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

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and of the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

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Web addenda

Pathology of pulmonary hypertension

Different pathological features characterise the diverse clinical pulmonary hypertension (PH) groups.[51,52]

- Group 1, pulmonary arterial hypertension (PAH): pathological changes predominantly affect the distal pulmonary arteries (<500 μm) with medial hypertrophy, intimal proliferative and fibrotic changes, adventitial thickening with mild to moderate perivascular inflammatory infiltrates and lymphoid neogenesis, complex lesions (plexiform, dilated lesions) and thrombotic lesions. Pulmonary veins are classically unaffected.
- Group 1′: includes mainly pulmonary veno-occlusive disease (PVOD) involving septal veins and pre-septal venules with occlusive fibrotic lesions, venous muscularization, patchy capillary proliferation with pulmonary capillary haemangiomatosis (PCH), pulmonary oedema, occult alveolar haemorrhage, lymphatic dilatation, lymph node enlargement (vascular transformation of the sinus) and inflammatory infiltrates. Distal pulmonary arteries are affected by medial hypertrophy and intimal fibrosis.
- Group 1″: persistent pulmonary hypertension of the newborn (PPHN) is characterized by changes in vasoreactivity and wall structure and decreases in pulmonary vascular density with reduced alveolarisation.
- Group 2: PH due to left heart disease (LHD) is characterised by enlarged and thickened pulmonary veins, pulmonary capillary dilatation, interstitial oedema, alveolar haemorrhage and lymphatic vessel and lymph node enlargement. Distal PA may be affected by medial hypertrophy and intimal fibrosis.
- Group 3: PH due to lung diseases and/or hypoxaemia is characterized by medial hypertrophy, intimal obstructive proliferation of the distal pulmonary artery (PA) and muscularisation of arterioles. A variable degree of destruction of the vascular bed in emphysematous or fibrotic areas may also be present.
- Group 4: PH due to chronic PA obstruction: chronic thromboembolic pulmonary hypertension (CTEPH) lesions include organized thrombi tightly attached to the medial layer in the elastic PA, replacing the normal intima. These may occlude the lumen or form different grades of stenosis, webs and bands.[53] A pulmonary microvascular disease can develop in the non-occluded and occluded areas that has similarities with PAH (with the exception of uncommon plexiform lesions in CTEPH) and patchy post-capillary remodelling related to bronchial-to-pulmonary venous shunting.[54,55] Collateral vessels from the systemic circulation (from bronchial, costal,

Web Table I **Condensed clinical classification of pulmonary hypertension (updated from Simonneau *et al.*[1])**

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease (Table 6)
1.4.5 Schistosomiasis
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1''. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Other
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Others

Web Table II **Anatomical-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (adapted from Simmoneau *et al.*[2])**

1. Type
1.1 Simple pre-tricuspid shunts
1.1.1 Atrial septal defect (ASD)
1.1.1.1 Ostium secundum
1.1.1.2 Sinus venosus
1.1.1.3 Ostium primum
1.1.2 Total or partial unobstructed anomalous pulmonary venous return
1.2 Simple post-tricuspid shunts
1.2.1 Ventricular septal defect (VSD)
1.2.2 Patent ductus arteriosus
1.3 Combined shunts
Describe combination and define predominant defect
1.4 Complex congenital heart disease
1.4.1 Complete atrioventricular septal defect
1.4.2 Truncus arteriosus
1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
1.4.5 Other
2. Dimension (specify for each defect if more than one congenital heart defect exists)
2.1 Haemodynamic (specify Qp/Qs)[a]
2.1.1 Restrictive (pressure gradient across the defect)
2.1.2 Non-restrictive
2.2 Anatomic[b]
2.2.1 Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)
3. Direction of shunt
3.1 Predominantly systemic-to-pulmonary
3.2 Predominantly pulmonary-to-systemic
3.3 Bidirectional
4. Associated cardiac and extracardiac abnormalities
5. Repair status
5.1 Unoperated
5.2 Palliated (specify type of operation/s, age at surgery)
5.3 Repaired (specify type of operation/s, age at surgery)

[a]Ratio of pulmonary (Qp) to systemic (Qs) blood flow.
[b]The size applies to adult patients.

diaphragmatic and coronary arteries) can grow to reperfuse areas distal to complete obstructions.

- Group 5: PH with unclear and/or multifactorial mechanisms includes heterogeneous conditions with different pathological pictures.

Pathobiology of pulmonary hypertension

Different pathobiological features[56–58] characterise the diverse clinical PH groups.

- Group 1: PAH has a multifactorial pathobiology. Excessive vasoconstriction has been related to abnormal function or expression of potassium channels in the smooth muscle cells and to endothelial dysfunction leading to chronically impaired production of vasodilator and antiproliferative agents such as nitric oxide (NO) and prostacyclin, along with overexpression of vasoconstrictor and proliferative substances such as thromboxane A_2 and endothelin-1. Many of these abnormalities both elevate vascular tone and promote vascular remodelling by proliferative changes involving endothelial and smooth muscle cells as well as fibroblasts and pericytes. Growth factors such as platelet-derived growth factor, fibroblast growth factor, transforming growth factor β (TGFβ) and bone morphogenic proteins play a role in the remodelling process. Reduced bone morphogenetic

protein receptor 2 (BMPR2) expression contributes to the pathobiology of heritable and other forms of PAH. Other cell types (inflammatory cells and platelets) and mediators (cytokines, chemokines, serotonin, etc.) play a role in PAH. Prothrombotic abnormalities have been demonstrated in PAH patients and thrombi are present in both the small distal pulmonary arteries and in proximal elastic pulmonary arteries. Autoimmunity is present in subgroups of PAH patients, as suggested by circulating autoantibody recognizing pulmonary vascular cells and detection of lymphoid neogenesis in the lungs of idiopathic PAH (IPAH) patients.

- Group 1′: In PVOD, bi-allelic *EIF2AK4* mutations, inflammation and exposure to toxic agents induce oxidative and inflammatory injuries.

Web Table III Developmental lung disease associated with pulmonary hypertension (adapted from Ivy *et al.*[3])

1. Congenital diaphragmatic hernia
2. Bronchopulmonary dysplasia
3. Alveolar capillary dysplasia (ACD)
4. ACD with misalignment of veins
5. Lung hypoplasia ("primary" or "secondary")
6. Surfactant protein abnormalities a. Surfactant protein B deficiency b. Surfactant protein C deficiency c. ATP-binding cassette A3 mutation d. Thyroid transcription factor 1/Nkx2.1 homeobox mutation
7. Pulmonary interstitial glycogenosis
8. Pulmonary alveolar proteinosis
9. Pulmonary lymphangiectasia

- Group 1″: In PPHN, endothelial cell dysfunction (with decreased NO production and activity) and impaired angiogenic mechanisms underlie abnormalities of lung vascular growth.
- Group 2: PH due to LHD: The mechanisms responsible for the increase in pulmonary arterial pressure (PAP) include passive backward transmission of the pressure elevation (isolated post-capillary PH, Table 3). In these cases pulmonary vascular resistance (PVR) is within the normal range. In other circumstances the elevation of PAP is greater than that of the pulmonary artery wedge pressure (PAWP), leading to an increase in PVR (combined post-capillary and pre-capillary PH, Table 3). The elevation of PVR is due to an increase in PA vasomotor tone and/or to fixed structural obstructive remodelling of the PA resistance vessels;[59] the former component of reactive PH is reversible under acute pharmacological testing, while the latter, characterized by medial hypertrophy and intimal proliferation of the pulmonary arteriole, does not respond to the acute challenge.[60]
- Group 3: PH due to lung diseases and/or hypoxia: The mechanisms involved include hypoxic vasoconstriction, mechanical stress of hyperinflated lungs, loss of capillaries, inflammation and toxic effects of cigarette smoke. There are also data supporting an endothelium-derived vasoconstrictor–vasodilator imbalance.
- Group 4: PH due to chronic PA obstruction: Non-resolution of acute embolic masses that later undergo fibrosis leading to mechanical obstruction of pulmonary arteries is believed to be an important pathobiological process in CTEPH. However, a mechanistic view of CTEPH as a disease exclusively caused by obliteration of central pulmonary arteries by pulmonary emboli is too simplistic. Pulmonary embolism (PE) could be followed by a pulmonary vascular remodelling process modified by infection, immune phenomena, inflammation and circulating and vascular-resident progenitor cells. Only a few specific thrombophilic factors, such as antiphospholipid antibodies, lupus anticoagulant and elevated factor VIII, have been statistically associated with CTEPH, and no abnormalities of fibrinolysis have been

Web Table IV Route of administration, half-life, dose ranges, increments, and duration of administration of the most commonly used agents for pulmonary vasoreactivity tests

Drug	Route	Half-life	Dose range[d]	Increments[e]	Duration[f]	Class[a]	Level[b]	Ref[c]
Nitric oxide	Inh	15–30 sec	10–20 ppm	-	5 min[g]	I	C	4, 5
Epoprostenol	i.v.	3 min	2–12 ng/kg/min	2 ng/kg/min	10 min	I	C	4, 6
Adenosine	i.v.	5–10 sec	50–350 μg/kg/min	50 μg/kg/min	2 min	IIa	C	7
Iloprost	Inh	30 min	5–20 μg	-	15 min	IIb	C	8

Inh = inhaled; i.v. = intravenous; NO = nitric oxide; ppm = parts per million.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Initial dose and maximal dose suggested.
[e]Increments of dose by each step.
[f]Duration of administration on each step.
[g]For NO a single step within the dose range is suggested.

Web Table V Functional classification of pulmonary hypertension modified after the NYHA functional classification according to the WHO 1998.[9]

Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
Class II – Patients with pulmonary hypertension 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.
Class III – Patients with pulmonary hypertension 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.
Class IV – Patients with pulmonary hypertension with 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.

NYHA = New York Heart Association; WHO = World Health Organization.

consistently demonstrated. Microvascular disease may be related to shear stress in non-obstructed areas, post-capillary remodelling related to bronchial-to-pulmonary venous shunting, pressure, inflammation and release of cytokines and vasculotrophic mediators.[55]

- Group 5: By definition, the pathobiology in this group is unclear or multifactorial.

Pulmonary arterial hypertension screening programme

The prognosis of PAH is significantly worse in patients with advanced disease.[61,62] PAH therapies delay clinical worsening[63] and data are accumulating suggesting that early treatment improves long-term outcome.[13,63,64] Screening is the systematic application of a test to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action among persons who have not sought medical attention on account of symptoms of that disorder.[65] Therefore screening for PH/PAH applies to asymptomatic individuals belonging to groups in which PH/PAH is highly prevalent, such as patients with systemic sclerosis (SSc),[66,67] *BMPR2* mutation carriers or relatives of patients with heritable PAH (HPAH),[68] patients with sickle cell disease (SCD) and patients with portal hypertension referred for liver transplantation.[69]

A screening method should use tools that are non-invasive, reproducible, associated with a high negative predictive value for the condition and cost effective.[61] In PH/PAH, these tools include pulmonary function tests (PFTs), circulating biomarkers and echocardiography. In SSc, PFTs have long been used as a screening tool, especially changes in diffusing capacity of the lung for carbon monoxide (DLCO).[70,71] An increased risk of PAH has been shown in adult SSc patients with a DLCO $<60\%$ of predicted.[67] There is now additional evidence suggesting that biomarkers [N-terminal pro-brain natriuretic peptide (NT-proBNP)], alone[72,73] or in combination with PFTs,[74] may identify patients at higher risk to present SSc-PAH. Finally, a recent study in patients undergoing right heart catheterization (RHC) as part of the evaluation of SSc suggested that, in the absence of PH, an increase in the transpulmonary pressure gradient (TPG) was associated with a higher risk of subsequently developing pre-capillary PH.[75] Echocardiography at rest remains the best way to estimate elevated pulmonary pressures. It has been used in large SSc-PAH screening programmes[67,76] by stratifying patients according to the level of PAPs estimated by the tricuspid regurgitant velocity (TRV). The recommendations for diagnostic management according to echocardiographic probability of PH in asymptomatic patients with or without risk factors for PAH or CTEPH are reported in Online Table IX. Conversely, exercise echocardiography has technical and methodological limitations and is not recommended for PH/PAH screening.[77–81]

Recent studies in SSc and SCD have demonstrated that asymptomatic PAH patients detected by screening can be missed by Doppler echocardiography (false negative), emphasizing the need for a multitest approach. In SSc, a composite measure has been proposed in the DETECT study.[67] In this study, adult SSc patients with >3-years disease duration and a DLCO $<60\%$ of predicted underwent non-invasive testing and RHC. A stepwise detection approach has been proposed with six simple clinical and biological assessments in step 1 of the algorithm determining referral to echocardiography. In step 2, the step 1 prediction score and two echocardiographic variables determined referral to RHC. The DETECT algorithm recommended RHC in 62% of patients (referral rate) and missed 4% of PAH patients (false negatives). Of those, 19% had RHC-confirmed PAH.[67] This screening approach is interesting, but there is currently no information on long-term outcomes in asymptomatic SSc-PAH patients screened thanks to the DETECT algorithm. Of note, the DETECT study did not provide recommendations regarding patients with a DLCO $\geq 60\%$ and its findings need to be validated in another cohort. Beyond initial screening, the frequency of non-invasive tests is unclear in asymptomatic subjects with a high risk of developing incident PAH. Annual screening with echocardiography, DLCO and NT-proBNP has been proposed in SSc patients.[66,82]

Pre-capillary PH is a known complication of SCD, but the prevalence SCD-PH has been overestimated in echocardiography based studies.[83] Two recent studies[84,85] employed similar methodologies and referred all patients with a screening TRV ≥ 2.5 m/s on echocardiography for confirmatory RHC. The prevalence of PH ranged from 6.2 to 10% (post-capillary PH in 3.3 and 6.2%, and pre-capillary PH in 2.9 and 3.8%, respectively). An exploratory post-hoc analysis found that calibrating TRV to ≥ 2.9 m/s or TRV between 2.5 and 2.8 m/s plus either NT-proBNP >164.5 pg/ml or a 6-minute walk distance (6MWD) <333 m reduced the number of RHC referrals compared with a single TRV threshold ≥ 2.5 m/s.[84]

BMPR2 mutation carriers have a lifetime risk of developing PAH of approximately 20%.[68,86] It is currently not possible to predict those who will ultimately develop PAH, although women are at increased risk compared with men.[86] In patients carrying a *BMPR2* mutation, the frequency of screening is unknown. At present, asymptomatic individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH patients in whom no causal mutations have been identified are offered yearly screening echocardiography.

Web Table VIA Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the endothelin pathway (Endothelin receptors antagonists)

Drug(s) tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main Results
Ambrisentan	ARIES-1[10]	202	12	No	6MWD	6MWD improved TTCW not improved
	ARIES-2[10]	192	12	No	6MWD	6MWD improved TTCW improved
Bosentan	Study-351[11]	32	12	No	6MWD	6MWD improved TTCW improved
	BREATHE-1[12]	213	16	No	6MWD	6MWD improved TTCW improved
	EARLY[13]	185	24	No, or Sildenafil (16%)	PVR, 6MWD	PVR improved TTCW improved 6MWD not improved
	BREATHE-5[14]	54	12	No	SaO_2, PVR	PVR improved 6MWD improved
	COMPASS-2[15]	334	99	Sildenafil	TTCW	TTCW not improved 6MWD improved NT-proBNP improved
Macitentan	SERAPHIN[16]	742	115	No, or Sildenafil, or Inh iloprost	TTCW	TTCW improved in monotherapy and combination

6MWD = 6-minute walking distance; PVR = pulmonary vascular resistance; SaO_2 = finger oxygen saturation; TTCW = time to clinical worsening.

Web Table VIB Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the nitric oxide pathway (Soluble guanylate cyclase stimulators, Phosphodiesterase type-5 inhibitors)

Drug(s) tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Riociguat	PATENT[17]	443	12	No, or bosentan, or prostanoids	6MWD	6MWD improved Haemodynamics improved
	PATENT plus[18]	30	18	Sildenafil	Supine SBP	Terminated for excess of SAE in the treated group
Sildenafil	SUPER-1[19]	277	12	No	6MWD	6MWD improved TTCW not improved
	Sastry[20]	22	12	No	TT	TT improved
	Singh[21]	20	6	No	6MWD	6MWD improved
	PACES[22]	264	16	Epoprostenol	6MWD	6MWD improved TTCW and haemodynamics improved
	Iversen[23]	20	12	Bosentan	6MWD	6MWD not improved
	Pfizer study A1481243	103	12	Bosentan	6MWD	6MWD not improved
Tadalafil	PHIRST[24]	405	16	No, or bosentan (54%)	6MWD	6MWD improved (In bosentan treated patients +23 m, 95% CI -2 to 48 m) TTCW improved
Vardenafil[a]	EVALUATION[25]	66	12	No	6MWD	6MWD improved TTCW improved

6MWD = 6-minute walking distance; SAE = serious adverse events; TTCW = time to clinical worsening; TT = treadmill test.
[a]This drug is not approved by the EMA at the time of publication of these guidelines.

Web Table VIC Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the prostacyclin pathway (Prostacyclin analogues and prostacyclin receptors agonists)

Drug(s) tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Beraprost[a]	ALPHABET[26]	130	12	No	6MWD	6MWD improved Haemodynamics not improved
	Barst[27]	116	52	No	CW	CW not improved
Epoprostenol	Rubin[28]	23	12	No	6MWD	6MWD improved Haemodynamics improved
	Barst[29]	81	12	No	6MWD	6MWD improved Haemodynamics improved Survival improved
	Badesch[30]	111	12	No	6MWD	6MWD improved
Inhaled Iloprost	AIR[31]	203	12	No	6MWD & FC	6MWD & WHO-FC improved Haemodynamics improved at peak
	STEP[32]	67	12	Bosentan	6MWD	6MWD improved (P = 0.051) TTCW improved
	COMBI[33]	40	12	Bosentan	6MWD	Terminated for futility 6MWD not improved No clinical improvement
Treprostinil	SC – Pivotal study[34]	470	12	No	6MWD	6MWD improved Haemodynamics improved Pain at infusion site
	Inhal[a] TRIUMPH[35]	235	12	Bosentan or sildenafil	6MWD	6MWD improvement (+20 m at peak, +12 m at trough) TTCW not improved
	PO[a]- Freedom M[36]	185	16	No	6MWD	6MWD improvement (+26 m at peak, +17 m at trough) TTCW not improved
	PO[a]- Freedom C1[37]	354	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
	PO[a]- Freedom C2[38]	310	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
Selexipag[a]	Phase - 2[39]	43	17	ERA and/or PDE-5i	PVR	PVR improved 6MWD not improved
	GRIPHON[40]	1156	74	ERA and/or PDE-5i	TTCW	TTCW improved

6MWD = six minute walking distance; CW = clinical worsening; PVR = pulmonary vascular resistance; TT = treadmill test; TTCW = time to clinical worsening.
[a]This drug is not approved by the EMA at the time of publication of these guidelines.

Web Table VID Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs testing initial combination therapy

Drug(s) tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Epoprostenol vs epoprostenol + bosentan	BREATHE-2[41]	33	12	No	PVR	PVR not improved 6MWD not improved
Ambrisentan or tadalafil vs ambrisentan + tadalafil	AMBITION[42]	500	78	No	TTCF	TTCF improved 6MWD improved

6MWD = 6-minute walking distance; TTCF = time to clinical failure; PVR = pulmonary vascular resistance.

Web Table VII Potentially significant drug interactions with pulmonary arterial hypertension drugs[a]

PAH drug	Mechanism of interaction	Interacting drug	Interaction
Ambrisentan	?	Cyclosporine Ketoconazole	Caution is required in the co-administration of ambrisentan with ketoconazole and cyclosporine.
Bosentan	CYP3A4 inducer	Sildenafil	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; bosentan levels increase 4-fold. Combination contraindicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course.
	CYP3A4 substrate	Ketoconazole	Bosentan levels increase 2-fold
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycaemic effect of glibenclamide. Combination contraindicated.
	CYP2C9 and CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels increase considerably. Combination contraindicated.
	CYP2C9 and CYP3A4 inducers	Rifampicin, phenytoin	Bosentan levels decrease by 58%. Need for dose adjustment uncertain.
	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increases warfarin metabolism, may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation but dose adjustment usually unnecessary.
	CYP2C9 and CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable.
Macitentan			To be determined
Selexipag			To be determined
Sildenafil[43]	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	HMG CoA reductase inhibitors	May increase simvastatin/atorvastatin levels through competition for metabolism. Sildenafil levels may increase. Possible increased risk of rhabdomyolysis.
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinovir increase sildenafil levels markedly.
	CYP3A4 inducer	Phenytoin	Sildenafil level may fall.
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase. May not require dose adjustment for a short course.
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment.
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment.
	cGMP	Nitrates, Nicorandil Molsidomine	Profound systemic hypotension, combination contraindicated.
Tadalafil[44]	CYP3A4 substrate	Bosentan	Tadalafil exposure decreases by 42%, no significant changes in bosentan levels.(44) May not require dose adjustment.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.
Riociguat[18]	cGMP	Sildenafil, other PDE-5 inhibitors	Hypotension, severe side effects, combination contraindicated.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.

cGMP = cyclic guanosine monophosphate; PDE-5 = phosphodiesterase type-5.
[a]This table is adapted from National Pulmonary Hypertension Centres of the UK and Ireland. Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice in the UK and Ireland. Heart 2008;94(suppl I):i1–41. See also updated official prescribing information for each compound.

An ongoing longitudinal study should clarify issues such as optimal screening strategies and predictors of progression to PAH in asymptomatic *BMPR2* carriers [DELPHI (NCT01600898)].

PAH screening is recommended in patients presenting for liver transplantation assessment. Doppler echocardiography is the only screening modality that has been systematically evaluated in portopulmonary hypertension (PoPH).[87] The recommendations for PAH screening are reported in Web Table X.

Quality of life measurements

Quality of life measures describe the patient's own perception of their health and how it affects them. This information is complementary to the typical clinical information collected by healthcare professionals. General quality of life questionnaires have been shown to be useful in PAH, including the 36-item Short Form Health Survey (SF-36),[91] whose Physical Component Score was prognostic in one study.[92] Since many generic quality of life questionnaires may

Web Table VIII Conditions of clinical group 5 that may cause pulmonary hypertension

Haematological disorders

a.Chronic haemolytic anaemia

The common feature of the haemolytic anaemias is that when there is intravascular haemolysis, there is release of cell-free haemoglobin into the plasma which scavenges the nitric oxide. A loss of nitric oxide, the physiological vasodilator of the pulmonary circulation, may cause vasoconstriction and vascular obstructive pathologic changes.

b.Sickle cell anaemia

Cells containing sickle cell haemoglobin (HbS) may sickle and be trapped in the microcirculation, resulting in local obstruction to blood flow. An additional factor leading to pulmonary hypertension (PH) is that these patients can suffer either functional or surgical asplenia, putting them at risk for thromboembolism and chronic thromboembolic pulmonary hypertension (CTEPH). There are, however, a few small uncontrolled studies, but the results of treatments such as bosentan and sildenafil are modest at best.

c.Beta-thalassaemia

PH in patients with thalassaemia is also multifactorial, involving intravascular haemolysis (see above), changes in the coagulation system, and local inflammation.

d.Hereditary spherocytosis/stomatocytosis

Hereditary stomatocytosis is a rare autosomal red cell membrane disorder and the red cells are subject to intravascular haemolysis. In addition, there is a high risk of thrombotic complications but, once again, this is often in association with splenectomy which is done to prevent the haemolysis.

e.Myeloproliferative disease

Chronic myeloproliferative disease (CMPD) is associated with PH. There are thought to be 2 main aetiologies.

1. CMPD may have excess risk of venous thrombosis.
2. CMPD may have pre-capillary proliferative vasculopathy. It is of interest that dasatinib, a tyrosine kinase inhibitor, which is one of treatments for chronic myeloid leukaemia, also appears to cause partially reversible PH.[45,46]

f. Splenectomy

Splenectomy causes an increased risk of CTEPH and also even idiopathic pulmonary arterial hypertension.

Systemic disorders associated with pulmonary hypertension

These disorders include sarcoidosis, histiocytosis, and lymphangiomyomatosis.

a.Sarcoidosis

PH occurs in 5–15%.[47] The cause of PH in sarcoidosis is multifactorial, including fibrosing lung disease, granulomata in the pulmonary arteries, fibrosing mediastinitis, pulmonary vasculitis, portopulmonary hypertension, and pulmonary veno-occlusive disease.[48]

b.Langerhans cell histiocytosis (LCH)

PH associated with parenchymal lung disease itself related to smoking.

c.Lymphangioleiomyomatosis (LAM)

PH associated with parenchymal lung disease occurs in approximately 7% of unselected patients with LAM.

Metabolic disorders

a.Thyroid disease

PH associated with hypo- or hyper-thyroidism.[50]

b.Glycogen storage diseases

Pathogenesis of PH unknown but may include pulmonary veno-occlusive disease. Enzyme replacement therapy seems to have little effect, unlike Gaucher's disease (see below).

c.Gaucher's disease

Approximately 30% of untreated patients with Gaucher's disease develop PH which is caused by a combination of factors including plugging of the vasculature by the abnormal macrophages, abnormal pulmonary vascular cell proliferation, and asplenia (see above).
Treatment with enzyme replacement therapy (ERT), which is now the dominant therapy for Gaucher's disease, may improve the PH. However, ERT initiation can also unmask underlying PH.

Other disorders

a. Chronic renal failure

PH is very common in end-stage renal disease and is multifactorial: anaemia, arteriovenous (A-V) fistulae (used for haemodialysis), both of which cause a high output state. It may be due to proliferative vascular dysfunction, related in part to uraemia which is also known to affect the systemic vessels. Most observers agree that PH in chronic renal failure is mostly venous in origin due to left ventricular dysfunction, which is in turn due to myocardial damage caused by the processes of renal failure.

b.Fibrosing mediastinitis

In PH due to fibrosing mediastinitis, the main pathology is obliteration of central veins and arteries by the fibrosing process.[47,48]

c.Tumours

Approximately 25% of patients dying with cancer die with tumour emboli in the pulmonary circulation. Tumours seem to be that particularly associated with PH are gastric, breast, ovary, lung, kidney and colon. Tumour cells migrate to the pulmonary circulation where they seem to cause a microangiopathy.

Web Table IX Diagnostic management suggested according to echocardiographic probability of pulmonary hypertension in asymptomatic patients with or without risk factors for pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[d,e]	Class[a]	Level[b]	With risk factors or associated conditions for PAH or CTEPH[d,e]	Class[a]	Level[b]	Ref[c]
Low	No work up for PAH required	III	C	Echo follow-up may be considered	IIb	C	
Intermediate	Echo follow-up should be considered	IIa	C	Echo follow-up is recommended	I	B	67, 76, 88
				If associated scleroderma, RHC should be considered[f]	IIa	B	8, 17,29
High	RHC should be considered[f]	IIa	C	RHC is recommended	I	C	

CTEPH = chronic thromboembolic pulmonary hypertension; Echo = echocardiographic; EO = expert opinion; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Applies to accidental findings during echocardiography performed for indications other than suspected PH. Recommendations regarding prospective institutional screening programmes for PAH or CTEPH are described in a dedicated section of the guidelines.
[e]These recommendations do not apply to patients with diffuse parenchymal lung disease or left heart disease.
[f]Depending on the presence of risk factors for PH group 2, 3 or 5.
Further investigation strategy may differ depending on whether risk factors/associated conditions suggest higher probability of PAH or CTEPH – see diagnostic algorithm (Figure 1).

Web Table X Recommendations for pulmonary arterial hypertension screening

Recommendations	Class[a]	Level[b]	Ref[c]
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B	66, 76
Resting echocardiography is recommended as a screening test in *BMPR2* mutation carriers or first-degree relatives of patients with HPAH and in patients with PoPH referred for liver transplantation.	I	C	69, 89,
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B	66, 67
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B	75
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B	67
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B	66, 90
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C	68
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C	79

DLCO = diffusing capacity of the lung for carbon monoxide; HPAH = heritable PAH; PAP = pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PFTs = pulmonary function tests; PH = pulmonary hypertension: PoPH = portopulmonary hypertension.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

not reflect well clinical status in PAH,[93] disease-specific questionnaires have been developed and validated. These include the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR),[94–96] emPHasis-10,[97] Minnesota Living with Heart Failure – PH[98,99] and Pulmonary Arterial Hypertension Symptom Scale (PAHSS)[100] questionnaires. Since there are no head-to-head comparisons it is not possible to recommend one over the others.

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