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)

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2022 ESC/ERS pulmonary hypertension guidelines incorporate changes and adaptations focusing on clinical management https://bit.ly/3QtUvb4

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1. Preamble

Guidelines summarize and evaluate available evidence, with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision-making of health professionals in their daily practice. However, guidelines are not a substitute for the patient's relationship with their practitioner. The final decisions concerning an individual patient must be made by the responsible health professional(s), based on what they consider to be the most appropriate in the circumstances. These decisions are made in consultation with the patient and caregiver as appropriate.

Guidelines are intended for use by health professionals. To ensure that all physicians have access to the most recent recommendations, both the European Society of Cardiology (ESC) and European Respiratory Society (ERS) make their guidelines freely available in their own journals. The ESC and ERS warn non-medical readers that the technical language may be misinterpreted and decline any responsibility in this respect.

Many Guidelines have been issued in recent years by the ESC and ERS. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The ERS and ESC guidance and procedure to formulate and issue clinical practice recommendations can be found on the societies' relevant website or journal (https://www.escardio.org/Guidelines and https://openres.ersjournals.com/content/8/1/00655-2021). The ESC and ERS Guidelines represent the official position of the ESC and ERS on a given topic and are regularly updated.

The panel of experts of these specific guidelines comprised an equal number of ERS and ESC members, including representatives from relevant subspecialty groups involved in the medical care of patients with this pathology.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/Guidelines). They have been compiled in a report and co-published in a supplementary document of the guidelines. This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arose during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC and ERS without any involvement from the health care industry.

The ESC Clinical Practice Guidelines (CPG) Committee and the ERS Guidelines Director reporting to the ERS Science Council supervise and co-ordinate the preparation of new guidelines. These Guidelines underwent extensive review by the ESC CPG Committee, the ERS Guidelines Working Group, and external experts. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of drafting. After appropriate revisions, the guidelines were signed off by all the experts in the Task Force. The finalized document was signed off by the ESC CPG Committee and endorsed by the ERS Executive Committee before being simultaneously published in the *European Heart Journal* (EHJ) and the *European Respiratory Journal* (ERJ). The decision to publish the guidelines in both journals was made to ensure adequate dissemination of the recommendations in both the cardiology and respiratory fields.

BOX 1 Abbreviations and acronyms	
6MWD	6-minute walking distance
6MWT	6-minute walking test
ABG	Arterial blood gas analysis
ACEi	Angiotensin-converting enzyme inhibitor
ALAT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
ASAT	Aspartate aminotransferase
ASIG	Australian Scleroderma Interest Group
BNP	Brain natriuretic peptide
BPA	Balloon pulmonary angioplasty
BPD	Bronchopulmonary dysplasia
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CCB	Calcium channel blocker
CDH	Congenital diaphragmatic hernia
cGMP	Cyclic guanosine monophosphate
CHD	Congenital heart disease
CI	Cardiac index; Confidence interval
cMRI	Cardiac magnetic resonance imaging
CO	Cardiac output
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for PH
COPD	Chronic obstructive pulmonary disease
CpcPH	Combined post- and pre-capillary pulmonary hypertension
CPET	Cardiopulmonary exercise testing
CPFE	Combined pulmonary fibrosis and emphysema
CT	Computed tomography
CTD	Connective tissue disease
CTEPD	Chronic thrombo-embolic pulmonary disease
CTEPH	Chronic thrombo-embolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiography
DECT	Dual-energy computed tomography
DLCO	Lung diffusion capacity for carbon monoxide
DPAH	Drug- or toxin-associated pulmonary arterial hypertension
dPAP	Diastolic pulmonary arterial pressure
DPG	Diastolic pressure gradient
DSA	Digital subtraction angiography
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EHJ	*European Heart Journal*
EMA	European Medicines Agency
EOV	Exercise oscillatory ventilation
ERA	Endothelin receptor antagonist
ERJ	*European Respiratory Journal*
ERN	European Reference Network
ERN-LUNG	European Reference Network on rare respiratory diseases
ERS	European Respiratory Society
ESC	European Society of Cardiology
EtD	Evidence to Decision
FPHR	French Pulmonary Hypertension Registry
FVC	Forced vital capacity
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HIV	Human immunodeficiency virus
HPAH	Heritable pulmonary arterial hypertension
HPS	Hepatopulmonary syndrome
HR	Hazard ratio
HR-QoL	Health-related quality of life
ICU	Intensive care unit

Continued

BOX 1 Continued	
IgG4	Immunogolobulin G4
ILD	Interstitial lung disease
IPAH	Idiopathic pulmonary arterial hypertension
IpcPH	Isolated post-capillary pulmonary hypertension
IP receptor	Prostacyclin I2 receptor
ISWT	Incremental shuttle walking test
i.v.	Intravenous
LA	Left atrium/left atrial
LAS	Lung allocation score
LHD	Left heart disease
LTx	Lung transplantation
LV	Left ventricle/left ventricular
LVAD	Left ventricular assist device
mPAP	Mean pulmonary arterial pressure
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NOAC	Novel oral anticoagulant
NT-proBNP	N-terminal pro-brain natriuretic peptide
OR	Odds ratio
PA	Pulmonary artery
PAC	Pulmonary arterial compliance
$PaCO_2$	Partial pressure of arterial carbon dioxide
PADN	Pulmonary artery denervation
PAH	Pulmonary arterial hypertension
PAH-CTD	Pulmonary arterial hypertension associated with connective tissue disease
PAH-SSc	Pulmonary arterial hypertension associated with systemic sclerosis
PAH-SYMPACT	Pulmonary Arterial Hypertension-Symptoms and Impact
PaO_2	Partial pressure of arterial oxygen
PAP	Pulmonary arterial pressure
PAVM	Pulmonary arteriovenous malformation
PAWP	Pulmonary arterial wedge pressure
PCH	Pulmonary capillary haemangiomatosis
PDE5i	Phosphodiesterase 5 inhibitor
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PET	Positron emission tomography
$P_{ET}CO_2$	End-tidal partial pressure of carbon dioxide
PFT	Pulmonary function test
PH	Pulmonary hypertension
PH-LHD	Pulmonary hypertension associated with left heart disease
PICO	Population, Intervention, Comparator, Outcome
PoPH	Porto-pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn
PROM	Patient-reported outcome measure
PVD	Pulmonary vascular disease
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
QI	Quality indicator
Qp/Qs	Pulmonary blood flow/systemic blood flow
RA	Right atrium/right atrial
RAP	Right atrial pressure
RCT	Randomized controlled trial
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
RHC	Right heart catheterization
RR	Relative risk
RV	Right ventricle/right ventricular
RVEF	Right ventricular ejection fraction
RV-FAC	Right ventricular fractional area change
RVOT AT	Right ventricular outflow tract acceleration time
SaO_2	Arterial oxygen saturation
s.c.	Subcutaneous

Continued

BOX 1 Continued

SCD	Sickle cell disease
sGC	Soluble guanylate cyclase
SGLT-2i	Sodium–glucose cotransporter-2 inhibitor
SLE	Systemic lupus erythematosus
SPAHR	Swedish Pulmonary Arterial Hypertension Registry
sPAP	Systolic pulmonary arterial pressure
SPECT	Single-photon emission computed tomography
SSc	Systemic sclerosis
SV	Stroke volume
SVI	Stroke volume index
SvO_2	Mixed venous oxygen saturation
TAPSE	Tricuspid annular plane systolic excursion
TGF-β	Transforming growth factor-β
TPR	Total pulmonary resistance
TR	Tricuspid regurgitation
TRPG	Tricuspid regurgitation pressure gradient
TRV	Tricuspid regurgitation velocity
TSH	Thyroid-stimulating hormone
V/Q	Ventilation perfusion
VE/VCO_2	Ventilatory equivalent for carbon dioxide
VKA	Vitamin K antagonist
VO_2	Oxygen uptake
VO_2/HR	Oxygen pulse
VTE	Venous thrombo-embolism
WHO-FC	World Health Organization functional class
WSPH	World Symposium on Pulmonary Hypertension
WU	Wood units

The task of developing the ESC/ERS Guidelines also included creating educational tools and implementation programmes for the recommendations, including condensed pocket guidelines versions, summary slides, a lay summary, and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access the full-text version of the guidelines, which is freely available via the ESC and ERS websites, and hosted on the EHJ and ERJ websites. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate, and implement all ESC Guidelines. Pulmonary national societies are also encouraged to share these guidelines with their members and develop a summary or editorials in their own language, if appropriate. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC/ERS Guidelines fully into account when exercising their clinical judgement, as well as in determining and implementing preventive, diagnostic, or therapeutic medical strategies. However, the ESC/ERS Guidelines do not override, in any way, the individual responsibility of health professionals to make appropriate and accurate decisions in considering each patient's health condition and in consulting with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription and, where appropriate, to respect the ethical rules of their profession in each country.

Off-label use of medication may be presented in these guidelines if a sufficient level of evidence shows that it can be considered medically appropriate to a given condition and if patients could benefit from the recommended therapy. However, the final decisions concerning an individual patient must be made by the responsible health professional, giving special consideration to:

- The specific situation of the patient. In this respect, it is specified that, unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest to do so, with regards to the quality, safety, and efficacy of care, and only after the patient has been fully informed and provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies, and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

Pulmonary hypertension (PH) is a pathophysiological disorder that may involve multiple clinical conditions and may be associated with a variety of cardiovascular and respiratory diseases. The complexity of managing PH requires a multifaceted, holistic, and multidisciplinary approach, with active involvement of patients with PH in partnership with clinicians. Streamlining the care of patients with PH in daily clinical practice is a challenging but essential requirement for effectively managing PH. In recent years, substantial progress has been made in detecting and managing PH, and new evidence has been timeously integrated in this fourth edition of the ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Reflecting the multidisciplinary input into managing patients with PH and interpreting new evidence, the Task Force included cardiologists and pneumologists, a thoracic surgeon, methodologists, and patients. These comprehensive clinical practice guidelines cover the whole spectrum of PH, with an emphasis on diagnosing and treating pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH).

2.1. What is new

One of the most important proposals from the 6th World Symposium on Pulmonary Hypertension (WSPH) was to reconsider the haemodynamic definition of PH [1]. After careful evaluation, the new definitions of PH have been endorsed and expanded in these guidelines, including a revised cut-off level for pulmonary vascular resistance (PVR) and a definition of exercise PH.

The classification of PH has been updated, including repositioning of vasoreactive patients with idiopathic pulmonary arterial hypertension (IPAH) and a revision of group 5 PH, including repositioning of PH in lymphangioleiomyomatosis in group 3.

Concerning the diagnosis of PH, a new algorithm has been developed aiming at earlier detection of PH in the community. In addition, expedited referral is recommended for high-risk or complex patients. Screening strategies are also proposed.

The risk-stratification table has been expanded to include additional echocardiographic and cardiac magnetic resonance imaging (cMRI) prognostic indicators. The recommendations for initial drug therapies have been simplified, building on this revised, three-strata, multiparametric risk model to replace functional classification. At follow-up, a four-strata risk-assessment tool is now proposed based on refined cut-off levels for World Health Organization functional class (WHO-FC), 6-minute walking distance (6MWD), and N-terminal pro-brain natriuretic peptide (NT-proBNP), categorizing patients as low, intermediate–low, intermediate–high, or high risk.

The PAH treatment algorithm has been modified, highlighting the importance of cardiopulmonary comorbidities, risk assessment both at diagnosis and follow-up, and the importance of combination therapies. Treatment strategies during follow-up have been based on the four-strata model intended to facilitate more granular decision-making.

The recommendations for managing PH associated with left heart disease (PH-LHD) and lung disease have been updated, including a new haemodynamic definition of severe PH in patients with lung disease.

In group 4 PH, the term chronic thrombo-embolic pulmonary disease (CTEPD) with or without PH has been introduced, acknowledging the presence of similar symptoms, perfusion defects, and organized fibrotic obstructions in patients with or without PH at rest. Interventional treatment by balloon pulmonary angioplasty (BPA) in combination with medical therapy has been upgraded in the therapeutic algorithm of CTEPH.

New standards for PH centres have been presented and, for the first time, patient representatives were actively involved in developing these guidelines.

Questions with direct consequences for clinical practitioners regarding each PH classification subgroup were selected and addressed, namely guidance on: initial treatment strategy for group 1 PH (Population, Intervention, Control, Outcome [PICO] I); use of oral phosphodiesterase 5 inhibitors (PDE5is) for the treatment of group 2 PH (PICO II); use of oral PDE5is for the treatment of group 3 PH (PICO III); and use of PH drugs prior to BPA for the treatment of group 4 PH (PICO IV). These questions were considered to be important because: most contemporary PH registries describe variable use of initial oral monotherapy and combination therapy; large case series show widespread use of PDE5is in group 2 PH, despite a class III recommendation in the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension; large case series show widespread use of PDE5is in group 3 PH, despite a class III recommendation in the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension; and there is no clear guidance for therapy with PH drugs in patients with inoperable CTEPH prior to BPA.

BOX 2 Selected revised recommendations (R) and new recommendations (N)				
New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
Right heart catheterization and vasoreactivity testing – Recommendation Table 1				
N			It is recommended that RHC comprises a complete set of haemodynamics and is performed following standardized protocols	I
R	Adenosine should be considered for performing vasoreactivity testing as an alternative Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative	IIa	Inhaled nitric oxide, inhaled iloprost, or i.v. epoprostenol are recommended for performing vasoreactivity testing	I
Diagnostic strategy – Recommendation Table 2				
N			It is recommended to assign an echocardiographic probability of PH, based on an abnormal TRV and the presence of other echocardiographic signs suggestive of PH (see Table 10)	I
N			It is recommended to maintain the current threshold for TRV (>2.8 m/s) for echocardiographic probability of PH according to the updated haemodynamic definition	I
N			Based on the probability of PH by echocardiography, further testing should be considered in the clinical context (*i.e.* symptoms and risk factors or associated conditions for PAH/CTEPH)	IIa
N			In symptomatic patients with intermediate echocardiographic probability of PH, CPET may be considered to further determine the likelihood of PH	IIb
Screening and improved detection of pulmonary arterial hypertension and chronic thrombo-embolic pulmonary hypertension – Recommendation Table 3				
N			In patients with SSc, an annual evaluation of the risk of having PAH is recommended	I
R	Resting echocardiography is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echocardiography, DLCO, and biomarkers	I	In adult patients with SSc of >3 years' disease duration, an FVC ⩾40%, and a DLCO <60%, the DETECT algorithm is recommended to identify asymptomatic patients with PAH	I
N			In patients with SSc, where breathlessness remains unexplained following non-invasive assessment, RHC is recommended to exclude PAH	I
N			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
N			Policies to evaluate the risk of having PAH should be considered in hospitals managing patients with SSc	IIa
R	RHC is recommended in all cases of suspected PAH associated with CTD	I	In symptomatic patients with SSc, exercise echocardiography or CPET, or CMR may be considered to aid decisions to perform RHC	IIb
N			In patients with CTD with overlap features of SSc, an annual evaluation of the risk of PAH may be considered	IIb
R	In PE survivors with exercise dyspnoea, CTEPH should be considered	IIa	In patients with persistent or new-onset dyspnoea or exercise limitation following PE, further diagnostic evaluation to assess for CTEPH/CTEPD is recommended	I
N			For symptomatic patients with mismatched perfusion lung defects beyond 3 months of anticoagulation for acute PE, referral to a PH/CTEPH centre is recommended after considering the results of echocardiography, BNP/NT-proBNP, and/or CPET	I

Continued

BOX 2 Continued				
New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
N			Counselling regarding the risk of PAH, and annual screening is recommended in individuals who test positive for PAH-causing mutations and in first-degree relatives of patients with HPAH	I
N			In patients referred for liver transplantation, echocardiography is recommended as a screening test for PH	I
N			Further tests (echocardiography, BNP/NT-proBNP, PFTs, and/or CPET) should be considered in symptomatic patients with CTD, portal hypertension, or HIV to screen for PAH	IIa
Evaluating the disease severity and risk of death in patients with pulmonary arterial hypertension – Recommendation Table 4				
N			For risk stratification at the time of diagnosis, the use of a three-strata model (low, intermediate, and high risk) is recommended, taking into account all available data including haemodynamics	I
N			For risk stratification during follow-up, the use of a four-strata model (low, intermediate–low, intermediate–high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary	I
R	Achievement/maintenance of an intermediate-risk profile should be considered an inadequate treatment response for most patients with PAH	IIa	In some PAH aetiologies and in patients with comorbidities, optimization of therapy should be considered on an individual basis while acknowledging that a low-risk profile is not always achievable	IIa
General measures and special circumstances – Recommendation Table 5				
R	Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	Supervised exercise training is recommended in patients with PAH under medical therapy	I
R	Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	Immunization of patients with PAH against SARS-CoV-2, influenza, and *Streptococcus pneumoniae* is recommended	I
R	Correction of anaemia and/or iron status may be considered in PAH patients	IIb	In the presence of iron-deficiency anaemia, correction of iron status is recommended in patients with PAH	I
N			In the absence of anaemia, iron repletion may be considered in patients with PAH with iron deficiency	IIb
R	Oral anticoagulant treatment may be considered in patients with IPAH, HPAH, and PAH due to use of anorexigens	IIb	Anticoagulation is not generally recommended in patients with PAH but may be considered on an individual basis	IIb
R	The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers, and ivabradine is not recommended in patients with PAH unless required by comorbidities (*i.e.* high blood pressure, coronary artery disease, or left HF)	III	The use of ACEis, ARBs, ARNIs, SGLT-2is, beta-blockers, or ivabradine is not recommended in patients with PAH unless required by comorbidities (*i.e.* high blood pressure, coronary artery disease, left HF, or arrhythmias)	III
R	In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg)	IIa	In-flight oxygen administration is recommended for patients using oxygen or whose arterial blood oxygen pressure is <8 kPa (60 mmHg) at sea level	I
R	In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	IIa	For interventions requiring anaesthesia, multidisciplinary consultation at a PH centre to assess risk and benefit should be considered	IIa
Women of childbearing potential – Recommendation Table 6				
R	It is recommended that PAH patients avoid pregnancy	I	It is recommended that women of childbearing potential with PAH are counselled at the time of diagnosis about the risks and uncertainties associated with becoming pregnant; this should include advice against becoming pregnant, and referral for psychological support where needed	I

Continued

BOX 2 Continued

New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
N			It is recommended to provide women of childbearing potential with PAH with clear contraceptive advice, considering the individual needs of the woman but recognizing that the implications of contraceptive failure are significant in PAH	I
N			It is recommended that women with PAH who consider pregnancy or who become pregnant receive prompt counselling in an experienced PH centre to facilitate genetic counselling and shared decision-making, and to provide psychological support to the patients and their families where needed	I
N			For women with PAH having termination of pregnancy, it is recommended that this be performed in PH centres, with psychological support provided to the patient and their family	I
N			For women with PAH who desire to have children, where available, adoption and surrogacy with pre-conception genetic counselling may be considered	IIb
N			As teratogenic potential has been reported in preclinical models for endothelin receptor antagonists and riociguat, these drugs are not recommended during pregnancy	III
Treatment of vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension – Recommendation Table 7				
R	Continuation of high doses of CCBs is recommended in patients with IPAH, HPAH, and DPAH in WHO-FC I or II with marked haemodynamic improvement (near normalization)	I	Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked haemodynamic improvement (mPAP <30 mmHg and PVR <4 WU)	I
N			In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered	IIa
Treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present without cardiopulmonary comorbidities[b] – Recommendation Table 8				
N			In patients with IPAH/HPAH/DPAH who present at high risk of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be considered[c]	IIa
N			In patients with IPAH/HPAH/DPAH who present at intermediate–low risk of death while receiving ERA/PDE5i therapy, addition of selexipag should be considered	IIa
N			In patients with IPAH/HPAH/DPAH who present at intermediate–high or high risk of death while receiving ERA/PDE5i therapy, the addition of i.v./s.c. prostacyclin analogues and referral for lung transplantation evaluation should be considered	IIa
N			In patients with IPAH/HPAH/DPAH who present at intermediate–low risk of death while receiving ERA/PDE5i therapy, switching from PDE5i to riociguat may be considered	IIb
Initial oral drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertensionwithout cardiopulmonary comorbidities – Recommendation Table 9				
R	Ambrisentan + tadalafil	I	Initial combination therapy with ambrisentan and tadalafil is recommended	I
N			Initial combination therapy with macitentan and tadalafil is recommended	I
R	Other ERA + PDE-5i	IIa	Initial combination therapy with other ERAs and PDE5is should be considered	IIa
N			Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended	III

Continued

BOX 2 Continued

New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
Sequential drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension – Recommendation Table 10				
N			It is recommended to base treatment escalations on risk assessment and general treatment strategies (see treatment algorithm)	I
R	Macitentan added to sildenafil	I	Addition of macitentan to PDE5is or oral/inhaled prostacyclin analogues is recommended to reduce the risk of morbidity/mortality events	I
N			Addition of oral treprostinil to ERA or PDE5i/riociguat monotherapy is recommended to reduce the risk of morbidity/mortality events	I
R	Bosentan added to sildenafil	IIb	Addition of bosentan to sildenafil is not recommended to reduce the risk of morbidity/mortality events	III
R	Riociguat added to bosentan	I	Addition of riociguat to bosentan should be considered to improve exercise capacity	IIa
Treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertensionwho present with cardiopulmonary comorbidities[b] – Recommendation Table 11				
N			In patients with IPAH/HPAH/DPAH and cardiopulmonary comorbidities, initial monotherapy with a PDE5i or an ERA should be considered	IIa
N			In patients with IPAH/HPAH/DPAH with cardiopulmonary comorbidities who present at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, additional PAH medications may be considered on an individual basis	IIb
Efficacy of intensive care management for pulmonary arterial hypertension – Recommendation Table 12				
N			When managing patients with right HF in the ICU, it is recommended to involve physicians with expertise, treat causative factors, and use supportive measures including inotropes and vasopressors, fluid management, and PAH drugs as appropriate	I
N			Mechanical circulatory support may be an option for selected patients as a bridge to transplantation or to recovery, and interhospital transfer should be considered if such resources are not available on site	IIa
Lung transplantation – Recommendation Table 13				
R	Lung transplantation is recommended soon after inadequate clinical response on maximal medical therapy	I	It is recommended that potentially eligible candidates are referred for LTx evaluation when they have an inadequate response to oral combination therapy, indicated by an intermediate–high or high risk or by a REVEAL risk score >7	I
N			It is recommended to list patients for LTx who present with a high risk of death or with a REVEAL risk score ⩾10 despite receiving optimized medical therapy including s.c. or i.v. prostacyclin analogues	I
Pulmonary arterial hypertensionassociated with drugs or toxins – Recommendation Table 14				
N			It is recommended to make a diagnosis of drug- or toxin-associated PAH in patients who had relevant exposure and in whom other causes of PH have been excluded	I
N			In patients with suspected drug- or toxin-associated PAH, it is recommended to discontinue the causative agent immediately whenever possible	I
N			Immediate PAH therapy should be considered in patients who present with intermediate/high-risk PAH at diagnosis	IIa

Continued

BOX 2 Continued

New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
N			Patients with low-risk PAH should be re-evaluated 3–4 months after discontinuing the suspected drug or toxin, and PAH therapy may be considered when the haemodynamics have not normalized	IIb
Pulmonary arterial hypertension associated with connective tissue disease – Recommendation Table 15				
N			In patients with PAH associated with CTD, treatment of the underlying condition according to current guidelines is recommended	I
Pulmonary arterial hypertension associated with human immunodeficiency virus infection – Recommendation Table 16				
N			In patients with PAH associated with HIV infection, antiretroviral treatment according to current guidelines is recommended	I
N			In patients with PAH associated with HIV infection, initial monotherapy should be considered, followed by sequential combination if necessary, taking into consideration comorbidities and drug–drug interactions	IIa
PAH associated with portal hypertension – Recommendation Table 17				
R	Echocardiographic assessment for signs of PH is recommended in symptomatic patients with liver disease or portal hypertension and in all candidates for liver transplantation	I	Echocardiography is recommended in patients with liver disease or portal hypertension with signs or symptoms suggestive of PH, and as a screening tool in patients evaluated for liver transplantation or transjugular portosystemic shunt	I
R	It is recommended that the treatment algorithm for patients with other forms of PAH should be applied to patients with PAH associated with portal hypertension, taking into account the severity of liver disease	I	In patients with PAH associated with portal hypertension, initial monotherapy should be considered, followed by sequential combination if necessary, taking into consideration the underlying liver disease and indication for liver transplantation	IIa
R	Liver transplantation may be considered in selected patients responding well to PAH therapy	IIb	Liver transplantation should be considered on an individual basis in patients with PAH associated with portal hypertension, as long as PVR is normal or near normal with PAH therapy	IIa
N			Drugs approved for PAH are not recommended for patients with portal hypertension and unclassified PH (*i.e.* elevated mPAP, high CO, and a normal PVR)	III
Shunt closure in patients with pulmonary-systemic flow ratio >1.5:1 based on calculated pulmonary vascular resistance – Recommendation Table 18				
N			In patients with ASD, VSD, or PDA and a PVR <3 WU, shunt closure is recommended	I
N			In patients with ASD, VSD, or PDA and a PVR of 3–5 WU, shunt closure should be considered	IIa
N			In patients with ASD and a PVR >5 WU that declines to <5 WU with PAH treatment, shunt closure may be considered	IIb
N			In patients with VSD or PDA and a PVR >5 WU, shunt closure may be considered after careful evaluation in specialized centres	IIb
N			In patients with ASD and a PVR >5 WU despite PAH treatment, shunt closure is not recommended	III
Pulmonary arterial hypertension associated with adult congenital heart disease – Recommendation Table 19				
N			Risk assessment is recommended for patients with persistent PAH after defect closure	I
N			Risk assessment should be considered in patients with Eisenmenger syndrome	IIa
R	Bosentan is recommended in WHO-FC III patients with Eisenmenger syndrome	I	Bosentan is recommended in symptomatic patients with Eisenmenger syndrome to improve exercise capacity	I
R	The use of supplemental iron treatment may be considered in patients with low ferritin plasma levels	IIb	Supplemental iron treatment should be considered in patients with iron deficiency	IIa

Continued

BOX 2 Continued

New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
R	Combination drug therapy may be considered in patients with Eisenmenger syndrome	IIb	In patients with PAH after corrected adult CHD, initial oral combination therapy with drugs approved for PAH should be considered for patients at low and intermediate risk, while initial combination therapy including i.v./s.c. prostacyclin analogues should be considered for patients at high risk	IIa
R	Combination drug therapy may be considered in patients with Eisenmenger syndrome	IIb	In patients with adult CHD, including Eisenmenger syndrome, sequential combination therapy should be considered if patients do not meet treatment goals	IIa
N			In women with Eisenmenger syndrome, pregnancy is not recommended	III
R	If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%	IIa	In patients with Eisenmenger syndrome, routine phlebotomy to lower elevated haematocrit is not recommended	III
Pulmonary arterial hypertension with signs of venous/capillary involvement – Recommendation Table 20				
R	A combination of clinical findings, physical examination, bronchoscopy, and radiological findings is recommended to diagnose PVOD/PCH	I	A combination of clinical and radiological findings, ABG, PFTs, and genetic testing is recommended to diagnose PAH with signs of venous and/or capillary involvement (PVOD/PCH)	I
N			In patients with PVOD/PCH, the use of drugs approved for PAH may be considered with careful monitoring of clinical symptoms and gas exchange	IIb
N			Lung biopsy is not recommended to confirm a diagnosis of PVOD/PCH	III
Paediatric pulmonary hypertension – Recommendation Table 21				
N			It is recommended to perform the diagnostic work-up, including RHC and acute vasodilator testing, and treat children with PH at centres with specific expertise in paediatric PH	I
R	A PH diagnostic algorithm work-up is recommended for diagnosis and definition of the specific aetiology group in paediatric PH patients	I	In children with PH, a comprehensive work-up for confirming diagnosis and specific aetiology is recommended (similar to that in adults, but adapted for age)	I
N			For confirming PH diagnosis, RHC is recommended, preferably before initiating any PAH therapy	I
N			In children with IPAH/HPAH, acute vasoreactivity testing is recommended to detect those who may benefit from calcium channel blocker therapy	I
N			It is recommended to define a positive response to acute vasoreactivity testing in children similar to adults by a reduction of mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg, with an increased or unchanged CO	I
R	A PAH-specific therapeutic algorithm is recommended in paediatric PH patients	I	In children with PAH, a therapeutic strategy based on risk stratification and treatment response is recommended, extrapolated from that in adults but adapted for age	I
R	Specific paediatric determinants of risk should be considered	IIa	It is recommended to monitor the treatment response in children with PAH by serially assessing a panel of data derived from clinical assessment, echocardiographic evaluation, biochemical markers, and exercise tolerance tests	I
N			Achieving and maintaining a low-risk profile should be considered as an adequate treatment response for children with PAH	IIa
N			It is recommended to screen infants with bronchopulmonary dysplasia for PH	I

Continued

BOX 2 Continued				
New or revised	**Recommendation in 2015 version**	**Class[a]**	**Recommendation in 2022 version**	**Class[a]**
N			In infants with (or at risk of) bronchopulmonary dysplasia and PH, treating lung disease, including hypoxia, aspiration, and structural airway disease, and optimizing respiratory support is recommended before initiating PAH therapy	I
N			In neonates and infants, a diagnostic and therapeutic approach to PH distinct from that in older children and adults should be considered, given the frequent association with developmental vascular and parenchymal lung disease	IIa
Pulmonary hypertension associated with left heart disease – Recommendation Table 22				
N			RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I
N			RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I
R	Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH centre for a complete diagnostic work-up and an individual treatment decision	IIa	For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended	I
N			In patients with LHD and CpcPH with a severe pre-capillary component (*e.g.* PVR >5 WU), an individualized approach to treatment is recommended	I
N			When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I
N			In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH	IIb
Pulmonary hypertension associated with lung disease and/or hypoxia – Recommendation Table 23				
R	Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease	I	If PH is suspected in patients with lung disease, it is recommended that echocardiography[d] be performed and results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging	I
R	Optimal treatment of the underlying lung disease, including long-term O_2 therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases	I	In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I
R	Referral to an expert centre is recommended in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction	I	In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[e]	I
N			In patients with lung disease and severe PH, an individualized approach to treatment is recommended	I
N			It is recommended to refer eligible patients with lung disease and PH for LTx evaluation	I
R	RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (*e.g.* LTx, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial)	III	In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I

Continued

BOX 2 Continued				
New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
N			Inhaled treprostinil may be considered in patients with PH associated with ILD	IIb
N			The use of ambrisentan is not recommended in patients with PH associated with IPF	III
N			The use of riociguat is not recommended in patients with PH associated with IIP	III
Chronic thrombo-embolic pulmonary hypertension and chronic thrombo-embolic pulmonary disease without pulmonary hypertension – Recommendation Table 24				
R	Lifelong anticoagulation is recommended in all patients with CTEPH	I	Lifelong therapeutic doses of anticoagulation are recommended in all patients with CTEPH	I
N			Antiphospholipid syndrome testing is recommended in patients with CTEPH	I
N			In patients with CTEPH and antiphospholipid syndrome, anticoagulation with VKAs is recommended	I
R	It is recommended that all patients with CTEPH receive assessment of operability and decisions regarding other treatment strategies made by a multidisciplinary team of experts	I	It is recommended that all patients with CTEPH are reviewed by a CTEPH team for the assessment of multimodality management	I
R	Surgical PEA in deep hypothermia circulatory arrest is recommended for patients with CTEPH	I	PEA is recommended as the treatment of choice for patients with CTEPH and fibrotic obstructions within pulmonary arteries accessible by surgery	I
R	Interventional BPA may be considered in patients who are technically inoperable or carry an unfavourable risk:benefit ratio for PEA	IIb	BPA is recommended in patients who are technically inoperable or have residual PH after PEA and distal obstructions amenable to BPA	I
R	Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	I	Riociguat is recommended for symptomatic patients with inoperable CTEPH or persistent/recurrent PH after PEA	I
N			Long-term follow-up is recommended after PEA and BPA, as well as for patients with CTEPH established on medical therapy	I
N			A multi-modality approach should be considered for patients with persistent PH after PEA and for patients with inoperable CTEPH	IIa
N			In patients with CTEPD without PH, long-term anticoagulant therapy should be considered on individual basis[f]	IIa
N			PEA or BPA should be considered in selected symptomatic patients with CTEPD without PH	IIa
N			Treprostinil s.c. may be considered in patients in WHO-FC III–IV who have inoperable CTEPH or persistent/recurrent PH after PEA	IIb
R	Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	IIb	Off-label use of drugs approved for PAH may be considered in symptomatic patients who have inoperable CTEPH	IIb
N			In patients with inoperable CTEPH, a combination of sGC stimulator/PDE5i, ERA, or parenteral prostacyclin analogues may be considered	IIb
N			BPA may be considered for technically operable patients with a high proportion of distal disease and an unfavourable risk:benefit ratio for PEA	IIb
Pulmonary hypertension centres – Recommendation Table 25				
N			It is recommended that PH centres maintain a patient registry	I
N			It is recommended that PH centres collaborate with patient associations	I

Continued

BOX 2 Continued

New or revised	Recommendation in 2015 version	Class[a]	Recommendation in 2022 version	Class[a]
N			Accreditation of the PH centres should be considered (*e.g.* https://ec.europa.eu/health/ern/assessment_en)	IIa
R	It should be considered that a referral centre follow at least 50 patients with PAH or CTEPH and should receive at least two new referrals per month with documented PAH or CTEPH	IIa	PH centres should follow-up a sufficient number of patients to maintain expertise (at least 50 patients with PAH or CTEPH and at least two new referrals per month with documented PAH or CTEPH), and consider establishing collaborations with high-volume centres	IIa

6MWD, 6-minute walking distance; ABG, arterial blood gas analysis; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ASD, atrial septal defect; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CCB, calcium channel blocker; CHD, congenital heart disease; CI, cardiac index; CMR, cardiac magnetic resonance; CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTD, connective tissue disease; CTEPD, chronic thrombo-embolic pulmonary disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; DLCO, lung diffusion capacity for carbon monoxide; DPAH, drug-associated pulmonary arterial hypertension; DPG, diastolic pressure gradient; ERA, endothelin receptor antagonist; FVC, forced vital capacity; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; ICU, intensive care unit; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; i.v., intravenous; LHD, left heart disease; LTx, lung transplantation; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PCH, pulmonary capillary haemangiomatosis; PDA, patent ductus arteriosus; PDE5i, phosphodiesterase 5 inhibitor; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PFTs, pulmonary function tests; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension associated with left heart disease; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RHC, right heart catheterization; RV, right ventricle; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; s.c., subcutaneous; sGC, soluble guanylate cyclase; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; SSc, systemic sclerosis; SVI, stroke volume index; TRV, tricuspid regurgitation velocity; VKA, vitamin K antagonist; VSD, ventricular septal defect; VTE, venous thrombo-embolism; WHO-FC, World Health Organization functional class; WU, Wood units. [a]Class of recommendation. [b]Cardiopulmonary comorbidities are predominantly encountered in elderly patients and include risk factors for HFpEF, such as obesity, diabetes, coronary heart disease, a history of hypertension, and/or a low DLCO. [c]Initial triple-combination therapy including i.v./s.c. prostacyclin analogues may also be considered in patients presenting at intermediate risk but severe haemodynamic impairment (*e.g.* RAP ⩾20 mmHg, CI <2.0 L/min/m^2, SVI <31 mL/m^2, and/or PVR ⩾12 WU). [d]Assessments should ideally be made when the patient is clinically stable, as exacerbations can significantly raise PAP. [e]This recommendation does not apply to patients with end-stage lung disease who are not considered candidates for LTx. [f]Long-term anticoagulant therapy is recommended when the risk of PE recurrence is intermediate or high, or when there is no history of VTE.

BOX 3 New recommendations developed with GRADE Evidence to Decision framework

Recommendations	Quality of evidence	Strength of recommendation	Class[a]	Level[b]
In patients with IPAH/HPAH/DPAH who present at low or intermediate risk of death, initial combination therapy with a PDE5i and an ERA is recommended	Low	Conditional	I	B
The use of PDE5i in patients with HFpEF and isolated post-capillary PH is not recommended	Low	Conditional	III	C
PDE5i may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	IIb	C
The use of PDE5i in patients with ILD and non-severe PH is not recommended	Very low	Conditional	III	C
In patients with CTEPH who are candidates for BPA, medical therapy should be considered prior to the intervention	Very low	Conditional	IIa	B

BPA, balloon pulmonary angioplasty; CTEPH, chronic thrombo-embolic pulmonary hypertension; DPAH, drug-associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; HPAH, heritable pulmonary arterial hypertension; HFpEF, heart failure with preserved ejection fraction; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension. [a]Class of recommendation. [b]Level of evidence.

2.2. Methods

Three main methodological approaches were used in these guidelines, depending on the type of questions addressed:

i) Four questions that were considered highly important were formulated in the PICO format, and assessed with full systematic reviews and application of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach [2] and the Evidence to Decision (EtD) framework [3] (see Supplementary Data, Section 2.1 for full methodology description and supportive material). The resulting recommendations were rated as strong or conditional, based on four potential levels of evidence (high, moderate, low, or very low; Tables 1 and 2). All Task Force members approved the recommendations. In addition, these recommendations were also presented and voted following the usual ESC approach.

ii) Eight questions that were considered of key importance (key narrative questions) were assessed with systematic literature searches and application of the EtD framework [6]. The evidence grading was performed following the usual ESC approach.

iii) The remaining topics of interest were assessed using the process commonly followed in ESC Guidelines. Structured literature searches were undertaken and grading tables, as outlined in Tables 3 and 4, were created to describe level of confidence in the recommendation provided and the quality of evidence supporting the recommendation. The Task Force discussed each draft recommendation during web-based conference calls dedicated to specific sections, followed by consensus modifications and an online vote on each recommendation. Only recommendations that were supported by at least 75% of the Task Force members were included in the guidelines. The recommendation tables were colour-coded for ease of interpretation.

TABLE 1 Strength of the recommendations according to GRADE

Recommendation strength	Rationale
Strong recommendation for	The panel is certain that desirable outweigh the undesirable effects
Conditional recommendation for	The panel is less confident that desirable outweigh the undesirable effects
Conditional recommendation against	The panel is less confident that undesirable outweigh the desirable effects
Strong recommendation against	The panel is certain that undesirable outweigh the desirable effects
No recommendation	The confidence in the results might be very low to make a recommendation, or the trade-offs between desirable and undesirable effects are finely balanced, or no data are available

Adapted from the ERS Handbook for Clinical Practice Guidelines [4].

TABLE 2 Quality of evidence grades and their definitions [5]

Quality	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

TABLE 3 Classes of recommendations

	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment or procedure	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

TABLE 4 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

3. Definitions and classifications

3.1. Definitions

The definitions for PH are based on haemodynamic assessment by right heart catheterization (RHC). Although haemodynamics represent the central element of characterizing PH, the final diagnosis and classification should reflect the whole clinical context and consider the results of all investigations.

Pulmonary hypertension is defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest (Table 5). This is supported by studies assessing the upper limit of normal pulmonary arterial pressure (PAP) in healthy subjects [7–9], and by studies investigating the prognostic relevance of increased PAP (key narrative question 1, Supplementary Data, Section 3.1) [10–12].

It is essential to include PVR and pulmonary arterial wedge pressure (PAWP) in the definition of pre-capillary PH, in order to discriminate elevated PAP due to pulmonary vascular disease (PVD) from that due to left heart disease (LHD), elevated pulmonary blood flow, or increased intrathoracic pressure (Table 5). Based on the available data, the upper limit of normal PVR and the lowest prognostically relevant threshold of PVR is ∼2 Wood units (WU) [7, 8, 13, 14]. Pulmonary vascular resistance depends on body surface area and age, with elderly healthy subjects having higher values. The available data on the

TABLE 5 Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
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

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units. Some patients present with elevated mPAP (>20 mmHg) but low PVR (⩽2 WU) and low PAWP (⩽15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH' (see text for further details).

best threshold for PAWP discriminating pre- and post-capillary PH are contradictory. Although the upper limit of normal PAWP is considered to be 12 mmHg [15], previous ESC/ERS Guidelines for the diagnosis and treatment of PH, as well as the recent consensus recommendation of the ESC Heart Failure Association [16], suggest a higher threshold for the invasive diagnosis of heart failure (HF) with preserved ejection fraction (HFpEF) (PAWP ⩾15 mmHg). In addition, almost all therapeutic studies of PAH have used the PAWP ⩽15 mmHg threshold. Therefore, it is recommended keeping PAWP ⩽15 mmHg as the threshold for pre-capillary PH, while acknowledging that any PAWP threshold is arbitrary and that the patient phenotype, risk factors, and echocardiographic findings, including left atrial (LA) volume, need to be considered when distinguishing pre- from post-capillary PH.

Patients with PAH are haemodynamically characterized by pre-capillary PH in the absence of other causes of pre-capillary PH, such as CTEPH and PH associated with lung diseases. All PH groups may comprise both pre- and post-capillary components contributing to PAP elevation. In particular, older patients may present with several conditions predisposing them to PH. The primary classification should be based on the presumed predominant cause of the pulmonary pressure increase.

Post-capillary PH is haemodynamically defined as mPAP >20 mmHg and PAWP >15 mmHg. Pulmonary vascular resistance is used to differentiate between patients with post-capillary PH who have a significant pre-capillary component (PVR >2 WU—combined post- and pre-capillary PH [CpcPH]) and those who do not (PVR ⩽2 WU—isolated post-capillary PH [IpcPH]).

There are patients with elevated mPAP (>20 mmHg) but low PVR (⩽2 WU) and low PAWP (⩽15 mmHg). These patients are frequently characterized by elevated pulmonary blood flow and, although they have PH, they do not fulfil the criteria of pre- or post-capillary PH. This haemodynamic condition may be described by the term 'unclassified PH'. Patients with unclassified PH may present with congenital heart disease (CHD), liver disease, airway disease, lung disease, or hyperthyroidism explaining their mPAP elevation. Clinical follow-up of these patients is generally recommended. In the case of elevated pulmonary blood flow, its aetiology should be explored.

As the groups of PH according to clinical classification represent different clinical conditions, there may be additional clinically relevant haemodynamic thresholds (*e.g.* for PVR) for the individual PH groups besides the general thresholds of the haemodynamic definition of PH, which are discussed in the corresponding sections.

Exercise PH, defined by an mPAP/cardiac output (CO) slope >3 mmHg/L/min between rest and exercise [17], has been re-introduced. The mPAP/CO slope is strongly age dependent and its upper limit of normal ranges from 1.6–3.3 mmHg/L/min in the supine position [17]. An mPAP/CO slope >3 mmHg/L/min is not physiological in subjects aged <60 years and may rarely be present in healthy subjects aged >60 years [17]. A pathological increase in pulmonary pressure during exercise is associated with impaired prognosis in patients with exercise dyspnoea [18] and in several cardiovascular conditions [19–22]. Although an increased mPAP/CO slope defines an abnormal haemodynamic response to exercise, it does not allow for differentiation between pre- and post-capillary causes. The PAWP/CO slope with a threshold >2 mmHg/L/min may best differentiate between pre- and post-capillary causes of exercise PH [23, 24].

3.2. Classifications

The basic structure of the classification from the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH [25, 26] and the Proceedings of the 6th WSPH [1] has been kept (Table 6). The general purpose of the clinical classification of PH remains to categorize clinical conditions associated with PH, based on similar pathophysiological mechanisms, clinical presentation, haemodynamic characteristics, and therapeutic management (Figure 1). The main changes are as follows:

i) The subgroups 'non-responders at vasoreactivity testing' and 'acute responders at vasoreactivity testing' have been added to IPAH as compared with the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH [25, 26]. In addition to patients with IPAH, some patients with heritable PAH (HPAH) or drug- or toxin-associated PAH (DPAH) might be acute responders.
ii) The groups 'PAH with features of venous/capillary (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis [PVOD/PCH]) involvement' and 'persistent PH of the newborn (PPHN)' have been included in group 1 (PAH) as compared with the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH and in line with the Proceedings of the 6th WSPH [1].
iii) 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

TABLE 6 Clinical classification of pulmonary hypertension

GROUP 1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.1.1 Non-responders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable[a]
1.3 Associated with drugs and toxins[a]
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
GROUP 2 PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction[b]
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease (*e.g.* high altitude)
3.6 Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thrombo-embolic PH
4.2 Other pulmonary artery obstructions[c]
GROUP 5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders[d]
5.2 Systemic disorders[e]
5.3 Metabolic disorders[f]
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

HF, heart failure; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease. [a]Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders. [b]Left ventricular ejection fraction for HF with reduced ejection fraction: ⩽40%; for HF with mildly reduced ejection fraction: 41–49%. [c]Other causes of pulmonary artery obstructions include: sarcomas (high or intermediate grade or angiosarcoma), other malignant tumours (*e.g.* renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), non-malignant tumours (*e.g.* uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis. [d]Including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders. [e]Including sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1. [f]Including glycogen storage diseases and Gaucher disease.

sleep apnoea is generally not a cause of PH, but PH is frequent in patients with hypoventilation syndromes causing daytime hypercapnia.

4. Epidemiology and risk factors

Pulmonary hypertension is a major global health issue. All age groups are affected. Present estimates suggest a PH prevalence of ∼1% of the global population. Due to the presence of cardiac and pulmonary causes of PH, prevalence is higher in individuals aged >65 years [29]. Globally, LHD is the leading cause of PH [29]. Lung disease, especially chronic obstructive pulmonary disease (COPD), is the second most common cause [29]. In the UK, the observed PH prevalence has doubled in the last 10 years and is currently 125 cases/million inhabitants [30]. Irrespective of the underlying condition, developing PH is associated with worsening symptoms and increased mortality [29]. In developing countries, CHD, some

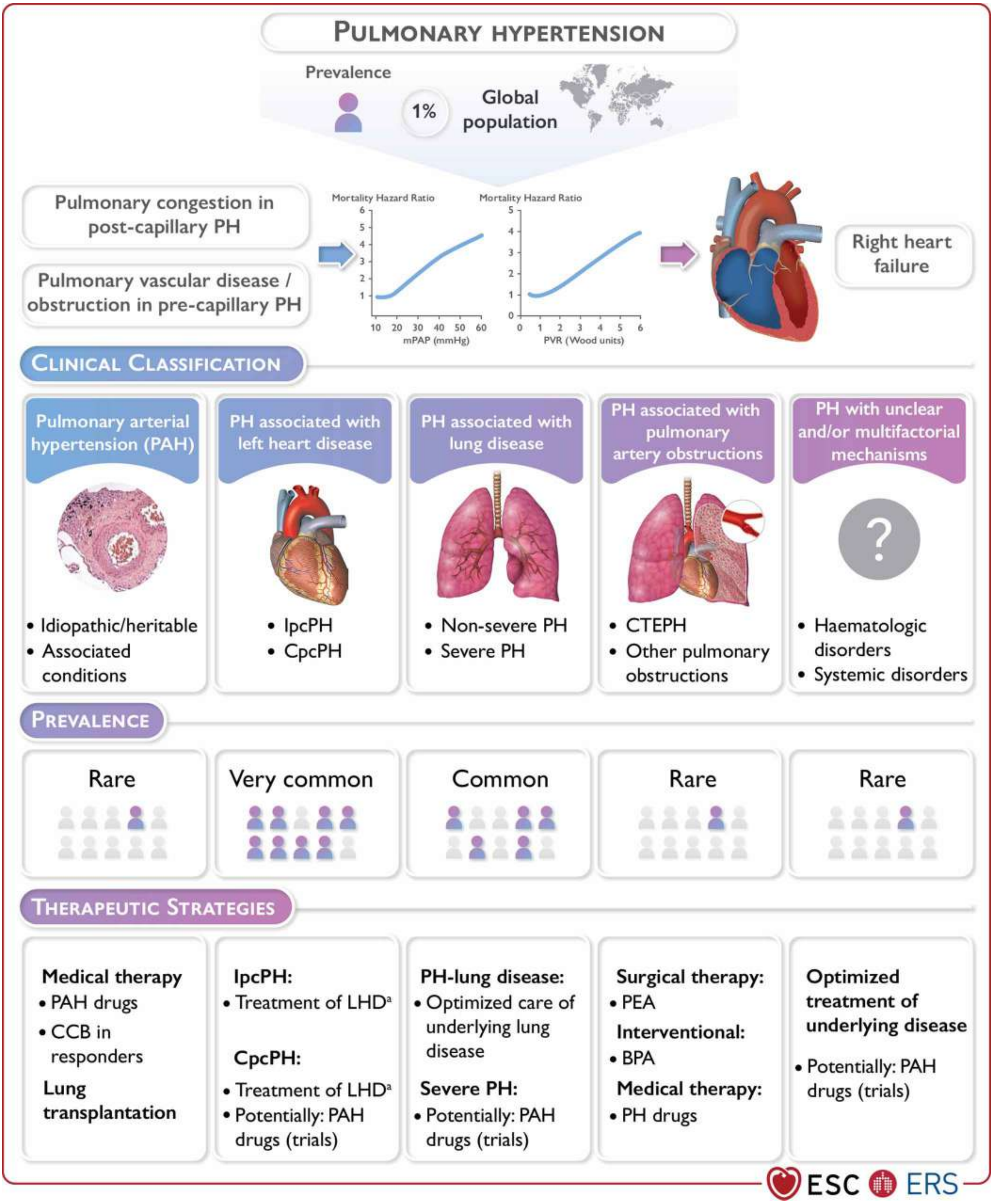

FIGURE 1 Central illustration. BPA, balloon pulmonary angioplasty; CCB, calcium channel blocker; CTEPH, chronic thrombo-embolic pulmonary hypertension; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; LHD, left heart disease; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension. [a]Treatment of heart failure according to the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [27]. Treatment of left-sided valvular heart disease according to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease [28].

TABLE 7 Drugs and toxins associated with pulmonary artery 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

[a]Pulmonary veno-occlusive disease.

infectious diseases (schistosomiasis, human immunodeficiency virus [HIV]), and high altitude represent important but under-studied causes of PH [29].

4.1. Group 1, pulmonary arterial hypertension

Recent registry data from economically developed countries indicate a PAH incidence and prevalence of ∼6 and 48–55 cases/million adults, respectively [31]. It has been thought to predominantly affect younger individuals, mostly females [32, 33]; this is currently true for HPAH, which affects twice as many females as males. However, recent data from the USA and Europe suggest that PAH is now frequently diagnosed in older patients (*i.e.* those aged ⩾65 years, who often present with cardiovascular comorbidities, resulting in a more equal distribution between sexes) [32]. In most PAH registries, IPAH was the most common subtype (50–60% of all cases), followed by PAH associated with connective tissue disease (CTD), CHD, and portal hypertension (porto-pulmonary hypertension [PoPH]) [32].

A number of drugs and toxins are associated with the development of PAH [1, 34–45]. The association between exposure to drugs and toxins and PAH is classified as definite or possible, as proposed at the 6th WSPH (Table 7) [1]. There is a definite association with drugs, with available data based on outbreaks, epidemiological case-control studies, or large multicentre series. A possible association is suggested by multiple case series or cases with drugs with similar mechanisms of action [1].

4.2. Group 2, pulmonary hypertension associated with left heart disease

In 2013, the Global Burden of Disease Study reported 61.7 million cases of HF worldwide, which represented almost a doubling since 1990 [46]. In Europe and the USA, >80% of patients with HF are aged ⩾65 years. Post-capillary PH, either isolated or combined with a pre-capillary component, is a frequent complication mainly in HFpEF, affecting at least 50% of these patients [47, 48]. The prevalence of PH increases with severity of left-sided valvular diseases, and PH can be found in 60–70% of patients with severe and symptomatic mitral valve disease [49] and in up to 50% of those with symptomatic aortic stenosis [50].

4.3. Group 3, pulmonary hypertension associated with lung diseases and/or hypoxia

Mild PH is common in advanced parenchymal and interstitial lung disease. Studies have reported that ∼1–5% of patients with advanced COPD with chronic respiratory failure or candidates for lung volume reduction surgery or lung transplantation (LTx) have an mPAP >35–40 mmHg [51, 52]. In idiopathic pulmonary fibrosis, an mPAP ⩾25 mmHg has been reported in 8–15% of patients upon initial work-up, with greater prevalence in advanced (30–50%) and end-stage (>60%) disease [52]. Hypoxia is a public health problem for the estimated 120 million people living at altitudes >2500 m. Altitude dwellers are at risk of developing PH and chronic mountain sickness. However, it remains unclear to what extent PH and right HF are public health problems in high-altitude communities; this should be addressed with updated methodology and large-scale population studies [53].

4.4. Group 4, pulmonary hypertension associated with chronic pulmonary artery obstruction

The number of patients diagnosed with CTEPH is increasing, probably due to a deeper understanding of the disease and more active screening for this condition in patients who remain dyspnoeic after pulmonary embolism (PE) or who have risk factors for developing CTEPH. Registry data indicate a CTEPH incidence and prevalence of 2–6 and 26–38 cases/million adults, respectively [31, 54, 55]. Patients with chronic thrombo-embolic pulmonary disease (CTEPD) without PH still represent a small proportion of the patients referred to CTEPH centres [56].

4.5. Group 5, pulmonary hypertension with unclear and/or multifactorial mechanisms

Group 5 PH consists of a complex group of disorders that are associated with PH [57]. The cause is often multifactorial and can be secondary to increased pre- and post-capillary pressure, as well as direct effects on pulmonary vasculature. The incidence and prevalence of PH in most of these disorders are unknown. However, high-quality registries have recently enabled estimation of PH prevalence in adult patients with sarcoidosis [58, 59]. Studies suggest that PH can be common and its presence is often associated with increased morbidity and mortality [58, 59].

5. Pulmonary hypertension diagnosis

5.1. Diagnosis

The diagnostic approach to PH is mainly focused on two tasks. The primary goal is to raise early suspicion of PH and ensure fast-track referral to PH centres 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.

5.1.1. Clinical presentation

Symptoms of PH are mainly linked to right ventricle (RV) dysfunction, and typically associated with exercise in the earlier course of the disease [25, 26]. The cardinal symptom is dyspnoea on progressively minor exertion. Other common symptoms are related to the stages and severity of the disease, and are listed in Figure 2 [60–62]. Potential clinical signs and physical findings are summarized in Figure 3 [60, 61]. Importantly, the physical examination may also be the key to identifying the underlying cause of PH (see Figure 3).

5.1.2. Electrocardiogram

Electrocardiogram (ECG) abnormalities (Table 8) may raise suspicion of PH, deliver prognostic information, and detect arrhythmias and signs of LHD. In adults with clinical suspicion of PH (*e.g.* unexplained dyspnoea on exertion), right axis deviation has a high predictive value for PH [63]. A normal ECG does not exclude the presence of PH, but a normal ECG in combination with normal biomarkers (BNP/NT-proBNP) is associated with a low likelihood of PH in patients referred for suspected PH or at risk of PH (*i.e.* after acute PE) [64, 65].

5.1.3. Chest radiography

Chest radiography presents abnormal findings in most patients with PH; however, a normal chest X-ray does not exclude PH [68]. Radiographic signs of PH include a characteristic configuration of the cardiac silhouette due to right heart (right atrium [RA]/RV) and PA enlargement, sometimes with pruning of the peripheral vessels. In addition, signs of the underlying cause of PH, such as LHD or lung disease, may be found (Table 9) [25, 60, 69, 70].

5.1.4. Pulmonary function tests and arterial blood gases

Pulmonary function tests (PFTs) and analysis of arterial blood gas (ABG) or arterialized capillary blood are necessary to distinguish between PH groups, assess comorbidities and the need for supplementary oxygen, and determine disease severity. The initial work-up of patients with suspected PH should comprise forced spirometry, body plethysmography, lung diffusion capacity for carbon monoxide (DLCO), and ABG.

In patients with PAH, PFTs are usually normal or may show mild restrictive, obstructive, or combined abnormalities [71, 72]. More severe PFT abnormalities are occasionally found in patients with PAH associated with CHD [73], and those with group 3 PH. The DLCO may be normal in patients with PAH, although it is usually mildly reduced [71]. A severely reduced DLCO (<45% of the predicted value) in the

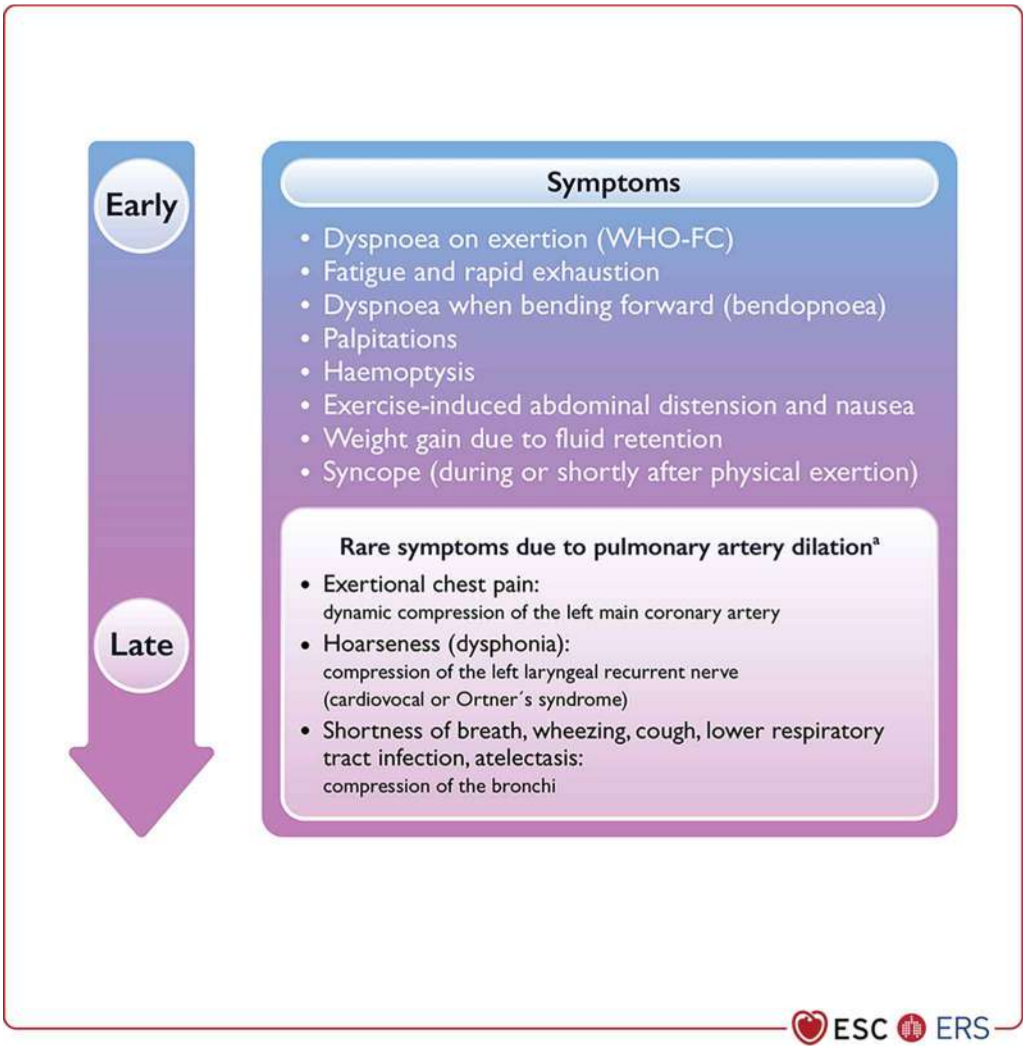

FIGURE 2 Symptoms in patients with pulmonary hypertension. WHO-FC, World Health Organization functional class. [a]Thoracic compression syndromes are found in a minority of patients with PAH with pronounced dilation of the pulmonary artery, and may occur at any disease stage and even in patients with otherwise mild functional impairment.

presence of otherwise normal PFTs can be found in PAH associated with systemic sclerosis (SSc), PVOD, in PH group 3—associated with emphysema, interstitial lung disease (ILD), or combined pulmonary fibrosis and emphysema—and in some PAH phenotypes [74]. A low DLCO is associated with a poor prognosis in several forms of PH [75–78].

Patients with PAH usually have normal or slightly reduced partial pressure of arterial oxygen (PaO_2). Severe reduction of PaO_2 might raise suspicion for patent foramen ovale, hepatic disease, other abnormalities with right-to-left shunt (*e.g.* septal defect), or low-DLCO-associated conditions.

Partial pressure of arterial carbon dioxide ($PaCO_2$) is typically lower than normal due to alveolar hyperventilation [79]. Low $PaCO_2$ at diagnosis and follow-up is common in PAH and associated with unfavourable outcomes [80]. Elevated $PaCO_2$ is very unusual in PAH and reflects alveolar hypoventilation, which in itself may be a cause of PH. Overnight oximetry or polysomnography should be performed if there is suspicion of sleep-disordered breathing or hypoventilation [81].

5.1.5. Echocardiography

Independent of the underlying aetiology, PH leads to RV pressure overload and dysfunction, which can be detected by echocardiography [82–84]. When performed accurately, echocardiography provides

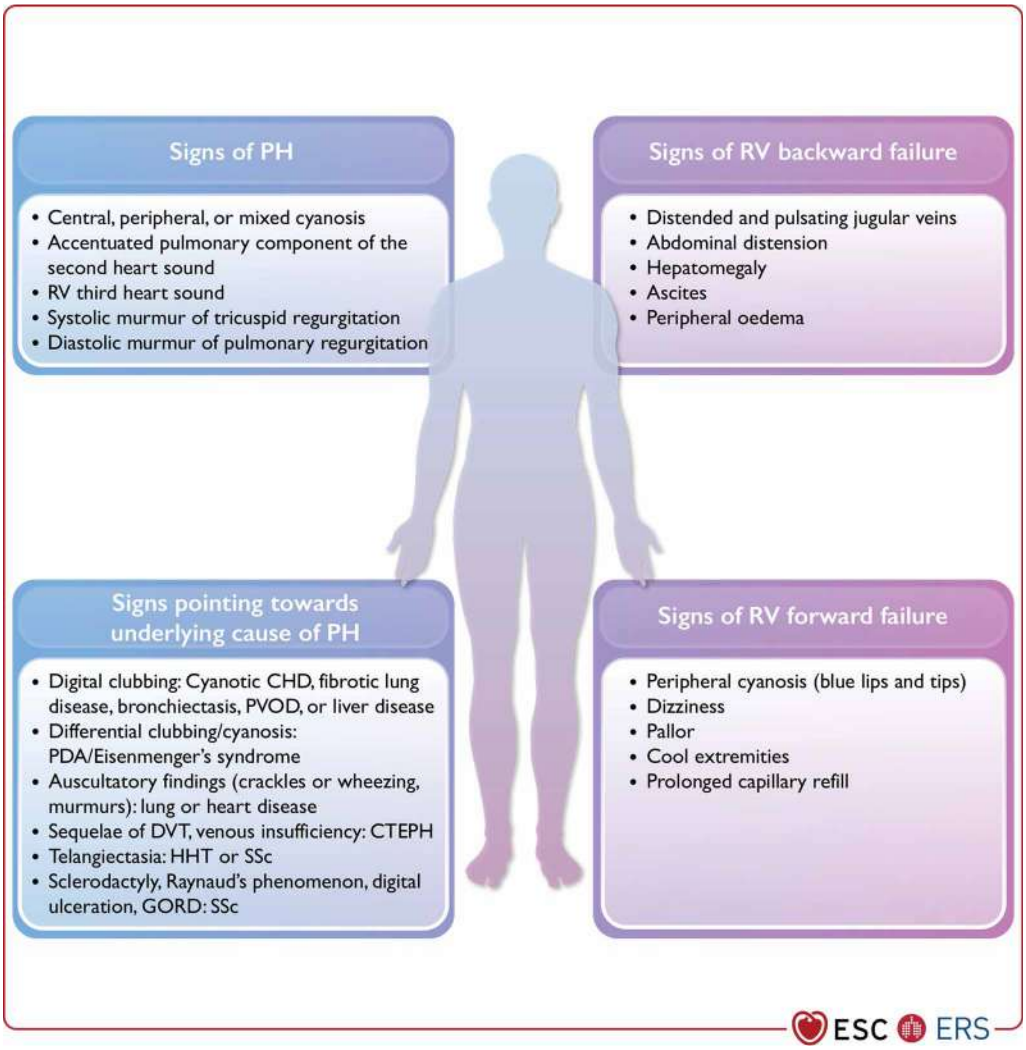

FIGURE 3 Clinical signs in patients with pulmonary hypertension. CHD, congenital heart disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; DVT, deep venous thrombosis; GORD, gastro-oesophageal reflux disease; HHT, hereditary haemorrhagic telangiectasia; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RV, right ventricle; SSc, systemic sclerosis.

TABLE 8 Electrocardiogram abnormalities in patients with pulmonary hypertension

Typical ECG abnormalities in PH [66]
• P pulmonale (P>0.25 mV in lead II)
• Right or sagittal axis deviation (QRS axis >90° or indeterminable)
• RV hypertrophy (R/S >1, with R >0.5 mV in V1; R in V1 + S in lead V5 >1 mV)
• Right bundle branch block—complete or incomplete (qR or rSR patterns in V1)
• RV strain pattern[a] (ST depression/T-wave inversion in the right precordial V1–4 and inferior II, III, aVF leads)
• Prolonged QTc interval (unspecific)[b]

ECG, electrocardiogram; PH, pulmonary hypertension; QTc, corrected QT interval; RV, right ventricular. [a]Present in advanced PH. [b]Patients with pulmonary arterial hypertension can present with a prolonged QTc interval (although non-specific), which may reflect RV dysfunction and delayed myocardial repolarization, and is an independent predictor of mortality [67].

TABLE 9 Radiographic signs of pulmonary hypertension and concomitant abnormalities

Signs of PH and concomitant abnormalities	Signs of left heart disease/ pulmonary congestion	Signs of lung disease
Right heart enlargement	Central air space opacification	Flattening of diaphragm (COPD/ emphysema)
PA enlargement (including aneurysmal dilatation)	Interlobular septal thickening 'Kerley B' lines	Hyperlucency (COPD/ emphysema)
Pruning of the peripheral vessels	Pleural effusions	Lung volume loss (fibrotic lung disease)
'Water-bottle' shape of cardiac silhouette[a]	Left atrial enlargement (including splayed carina)	Reticular opacification (fibrotic lung disease)
	Left ventricular dilation	

COPD, chronic obstructive pulmonary disease; PA, pulmonary artery; PH, pulmonary hypertension. [a]May be present in patients with PH with advanced right ventricular failure and moderate pericardial effusion.

comprehensive information on right and left heart morphology, RV and LV function, and valvular abnormalities, and gives estimates of haemodynamic parameters. Echocardiography is also a valuable tool with which to detect the cause of suspected or confirmed PH, particularly with respect to PH associated with LHD or CHD. Yet, echocardiography alone is insufficient to confirm a diagnosis of PH, which requires RHC.

Given the heterogeneous nature of PH and the peculiar geometry of the RV, there is no single echocardiographic parameter that reliably informs about PH status and underlying aetiology. Therefore, a comprehensive echocardiographic evaluation for suspected PH includes estimating the systolic pulmonary arterial pressure (sPAP) and detecting additional signs suggestive of PH, aiming at assigning an echocardiographic level of probability of PH. Echocardiographic findings of PH, including estimating pressure and signs of RV overload and/or dysfunction, are summarized in Figure 4.

Estimates of sPAP are based on the peak tricuspid regurgitation velocity (TRV) and the TRV-derived tricuspid regurgitation pressure gradient (TRPG)—after excluding pulmonary stenosis—taking into account non-invasive estimates of RA pressure (RAP). Considering the inaccuracies in estimating RAP and the amplification of measurement errors by using derived variables [85–87], 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; however, the presence or absence of PH cannot be reliably determined by TRV alone [88]. Lowering the TRV threshold in view of the revised haemodynamic definition of PH is not supported by available data (key narrative question 2, Supplementary Data, Section 5.1) [89–92]. Tricuspid regurgitation (TR) velocity may underestimate (*e.g.* in patients with severe TR) [28] or overestimate (*e.g.* in patients with high CO in liver disease or sickle cell disease [SCD] [93, 94], misinterpretation of tricuspid valve closure artefact for the TR jet, or incorrect assignment of a peak TRV in the case of maximum velocity boundary artefacts) pressure gradients. Hence, additional variables related to RV morphology and function are used to define the echocardiographic probability of PH (Table 10) [82–84, 95], which may then be determined as low, intermediate, or high. When interpreted in a clinical context, this probability can be used to decide the need for further investigation, including cardiac catheterization in individual patients (Figure 5).

Echocardiographic measures of RV function include the tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RV-FAC), RV free-wall strain, and tricuspid annulus velocity (S′ wave) derived from tissue Doppler imaging, and potentially RV ejection fraction (RVEF) derived from 3D echocardiography. Furthermore, the TAPSE/sPAP ratio—representing a non-invasive measure of RV–PA coupling [96]—may aid in diagnosing PH [90, 97, 98]. The pattern of RV outflow tract (RVOT) blood flow (mid-systolic 'notching') may suggest pre-capillary PH [99, 100].

To separate between group 2 PH and other forms of PH, and to assess the likelihood of left ventricle (LV) diastolic dysfunction, LA size and signs of LV hypertrophy should always be measured, and Doppler echocardiographic signs (*e.g.* E/A ratio, E/E′) should be assessed even if the reliability of the latter is considered low [16]. To identify CHD, 2D Doppler and contrast examinations are helpful, but

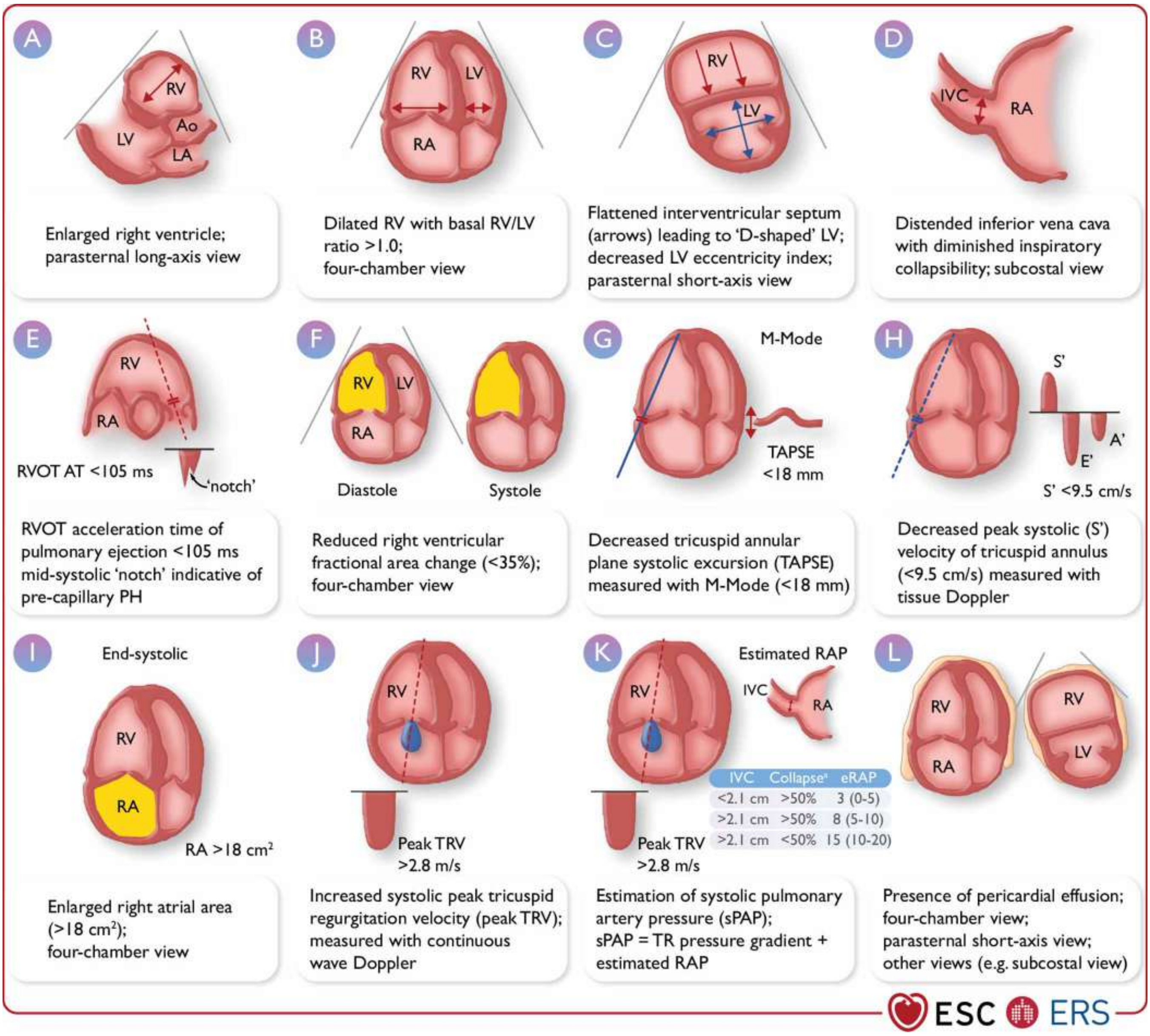

FIGURE 4 Transthoracic echocardiographic parameters in the assessment of pulmonary hypertension. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PH, pulmonary hypertension; RA, right atrium; RAP, right atrial pressure; RV, right ventricle; RVOT AT, right ventricular outflow tract acceleration time; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TRV, tricuspid regurgitation velocity. [a]Refers to collapse on inspiration.

transoesophageal contrast echocardiography or other imaging techniques (*e.g.* computer tomography [CT] angiography, cMRI) are needed in some cases to detect or exclude sinus venosus atrial septal defects, patent ductus arteriosus, and/or anomalous pulmonary venous return [101]. The clinical value of exercise Doppler echocardiography in identifying exercise PH remains uncertain because of the lack of validated criteria and prospective confirmatory data. In most cases, increases in sPAP during exercise are caused by diastolic LV dysfunction [16].

5.1.6. Ventilation/perfusion lung scan

A ventilation/perfusion (V/Q) lung scan (planar or single-photon emission computed tomography [SPECT]) is recommended in the diagnostic work-up of patients with suspected or newly diagnosed PH, to rule out or detect signs of CTEPH [102, 103]. The V/Q SPECT is superior to planar imaging and is the

TABLE 10 Additional echocardiographic signs suggestive of pulmonary hypertension[a]

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and RA
RV/LV basal diameter/area ratio >1.0	RVOT AT <105 ms and/or mid-systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LVEI >1.1 in systole and/ or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm^2
TAPSE/sPAP ratio <0.55 mm/mmHg	PA diameter >AR diameter PA diameter >25 mm	

AR, aortic root; IVC, inferior vena cava; LV, left ventricle; LVEI, left ventricle eccentricity index; PA, pulmonary artery; RA, right atrium; RV, right ventricle; RVOT AT, right ventricular outflow tract acceleration time; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity. [a]Signs contributing to assessing the probability of PH in addition to TRV (see Figure 5). Signs from at least two categories (A/B/C) must be present to alter the level of echocardiographic probability of PH.

methodology of choice; however, SPECT has been widely evaluated in assessing PE, but not to the same degree in CTEPH [68]. In the absence of parenchymal lung disease, a normal perfusion scan excludes CTEPH with a negative predicted value of 98% [104, 105]. In most patients with PAH, V/Q scintigraphy

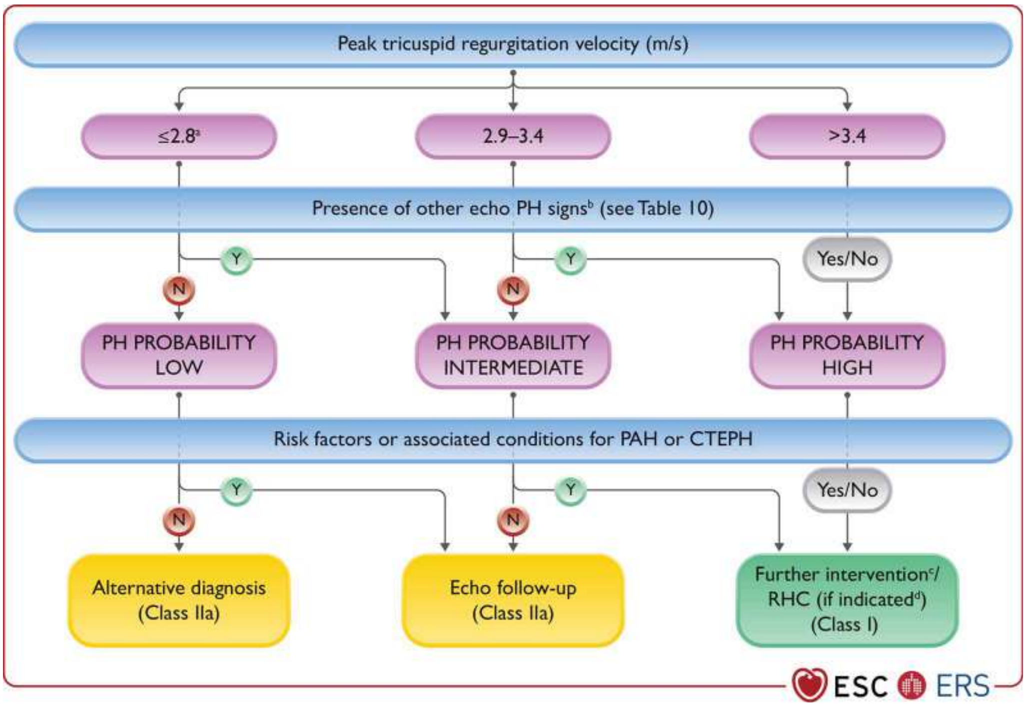

FIGURE 5 Echocardiographic probability of pulmonary hypertension and recommendations for further assessment. CPET, cardiopulmonary exercise testing; CTEPH, chronic thrombo-embolic pulmonary hypertension; echo, echocardiography; LHD, left heart disease; N, no; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; TRV, tricuspid regurgitation velocity; Y, yes. [a]Or unmeasurable. The TRV threshold of 2.8 m/s was not changed according to the updated haemodynamic definition of PH. [b]Signs from at least two categories in Table 10 (A/B/C) must be present to alter the level of echocardiographic probability of PH. [c]Further testing may be necessary (*e.g.* imaging, CPET). [d]RHC should be performed if useful information/a therapeutic consequence is anticipated (*e.g.* suspected PAH or CTEPH), and may not be indicated in patients without risk factors or associated conditions for PAH or CTEPH (*e.g.* when mild PH and predominant LHD or lung disease are present).

is normal or shows a speckled pattern but no typical perfusion defects characteristic of PE or CTEPH, whereas matched V/Q defects may be found in patients with lung disease (*i.e.* group 3 PH). Non-matched perfusion defects similar to those seen in CTEPH may be present in 7–10% of patients with PVOD/PCH or PAH [106, 107]. Deposition of the perfusion agent in extrapulmonary organs may hint to cardiac or pulmonary right-to-left shunting and has been reported in CHD, hepato-pulmonary syndrome, and pulmonary arteriovenous malformations (PAVMs) [68].

5.1.7. Non-contrast and contrast-enhanced chest computed tomography examinations, and digital subtraction angiography

Computed tomography (CT) imaging may provide important information for patients with unexplained dyspnoea or suspected/confirmed PH. The CT signs suggesting the presence of PH include an enlarged PA diameter, a PA-to-aorta ratio >0.9, and enlarged right heart chambers [68]. A combination of three parameters (PA diameter ⩾30 mm, RVOT wall thickness ⩾6 mm, and septal deviation ⩾140° [or RV:LV ratio ⩾1]) is highly predictive of PH [108]. Non-contrast chest CT can help determine the cause of PH when there are features of parenchymal lung disease, and may also point towards the presence of PVOD/PCH by showing centrilobular ground-glass opacities (which may also be found in PAH), septal lines, and lymphadenopathy [68].

Computed tomography pulmonary angiography (CTPA) is mainly used to detect direct or indirect signs of CTEPH, such as filling defects (including thrombus adhering to the vascular wall), webs or bands in the PAs, PA retraction/dilatation, mosaic perfusion, and enlarged bronchial arteries. Importantly, the diagnostic accuracy of CTPA for CTEPH is limited (at the patient level, sensitivity and specificity are 76% and 96%, respectively) [109], but was reported to be higher when modern, high-quality multi-detector CT scanners were used and when interpreted by experienced readers [109, 110]. Computed tomography pulmonary angiography may also be used to detect other cardiovascular abnormalities, including intracardiac shunts, abnormal pulmonary venous return, patent ductus arteriosus, and PAVMs.

In patients presenting with a clinical picture of acute PE, chest CT may be helpful in detecting signs of hitherto undetected CTEPH, which may include the presence of the above CTEPH signs, and RV hypertrophy as a sign for chronicity [111, 112]. Detecting 'acute on chronic' PE is important, as it may impact the management of patients with presumed acute PE.

Dual-energy CT (DECT) angiography and iodine subtraction mapping may provide additional diagnostic information by creating iodine maps [113], which reflect lung perfusion, thereby possibly increasing the diagnostic accuracy for CTEPH [114]. Although increasingly used, the diagnostic value of DECT in the work-up of patients with PH has not been established.

Digital subtraction angiography (DSA) is mainly used to confirm the diagnosis of CTEPH and to assess treatment options (*i.e.* operability or accessibility for BPA). Most centres use conventional two- or three-planar DSA. However, C-arm CT imaging may provide a higher spatial resolution, potentially identifying more target vessels for BPA and providing procedural guidance [115, 116].

5.1.8. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging accurately and reproducibly assesses atrial and ventricular size, morphology, and function. Additional information on RV/LV myocardial strain can be obtained by applying tagging or by post-processing feature tracking. In addition, cMRI can be used to measure blood flow in the PA, aorta, and vena cava, allowing for quantifying stroke volume (SV), intracardiac shunt, and retrograde flow. By combining contrast magnetic resonance (MR) angiography and pulmonary perfusion imaging with late gadolinium-enhancement imaging of the myocardium, a complete picture of the heart and pulmonary vasculature can be obtained (see Supplementary Data, Table S2 for cMRI indices and normal values). A limitation is that there is no established method with which to estimate PAP. Even though the cost and availability of the technique precludes its use in the early diagnosis of PAH, it is sensitive in detecting early signs of PH and diagnosing CHD [117].

5.1.9. Blood tests and immunology

The initial diagnostic assessment of patients with newly diagnosed PH/PAH aims to identify comorbidities and possible causes or complications of PH. Laboratory tests that should be obtained at the time of PH diagnosis include: blood counts (including haemoglobin [Hb]); serum electrolytes (sodium, potassium); kidney function (creatinine, calculation of estimated glomerular filtration rate, and urea); uric acid; liver parameters (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, γ-glutamyl transpeptidase, bilirubin); iron status (serum iron, transferrin saturation, and ferritin); and BNP or

NT-proBNP. In addition, serological studies should include testing for hepatitis viruses and HIV. Basic immunology laboratory work-up is recommended, including screening tests for anti-nuclear antibodies, anti-centromere antibodies, and anti-Ro. Screening for biological markers of antiphospholipid syndrome is recommended in patients with CTEPH. Additional thrombophilia screening is not generally recommended, unless therapeutic consequences are to be expected [118]. Pulmonary arterial hypertension and other forms of severe PH can be associated with thyroid function disorders; hence, laboratory screening should include at least thyroid-stimulating hormone.

5.1.10. Abdominal ultrasound

An abdominal ultrasound examination should be part of the comprehensive diagnostic work-up of patients with newly diagnosed PH, particularly if liver disease is suspected. A major objective is to search for liver disease and/or portal hypertension, or portocaval shunt (Abernethy malformation). During the course of the disease, patients with PH may develop secondary organ dysfunction mainly affecting the liver and kidneys [119]. In these patients, abdominal ultrasound is needed for differential diagnostic reasons and to assess the extent of organ damage.

5.1.11. Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is a useful tool to assess the underlying pathophysiologic mechanisms leading to exercise intolerance. Patients with PAH show a typical pattern, with a low end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$), high ventilatory equivalent for carbon dioxide (VE/VCO_2), low oxygen pulse (VO_2/HR), and low peak oxygen uptake (VO_2) [120]. These findings should prompt consideration of PVD. In patients with LHD or COPD, such a pattern may indicate an additional pulmonary vascular limitation [121, 122]. In populations at risk of PAH, such as those with SSc, a normal peak VO_2 seems to exclude the diagnosis of PAH [123].

5.1.12. Right heart catheterization, vasoreactivity, exercise, and fluid challenge

5.1.12.1. Right heart catheterization

Right heart catheterization is the gold standard for diagnosing and classifying PH. Performing RHC requires expertise and meticulous methodology following standardized protocols. In addition to diagnosing and classifying PH, clinical indications include haemodynamic assessment of heart or LTx candidates [124] and evaluating congenital cardiac shunts. Interpreting invasive haemodynamics should be done in the context of the clinical picture and other diagnostic investigations. When performed in PH centres, the frequencies of serious adverse events (1.1%) and procedure-related mortality (0.055%) are low [125]. A known thrombus or tumour in the RV or RA, recently implanted (<1 month) pacemaker, mechanical right heart valve, TriClip, and an acute infection are contraindications to RHC; the risk:benefit ratio should be individually assessed before each examination and discussed with the patient. The most feared complication of RHC is perforation of a PA.

The adequate preparation of patients for RHC is of major relevance. Pre-existing medical conditions should be optimally controlled at the time of the examination (particularly blood pressure and volume control). In the supine position, the mid-thoracic level is recommended as the zero reference level, which is at the level of the LA in most patients [126].

For a complete assessment of cardiopulmonary haemodynamics, all measures listed in Table 11 must be measured or calculated. Incomplete assessments must be avoided, as this may lead to misdiagnosis. As a minimum, mixed venous oxygen saturation (SvO_2) and arterial oxygen saturation (SaO_2) should be determined. A stepwise assessment of oxygen saturation should be performed in patients with SvO_2 >75% and whenever a left-to-right shunt is suspected. Cardiac output (CO) should be assessed by the direct Fick method or thermodilution (mean values of at least three measurements). The indirect Fick method is considered to be less reliable than thermodilution [127]; however, thermodilution should not be used in the presence of shunts. Pulmonary vascular resistance ([mPAP−PAWP]/CO) should be calculated for each patient. All pressure measurements, including PAWP, should be performed at end expiration (without breath-holding manoeuvre). In patients with large intrathoracic pressure changes during the respiratory cycle (*i.e.* COPD, obesity, during exercise), it is appropriate to average over at least three to four respiratory cycles. If no reliable PAWP curve can be obtained, or if the PAWP values are implausible, additional measurement of LV end-diastolic pressure should be considered to avoid misclassification. Saturations taken with the catheter in the wedged position can confirm an accurate PAWP [128].

5.1.12.2. Vasoreactivity testing

The purpose of vasoreactivity testing in PAH is to identify acute vasoresponders who may be candidates for treatment with high-dose calcium channel blockers (CCBs). Pulmonary vasoreactivity testing is only

TABLE 11 Haemodynamic measures obtained during right heart catheterization

	Normal value
Measured variables	
Right atrial pressure, mean (RAP)	2–6 mmHg
Pulmonary artery pressure, systolic (sPAP)	15–30 mmHg
Pulmonary artery pressure, diastolic (dPAP)	4–12 mmHg
Pulmonary artery pressure, mean (mPAP)	8–20 mmHg
Pulmonary arterial wedge pressure, mean (PAWP)	⩽15 mmHg
Cardiac output (CO)	4–8 L/min
Mixed venous oxygen saturation (SvO_2)[a]	65–80%
Arterial oxygen saturation (SaO_2)	95–100%
Systemic blood pressure	120/80 mmHg
Calculated parameters	
Pulmonary vascular resistance (PVR)[b]	0.3–2.0 WU
Pulmonary vascular resistance index (PVRI)	3–3.5 WU m^2
Total pulmonary resistance (TPR)[c]	<3 WU
Cardiac index (CI)	2.5–4.0 L/min/m^2
Stroke volume (SV)	60–100 mL
Stroke volume index (SVI)	33–47 mL/m^2
Pulmonary arterial compliance (PAC)[d]	>2.3 mL/mmHg

WU, Wood units. [a]Derived from blood sample taken from the pulmonary artery; compartmental oximetry to exclude an intracardiac shunt is recommended when SvO2 0.75%. [b]PVR, (mPAP−PAWP)/CO. [c]TPR, mPAP/CO. [d]PAC, SV/(sPAP−dPAP).

recommended in patients with IPAH, HPAH, or DPAH. Inhaled nitric oxide [129] or inhaled iloprost [130, 131] are the recommended test compounds for vasoreactivity testing (Table 12). There is similar evidence for intravenous (i.v.) epoprostenol, but due to incremental dose increases and repetitive measurements, testing takes much longer and is therefore less feasible [129]. Adenosine i.v. is no longer recommended due to frequent side effects [132]. A positive acute response is defined as a reduction in mPAP by ⩾10 mmHg to reach an absolute value ⩽40 mmHg, with increased or unchanged CO [129]. In patients with PH-LHD, vasoreactivity testing is restricted to evaluating heart transplantation candidacy (see Section 8.1), and in patients with PH in the context of CHD with initial systemic-to-pulmonary shunting, vasoreactivity testing can be performed to evaluate the possibility of defect closure (see Section 7.5) [101].

5.1.12.3. Exercise right heart catheterization

Right heart catheterization is the gold standard method to assess cardiopulmonary haemodynamics during exercise and to define exercise PH [133]. The main reason to perform exercise RHC is to investigate patients with unexplained dyspnoea and normal resting haemodynamics in order to detect early PVD or left heart dysfunction. In addition, exercise haemodynamics may reveal important prognostic and functional information in patients at risk of PAH and CTEPH [22, 134, 135]. To maximize the amount of information, exercise RHC may be combined with CPET. According to the available data and experience,

TABLE 12 Route of administration, half-life, dosages, and duration of administration of the recommended test compounds for vasoreactivity testing in pulmonary arterial hypertension

Compound	Route	Half-life	Dosage	Duration
Nitric oxide [129]	inh	15–30 s	10–20 p.p.m.	5–10 min[a]
Iloprost [130, 131]	inh	30 min	5–10 μg[b]	10–15 min[c]
Epoprostenol [129]	i.v.	3 min	2–12 ng/kg/min	10 min[d]

Inh, inhaled; i.v., intravenous. [a]Measurement as a single step within the dose range. [b]At mouth piece. [c]Measurement as a single step, temporize full effect. [d]Incremental increase in 2 ng/kg/min intervals, duration of 10 min at each step.

exercise RHC is not associated with an additional risk of complications compared with resting RHC and CPET [133].

Incremental exercise tests (step or ramp protocol) with repeated haemodynamic measurements provide the most clinical information on pulmonary circulation. The minimally required haemodynamic variables measured at each exercise level include mPAP, sPAP, diastolic PAP (dPAP), PAWP, CO, heart rate, and systemic blood pressure. In addition, RAP, SvO_2, and SaO_2 should at least be measured at rest and peak exercise. Total pulmonary resistance (TPR), PVR, and cardiac index (CI) should be calculated at each exercise level, as well as arteriovenous difference in oxygen at peak exercise. The mPAP/CO and PAWP/CO slopes should also be calculated [136, 137]. In patients with early PVD, PVR may be normal or mildly elevated at rest, but may change during exercise with a steep increase in mPAP, reflected by an mPAP/CO slope >3 mmHg/L/min, while the PAWP/CO slope usually remains <2 mmHg/L/min. Patients with left heart dysfunction, such as those with HFpEF [23] and/or dynamic mitral regurgitation [138], and a normal PAWP at rest, usually show a steep increase in mPAP and PAWP (and mPAP/CO, PAWP/CO slope) during exercise.

According to recent studies, a PAWP/CO slope >2 mmHg/L/min may be helpful in recognizing an abnormal PAWP increase and, therefore, a cardiac exercise limitation, especially in patients with PAWP 12–15 mmHg at rest [23, 24, 139]. A PAWP cut-off of >25 mmHg during supine exercise has been recommended for diagnosing HFpEF [16]. In patients with lung disease, increased intrathoracic pressure may contribute to mPAP elevation; this is exaggerated during exercise and can be recognized by a concomitant increase in RAP [140]. Some exercise haemodynamics are age dependent, with healthy elderly subjects presenting with steeper mPAP/CO and PAWP/CO slopes than healthy young individuals [9, 141].

5.1.12.4. Fluid challenge

Fluid challenge may reveal LV diastolic dysfunction in patients with PAWP ⩽15 mmHg, but a clinical phenotype suggestive of LHD. Most available data are derived from studies aiming to uncover HFpEF (increase in PAWP) rather than identify group 2 PH (increase in PAP; see Section 8.1). It is generally accepted that rapid infusion (over 5–10 min) of ∼500 mL (7–10 mL/kg) of saline would be sufficient to detect an abnormal increase in PAWP to ⩾18 mmHg (suggestive of HFpEF) [142], although validation and long-term evaluation of these data are needed [143]. There are insufficient data on the haemodynamic response to fluid challenge in patients with PAH. Recent data suggest that passive leg raise during RHC may also help to uncover occult HFpEF [144].

RECOMMENDATION TABLE 1 Recommendations for right heart catheterization and vasoreactivity testing

Recommendations	Class[a]	Level[b]
Right heart catheterisation (RHC)		
RHC is recommended to confirm the diagnosis of PH (especially PAH or CTEPH), and to support treatment decisions [25, 26]	I	B
In patients with suspected or known PH, it is recommended to perform RHC in experienced centres [125]	I	C
It is recommended that RHC comprises a complete set of haemodynamics and is performed following standardized protocols [25, 26, 145]	I	C
Vasoreactivity testing		
Vasoreactivity testing is recommended in patients with I/H/DPAH to detect patients who can be treated with high doses of a CCB [129, 146]	I	B
It is recommended that vasoreactivity testing is performed at PH centres	I	C
It is recommended to consider a positive response to vasoreactivity testing by a reduction in mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg with an increased or unchanged CO[c] [129]	I	C
Inhaled nitric oxide, inhaled iloprost, or i.v. epoprostenol are recommended for performing vasoreactivity testing [129–132]	I	C
Vasoreactivity testing, for identifying candidates for CCB therapy, is not recommended in patients with PAH other than I/H/DPAH, and in PH groups 2, 3, 4, and 5 [124, 129]	III	C

CCB, calcium channel blocker; CO, cardiac output; CTEPH, chronic thrombo-embolic pulmonary hypertension; I/H/DPAH, idiopathic, heritable, drug-associated pulmonary arterial hypertension; i.v., intravenous; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterisation. [a]Class of recommendation. [b]Level of evidence. [c]Testing should also be performed in patients with a baseline mPAP ⩽40 mmHg, in whom the same responder criteria apply.

5.1.13. Genetic counselling and testing

Mutations in PAH genes have been identified in familial PAH, IPAH, PVOD/PCH, and anorexigen-associated PAH (Table 13) [148]. The screening recommendations herein specifically relate to patients with an a priori diagnosis of PAH and not 'at-risk' populations being screened for PAH (see Section 5.3). All patients with these conditions should be informed about the possibility of a genetic condition and that family members could carry a mutation that increases the risk of PAH, allowing for screening and early diagnosis [33, 148]. Even if genetic testing is not performed, family members should be made aware of early signs and symptoms, to ensure that a timely and appropriate diagnosis is made [148].

Genetic counselling by appropriately trained PAH providers or geneticists should be performed prior to genetic testing, to address the complex questions related to penetrance, genetically at-risk family members, reproduction, genetic discrimination, and psychosocial issues. Careful genetic counselling with genetic counsellors or medical geneticists is critical prior to genetic testing for asymptomatic family members [148].

If the familial mutation is known and an unaffected family member tests negative for that mutation, the risk of PAH for that person is the same as for the general population [148].

Many of the less common mutations outlined have a potential additional set of syndromic features. These are summarized in Table 13 where specific clinical history, examination, and investigations are suggested. In particular, clinicians should undertake a thorough history and examination, as syndromic PAH diagnoses may be missed if not interrogated. For example, in one of the largest studies to date, *TBX4*, *ALK1*, and *ENG* mutations were represented in the top six most common genetic findings in adults with previously diagnosed IPAH [149]. These findings have been confirmed and extended in international genetics consortia in 4241 patients with PAH [150]. It is therefore apparent that there is either phenotypic heterogeneity of these syndromes or missed diagnostic features. As more genes associated with PAH are discovered, it will become increasingly difficult to individually test for each. Next-generation sequencing has enabled the development of gene panels to simultaneously interrogate several genes [151]. It is, however, important to check the genes included in the panel at the time of testing, since the composition changes as genetic discoveries advance.

5.2. Diagnostic algorithm

A multistep, pragmatic approach to diagnosis should be considered in patients with unexplained dyspnoea or symptoms/signs raising suspicion of PH. This strategy is depicted in detail in Figure 6 and Table 14. The diagnostic algorithm does not address screening for specific groups at risk of PH.

5.2.1 Step 1 (suspicion)

Patients with PH are likely to be seen by first-line physicians, mainly general practitioners, for non-specific symptoms. Initial evaluation should include a comprehensive medical (including familial) history, thorough physical examination (including measurement of blood pressure, heart rate, and pulse oximetry), blood test to determine BNP/NT-proBNP, and resting ECG. This first step may raise a suspicion of a cardiac or respiratory disorder causing the symptoms.

5.2.2. Step 2 (detection)

The second step includes classical, non-invasive lung and cardiac testing. Among those tests, echocardiography is an important step in the diagnostic algorithm (Figure 6), as it assigns a level of probability of PH, irrespective of the cause. In addition, it is an important step in identifying other cardiac disorders. Based on this initial assessment, if causes other than PH are identified and/or in case of low probability of PH, patients should be managed accordingly.

5.2.3. Step 3 (confirmation)

Patients should be referred to a PH centre for further evaluation in the following situations: (1) when an intermediate/high probability of PH is established; (2) in the presence of risk factors for PAH, or a history of PE. A comprehensive work-up should be performed, with the goal of establishing the differential diagnoses and distinguishing between the various causes of PH according to the current clinical classification. The PH centre is responsible for performing an invasive assessment according to the clinical scenario.

At any time, warning signs must be recognized, as they are associated with worse outcomes and warrant immediate intervention. Such warning signs include: rapidly evolving or severe symptoms (WHO-FC III/

TABLE 13 Phenotypic features associated with pulmonary arterial hypertension mutations

Gene	Pulmonary hypertension phenotypic association	Putative molecular mechanism	Inheritance pattern	Potential distinguishing clinical and examination features	Investigations	Populations	Reference
BMPR2	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Paediatric and adult	[152]
ATP13A3		Unknown	Autosomal dominant			Adult	[149]
AQP1		Unknown	Autosomal dominant			Adult	[149]
ABCC8		Haploinsufficiency	Autosomal dominant			Adult	[153]
KCNK3		Haploinsufficiency	Autosomal dominant			Adult	[154]
SMAD9		Haploinsufficiency	Autosomal dominant			Adult	[155]
Sox17	Heritable and idiopathic PAH Congenital heart disease	Unknown	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Paediatric and adult	[149]
CAV1	Heritable and idiopathic PAH Lipodystrophy	Gain of function; dominant negative	Autosomal dominant	Deficiency of subcutaneous adipose tissue	Fasting triglyceride and leptin levels	Paediatric and adult	[156]
TBX4	Heritable and idiopathic PAH Small patella syndrome (ischiopatellar dysplasia) Parenchymal lung disease Bronchopulmonary dysplasia Persistent pulmonary hypertension of the neonate	Unknown	Autosomal dominant	Patellar aplasia Skeletal abnormalities, in particular pelvis, knees, and feet	Skeletal X-rays: pelvis, knees, and feet CT chest: diffuse parenchymal lung disease	Paediatric and (less commonly) adult	[149, 157]
EIF2AK4	Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis	Loss of function	Autosomal recessive	Distal phalangeal clubbing	Reduced DLCO CT chest: interlobular septal thickening and mediastinal lymphadenopathy, and centrilobular ground-glass nodular opacities	Adult	[158]
KDR	Heritable and idiopathic PAH	Loss of function	Autosomal dominant	No specific or diagnostic clinical features described	Possible reduced DLCO	Older-onset adult	[159]
ENG		Unknown	Autosomal dominant	Telangiectasia	Iron-deficiency anaemia	Adult and paediatric	[160]
ACVRL1	Heritable and idiopathic PAH; hereditary haemorrhagic telangiectasia	Haploinsufficiency	Autosomal dominant	Abnormal blood vessel formation	Presence on imaging of pulmonary, hepatic, cerebral, or spinal arteriovenous malformations	Adult and paediatric	[160]
GDF2		Haploinsufficiency	Autosomal dominant	Visceral arteriovenous malformations Bleeding diathesis	Invasive endoscopic assessment of gastrointestinal telangiectasia	Adult and paediatric	[149]

CT, computed tomography; DLCO, lung diffusion capacity for carbon monoxide; PAH, pulmonary arterial hypertension.

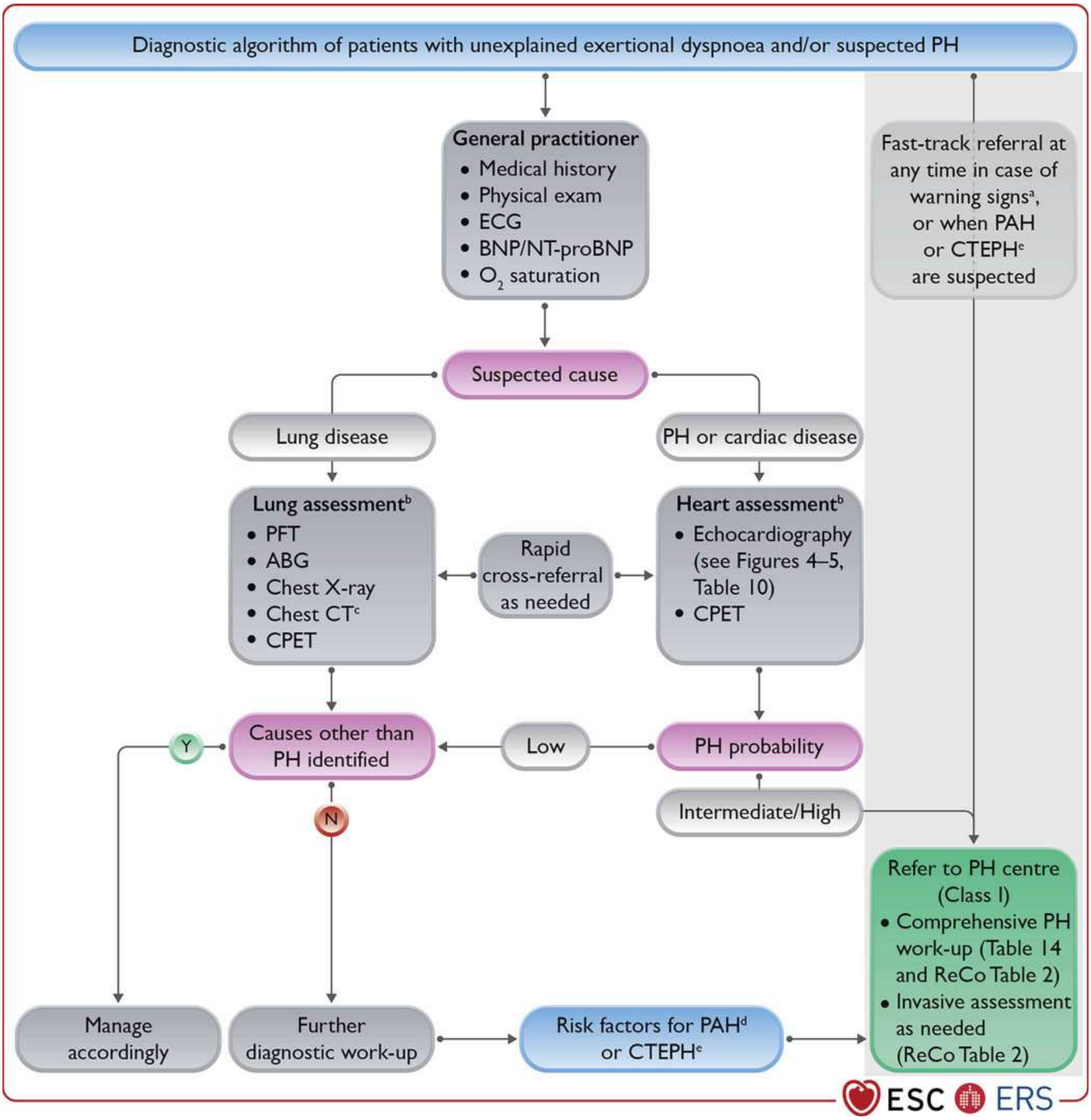

FIGURE 6 Diagnostic algorithm of patients with unexplained dyspnoea and/or suspected pulmonary hypertension. ABG, arterial blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thrombo-embolic pulmonary hypertension; ECG, electrocardiogram; HIV, human immunodeficiency virus; N, no; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PFT, pulmonary function tests; PH, pulmonary hypertension; ReCo, recommendation; Y, yes. [a]Warning signs include rapid progression of symptoms, severely reduced exercise capacity, pre-syncope or syncope on mild exertion, signs of right heart failure. [b]Lung and heart assessment by specialist as per local practice. [c]As indicated; CT pulmonary angiography recommended if PH suspected. [d]Includes connective tissue disease (especially systemic sclerosis), portal hypertension, HIV infection, and family history of PAH. [e]History of PE, permanent intravascular devices, inflammatory bowel diseases, essential thrombocythaemia, splenectomy, high-dose thyroid hormone replacement, and malignancy.

TABLE 14 Characteristic diagnostic features of patients with different forms of pulmonary hypertension

Diagnostic tool	Characteristic findings/features	Group 1 (PAH)	Group 2 (PH associated with left heart disease)	Group 3 (PH associated with lung disease)	Group 4 (PH associated with pulmonary artery obstructions)
5.1.1 Clinical presentation	Clinical features	Variable age, but young, female patients may be predominantly affected[a] [161] Clinical presentation depends on associated conditions and phenotype See section 5.1.1	Mostly elderly patients, female predominance in case of HFpEF [161] History and clinical findings suggestive of LHD	Mostly elderly patients, male predominance [161] History and clinical findings suggestive of lung disease Smoking history common	Variable age, but elderly male and female equally affected History of VTE (CTEPH may occur in the absence of a VTE history) Risk factors for CTEPH See section 10.1
	Oxygen requirement for hypoxaemia	Uncommon, except for conditions with low DLCO or right-to-left shunting	Uncommon	Common, often profound hypoxaemia in severe PH	Uncommon; common in severe cases with predominantly distal pulmonary artery occlusions
5.1.3 Chest radiography		RA/RV/PA size ↑ Pruning of peripheral vessels	LA/LV size ↑ Cardiomegaly Occasional signs of congestion (interstitial oedema/Kerley lines, alveolar oedema, pleural effusion)	Signs of parenchymal lung disease	RA/RV/PA size ↑ Number and size of peripheral vessels ↓ Occasional signs of pulmonary infarction
5.1.4 Pulmonary function tests and ABG	Spirometry/PFT impairment	Normal or mildly impaired	Normal or mildly impaired	Abnormal as determined by the underlying lung disease	Normal or mildly impaired
	DLCO	Normal or mild-to-moderately reduced (low DLCO in SSc-PAH, PVOD, and some IPAH phenotypes)	Normal or mild-to-moderately reduced, especially in HFpEF	Often very low (<45% predicted)	Normal or mild-to-moderately reduced
	Arterial blood gas				
	PaO_2	Normal or reduced	Normal or reduced	Reduced	Normal or reduced
	$PaCO_2$	Reduced	Usually normal	Reduced, normal, or increased	Normal or reduced
5.1.5 Echocardiography		Signs of PH (increased sPAP, enlarged RA/RV) Congenital heart defects may be present See section 5.1.5	Signs of LHD (HFrEF, HFpEF, valvular) and PH (increased sPAP, enlarged RA/RV) See section 8	Signs of PH (increased sPAP, enlarged RA/RV) See section 5.1.5	Signs of PH (increased sPAP, enlarged RA/RV) See section 5.1.5
5.1.6 Lung scintigraphy	Planar – SPECT V/Q	Normal or matched	Normal or matched	Normal or matched	Mismatched perfusion defect
5.1.7 Chest CT		Signs of PH or PVOD See section 5.1.7	Signs of LHD Pulmonary oedema Signs of PH	Signs of parenchymal lung disease Signs of PH	Intravascular filling defects, mosaic perfusion, enlarged bronchial arteries Signs of PH
5.1.11 Cardiopulmonary exercise testing		High VE/VCO_2 slope Low $PETCO_2$, decreasing during exercise No EOV	Mildly elevated VE/VCO_2 slope Normal $PETCO_2$, increasing during exercise EOV	Mildly elevated VE/VCO_2 slope Normal $PETCO_2$, increasing during exercise	High VE/VCO_2 slope Low $PETCO_2$, decreasing during exercise No EOV
5.1.12 Right heart catheterization		Pre-capillary PH	Post-capillary PH	Pre-capillary PH	Pre- (or post-) capillary PH

ABG, arterial blood gas analysis; CT, computed tomography; CTEPH, chronic thrombo-embolic pulmonary hypertension; DLCO, Lung diffusion capacity for carbon monoxide; EOV, exercise oscillatory ventilation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IPAH, idiopathic pulmonary arterial hypertension; LA, left atrium; LHD, left heart disease; LV, left ventricle; PA, pulmonary artery; PaCO2, partial pressure of arterial carbon dioxide; PAH, pulmonary arterial hypertension; PaO2, partial pressure of arterial oxygen; PETCO2, end-tidal partial pressure of carbon dioxide; PFT, pulmonary function test; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RA, right atrium; RV, right ventricle; sPAP, systolic pulmonary arterial pressure; SPECT, single-photon emission computed tomography; SSc-PAH, systemic sclerosis-associated pulmonary arterial hypertension; VE/VCO2, ventilatory equivalent for carbon dioxide; V/Q, ventilation perfusion scintigraphy; VTE, venous thrombo-embolism. ↓, reduced; ↑, increased. [a]However, it may affect individuals of all ages and sexes; diagnosis in males should not be delayed.

IV), clinical signs of RV failure, syncope, signs of low CO state, poorly tolerated arrhythmias, and compromised or deteriorated haemodynamic status (hypotension, tachycardia). Such cases must be immediately managed as inpatients for initial work-up at a nearby hospital or PH centre. The presence of RV dysfunction by echocardiography, elevated levels of cardiac biomarkers, and/or haemodynamic instability must prompt referral to a PH centre for immediate assessment.

This diagnostic process emphasizes the importance of sufficient awareness and collaboration between first-line, specialized medicine and PH centres. Effective and rapid collaboration between each partner permits earlier diagnosis and management, and improves outcomes.

RECOMMENDATION TABLE 2 Recommendations for diagnostic strategy

Recommendation	Class[a]	Level[b]
Echocardiography		
Echocardiography is recommended as the first-line, non-invasive, diagnostic investigation in suspected PH [82, 84, 91]	I	B
It is recommended to assign an echocardiographic probability of PH, based on an abnormal TRV and the presence of other echocardiographic signs suggestive of PH (see Table 10) [91, 92, 162]	I	B
It is recommended to maintain the current threshold for TRV (>2.8 m/s) for echocardiographic probability of PH according to the updated haemodynamic definition [88]	I	C
Based on the probability of PH by echocardiography, further testing should be considered in the clinical context (*i.e.* symptoms and risk factors or associated conditions for PAH/CTEPH) [92]	IIa	B
In symptomatic patients with intermediate echocardiographic probability of PH, CPET may be considered to further determine the likelihood of PH [123, 163]	IIb	C
Imaging		
Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to assess for CTEPH [105]	I	C
CT pulmonary angiography is recommended in the work-up of patients with suspected CTEPH [104]	I	C
Routine biochemistry, haematology, immunology, HIV testing, and thyroid function tests are recommended in all patients with PAH, to identify associated conditions	I	C
Abdominal ultrasound is recommended for the screening of portal hypertension [164]	I	C
Chest CT should be considered in all patients with PH	IIa	C
Digital subtraction angiography should be considered in the work-up of patients with CTEPH	IIa	C
Other diagnostic tests		
Pulmonary function tests with DLCO are recommended in the initial evaluation of patients with PH [78]	I	C
Open or thoracoscopic lung biopsy is not recommended in patients with PAH	III	C

CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thrombo-embolic pulmonary hypertension; DLCO, Lung diffusion capacity for carbon monoxide; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; TRV, tricuspid regurgitation velocity. [a]Class of recommendation. [b]Level of evidence.

5.3. Screening and early detection

Despite the advent of PAH therapies that prevent clinical worsening [166–168] and effective interventions for CTEPH [102], the time from symptom onset to PH diagnosis remains at >2 years [169, 170], with most patients presenting with advanced disease. Decreasing the time to diagnosis may reduce emotional uncertainty in patients [171], reduce the use of health care resources, and enable treatment at an earlier stage when therapies may be more effective [172].

A proposed multifaceted approach [172] to facilitate an earlier diagnosis includes: (1) screening asymptomatic, high-risk groups (with high prevalence or where the diagnosis significantly impacts the proposed intervention), including individuals with SSc (prevalence: 5–19%) [173, 174], *BMPR2* mutation carriers (14–42%) [33], first-degree relatives of patients with HPAH [148], and patients undergoing assessment for liver transplantation (2–9%) [175]; (2) early detection of symptomatic patients in *at-risk* groups with conditions such as portal hypertension [176], HIV infection (0.5%) [177], and non-SSc CTD, where the lower prevalence rates do not support asymptomatic screening; and (3) applying population-based strategies by deploying early detection approaches in PE follow-up clinics [178, 179], breathlessness clinics [172], or in at-risk patients identified from their health care behaviour and/or previous investigations [180].

Screening can be defined as the systematic application of a test or tests to identify at-risk, asymptomatic individuals. Screening approaches can also be extended to individuals who would not otherwise have sought medical attention on account of their symptoms, to facilitate early detection. Tools used to screen for PH have primarily been assessed, but not exclusively, in SSc [172, 174], and include blood biomarkers (NT-proBNP), ECG, echocardiography (primarily using estimates of sPAP at rest, but also exercise studies) [182], PFTs (DLCO and forced vital capacity [FVC]/DLCO ratio), and exercise testing including CPET (which has been used in combination with screening algorithms to reduce the need for RHC) [123, 163].

5.3.1. Systemic sclerosis

In SSc, the prevalence of PAH is 5–19% [174], with an annual incidence of developing PAH of 0.7–1.5% [183–185]. Evidence for the clinical value of detecting PAH early in SSc was provided by a screening programme [186], which showed less severe haemodynamic impairment and better survival in screened patients compared with a contemporaneous, non-screened cohort [187], providing a strong rationale for screening for PAH in patients with SSc.

The diagnostic accuracy of echocardiography or other tests alone in detecting PAH is suboptimal [173]. Several screening algorithms have been studied using a combination of clinical features, echocardiography, PFTs, and NT-proBNP to select patients with SSc for RHC (DETECT [173]; Australian Scleroderma Interest Group [ASIG] [188]). Such combined approaches have improved diagnostic accuracy compared with the use of echocardiography, NT-proBNP, or PFTs alone, and are able to prevent unnecessary RHC and identify patients with mPAP 21–24 mmHg [189]. Therefore, a multimodal approach is warranted when screening patients with SSc for PAH; the echocardiographic assessment should follow the strategy described in Section 5.1.5.

Beyond initial screening, the frequency with which screening should be undertaken in asymptomatic subjects with SSc is unclear. A study from the Australian Scleroderma Study Cohort, where annual screening was recommended (some patients were screened up to 10 times), noted that most patients were diagnosed with PAH at their first screening; however, those diagnosed on subsequent screening had a lower mPAP, PVR, and WHO-FC, and better survival than those diagnosed at first screening [190]. Based on current evidence, annual screening for PAH in patients with SSc is sufficient. Given the financial and emotional cost associated with regular screening, stratifying subjects with SSc into those at highest and lowest risk of PAH would be desirable. Risk factors for PAH include: (1) clinical and demographic factors (*i.e.* breathlessness, longer disease duration, sicca symptoms, digital ulceration, older age, and male sex); and (2) the results of investigations (*e.g.* positive anti-centromere antibody profile, mild ILD, low DLCO, elevated FVC/DLCO ratio, or elevated NT-proBNP) [174, 191]. A recent meta-analysis showed that reduced digital capillary density, as assessed by video-capillaroscopy, or progression to a severe active/late pattern of vascular involvement is also a risk factor for PAH [192]. In addition to identifying patients at increased risk of PAH, a simple prediction model integrating symptoms, DLCO, and NT-proBNP identified subjects at very low probability of PAH who could potentially avoid further specific testing for PH [183]. Furthermore, CPET may help to identify patients with SSc with a low risk of having PAH and thus to avoid unnecessary RHC [123].

The recommendations on screening for PAH in SSc have been established based on key narrative question 3 (Supplementary Data, Section 5.2).

5.3.2. BMPR2 mutation carriers

In the evolving list of genes known to be associated with PAH, experience is largely restricted to *BMPR2* mutation carriers who carry a lifetime risk of developing PAH of ∼20%, with penetrance higher in female carriers (42%) compared with male carriers (14%) [33, 148, 193]. There is currently no accepted screening strategy for evaluating PAH in *BMPR2* mutation carriers. At present, based on expert consensus, asymptomatic relatives who screen positive for PAH-causing mutations are often offered yearly screening echocardiography [25, 26] The DELPHI-2 study, which prospectively screened carriers and relatives, recently demonstrated a 9.1% pick up over 47±27 months of PAH, with 2/55 diagnosed at baseline and 3/55 at follow-up; this equates to an incidence of 2.3%/year [33]. The screening schedule included ECG, NT-proBNP, DLCO, echocardiography, CPET, and optional RHC; however, none of the cases would have been picked up by echocardiography alone. Screening programmes should adopt a multimodal approach, although the optimal strategy and screening period remains undefined and will require multinational, multicentre study.

5.3.3. Portal hypertension

An estimated 1–2% of patients with liver disease and portal hypertension develop PoPH [176, 194], which is of particular relevance in patients considered for transjugular portosystemic shunting or liver transplantation. In such patients, echocardiography is recommended to screen for PAH, even in the absence of symptoms. By using echocardiography, sPAP can be measured in ∼80% of patients with portal hypertension, which aids decisions to perform RHC. In patients assessed for liver transplantation, one study showed that an sPAP of >50 mmHg had 97% sensitivity and 77% specificity for detecting moderate-to-severe PAH [195]. Other investigators have recommended RHC when sPAP is >38 mmHg [196]. When screening for PoPH, it is advised to assess the echocardiographic probability of PH (see Section 5.1.5). In agreement with the International Liver Transplant Society, for patients awaiting liver transplantation, it is recommended to reassess for PAH annually, although the optimal interval remains unclear [175].

5.3.4. Pulmonary embolism

Chronic thrombo-embolic pulmonary hypertension is an uncommon and under-diagnosed complication of acute PE [112]. The reported cumulative incidence of CTEPH after acute, symptomatic PE ranges 0.1–11.8%, depending on the collective investigated [112, 178, 197–199]. A systematic review and meta-analysis reported a CTEPH incidence of 0.6% in all patients with acute PE, 3.2% in survivors, and 2.8% in survivors without major comorbidities [178]. A multicentre, observational, screening study reported a CTEPH incidence of 3.7/1000 patient-years and a 2 year cumulative incidence of 0.79% following acute PE [200]. A recent prospective observational study (FOCUS, Follow-up After Acute Pulmonary Embolism) showed a cumulative 2 year incidence of 2.3% and 16.0% for CTEPH and post-PE impairment, respectively, which were both associated with a higher risk of rehospitalization and death [201]. Due to insufficient awareness, some patients may have a delayed diagnosis of CTEPH because they may initially be misclassified as acute PE [112]. In this context, the current guidelines do not recommend routine follow-up of patients with PE by imaging methods of the pulmonary vascular tree, but suggest evaluating the index imaging test used to diagnose acute PE for signs of CTEPH. Echocardiography is the preferred first-line diagnostic test in patients with suspected CTEPH [103].

Up to 50% of patients have persistent perfusion defects after an acute PE; however, the clinical relevance is unclear [202–204]. All patients in whom symptoms can be attributed to post-thrombotic deposits within PAs are considered to have CTEPD, with or without PH [54]. While persistent dyspnoea is common after acute PE [205], the prevalence of CTEPD without PH is unknown and requires further study (see Section 10.1). A study exploring screening for CTEPH following acute PE identified, using echocardiography, a low yield of additional CTEPH diagnoses in asymptomatic patients [206]. Current PE guidelines recommend that further diagnostic evaluation may be considered in asymptomatic patients with risk factors for CTEPH at 3–6 months' follow-up [103, 207]. Approaches to early detection of CTEPH following acute PE are based on identifying patients at increased risk [208]. In patients with persistent or new-onset dyspnoea after PE, non-invasive approaches use echocardiography to assess for PH and cross-sectional imaging to assess for persistent perfusion defects. Limited data exist on strategies using DECT, CT lung subtraction iodine mapping, or 3D MR perfusion imaging. Scoring systems, including the Leiden CTEPH rule-out criteria [206, 209] can be used to inform diagnostic strategies. Cardiopulmonary exercise testing may identify characteristic features of exercise limitation due to PVD, or suggest an alternative diagnosis. The optimal timing for assessing symptoms to aid early detection of CTEPH may be 3–6 months after acute PE, coinciding with the routine evaluation of anticoagulant treatment, but earlier assessment may be necessary in highly symptomatic or deteriorating patients [54, 103].

RECOMMENDATION TABLE 3 Recommendations for screening and improved detection of pulmonary arterial hypertension and chronic thrombo-embolic pulmonary hypertension

Recommendations	Class[c]	Level[b]
Systemic sclerosis		
In patients with SSc, an annual evaluation of the risk of having PAH is recommended [183, 186]	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 [173, 186]	I	B

Continued

RECOMMENDATION TABLE 3 Continued

Recommendations	Class[c]	Level[b]
In patients with SSc, where breathlessness remains unexplained following non-invasive assessment, RHC is recommended to exclude PAH [185–187]	I	C
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 [172, 173, 186, 188, 190]	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
CTEPH/CTEPD		
In patients with persistent or new-onset dyspnoea or exercise limitation following PE, further diagnostic evaluation to assess for CTEPH/CTEPD is recommended [103]	I	C
For symptomatic patients with mismatched perfusion lung defects beyond 3 months of anticoagulation for acute PE, referral to a PH/CTEPH centre is recommended after considering the results of echocardiography, BNP/NT-proBNP, and/or CPET [203, 206]	I	C
Other		
Counselling regarding the risk of PAH, and annual screening is recommended in individuals who test positive for PAH-causing mutations and in first-degree relatives of patients with HPAH [33]	I	B
In patients referred for liver transplantation, echocardiography is recommended as a screening test for PH	I	C
Further tests (echocardiography, BNP/NT-proBNP, PFTs, and/or CPET) should be considered in symptomatic patients with CTD, portal hypertension, or HIV to screen for PAH [172]	IIa	B

BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; CTD, connective tissue disease; CTEPD, chronic thrombo-embolic pulmonary disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; DLCO, Lung diffusion capacity for carbon monoxide; FVC, forced vital capacity; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterisation; SSc, systemic sclerosis. [a]Class of recommendation. [b]Level of evidence.

6. Pulmonary arterial hypertension (group 1)

6.1. Clinical characteristics

The symptoms of PAH are non-specific and mainly related to progressive RV dysfunction (see Section 5.1.1) as a consequence of progressive pulmonary vasculopathy (Figure 7). The presentation of PAH may be modified by diseases that are associated with PAH, as well as comorbidities. More detailed descriptions of the individual PAH subsets are reported in Section 7.

6.2. Severity and risk assessment

6.2.1. Clinical parameters

Clinical assessment is a key part of evaluating patients with PAH, as it provides valuable information for determining disease severity, improvement, deterioration, or stability. At follow-up, changes in WHO-FC (Table 15), episodes of chest pain, arrhythmias, haemoptysis, syncope, and signs of right HF provide important information. Physical examination should assess heart rate, rhythm, blood pressure, cyanosis, enlarged jugular veins, oedema, ascites, and pleural effusions. The WHO-FC is one of the strongest predictors of survival, both at diagnosis and follow-up [210–212], and worsening WHO-FC is one of the most alarming indicators of disease progression, which should trigger further investigations to identify the cause(s) of clinical deterioration [210, 213, 214].

6.2.2. Imaging

Imaging of the heart plays an essential role in the follow-up of patients with PAH. Several echocardiographic and cMRI parameters have been proposed to monitor RV function during the course of PAH. Table S2 provides a list of imaging parameters and relative cut-off values associated with increased and decreased risk of adverse events.

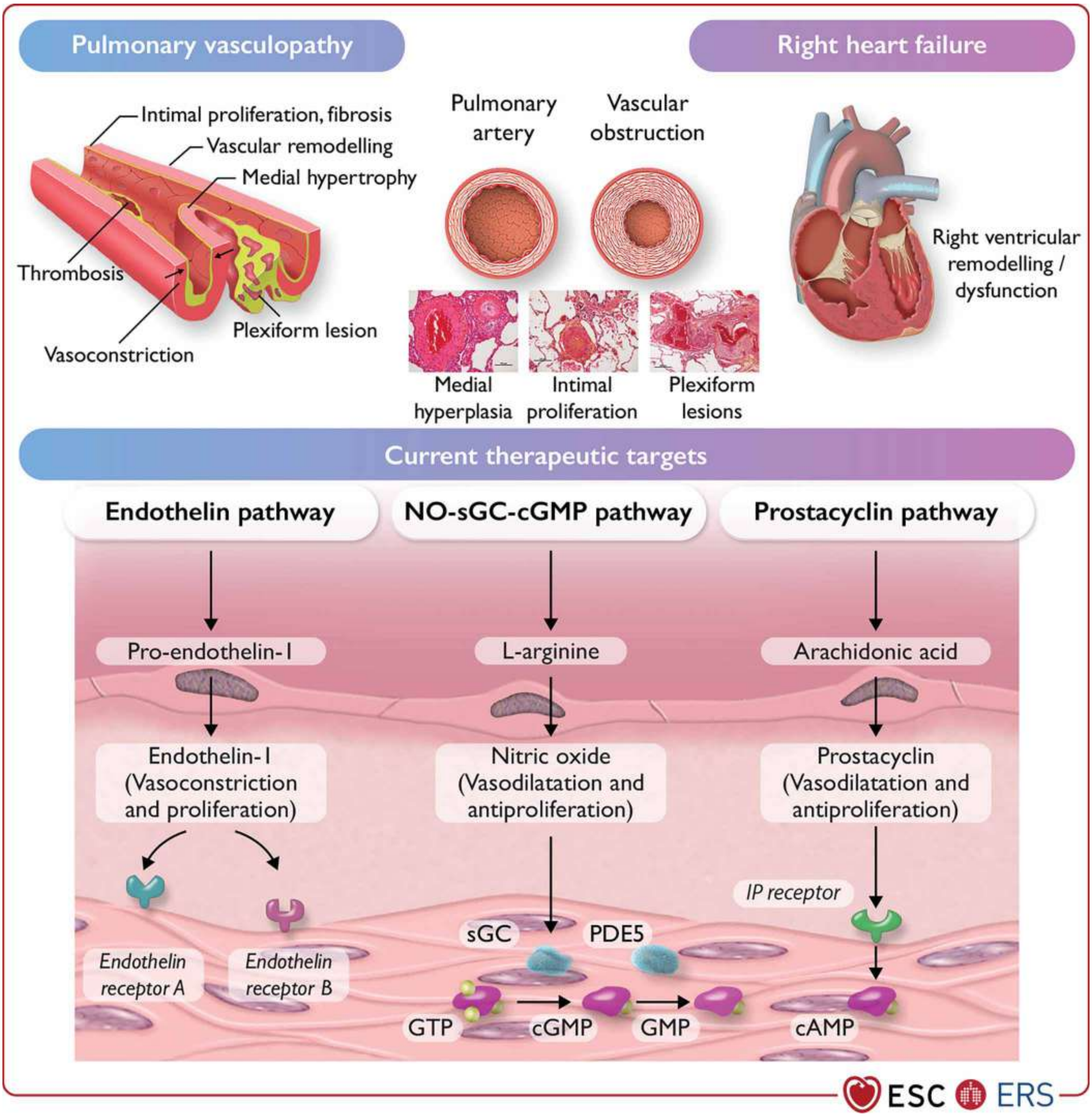

FIGURE 7 Pathophysiology and current therapeutic targets of pulmonary arterial hypertension (group 1). cAMP, cyclic adenosine monophosphate; (c)GMP, (cyclic) guanosine monophosphate; GTP, guanosine-5′-triphosphate; IP receptor, prostacyclin I2 receptor; NO, nitric oxide; PDE5, phosphodiesterase 5; sGC, soluble guanylate cyclase.

6.2.2.1. Echocardiography

Echocardiography is a widely available imaging modality and is readily performed at the patient's bedside. It is crucial that a high-quality echocardiographic assessment by PH specialists is undertaken to reduce intraobserver and interobserver variability. Of note, estimated sPAP at rest is not prognostic and irrelevant to therapeutic decision-making [212, 215, 216]. An increase in sPAP does not necessarily reflect disease progression and a decrease in sPAP does not necessarily reflect improvement.

TABLE 15 World Health Organization classification of functional status of patients with pulmonary hypertension

Class	Description[a]
WHO-FC I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
WHO-FC II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
WHO-FC III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
WHO-FC IV	Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

PH, pulmonary hypertension; WHO-FC, World Health Organization functional class. [a]Functional classification of PH modified after the New York Heart Association functional classification according to the World Health Organization 1998 [147].

Despite the complex geometry of the right heart, echocardiographic surrogates of the true right heart dimensions, which include a description of RV and RA areas, and the LV eccentricity index, provide useful clinical information in PAH [217, 218]. Right ventricular dysfunction can be evaluated measuring fractional area change, TAPSE, tissue Doppler, and 2D speckle tracking myocardial strain recording of RV free-wall motion, all of which represent isovolumetric and ejection-phase indices of load-induced RV pump failure [219–224]. The rationale for the reported measurements is strong, as RV systolic function metrics assess the adaptation of RV contractility to increased afterload, and increased right heart dimension and inferior vena cava dilation reflect failure of this mechanism, hence maladaptation [225]. Pericardial effusion and tricuspid regurgitation (TR) grading further explore RV overload and are of prognostic relevance in these patients [218, 226–228]. All of these variables are physiologically interdependent and their combination provides additional prognostic information over single measurements [223].

Echocardiography also enables combined parameters to be measured, such as the TAPSE/sPAP ratio, which is tightly linked to RV–PA coupling and predicts outcome [96, 97]. Echocardiographic measurements of RV and RA sizes combined with LV eccentricity index are crucial for assessing RV reverse remodelling as an emerging marker of treatment efficacy [220, 229]. Three-dimensional echocardiography may achieve better estimation than standard 2D assessment, but underestimations of volumes and ejection fraction have been reported, and technical issues are, as yet, unresolved [230].

6.2.2.2. Cardiac magnetic resonance imaging

The role of cMRI in evaluating patients with PAH has been addressed in several studies, and RV volumes, RVEF, and SV are essential prognostic determinants in PAH [225, 231–236]. In patients with PAH, initial cMRI measurements added prognostic value to current risk scores [231, 232]. In addition, risk assessment at 1 year of follow-up based on cMRI was at least equal to risk assessment based on RHC [237]. The cMRI risk-assessment variables based on the current literature are included in Table 16 [117, 225, 231–235, 237]. The stroke volume index (SVI) cut-off levels are based on the consensus of the literature [238]; a change of 10 mL in SV (LV end-diastolic volume−LV end-systolic volume) during follow-up is considered clinically significant [239]. The value of cMRI in the follow-up of patients has been shown in several studies, and cMRI enables treatment effects to be monitored and treatment strategies adapted in time to prevent clinical failure [240–242].

6.2.3. Haemodynamics

Cardiopulmonary haemodynamics assessed by RHC provide important prognostic information, both at the time of diagnosis and at follow-up [129, 212, 213, 216, 238, 243–248]. Currently available risk-stratification tools include haemodynamic variables for prognostication: RAP and PVR in REVEAL risk scores [213, 249, 250], and RAP, CI, and SvO_2 in the ESC/ERS risk-stratification table [25, 26]. The mPAP provides little prognostic information, except in acute vasodilator responders [129]. A recent study

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%

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO2, ventilatory equivalents for carbon dioxide; VO2, oxygen uptake; WHO-FC, World Health Organization functional class. [a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient. [b]Repeated episodes of syncope even with little or regular physical activity. [c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities. [d]To harmonize with the four-strata model shown in Table 18, the BNP and NT-proBNP cut-off levels have been updated from the 2015 version based on data from the REVEAL registry, acknowledging that the European validation studies have used the original cut-off levels [274, 292, 293, 295, 296, 302]. [e]cMRI parameters adapted from Section 6.2.2.2.

from France, which combined clinical and haemodynamic parameters, found that WHO-FC, 6MWD, RAP, and SVI (but not SV and SvO_2) were independent predictors of outcome [238].

To refine the risk-stratification table (Table 16), SVI criteria are now added with the cut-off values of >38 mL/m^2 and <31 mL/m^2 to determine low-risk and high-risk status, respectively [238].

The optimal timing of follow-up RHC has not been determined. While some centres regularly perform invasive follow-up assessments, others perform them as clinically indicated, and there is no evidence that any of these strategies is associated with better outcomes (Table 17).

6.2.4. Exercise capacity

The 6-minute walking test (6MWT) is the most widely used measure of exercise capacity in PH centres. The 6MWT is easy to perform, inexpensive, and widely accepted by patients, health professionals, and medicines agencies as an important and validated variable in PH. As with all PH assessments, 6MWT results must always be interpreted in the clinical context. The 6MWD is influenced by factors such as sex, age, height, weight, comorbidities, need for oxygen, learning curve, and motivation. Test results are usually given in absolute distance (metres) rather than the percentage of predicted values. Change in 6MWD is one of the most commonly used parameters in PAH clinical trials as a primary endpoint, key secondary endpoint, or component of clinical worsening [251]. A recent investigation showed that the best absolute-threshold values for 1 year mortality and 1 year survival, respectively, were 165 m and 440 m,

TABLE 17 Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

	At baseline	3–6 months after changes in therapy[a]	Every 3–6 months in stable patients[a]	In case of clinical worsening
Medical assessment (including WHO-FC)	Green	Green	Green	Green
6MWT	Green	Green	Green	Green
Blood test (including NT-proBNP)[b,c]	Green	Green	Green	Green
ECG	Green	Green	Green	Green
Echocardiography or cMRI	Green	Green	Orange	Green
ABG or pulse oximetry[d]	Green	Green	Green	Green
Disease-specific HR-QoL	Orange	Orange	Orange	Orange
CPET	Orange	Orange	Orange	Orange
RHC	Green	Yellow	Orange	Yellow

6MWT, 6-minute walking test; ABG, arterial blood gas analysis; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BNP, brain natriuretic peptide; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; HR-QoL, health-related quality of life; INR, international normalized ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; TSH, thyroid-stimulating hormone; WHO-FC, World Health Organization functional class. Green: is indicated; yellow: should be considered; orange: may be considered. [a]Intervals to be adjusted according to patient needs, PAH aetiology, risk category, demographics, and comorbidities. [b]Basic laboratory tests include blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT, bilirubin, and BNP/NT-proBNP. [c]Extended laboratory tests (*e.g.* TSH, troponin, uric acid, iron status, etc.) according to clinical circumstances. [d]ABG should be performed at baseline but may be replaced by pulse oximetry in stable patients at follow-up.

respectively [252]. Improvements in 6MWD have had less predictive value than deterioration on key clinical outcomes (mortality and survival) [250, 252, 253]. These results are consistent with observations from clinical trials and registries [254, 255]; however, there is no single threshold that would apply to all patients [256]. Some studies have also suggested that adding SaO_2 measured by pulse oximetry and heart rate responses may improve prognostic relevance [246, 257]. Hypoxaemia observed during the 6MWT is associated with worse survival, but these findings still await confirmation in large multicentre studies.

The incremental shuttle walking test (ISWT) is an alternative maximal test for assessing patients with PAH. The ISWT has a potential advantage over the 6MWT in that it does not have a ceiling effect; furthermore, it keeps the simplicity of a simple-to-perform field test, in contrast to CPET. However, the ISWT experience in PAH is currently limited [258].

Cardiopulmonary exercise testing is a non-invasive method for assessing functional capacity and exercise limitation. It is usually performed as a maximal exercise test, and is safe even in patients with severe exercise limitation [259, 260]. Most PH centres use an incremental ramp protocol, although the test has not yet been standardized for this patient population. Robust prognostic evidence for peak VO_2 and VE/VCO_2 has been found in three studies, all powered for multivariable analysis [261–263]. When associated with SVI, peak VO_2 provided useful information to further stratify patients with PAH at intermediate risk [264]. However, the added value of CPET on top of common clinical and haemodynamic variables remains largely unexplored.

6.2.5. Biochemical markers

Considerable efforts have been made to identify additional biomarkers of PVD, addressing prognosis [265–272], diagnosis, and differentiation of PH subtypes [270, 273–276], as well as PAH treatment response [266]. Emerging proteins related to PAH and vascular remodelling include bone morphogenetic proteins 9 and 10 and translationally controlled tumour protein [270, 277, 278]. Proteome-wide screening in IPAH and HPAH identified a multimarker panel with prognostic information in addition to the REVEAL risk score [271]. Another study found that early development of SSc-associated PAH (PAH-SSc) was predicted by high circulating levels of C-X-C motif chemokine 4 in patients with SSc [276]. However, none of these biomarkers have been introduced in clinical practice.

Thus, BNP and NT-proBNP remain the only biomarkers routinely used in clinical practice at PH centres, correlating with myocardial stress and providing prognostic information [279]. Brain natriuretic peptide and NT-proBNP are not specific for PH, as they can be elevated in other forms of heart disease, exhibiting great variability. The previously proposed cut-off levels of BNP (<50, 50–300, and >300 ng/L) and NT-proBNP (<300, 300–1400, and >1400 ng/L) for low, intermediate, and high risk, respectively, in the ESC/ERS risk-assessment model at baseline and during follow-up are prognostic for long-term outcomes and can be used to predict response to treatment [266]. Refined cut-off values for BNP (<50, 50–199, 200–800, and >800 ng/L) and NT-pro-BNP (<300, 300–649, 650–1100, and >1100 ng/L) for low, intermediate–low, intermediate–high, and high risk, respectively, have recently been introduced as part of a four-strata risk-assessment strategy (see Section 6.2.7) [280].

6.2.6. Patient-reported outcome measures

A patient-reported outcome measure (PROM) is a term for health outcomes that are 'self-reported' by the patient. It is the patient's experience of living with PH and its impact on them and their caregivers, including symptomatic, intellectual, psychosocial, spiritual, and goal-orientated dimensions of the disease and its treatment. Despite treatment advances improving survival, patients with PAH present with a range of non-specific yet debilitating symptoms, which affect health-related quality of life (HR-QoL) [281, 282].

Patient-reported outcome measures remain an underused outcome measure. Tools validated in patients with PAH should be used to assess HR-QoL [282, 283] in individual patients. There has been a reliance on generic PROMs, which have been studied in patients with PAH but may lack sensitivity to detect changes in PAH [284, 285]. To address this, a number of PH-specific HR-QoL instruments have been developed and validated (*e.g.* Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR] [286], emPHasis-10 [282, 287], Living with Pulmonary Hypertension [288], and Pulmonary Arterial Hypertension-Symptoms and Impact [PAH-SYMPACT]) [289]. These disease-specific PROMs track functional status, clinical deterioration, and prognosis in PAH, and are more sensitive to the differences in the risk status than generic PROMs [290, 291]. In addition, HR-QoL scores provide independent prognostic information [287].

6.2.7. Comprehensive prognostic evaluation, risk assessment, and treatment goals

In the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH, risk assessment was based on a multiparametric approach using a three-strata model to classify patients at low, intermediate, or high risk of death. Originally, these strata were based on estimated 1 year mortality rates of <5%, 5–10%, and >10%, respectively [25, 26]. Since then, registry data have shown that observed 1 year mortality rates in the intermediate- and high-risk groups were sometimes higher than predicted (*i.e.* up to 20% in the intermediate-risk group and >20% in the high-risk group). These numbers have been updated accordingly in the revised three-strata risk model (Table 16) [292–294].

Several abbreviated approaches of the 2015 ESC/ERS risk-stratification tool have been introduced and independently validated using the Swedish Pulmonary Arterial Hypertension Registry (SPAHR) [292], the Comparative, Prospective Registry of Newly Initiated Therapies for PH (COMPERA) [293], and the French PH Registry (FPHR) [295]. Other risk-stratification tools have been developed from the US REVEAL, including the REVEAL 2.0 risk score calculator, and an abridged version (REVEAL Lite 2) [249, 296]. In all these studies, WHO-FC, 6MWD, and BNP/NT-proBNP emerged as the variables with the highest predictive value.

The main limitation of the 2015 ESC/ERS three-strata, risk-assessment tool is that 60–70% of the patients are classified as intermediate risk [274, 293–295, 297–303]. An initial attempt to substratify the intermediate-risk group has been proposed, using a modified mean score in the SPAHR equation (with low–intermediate, 1.5–1.99 and high–intermediate, 2.0–2.49 as cut-offs), where the high–intermediate group was associated with worse survival [302]. There have also been attempts to further improve risk stratification by exploring the additional value of new biomarkers [304], or by measuring RV structure and function by echocardiography and cMRI [231, 305, 306]. Other strategies have included incorporating renal function [307] or combining 6MWD with TAPSE/sPAP ratio [96, 97]; however, all of these strategies have to be further validated.

Two recent registry studies have evaluated a four-strata, risk-assessment tool based on refined cut-off levels for WHO-FC, 6MWD, and NT-proBNP (Table 18) [280, 308]. Patients were categorized as low,

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	<50	50–199	200–800	>800
NT-proBNP, ng/L	<300	300–649	650–1100	>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.

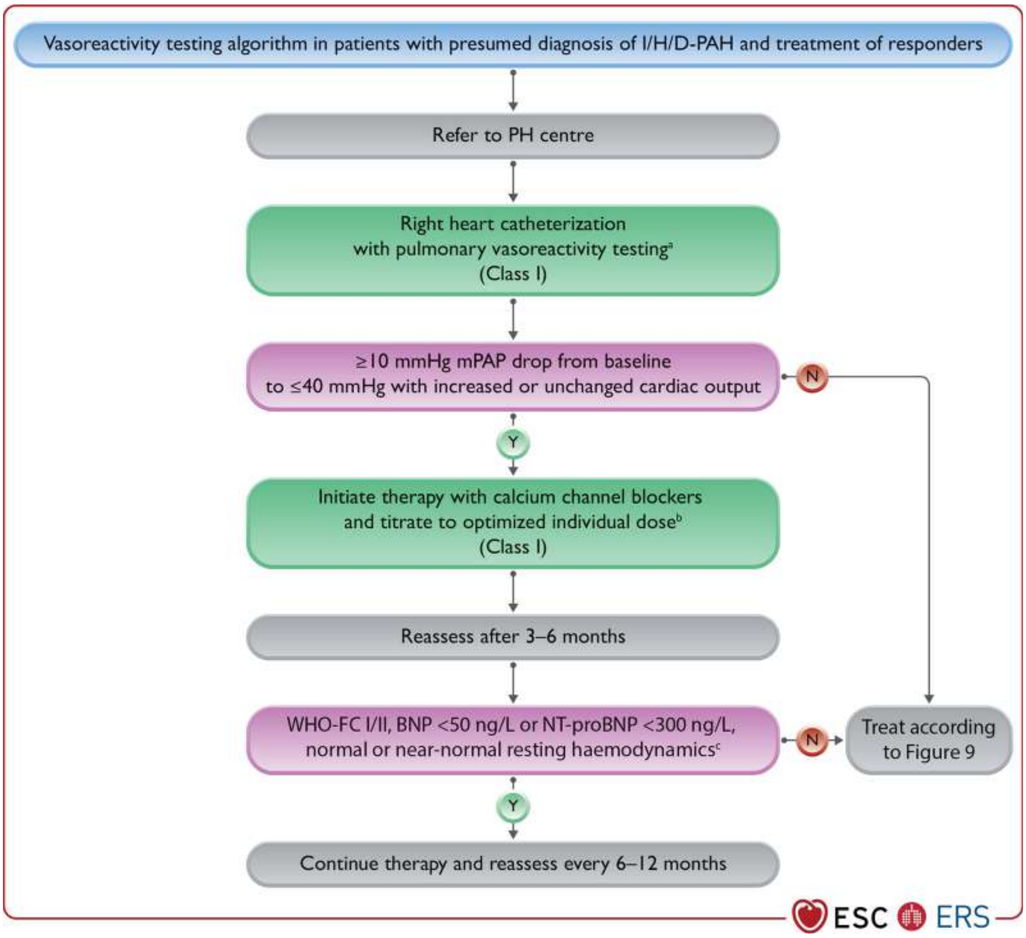

FIGURE 8 Vasoreactivity testing algorithm of patients with presumed diagnosis of idiopathic, heritable, or drug-associated pulmonary arterial hypertension. BNP, brain natriuretic peptide; I/H/D-PAH, idiopathic, heritable, drug-associated pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; N, no; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization functional class; WU, Wood units; Y, yes. [a]Inhaled nitric oxide and inhaled iloprost are recommended; intravenous epoprostenol can be used if inhaled nitric oxide or inhaled iloprost are unavailable. [b]See text for details. [c]mPAP ⩽30 mmHg and PVR ⩽4 WU.

intermediate–low, intermediate–high, or high risk. Together, these studies included >4000 patients with PAH and showed that the four-strata model performed at least as well as the three-strata model in predicting mortality. The four-strata model predicted survival in patients with IPAH, HPAH, DPAH, and PAH associated with CTD (including the SSc subgroup), and in patients with PoPH. The observed 1-year mortality rates in the four risk strata were 0–3%, 2–7%, 9–19%, and >20%, respectively. Compared with the three-strata model, the four-strata model was more sensitive to changes in risk from baseline to follow-up, and these changes were associated with changes in the long-term mortality risk. The main advantage of the four-strata model over the three-strata model is better discrimination within the intermediate-risk group, which helps guide therapeutic decision-making (see Section 6.3.4). For these reasons, the four-strata model is included in the updated treatment algorithm (see Figure 9). However, the three-strata model is maintained for initial assessment, which should be comprehensive and include echocardiographic and haemodynamic variables, for which cut-off values for the four-strata model have yet to be established.

Several studies have identified WHO-FC, 6MWD, and BNP/NT-proBNP as the strongest prognostic predictors [293, 295, 296]. With the abbreviated risk-assessment tools, missing values become an important limitation. REVEAL Lite 2 provides accurate prediction when one key variable (WHO-FC, 6MWD, or BNP/NT-proBNP) is unavailable, but is no longer accurate when two of these variables are missing [293, 296]. The original three-strata SPAHR/COMPERA risk tool was developed with at least two variables available, while the four-strata model was developed and validated in patients for whom all three variables were available. It is therefore recommended to use at least these three variables for risk stratification. However, two components may be used when variables are missing, especially when a functional criterion (WHO-FC or 6MWD) is combined with BNP or NT-proBNP [296].

Collectively, the available studies support a risk-based, goal-orientated treatment approach in patients with PAH, where achieving and/or maintaining a low-risk status is favourable and recommended (key narrative question 4, Supplementary Data, Section 6.1) [298, 300, 303, 309, 310]. For risk stratification at diagnosis, use of the three-strata model is recommended taking into account as many factors as possible (Table 16), with a strong emphasis on disease type, WHO-FC, 6MWD, BNP/NT-proBNP, and haemodynamics. At follow-up, the four-strata model (Table 18) is recommended as a basic risk-stratification tool, but additional variables should be considered as needed, especially right heart imaging and haemodynamics. At any stage, individual factors such as age, sex, disease type, comorbidities, and kidney function should also be considered.

RECOMMENDATION TABLE 4 Recommendations for evaluating the disease severity and risk of death in patients with pulmonary arterial hypertension

Recommendations	Class[a]	Level[b]
It is recommended to evaluate disease severity in patients with PAH with a panel of data derived from clinical assessment, exercise tests, biochemical markers, echocardiography, and haemodynamic evaluations [212, 213, 216, 249, 292, 293, 295, 296, 302, 307]	I	B
Achieving and maintaining a low-risk profile on optimised medical therapy is recommended as a treatment goal in patients with PAH [210, 212, 213, 216, 298, 300, 303, 309, 310]	I	B
For risk stratification at the time of diagnosis, the use of a three-strata model (low, intermediate, and high risk) is recommended, taking into account all available data, including haemodynamics [292, 293, 295]	I	B
For risk stratification during follow-up, the use of a four-strata model (low, intermediate-low, intermediate-high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary [280, 308]	I	B
In some PAH aetiologies and in patients with comorbidities, optimisation of therapy should be considered on an individual basis while acknowledging that a low-risk profile is not always achievable [293, 294, 299, 311]	IIa	B

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class. [a]Class of recommendation. [b]Level of evidence.

6.3. Therapy

According to the revised haemodynamic definition, PAH may be diagnosed in patients with mPAP >20 mmHg and PVR >2 WU. Yet, the efficacy of drugs approved for PAH has only been demonstrated in patients with mPAP ⩾25 mmHg and PVR >3 WU (see Supplementary Data, Table S1). No data are

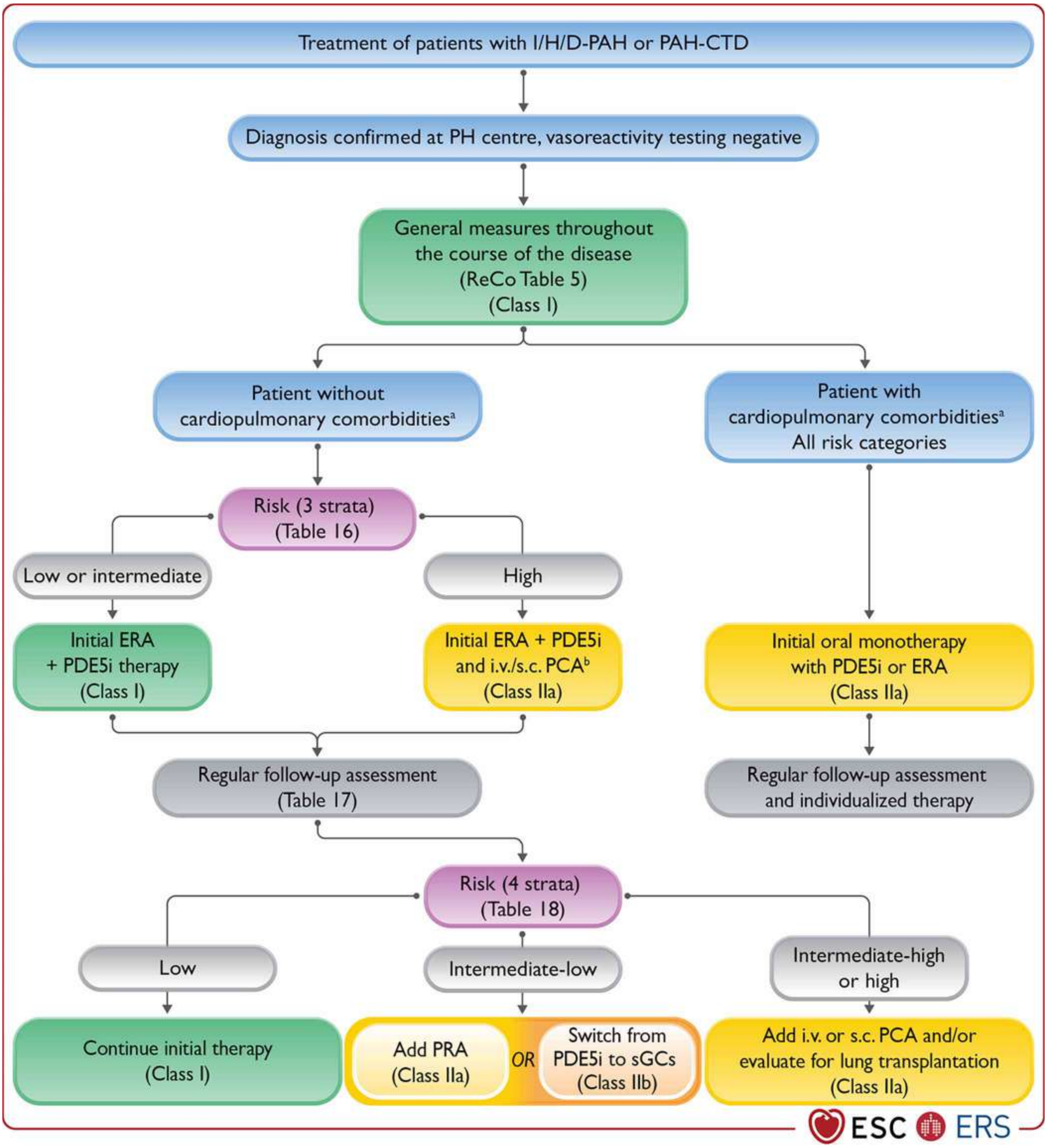

FIGURE 9 Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated pulmonary arterial hypertension. DLCO, lung diffusion capacity for carbon monoxide; ERA, endothelin receptor antagonist; I/H/D-PAH, idiopathic, heritable, or drug-associated pulmonary arterial hypertension; i.v., intravenous; PAH-CTD, PAH associated with connective tissue disease; PCA, prostacyclin analogue; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; ReCo, recommendation; s.c., subcutaneous; sGCs, soluble guanylate cyclase stimulator. [a]Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease; pulmonary comorbidities may include signs of mild parenchymal lung disease and are often associated with a low DLCO (<45% of the predicted value). [b]Intravenous epoprostenol or i.v./s.c. treprostinil.

available for the efficacy of drugs approved for PAH in patients whose mPAP is <25 mmHg and whose PVR is <3 WU. Hence, for such patients, the efficacy of drugs approved for PAH has not been established. The same is true for patients with exercise PH, who, by definition, do not fulfil the diagnostic criteria for PAH. Patients at high risk of developing PAH, for instance patients with SSc or family members of patients with HPAH, should be referred to a PH centre for individual decision-making.

6.3.1. General measures

Managing patients with PAH requires a comprehensive treatment strategy and multidisciplinary care. In addition to applying PAH drugs, general measures and care in special situations represent integral components of optimized patient care. In this context, the systemic consequences of PH and right-sided HF, often contributing to disease burden, should be appropriately managed [119].

6.3.1.1. Physical activity and supervised rehabilitation

The 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH suggested that patients with PAH should be encouraged to be active within symptom limits [25, 26]. Since then, additional studies have shown the beneficial impact of exercise training on exercise capacity (6MWD) and quality of life [312–316]. A large, randomized controlled trial (RCT) in 11 centres across 10 European countries, including 116 patients with PAH/CTEPH on PAH drugs, showed a significant improvement in 6MWD of 34.1±8.3 m, quality of life, WHO-FC, and peak VO_2 compared with standard of care [315]. Since most of the studies included patients who were stable on medical treatment, patients with PAH should be treated with the best standard of pharmacological treatment and be in a stable clinical condition before embarking on a supervised rehabilitation programme. Establishing specialized rehabilitation programmes for patients with PH would further enhance patient access to this intervention [317].

6.3.1.2. Anticoagulation

There are several reasons to consider anticoagulation in patients with PAH. Histopathological specimens from PAH patients' lungs have shown *in situ* thrombosis of pulmonary vessels. Patients with CHD or PA aneurysms may develop thrombosis of the central PAs. Abnormalities in the coagulation and fibrinolytic system indicating a pro-coagulant state have been reported in patients with PAH [318].

Data from RCTs on anticoagulation in PAH are lacking, and registry data have yielded conflicting results. The largest registry analysis so far suggested a potential survival benefit associated with anticoagulation in patients with IPAH [319], but this finding was not confirmed by others [320]. Two recent meta-analyses also concluded that using anticoagulants may improve survival in patients with IPAH [321, 322]; however, none of the included studies were methodologically robust. Despite the lack of evidence, registry data obtained between 2007 and 2016 showed that anticoagulation was used in 43% of patients with IPAH [293]. In PAH associated with SSc, registry data and meta-analyses uniformly indicated that anticoagulation may be harmful [320–322]. In CHD, there are also no RCTs on anticoagulation. There is also no consensus about the use of anticoagulants in patients who have permanent i.v. lines for therapy with prostacyclin analogues; this is left to local centre practice.

As anticoagulation is associated with an increased bleeding risk, and in the absence of robust data, no general recommendation has been made for or against the use of anticoagulants in patients with PAH; therefore, individual decision-making is required.

6.3.1.3. Diuretics

Right HF is associated with systemic fluid retention, reduced renal blood flow, and activation of the renin–angiotensin–aldosterone system. Increased right-sided filling pressures are transmitted to the renal veins, increasing interstitial and tubular hydrostatic pressure within the encapsulated kidney, which decreases net glomerular filtration rate and oxygen delivery [119].

Avoiding fluid retention is one of the key objectives in managing patients with PH. Once these patients develop signs of right-sided HF and oedema, restricting fluid intake and using diuretics is recommended. The three main classes of diuretics—loop diuretics, thiazides, and mineralocorticoid receptor antagonists—are used as monotherapy or in combination, as determined by the patient's clinical need and kidney function. Patients requiring diuretic therapy should be advised to regularly monitor their body weight and to seek medical advice in case of weight gain. Close collaboration between patients, PH centres, especially PH nurses, and primary care physicians plays a vital role. Kidney function and serum electrolytes should be regularly monitored, and intravascular volume depletion must be avoided as it may cause a further decline in CO and systemic blood pressure. Physicians should bear in mind that fluid retention and oedema may not necessarily signal right-sided HF, but may also be a side effect of PAH therapy [323].

6.3.1.4. Oxygen

Although oxygen administration reduces PVR and improves exercise tolerance in patients with PAH, there are no data to suggest that long-term oxygen therapy has sustained benefits on the course of the disease. Most patients with PAH, except those with CHD and pulmonary-to-systemic shunts, have minor degrees of arterial hypoxaemia at rest, unless they have a patent foramen ovale. Data show that nocturnal oxygen therapy does not modify the natural history of advanced Eisenmenger syndrome [324]. In the absence of robust data on the use of oxygen in patients with PAH, guidance is based on evidence in patients with COPD [325]; when PaO_2 is <8 kPa (60 mmHg; alternatively, SaO_2 <92%) on at least two occasions, patients are advised to take oxygen to achieve a PaO_2 >8 kPa. Ambulatory oxygen may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise [326, 327]. Nocturnal oxygen therapy should be considered in case of sleep-related desaturation [328].

6.3.1.5. Cardiovascular drugs

No data from rigorous clinical trials are available on the usefulness and safety of drugs that are effective in systemic hypertension or left-sided HF, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor–neprilysin inhibitors (ARNIs), sodium–glucose cotransporter-2 inhibitors (SGLT-2is), beta-blockers, or ivabradine in patients with PAH. In this group of patients, these drugs may lead to potentially dangerous drops in blood pressure, heart rate, or both. Likewise, the efficacy of digoxin/digitoxin has not been documented in PAH, although these drugs may be administered to slow ventricular rate in patients with PAH who develop atrial tachyarrhythmias.

6.3.1.6. Anaemia and iron status

Iron deficiency is common in patients with PAH and is defined by serum ferritin <100 µg/L, or serum ferritin 100–299 µg/L and transferrin saturation <20% [329]. The underlying pathological mechanisms are complex [330–333]. In patients with PAH, iron deficiency is associated with impaired myocardial function, aggravated symptoms, and increased mortality risk [333, 334]. Based on these data, regular monitoring of iron status (serum iron, ferritin, transferrin saturation, soluble transferrin receptors) is recommended in patients with PAH.

In patients with severe iron deficiency anaemia (Hb <7–8 g/dL), i.v. supplementation is recommended [335–337]. Oral iron formulations containing ferrous (Fe^{2+}) sulfate, ferrous gluconate, and ferrous fumarate are often poorly tolerated, and drug efficacy may be impaired in patients with PAH [330, 331]. Ferric maltol is a new, orally available formulation of ferric (Fe^{3+}) iron and maltol. One small, open-label study suggested good tolerability and efficacy in patients with severe PH with mild-to-moderate iron deficiency and anaemia [338]. In contrast, two small, 12 week, randomized, cross-over trials studying iron supplementation in PAH patients without anaemia provided no significant clinical benefit [339]. Randomized controlled trials comparing oral and i.v. iron supplementation in patients with PAH are lacking.

6.3.1.7. Vaccination

As a general health care measure, it is recommended that patients with PAH be vaccinated at least against influenza, *Streptococcus pneumoniae*, and SARS-CoV-2.

6.3.1.8. Psychosocial support

Receiving a diagnosis of PH—often after a substantial delay—and experiencing the physical limitations have a substantial impact on psychological, emotional, and social aspects of patients and their families. Symptoms of depression and anxiety, as well as adjustment disorders, have a high prevalence in patients with PAH. Pulmonary arterial hypertension also has grave repercussions on ability to work and income [281, 340–344].

Empathic and hopeful communication is essential for physicians caring for patients with PAH. Awareness and knowledge about the disease and its treatment options empower patients to engage in shared decision-making. Adequate diagnostic screening tools are the key to identifying patients in need of referral for psychological/psychiatric support, including psychopharmacological medication [345], or social assistance. Patient support groups may play an important role, and patients should be advised to join such groups. Given the life-limiting character of PAH, advanced care planning with referral to specialist palliative care services should be supported at the right time [346].

6.3.1.9. Adherence to treatments

Adhering to medical therapy is key to successfully managing PAH. In general, factors that affect adherence are patient related (*e.g.* demographics, cognitive impairment, polypharmacy, adverse reactions/side effects, psychological health, health literacy, patient understanding of the treatment rationale, and comorbidities), physician related (expertise, awareness of guidelines, and multidisciplinary team approach), and health care system related (work setting, access to treatments, and cost) [347].

Recent studies have indicated that adherence to drug therapy in patients with PAH may be suboptimal [348, 349]. Given the complexity of PAH treatment, potential side effects, and risks associated with treatment interruptions, adherence should be periodically monitored by a member of the multidisciplinary team, to identify non-adherence and any changes to the treatment regimen spontaneously triggered by patients or non-expert physicians. To promote adherence, it is important to ensure that patients are involved in care decisions and appropriately informed about treatment options and rationale, expectations, side effects, and potential consequences of non-adherence. Patients should be advised that any changes in treatment should be made in cooperation with the PH centre.

6.3.2. Special circumstances

6.3.2.1. Pregnancy and birth control

6.3.2.1.1. Pregnancy. Historically, pregnancy in women with PAH and other forms of severe PH has been associated with maternal mortality rates of up to 56% and neonatal mortality rates of up to 13% [350]. With improved treatment of PAH and new approaches to managing women during pregnancy and the peri-partum period, maternal mortality has declined but remains high, ranging 11–25% [351–355]. For these reasons, previous ESC/ERS Guidelines for the diagnosis and treatment of PH have recommended that patients with PAH should avoid pregnancy [25, 26]. However, there are reports of favourable pregnancy outcomes in women with PH, including, but not limited to, women with IPAH who respond to CCB therapy [353, 354, 356, 357]. Nonetheless, pregnancy remains associated with unforeseeable risks, and may accelerate PH progression [358]. Women with PH can deteriorate at any time during or after pregnancy. Therefore, physicians have a responsibility to inform patients about the risks of pregnancy, so that women and their families can make informed decisions.

Women with poorly controlled disease, indicated by an intermediate- or high-risk profile and signs of RV dysfunction, are at high risk of adverse outcomes; in the event of pregnancy, they should be carefully counselled and early termination should be advised. For patients with well-controlled disease, a low-risk profile, and normal or near-normal resting haemodynamics who consider becoming pregnant, individual counselling and shared decision-making are recommended. In such cases, alternatives such as adoption and surrogacy may also be explored. Pre-conception genetic counselling should also be considered in HPAH.

Women with PH who become pregnant or present during pregnancy with newly diagnosed PAH should be treated, whenever possible, in centres with a multidisciplinary team experienced in managing PH in pregnancy. If pregnancy is continued, PAH therapy may have to be adjusted. It is recommended to stop endothelin receptor antagonists (ERAs), riociguat, and selexipag because of potential or unknown teratogenicity [359]. Despite limited evidence, CCBs, PDE5is, and inhaled/i.v./subcutaneous (s.c.) prostacyclin analogues are considered safe during pregnancy [356, 360].

Pregnancy in PH is a very sensitive topic and requires empathic communication. Psychological support should be offered whenever needed.

6.3.2.1.2. Contraception. Women with PH of childbearing potential should be provided with clear contraceptive advice, considering the individual needs of the woman but recognizing that the implications of contraceptive failure are significant in PH. With appropriate use, many forms of contraception, including oral contraceptives, are highly effective. In patients treated with bosentan, reduced efficacy of hormonal contraceptives should be carefully considered [361]. Using hormonal implants or an intrauterine device are alternative options with low failure rates. Surgical sterilization may be considered but is associated with peri-operative risks. Emergency post-coital hormonal contraception is safe in PH.

6.3.2.2. Surgical procedures

Surgical procedures in patients with PH are associated with an elevated risk of right HF and death. In a prospective, multinational registry including 114 patients with PAH who underwent non-cardiac and non-obstetric surgery, the peri-operative mortality rate was 2% in elective procedures and 15% in emergency procedures [362]. The mortality risk was associated with the severity of PH. The decision to perform surgery should be made by a multidisciplinary team involving a PH physician, and must be based on an individual risk:benefit assessment considering various factors, including indication, urgency, PH severity, and patient preferences. Risk scores to predict the peri-operative mortality risk have been developed but require further validation [363]. General recommendations cannot be made. The same is true regarding the preferred mode of anaesthesia. Pre-operative optimization of PAH therapy should be attempted whenever possible (see also the 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery) [364].

6.3.2.3. Travel and altitude

Hypobaric hypoxia may induce arterial hypoxaemia, additional hypoxic pulmonary vasoconstriction, and increased RV load in PAH [365, 366]. Cabin aircraft pressures are equivalent to altitudes up to 2438 m [367], at which the PaO_2 decreases to that of an inspired O_2 fraction of 15.1% at sea level [365]. However, evidence suggests that short-term (less than 1 day) normobaric hypoxia is generally well tolerated in clinically stable patients with PAH [365, 368–372]. In-flight oxygen administration is advised for patients using oxygen at sea level and for those with PaO_2 <8 kPa (60 mmHg) or SaO_2 <92% [25, 26, 325, 369, 372]. An oxygen flow rate of 2 L/min will raise inspired oxygen pressure to values as at sea level, and patients already using oxygen at sea level should increase their oxygen flow rate [25, 26, 373].

As the effects of moderate to long-term (hours–days) hypoxia exposure in PAH remain largely unexplored [374, 375], patients should avoid altitudes >1500 m without supplemental oxygen [25, 26, 369]. However, patients with PAH who are not hypoxaemic at sea level have tolerated day trips to 2500 m reasonably well [376]. Patients should travel with written information about their disease, including a medication list, bring extra doses of their medication, and be informed about local PH centres near their travel destination [25, 26].

RECOMMENDATION TABLE 5 Recommendations for general measures and special circumstances

Recommendations	Class[a]	Level[b]
General measures		
Supervised exercise training is recommended in patients with PAH under medical therapy [314, 315, 317]	I	A
Psychosocial support is recommended in patients with PAH	I	C
Immunization of patients with PAH against SARS-CoV-2, influenza, and *Streptococcus pneumoniae* is recommended	I	C
Diuretic treatment is recommended in patients with PAH with signs of RV failure and fluid retention	I	C
Long-term oxygen therapy is recommended in patients with PAH whose arterial blood oxygen pressure is <8 kPa (60 mmHg)[c]	I	C
In the presence of iron-deficiency anaemia, correction of iron status is recommended in patients with PAH	I	C
In the absence of anaemia, iron repletion may be considered in patients with PAH with iron deficiency	IIb	C
Anticoagulation is not generally recommended in patients with PAH but may be considered on an individual basis	IIb	C
The use of ACEis, ARBs, ARNIs, SGLT-2is, beta-blockers, or ivabradine is not recommended in patients with PAH unless required by comorbidities (*i.e.* high blood pressure, coronary artery disease, left HF, or arrhythmias)	III	C
Special circumstances		
In-flight oxygen administration is recommended for patients using oxygen or whose arterial blood oxygen pressure is <8 kPa (60 mmHg) at sea level	I	C
For interventions requiring anaesthesia, multidisciplinary consultation at a PH centre to assess risk and benefit should be considered	IIa	C

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HF, heart failure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RV, right ventricle; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SGLT-2i, sodium–glucose cotransporter-2 inhibitor. [a]Class of recommendation. [b]Level of evidence. [c]Measured on at least two occasions.

RECOMMENDATION TABLE 6 Recommendations for women of childbearing potential

Recommendations	Class[a]	Level[b]
It is recommended that women of childbearing potential with PAH are counselled at the time of diagnosis about the risks and uncertainties associated with becoming pregnant; this should include advice against becoming pregnant, and referral for psychological support where needed	I	C

Continued

RECOMMENDATION TABLE 6 Continued

Recommendations	Class[a]	Level[b]
It is recommended to provide women of childbearing potential with PAH with clear contraceptive advice, considering the individual needs of the woman but recognizing that the implications of contraceptive failure are significant in PAH	I	C
It is recommended that women with PAH who consider pregnancy or who become pregnant receive prompt counselling in an experienced PH centre, to facilitate genetic counselling and shared decision-making, and to provide psychological support to the patients and their families where needed	I	C
For women with PAH having termination of pregnancy, it is recommended that this be performed in PH centres, with psychological support provided to the patient and their family	I	C
For women with PAH who desire to have children, where available, adoption and surrogacy with pre-conception genetic counselling may be considered	IIb	C
As teratogenic potential has been reported in preclinical models for endothelin receptor antagonists and riociguat, these drugs are not recommended during pregnancy [359, 377]	III	B

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension. [a]Class of recommendation. [b]Level of evidence.

6.3.3. Pulmonary arterial hypertension therapies

6.3.3.1. Calcium channel blockers

Patients with PAH who respond favourably to acute vasoreactivity testing (Figure 8) may respond favourably to treatment with CCBs [129, 146]. Less than 10% of patients with IPAH, HPAH, or DPAH are responders, while an acute vasodilator response does not predict a favourable long-term response to CCBs in patients with other forms of PAH [129, 146, 378]. The CCBs that have predominantly been used in PAH are nifedipine, diltiazem, and amlodipine [129, 146]. Amlodipine and felodipine are increasingly being used in clinical practice due to their long half-life and good tolerability. The daily doses that have shown efficacy in PAH are relatively high and they must be reached progressively (Table 19). The most common adverse events are systemic hypotension and peripheral oedema.

Patients who meet the criteria for a positive acute vasodilator response and treated with CCBs should be closely followed for safety and efficacy, with a complete reassessment after 3–6 months of therapy, including RHC. Additional acute vasoreactivity testing should be performed at re-evaluation to detect persistent vasodilator response, supporting possible increases in CCB dosage. Patients with a satisfactory chronic response present with WHO-FC I/II and marked haemodynamic improvement (ideally, mPAP <30 mmHg and PVR <4 WU) while on CCB therapy. In the absence of a satisfactory response, additional PAH therapy should be instituted. In some cases, a combination of CCBs with approved PAH drugs is required because of clinical deterioration with CCB withdrawal attempts. Patients who have not undergone a vasoreactivity study or those with a negative test should not be started on CCBs because of potentially severe side effects (*e.g.* severe hypotension, syncope, and RV failure), unless prescribed at standard doses for other indications [379].

RECOMMENDATION TABLE 7 Recommendations for the treatment of vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension

Recommendations	Class[a]	Level[b]
High doses of CCBs are recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing	I	C
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH, or DPAH treated with high doses of CCBs	I	C
Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked haemodynamic improvement (mPAP <30 mmHg and PVR <4 WU)	I	C
Initiating PAH therapy is recommended in patients who remain in WHO-FC III or IV or those without marked haemodynamic improvement after high doses of CCBs	I	C
In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered	IIa	C

Continued

RECOMMENDATION TABLE 7 Continued		
Recommendations	**Class[a]**	**Level[b]**
CCBs are not recommended in patients without a vasoreactivity study or non-responders, unless prescribed for other indications (*e.g.* Raynaud's phenomenon)	III	C

CCB, calcium channel blocker; DPAH, drug-associated pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WHO-FC, World Health Organization functional class; WU, Wood units. [a]Class of recommendation. [b]Level of evidence.

6.3.3.2. Endothelin receptor antagonists

Binding of endothelin-1 to endothelin receptors A and B on PA smooth-muscle cells promotes vasoconstriction and proliferation (Figure 7) [380]. Endothelin B receptors are mostly expressed on pulmonary endothelial cells, promoting vasodilation through accelerated production of prostacyclin and

TABLE 19 Dosing of pulmonary arterial hypertension medications in adults

	Starting dose	**Target dose**
Calcium channel blockers		
Amlodipine	5 mg o.d.	15–30 mg o.d.[a]
Diltiazem	60 mg b.i.d.[b]	120–360 mg b.i.d.[b]
Felodipine	5 mg o.d.	15–30 mg o.d.[a]
Nifedipine	10 mg t.i.d.	20–60 mg b.i.d. or t.i.d.
Endothelin receptor antagonists (oral administration)		
Ambrisentan	5 mg o.d.	10 mg o.d.
Bosentan	62.5 mg b.i.d.	125 mg b.i.d.
Macitentan	10 mg o.d.	10 mg o.d.
Phosphodiesterase 5 inhibitors (oral administration)		
Sildenafil	20 mg t.i.d.	20 mg t.i.d.[c]
Tadalafil	20 or 40 mg o.d.	40 mg o.d.
Prostacyclin analogues (oral administration)		
Beraprost sodium	20 µg t.i.d.	Maximum tolerated dose up to 40 µg t.i.d.
Beraprost extended release	60 µg b.i.d.	Maximum tolerated dose up to 180 µg b.i.d.
Treprostinil	0.25 mg b.i.d. or 0.125 mg t.i.d.	Maximum tolerated dose
Prostacyclin receptor agonist (oral administration)		
Selexipag	200 µg b.i.d.	Maximum tolerated dose up to 1600 µg b.i.d.
Soluble guanylate cyclase stimulator (oral administration)		
Riociguat[d]	1 mg t.i.d.	2.5 mg t.i.d.
Prostacyclin analogues (inhaled administration)		
Iloprost[e]	2.5 µg 6–9 times per day	5.0 µg 6–9 times per day
Treprostinil[e]	18 µg 4 times per day	54–72 µg 4 times per day
Prostacyclin analogues (i.v. or s.c. administration)		
Epoprostenol i.v.	2 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 16–30 ng/kg/min, with wide individual variability
Treprostinil s.c. or i.v.	1.25 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 25–60 ng/kg/min, with wide individual variability

b.i.d., twice daily; i.v., intravenous; o.d., once daily; s.c., subcutaneous; t.i.d., three times daily. Dosages are those commonly used in clinical practice. This does not exclude the use of alternative dosages. [a]The daily dosages of amlodipine and felodipine can be administered in a single dose or divided into two doses. [b]There are different release formulations of diltiazem, some of which should be administered o.d. or t.i.d. [c]Sildenafil is approved at a dose of 20 mg t.i.d. but doses used in practice vary widely and are sometimes higher. [d]In patients at risk of systemic hypotension, riociguat may be started at 0.5 mg t.i.d. [e]Doses provided are for nebulizers and may differ with the use of other formulations and other inhalation devices.

nitric oxide, and clearance of endothelin-1 [380]. Nevertheless, selective blocking of endothelin A receptors alone or non-selective blocking of both A and B receptors has shown similar effectiveness in PAH [380]. Endothelial receptor antagonists have teratogenic effects and should not be used during pregnancy [381].

6.3.3.2.1. Ambrisentan. Ambrisentan is an oral ERA that preferentially blocks the endothelin A receptors. The approved dosages in adults are 5 mg and 10 mg o.d. In patients with PAH, it has demonstrated efficacy for symptoms, exercise capacity, haemodynamics, and time to clinical worsening [382]. An increased incidence of peripheral oedema was reported with ambrisentan use, while there was no increased incidence of abnormal liver function.

6.3.3.2.2. Bosentan. Bosentan is an oral, dual ERA that improves exercise capacity, WHO-FC, haemodynamics, and time to clinical worsening in patients with PAH [383]. The approved target dose in adults is 125 mg b.i.d. Dose-dependent increases in liver transaminases can occur in ∼10% of treated patients (reversible after dose reduction or discontinuation) [384]. Thus, liver function testing should be performed monthly in patients receiving bosentan [384]. Due to pharmacokinetic interactions, bosentan may render hormonal contraceptives unreliable and lower serum levels of warfarin, sildenafil, and tadalafil [361, 385–387].

6.3.3.2.3. Macitentan. Macitentan is an oral, dual ERA that has been found to increase exercise capacity and reduce a composite endpoint of clinical worsening in patients with PAH [167]. While no liver toxicity has been shown, a reduction in Hb to ⩽8 g/dL was observed in 4.3% of patients receiving 10 mg of macitentan [167].

6.3.3.3. Phosphodiesterase 5 inhibitors and guanylate cyclase stimulators

Stimulating soluble guanylate cyclase (sGC) by nitric oxide results in production of the intracellular second messenger cyclic guanosine monophosphate (cGMP) (Figure 7). This pathway is controlled by a negative feedback loop through degradation of cGMP via different phosphodiesterases, among which subtype 5 (PDE5) is abundantly expressed in the pulmonary vasculature [388]. Phosphodiesterase 5 inhibitors and sGC stimulators must not be combined with each other and with nitrates, as this can result in systemic hypotension [389].

6.3.3.3.1. Sildenafil. Sildenafil is an orally active, potent, and selective inhibitor of PDE5. Several RCTs of patients with PAH treated with sildenafil (with or without background therapy) have confirmed favourable results on exercise capacity, symptoms, and/or haemodynamics [390–392]. The approved dose of sildenafil is 20 mg t.i.d. Most side effects of sildenafil are mild to moderate and mainly related to vasodilation (headache, flushing, and epistaxis).

6.3.3.3.2. Tadalafil. Tadalafil is a once-daily administered PDE5i. An RCT of 406 patients with PAH (53% on background bosentan therapy) treated with tadalafil at doses up to 40 mg o.d. showed favourable results on exercise capacity, symptoms, haemodynamics, and time to clinical worsening [393]. The side effect profile was similar to that of sildenafil.

6.3.3.3.3. Riociguat. While PDE5is augment the nitric oxide–cGMP pathway by slowing cGMP degradation, sGC stimulators enhance cGMP production by directly stimulating the enzyme, both in the presence and absence of endogenous nitric oxide [394]. An RCT of 443 patients with PAH (44% and 6% on background therapy with ERAs or prostacyclin analogues, respectively) treated with riociguat up to 2.5 mg t.i.d. showed favourable results on exercise capacity, haemodynamics, WHO-FC, and time to clinical worsening [395]. The side effect profile was similar to that of PDE5is.

6.3.3.4. Prostacyclin analogues and prostacyclin receptor agonists

The prostacyclin metabolic pathway (Figure 7) is dysregulated in patients with PAH, with less prostacyclin synthase expressed in PAs and reduced prostacyclin urinary metabolites [396]. Prostacyclin analogues and prostacyclin receptor agonists induce potent vasodilation, inhibit platelet aggregation, and also have both cytoprotective and anti-proliferative activities [397]. The most common adverse events observed with these compounds are related to systemic vasodilation and include headache, flushing, jaw pain, and diarrhoea.

6.3.3.4.1. Epoprostenol. Epoprostenol has a short half-life (3–5 min) and needs continuous i.v. administration via an infusion pump and a permanent tunnelled catheter. A thermo-stable formulation is available to maintain stability up to 48 h [398]. Its efficacy has been demonstrated in three unblinded RCTs in patients with IPAH (WHO-FC III and IV) [399, 400] and SSc-associated PAH [401].

Epoprostenol improved symptoms, exercise capacity, haemodynamics, and mortality [399]. Long-term, persistent efficacy has also been shown in IPAH [212, 245], as well as in other associated PAH conditions [402–404]. Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. Recommendations for preventing central venous catheter bloodstream infections have been proposed [405, 406].

6.3.3.4.2. Iloprost. Iloprost is a prostacyclin analogue approved for inhaled administration. Inhaled iloprost has been evaluated in one RCT, in which six to nine repetitive iloprost inhalations were compared with placebo in treatment-naïve patients with PAH or CTEPH [407]. The study showed an increase in exercise capacity and improvement in symptoms, PVR, and clinical events in the iloprost group compared with the placebo group.

6.3.3.4.3. Treprostinil. Treprostinil is available for s.c., i.v., inhaled, and oral administration. Treprostinil s.c. improved exercise capacity, haemodynamics, and symptoms in PAH [408]. Infusion-site pain was the most common adverse effect, which led to treatment discontinuation in 8% of cases [408]. Based on its chemical stability, i.v. treprostinil may also be administered via implantable pumps, improving convenience and likely decreasing the occurrence of line infections [409, 410].

Inhaled treprostinil improved the 6MWD, NT-proBNP, and quality of life measures in patients with PAH on background therapy with either bosentan or sildenafil [411]. Inhaled treprostinil is not approved in Europe.

Oral treprostinil has been evaluated in two RCTs of patients with PAH on background therapy with bosentan and/or sildenafil. In both trials, the primary endpoint—6MWD—did not reach statistical significance [412, 413]. An additional RCT in treatment-naïve patients with PAH showed improved 6MWD [414]. An event-driven RCT that enrolled 690 patients with PAH demonstrated that oral treprostinil reduced the risk of clinical worsening events in patients who were receiving oral monotherapy with ERAs or PDE5is [415]. Oral treprostinil is not approved in Europe.

6.3.3.4.4. Beraprost. Beraprost is a chemically stable and orally active prostacyclin analogue. Two RCTs have shown a modest, short-term improvement in exercise capacity in patients with PAH [416, 417]; however, there were no haemodynamic improvements or long-term outcome benefits. Beraprost is not approved in Europe.

6.3.3.4.5. Selexipag. Selexipag is an orally available, selective, prostacyclin receptor agonist that is chemically distinct from prostacyclin, with different pharmacology. In a pilot RCT in patients with PAH (receiving stable ERA and/or PDE5i therapy), selexipag reduced PVR after 17 weeks [418]. An event-driven, phase 3 RCT that enrolled 1156 patients [419] showed that selexipag alone or on top of mono or double therapy with an ERA and/or a PDE5i reduced the relative risk of composite morbidity/mortality events by 40%. The most common side effects were headache, diarrhoea, nausea, and jaw pain.

6.3.4. Treatment strategies for patients with idiopathic, heritable, drug-associated, or connective tissue disease-associated pulmonary arterial hypertension

Pulmonary arterial hypertension is a rare and life-threatening disease and should be managed, where possible, at PH centres in close collaboration with the patient's local physicians.

This section describes drug treatment and is focused on non-vasoreactive patients with IPAH/HPAH/DPAH and on patients with PAH associated with connective tissue disease (PAH-CTD). Information on the dosing of PAH medication is summarized in Table 19. For other forms of PAH, treatment strategies have to be modified (see Section 7). The approach to vasoreactive patients with IPAH/HPAH/DPAH is described in Section 6.3.3.1.

In addition to targeted drug treatment, the comprehensive management of patients with PAH includes general measures that may include supplementary oxygen, diuretics to optimize volume status, psychosocial support, and standardized exercise training (Section 6.3.1) [315]. Prior to the treatment decisions, patients and their next of kin should be provided with appropriate and timely information about the risks and benefits of the treatment options so they can make the final, informed, and joint decision about the treatment with the medical team. Treatment decisions in patients with IPAH/HPAH/DPAH or PAH-CTD should be stratified according to the presence or absence of cardiopulmonary comorbidities (Section 6.3.4.3) and according to disease severity assessed by risk stratification (Section 6.2.7).

6.3.4.1. Initial treatment decision in patients without cardiopulmonary comorbidities

The initial treatment of patients with PAH should be based on a comprehensive, multiparameter risk assessment, considering disease type and severity, comorbidities, access to therapies, economic aspects, and patient preference.

The following considerations predominantly apply to patients with IPAH/HPAH/DPAH or PAH-CTD without cardiopulmonary comorbidities, as patients with comorbidities were under-represented in the clinical studies addressing treatment strategies and combination therapy in patients with PAH. Treatment considerations for patients with PAH and cardiopulmonary comorbidities are summarized in Section 6.3.4.3.

For patients presenting at low or intermediate risk, initial combination therapy with an ERA and a PDE5i is recommended. This approach was assessed in the AMBITION study, which compared initial combination therapy using ambrisentan at a target dose of 10 mg o.d. and tadalafil at a target dose of 40 mg o.d. with initial monotherapy with either drug [166]. AMBITION predominantly included patients with IPAH/HPAH/DPAH or PAH-CTD. The primary endpoint was the time to first clinical failure event (a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response). The hazard ratio (HR) for the primary endpoint in the combination-therapy group *versus* the pooled monotherapy group was 0.50 (95% confidence interval [CI], 0.35–0.72; $P<0.001$) and there were significant improvements in 6MWD and NT-proBNP with initial combination therapy. At the end of the study, 10% of the patients assigned to initial combination therapy had died compared with 14% of the patients assigned to initial monotherapy (HR 0.67; 95% CI, 0.42–1.08) [420].

In the TRITON study, treatment-naïve patients with PAH were assigned to initial dual-combination therapy with macitentan and tadalafil, or initial triple-combination therapy with macitentan 10 mg o.d., tadalafil at a target dose of 40 mg o.d., and selexipag up to 1600 µg o.d [421]. TRITON predominantly included patients with IPAH/HPAH/DPAH or PAH-CTD. At week 26, PVR was reduced by 52% and 54%, with double- or triple-combination therapy, respectively, and 6MWD had increased by 55 m and 56 m, respectively. The geometric means of the NT-proBNP ratio from baseline to week 26 were 0.25 and 0.26, respectively. Hence, TRITON did not show a benefit of oral triple- *versus* oral double-combination therapy but confirmed that substantial improvements in haemodynamics and exercise capacity can be obtained with initial ERA/PDE5i combination therapy. Further studies are needed to determine whether oral triple-combination therapy impacts long-term outcomes.

Based on the evidence generated by these and other studies [303, 422–424], initial dual-combination therapy with an ERA and a PDE5i is recommended for newly diagnosed patients who present at low or intermediate risk. Initial oral triple-combination therapy is not recommended, given the current lack of evidence supporting this strategy. In patients presenting at high risk, initial triple-combination therapy including an i.v./s.c. prostacyclin analogue should be considered [426, 427]. While it is acknowledged that the evidence for this approach is limited to case series, there is consensus that this strategy has the highest likelihood of success, especially in view of registry data from France showing that initial triple-combination therapy including an i.v./s.c. prostacyclin analogue was associated with better long-term survival than monotherapy or dual-combination therapy [428]. Initial triple-combination therapy including an i.v./s.c. prostacyclin analogue should also be considered in patients at intermediate risk presenting with severe haemodynamic impairment (*e.g.* RAP $\geqslant$20 mmHg, CI <2.0 L/min/m^2, SVI <31 mL/m^2, and/or PVR $\geqslant$12 WU) [238, 426].

The recommendations for initial oral double-combination therapy are based on PICO question I (Supplementary Data, Section 6.2). Although the quality of evidence is low, initial oral combination therapy with an ERA and a PDE5i achieves important targets in symptom improvement (functional class), exercise capacity, cardiac biomarkers, and reduction of hospitalizations.

RECOMMENDATION TABLE 8A Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present without cardiopulmonary comorbidities[a]

Recommendations	Class[b]	Level[c]
Recommendations for initial therapy		
In patients with IPAH/HPAH/DPAH who present at high risk of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be considered[d]	IIa	C

Continued

RECOMMENDATION TABLE 8A Continued

Recommendations	Class[b]	Level[c]
Recommendations for treatment decisions during follow-up		
In patients with IPAH/HPAH/DPAH who present at intermediate–low risk of death while receiving ERA/PDE5i therapy, addition of selexipag should be considered [419]	IIa	B
In patients with IPAH/HPAH/DPAH who present at intermediate–high or high risk of death while receiving ERA/PDE5i therapy, addition of i.v./s.c. prostacyclin analogues and referral for LTx evaluation should be considered	IIa	C
In patients with IPAH/HPAH/DPAH who present at intermediate–low risk of death while receiving ERA/PDE5i therapy, switching from PDE5i to riociguat may be considered [429]	IIb	B

RECOMMENDATION TABLE 8B Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present without cardiopulmonary comorbidities[a]

Recommendations	GRADE Quality of evidence	GRADE Strength of recommendation	Class[b]	Level[c]
Recommendations for initial therapy				
In patients with IPAH/HPAH/DPAH who present at low or intermediate risk of death, initial combination therapy with a PDE5i and an ERA is recommended [166]	Low	Conditional	I	B

CI, cardiac index; DLCO, Lung diffusion capacity for carbon monoxide; DPAH, drug-associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; HFpEF, heart failure with preserved ejection fraction; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; i.v., intravenous; LTx, lung transplantation; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PVR, pulmonary vascular resistance; RAP, right atrial pressure; s.c., subcutaneous; SVI, stroke volume index; WU, Wood units. [a]Cardiopulmonary comorbidities are predominantly encountered in elderly patients and include risk factors for HFpEF such as obesity, diabetes, coronary heart disease, a history of hypertension, and/or a low DLCO. [b]Class of recommendation. [c]Level of evidence. [d]Initial triple-combination therapy including i.v./s.c. prostacyclin analogues may also be considered in patients presenting at intermediate risk but severe haemodynamic impairment (*e.g.* RAP ⩾20 mmHg, CI <2.0 L/min/m^2, SVI <31 mL/m^2, and/or PVR ⩾12 WU).

RECOMMENDATION TABLE 9 Recommendations for initial oral drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension without cardiopulmonary comorbidities

Recommendations	Class[a]	Level[b]
Initial combination therapy with ambrisentan and tadalafil is recommended [166, 420, 423]	I	B
Initial combination therapy with macitentan and tadalafil is recommended [421, 430]	I	B
Initial combination therapy with other ERAs and PDE5is should be considered [303]	IIa	B
Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended [421]	III	B

ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase 5 inhibitor. [a]Class of recommendation. [b]Level of evidence.

6.3.4.2. Treatment decisions during follow-up in patients without cardiopulmonary comorbidities

Patients with PAH require regular follow-up, including risk stratification and an assessment of patient concordance with therapy. Patients who achieve a low-risk status have a much superior long-term survival compared with patients with intermediate- or high-risk status [292, 295, 296]. Achieving and maintaining a low-risk profile is therefore a key objective in managing patients with PAH.

Several clinical trials have assessed the safety and efficacy of sequential combination therapy in patients with PAH. SERAPHIN enrolled 742 patients with PAH, mostly with IPAH/HPAH/DPAH and PAH-CTD, of whom 63.7% were receiving other PAH medication at the time of enrolment, mostly sildenafil [167]. In the subgroup of patients with background PAH therapy, macitentan at a daily dose of 10 mg reduced the risk of clinical worsening events compared with placebo (HR 0.62; 95% CI, 0.43–0.89) [167].

GRIPHON assessed the safety and efficacy of selexipag [419]. This study enrolled 1156 patients with PAH, also mostly with IPAH/HPAH/DPAH or PAH-CTD, who were treatment naïve or receiving background therapy with an ERA, PDE5i, or a combination of both. Selexipag at a dose of up to 1600 µg b.i.d. was associated with a reduced risk of clinical worsening events independent of the background medication. In patients receiving ERA/PDE5i combination therapy (n=376), the risk of clinical worsening events was lower with selexipag than with placebo (HR 0.63; 95% CI, 0.44–0.90) [431].

The effects of combination therapy on long-term survival in patients with PAH remain unclear. A 2016 meta-analysis demonstrated that combination therapy (initial and sequential) was associated with a significant risk reduction for clinical worsening (relative risk [RR] 0.65; 95% CI, 0.58–0.72; P<0.0001) [432]; however, all-cause mortality was not improved (RR 0.86; 95% CI, 0.72–1.03; P=0.09) and a substantial proportion of patients had clinical worsening events or died despite receiving combination therapy. In addition, registry data showed that the use of combination therapy increased since 2015 but there was no clear improvement in overall survival rates [428, 433, 434]. These data were corroborated by a study showing that less than half of patients receiving initial combination therapy with an ERA and a PDE5i achieved and maintained a low-risk profile [422].

Switching from PDE5is to riociguat has also been investigated as a treatment-escalation strategy [429, 435]. REPLACE was a randomized, controlled, open-label study that enrolled patients on a PDE5i-based therapy who were in WHO-FC III and had a 6MWD of 165–440 m [429]. The study predominantly included patients with IPAH/HPAH/DPAH or PAH-CTD who were randomized to continue their PDE5i or to switch from a PDE5i to riociguat up to 2.5 mg t.i.d. The study met its primary endpoint, termed 'clinical improvement', which was a composite of pre-specified improvements in 6MWD, WHO-FC, and NT-proBNP at week 24. Clinical improvement at week 24 was demonstrated in 41% of the patients who switched to riociguat and in 20% of the patients who maintained their PDE5i (odds ratio [OR] 2.78; 95% CI, 1.53–5.06; P=0.0007). In addition, fewer patients in the riociguat group experienced a clinical worsening event (OR 0.10; 95% CI, 0.01–0.73; P=0.0047).

Based on the evidence summarized above, the following recommendations for treatment decisions during follow-up are:

i) In patients who achieve a low-risk status with their initial PAH therapy, continuation of treatment is recommended.
ii) In patients who are at intermediate–low risk despite receiving ERA/PDE5i therapy, adding selexipag should be considered to reduce the risk of clinical worsening. In these patients, switching from PDE5i to riociguat may also be considered.
iii) In patients who are at intermediate–high or high risk while receiving oral therapies, the addition of i.v. epoprostenol or i.v./s.c. treprostinil and referral for LTx evaluation should be considered [309, 436]. If adding i.v./s.c. prostacyclin analogues is unfeasible, adding selexipag or switching from PDE5i to riociguat may be considered.

RECOMMENDATION TABLE 10 Recommendations for sequential drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension

Recommendations	Class[a]	Level[b]
General recommendation for sequential combination therapy		
It is recommended to base treatment escalations on risk assessment and general treatment strategies (see Figure 9)	I	C
Evidence from studies with a composite morbidity/mortality endpoint as primary outcome measure		
Addition of macitentan to PDE5is or oral/inhaled prostacyclin analogues is recommended to reduce the risk of morbidity/mortality events [167, 168, 437]	I	B
Addition of selexipag to ERAs[c] and/or PDE5is is recommended to reduce the risk of morbidity/mortality events [418, 419]	I	B
Addition of oral treprostinil to ERA or PDE5i/riociguat monotherapy is recommended to reduce the risk of morbidity/mortality events [412, 413, 415]	I	B
Addition of bosentan to sildenafil is not recommended to reduce the risk of morbidity/mortality events [419]	III	B

Continued

RECOMMENDATION TABLE 10 Continued

Recommendations	Class[a]	Level[b]
Evidence from studies with change in 6MWD as primary outcome measure		
Addition of sildenafil to epoprostenol is recommended to improve exercise capacity [392, 438]	I	B
Addition of inhaled treprostinil to sildenafil or bosentan monotherapy should be considered to improve exercise capacity [411, 439]	IIa	B
Addition of riociguat to bosentan should be considered to improve exercise capacity [395, 440]	IIa	B
Addition of tadalafil to bosentan may be considered to improve exercise capacity [393]	IIb	C
Addition of inhaled iloprost to bosentan may be considered to improve exercise capacity [441, 442]	IIb	B
Addition of ambrisentan to sildenafil may be considered to improve exercise capacity [443]	IIb	C
Addition of bosentan to sildenafil may be considered to improve exercise capacity [419, 444]	IIb	C
Addition of sildenafil to bosentan may be considered to improve exercise capacity [444–446]	IIb	C
Other sequential double- or triple-combination therapies may be considered to improve exercise capacity and/or alleviate PH symptoms	IIb	C
Evidence from studies with safety of combination therapy as primary outcome measure		
Combining riociguat and PDE5is is not recommended[d] [389]	III	B

6MWD, 6-minute walking distance; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension. [a]Class of recommendation. [b]Level of evidence. [c]ERAs used in the GRIPHON study were bosentan and ambrisentan. [d]The PATENT plus study investigated the combination of sildenafil and riociguat; however, combining riociguat with any PDE5i is contraindicated.

6.3.4.3. Pulmonary arterial hypertension with cardiopulmonary comorbidities

Over the past decade, the demographics and characteristics of patients with IPAH have changed, especially in industrialized countries [447]. In several contemporary registries, the average age of patients diagnosed with IPAH is ∼60 years or older [161, 295, 299, 447, 448]. Many elderly patients have cardiopulmonary comorbidities, making the distinction from group 2 and group 3 PH challenging. Among elderly patients diagnosed with IPAH, two main disease phenotypes have emerged. One phenotype (herein called the left heart phenotype) consists of elderly, mostly female patients with risk factors for HFpEF (*e.g.* hypertension, obesity, diabetes, or coronary heart disease) but pre-capillary PH rather than post-capillary PH [449, 450]; ∼30% of these patients have a history of atrial fibrillation [161]. The other phenotype (called the cardiopulmonary phenotype) consists of elderly, predominantly male patients who have a low DLCO (<45% of the predicted value), are often hypoxaemic, have a significant smoking history, and have risk factors for LHD [77, 78, 161, 451]. In a cluster analysis of 841 newly diagnosed patients with IPAH from the COMPERA registry, 12.6% had a classic phenotype of young, mostly female patients without cardiopulmonary comorbidities, while 35.8% presented with a left heart phenotype and 51.6% with a cardiopulmonary phenotype [161].

There are no evidence-based rules for determining a patient's phenotype. The AMBITION study used the presence of more than three risk factors for LHD together with certain haemodynamic criteria to exclude patients from the primary analysis [166]. However, the COMPERA cluster analysis mentioned above found that the presence of a single risk factor may change the phenotype [161]. Pending further data, it is the overall profile that should be used to determine a patient's phenotype.

Compared with patients without cardiopulmonary comorbidities, patients with cardiopulmonary comorbidities respond less well to PAH medication, are more likely to discontinue this medication due to efficacy failure or lack of tolerability, are less likely to reach a low-risk status, and have a higher mortality risk. While the age-adjusted mortality of patients with the left heart phenotype seems to be similar to that of patients with classical PAH, patients with a cardiopulmonary phenotype and a low DLCO have a particularly high mortality risk [77, 78, 161, 450, 451].

As patients with cardiopulmonary comorbidities were under-represented in or excluded from PAH trials, no evidence-based treatment recommendations can be made for this patient population. Registry data suggest that most physicians use PDE5is as primary treatment for these patients. Endothelin receptor antagonists or PDE5i/ERA combinations are occasionally used, but the drug discontinuation rate is higher than in patients with classical PAH [447, 450]. A subgroup analysis from AMBITION, which assessed the response to PAH therapy in 105 patients who were excluded from the primary analysis set because of a left heart phenotype, found that these patients—compared with patients in the primary analysis set—had less clinical improvement and a higher likelihood of drug discontinuations due to safety and tolerability with both monotherapy and initial combination therapy [449]. Data from the ASPIRE registry demonstrated that patients with IPAH and a cardiopulmonary phenotype had less improvement in exercise capacity and PROMs compared with patients with classical IPAH [451].

In patients with a left heart phenotype, ERA therapy is associated with an elevated risk of fluid retention [449]. Moreover, in patients with a cardiopulmonary phenotype, PAH medication may cause a decline in the peripheral oxygen saturation [452]. There is little published experience on the use of prostacyclin analogues or prostacyclin receptor agonists in this patient population [453].

The lack of solid evidence for treating elderly patients with PAH and cardiopulmonary comorbidities makes treatment recommendations challenging, and patients should be counselled accordingly. In the absence of evidence on treatment strategies in these patients, risk stratification is of limited usefulness in guiding therapeutic decision-making. Initial monotherapy (see Supplementary Data, Table S3) is recommended for most of these patients, with PDE5is being the most widely used compounds according to registry data [161]. Further treatment decisions should be made on an individual basis in collaboration with the PH centre and local physicians.

The treatment algorithm for patients with PAH is shown in Figure 9 and the accompanying section describing the treatment algorithm.

RECOMMENDATION TABLE 11 Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present with cardiopulmonary comorbidities[a]

Recommendations	Class[b]	Level[c]
Recommendations for initial therapy		
In patients with IPAH/HPAH/DPAH and cardiopulmonary comorbidities, initial monotherapy with a PDE5i or an ERA should be considered	IIa	C
Recommendations for treatment decisions during follow-up		
In patients with IPAH/HPAH/DPAH with cardiopulmonary comorbidities who present at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, additional PAH medications may be considered on an individual basis	IIb	C

DPAH, drug-associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor. [a]Cardiopulmonary comorbidities are predominantly encountered in elderly patients and include risk factors for HFpEF such as obesity, diabetes, coronary heart disease, a history of hypertension, and/or a low DLCO. [b]Class of recommendation. [c]Level of evidence.

6.3.5. Drug interactions

Among PAH drugs, clinically relevant pharmacokinetic interactions are observed between bosentan and sildenafil (reduced sildenafil plasma concentration [385]), bosentan and hormonal contraceptives (reduced contraception efficacy [361]), and bosentan and vitamin K antagonists (VKAs) (potential need for VKA dose adjustment [386]). Additional pharmacokinetic interactions of potential clinical relevance are listed in Supplementary Data, Table S4.

6.3.6. Interventional therapy

6.3.6.1. Balloon atrial septostomy and Potts shunt

Balloon atrial septostomy [454, 455], by creating an interatrial shunt, and Potts shunt [456–459], by connecting the left PA and descending aorta, aim to decompress the right heart and increase systemic blood flow, thereby improving systemic oxygen transport despite arterial oxygen desaturation. As these procedures are complex and associated with high risk, including substantial procedure-related mortality, they are rarely performed in patients with PAH and may only be considered in centres with experience in the techniques.

6.3.6.2. Pulmonary artery denervation

The rationale for performing a PA denervation (PADN) is based on the increased sympathetic overdrive characterizing PAH, which is associated with poor outcome [460, 461]. Although the contribution of this mechanism to developing PAH is not completely understood, it is associated with vasoconstriction and vascular remodelling through a baroreflex mediated by stretch receptors located at the bifurcation of the Pas [462, 463]. Applying radiofrequency at the latter acutely and chronically improves haemodynamic variables [464]. However, there is little evidence yet from multicentre RCTs demonstrating a benefit of

PADN in patients already receiving recommended medical therapy. A small multicentre study tested the feasibility of PADN using an intravascular ultrasound catheter in patients receiving dual or triple therapy for PAH [465]; the procedure was safe and associated with a reduction in PVR, and increases in 6MWD and daily activity. Although potentially promising, PADN should be considered experimental.

6.3.7. Advanced right ventricular failure

6.3.7.1. Intensive care unit management

Patients with PH may require intensive care treatment for right HF, comorbidities (including major surgery), or both. The mortality risk is high in such patients [466, 467], and specialized centres should be involved whenever possible. In addition to basic intensive care unit (ICU) standards, RV function in these patients should be carefully monitored. Non-specific clinical signs of right HF with low CO include pale skin with peripheral cyanosis, hypotension, tachycardia, declining urine output, and increasing lactate levels. Non-invasive monitoring should include biomarkers (NT-proBNP and troponin) and echocardiography. Minimum invasive monitoring consists of an upper body central venous catheter to measure central venous pressure and central venous oxygen saturation, the latter reflecting CO. Right heart catheterization or other forms of advanced haemodynamic assessment should be considered in patients with advanced right HF or in complex situations [468].

Treating right HF should focus on treatable triggers such as infection, arrhythmia, anaemia, and other comorbidities. Fluid management is of utmost importance in these patients, most of whom require a negative fluid balance to reduce RV pre-load, thereby improving RV geometry and function [468]. Patients with a low CO may benefit from treatment with inotropes; dobutamine and milrinone are the most frequently used substances in this setting. Maintaining the mean systemic blood pressure >60 mmHg is a key objective when treating right HF, and patients with persistent hypotension may require vasopressors such as norepinephrine or vasopressin. Intubation and invasive mechanical ventilation should be avoided whenever possible in patients with advanced RV failure because of a high risk of further haemodynamic deterioration and death. Pulmonary arterial hypertension medication should be considered on an individual basis, taking into account underlying disease, comorbidities, and existing medication. In patients with newly diagnosed PAH presenting with low CO, combination therapy including i.v./s.c. prostacyclin analogues should be considered [426].

6.3.7.2. Mechanical circulatory support

In specialist centres, various forms of mechanical circulatory support are available for managing RV failure, with veno-arterial extracorporeal membrane oxygenation (ECMO) being the most widely used approach. Mechanical circulatory support has become an established bridging tool to transplantation in patients with irreversible right HF, but is occasionally used as a bridge to recovery in patients with treatable causes and potentially reversible RV failure [468]. No general recommendations can be made regarding the indication for mechanical circulatory support, which needs to be individualized, considering patient factors and local resources [469, 470]. Long-term mechanical support analogous to left ventricular assist devices (LVADs) is not yet available for patients with PH and end-stage right HF.

RECOMMENDATION TABLE 12 Recommendations for intensive care management for pulmonary arterial hypertension

Recommendations	Class[a]	Level[b]
When managing patients with right HF in the ICU, it is recommended to involve physicians with expertise, treat causative factors, and use supportive measures, including inotropes and vasopressors, fluid management, and PAH drugs, as appropriate	I	C
Mechanical circulatory support may be an option for selected patients as bridge to transplantation or to recovery, and interhospital transfer should be considered if such resources are not available on site	IIa	C

HF, heart failure; ICU, intensive care unit; PAH, pulmonary arterial hypertension. [a]Class of recommendation. [b]Level of evidence.

6.3.8. Lung and heart–lung transplantation

Lung transplantation remains an important treatment option for patients with PAH refractory to optimized medical therapy. In patients with PAH, referral to an LTx centre should be considered early (Table 20): 1) when they present with an inadequate response to treatment despite optimized combination therapy; 2) when they present with an intermediate–high or high risk of death (*i.e.* 1-year mortality >10% when estimated with established risk-stratification tools) [471] (see Section 6.2.7), which exceeds the current mortality rate after LTx [472]; 3) when patients have a disease variant that poorly responds to medical therapy, such as PVOD or PCH.

TABLE 20 Criteria for lung transplantation and listing in patients with pulmonary arterial hypertension

Referral	
	Potentially eligible patients for whom LTx might be an option in case of treatment failure
	ESC/ERS intermediate–high or high risk or REVEAL risk score >7 on appropriate PAH medication
	Progressive disease or recent hospitalization for worsening PAH
	Need for i.v. or s.c. prostacyclin therapy
	Known or suspected high-risk variants, such as PVOD or PCH, systemic sclerosis, or large and progressive pulmonary artery aneurysms
	Signs of secondary liver or kidney dysfunction due to PAH or other potentially life-threatening complications, such as recurrent haemoptysis
Listing	
	Patient has been fully evaluated and prepared for transplantation
	ESC/ERS high risk or REVEAL risk score >10 on appropriate PAH medication, usually including i.v. or s.c. prostacyclin analogues
	Progressive hypoxaemia, especially in patients with PVOD or PCH
	Progressive, but not end-stage liver or kidney dysfunction due to PAH, or life-threatening haemoptysis

ERS, European Respiratory Society; ESC, European Society of Cardiology; i.v., intravenous; LTx, lung transplantation; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PVOD, pulmonary veno-occlusive disease; s.c., subcutaneous.

Both heart–lung and bilateral LTx have been performed for PAH. Currently, most patients receive bilateral LTx, while combined heart–lung transplantation is reserved for patients who have additional non-correctable cardiac conditions [473]. With the introduction of the lung allocation score (LAS), waiting list mortality has decreased and the odds of receiving a donor organ have increased [474]. In some countries, an 'exceptional LAS' can be obtained for patients with severe PH. Some other countries not using the LAS have successfully implemented high-priority programmes for these patients [475]. The patient and their next of kin should be fully engaged in the transplant assessment process and informed of the risks and benefits, and the final decision should be jointly made between the patient and medical team (see Section 6.3.1.8). For patients with PAH who survive the early post-transplant period, long-term outcomes are good. A study found that for primary transplant patients with IPAH who survived to 1 year, conditional median survival was 10.0 years [476].

RECOMMENDATION TABLE 13 Recommendations for lung transplantation

Recommendations	Class[a]	Level[b]
It is recommended that potentially eligible candidates are referred for LTx evaluation when they have an inadequate response to oral combination therapy, indicated by an intermediate–high or high risk or by a REVEAL risk score >7	I	C
It is recommended to list patients for LTx who present with a high risk of death or with a REVEAL risk score ⩾10 despite receiving optimized medical therapy including s.c. or i.v. prostacyclin analogues	I	C

i.v., intravenous; LTx, lung transplantation; s.c., subcutaneous. [a]Class of recommendation. [b]Level of evidence.

6.3.9. Evidence-based treatment algorithm

A treatment algorithm for patients with IPAH/HPAH/DPAH or PAH-CTD is shown in Figure 9. The evidence supporting this algorithm has mainly been generated in patients with IPAH/HPAH/DPAH or PAH-CTD who present without cardiopulmonary comorbidities. Patients with HIV-associated PAH, PoPH, and PAH associated with congenital heart disease were not enrolled or under-represented in most PAH therapy trials. Treatment recommendations for these patients are provided in Section 7.

6.3.10. Diagnosis and treatment of pulmonary arterial hypertension complications

6.3.10.1. Arrhythmias

The most common types of arrhythmias observed in PAH are supraventricular, mainly atrial fibrillation and atrial flutter, while the frequency of ventricular arrhythmias and bradyarrhythmias appears to be considerably lower [477–479]. Of note, age is an independent risk factor for atrial arrhythmias.

In prospective studies, the incidence of atrial arrhythmias was 3–25% over an observation time of 5 years in cohorts primarily containing patients with IPAH [479–481].

In the absence of specific evidence for PAH, managing anticoagulation in patients with PAH and atrial arrhythmia should follow the recommendations for patients with other cardiac conditions [477].

Patients with PAH are especially sensitive to haemodynamic stress during atrial arrhythmias due to tachycardia and loss of atrioventricular synchrony. Maintaining sinus rhythm is an important treatment objective in these patients. New-onset arrhythmias frequently lead to clinical deterioration and are associated with increased mortality [481]. Observational studies have shown that a variety of rhythm control strategies are feasible, including pharmacological cardioversion with anti-arrhythmic drugs, electrical cardioversion, and invasive catheter ablation procedures. To achieve or maintain a stable sinus rhythm, prophylaxis with anti-arrhythmic drugs without negative inotropic effects, such as oral amiodarone, should be considered, even if specific data regarding their efficacy are lacking. Low-dose beta-blockers and/or digoxin may be used on an individual patient basis.

Catheter ablation is the preferred approach in managing atrial flutter and some other atrial tachycardias, although catheter ablation in patients with PAH is often more technically challenging than in patients with a structurally normal right heart chamber [482]. The safety and efficacy of ablation techniques for atrial fibrillation specifically in the PAH population are uncertain, and it is possible that, due to remodelling of the RA, non-pulmonary vein triggers may play a more important role than in patients without PAH [483].

6.3.10.2. Haemoptysis

Haemoptysis, ranging from mild to life-threatening, may occur in all forms of PH but is particularly common in HPAH and PAH associated with CHD. Pulmonary bleeding frequently originates from enlarged bronchial arteries [484–486]; hence, the diagnostic evaluation of patients with PAH and haemoptysis should include a contrast-enhanced CT scan with an arterial phase. Even if the source of bleeding cannot be determined, embolization of enlarged bronchial arteries is recommended in patients who present with moderate-to-severe haemoptysis or recurrent episodes of mild haemoptysis. Lung transplant should be considered in patients with recurrent and severe haemoptysis despite optimized treatment.

6.3.10.3. Mechanical complications

Mechanical complications in patients with PAH usually arise from progressive dilatation of the PA and include PA aneurysms, rupture, and dissection, and compression of adjacent structures such as the left main coronary artery, pulmonary veins, main bronchi, and recurrent laryngeal nerves [487–492].

Pulmonary artery aneurysm was independently related to an increased risk of sudden cardiac death in one study [492]. Symptoms and signs are non-specific; in most cases, patients are asymptomatic and these complications are incidentally diagnosed. Pulmonary artery aneurysms are usually detected during echocardiography and best visualized by contrast-enhanced CT or MRI. Treatment options for asymptomatic PA aneurysm or PA dissection are not well defined. LTx has to be considered on an individual basis [490, 493].

For patients with left main coronary artery compression syndrome, percutaneous coronary stenting is an effective and safe treatment [62]. For patients with asymptomatic left main coronary artery compression or non-severe compromise of its anatomy, evaluation with intravascular ultrasound or coronary pressure wire may help to avoid unnecessary interventions [494].

6.3.11. End-of-life care and ethical issues

The clinical course of PAH may be characterized by progressive deterioration and occasional episodes of acute decompensation. Life expectancy is difficult to predict, as patients may either die slowly because of progressive right HF or experience sudden death.

Patient-orientated care is essential in managing PAH. Information about disease severity and possible prognosis should be provided at initial diagnosis but empathic and hopeful communication, as well as yielding hope, is essential, in line with Section 6.3.1.8. At the right time, open and sensitive communication will enable advanced planning and discussion of a patient’s fears, concerns, and wishes, and will ultimately contribute to making the final, well-informed, and joint decision about treatment with the medical team.

Patients approaching end of life require frequent assessment of their full needs by a multidisciplinary team. In advanced stages, recognizing that cardiopulmonary resuscitation in severe PAH has a poor outcome may enable a do not resuscitate order; this may facilitate patients being in their preferred place of care at end of life. Attention should be given to controlling distressing symptoms and prescribing appropriate drugs while withdrawing medication that is no longer needed, which may include PAH medication. Well-informed psychological, social, and spiritual support is also vital. Specialist palliative care should be consulted for patients whose needs are beyond the expertise of the PH team [346].

6.3.12. New drugs in advanced clinical development (phase 3 studies)

Pulmonary arterial hypertension remains an incurable condition with a high mortality rate, despite use of PAH drugs mainly targeting imbalance of vasoactive factors. Novel agents, which are currently in phase 3 development, are ralinepag and sotatercept. Ralinepag is an orally available prostacyclin receptor agonist, which, in a phase 2 RCT that included 61 patients with PAH, improved PVR compared with placebo after 22 weeks of therapy [495]. Sotatercept—a fusion protein comprising the extracellular domain of the human activin receptor type IIA linked to the Fc domain of human immunoglobulin G1—acts as a ligand trap for members of the transforming growth factor (TGF)-β superfamily, thus restoring balance between growth-promoting and growth-inhibiting pathways [496]. In a phase 2 RCT that included 106 patients with PAH treated over 24 weeks, s.c. sotatercept reduced PVR in patients receiving background PAH therapy [496]; improvements were also observed in 6MWD and NT-proBNP [496].

7. Specific pulmonary arterial hypertension subsets

7.1. Pulmonary arterial hypertension associated with drugs and toxins

Several drugs and toxins are associated with developing PAH or PVOD/PCH. Historically, certain appetite suppressants and toxic rapeseed oil were the most prominent examples, whereas methamphetamines, interferons, and some tyrosine kinase inhibitors are more common causes nowadays (Table 7). Pulmonary arterial hypertension is a rare complication in patients exposed to these drugs, and many of these drugs have also been linked to other pulmonary complications such as parenchymal lung disease or pleural effusions. These pulmonary complications may occur concurrently.

Methamphetamine-associated PAH has mainly been reported from the USA, where some centres have found that 20–29% of their otherwise idiopathic cases of PAH were associated with methamphetamine use [497, 498]. Compared with patients with IPAH, those with methamphetamine-associated PAH had more severe haemodynamic impairment and a higher mortality risk [498]. Alpha and beta interferons have also been associated with developing PAH [499]. The same is true of some tyrosine kinase inhibitors, especially dasatinib, but also bosutinib and ponatinib [40, 500].

Drug- or toxin-induced PAH should always be considered in patients presenting with unexplained exertional dyspnoea or other warning signs. The diagnostic approach should be the same as in other forms of PH, and the diagnosis is usually made by excluding other forms of PH in patients who have been exposed to drugs associated with developing PAH.

Treatment of DPAH follows the same basic principles as treating other forms of PAH. Importantly, partial or full reversal of PAH has been reported after discontinuing the causative agent, at least for interferons and dasatinib [499, 500]. Hence, multidisciplinary management of the patient should include discontinuing the presumed causative agents once PAH is diagnosed (also see the 2022 ESC Guidelines on Cardio-Oncology) [501]. In patients with mild PH and a low-risk profile, discontinuing the trigger alone may be sufficient, and it is recommended that these patients be observed over 3–4 months before considering PAH therapy. Pulmonary arterial hypertension therapy should be initiated in patients who do not normalize their haemodynamics after withdrawing or in patients presenting with more advanced PAH at diagnosis. Unlike in other forms of PAH, de-escalation of PAH therapy is often possible during the course of the disease [500]. Physicians should bear in mind that DPAH may have features of PVOD/PCH, especially in patients treated with alkylating agents such as mitomycin C or cyclophosphamide. Health professional awareness is essential in identifying cases of DPAH and reporting adverse effects of pharmaceutical products.

RECOMMENDATION TABLE 14 Recommendations for pulmonary arterial hypertension associated with drugs or toxins

Recommendations	Class[a]	Level[b]
It is recommended to make a diagnosis of drug- or toxin-associated PAH in patients who had relevant exposure and in whom other causes of PH have been excluded	I	C

Continued

RECOMMENDATION TABLE 14 Continued		
Recommendations	**Class[a]**	**Level[b]**
In patients with suspected drug- or toxin-associated PAH, it is recommended to discontinue the causative agent whenever possible	I	C
Immediate PAH therapy should be considered in patients who present with intermediate/high-risk PAH at diagnosis	IIa	C
Patients with low-risk PAH should be re-evaluated 3–4 months after discontinuing the suspected drug or toxin, and PAH therapy may be considered when the haemodynamics have not normalized	IIb	C

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension. [a]Class of recommendation. [b]Level of evidence.

7.2. Pulmonary arterial hypertension associated with connective tissue disease

Pulmonary arterial hypertension is a well-known pulmonary vascular complication of SSc [173, 502–504], systemic lupus erythematosus (SLE) [505–507], mixed CTD [506], and, rarely, dermatomyositis [508] and Sjögren's syndrome [509]. Conversely, the relationship between rheumatoid arthritis and PAH is not established [510]. After IPAH, PAH-CTD is the second most prevalent type of PAH in western countries [511].

Systemic sclerosis, particularly in its limited variant, represents the main cause of PAH-CTD in Europe and the USA (SLE being more common in Asia) [173, 502, 506]. The prevalence of pre-capillary PH in large cohorts of patients with SSc is 5–19% [173, 502]. In these patients, PH may occur in association with ILD [504, 512] or as a result of PAH [173, 502–504, 506], sometimes with features of venous/capillary involvement [504, 513]. Moreover, group 2 PH-LHD is also common due to myocardial SSc involvement [504, 514]. Of note, patients with SLE may also present with PAH, LHD, ILD, and CTEPH (mostly in the setting of antiphospholipid syndrome). It is therefore essential to carefully determine which mechanism is operative in a given patient, since this will dictate treatment in the context of a multifaceted disease.

Cluster analysis performed in patients with SSc has shown that pre-capillary PH can be characterized into distinct clusters that differ in prognosis [503]. One cluster, characterized by the presence of extensive ILD, and another by severely impaired haemodynamics carried a dismal prognosis, while the two others showed either the absence of ILD or the presence of limited ILD, with mild-to-moderate risk PAH and a relatively favourable overall prognosis [503].

7.2.1. Epidemiology and diagnosis

There is a strong female predominance in PAH-CTD (female/male ratio 4:1), and mean age at diagnosis is commonly >50 years, especially in SSc [173, 502–511, 513, 515, 516]. In the setting of a CTD, patients may present with concomitant disorders such as ILD, and have shorter survival compared with patients with IPAH [503]. The unadjusted risk of death for PAH-SSc compared with IPAH is 2.9, and the predictors of outcome are broadly similar to those for IPAH [516, 517]. Symptoms and clinical presentation are also similar to IPAH, and some patients thought to have IPAH can be identified as having an associated CTD by careful clinical examination and immunological screening tests. Chest CT is recommended for evaluating the presence of associated ILD or PVOD/PCH [504, 513, 515]. An isolated reduction of DLCO is common in PAH-CTD [173, 502–504].

Resting echocardiography combined with other tests is recommended as a screening test in asymptomatic patients with SSc, followed by annual assessments. Screening/early detection is discussed in Section 5.3.1. In other CTDs, PH screening in the absence of suggestive symptoms is not recommended, while echocardiography should be performed in the presence of symptoms. As in other forms of PAH, RHC is recommended in all cases of suspected PAH-CTD to confirm diagnosis, determine severity, and rule out LHD [504].

7.2.2. Therapy

Drugs for PAH should be prescribed in PAH-CTD according to the same treatment algorithm as in IPAH (Figure 9). Patients with PAH-CTD have been included in most of the major RCTs for regulatory approval of PAH therapy [518]. Some aspects of PAH-CTD treatment differ according to the associated CTD [506]. Immunosuppressive therapy combining glucocorticosteroids and cyclophosphamide may result in clinical improvement in patients with SLE- or mixed CTD-associated PAH [506], while it is not recommended in

PAH-SSc [519]. Patients with SSc and other CTDs may have ILD and/or HFpEF, which needs to be considered when initiating PAH therapy [504, 515]. In SSc, the long-term risk/benefit ratio of oral anticoagulation is unfavourable because of an increased risk of bleeding, while VKAs are recommended in PAH-CTD with a thrombophilic predisposition (*e.g.* antiphospholipid syndrome) [319].

Subgroup analyses of patients with PAH-SSc enrolled in RCTs performed with monotherapy or combination therapy of ERAs, PDE5is, sGC stimulators, prostacyclin receptor agonists, epoprostenol, and prostacyclin analogues have shown positive effects *versus* placebo [301, 401, 519, 520]. In some of these trials, the magnitude of the response in the PAH-CTD subgroup was lower than in the IPAH subgroup [519, 520]. Continuous i.v. epoprostenol therapy improved exercise capacity, symptoms, and haemodynamics in a 3-month RCT in PAH-SSc [401]. However, a retrospective analysis showed a better effect of i.v. epoprostenol on survival in IPAH compared with PAH-SSc [521]. The choice of PAH therapy in the context of SSc and its systemic manifestations may consider other vascular damage such as digital ulcers [522].

Connective tissue disease should not be considered as an a priori contraindication for LTx [523]. This has been extensively studied in SSc, where a multidisciplinary approach optimizing SSc management before, during, and after surgery is recommended [523]. Indications and contraindications for transplantation have to be adapted to the specificities of CTD, with a special focus on digestive (gastro-oesophageal reflux disease and intestinal disease), cardiac, renal, and cutaneous involvement [523].

RECOMMENDATION TABLE 15 Recommendations for pulmonary arterial hypertension associated with connective tissue disease

Recommendations	Class[a]	Level[b]
In patients with PAH associated with CTD, treatment of the underlying condition according to current guidelines is recommended [166, 167, 419, 524]	I	A
In patients with PAH associated with CTD, the same treatment algorithm as for patients with IPAH is recommended	I	C

PAH-CTD, pulmonary arterial hypertension associated with connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension. [a]Class of recommendation. [b]Level of evidence.

7.3. Pulmonary arterial hypertension associated with human immunodeficiency virus infection

The use of highly active antiretroviral therapy (HAART), and advances in managing opportunistic infections have contributed to increased life expectancy in patients with HIV [525, 526]. Consequently, the spectrum of complications has shifted towards other long-term conditions, including PAH. Clinical and histopathological findings in PAH associated with HIV infection (PAH-HIV) share many similarities with IPAH [1, 527]. With the availability of HAART given in combination with PAH therapies, the prognosis of PAH-HIV has markedly improved in recent years [526, 528]. In addition, the incidence of PAH-HIV has declined in parallel with the increasing availability of HAART [528]. Taken together, these effects on survival and incidence have resulted in a stable PAH prevalence in patients with HIV over recent decades. A French population study indicated that the prevalence of PAH in individuals with HIV infection was 0.46%, which is very similar to the prevalence before the HAART era [177].

The pathogenesis of PAH-HIV remains unclear. There is no evidence of a direct role of HIV in the pathogenesis of PAH and, although present in inflammatory cells in the lungs, the virus itself has never been found in pulmonary vascular lesions of patients with PAH-HIV [529]. This suggests that an indirect action of viral infection on inflammation and growth factors may act as a trigger in a predisposed patient.

7.3.1. Diagnosis

Pulmonary arterial hypertension associated with HIV shares a clinical presentation with IPAH. Before the availability of HAART most patients were in WHO-FC III or IV at diagnosis. Nowadays, patients are diagnosed with much less severe symptoms and haemodynamics. Patients may present with other risk factors for PAH such as liver disease (chronic viral hepatitis B or C) or exposure to drugs or toxins. Patients with PAH-HIV are more likely to be male and i.v. drug abusers [403, 526]. There is no correlation between the severity of PAH and the stage of HIV infection or the degree of immunodeficiency [403, 530]. Because of its low prevalence, asymptomatic patients with HIV should not be screened for PAH. However, echocardiography should be performed in patients with unexplained dyspnoea to detect HIV-related cardiovascular complications such as myocarditis, cardiomyopathy, or PAH. Right heart catheterization is mandatory to confirm the diagnosis of PAH-HIV and to rule out LHD [527].

Pulmonary arterial hypertension is an independent risk factor for death in patients with HIV. In the 1990s, before the availability of HAART, patients with PAH-HIV had poor outcomes, with a 3 year survival of <50% [403]. The overall survival has now improved and patients with PAH-HIV have a better prognosis than most patients with other forms of PAH [526].

7.3.2. Therapy

Current recommendations for the treatment of PAH-HIV are largely based on data from IPAH [25, 26].

Treatment of PAH-HIV with HAART has improved functional status and survival in some retrospective studies [525, 526, 531]. The use of HAART in PAH-HIV is therefore recommended, irrespective of viral load and CD4+ cell count.

Anticoagulation is not recommended because of an increased risk of bleeding and drug interactions [319, 527]. Patients with PAH-HIV are usually non-responders to acute vasoreactivity testing and therefore should not receive CCBs [378].

The prospective, open-label, BREATHE-4 study showed that bosentan markedly improved WHO-FC, exercise capacity, quality of life, and haemodynamics after 16 weeks in patients with PAH-HIV [532]. In a long-term, retrospective series, bosentan therapy was associated with haemodynamic normalization in 10/59 patients [533]. Bosentan potentially interacts with antiretroviral drugs, and close monitoring is required when combined with HAART. Very few patients with PAH-HIV have been included in RCTs with ambrisentan and macitentan, and no definite conclusion can be drawn from those studies.

Positive effects of sildenafil and tadalafil in PAH-HIV have been established in case studies [534, 535]. Interactions have been reported between PDE5is and protease inhibitors, resulting in major increases in PDE5i concentrations; these drugs should be introduced at low dosages with careful monitoring of potential side effects, including hypotension [536, 537]. There are no data on the use of the sGC stimulator riociguat in PAH-HIV.

Treatment with i.v. epoprostenol resulted in significant improvement in WHO-FC, exercise capacity, haemodynamics, and survival in selected patients with PAH-HIV [403, 538]. There are very few data on the use of i.v. or s.c. treprostinil or inhaled iloprost in PAH-HIV [539, 540].

There are no clinical trial data on the use of combination therapy for PAH-HIV. Given the lack of supporting evidence and potential safety concerns when PAH drugs are co-administered with antiretroviral drugs, initial monotherapy with PAH medication is recommended, followed by an individualized use of combination therapy in patients who do not reach a low-risk profile.

RECOMMENDATION TABLE 16 Recommendations for pulmonary arterial hypertension associated with human immunodeficiency virus infection

Recommendations	Class[a]	Level[b]
In patients with PAH associated with HIV infection, antiretroviral treatment according to current guidelines is recommended [541, 542]	I	A
In patients with PAH associated with HIV infection, initial monotherapy should be considered, followed by sequential combination if necessary, taking into consideration comorbidities and drug–drug interactions	IIa	C

HIV, Human immunodeficiency virus; PAH, pulmonary arterial hypertension. [a]Class of recommendation. [b]Level of evidence.

7.4. Pulmonary arterial hypertension associated with portal hypertension

Pulmonary arterial hypertension associated with portal hypertension, commonly referred to as PoPH, develops in 2–6% of patients with portal hypertension, with or without liver disease. In PAH registries, PoPH represents 5–15% of the patients [543–545]. Rarely, some patients with PoPH have portosystemic shunts in the absence of portal hypertension (congenital extrahepatic cavoportal shunts) [546]. However, PoPH is distinct from hepatopulmonary syndrome (HPS), which is characterized by intrapulmonary vascular dilatations and hypoxaemia. Of note, HPS and PoPH can occur sequentially or concurrently in patients with portal hypertension [547].

7.4.1. Diagnosis

The diagnosis of PoPH is based on the presence of otherwise unexplained pre-capillary PH in patients with portal hypertension or a portosystemic shunt. The diagnostic approach is the same as in other patients with suspected or newly detected PH. Transthoracic echocardiography is usually the first non-invasive assessment in patients with suspected PH, and echocardiography is also recommended as a screening tool in patients evaluated for liver transplantation. As patients with liver disease often have an elevated CO, TRV tends to overestimate PAP in these patients. Hence, RHC with comprehensive haemodynamic assessment is essential to confirm the diagnosis of PH and to distinguish PAH (with elevated PVR) from unclassified PH (with a normal PVR).

7.4.2. Therapy

Patients with unclassified PH (*i.e.* mPAP >20 mmHg, elevated CO, and PVR ⩽2.0 WU) should be regularly followed-up but should not be treated with drugs approved for PAH.

In patients with an established diagnosis of PoPH, treatment should follow the same general principles as in other patients with PAH, taking into account the severity of underlying liver disease, the indication for liver transplantation, and the potential effects of PAH medication on gas exchange, which may deteriorate with vasodilators in patients with PoPH [548, 549]. All drugs approved for PAH can principally be used to treat patients with PoPH, bearing in mind that these patients are usually excluded from registration studies. Nevertheless, various case series support the use of approved PAH medication in patients with PoPH. The largest series published so far reported on 574 patients with PoPH treated with various PAH drugs, mostly PDE5is or ERAs, alone and in combination [545]. Most patients (56.8%) were in Child–Pugh class A at the time of PAH diagnosis. At the first follow-up, which took place 4.5 months after starting treatment, improvements were seen in haemodynamics, WHO-FC, 6MWD, and BNP/NT-proBNP; survival at 5 years was 51%. In patients presenting with mild liver disease, the main causes of death were PAH progression and malignancy, whereas complications of liver disease were the most common causes of death in patients with advanced liver disease. The 5 year survival of patients who underwent liver transplantation (*n*=63) was 81%.

The only RCT dedicated to the treatment of PoPH was PORTICO, a 12 week study that randomized 85 patients to macitentan (*n*=43) or placebo (*n*=42) [168]. PORTICO met its primary endpoint, demonstrating a significant reduction in PVR from baseline (ratio of geometric mean 0.65; 95% CI, 0.59–0.72; $P<0.0001$). There were, however, no differences between the two treatment groups in secondary outcome measures, including WHO-FC, 6MWD, and NT-proBNP.

7.4.2.1. Liver transplantation

Porto-pulmonary hypertension is not per se an indication for liver transplantation. Pulmonary arterial hypertension poses a major threat to patients who undergo liver transplantation when indicated for the severity of liver disease. In a historical series from the Mayo Clinic, severe PAH with mPAP ⩾50 mmHg was associated with a 100% peri-operative mortality rate. In patients with mPAP 35–50 mmHg and PVR >3.0 WU, mortality was still 50% [550]. In liver transplantation candidates with PAH, targeted medical therapy successfully improves haemodynamics and establishes eligibility for transplantation [545, 551–554]. However, haemodynamic criteria for successful liver transplantation have not been firmly established. The International Liver Transplant Society proposed haemodynamic targets of mPAP <35 mmHg and PVR <5 WU, or mPAP ⩾35 mmHg and PVR <3 WU in patients receiving PAH therapy, while acknowledging that these criteria need to be further validated [175]. An mPAP ⩾45 mmHg is regarded as an absolute contraindication to liver transplantation [175].

In patients with PoPH who successfully underwent liver transplantation, de-escalation or discontinuation of PAH medication is often feasible, but this has to be performed on an individual basis [551, 554].

RECOMMENDATION TABLE 17 Recommendations for pulmonary arterial hypertension associated with portal hypertension

Recommendations	Class[a]	Level[b]
Echocardiography is recommended in patients with liver disease or portal hypertension with signs or symptoms suggestive of PH, and as a screening tool in patients evaluated for liver transplantation or transjugular portosystemic shunt	I	C
It is recommended that patients with PAH associated with portal hypertension are referred to centres with expertise in managing both conditions	I	C

Continued

RECOMMENDATION TABLE 17 Continued

Recommendations	Class[a]	Level[b]
In patients with PAH associated with portal hypertension, initial monotherapy should be considered, followed by sequential combination if necessary, taking into consideration the underlying liver disease and the indication for liver transplantation	IIa	C
Liver transplantation should be considered on an individual basis in patients with PAH associated with portal hypertension, as long as PVR is normal or near normal with PAH therapy	IIa	C
Drugs approved for PAH are not recommended for patients with portal hypertension and unclassified PH, *i.e.* elevated mPAP, high CO, and a normal PVR	III	C

mPAP, mean pulmonary arterial pressure; CO, cardiac output; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance. [a]Class of recommendation. [b]Level of evidence.

7.5. Pulmonary arterial hypertension associated with adult congenital heart disease

The presence of PH in adults with CHD has a negative impact on the natural course of CHD, and worsens clinical status and overall outcome [555]. Pulmonary arterial hypertension associated with adult CHD is included in group 1 of the PH clinical classification (Table 6) and represents a heterogeneous patient population. Post-capillary PH in adult CHD (*e.g.* systolic or diastolic, systemic, ventricular dysfunction in combination with shunt lesions or complex adult CHD, and systemic atrioventricular valve dysfunction) should be excluded to determine further management. A specific clinical classification (Table 21) is provided to better characterize PAH associated with adult CHD. Some complex CHDs are associated with congenital abnormalities of the pulmonary vascular tree leading to segmental PH. In segmental PH, one or more, but not all, segments of the lung(s) are hypertensive and each hypertensive area may present with PH of different severity, while other parts of the lung vasculature may be hypoplastic. Pulmonary atresia with ventricular septal defect and systemic-to-pulmonary collaterals is the most frequent condition, but other complex CHDs may also lead to segmental PH.

Approximately 3–7% of patients with adult CHD will eventually develop PAH; it is more frequently encountered in females, and the incidence depends on the underlying lesion and increases with age and age at defect closure [556]. The estimated prevalence of PAH in patients after correcting a simple cardiac defect is 3% [557]. The epidemiology of PAH associated with adult CHD is expected to change due to

TABLE 21 Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1) Eisenmenger syndrome
Includes all large intra- and extracardiac defects that begin as systemic-to-pulmonary shunts and progress to severely elevated PVR and to reverse (pulmonary-to-systemic) or bidirectional shunting. Cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present. Closing the defects is contraindicated.

2) PAH associated with prevalent systemic-to-pulmonary shunts
- Correctable[a]
- Non-correctable

Include moderate-to-large defects. PVR is mildly to moderately increased and systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3) PAH with small/coincidental[b] defects
Markedly elevated PVR in the presence of cardiac defects considered haemodynamically non-significant (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography), which themselves do not account for the development of elevated PVR. The clinical picture is very similar to IPAH. Closing the defects is contraindicated.

4) PAH after defect correction
Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant, post-operative, haemodynamic lesions.

IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance. [a]With surgery or intravascular percutaneous procedure, see also the Recommendation Table 18 for shunt closure. [b]The size applies to adult patients. However, also in adults, the simple diameter may be insufficient for defining the haemodynamic relevance of the defect, and also the pressure gradient, the shunt size and direction, and the pulmonary-to-systemic flows ratio should be considered.

advances in diagnostic and therapeutic paediatric cardiology, resulting in fewer patients with simple adult CHD and more patients with complex lesions and/or closed defects who develop PAH in adulthood [558].

The clinical presentation of Eisenmenger syndrome, an advanced form of adult CHD-associated PAH, is characterized by the multiorgan effects of chronic hypoxaemia, including cyanosis, and haematological changes, including secondary erythrocytosis and thrombocytopenia; the main symptoms are dyspnoea, fatigue, and syncope. Eisenmenger syndrome may also present with haemoptysis, chest pain, cerebrovascular accidents, brain abscesses, coagulation abnormalities, and sudden death. Patients with adult CHD and Down syndrome are at an increased risk of developing Eisenmenger syndrome.

7.5.1. Diagnosis and risk assessment

The diagnostic work-up of PAH associated with adult CHD should be based on the presence of symptoms and includes medical history, physical examination, PFTs, ABG, imaging (especially echocardiography), and exercise and laboratory testing. Of note, standard echocardiographic criteria for detecting PH may not be applicable in complex adult CHD [559]. Right heart catheterization with compartmental oximetry for calculating pulmonary blood flow/systemic blood flow (Qp/Qs) is required to confirm PAH diagnosis and guide therapeutic interventions. Thermodilution should be avoided in the presence of intracardiac shunts, and direct Fick is the most accurate method. Pulmonary vascular resistance may be overestimated due to erythrocytosis [560]. Interpreting invasive haemodynamics (see Section 5.1.12) should be made in the context of multiparametric assessment of exercise capacity, laboratory testing, and imaging.

Predictors of worse outcomes in adult CHD-associated PAH are WHO-FC III–IV, exercise intolerance assessed by 6MWD or peak VO_2, history of hospitalization for right HF, biomarkers (NT-proBNP >500 pg/mL, C-reactive protein >10 mg/mL, high serum creatinine, and low albumin levels), iron deficiency, and echocardiographic indices of RV dysfunction [559, 561]. When compared with patients with IPAH, patients with Eisenmenger syndrome may have a relatively stable long-term clinical course. The right ventricle is unloaded by the right-to-left shunt, sustaining CO at the expense of hypoxaemia and cyanosis. However, due to immortal time bias, prognosis of Eisenmenger syndrome is not as favourable as previously thought [562].

As in other forms of PAH, risk assessment is important to guide therapy, and specific risk factors have been described in Eisenmenger syndrome. A large multicentre study showed that mortality in adults with Eisenmenger syndrome was predicted by the presence of pre-tricuspid shunt, advancing age, low rest oxygen saturation, absence of sinus rhythm, and presence of pericardial effusion [563].

7.5.2. Therapy

Outcomes in adult CHD-associated PAH have improved with the availability of new PAH therapies, advances in surgical and peri-operative management, and a team-based, multidisciplinary approach in PH centres. These patients should be managed by specialized health professionals. Patient education, behavioural modifications, and social and psychological support are all important aspects of management.

Shunt closure (surgical or interventional) may only be considered in patients with prevalent systemic-to-pulmonary shunting without significantly increased PVR. Criteria for defect closure based on Qp/Qs ratio and (baseline and/or after targeted PAH treatment) PVR have been proposed by the 2020 ESC Guidelines for the management of adult congenital heart disease [101]. Decisions on shunt closure should not be made on haemodynamic numbers alone, and a multiparametric strategy should be followed. For instance, shunt closure is not indicated in the case of desaturation during exercise in the 6MWT or CPET, or when there is secondary erythrocytosis suggesting dynamic reversal of shunt. There is no evidence for a long-term benefit of a treat-and-repair approach in patients with adult CHD-associated PAH with prevalent systemic-to-pulmonary shunts; therefore, there is a need for future prospective studies [564]. Defect closure is contraindicated in all patients with Eisenmenger syndrome, and may also adversely affect patients with small/coincidental defects that behave similarly to IPAH [565]. There are no prospective data available on the usefulness of vasoreactivity testing, balloon closure testing, or lung biopsy for assessing operability and normalization of PVR after closure [566].

Patients with adult CHD-associated PAH may present with clinical deterioration in different circumstances, such as arrhythmia, during non-cardiac surgery requiring general anaesthesia, dehydration or bleeding, thrombo-embolism, and lung infections. Surgeries should be limited to those deemed essential, and performed in specialized centres with anaesthetists experienced in adult CHD and PAH. Endocarditis should be suspected in patients with sepsis, whereas a cerebral abscess should be excluded in those with neurological symptoms or new headache, especially in those with low oxygen saturations and complex anatomies. It is recommended to avoid strenuous exercise, but mild and moderate activities seem to be beneficial [567]. Patients should receive all recommended vaccinations and endocarditis prophylaxis in the presence of cyanosis. Although pregnant patients with left-to-right shunts and stable, well-controlled PAH have tolerated pregnancy well under specialized care, pregnancy is still associated with both high maternal mortality and foetal complications in Eisenmenger syndrome and should be discouraged in this setting [568, 569]; hence, effective contraception is highly recommended. Levonorgestrel-based, long-acting, reversible contraception implants or intrauterine devices have been recommended for these patients [570].

Secondary erythrocytosis is beneficial for adequate oxygen transport and delivery, and routine phlebotomy should be avoided whenever possible. Symptoms of hyperviscosity in the presence of haematocrit >65% should be approached with appropriate hydration. Iron deficiency should be corrected. When i.v. iron supplementation is administered, special care should be taken to avoid air emboli during administration [571]. Supplemental oxygen therapy has not been shown to impact survival.

Oral anticoagulant treatment with VKAs may be considered in patients with large PA aneurysms with thrombus, atrial arrhythmias, and previous thrombo-embolic events, but with low bleeding risk. In patients with very high Hb levels (>20 mg/dL), standard international normalized ratio measures are less accurate, and citrate-adjusted blood bottles must be used. Regarding using novel oral anticoagulants (NOACs), a large, nationwide, German, adult CHD database (including 106 NOAC-treated patients with Eisenmenger syndrome) showed that NOAC users had higher long-term risk of bleeding, major adverse cardiovascular events, and mortality compared with those on VKAs, suggesting that initiating NOACs should be reserved for experienced adult CHD centres, carefully weighing potential benefits and risks [572, 573].

Compared with other group 1 subgroups, limited data exist on the use of drugs approved for PAH in patients with adult CHD-associated PAH. Bosentan improved 6MWD and decreased PVR in patients with Eisenmenger syndrome in WHO-FC III [574]. Patients with more complex lesions were less likely to respond to PAH therapies compared with patients with simple lesions. An RCT investigating the efficacy of macitentan found no effect on 6MWD in a mixed cohort of patients with Eisenmenger syndrome (6MWD improved in both treatment and placebo arms), although decreases in NT-proBNP and PVR were noted in the macitentan arm [575].

Experiences with other ERAs and PDE5is have shown favourable functional and haemodynamic results in Eisenmenger syndrome [576]. In a small, single-centre, pilot study, adding nebulized iloprost to a background of oral PAH therapy failed to improve 6MWD in Eisenmenger syndrome [577]. In case symptoms persist or in clinical deterioration, a sequential and symptom-orientated treatment strategy is recommended in Eisenmenger syndrome, starting with an oral ERA (or PDE5i) and escalating therapy. Should symptoms not adequately improve with oral therapies, i.v./s.c. options should be proactively considered [578]. There is a theoretical risk of paradoxical embolism in right-to-left shunt lesions with the presence of a central venous catheter for i.v. therapy; therefore, s.c. prostacyclin analogue infusion may be considered.

The effect of PAH therapies in patients with prevalent systemic-to-pulmonary shunts is less well established. Patients with small/coincidental defects should be treated with PAH medication [557]. This is also the case for patients with PAH after defect correction who have increased mortality compared with those with Eisenmenger syndrome [579]. These patients were included in major RCTs with PAH therapies and should be evaluated based on comprehensive risk assessment (Table 16) [580]. The effect of PAH therapies in patients with segmental PH remains a matter of debate [101, 581]. While some series have reported promising results, there have been cases where therapies were not tolerated [581]. Similarly, using PAH therapies in Fontan circulation has yielded conflicting results, and results of further studies are awaited [582–584].

Heart–lung transplantation or LTx with heart surgery is an option in highly selected cases not responsive to medical treatment; however, it is limited by organ availability and lesion complexity. Mortality is high during the first year after surgery, especially after heart–lung transplantation, but remains relatively low thereafter [585].

RECOMMENDATION TABLE 18 Recommendations for shunt closure in patients with pulmonary–systemic flow ratio >1.5:1 based on calculated pulmonary vascular resistance

Recommendations	Class[a]	Level[b]
In patients with ASD, VSD, or PDA and a PVR <3 WU, shunt closure is recommended	I	C
In patients with ASD, VSD, or PDA and a PVR of 3–5 WU, shunt closure should be considered	IIa	C
In patients with ASD and a PVR >5 WU that declines to <5 WU with PAH treatment, shunt closure may be considered	IIb	C
In patients with VSD or PDA and a PVR >5 WU, shunt closure may be considered after careful evaluation in specialized centres	IIb	C
In patients with ASD and a PVR >5 WU despite PAH treatment, shunt closure is not recommended	III	C

ASD, atrial septal defect; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; VSD, ventricular septal defect; WU, Wood units. Decisions on shunt closure should not be made on haemodynamic numbers alone; a multiparametric strategy should be followed (see Section 7.5.2). [a]Class of recommendation. [b]Level of evidence.

RECOMMENDATION TABLE 19 Recommendations for pulmonary arterial hypertension associated with adult congenital heart disease

Recommendations	Class[a]	Level[b]
Risk assessment		
Risk assessment is recommended for patients with persistent PAH after defect closure	I	C
Risk assessment should be considered in patients with Eisenmenger syndrome	IIa	C
Treatment		
Bosentan is recommended in symptomatic patients with Eisenmenger's syndrome to improve exercise capacity [574]	I	B
In patients with Eisenmenger syndrome, the use of supplemental oxygen therapy should be considered in cases where it consistently increases arterial oxygen saturation and reduces symptoms	IIa	C
Supplemental iron treatment should be considered in patients with iron deficiency	IIa	C
In patients with adult CHD, including Eisenmenger syndrome, other ERAs, PDE5is, riociguat, prostacyclin analogues, and prostacyclin receptor agonists should be considered	IIa	C
In patients with PAH after corrected adult CHD, initial oral combination therapy with drugs approved for PAH should be considered for patients at low and intermediate risk, while initial combination therapy including i.v./s.c. prostacyclin analogues should be considered for patients at high risk	IIa	C[c]
In patients with adult CHD, including Eisenmenger syndrome, sequential combination therapy should be considered if patients do not meet treatment goals	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with Eisenmenger syndrome with pulmonary artery thrombosis	IIb	C
In women with Eisenmenger syndrome, pregnancy is not recommended	III	C
In patients with Eisenmenger syndrome, routine phlebotomy to lower elevated haematocrit is not recommended	III	C

CHD, congenital heart disease; ERA, endothelin receptor antagonist; i.v., intravenous; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; s.c., subcutaneous. [a]Class of recommendation. [b]Level of evidence. [c]Level of evidence differs from the 2020 ESC Guidelines for the management of adult congenital heart disease because the number of patients with adult CHD included in the AMBITION study was very low.

7.6. Pulmonary arterial hypertension associated with schistosomiasis

Schistosomiasis is one of the most common chronic infectious diseases worldwide, affecting around 200 million people [586, 587]. Schistosomiasis-associated PAH is present in 5% of patients with the hepatosplenic form of the disease [586]. It is thus a leading cause of PAH, especially in some regions of South America, Africa, and Asia. Compared with patients with IPAH, patients with schistosomiasis-associated PAH present with higher CO and lower PVR, and have a better survival [587]. Registry data suggest that survival in schistosomiasis-associated PAH has improved in recent years with the use of PAH drugs [588].

7.7. Pulmonary arterial hypertension with signs of venous/capillary involvement

The common risk factors, identical genetic substrate, and indistinguishable clinical presentations of PCH and PVOD necessitate their consideration as a single disease belonging to the group 1 PH spectrum of diseases (PAH with signs of venous/capillary involvement) [1, 425, 589]. In PVOD/PCH, post-capillary lesions affecting septal veins and pre-septal venules consist of loose, fibrous remodelling of the intima that may totally occlude the lumen [1, 425, 589, 590]. These changes are frequently associated with PCH consisting of capillary ectasia and proliferation, with doubling and tripling of the alveolar septal capillary layers that may be focally distributed within the alveolar interstitium [425, 590].

The proportion of patients with IPAH that fulfil the criteria for PVOD/PCH is ∼10%, resulting in a lowest estimate of PVOD/PCH incidence and prevalence of <1 case/million [425]. In contrast to IPAH, there is a male predominance in PVOD/PCH and its prognosis is worse [425, 589, 591]. Familial PVOD/PCH typically occurs in the young siblings of one generation, with unaffected and sometimes consanguineous parents, indicating that the disease segregates as a recessive trait [158, 425, 591]. Biallelic mutations in the *EIF2AK4* gene cause heritable PVOD/PCH [158]. In addition, PVOD/PCH can complicate the course of associated conditions, such as SSc [425], or be associated with exposure to environmental triggers, such as alkylating agents (cyclophosphamide, mitomycin C) [34] and solvents (trichloroethylene) [38].

7.7.1. Diagnosis

Most patients complain of non-specific dyspnoea on exertion and fatigue [590]. Physical examination may reveal digital clubbing and bibasal crackles on lung auscultation [590]. Pulmonary arterial hypertension and PVOD/PCH share the same haemodynamic profile as pre-capillary PH [590, 591]. The PAWP is not elevated because the pulmonary vascular changes occur in small venulae and capillaries, while the LA filling pressure remains normal [590, 591]. A diagnosis of PVOD/PCH is based on the results of tests suggesting venous post-capillary involvement, chronic interstitial pulmonary oedema, and capillary proliferation [1, 590, 591]. These tests include PFTs (decreased DLCO, frequently <50% theoretical values), ABG (hypoxaemia), and non-contrast chest CT (subpleural thickened septal lines, centrilobular ground-glass opacities, and mediastinal lymphadenopathy) [1, 425, 589, 591, 592]. Importantly, these patients are at risk of drug-induced pulmonary oedema with PAH therapy, a finding suggestive of PVOD/PCH [425, 591]. Detecting biallelic *EIF2AK4* mutations is sufficient to confirm a diagnosis of heritable PVOD/PCH [158, 591, 592]. Lung biopsy is hazardous in PH and is not recommended for diagnosing PVOD/PCH [1, 425].

7.7.2. Therapy

There is no established medical therapy for PVOD/PCH [425]. Compared with IPAH, PVOD/PCH has a poor prognosis and limited response to PAH therapy, with a risk of pulmonary oedema due to pulmonary venous obstruction [425, 591]. However, there are reports of incomplete and transient clinical improvement in individual patients with PVOD/PCH treated with PAH therapy, which should be used with great caution in this setting [425, 591]. Diuretics, oxygen therapy, and slow titration of PAH therapy can be used on an individual basis [425]. Therefore, therapy for PVOD/PCH should be undertaken at centres with extensive experience in managing PH, and patients should be fully informed about the risks [425]. Anecdotal reports suggest a potential benefit of immunomodulatory treatments, but this approach requires further study [593]. The only curative therapy for PVOD/PCH is LTx, and eligible patients should be referred to a transplant centre for evaluation upon diagnosis [425, 591]. Pathological examination of the explanted lungs will confirm the diagnosis [590].

RECOMMENDATION TABLE 20 Recommendations for pulmonary arterial hypertension with signs of venous/capillary involvement

Recommendations	Class[a]	Level[b]
A combination of clinical and radiological findings, ABG, PFTs, and genetic testing is recommended to diagnose PAH with signs of venous and/or capillary involvement (PVOD/PCH) [591]	I	A
Identification of biallelic *EIF2AK4* mutations is recommended to confirm a diagnosis of heritable PVOD/PCH [158, 591]	I	A
Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is recommended as soon as the diagnosis is established	I	C
In patients with PVOD/PCH, the use of drugs approved for PAH may be considered with careful monitoring of clinical symptoms and gas exchange	IIb	C

Continued

RECOMMENDATION TABLE 20 Continued

Recommendations	Class[a]	Level[b]
Lung biopsy is not recommended to confirm a diagnosis of PVOD/PCH	III	C

ABG, arterial blood gas analysis; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PFT, pulmonary function test; PVOD, pulmonary veno-occlusive disease. [a]Class of recommendation. [b]Level of evidence.

7.8. Paediatric pulmonary hypertension

Pulmonary hypertension may present at all ages, including in infants and children. Pulmonary hypertension in childhood shares many common features with PH in adulthood; however, there are also important differences, which concern epidemiology, aetiology, genetic background, age-dependent diagnostic and treatment approaches, and disease monitoring. An important and conceptually distinctive feature of paediatric PH is injury to developing foetal, neonatal, or paediatric lung circulation.

7.8.1. Epidemiology and classification

The reported annual incident rate for paediatric PH is 64/million children [594]. The distribution of the various aetiologies of PH in childhood differs from PH in adulthood [594–596]. Pulmonary arterial hypertension is the most frequent type of PH in children, with the vast majority (82%) of cases being infants with transient PAH (*i.e.* PPHN or repairable cardiac shunt defects). Of the remaining children with PAH, most have either IPAH, HPAH, or irreversible CHD-associated PAH. The reported incidences of IPAH/HPAH and (non-transient) CHD-associated PAH are 0.7 and 2.2/million children, respectively, with a prevalence of 4.4 and 15.6/million children, respectively [594]. Other conditions associated with PAH (Table 6) do occur in children but are rare.

Another significant proportion (34–49%) of children with non-transient PH are neonates and infants with PH associated with respiratory disease, especially developmental lung diseases, including bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH), and congenital pulmonary vascular abnormalities [594–598]. These children form a prominent and distinctive group in paediatric PH and are currently classified as PH group 3 associated with developmental lung disease (Table 6; Table S7). A significant and growing proportion of children with PH associated with respiratory disease is made up of pre-term infants with BPD. Also, newly recognized genetic developmental lung disorders—including alveolar capillary dysplasia, *TBX4*-mutation-related lung disorders, and surfactant abnormalities—are currently classified in this category (Figure 10) [599].

Another distinctive feature of PH in children is the high burden of genetic disorders. Childhood PH is often associated with chromosomal, genetic, and syndromic anomalies (11–52%). Like in adults, gene mutations implicated in the pathogenesis of HPAH are found in 20–30% of sporadic cases, where paediatric HPAH seems to be characterized by an enrichment in *TBX4* and *ACVRL1* variations [600, 601]. Additionally, 17% of children with PAH have other disorders known to be associated with PAH, including trisomy 21. Finally, 23% of children with PAH have copy number variations not previously associated with PH [600, 602, 603].

Given the frequent association of paediatric PAH with chromosomal, genetic, and syndromic anomalies (for which the mechanistic basis for PAH is generally uncertain), genetic testing may be considered for defining aetiology and comorbidities, stratifying risk, and identifying family members at risk; however, this should be after appropriate expert genetic counselling for the child and family (see Section 5.1.13).

The clinical PH classification (Table 6) is also followed for paediatric PH. To improve applicability of this classification in infants and children with PH, it has been adapted to give room to PH associated with various congenital cardiovascular and pulmonary diseases or specific paediatric conditions (Tables S5–S8) [599].

7.8.2. Diagnosis and risk assessment

Historically, the definition of PH in children aged >3 months has been the same as in adults. The definition for PH has now been redefined to mPAP >20 mmHg in adults as well as in children. The impact of an mPAP 21–24 mmHg on outcomes in children is unknown. However, in the interest of consistency and to facilitate transition from paediatric to adult PH care, it is recommended that the updated definition

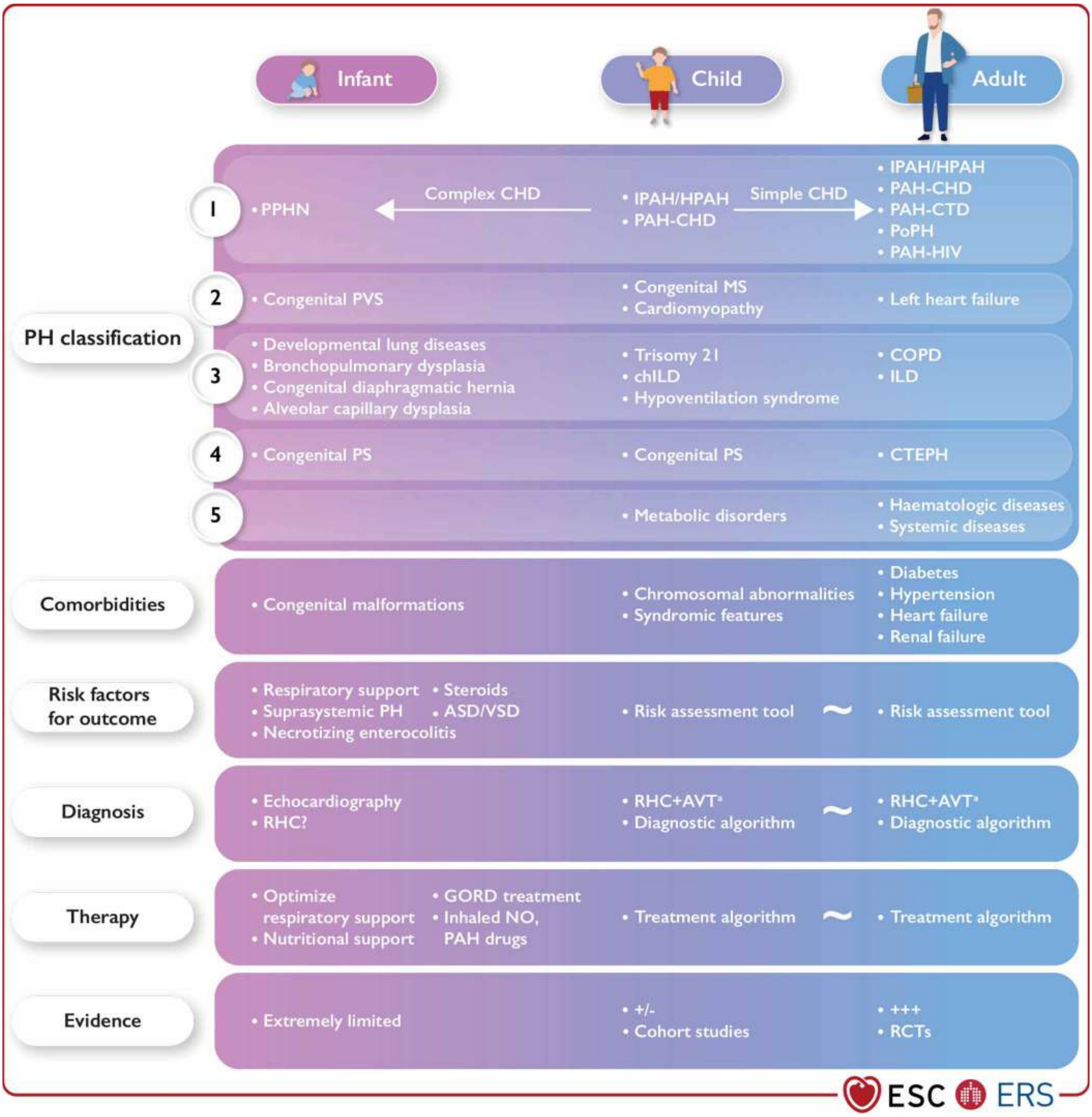

FIGURE 10 Neonatal and paediatric *versus* adult pulmonary hypertension. ASD, atrial septal defect; AVT, acute vasoreactivity testing; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; GORD, gastro-oesophageal reflux disease; HPAH, heritable pulmonary arterial hypertension; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; MS, mitral stenosis; NO, nitric oxide; PAH, pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart disease; PAH-CTD, PAH associated with connective tissue disease; PAH-HIV, PAH associated with HIV infection; PH, pulmonary hypertension; PoPH, porto-pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PS, pulmonary arterial stenosis; PVS, pulmonary vein stenosis; RCT, randomized controlled trial; RHC, right heart catheterization; VSD, ventricular septal defect. [a]In patients with idiopathic, heritable or drug-associated PAH. Pulmonary hypertension in neonates and infants significantly differs in aetiology, pathophysiology, risk assessment, and treatment from older children and adults, while PH in older children has more similarities with PH in adults.

for PH also be followed in children. No treatment recommendations currently exist for this group of children (mPAP 21–24 mmHg).

Regarding the newly introduced criterion to include PVR >2 WU to identify pre-capillary PH in adults, PVR had previously been included in the definition for PAH in children. In children, blood flows are traditionally indexed assuming that systemic and pulmonary blood flows change proportionally with body size, while the transpulmonary pressure gradient does not. Since blood flow is the denominator in the equation for calculating PVR, the need for indexing of PVR in children is emphasized, and the criterion of pulmonary vascular resistance index (PVRI) ⩾3 WU·m^2 in the definition for PAH in children remains unchanged [599].

Since the aetiology of paediatric PH is very diverse, a methodical and comprehensive diagnostic approach is crucial to reach an accurate diagnosis and treatment plan. As in adults, IPAH is a diagnosis 'per exclusion'. A diagnostic work-up, similar to that in adults but customized for paediatric PH, is recommended [599]. Pre-term infants with BPD should be screened for PH, since PH is prevalent in this population and seriously affects outcome [604].

Also in children, RHC is the gold standard for definitively diagnosing and establishing the nature of PH, and provides important data for stratifying risk [604a, 605]. To identify those suitable for high-dose CCB treatment, acute vasoreactivity testing is recommended in children with IPAH/HPAH. The criteria used in adults for a positive acute response have identified children who will show sustained benefit from CCB therapy; however, these criteria do not define reversibility of PAH or operability in children with CHD. Since RHC in children with PH may be associated with major complications (in 1–3% of cases, especially in young infants and those in worse clinical condition), risks and benefits have to be balanced in the individual child [605]. Heart catheterization in children with PAH should be exclusively performed in experienced paediatric PH centres. Indications for repeated RHC in children with PH are currently not well defined.

Treatment of children with PAH is based on risk stratification [599]. Predictors of worse outcome in paediatric PAH are similar to those in adults, and include clinical evidence of RV failure, progression of symptoms, WHO-FC III–IV, certain echocardiographic parameters (*e.g.* TAPSE), and elevated serum NT-proBNP. A 6MWD <350 m has also been suggested as a predictor of worse outcome in paediatric PH, but its value in young children is less established. Further prognosticators identified in paediatric PAH are failure to thrive and haemodynamic variables, such as RAP >10 mmHg, the ratio of mean pulmonary-to-systemic blood pressure >0.75, and PVRI >20 WU·m^2 [602, 606, 607]. Paediatric risk-assessment tools based on these parameters have been retrospectively validated in observational paediatric registries [599, 604a].

7.8.3. Therapy

The ultimate goal of treatment should be to improve survival and facilitate normal childhood activities without limitations. In the absence of RCTs in paediatric PAH, recommended treatment algorithms are extrapolated from those in adults and enhanced with data from observational studies in children with PAH [599].

Observational cohort studies support treatment algorithms designed for adults to be used for children (including the superiority of combination therapy over monotherapy) [608]. Drugs investigated in children, with or without formal approval by the European Medicines Agency (EMA) for treating children with PAH, are shown in Table 22.

A paediatric treatment algorithm, derived from that for adults, is based on risk stratification, recommending general measures, high-dose CCB therapy for responders to acute vasoreactivity testing (where close follow-up is mandatory, as some patients may fail long-term therapy), oral or inhaled combination therapy for children at low risk, and combination therapy with i.v./s.c. prostacyclin analogues for those at high risk [599].

In the case of insufficient response to recommended drug therapy, or when drugs are unavailable, a Potts shunt (a surgical or interventional connection between the left PA and the descending aorta), BAS, or LTx may be considered in children with severe PH (see Sections 6.3.6.1 and 6.3.8) [599]. Reported clinical experience with Potts shunts is limited to just over 100 patients, predominantly children, with a mortality of 12–25% and long-term clinical benefit in a subset of children with long-term follow-up [456–459].

TABLE 22 Use of pulmonary arterial hypertension therapies in children

Drug	Paediatric study data	European Medicines Agency approval for use in children with PAH	Ref.
Phosphodiesterase 5 inhibitors (oral)			
Sildenafil	RCT, open-label extension: tolerability, efficacy	Yes, for ⩾1 year of age Recommended dosing: <20 kg: 30 mg/day in 3 doses; ⩾20 kg: 60 mg/day in 3 doses Avoid higher dosing in children (>3 mg/kg/day)	[613, 614]
Tadalafil	RCT, open-label: safety, tolerability, pharmacokinetics	No Suggested dosing: 0.5–1 mg/kg/day in 1 dose Max: 40 mg/day Evaluated only in children aged >3 years	[615, 616]
Endothelin receptor antagonists (oral)			
Bosentan	Open-label, uncontrolled: safety, tolerability, pharmacokinetics, efficacy	Yes, for ⩾1 year of age Paediatric formulation Recommended dosing: 4 mg/kg/day in 2 doses Max: 250 mg/day	[617–620]
Ambrisentan	Open-label, uncontrolled: safety, tolerability, pharmacokinetics	Yes, for children aged >8 years Recommended dosing: 2.5–10 mg/day in one dose	[621, 622]
Macitentan	Insufficient data in children Open-label, ongoing: efficacy, safety, pharmacokinetics in children aged 2–18 years	No	
Prostacyclin analogues (i.v./s.c.)			
Epoprostenol i.v.	Cohort studies, retrospective	No Suggested dosing: Starting dose: 1–2 ng/kg/min without a known maximum In children, a stable dose is usually 40–80 ng/kg/min Dose increases may be required	[623–626]
Treprostinil i.v./s.c.	Cohort studies, retrospective: pharmacokinetics	No Suggested dosing: Starting dose: 2 ng/kg/min without a known maximum In children, a stable dose is usually 50–100 ng/kg/min Dose increases may be required	[624, 626, 627]
Other			
Iloprost (inhaled)	Insufficient data in children Small case series, retrospective	No	
Selexipag (oral)	Insufficient data in children Randomized, placebo-controlled, add-on, ongoing: safety, tolerability, pharmacokinetics in children aged 2–18 years	No	
Riociguat (oral)	Insufficient data in children Open-label, ongoing: safety, tolerability, pharmacokinetics in children aged 6–18 years	No	

i.v., intravenous; PAH, pulmonary arterial hypertension; RCT, randomized controlled trial; s.c., subcutaneous.

Monitoring of treatment effect and disease course is pivotal in managing all patients with PAH (adults and in children). In children with PAH, clinical risk scores including WHO-FC, TAPSE, and serum NT-proBNP are potential treatment targets for goal-orientated treatment [604a, 609].

Contemporary treatment algorithms for infants with PPHN have been proposed but are outside the scope of these guidelines [610].

The recommendations discussed above apply to children with PAH, whereas the specific group of infants with neonatal PVD, mostly classified as PH associated with developmental lung disease and with heterogeneous aetiology, require a distinct and customized approach (Figure 10).

In pre-term infants with BPD and PH, the underlying lung disease should primarily be treated. Frequently, these infants are additionally treated with therapies for PAH, including sildenafil and bosentan; however, these are not approved by the EMA for use in infants with group 3 PH and developmental lung diseases (BPD, CDH). Their effects on outcomes in this population are unclear, and data enabling robust treatment recommendations are lacking. These children should be treated by multidisciplinary teams involving cardiologists, neonatologists, pulmonologists, and nutritionists. Pulmonary hypertension in these infants may disappear with lung healing, although long-term cardiovascular sequelae have been reported [611, 612].

RECOMMENDATION TABLE 21 Recommendations for paediatric pulmonary hypertension

Recommendations	Class[a]	Level[b]
Children		
It is recommended to perform the diagnostic work-up, including RHC and acute vasodilator testing, and treat children with PH at centres with specific expertise in paediatric PH	I	C
In children with PH, a comprehensive work-up for confirming diagnosis and specific aetiology is recommended (similar to that in adults, but adapted for age)	I	C
For confirming PH diagnosis, RHC is recommended, preferably before initiating any PAH therapy	I	C
In children with IPAH/HPAH, acute vasoreactivity testing is recommended to detect those who may benefit from CCB therapy	I	C
It is recommended to similarly define a positive response to acute vasoreactivity testing in children and adults by a reduction in mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg, with an increased or unchanged CO	I	C
In children with PAH, a therapeutic strategy based on risk stratification and treatment response is recommended, extrapolated from that in adults but adapted for age	I	C
It is recommended to monitor the treatment response in children with PAH by serially assessing a panel of data derived from clinical assessment, echocardiographic evaluation, biochemical markers, and exercise tolerance tests	I	C
Achieving and maintaining a low-risk profile should be considered as an adequate treatment response for children with PAH	IIa	C
Infants		
It is recommended to screen infants with bronchopulmonary dysplasia for PH [628, 629]	I	B
In infants with (or at risk of) bronchopulmonary dysplasia and PH, treating lung disease—including hypoxia, aspiration, and structural airway disease—and optimizing respiratory support is recommended before initiating PAH therapy [630]	I	B
In neonates and infants, a diagnostic and therapeutic approach to PH distinct from that in older children and adults should be considered, given the frequent association with developmental vascular and parenchymal lung disease	IIa	C

CCB, calcium channel blocker; CO, cardiac output; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization. [a]Class of recommendation. [b]Level of evidence.

8. Pulmonary hypertension associated with left heart disease (group 2)

8.1. Definition, prognosis, and pathophysiology

Among patients with LHD, PH and RV dysfunction are frequently present and associated with high mortality [47]. This includes patients with HF with reduced, mildly reduced, or preserved ejection fraction (HFrEF, HFmrEF, or HFpEF), left-sided valvular heart disease, and congenital/acquired cardiovascular conditions leading to post-capillary PH [13, 631–635]. Arguably, PH-LHD represents the most prevalent form of PH, accounting for 65–80% of cases [47].

Consistent with the general definitions of PH, PH-LHD (group 2 PH) is defined by an mPAP >20 mmHg and a PAWP >15 mmHg. Within this haemodynamic condition of post-capillary PH, IpcPH is defined by PVR ⩽2 WU and CpcPH by PVR >2 WU (Table 5). 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 [142].

Across the spectrum of LHD, increases in PAP and PVR are associated with an increased disease burden and a worse outcome [13, 631, 633, 635]. In a large patient cohort—predominantly with post-capillary PH—a PVR ⩾2.2 WU was associated with adverse outcomes and considered abnormal [13]. However, even within this subgroup of patients with LHD and CpcPH, the risk of mortality increases with progressive elevation in PVR. In patients with advanced HFrEF and those with HFpEF or valvular heart disease, a PVR >5 WU carries additional prognostic information and is considered clinically meaningful by physicians [142, 450, 631–639]. Elevated PVR also appears to be associated with decreased survival in special situations, such as in patients undergoing interventions for correcting valvular heart disease [634], heart transplantation [142, 633], or LVAD implantation [142, 637]. Based on available data, a PVR >5 WU may indicate a severe pre-capillary component, the presence of which may prompt physicians to refer patients to PH centres for specialized care.

The prevalence of PH in patients with LHD is difficult to assess and depends on the methodology of diagnostic testing (echocardiography or invasive haemodynamics), cut-off values used to define PH, and populations studied. Observational studies suggest an estimated prevalence of PH of 40–72% in patients with HFrEF and 36–83% in those with HFpEF [48, 639–643]. When PVR is used to define a pre-capillary component in patients with HF and post-capillary PH, ∼20–30% of patients are categorized as having CpcPH [47, 644, 645]. In patients with valvular heart disease, echocardiographic studies have shown that PH is present in up to 65% of patients with symptomatic aortic stenosis [646–651], while virtually all patients with severe mitral valve stenosis develop PH [652], which can also be found in most patients with significant degenerative or functional mitral regurgitation.

The pathophysiology of PH-LHD combines several mechanisms (Figure 11): 1) an initial passive increase in LV filling pressures and backward transmission into the pulmonary circulation; 2) PA endothelial dysfunction (including vasoconstriction); 3) vascular remodelling (which may occur in both venules and/or arterioles); 4) RV dilatation/dysfunction and functional TR [653–656]; and 5) altered RV–PA coupling [656, 657]. The haemodynamic profile of CpcPH *versus* IpcPH and elevated PVR reflects pulmonary vascular abnormalities, which contribute to an increased RV afterload. Resulting dysfunction of the RV is frequent and associated with a worse prognosis in patients with PH-LHD. In HFpEF, where RV dysfunction may occur via distinct mechanisms (Figure S1), deterioration of RV, but not LV systolic function, has been observed over time, and both prevalent and incident RV dysfunction are predictors of mortality [658].

The occurrence of PH in patients with LHD may also be due to other causes, including undetected CTEPH or PAH. Further, respiratory comorbidities such as COPD and sleep apnoea are also common in patients with LHD and may contribute to PH and impact prognosis. Patients with HFpEF and PH associated with HFpEF [75, 76] may also present with a low DLCO, which is an independent predictor of outcome [75].

8.2. Diagnosis

In patients with LHD, symptoms (*e.g.* exertional dyspnoea) and physical signs of PH (*e.g.* peripheral oedema) frequently overlap with those of the underlying left heart condition and are mostly non-specific. However, while pulmonary congestion or pleural effusion indicate LHD as the underlying cause of PH, other features may suggest the presence of relevant PH (see Section 5.1.1).

Routine diagnostic tests including BNP/NT-proBNP, ECG, and echocardiography may show signs of underlying LHD, but may also indicate PH. While BNP/NT-proBNP cannot discriminate between left- or right-sided HF, ECG findings such as right axis deviation or RV strain may suggest the presence of PH in patients with LHD. Echocardiography can diagnose HFrEF and HFpEF; identify specific cardiac conditions, including those with restrictive filling pattern; and diagnose additional valvular heart disease; it may also detect elevated sPAP and other features of PH (RA area, PA enlargement, RV/LV ratio, LV eccentricity index, RV forming the apex), leading to an echocardiographic probability of PH (see Section 5.1.5). A stepwise, composite echocardiographic score may discriminate pre- *versus*

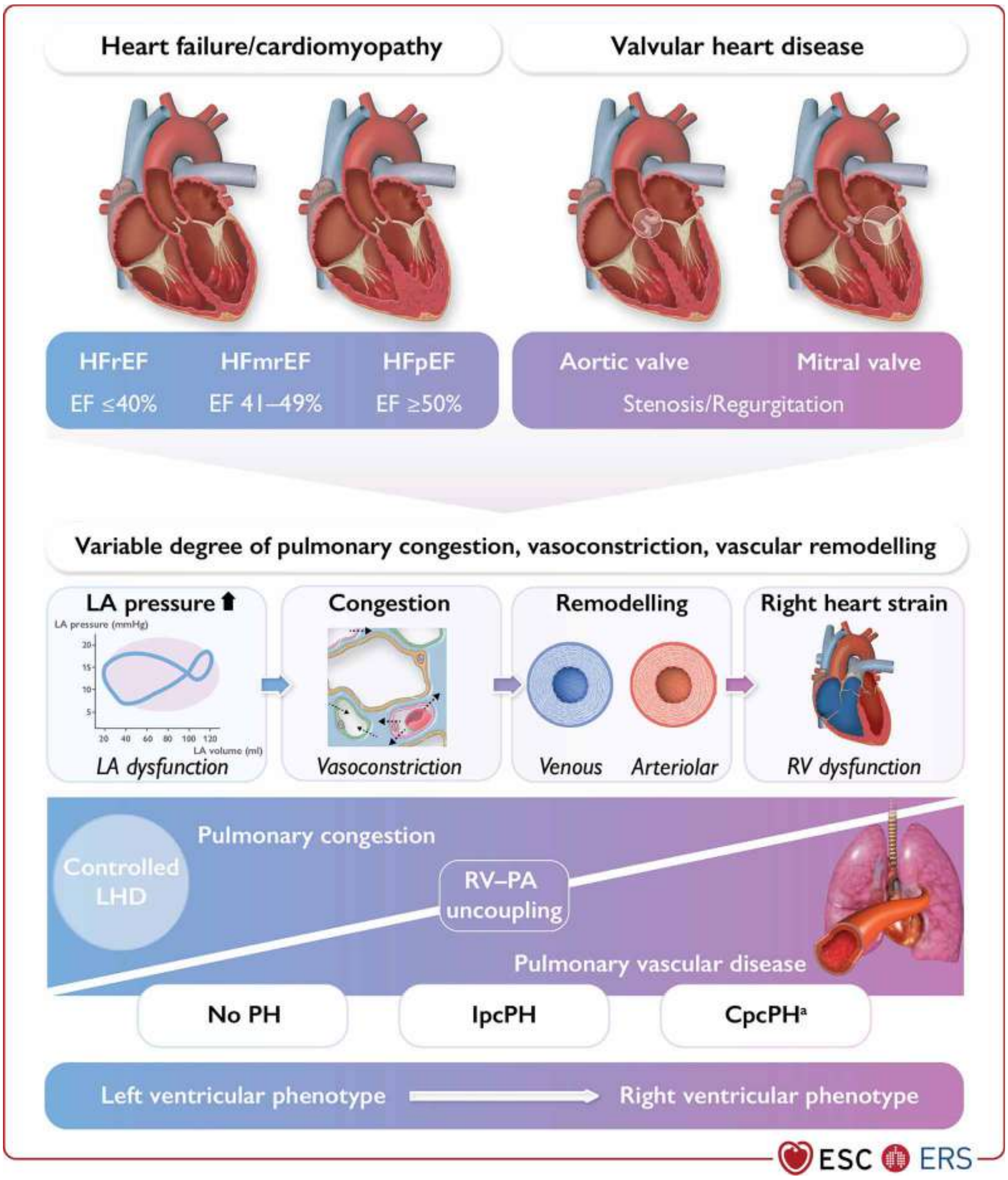

FIGURE 11 Pathophysiology of pulmonary hypertension associated with left heart disease (group 2). CpcPH, combined post- and pre-capillary pulmonary hypertension; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IpcPH, isolated post-capillary pulmonary hypertension; LA, left atrial; LHD, left heart disease; RV, right ventricle/right ventricular; PA, pulmonary artery; PH, pulmonary hypertension. [a]CpcPH is defined by post-capillary PH and PVR >2 WU; a PVR >5 WU may be considered a severe pre-capillary component.

post-capillary PH and predict PVD in patients with LHD [659, 660]. Additional information may be gathered from further testing, including biomarkers, imaging-derived markers of RV dysfunction, and CPET-derived variables [142].

Given the complexity and variability of cardiopulmonary haemodynamics in patients with LHD, the distinction between post- and pre-capillary PH and the diagnosis of PH-LHD *versus* other forms of PH can be challenging. Diagnostic clues in the evaluation of suspected PH in LHD include: 1) diagnosis and control of the underlying LHD; 2) evaluation for PH and patient phenotyping; and 3) invasive haemodynamic evaluation, when indicated.

8.2.1. Diagnosis and control of the underlying left heart disease

Patients with suspected PH-LHD will have an established diagnosis of LHD, such as HFrEF/HFmrEF, HFpEF, valvular heart disease, and/or CHD. The distinction between PH associated with HFpEF and other forms of PH (*e.g.* PAH, CTEPH) may be challenging, particularly given the increased burden of cardiovascular comorbidities in real-world PAH populations [142, 293, 450, 661]. In this context, validated scores for diagnosing HFpEF (HFA-PEFF, H2FPEF) [16, 662, 663] may be helpful for detecting it as an underlying condition in PH, and the presence or absence of risk factors for PAH or CTEPH should be determined. Patients with signs of predominant RV strain and/or PH should be further evaluated. Patients should be assessed or reassessed when they are fully recompensated and in a clinically stable condition.

8.2.2. Evaluation of pulmonary hypertension and patient phenotyping

Patients with LHD and suspected PH should be evaluated following the diagnostic strategy for PH (see Section 5). This requires identifying clinical features and a multimodal approach using non-invasive diagnostic tests such as echocardiography, ECG, and BNP/NT-proBNP levels. In the presence of mild PH and predominant LHD, no further testing may be necessary. Otherwise, CTEPH and significant lung disease should be ruled out by V/Q scan and PFTs, and additional cardiac imaging including cMRI may be considered in selected cases. For phenotyping, a combination of variables may help to determine the likelihood of LHD, and HFpEF in particular, *versus* other causes of PH (Table 23). Pulmonary hypertension associated with left heart disease is likely in the presence of known cardiac disease, multiple cardiovascular comorbidities/risk factors, atrial fibrillation at diagnosis, and specific imaging findings (LV hypertrophy, increased LA size, and reduced LA strain). Although exercise echocardiography has been proposed to uncover HFpEF, it is unable to diagnose or classify PH in this context. A combination of clinical findings and phenotyping is required to decide about the need for further invasive assessment.

8.2.3. Invasive assessment of haemodynamics

The decision to perform cardiac catheterization and to invasively assess cardiopulmonary haemodynamics 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. In patients with a high likelihood of LHD as the main cause of PH, or with established underlying LHD and mild PH (Table 23), invasive assessment for PH is usually not indicated. Indications for RHC in LHD include: (1) suspected PAH or CTEPH; (2) suspected CpcPH with a severe pre-capillary component, where further information will aid phenotyping and treatment decisions (Figure S2); and (3) advanced HF and evaluation for heart transplantation. While several haemodynamic measures (mPAP, PVR, pulmonary arterial compliance [PAC], transpulmonary pressure gradient, and DPG) are associated with outcomes in PH-LHD [142, 632, 635], the most robust and consistent data are available for PVR. Invasive assessment should be conducted in experienced centres, when management of the underlying LHD has been optimized and patients are in a clinically stable condition. With respect to respiratory variations of intrathoracic pressures, all pressure readings should be taken at end-expiration.

Additional testing during RHC may be useful for distinguishing between PAH and HFpEF [18, 23, 664–669], and to uncover LHD in patients with a high likelihood of PH-LHD and normal resting PAWP [670–673]; both exercise testing and fluid challenge may be considered in special situations (see Section 5.1.12). Conditions associated with reduced LV diastolic compliance or valvular heart disease may be associated with a rapid increase in PAWP when challenged with increased systemic venous return [674]. While the upper limit of normal remains controversial [142, 143, 665, 667], a PAWP cut-off of >18 mmHg has been suggested to identify HFpEF as the underlying cause of PH, despite normal PAWP at baseline [143]. While this may help to classify PH, therapeutic consequences of such testing remain to be determined.

As differentiating between severe PH associated with HFpEF and IPAH with cardiac comorbidities is challenging, patients with an unclear diagnosis, particularly those with a predominant pre-capillary component (*e.g.* PVR >5 WU), should be referred to a PH centre for individualized management.

8.3. Therapy

The primary strategy in managing PH-LHD is optimizing treatment of the underlying cardiac disease. Nevertheless, a pathophysiological sequence ranging from left-sided heart disease via pulmonary circulation to chronic right heart strain (at rest or exercise) is present in many patients [47]. Since deterioration of RV function over time is associated with poor outcomes in HFpEF [658], preserving RV function should be considered an important treatment goal. Diuretics remain the cornerstone of medical therapy in the presence of fluid retention due to PH-LHD.

TABLE 23 Patient phenotyping and likelihood for left heart disease as cause of pulmonary hypertension

Feature	PH-LHD unlikely	Intermediate probability	PH-LHD likely
Age	<60 years	60–70 years	>70 years
Obesity, hypertension, dyslipidaemia, glucose intolerance/diabetes	No factors	1–2 factors	>2 factors
Presence of known LHD	No	Yes	Yes
Previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Permanent/persistent
Structural LHD	No	No	Present
ECG	Normal or signs of RV strain	Mild LVH	LBBB or LVH
Echocardiography	No LA dilation E/e′ <13	No LA dilation Grade <2 mitral flow	LA dilation (LAVI >34 mL/m^2) LVH Grade >2 mitral flow
CPET	High VE/VCO_2 slope No EOV	Elevated VE/VCO_2 slope EOV	Mildly elevated VE/VCO_2 slope EOV
cMRI	No left-heart abnormalities		LVH LA dilation (strain or LA/RA >1)

cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; E/e′, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; ECG, electrocardiogram; EOV, exercise oscillatory ventilation; LA, left atrial; LAVI, left atrial volume index; LBBB, left bundle branch block; LHD, left heart disease; LVH, left ventricular hypertrophy; PH, pulmonary hypertension; PH-LHD, left heart disease associated with pulmonary hypertension; RA, right atrium; RV, right ventricle; VE/VECO2, ventilatory equivalents for carbon dioxide. Assigning the likelihood of LHD as a cause of PH. This assessment may help to decide which patients should undergo a full work-up, including invasive haemodynamic assessment (see Figure 11 and Figure S2).

There is limited and conflicting evidence for the use of drugs approved for PAH in patients with group 2 PH. Some medications may have variable and potentially detrimental effects in such patients and are therefore not indicated in PH-LHD. Management strategies for PH in various left heart aetiologies are described below.

8.3.1. Pulmonary hypertension associated with left-sided heart failure

8.3.1.1. Heart failure with reduced ejection fraction

Patients with HFrEF or HFmrEF require guideline-directed treatment including established medical and interventional therapies [27]. In patients with advanced HFrEF, implanting an LVAD may significantly reduce or even normalize mPAP [675], although this is not achieved in all patients [676], and an increased DPG emerged as a negative prognostic factor after LVAD implantation [677]. With regards to PAH drugs, bosentan was assessed in an RCT of patients with PH associated with HFrEF [678], showing no efficacy but an increase in adverse events compared with placebo, predominantly related to fluid retention. Small studies have suggested that sildenafil may improve haemodynamics and exercise capacity in PH and HFrEF [679–681], but RCTs are lacking.

8.3.1.2. Heart failure with preserved ejection fraction

In patients with HFpEF, blood pressure, volume load, and risk factors should be controlled, which may lower filling pressures and PAP [27]. Recently, the SGLT-2i empagliflozin improved outcomes in patients with an LV ejection fraction of 40–60% [682]. Endothelin receptor antagonists have not proved successful in this population, as both bosentan [683] and macitentan [684] failed to show efficacy but rather led to more adverse events (fluid retention) *versus* placebo in patients with HFpEF-associated PH and HF with ejection fraction >35%-associated CpcPH, respectively. Phosphodiesterase 5 inhibitors were assessed in two small RCTs in patients with HFpEF and PH with distinct haemodynamic characteristics. In patients with a predominantly IpcPH profile, sildenafil had no effect on mPAP (primary endpoint) or other haemodynamic and clinical measures *versus* placebo [685]. In patients with a predominantly CpcPH profile, sildenafil improved haemodynamics, RV function, and quality of life at 6 and 12 months *versus* placebo [686]. Furthermore, retrospective analyses and registry data suggested improvements in exercise capacity with PDE5i therapy in patients with HFpEF-associated CpcPH and with a severe pre-capillary component (PVR mostly >5 WU) [450, 687].

8.3.1.3. Interatrial shunt devices

Recent data suggest that specific interventions may be considered in selected cases of HFpEF, such as interatrial shunt devices to unload the left heart. While this was associated with short-term improvements in pulmonary vascular function [688], the long-term effect on the pulmonary circulation remains unknown. The recent REDUCE LAP-HF II trial failed to show a reduction in HF events after placement of an atrial shunt device in a population of HF patients with LVEF ⩾40% [689], with worse outcomes in the presence of PVD [690]. In addition, a sustained increase in PA blood flow may be a matter of concern, as this may trigger vascular remodelling in patients with pre-existing PH.

8.3.1.4. Remote pulmonary arterial pressure monitoring in heart failure

The importance of decongestion in patients with HF is underscored by the use of implantable pressure sensors, remotely monitoring PAP as a surrogate of left-sided filling pressure. Pulmonary arterial pressure-based adjustment of HF therapy substantially reduced HF hospitalizations and improved outcomes in both patients with HFpEF and HFrEF [691–694], with adjustment of diuretic therapy being the most prominent therapeutic consequence. Further strategies to optimize management depending on the haemodynamic phenotype in PH-LHD remain to be established. In HFrEF, novel medical therapies such as ARNIs and SGLT-2is reduced remotely monitored PAP and diuretic use [695–698], potentially providing opportunities to further optimize PAP-guided HF therapy.

8.3.2. Pulmonary hypertension associated with valvular heart disease

Pulmonary hypertension frequently occurs as a consequence of valvular heart disease. While surgical or interventional approaches for valvular repair improve cardiopulmonary haemodynamics by reducing PAWP and PAP and improving forward SV [699], persistent PH after correcting valvular heart disease is frequent and associated with adverse outcomes [634, 700].

8.3.2.1. Mitral valve disease

Both mitral stenosis and regurgitation regularly lead to post-capillary PH. Functional (secondary) mitral regurgitation occurs in both HFrEF and HFpEF, and is an important contributor to PH in LHD. Reducing mitral regurgitation according to the recommendations of the 2021 ESC/EACTS Guidelines for the management of valvular heart disease [28] has a crucial role in improving haemodynamics in patients with HFrEF, as this reduces mPAP and PAWP and improves the CI [699]. Nevertheless, registry data have demonstrated that even moderately elevated sPAP negatively impacts post-procedural outcomes after catheter-based therapy [700].

8.3.2.2. Aortic stenosis

In patients with aortic stenosis undergoing surgical or catheter-based aortic valve repair, pre-interventional PH is associated with a higher risk of in-hospital adverse events and adverse long-term outcomes [646–651]. Although post-procedural improvement in PH correlates with symptom relief and favourable outcomes, persistence of PH is common, and even moderate PH is associated with a higher all-cause mortality [646–651].

Of note, medical therapy of PH post-valvular repair may be harmful. A randomized study of 231 patients with surgically corrected valvular heart disease and persistent PH showed that sildenafil therapy *versus* placebo was associated with worse outcome when compared with placebo [701]; however, this study did not distinguish between different types of PH (pre-capillary, IpcPH, and CpcPH).

8.3.2.3. Tricuspid regurgitation

Severe TR is associated with volume overload, increased RV workload, and maladaptive remodelling, leading to symptomatic right HF and impaired survival [702, 703]. While primary TR is relatively rare, functional TR may arise from annular dilation in the presence of both PH and LHD. Transcatheter tricuspid valve interventions have recently emerged, aiming at reducing TR and RV volume overload. Of note, correcting TR in patients with PAH or PH in (non-valvular) LHD with significantly elevated PVR and/or RV dysfunction must be considered with great caution, as this may be hazardous [704]. Right ventricle–PA coupling is an independent predictor of all-cause mortality in such patients [705]. Patient selection appears crucial, and a comprehensive diagnostic approach integrating imaging modalities and invasive haemodynamic assessment is necessary in the evaluation process prior to tricuspid valve repair, particularly since echocardiography underestimates sPAP in the presence of severe TR.

8.3.3. Recommendations on the use of drugs approved for PAH in PH-LHD

The recommendations on the use of drugs approved for PAH in patients with PH-LHD have been established based on key narrative question 5 (Supplementary Data, Section 8.3).

The recommendations on the use of PDE5is in patients with CpcPH associated with HFpEF are based on PICO question II (Supplementary Data, Section 8.4). Two RCTs that enrolled patients with HFpEF and PH were identified, but no study that specifically enrolled patients with HFpEF and CpcPH. Harmful effects cannot be excluded, even if the available data from clinical studies, case series, and registries suggest that PDE5is may be safely administered to patients with HFpEF-associated CpcPH. As a result, a general recommendation for or against the use of PDE5is in patients with HFpEF and CpcPH cannot be made. However, it is clinically relevant to make a recommendation against their use for patients with HFpEF and IpcPH.

RECOMMENDATION TABLE 22A Recommendations for pulmonary hypertension associated with left heart disease

Recommendation	Class[a]	Level[b]
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH [27, 28]	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended [29, 47, 142]	I	C
In patients with LHD and CpcPH with a severe pre-capillary component (*e.g.* PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH [133, 143]	IIb	C
Drugs approved for PAH are not recommended in PH-LHD[c] [631, 678, 683, 684, 701, 706]	III	A

RECOMMENDATION TABLE 22B Recommendations for pulmonary hypertension associated with left heart disease

Recommendations	GRADE		Class[a]	Level[b]
	Quality of evidence	Strength of recommendation		
No recommendation can be given for or against the use of PDE5is in patients with HFpEF and combined post- and pre-capillary PH	Low	None		
The use of PDE5is in patients with HFpEF and isolated post-capillary PH is not recommended	Low	Conditional	III	C

CpcPH, combined post- and pre-capillary PH; ERA, endothelin receptor antagonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LHD, left heart disease; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PDE5is, phosphodiesterase 5 inhibitors; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension associated with left heart disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricular; WU, Wood units. [a]Class of recommendation. [b]Level of evidence. [c]Safety concerns have been identified when ERAs are used in patients with HF (HFpEF and HFrEF, with or without PH) and when sildenafil is used in patients with persistent PH after correction of valvular heart disease.

9. Pulmonary hypertension associated with lung diseases and/or hypoxia (group 3)

Pulmonary hypertension is frequently observed in patients with COPD and/or emphysema, ILD, combined pulmonary fibrosis and emphysema (CPFE), and hypoventilation syndromes [52, 165, 707, 708]. Pulmonary hypertension is uncommon in obstructive sleep apnoea unless other conditions coexist, such as COPD or daytime hypoventilation [709]. At high altitude (>2500 m) hypoxia-induced PH is thought to affect >5% of the population, the development of PH being related to geography and genetic factors [710].

A PH screening study performed on a large cohort of >100 patients with lymphangioleiomyomatosis confirmed that PH is usually mild in that setting: from six patients (5.7%) presenting with pre-capillary PH, none had mPAP >30 mmHg and PH was associated with PFT alteration, suggesting that the rise in mPAP is associated with parenchymal involvement [711]. Thus, PH in lymphangioleiomyomatosis is now classified in group 3 PH [1].

In patients with lung disease, PH is categorized as non-severe or severe, depending on haemodynamic findings (Figure 12). In the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH, severe PH was defined by mPAP >35 mmHg or mPAP ⩾25 mmHg with CI <2.5 L/min/m^2 [25, 26]. However, two recent studies have demonstrated that a PVR >5 WU is a better threshold for predicting worse prognosis in

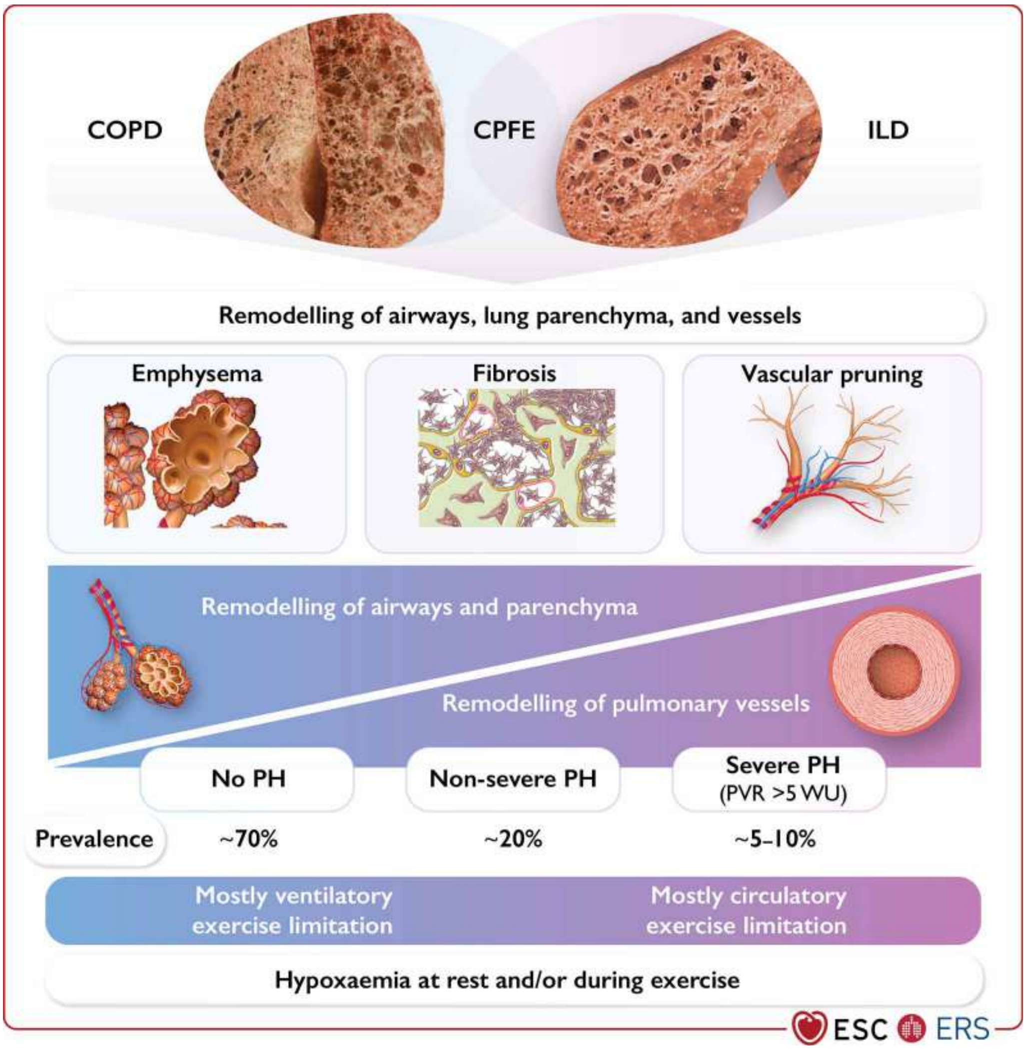

FIGURE 12 Pathophysiology of pulmonary hypertension associated with lung disease (group 3). COPD, chronic obstructive pulmonary disease; CPFE, combined pulmonary fibrosis and emphysema; ILD, interstitial lung disease; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units. Shown are underlying lung diseases (upper panel); contributing pathogenic pulmonary alterations of airways, parenchyma, and vessels (middle panel); and the relation of airway/parenchymal remodelling and vascular remodelling to the degree of PH and its consequences for exercise limitation (ventilatory *versus* circulatory, lower panel).

patients with PH associated with both COPD and ILD [712, 713]. Based on these data, the current guidelines used PVR to distinguish between non-severe PH (PVR ⩽5 WU) and severe PH (PVR >5 WU). Whereas non-severe PH is common in advanced COPD and ILD defined by spirometric criteria, severe PH is uncommon, occurring in 1–5% of cases of COPD and <10% of patients with advanced ILD, with limited data in obesity hypoventilation syndrome [714, 715]. Even non-severe PH in lung disease negatively impacts symptoms and survival, and is associated with increased hospitalization [715–717]. Patients with lung disease and severe PH have a worse outcome than those with non-severe PH, providing evidence that this distinction has clinical significance [51, 712, 713, 718, 719]. It is noteworthy that developing severe PH is largely independent of spirometry but usually accompanied by hypoxaemia, low $PaCO_2$, and a significant reduction in DLCO [51, 714, 718, 719].

Pulmonary hypertension presenting in patients with lung disease may be due to a number of causes, including undiagnosed CTEPH or PAH [714, 720]. Cardiac comorbidities are also common in patients with lung disease and may contribute to PH. A number of distinct phenotypes of PH in patients with lung disease, including a pulmonary vascular phenotype, have been proposed [51, 720]. The pulmonary vascular phenotype is characterized by better preserved spirometry, low DLCO, hypoxaemia, a range of parenchymal involvement on lung imaging, and a circulatory limitation to exercise [51, 714, 718–722]. Recent studies have shown that the clinical characteristics, disease trajectory, response to treatment [451, 718, 719], and histological correlates [723, 724] of patients with severe PH and minor lung disease are different to those in patients with IPAH, including a poorer prognosis.

9.1. Diagnosis

In patients with lung disease, symptoms of PH, especially exertional dyspnoea, overlap with those of the underlying condition. Physical findings may also be non-specific, for example: ankle swelling is common during episodes of ventilatory failure in COPD, where activation of the renin–angiotensin–aldosterone system may cause fluid retention, usually in the setting of preserved RV function.

Non-invasive tests—such as ECG showing right axis deviation or RV strain, elevated levels of BNP/NT-proBNP, CPET, or features on cross-sectional imaging—may suggest the diagnosis of PH in patients with lung disease [725, 726]. Echocardiography remains the most widely used non-invasive diagnostic tool for assessing PH; however, the accuracy of echocardiography in patients with advanced respiratory diseases is low, with a TRV unmeasurable in >50% of patients in some studies, and there is a tendency to overestimate PAP and misclassify patients with PH [86, 87, 727]. More recent data suggest that a stepwise, composite, echocardiographic score can identify patients with severe PH, with and without an estimate of TRV, using other echocardiographic features including RA area, RV:LV ratio, and LV eccentricity index [728]. Where PH is suspected, combining echocardiography with a contrast-enhanced CT may aid diagnostic assessment and disease classification [108, 729–731]. Pulmonary artery enlargement, RV outflow hypertrophy, and increased RV:LV ratio may suggest a diagnosis of PH [108]. Ideally, assessments should be made or repeated when the patient is clinically stable, as exacerbations can significantly raise PAP.

Key parts of evaluating suspected PH in lung disease include integrating: 1) the presence or absence of risk factors for PAH, CTEPH, or LHD; 2) clinical features, including disease trajectory (*e.g.* rapid recent deterioration *versus* gradual change over years, and oxygen requirements); 3) PFTs, including DLCO and blood gas analysis; 4) NT-proBNP measurements, ECG, and echocardiography; and 5) cross-sectional imaging with contrast-enhanced CT, SPECT, or V/Q lung scan and, in selected cases, cMRI [732] to assess the need for RHC. Cardiopulmonary exercise testing may be helpful in assessing ventilatory or cardiac limitation in patients with lung disease [121, 733], although data are limited regarding its clinical use in identifying patients with PH in lung disease.

Indications for RHC in lung disease include assessment for surgical treatments (selected patients considered for LTx and lung volume reduction surgery), suspected PAH or CTEPH, and where further information will aid phenotyping of disease and consideration of therapeutic interventions (Figure S3) [712, 718, 734]. Such testing should ideally be conducted in PH centres when patients are clinically stable and treatment of underlying lung disease has been optimized. Consideration should be given to how pressure measurements are made, due to the impact of changing intrathoracic pressures on pulmonary haemodynamics during the respiratory cycle (see Section 5.1.12) [735].

9.2. Therapy

The therapeutic approach to group 3 PH starts with optimizing the treatment of the underlying lung disease, including supplementary oxygen and non-invasive ventilation, where indicated, as well as enrolment into pulmonary rehabilitation programmes [736]. There is limited and conflicting evidence for the use of medication approved for PAH in patients with group 3 PH, and these drugs may have variable and sometimes detrimental effects on haemodynamics, exercise capacity, gas exchange, and outcomes in this patient population [181, 737–740].

9.2.1. Pulmonary hypertension associated with chronic obstructive pulmonary disease or emphysema

Studies using drugs approved for PAH in patients with PH associated with COPD or emphysema have yielded conflicting results and are mostly limited by small sample size, short duration, and insufficient haemodynamic characterization of PH [739, 741, 742]. In a 16 week RCT of 28 patients with COPD and severe PH confirmed by RHC, sildenafil therapy resulted in statistically significant improvements in PVR and quality of life [743]. Registry data identified that ∼30% of patients with COPD and severe PH, predominantly treated with PDE5is, had improved WHO-FC, 6MWD, and PVR *versus* baseline, and those with a treatment response had improved transplant-free survival [51, 718]. However, in the absence of large randomized trials, the evidence is insufficient to support the general use of medication approved for PAH in patients with COPD and PH. Patients with COPD and suspected or confirmed severe PH should be referred to PH centres for individual decision-making.

9.2.2. Pulmonary hypertension associated with interstitial lung disease

Numerous phase 2 and phase 3 studies have investigated the use of ERAs to treat ILD, all with negative results [740, 744, 745]. In addition, the PDE5i sildenafil has been investigated in phase 3 trials of patients with ILD, also with negative results [746, 747]. Few data from RCTs are available for patients with PH associated with ILD, and many of the studies performed for this indication [748, 749] suffered from the same limitations as the aforementioned studies in PH associated with COPD. In addition, there were several adverse safety signals: ambrisentan was associated with an increased risk of clinical worsening in patients with ILD with and without PH [740, 750], while riociguat was associated with an increased risk of clinical worsening events, including potential excess mortality, in patients with PH associated with idiopathic interstitial pneumonia [181].

In contrast, promising results have been obtained with the use of inhaled treprostinil. A phase 3 RCT (INCREASE) examined inhaled treprostinil at a target dose of 72 µg given four times daily in 326 patients with PH associated with ILD [734, 751]. The PH diagnosis was confirmed by RHC within 1 year prior to enrolment. At week 16, the placebo-corrected 6MWD improved by 31 m with inhaled treprostinil. There were also improvements in NT-proBNP and clinical worsening events, the latter driven by a lower proportion of patients whose 6MWD declined by >15% from baseline.

Given the significant impact of even non-severe PH in patients with lung disease, eligible patients should be referred for LTx evaluation. In patients with ILD and PH, inhaled treprostinil may be considered based on the findings from the INCREASE study, but further data are needed, especially on long-term outcomes. The routine use of other medication approved for PAH is not recommended in patients with ILD and non-severe PH. For patients with severe PH and/or severe RV dysfunction, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended for careful evaluation, to facilitate entry into RCTs, and consider PAH therapies on an individual basis (Figure S3). Registry data show that some patients with group 3 PH are being treated with PAH medication, predominantly PDE5is [718, 752, 753], but it is unclear if and to what extent these patients benefit from this treatment.

9.2.3. Recommendations on the use of drugs approved for PAH in PH associated with lung disease

The recommendations on the use of drugs approved for PAH in patients with PH associated with COPD and ILD have been established based on key narrative questions 6 and 7 (Supplementary Data, Sections 9.1 and 9.2, respectively).

The recommendations on the use of PDE5is in patients with severe PH associated with ILD are based on PICO question III (Supplementary Data, Section 9.3). There are no direct data from RCTs on the safety, tolerability, and efficacy of PDE5is in patients with PH associated with ILD. The indirect data included in the guidelines do not enable firm conclusions to be drawn. Given the lack of robust evidence, the Task Force members felt unable to provide a recommendation for or against the use of PDE5is in patients with ILD and severe PH, and recommend that these patients are referred to a PH centre for individualized decision-making.

RECOMMENDATION TABLE 23A Recommendations for pulmonary hypertension associated with lung disease and/or hypoxia

Recommendations	Class[a]	Level[b]
If PH is suspected in patients with lung disease, it is recommended that echocardiography[c] be performed and results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging	I	C
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I	C
In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[d]	I	C
In patients with lung disease and severe PH, an individualized approach to treatment is recommended	I	C
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation	I	C
In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I	C
Inhaled treprostinil may be considered in patients with PH associated with ILD [734]	IIb	B
The use of ambrisentan is not recommended in patients with PH associated with IPF [740]	III	B
The use of riociguat is not recommended in patients with PH associated with IIP [181]	III	B
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]	III	C

RECOMMENDATION TABLE 23B Recommendations for pulmonary hypertension associated with lung disease and/or hypoxia

Recommendations	GRADE		Class[a]	Level[b]
	Quality of evidence	Strength of recommendation		
PDE5is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	IIb	C
The use of PDE5is in patients with ILD and non-severe PH is not recommended	Very low	Conditional	III	C

ABG, arterial blood gas analysis; CT, computed tomography; DLCO, Lung diffusion capacity for carbon monoxide; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; LTx, lung transplantation; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterization. [a]Class of recommendation. [b]Level of evidence. [c]Assessments should ideally be made when the patient is clinically stable, as exacerbations can significantly raise pulmonary artery pressure. [d]This recommendation does not apply to patients with end-stage lung disease who are not considered candidates for LT. [e]This does not include inhaled treprostinil, which may be considered in patients with PH associated with ILD, irrespective of PH severity.

10. Chronic thrombo-embolic pulmonary hypertension (group 4)

All patients whose symptoms can be attributed to post-thrombo-embolic fibrotic obstructions within the PA are considered to have CTEPD with or without PH; CTEPH remains the preferred term for patients with PH, as defined in Section 3.1 (Table 5) [54]. Chronic thrombo-embolic pulmonary disease describes symptomatic patients with mismatched perfusion defects on V/Q scan and with signs of chronic, organized, fibrotic clots on CTPA or DSA, such as ring-like stenoses, webs/slits, and chronic total occlusions (pouch lesions or tapered lesions), after at least 3 months of therapeutic anticoagulation. Pulmonary hypertension in this setting is not only a consequence of PA obstruction by organized fibrotic clots but can also be related to the associated microvasculopathy. In those patients without PH at rest, breathlessness could be due to exercise PH (see definition in Section 3.1, Table 5) and/or increased dead space ventilation [54]. Excluding ventilatory limitation, deconditioning and psychogenic hyperventilation syndrome by CPET and LV myocardial or valvular disease by echocardiography is of upmost importance when making therapeutic decisions in patients with CTEPD without PH.

10.1. Diagnosis

Chronic thrombo-embolic pulmonary hypertension is a common and important cause of PH, with a distinct management strategy. Thus, the possibility of CTEPH should be carefully considered in all patients with PH

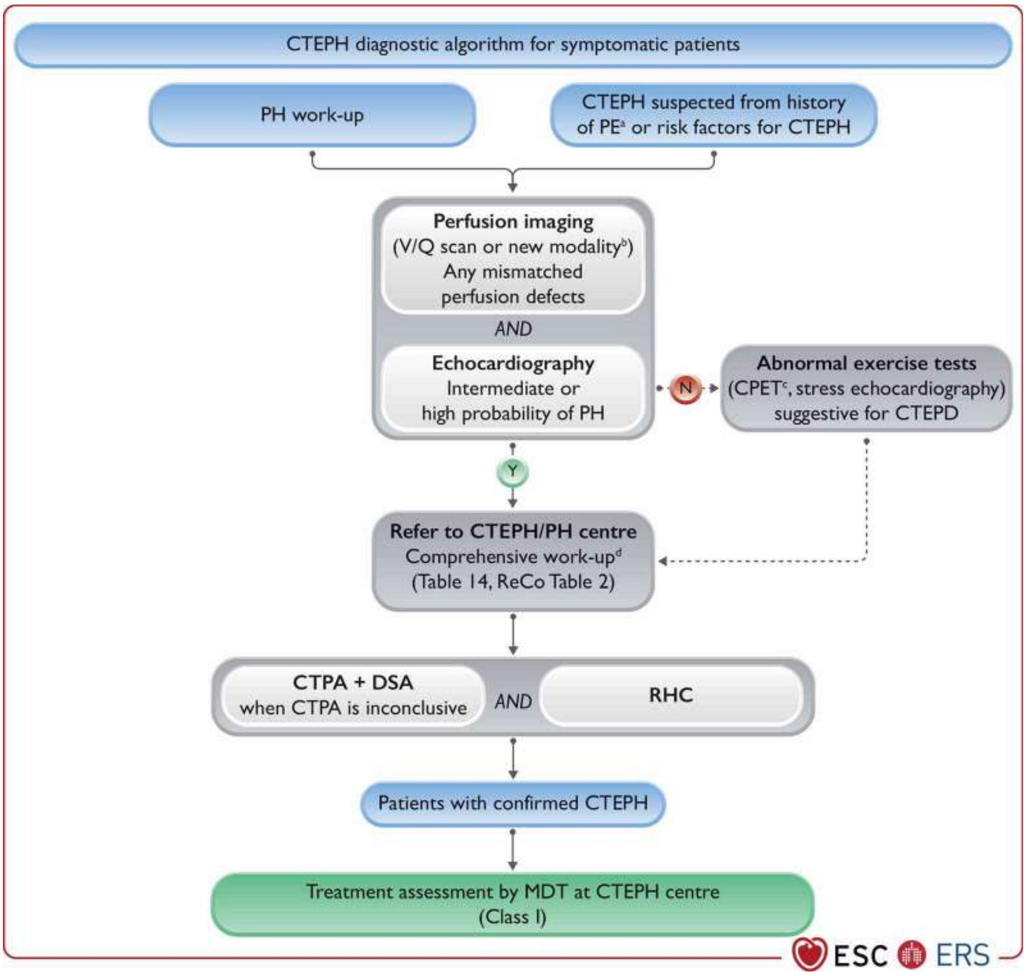

FIGURE 13 Diagnostic strategy in chronic thrombo-embolic pulmonary hypertension. CPET, cardiopulmonary exercise test; CTEPD, chronic thrombo-embolic pulmonary disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; DECT, dual-energy computed tomography; DSA, digital subtraction angiography; MDT, multidisciplinary team; MRI, magnetic resonance imaging; N, no; PE, pulmonary embolism; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; PH, pulmonary hypertension; ReCo, recommendation; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; V/Q, ventilation/perfusion; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2/HR, oxygen pulse; VO_2, oxygen uptake; Y, yes. [a]CTEPH suspected from history of PE, including elevated sPAP on echocardiography and signs suggesting CTEPH on CTPA performed at the time of the acute PE (Section 5.1.7). [b]Alternative perfusion imaging techniques—such as iodine subtraction mapping, DECT, and MRI perfusion—are currently under evaluation. [c]Typical pattern, including low $P_{ET}CO_2$, high VE/VCO_2, low VO_2/HR, and low peak VO_2 (Section 5.1.11). [d]Comprehensive work-up after 3 months of therapeutic anticoagulation or sooner in unstable or rapidly deteriorating patients. Ideally, CTPA, DSA, and RHC are performed in CTEPH centres, but they are sometimes performed in PH centres, depending on the country and organization.

(Figure 13). In the context of acute PE, CTEPH should be considered: 1) if radiological signs (detailed in Section 5.1.7) suggest CTEPH on the CTPA performed to diagnose PE [112], and/or if estimated sPAP is >60 mmHg [112] on echocardiogram; 2) when dyspnoea or functional limitations persist in the clinical course post-PE [754]; and 3) in asymptomatic patients with risk factors for CTEPH or a high CTEPH prediction score [755]. Clinical conditions such as permanent intravascular devices (pacemaker, long-term central lines, ventriculoatrial shunts), inflammatory bowel diseases, essential thrombocythaemia, polycythaemia vera, splenectomy, antiphospholipid syndrome, high-dose thyroid hormone replacement, and malignancy are risk factors for CTEPH [54, 103, 756].

Alternative causes of PA obstructions (also included in group 4 of the PH classification)—including PA sarcomas, other malignant tumours (*e.g.* renal carcinoma, uterine carcinoma, and germ-cell tumours of the testis), non-malignant tumours (*e.g.* uterine leiomyoma), arteriitis without CTD, congenital or acquired PA stenoses, parasites (hydatid cyst), and foreign-body embolism—have to be considered in the differential diagnosis of CTEPD [757]. They can be explored by specific additional imaging such as ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography (PET) scan, which can provide additional information when PA sarcoma is suspected [758].

Ventilation/perfusion scintigraphy [207] remains the most effective tool in excluding CTEPD. Alternative perfusion imaging techniques—such as iodine subtraction mapping, DECT, and MRI perfusion—have numerous theoretical advantages over V/Q but are more technically challenging and expensive, have limited availability, and currently lack multicentre validation.

Computed tomography pulmonary angiography with bi-planar reconstruction is broadly used for diagnosing CTEPD and assessing operability, but a negative CTPA, even if high quality, does not exclude CTEPD, as distal disease can be missed. Digital subtraction angiography is still used to assess treatment options when CTPA is inconclusive. Selective segmental angiography, cone-beam CT, and area detector CT allow for more accurate visualization of subsegmental vasculature and are useful for procedural guidance for BPA. The benefits of the new technologies require validating in prospective trials before being recommended for routine clinical use; a large, European, multicentre study is currently ongoing [759].

10.2. Therapy

The CTEPH treatment algorithm includes a multimodal approach of combinations of pulmonary endarterectomy (PEA), BPA, and medical therapies to target the mixed anatomical lesions: proximal, distal, and microvasculopathy, respectively (Figures 14 and 15).

General measures recommended for PAH also apply to CTEPH, including supervised exercise training, which is effective and safe in inoperable CTEPH patients [760], as well as early after PEA [761].

Lifelong therapeutic anticoagulation is recommended for patients with CTEPH, as recurrent pulmonary thrombo-embolism accompanied by insufficient clot resolution are key pathophysiological features of this disease. There are no RCTs in CTEPH with any of the approved anticoagulants; however, despite this lack of evidence, VKAs are recommended by experts, and are most widely used as background therapy for patients with CTEPH. More recently, NOACs have more frequently been used as alternatives to VKAs, again, lacking evidence from RCTs. A retrospective case series from the UK and a multicentre prospective registry (EXPERT) showed comparable bleeding rates for VKAs and NOACs in CTEPH, but recurrent venous thrombo-embolism rates were higher in those receiving NOACs [762, 763]. In patients with antiphospholipid syndrome (10% of the CTEPH population), VKAs are recommended [103, 764, 765]. Screening for antiphospholipid syndrome should be performed at CTEPH diagnosis. In the absence of any evidence in favour or against prolonged anticoagulation in patients with CTEPD without PH, long-term anticoagulant therapy is based on individual decision-making. It is recommended when the risk of PE recurrence is intermediate or high, thereby following the 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism (Table 11) [103].

10.2.1. Surgical treatment

Surgical PEA is the treatment of choice for patients with accessible PA lesions [102]. As surgery may normalize pulmonary haemodynamics (65% decrease in PVR) [766] and functional capacity, an expert multidisciplinary team including an experienced PEA surgeon (on-site or closely collaborating) is mandatory for evaluating operability and deciding final treatment [102].

Operability is based on team experience, accessibility of PA lesions, correlation between severity of PH and degree of PA obstructions, and comorbidities [767]. The surgical technique is complex but well standardized with >30 years of experience. It consists of a complete bilateral endarterectomy of the PAs down to segmental and subsegmental levels in phases of deep hypothermic circulatory arrest (Figure 15) [767, 768]. In CTEPH centres, surgical outcomes are favourable, with peri-operative mortality rates <2.5% due to improved management of cardiac and pulmonary complications and well-established use of ECMO [768]. Post-operative PH is frequently observed (∼25%) [766], but long-term outcomes after PEA surgery are excellent regarding survival (averaging 90% at 3 years) and quality of life [769–771], even in patients with distal PA obstructions [772]. On the other hand, patients with proximal operable disease declining surgery have a poor long-term outcome, with a 5 year survival of 53% compared with 83% in patients undergoing PEA [773]. Therefore, PEA should be offered to all operable patients with a favourable risk: benefit ratio, ideally during a personal consultation between the patient and the PEA surgeon [102].

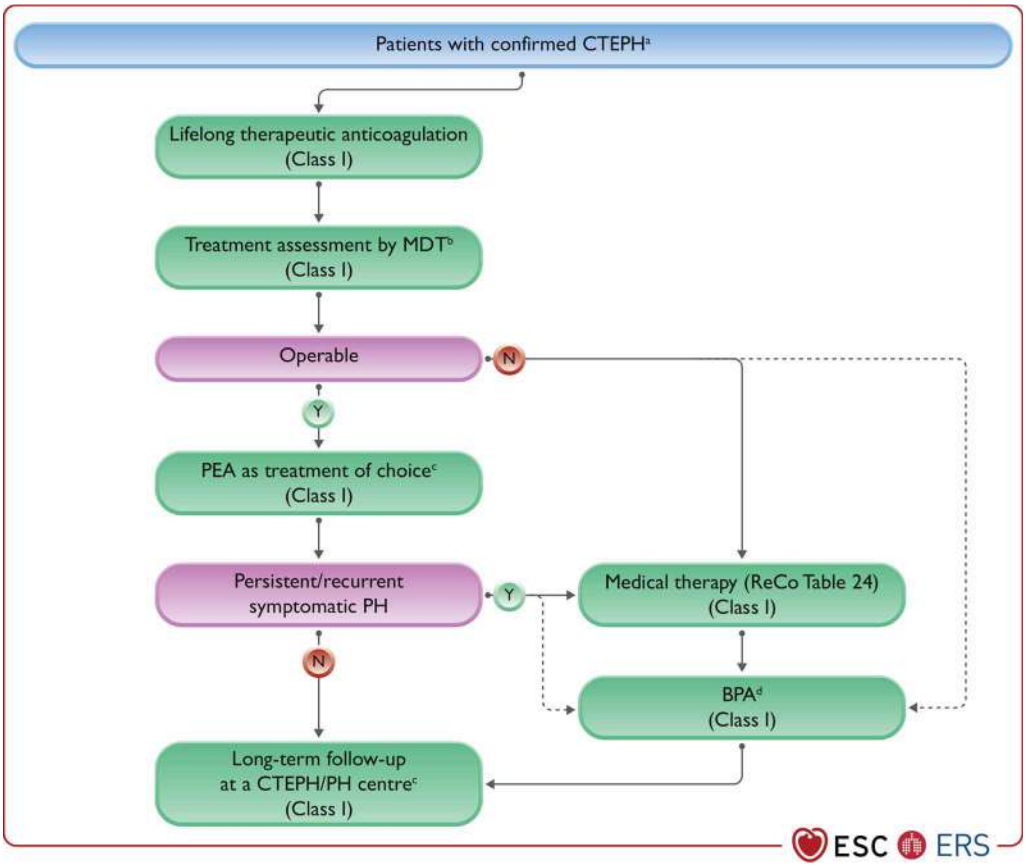

FIGURE 14 Management strategy in chronic thrombo-embolic pulmonary hypertension. BPA, balloon pulmonary angioplasty; CTEPD, chronic thrombo-embolic pulmonary disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; MDT, multidisciplinary team; N, no; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; ReCo, recommendation; WU, Wood units; Y, yes. [a]Selected symptomatic patients with CTEPD without PH can also be treated by PEA and BPA. [b]MDT meeting can be virtual. [c]Treatment assessment may differ, depending on the level of expertise in PEA and BPA. [d]For inoperable patients with PVR >4 WU, medical therapy should be considered prior to BPA; there are limited data on BPA as first-line therapy.

Selected symptomatic patients with CTEPD without PH can be successfully treated by PEA, with clinical and haemodynamic improvements at rest and exercise [135, 774]. Those patients would require careful discussion to balance risk and benefit.

10.2.2. Medical therapy

To manage the microvascular component of CTEPH (Figure 15), medical therapies have been used off-label based on uncontrolled studies and/or regional approvals. Meanwhile, three RCTs have successfully been conducted. The first phase 3 RCT investigated the efficacy of riociguat in patients with inoperable CTEPH or those with persistent/recurrent PH after PEA [775]. Riociguat, after 16 weeks of therapy, improved 6MWD and reduced PVR by 31% compared with placebo, and is approved for this indication. Treprostinil s.c. was investigated in a phase 3 RCT, which showed improved 6MWD at week 24 in patients with inoperable CTEPH or those with persistent/recurrent PH after PEA receiving a high dose compared with a low dose [776]; s.c. treprostinil is approved for this indication. In a phase 2 study including only patients with inoperable CTEPH, macitentan 10 mg improved PVR and 6MWD *versus* placebo at 16 and 24 weeks, respectively [777]. A phase 3 RCT is ongoing to evaluate the safety and efficacy of macitentan 75 mg in inoperable or persistent/recurrent CTEPH (NCT04271475).

Other medical therapies—PDE5is (*e.g.* sildenafil) and ERAs (*e.g.* bosentan)—have been used off-label, as their efficacy in inoperable CTEPH has not been proven by RCTs or registry data [769, 778, 779].

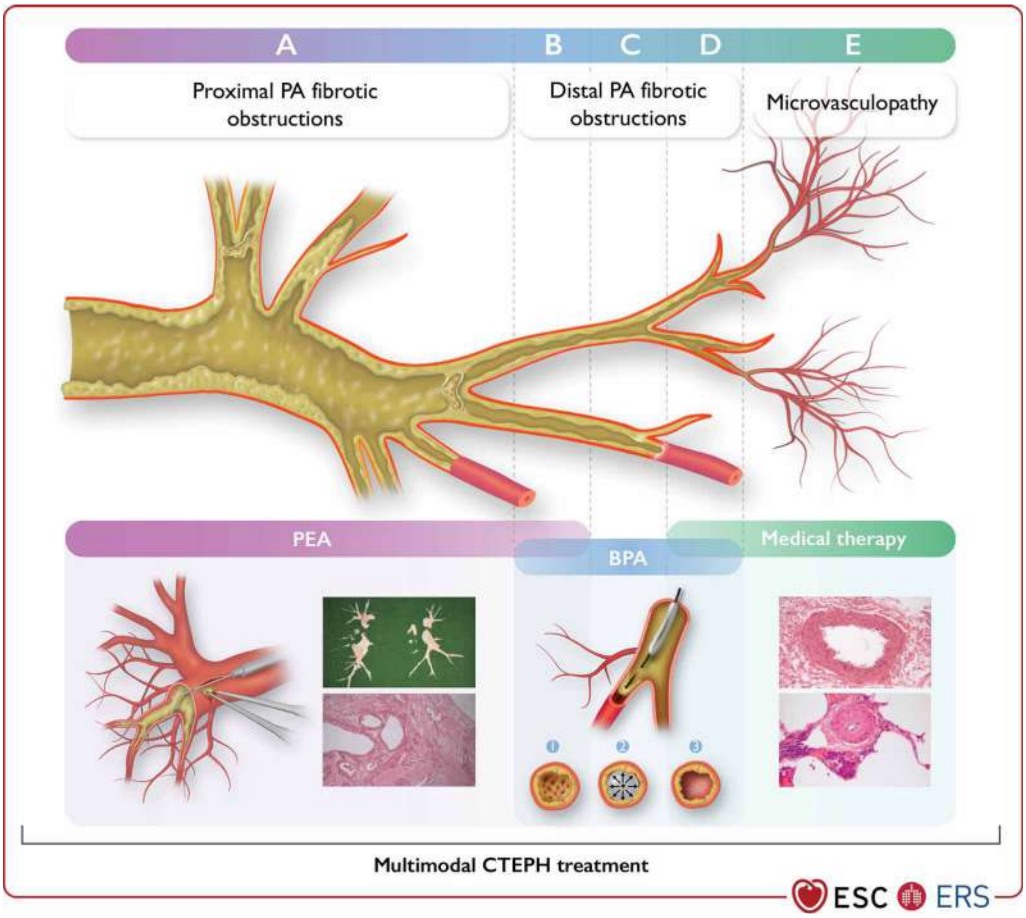

FIGURE 15 Overlap in treatments/multimodality approaches in chronic thrombo-embolic pulmonary hypertension. BPA, balloon pulmonary angioplasty; CTEPH, chronic thrombo-embolic pulmonary hypertension; PA, pulmonary artery; PEA, pulmonary endarterectomy. Top panels: (*A*) Proximal PA fibrotic obstructions (vessel diameter 10–40 mm). (*B*) Distal segmental and subsegmental PA fibrotic obstruction potentially suitable for both PEA and BPA interventions (vessel diameter 2–10 mm). (*C*) Distal subsegmental PA fibrotic obstructions form a web-lesion in a subsegmental branch of the PA suitable for BPA interventions (vessel diameter 0.5–5 mm). (*D*) Distal subsegmental PA fibrotic obstructions form web-like lesions, which might be accompanied by microvasculopathy (vessel diameter <0.5 mm). (*E*) Microvasculopathy (vessel diameter <0.05 mm) treated with medical therapy. Bottom panels: (*A*) bottom left: PEA; vessel diameter (0.2–3 cm). The right PA is opened and the suction dissector is introduced between the artery wall and fibrosis. Following the inside of the artery down to segmental and subsegmental levels, the fibrotic material is subsequently freed from the wall and removed with forceps. (*A*) bottom right: PEA specimen with 'tails' to subsegmental branches of the PA; cross-section of partially organized and permeabilized thrombotic lesion of the large PA dissected during PEA. (*B*, *C*, *D*) The wire is introduced between the fibrotic material (*1*), then the balloon is inflated, leading to a rupture of the web (*2*). Fibrotic material is connected to the vessel wall (*3*). (*E*) Small muscular PA displaying eccentric intimal fibrosis involving intimal thickening and proliferation—target for medical therapies.

However, oral combination therapy, including PDE5is and ERAs, is common practice in patients with CTEPH with severe haemodynamic compromise [780].

10.2.3. Interventional treatment

Balloon pulmonary angioplasty (Figure 15) has become an established treatment for selected patients with inoperable CTEPH or persistent/recurrent PH after PEA, improving haemodynamics (PVR decrease 49–66%), right heart function, and exercise capacity [781–794]. Long-term outcomes are promising, but evidence is still scarce [795].

A staged interventional procedure with a limited number of dilated PA segments per session is preferred [102, 788]. The number of sessions needed and haemodynamic results are dependent on experience [781]. While BPA is effective, it is associated with serious complications, which may be fatal. Procedural and post-interventional complications include vascular injury due to wire perforation, and lung injury with haemoptysis and/or hypoxia [102, 781, 796, 797]. As with all interventional procedures, a significant learning curve has been shown, with reducing complication rates over time [781]; therefore, this procedure should be performed in high-volume CTEPH centres. As the rates of interventional complications can be reduced by medical pre-treatment, patients with a PVR >4 WU should be treated before BPA (Figure 15) [798].

Selected symptomatic patients with CTEPD without PH and segmental/subsegmental lesions can successfully be treated by BPA, with clinical and haemodynamic improvements at rest and exercise [799].

Preliminary data on PADN point towards improved exercise capacity and pulmonary haemodynamics in patients with persistent PH after PEA [800]; further confirmation is being awaited.

10.2.4. Multimodal treatment

Multimodal therapy including surgery, medication, and intervention is offered to selected patients with CTEPH (Figure 15) [102].

Using medical therapy in patients with high pre-operative PVR to improve pulmonary haemodynamics before PEA is common practice but still controversial, as it is felt to delay timely surgical referral and therefore definitive treatment [801–803].

A significant proportion of symptomatic patients may have persistent or recurrent PH following PEA, which may also benefit from medical and/or interventional therapies (Figure 15) [804–806]. An mPAP ⩾30 mmHg has been associated with initiation of medical therapies post-PEA, and an mPAP ⩾38 mmHg and PVR ⩾5 WU with worse long-term survival [806].

Some patients with CTEPH may have mixed anatomical lesions, with surgically accessible lesions in one lung and inoperable lesions in the other lung. Such patients might benefit from a combined approach with BPA (prior to or at the same time as surgery) and PEA to decrease the surgical risk and improve the final result [807].

The recommendations on BPA and medical therapy in patients with inoperable CTEPH have been established based on key narrative question 8 (Supplementary Data, Section 10.1).

The recommendation on the use of medical therapy before interventional therapy in patients with CTEPH who are considered inoperable but candidates for BPA is based on PICO question IV (Supplementary Data, Section 10.2). The included evidence suggests that pre-treatment improves pulmonary haemodynamics and safety of the procedure. This is confirmed by the clinical experience of Task Force members. However, due to the low certainty of the evidence, the recommendation is conditional.

10.2.5. Follow-up

Regardless of the result of PEA/BPA, patients should be regularly followed-up, including invasive assessment with RHC 3–6 months after intervention, allowing for consideration of a multimodal treatment approach. After successful treatment, yearly non-invasive follow-up, including echocardiography and an evaluation of exercise capacity, is indicated because recurrent PH has been described (Figure 14) [806].

Risk assessment with either the ESC/ERS or REVEAL risk score developed for PAH has been validated in medically treated patients with CTEPH [300, 808, 809], but it is unknown if its use has any therapeutic implication or affects outcome.

There are no data or consensus on what is the therapeutic target after PEA/BPA or medical therapy in CTEPH. Most experts accept achieving a good functional class (WHO-FC I–II) and/or normalization or near normalization of haemodynamics at rest, obtained at RHC 3–6 months post-procedure (PEA or last BPA), and improvement in quality of life.

10.3. Chronic thrombo-embolic pulmonary hypertension team and experience criteria

To optimize patients' outcomes, CTEPH centres should fulfil criteria for a PH centre (Section 12) and have a CTEPH multidisciplinary team consisting of a PEA surgeon, BPA interventionist, PH specialist, and thoracic radiologist, trained in high-volume PEA and/or BPA centres. The team should meet regularly to review new referrals and post-treatment follow-up cases. Ideally, CTEPH centres should have PEA activities (>50/year) [810] and BPAs (>30 patients/year or >100 procedures/year) [781], as these figures have been associated with better outcome. The CTEPH centres should also manage medically treated patients. Based on regional requirements, these numbers may be adjusted for the country's population, ideally concentrating care and expertise in high-volume centres.

RECOMMENDATION TABLE 24A Recommendations for chronic thrombo-embolic pulmonary hypertension and chronic thrombo-embolic pulmonary disease without pulmonary hypertension

Recommendations	Class[a]	Level[b]
CTEPH		
Lifelong, therapeutic doses of anticoagulation are recommended in all patients with CTEPH [762]	I	C
Antiphospholipid syndrome testing is recommended in patients with CTEPH	I	C
In patients with CTEPH and antiphospholipid syndrome, anticoagulation with VKAs is recommended [103, 764, 765]	I	C
It is recommended that all patients with CTEPH are reviewed by a CTEPH team for the assessment of multi-modality management [54]	I	C
PEA is recommended as the treatment of choice for patients with CTEPH and fibrotic obstructions within pulmonary arteries accessible by surgery [54, 102]	I	B
BPA is recommended in patients who are technically inoperable or have residual PH after PEA and distal obstructions amenable to BPA [54, 102, 783, 784, 789, 793, 798, 811]	I	B
Riociguat is recommended for symptomatic patients with inoperable CTEPH or persistent/recurrent PH after PEA [775]	I	B
Long-term follow-up is recommended after PEA and BPA, as well as for patients with CTEPH established on medical therapy [782, 805, 806, 812]	I	C
A multi-modality approach should be considered for patients with persistent PH after PEA and for patients with inoperable CTEPH [804, 805, 812]	IIa	C
Treprostinil s.c. may be considered in patients in WHO-FC III–IV who have inoperable CTEPH or persistent/recurrent PH after PEA [776]	IIb	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have inoperable CTEPH [55, 777–779, 801, 803]	IIb	B
In patients with inoperable CTEPH, a combination of sGC stimulator/PDE5i, ERA, [777] or parenteral prostacyclin analogues [776] may be considered	IIb	C
BPA may be considered for technically operable patients with a high proportion of distal disease and an unfavourable risk:benefit ratio for PEA	IIb	C
CTEPD without PH		
In patients with CTEPD without PH, long-term anticoagulant therapy should be considered on individual basis[c]	IIa	C
PEA or BPA should be considered in selected symptomatic patients with CTEPD without PH	IIa	C

RECOMMENDATION TABLE 24B Recommendations for chronic thrombo-embolic pulmonary hypertension and chronic thrombo-embolic pulmonary disease without pulmonary hypertension

Recommendations	GRADE Quality of evidence	GRADE Strength of recommendation	Class[a]	Level[b]
In patients with CTEPH who are candidates for BPA, medical therapy should be considered prior to the intervention [798]	Very low	Conditional	IIa	B

BPA, balloon pulmonary angioplasty; CTEPD, chronic thrombo-embolic pulmonary disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PEA, pulmonary endarterectomy; PE, pulmonary embolism; PH, pulmonary hypertension; s.c., subcutaneous; sGC, soluble guanylate cyclase; VKA, vitamin K antagonist; WHO-FC, World Health Organization functional class. [a]Class of recommendation. [b]Level of evidence. [c]Long-term anticoagulant therapy is recommended when the risk of PE recurrence is intermediate or high [103], or when there is no history of venous thrombo-embolism

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	

11. Pulmonary hypertension with unclear and/or multifactorial mechanisms (group 5)

Pulmonary hypertension with unclear and/or multifactorial mechanisms (Table 24) includes several conditions that may be complicated by complex and sometimes overlapping pulmonary vascular involvement. Although group 5 PH represents less-studied forms of PH, it constitutes a significant part of the worldwide burden of PH [1]. Group 5 PH includes: haematological disorders, such as SCD and chronic myeloproliferative neoplasms; systemic disorders, such as sarcoidosis; metabolic diseases, such as glycogen storage disease; and others, such as chronic renal failure, pulmonary tumour thrombotic microangiopathy, and fibrosing mediastinitis. A common feature of these diseases is that the mechanisms of PH are poorly understood and contributing factors may include, alone or in combination: hypoxic pulmonary vasoconstriction, pulmonary vascular remodelling, thrombosis, fibrotic destruction and/or extrinsic compression of pulmonary vasculature, pulmonary vasculitis, high-output cardiac failure, and left HF. These patients need careful assessment and treatment should be directed to the underlying condition.

11.1. Haematological disorders

In haemoglobinopathies and chronic haemolytic anaemias, including SCD, PH has emerged as a major cause of morbidity and mortality. The prevalence of PH confirmed by RHC was 6–10% in studies of adult patients with stable SCD [93, 94, 813]. Patients with SCD with pre-capillary PH are more commonly homozygous for haemoglobin S, while some have S-β0 thalassaemia (S-β0 thal) or haemoglobin SCD [814]. Thrombotic lesions are a major component of PH related to SCD, more frequently in haemoglobin SCD [814]. Patients with PH and SCD should be followed by multidisciplinary SCD and PH teams, since treatment of the anaemia is a key part of management [814]. There is a lack of data to support the use of PAH drugs in patients with SCD-associated PH. In a study in patients with SCD with TRV ⩾2.7 m/s and a 6MWD of 150–500 m, sildenafil showed no treatment effect on 6MWD, TRV, or NT-proBNP, but appeared to increase hospitalization rates for pain [815]. Preliminary evidence supports the short- and long-term benefits of chronic blood-exchange transfusions in patients with pre-capillary PH complicating SCD [816]. Pre-capillary PH complicating SCD has an important impact on survival, with an overall death rate of 2.0–5.3% in different populations with similar follow-up (26 months and 18 months, respectively) [94, 817]. In β-thalassaemia, invasive haemodynamic evaluation confirmed pre-capillary PH in 2.1% of cases, while a post-capillary profile was found in 0.3% [818]. Potential treatment strategies are awaiting an enhanced understanding of the pathophysiological mechanisms. In spherocytosis, splenectomy is a risk factor for CTEPH [819].

Multiple causes of PH have been described in patients with chronic myeloproliferative disorders [820]. In chronic myelogenous leukaemia, spleen enlargement and anaemia can give rise to hyperkinetic syndrome. Hepatosplenic enlargement can also cause PoPH. Cases of potentially reversible DPAH have been described with dasatinib, bosutinib, and ponatinib. In polycythaemia vera and essential thrombocythaemia, there is an increased risk of venous thrombo-embolic disease and CTEPH; moreover, a blood clot within the hepatic veins can lead to Budd–Chiari syndrome and subsequent PoPH. Pulmonary extramedullary haematopoiesis complicating idiopathic or secondary myelofibrosis may also contribute to dyspnoea and PH.

Group 5 PH may be described in other haematological disorders, such as common variable immunodeficiency; immunoglobulin G4 (IgG4)-related disease; Castleman disease; and polyneuropathy, organomegaly, endocrinopathy, monoclonal immunoglobulin, skin changes (POEMS) syndrome [821–823].

11.2. Systemic disorders

The reported prevalence of PH in patients with sarcoidosis is 6–20% [824]. The causes are multifactorial, including fibrosing lung disease, granulomata in the PAs and/or pulmonary veins, fibrosing mediastinitis and/or extrinsic compression by lymph nodes, pulmonary vasculitis, CTEPH, and PoPH [58, 825]. It is associated with significant morbidity and increased mortality compared with sarcoidosis without PH [58, 825]. In a registry, factors independently associated with outcomes included physiological (forced expiratory volume in 1 s/FVC ratio and DLCO) and functional (6MWD) parameters [58]. In a large study of severe, sarcoidosis-associated PH, PAH drugs improved short-term pulmonary haemodynamics without improving 6MWD [59]. Small RCTs have suggested efficacy of PAH drugs in these patients, which requires confirmation in larger studies [826]. Corticosteroids or immunosuppressive therapy may improve haemodynamics in selected patients with active granulomatous disease. Of note, when pulmonary vascular compression is suspected (fibrosing mediastinitis and/or extrinsic compression by lymph nodes), results from pulmonary angiography and PET scans provide additional information justifying endovascular and/or anti-inflammatory approaches. Long-term survival remains poor in sarcoidosis-associated PH, which makes LTx a reasonable option for selected severe cases.

In pulmonary Langerhans's cell histiocytosis, diminished exercise capacity does not appear to be due to ventilatory limitation but may be related to pulmonary vascular dysfunction. In 29 patients with PH associated with pulmonary Langerhans's cell histiocytosis, PAH drugs improved haemodynamics without worsening oxygen levels [827].

Pulmonary hypertension associated with neurofibromatosis type 1 is a rare but severe complication characterized by female predominance (female/male ratio 3.9:1) [828]. Specific pulmonary vascular involvement exists in these patients, and despite a potential short-term benefit of PAH drugs, prognosis remains poor, and LTx should be considered in selected patients with severe disease. In the presence of dyspnoea, screening for ILD by non-contrast CT and for PH by echocardiography is required [828].

11.3. Metabolic disorders

Glycogen storage diseases are caused by genetic alterations of glycogen metabolism, and PH case reports have been related to glycogen storage disease type 1 and 2 [829]. The occurrence of PH has predominantly been described in glycogen storage disease type 1, where it may partly be due to vasoconstrictive amines such as serotonin. Drugs for PAH have been used in some cases [830].

Untreated patients with Gaucher disease may develop PH, which is caused by a combination of factors, including asplenia, plugging of the vasculature by abnormal macrophages, and pulmonary vascular remodelling. Treatment with enzyme-replacement therapy may improve PH.

11.4. Chronic kidney failure

Although commonly recognized in chronic renal failure, the pathogenesis of PH remains poorly understood and PH is observed in patients prior to and while receiving different dialysis modalities [831]. A recent RHC study of 3504 patients with chronic kidney disease found that CpcPH was the most common phenotype, and the phenotype with the highest mortality [832]. Post-capillary PH has been described in 65% of patients receiving haemodialysis and 71% of patients without kidney replacement [833].

11.5. Pulmonary tumour thrombotic microangiopathy

Pulmonary tumour thrombotic microangiopathy describes tumour-cell microemboli with occlusive fibrointimal remodelling in small PAs, pulmonary veins, and lymphatics. It is a rare cause of PH, which arises due to multiple mechanisms, but probably remains under-diagnosed, as evidenced by autopsy findings [834]. The disorder is associated with carcinomas, notably gastric carcinoma. Progressive vessel occlusion ultimately results in PH, which is often severe, of sudden onset, rapidly progressive, and accompanied by progressive hypoxaemia. Chest CT may show patchy ground-glass and septal markings (masquerading as PVOD).

11.6. Fibrosing mediastinitis

Fibrosing mediastinitis is caused by fibrous tissue proliferating in the mediastinum, encasing mediastinal viscera and compressing mediastinal bronchovascular structures [835]. Pre- or post-capillary PH can complicate the course of fibrosing mediastinitis due to extrinsic compression of the PAs and/or pulmonary veins. Fibrosing mediastinitis can be idiopathic or caused by irradiation, infection (tuberculosis, histoplasmosis), and systemic diseases, such as sarcoidosis and IgG4-related disease, a fibroinflammatory disease characterized by elevated serum IgG4 levels with infiltration of IgG4+ plasma cells and severe fibrosis in affected tissues [821]. Treatment should be directed to the underlying condition. No clear clinical improvement has been described with PAH drugs. Surgical and endovascular procedures have been proposed to de-obstruct or bypass the arterial and/or venous compressions.

In the absence of positive RCTs studying the use of PAH drugs for treating group 5 PH, treating the underlying disorder remains the standard of care [836]. Importantly, some of the diseases described in Table 24 may have a pulmonary venous component that could be made worse with PAH drugs, implying that off-label use of drugs approved for PAH should be considered with great caution, if at all. Placebo-controlled, randomized trials are currently recruiting in well-phenotyped subgroups of PH with unclear and/or multifactorial mechanisms, such as sarcoidosis-associated PH.

12. Definition of a pulmonary hypertension centre

While PH is not an uncommon condition, severe forms of PH, especially PAH and CTEPH, require highly specialized management. Since medical centres with multidisciplinary teams and a high volume of patients generally offer best standard of care, which translates into better clinical outcomes, establishing PH centres is clinically and economically highly desirable and is supported by patient organizations and scientific societies. The purpose of a PH centre is to: receive new referrals; assess and investigate the cause of PH; carefully phenotype and routinely manage patients with medical, interventional, and surgical approaches; work closely with other health care providers to achieve the best outcomes for patients; undertake audits (reporting patient case mix and quality indicators); and be involved in clinical and translational research, and education. The requirements—comprising definition, multidisciplinary structure, number of cases, procedures, and staffing levels, as well as the skills and resources needed in a PH referral centre—are described below and in Figure 16. Criteria for paediatric and CTEPH centres are described elsewhere (Sections 7.8.3 and 10.3, respectively).

12.1. Facilities and skills required for a pulmonary hypertension centre

Pulmonary hypertension centres care for a sufficient number of patients on PH therapy, as well as new referrals, to warrant this status. According to the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH and the European Reference Network on rare respiratory diseases (ERN-LUNG) competency requirements, the ideal number of patients seen by an adult centre each year is no fewer than 200, of which at least half have a final diagnosis of PAH; a PH centre follows at least 50 patients with PAH or CTEPH and receives at least two new referrals per month with documented PAH or CTEPH [25, 26, 837–839]. These numbers can be adapted according to specific country characteristics (small population, large geographical area) provided that strong working collaborations are established with high-volume centres. This is currently facilitated by the availability of secure virtual platforms (*e.g.* ERN clinical patient management system) [840].

Proper training of staff members includes core competencies, such as those outlined in the ERS Pulmonary Vascular Diseases Continuing Professional Development framework [841], and builds on entrustable professional activities, described in the ESC Core Curriculum [842].

Clinical, laboratory, and imaging facilities include: a ward where health care providers have expertise in PH; a specialist outpatient service; an intermediate/ICU; 24/7 emergency care; an interventional radiology unit; diagnostic investigations, including echocardiography, CT scanning, nuclear medicine, MRI, exercise tests, and PFTs; a cardiac catheterization laboratory; access to genetic counselling and testing; and fast and easy access to cardiothoracic and vascular surgery. Key diagnostic procedures are performed in sufficient numbers to guarantee expertise (*e.g.* ERN-LUNG requirements) [837]. In analogy with the 'advanced heart failure units' [843], PH centres offer the full range of PAH therapies available in their country (including i.v./s.c. prostacyclin derivatives) and have early referral protocols to CTEPH, LTx, and rehabilitation centres. Since evaluation and early availability of new drugs and techniques are critical, PH centres participate in collaborative clinical research.

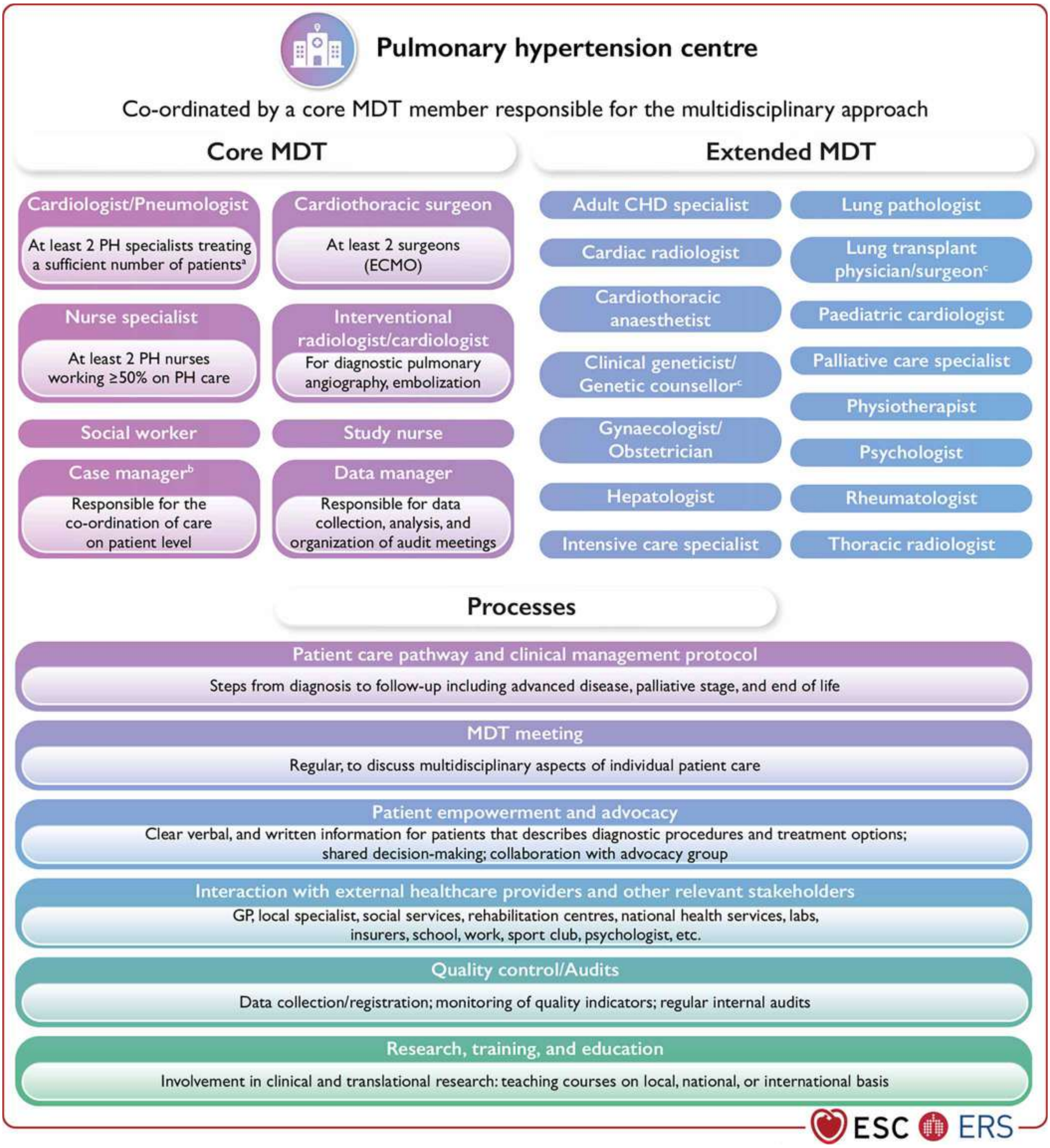

FIGURE 16 Pulmonary hypertension centre schematic. CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; GP, general practitioner; MDT, multidisciplinary team; PH, pulmonary hypertension. [a]Number adapted according to specific country characteristics. [b]Case manager can be a nurse specialist, social worker, physiotherapist, or administrative assistant in function of the centre organization. [c]Can be located in partner centres. Adapted from Biganzoli *et al.* [846].

Regular multidisciplinary team meetings, including core members and on-demand invited members (extended multidisciplinary team) as needed (Figure 16), are required to establish and adapt individual patient care pathways. Case management (co-ordination of individual patient pathways) should include administrative, social, and care support. Remote accessibility of the PH centre by phone, mail, or other is a vital part of the care. Strategies have to be implemented in order to improve health literacy and shared decision-making, with the support of dedicated patient decision tools. Transitioning from a paediatric PH centre to an adult PH centre requires adequate planning to prevent gaps in care. Involving national and/or international patient associations helps to design patient-centric care and to spread medical knowledge among patients and their carers.

Pulmonary hypertension centres should record patients' data using local, national, or international patient registries, and be able to report process indicators (compliance with diagnostic and treatment guidelines, including LTx) and outcome indicators, such as WHO-FC, exercise capacity, haemodynamics, quality of life, complications, and survival. They should undergo regular audits to assess the quality of delivered care.

RECOMMENDATION TABLE 25 Recommendations for pulmonary hypertension centres

Recommendations	Class[a]	Level[b]
It is recommended that PH centres provide care by a multidisciplinary team (cardiologist, pneumologist, rheumatologist, nurse specialist, radiologist, psychological and social work support, and appropriate on-call expertise)	I	C
It is recommended that PH centres have direct links and quick referral patterns to other services (such as genetic counselling, PEA/BPA, LTx, and adult congenital heart disease service)	I	C
It is recommended that PH centres maintain a patient registry	I	C
It is recommended that PH centres collaborate with patient associations	I	C
Accreditation of the PH centres should be considered (*e.g.* https://ec.europa.eu/health/ern/assessment_en)	IIa	C
PH centres' participation in collaborative clinical research should be considered	IIa	C
PH centres should follow-up of a sufficient number of patients to maintain expertise (at least 50 patients with PAH or CTEPH and at least two new referrals per month with documented PAH or CTEPH), and consider establishing collaborations with high-volume centres	IIa	C

BPA, balloon pulmonary angioplasty; CTEPH, chronic thrombo-embolic pulmonary hypertension; LTx, lung transplantation; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension. [a]Class of recommendation. [b]Level of evidence.

12.2. European Reference Network

In 2017, the European Commission launched European Reference Networks (ERNs) for rare diseases that included the ERN-LUNG with a PH core network. European Reference Networks are patient-centred networks of commissioned centres offering guidance and cross-border best standard of care in the European Union. The PH network includes over 20 full members, contributing each year ∼1500 new patients with PAH or CTEPH [844]. It also includes UK supporting centres, and affiliated partners (who do not necessarily have to fulfil the minimum competency criteria of the ERN-LUNG PH network). The ERN-LUNG requires and monitors standards for these centres.

12.3. Patient associations and patient empowerment

Pulmonary hypertension centres should inform patients about patient associations and encourage them to join such groups. Patient associations are a valuable resource for managing patients, as they provide educational and emotional support, and can have positive effects on coping, confidence, and outlook [845]. It is recommended that PH centres collaborate with patient associations on initiatives to empower patients and improve the patient experience, addressing issues such as health literacy, digital skills, healthy lifestyles, mental health, and self-management. Health care can be delivered more effectively and efficiently if patients are full partners in the process.

13. Key messages

1) The haemodynamic definition of PH has been updated as mPAP >20 mmHg. The definition of PAH also implies a PVR >2 WU and PAWP ⩽15 mmHg. These cut-off values better reflect the limits of normal ranges, but do not yet translate into new therapeutic recommendations, since the efficacy of PAH therapy in patients with PVD and an mPAP 21–24 mmHg and/or PVR 2–3 WU is still unknown.
2) The main diagnostic algorithm for PH has been simplified following a three-step approach, from suspicion by first-line physicians, detection by echocardiography, and confirmation with RHC in PH centres. Warning signs associated with worse outcomes have been identified, which justify immediate referral and management in PH centres.

3) Screening strategies for PAH in patients with SSc and in those at risk of HPAH are proposed based on the results of published cohort studies. Their implementation may shorten the time from symptom onset to diagnosis of PAH.
4) An improved recognition of CT and echocardiographic signs of CTEPH at the time of an acute PE event, together with a systematic follow-up of patients with acute PE, as indicated in the 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism, should help to remediate the underdiagnosis of CTEPH.
5) The three-strata risk-stratification assessment in PAH has been refined after being validated in multiple registries. The MRI and echocardiographic criteria have been added to the ESC/ERS table, refining non-invasive evaluation at diagnosis.
6) A four-strata risk stratification, dividing the large, intermediate-risk group into intermediate–low and intermediate–high risk, is proposed at follow-up.
7) The treatment algorithm for PAH has been simplified, with a clear focus on risk assessment, cardiopulmonary comorbidities, and treatment goals. Initial combination therapy and treatment escalation at follow-up when appropriate are current standards.
8) The Task Force has attempted to close the gap between paediatric and adult PAH care, with therapeutic and follow-up strategies based on risk stratification and treatment response, extrapolated from that in adults but adapted for age.
9) The recommendations on sex-related issues in patients with PAH, including pregnancy, have been updated, with information and shared decision-making as key points.
10) The recommendations for rehabilitation and exercise programmes in PH have been updated following the release of additional supportive evidence.
11) For the first time, there is a recommendation for PH medical therapy in group 3 PH, based on a single positive RCT in patients with ILD.
12) The concept of CTEPD with or without PH has been introduced, enabling further research on the natural history and management in the absence of PH.
13) The treatment algorithm for CTEPH has been modified, including multimodal therapy with surgery, PH drugs, and BPA.

14. Gaps in evidence

14.1. Pulmonary arterial hypertension (group 1)

- The efficacy and safety of PAH drugs in group 1 patients with an mPAP 21–24 mmHg, PVR 2–3 WU, and exercise PH has to be established.
- The role of PAH drugs in different PAH subgroups, including schistosomiasis-associated PAH, needs to be explored.
- Risk-stratification assessment in PAH needs to be further prospectively validated through goal-orientated outcome studies, and optimized for patients with PAH and comorbidities.
- New PAH phenotypes observed in patients with significant cardiopulmonary comorbidities are common and should be the focus of more research.
- The importance of PAH patient phenotypes and the relevance of comorbidities on treatment goals and outcomes must be further evaluated.
- The impact of PAH therapies and treatment strategies on survival needs to be further assessed.
- Pulmonary arterial hypertension drugs targeting novel pathways are emerging and the impact of add-on use of this medication on outcomes has to be evaluated in RCTs.
- The role of RV imaging techniques (echocardiography, cMRI) in diagnosing and stratifying risk in PAH needs to be further studied. The proposed cut-off values for risk stratification need to be properly validated in multicentre studies.
- The role of CPET in the early diagnosis of PAH in populations at risk of developing PAH, and in assessing prognosis in PAH on top of clinical and haemodynamic data, needs further investigation.
- The role of exercise echocardiography and exercise RHC in patients at risk of developing PAH, with abnormal CPET but normal rest echocardiogram, also needs further evaluation.
- The use of mechanical circulatory support, particularly in reversible PH or in patients with advanced right HF with an exit strategy (such as LTx), has to be further studied.
- Differences in natural history and treatment response between adults and children should be further investigated.
- Further studies are needed on the effects of PADN in PAH and in other PH groups.
- The impact of centre volume, organization, and expertise on treatment outcome needs further investigation.

14.2. Pulmonary hypertension associated with left heart disease (group 2)

- The management of patients with group 2 PH needs further study with RCTs.
- Additional research is needed to facilitate non-invasive diagnosis of HFpEF-associated PH and distinguishing it from PAH.
- The role of fluid challenge and exercise testing to reveal left HF needs further validation.
- Further studies focusing on PDE5is in patients with HFpEF and a CpcPH phenotype are needed and currently underway.
- The effects that new HF medication (ARNIs, SGLT-2is) has on PH, through reverse remodelling of the LV, need further investigation.

14.3. Pulmonary hypertension associated with lung diseases and/or hypoxia (group 3)

- The management of patients with group 3 PH has to be further studied in RCTs.
- Refining phenotypes will be crucial, as this will inform development of trials.
- Clinical relevance and therapeutic implications of severe PH in lung disease need to be investigated.
- Long-term data on the effects of inhaled treprostinil (and other PAH drugs) in patients with PH associated with lung disease are needed.
- The impact of the hypobaric and hypoxic environment of the >150 million people living at >2500 m altitude has to be clarified, and studies need to be performed to assess potential treatment strategies for PH.

14.4. Chronic thrombo-embolic pulmonary hypertension (group 4)

- The differentiation between acute and chronic PE in imaging (CTPA) has to be improved.
- In patients with suspected CTEPH, the diagnostic role of DECT or iodine subtraction mapping *versus* V/Q lung scintigraphy has to be validated.
- The effect of drug therapy on the outcome of patients with CTEPH needs to be established.
- The treatment goals in patients with CTEPH have to be clarified, as it is still unclear if normalizing mPAP and PVR translates into improved outcomes.
- The role of BPA *versus* PEA should be further clarified: which treatment in which patient? Are they equivalent for the treatment of segmental/subsegmental disease?
- In inoperable CTEPH or persistent/recurrent PH after PEA, the potential role of combination therapy of PH drugs must be assessed.
- The role of medical treatments as bridges to interventional and operative treatments needs to be formally tested.
- Randomized controlled trials are needed to discriminate the effects of PEA and early follow-up rehabilitation.
- The effect of PEA, BPA, and medical therapy on patients with CTEPD without PH is not established.

14.5. Pulmonary hypertension with unclear and/or multifactorial mechanisms (group 5)

- Further research needs to inform management of group 5 PH, such as SCD-associated PH and sarcoidosis-associated PH.

15. 'What to do' and 'What not to do' messages from the Guidelines

BOX 4 'What to do' and 'What not to do' messages from the Guidelines

Recommendations	Class[a]	Level[b]
Recommendations for right heart catheterization and vasoreactivity testing		
Right heart catheterization		
It is recommended that RHC is performed to confirm the diagnosis of PH (especially PAH or CTEPH), and to support treatment decisions	I	B
In patients with suspected or known PH, it is recommended that RHC is performed in experienced centres	I	C
It is recommended that RHC comprises a complete set of haemodynamics and is performed following standardized protocols	I	C

Continued

BOX 4 Continued

Recommendations	Class[a]	Level[b]
Vasoreactivity testing		
Vasoreactivity testing is recommended in patients with I/H/DPAH to detect patients who can be treated with high doses of a CCB	I	B
It is recommended that vasoreactivity testing is performed at PH centres	I	C
It is recommended to consider a positive response to vasoreactivity testing by a reduction of mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg with an increased or unchanged CO[c]	I	C
Inhaled nitric oxide, inhaled iloprost, or i.v. epoprostenol are recommended for performing vasoreactivity testing	I	C
Vasoreactivity testing, for identifying candidates for CCB therapy, is not recommended in patients with PAH other than I/H/DPAH, and in PH groups 2, 3, 4, and 5	III	C
Recommendations for diagnostic strategy		
Echocardiography		
Echocardiography is recommended as the first-line, non-invasive, diagnostic investigation in suspected PH	I	B
It is recommended to assign an echocardiographic probability of PH, based on an abnormal TRV and the presence of other echocardiographic signs suggestive of PH (see Table 10)	I	B
It is recommended to maintain the current threshold for TRV (>2.8 m/s) for echocardiographic probability of PH according to the updated haemodynamic definition	I	C
Imaging		
Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to assess for CTEPH	I	C
CT pulmonary angiography is recommended in the work-up of patients with suspected CTEPH	I	C
Routine biochemistry, haematology, immunology, HIV testing, and thyroid function tests are recommended in all patients with PAH, to identify associated conditions	I	C
Abdominal ultrasound is recommended for the screening of portal hypertension	I	C
Other diagnostic tests		
Pulmonary function tests with DLCO are recommended in the initial evaluation of patients with PH	I	C
Open or thoracoscopic lung biopsy is not recommended in patients with PAH	III	C
Recommendations for screening and improved detection of pulmonary arterial hypertension and chronic thrombo-embolic pulmonary hypertension		
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
CTEPH/CTEPD		
In patients with persistent or new-onset dyspnoea or exercise limitation following PE, further diagnostic evaluation to assess for CTEPH/CTEPD is recommended	I	C
For symptomatic patients with mismatched perfusion lung defects beyond 3 months of anticoagulation for acute PE, referral to a PH/CTEPH centre is recommended after considering the results of echocardiography, BNP/NT-proBNP, and/or CPET	I	C
Other		
Counselling regarding the risk of PAH and annual screening is recommended in individuals who test positive for PAH-causing mutations and in first-degree relatives of patients with HPAH	I	B
In patients referred for liver transplantation, echocardiography is recommended as a screening test for PH	I	C
Recommendations for evaluating the disease severity and risk of death in patients with pulmonary arterial hypertension		
It is recommended to evaluate disease severity in patients with PAH with a panel of data derived from clinical assessment, exercise tests, biochemical markers, echocardiography, and haemodynamic evaluations	I	B
Achieving and maintaining a low-risk profile on optimized medical therapy is recommended as a treatment goal in patients with PAH	I	B
For risk stratification at the time of diagnosis, the use of a three-strata model (low, intermediate, and high risk) is recommended, taking into account all available data including haemodynamics	I	B
For risk stratification during follow-up, the use of a four-strata model (low, intermediate–low, intermediate–high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary	I	B

Continued

BOX 4 Continued

Recommendations	Class[a]	Level[b]
Recommendations for general measures and special circumstances		
General measures		
Supervised exercise training is recommended in patients with PAH under medical therapy	I	A
Psychosocial support is recommended in patients with PAH	I	C
Immunization of patients with PAH against SARS-CoV-2, influenza, and Streptococcus pneumoniae is recommended	I	C
Diuretic treatment is recommended in patients with PAH with signs of RV failure and fluid retention	I	C
Long-term oxygen therapy is recommended in patients with PAH whose arterial blood oxygen pressure is <8 kPa (60 mmHg)[d]	I	C
In the presence of iron-deficiency anaemia, correction of iron status is recommended in patients with PAH	I	C
The use of ACEis, ARBs, ARNIs, SGLT-2is, beta-blockers, or ivabradine is not recommended in patients with PAH unless required by comorbidities (*i.e.* high blood pressure, coronary artery disease, left HF, or arrhythmias)	III	C
Special circumstances		
In-flight oxygen administration is recommended for patients using oxygen or whose arterial blood oxygen pressure is <8 kPa (60 mmHg) at sea level	I	C
Recommendations for women of childbearing potential		
It is recommended that women of childbearing potential with PAH are counselled at the time of diagnosis about the risks and uncertainties associated with becoming pregnant; this should include advice against becoming pregnant, and referral for psychological support where needed	I	C
It is recommended to provide women of childbearing potential with PAH with clear contraceptive advice, considering the individual needs of the woman but recognizing that the implications of contraceptive failure are significant in PAH	I	C
It is recommended that women with PAH who consider pregnancy or who become pregnant eceive prompt counselling in an experienced PH centre, to facilitate genetic counselling and shared decision-making, and to provide psychological support to the patients and their families where needed	I	C
For women with PAH having termination of pregnancy, it is recommended that this be performed in PH centres with psychological support provided to the patient and their family	I	C
As teratogenic potential has been reported in preclinical models for endothelin receptor antagonists and riociguat, these drugs are not recommended during pregnancy	III	B
Recommendations for the treatment of vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension		
High doses of CCBs are recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing	I	C
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH, or DPAH treated with high doses of CCBs	I	C
Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked haemodynamic improvement (mPAP <30 mmHg and PVR <4 WU)	I	C
Initiating PAH therapy is recommended in patients who remain in WHO-FC III or IV or those without marked haemodynamic improvement after high doses of CCBs	I	C
CCBs are not recommended in patients without a vasoreactivity study or non-responders, unless prescribed for other indications (*e.g.* Raynaud's phenomenon)	III	C
Recommendations for initial oral drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension without cardiopulmonary comorbidities[e]		
Initial combination therapy with ambrisentan and tadalafil is recommended	I	B
Initial combination therapy with macitentan and tadalafil is recommended	I	B
Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended	III	B
Recommendations for sequential drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension		
General recommendation for sequential combination therapy		
It is recommended to base treatment escalations on risk assessment and general treatment strategies (see treatment algorithm)	I	C
Evidence from studies with a composite morbidity/mortality endpoint as primary outcome measure		
The addition of macitentan to PDE5is or oral/inhaled prostacyclin analogues is recommended to reduce the risk of morbidity/mortality events	I	B
The addition of selexipag to ERAs[f] and/or PDE5is is recommended to reduce the risk of morbidity/mortality events	I	B
The addition of oral treprostinil to ERA or PDE5i/riociguat monotherapy is recommended to reduce the risk of morbidity/mortality events	I	B

Continued

BOX 4 Continued

Recommendations	Class[a]	Level[b]
The addition of bosentan to sildenafil is not recommended to reduce the risk of morbidity/ mortality events	III	B
Evidence from studies with change in 6MWD as primary outcome measure		
Addition of sildenafil to epoprostenol is recommended to improve exercise capacity	I	B
Evidence from studies with safety of combination therapy as primary outcome measure		
Combining riociguat and PDE5is is not recommended[g]	III	B
Recommendations for intensive care management for pulmonary arterial hypertension		
When managing patients with right HF in the ICU, it is recommended to involve physicians with expertise, treat causative factors, and use supportive measures, including inotropes and vasopressors, fluid management, and PAH drugs as appropriate	I	C
Recommendations for lung transplantation		
It is recommended that potentially eligible candidates are referred for LTx evaluation when they have an inadequate response to oral combination therapy, indicated by an intermediate–high or high risk or by a REVEAL risk score >7	I	C
It is recommended to list patients for LTx who present with a high risk of death or with a REVEAL risk score ⩾10 despite receiving optimized medical therapy including s.c. or i.v. prostacyclin analogues	I	C
Recommendations for pulmonary arterial hypertension associated with drugs or toxins		
It is recommended to make a diagnosis of drug- or toxin-associated PAH in patients who had relevant exposure and in whom other causes of PH have been excluded	I	C
In patients with suspected drug- or toxin-associated PAH, it is recommended to discontinue the causative agent whenever possible	I	C
Recommendations for pulmonary arterial hypertension associated with connective tissue disease		
In patients with PAH associated with CTD, treatment of the underlying condition according to current guidelines is recommended	I	A
In patients with PAH associated with CTD, the same treatment algorithm as for patients with IPAH is recommended	I	C
Recommendations for pulmonary arterial hypertension associated with human immunodeficiency virus infection		
In patients with PAH associated with HIV infection, antiretroviral treatment according to current guidelines is recommended	I	A
Recommendations for pulmonary arterial hypertension associated with portal hypertension		
Echocardiography is recommended in patients with liver disease or portal hypertension with signs or symptoms suggestive of PH, and as a screening tool in patients evaluated for liver transplantation or transjugular portosystemic shunt	I	C
It is recommended that patients with PAH associated with portal hypertension are referred to centres with expertise in managing both conditions	I	C
Drugs approved for PAH are not recommended for patients with portal hypertension and unclassified PH (*i.e.* elevated mPAP, high CO, and a normal PVR)	III	C
Recommendations for shunt closure in patients with pulmonary-systemic flow ratio >1.5:1 based on calculated pulmonary vascular resistance		
In patients with ASD, VSD, or PDA and a PVR <3 WU, shunt closure is recommended	I	C
In patients with ASD and a PVR >5 WU despite PAH treatment, shunt closure is not recommended	III	C
Recommendations for pulmonary arterial hypertension associated with adult congenital heart disease		
Risk assessment		
Risk assessment is recommended for patients with persistent PAH after defect closure	I	C
Treatment		
Bosentan is recommended in symptomatic patients with Eisenmenger syndrome to improve exercise capacity	I	B
In women with Eisenmenger syndrome, pregnancy is not recommended	III	C
In patients with Eisenmenger syndrome, routine phlebotomy to lower elevated haematocrit is not recommended	III	C
Recommendations for pulmonary arterial hypertension with signs of venous/capillary involvement		
A combination of clinical and radiological findings, ABG, PFTs, and genetic testing is recommended to diagnose PAH with signs of venous and/or capillary involvement (PVOD/PCH)	I	A
Identification of biallelic *EIF2AK4* mutations is recommended to confirm a diagnosis of heritable PVOD/PCH	I	A
Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is recommended as soon as the diagnosis is established	I	C
Lung biopsy is not recommended to confirm a diagnosis of PVOD/PCH	III	C
Recommendations for paediatric pulmonary hypertension		
Children		
It is recommended to perform the diagnostic work-up, including RHC and acute vasodilator testing, and treat children with PH at centres with specific expertise in paediatric PH	I	C

Continued

BOX 4 Continued

Recommendations	Class[a]	Level[b]
In children with PH, a comprehensive work-up for confirming diagnosis and specific aetiology is recommended (similar to that in adults, but adapted for age)	I	C
For confirming PH diagnosis, RHC is recommended, preferably before initiating any PAH therapy	I	C
In children with IPAH/HPAH, acute vasoreactivity testing is recommended to detect those who may benefit from CCB therapy	I	C
It is recommended to similarly define a positive response to acute vasoreactivity testing in children and adults by a reduction in mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg, with an increased or unchanged CO	I	C
In children with PAH, a therapeutic strategy based on risk stratification and treatment response is recommended, extrapolated from that in adults, but adapted for age	I	C
It is recommended to monitor the treatment response in children with PAH by serially assessing a panel of data derived from clinical assessment, echocardiographic evaluation, biochemical markers, and exercise tolerance tests	I	C
Infants		
It is recommended to screen infants with bronchopulmonary dysplasia for PH	I	B
In infants with (or at risk of) bronchopulmonary dysplasia and PH, treating lung disease—including hypoxia, aspiration, and structural airway disease—and optimizing respiratory support is recommended before initiating PAH therapy	I	B
Recommendations for pulmonary hypertension associated with left heart disease		
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended	I	C
In patients with LHD and CpcPH with a severe pre-capillary component (*e.g.* PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
Drugs approved for PAH are not recommended in PH-LHD[h]	III	A
Recommendations for pulmonary hypertension associated with lung disease and/or hypoxia		
If PH is suspected in patients with lung disease, it is recommended that echocardiography[i] be performed and results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging	I	C
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I	C
In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[j]	I	C
In patients with lung disease and severe PH, an individualized approach to treatment is recommended	I	C
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation	I	C
In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I	C
The use of ambrisentan is not recommended in patients with PH associated with IPF	III	B
The use of riociguat is not recommended in patients with PH associated with IIP	III	B
The use of PAH medications is not recommended in patients with lung disease and non-severe PH[k]	III	C
Recommendations for chronic thrombo-embolic pulmonary hypertension and chronic thrombo-embolic pulmonary disease without pulmonary hypertension		
CTEPH		
Lifelong, therapeutic doses of anticoagulation are recommended in all patients with CTEPH	I	C
Antiphospholipid syndrome testing is recommended in patients with CTEPH	I	C
In patients with CTEPH and antiphospholipid syndrome, anticoagulation with VKAs is recommended	I	C
It is recommended that all patients with CTEPH are reviewed by a CTEPH team for the assessment of multi-modality management	I	C
PEA is recommended as the treatment of choice for patients with CTEPH and fibrotic obstructions within pulmonary arteries accessible by surgery	I	B

Continued

BOX 4 Continued

Recommendations	Class[a]	Level[b]
BPA is recommended in patients who are technically inoperable or have residual PH after PEA and distal obstructions amenable to BPA	I	B
Riociguat is recommended for symptomatic patients with inoperable CTEPH or persistent/recurrent PH after PEA	I	B
Long-term follow-up is recommended after PEA and BPA, as well as for patients with CTEPH established on medical therapy	I	C
Recommendations for pulmonary hypertension centres		
It is recommended that PH centres provide care by a multidisciplinary team (cardiologist, pneumologist, rheumatologist, nurse specialist, radiologist, psychological and social work support, appropriate on-call expertise)	I	C
It is recommended that PH centres have direct links and quick referral patterns to other services (such as genetic counselling, PEA/BPA, LTx, adult congenital heart disease service)	I	C
It is recommended that PH centres maintain a patient registry	I	C
It is recommended that PH centres collaborate with patient associations	I	C

6MWD, 6-minute walking distance; ABG, arterial blood gas analysis; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ASD, atrial septal defect; BNP/NT-proBNP, brain natriuretic peptide/N-terminal pro-brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CCB, calcium channel blocker; CpcPH, combined post- and pre-capillary pulmonary hypertension; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTD, connective tissue disease; CTEPD, chronic thrombo-embolic pulmonary disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; DLCO, Lung diffusion capacity for carbon monoxide; DPAH, drug-associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; FVC, forced vital capacity; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; ICU, intensive care unit; I/H/DPAH, idiopathic, heritable, drug-associated pulmonary arterial hypertension; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; i.v., intravenous; LHD, left heart disease; LTx, lung transplantation; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PCH, pulmonary capillary haemangiomatosis; PDA, patent ductus arteriosus; PDE5i, phosphodiesterase 5 inhibitor; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PFTs, pulmonary function tests; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension associated with left heart disease; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricular; s.c., subcutaneous; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; SSc, systemic sclerosis; TRV, tricuspid regurgitation velocity; VKA, vitamin K antagonist; VSD, ventricular septal defect; WHO-FC, World Health Organization functional class; WU, Wood units. [a]Class of recommendation. [b]Level of evidence. [c]Testing should also be performed in patients with a baseline mPAP ⩽40 mmHg, in whom the same responder criteria apply. [d]Measured on at least two occasions. [e]Cardiopulmonary comorbidities are predominantly encountered in elderly patients and include risk factors for HFpEF such as obesity, diabetes, coronary heart disease, a history of hypertension, and/or a low DLCO. [f]ERA used in the GRIPHON study were bosentan and ambrisentan. [g]The PATENT plus study investigated the combination of sildenafil and riociguat; however, combining riociguat with any PDE5i is contraindicated. [h]Safety concerns have been identified when ERAs are used in patients with HF (HFpEF and HFrEF, with or without PH) and when sildenafil is used in patients with persistent PH after correction of valvular heart disease. [i]Assessments should ideally be made when the patient is clinically stable, as exacerbations can significantly raise pulmonary artery pressure. [j]This recommendation does not apply to patients with end-stage lung disease who are not considered candidates for LTx. [k]This does not include inhaled treprostinil, which may be considered in patients with PH associated with ILD irrespective of PH severity.

16. Quality indicators

Quality indicators (QIs) are tools that may be used to evaluate care quality, including structural, process, and outcomes of care [847]. They may also serve as a mechanism for enhancing adherence to guideline recommendations through associated quality-improvement initiatives and benchmarking of care providers [848, 849]. As such, the role of QIs in improving care and outcomes for cardiovascular disease is increasingly being recognized by health care authorities, professional organizations, payers, and the public [847].

The ESC understands the need for measuring and reporting quality and outcomes of cardiovascular care, and has established methods for developing the ESC QIs for the quantification of care and outcomes for cardiovascular diseases [847]. To date, the ESC has developed QI suites for a number of cardiovascular diseases [850–852] and embedded these in respective ESC Clinical Practice guidelines [27, 477, 853, 854]. Furthermore, the ESC aims to integrate its QIs with clinical registries such as the EurObservational

BOX 5 'What to do' and 'What not to do' messages developed with GRADE Evidence to Decision framework

Recommendations	Quality of evidence	Strength of recommendation	Class[a]	Level[b]
In patients with IPAH/HPAH/DPAH who present at low or intermediate risk of death, initial combination therapy with a PDE5i and an ERA is recommended	Low	Conditional	I	B
The use of PDE5i in patients with HFpEF and isolated post-capillary PH is not recommended	Low	Conditional	III	C
The use of PDE5i in patients with ILD and non-severe PH is not recommended	Very low	Conditional	III	C

DPAH, drug-associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; HPAH, heritable pulmonary arterial hypertension; HFpEF, heart failure with preserved ejection fraction; ILD, interstitial lung disease; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension. [a]Class of recommendation. [b]Level of evidence.

Research Programme and the European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) project [855] to provide real-world data about the patterns and outcomes of care for cardiovascular disease across Europe.

In parallel with the writing of this Clinical Practice Guideline, a process has been initiated to develop QIs for patients with PH using the ESC methodology and through collaboration with domain experts and the Heart Failure Association of the ESC. Such QIs may be used for evaluating the quality of care for patients with PH, and enable important aspects of care delivery to be captured. These QIs, alongside their specifications and development process, will be published separately.

17. Supplementary data

This article has supplementary data that includes background information and detailed discussion of the data that have provided the basis of the guidelines, and includes key narrative questions (1–8) and PICO questions (I–IV)

18. Data availability statement

No new data were generated or analysed in support of this research.

19. Other information and notes

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ESC subspecialty communities having participated in the development of this document: *Associations*: Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), and Heart Failure Association (HFA); *Councils*: Council on Cardiovascular Genomics; *Working Groups*: Adult Congenital Heart Disease, Pulmonary Circulation and Right Ventricular Function, Thrombosis; *Patient Forum*.

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All experts involved in the development of these guidelines have submitted declarations of interest. These have been compiled in a report and simultaneously published in a supplementary document to the guidelines.

20. Appendix

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