Navigating the identification, diagnosis and management of pulmonary hypertension using the updated ESC/ERS guidelines

Host: Marc Humbert

Speaker: Simon Gibbs

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– **Actelion:** consultancy (current), board or advisory committee (current), speaker (current)
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– **GSK:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
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– **Pfizer:** consultancy (current), board or advisory committee (current), speaker (current), research support (past)

Navigating the identification, diagnosis and management of pulmonary hypertension using updated ESC/ERS guidelines

Case 1

Simon Gibbs
Imperial College London &
Hammersmith Hospital, London, UK

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– **United Therapeutics:** educational grant (current)

Abbreviations we shall use

- PH, pulmonary hypertension
- PAH, pulmonary arterial hypertension
- CTEPH, chronic thromboembolic pulmonary hypertension
- RV, right ventricle

69 y old female: presenting complaint

2 years	**gradual onset breathlessness on exertion**
18 months	**ankle swelling**
2 weeks	**admitted to local hospital: poor exercise tolerance and low oxygen saturation** **echo: ? pulmonary hypertension** **treated with diuretics and oxygen** **Referred to Hammersmith Hospital**

69 y old female

WHO functional class III

Breathless walking 10 – 15 m on the level

No orthopnoea, paroxysmal nocturnal dyspnoea, syncope, angina or palpitations

<u>Past history</u>

- **Systemic hypertension**
- **Diabetes mellitus type II**
- **Chronically impaired renal function (eGFR 34 ml/min)**
- **Hypercholesterolaemia**
- **Cholecystectomy**

69 y old female

Ex smoker 20 y previously; 20 pack years

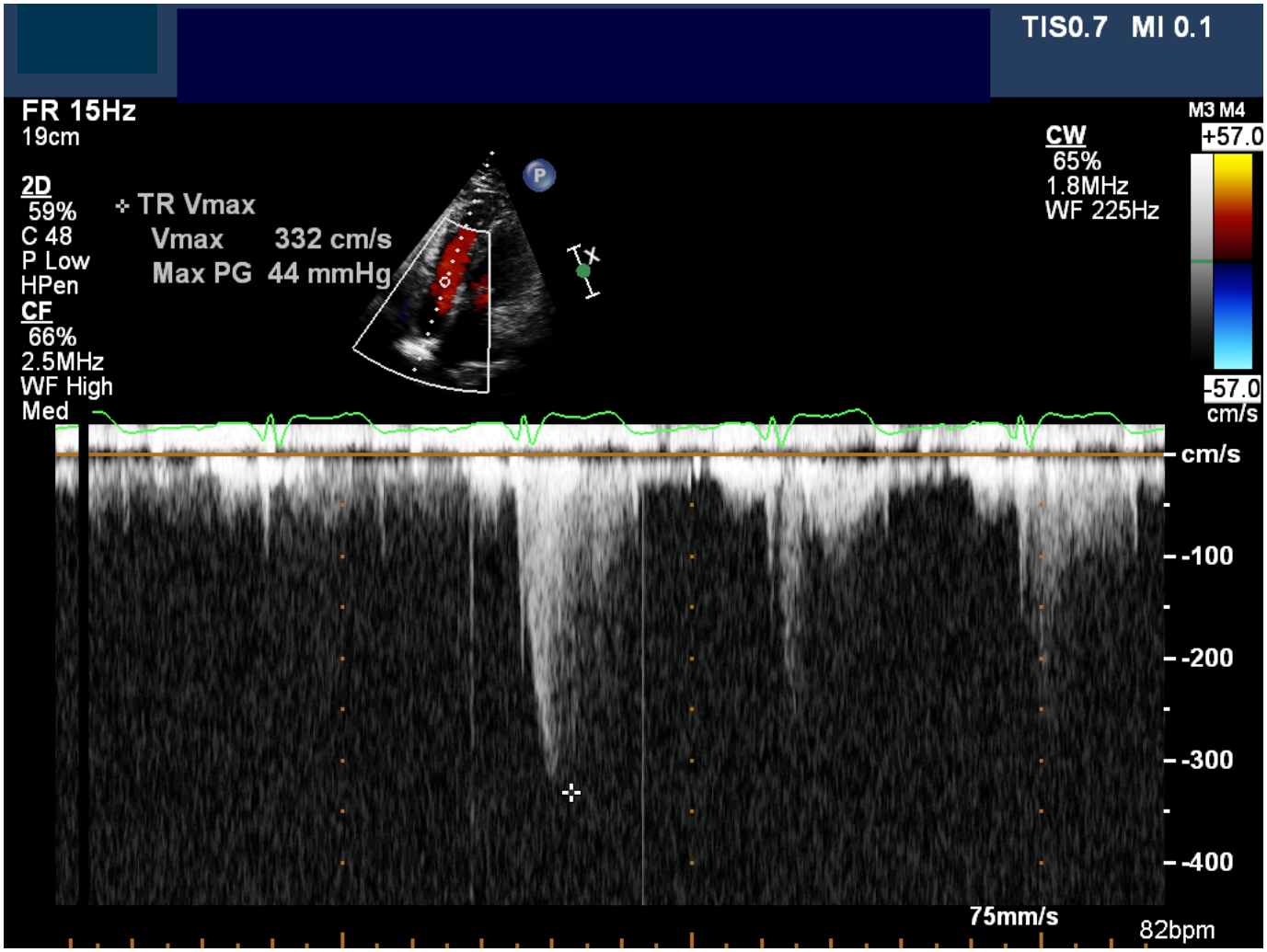
Treatment included:

- **furosemide 40 mg od**
- **bisoprolol 5 mg od**
- **ramipril 2.5 mg od**
- **atorvastatin 40 mg od**
- **gliclazide MR 30 mg od**

69 y old female: examination

Well perfused
Heart rate 80 bpm
BP 135/74
Jugular venous pressure +7 cm by inspection
Respiratory rate 18 per min
Oxygen saturation on oxygen 2l/min = 85%
Loud P2
Chest clear
Mild ankle swelling

Echocardiogram tricuspid regurgitation velocity



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Question: In this patient with a tricuspid regurgitation velocity of 3.3 m/s:

- This velocity translates to a mean pulmonary artery pressure of 24 mm Hg
- Pulmonary hypertension is not likely to be clinically significant and the patient should be discharged
- The patient requires cardiac catheterization
- Further echocardiographic measurements should be made at this stage
- A repeat echocardiogram should be undertaken in 4 - 6 months

Echocardiographic probability of PH in symptomatic patients with a suspicion of PH

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

PH = pulmonary hypertension.

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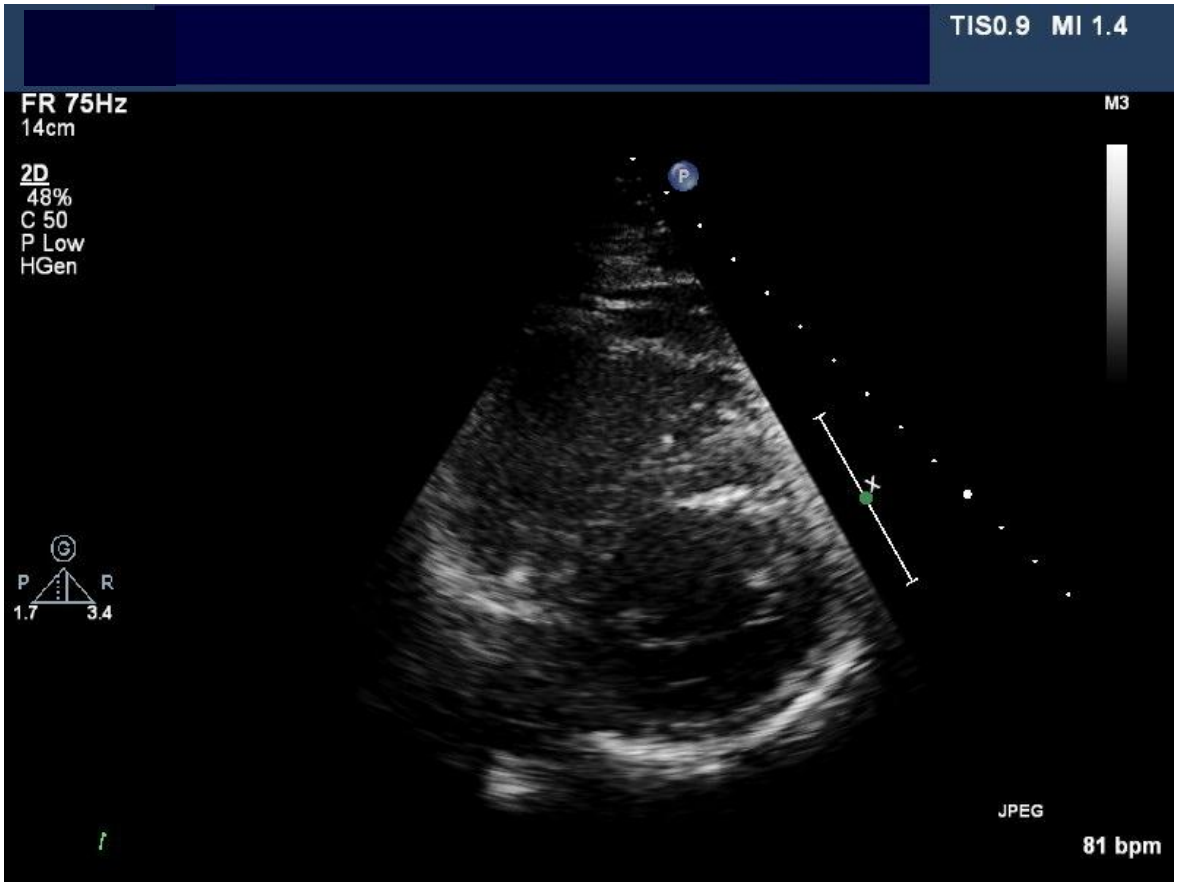
Echocardiogram parasternal short axis



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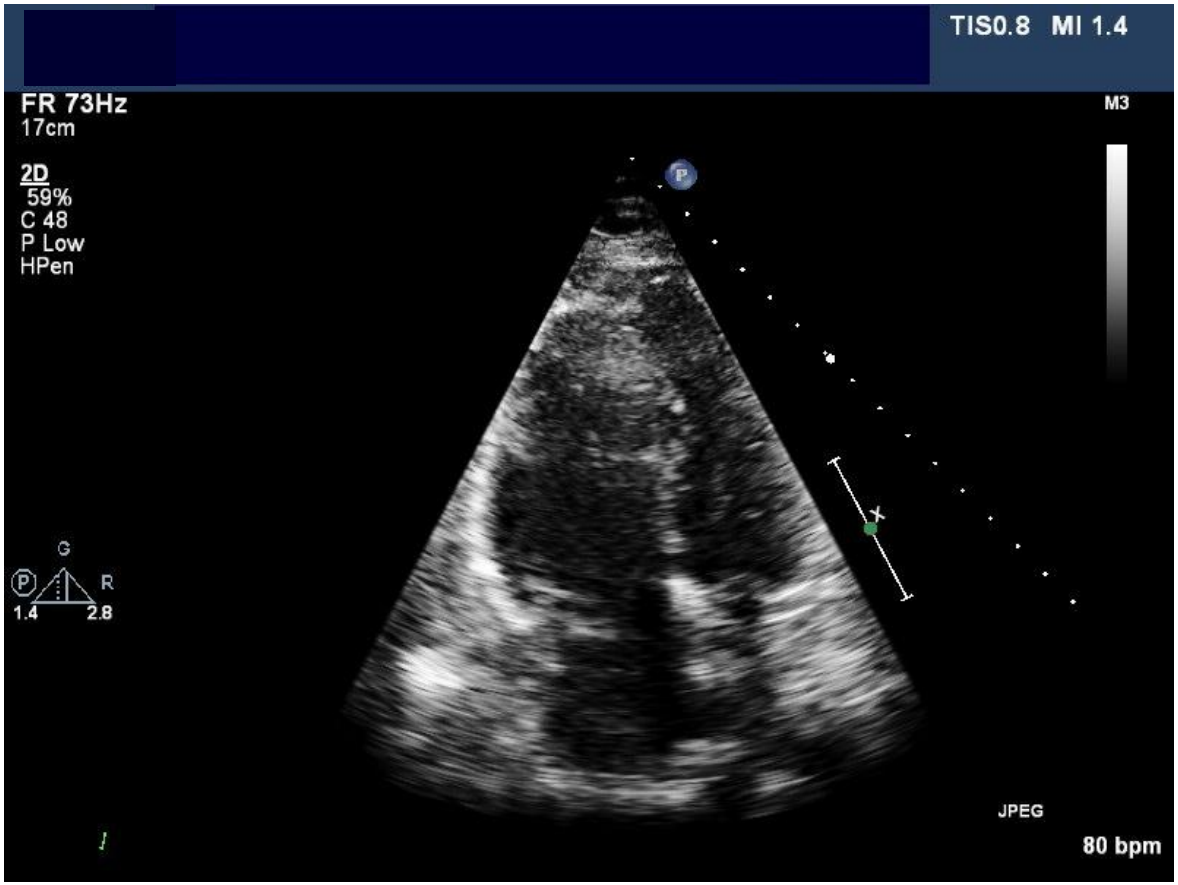
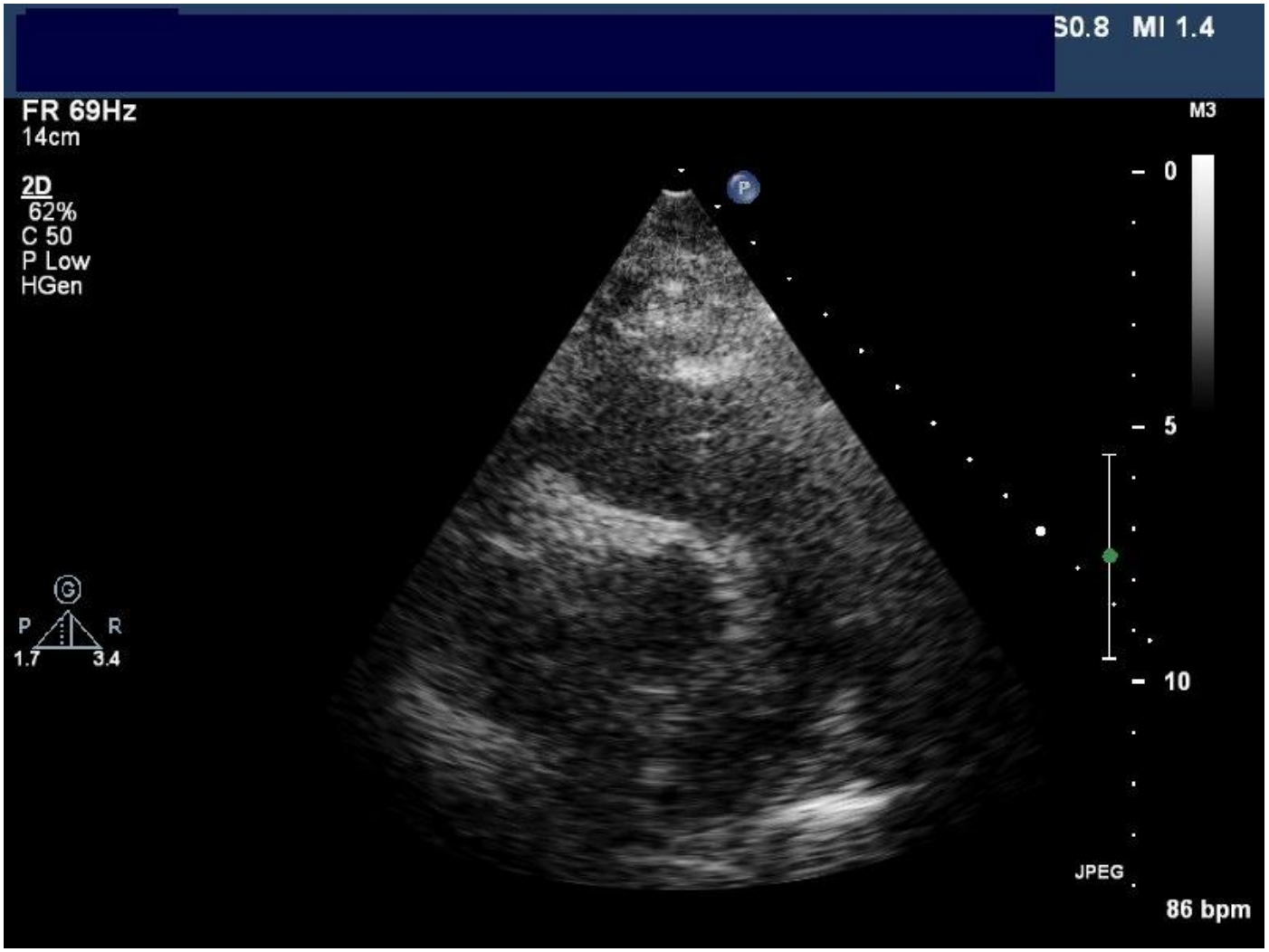
Echocardiogram apical 4 chamber



Echocardiogram pulmonary artery 29 mm



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Echocardiographic signs suggesting PH used to assess the probability of PH in addition to tricuspid regurgitation velocity measurements

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 m/sec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm	

[a]Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

For more details of echocardiographic assessment of the right heart:

Rudski LG et al J Am Soc Echocardiogr 2010;23:685-713
Lang RM et al Eur Heart J Cardiovasc Imaging 2015;16:233-71.

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Diagnostic management according to echocardiographic probability of PH in patients with symptoms, without risk factors for PAH or CTEPH

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[c]	Class[a]	Level[b]
Low	Alternative diagnosis should be considered	IIa	C
Intermediate	Alternative diagnosis, echo follow-up, should be considered	IIa	C
	Further investigation of PH may be considered[d]	IIb	
High	Further investigation of PH (including RHC[d]) is recommended	I	C

CTEPH = chronic thromboembolic pulmonary hypertension; Echo = echocardiographic; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization.
[a]Class of recommendation. [b]Level of evidence. [c]These recommendations do not apply to patients with diffuse parenchymal lung disease or left heart disease. [d]Depending on the presence of risk factors for PH Group 2, 3 or 5. Further investigation strategy may differ depending on whether risk factors/associated conditions suggest higher probability of PAH or CTEPH – see diagnostic algorithm.

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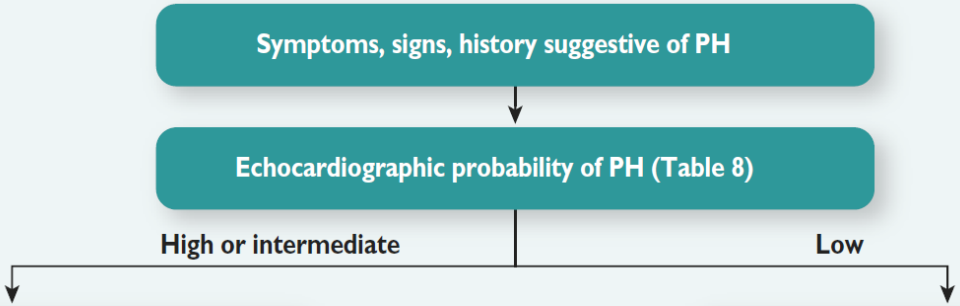
Diagnostic algorithm for pulmonary hypertension



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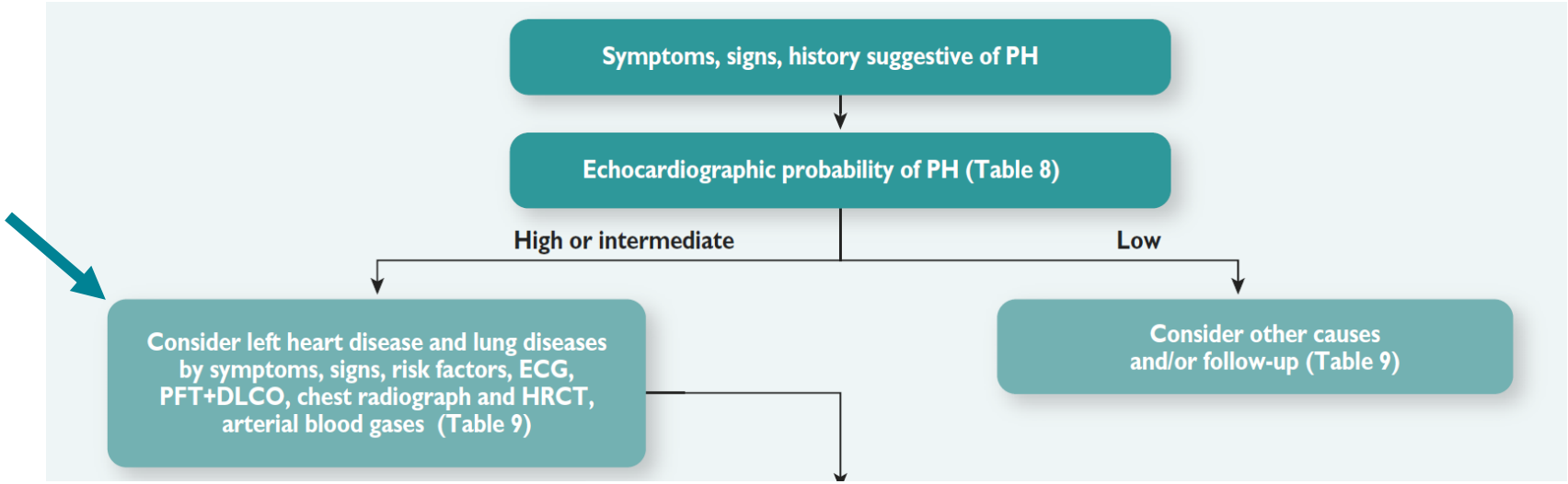

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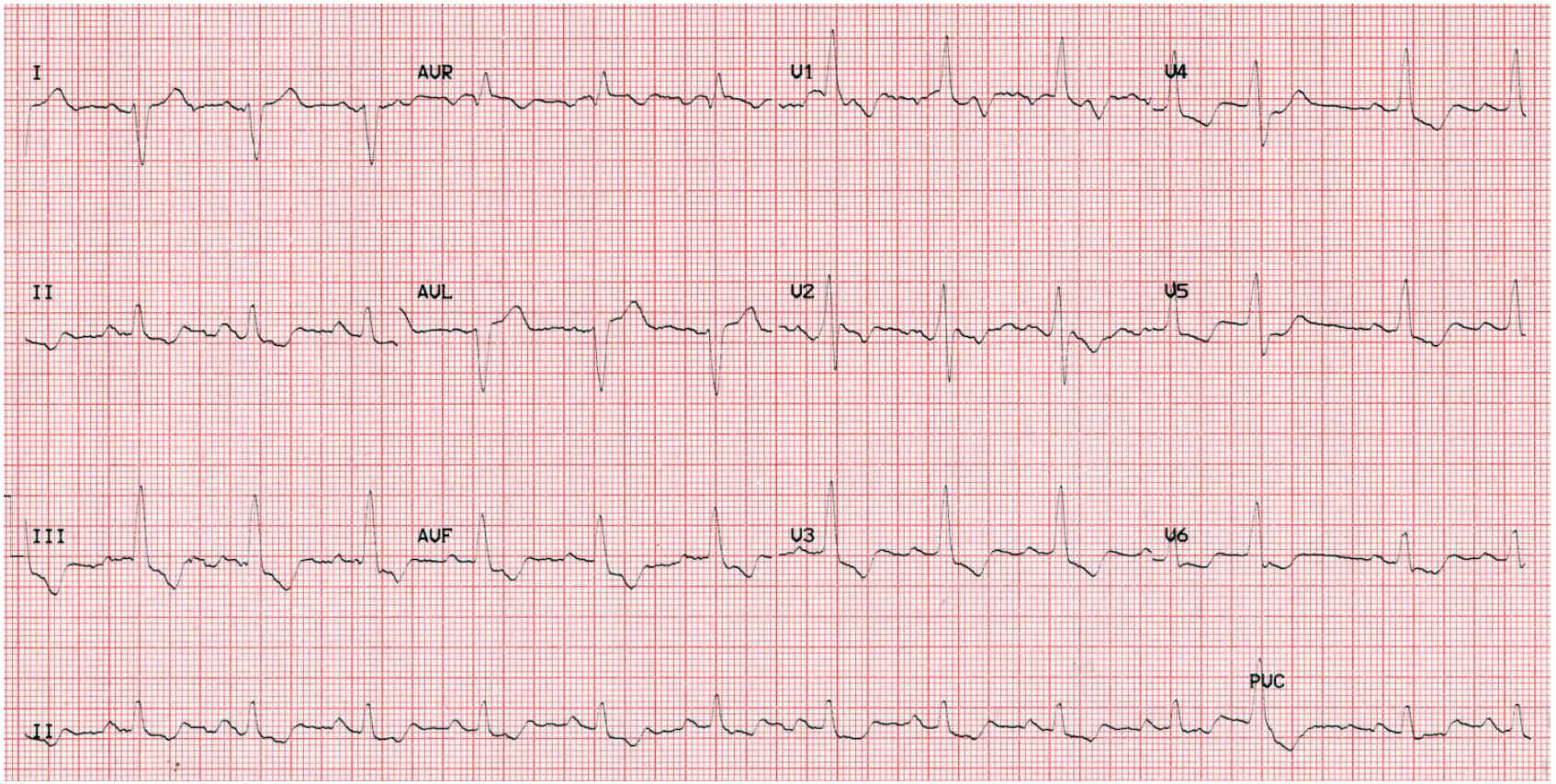
Resting ECG on admission



Lung function

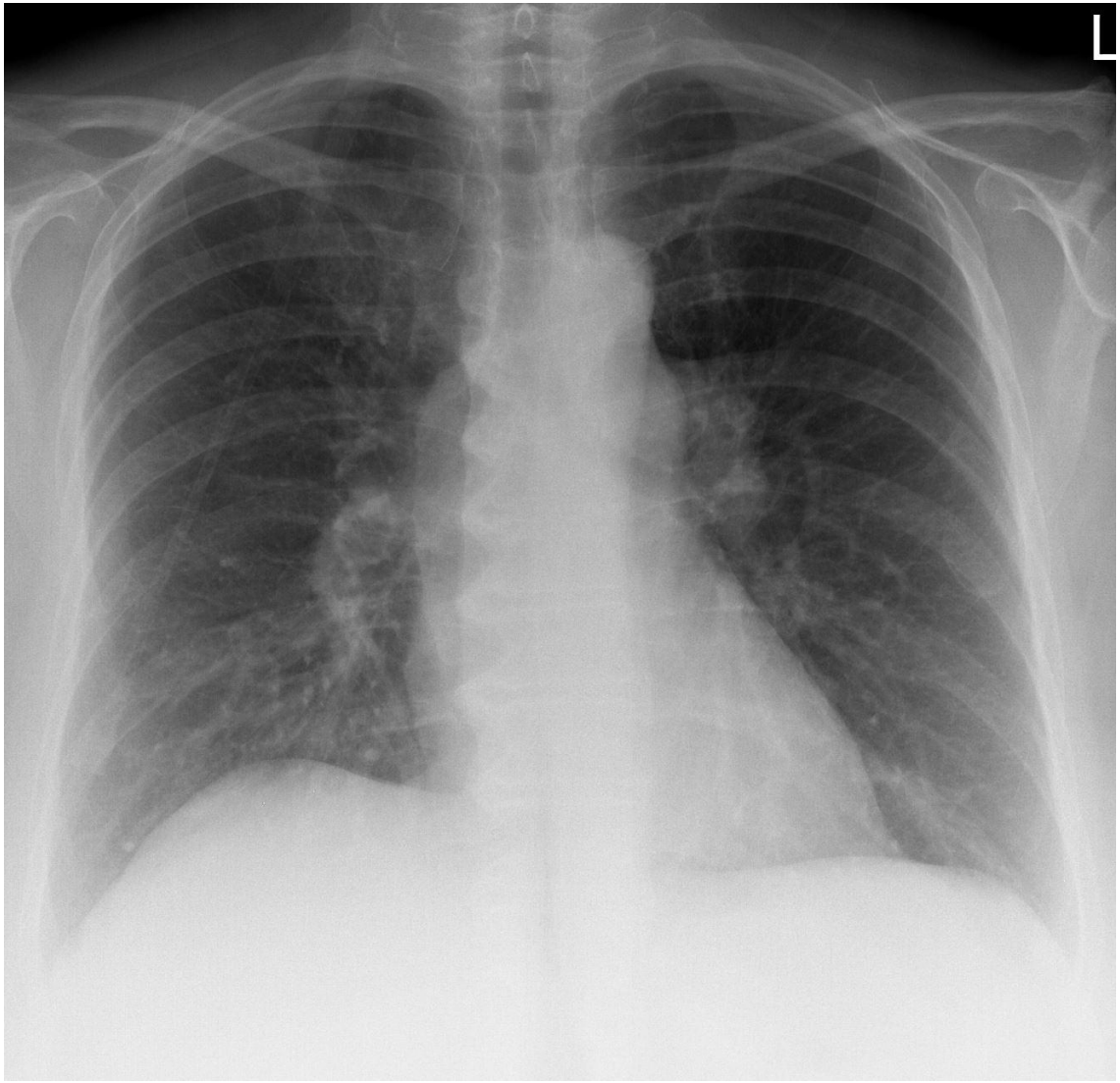
FEV1	**2.36 l**	**119% predicted**
FVC	**3.18 l**	**133%**
FEV1/FVC	**74%**	

Gas diffusion and static lung volumes were not measured because the patient was unwilling to come off oxygen.

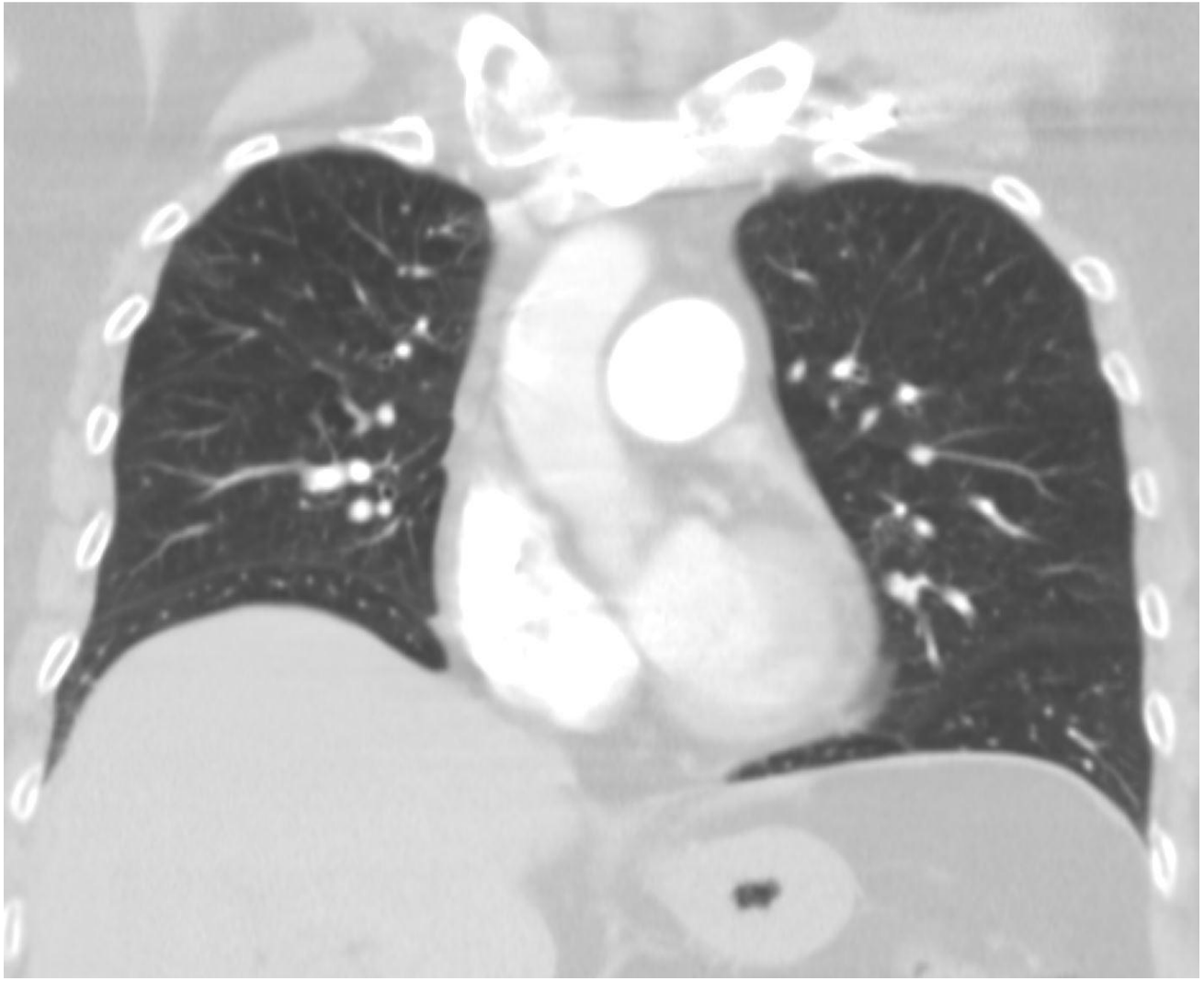
<u>On 2 l/min oxygen:</u>

pH	**7.45**
PCO2	**4.3 kPa**
pO2	**7.2 kPa**
Bicarbonate	**24.0 mmol/l**

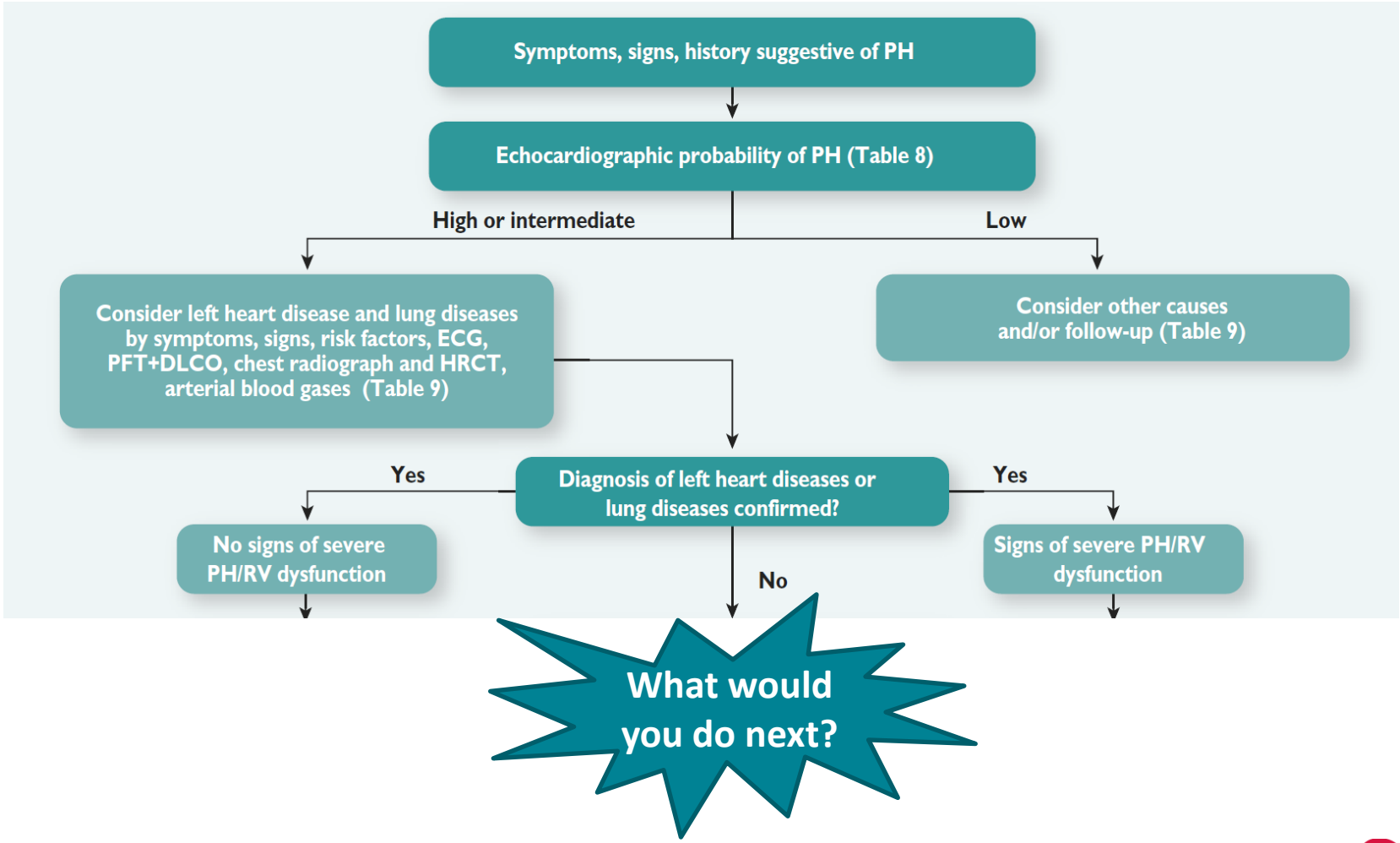
Chest radiograph on admission



Coronal CT showing dilated pulmonary artery and normal lung parenchyma with preserved volumes; CTPA showed no thromboembolism



Diagnostic algorithm for pulmonary hypertension



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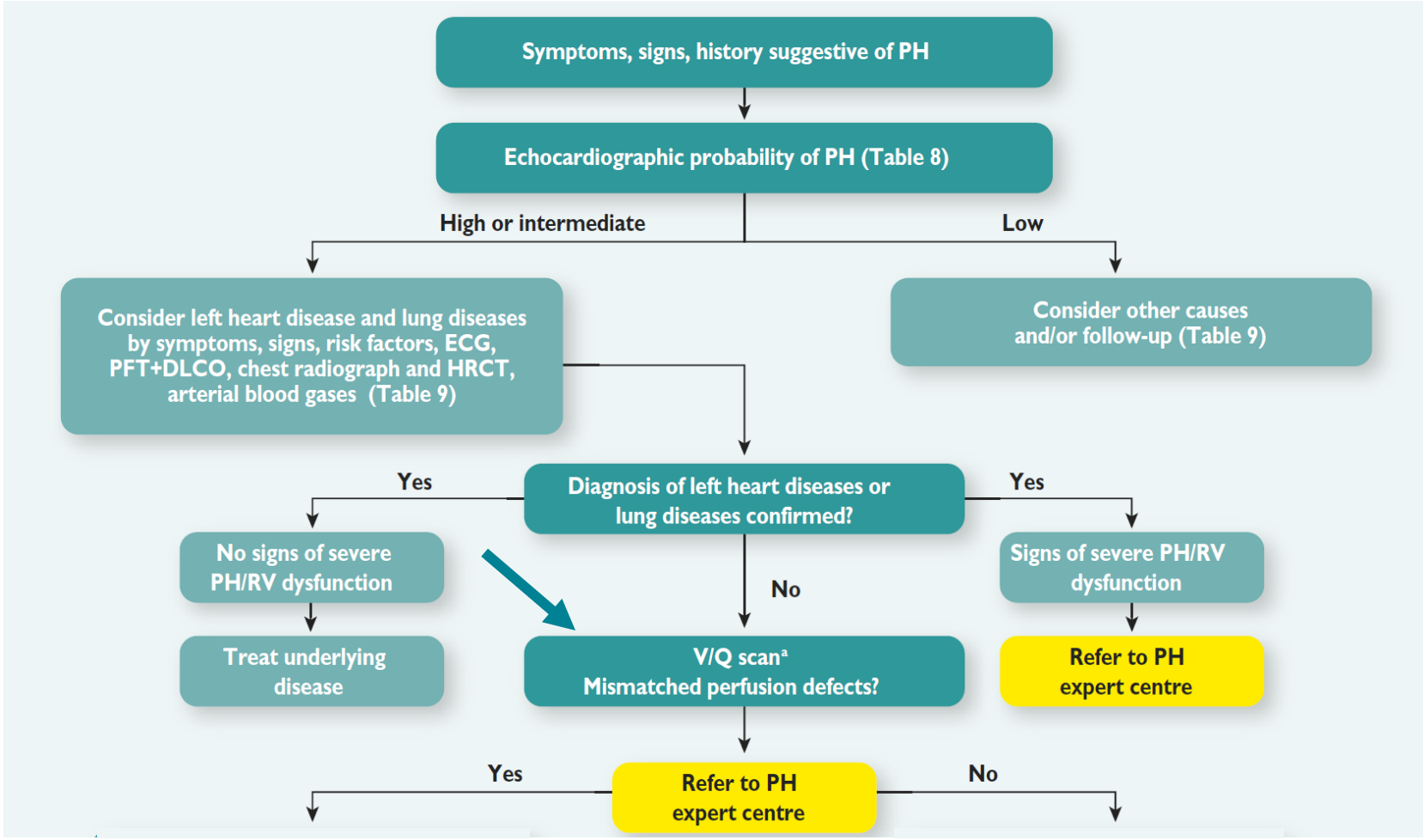
Question: What would you do next?

- The clinical picture now looks like COPD: commence therapy for COPD
- Arrange a ventilation perfusion scan
- Undertake cardiac catheterization
- Arrange a dual energy CT scan
- Arrange a cardiopulmonary exercise test

Diagnostic algorithm for pulmonary hypertension



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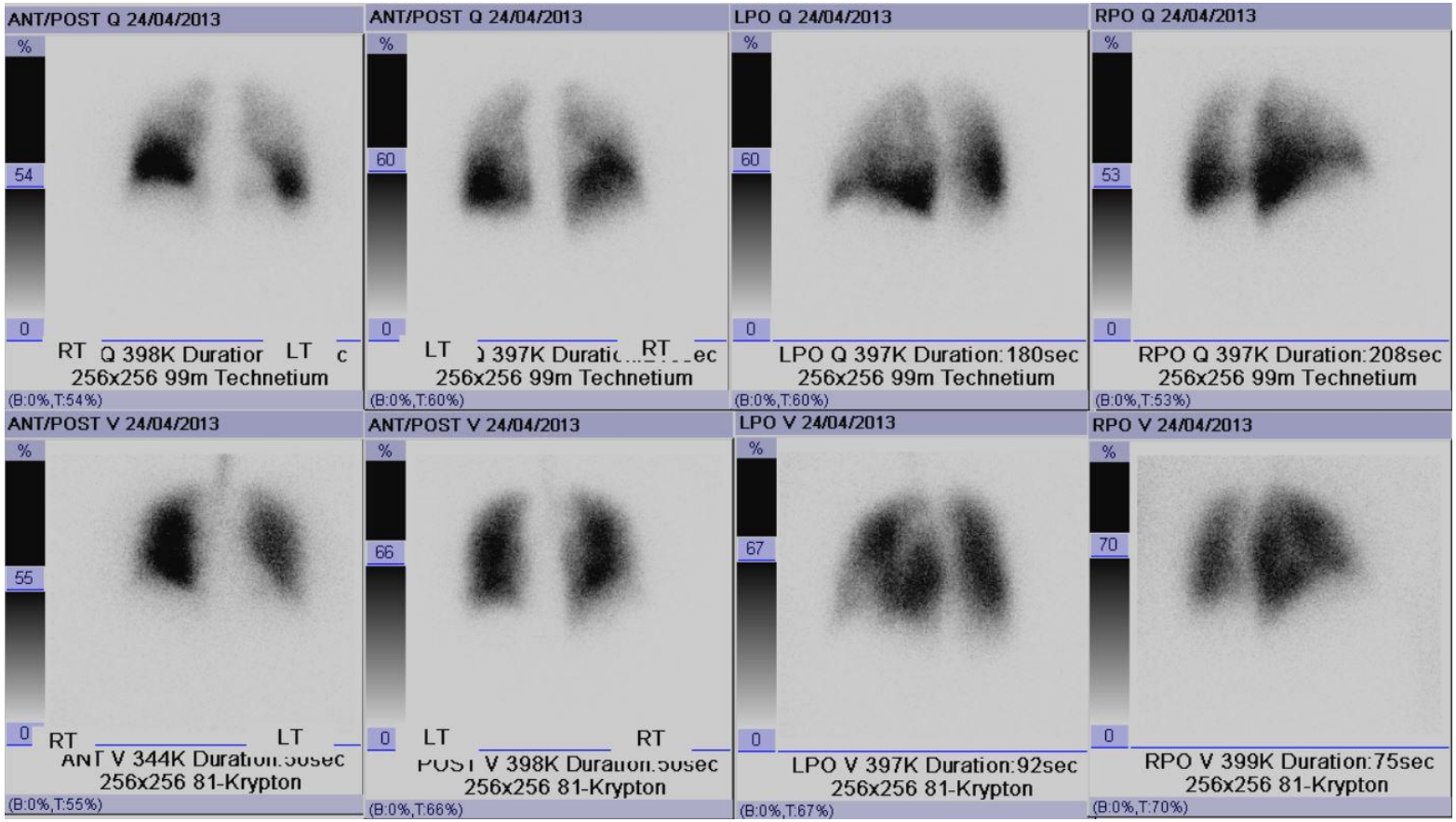
Ventilation perfusion scan: bilateral reduced upper lobe perfusion and normal ventilation scan



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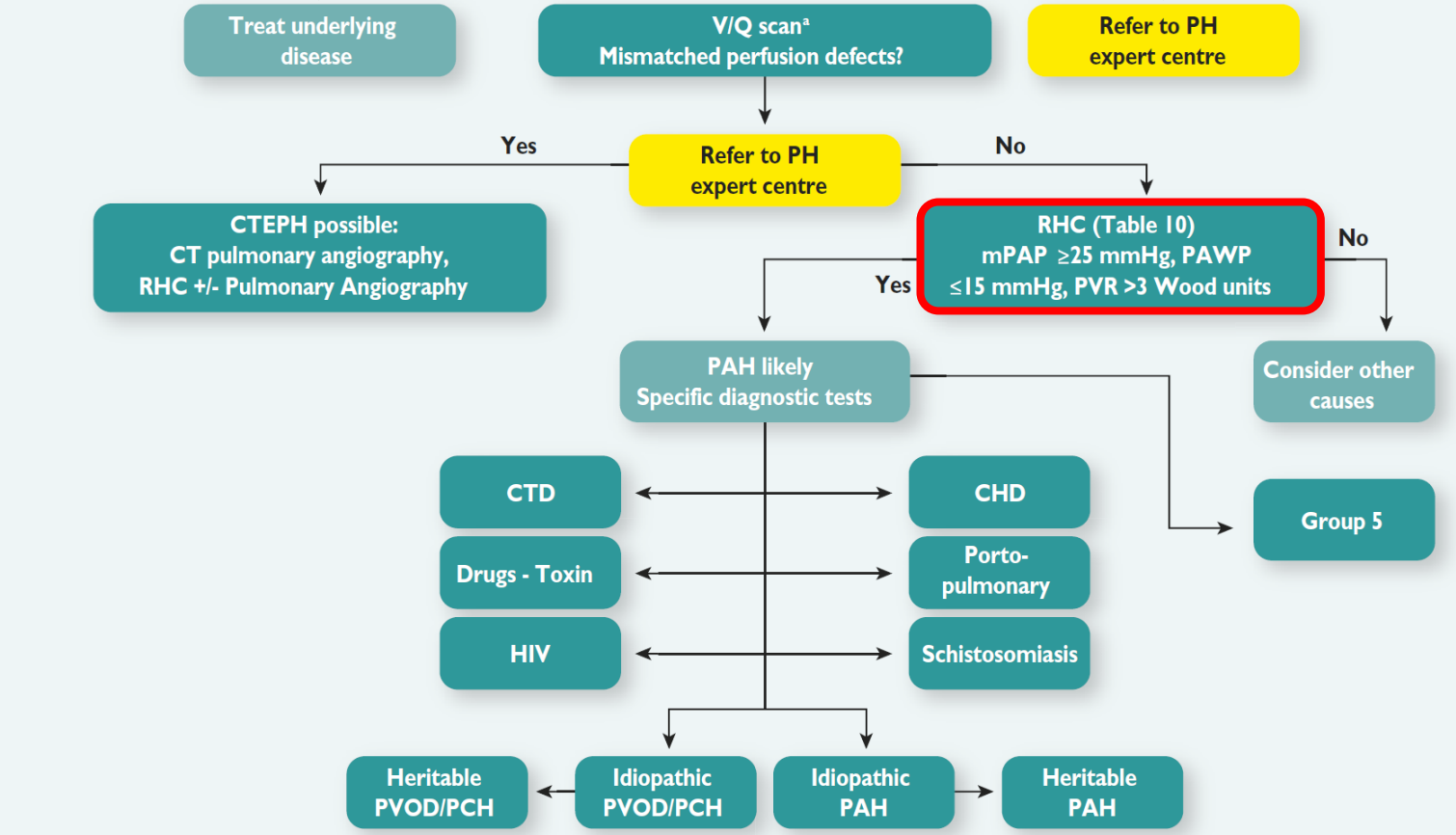
Diagnostic algorithm for pulmonary hypertension



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomathosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

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Recommendations for right heart catheterization in pulmonary hypertension

Recommendations	Class[a]	Level[b]
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (Group 1) and to support treatment decisions.	I	C
In patients with PH, it is recommended to perform RHC in expert centres (Table 34) as it is technically demanding and may be associated with serious complications.	I	B
RHC should be considered in pulmonary arterial hypertension (Group 1) to assess treatment effect of drugs (Table 12).	IIa	C

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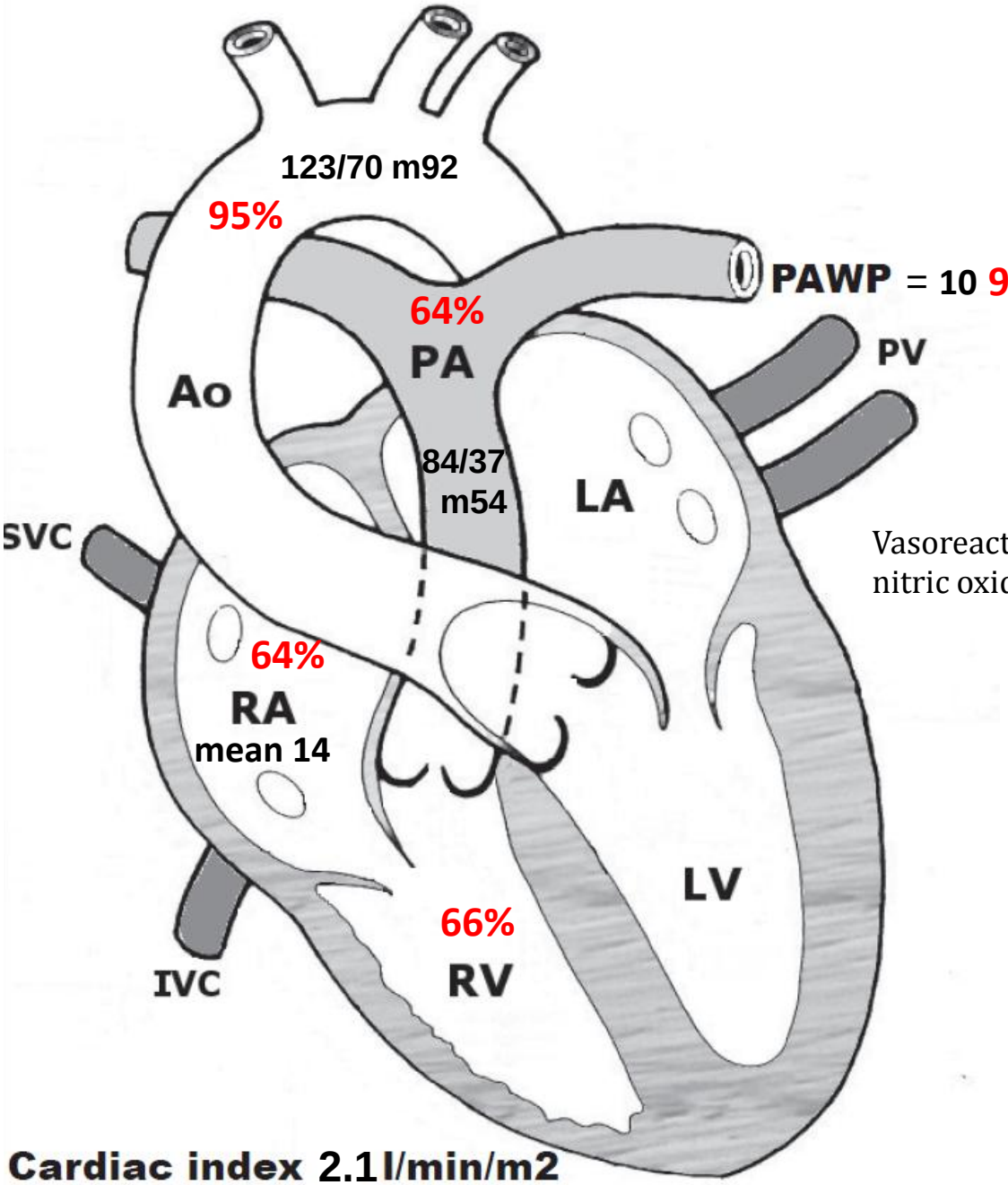
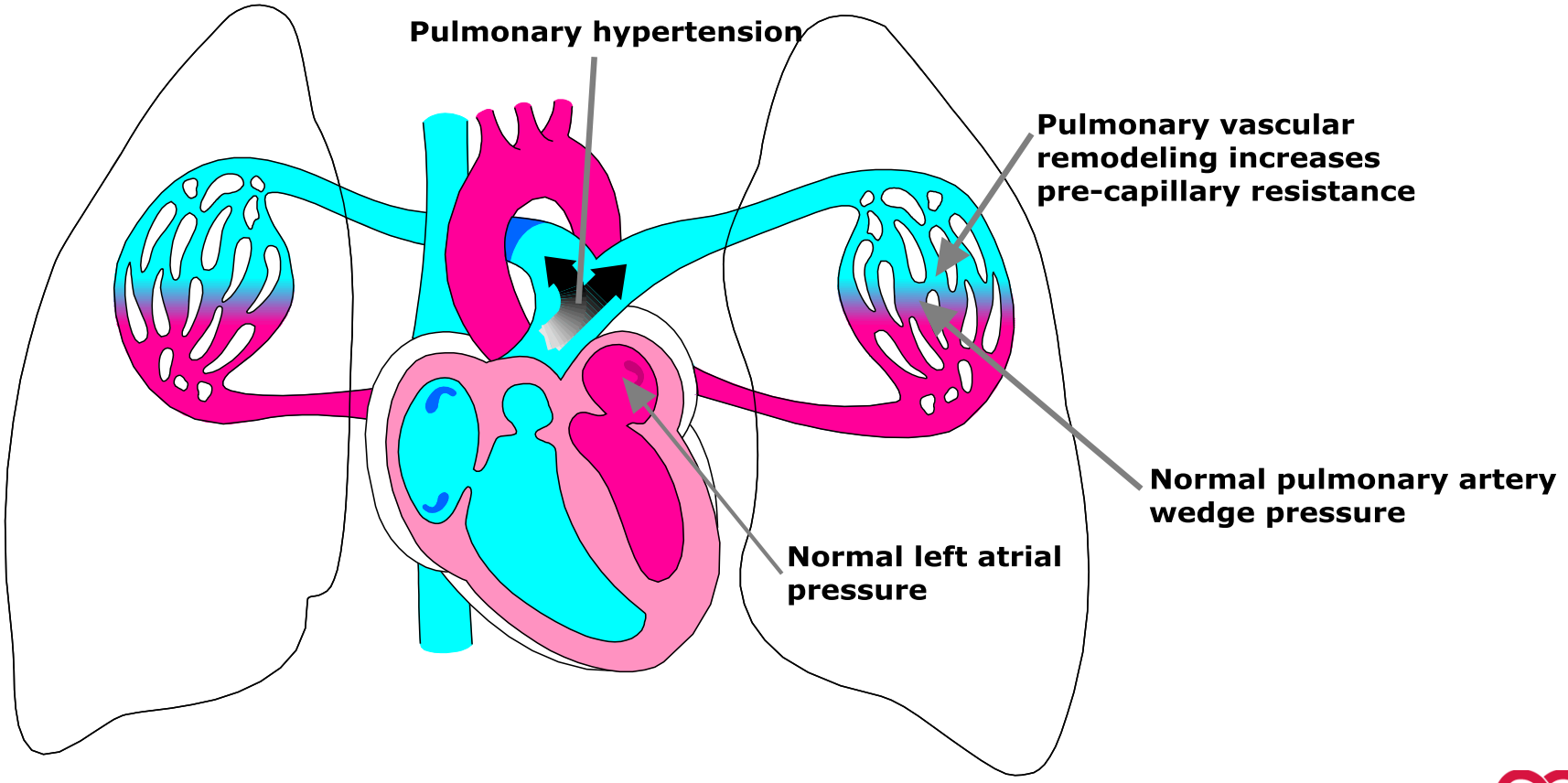


Vasoreactivity study with nitric oxide negative

Cardiac index 2.1 l/min/m2

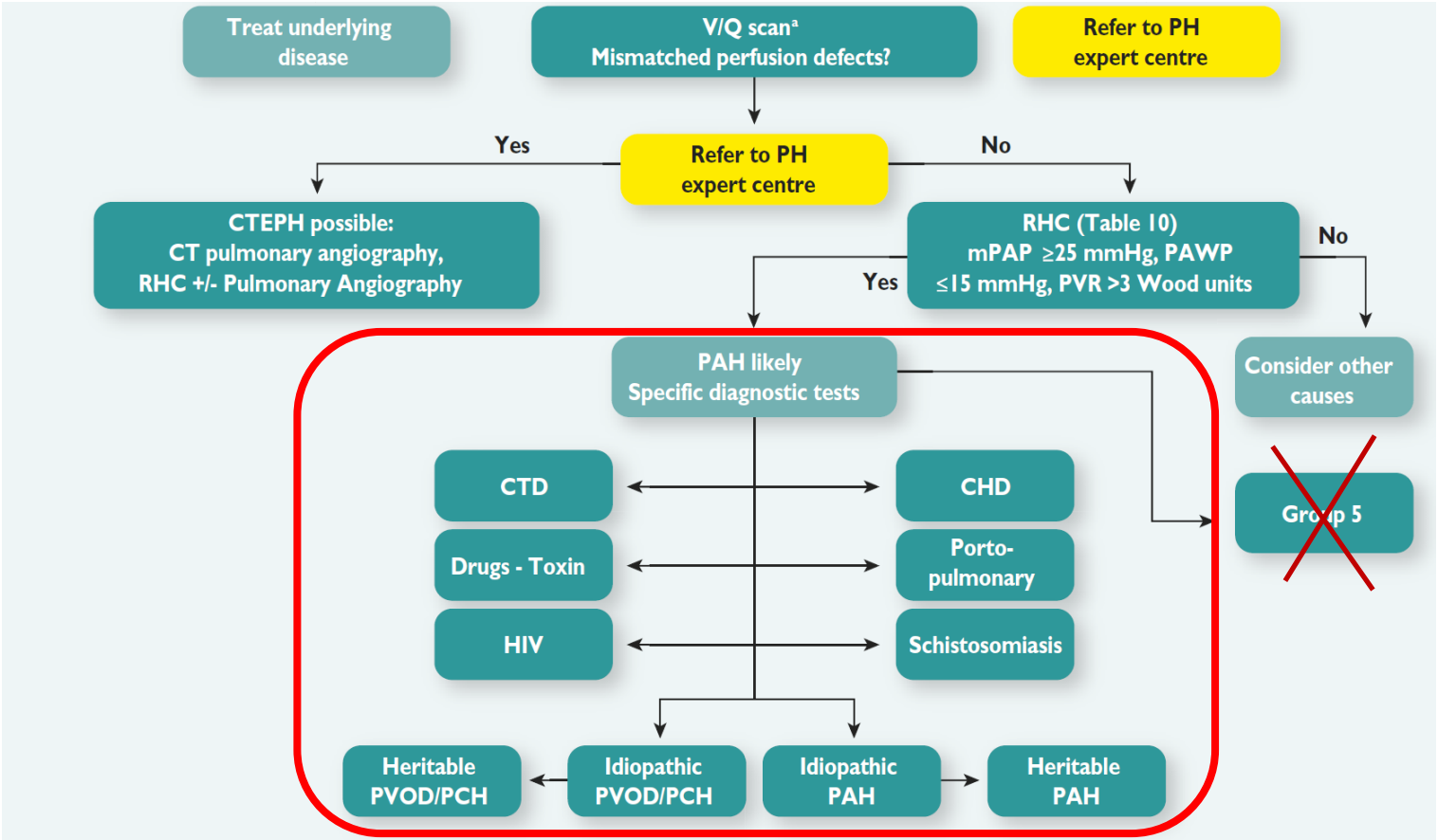
Pulmonary vascular resistance 12.6 Wood units

Pulmonary Arterial Hypertension
PAPm ≥ 25 mmHg; PAWP ≤ 15 mmHg; PVR > 3 Wood units



PAPm, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance

Diagnostic algorithm for pulmonary hypertension



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What type of PAH?

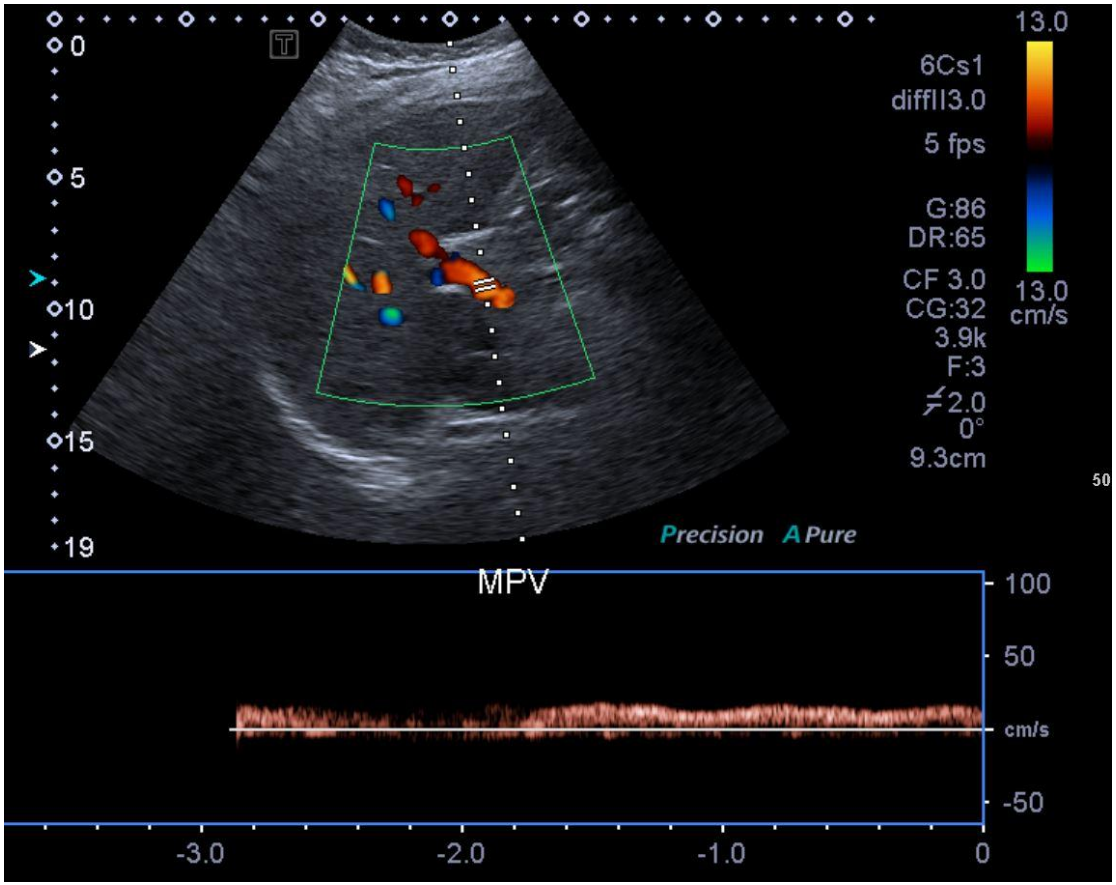
History

- No history of exposure to drugs / toxins associated with PAH
- No history of travel outside Europe
- No history of congenital heart disease
- Two generation family history negative

Blood tests

- Autoimmune screen negative including antinuclear antigen, double stranded DNA ELISA, ANCA, antiphospholipid antibodies
- HIV-1 and HIV-2 serology negative
- Hepatitis B and C negative
- Liver function tests were within normal limits

Liver ultrasound showing normal portal blood flow



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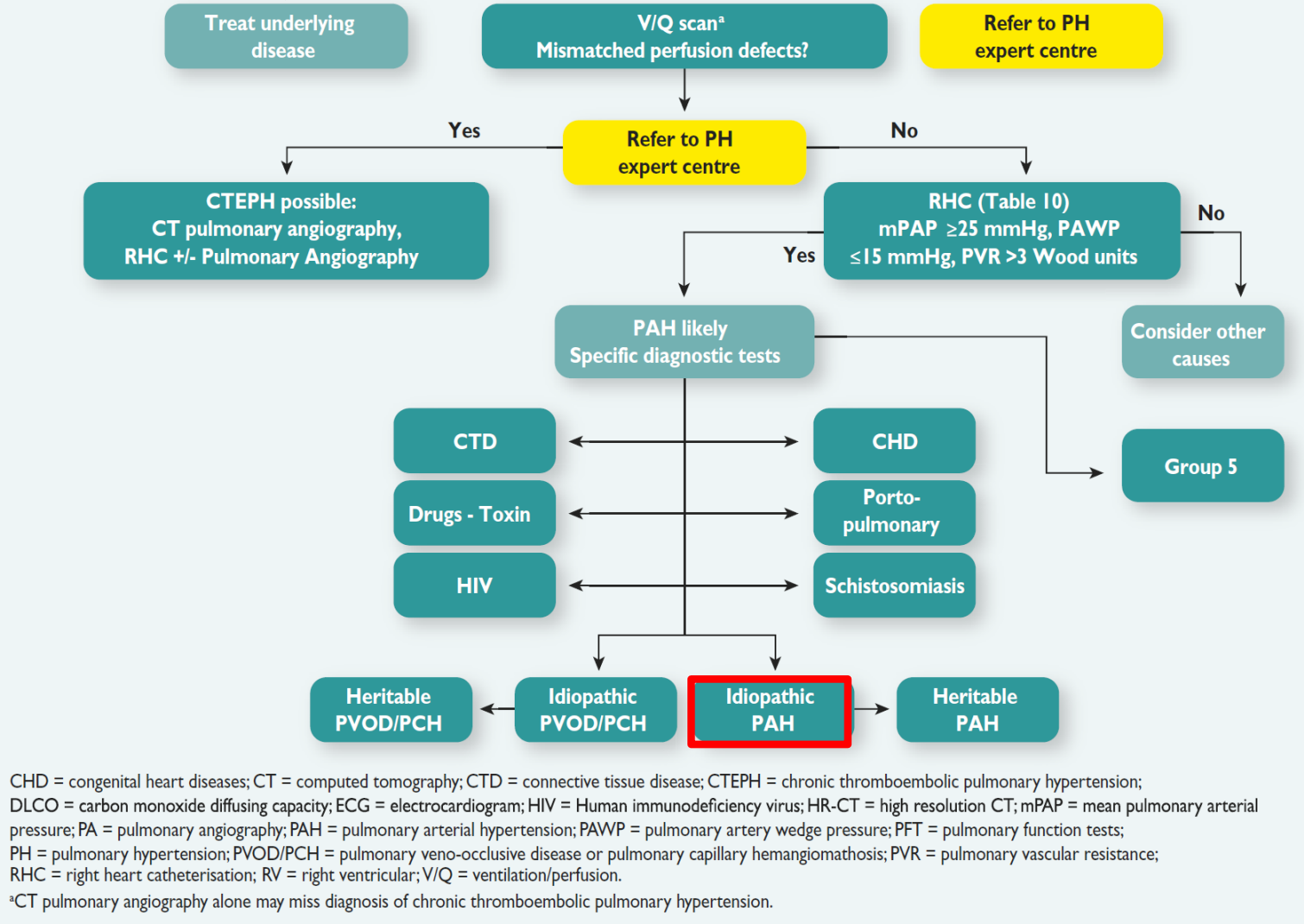
Diagnostic algorithm for pulmonary hypertension



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Comprehensive clinical classification of pulmonary hypertension

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 diseases (Table 5)
  - 1.4.5 Schistosomiasis

Pulmonary arterial hypertension describes a group of PH patients with **pre-capillary PH with a PVR >3 Wood units**

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

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

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)[a]

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 thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	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 36–44.9	Peak VO_2 <11 ml/min/kg (<35 % pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65 %	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60 %

[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.
[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity.

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Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure			Present
Progression of symptoms		Slow	
Syncope	No		
WHO functional class		III	
6MWD			<165 m
Cardiopulmonary exercise testing			
NT-proBNP plasma levels		BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion		
Haemodynamics		RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	

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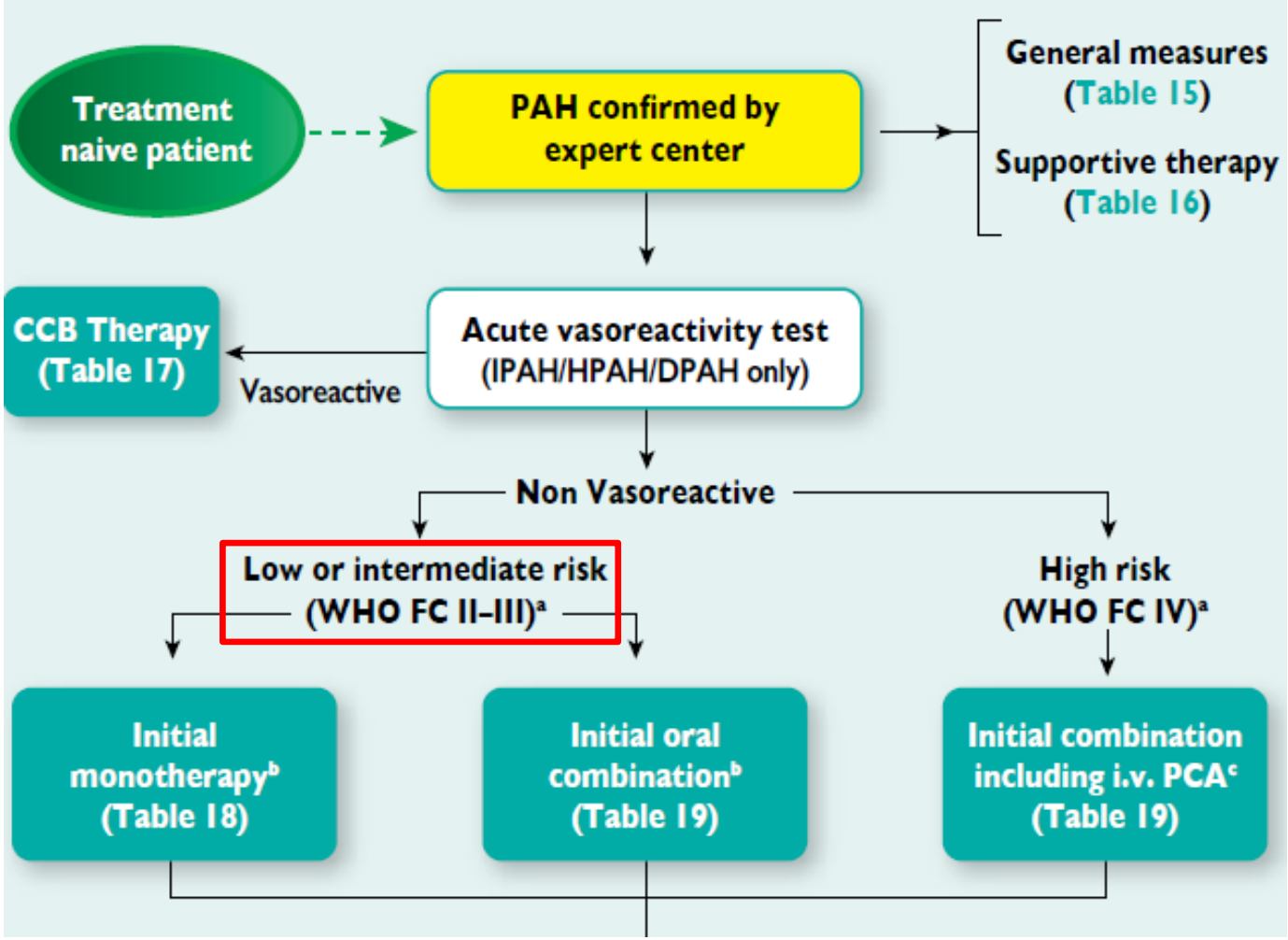
Question: What treatment of PAH do you recommend?

1. Calcium channel blocker
2. Phosphodiesterase 5 inhibitor or a soluble guanylate cyclase stimulator
3. Endothelin receptor antagonist
4. Intravenous epoprostenol with/without a phosphodiesterase 5 inhibitor or an endothelin receptor antagonist
5. Combination of 2 and 3

Treatment algorithm for pulmonary arterial hypertension



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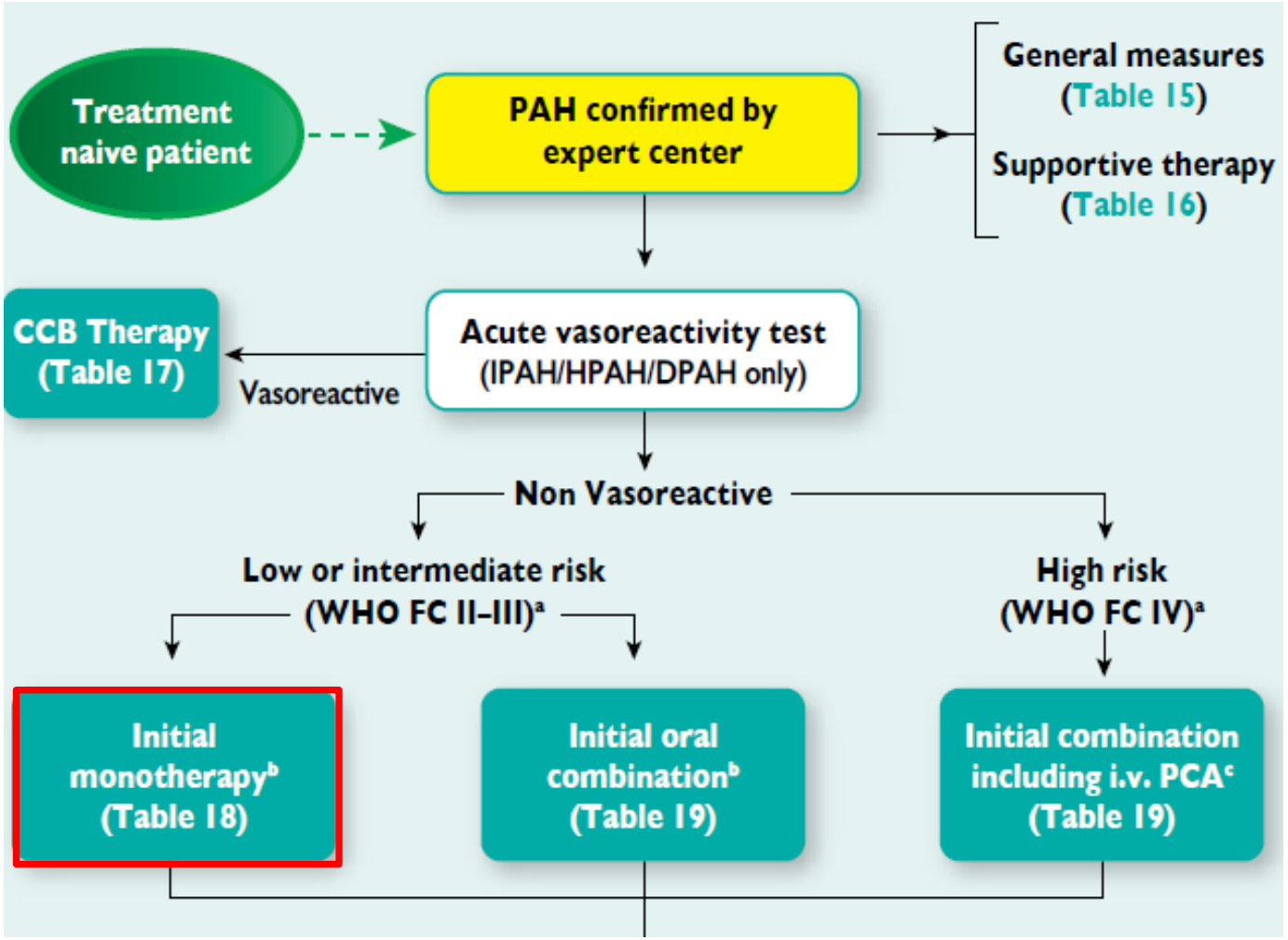
Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75

Treatment algorithm for pulmonary arterial hypertension



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PAH treatment

- **Sildenafil 20 mg TDS**
- Warfarin to maintain INR 2-3
- Long-term oxygen therapy 3l/min
- Furosemide 40 mg
- Bisoprolol discontinued

Risk assessment after 3 months monotherapy

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	
Progression of symptoms	No		
Syncope	No		
WHO functional class		III	
6MWD			<165 m
Cardiopulmonary exercise testing		Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	
NT-proBNP plasma levels		BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion		
Haemodynamics			

[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.
[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity.

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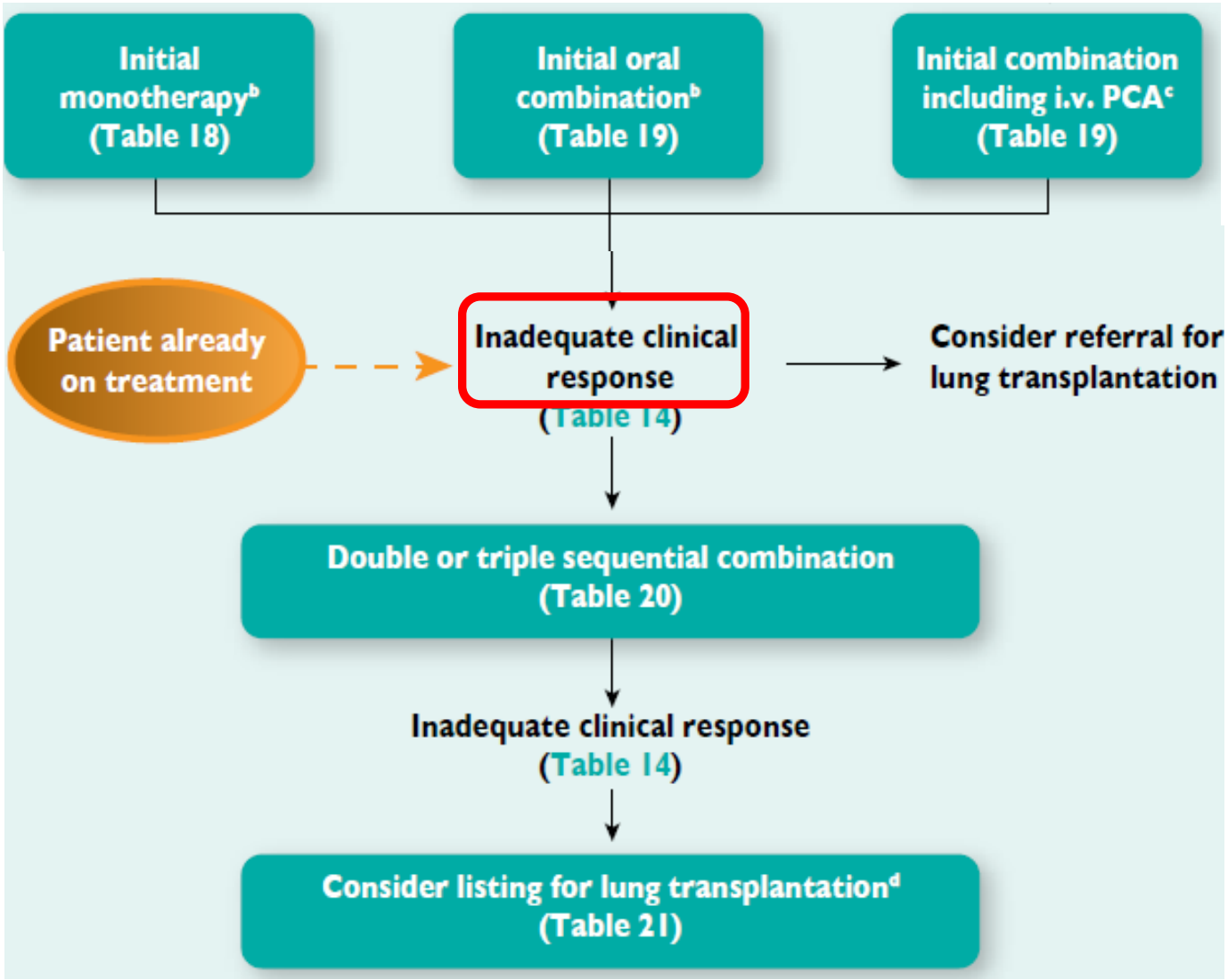
Treatment algorithm for pulmonary arterial hypertension



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PAH treatment: sequential combination

- **Ambrisentan 10 mg OD**
- **Sildenafil 20 mg TDS**
- **Warfarin to maintain INR 2-3**
- **Long-term oxygen therapy 3l/min**
- **Furosemide 40 mg**

Risk assessment after 6 months dual oral combination

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	
Progression of symptoms	No		
Syncope	No		
WHO functional class		III	
6MWD		165–440 m	
Cardiopulmonary exercise testing		Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	
NT-proBNP plasma levels		BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion		
Haemodynamics			

[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.
[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity.

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PAH treatment: sequential combination at 6 months treatment

- **Nebulized iloprost 2.5 mcg uptitrated to 5 mcg six times/day**
- **Ambrisentan 10 mg OD**
- **Sildenafil 20 mg TDS**
- **Warfarin to maintain INR 2-3**
- **Long-term oxygen therapy 2l/min**
- **Furosemide 40 mg**

Summary

A 69 year old female presented with 2 years worsening breathlessness and ankle swelling in WHO functional class III.

Investigations confirmed a diagnosis of idiopathic PAH which was treated with sequential monotherapy. Although she improved, she remained at intermediate risk. Treatment has been escalated with the aim of achieving a low risk state.

Key messages

- **Echocardiography is the first investigation of choice in patients with suspected pulmonary hypertension**
- **Follow the diagnostic algorithm**
- **Risk assessment guides treatment of PAH**