PULMONARY HYPERTENSION (PH) – 2022 ESC/ERS Guidelines

DIAGNOSTIC APPROACH FOR PATIENTS WITH SUSPECTED PH (see fig 1)

Step 1 (suspicion)

PH is usually suspected in patients with unexplained dyspnea and/or echocardiographic findings.

Echocardiography remains an important tool to estimate the probability of PH and RV function. The tricuspid regurgitation maximal velocity (TR max vel) and additional echocardiographic signs of PH can stratify patients into low, intermediate, or high probability of PH (see Fig 2).

- TR max vel:
  - ≤2.8 indicates low probability of PH
  - 2.8 – 3.4 indicates intermediate probability of PH
  - >3.4 indicates high probability of PH
- The TAPSE (tricuspid annular plane systolic excursion/sPAP) is an index of RV function.
  - A value ≥20 mm indicates preserved RV function
  - Values between 16 and 20 mm are borderline
  - A value ≤16 mm indicates reduced RV function
- The TAPSE/sPAP ratio is a new addition to the echocardiographic probability assessment. It is a noninvasive assessment of RV and pulmonary artery coupling and a ratio <0.55 mm/mmHg is suggestive of PH.
- Flattened interventricular septum leading to 'D-shaped' LV indicates significant RV pressure overload and probable RV dysfunction.

Step 2 (detection)

Once PH is suspected, the next step is identification of a clinical phenotype known to be associated with PH.

- Medical history
  - Risk factors for group 1-PAH (connective tissue disease, portal hypertension, congenital heart disease, HIV infection, pulmonary veno-oclussive disease/pulmonary capillary hemangiomatosis (PVOD/PCH are rare), and drugs/toxins)
  - Comorbidities including systemic HTN, DM, CAD, AF, VTE, CKD, anemia, and old age
  - Smoking and environmental exposure
- Work up
  - Echocardiogram
  - PFTs
  - ABGs
  - 6 MWT
  - HRCT
  - ANA, HIV test and liver US-liver enzymes if PAH suspected
  - PSG study if OSA-OHS suspected. Alternatively, overnight oximetry to screen both nocturnal hypoxemia and sleep disorder breathing
  - If no evidence of LHD, lung diseases, or hypoventilation syndrome
    - Request CTA chest with PE protocol and or V/Q scan and investigate for clinical conditions associated with PH of unclear mechanisms (group 5).

Step 3 (confirmation)

RHC must be performed to confirm the diagnosis of PH and to support treatment decisions.

The decision to perform RHC should depend on the presence of an intermediate to high echocardiographic probability of PH and should be determined by the need to obtain relevant information for prognostication or management.

RHC is usually recommended in the following conditions:

- Patients with *high* echocardiographic probability of PH.
- Patients with *intermediate* echocardiographic probability of PH
    - With risk factors for PAH or CTPH.
    - Suspected CpcPH with a severe pre-capillary component where the severity of PH is not sufficiently explained by the underlying conditions and further information will aid phenotyping and treatment decisions.
        - A significantly increased PVR defined as >5 WU may indicate a severe pre-capillary component and therefore patient may potentially benefit from pulmonary vasodilators which may prompt referral patients to PH center for specialized care.

RHC is not usually recommended in the following conditions:

- Patients with a *low* echocardiographic probability of PH
    - Without risk factors for PAH or CTPH.
        - No further PH work up needed. An alternate diagnosis needs to be considered.
    - With risk factors for PAH or CTPH.
        - Echocardiogram follow-up is recommended.
- Patients with *intermediate* echocardiographic probability of PH
    - Without risk factors for PAH or CTPH.
        - Echocardiogram follow-up is recommended.
    - With LHD or lung diseases and/or hypoxemia with intermediate echocardiographic probability of PH suggesting that PH is sufficiently explained by the underlying condition.

Best practice suggests that echocardiogram and RHC should be performed in stable, non-acute clinical conditions for the differential diagnosis of PH.

In patients with a PAWP 13–15 mmHg and high/intermediate probability of PH associated with HFpEF, a provocative testing-fluid challenge should be considered to uncover PH due to HFpEF.

- PAWP >18 mmHg immediately after administration of 500 mL of saline over 5-10 min or leg raising maneuver over 2 min is considered abnormal suggesting HFpEF as the underlying cause of PH.

Vasoreactivity testing:

- Indications
    - To identify a small subset of PAH patients who can respond to calcium channel blocker therapy.
    - Include only patients who are most likely to be vasoreactive
        - IPAH
        - Heritable PAH
        - PAH associated with drug/toxin
- Contraindications
    - SBP <90 mmHg
    - CI <2 L/min/m2
    - Functional class IV
- Test positivity
    - mPAP decreases >10 mmHg and to a value of <40 mmHg
    - Increased or unchanged CO
    - Minimally reduced or unchanged BP

Vasodilators for vasoreactivity testing

- Inhaled nitric oxide 20 ppm
- Epoprostenol IV infusion

    - Start at 1 to 2 ng/Kg/min and increased by 2 ng/Kg/min every 5-10 min in clinically significant fall in BP, increase in HR, or adverse symptoms develop to maximal dose of 12 ng/Kg/min
- Adenosine IV infusion
    - Start at 50 mcg/Kg/min and increased every 2 minutes until uncomfortable symptoms developed or a maximal dose of 200-350 mcg/Kg/min

Indications for direct LVEDP measurement:

- If PAWP is elevated and the accuracy of PAWP is in question, blood oxygen saturation should be determined in the wedge position. If the PAWP oxygen saturation is <90%, direct LVEDP measurement should be obtained.
- If pre-test probability of PH-HFpEF is low and PAWP >15 mmHg, direct LVEDP measurement should be obtained.

New Definition and Hemodynamic and Clinical Groups Classification

- *Note a change from mPAP >20 mmHg rather than >25 mmHg*
- *Note a change from* PVR >2 WU *rather than* PVR ⩾3 WU

Haemodynamic definitions	mPAP	PVR	PAWP
PH	>20 mmHg		
Pre-capillary PH	>20 mmHg	>2 WU	⩽15 mmHg
Isolated post-capillary PH	>20 mmHg	⩽2 WU	>15 mmHg
Combined post- and pre-capillary PH	>20 mmHg	>2 WU	>15 mmHg
Unclassified PH[#]	>20 mmHg	⩽2 WU	⩽15 mmHg
Exercise PH	mPAP/CO slope >3 mmHg·min·L^{-1} between rest and exercise		

Unclassified PH refers to a hemodynamic pattern that does not fulfil the criteria of precapillary PH or IpcPH or CpcPH. It is due to elevated pulmonary blood flow and is characterized by elevated pulmonary artery pressure with normal PAWP and normal PVR.

- May be present in patients with liver disease, congenital heart disease, or hyperthyroidism
- We also encounter this scenario when using the Fick rather than thermodilution method to estimate the cardiac output (CO). In general, Fick method tend to overestimate the CO. Alternatively, the thermodilution method underestimate the CO in the presence of significant tricuspid regurgitation and overestimate it in the presence of cardiac shunt.
- The thermodilution method is usually preferred even with the risk of some underestimation with severe TR because is a better predictor of survival outcome.
- Clinical follow-up of these patients is generally recommended and its etiology should be explored.

Clinical groups

Group 1: PAH

- Idiopathic – patients with no clinical phenotype identified
    - Non-responders at vasoreactivity testing
    - Acute responders at vasoreactivity testing
- Heritable
- Associated with drug or toxin induced
- Associated with:
    - Connective tissue disease
    - HIV infection
    - Portal hypertension
    - Congenital heart disease

    - Schistosomiasis
    - PAH with features of venous/capillary (PVOD/PCH) involvement
    - Persistent PH of the newborn

Group 2: PH associated with left heart disease (LHD)

- HFpEF
- HFrEF
- Valve heart disease

Group 3: PH associated with to lung diseases and/or hypoxemia. A PVR threshold of >5 WU has been chosen to differentiate severe from non-severe PH in group 3 PH.

- COPD/emphysema
- ILD
- Hypoventilation syndromes with hypoxemia and daytime hypercapnia

Group 4: PH associated with pulmonary artery obstructions

- CTEPH
- Other rare pulmonary artery obstructions (malignant tumors and fibrosing mediastinitis)

Group 5: PH with unclear and/or multifactorial mechanisms

- Hematologic disorders (sickle cell disease, beta thalassemia, and myeloproliferative disorders
- Systemic disorders (sarcoidosis, pulmonary Langerhans histiocytosis, neurofibromatosis, LAM is now reclassified into group 3)
- End-stage kidney disease with or without hemodialysis

Hemodynamic classification and clinical groups association

- Group 1: pre-capillary PH.
- Group 2: isolated post-capillary (IpcPH) or combined post and pre-capillary PH (CpcPH).
- Group 3: pre-capillary PH unless associated with co-existing LHD
- Group 4: pre-capillary PH unless associated with co-existing LHD
- Group 5:
    - Precapillary PH (e.g., hemoglobinopathies or myeloproliferative disease)
    - IpcPH or CpcPH

Combined post and pre-capillary PH is more commonly seen in patients with LHD that develop primary increase in PVR, in patients with chronic hypoxemic respiratory failure with co-existing LHD, and in some patients in clinical group 5.

TREATMENT

Differentiating between severe PH associated with groups 2 through 5 with a predominant pre-capillary component and IPAH with cardiac or pulmonary comorbidities is challenging. Patients should be referred to a PH center for individualized management.

Group 1: PAH – treatment

General supportive measures

- Supplemental O2 targeting O2 Sat 90-96%
    - Hypoxemia can be due to V/Q mismatch, deceased DLCO, decreased CO, or opening of intrapulmonary or intracardiac shunts
- Activity is encouraged within symptom limits
- Fluid restriction and diuresis to achieve euvolemia
- Anticoagulation

- No recommendation has been made for or against the use of anticoagulants
  - Has fallen out of favor in the USA after the REVEAL study
- May be harmful in patients with systemic sclerosis

Pharmacologic Treatment
Initial risk assessment using the model recommended by the ESC/ERS should be established to guide patient-centered treatment decisions (see fig 4 and 5).

To guide treatment during follow-ups the following three noninvasive parameters should be used:

- WHO functional class
- 6 MWT
- ProBNP or BNP

Group 2: PH associated with LHD – treatment

- The primary strategy in managing PH-LHD is optimizing treatment of the underlying cardiac disease.
- Use of pulmonary vasodilators including PDE5 inhibitors in patients with PH-LHD.
  - Are not beneficial and can be harmful in patients with valve heart disease with HFrEF as well as in patients with persistence of PH after valvular heart repair.
  - Not indicated in patients with HFpEF and IpcPH.
  - May be beneficial (evidence is modest at best and only with sildenafil) in patients with HFpEF and CpcPH with a severe pre-capillary component defined as a PVR >5 WU.

Group 3 – PH associated with lung diseases and/or hypoxemia

Similar to group 2 PH, the primary strategy in managing PH associated with lung disease is optimizing treatment of the underlying lung disease.

- Former guidelines recommended against the use of PAH-specific therapy in this group due to concerns regarding worsening ventilation/perfusion (V/Q) mismatch and a lack of evidence demonstrating significant benefits.
- However, following the results of the phase 3 INCREASE trial, inhaled treprostinil can now be considered in subjects with ILD and severe PH.
  - A PVR threshold of >5 WU has been chosen to differentiate severe from non-severe PH in group 3 PH.
- Early referral to lung transplantation

Group 4: PH associated with pulmonary artery obstructions

Patients should be referred to a PH center for consideration of pulmonary endarterectomy, balloon pulmonary angioplasty and/or medical therapy.

Group 5: PH with unclear and/or multifactorial mechanisms

This group comprises a heterogeneous mix of disorders that may be complicated by PH but the mechanisms driving PH are often poorly understood and frequently multifactorial in nature.

PH-tailored treatments have been limited; however, there has been some progress in the field of sarcoidosis-associated PH but still no robust evidence.

2022 ESC/ERS Guidelines pearls

In summary, it is an endorsement of the 6th World Symposium on PH including using mPAP >20 mmHg to define PH.

The major innovations were:

- Using >2 WU rather than ≥3 WU to define elevation of PVR. To my knowledge, this has not been endorsed by other societies.
- In group 4 PH, the term chronic thrombo-embolic pulmonary disease (CTEPD) with or without PH was officially introduced, acknowledging the presence of similar symptoms, perfusion defects, and organized fibrotic obstructions in patients with or without PH at rest.
- Instead of the general term 'sleep-disordered breathing', the term 'hypoventilation syndromes' should be used within group 3 to describe conditions with increased risk of PH. Sole nocturnal obstructive sleep apnea is generally not a cause of PH, but PH is frequent in patients with hypoventilation syndromes causing daytime hypercapnia.
- Considering the inaccuracies in estimating RAP and the amplification of measurement errors by using derived variables, these guidelines recommend using the peak TRV (and not the estimated sPAP) as the key variable for assigning the echocardiographic probability of PH. A peak TRV >2.8 m/s may suggest PH and >3.4 m/s is very likely consistent with PH.
- The diastolic pressure gradient (DPG) (calculated as the difference between dPAP and PAWP) is no longer used to distinguish between IpcPH and CpcPH because of conflicting data on prognostication in LHD

Fig 1. Diagnostic approach (taken from NEJM 385;25 nejm.org December 16, 2021).

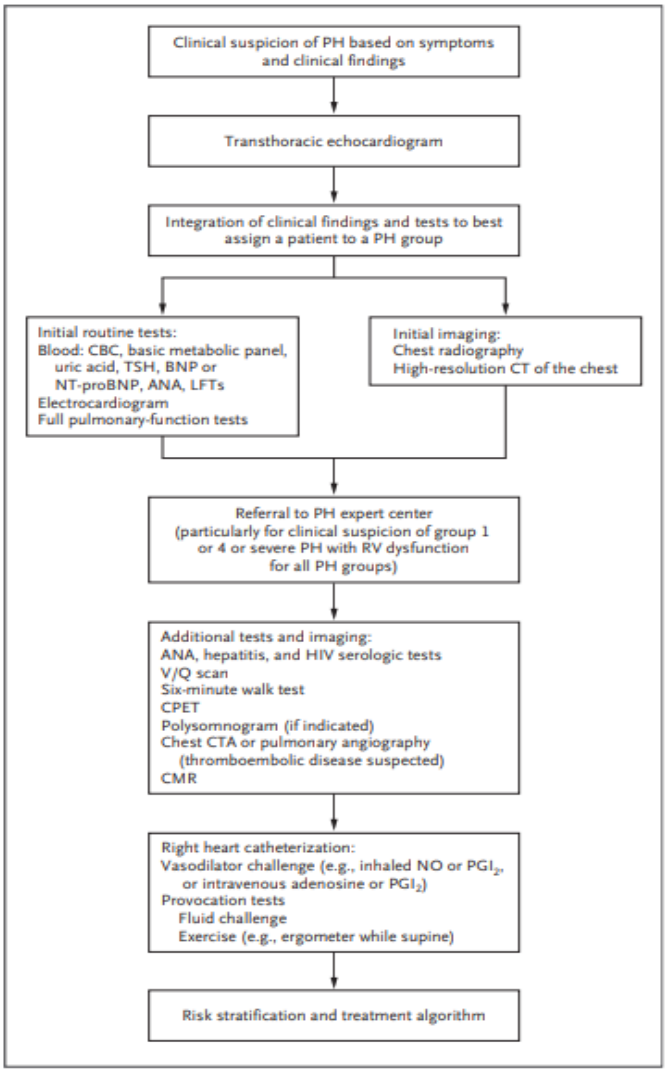

Fig 2. Probability of PH

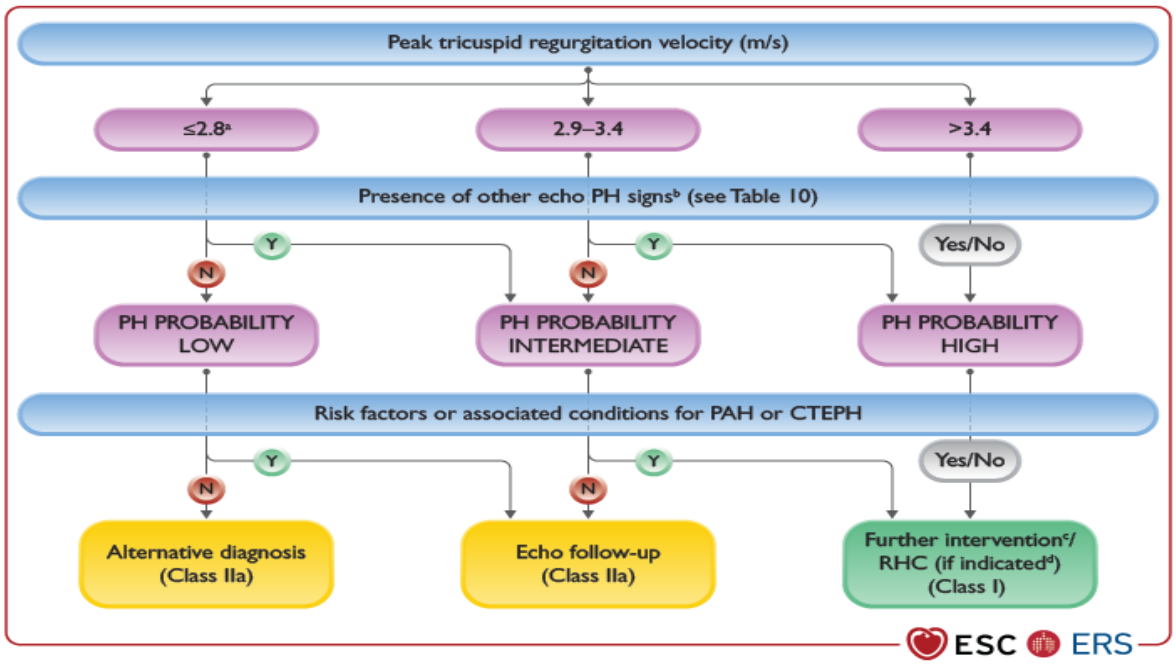

Fig 3. Therapeutic strategies

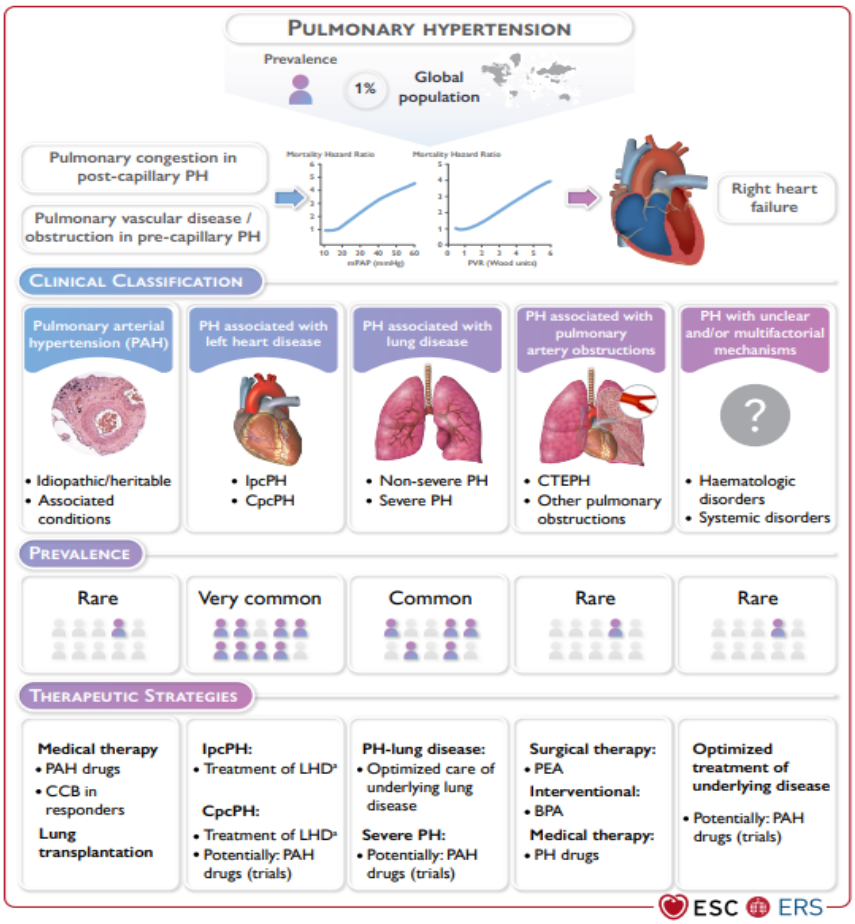

Fig 4. Comprehensive risk assessment in pulmonary arterial hypertension

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%

Fig 5. Treatment Algorithm for Confirmed PAH (taken from NEJM 385;25 nejm.org December 16, 2021).

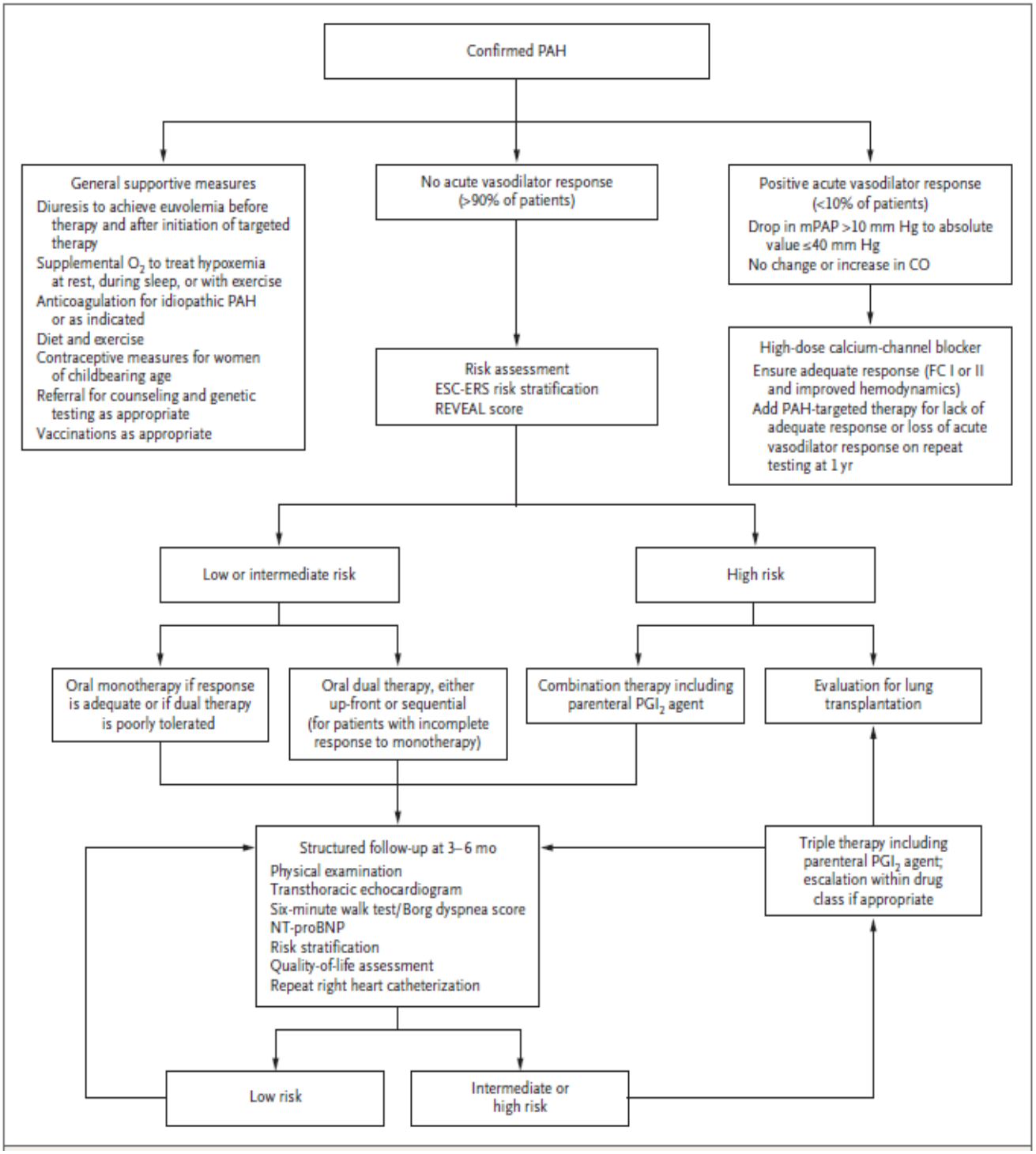

Fig 6. IpcPH and CpcPH