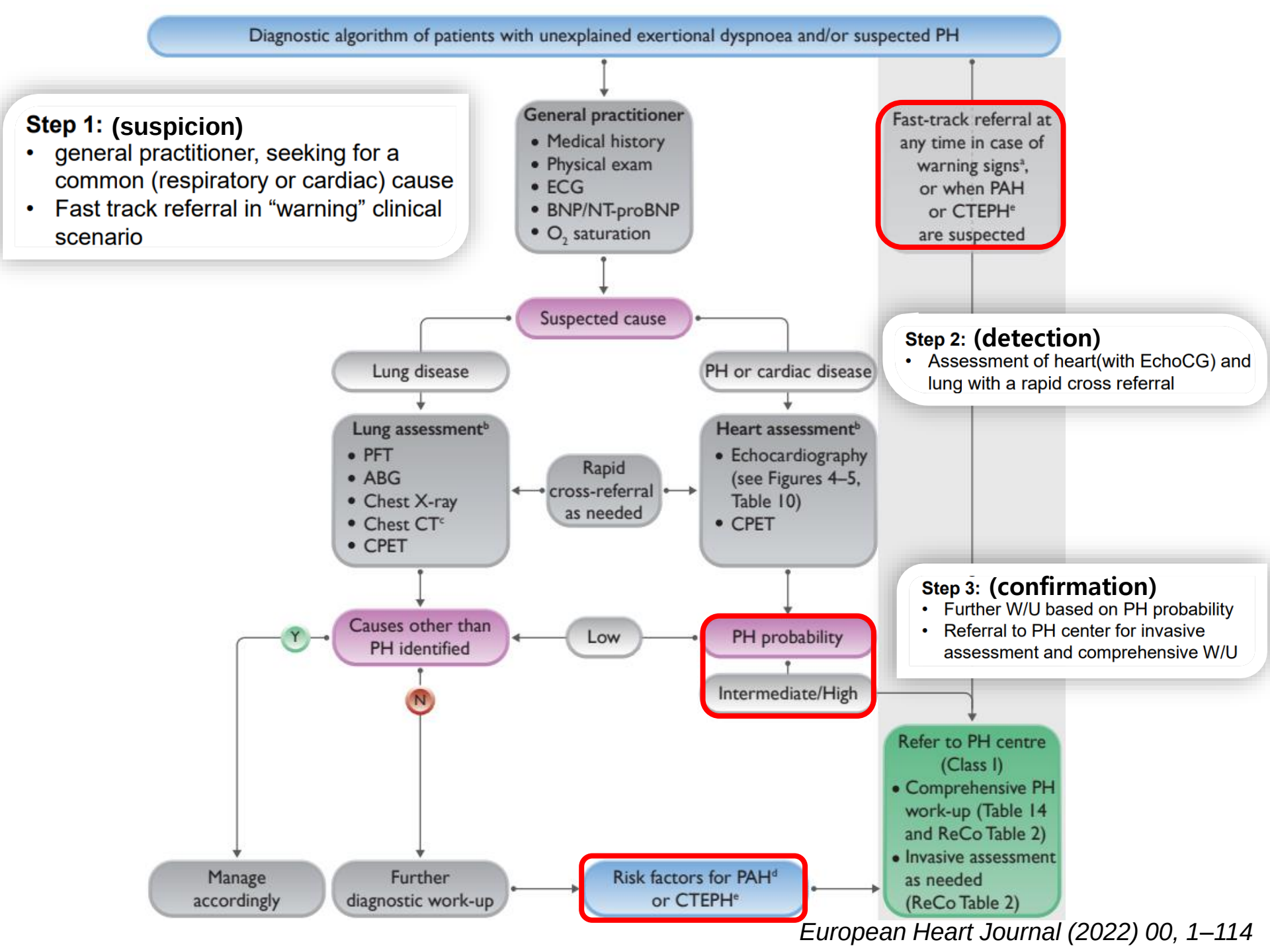
- Refer to PH center for further evaluation

  1) intermediate/high probability of PH
  2) in the presence of RF for PAH, or a history of PE

- Warning signs must be recognized

  1) rapidly evolving/severe symptoms(WHO-FC III/IV)
  2) syncope, signs of low CO state, poorly tolerated arrhythmias, hypotension/tachycardia
  3) clinical signs of RV failure
  4) RV dysfunction by echocardiography, elevated cardiac biomarkers





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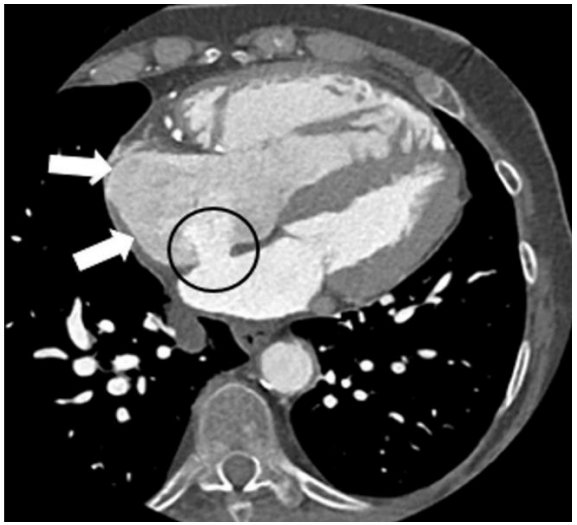
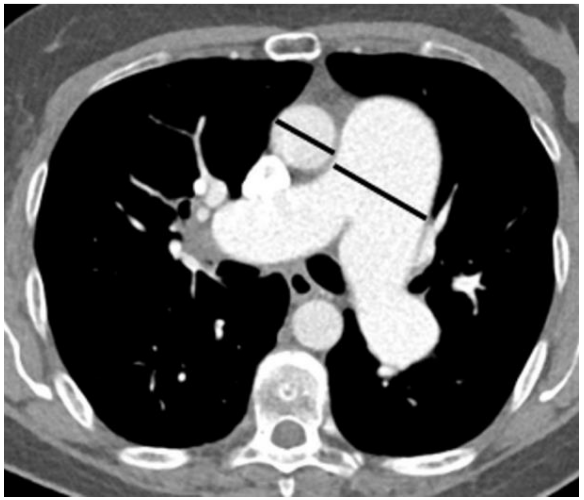
Radiographic signs of PH





Signs of PH and concomitant abnormalities	Signs of left heart disease/ pulmonary congestion	Signs of lung disease
Right heart enlargement	Central air space opacification	Flattening of diaphragm (COPD/ emphysema)
PA enlargement (including aneurysmal dilatation)	Interlobular septal thickening 'Kerley B' lines	Hyperlucency (COPD/ emphysema)
Pruning of the peripheral vessels	Pleural effusions	Lung volume loss (fibrotic lung disease)
'Water-bottle' shape of cardiac silhouette[a]	Left atrial enlargement (including splayed carina) Left ventricular dilation	Reticular opacification (fibrotic lung disease)

CHEST 2019; 156(2):211-227

Echocardiographic probability of PH

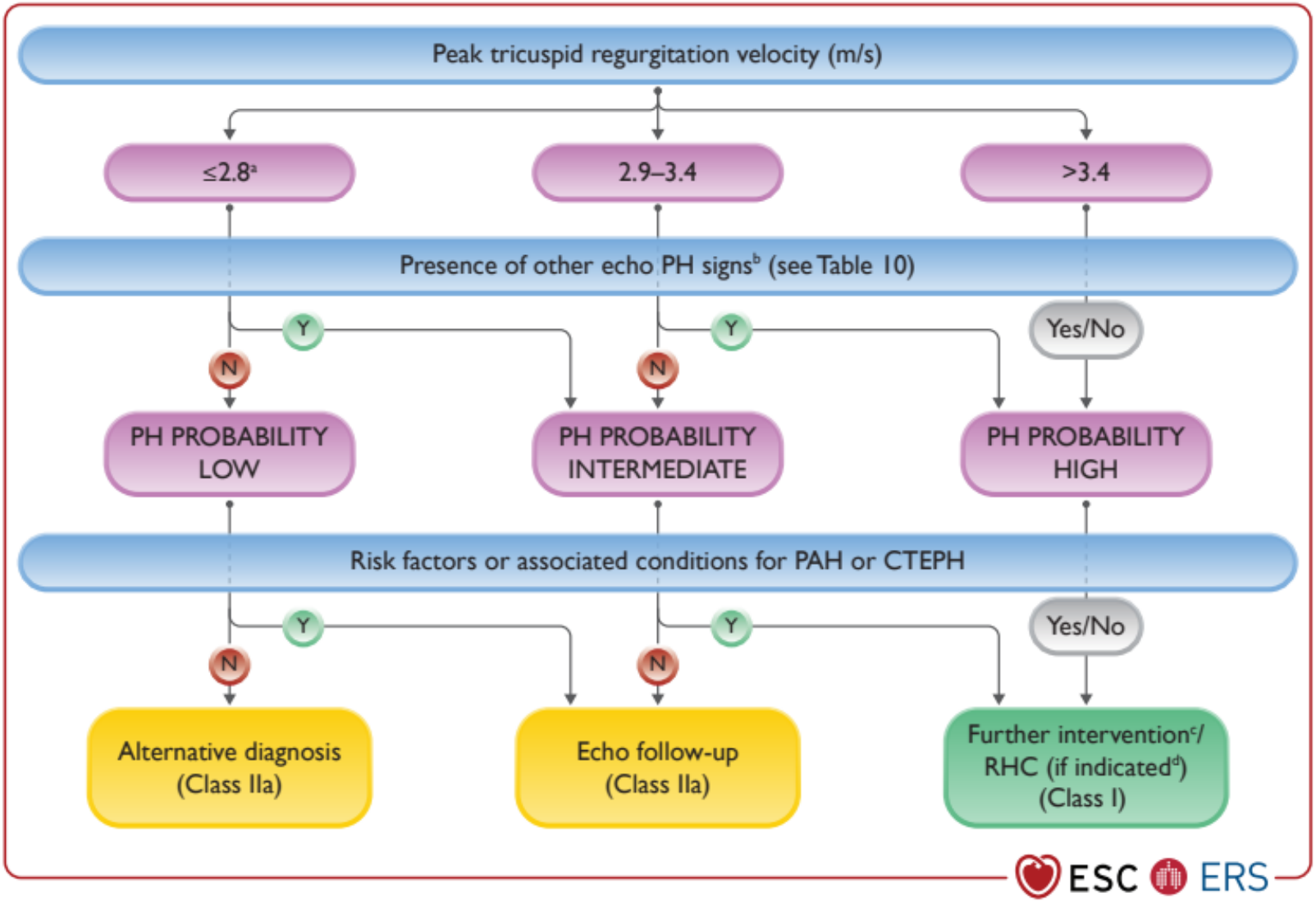


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Table 10 Additional echocardiographic signs suggestive of pulmonary hypertension

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	

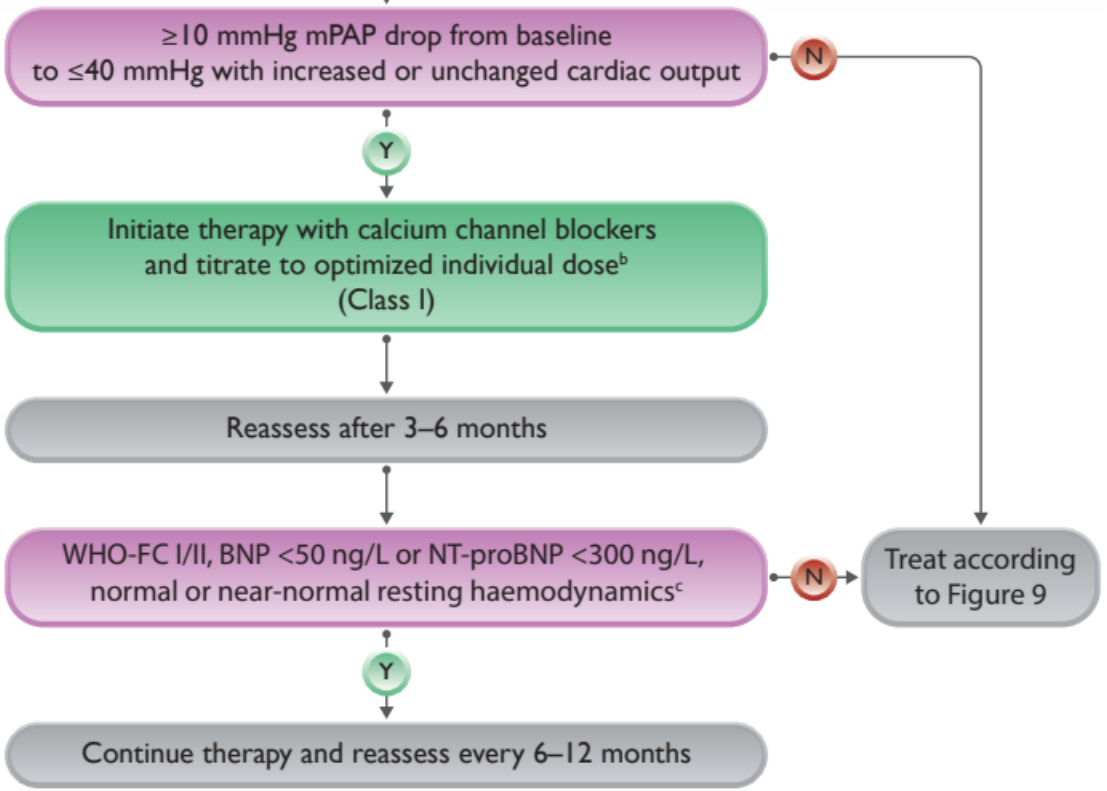
Tricuspid annular plane systolic excursion (TAPSE) 삼첨판륜 수축기 이동거리

Vasoreactivity testing algorithm in patients with presumed diagnosis of I/H/D-PAH and treatment of responders

Table 12 **Route of administration, half-life, dosages, and duration of administration of the recommended test compounds for vasoreactivity testing in pulmonary arterial hypertension**

Compound	Route	Half-life	Dosage	Duration
Nitric oxide[129]	inh	15–30 s	10–20 p.p.m.	5–10 min[a]
Iloprost[130,131]	inh	30 min	5–10 µg[b]	10–15 min[c]
Epoprostenol[129]	i.v.	3 min	2–12 ng/kg/min	10 min[d]

IV Adenosine is no longer recommended d/t frequent S/E



ESC ERS

Treatment of PH/PAH

General measures

2015

Recommendations		
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens.	IIb	C

General measures		
Supervised exercise training is recommended in patients with PAH under medical therapy[314,315,317]	I	A
Psychosocial support is recommended in patients with PAH	I	C
Immunization of patients with PAH against SARS-CoV-2, influenza, and *Streptococcus pneumoniae* is recommended	I	C
Diuretic treatment is recommended in patients with PAH with signs of RV failure and fluid retention	I	C
Long-term oxygen therapy is recommended in patients with PAH whose arterial blood oxygen pressure is <8 kPa (60 mmHg)[c]	I	C
In the presence of iron-deficiency anaemia, correction of iron status is recommended in patients with PAH	I	C
In the absence of anaemia, iron repletion may be considered in patients with PAH with iron deficiency	IIb	C
Anticoagulation is not generally recommended in patients with PAH but may be considered on an individual basis	IIb	C
The use of ACEis, ARBs, ARNIs, SGLT-2is, beta-blockers, or ivabradine is not recommended in patients with PAH unless required by comorbidities (i.e. high blood pressure, coronary artery disease, left HF, or arrhythmias)	III	C

Special circumstances		
In-flight oxygen administration is recommended for patients using oxygen or whose arterial blood oxygen pressure is <8 kPa (60 mmHg) at sea level	I	C
For interventions requiring anaesthesia, multidisciplinary consultation at a PH centre to assess risk and benefit should be considered	IIa	C

Recommendations for women of childbearing potential

2015

Recommendations	Class	Level
It is recommended to avoid pregnancy in patients with PAH.	I	C

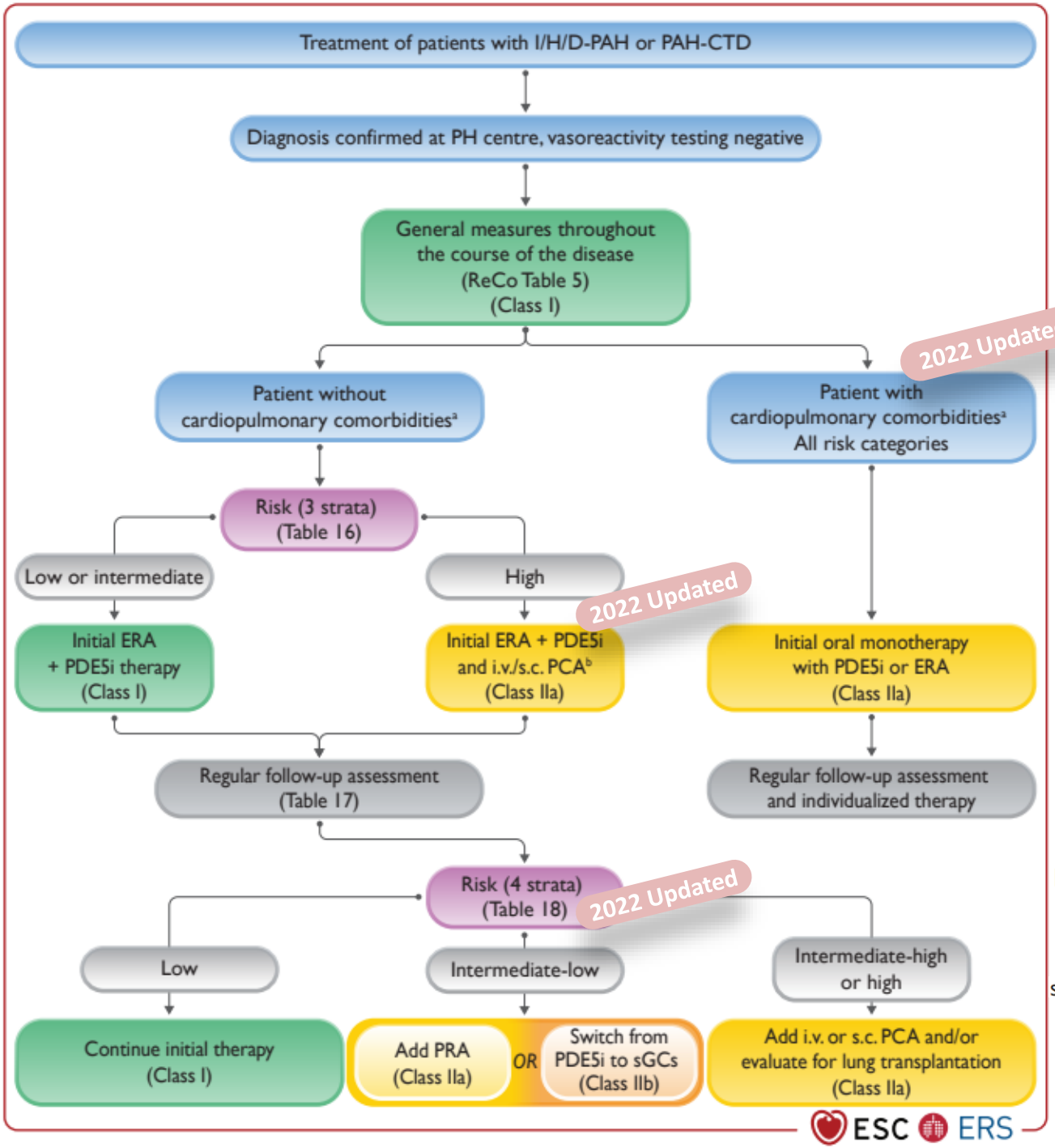
2022 Updated

Recommendations	Class[a]	Level[b]
It is recommended that women of childbearing potential with PAH are counselled at the time of diagnosis about the risks and uncertainties associated with becoming pregnant; this should include advice against becoming pregnant, and referral for psychological support where needed	I	C
It is recommended to provide women of childbearing potential with PAH with clear contraceptive advice, considering the individual needs of the woman but recognizing that the implications of contraceptive failure are significant in PAH	I	C
It is recommended that women with PAH who consider pregnancy or who become pregnant receive prompt counselling in an experienced PH centre, to facilitate genetic counselling and shared decision-making, and to provide psychological support to the patients and their families where needed	I	C
For women with PAH having a termination of pregnancy, it is recommended that this be performed in PH centres, with psychological support provided to the patients and their families	I	C

Comprehensive risk assessment in PAH
(three-strata model)

2022 Updated

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%



a. **Cardiopulmonary comorbidities:** a/w an **increased risk of left ventricular diastolic dysfunction**, and include obesity, HTN, DM, and coronary heart disease; **Pulmonary comorbidities :** include signs of **mild parenchymal lung disease** and are often a/w a **low DLCO (<45% predicted value)**

PRA, prostacyclin receptor agonist
: Selexipag

sGCs, soluble guanylate cyclase stimulator
: Riociguat

Table 17 **Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension**

	At baseline	3–6 months after changes in therapy[a]	Every 3–6 months in stable patients[a]	In case of clinical worsening
Medical assessment (including WHO-FC)				
6MWT				
Blood test (including NT-proBNP)[b,c]				
ECG				
Echocardiography or cMRI				
ABG or pulse oximetry[d]				
Disease-specific HR-QoL				
CPET				
RHC				

indicated; should be considered; may be considered.

Table 18 **Variables used to calculate the simplified four-strata risk-assessment tool**

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

Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer

Take Home Points

- **The hemodynamic definition of PH has been updated as mPAP >20mmHg.**
  - The definition of PAH also implies a PAWP ≤15 mmHg & PVR >2 WU.
- **The main diagnostic algorithm for PH has been simplified following**
  - **a three-step approach :** suspicion by first-line physicians, detection by echocardiography, and confirmation with RHC in PH centers
  - Rapid referral for Warning signs
- **Risk assessment & Treatment algorithm in PAH**
  - **The three-strata risk-stratification assessment at diagnosis.**
  - **A four-strata risk stratification at follow-up**
  - Initial combination therapy in non-Cardiopulmonary comorbidities
- **In group 3 PH,**
  - **Severe PH-LD** : mPAP > 35mmHg → PVR > 5WU
  - PAH drugs may be considered in severe PH-LD
  - inhaled treprostinil is the first FDA-approved drug for PH-ILD


서울케어
Thank you !