Update on Pulmonary Hypertension

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Disclosures

- Acceleron – Advisory Panel, Research Support
- Actelion J&J – Advisory Panel, Consultant, Speakers Bureau
- Bayer – Speakers Bureau
- Bellerophon – Clinical Research Support
- Roche – Clinical Research Support
- United Therapeutics - Speakers Bureau, Consultant, Advisory Panel, Clinical Research Support

Objectives

- Review current classification system for pulmonary hypertension (PH) with an emphasis on rare types which require specialized referral.
- Review key elements of workup which often separate pulmonary arterial hypertension from other types of PH.
- Briefly review modern approaches to therapy and risk stratification of patients with pulmonary arterial hypertension (PAH).

ESC European Society of Cardiology

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

ESC/ERS GUIDELINES

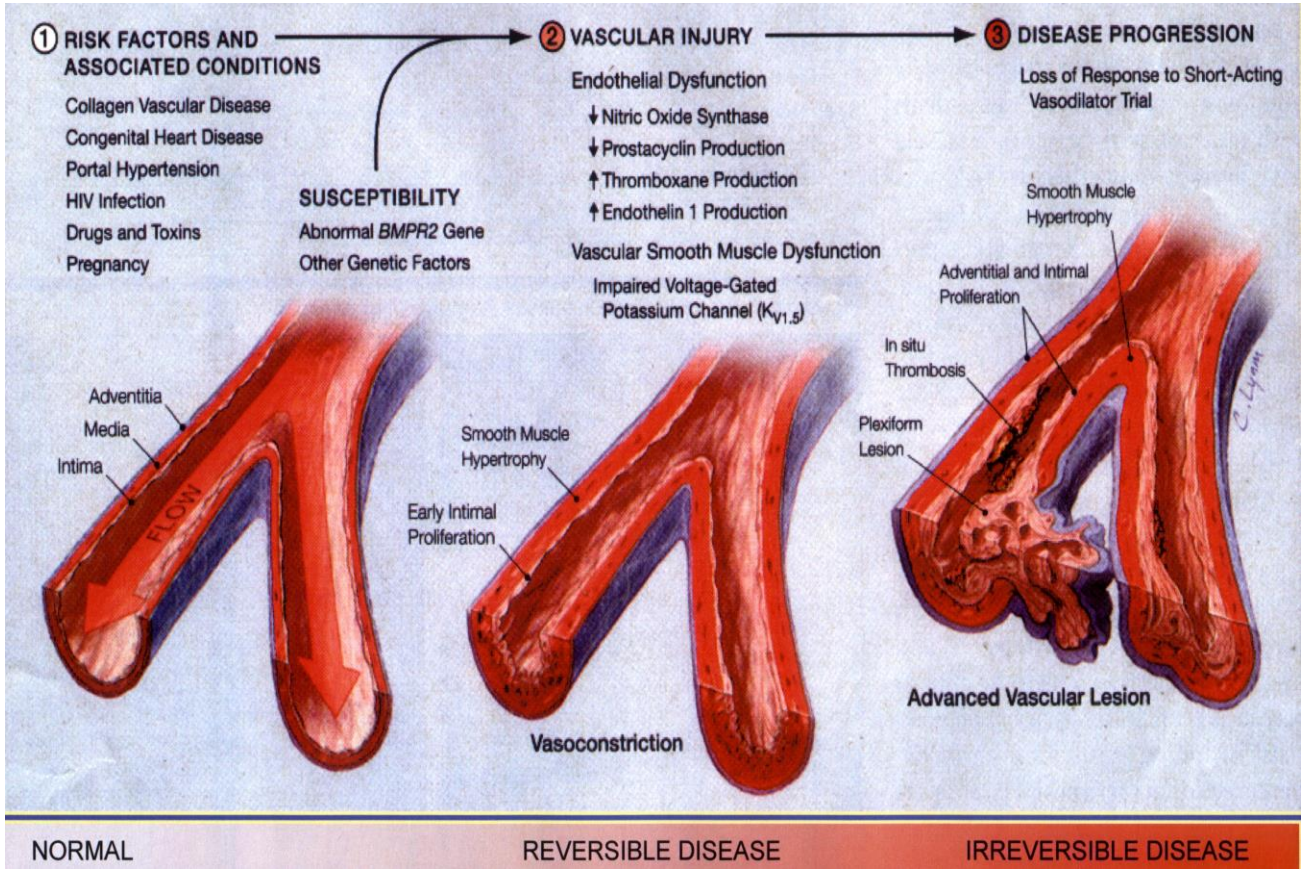
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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).

Definition, Classification, Pathophysiology

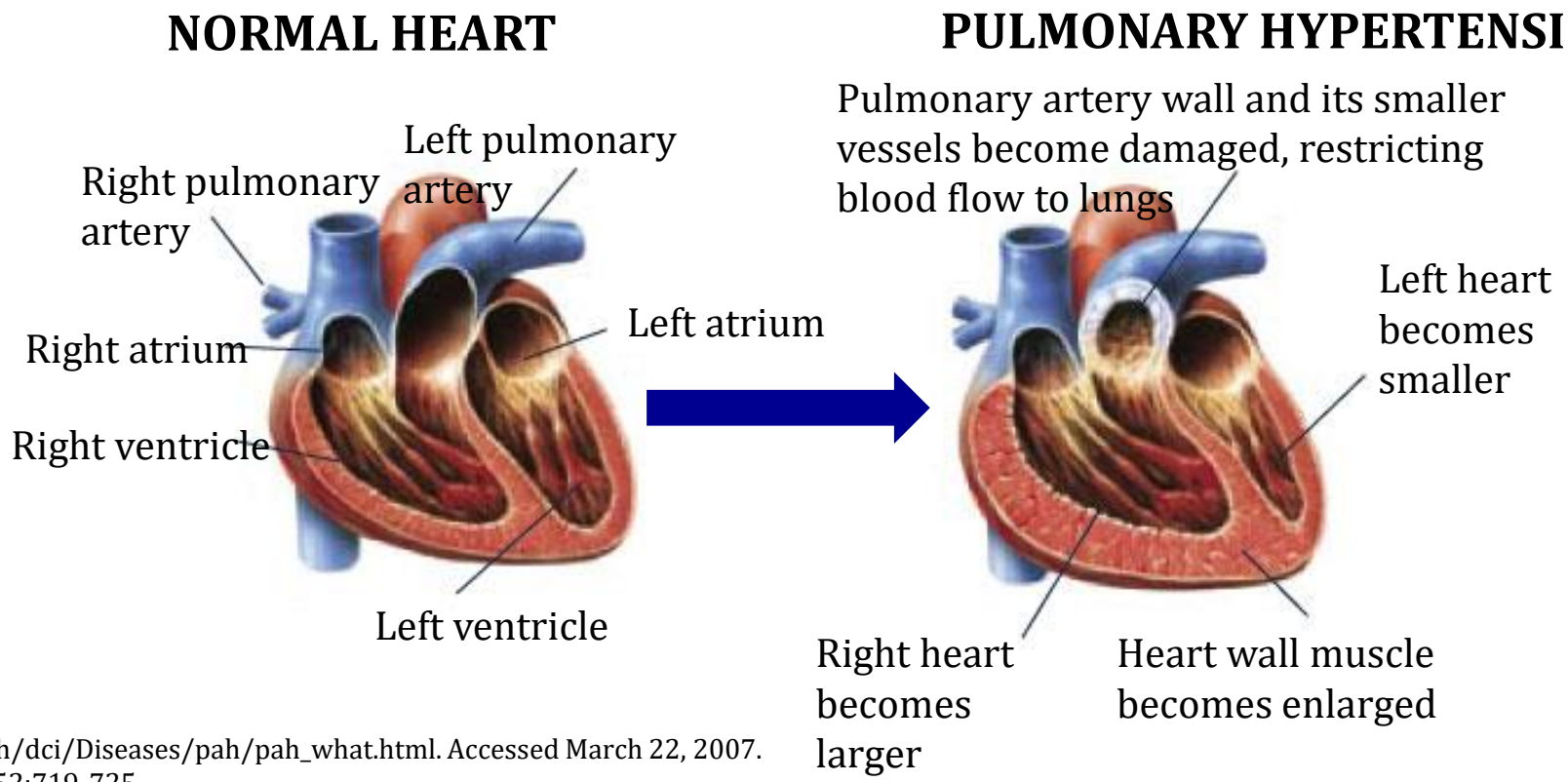
Pathophysiology in IPAH



Gaine, JAMA, 2000

Gaine, JAMA, 2000

The Basics: The Heart in PAH[1-3]



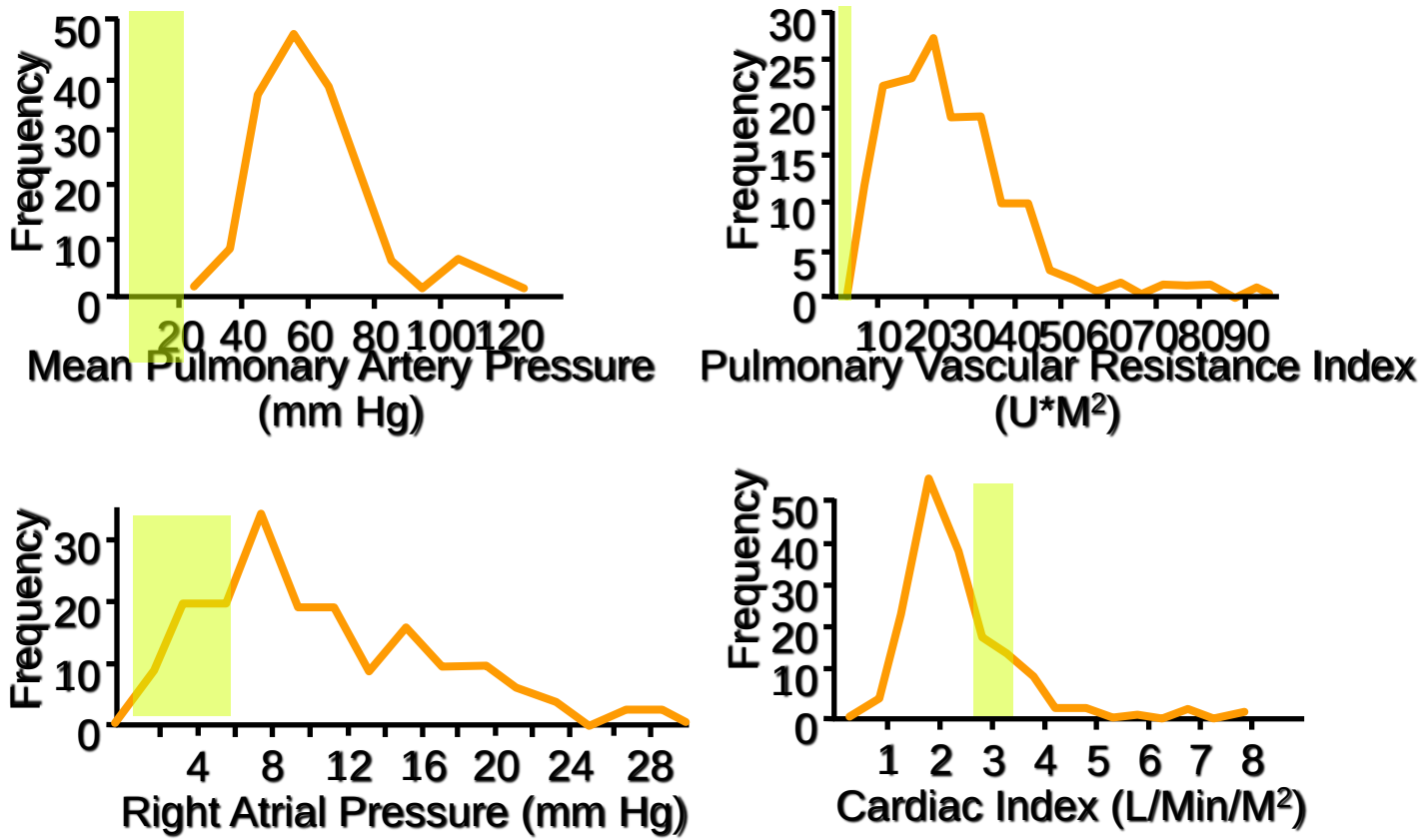
1. Farber H, et al. *N Engl J Mec*
2. http://www.nhlbi.gov/health/dci/Diseases/pah/pah_what.html. Accessed March 22, 2007.
3. Gaine S, et al. *Lancet*. 1998;352:719-725.

Hemodynamic and Physiologic Classifications of PH

Definition	Hemodynamic characteristics
PH	mPAP >20 mmHg Previous mPAP >25 mm Hg
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

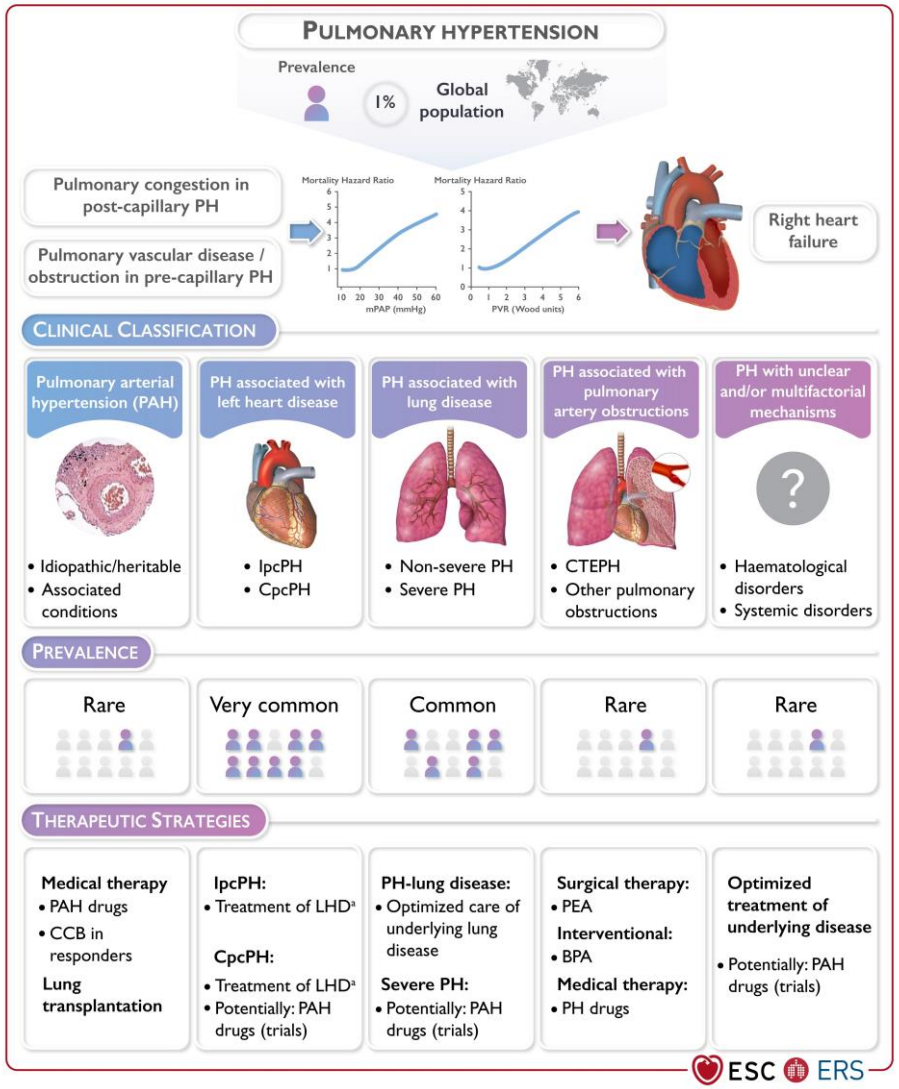
European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

Typical Hemodynamic Picture of Pulmonary Arterial Hypertension



Rich S et al. *Ann Intern Med*. 1987;107:216-223.

- Classification System for PH
  - I - Pulmonary Arterial Hypertension
  - II - PH Associated with Left Heart Disease
  - III - PH Associated with Lung Disease
  - IV- PH Associated with Pulmonary Artery Occlusions
  - V - PH with Unclear and/or Multifactorial Mechanisms



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PAH Classification (Expanded)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable
- 1.3 Associated with drugs and toxins
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

Adapted from: European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

Epidemiology

Epidemiology of IPAH (PPH) NIH Registry (1987)

- 187 patients followed over 7 years
- mPAP: 60 mm/Hg; CI: 2.3 l/min; PVRI: 26 Wood units
- Mean age at diagnosis: 36 years
- Almost 2:1 female-to-male ratio
- Family history positive in 6% of patients
- Mean duration of symptoms before diagnosis: 2 years
- Incidence: ~2 cases per 1,000,000

Rich S, et al. *Ann Intern Med*. 1987;107:216-223.

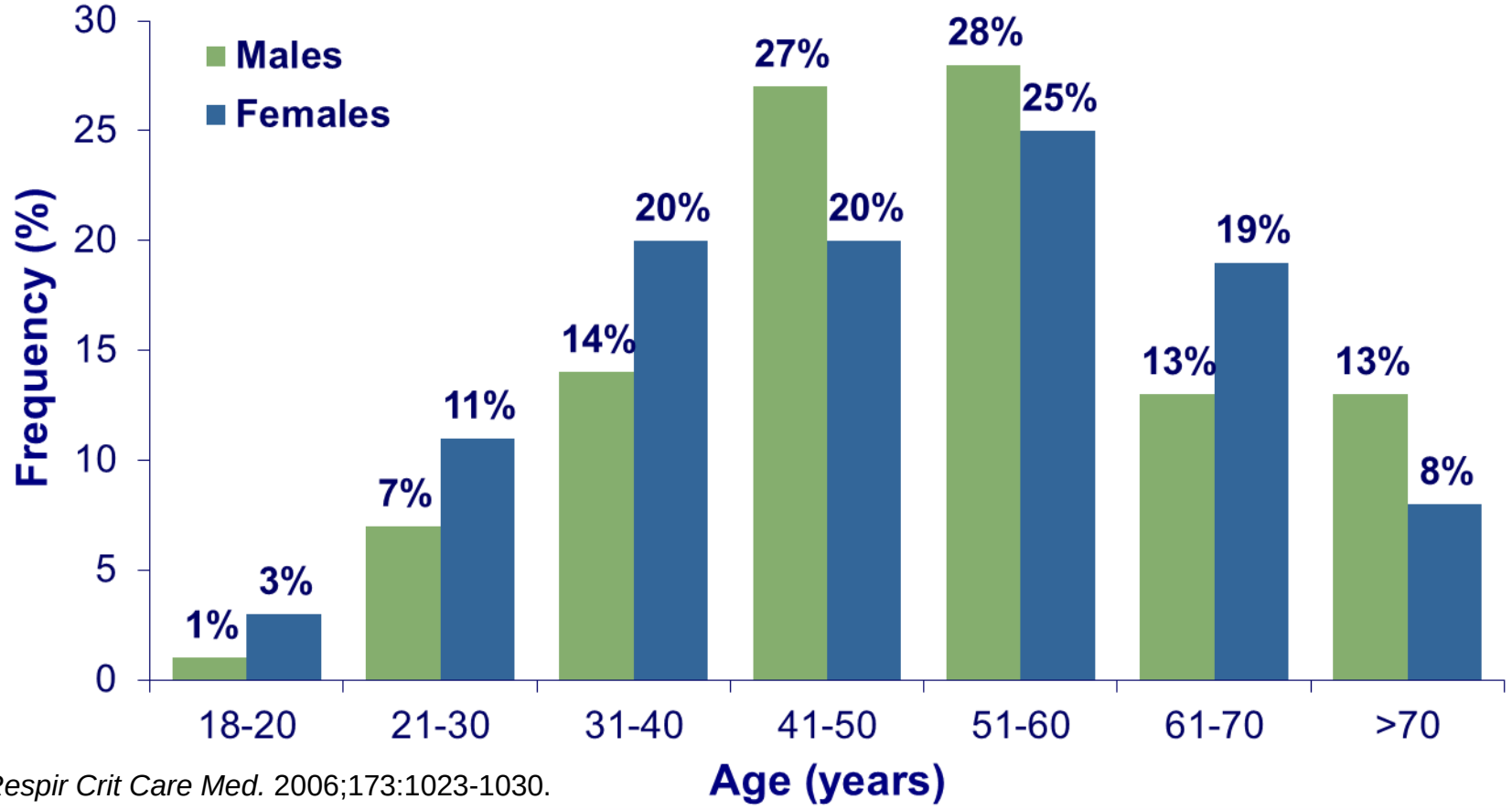
Epidemiology of PAH French Registry (2006)

- Enrolled patients newly diagnosed with PAH from October 2002 to October 2003
- Prevalence: 15 cases per million
  - IPAH = 5.9 per million
- Mean time between onset of symptoms and diagnosis: 27 months
- 88.4% 1-year survival for whole cohort
  - 89.3% in IPAH, familial and anorexigen group vs 71.8% predicted (NIH)
  - French university hospitals
- 674 patients

Humbert M, et al. *Am J Respir Crit Care Med.* 2006;173:1023-1030.

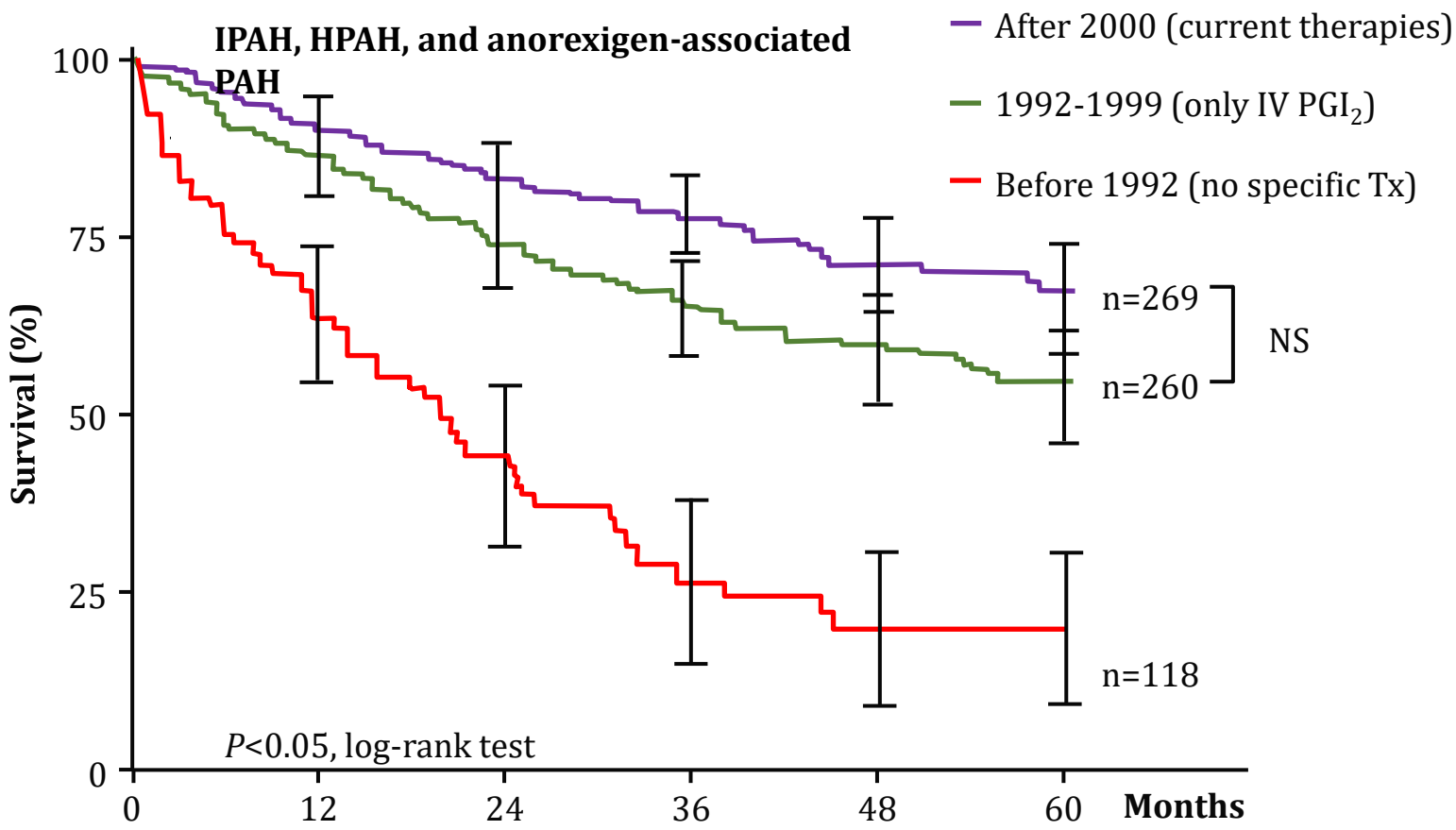
PAH May Occur at All Ages:

Distribution of Patients According to Age Based on Sex



Humbert M, et al. *Am J Respir Crit Care Med.* 2006;173:1023-1030.

PAH Prognosis with Modern Therapeutics



Adapted from: Sitbon et al. Slides presented at European Respiratory Society; September 16-18, 2007; Stockholm, Sweden.

Diagnosis: History, Physical and Testing

When to Suspect PAH:
Unexplained chronic dyspnea + one or more of the following:

- Presence of a systemic disorder or drug exposure known to be associated with PAH
- Review of systems/Exam/Testing Consistent
  - Physical exam findings consistent with PH
  - Study findings consistent with PAH
    - ECG
    - Echo
    - Right Heart Catheterization

Diagnosing PAH in Primary Care Setting: Who Is At Risk?

- Patients with connective tissue disorders
- Patients with congenital heart defects, including repaired shunts
- Patients exposed to drugs and toxins associated with PAH
- Patients with liver disease and portal hypertension
- Patients with HIV disease
- Patients with a family history of PAH
- Idiopathic PAH is an extremely rare condition – the vast majority of PAH seen in a primary care setting will be attributable to causative (secondary) conditions

Brown LM, et al. *Chest*. 2011;140(1):19-26.

History of Systemic Disease and Type V PH

TABLE 24 Pulmonary hypertension with unclear and/or multi-factorial mechanisms

Disorders associated with pulmonary hypertension	
1) Haematological disorders	Inherited and acquired chronic haemolytic anaemia • Sickle cell disease • β-thalassaemia • Spherocytosis • Stomatocytosis • Autoimmune disorders Chronic myeloproliferative disorders • Chronic myelogenous leukaemia • Polycythaemia vera • Idiopathic myelofibrosis • Essential thrombocytopenia • Others
2) Systemic disorders	Sarcoidosis Pulmonary Langerhans's cell histiocytosis Neurofibromatosis type 1
3) Metabolic disorders	Glycogen storage disease Gaucher disease
4) Chronic renal failure with/without haemodialysis	
5) Pulmonary tumour thrombotic microangiopathy	
6) Fibrosis mediastinitis	

European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

Table 7 **Drugs and toxins associated with pulmonary arterial hypertension**

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

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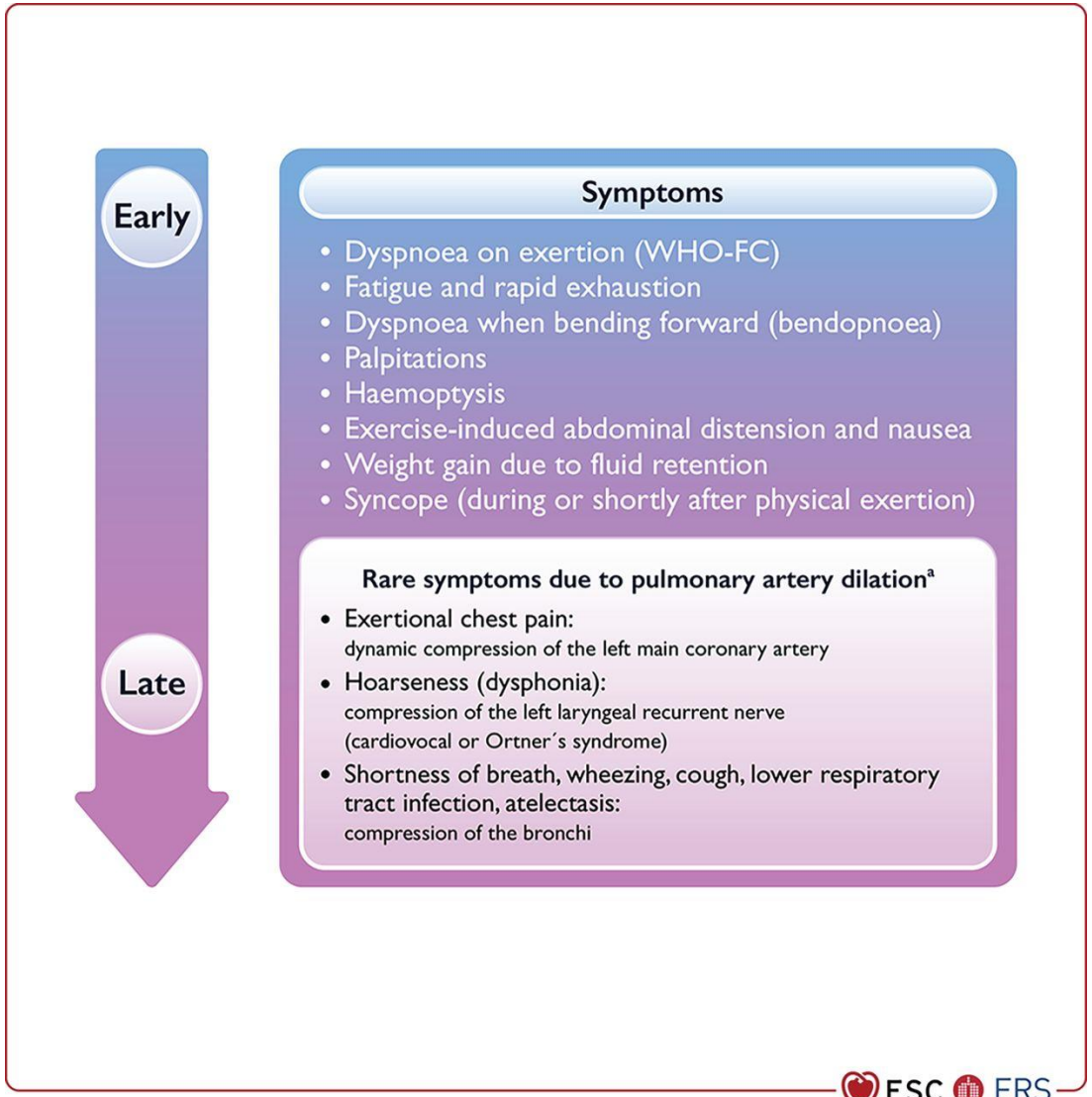
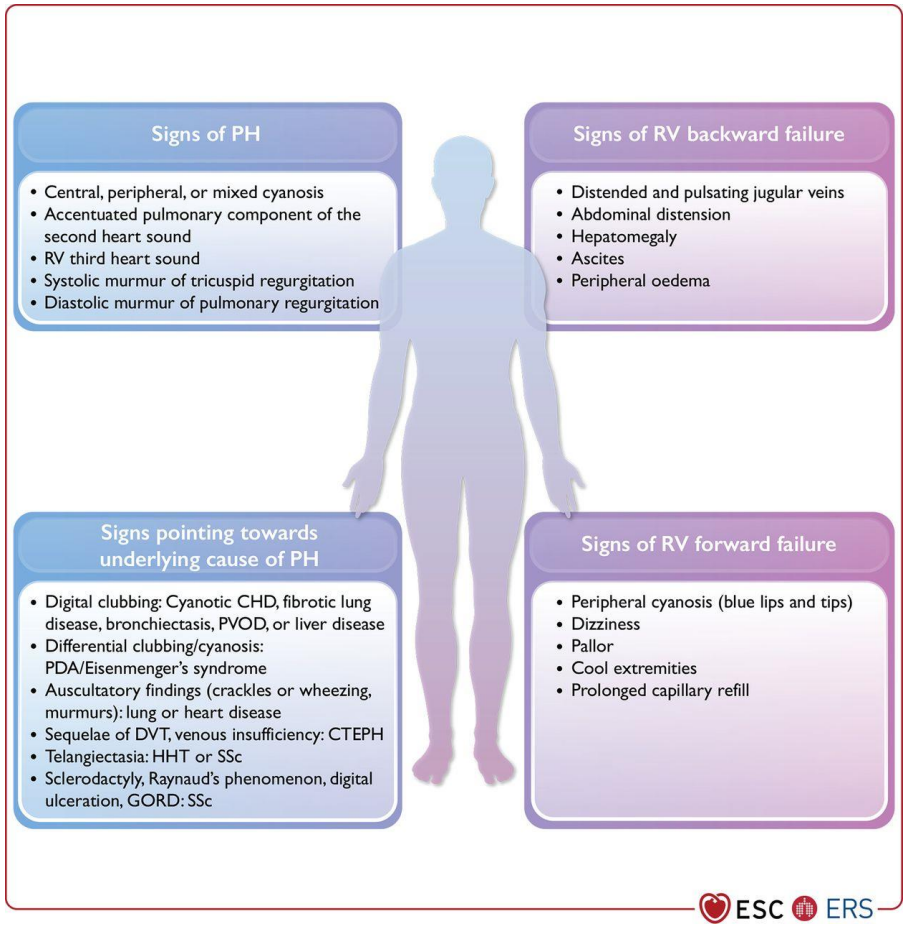
Symptoms in patients with pulmonary hypertension.



Marc Humbert et al. Eur Respir J doi:10.1183/13993003.00879-2022

Physical Exam Findings Consistent with PAH



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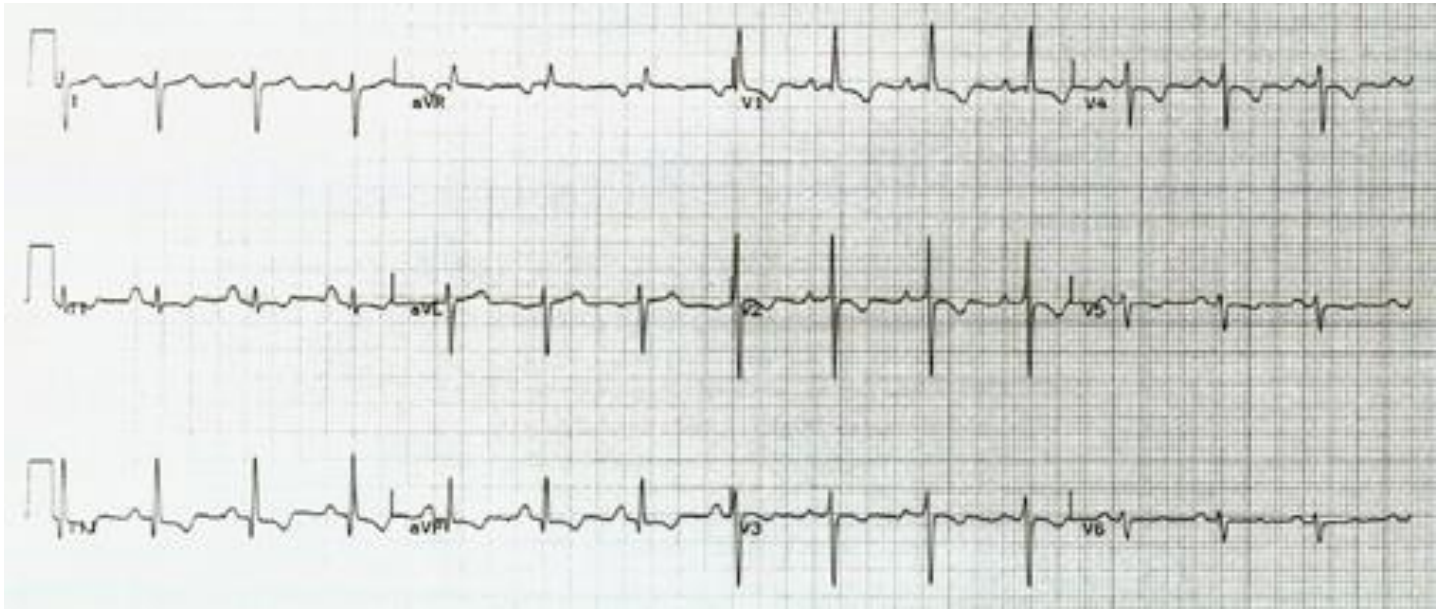
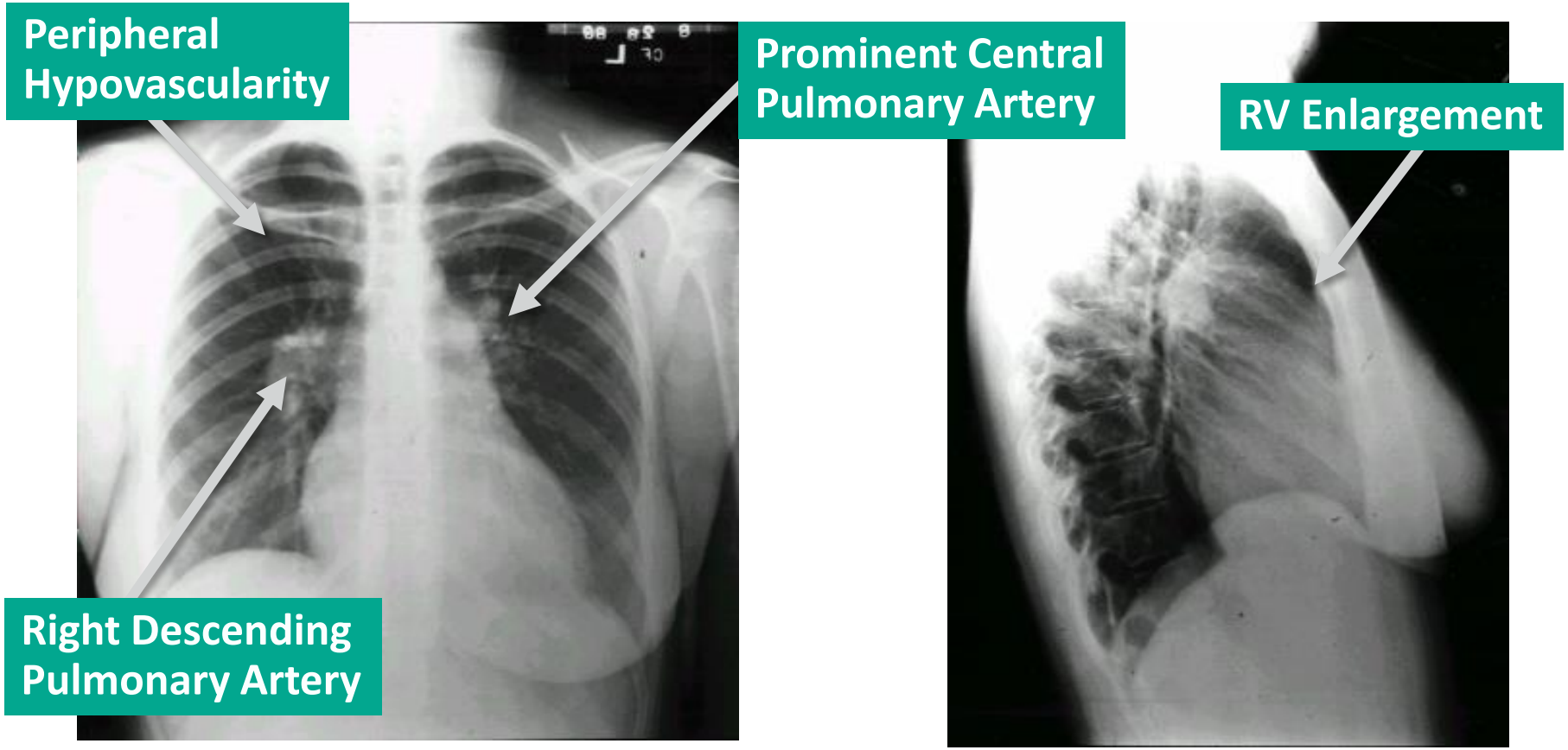
Electrocardiogram Findings Accompanying PAH

- P pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block, QTc prolongation[1]



[1] Humbert M, et al. *Eur Heart J* 2022; 00:1-114

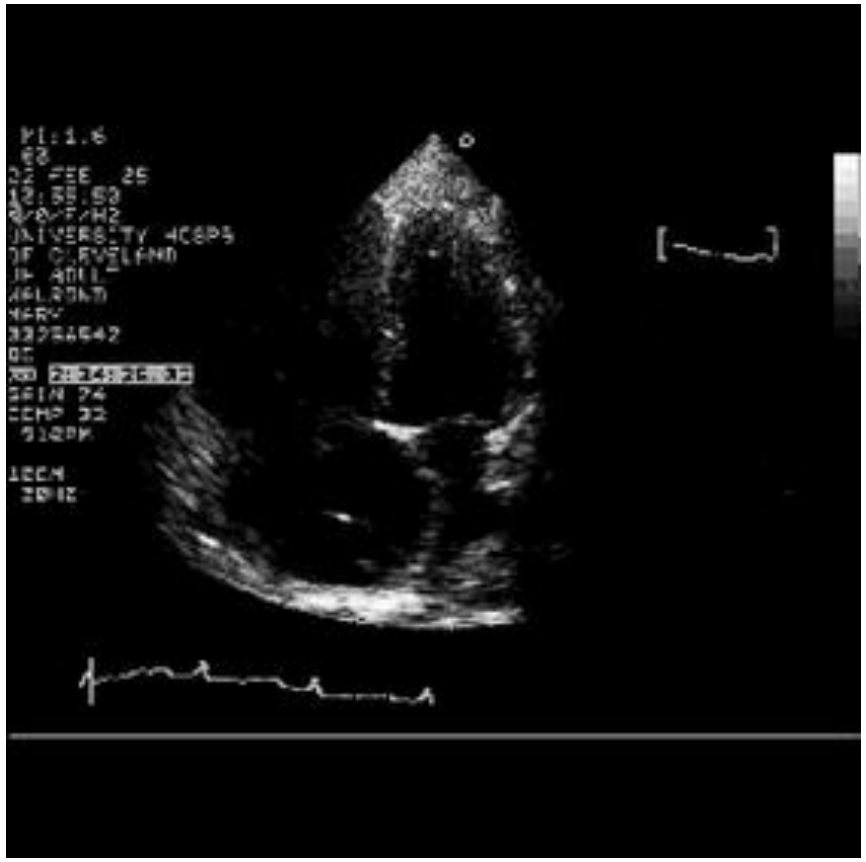
The CXR in PAH



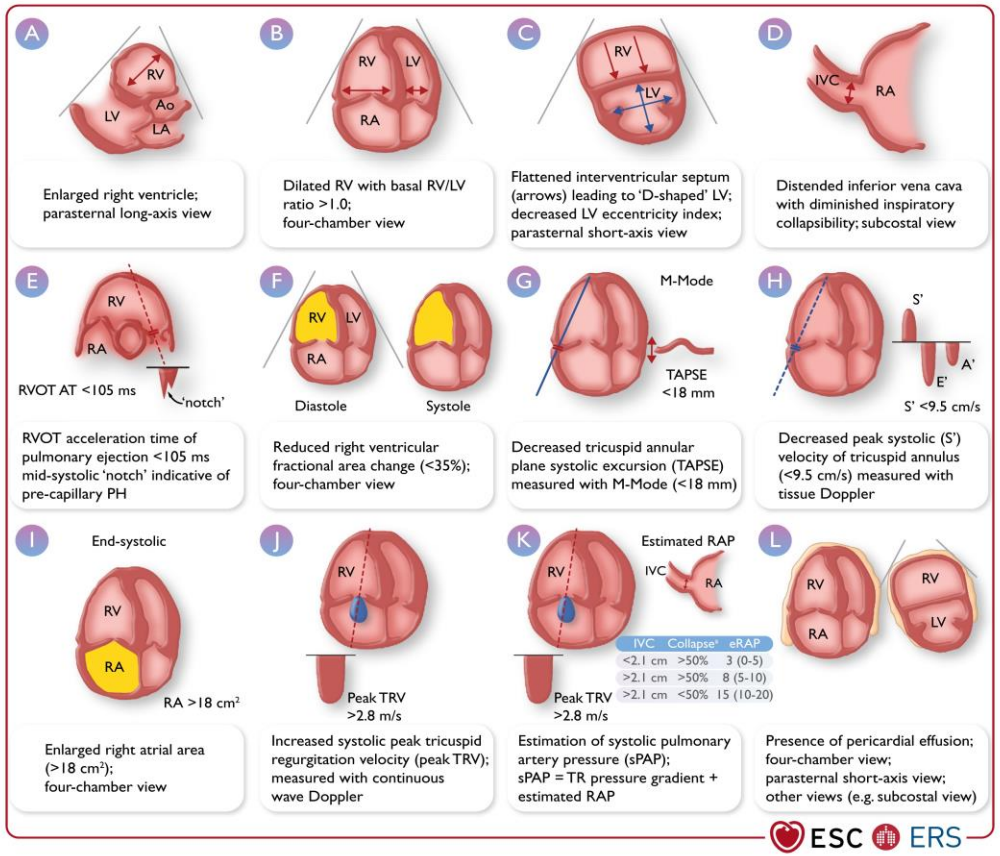
McLaughlin VV, et al. *JACC.* 2009;53:1573-1619.

Echocardiography in PAH

- T R
- RVE
- RAE
- RVH
- Flattening of IVS
- Dilated IVC



Transthoracic echocardiographic parameters associated with pulmonary arterial hypertension.



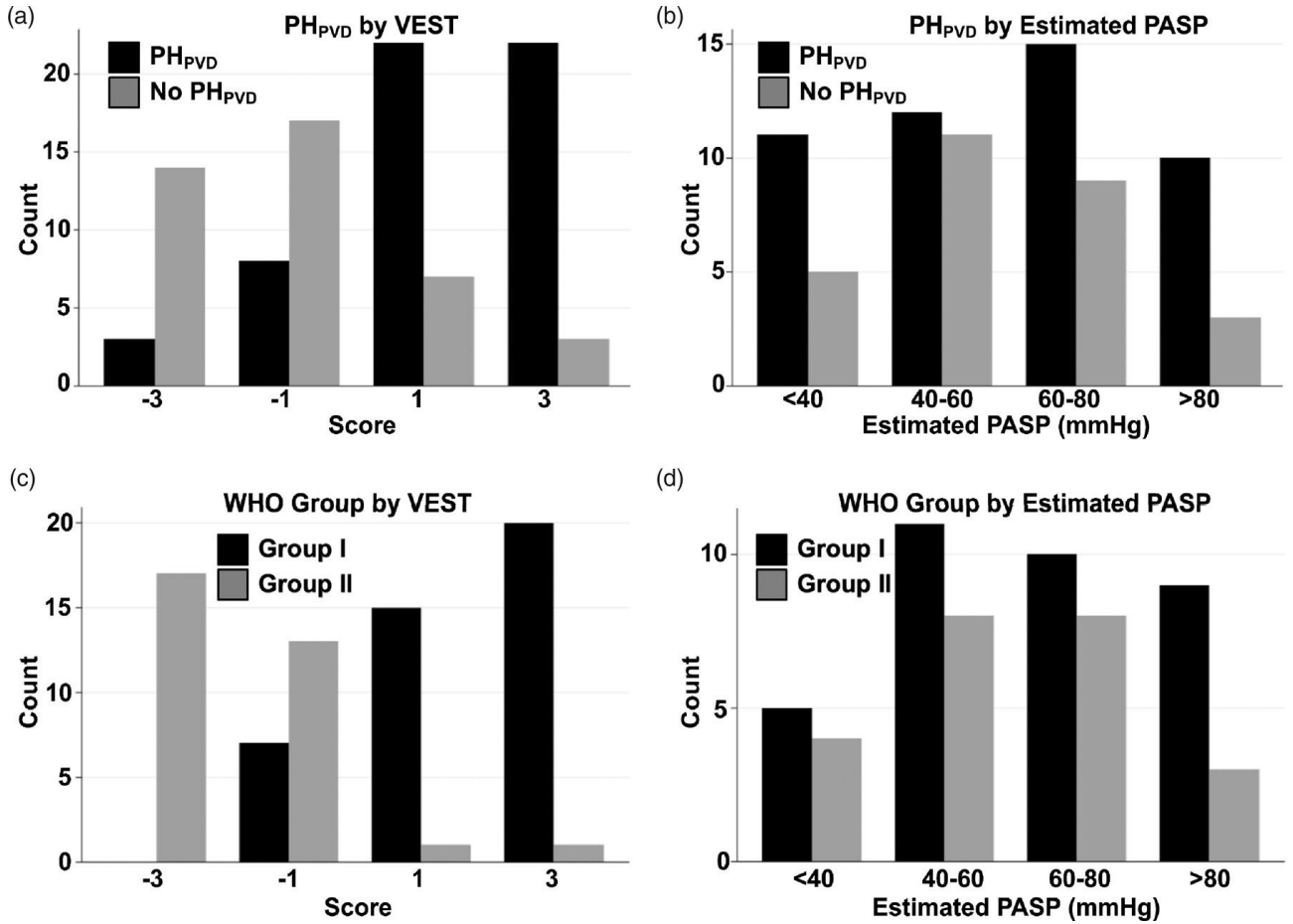
European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

Virtual Echocardiographic Screening Tool and Diagnostic Likelihood of Type I vs Type II PH

Echocardiographic parameter	Yes	No
Mitral E:e', lateral ≤10 [a]	+1	–1
Qualitative left atrial size normal or mildly enlarged	+1	–1
Systolic interventricular septal flattening	+1	–1

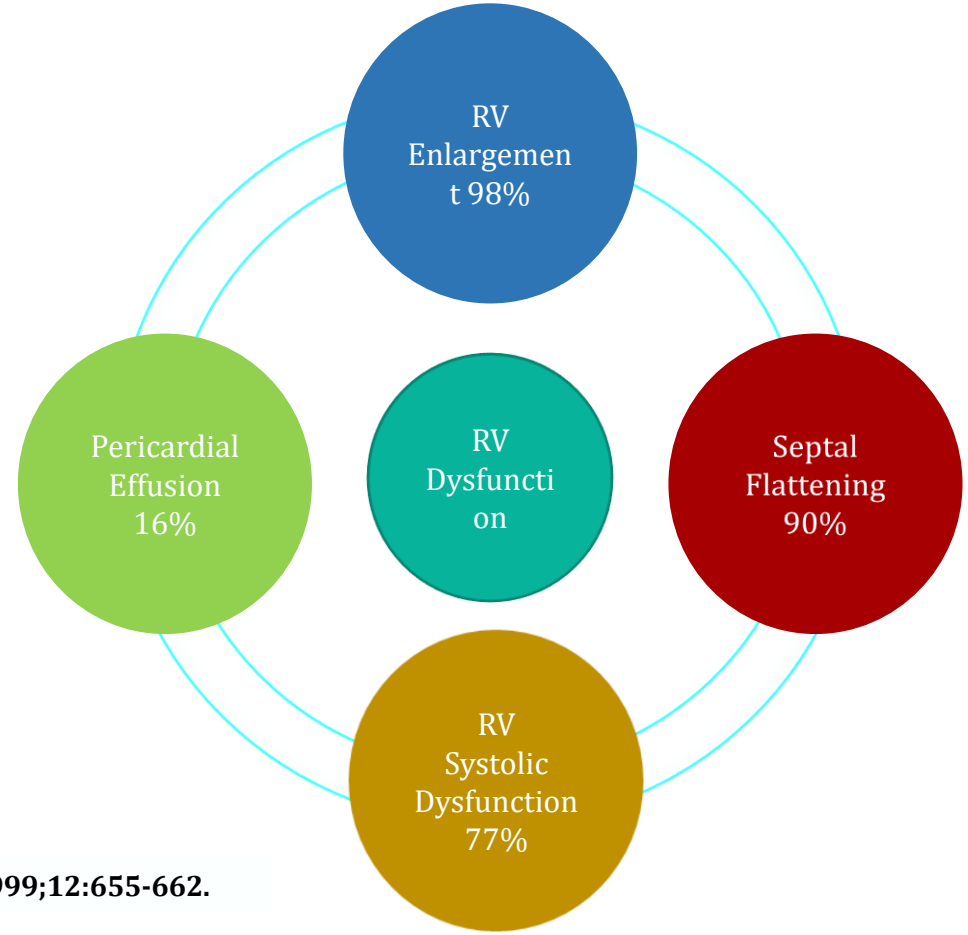
Pulm. circ., Volume: 10, Issue: 3, Pages: 1-10, First published: 01 September 2020, DOI: (10.1177/2045894020950225)

Virtual echocardiography screening tool to differentiate hemodynamic profiles in pulmonary hypertension



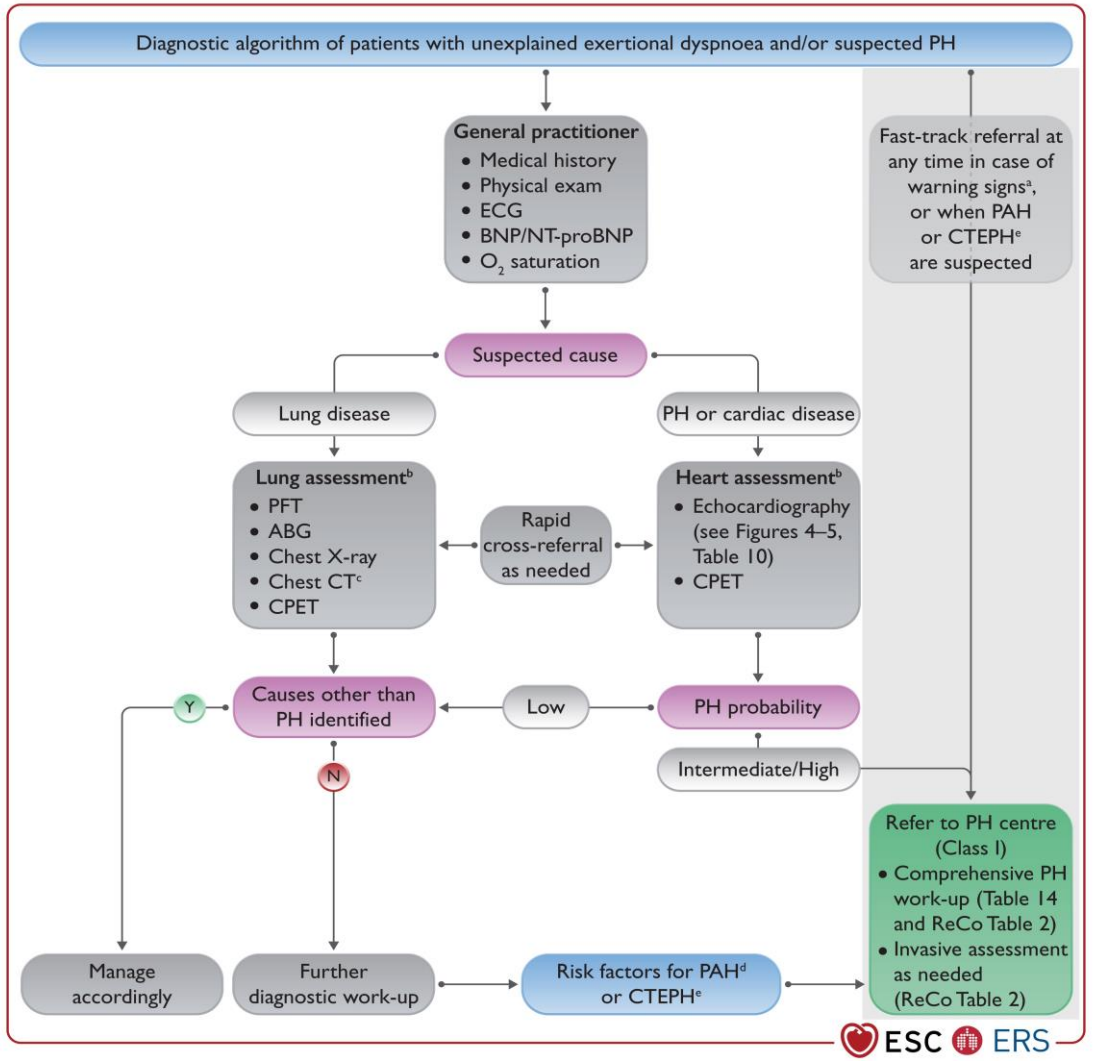
Pulm. circ., Volume: 10, Issue: 3, Pages: 1-10, First published: 01 September 2020, DOI: (10.1177/2045894020950225)

A Normal Echo is Uncommon in PAH



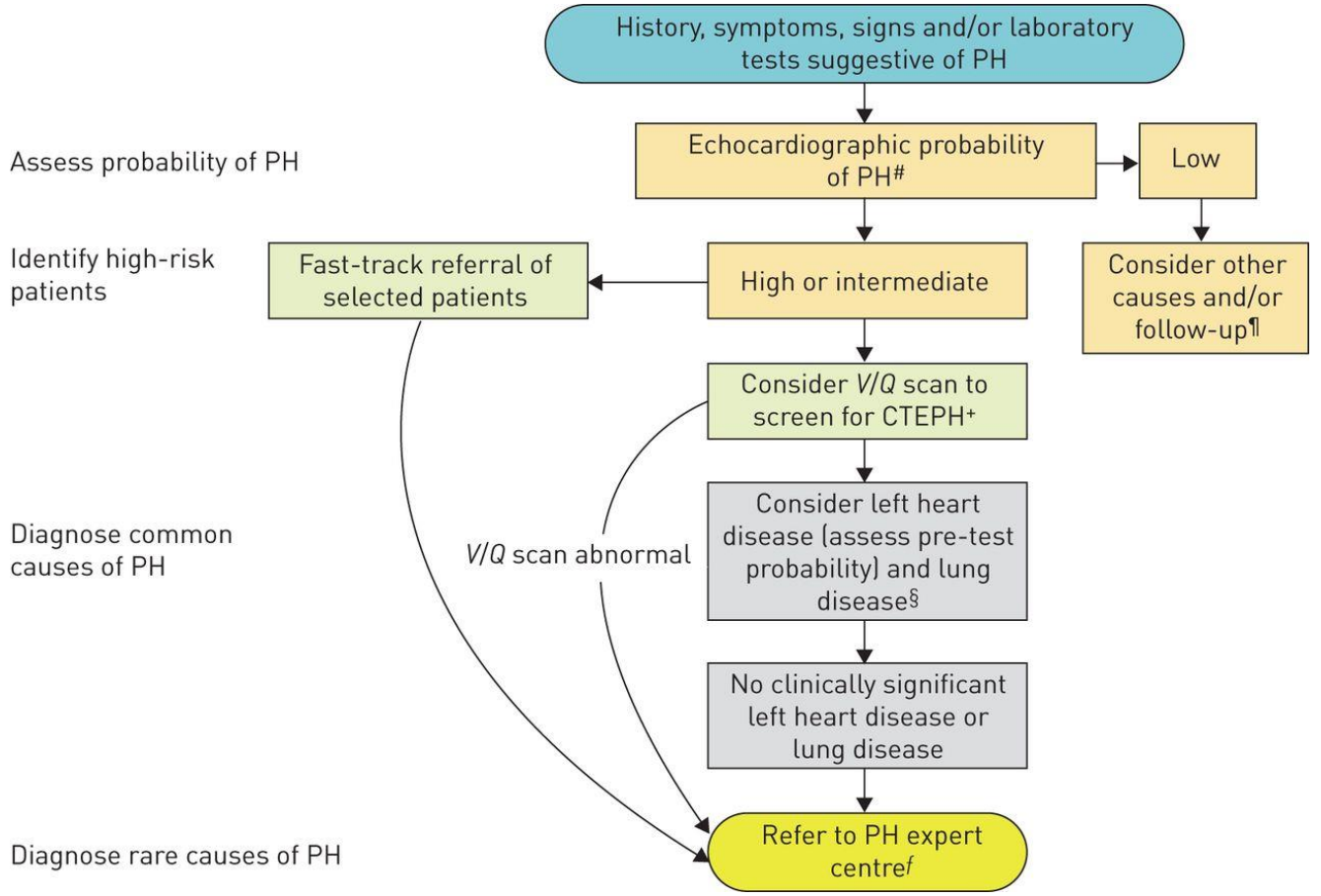
Bossone E, et al. *J Am Soc Echocardiogr.* 1999;12:655-662.

- Focus of a primary PH workup
  - The primary goal is to raise early suspicion of PH and ensure fast-track referral to PH centers in patients with a high likelihood of PAH, CTEPH, or other forms of severe PH.
  - The second objective is to identify underlying diseases, especially LHD (group 2 PH) and lung disease (group 3 PH), as well as comorbidities, to ensure proper classification, risk assessment, and treatment.



European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

ESC Simplified Approach to Diagnosis of PAH



Frost et al. Eur Respir J 2019; 53: 1801897

Summary of diagnostic features of PAH

- History of systemic disease or drugs associated with PH.
- Physical exam consistent with R heart overload
- ECG with RVH and strain
- Echocardiogram with significant R ventricular and R atrial enlargement in isolation and NOT with features consistent with L heart disease (which is very common).

Illustrative Case PAH

Case 1 - History

- 32-year-old female her for an initial evaluation of pulmonary arterial hypertension. She is referred for progressive complaints of shortness of breath on exertion that worsened after a tubal ligation that was preformed approximately 1 year before. CT angio was performed 4 months prior to consultation and was negative for PE. Patient also states she has a dry cough, occasional chest pain, fatigue and dizziness. She has never had a syncopal episode. She has never been tested for OSA. She is a former smoker; 1 pack per week for 16 years. Quit 3 years ago. (-) family history of VTE, cardiac disease.

Initial Data

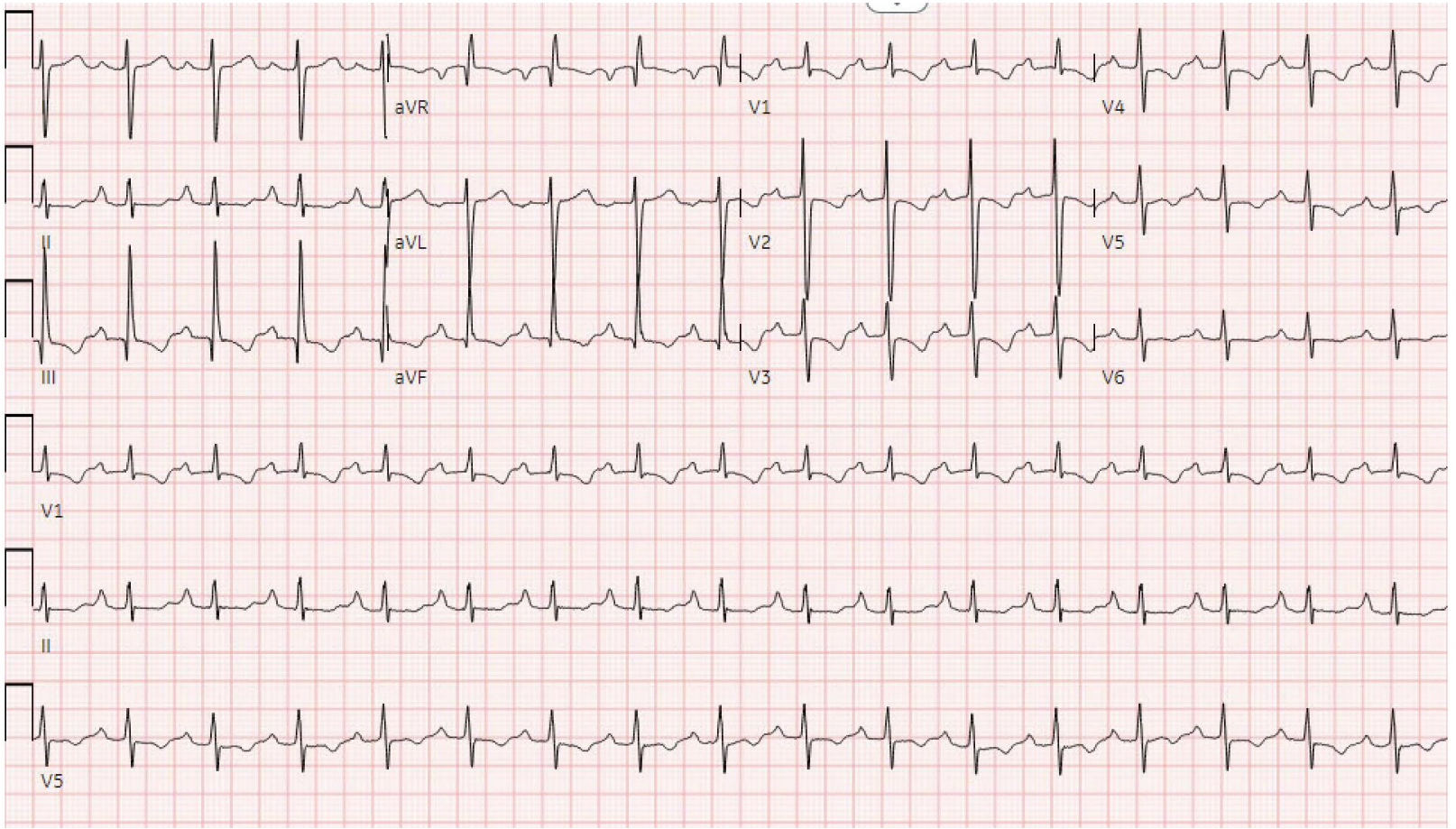
Physical Exam

- Normal appearing
- (+) 6 cm JVD
- HRRR, ↑ P2, II/VI SEM LLSB
- Lungs clear
- (-) Abdominal Exam
- (-) Clubbing or cyanosis
- 1-2+ LE edema

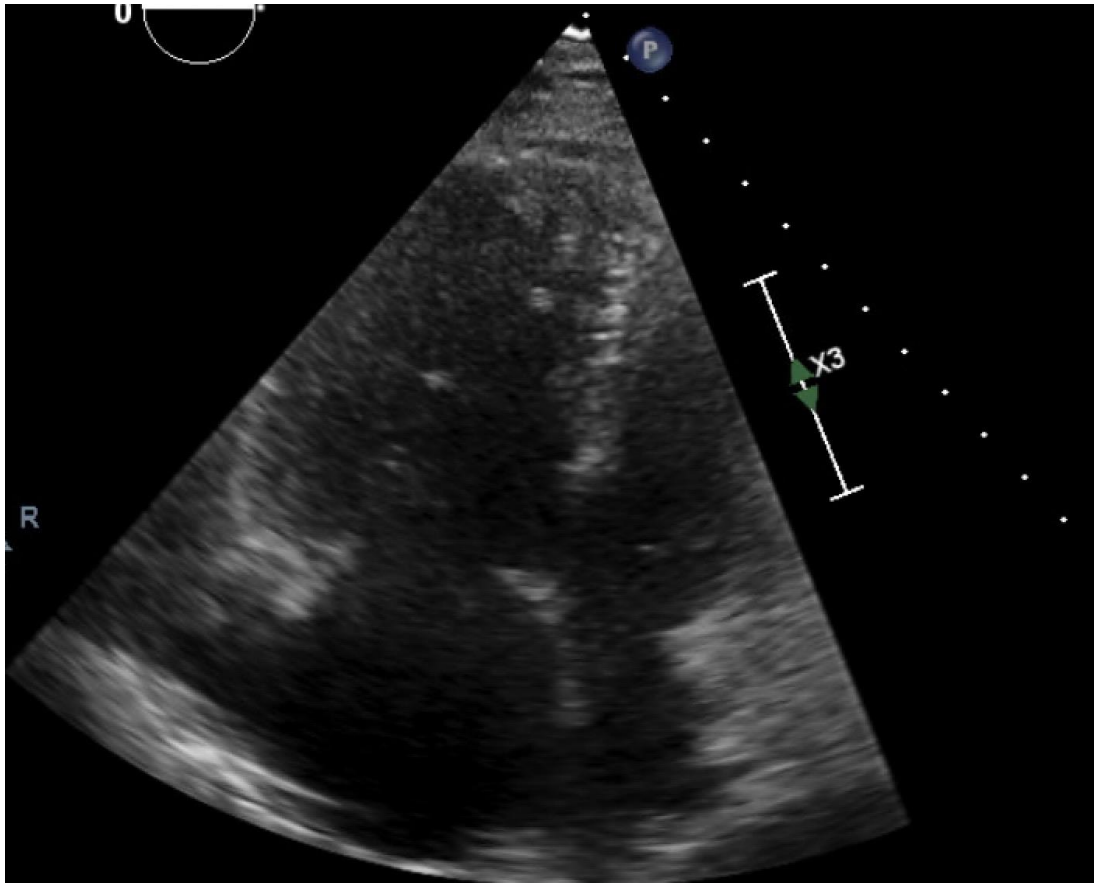
Laboratory Data

- Normal Chem Complete
- Normal CBC and differential
- Normal lactate
- BNP = 225 pg/ml
- Normal Spirometry
- 6 minute walk significantly reduced. 261 m 97%, HR 86-> 122, BORG = 4

ECG

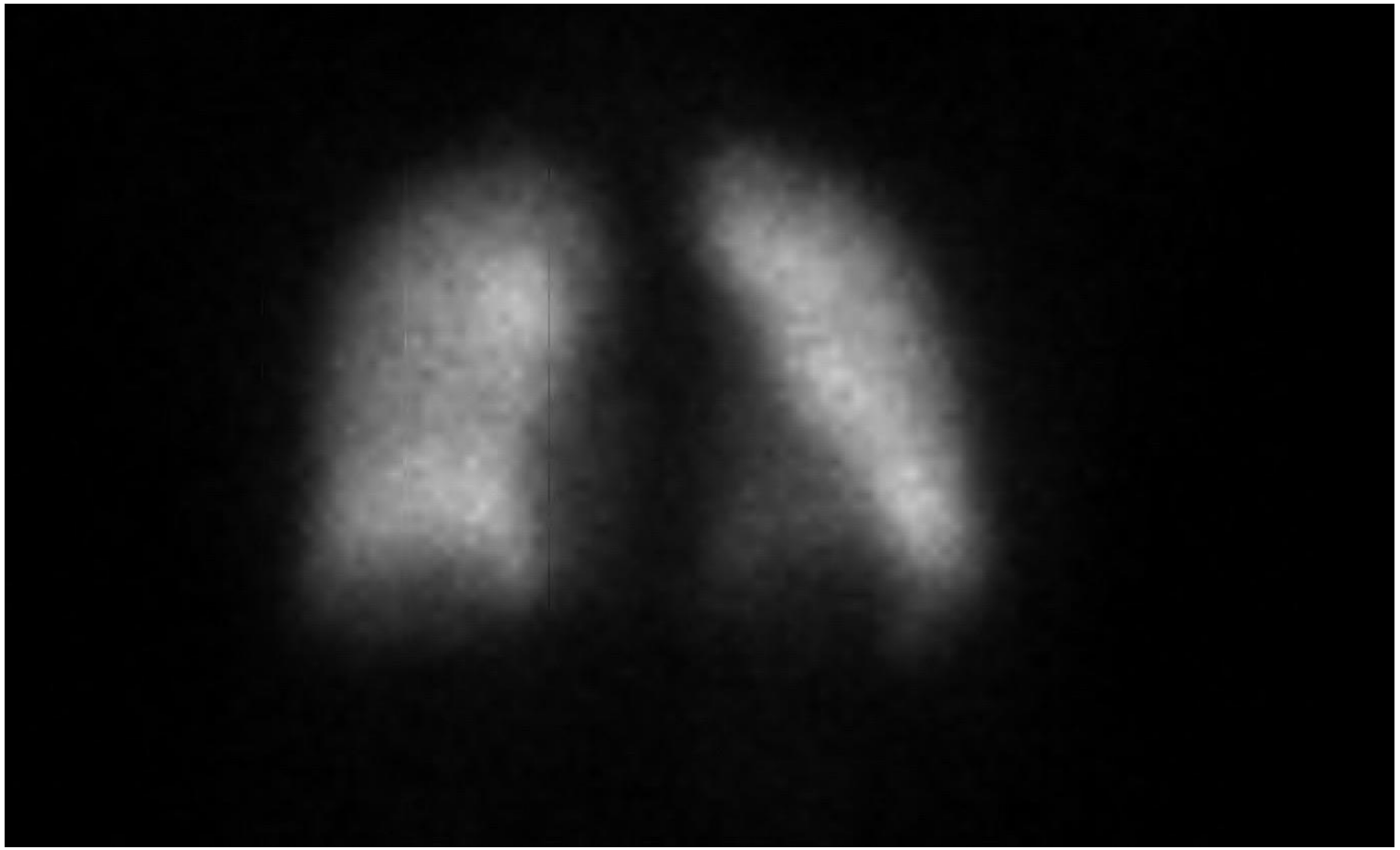


Echocardiogram



- Normal LV
- RV is severely enlarged with reduced function and mild to moderately dilated RA.
- Positive bubble study. (Grade 1)
- Trace Mitral valve regurgitation, normal aortic valve
- Moderate TR, RVSP = 83 mm Hg, TAPSE =16 mm,

V/Q



Cardiac Catheterization

- Aortic BP 117/81
- RV = 84/8
- PAP = 84/43 , mean = 59 mm Hg
- LVEDP = PCWP = 9 mm Hg
- RA = 15 mm Hg
- CI =1.7 by Fick
- SpO2 without step-up
- PVR = 17.9 WU
- No response to 20 ppm NO,

Initial Therapy

- Triple therapy planned.
  - Infusion epoprostenol -> Treprostinil (In ICU) (MVO2 49->62%)
  - Macitentan 10mg (Week 2)
  - Tadalafil 40 mg daily (Week 3-4)
- Follow up at 4 and 8 weeks and 1-2x weekly on telephone
- At 4 weeks coincident with clinical genetics referral. “I think you take care of my uncle who has the same thing”

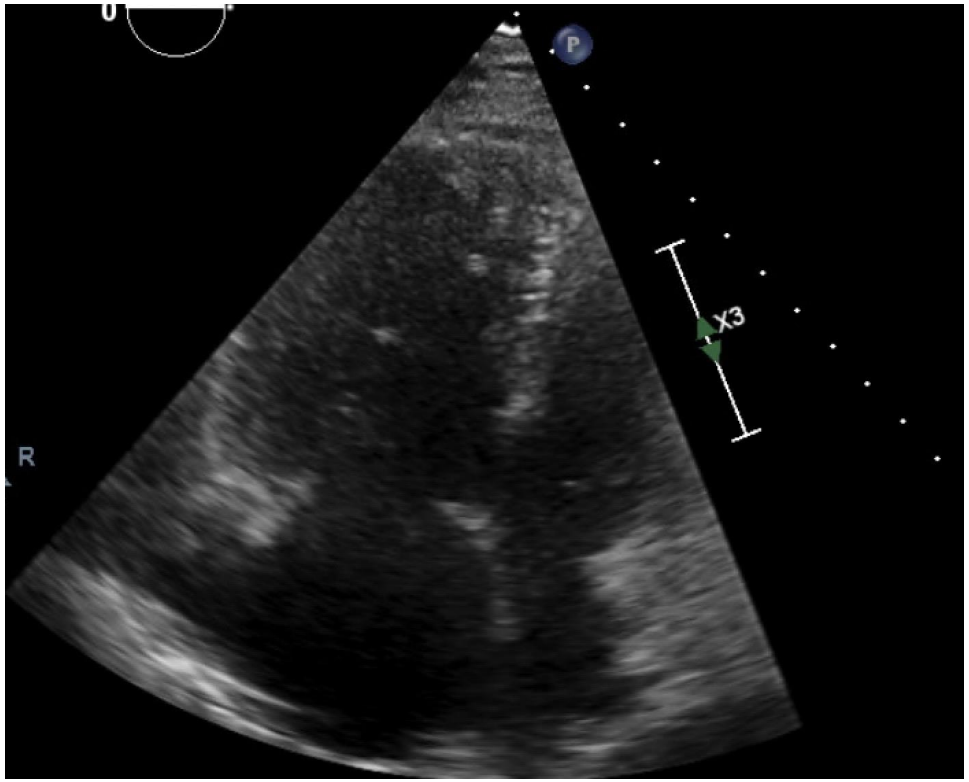
8 Week Clinic Visit

Clinical/Lab	Presentation	8 weeks
6 Minute Walk	261 m	409 m
BNP	225 pg/ml	46 pg/ml
Edema	1-2+	0
FC	IV	II-III

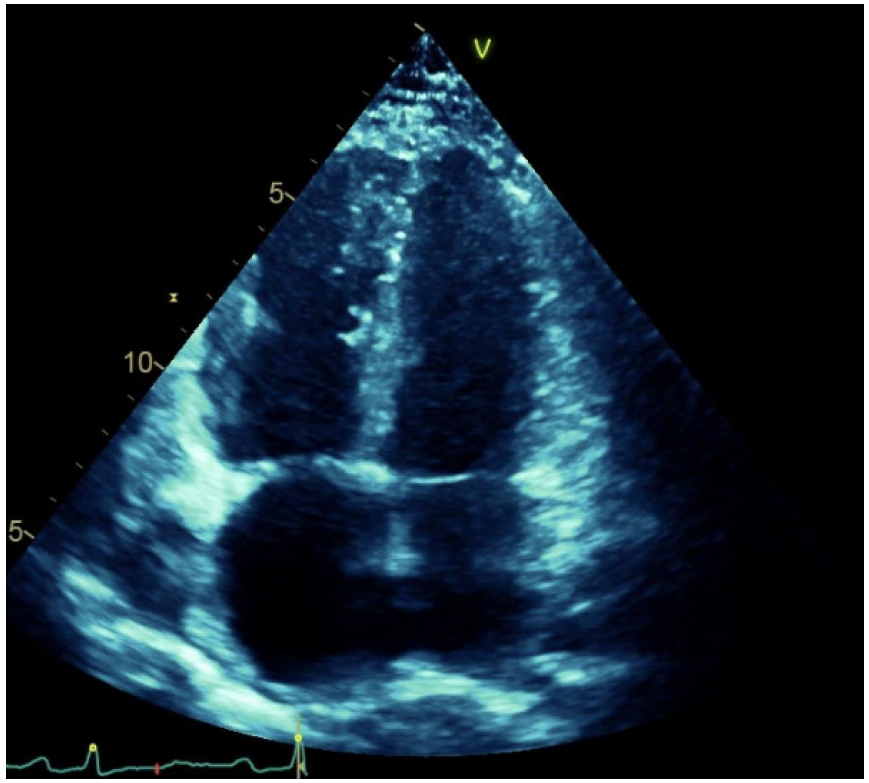
Since presentation, patient found out that an estranged relative also was reported with PAH. When we learned this, patient was referred to clinical genetics. She tested (+) for BMPR2 mutation.

8 Week Clinic Follow Up

Initial



8 Week Post Treatment

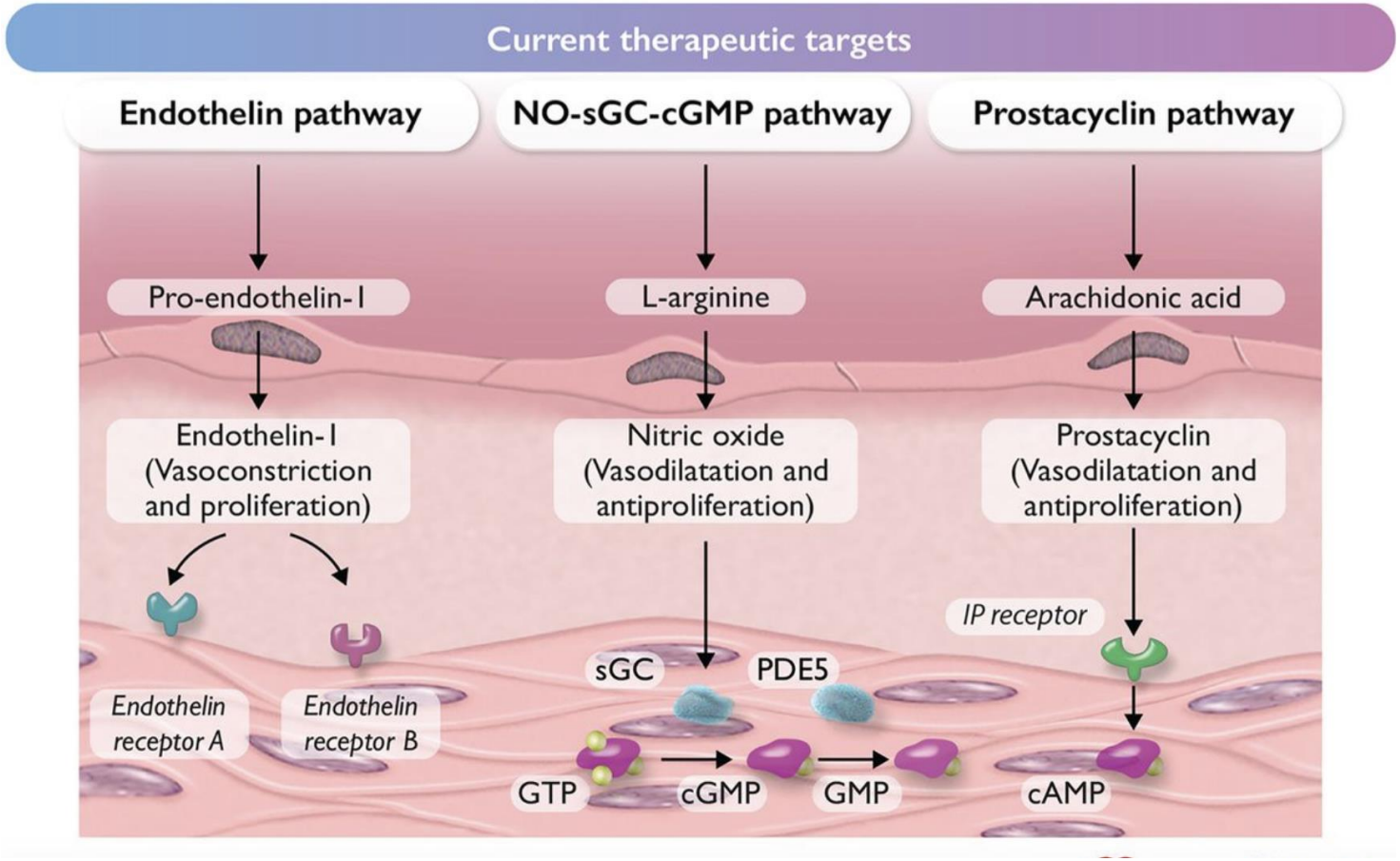


Summary Case 1

- ”Classic” genetically associated PAH
- Presenting late and high risk (80% FC III or IV)
- mPAP > 50 mm Hg
- Decreased CI
- Very High PVR
- Significant RV/RA dilation and dysfunction
- NO response (-)
- CTEPH excluded

Therapy of PAH

Current therapeutic targets of pulmonary arterial hypertension (group 1)

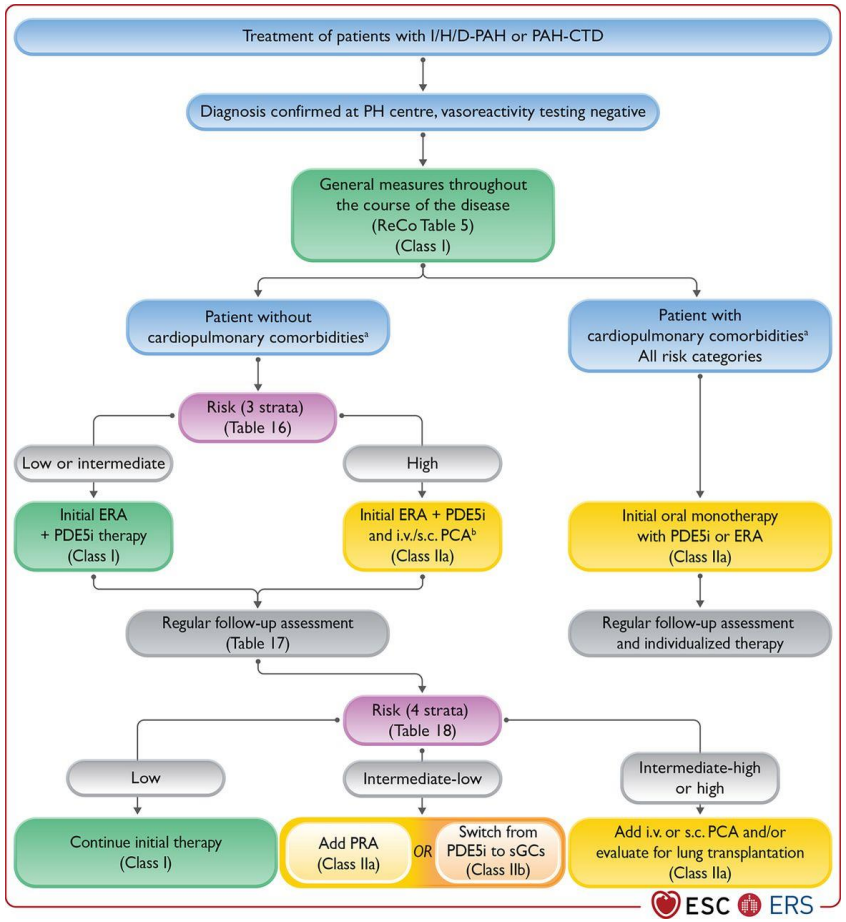


Marc Humbert et al. Eur Respir J
doi:10.1183/13993003.00879-2022

Approach to Therapy of PAH

- Secure diagnosis with right heart catheterization and exclusion of chronic thromboembolic disease.
- Refer to PAH center
- Assess risk
- General Measures (oxygen, diuretic, vaccination, anemia treatment, prevention of pregnancy, physical rehabilitation in treated patients)
- Initiate (combination) therapy based on risk
- Reassessment of risk at 1-3 month intervals
- Escalation of therapy if not low risk

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



Marc Humbert et al. Eur Respir J doi:10.1183/13993003.00879-2022

3 Strata Risk Assessment

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%

Adapted from:European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

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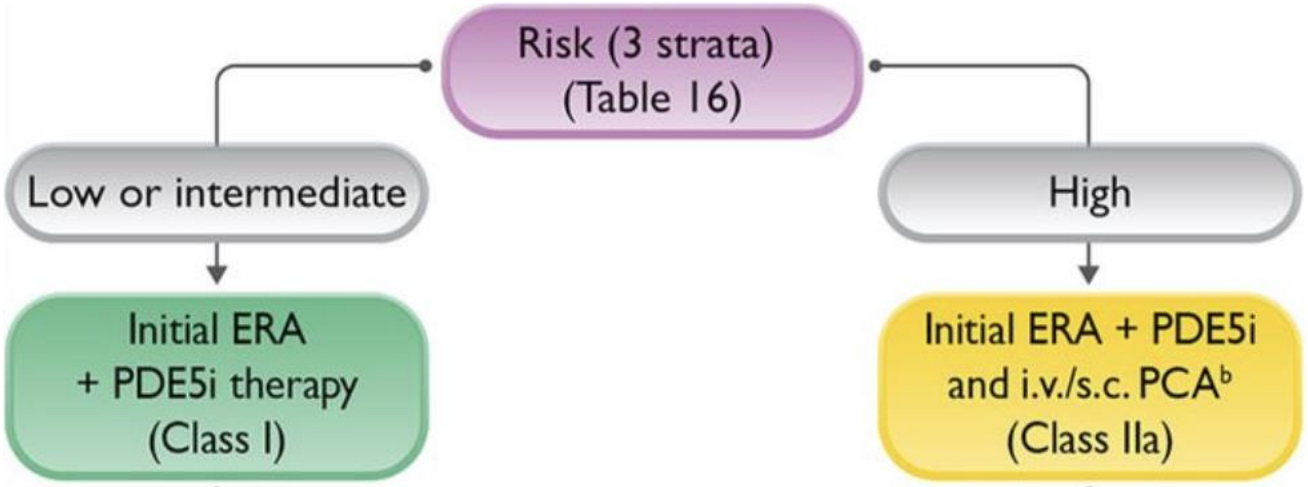

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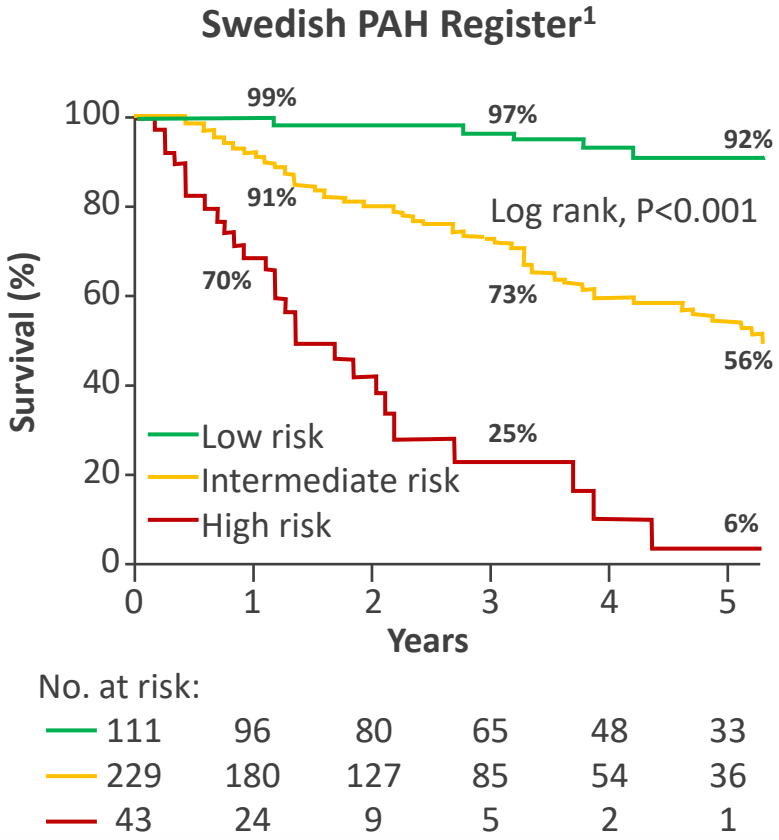
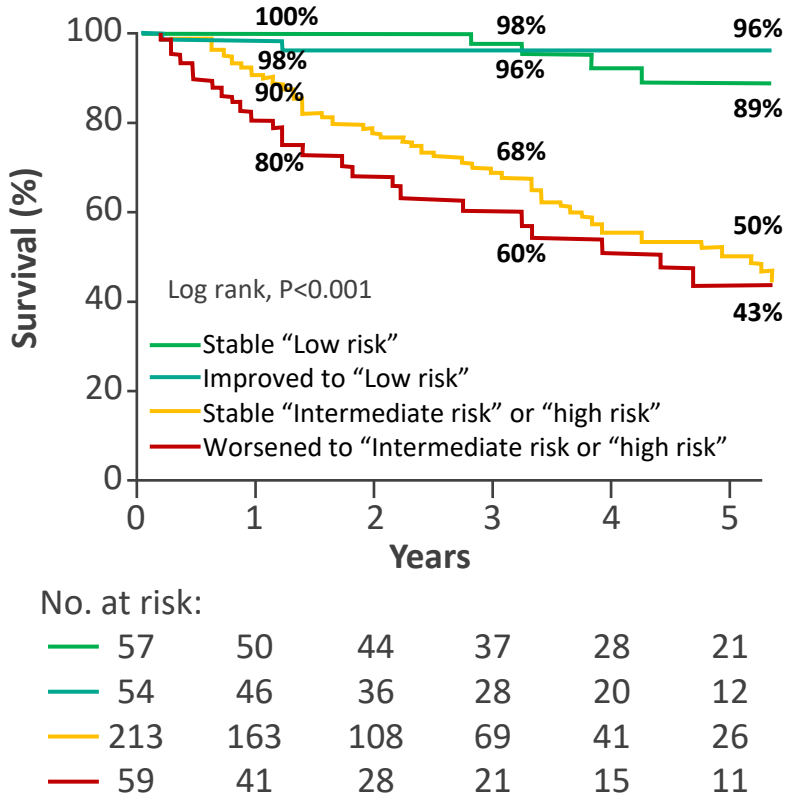
Risk Stratification at Follow up Within the Year after Diagnosis on Therapy



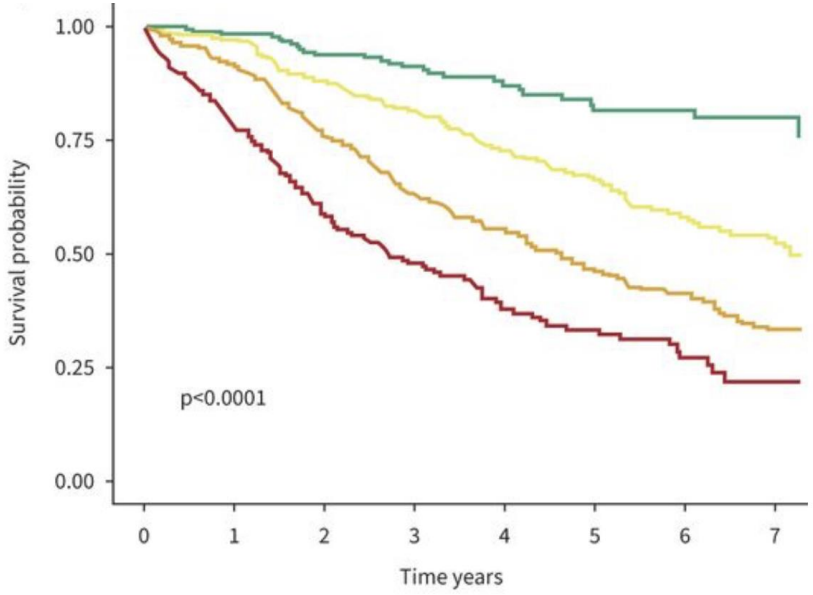
Kylhammar D. et al. *European Heart Journal*, Volume 39, Issue 47, 14 December 2018, Pages 4175–4181

Improvement or Decline in Risk Profile and Survival



Kylhammar D. et al. *European Heart Journal*, Volume 39, Issue 47, 14 December 2018, Pages 4175–4181

Analysis of COMPERA Database Follow Up Survival – 4 Strata Risk



Number at risk								
Low risk	240	189	154	126	95	66	53	39
Intermediate–low risk	395	322	255	205	160	119	80	59
Intermediate–high risk	534	413	289	212	162	107	76	56
High risk	245	159	104	69	48	32	19	9

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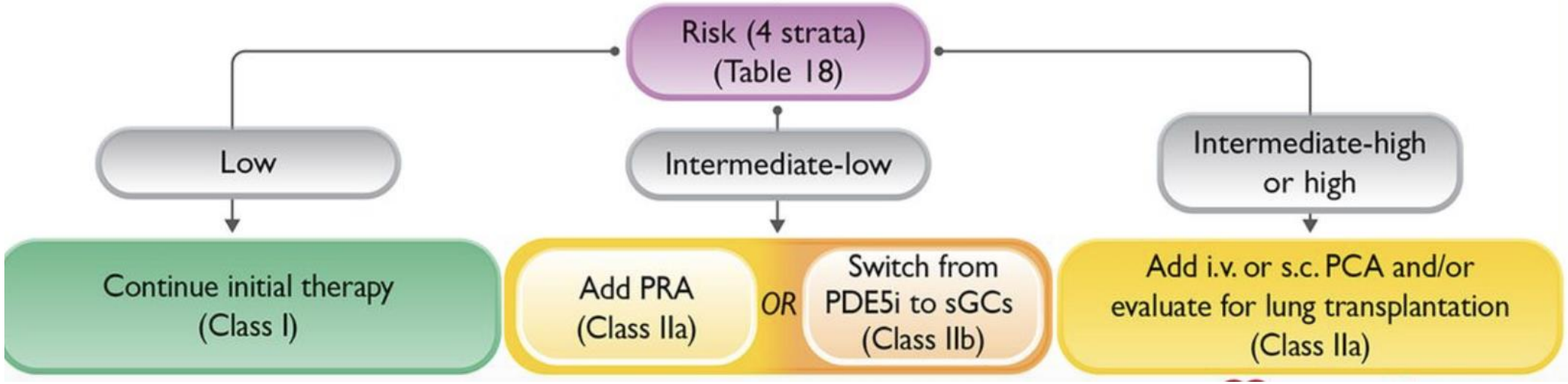
Four Strata Risk Assessment

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

European Heart Journal, ehac237, https://doi.org/10.1093/eurheartj/ehac237 26 August 2022

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



Marc Humbert et al. Eur Respir J doi:10.1183/13993003.00879-2022

Summary

- Review current classification system for pulmonary hypertension (PH) with an emphasis on rare types which require specialized referral.
- Review key elements of workup which often separate pulmonary arterial hypertension from other types of PH.
- Briefly review modern approaches to therapy and risk stratification of patients with pulmonary arterial hypertension (PAH).