2015 ESC/ERS Guidelines:

Pulmonary Hypertension Definitions and Diagnosis

Eur Heart J, 2015 doi: 10.1093/eurheartj/ehv317

Eur Respir J, 2015 doi: 10.1183/13993003.01032-2015

Adam Torbicki, CMKP, ECZ-Otwock

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- **Lectures/consultancy and/or research fees:**
  - Actelion
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  - Sanofi
  - United Therapeutics

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)
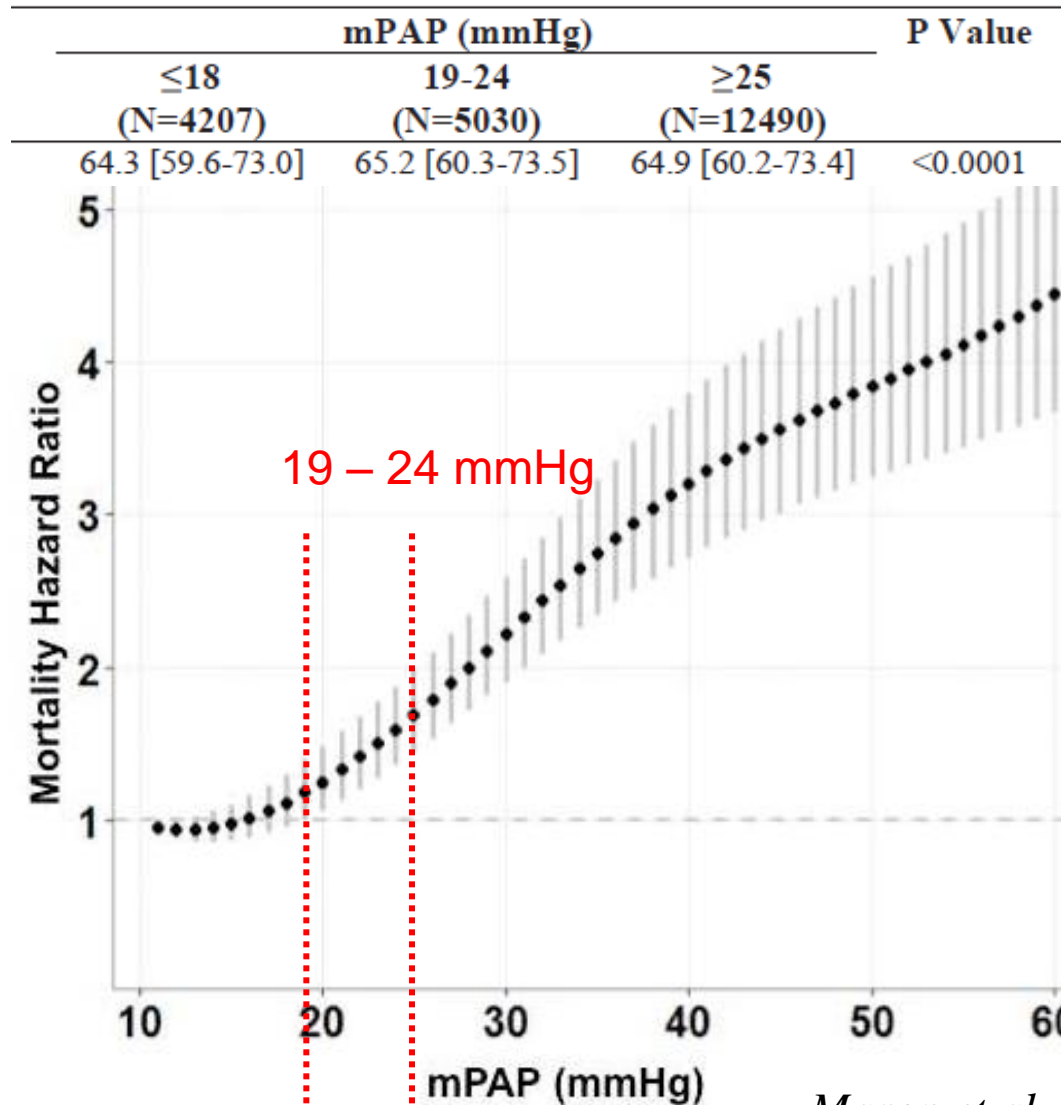
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Speaker

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Definition of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All

RHC

Association of Borderline Pulmonary Hypertension With Mortality and Hospitalization in a Large Patient Cohort: Insights From the VA-CART Program

	mPAP (mmHg)		P Value
≤18 (N=4207)	19-24 (N=5030)	≥25 (N=12490)	
64.3 [59.6-73.0]	65.2 [60.3-73.5]	64.9 [60.2-73.4]	<0.0001

19 – 24 mmHg

Mortality Hazard Ratio

mPAP (mmHg)

Maron et al. Circulation 2016.

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

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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Haemodynamic definitions 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

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.
[a]All values measured at rest; see also section 7.
[b]According to Table 4.
[c]Wood Units are preferred to dynes.s.cm^{-5}.

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Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
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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]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.
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> **65 year old male, HT, AF smoker with mild COPD chronic myeloid leukemia treated with dasatanib history of acute PE**

PH-specific treatement indicated ?

I. Pulmonary arterial hypertension

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YES !

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Cautiously...

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Not indicated potentially dangerous

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Not indicated no data ...

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Diagnosing pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg **RHC**	All

Strategy which would:

- **Acknowledge the need for RHC before introduction of any specific PH Tx**

- **Limit the need for RHC performed for diagnostic purposes in patients most likely belonging to PH groups 2,3,5**

- **Accept the areas of overlap between PH groups and „multifactorial" PH...**

- **Acknowledge the critical role of referral centers**

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Diagnostic investigations utilized in patients with pulmonary hypertension

- Electrocardiogram
- Chest radiograph
- Echocardiography
- Pulmonary function tests and arterial blood gases
- Ventilation/perfusion lung scan
- High-resolution computed tomography, contrast enhanced computed tomography
- Cardiac magnetic resonance imaging
- Blood tests and immunology
- Abdominal ultrasound scan
- Right heart catheterization and vasoreactivity
- Pulmonary Angiography

Echocardiography in suspected pulmonary hypertension

- Should be performed when pulmonary hypertension is suspected

- Echo is not sufficient to support a PH-specific treatment decision: cardiac catheterization is required

- Echocardiographic examination is used to assign a level of probability of pulmonary hypertension

- Probability of pulmonary hypertension should not be defined only by a cut off value of peak tricuspid regurgitation velocity

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Echocardiographic probability of pulmonary hypertension in __symptomatic patients__ with a suspicion of pulmonary hypertension

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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Echocardiographic signs suggesting pulmonary hypertension (in addition to tricuspid regurgitation velocity measurements)

RV>LV domination	RV/PA coupling	RV failure
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.

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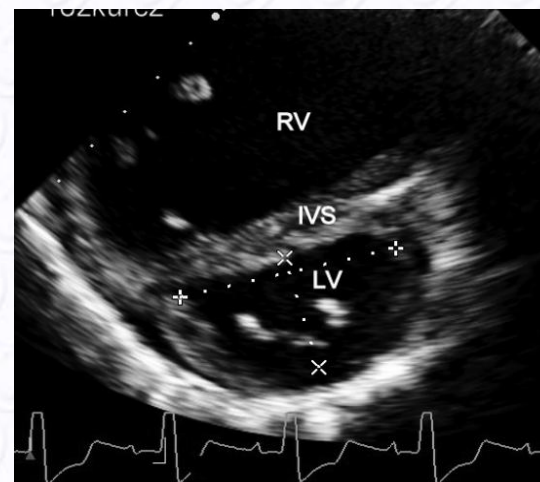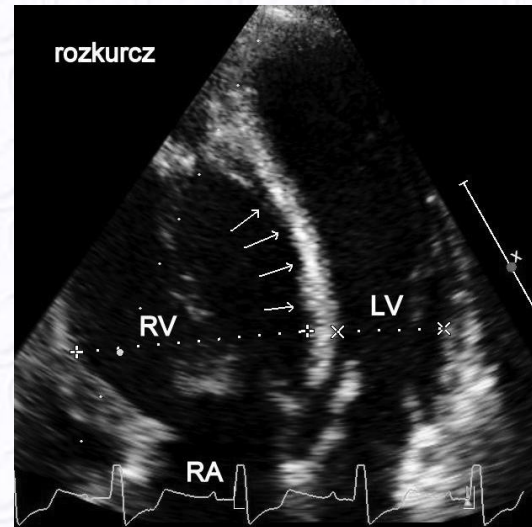
Echocardiographic signs suggesting pulmonary hypertension (in addition to tricuspid regurgitation velocity measurements)

RV failure

Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)

Right atrial area (end-systole) >18 cm²

Echocardiographic signs suggesting pulmonary hypertension (in addition to tricuspid regurgitation velocity measurements)

AcT = 55 ms
Vmax = 52 cm/s

RV/PA coupling

Right ventricular outflow Doppler acceleration time <105 m/sec and/or midsystolic notching

Early diastolic pulmonary regurgitation velocity >2.2 m/sec

PA diameter >25 mm

Vel 220 cm/s
PG 19 mmHg
Vel 345 cm/s
PG 48 mmHg

2D
47%
C 50
P Low
HGen

Ao   MPA

RPA

LPA

Asc Ao Diam 2.7 cm
MPA Diam   6.1 cm

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Echocardiographic signs suggesting pulmonary hypertension (in addition to tricuspid regurgitation velocity measurements)
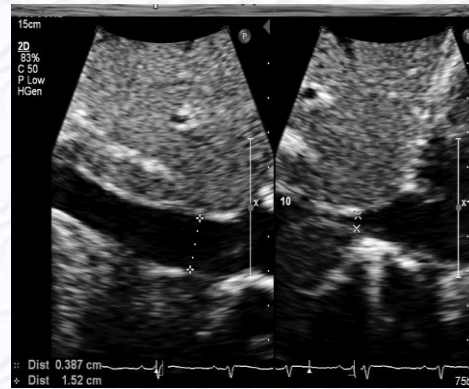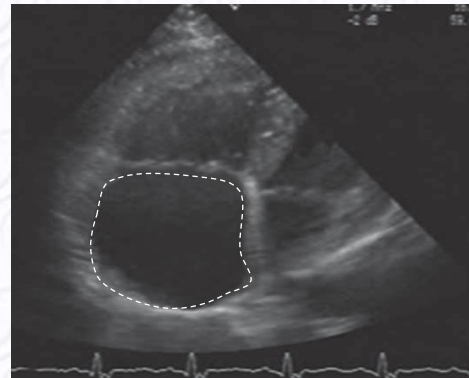
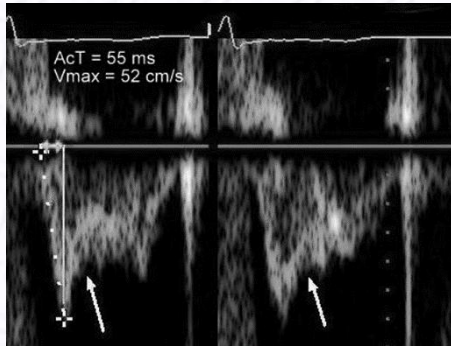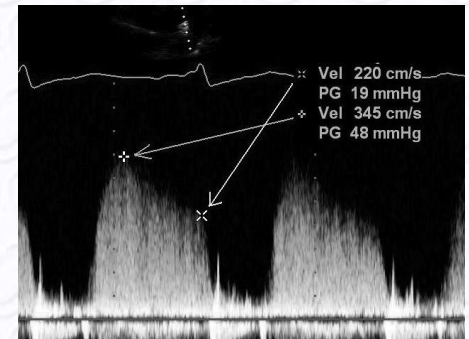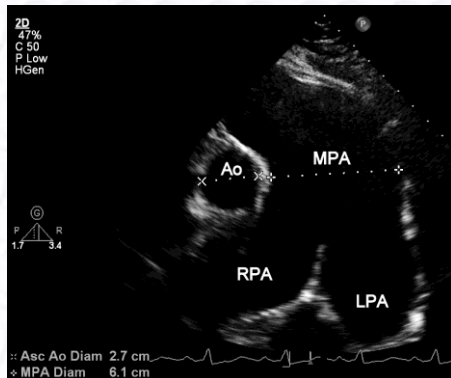| RV>LV domination	RV/PA coupling	RV failure
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	PA diameter >25 mm	

No…

[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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Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurements

RV>LV domination	RV/PA coupling	RV failure
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	PA diameter >25 mm	

ᵃEchocardiographic 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.

YES !

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Echocardiographic probability of pulmonary hypertension in <u>symptomatic patients</u> with a suspicion of pulmonary hypertension

TRV ?

IVC 30mm

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	Intermediate
2.9–3.4	Yes	High
>3.4	Not required	High

PH = pulmonary hypertension.

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PH = pulmonary hypertension.

IVC 30mm
RV/LV > 1

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Echocardiographic probability of pulmonary hypertension in <u>symptomatic patients</u> with a suspicion of pulmonary hypertension

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Diagnostic management according to echocardiographic probability of PH in patients with symptoms, with or 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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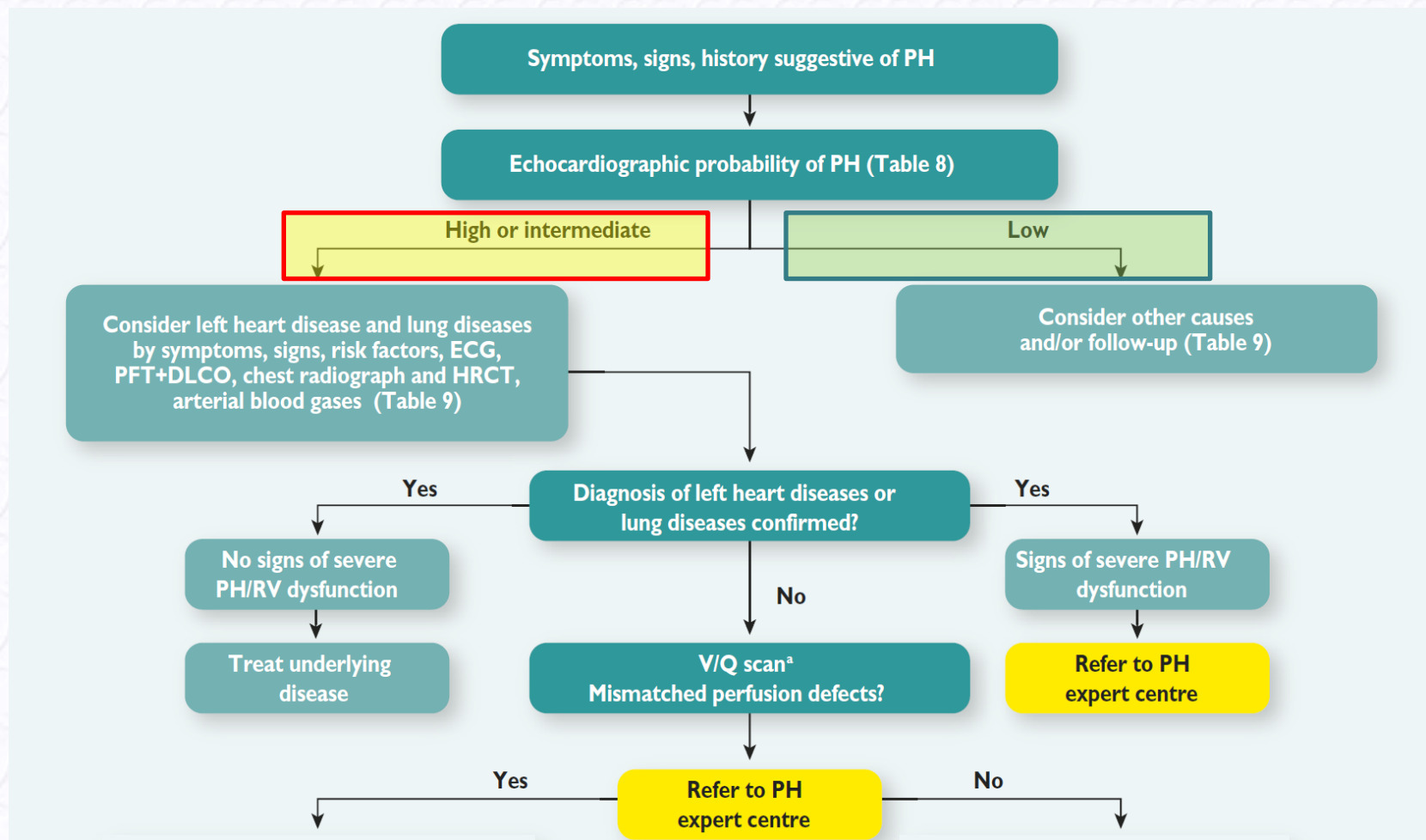
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Echocardiographic probability of PH	With risk factors or associated conditions for PAH or CTEPH[c]	Class[a]	Level[b]
Low	Echo follow-up should be considered	IIa	C
Intermediate	Further assessment of PH including RHC should be considered[c]	IIa	B
High	Further investigation of PH[d] including RHC is recommended	I	C

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Diagnostic algorithm for pulmonary hypertension - 1

Diagnostic algorithm for pulmonary hypertension - 1

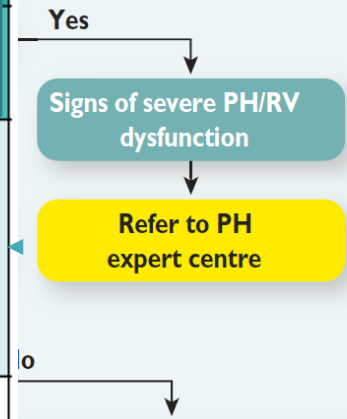Symptoms, signs, history suggestive of PH

↓

Echocardiographic probability of PH (Table 8)

High or intermediate

Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases (Table 9)

Low

Consider other causes and/or follow-up (Table 9)

Yes

Signs of severe PH/RV dysfunction

Refer to PH expert centre

No

RV>LV domination	RV/PA coupling	RV failure
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)
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	PA diameter >25 mm	

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Diagnostic algorithm for pulmonary hypertension - 2

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.

ªCT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

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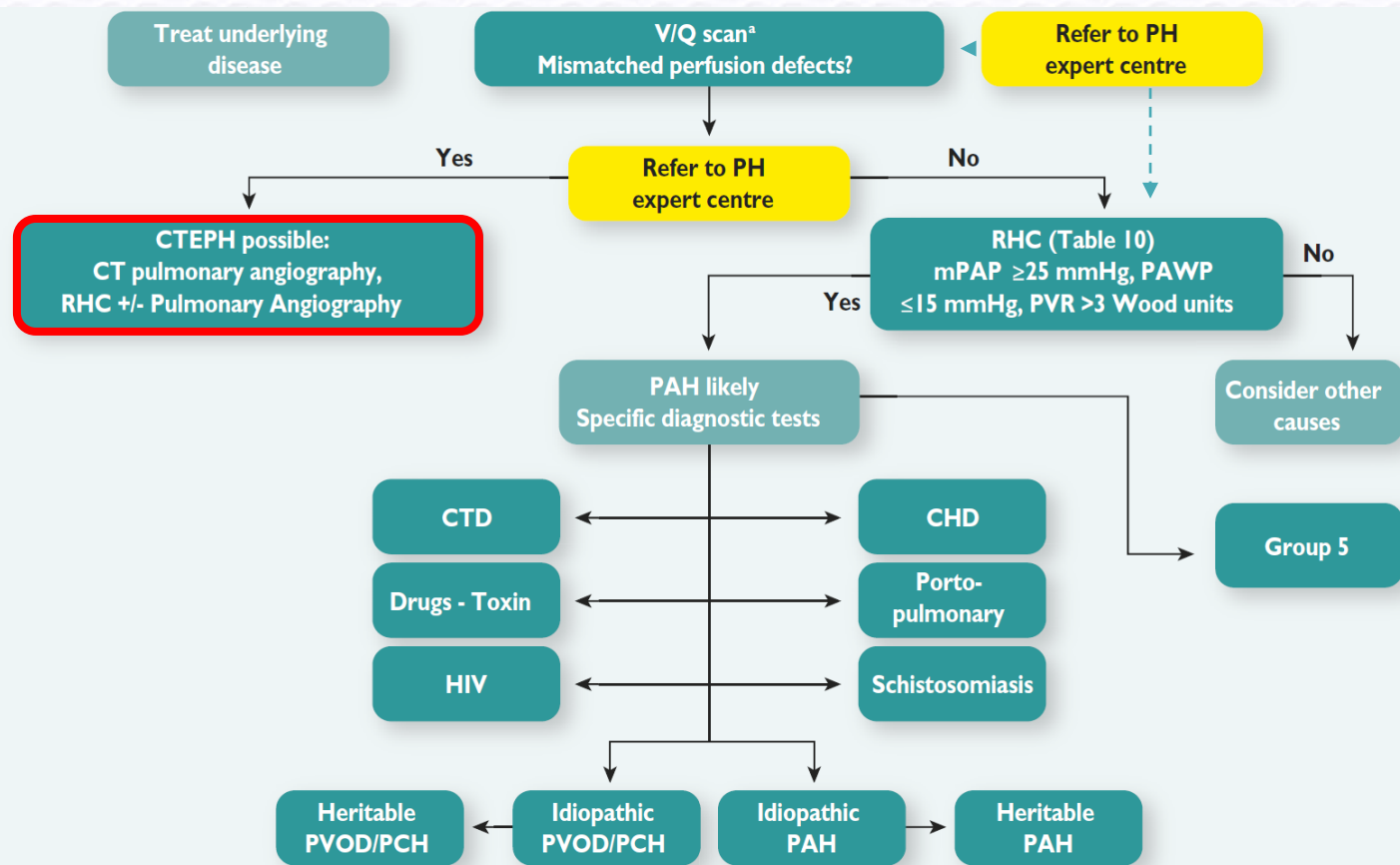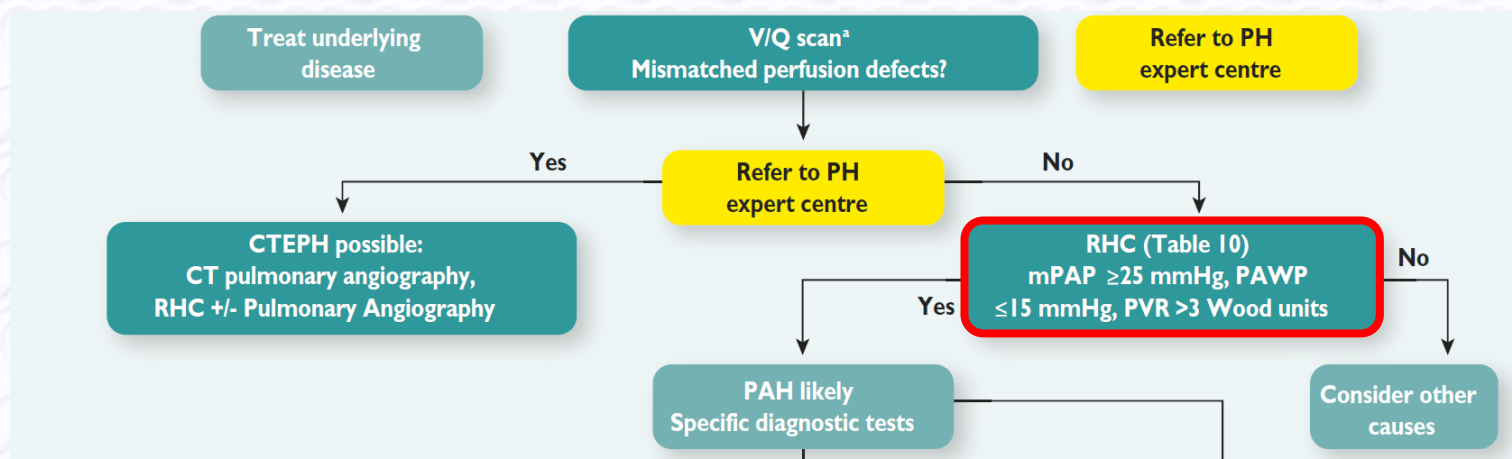EUROPEAN SOCIETY OF CARDIOLOGY®

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Diagnostic algorithm for pulmonary hypertension - 2

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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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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

Additional diagnostic innformation from RHC beyond mPAP >25mmHg

65 year old male, HT, AF	[group 2]	PAWP > 15 mmHg
smoker with mild COPD	[group 3],	respiratory PAP swings
chronic myeloid leukemia (*)	[group 5]	PVR < 3 U (anemia?)
treated with dasatanib (*),	[group 1]	PVR > 3 U
with mild V/Q mismatch	[group 4]	RHC with PA angio

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Subgroup 1′ pulmonary veno-occlusive disease

Symptoms signs and ABG

- dyspnea on exertion, basal crackles, digital clubbing,
- low DLCO

Imaging/HRCT:

- Subpleural thickened septae
- Centrilobular ground glass opacities
- Mediastinal lymphadenopathy

FOB with BAL

- Hemosiderin-laden macrophages

RHC

- **Normal PAWP !**

Eur Heart J 2015, Eur Respir J, 2015

Recommendations for pulmonary veno-occlusive disease

Recommendations	Class[a]	Level[b]
A combination of clinical findings, physical examination, bronchoscopy and radiological findings is recommended to diagnose PVOD/PCH.	I	C
Identification of a bi-allelic *EIF2AK4* mutation is recommended to confirm a diagnosis of heritable PVOD/PCH without histological confirmation.	I	B
Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is indicated as soon as the diagnosis is established.	I	C
Patients with PVOD/PCH should be managed only in centres with extensive experience in PH due to the risk of lung oedema after the initiation of PAH therapy.	IIa	C

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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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Recommendations for right heart catheterization in pulmonary hypertension

Recommendations	Class[a]	Level[b]
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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
RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 23).	I	C
RHC is recommended in patients with PH due to left heart disease (Group 2) or lung disease (Group 3) if organ transplantation is considered.	I	C
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP.	IIa	C
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist differential diagnosis and support treatment decisions.	IIb	C
RHC is indicated in patients with Chronic Thromboembolic Pulmonary Hypertension (Group 4) to confirm diagnosis and support treatment decisions.	I	C

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Recommendations for pulmonary arterial hypertension screening

Recommendations	Class [a]	Level [b]
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B
Resting echocardiography is recommended as a screening test in *BMPR2* mutation carriers or first-degree relatives of patients with HPAH and in patients with PoPH referred for liver transplantation.	I	C
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C

DLCO = diffusing capacity of the lung for carbon monoxide; HPAH = heritable PAH; PAP = pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PFTs = pulmonary function tests; PH = pulmonary hypertension: PoPH = portopulmonary hypertension.
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Conclusions

- Echocardiography should be performed when pulmonary hypertension is suspected

- Echocardiography is not sufficient to support a treatment decision about PAH drug therapies: cardiac catheterization is required

- It is recommended that right heart catheterization be performed in expert centres,

- Screening is recommended/should be considered in selected asymptomatic populations at risk of PAH

- The new diagnostic algorithm should help in more systematic approach to PH diagnosis and management decisions

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- **Thank you...**

Symptoms, signs, history suggestive of PH

Echocardiographic probability of PH

High or intermediate | Low

Consider left heart disease and lung disease (symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, ABG)

Consider other causes and/or follow-up

Diagnosis of left heart disease or lung disease confirmed?

Yes → Signs of severe PH/RV dysfunction

No

No

Yes

V/Q scan Unmatched perfusion defects?

CTEPH or PAH likely

YES

No

Chest CT angiography

PAH likely

Refer to PH expert centre

Consider pulmonary angiograpy

RHC PAP ≥ 25 mmHg, PAWP/LVEDP ≤ 15 mmHg, PVR>3 U

Other specific diagnostic tests

Group 4 PH

Other PA occlusions | CTEPH

Group 1/1' PH

PAH | PVOD/PCH

Group 5 PH

Group 2 or 3 PH