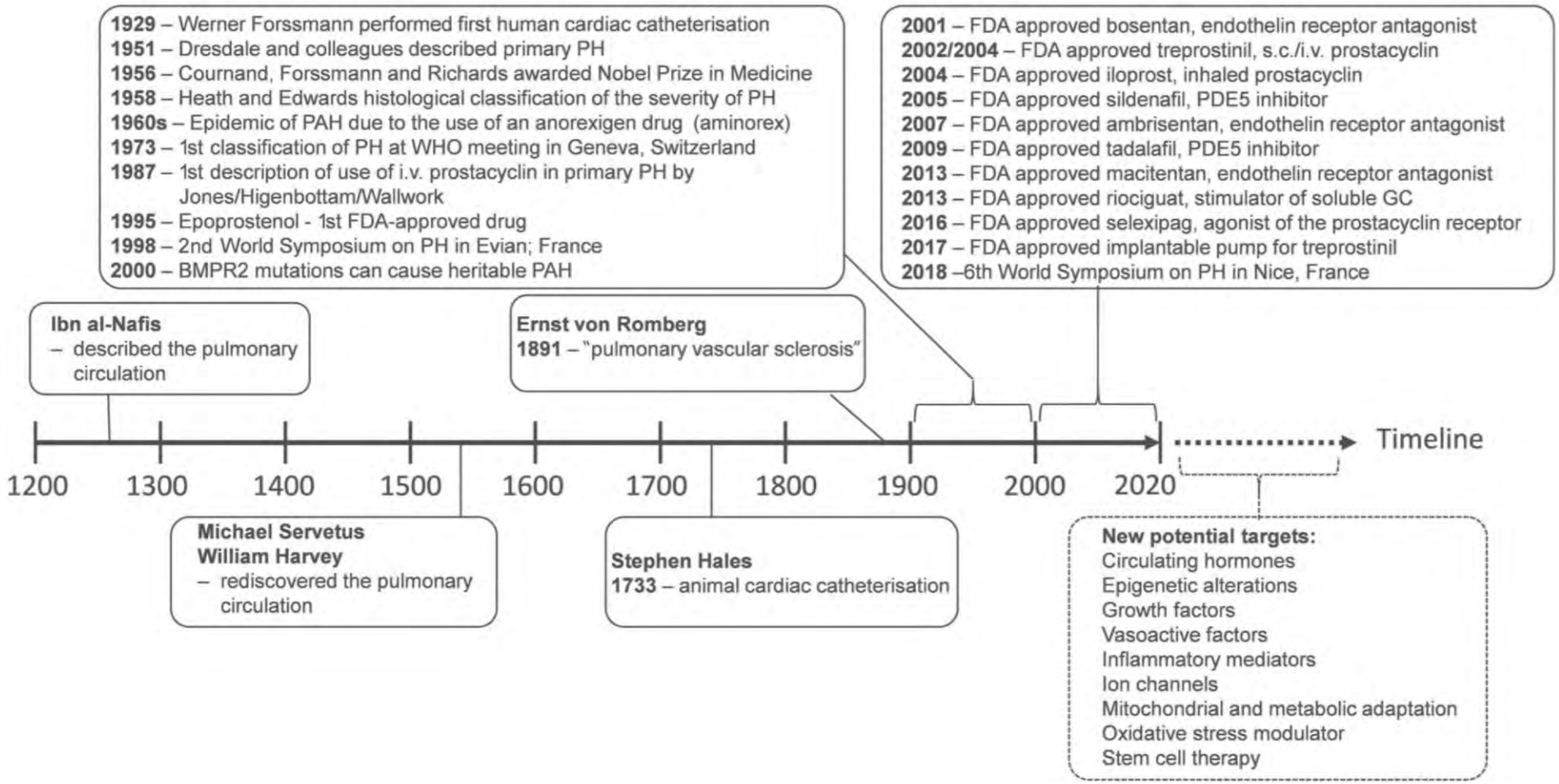
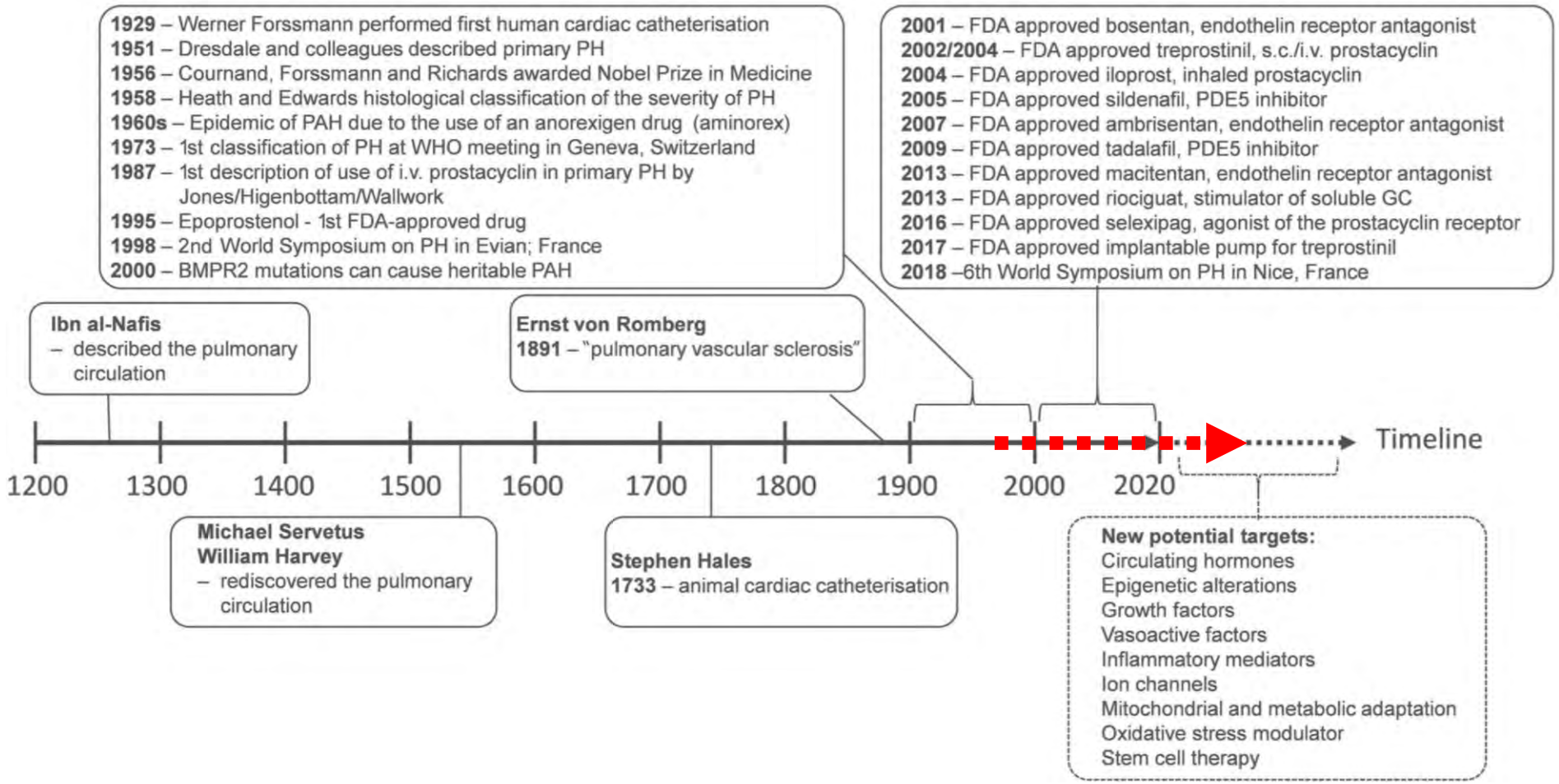
Πνευμονική αρτηριακή υπέρταση: Γενικές αρχές & αντιμετώπιση στη συστηματική σκληροδερμία

Αναστασία Ανθη

Α΄ Κλινική Εντατικής Θεραπείας & Ιατρείο Πνευμονικής Υπέρτασης
Γ.Ν.Α.«Ο ΕΥΑΓΓΕΛΙΣΜΟΣ»



Br J Pharmacol. 2020;1–25.



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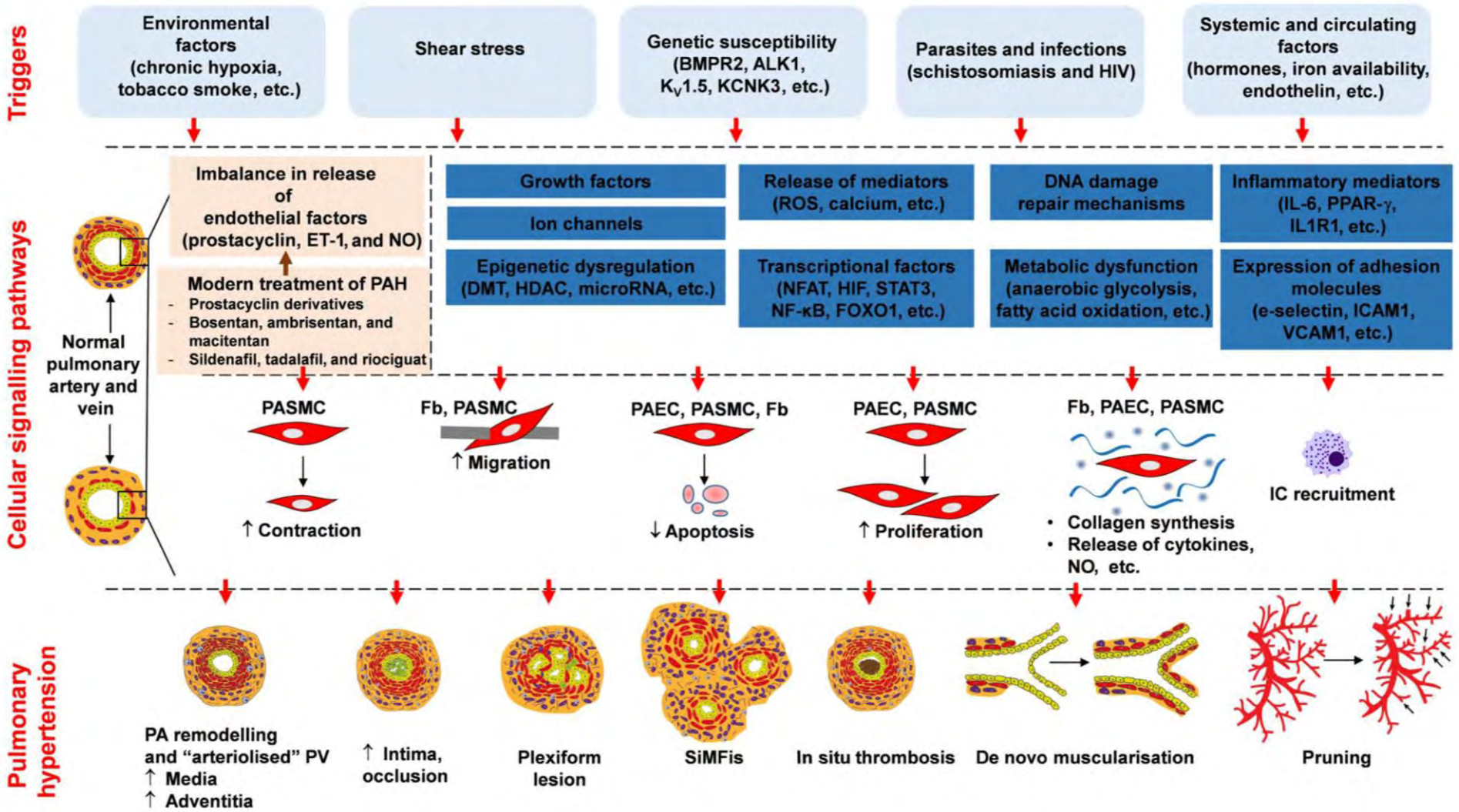
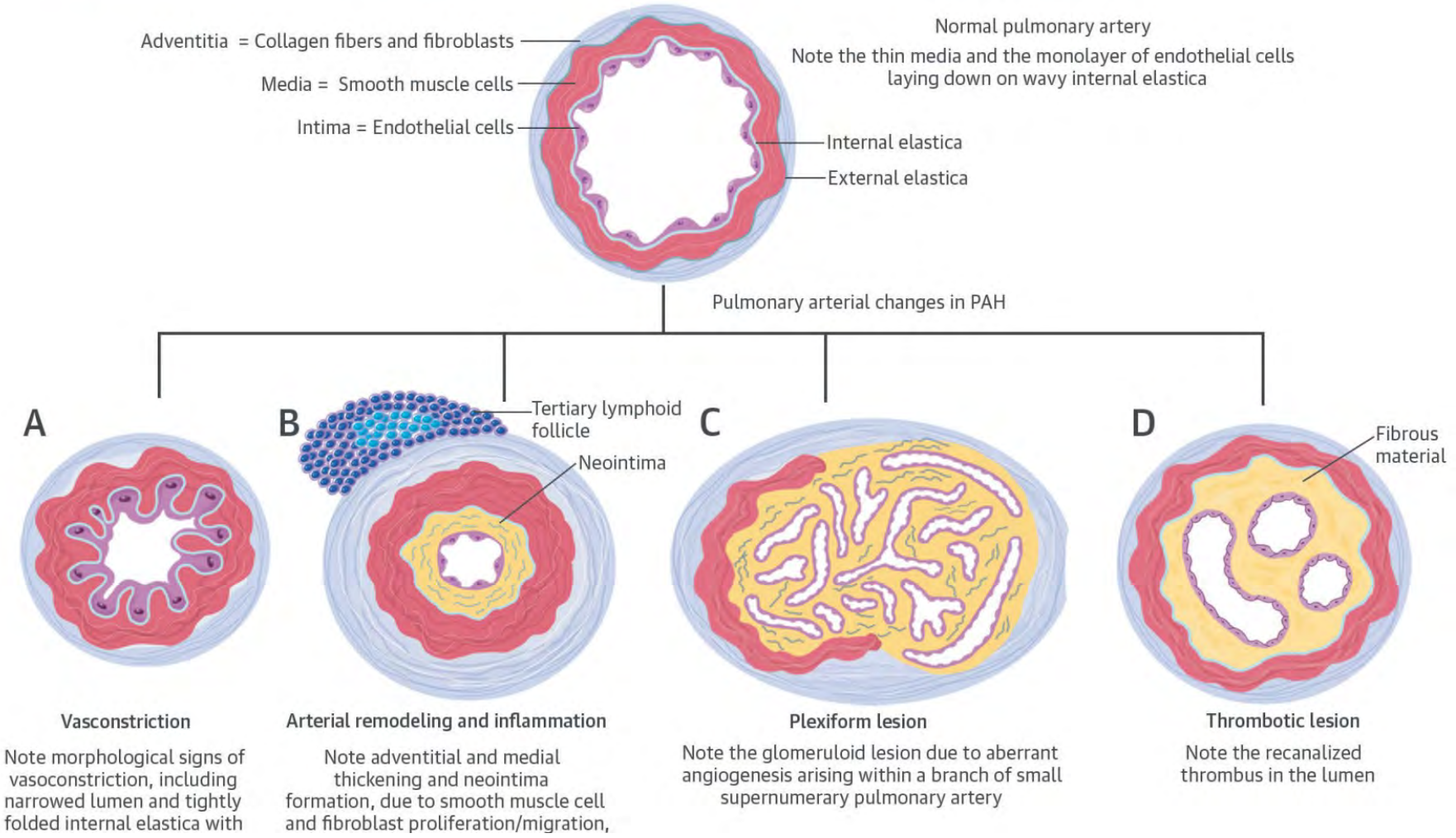


Br J Pharmacol. 2020;1–25.

FIGURE 1 **Pathobiology of PAH**



McLaughlin et al. JACC 2015;65:1976–97

Geneva, 1973:

1st world symposium on PH

Classification of PH

primary/ secondary PH

Classification of PH

primary/ secondary PH

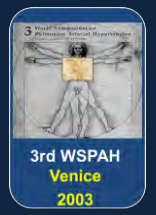
Geneva, 1973:

1st world symposium on PH

Evian, 1998:

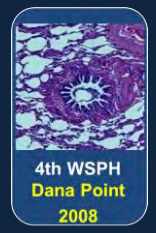
2nd world symposium on PH

5 groups



Venice, 2003:

3rd world symposium on PH »



Dana Point, 2008:

4th world symposium on PH »

Nice, 2013:

5th world symposium on PH »

Nice, 2018:

6th world symposium on PH »

Clinical classification of Pulmonary Hypertension (ESC/ERS guidelines 2015)

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

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1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

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)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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Categorization of multiple clinical conditions into 5 groups according to their similar:

- **clinical presentation**
- **pathological findings**
- **haemodynamic characteristics &**
- **treatment strategy**

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SSc-PAH

- **is a leading cause of PAH in the western world**
- **represents ≈ 15–30% of PAH in most registries**

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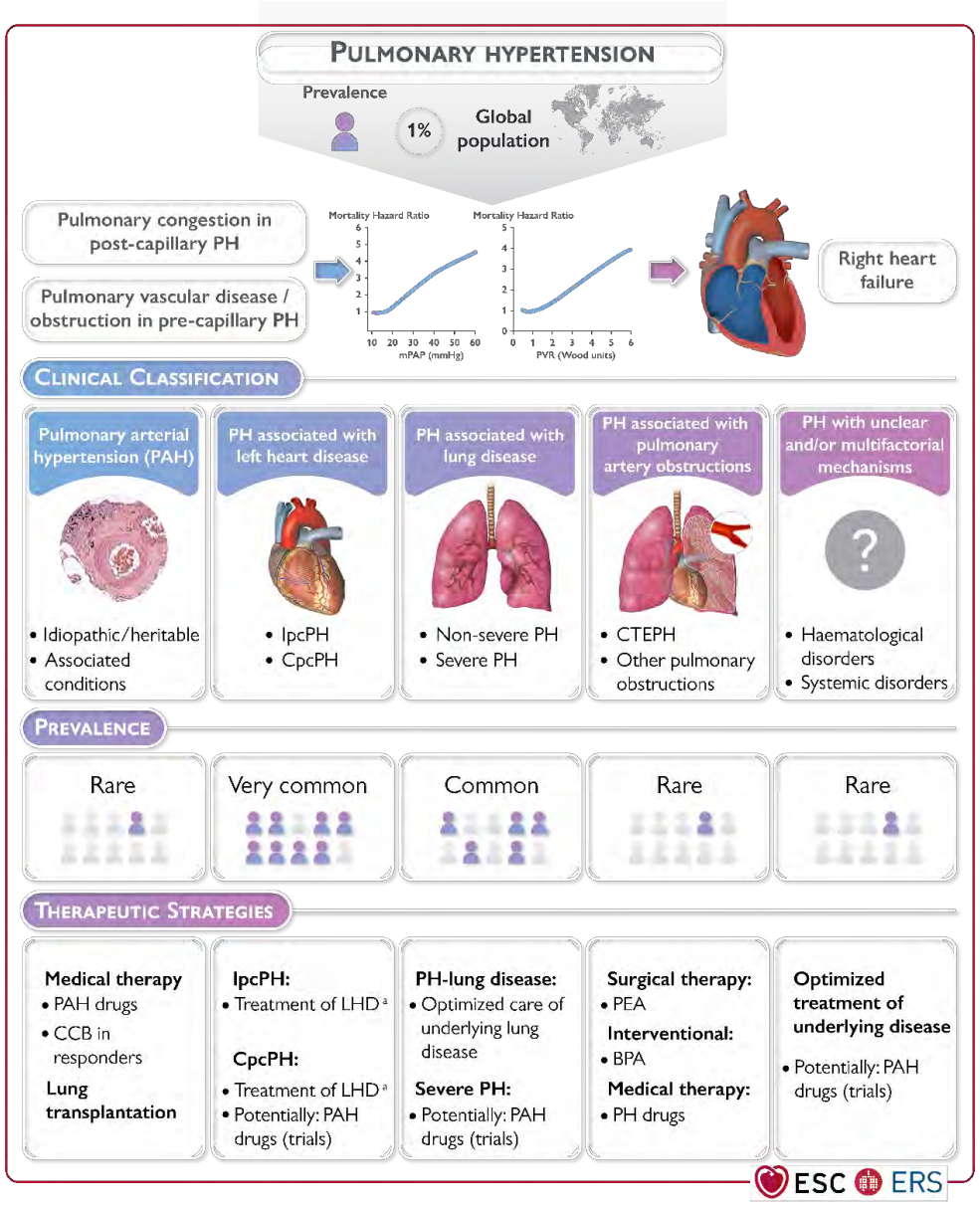
Figure 1

Central illustration



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Haemodynamic definition of Pulmonary Hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

PH guidelines 2015

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

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
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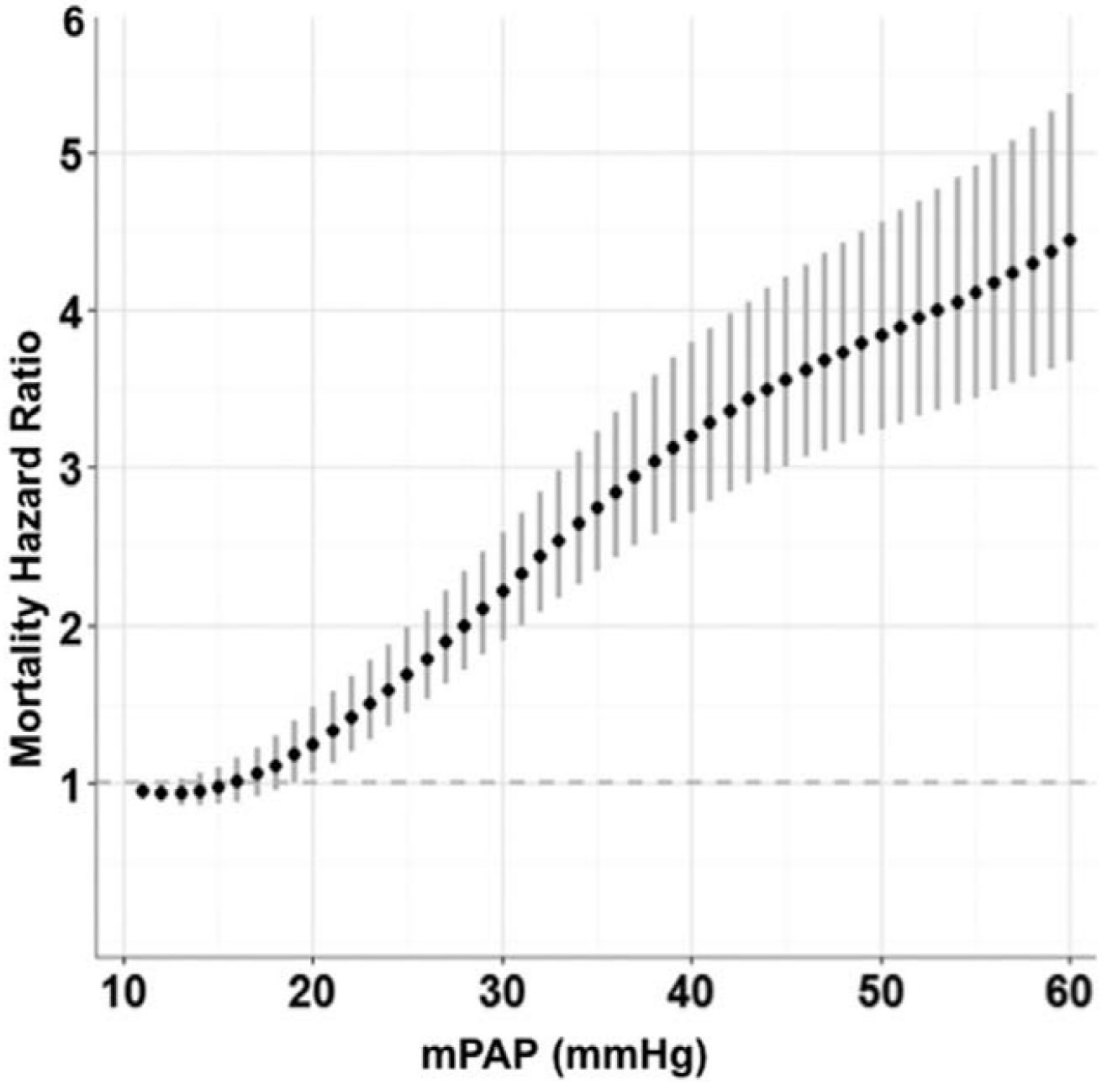
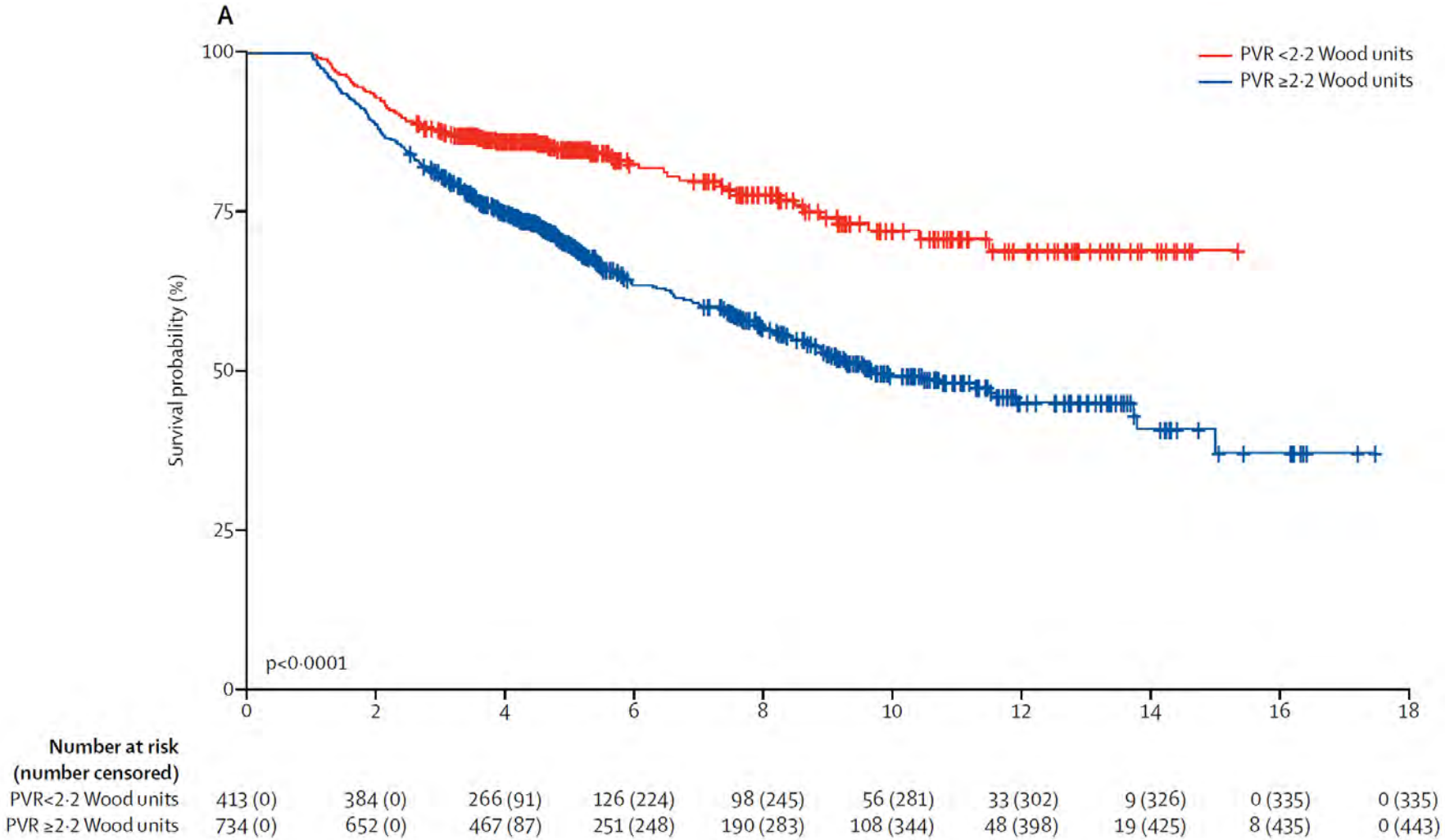
Borderline Pulmonary Hypertension Increases Mortality



borderline PH: mPAP 19- 24 mm Hg

Circulation. 2016;133:1240-1248

Probability of all-cause mortality according to PVR of ≥2·2 WU versus <2·2 WU in pts with mPAP ≥19 mm Hg & PAWP of ≤15 mm Hg



Maron BA et al. Lancet RM, July 2020

Kovacs and Olschewski *Arthritis Research & Therapy* (2015) 17:123
DOI 10.1186/s13075-015-0649-7

arthritis research&therapy

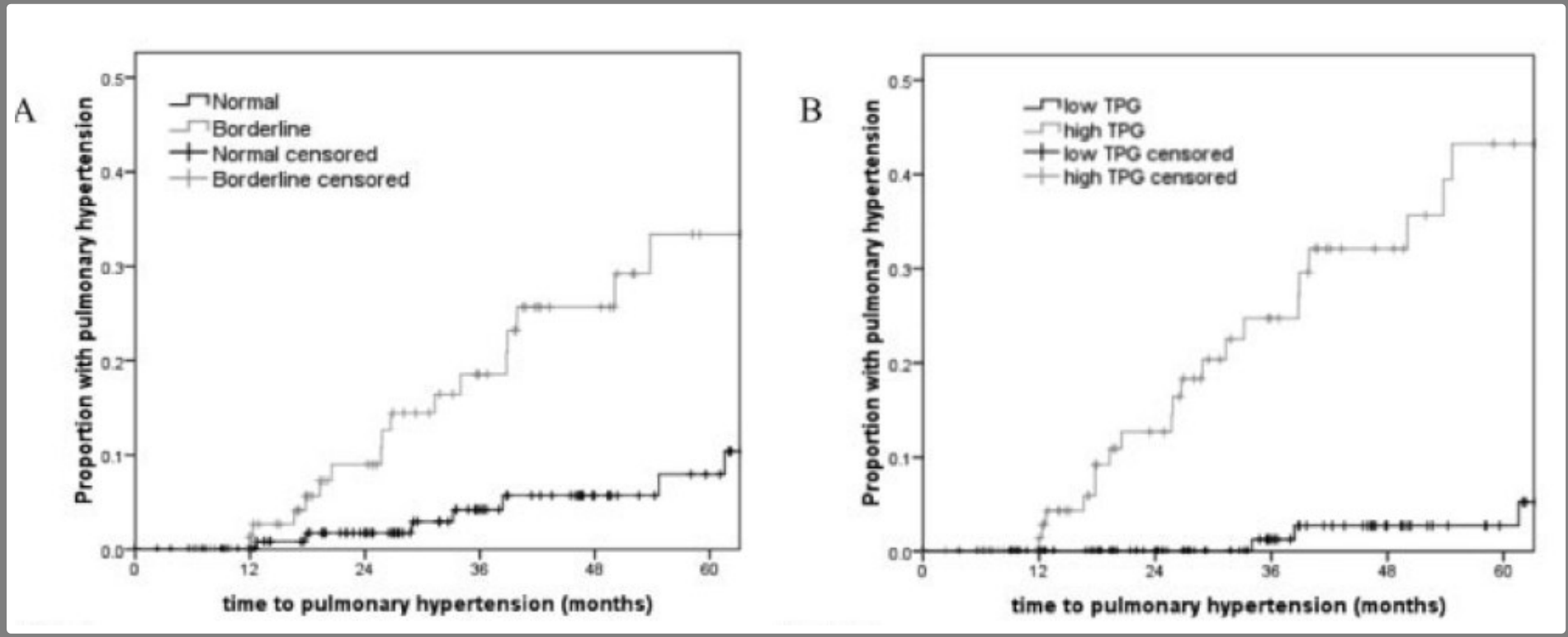
EDITORIAL Open Access

Borderline pulmonary pressures in scleroderma - a 'pre-pulmonary arterial hypertension' condition?

Gabor Kovacs[1,2*] and Horst Olschewski[1,2]

Borderline Mean Pulmonary Artery Pressure in Patients With Systemic Sclerosis

Transpulmonary Gradient Predicts Risk of Developing Pulmonary Hypertension



Valerio CJ et al. ARTHRITIS & RHEUMATISM 2013; 65(4): 1074-84

Borderline Mean Pulmonary Artery Pressure in Patients With Systemic Sclerosis

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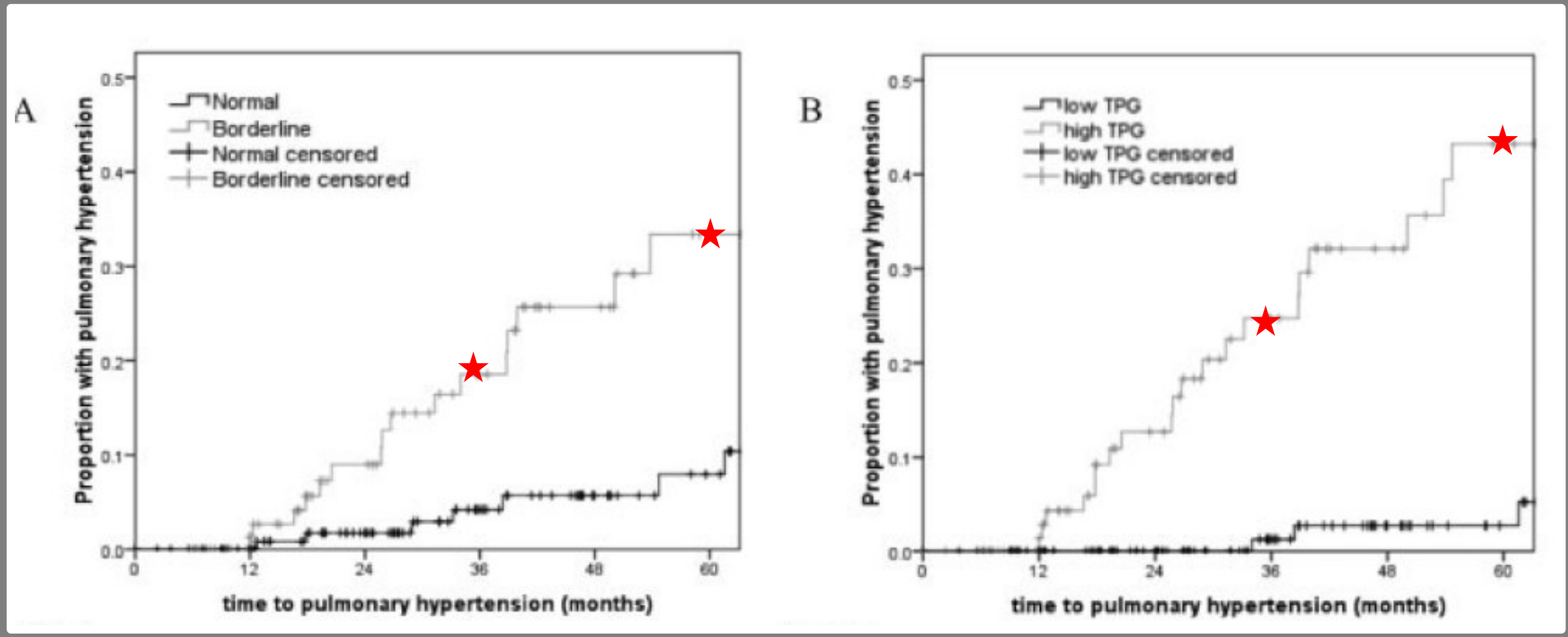


Valerio CJ et al. ARTHRITIS & RHEUMATISM 2013; 65(4): 1074-84

CASE: 1

Γυναίκα, 53 ετών (2014)

Παραπέμπεται για διερεύνηση δύσπνοιας κοπώσεως απο τριμήνου

<u>Ατομικό αναμνηστικό</u>

21 ετών : σ. Raynaud

31 ετών: σ. CREST

Calcinosis
Raynaud's phenomenon
Esophageal dysfunction
Sclerodactyly
Telangiectasias

CASE: 1

7/ 2014

WHO class	II	
Echocardiography		
TRV	2,7	m/s
NT-pro BNP	79	pg/ml
PFT's		
FVC	98	%
FEV1	93	%
TLC	93	%
DLCO	45	%

CASE: 1

Right Heart Catheterization

7/ 2014

RAP	2	mmHg
PAP	38/12/21	mmHg (S/D/M)
PAWP	7	mmHg
CO	4	l/min
CI	2,6	l/min/m^2
PVR	3,5	Wood Units
SvO2	74	%

CASE: 1

	7/ 2014	4/2017	
WHO class	II	III	
Echocardiography			
TRV	2,7	3,5	m/s
NT-pro BNP	79	3695	pg/ml
PFT's			
FVC	98	88	%
FEV1	93	78	%
TLC	93	91	%
DLCO	45	31	%

CASE: 1

Right Heart Catheterization

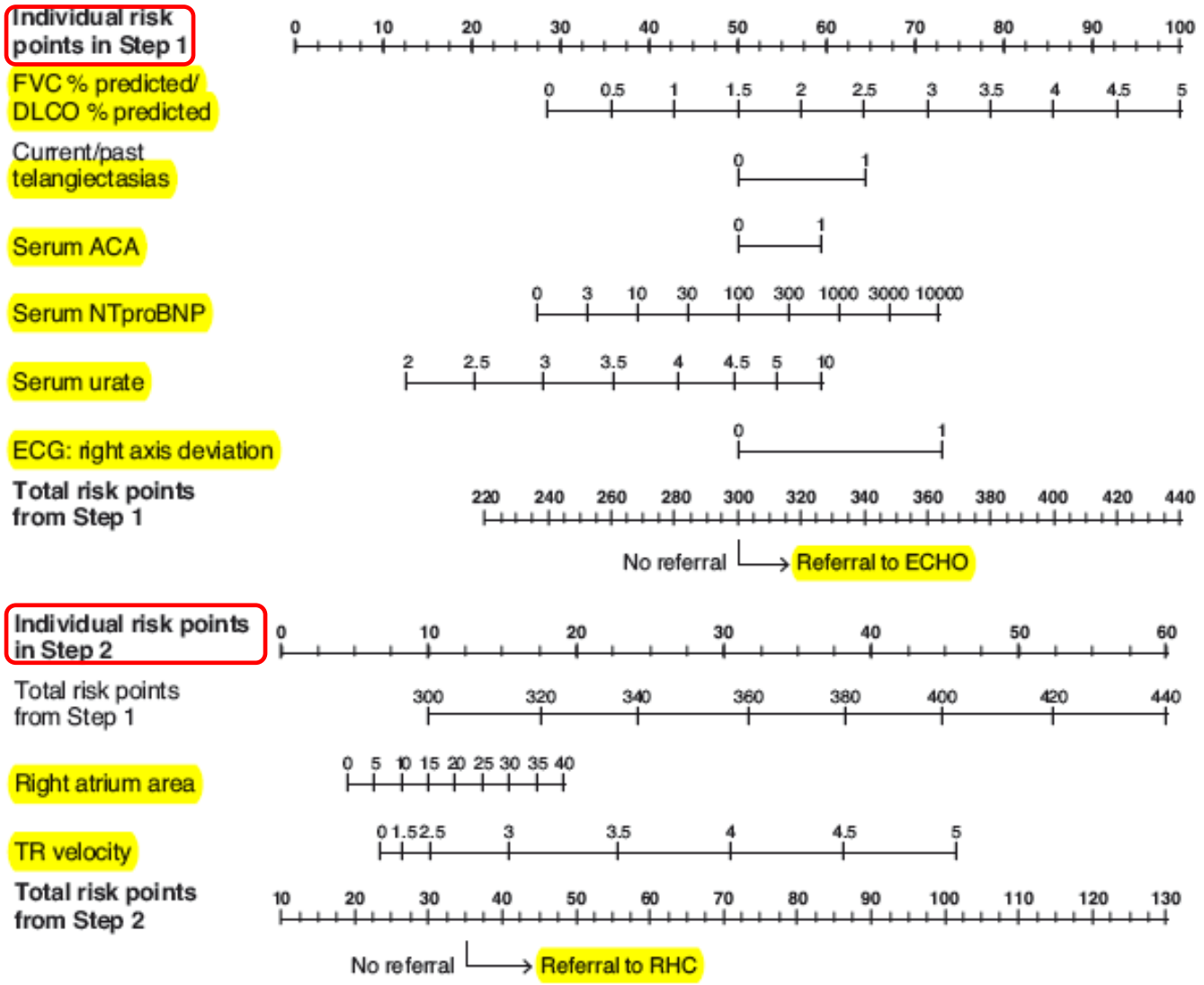
	7/ 2014	4/2017	
RAP	2	7	mmHg
PAP	38/12/21	65/31/42	mmHg (S/D/M)
PAWP	7	10	mmHg
CO	4	3,2	l/min
CI	2,6	2	l/min/m^2
PVR	3,5	10	Wood Units
SvO2	74	63	%

Recommendations for screening and improved detection of PAH and CTEPH (1)

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

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Figure 3. *Nomograms for practical application of the DETECT algorithm.*



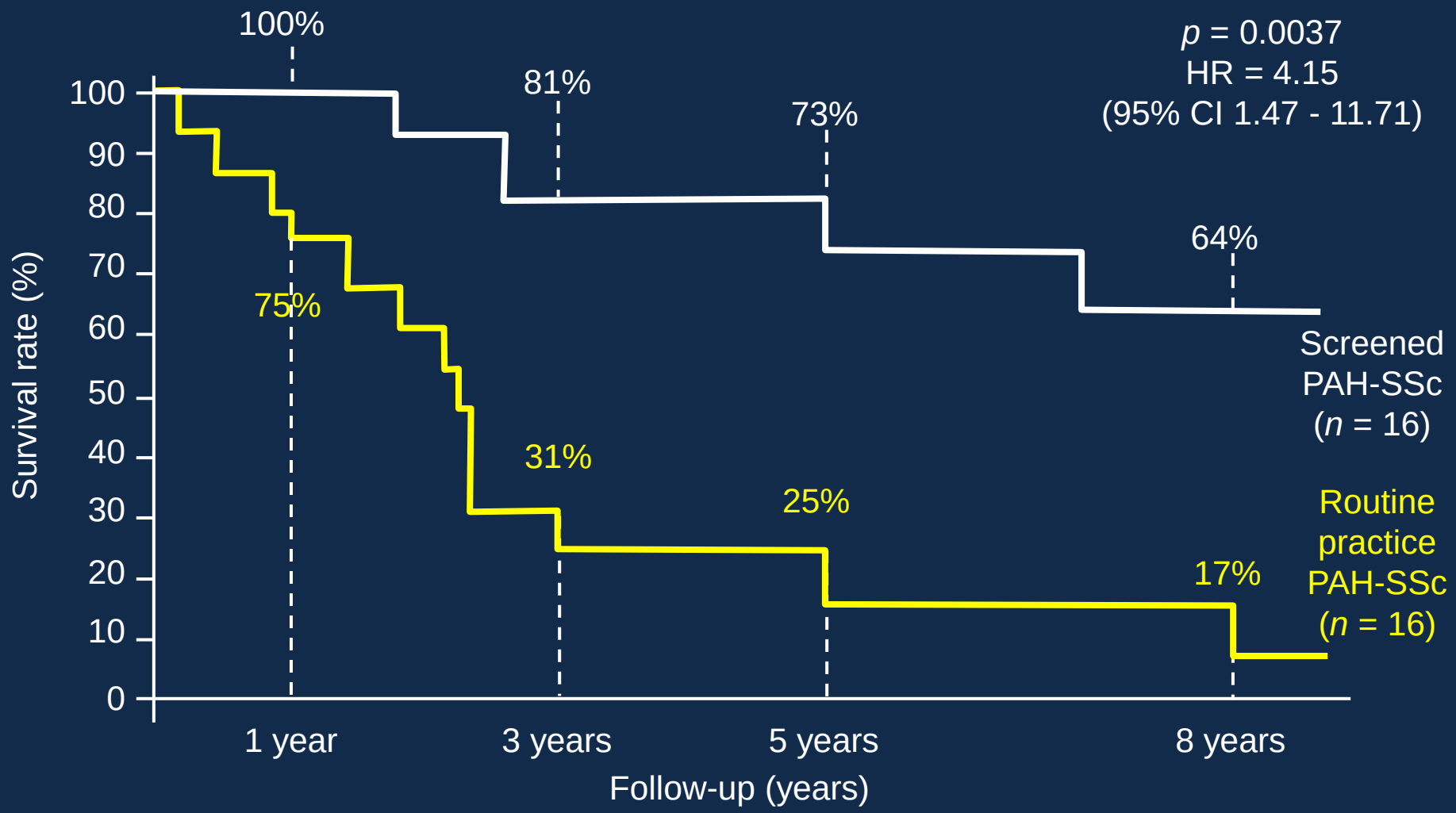
Coghlan JG, et al. Ann Rheum Dis 2013

Recommendations for screening and improved detection of PAH and CTEPH (2)

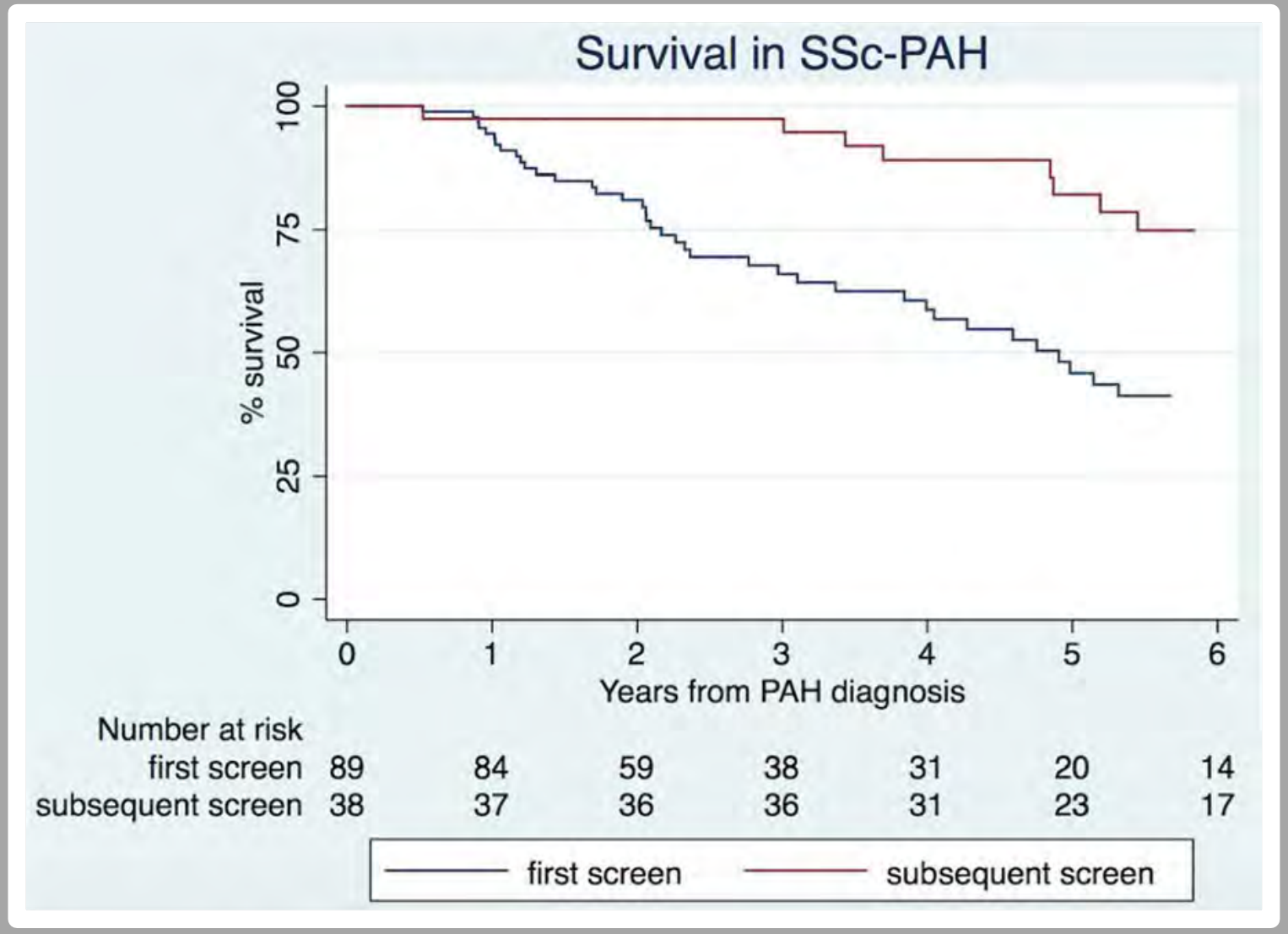
Recommendations	Class	Level
Systemic sclerosis (continued)		
Assessing the risk of having PAH, based on an evaluation of breathlessness, in combination with echocardiogram or PFTs and BNP/NT-proBNP, should be considered in patients with SSc	IIa	B
Policies to evaluate the risk of having PAH should be considered in hospitals managing patients with SSc	IIa	C
In symptomatic patients with SSc, exercise echocardiography or CPET, or CMR may be considered to aid decisions to perform RHC	IIb	C
In patients with CTD with overlap features of SSc, an annual evaluation of the risk of PAH may be considered	IIb	C

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Screening improves long-term outcomes in SSc patients



Humbert M, *et al. Arthritis Rheum* 2011; 63:3522-30.



Morrisroe et al. Arthritis Research & Therapy (2017) 19:42

The ‘great wait’ for diagnosis in pulmonary arterial hypertension (EDITORIAL)

Respirology 2020; 25: 790–792

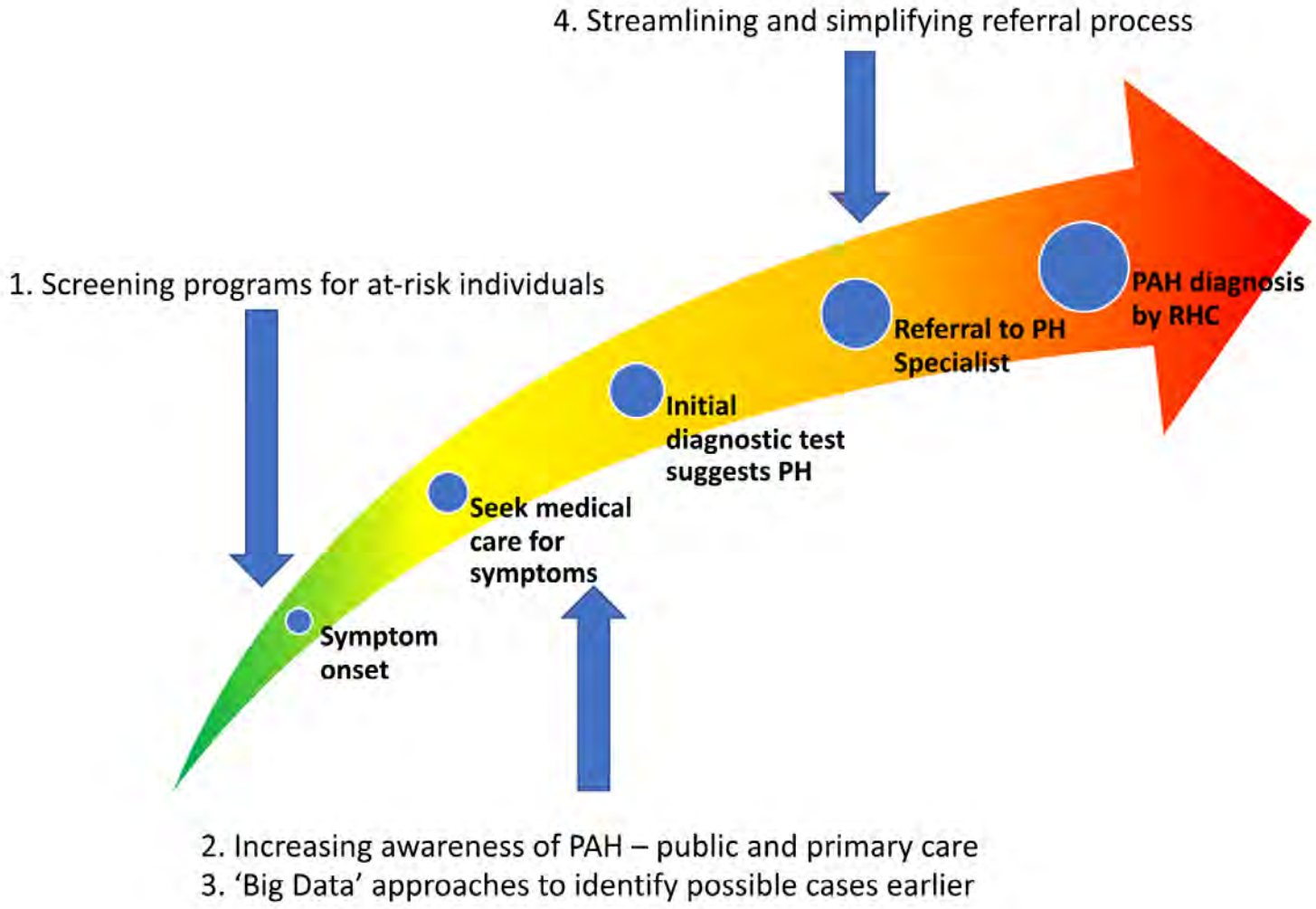


Figure 2

Symptoms in patients with pulmonary hypertension

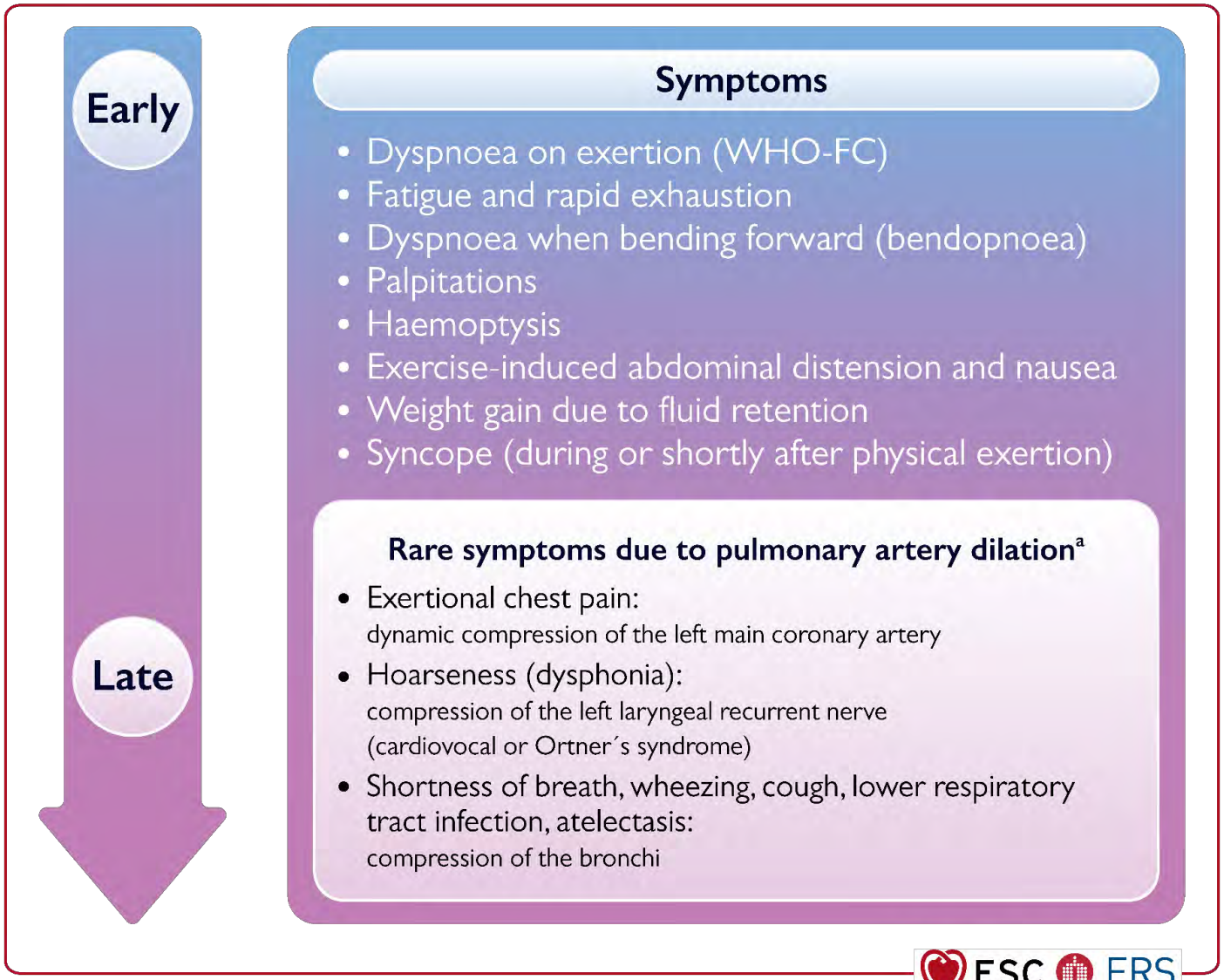


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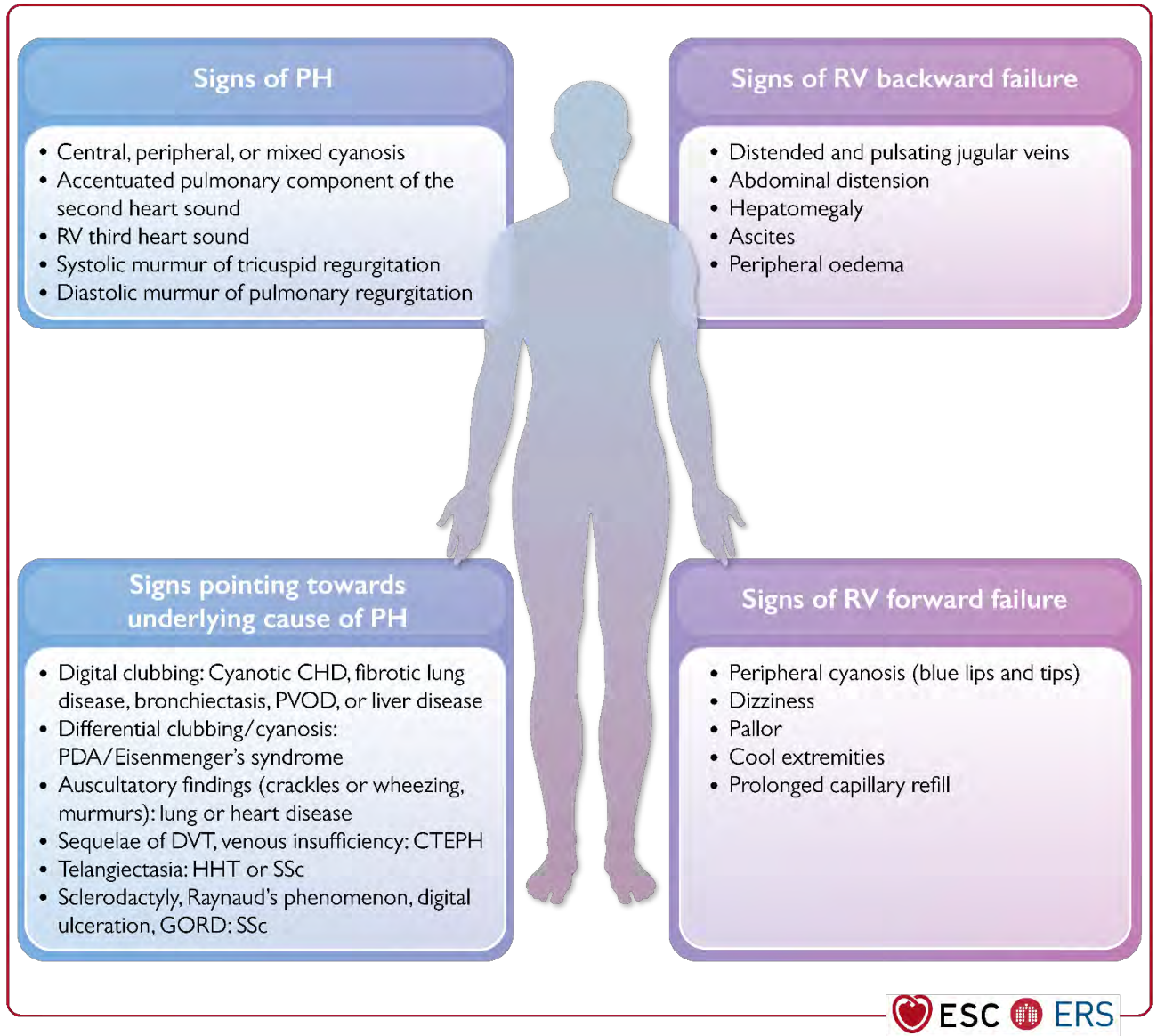
Figure 3

Clinical signs in patients with pulmonary hypertension



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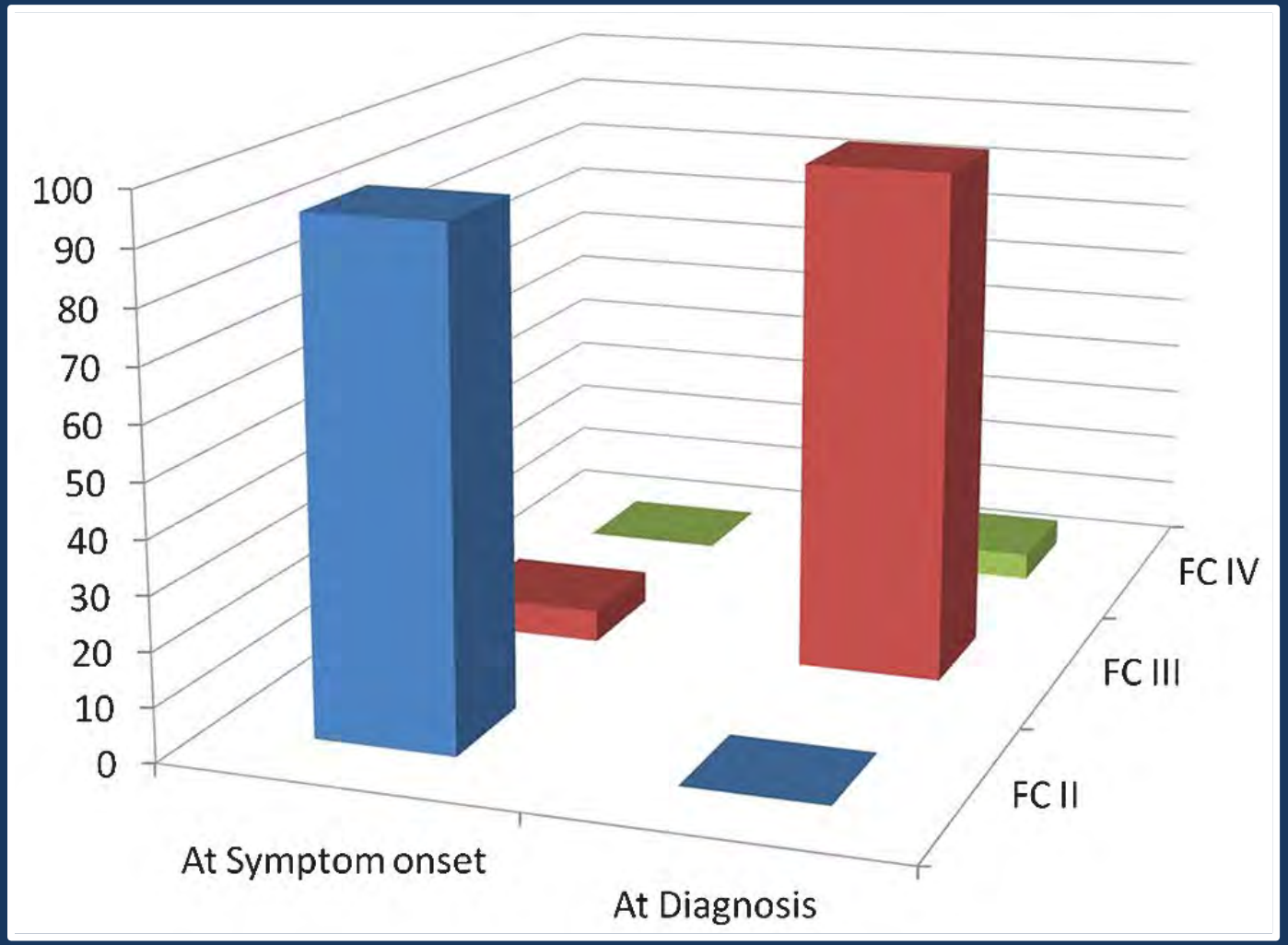
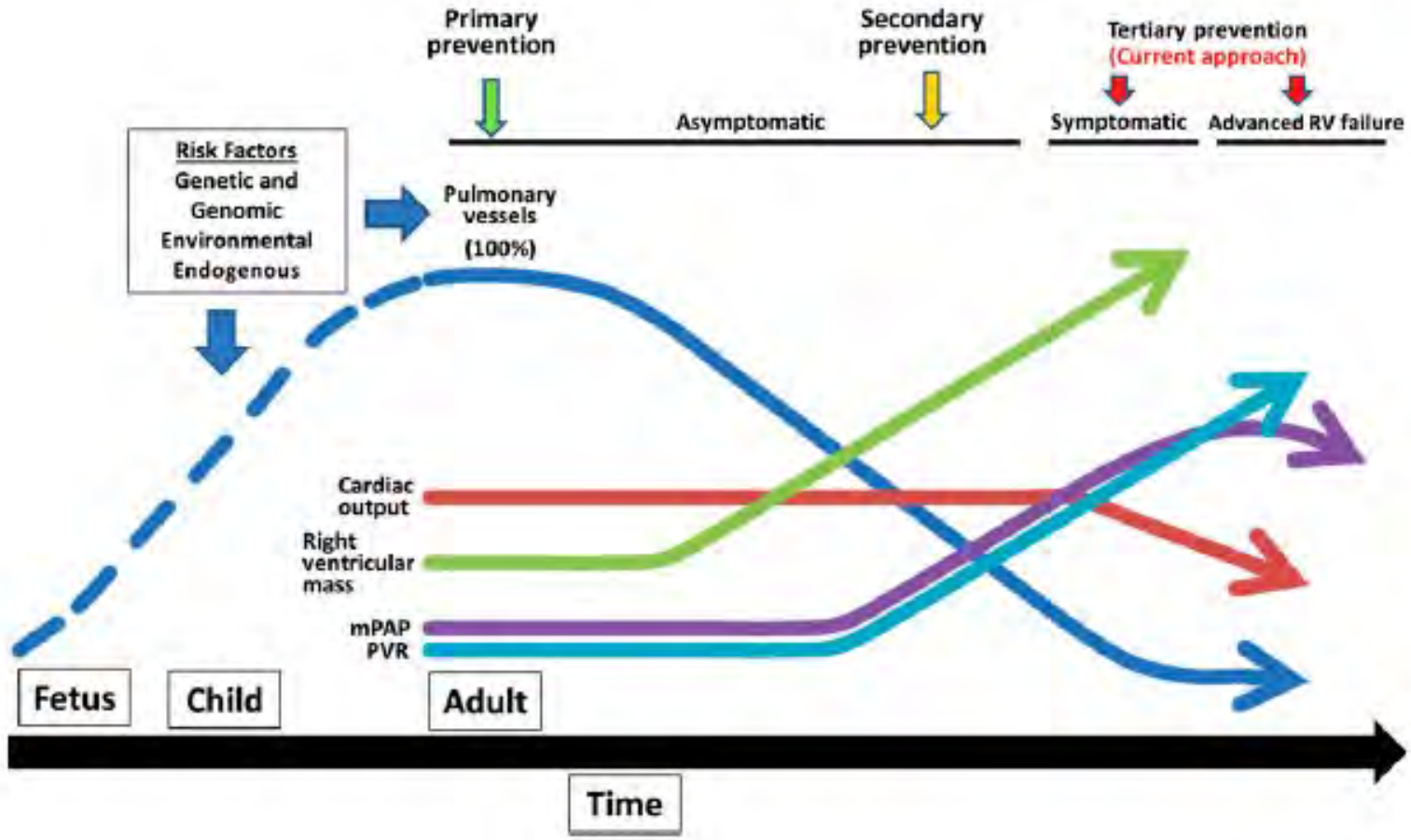


Strange et al.: Pulmonary Circulation, January-March 2013

State of the Science in PAH



Ann Am Thorac Soc Vol 11, Supplement 3, pp S178–S185, Apr 2014

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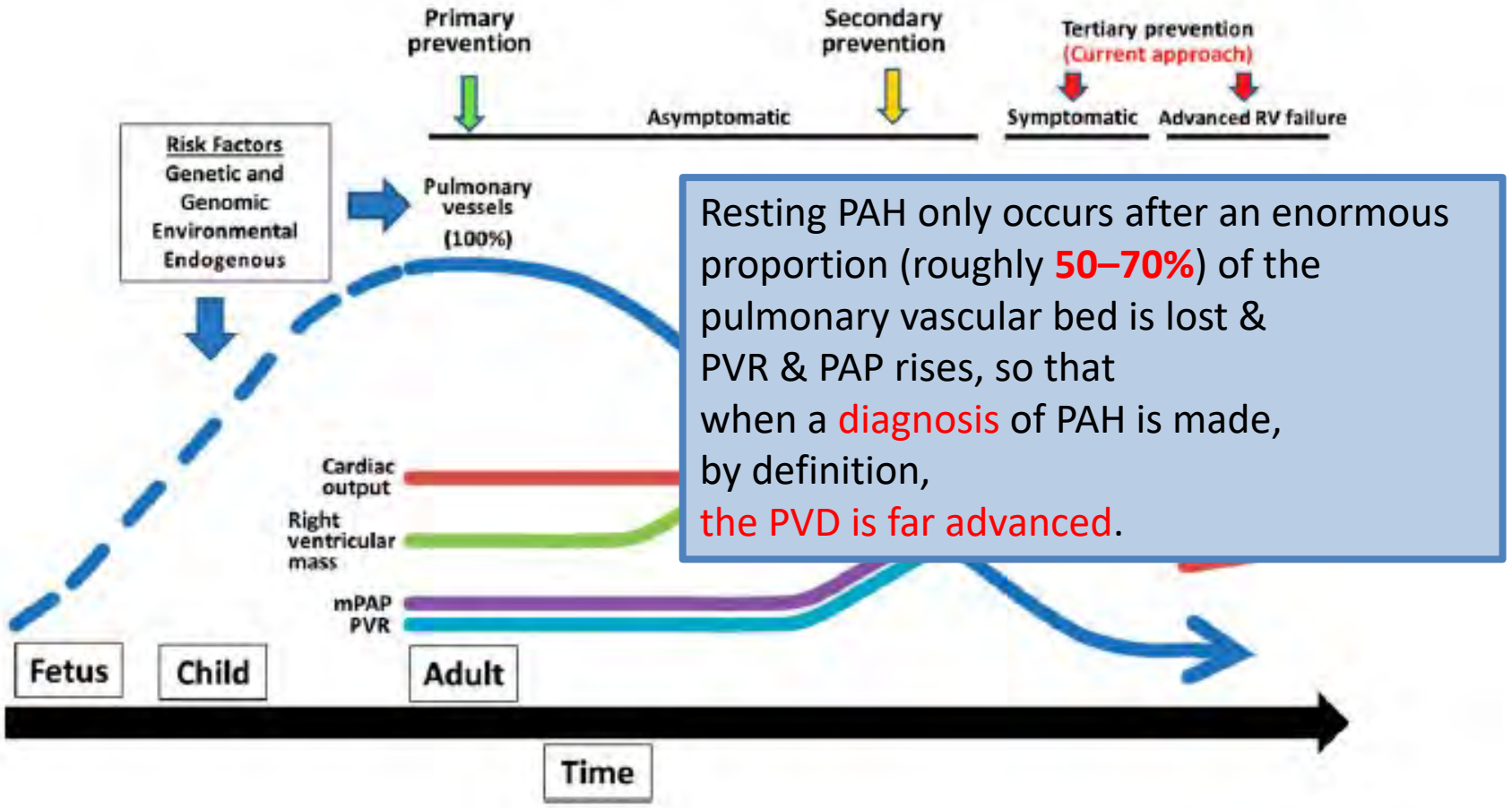
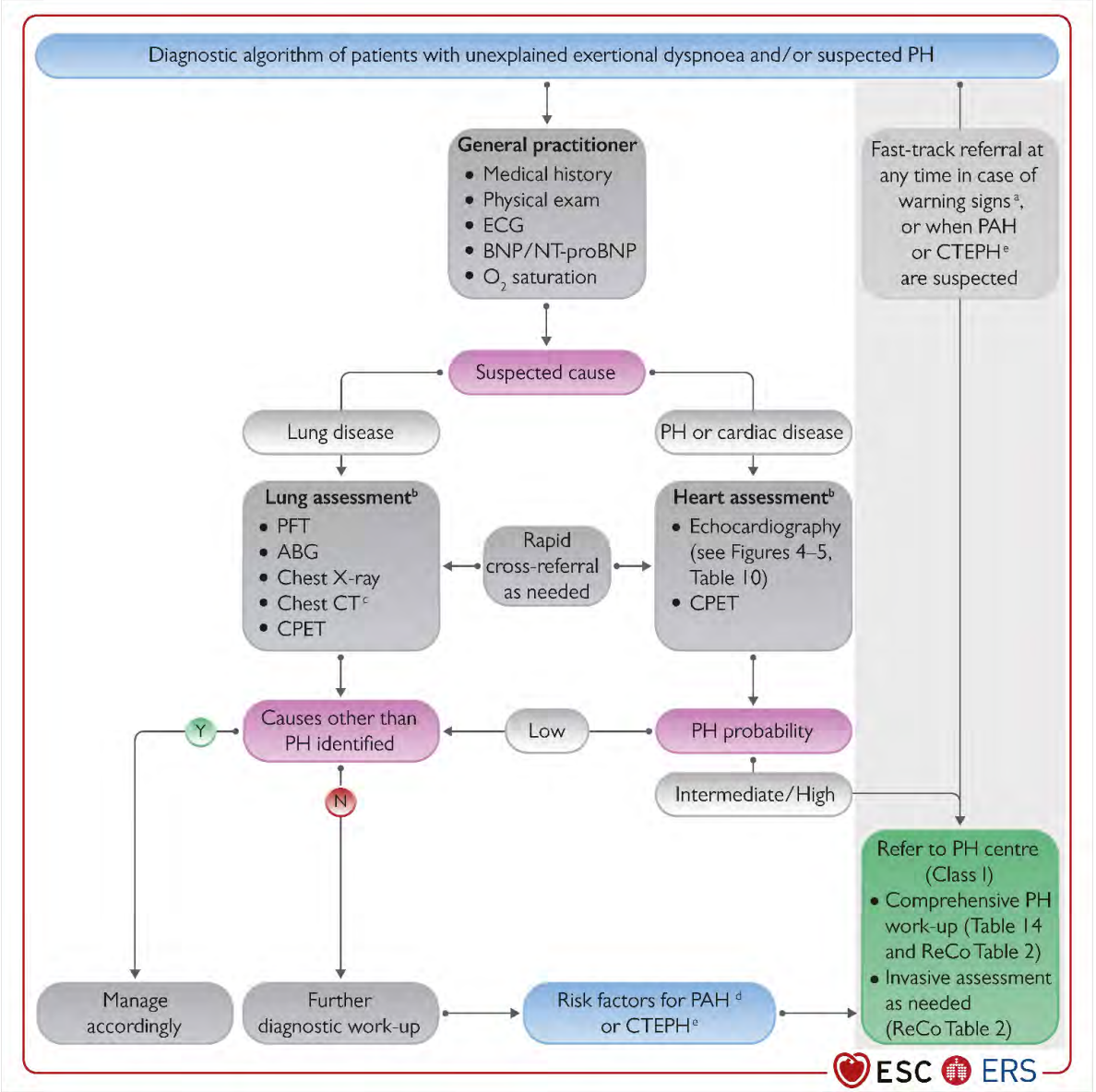


Resting PAH only occurs after an enormous proportion (roughly **50–70%**) of the pulmonary vascular bed is lost & PVR & PAP rises, so that when a diagnosis of PAH is made, by definition, the PVD is far advanced.

Ann Am Thorac Soc Vol 11, Supplement 3, pp S178–S185, Apr 2014

Figure 6

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



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Figure 6

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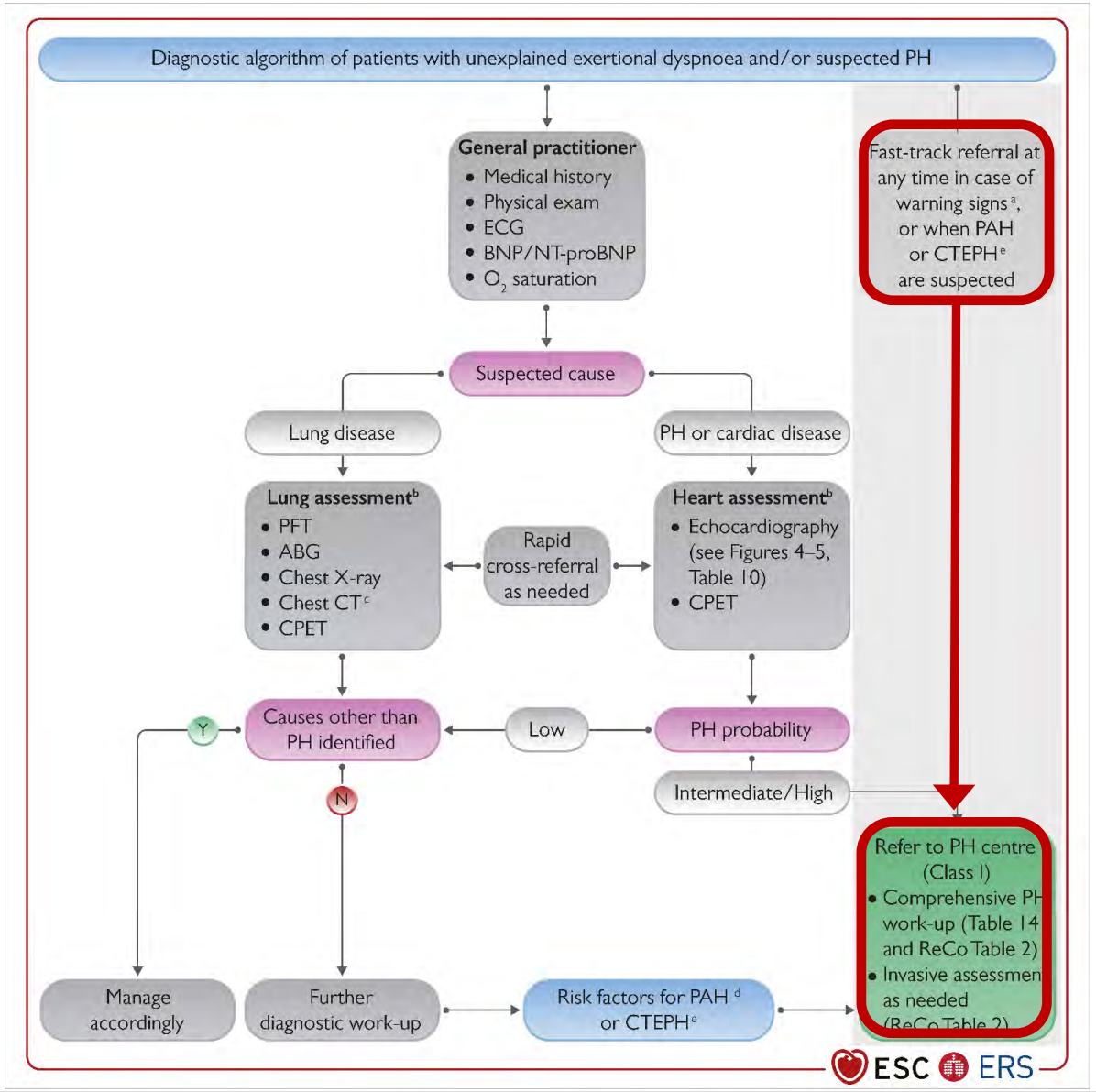

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
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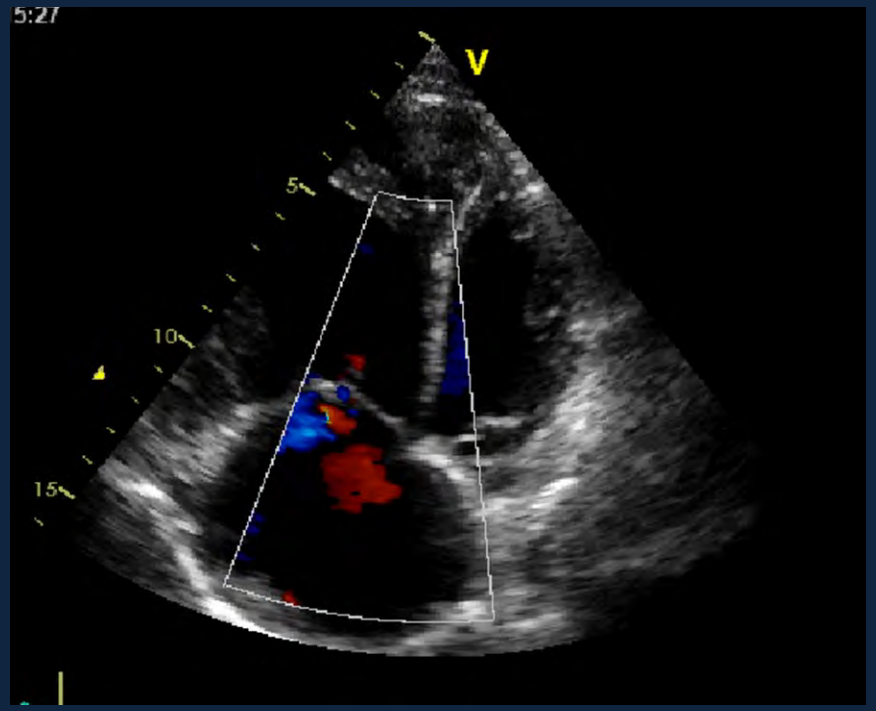
CASE: 2

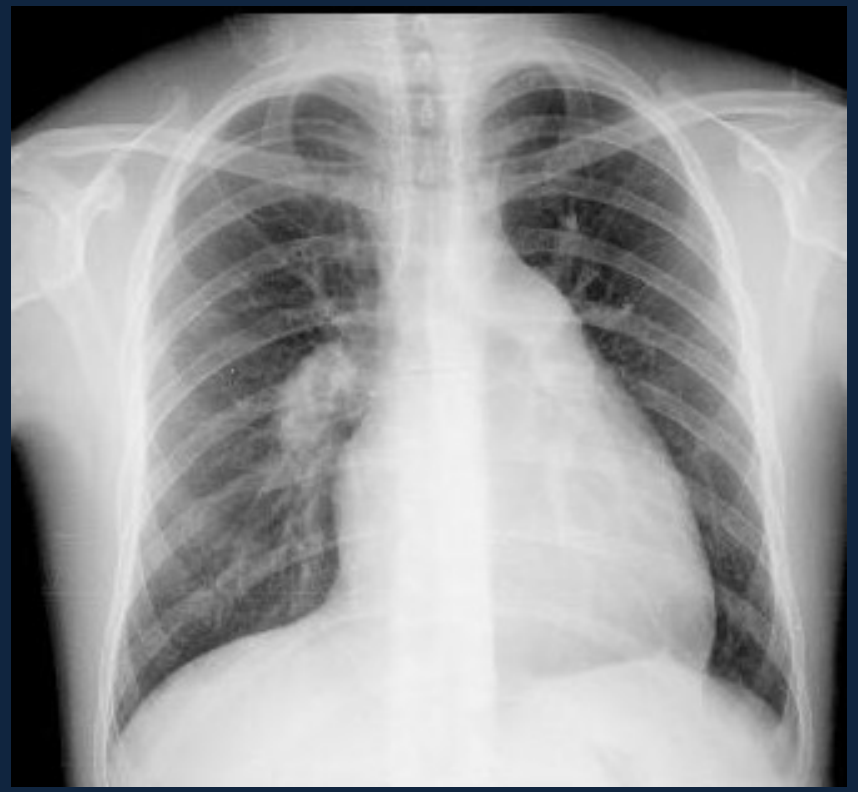
- άνδρας, 21 ετών
- δύσπνοια κοπώσεως
- συγκοπτικό επεισόδιο



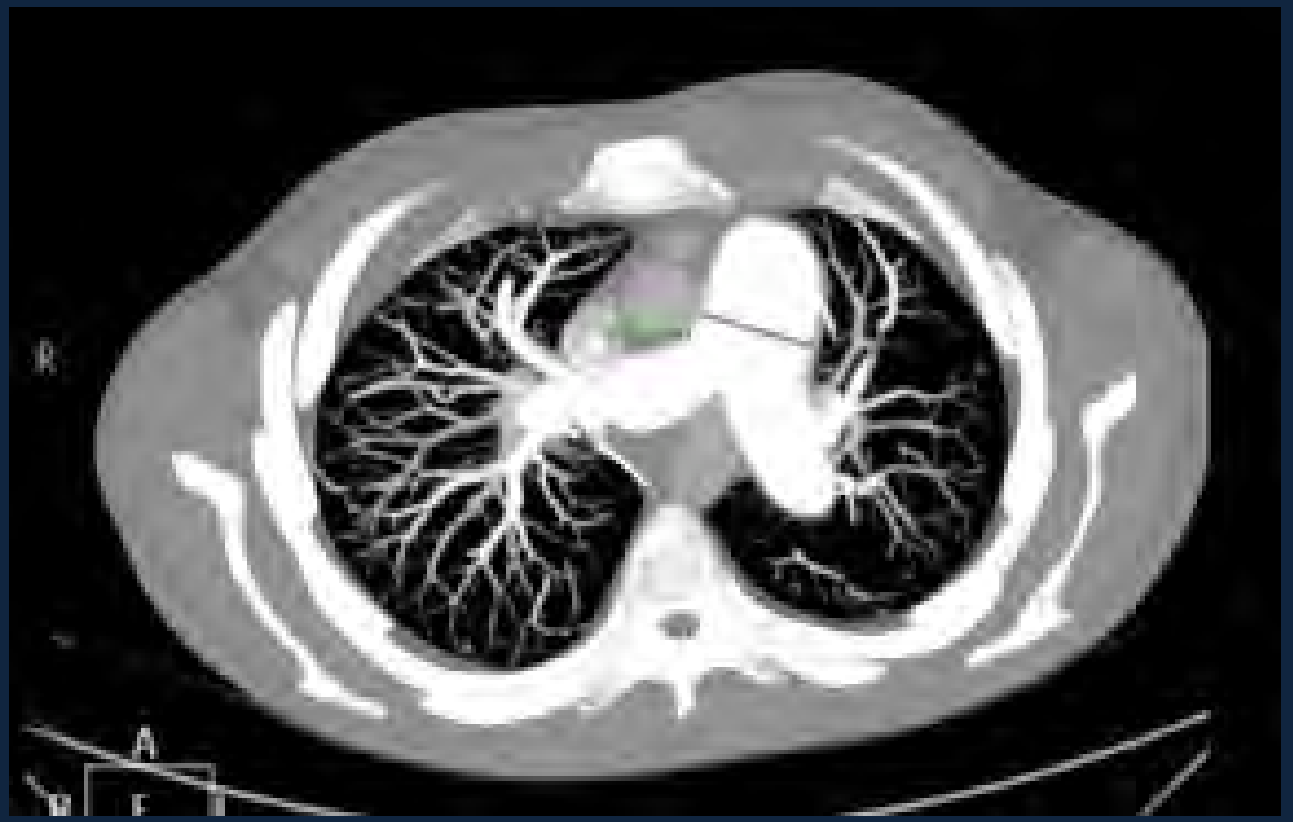
TVR= 4,8 m/sec
eSPAP= 110 mmHg

CASE: 2

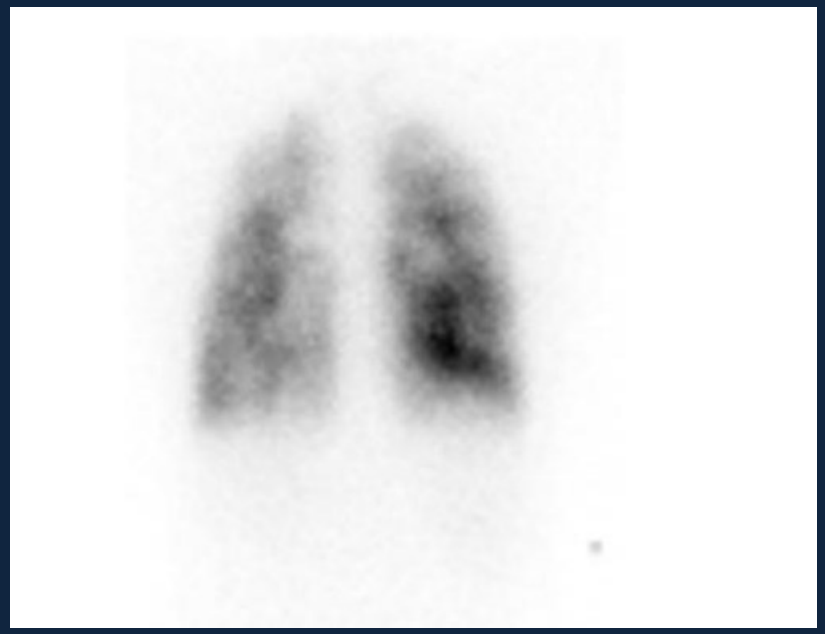
- άνδρας, 21 ετών
- δύσπνοια κοπώσεως
- συγκοπτικό επεισόδιο



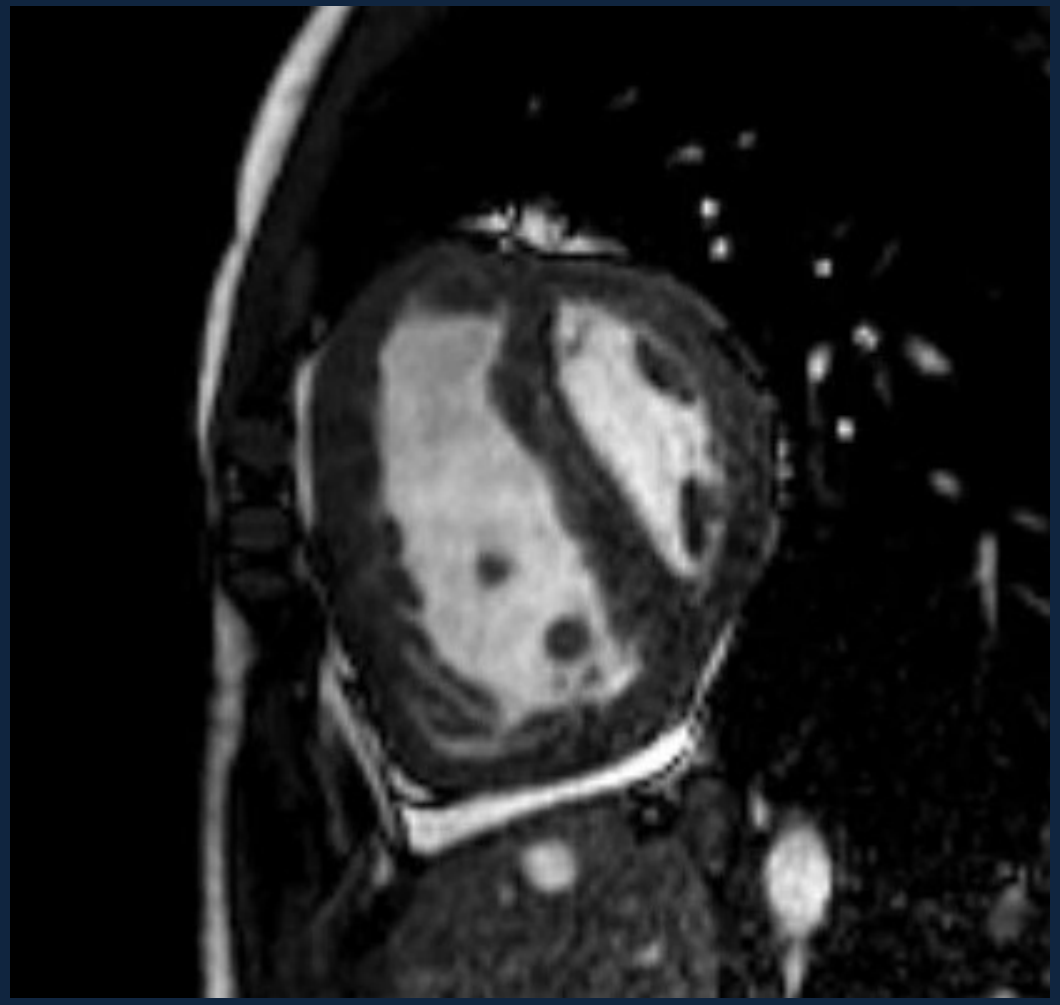
CASE: 2



CASE: 2



CASE: 2



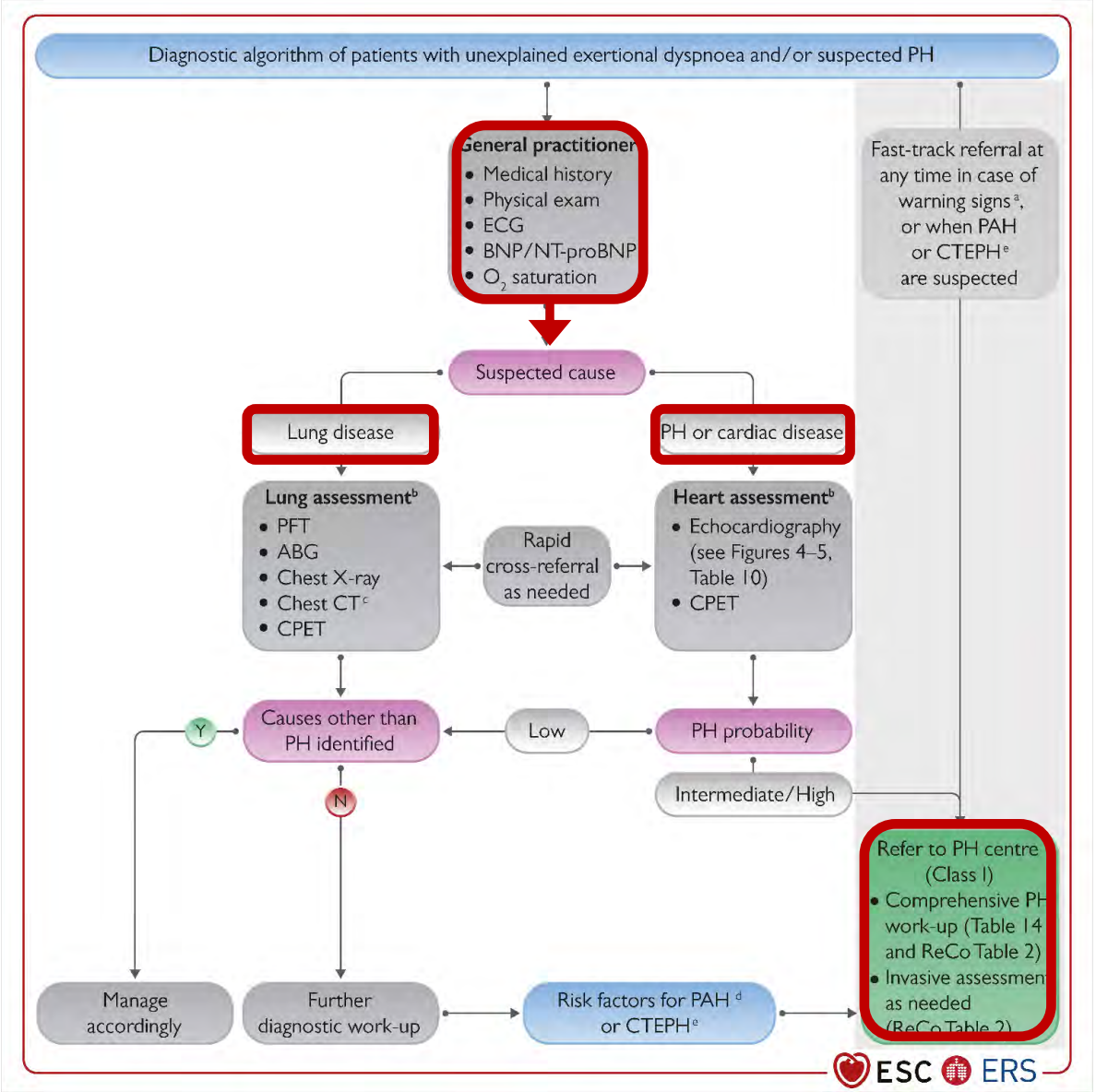
CASE: 2

Right Heart Catheterization

RAP	7	mmHg
PAP	140/79/100	mmHg (S/D/M)
PAWP	12	mmHg
CO	3,5	l/min
CI	2	$l/min/m^2$
PVR	25	Wood Units
SvO2	61	%

Figure 6

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



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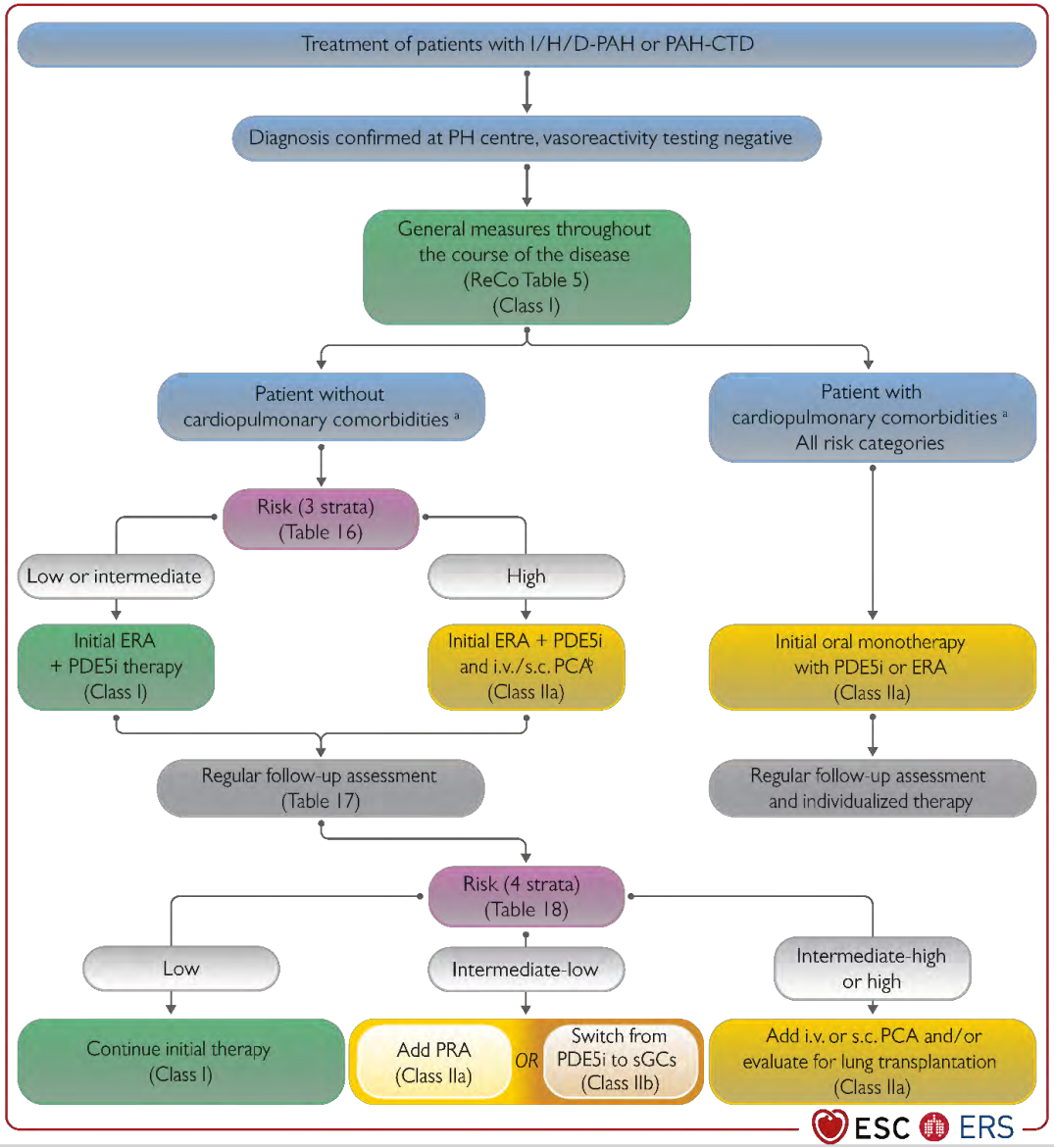
- PAH-CTD is the 2nd most prevalent type of PAH in western countries
- Systemic sclerosis represents the main cause of PAH-CTD

- The prevalence of pre-capillary PH in pts with SSc is 5–19% (ILD, PAH, PVOD)
- Group 2 PH-LHD is also common due to myocardial SSc involvement

- *It is essential to determine <u>which mechanism is operative in a given patient</u>*

Figure 9

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



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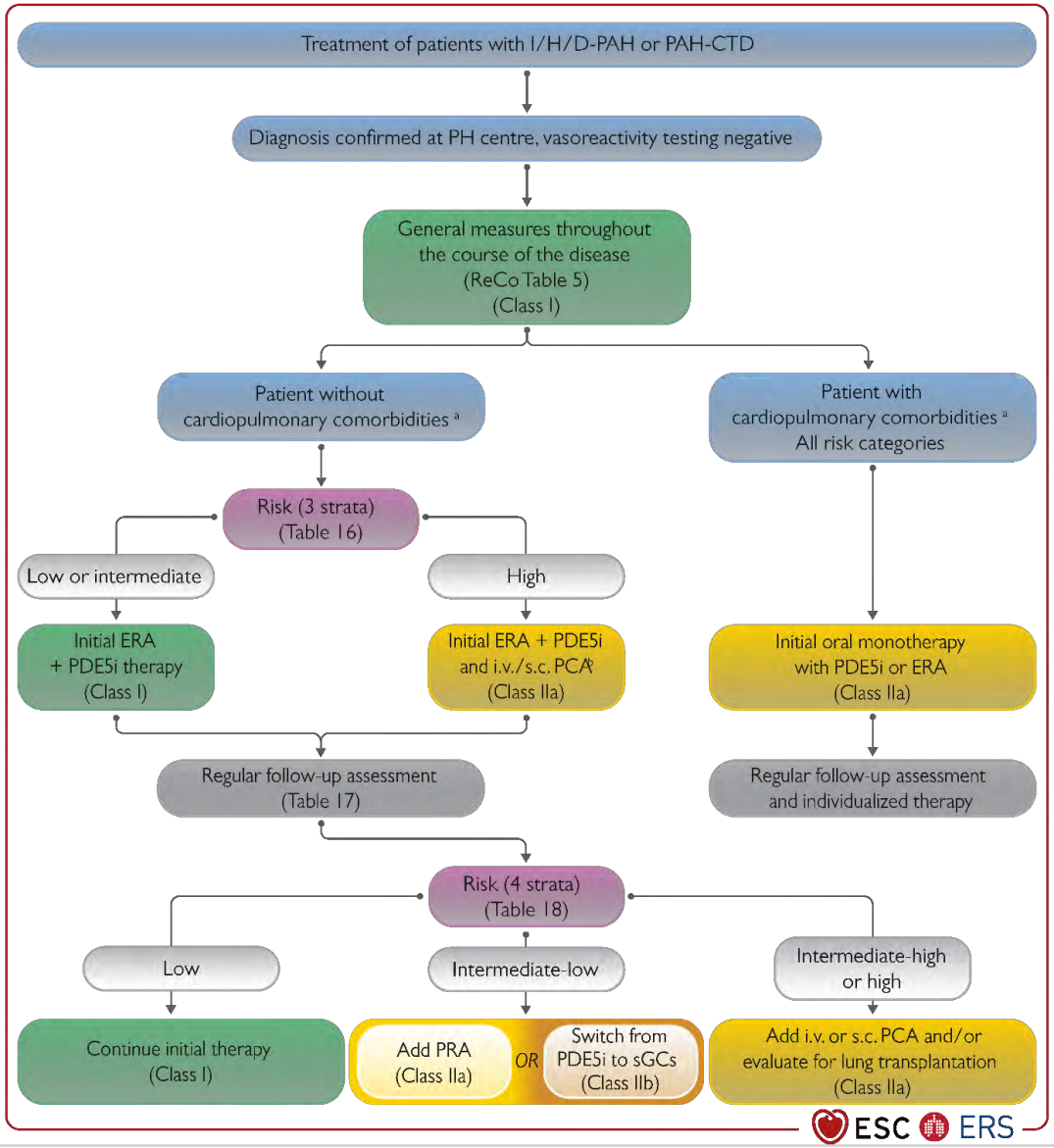

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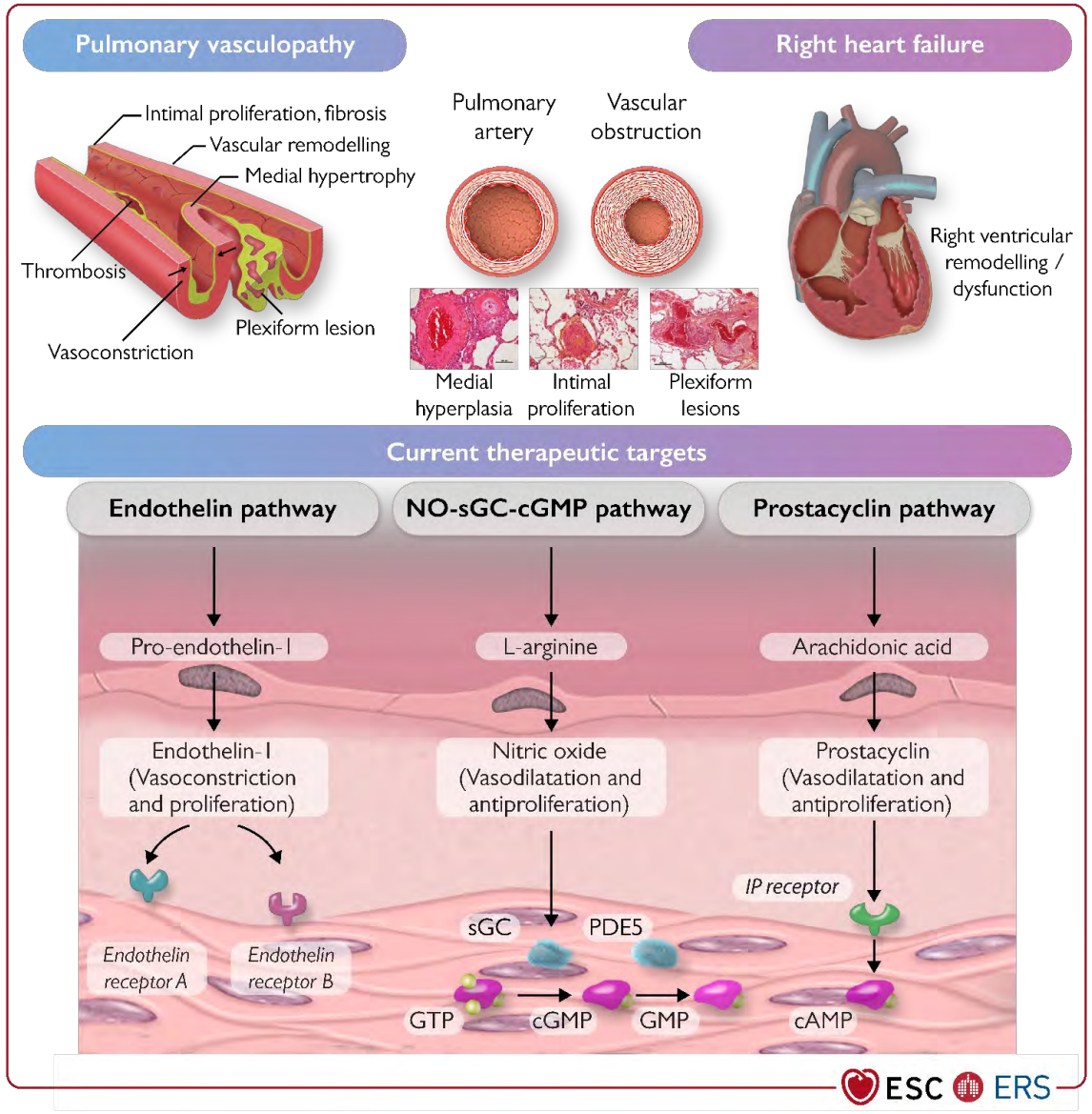
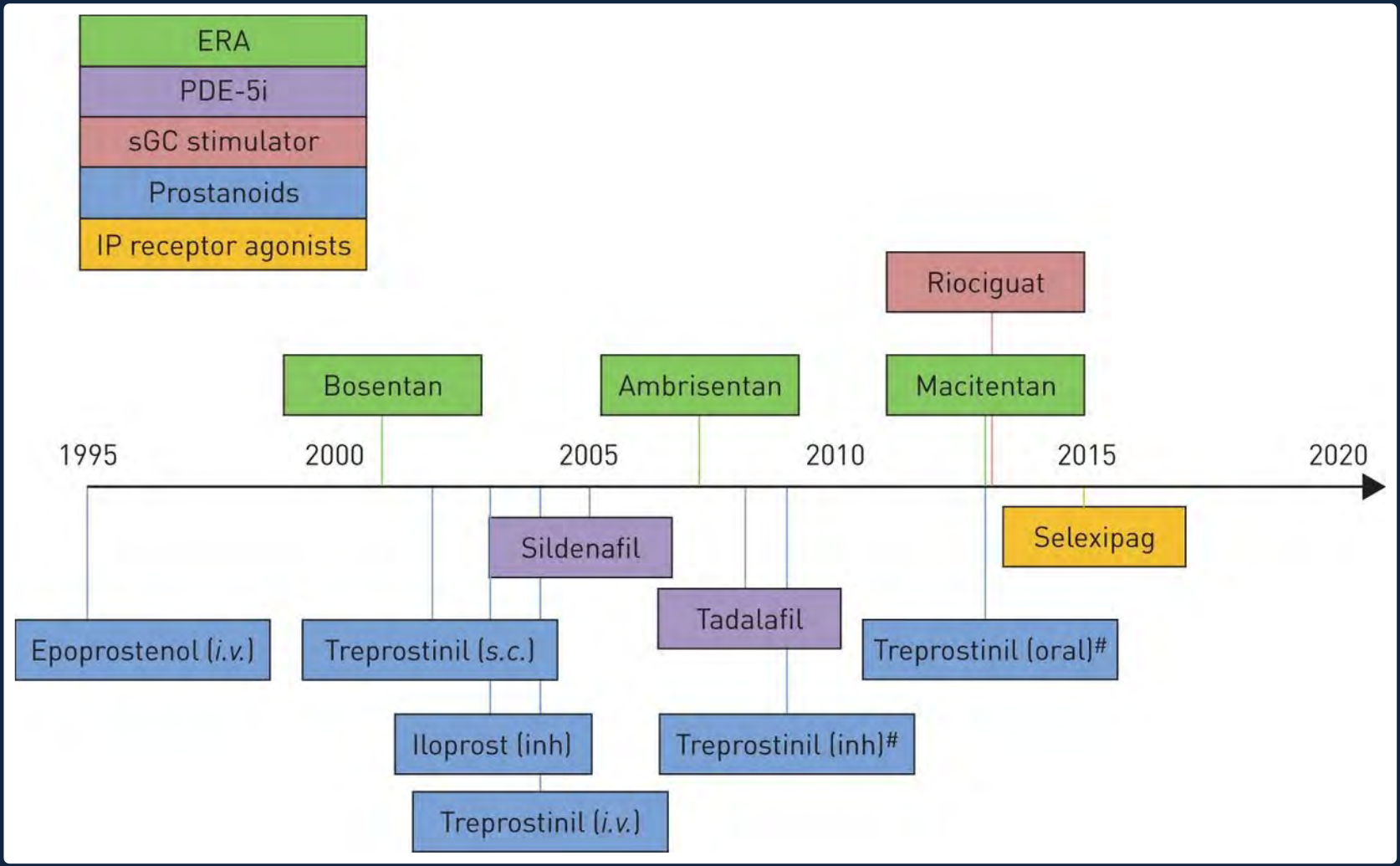
Figure 7

Pathophysiology and current therapeutic targets of pulmonary arterial hypertension (group 1)



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Timeline of approval of therapies for pulmonary arterial hypertension



Sean Gaine & Vallerie McLaughlin Eur Respir Rev 2017

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

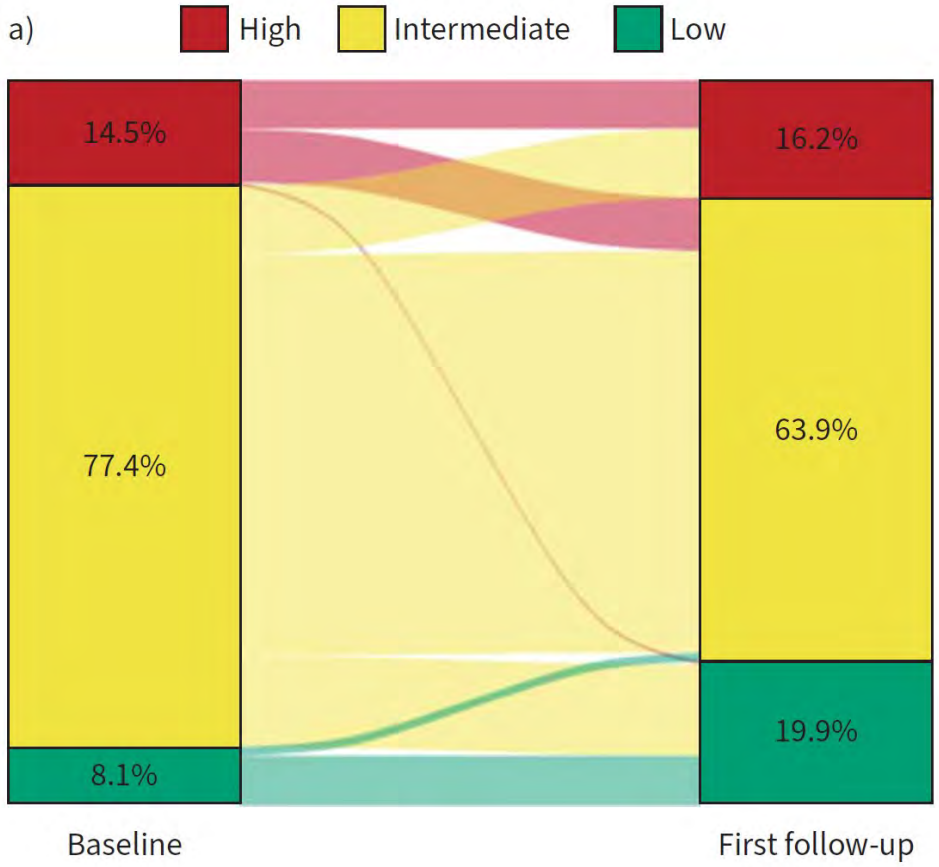
Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	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%

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

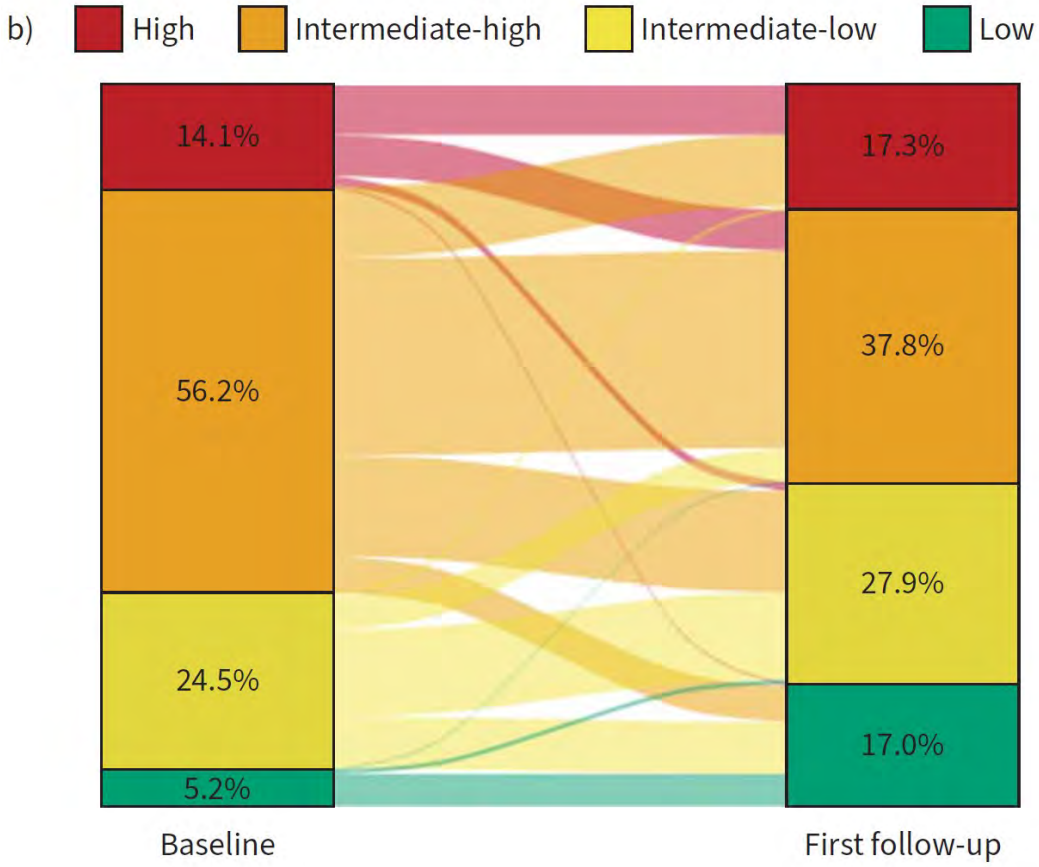
Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.
Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.
[a]WHO-FC I and II are assigned 1 point as both are associated with good long-term survival.

three-stratum risk model



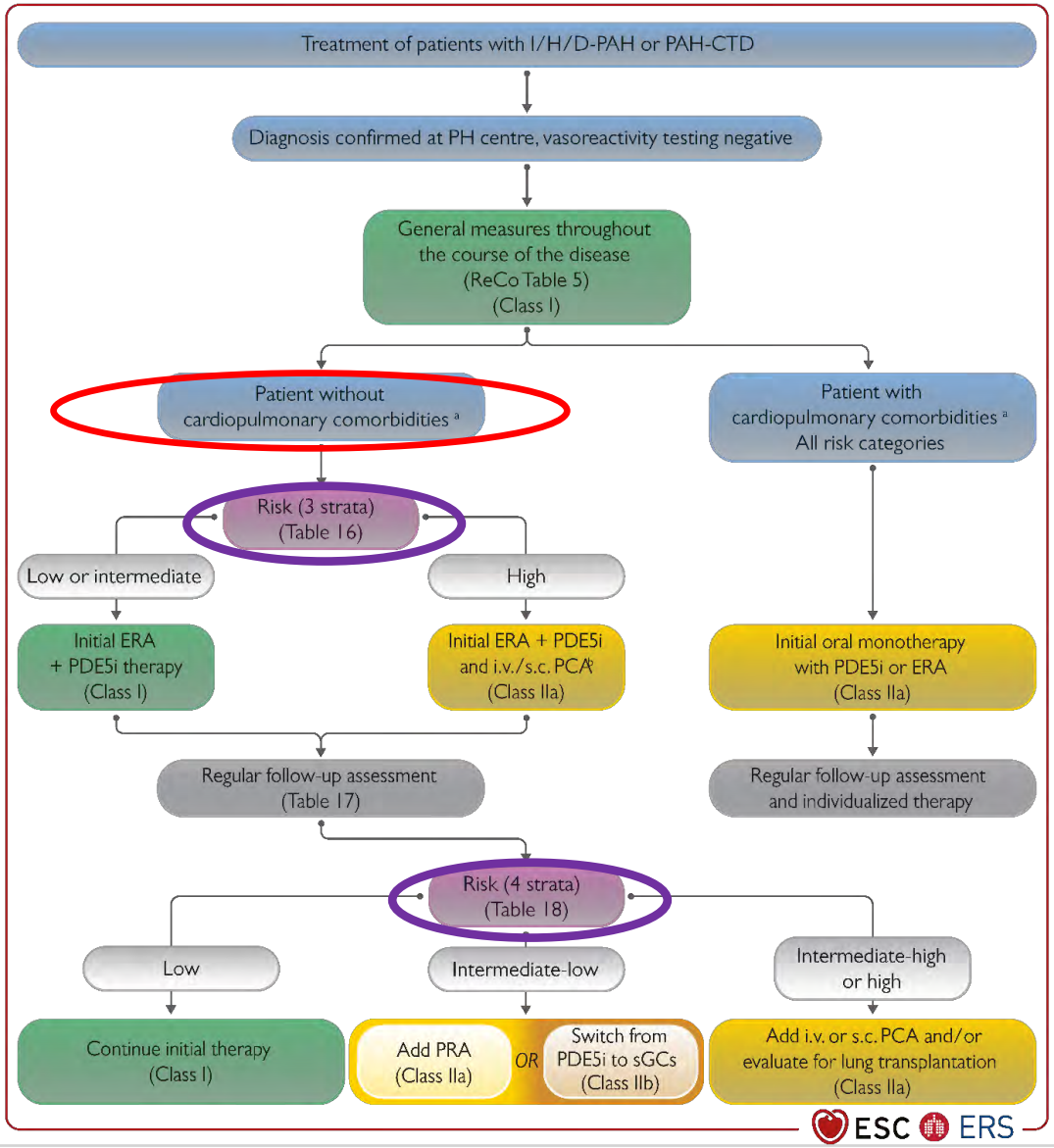
four-stratum risk model



Eur Respir J 2022; 60: 2102311

Figure 9

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



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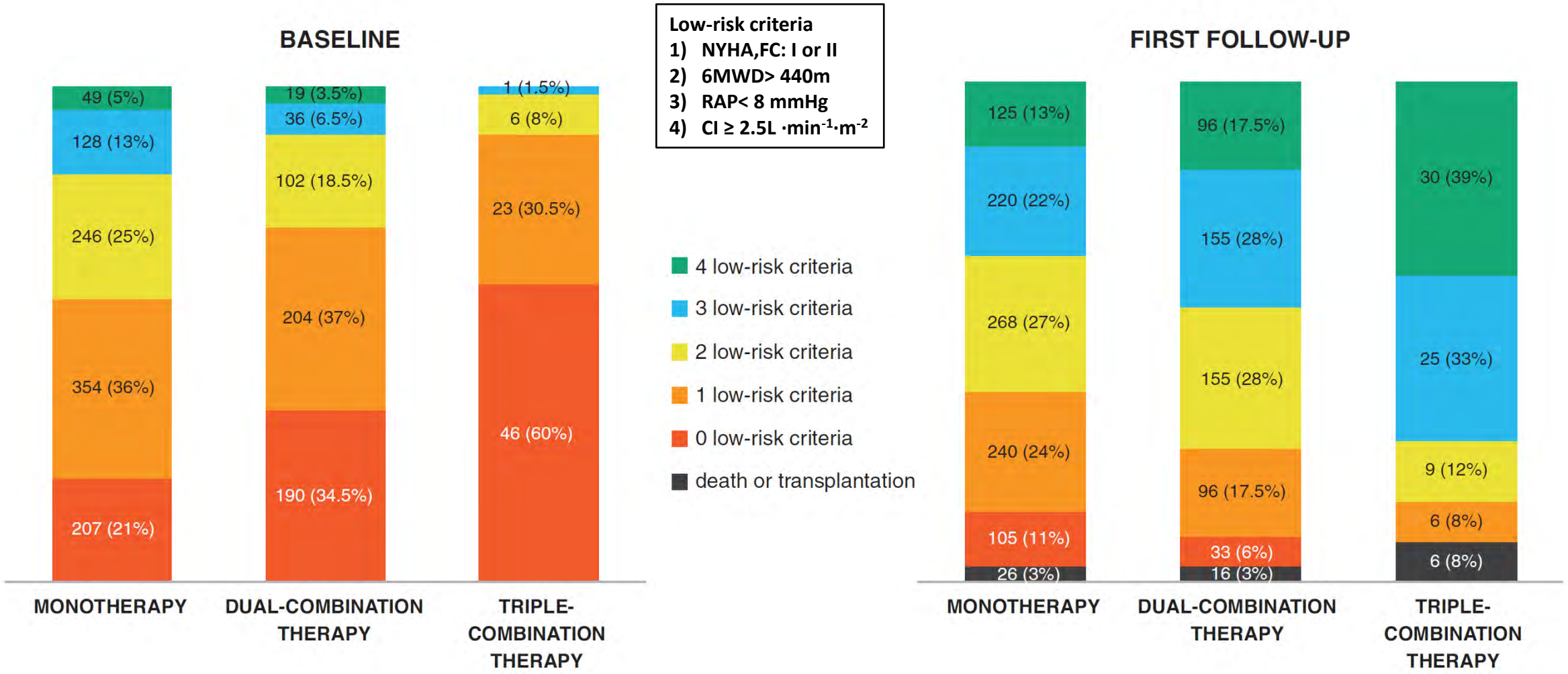
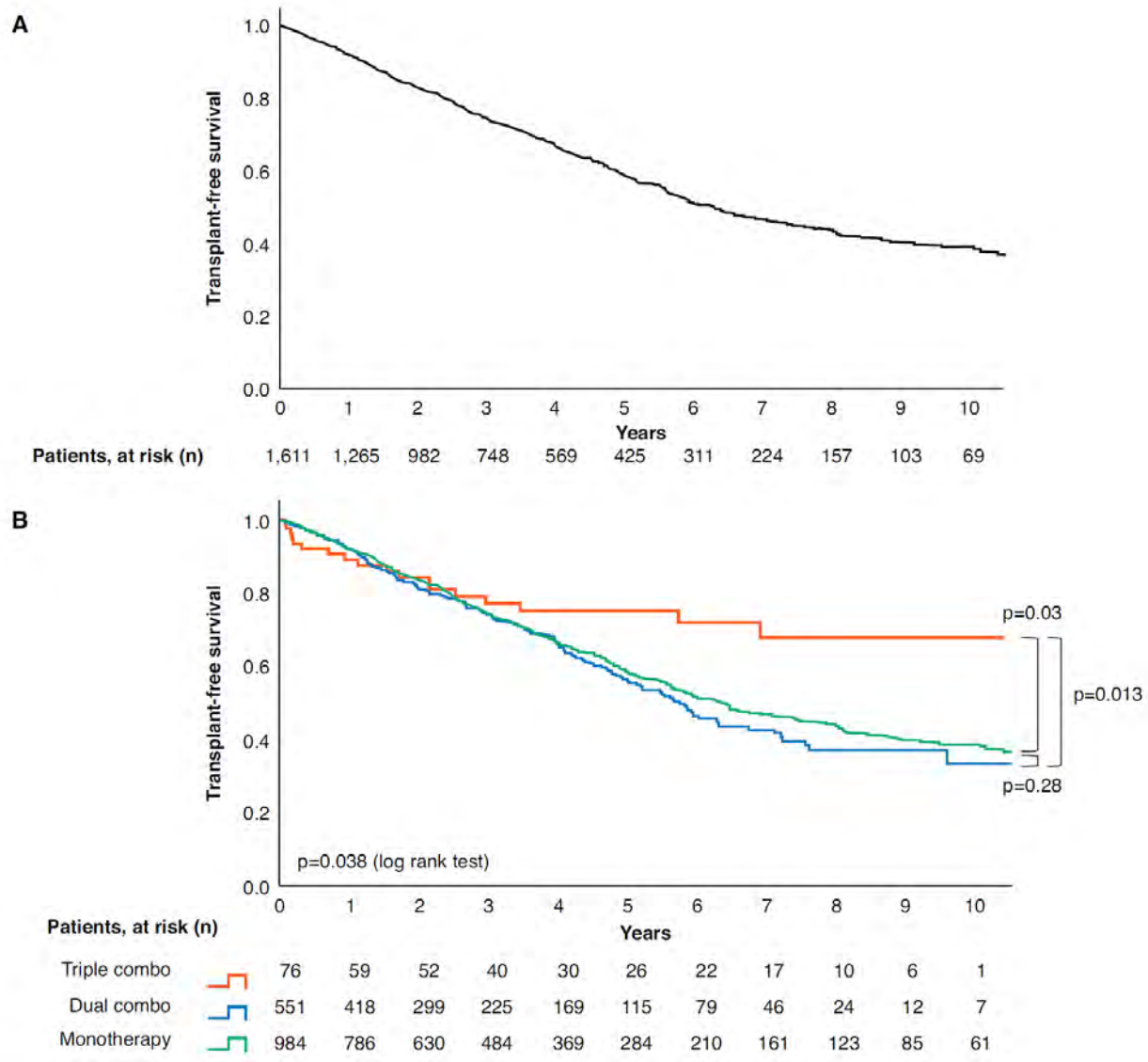
Association between Initial Treatment Strategy & Long-Term Survival in PAH



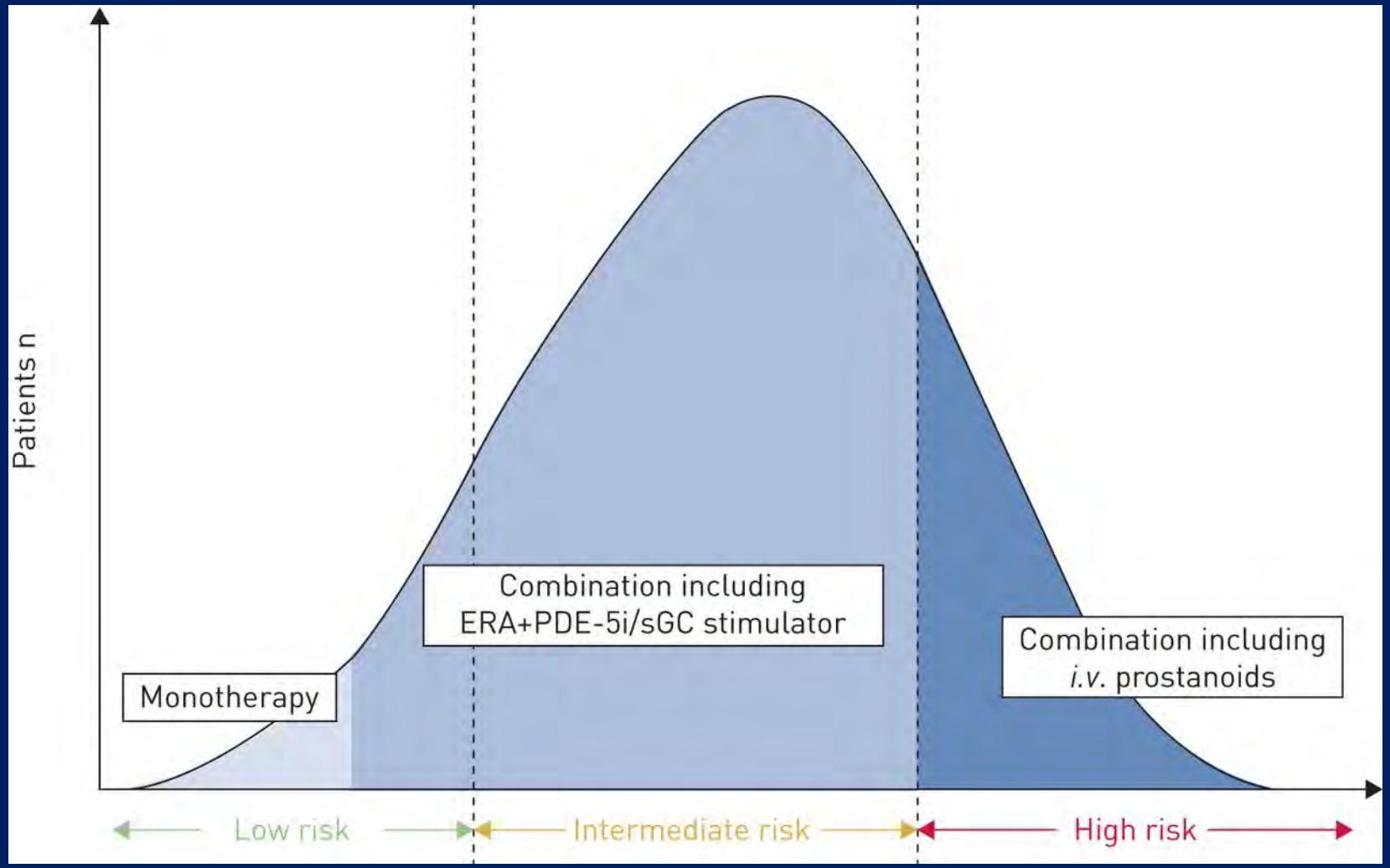
Boucly A et al. AJRCCM 2021; 204(7):842-854

Association between Initial Treatment Strategy & Long-Term Survival in PAH



Boucly A et al. AJRCCM 2021; 204(7):842-854

Initial management of pulmonary arterial hypertension in the current era



Sean Gaine & Vallerie McLaughlin Eur Respir Rev 2017

CASE: 3

Ανδρας, 60 ετών

Προσέρχεται λόγω δύσπνοιας κοπώσεως απο διετίας

<u>Ατομικό αναμνηστικό</u>

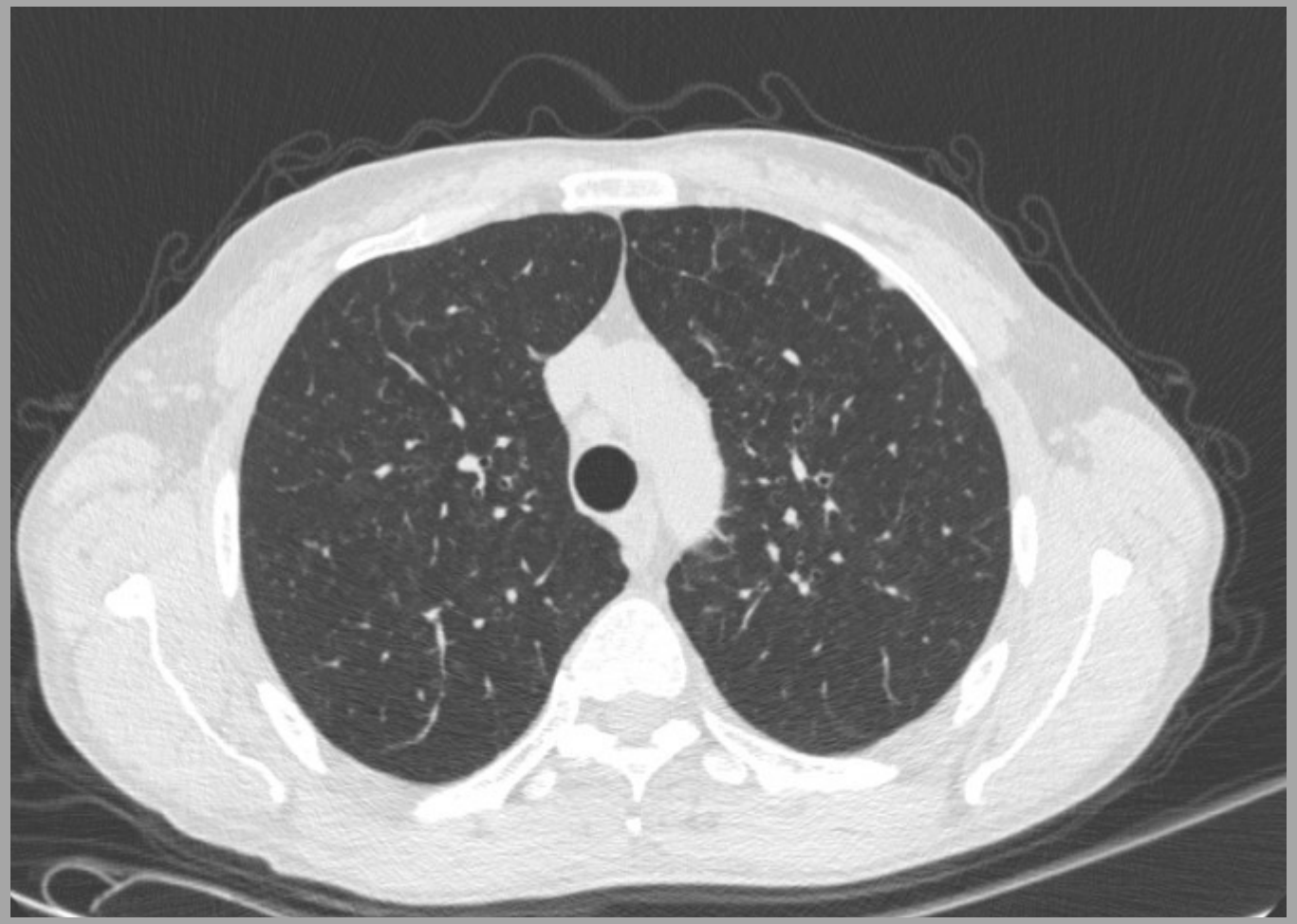
- **Υπέρταση απο διετίας**
- **Συστηματικό Σκληρόδερμα απο 10ετίας**

CASE: 3

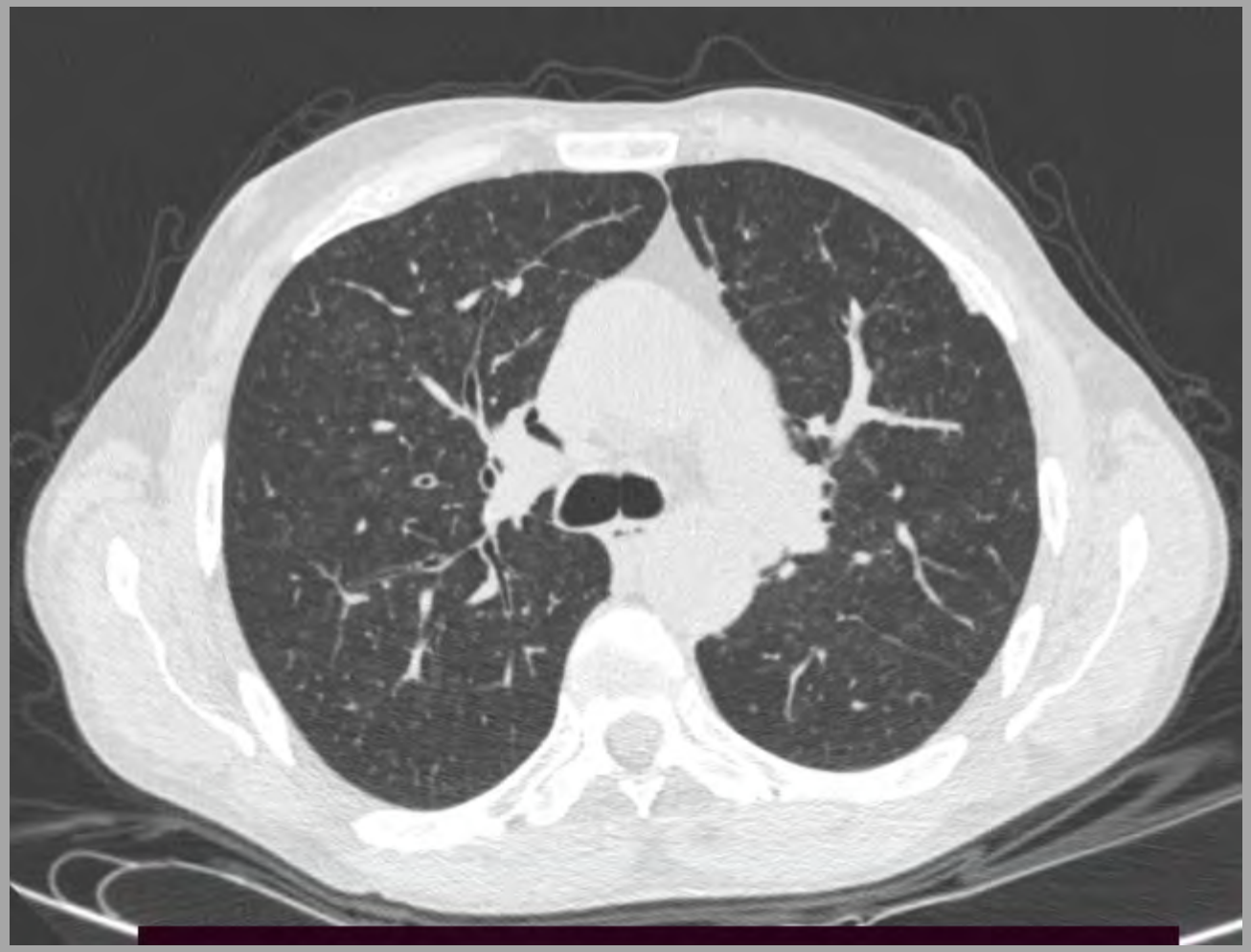
6/ 2020

WHO class	II late	
6MWD	480	m
Echocardiography		
TRV	3,3	m/s
PFT's		
FVC	95	%
FEV1	88	%
TLC	84	%
DLCO	48	%

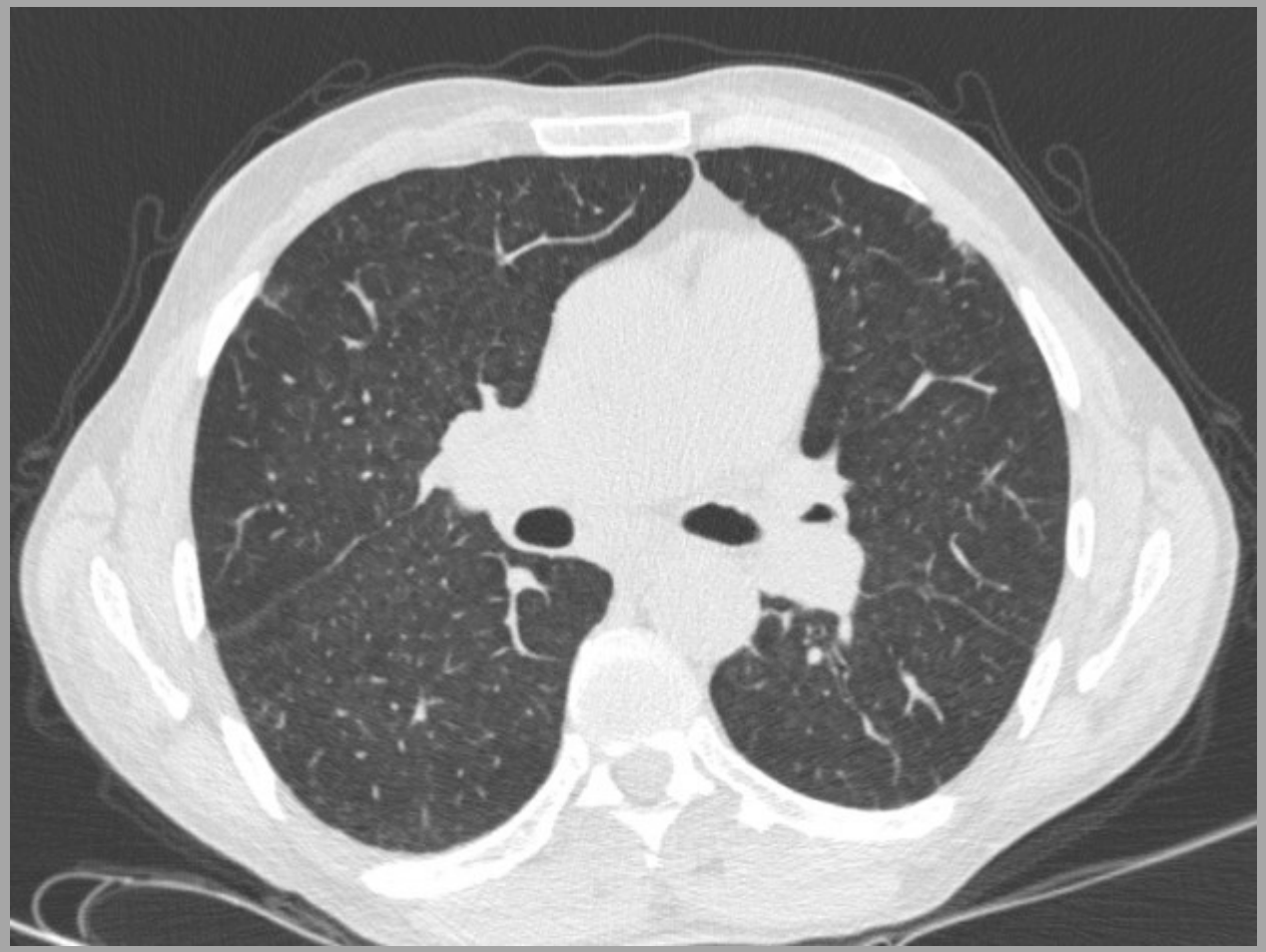
CASE: 3



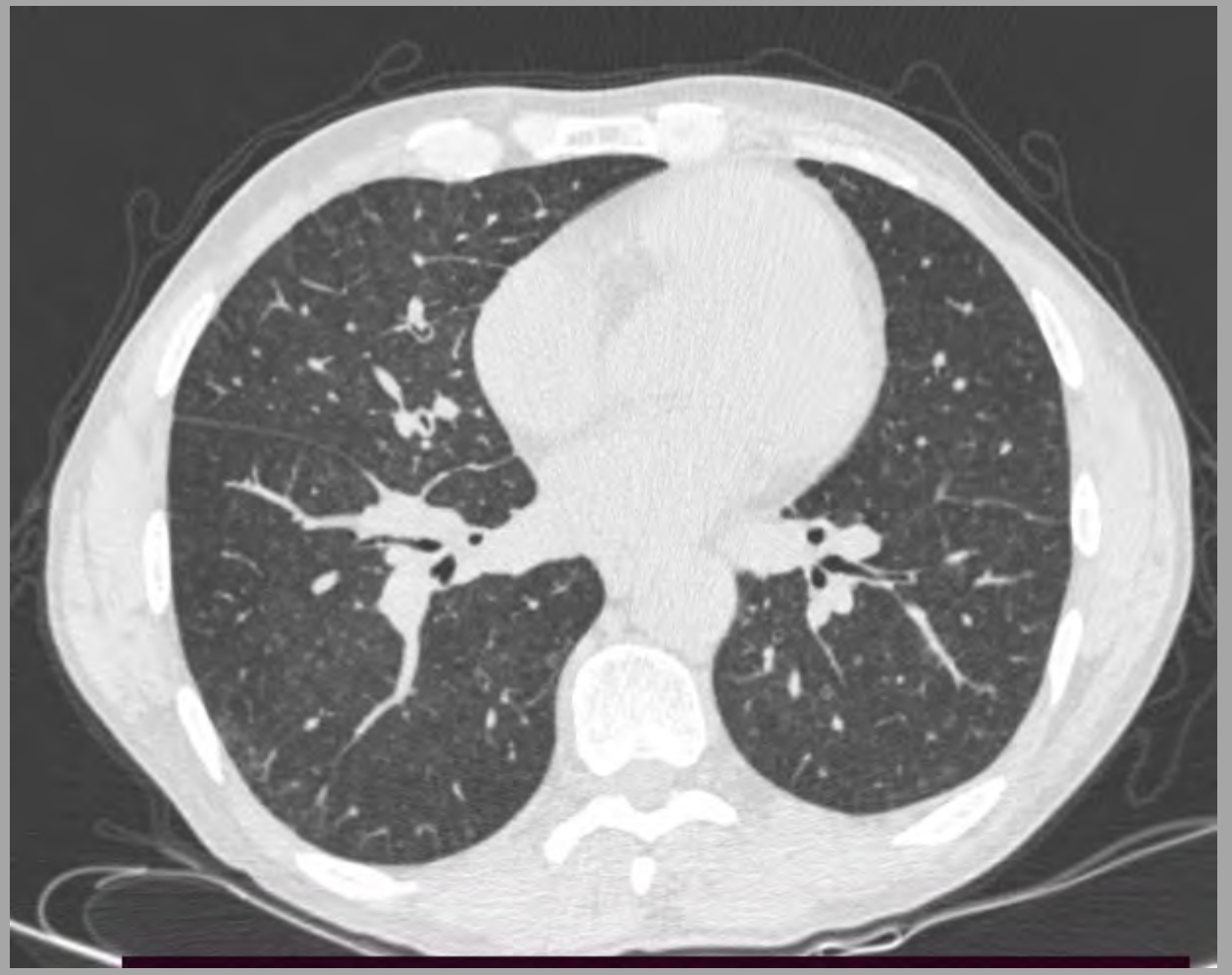
CASE: 3



CASE: 3



CASE: 3



CASE: 3

Right Heart Catheterization

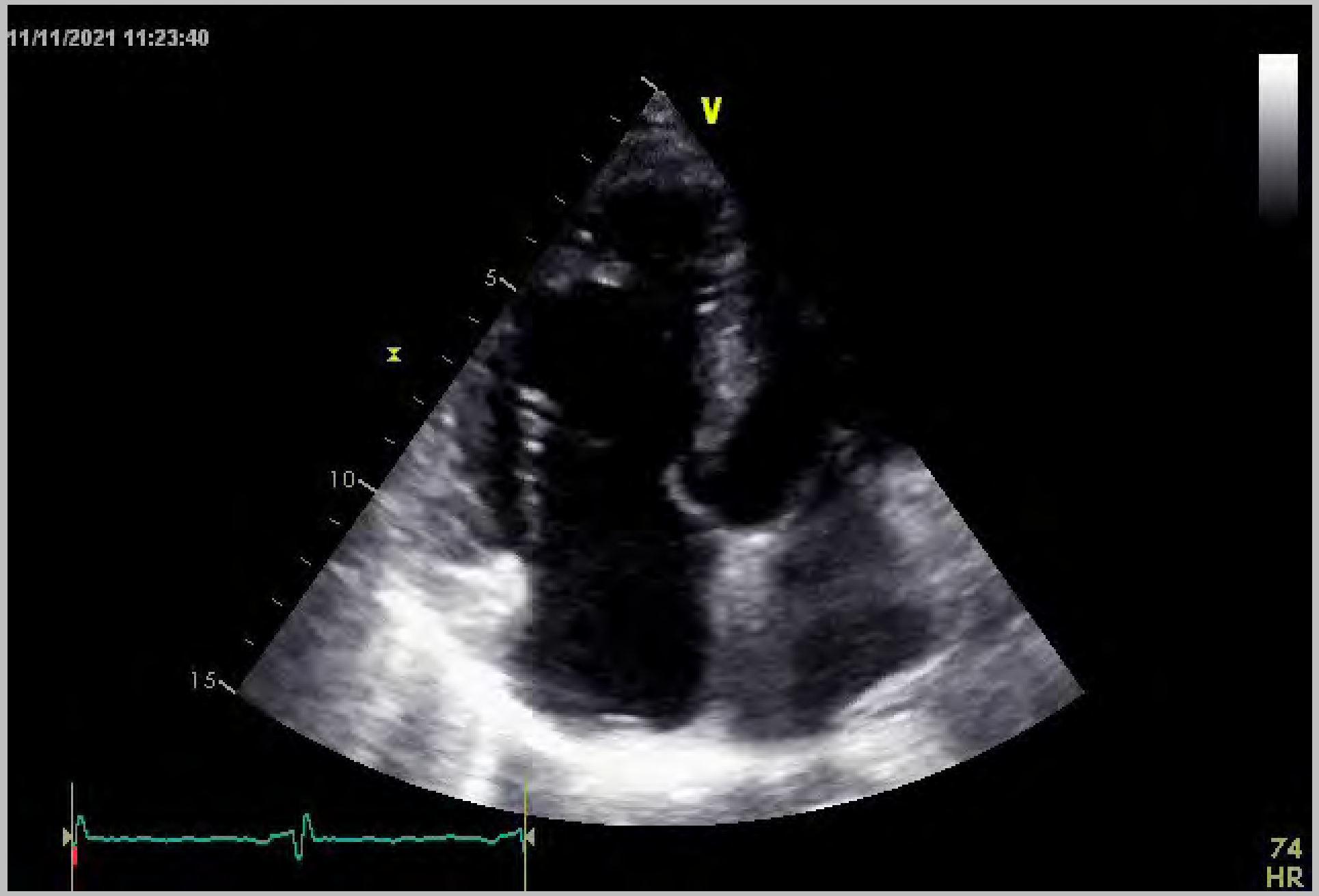
6/ 2020

RAP	4	mmHg
PAP	48/18/28	mmHg (S/D/M)
PAWP	5	mmHg
CO	4,8	l/min
CI	2,7	l/min/m^2
PVR	4,8	Wood Units
SvO2	78	%

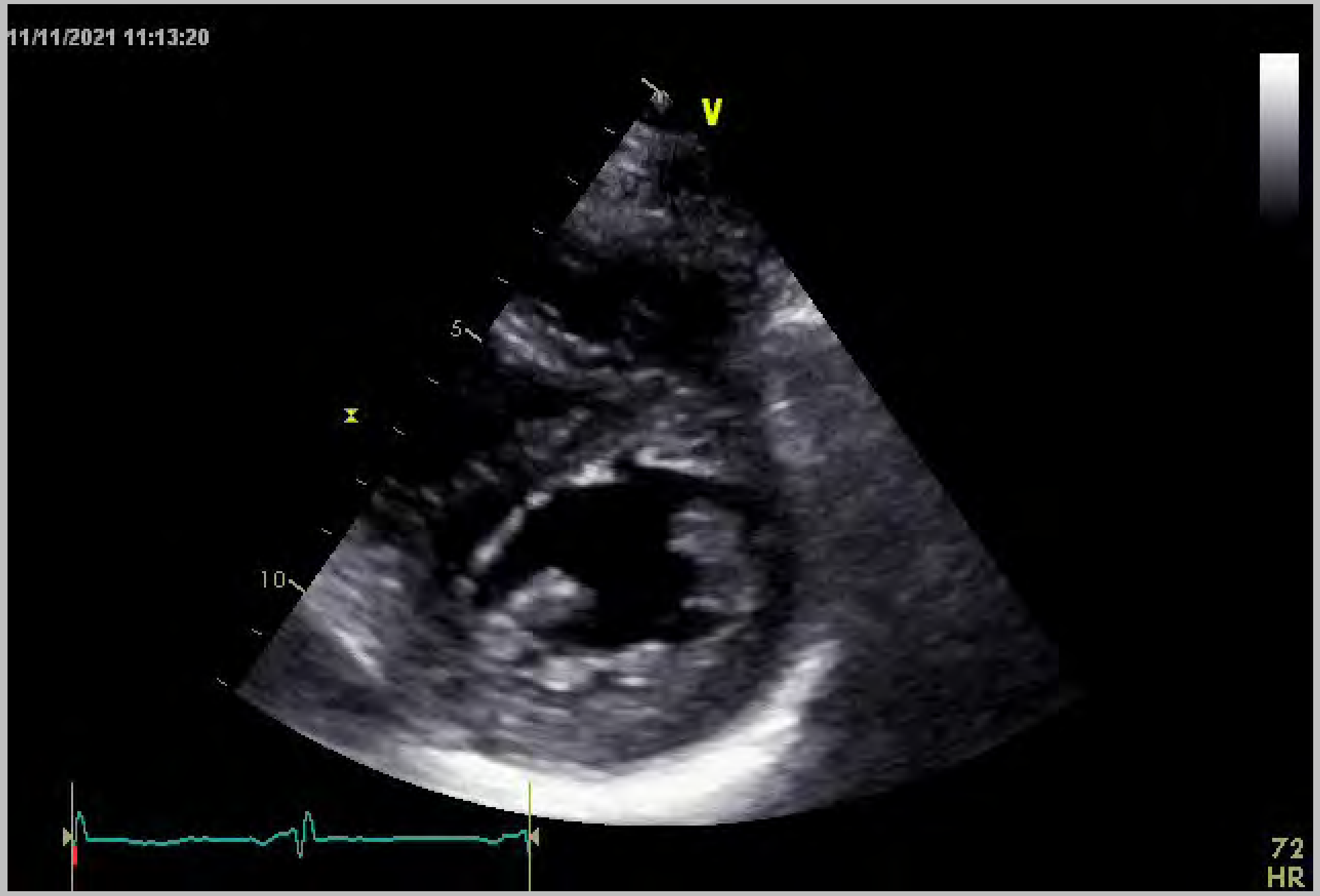
CASE: 3

	6/ 2020	11/ 2021	
WHO class	II late	III	
6MWD	480	N/U	m
Echocardiography			
TRV	3,3	4,3	m/s
PFT's			
FVC	95	98	%
FEV1	88	93	%
TLC	84	99	%
DLCO	48	31	%

CASE: 3



CASE: 3



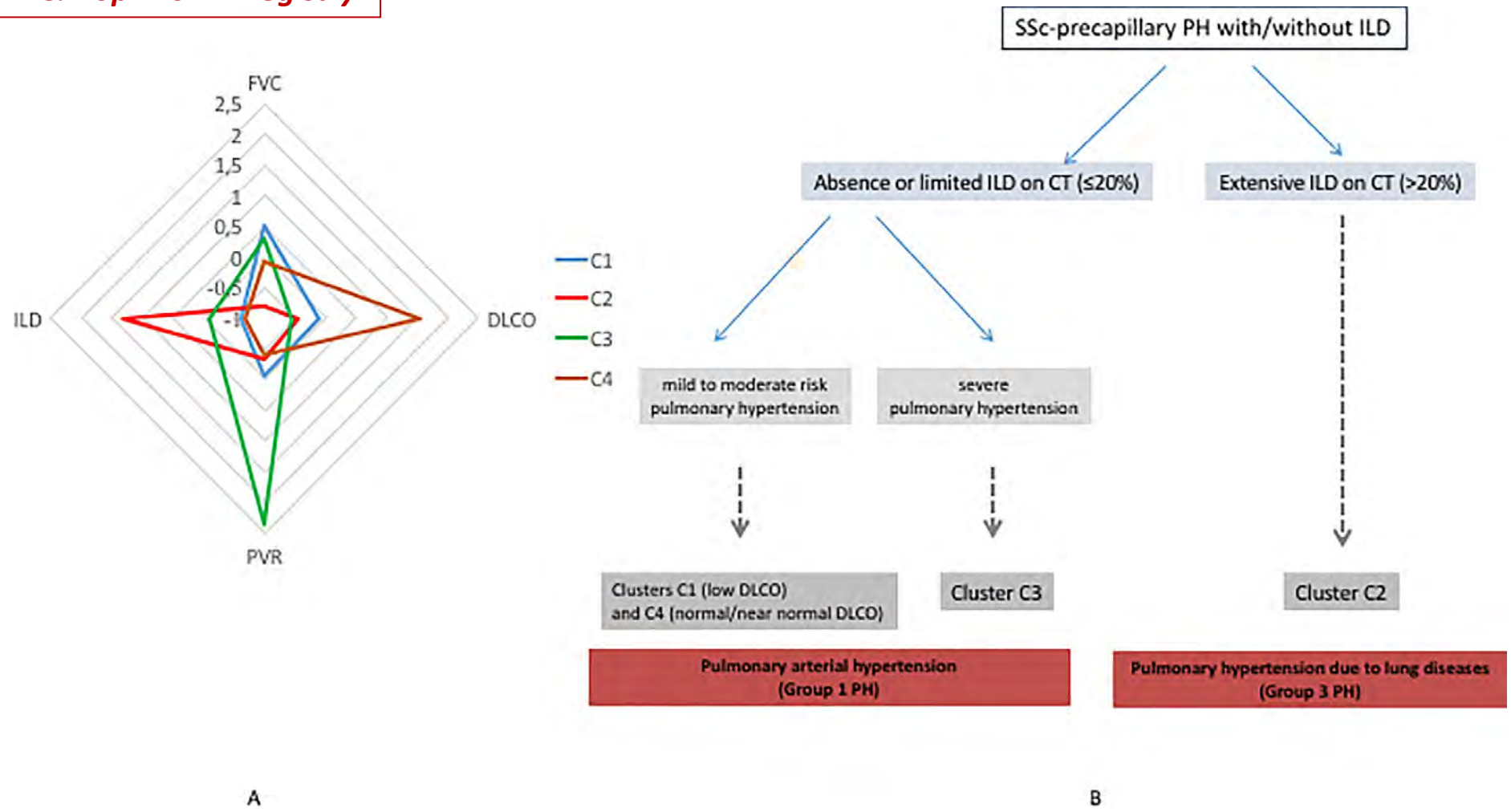
CASE: 3

Right Heart Catheterization

	6/ 2020	11/2021	
RAP	4	6	mmHg
PAP	48/18/28	76/26/43	mmHg (S/D/M)
PAWP	5	7	mmHg
CO	4,8	3,7	l/min
CI	2,7	2,1	l/min/m^2
PVR	4,8	9,7	Wood Units
SvO2	78	70	%

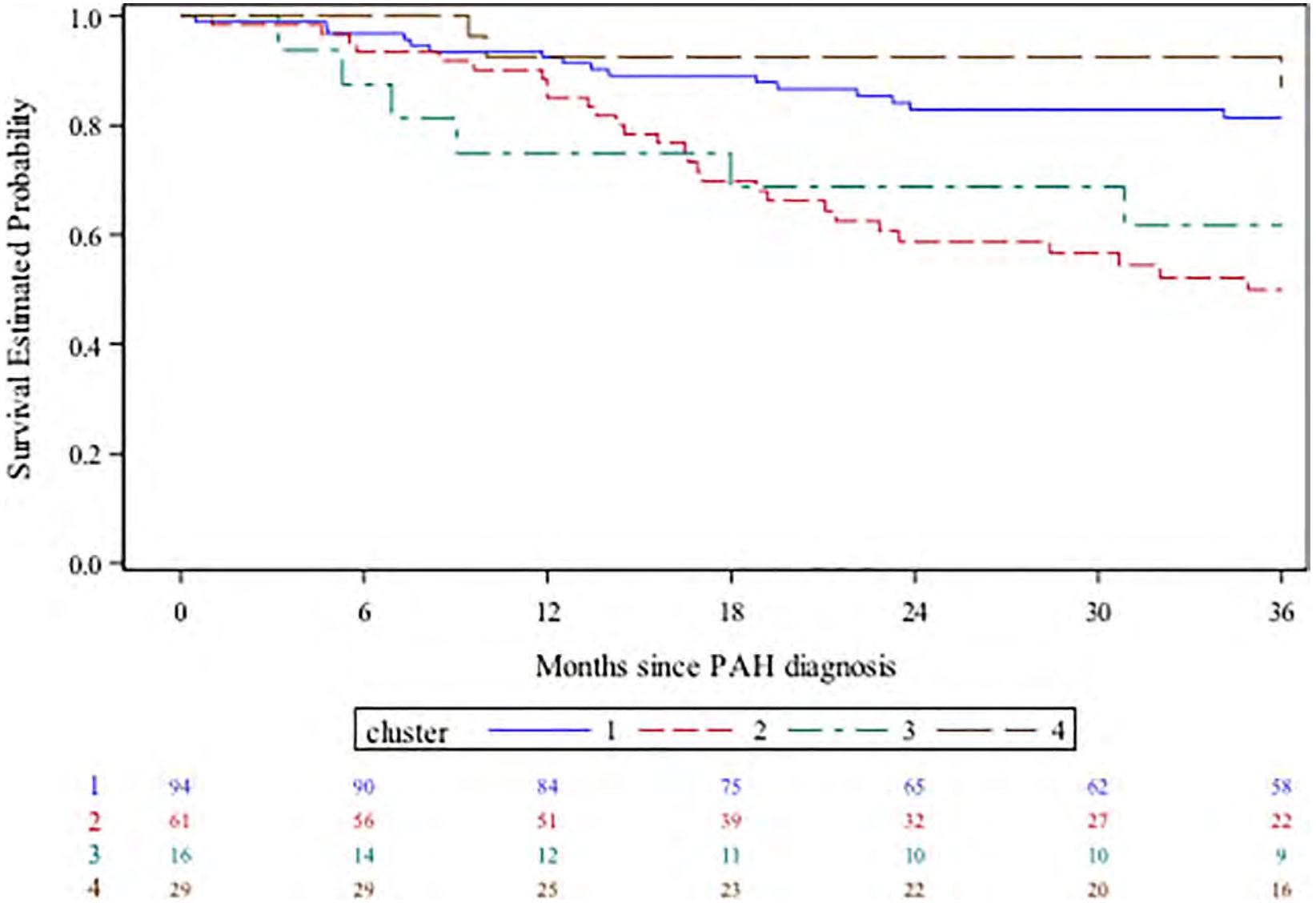
Clinical phenotypes in scleroderma-associated PH

French PH network & Hopkins PH Registry



PLOS ONE | https://doi.org/10.1371/journal.pone.0197112 May, 2018

Clinical phenotypes in scleroderma-associated PH



PLOS ONE | https://doi.org/10.1371/journal.pone.0197112 May, 2018

CASE: 4

Γυναίκα, 52 ετών
Παραπέμπεται για περαιτέρω αξιολόγηση

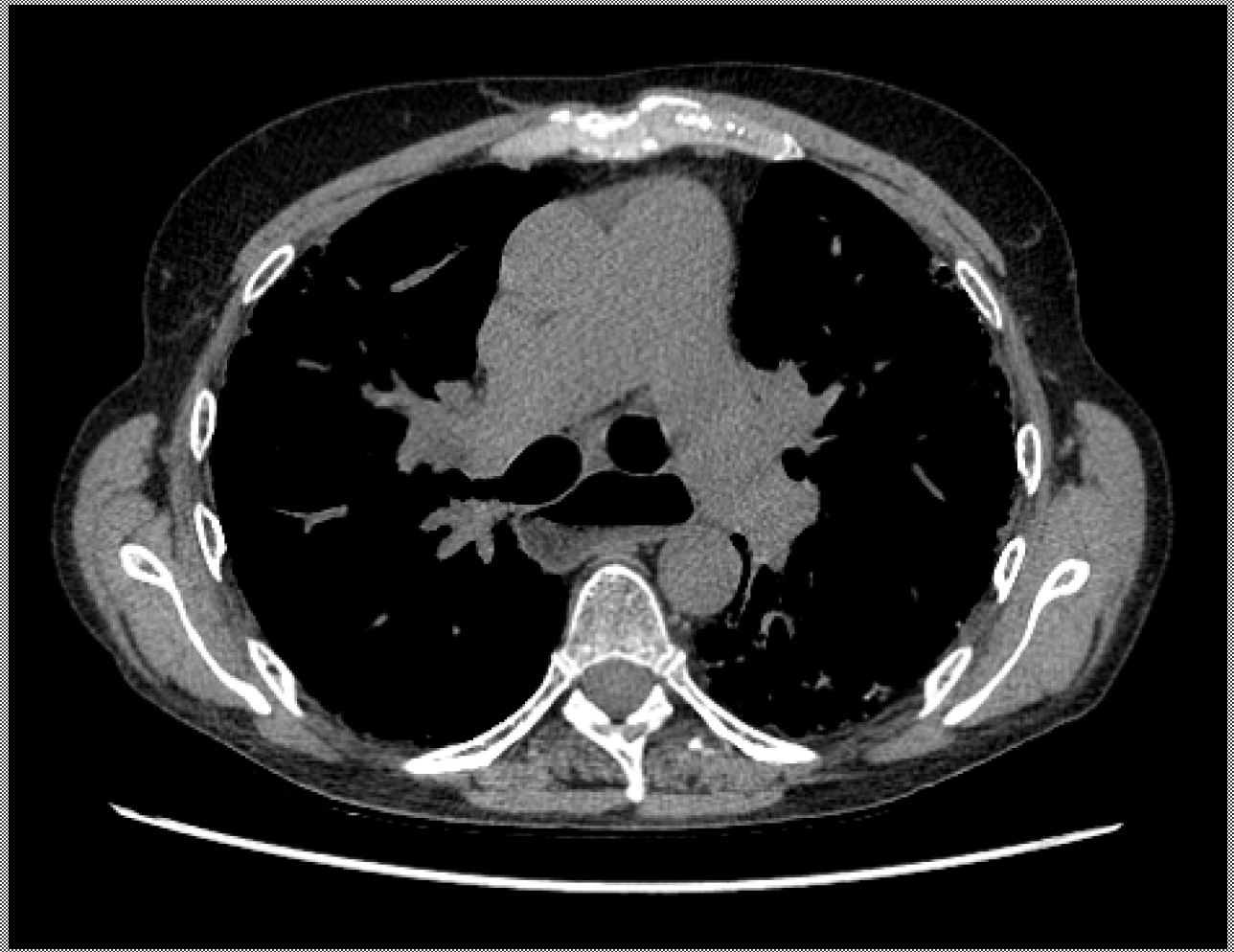
<u>Ατομικό αναμνηστικό</u>

- **Σκληρόδερμα απο 25ετίας**
- **Διάγνωση PAH απο 4ετίας/ σε διπλή αγωγή (ERA, PD5I)**
- **Συνεχής οξυγονοθεραπεία απο έτους**

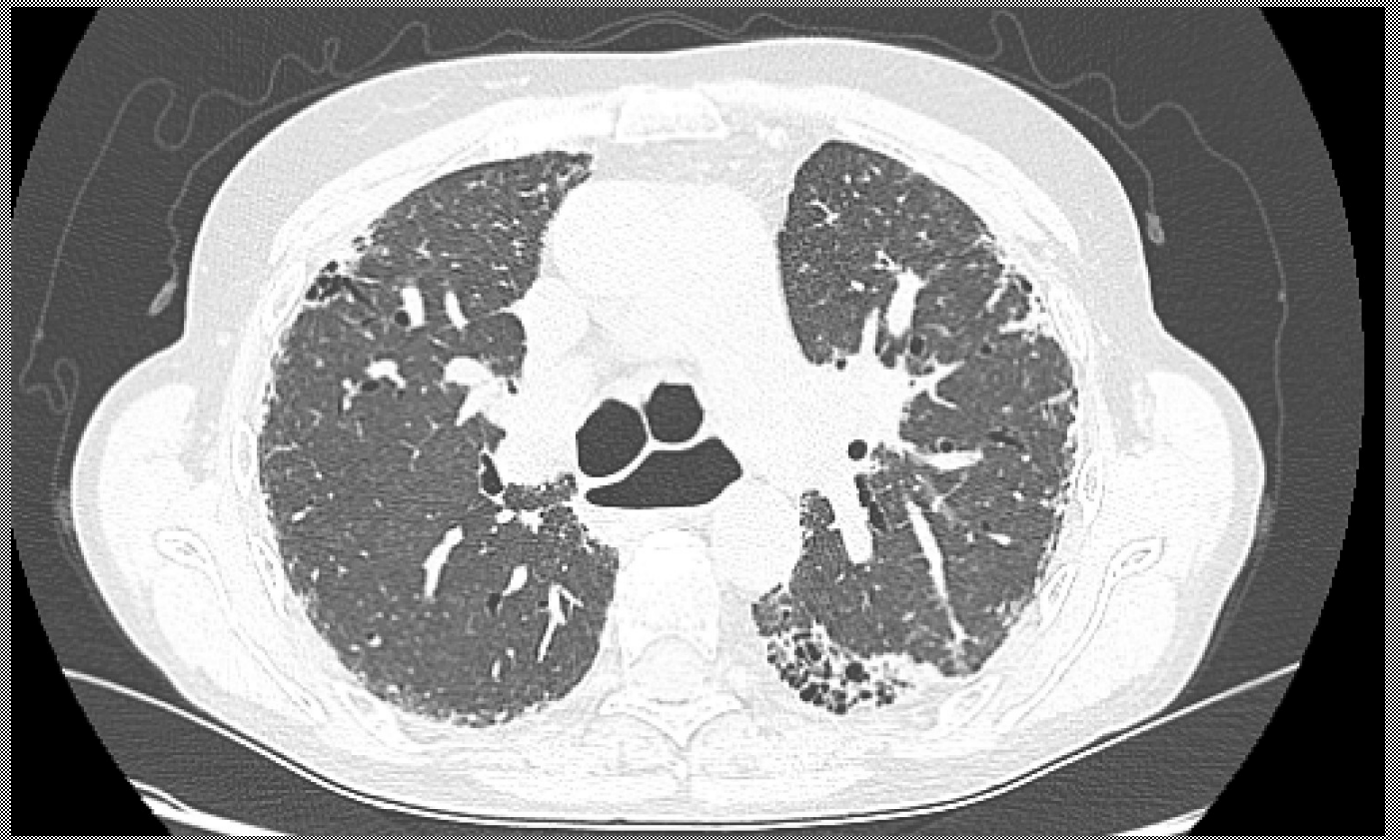
- **WHO class III late**

- **Echocardiography**
  TRV 4,5 m/s

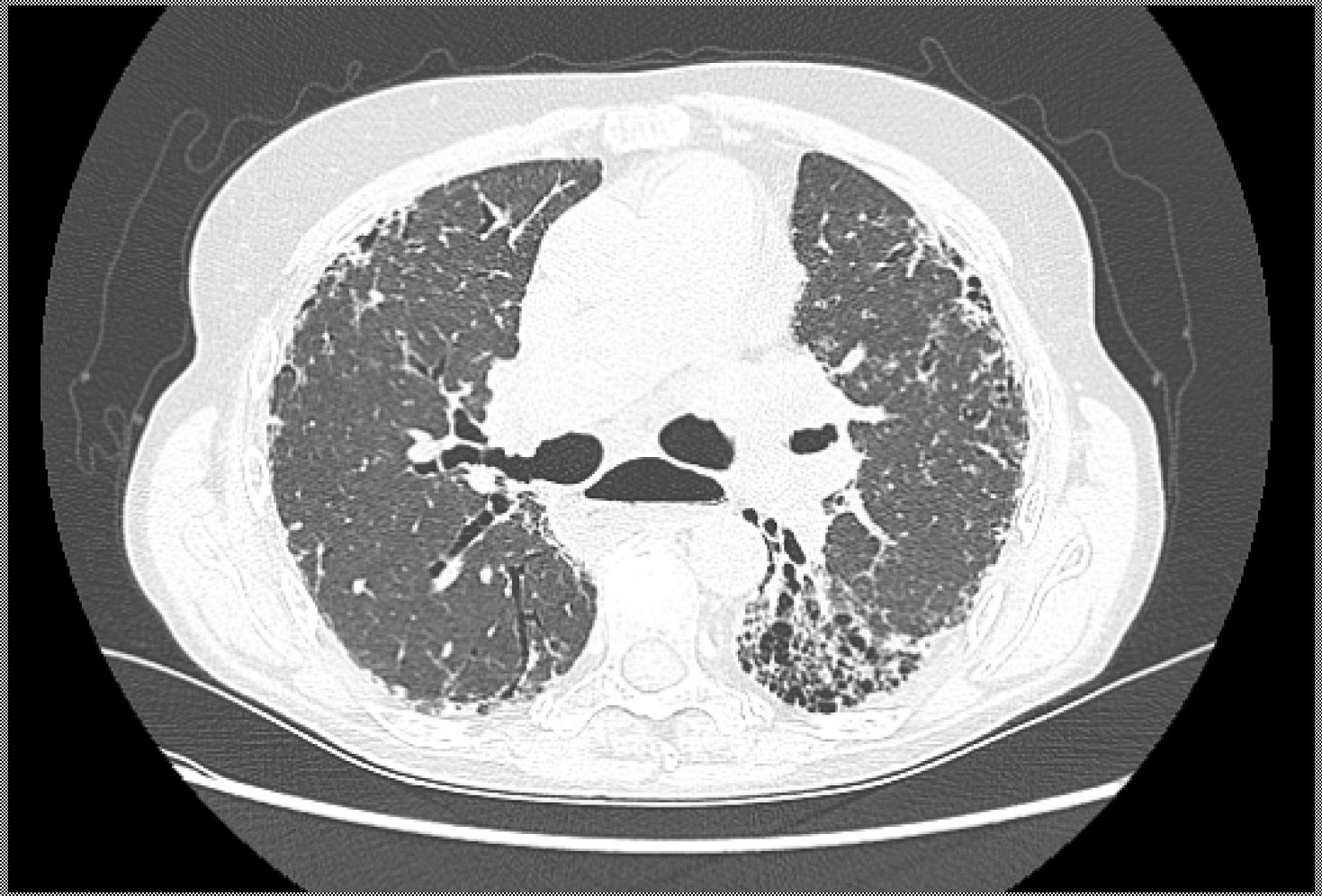
CASE: 4



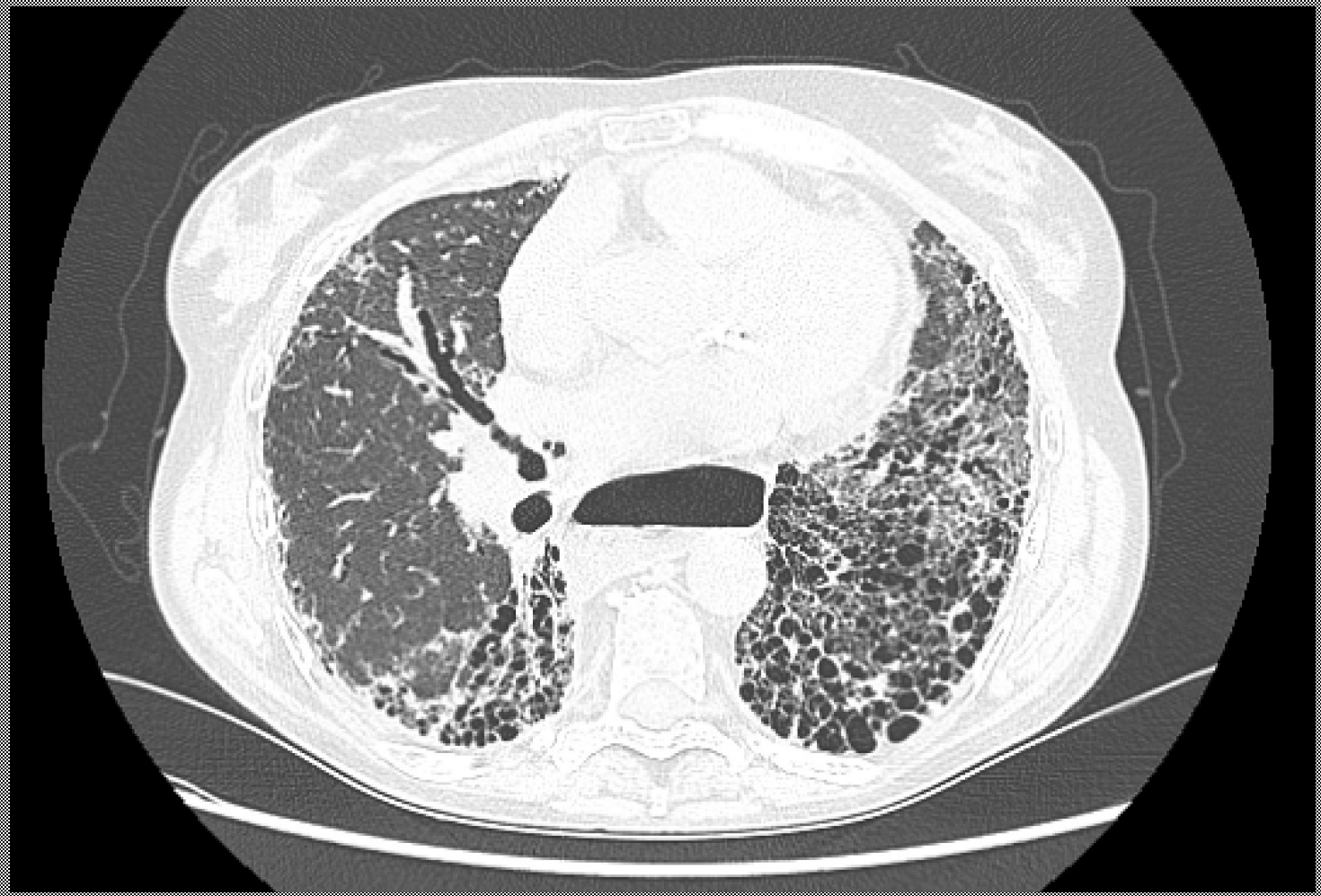
CASE: 4



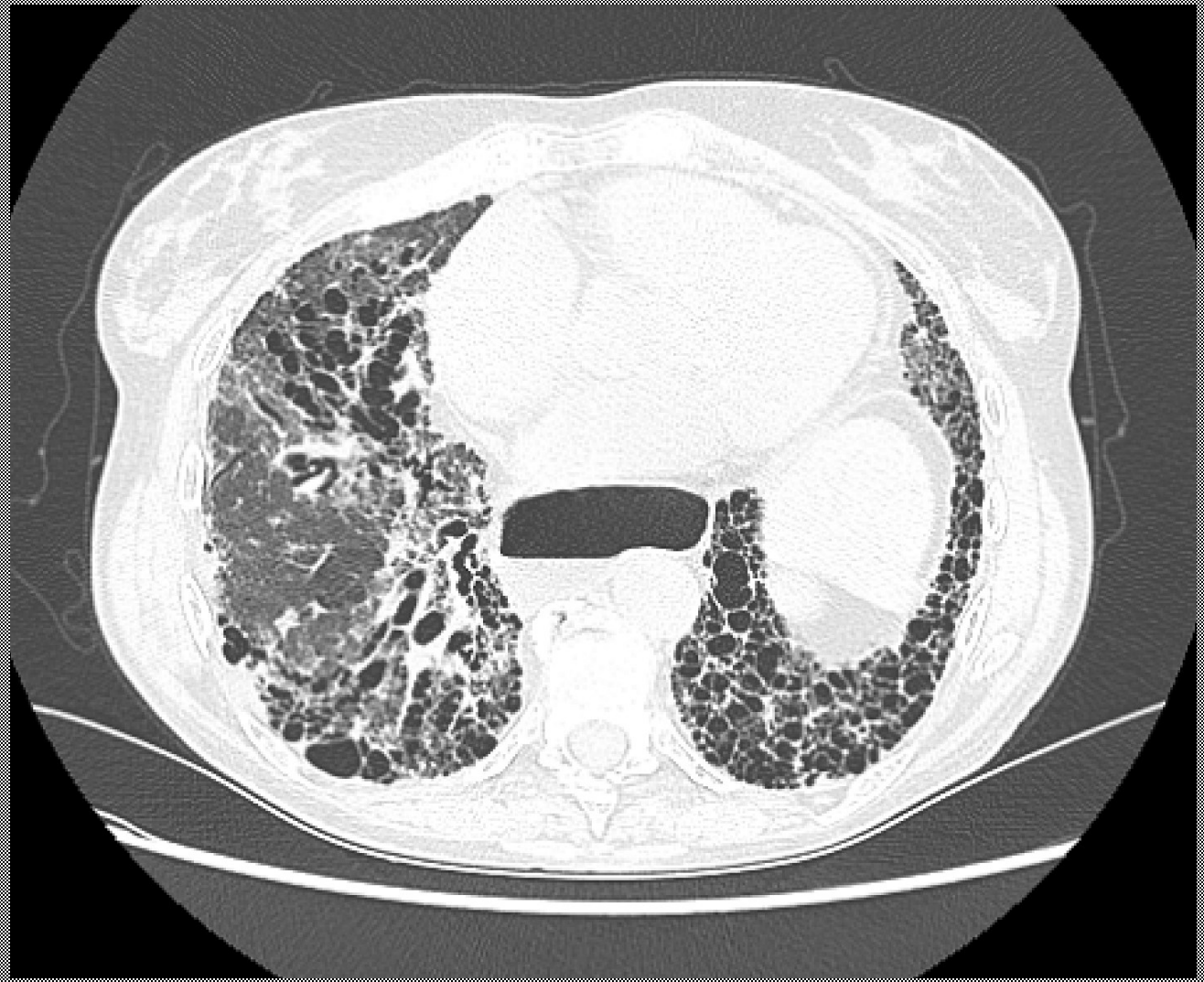
CASE: 4



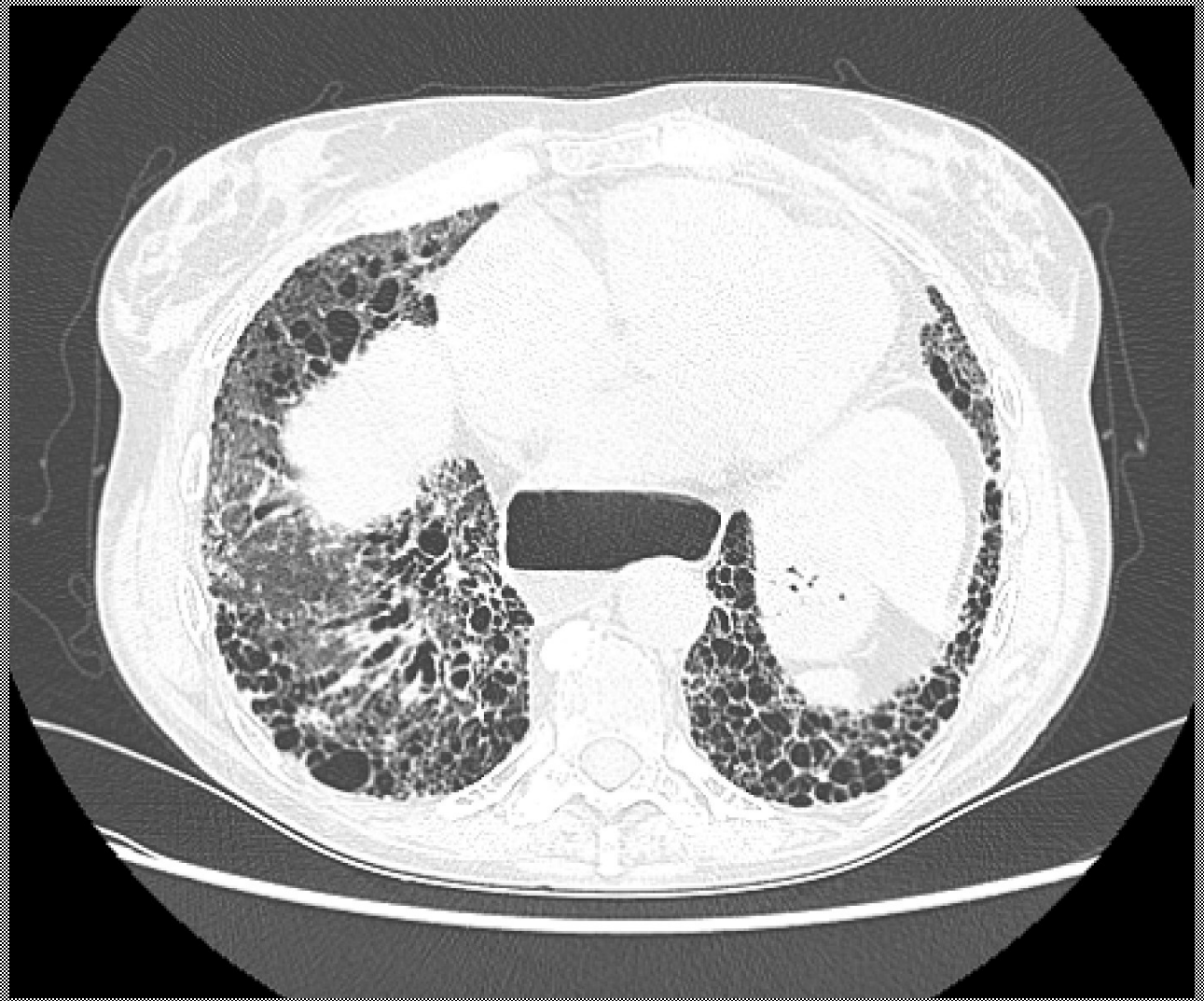
CASE: 4



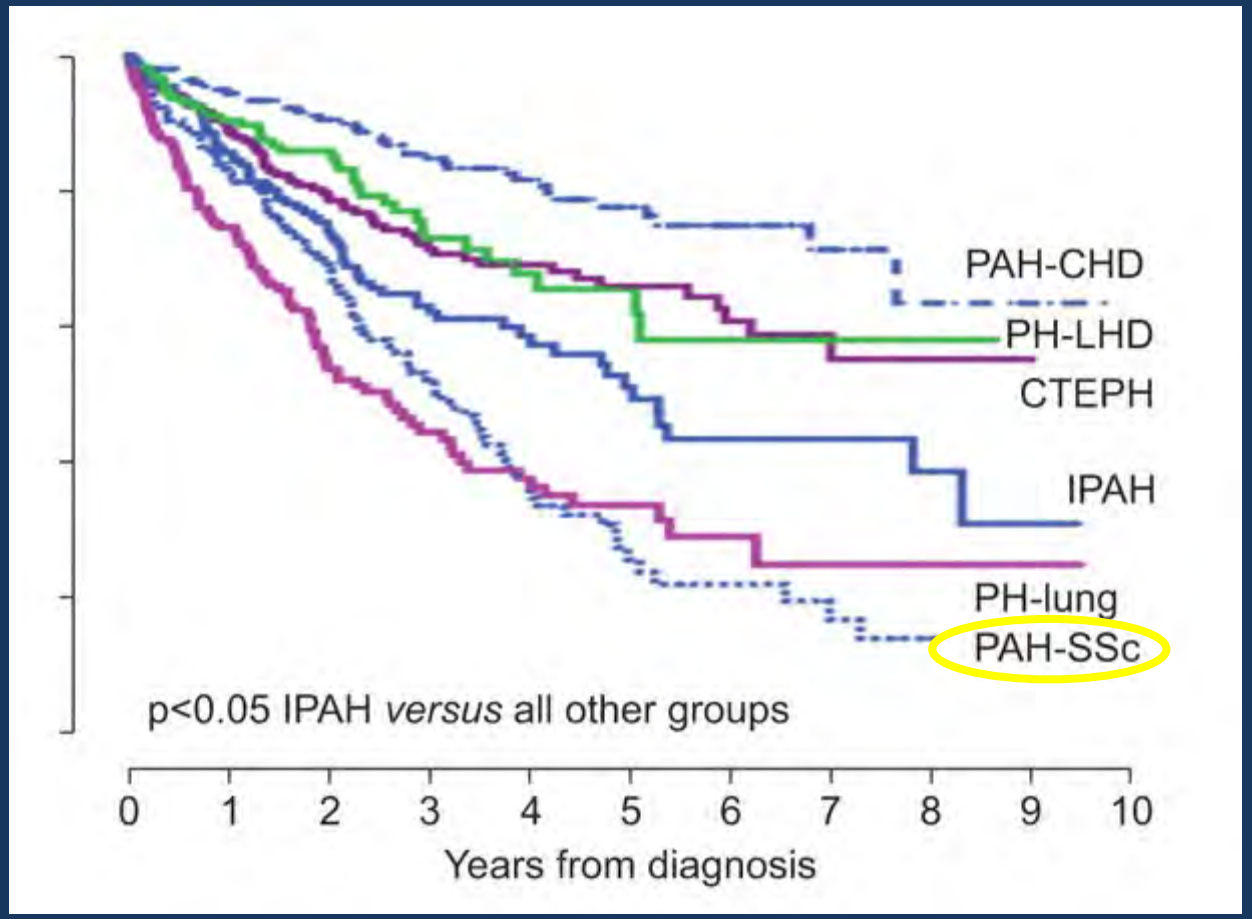
CASE: 4



CASE: 4



Cumulative survival from date of diagnosis for common diagnostic subgroups of PH



Hurdman J et al. Eur Respir J 2012; 39: 945–955

What is new (5)

Screening and improved detection of PAH and CTEPH (continued)			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
		In patients with SSc, where breathlessness remains unexplained following non-invasive assessment, RHC is recommended to exclude PAH	**I**
		Assessing the risk of having PAH, based on an evaluation of breathlessness, in combination with echocardiogram or PFTs and BNP/NT-proBNP, should be considered in patients with SSc	**IIa**
		Policies to evaluate the risk of having PAH should be considered in hospitals managing patients with SSc	**IIa**

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