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REVIEW

Implementing the ESC/ERS pulmonary hypertension guidelines: real-life cases from a national referral centre

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ABSTRACT: Pulmonary hypertension (PH) comprises a heterogeneous group of disorders characterised by increased pulmonary vascular resistance that results in progressive right ventricular failure. In order to translate current evidence into routine clinical practice, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) have recently jointly proposed evidence-based guidelines for the optimal management of different PH patient groups. This article describes a series of clinical cases of PH due to various aetiologies that were referred to a large national PH expert referral centre. In each case, the assessment and therapeutic approach undertaken is described in the context of the new ECS/ERS guidelines. The routine diagnostic work-up of suspected idiopathic pulmonary arterial hypertension (PAH) and recommended treatments for patients with functional class II, III and IV disease is emphasised. Familial screening and management of heritable PAH is discussed. Appropriate investigation and therapeutic strategies for patients with chronic thromboembolic disease and PH that is associated with congenital heart disease, pulmonary veno-occlusive disease and systemic sclerosis are also highlighted.

The term pulmonary hypertension (PH) describes a group of devastating and life-limiting diseases, defined by a mean pulmonary artery pressure ($\bar{P}_{pa}$) $\geqslant$25 mmHg at rest [1–8]. PH remains poorly characterised as it is a rare disorder and because there is an incomplete understanding of the diverse underlying pathogenic conditions and mechanisms. Furthermore, effective treatment approaches available to clinicians have traditionally been limited. However, the past decade has witnessed a significant increase in our knowledge base, leading to novel medical, surgical and supportive therapeutic options for patients. In addition, international collaborative efforts have directly led to the development of regularly updated proceedings and guidelines [1, 2, 9]. The recent publication of the joint European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines is a major event in our community and it thus appeared timely to comment on these guidelines with real-life cases managed according to this approach [1, 2]. Indeed, it is essential to implement these guidelines in day-to-day care of this fragile patient population [4, 10]. This article describes a number of real-life clinical cases and focuses on the management approaches employed at a large national pulmonary vascular disease referral centre. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as presented in tables 1 and 2.

CASE 1: DIAGNOSTIC WORK-UP IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

Case report

A 30-yr-old female presented with progressive dyspnoea associated with intermittent episodes of dizziness. She was a nonsmoker and had no history of venous thromboembolism, Raynaud's phenomenon or exposure to anorexigens. Family history was noncontributory. At initial assessment after referral to a PH expert centre she was deemed to be in World Health Organization (WHO) functional class III. Physical examination was remarkable only for a loud second heart sound over the pulmonic valve. There was no clinical

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TABLE 1 ESC/ERS guidelines: classes of recommendations

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

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evidence of connective tissue disease (CTD). Transthoracic echocardiography revealed dilated right heart chambers, moderate impairment of right ventricular contractility and a systolic P_{pa} estimated to be 70 mmHg. Her 6-min walk distance (6MWD) was 310 m. Pulmonary function tests (PFTs) and arterial blood gas analysis were within normal limits. The only abnormality observed on high-resolution computed tomography (HRCT) was mild dilatation of the pulmonary arteries. Ventilation/perfusion lung scintigraphy demonstrated some subsegmental mismatched defects but findings were not consistent with a diagnosis of chronic thromboembolic PH (CTEPH). Testing for infection with hepatitis B, hepatitis C and HIV was negative and liver function tests were normal. Portal hypertension was excluded by abdominal ultrasound. The patient proceeded to diagnostic right heart catheterisation (RHC), which confirmed severe pre-capillary PH ($\bar{P}_{pa}$ 55 mmHg, pulmonary capillary wedge pressure (P_{pcw}) 8 mmHg, cardiac index (CI) 2.88 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance (PVR) 694 $dyn \cdot s \cdot cm^{-5}$). Acute vasodilator testing with inhaled nitric oxide was negative. As no identifiable underlying cause was revealed by the various investigations performed for the work-up of PH in this patient, a diagnosis of idiopathic pulmonary arterial hypertension (PAH) was established and endothelin receptor antagonist therapy was instituted. Oral anticoagulation for a target international normalised ratio (INR) of 2–3 was initiated, and the patient was advised on effective contraception measures as well as avoidance of excessive physical activity. A clinical and haemodynamic re-evaluation after 4 months was scheduled.

TABLE 2 ESC/ERS guidelines: levels of evidence

Level of evidence A	Data derived from multiple randomised clinical trials[#] or meta-analyses.
Level of evidence B	Data derived from multiple randomised clinical trials[#] or large nonrandomised studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

[#]: or large accuracy or outcome trial(s) in the case of diagnostic tests or strategies. Reproduced from [1] with permission from the publisher.

Commentary: relevance to ESC/ERS guidelines

PH has been defined as an increase in $\bar{P}_{pa} \geqslant 25$ mmHg at rest, as assessed by RHC.

The definition of PH on exercise as a $\bar{P}_{pa} \geqslant 30$ mmHg is not supported by published data and healthy individuals can reach much higher values. Thus no definition for PH on exercise as assessed by RHC can be provided at the present time.

According to various combinations of values of P_{pcw}, PVR and cardiac output (CO), different haemodynamic definitions of PH are shown in table 3.

To avoid possible confusion among the terms PH and PAH, the specific definitions have been included in table 4.

Compared with the previous version of the clinical classification, a number of changes have been made (table 5). 1) In group 1, corresponding to PAH, the term familial PAH has been replaced by heritable PAH that includes clinically sporadic idiopathic PAH with germline mutations and clinical familial cases with or without identified germline mutations. 2) Associated PAH includes conditions that can have a similar clinical presentation to that seen in idiopathic PAH with identical histological findings, and accounts for approximately half of all PAH patients. Schistosomiasis and chronic haemolytic anaemia have been now included among the associated PAH forms. 3) A group 1′ has been created, which includes pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH), as these disorders share some characteristics with idiopathic PAH but also demonstrate a number of differences.

TABLE 3 ESC/ERS guidelines: haemodynamic definitions of pulmonary hypertension (PH)[#]

Definition	Characteristics	Clinical group(s)[¶]
PH	$\bar{P}_{pa} \geqslant 25$ mmHg	All
Pre-capillary PH	$\bar{P}_{pa} \geqslant 25$ mmHg	1. Pulmonary arterial hypertension
	$P_{pcw} \leqslant 15$ mmHg	3. PH due to lung diseases
	CO normal or reduced[+]	4. Chronic thromboembolic PH
		5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	$\bar{P}_{pa} \geqslant 25$ mmHg	2. PH due to left heart disease
	$P_{pcw} > 15$ mmHg	
	CO normal or reduced[+]	
Passive	TPG $\leqslant 12$ mmHg	
Reactive (out of proportion)	TPG > 12 mmHg	

$\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; TPG: transpulmonary pressure gradient ($\bar{P}_{pa}$-$\bar{P}_{pcw}$). [#]: all values measured at rest; [¶]: according to table 5; [+]: high CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia, hyperthyroidism, *etc.* Reproduced from [1] with permission from the publisher.

TABLE 4 ESC/ERS guidelines: important definitions

PH is a haemodynamic and pathophysiological condition defined as an increase in $\bar{P}_{pa}$ $\geqslant$25 mmHg at rest as assessed by right heart catheterisation (table 3). PH can be found in multiple clinical conditions (table 5).

The definition of PH on exercise as a $\bar{P}_{pa}$ >30 mmHg as assessed by right heart catheterisation is not supported by published data.

PAH (group 1) is a clinical condition characterised by the presence of pre-capillary PH (table 3) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases (table 5). PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation (table 5).

PH: pulmonary hypertension; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension. Reproduced from [1] with permission from the publisher.

The evaluation process of a patient with suspected PH requires a series of investigations intended to confirm the diagnosis, clarify the clinical group of PH and the specific aetiology within the PAH group, and evaluate the functional and haemodynamic impairment.

Since PAH, and particularly idiopathic PAH, is a diagnosis of exclusion, a diagnostic algorithm may be useful as a starting point in any case of suspected PH (fig. 1), as follows:

1) The symptoms of PAH are nonspecific and include breathlessness, fatigue, weakness, angina, syncope and abdominal distension. In 90% of patients with idiopathic PAH the chest radiograph is abnormal at the time of diagnosis. The ECG may provide suggestive or supportive evidence of PH by demonstrating right ventricular hypertrophy and strain, and right atrial dilatation.

2) Transthoracic echocardiography provides several variables that correlate with right heart haemodynamics, including P_{pa}, and should always be performed in the case of suspected PH. The estimation of P_{pa} during echocardiography is based on the peak velocity of the jet of tricuspid regurgitation. Other echocardiographic variables that might reinforce suspicion of PH include an increased velocity of pulmonic valve regurgitation, short acceleration time of right ventricular ejection into the pulmonary artery, increased dimensions of right heart chambers, abnormal shape and function of the interventricular septum, increased right ventricular wall thickness, and dilatation of the main pulmonary artery.

3) PFTs and arterial blood gases will identify the contribution of underlying airway or parenchymal lung disease. Patients with PAH usually have decreased diffusion capacity for carbon monoxide ($D_{L,CO}$) and mild to moderate reduction of lung volumes.

4) The ventilation/perfusion lung scan should be performed in patients with PH to look for potentially treatable CTEPH. The ventilation/perfusion scan remains the screening method of choice for CTEPH and a normal or low probability effectively excludes CTEPH with a sensitivity >90% and a specificity >94%.

TABLE 5 ESC/ERS guidelines: updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

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

2 PH due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 PH 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 abnormalities

4 Chronic thromboembolic PH

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

PAH: pulmonary arterial hypertension; BMPR2: bone morphogenetic protein receptor, type 2; ALK-1: activin receptor-like kinase 1; APAH: associated pulmonary arterial hypertension. Reproduced from [11] with permission from the publisher.

5) HRCT facilitates the diagnosis of interstitial lung disease and emphysema and may be very helpful where there is a suspicion of PVOD or PCH.

6) Liver cirrhosis and/or portal hypertension can be reliably excluded by the use of abdominal ultrasound.

7) Routine biochemistry, haematology and thyroid function tests are required in all patients, as well as a number of other essential blood tests. Serological testing is important to detect underlying CTD, HIV and hepatitis.

RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment and to test the

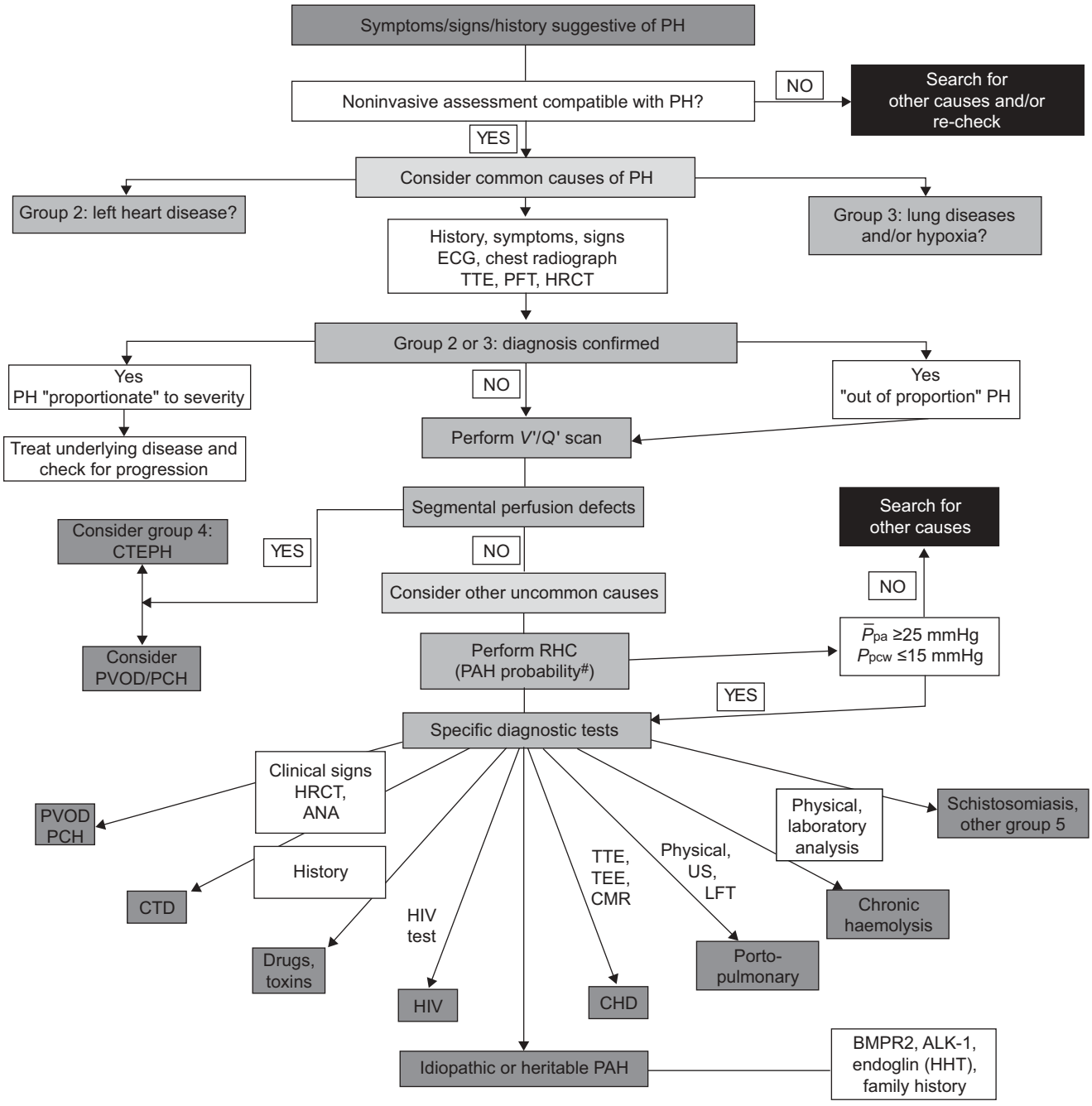

FIGURE 1. Diagnostic algorithm. ALK-1: activin-receptor-like kinase; ANA: antinuclear antibodies; BMPR2: bone morphogenetic protein receptor 2; CHD: congenital heart disease; CMR: cardiac magnetic resonance; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; HHT: hereditary haemorrhagic telangiectasia; HRCT: high-resolution computed tomography; LFT: liver function tests; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PCH: pulmonary capillary haemangiomatosis; P_{pcw}: pulmonary capillary wedge pressure; PFT: pulmonary function test; PH: pulmonary hypertension; PVOD: pulmonary veno-occlusive disease; RHC: right heart catheterisation; TEE: trans-oesophageal echocardiography; TTE: transthoracic echocardiography; US: ultrasonography; *V'/Q'* scan: ventilation/perfusion lung scan. #: refer also to table 9. Reproduced from [1] with permission from the publisher.

vasoreactivity of the pulmonary circulation. The following variables must be recorded during RHC. 1) P_{pa} (systolic, diastolic and mean), right atrial pressure, P_{pcw} and right ventricular pressure. CO must be measured in triplicate, preferably by thermodilution or by the Fick method. 2) Adequate recording of P_{pcw} is required for the differential diagnosis of PH due to left heart disease.

Special awareness should be directed towards patients with associated conditions and/or risk factors for development of PAH, such as family history, CTD, congenital heart disease (CHD), HIV infection, portal hypertension, haemolytic anaemia or a history of intake of drugs and toxins known to induce PAH. If noninvasive assessment is compatible with PH, clinical history, symptoms, signs, ECG, chest radiograph, transthoracic

TABLE 6 ESC/ERS guidelines: functional classification of pulmonary hypertension modified after the New York Heart Association functional classification according to the World Health Organization

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.

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echocardiogram, PFTs and HRCT of the chest are requested to identify the presence of group 2 left heart disease or group 3 lung diseases. If a ventilation/perfusion scan shows multiple segmental perfusion defects, a diagnosis of group 4 CTEPH should be suspected. The final diagnosis of CTEPH (and the assessment of suitability for pulmonary endarterectomy) will require computed tomography (CT) angiography, RHC and selective pulmonary angiography.

TABLE 7 ESC/ERS guidelines: recommendations for pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD)

Statement	Class#	Level¶
In patients with PAH associated with CTD the same treatment algorithm as in patients with idiopathic PAH is recommended	I	A
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with scleroderma spectrum of diseases	I	B
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with all other CTDs	I	C
RHC is indicated in all cases of suspected PAH associated with CTD, in particular if specific drug therapy is considered	I	C
Oral anticoagulation should be considered on an individual basis	IIa	C
Echocardiographic screening for the detection of PH may be considered in asymptomatic patients with the scleroderma spectrum of disease	IIb	C

PH: pulmonary hypertension; RHC: right heart catheterisation. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publishers.

The clinical assessment of the patient has a pivotal role in the choice of the initial treatment, the evaluation of the response to therapy, and the possible escalation of therapy if needed. Despite large interobserver variation in the measurement, WHO functional class (table 6) remains a powerful predictor of survival. In untreated patients with idiopathic or heritable PAH, historical data showed a median survival of 6 months for WHO functional class IV, 2.5 yrs for WHO functional class III, and 6 yrs for WHO functional classes I and II.

CASE 2: SYSTEMIC SCLEROSIS-ASSOCIATED PAH

Case report

A 37-yr-old female with limited systemic sclerosis (LSSc) was referred by her rheumatologist for assessment of increasing exercise intolerance associated with effort-induced chest discomfort and dizziness. Physical examination was remarkable for an accentuated pulmonic component of the second heart sound, a parasternal heave and mucocutaneous features consistent with LSSc. Auscultation of the lungs was unremarkable and there was no clinical evidence of right heart failure. Transthoracic echocardiography revealed a left ventricle compromised by markedly dilated right heart chambers with associated paradoxical motion of the interventricular septum and a 1-cm circumferential noncompressive pericardial effusion. Spirometry and lung volume measurements were normal and there was no evidence of interstitial lung disease on HRCT of the chest. RHC confirmed severe pre-capillary PH ($\bar{P}_{pa}$

TABLE 8 ESC/ERS guidelines: arbitrary criteria for estimating the presence of pulmonary hypertension (PH) based on tricuspid regurgitation peak velocity and Doppler-calculated systolic pulmonary arterial pressure (P_{pa}) at rest (assuming a normal right atrial pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH

Criteria	Class#	Level¶
Echocardiographic diagnosis: PH unlikely		
Tricuspid regurgitation velocity $\leqslant$2.8 m·s^{-1}, systolic P_{pa} $\leqslant$36 mmHg and no additional echocardiographic variables suggestive of PH	I	B
Echocardiographic diagnosis: PH possible		
Tricuspid regurgitation velocity $\leqslant$2.8 m·s^{-1}, systolic P_{pa} $\leqslant$36 mmHg, but presence of additional echocardiographic variables suggestive of PH	IIa	C
Tricuspid regurgitation velocity 2.9–3.4 m·s^{-1}, systolic P_{pa} 37–50 mmHg with/without additional echocardiographic variables suggestive of PH	IIa	C
Echocardiographic diagnosis: PH likely		
Tricuspid regurgitation velocity >3.4 m·s^{-1}, systolic P_{pa} >50 mmHg, with/without additional echocardiographic variables suggestive of PH	I	B
Exercise Doppler echocardiography is not recommended for screening of PH	III	C

#: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

TABLE 9 ESC/ERS guidelines: probability of pulmonary arterial hypertension (PAH) diagnosis and suggested management according to the echocardiographic diagnosis of pulmonary hypertension (PH) (table 8), symptoms and additional clinical information

	Class#	Level¶
Low probability for PAH diagnosis		
Echocardiographic diagnosis of ''PH unlikely'', no symptoms: no additional work-up is recommended	I	C
Echocardiographic diagnosis of ''PH unlikely'', presence of symptoms and of associated conditions or risk factors for group 1–PAH: echocardiographic follow-up is recommended	I	C
Echocardiographic diagnosis of ''PH unlikely'', presence of symptoms and absence of associated conditions or risk factors for group 1–PAH: evaluation of other causes for the symptoms is recommended	I	C
Intermediate probability for PAH		
Echocardiographic diagnosis of ''PH possible'', no symptoms and absence of associated conditions or risk factors for group 1–PAH: echo-cardiographic follow-up is recommended	I	C
Echocardiographic diagnosis of ''PH possible'', presence of symptoms and of associated conditions or risk factors for group 1–PAH: RHC may be considered	IIb	C
Echocardiographic diagnosis of ''PH possible'', presence of symptoms and absence of associated conditions or risk factors for group 1–PAH: alternative diagnosis and echocardiographic follow-up may be considered. If symptoms at least moderate RHC may be considered	IIb	C
High probability for PAH		
Echocardiographic diagnosis of ''PH likely'', with symptoms and presence/absence of associated conditions or risk factors for group 1–PAH: RHC is recommended	I	C
Echocardiographic diagnosis of ''PH likely'', without symptoms and presence/absence of associated conditions or risks factors for group 1–PAH: RHC should be considered	IIa	C

RHC: right heart catheterisation. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

73 mmHg, PVR 1,950 dyn·s·cm^{-5} and P_{pcw} 10 mmHg) with evidence of volume overload (right atrial pressure 20 mmHg) and no acute vasodilator response to inhaled nitric oxide. The patient was deemed to be in WHO functional class III and was commenced on treatment with oral endothelin receptor antagonist. In addition, diuretics and anticoagulation with a target INR of 2.0–3.0 were initiated. Monthly surveillance of liver transaminases was advised and effective contraceptive measures suggested. At re-evaluation after 4 months of therapy, the patient reported a symptomatic improvement and her 6MWD increased to 365 m from a baseline of 250 m. There was also a modest improvement in the pulmonary haemodynamic profile at repeat RHC ($\bar{P}_{pa}$ 65 mmHg, PVR 1,800 dyn·s·cm^{-5} and right atrial pressure 15 mmHg).

TABLE 10 Case 3: invasive pulmonary haemodynamics

	Baseline	After 500 mL fluid challenge
P_{ra} mmHg	7	13
$\bar{P}_{pa}$ mmHg	26	33
P_{pcw} mmHg	8	21
CO L·min^{-1}	4.82	5.43
CI L·min^{-1}·m^{-2}	2.71	3.02
PVR dyn·s·cm^{-5}	299	177

P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance.

Commentary: relevance to ESC/ERS guidelines

PAH is a well-known complication of CTD such as systemic sclerosis, systemic lupus erythematosus, mixed CTD and, to a lesser extent, rheumatoid arthritis, dermatomyositis and Sjögren's syndrome. PAH associated with CTD is the second most prevalent type of PAH after idiopathic PAH.

Systemic sclerosis, particularly in its limited variant, represents the main CTD associated with PAH. The prevalence of haemodynamically proven PAH in large cohorts of patients with systemic sclerosis is between 7% and 12%. Compared with idiopathic PAH, patients with CTD and PAH are mainly females (female to male ratio 4:1), are older (mean age at diagnosis 66 yrs), may present concomitant disorders (pulmonary fibrosis and left heart disease) and have shorter survival.

Echocardiographic screening for the detection of PH has been recommended annually in asymptomatic patients with the scleroderma spectrum of diseases but only in the presence of symptoms in other CTD (table 7).

The reliability of several tricuspid regurgitation velocity cut-off values, using RHC as reference, has been assessed in two large screening studies. A trial evaluating the reliability of prospective screening of patients with scleroderma, based on tricuspid regurgitation velocity >2.5 m·s^{-1} in symptomatic patients or >3.0 m·s^{-1} irrespective of symptoms, found that 45% of cases of echocardiographic diagnoses of PH were falsely positive. Another trial selected a tricuspid regurgitation pressure gradient >40 mmHg (tricuspid regurgitation velocity >3.2 m·s^{-1}) with an assumed right atrial pressure of 10 mmHg as the cut-off value for diagnosis of PH. Those criteria were recently prospectively applied in systemic sclerosis patients.

In tables 8 and 9, the ESC/ERS task force suggests arbitrary criteria for detecting the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated systolic P_{pa} at rest (assuming a normal right atrial pressure of 5 mmHg) and additional echocardiographic variables suggestive of PH.

CASE 3: SYSTEMIC SCLEROSIS-ASSOCIATED POST-CAPILLARY PH

Case report

A 67-yr-old female in whom LSSc was diagnosed 11 yrs previously was referred for assessment of PH. She reported worsening dyspnoea on exertion over the preceding several

TABLE 11 ESC/ERS guidelines: factors favouring diagnosis of left ventricular diastolic dysfunction in the presence of pulmonary hypertension as assessed by Doppler echocardiography

Clinical features
Age >65 yrs
Elevated systolic blood pressure
Elevated pulse pressure
Obesity, metabolic syndrome
Hypertension
Coronary artery disease
Diabetes mellitus
Atrial fibrillation
Echocardiography
Left atrial enlargement
Concentric remodelling of the LV (relative wall thickness >0.45)
LV hypertrophy
Presence of echocardiographic indicators of elevated LV filling pressure [13, 14]
Interim evaluation (after echocardiography)
Symptomatic response to diuretics
Exaggerated increase in systolic blood pressure with exercise
Re-evaluation of chest radiograph consistent with heart failure [14]

LV: left ventricle. Modified from [15] with permission from the publisher.

months associated with intermittent episodes of chest discomfort and mild leg swelling, in addition to severe Raynaud's phenomenon and gastro-oesophageal reflux symptoms. Physical examination was remarkable for severe calcinosis involving both hands and extensive telangiectasia. She was normotensive and there was no clinical evidence of cardiac failure. PFTs revealed normal spirometry and lung volume measurements and a $D_{L,CO}$ of 60% predicted. She was referred to an expert centre for evaluation of suspected PAH as transthoracic echocardiography demonstrated enlarged right heart chambers and an estimated systolic P_{pa} of 50 mmHg with normal left ventricular function, mild left atrial enlargement, normal valvular structure and a normal pericardium. At review, she was in WHO functional class III with a 6MWD of 320 m. HRCT showed mild bibasal interstitial infiltrates. Liver function tests, blood gas analysis, lung scintigraphy, abdominal ultrasound and polysomnography were normal and HIV test was negative. RHC was performed and confirmed mild PH ($\bar{P}_{pa}$ 26 mmHg) with normal P_{pcw} (table 10). Because of the strong suspicion of underlying left heart disease, a fluid challenge (500 mL saline over 10 min) was administered and repeat measurements of pulmonary haemodynamics were made, revealing a profile consistent with post-capillary PH in the context of diastolic left heart disease associated with scleroderma (table 10).

TABLE 12 ESC/ERS guidelines: recommendations for pulmonary hypertension (PH) due to left heart disease

Statement	Class#	Level¶
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	I	C
Patients with "out of proportion" PH due to left heart disease (table 3) should be enrolled in RCTs targeting PH specific drugs	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography	IIb	C
Invasive measurements of P_{pcw} or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease	IIb	C
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease	IIb	C
The use of PAH specific drug therapy is not recommended in patients with PH due to left heart disease	III	C

RCT: randomised controlled trial; P_{pcw}: pulmonary capillary wedge pressure; LV: left ventricular; RHC: right heart catheterisation; PAH: pulmonary arterial hypertension. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

Commentary: relevance to ESC/ERS guidelines

The diagnostic approach to PH due to left heart disease is similar to that for PAH, doppler echocardiography being the best tool for screening purposes.

Left ventricle diastolic dysfunction should be suspected in the presence of a dilated left atrium, atrial fibrillation, characteristic changes in mitral flow profile, pulmonary venous flow profile, and mitral annulus tissue Doppler signals and left ventricle hypertrophy. Characteristic clinical and echocardiographic features of PH associated with left ventricle diastolic dysfunction are listed in table 11.

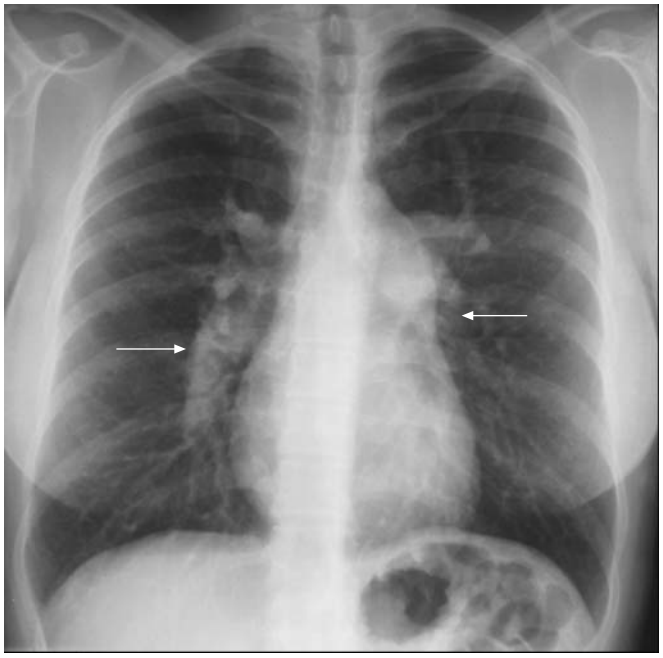

FIGURE 2. Chest radiograph showing markedly dilated pulmonary arteries (arrows).

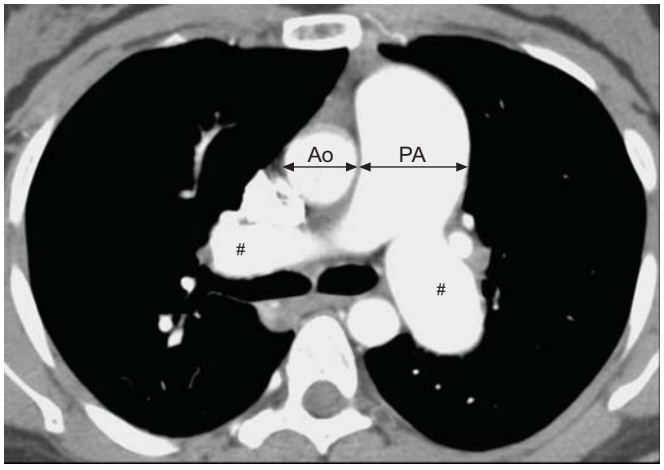

FIGURE 3. Contrast-enhanced computed tomography of the chest of a patient with pulmonary arterial hypertension associated with congenital heart disease (large atrial septal defect). Massive dilatation of the pulmonary arterial trunk and branches (#). The ratio of the diameter of aorta (Ao) to the diameter of main pulmonary artery (PA) is >1.5.

Adequate recording of P_{pcw} is required for the differential diagnosis of PH due to left heart disease. In rare cases, left heart catheterisation may be required for direct assessment of left ventricular end-diastolic pressure.

A P_{pcw} >15 mmHg excludes the diagnosis of pre-capillary PAH.

One of the most challenging differential diagnoses of PAH is heart failure with normal left ventricular ejection fraction and diastolic dysfunction. In this population, P_{pcw} may be mildly elevated or at the higher end of the normal range at rest. P_{pcw} and left ventricular end-diastolic pressure can be ''pseudo-normal'', especially when patients have been treated with diuretics. In this setting, exercise haemodynamic volume challenge has been proposed to identify left ventricular dysfunction, but these diagnostic tools require further standardisation.

An elevated transpulmonary gradient ($\bar{P}_{pa}$-$\bar{P}_{pcw}$) >12 mmHg is suggestive of intrinsic changes in the pulmonary circulation overriding the passive increase in P_{pcw}.

Recommendations for PH due to left heart disease are summarised in table 12.

CASE 4: PAH AND CONGENITAL HEART DISEASE

Case report

A 24-yr-old female was referred for assessment of suspected PH. Except for mild asthma treated with a short-acting β_2-adrenergic agonist, she had no significant personal or familial medical history and denied illicit drug or appetite suppressant intake. 2 months before admission, a chest radiograph was performed for tuberculosis contact screening and revealed markedly dilated pulmonary arteries (fig. 2). She reported mild dyspnoea on exertion (WHO functional class II) over the preceding several months. Physical examination revealed an accentuated second heart sound over the pulmonic valve but was otherwise normal. ECG showed right ventricular hypertrophy and an incomplete right bundle branch block pattern. 6MWD was 505 m, during which a decrease in arterial oxygen saturation to 87% was recorded. Echocardiography demonstrated a large atrial septal defect of the posterior ostium secundum (15×15 mm) associated with a bi-directional shunt that was predominantly right to left. Significant tricuspid regurgitation was also noted and systolic P_{pa} was estimated at 55 mmHg. Systemic and pulmonary venous returns were normal. Contrast-enhanced chest CT was remarkable for massive dilatation of the pulmonary arteries associated with marked right ventricular hypertrophy and dilatation (fig. 3). RHC confirmed PAH with a pre-capillary pattern: $\bar{P}_{pa}$ 57 mmHg, P_{pcw} 3 mmHg, and PVR 880 dyn·s·cm^{-5}. The pressures in right and left atria were equivalent at 3 mmHg. The pulmonary CI measured by the Fick method was 3.2 L·min^{-1}·m^{-2} and the systemic CI was 2.6 L·min^{-1}·m^{-2}, resulting in a pulmonary to systemic CI ratio of 1.22. Because of the high level of PVR and the presence of right-to-left shunt, repair surgery was not performed. Instead, oral specific PAH therapy with an endothelin receptor antagonist was initiated. After 6 months, the patient remained in WHO functional class II with a moderate clinical and haemodynamic improvement (70 m increase in 6MWD and 25% reduction in PVR). Repeat echocardiography confirmed persistence of the right-to-left shunt. Specific PAH therapy was therefore maintained and repair surgery was definitively contraindicated.

TABLE 13 ESC/ERS guidelines: clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (PAH)

A. Eisenmenger's syndrome

Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis and multiple organ involvement are present.

B. PAH associated with systemic-to-pulmonary shunts

In these patients with moderate-to-large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

C. PAH with small# defects

In cases with small defects (usually ventricular septal defects, 1 cm and atrial septal defects, 2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

D. PAH after corrective cardiac surgery

In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery.

PVR: pulmonary vascular resistance. #: the size applies to adult patients. Reproduced from [1] with permission from the publisher.

Commentary: relevance to ESC/ERS guidelines

PAH associated with CHD is included in group 1 of the PH clinical classification. A specific clinical classification (table 13) and an anatomical–pathophysiological classification (table 14) are useful to better define each individual patient with PAH associated with CHD.

TABLE 14 ESC/ERS guidelines: anatomical–pathophysiological classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

1 Type
- 1.1 Simple pre-tricuspid shunts
  - 1.1.1 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 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 Q_P/Q_S)#
  - 2.1.1 Restrictive (pressure gradient across the defect)
  - 2.1.2 Nonrestrictive
- 2.2 Anatomical¶
  - 2.2.1 Small to moderate (ASD $\leqslant$2.0 cm and VSD $\leqslant$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)

ASD: atrial septal defect; VSD: ventricular septal defect. #: ratio of pulmonary (Q_P) to systemic (Q_S) blood flow; ¶: the size applies to adult patients. Modified from [16] with permission from the publisher.

The persistent exposure of the pulmonary vasculature to increased blood flow due to systemic-to-pulmonary shunts as well as increased pressure may result in a typical pulmonary obstructive arteriopathy that leads to the increase of PVR. If PVR approaches or exceeds systemic vascular resistance, the shunt is reversed (Eisenmenger's syndrome).

In patients listed for lung or heart–lung transplantation when no medical treatment was available, Eisenmenger's syndrome had better survival compared with idiopathic PAH, with a 3-yr survival rate of 77% compared with 35% for untreated idiopathic PAH.

Recommendations for PAH associated with congenital cardiac shunts are summarised in table 15.

TABLE 15 ESC/ERS guidelines: recommendations for pulmonary arterial hypertension associated with congenital cardiac shunts

Statement	Class#	Level¶
The ERA bosentan is indicated in WHO FC III patients with Eisenmenger's syndrome	I	B
Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in patients with Eisenmenger's syndrome	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is $>$65%	IIa	C
Combination therapy may be considered in patients with Eisenmenger's syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome	III	C

ERA: endothelin receptor antagonist; WHO FC: World Health Organization functional class; PA: pulmonary arterial; CCB: calcium channel blockers. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

CASE 5: HERITABLE PAH

Case report

A 10-yr-old male presented with a 2-month history of progressive dyspnoea on exertion. Clinical examination revealed an accentuated second heart sound over the pulmonic valve. Although the child had no medical history, a strong familial history of PAH had previously been established (fig. 4). 10 yrs earlier, the patient's father had been diagnosed with severe PAH at age 30 yrs that was initially deemed idiopathic given the absence of familial history at time of diagnosis. However, 2 yrs thereafter, the patient's paternal grandmother was also diagnosed with severe PAH. She had developed symptoms at age 52 yrs, presenting in WHO functional class III with marked haemodynamic impairment. A screening of point mutations and large rearrangements of bone morphogenetic protein receptor type 2 (*BMPR2*) gene found a c.418+3A$>$T mutation (a defect that affects a putative spicing regulatory element in intron 3), thereby confirming the diagnosis of heritable PAH. Genetic counselling sessions were conducted with family members in order to provide information on the risks of developing PAH and to inform them of disease symptoms and signs. These interventions helped facilitate the early referral of the child to a PAH referral centre in order to expedite a diagnostic work-up. RHC confirmed severe PAH ($\bar{P}_{pa}$ 73 mmHg, CI 2.71 $L \cdot min^{-1} \cdot m^{-2}$ and PVR 1,510 $dyn \cdot s \cdot cm^{-5}$) and endothelin receptor antagonist therapy was initiated. However, after 6 months of treatment there was only a modest

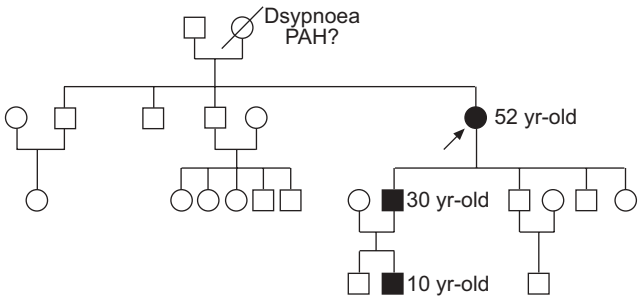

FIGURE 4. Genealogical tree of heritable pulmonary arterial hypertension (PAH) with *BMPR2* mutation, demonstrating the phenomenon of genetic anticipation. PAH in the first generation was diagnosed at age 52 yrs, then at age 30 yrs in the second generation and at age 10 yrs for the last generation.

clinical and haemodynamic improvement, justifying the addition of a phosphodiesterase-5 (PDE-5) inhibitor.

Commentary: relevance to ESC/ERS guidelines

When PAH occurs in a familial context, germline mutations in the *BMPR2* gene are detected in $\geqslant$70% of cases.

Mutations of this gene can also be detected in 11–40% of apparently sporadic cases, thus representing the major genetic predisposing factor for PAH.

The *BMPR2* gene encodes a type 2 receptor for bone morphogenetic proteins, which belong to the transforming growth factor-β superfamily, involved in the control of vascular cell proliferation.

Mutations of other receptors for these substances, such as *activin receptor-like kinase 1* (*ALK-1* or *ACVRL-1*) and endoglin, have been identified mostly in PAH patients with a personal or family history of hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome).

CASE 6: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Case report

A 21-yr-old male professional soccer player presented with a 1-yr history of exercise intolerance and intermittent pleuritic chest pain. He was a cigarette smoker (2 pack-yrs) but otherwise had no significant past medical history, denied previous illicit or performance-enhancing drug intake and had no personal or family history of venous thromboembolism. Initial chest radiograph, PFTs and echocardiography were negative and no further exams were performed. The patient represented 18 months later with worsening of breathlessness. Repeat echocardiography showed moderately dilated right heart chambers with an estimated systolic P_{pa} of 55 mmHg. A working diagnosis of pulmonary embolism was made; however, both CT pulmonary angiography and lower limb compression ultrasonography were normal. 1 month later, he represented with severe pleuritic chest pain. On this occasion, ventilation/perfusion lung scintigraphy confirmed bilateral pulmonary emboli and compression ultrasonography identified a left leg deep vein thrombosis. Anticoagulation therapy was therefore initiated. 4 months thereafter, the patient had persistent WHO functional class II symptoms. Repeat echocardiography demonstrated persistent PH (systolic P_{pa} 60 mmHg). 6MWD was 540 m. Thrombophilia screening was negative. RHC confirmed mild PH at rest with a significant increase in $\bar{P}_{pa}$ with exercise at 100 W (table 16). Repeat CTPA and formal pulmonary angiography confirmed the presence of chronic thromboembolic disease in a proximal distribution (fig. 5a and b) and treatment by pulmonary thromboendarterectomy (PEA) was proposed. However, the patient declined surgery, though agreed to continue oral anticoagulation. 18 months later, he was readmitted with increasing breathlessness. The patient was in WHO functional class III and 6MWD was 477 m (decrease of 63 m from baseline). Haemodynamic reassessment confirmed worsening PH (table 16) while progressive occlusive vasculopathy was noted

TABLE 16 Case 6: clinical data

	First evaluation		After 18 months of evolution without PEA	6 months after PEA
	At rest	Exercise (100 W)		
WHO functional class	II		III	I
6MWD m	540		477	748
P_{ra} mmHg	2	NA	6	4
$\bar{P}_{pa}$ mmHg	31	69	43	18
P_{pcw} mmHg	2	NA	4	6
CO L·min^{-1}	4.6	12.3	4.7	5.8
TPR dyn·s·cm^{-5}	539	449	732	248
S_{V,O_2} %	68	27	63	73
Decision for therapy	VKA		VKA	VKA
	Patient declined PEA		Patient accepted PEA	

PEA: pulmonary thromboendarterectomy; WHO: World Health Organization; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; TPR: total pulmonary resistance; S_{V,O_2}: mixed venous oxygen saturation; VKA: oral vitamin K antagonist anticoagulation.

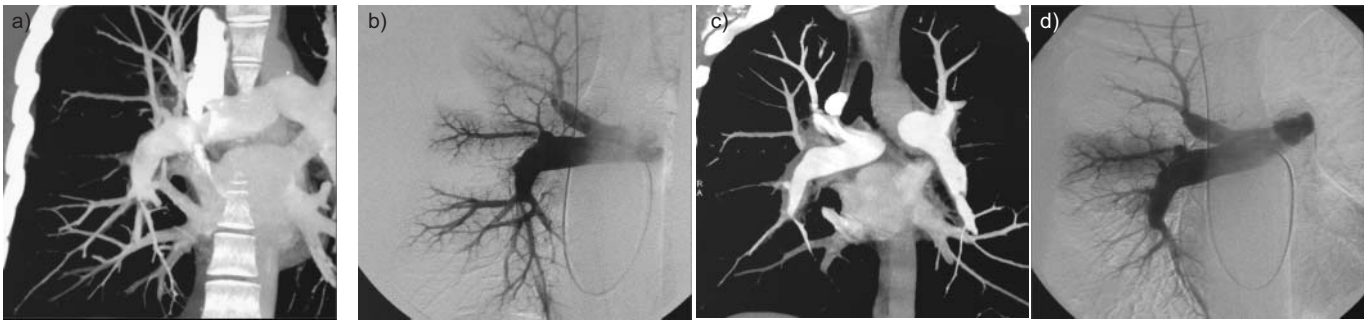

FIGURE 5. Case 6. a) Computed tomography pulmonary angiography and b) formal pulmonary angiography confirmed the presence of chronic thromboembolic disease. c) and d) Progressive occlusive vasculopathy was noted on repeat imaging studies.

on repeat imaging studies (fig. 5c and d). On this occasion, the patient proceeded to PEA during which obstructing material was successfully removed from all major pulmonary artery branches. His post-operative course was unremarkable and oral anticoagulation was recommenced. At follow-up 6 months later, he was asymptomatic and repeat RHC confirmed normal pulmonary haemodynamics (table 16).

Commentary: relevance to ESC/ERS guidelines

CTEPH is one of the most prevalent forms of PH. Nevertheless, it is almost impossible to determine the overall prevalence of CTEPH since not all of these patients have a history of acute pulmonary embolism.

Any patient with unexplained PH should be evaluated for the presence of CTEPH. 1) A normal ventilation/perfusion scan rules out CTEPH. 2) Multi-row CT angiography is indicated when the ventilation/perfusion lung scan is indeterminate or reveals perfusion defects. Even in the era of modern multi-row CT scanners, there is not yet enough evidence to suggest that a normal CT angiography excludes the presence of operable CTEPH.

Once ventilation/perfusion scanning and/or CT angiogram show signs compatible with CTEPH, the patient should be referred to a centre with expertise in the medical and surgical management of these patients.

To determine the appropriate therapeutic strategy, invasive tools, including RHC and traditional pulmonary angiography, are usually required. The final diagnosis of CTEPH is based on the presence of pre-capillary PH in patients with multiple chronic/organised occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental and subsegmental).

The decision on how to treat patients with CTEPH should be made at an experienced centre based upon interdisciplinary discussion among internists, radiologists, and expert surgeons: 1) PEA is the treatment of choice for patients with CTEPH, as it is a potentially curative option; 2) patients with CTEPH should receive life-long anticoagulation, usually with vitamin K antagonists adjusted to a target INR of 2.0–3.0.

Recommendations for PH due to CTEPH are summarised in table 17.

CASE 7: ACUTE VASOREACTIVITY TEST RESPONDER

Case report

A 69-yr-old female presented with a 3-month history of dyspnoea and exercise intolerance. Her past medical history was significant for breast cancer diagnosed 2 yrs previously treated by surgery and adjuvant combination cytotoxic therapy with cyclophosphamide, 5-fluoro-uracil and farmorubicin. At the time of initial referral, she was in WHO functional class III.

TABLE 17 ESC/ERS guidelines: recommendations for chronic thromboembolic pulmonary hypertension (CTEPH)

Statement	Class[#]	Level[¶]
The diagnosis of CTEPH is based on the presence of pre-capillary PH ($\bar{P}_{pa}$ ⩾25 mmHg, P_{pcw} ⩽15 mmHg, PVR>2 Wood units) in patients with multiple chronic/organised occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental)	I	C
In patients with CTEPH lifelong anticoagulation is indicated	I	C
Surgical pulmonary endarterectomy is the recommended treatment for patients with CTEPH	I	C
Once perfusion scanning and/or CT angiography show signs compatible with CTEPH, the patient should be referred to a centre with expertise in surgical pulmonary endarterectomy	IIa	C
The selection of patients for surgery should be based on the extent and location of the organised thrombi, on the degree of PH, and on the presence of comorbidities	IIa	C
PAH-specific drug therapy may be indicated in selected CTEPH patients such as patients not candidates for surgery or patients with residual PH after pulmonary endarterectomy	IIb	C

PH: pulmonary hypertension; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; CT: computed tomography; PAH: pulmonary arterial hypertension. [#]: class of recommendation; [¶]: level of evidence. Reproduced from [1] with permission from the publisher.

TABLE 18 Case 7: clinical characteristics

	First evaluation		After 12 months of high-dose CCB	
	At rest	Acute vasodilator testing	At rest	Acute vasodilator testing
WHO functional class	III		II	
6MWD m	210		310	
P_{ra} mmHg	6	5	6	6
$\bar{P}_{pa}$ mmHg	52	25	31	23
P_{pcw} mmHg	10	6	11	9
CO L·min^{-1}	6.6	7.3	7.0	6.8
PVR dyn·s·cm^{-5}	509	208	286	200

CCB: calcium channel blockers; WHO: World Health Organization; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; PVR: pulmonary vascular resistance.

Clinical examination revealed an accentuated second heart sound over the pulmonic valve without evidence of cardiac failure. Transthoracic echocardiography estimated systolic P_{pa} 62 mmHg. Additional routine diagnostic testing for an underlying cause of PH was negative. The patient proceeded to RHC in order to confirm the diagnosis and assess severity of haemodynamic impairment. This revealed severe pre-capillary PH ($\bar{P}_{pa}$ 52 mmHg and PVR 509 dyn·s·cm^{-5}) with a preserved CO and no evidence of hypervolaemia (table 18). An acute vasodilator challenge testing using inhaled nitric oxide at a dose of 10 ppm was then performed to assess for vasoreactivity. This showed a significant acute vasodilator response with near normalisation of $\bar{P}_{pa}$, reduction in PVR and an associated increase in CI (table 18). A treatment with high-dose oral calcium channel antagonist (CCB) therapy was therefore initiated and titrated up to the maximum tolerated dose, in conjunction with oral anticoagulation. At haemodynamic reassessment 12 months later, the patient had improved to WHO functional class II and had increased her 6MWD from 210 m to 310 m. Subsequent RHC confirmed a sustained favourable pulmonary haemodynamic response and the dose of oral CCB was increased because of persistence of an acute vasoreactivity to inhaled nitric oxide.

Commentary: relevance to ESC/ERS guidelines

In PAH, vasoreactivity testing should be performed at the time of diagnostic RHC to identify patients who may benefit from long-term therapy with CCBs.

Acute vasodilator challenge should only be performed with short-acting, safe and easy to administer drugs with no or limited systemic effects. Currently the agent most used in acute testing is nitric oxide based on previous experience; *i.v.* epoprostenol or *i.v.* adenosine may also be used as an alternative (but with a risk of systemic vasodilator effects) (table 19). Due to the risk of potentially life-threatening complications, the use of CCBs given orally or *i.v.* as an acute test is discouraged.

A positive acute response (positive acute responder) is defined as a reduction of $\bar{P}_{pa} \geqslant 10$ mmHg to reach an absolute value of $\bar{P}_{pa} \leqslant 40$ mmHg with an increased or unchanged CO. Only 10% of patients with idiopathic PAH will meet these criteria (table 20).

Positive acute responders are most likely to show a sustained response to long-term treatment with high doses of CCBs and they are the only patients that can safely be treated with this type of therapy. About half of idiopathic PAH-positive acute responders are also positive long-term responders to CCBs and only in these cases is the continuation of a CCB as a single treatment warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with CCBs in patients with other PAH types, such as heritable PAH, CTD, and HIV patients is less clear than in idiopathic PAH. Nevertheless, experts recommend performing acute vasoreactivity studies in these patients and to look for a long-term response to CCBs in those in whom the test is positive.

TABLE 19 ESC/ERS guidelines: 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[#]	Increments[¶]	Duration[+]
Epoprostenol	Intravenous	3 min	2–12 ng·kg^{-1}·min^{-1}	2 ng·kg^{-1}·min^{-1}	10 min
Adenosine	Intravenous	5–10 s	50–350 μg·kg^{-1}·min^{-1}	50 μg·kg^{-1}·min^{-1}	2 min
Nitric oxide	Inhaled	15–30 s	10–20 ppm		5 min[§]

[#]: initial dose and maximal tolerated dose suggested (maximal dose limited by side-effects such as hypotension, headache, flushing, *etc.*); [¶]: increments of dose by each step; [+]: duration of administration on each step; [§]: for nitric oxide, a single step within the dose range is suggested. Reproduced from [1] with permission from the publisher.

TABLE 20 ESC/ERS guidelines: recommendations for right heart catheterisation (RHC) (A) and vasoreactivity testing (B)

	Class[#]	Level[¶]
A. RHC		
RHC is indicated in all patients with PAH to confirm the diagnosis, to evaluate the severity and when PAH specific drug therapy is considered	I	C
RHC should be performed for confirmation of efficacy of PAH-specific drug therapy	IIa	C
RHC should be performed for confirmation of clinical deterioration and as baseline for the evaluation of the effect of treatment escalation and/or combination therapy	IIa	C
B. Vasoreactivity testing		
Vasoreactivity testing is indicated in patients with IPAH, heritable PAH and PAH associated with anorexigen use to detect patients who can be treated with high doses of a CCB	I	C
A positive response to vasoreactivity testing is defined as a reduction of $\bar{P}_{pa} \geqslant 10$ mmHg to reach an absolute value of $\bar{P}_{pa} \leqslant 40$ mmHg with an increased or unchanged CO	I	C
Vasoreactivity testing should be performed only in referral centres	IIa	C
Vasoreactivity testing should be performed using nitric oxide as vasodilator	IIa	C
Vasoreactivity testing may be performed in other types of PAH	IIb	C
Vasoreactivity testing may be performed using *i.v.* epoprostenol or *i.v.* adenosine	IIb	C
The use of an oral or *i.v.* CCB in acute vasoreactivity testing is not recommended	III	C
Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with other PH groups (groups 2, 3, 4 and 5)	III	C

PAH: pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; CCB: calcium channel blocker; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CO: cardiac output; PH: pulmonary hypertension. [#]: class of recommendation; [¶]: level of evidence. Reproduced from [1] with permission from the publisher.

TABLE 21 ESC/ERS guidelines: recommendations for general measures

Statement	Class[#]	Level[¶]
It is recommended to avoid pregnancy in patients with PAH	I	C
Immunisation of PAH patients against influenza and pneumococcal infection is recommended	I	C
Physically deconditioned PAH patients should be considered for supervised exercise rehabilitation	IIa	B
Psychosocial support should be considered in patients with PAH	IIa	C
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	C
Epidural anaesthesia instead of general anaesthesia should be utilised, if possible, for elective surgery	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in patients with PAH	III	C

PAH: pulmonary arterial hypertension; WHO FC: World Health Organization functional class. [#]: class of recommendation; [¶]: level of evidence. Reproduced from [1] with permission from the publisher.

The CCBs that have been predominantly used in reported studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two. The choice of CCB is based upon the patient's heart rate at baseline, with a relative bradycardia favouring nifedipine and amlodipine and a relative tachycardia favouring diltiazem. The daily doses of these drugs that have shown efficacy in idiopathic PAH are relatively high, 120–240 mg for nifedipine, 240–720 mg for diltiazem, and up to 20 mg for amlodipine.

Patients with idiopathic PAH who meet the criteria for a positive vasodilator response and are treated with a CCB should be followed closely for both safety and efficacy with an initial reassessment after 3–4 months of therapy including RHC. If the patient does not show an adequate response, defined as being in WHO functional class I or II and with a marked haemodynamic improvement, additional PAH therapy should be instituted.

Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on a CCB because of potential severe side-effects.

CASE 8: IDIOPATHIC PAH WITH WHO FUNCTIONAL CLASS II SYMPTOMS

Case report

A 48-yr-old male was referred for evaluation of breathlessness associated with effort-associated palpitations and chest discomfort. He reported that his symptoms occurred with moderate exertion and was therefore deemed to be in WHO functional class II. He denied dizziness, syncope or ankle swelling. The only positive sign elicited on physical examination was an accentuated pulmonary component to the second heart sound. Baseline 6MWD was 450 m. RHC confirmed precapillary PH of moderate severity without associated acute vasodilator response (right atrial pressure 2 mmHg, $\bar{P}_{pa}$ 35 mmHg, P_{pcw} 5 mmHg, PVR 260 dyn·s·cm^{-5} and CI 5.6 L·min^{-1}·m^{-2}). Routine testing to assess for underlying causes of PH was negative and a diagnosis of idiopathic PAH was made. He was commenced on PAH-specific therapy with an endothelin antagonist in addition to oral anticoagulation. At reassessment after 6 months of treatment, he remained in WHO functional class II, had a 6MWD of 466 m and showed a stable pulmonary haemodynamic profile (right atrial pressure 7 mmHg; $\bar{P}_{pa}$ 39 mmHg; P_{pcw} 8 mmHg; PVR 238 dyn·s·cm^{-5} and CI 5.8 L·min^{-1}·m^{-2}). He was reassessed thereafter on a 6-monthly basis. On each occasion, he was

TABLE 22 ESC/ERS guidelines: recommendations for supportive therapy

Statement	Class[#]	Level[¶]
Diuretic treatment is indicated in PAH patients with signs of RV failure and fluid retention	I	C
Continuous long-term O_2 therapy is indicated in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[+]	I	C
Oral anticoagulant treatment should be considered in patients with IPAH, heritable PAH and PAH due to use of anorexigens	IIa	C
Oral anticoagulant treatment may be considered in patients with APAH	IIb	C
Digoxin may be considered in patients with PAH who develop atrial tachyarrhythmias to slow ventricular rate	IIb	C

PAH: pulmonary arterial hypertension; RV: right ventricular; IPAH: idiopathic PAH; APAH: associated PAH. [#]: class of recommendation; [¶]: level of evidence; [+]: see also recommendations for PAH associated with congenital cardiac shunts (table 15). Reproduced from [1] with permission from the publisher.

noted to be in WHO functional class II and had stable exercise capacity, as evidenced by 6MWD consistently in the 475–500 m range. Treatment was therefore continued without modification. Since diagnosis of PAH 5 yrs ago, the patient has shown no evidence of clinical or haemodynamic deterioration.

Commentary: relevance to ESC/ERS guidelines

The management of PAH patients includes general and supportive measures, as follows. 1) Patients should avoid excessive physical activity that leads to distressing symptoms, but when physically deconditioned may undertake supervised exercise rehabilitation. 2) Pregnancy is associated with 30–50% mortality in patients with PAH and, as a consequence, pregnancy is contraindicated in PAH. There is less consensus relating to the most appropriate methods of birth control. Barrier contraceptive methods are safe and progesterone-only preparations are effective approaches to contraception and avoid potential issues of oestrogens. 3) Patients should avoid going to altitudes above 1,500–2,000 m without supplemental oxygen. 4) It is recommended to vaccinate against influenza and pneumococcal pneumonia.

Recommendations for general measures are summarised in table 21.

Advice regarding the target INR in patients with idiopathic PAH varies from 1.5–2.5 in most centres of North America to 2.0–3.0 in European centres.

Diuretic treatment is indicated in PAH patients with signs of right ventricular failure and fluid retention.

When arterial blood oxygen pressure is consistently <8 kPa (60 mmHg) patients are advised to take oxygen to achieve a arterial blood oxygen pressure of.8 kPa for $\geqslant$15 h·day^{-1}.

Recommendations for general measures are summarised in table 22.

TABLE 23 ESC/ERS guidelines: recommendations for efficacy of specific drug therapy, balloon atrial septostomy and lung transplantation for pulmonary arterial hypertension (group 1) according to World Health Organization functional class (WHO FC)

Measure/treatment		Classes of recommendation–level of evidence		
		WHO FC II	WHO FC III	WHO FC IV
Calcium channel blockers		I–C[#]	I–C[#]	–
Endothelin receptor antagonists	Ambrisentan	I–A	I–A	IIa–C
	Bosentan	I–A	I–A	IIa–C
	Sitaxentan	IIa–C	I–A	IIa–C
Phosphodiesterase type-5 inhibitors	Sildenafil	I–A	I–A	IIa–C
	Tadalafil[¶]	I–B	I–B	IIa–C
Prostanoids	Beraprost	–	IIb–B	–
	Epoprostenol (intravenous)	–	I–A	I–A
	Iloprost (inhaled)	–	I–A	IIa–C
	Iloprost (intravenous)	–	IIa–C	IIa–C
	Treprostinil (subcutaneous)	–	I–B	IIa–C
	Treprostinil (intravenous)	–	IIa–C	IIa–C
	Treprostinil (inhaled)[¶]	–	I–B	IIa–C
Initial drugs combination therapy		–	–	IIa–C
Sequential drugs combination therapy		IIa–C	IIa–B	Iia–B
Balloon atrial septostomy		–	I–C	I–C
Lung transplantation		–	I–C	I–C

[#]: only in responders to acute vasoreactivity tests, I for idiopathic pulmonary arterial hypertension (PAH), heritable PAH and PAH due to anorexigens; IIa for associated PAH conditions; [¶]: under regulatory review in the European Union. Reproduced from [1] with permission from the publisher.

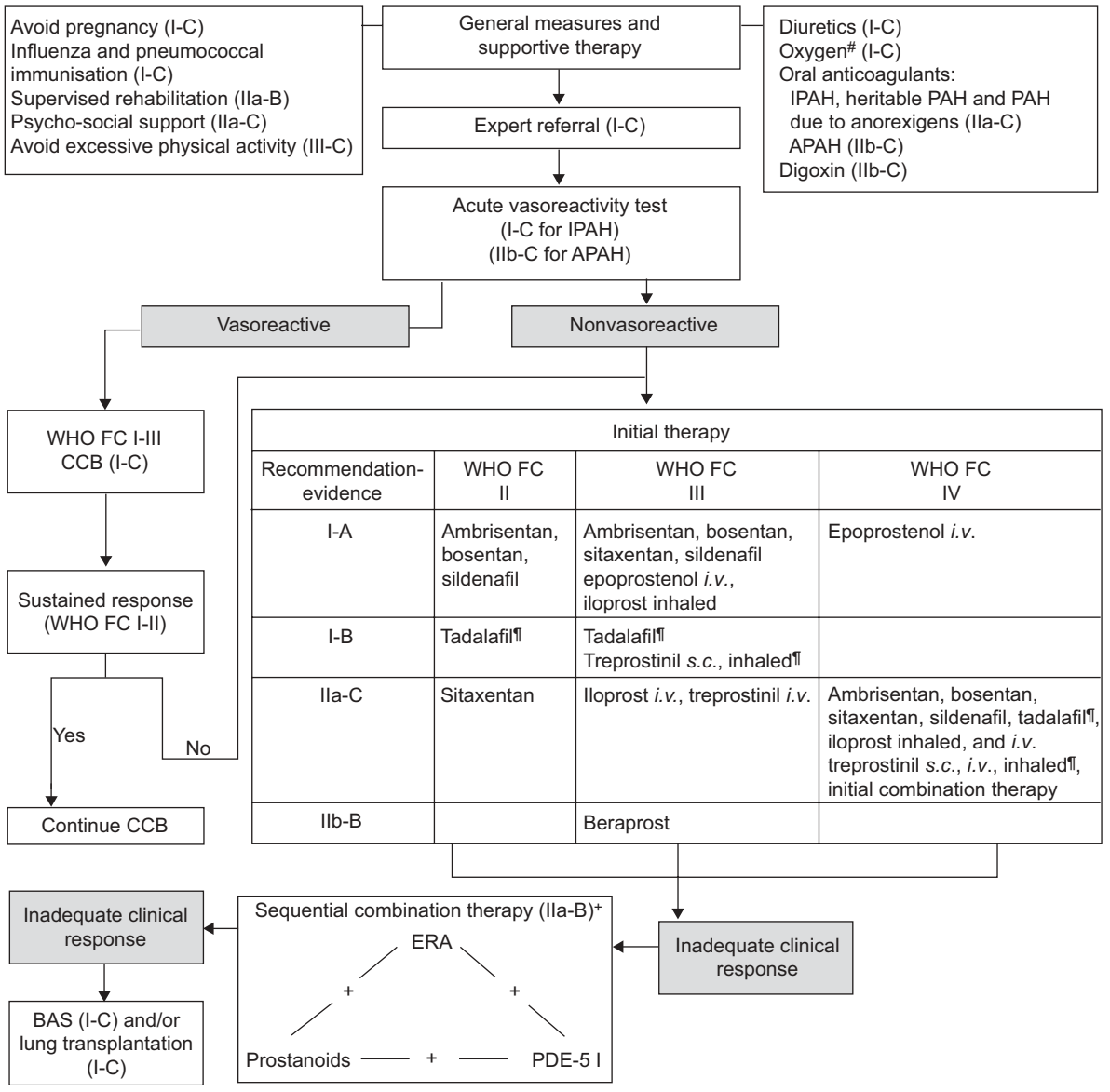

FIGURE 6. Evidence-based treatment algorithm for pulmonary arterial hypertension patients (PAH; for group 1 patients only). APAH: associated PAH; BAS: balloon atrial septostomy; CCB: calcium channel blocker; ERA: endothelin receptor antagonist; IPAH: idiopathic PAH; PDE-5I: phosphodiesterase type-5 inhibitor; WHO FC: World Health Organization functional class. #: to maintain arterial blood O_2 pressure >8 kPa (60 mmHg); ¶: under regulatory review in the European Union; +: IIa-C for WHO FC II. Reproduced from [1] with permission from the publisher.

As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. In this case the choice of the drug is dependent on a variety of factors, including the approval status, the route of administration, the side-effect profile, patients' preferences and physicians' experience.

Classes of recommendations and level of evidence for first-line therapy in PAH patients (group 1) depends on the WHO functional class (table 23). Nonresponders to acute vasoreactivity testing who are in WHO functional class II should be treated with an endothelin receptor agonist or a PDE-5 inhibitor.

CASE 9: IDIOPATHIC PAH WITH WHO FUNCTIONAL CLASS IV SYMPTOMS TREATED BY FIRST-LINE COMBINATION THERAPY

Case report

A 27-yr-old female with previously well-controlled asthma since childhood was referred for evaluation of a 1-month history of progressive dyspnoea unresponsive to augmentation of inhaled corticosteroids. There was no family history of pulmonary vascular disease. At presentation she was in WHO functional class IV, being breathless on minimal exertion and having experienced several pre-syncopal episodes. Physical examination revealed a loud pulmonic component to the second heart sound and a soft pansystolic murmur over the tricuspid valve without

TABLE 24 Case 10: clinical characteristics

Treatment at evaluation	None	ERA (for 4 months)	ERA and PDE-5I (for 5 months)	ERA, PDE-5I and *i.v.* prostacyclin (for 4 months)
WHO functional class	III	III	III	II
6MWD m	519	525	441	601
P_{ra} mmHg	7	8	8	3
$\bar{P}_{pa}$ mmHg	55	60	65	47
CI L·min^{-1}·m^{-2}	2.01	2.5	2.09	3.35
PVR dyn·s·cm^{-5}	1248	1066	1368	649
BNP pg·mL^{-1}		217	360	62
Modification of specific PAH therapy	Initiation of ERA	Addition of PDE5-I	Addition of *i.v.* prostacyclin	No change

ERA: endothelin receptor agonist; PDE5-I: phosphodiesterase type-5 inhibitor; WHO: World Health Organization; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; $\bar{P}$pa: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; BNP: brain natriuretic peptide; PAH: pulmonary arterial hypertension.

jugular venous distension or peripheral oedema. Chest radiograph demonstrated an enlarged heart and clear lung fields. Transthoracic echocardiography revealed a systolic P_{pa} >100 mmHg and associated dilated right heart chambers without evidence of intracardiac shunt. Arterial blood gas analysis showed a respiratory alkalosis pattern and hypoxaemia. Antinuclear antibody, anti-double-stranded DNA, rheumatoid factor and HIV test were negative. Abdominal ultrasound showed no evidence of portal hypertension. PFTs demonstrated normal airway function and lung volumes, but a $D_{L,CO}$ of 60% pred. Lung scintigraphy was unremarkable. The patient's 6MWD was 150 m, during which an oxygen desaturation to 81% was recorded, despite the use of supplementary oxygen. RHC confirmed severe pre-capillary PH with $\bar{P}_{pa}$ 74 mmHg, PVR 1,450 dyn·s·cm^{-5}, CI 1.9 L·min^{-1}·m^{-2} and a mixed venous oxygen saturation of 57%. Acute vasodilator testing with nitric oxide was negative. Because of the severity of the patient's symptoms, advanced functional class, marked limitation of exercise capacity and significant haemodynamic impairment, a decision was made to initiate a dual targeted therapy regimen with combination continuous *i.v.* prostacyclin and oral endothelin antagonist.

Commentary: relevance to ESC/ERS guidelines

The treatment algorithm (fig. 6) does not apply to patients in other clinical groups, and in particular not to patients with PH associated with group 2 (left heart disease) or with group 3 (lung diseases). In addition, the different treatments have been evaluated by randomised controlled trials mainly in idiopathic PAH, heritable PAH, PAH due to anorexigen drugs, and in PAH associated with CTD or with CHD (surgically corrected or not). The grades of recommendation and levels of evidence for the other PAH subgroups are lower.

The suggested initial approach after the diagnosis of PAH is the adoption of the general measures, the initiation of the supportive therapy and referral to an expert centre. Acute vasoreactivity testing should be performed in all patients with group 1 PAH. Vasoreactive patients should be treated with optimally tolerated doses of CCBs.

Nonresponders to acute vasoreactivity testing, or responders who remain in (or progress to) WHO functional class III should be considered candidates for treatment with an endothelin receptor agonist, a PDE-5 inhibitor, or a prostanoid.

TABLE 25 ESC/ERS guidelines: parameters with established importance for assessing disease severity, stability and prognosis in pulmonary arterial hypertension

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO FC	IV
Longer (>500 m)[#]	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL·min^{-1}·kg^{-1}	Cardiopulmonary exercise testing	Peak O_2 consumption <12 mL·min^{-1}·kg^{-1}
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE[¶] >2.0 cm	Echocardiographic findings[¶]	Pericardial effusion TAPSE[¶] <1.5 cm
P_{ra} <8 mmHg and CI ⩾2.5 L·min^{-1}·m^{-2}	Haemodynamics	P_{ra} >15 mmHg or CI ⩽2.0 L·min^{-1}·m^{-2}

RV: right ventricular; WHO FC: World Health Organization functional class; 6MWT: 6-min walk test; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; TAPSE: tricuspid annular plane systolic excursion; P_{ra}: right atrial pressure; CI: cardiac index. [#]: depending on age; [¶]: TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients. Reproduced from [17] with permission from the publisher.

TABLE 26 ESC/ERS guidelines: definition of inadequate response to pulmonary arterial hypertension treatments

Inadequate clinical response for patients who were initially in WHO FC II or III:
1) Resulting clinical status defined as stable and not satisfactory
2) Resulting clinical status defined as unstable and deteriorating
Inadequate clinical response for patients who were initially in WHO FC IV:
1) No rapid improvement to WHO FC III or better
2) Resulting clinical status defined as stable and not satisfactory

WHO FC: World Health Organization functional class. Reproduced from [1] with permission from the publisher.

Continuous *i.v.* epoprostenol is recommended as first-line therapy for WHO functional class IV PAH patients, because of the survival benefit in this subset. In WHO functional class IV patients, initial combination therapy should also be considered.

CASE 10: INADEQUATE RESPONSE TO PAH THERAPY

Case report

A previously healthy 39-yr-old female presented to her local hospital with a 1-month history of progressive dyspnoea associated with exercise-induced palpitations. She reported that her symptoms had begun approximately 1 month after the birth of her third child. Initial transthoracic echocardiography demonstrated enlarged right heart chambers with estimated systolic P_{pa} 100 mmHg without evidence of intracardiac shunt. She was referred to an expert centre for further evaluation. Initial RHC confirmed severe pre-capillary PH ($\bar{P}_{pa}$ 55 mmHg, PVR 1,250 dyn·s·cm^{-5}, CI 2.0 L·min^{-1}·m^{-2}; table 24) without acute vasodilator response. A diagnosis of idiopathic PAH was made after additional investigations for associated causes of PH were negative. As she was deemed to be in functional class III, with a baseline 6MWD of 519 m, oral endothelin antagonist therapy was initiated.

When the patient was reassessed after 4 months of treatment, she was still in functional class III with a similar 6MWD and haemodynamic profile that showed only a modest improvement (table 24). Because of a lack of improvement in either subjective or objective parameters, a decision was made to add oral PDE-5 inhibitor therapy. At subsequent re-evaluation 6 months after this therapeutic modification, there was both a clinical worsening (80 m reduction in 6MWD) and haemodynamic deterioration (increased $\bar{P}_{pa}$ and PVR, with associated significant reduction in CI; table 24). In view of this objectively defined deterioration in spite of dual oral targeted therapy, continuous *i.v.* prostacyclin was added to her treatment regimen. At the next assessment after 6 months of this three-drug combination approach, a marked clinical and haemodynamic improvement was observed (table 24). 3 yrs after initiation of triple therapy the patient is alive and well.

Commentary: relevance to ESC/ERS guidelines

Regular evaluation of patients with PAH should focus on variables with established prognostic importance, as outlined above. Treatment decisions should be based on parameters that reflect symptoms and exercise capacity and that are relevant in terms of predicting outcome. Table 25 lists several parameters of known prognostic importance that are widely used as follow-up tools. Patients with better or worse prognosis are separated by an intermediate group for which prognostication is more difficult.

Based on the clinical, noninvasive and invasive findings the clinical condition of a patient can be defined as stable and satisfactory, stable but not satisfactory, unstable and deteriorating, as follows. 1) Stable and satisfactory. Patients in this condition should fulfil the majority of the findings listed in the ''better prognosis'' column. 2) Stable and not satisfactory. This is a patient who, although stable, has not achieved the status that the patient and treating physician would consider desirable. Some of the limits described above for a stable and satisfactory condition and included in the ''better prognosis'' column are not fulfilled. These patients require re-evaluation and consideration for additional or different treatment following full assessment. 3) Unstable and deteriorating. Patients in this condition fulfil the majority of the findings listed in the ''worse prognosis'' column.

A goal-oriented treatment strategy is recommended in patients with PAH. Treatment goals for PAH patients that may be

TABLE 27 ESC/ERS guidelines: suggested assessments and timing for the follow-up of patients with pulmonary arterial hypertension

	At baseline (prior to therapy)	Every 3–6 months[#]	3–6 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO FC/ECG	X	X	X	X
6MWT[¶]	X	X	X	X
Cardiopulmonary exercise testing[¶]	X		X	X
BNP/NT-proBNP	X	X	X	X
Echocardiography	X		X	X
RHC	X[+]		X[§]	X[§]

WHO-FC: World Health Organization functional class; X: assessment is suggested; 6MWT: 6-min walk test; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; RHC: right heart catheterisation. [#]: intervals should to be adjusted to individual patients needs; [¶]: usually one of the two exercise tests is performed; [+]: is recommended (table 20); [§]: should be performed (table 20). Reproduced from [1] with permission from the publisher.

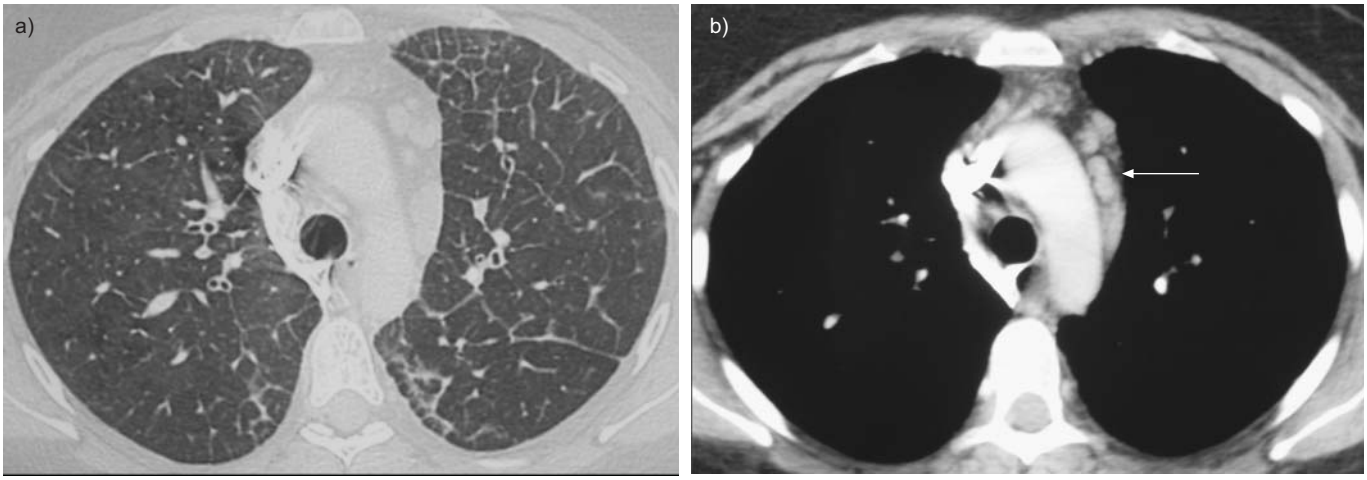

FIGURE 7. High-resolution computed tomography in a pulmonary veno-occlusive disease patient showing septal lines and ground-glass opacities (a) associated with mediastinal lymph node enlargement (arrow, b).

considered are those listed in the ''stable and satisfactory definition'' and in the ''better prognosis'' column.

In the case of inadequate clinical response (table 26), sequential combination therapy should be considered. Combination therapy can include either an endothelin receptor agonist plus a PDE-5 inhibitor, or a prostanoid plus an endothelin receptor agonist, or a prostanoid plus a PDE-5 inhibitor. Appropriate protocols for timing and dosing to limit possible side-effects of the combination have still to be defined. In expert centres triple combination therapy is also considered.

Balloon atrial septostomy and/or lung transplantation are indicated for PAH with inadequate clinical response despite optimal medical therapy or where medical treatments are unavailable. These procedures should be performed only in experienced centres.

Suggested follow-up strategies for patients with PAH are reported in table 27.

CASE 11: PULMONARY VENO-OCCLUSIVE DISEASE

Case report

A previously healthy 37-yr-old female cigarette smoker (8 pack-yrs) was referred with a 2-month history of intermittent chest pain on a background of a 2-yr history of progressive dyspnoea. On admission, the patient was in WHO functional class IV; physical examination revealed a loud pulmonic component to the second heart sound and normal pulmonary auscultation. ECG demonstrated complete right bundle branch block. Arterial blood gases showed severe hypoxaemia at rest (arterial oxygen tension (P_{a,O_2}) 5.8 kPa) while PFTs found normal values for forced expiratory volume in 1 s, forced vital capacity and total lung capacity, associated with a moderate impairment of $D_{L,CO}$ (52%). Echocardiography estimated systolic P_{pa} at 72 mmHg. RHC confirmed severe pre-capillary PH with normal left heart filling pressures ($\bar{P}_{pa}$ 68 mmHg, right atrial pressure 9 mmHg, P_{pcw} 11 mmHg, CI 2.27 $L \cdot min^{-1} \cdot m^{-2}$ and PVR 1,010 $dyn \cdot s \cdot cm^{-5}$). Acute vasodilatator testing with nitric oxide showed a degree of vasoreactivity that was insufficient to fulfil criteria for an acute vasodilator response (decrease in $\bar{P}_{pa}$ to 56 mmHg without change in CI). 6MWD was not feasible. Ventilation/perfusion lung scintigraphy found multiple mismatched subsegmentary perfusion defects. HRCT showed patchy areas of centrilobular ground-glass opacification, septal lines and mediastinal lymph node enlargement (fig. 7). This combination of radiological abnormalities associated with low P_{a,O_2} at rest and low $D_{L,CO}$ was highly suggestive of a diagnosis of PVOD. Neither surgical nor transbronchial lung biopsy, being contraindicated in suspected PVOD, was performed. The patient was hospitalised in the intensive care unit and treated with oxygen, diuretics and dobutamine. Because of the poor prognosis associated with PVOD, the risk of life-threatening pulmonary oedema with specific PAH therapy and the requirement for inotropic support in this case, the patient was listed for urgent double-lung transplantation and was transplanted 1 week later. The diagnosis of PVOD was confirmed by pathological assessment of the explanted lungs.

Commentary: relevance to ESC/ERS guidelines

Both PVOD and PCH are uncommon conditions, but are increasingly recognised as causes of PAH. They have been classified in a specific subgroup (group 1′) of the clinical classification for the pathological, clinical and therapeutic differences with the other forms of PAH included in group 1.

The diagnosis of PVOD can be established with a high probability by the combination of clinical suspicion, physical examination, bronchoscopy and radiological findings. Most patients complain of dyspnoea on exertion and fatigue, a clinical presentation that is indistinguishable from idiopathic PAH. Physical examination may reveal digital clubbing and bibasal crackles on lung auscultation, these being unusual in other forms of PAH. Case series suggest that patients with PVOD are more severely hypoxaemic and have a much lower $D_{L,CO}$ than in other forms of PAH. HRCT scanning is the investigation of choice. Typical findings suggestive of PVOD are the presence of subpleural thickened septal lines, centrilobular ground-glass opacities and mediastinal lymphadenopathy. Because PVOD may be associated with occult alveolar haemorrhage, bronchoscopy with bronchoalveolar lavage may be a useful tool in the diagnostic strategy. This noninvasive approach may avoid lung biopsy in most of the cases.

TABLE 28 ESC/ERS guidelines: recommendations for pulmonary veno-occlusive disease (PVOD)

Statement	Class#	Level¶
Referral of patients with PVOD to a transplant centre for evaluation is indicated as soon as the diagnosis is established	I	C
Patients with PVOD should be managed only in centres with extensive experience in PAH due to the risk of lung oedema after the initiation of PAH-specific drug therapy	IIa	C

PAH: pulmonary arterial hypertension. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

Haemodynamic presentation of PVOD is similar to idiopathic PAH. Importantly, P_{pcw} is almost invariably normal because the pathological changes occur in small venulae and do not affect the larger pulmonary veins.

There is no established medical therapy for PVOD. Most importantly, vasodilators and especially prostanoids must be used with great caution because of the high risk of pulmonary oedema (table 28).

There are reports of sustained clinical improvement in individual patients treated with these medications. Therefore, therapy for PVOD should be undertaken only at centres with extensive experience in the management of PH, and patients should be fully informed about the risks.

Atrial septostomy may be considered but is usually limited by hypoxaemia. The only curative therapy for PVOD and PCH is lung transplantation, and similarly to idiopathic PAH there are no reports of recurrence of disease following transplantation. Patients with PVOD should be referred to a transplant centre for evaluation as soon as the diagnosis is established.

CONCLUSION

We hope that these real-life cases and their accompanying commentaries have emphasised the high clinical relevance of the ESC and ERS guidelines, which should be largely disseminated and implemented. On this occasion, the authors wish to thank N. Galiè, University of Bologna, Bologna, Italy, who chaired the PH guidelines group, and all task force members, as well as members of the guideline committees from the ESC and the ERS.

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STATEMENT OF INTEREST

D. Montani, X. Jaïs, F. Parent, O. Sitbon and G. Simonneau have relationships with drug companies including Actelion, BayerSchering, GlaxoSmithKline, Pfizer and United Therapeutics. In addition to being an investigator in trials involving these companies, relationships include consultancy services and membership of scientific advisory boards. M. Humbert has relationships with drug companies including AB Science, Actelion, Altair, Amgen, Astrazeneca, Chiesi, GlaxoSmithKline, MSD, Novartis and Pfizer. In addition to being an investigator in trials involving these companies, relationships include consultancy services and membership of scientific advisory boards.

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