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ESC Guidelines

Guidelines on diagnosis and treatment of pulmonary arterial hypertension

The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology

Task Force members: Nazzareno Galiè (Chairperson)[1] (Italy), Adam Torbicki (Poland), Robyn Barst (USA), Philippe Dartevelle (France), Sheila Haworth (UK), Tim Higenbottam (UK), Horst Olschewski (Germany), Andrew Peacock (UK), Giuseppe Pietra (Switzerland), Lewis J. Rubin (USA), Gerald Simonneau (Co-Chairperson) (France)

ESC Committee for Practice Guidelines (CPG): Silvia G. Priori (Chairperson) (Italy), Maria Angeles Alonso Garcia (Spain), Jean-Jacques Blanc (France), Andrzej Budaj (Poland), Martin Cowie (UK), Veronica Dean (France), Jaap Deckers (The Netherlands), Enrique Fernandez Burgos (Spain), John Lekakis (Greece), Bertil Lindahl (Sweden), Gianfranco Mazzotta (Italy), Keith McGregor (France), João Morais (Portugal), Ali Oto (Turkey), Otto A. Smiseth (Norway)

Document reviewers: Gianfranco Mazzotta (CPG Review Coordinator) (Italy), Joan Albert Barbera (Spain), Simon Gibbs (UK), Marius Hoeper (Germany), Marc Humbert (France), Robert Naeije (Belgium), Joanna Pepke-Zaba (UK)

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[1] Corresponding author. Nazzareno Galiè, MD, Institute of Cardiology, University of Bologna, Via Massarenti, 9, 40138 Bologna, Italy. Tel.: + 39 051 349858; fax: +39 051 344859.

E-mail addresses: n.galie@bo.nettuno.it, amanes@orsolamalpighi.med.unibo.it (N. Galiè)

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Preamble

Guidelines and Expert Consensus Documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and by different organisations and other related societies. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilisation of health resources.

The *ESC Committee for Practice Guidelines* (*CPG*) supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by Task Forces, expert groups or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatments and the Level of Evidence as indicated in the tables below:

Classes of Recommendations	
Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective;
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment;
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[a]	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

[a] Use of Class III is discouraged by the ESC.

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

Introduction

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterised by a progressive increase of pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death.[1] The median life expectancy from the time of diagnosis in patients with idiopathic PAH (IPAH), formerly known as primary pulmonary hypertension (PPH), before the availability of disease-specific (targeted) therapy, was 2.8 years through the mid-1980s.[2] PAH includes IPAH[3] and pulmonary hypertension associated with various conditions such as connective tissue diseases (CTD), congenital systemic-to-pulmonary shunts, portal hypertension and Human Immunodeficiency Virus (HIV) infection.[4] All these conditions share equivalent obstructive pathological changes of the pulmonary microcirculation[5,6] suggesting shared pathobiological processes among the disease spectrum of PAH.[7]

In the past decade, we have witnessed major advances in our understanding of the mechanism of disease development, in the diagnostic process, and in the treatment of PAH.

The identification of mutations in the bone morphogenetic protein receptor 2 (BMPR2) in the majority of cases of familial PAH (FPAH) has been a major advance in the elucidation of the pathogenic sequence in PAH.[8,9] A variety of cellular abnormalities have been described in the pulmonary vasculature of affected patients that may play important roles in the development and progression of PAH.[7] These include pulmonary endothelial dysfunction[10] characterised by altered synthesis of nitric oxide, thromboxane A2, prostacyclin and endothelin, impaired potassium channels and altered expression of the serotonin transporter in the smooth muscle cells and enhanced matrix production in the adventitia.[7]

The diagnosis is now more clearly defined according to a new clinical classification and with consensus reached on algorithms of various investigative tests and procedures that exclude other causes and ensure an accurate diagnosis of PAH.[11] In addition, non-invasive markers of disease severity, either biomarkers or physiological tests that can be widely applied, have been proposed to reliably monitor the clinical course.[11,12]

Finally, the numerous controlled clinical trials performed recently in PAH can allow us to abandon a clinical-based treatment strategy and adopt an evidence-based therapy that includes new classes of drugs such as prostanoids,[13] endothelin receptor antagonists[14] and type 5 phosphodiesterase inhibitors.[15]

The present guidelines are intended to provide clear and concise indications for the practical use of the new clinical classification, and a brief description of the new pathological classification and of the recent pathogenetic insights. The diagnostic process will be discussed in order to propose a logical sequence of investigations for aetiology identification, disease assessment and follow-up. Special emphasis will be devoted to the evidence-based treatment algorithm that has been defined according to the ESC proposals for the Level of Evidence classification and the Grade of Recommendation[16] for the available therapies.

Clinical classification of pulmonary hypertension

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (PAP) >25 mmHg at rest or >30 mmHg with exercise.[17] Current classification of PH is presented in Table 1. It is a result of extensive discussion and represents a consensus accommodating our present understanding of pathophysiology as well as of clinical-based differences or similarities within PH. Understanding and correct clinical application of the classification should be aided by the following discourse.

PH was previously classified into 2 categories: PPH or secondary PH depending on the absence or the presence of identifiable causes or risk factors.[3,17] The diagnosis of PPH was one of exclusion after ruling out all causes of PH.

In 1998, during the Second World Meeting on PH held in Evian – France, a clinical-based classification of PH was proposed.[18] The aim of the ''Evian classification'' was to individualise different categories sharing similarities in pathophysiological mechanisms, clinical presentation and therapeutic options. Such a clinical

Table 1 Clinical classification of pulmonary hypertension — Venice 2003

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
      1.3.1. Connective tissue disease
      1.3.2. Congenital systemic to pulmonary shunts
      1.3.3. Portal hypertension
      1.3.4. HIV infection
      1.3.5. Drugs and toxins
      1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
   1.4. Associated with significant venous or capillary involvement
      1.4.1. Pulmonary veno-occlusive disease (PVOD)
      1.4.2. Pulmonary capillary haemangiomatosis (PCH)
   1.5. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension associated with left heart diseases
   2.1. Left-sided atrial or ventricular heart disease
   2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Sleep disordered breathing
   3.4. Alveolar hypoventilation disorders
   3.5. Chronic exposure to high altitude
   3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   4.1. Thromboembolic obstruction of proximal pulmonary arteries
   4.2. Thromboembolic obstruction of distal pulmonary arteries
   4.3. Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
5. Miscellaneous
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

classification is essential in communicating about individual patients, in standardising diagnosis and treatment, in conducting trials with homogeneous groups of patients, and lastly in analysing novel pathobiological abnormalities in well characterised patient populations. Obviously, a clinical classification does not preclude other classifications such as a pathological classification based on histological findings, or a functional classification based on the severity of symptoms. The 2003 Third World Symposium on PAH held in Venice—Italy provided the opportunity to assess the impact and the usefulness of the Evian classification and to propose some modifications.

It was decided to maintain the general architecture and philosophy of the Evian classification. However, some modifications have been proposed, mainly: to abandon the term ''primary pulmonary hypertension — PPH'' and to replace it with ''idiopathic pulmonary arterial hypertension — IPAH'', to reclassify pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH), to update risk factors and associated conditions for PAH, and to propose some guidelines in order to improve the classification of congenital systemic-to-pulmonary shunts (Table 1). The aim of these modifications was to make the ''Venice clinical classification'' more comprehensive, easier to follow and widespread as a tool.

Idiopathic pulmonary arterial hypertension

The term PPH was retained in the Evian classification because of its common use and familiarity, and because it was emblematic of 50 years of intense scientific and clinical research. However, the use of the term ''primary'' facilitated the reintroduction of the term ''secondary'' that was abandoned in the Evian version because it was used to describe very heterogeneous conditions. In order to avoid any possible confusion in Venice it was decided that the first category termed ''pulmonary arterial hypertension — PAH'' should include three main subgroups: [1.1] idiopathic pulmonary arterial hypertension — IPAH, [1.2] familial pulmonary arterial hypertension — FPAH and [1.3] pulmonary arterial hypertension related to risk factors or associated conditions — APAH.

Risk factors and associated conditions

A risk factor for PH is any factor or condition that is suspected to play a predisposing or facilitating role in the development of the disease. Risk factors may include drugs and chemicals, diseases or phenotype (age, gender). The term of ''associated conditions'' is used when

a statistically significantly increased incidence of PAH is found with a given predisposing factor, without, however, meeting ''Koch's postulate'' for causal relationship. Since the absolute risk of known risk factors for PAH is generally low, individual susceptibility or genetic predisposition is likely to play an important role. During the Evian meeting in 1998, different risk factors and associated conditions were categorised according to the strength of their association with PH and their probable causal role. ''Definite'' indicates an association based on several concordant observations including a major controlled study or an unequivocal epidemic. ''Very likely'' indicates several concordant observations (including large case series and studies) that are not attributable to identified causes. ''Possible'' indicates an association based on case series, registries or expert opinions. ''Unlikely'' indicates risk factors that were suspected but for which controlled studies failed to demonstrate any association.

According to the strength of the evidence, Table 2 summarises, risk factors and associated conditions already known[19] and novel ''possible'' risk factors for PAH that were identified recently, according to several case series or case reports. The new possible risk factors include haematological conditions such as asplenia secondary to surgical splenectomy,[20] sickle cell disease,[21] β-thalassaemia[22] and chronic myeloproliferative disorders[23] (polycythaemia vera, essential thrombocytaemia and myelofibrosis with myeloid metaplasia accompanying chronic myeloid leukaemia or the myelodysplastic syndrome). Possible risk factors include also rare genetic or metabolic diseases such as type 1a glycogen storage disease (Von Gierke disease),[24] Gaucher's disease[25] and hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu disease).[26]

Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis

In the Evian classification, PVOD was included in the pulmonary venous hypertension category that consists predominantly of left-sided heart diseases and PCH was included in the last and heterogeneous group of PH caused by diseases that directly affect the pulmonary vasculature. The similarities in the pathological features and clinical presentation, along with the possible occurrence of pulmonary oedema during epoprostenol therapy, suggest that these disorders may overlap. Accordingly, it seems logical to include PVOD and PCH within the same group, most appropriately within the category of PAH. In fact, the clinical presentation of PVOD and PCH is generally similar to that of IPAH and the risk factors or conditions associated with PAH and PVOD/PCH are similar and include the scleroderma spectrum of the disease, HIV infection, and the use of anorexigens. Thus, in the new clinical classification (Table 1), the PAH Clinical classification group 1 includes another subgroup termed PAH associated with significant venous or capillary involvement (Clinical class 1.4).

Table 2 Risk factors and associated conditions classified according to the level of evidence

1. Drugs and toxins
   - 1.1. Definite
     - Aminorex
     - Fenfluramine
     - Dexfenfluramine
     - Toxic rapeseed oil
   - 1.2. Very likely
     - Amphetamines
     - L-tryptophan
   - 1.3. Possible
     - Meta-amphetamines
     - Cocaine
     - Chemotherapeutic agents
   - 1.4. Unlikely
     - Antidepressants
     - Oral contraceptives
     - Oestrogen therapy
     - Cigarette smoking
2. Demographic and medical conditions
   - 2.1. Definite
     - Gender
   - 2.2. Possible
     - Pregnancy
     - Systemic hypertension
   - 2.3. Unlikely
     - Obesity
3. Diseases
   - 3.1. Definite
     - HIV Infection
   - 3.2. Very likely
     - Portal hypertension/liver disease
     - Connective tissue diseases
     - Congenital systemic-pulmonary cardiac shunts
   - 3.3. Possible
     - Thyroid disorders
     - Haematological conditions
       - – Asplenia secondary to surgical splenectomy
       - – Sickle cell disease
       - – β-thalassaemia
       - – Chronic myeloproliferative disorders
     - Rare genetic or metabolic diseases
       - –Type 1a glycogen storage disease (Von Gierke disease)
       - –Gaucher's disease
       - –Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu disease)

HIV: human immunodeficiency virus.

Classification of congenital systemic-to-pulmonary shunts

The proposed classification of congenital systemic-to-pulmonary shunts takes into account the type and the dimensions of the defect, the presence of associated extracardiac abnormalities and the correction status (Table 3). All these factors are relevant for the development of PH and Eisenmenger physiology and the prognosis.

Eisenmenger syndrome can be caused by simple or complex (about 30% of cases) congenital heart defects.[27]

Table 3 Classification of congenital systemic-to-pulmonary shunts

1. Type
Simple
Atrial septal defect (ASD)
Ventricular septal defect (VSD)
Patent ductus arteriosus
Total or partial unobstructed anomalous pulmonary venous return
Combined
Describe combination and define prevalent defect if any
Complex
Truncus arteriosus
Single ventricle with unobstructed pulmonary blood flow
Atrioventricular septal defects
2. Dimensions
Small (ASD $\leqslant$ 2.0 cm and VSD $\leqslant$ 1.0 cm)
Large (ASD > 2.0 cm and VSD > 1.0 cm)
3. Associated extracardiac abnormalities
4. Correction status
Non-corrected
Partially corrected (age)
Corrected: spontaneously or surgically (age)

Among simple defects, ventricular septal defects appear to be the most frequent, followed by atrial septal defects and patent ductus arteriosus.[27] It is calculated that 10% of patients with ventricular septal defects of any size that are older than 2 years can develop Eisenmenger syndrome as compared to 4–6% of subjects with atrial septal defects.[28,29] For patients with large defects, almost all cases with truncus arteriosus, 50% of cases with ventricular septal defects and 10% of those with atrial septal defects will develop PAH and pulmonary vascular disease.[30] In patients with atrial septal defects, those with sinus venosus defects have an higher incidence of PAH (16%) as compared to ostium secundum defects (4%).[31]

The development of PAH with pulmonary vascular disease appears to be related to the size of the defect. In fact, with small- to moderate-size ventricular septal defects only 3% of patients develop PH.[32,33] In contrast with larger defects (>1.5 cm in diameter), 50% will be affected. In case of small defects (ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo) the exact pathophysiological role of the heart defect on the development of PAH is unknown.

In some patients severe PAH can be detected after ''successful'' correction of the heart defect. In many of these cases it is not clear if irreversible pulmonary vascular lesions were already present before the surgical intervention or if the pulmonary vascular disease has progressed despite a successful correction. Usually an early correction prevents the subsequent development of PAH.

Pathology of pulmonary arterial hypertension

PAH includes various forms of PH of different aetiologies but similar clinical presentation, and in many cases similar response to medical treatment. Histopathological changes in various forms of PAH are qualitatively similar[5] but with quantitative differences in the distribution and prevalence of pathological changes in the different components of the pulmonary vascular bed (arterioles, capillaries or veins). The following updated pathological classification has been proposed at the Third World Symposium on PAH of Venice (Table 4).[6]

Pulmonary arteriopathy

The main histopathological features of pulmonary arteriopathy include medial hypertrophy, intimal thickening, adventitial thickening and complex lesions.

Medial hypertrophy is an increase in the cross sectional area of the media of pre and intra-acinar pulmonary arteries. It is due to both hypertrophy and hyperplasia of smooth muscle fibers as well as increase in connective tissue matrix and elastic fibers in the media of muscular arteries.

Intimal thickening may be concentric laminar, eccentric or concentric non-laminar. Ultrastructurally and immuno-histochemically the intimal cells show features of fibroblasts, myofibroblasts and smooth muscle cells.

Adventitial thickening occurs in most cases of PAH but it is more difficult to evaluate.

Complex lesions. The plexiform lesion is a focal proliferation of endothelial channels lined by myofibroblasts, smooth muscle cells and connective tissue matrix. These lesions are at an arterial branching point or at the origin of a supernumerary artery, distally to marked obliterative intimal thickening of the parent artery. The frequency of the plexiform lesions in PAH remains undetermined. Arteritis may be associated with plexiform lesions and it is characterised by a necrosis of the arterial wall with fibrinoid insudation and infiltration with inflammatory cells.

All the above changes are seen typically in clinical classification (Table 1) groups 1.1 (IPAH), 1.2 (FPAH) and 1.3 (APAH).

Pulmonary occlusive venopathy (also called pulmonary veno-occlusive disease)

Pulmonary occlusive venopathy accounts for a relatively small proportion of cases of PH; main histo-pathological features consist of extensive and diffuse occlusion of pulmonary venules and veins of various sizes. The luminal occlusion can be either solid or eccentric. In addition, the media may be thickened. In pulmonary occlusive venopathy, large amounts of haemosiderin are found both within the cytoplasm of alveolar macrophages and type II pneumocytes, as well as deposits in the interstitium. The capillary vessels are engorged and prominent and they may be so tortuous as to mimic pulmonary capillary haemangiomatosis. Pulmonary arterioles can show remodelling with medial hypertrophy and intimal fibrosis. Plexiform lesions and fibrinoid arteritis are not described in pulmonary occlusive venopathy. The pulmonary interstitium frequently shows oedema in the

Table 4 Pathological classification of vasculopathies of pulmonary hypertension

(1) Pulmonary arteriopathy[a] (pre-and intra-acinar arteries)
Subsets
- Pulmonary arteriopathy with isolated medial hypertrophy
- Pulmonary arteriopathy with medial hypertrophy and intimal thickening (cellular, fibrotic)
  - Concentric laminar
  - Eccentric, concentric non-laminar
- Pulmonary arteriopathy with plexiform and/or dilatation lesions or arteritis
- Pulmonary arteriopathy with isolated arteritis

(1a) As above but with coexisting venous-venular changes[a] (cellular and/or fibrotic intimal thickening, muscularisation)

(2) Pulmonary occlusive venopathy[b] (veins of various size and venules) with or without coexisting arteriopathy

(3) Pulmonary microvasculopathy[c] with or without coexisting arteriopathy and/or venopathy

(4) Unclassifiable
Atypical histopathological features or inadequate sampling of blood vessels

[a] These changes are seen typically in clinical classification (Table 1) groups 1.1 (idiopathic pulmonary arterial hypertension), 1.2 (familial pulmonary arterial hypertension) and 1.3 (associated pulmonary arterial hypertension).
[b] These changes are seen typically in clinical classification (Table 1) group 1.4.1 (pulmonary venoocclusive disease).
[c] These changes are seen typically in clinical classification (Table 1) group 1.4.2 (pulmonary capillary haemangiomatosis).

lobular septa, which may progress to interstitial fibrosis. Lymphatics within the lung and pleura are also dilated. These changes are seen typically in clinical classification (Table 1) group 1.4.1 (PVOD).

Pulmonary microvasculopathy (also called pulmonary capillary haemangiomatosis)

Pulmonary microvasculopathy is another rare condition characterised by localised capillary proliferation within the lung. The distribution of pulmonary microvasculopathy is usually panlobar and patchy. The abnormal proliferating capillaries infiltrate the walls of arteries and veins invading muscular walls and occluding the lumen. In the areas of capillary proliferation, pulmonary haemosiderosis, characterised by haemosiderin-laden macrophages and type II pneumocytes, is also present. Similar to pulmonary occlusive venopathy, the pulmonary arteries in pulmonary microvasculopathy show marked muscular hypertrophy and intimal thickening. These changes are seen typically in clinical classification (Table 1) group 1.4.2 (PCH).

Finally, there are unclassifiable conditions with atypical histopathological features or inadequate sampling of blood vessels.

Pathogenesis of pulmonary arterial hypertension

The exact processes that initiate the pathological changes seen in PAH are still unknown even if we now understand more of the mechanisms involved. It is recognised that PAH has a multi-factorial pathobiology that involves various biochemical pathways and cell types. The increase of PVR is related to different mechanisms including vasoconstriction, obstructive remodelling of the pulmonary vessel wall, inflammation and thrombosis.

Pulmonary vasoconstriction is believed to be an early component of the pulmonary hypertensive process.[34] Excessive vasoconstriction has been related to abnormal function or expression of potassium channels in the smooth muscle cells[35] and to endothelial dysfunction.[10] Reduced plasma levels of a vasodilator and antiproliferative substance such as Vasoactive Intestinal Peptide has been shown in patients with PAH.[36]

Endothelial dysfunction leads to chronically impaired production of vasodilators such as nitric oxide (NO) and prostacyclin along with overexpression of vasoconstrictors such as thromboxane A_2 (TxA_2) and endothelin-1 (ET-1).[10] Many of these abnormalities both elevate vascular tone and promote vascular remodelling.

The process of pulmonary vascular remodelling involves all layers of the vessel wall and is characterised by proliferative and obstructive changes that involve several cell types including endothelial, smooth muscle and fibroblasts.[6,7] In addition, in the adventitia there is increased production of extracellular matrix including collagen, elastin, fibronectin, and tenascin.[37] Angiopoietin-1, an angiogenic factor essential for vascular lung development, seems to be upregulated in cases of PH correlating directly with the severity of the disease.[38]

Also inflammatory cells and platelets may play a significant role in PAH. In fact, inflammatory cells are ubiquitous in PAH pathological changes and pro-inflammatory cytokines are elevated in the plasma of PAH patients.[39] Alterations in the metabolic pathways of serotonin, a pulmonary vasoconstrictor substance stored in platelets, have also been detected in PAH patients.[40]

Prothrombotic abnormalities have been demonstrated in PAH patients[41] and thrombi are present in both microcirculation and elastic pulmonary arteries.[6] In fact, fibrinopeptide A levels that reflect thrombin activity,[42] and TxA_2 levels,[43] are both elevated in patients with IPAH.

Despite the identification of mutations in the BMPR2 in the majority of cases of familial PAH,[8,9] the pathobiological links between this genetic abnormality and the development of pulmonary vascular hypertensive disease

have not been clarified. On the other hand, the high frequency of ''true'' sporadic IPAH cases and reduced penetrance of familial PAH (only 20% of BMPR2 gene mutation carriers manifest the disease), suggests that additional triggers are required for the development of the condition. Mechanisms could be second somatic mutations within an unstable BMPR-2 pathway,[44] polymorphisms for genes related to PAH [serotonin transporter gene (5HTT),[40] nitric oxide synthase (ec-NOS) gene[45] and carbamyl-phosphate synthase (CPS) gene[46]] or any stimulus able to disrupt pulmonary vascular cells growth control. In addition there may be further genes, possibly related to the BMP/TGF-β_v pathway, to be identified. Indeed, mutations in the TGF-β_v receptors, activin-receptor-like kinase 1 (ALK-1) and endoglin, have been identified in PAH patients with a personal or family history of hereditary haemorrhagic telangiectasia, i.e. Osler–Weber–Rendu.[26,47]

Even if many pathobiological mechanisms have been identified in the cells and tissues of PAH patients, the exact interactions between these mechanisms in initiating and progressing the pathological processes are not well understood. Possible theoretical pathways (Fig. 1) include the classical interaction between genetic predisposition and risk factors that may induce changes in different cell types (smooth muscle cells, endothelial cells, inflammatory cells, platelets) and in the extracellular matrix of pulmonary microcirculation. The imbalance between thrombogenic, mitogenic, proinflammatory and vasoconstrictive factors as opposed to anticoagulant, antimitotic and vasodilating mechanisms may initiate and perpetuate interacting processes such as vasoconstriction, proliferation, thrombosis and inflammation in the lung microcirculation. These mechanisms are responsible for the initiation and progression of pathological obstructive changes typical of PAH. The consequent increase of PVR leads to right ventricular overload and eventually to right ventricular failure and death.

Future studies are required to find which, if any, of these abnormalities initiates PAH and which are best targeted to cure the disease.

Diagnostic strategy

The diagnostic process of PH requires a series of investigations that are intended to make the diagnosis, to clarify the clinical class of PH and the type of PAH and to evaluate the functional and haemodynamic impairment. For practical purposes it can be useful to adopt a sequential approach that includes four stages (Fig. 2):

I. Clinical suspicion of pulmonary hypertension
II. Detection of pulmonary hypertension
III. Pulmonary hypertension clinical class identification
IV. Pulmonary arterial hypertension evaluation (type, functional capacity, haemodynamics)

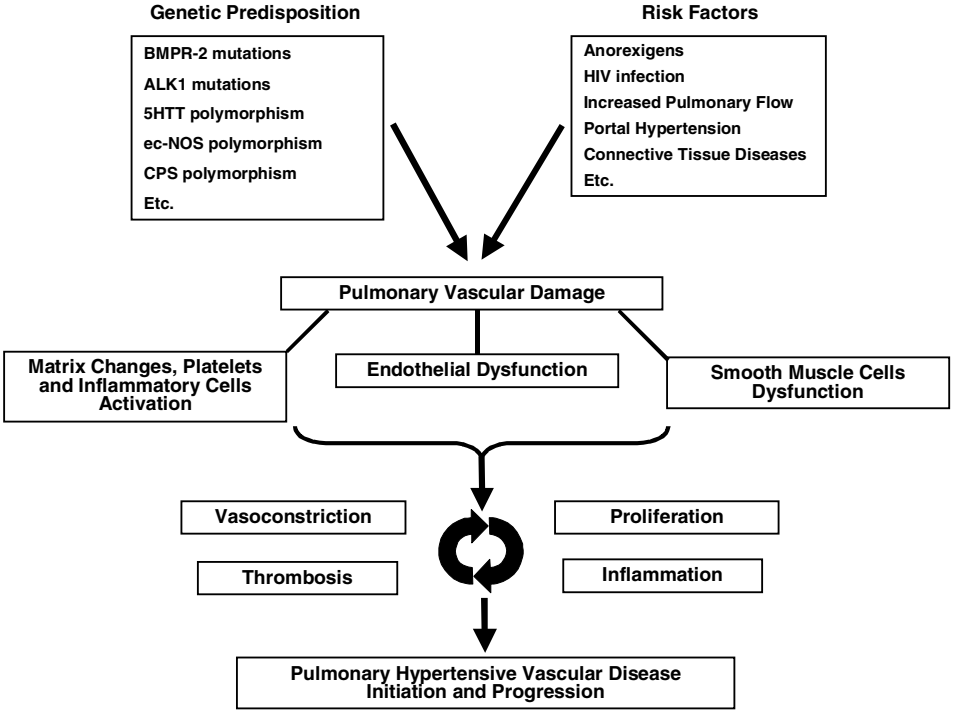

Fig. 1 Pulmonary arterial hypertension: potential pathogenetical and pathobiologic mechanisms. BMPR-2: bone morphogenetic receptor protein 2 gene; ALK 1: activin-receptor-like kinase 1 gene; 5-HTT: serotonin transporter gene; ec-NOS: nitric oxide synthase gene; CPS: carbamyl-phosphate synthetase gene.

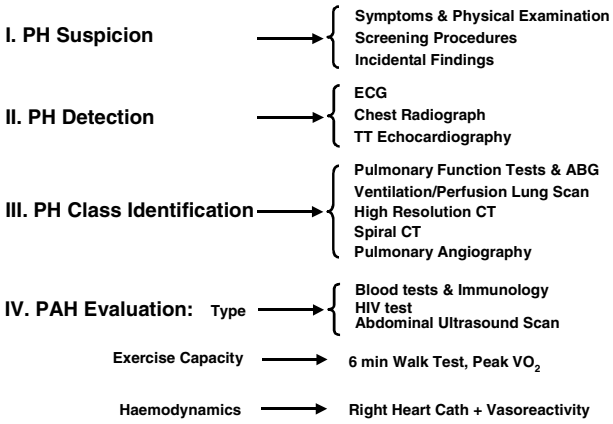

Fig. 2 Pulmonary hypertension diagnostic approach. ABG: arterial blood gases; CT: computerised tomography; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; TT: transthoracic; VO_2: oxygen consumption; Cath: catheterisation.

Clinical suspicion of pulmonary hypertension

The clinical suspicion of PH should arise in any case of breathlessness without overt signs of specific heart or lung disease or in patients with underlying lung or heart disease whenever there is increasing dyspnoea unexplained by the underlying disease itself. The *symptoms of PH*[48] can also include fatigue, weakness, angina, syncope, and abdominal distension. Symptoms at rest are reported only in very advanced cases.

The *physical signs of PH*[48] may require experience to be appreciated. They include left parasternal lift, accentuated pulmonary component of S2, pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency and right ventricular S3. Jugular vein distension, hepatomegaly, peripheral oedema, ascites and cool extremities characterise patients in a more advanced state with right ventricular failure at rest. Central cyanosis (and sometime peripheral cyanosis and mixed forms) may also be present. Lung sounds are usually normal.

The clinical suspicion is raised when symptoms and signs are present in subjects with conditions that can be associated with PAH such as CTD, portal hypertension, HIV infection and congenital heart diseases with systemic-to-pulmonary shunts. In the presence of these predisposing abnormalities some experts support a rationale for periodic screening assessments to identify asymptomatic patients in the early stage of PH[49] (see Specific Conditions below).

Finally, PH can be suspected when abnormal *electrocardiographic, chest radiograph or echocardiographic findings*, are detected in the course of procedures performed for other clinical reasons.

Detection of pulmonary hypertension

The detection phase requires investigations that are able to confirm the diagnosis of PH. They include the electrocardiogram (ECG), the chest radiograph and transthoracic Doppler-echocardiography.

ECG

The ECG may provide suggestive or supportive evidence of PH by demonstrating right ventricular hypertrophy and strain, and right atrial dilation. Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with IPAH.[48] However, the ECG has inadequate sensitivity (55%) and specificity (70%) to be a screening tool for detecting significant PAH.[50] A normal ECG does not exclude the presence of severe PH.

Chest radiograph

In 90% of IPAH patients the chest radiograph is abnormal at the time of diagnosis.[48] Findings include central pulmonary arterial dilatation which contrasts with 'pruning' (loss) of the peripheral blood vessels. Right atrial and ventricular enlargement may be seen and it progresses in more advanced cases. The chest radiograph allows associated moderate-to-severe lung disease or pulmonary venous hypertension due to left heart abnormalities to be reasonably excluded. However, a normal chest radiograph does not exclude mild post capillary pulmonary hypertension including left-heart disease or pulmonary veno-occlusive disease.

Transthoracic Doppler-echocardiography

Transthoracic Doppler-echocardiography (TTE) is an excellent non-invasive screening test for the patient with suspected PH. TTE estimates pulmonary artery systolic pressure (PASP) and can provide additional information about the cause and consequences of PH. PASP is equivalent to right ventricular systolic pressure (RVSP) in the absence of pulmonary outflow obstruction. RVSP is estimated by measurement of the systolic regurgitant tricuspid flow velocity v and an estimate of right atrial pressure (RAP) applied in the formula: $RVSP = 4v^2 + RAP$. RAP is either a standardised value, or estimated value from characteristics of the inferior vena cava[51] or from jugular venous distension. Tricuspid regurgitant jets can be assessed in the majority (74%) of patients with PH.[52] Most studies report a high correlation (0.57—0.93) between TTE and right heart catheterisation (RHC) measurements of PASP.[53] However, in order to minimise false positives[54] it is important to identify specific values for the definition of PH as assessed by TTE.

The range of RVSP among healthy controls has been well characterised. Among a broad population of male and female subjects ranging from 1 to 89 years old, RVSP was reported as 28 ± 5 mmHg (range 15—57 mmHg). RVSP increases with age and body mass index.[55] According to these data mild PH can be defined as a PASP of approximately 36—50 mmHg or a resting tricuspid regurgitant velocity of 2.8—3.4 m/s (assuming a normal RAP of 5 mmHg). It should be noted that also with this definition a number of false positive diagnoses can be anticipated especially in aged subjects and confirmation with RHC is required in symptomatic patients (NYHA class II—III). In asymptomatic subjects (NYHA class I) a concomitant CTD should be excluded and echocardiography should be repeated in six months. It should be noted that defining the level for an elevated RVSP does not define the

point at which an increased RVSP is clinically important, is predictive of future consequences and/or requires specific treatments. Also the possibility of false negative Doppler-echocardiographic results should be considered in case of high clinical suspicion.[56]

Additional echocardiographic and Doppler parameters are important for diagnosis confirmation and assessment of severity of PH including right and left ventricular dimensions and function, tricuspid, pulmonary and mitral valve abnormalities, right ventricular ejection and left ventricular filling characteristics, inferior vena cava dimensions and pericardial effusion size.[57,58]

Besides identification of PH, TTE also allows a differential diagnosis of possible causes and virtually starts the phases III and IV of the diagnostic process. TTE can recognise left heart valvular and myocardial diseases responsible for pulmonary venous hypertension (Clinical Class 2), and congenital heart diseases with systemic-to-pulmonary shunts can be easily identified (Clinical Class 1.3.2). The venous injection of agitated saline as contrast medium can help the identification of patent foramen ovale or small sinus venosus type atrial septal defects that can be overlooked on the standard TTE examination. Trans-oesophageal echocardiography (TEE) is rarely required and is usually used to confirm the presence, and assess the exact size, of small atrial septal defects.

Pulmonary hypertension clinical class identification

The next step after the detection of PH is the identification of the Clinical Class according to the clinical classification of Venice (Table 1).[1] This is accomplished by the use of essential tests such as TTE (as specified above), pulmonary function tests (PFT) (including arterial blood gas sample) and ventilation and perfusion (V/Q) lung scan. If required, in particular circumstances additional tests can be performed such as chest high resolution CT (HRCT), spiral CT and pulmonary angiography.

Pulmonary function tests and arterial blood gases

PFTs and arterial blood gas sampling can identify the contribution of underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (DL_{CO}) [typically in the range of 40–80% predicted] and mild to moderate reduction of lung volumes. The arterial oxygen tension (PaO_2) is normal or only slightly lower than normal and arterial carbon dioxide tension ($PaCO_2$) is decreased as a result of alveolar hyperventilation. Chronic obstructive pulmonary disease as a cause of hypoxic PH, is diagnosed on the evidence of irreversible airflow obstruction,[59] usually by measuring the forced expired volume in one second (FEV1). These patients often have a normal or increased $PaCO_2$ together with airflow limitation and increased residual volumes and reduced DL_{CO}. Emphysema is now diagnosed using HRCT. A decrease in lung volume together with a decrease in DL_{CO} may indicate a diagnosis of interstitial lung disease (ILD). Again the HRCT is the principle way of assessing the severity of ILD.[60] If clinically suspected, screening overnight oximetry and polisomnography will exclude significant obstructive sleep apnoea/hypopnoea and nocturnal desaturation.

Ventilation and perfusion (V/Q) lung scan

In PAH the lung V/Q scans may be entirely normal. However, they may also show small peripheral non-segmental defects in perfusion. These are normally ventilated and thus represent V/Q mismatch. Lung V/Q scan provides a means of diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH, Clinical Class 4).[61] In CTEPH the perfusion defects are usually found in lobar and segmental regions leading to segmental defects in the perfusion image. As these areas are normally ventilated, the perfusion defects are described as being unmatched by ventilation defects. V/Q scanning showed sensitivity of 90–100% with specificity of 94–100% for distinguishing between IPAH and CTEPH.[61] A caveat is that unmatched perfusion defects are also seen in veno-occlusive disease. Such a patient requires careful further investigation (see section on HRCT). In patients with parenchymal lung disease the perfusion defects are *matched* by ventilation defects.

High resolution CT of the lung

HRCT provides detailed views of the lung parenchyma and facilitates the diagnosis of ILD and emphysema. The presence of interstitial markings similar to those seen with advanced left ventricular failure such as diffuse central ground-glass opacification and thickening of interolobular septa suggest pulmonary veno-occlusive disease; additional findings are lymphadenopathy, pleural shadows and effusions.[62] Diffuse bilateral thickening of the interlobular septae and the presence of small, centrilobular, poorly circumscribed nodular opacities suggest pulmonary capillary haemangiomatosis.

Contrast enhanced spiral CT of the lung, pulmonary angiography and magnetic resonance imaging

Contrast-enhanced spiral (or helical) CT is indicated in pulmonary hypertensive patients when the V/Q lung scintigraphy shows segmental or sub-segmental defects of perfusion with normal ventilation, i.e. evidence of a V/Q mismatch and may demonstrate central chronic pulmonary thromboemboli. CT features of chronic thromboembolic disease are complete occlusion of pulmonary arteries, eccentric filling defects consistent with thrombi, recanalisation, and stenoses or webs.[63,64]

Traditional pulmonary angiography is still required in the work-up of CTEPH to better identify patients that can benefit from the intervention of endarterectomy.[61] Pulmonary angiography is more accurate in the identification of distal obstructions and it is indicated also in cases of inconclusive contrast-enhanced spiral CT in patients with clinical and lung scintigraphy suspicion of CTEPH. This procedure can be safely performed by experienced staff in patients with severe PH. Useful technical details include the utilisation of modern contrast media,

right and left main branch selective injections and multiple views.

Magnetic resonance imaging is increasingly used in patients with PAH for the evaluation of pathological and functional changes of both heart and pulmonary circulation.[63] However, additional experience is needed before introducing this tool in the routine assessment of patients with PAH.

Pulmonary arterial hypertension evaluation (type, exercise capacity, haemodynamics)

When the Clinical Class of PAH (Clinical Class 1) has been determined, additional investigations may be required for the exact identification of the type of PAH and for the assessment of exercise capacity and haemodynamics.

Blood tests and immunology

Routine biochemistry, haematology and thyroid function tests are required. Thrombophilia screen should be performed including antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies). CTD are diagnosed primarily on clinical and laboratory criteria and an autoimmune screen consists of antinuclear antibodies (ANA), including anti-centromere antibody, anti-SCL70 and RNP. About one third of patients with IPAH have positive but low antinuclear antibody titre ($\leqslant$1:80 dilutions).[65] Patients with a substantially elevated ANA and/or suspicious clinical features require further serological assessment and rheumatology consultation. Finally, all patients should be consented for and undertake a HIV serology test.

Abdominal ultrasound scan

Liver cirrhosis and/or portal hypertension can be reliably excluded by the use of abdominal ultrasound scan. The colour-Doppler examination also allows the differentiation between passive portal hypertension, due to right heart failure, from portal hypertension caused by an increase in the trans-hepatic venous gradient associated with liver cirrhosis. The use of contrast agents may improve the diagnosis.[66] Portal hypertension can be confirmed by the detection of an increased gradient between free and occluded (wedge) hepatic vein pressure at the time of RHC (see Porto-pulmonary hypertension).[67]

Exercise capacity

The objective assessment of exercise capacity in patients with PAH is an important instrument for evaluating disease severity[68,69] and treatment effect.[70,71] The most commonly used exercise tests for PH are the six-minute walk test and cardiopulmonary exercise testing with gas exchange measurement.

The *six-minute walk test* (6MWT) is technically simple and inexpensive.[72] It is predictive of survival in IPAH and also correlates inversely with NYHA functional status severity.[68] 6MWT is usually combined with the Borg score that assesses the subjective level of dyspnoea with the exercise. Reduction of arterial oxygen saturation >10% during 6MWT increases mortality risk 2.9 times over a median follow-up of 26 months.[73] 6MWT is the traditional ''primary'' end point for the great majority of controlled clinical trials performed in PAH.[70]

Cardiopulmonary exercise testing (CPET) allows measurement of ventilation and pulmonary gas exchange during exercise testing providing additional ''pathophysiologic'' information to that derived from standard exercise testing. PAH patients show reduced peak VO_2, reduced peak work rate, reduced ratio of VO_2 increase to work rate increase, reduced anaerobic threshold and reduced peak oxygen pulse; they show also increased VE and VCO_2 slope representative of ventilatory inefficiency.[69] Peak VO_2 is correlated with the prognosis of PAH patients.[69]

CPET has been used in recent multicentre trials but it failed to confirm improvements observed with 6MWT.[74,75] A possible explanation for these findings is that CPET is technically more difficult than 6MWT and its results may be influenced by the experience of the centres. An alternative explanation may relate to a lack of sensitivity of CPET in measuring response to treatment which has less effect on maximal as opposed to submaximal exercise.

Haemodynamics

RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment and to test the vasoreactivity of the pulmonary circulation. The following parameters should always be assessed: heart rate, RAP, PAP (systolic, diastolic and mean), pulmonary capillary wedge pressure (PWP), cardiac output (by thermodilution, or the Fick method in cases of systemic-to-pulmonary shunts), blood pressure, pulmonary and systemic vascular resistance, arterial and mixed venous oxygen saturation (and superior vena cava saturation in cases of systemic-to-pulmonary shunts).

PAH is defined by a mean PAP >25 mmHg at rest or >30 mmHg with exercise, by a PWP $\leqslant$15 mmHg and by PVR >3 mmHg/l/min (Wood units). Left heart catheterisation is required in the rare circumstances in which a reliable PWP cannot be measured.

Confirmation of diagnosis by RHC is required in cases of symptomatic patients (NYHA class II and III) with mild PH as assessed by Doppler echocardiography (see above for definition) to identify subjects needing further diagnostic and therapeutic procedures. The assessment of PWP may allow the distinction between arterial and venous PH in patients with concomitant left heart diseases.

RHC is important also in patients with definite moderate-to-severe PAH because the haemodynamic variables have prognostic relevance.[2]

Elevated mean RAP, mean PAP and reduced cardiac output and central venous O_2 saturation identify IPAH patients with the worst prognosis. Haemodynamic measurements have been used to estimate the natural history of IPAH in an individual patient by the use of a prediction equation[2] that has also been utilised for assessing the long-term effects of new treatments on survival.[76–78] However, this formula has been derived by patients on

conventional therapy followed up almost 15–20 years ago that may not represent an appropriate ''control'' group for current PAH populations.

Uncontrolled studies have suggested that long-term administration of calcium-channel blockers (CCB) prolongs survival in the rare case of acutely responsive patients compared with unresponsive patients.[79] It is generally accepted that patients who may benefit from long-term CCB can be identified by an acute vasodilator challenge performed during RHC.[80] However, it has been proposed that the definitive recognition of patients who benefit from CCB treatment requires both (1) the demonstration of a positive acute vasoreactive response and (2) the confirmation of a sustained response to long term treatment to CCB.[81]

Acute vasodilator testing should only be done using short-acting pulmonary vasodilators at the time of the initial RHC in experienced centres to minimise the potential risks.[82] Currently the agents used in acute testing are intravenous (iv) prostacyclin or adenosine and inhaled nitric oxide.[83,84] Half-lives, dose ranges, increments and duration of administration for these compounds are provided in Table 5.

A positive acute vasoreactive response (*positive acute responders*) is defined as a reduction of mean PAP $\geqslant$10 mmHg to reach an absolute value of mean PAP $\leqslant$40 mmHg with an increase or unchanged cardiac output.[11,81,85] Generally, only about 10–15% of IPAH will meet these criteria.[81,83] Positive acute responders are most likely to show a sustained response to long-term treatment with high doses of CCB and are the only patients that can safely be treated with this type of therapy. An empiric treatment with CCB without acute vasoreactivity test is strongly discouraged due to possible severe adverse effects.

Positive long-term responders to high dose CCB treatment are defined as patients being in NYHA functional class I or II with near normal haemodynamics after several months of treatment with CCB alone. Only about a half of IPAH positive acute responders are also positive long-term responders[81] to CCB and only in these cases the continuation of CCB as single treatment is warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with CCB in patients with PAH associated with underlying processes, such as CTD or congenital heart disease, is less clear as compared to IPAH.[81,86] However, experts suggest also in these cases to test patients for acute vasoreactivity and to look for a long-term response to CCB in appropriate subjects.

Lung biopsy

Open or thoracoscopic lung biopsy entails substantial risks of morbidity and mortality. Because of the low likelihood of altering the diagnosis and treatment, routine biopsy is discouraged.

Assessment of severity

Several variables have been shown to predict prognosis in IPAH when assessed at baseline or after targeted treatments.[71] Very little information is available in other conditions such as PAH associated with CTD, congenital systemic to pulmonary shunts, HIV infection or portal hypertension. In these circumstances, additional factors may contribute to the overall outcome. In fact, PAH associated with CTD disorders has a worse prognosis than IPAH patients, whereas patients with PAH associated with congenital systemic-to-pulmonary shunts have a more slowly progressive course than IPAH patients.

In practice, the prognostic value of a single variable in the individual patient may be less than the value of multiple concordant variables (Table 6).

Clinical variables

Among clinical variables, baseline NYHA functional classification has a definite prognostic predictive value in patients with IPAH on conventional treatment.[2] This predictive value is conserved when NYHA classification is assessed either before or 3 months after the initiation of epoprostenol treatment.[77,87] History of right heart failure before the initiation of epoprostenol treatment has a negative predictive value.[87] The World Health Organisation (WHO) classification proposed in Evian is an adaptation of the NYHA system for PAH and many clinicians refer to both classifications which are nearly identical as NYHA/WHO functional classification (Table 7).[11,12]

Exercise capacity

Several authors have shown that the 6MWT is of great prognostic value in PAH: Miyamoto et al.[68] showed that

Table 5 Route of administration, half-lives, dose ranges, increments and duration of administration of the most used substances on pulmonary vasoreactivity tests

Drug	Route	Half-life	Dose range[a]	Increments[b]	Duration[c]
Epoprostenol	Intravenous	3 min	2–12 ng/kg/min	2 ng/kg/min	10 min
Adenosine	Intravenous	5–10 s	50–350 μg/kg/min	50 μg/kg/min	2 min
Nitric oxide	Inhaled	15–30 s	10–20 ppm	–	5 min[d]

[a] Initial dose and maximal dose suggested.
[b] Increments of dose by each step.
[c] Duration of administration on each step.
[d] For NO a single step within the dose range is suggested.

Table 6 Prognostic parameters in patients with idiopathic pulmonary arterial hypertension

Clinical parameters
NYHA functional classification
NYHA functional class on chronic epoprostenol treatment
History of right heart failure
Exercise capacity
6MWT distance
6MWT distance on chronic epoprostenol treatment
Peak VO_2
Echocardiographic parameters
Pericardial effusion
Right atrial size
Left ventricular eccentricity index
Doppler right ventricular (Tei) index
Haemodynamics
Right atrial pressure
Mean PAP
Cardiac output
Mixed venous O_2 saturation
Positive acute response to vasoreactivity tests
Fall in pulmonary vascular resistance <30% after 3 months of epoprostenol
Blood tests
Hyperuricaemia
Baseline Brain natriuretic peptide
Brain natriuretic peptide after 3 months therapy
Troponin — detectable, especially persistent leakage
Plasma norepinephrine
Plasma endothelin-1

6MWT: six-minute walk test; NYHA: New York Heart Association.

patients with IPAH walking less than 332 m had a significantly lower survival rate than those walking farther. In another study it has been calculated that there is an 18% reduction in the risk of death per additional 50 m walked in patients with IPAH.[73] Preliminary data show also that arterial oxygen desaturation >10% during 6MWT increases mortality risk 2.9 times over a median follow-up of 26 months.[73] Patients in NYHA functional class III or IV walking $\leqslant$250 m before the initiation of epoprostenol or <380 m after three months of epoprostenol treatment portend a worst prognosis as compared to patients walking farther.[87] Absolute change of 6MWT distance with epoprostenol has not been found to be of prognostic value.

Peak VO_2 <10.4 ml/kg/min as assessed by CPET is correlated with a worse prognosis in PAH patients.[69]

Echocardiographic parameters

The presence and size of a pericardial effusion as assessed by TTE has a clear prognostic relevance in patients with IPAH.[88,89] In addition, right atrial size and left ventricular eccentricity index are predictive of the outcome of IPAH subjects.[89]

Doppler right ventricular[90] index, i.e. Tei index, is a variable which assesses both systolic and diastolic function of the right ventricle and has been found to have prognostic relevance in PAH.[91]

Haemodynamics

Elevated mean RAP and PAP at baseline, as well as reduced cardiac output and central venous O_2 saturation, identify IPAH patients with a worst prognosis.[2] Patients with a positive acute response to vasoreactivity tests have a better prognosis when compared to non-responders.[79,83,92]

On univariate analysis, the baseline haemodynamic variables associated with a poor outcome in IPAH patients subsequently treated with epoprostenol are reported to be RAP >12 mmHg, and mean pulmonary artery pressure <65 mmHg[87] even if this last finding has not been confirmed by other series.[77] After 3 months of epoprostenol, a fall in PVR <30% relative to baseline is associated with a poor prognosis.[87]

Blood tests

Hyperuricaemia occurs with high frequency in patients with PH and correlates with haemodynamic abnormalities, e.g. elevated RAP and increased mortality in IPAH.[93] Brain natriuretic peptide is elevated in right ventricular pressure overload and correlates with severity of right ventricular dysfunction and mortality in PAH.[94]

Additional neurohormonal plasma levels correlate with survival e.g. norepinephrine[95] and ET-1.[96] Recently troponin[97] levels both at baseline and after targeted

Table 7 NYHA/WHO Classification of functional status of patients with pulmonary hypertension[11,12]

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or pre-syncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

treatments have been found to have prognostic relevance in PAH patients.

Treatment

The treatment of PAH has been traditionally characterised by few and difficult options.[98] Recently, we have faced a dramatic change from the slow progress in the past decades to the remarkable number of randomised controlled trials (RCT) accomplished in the last few years. However we have also inherited different treatments that are generally accepted to be efficacious (e.g. oral anticoagulants, oxygen, CCBs), although not supported by RCT and not formally approved by Regulatory Agencies for the specific PAH indication.

The objective of this section is to review each form of therapy according to the Level of Evidence classification as suggested by the Committee for Practice Guidelines of the European Society of Cardiology.[16] In addition, we will provide the Grade of Recommendation[16] that will take into account the clinical efficacy of treatments that, for different reasons, have not been tested in RCTs such as oral anticoagulants, oxygen, CCBs, balloon atrial septostomy and/or lung transplantation. Furthermore, we will provide information concerning current country-specific regulatory approval and labelling for each compound. Finally, we will propose an evidence-based treatment algorithm[85] that is intended to provide a guide to the selective use of each form of therapy.

Introduction to level of evidence and grade of recommendation

The grading system for the *Level of Evidence* is substantially based on the number of favourable RCTs performed with a given treatment strategy[16] (Table 8) and has been adapted to the specific requirements of a rare disease. The only difference is that we did not include in category B ''non-randomised studies'' because all these studies in PAH are rather small therefore they are included in category C. In category B we included the wording ''multiple randomised clinical trials with heterogeneous results'' because this situation may happen (and has happened) and this definition is more comprehensive even if the final result is that ''a single randomised clinical trial'' resulted positive. The analysis takes into consideration the studies and the RCTs on PAH patients published in peer-reviewed journals or presented in recent major meetings.

The grading system for the *Level of Evidence* based on the number of RCTs may present some limitations that need to be taken into account and possibly corrected.[99] In fact, the level of evidence may change over time as a result of additional studies performed. In addition, the grading system does not address the sample sizes of the RCTs as ''small'' RCTs are given the same weight as larger ones. Moreover, the *Level of Evidence* for efficacy should not be confused with the *Level of Clinical Efficacy*, which depends on the net pharmacodynamic effects of the compound and on possible side effects and shortcomings (e.g. complexity of the route of administration). For example, a treatment strategy with better results but with only one or no RCTs is rated respectively B or C, as compared with a therapy with poorer results and greater side effects assessed in more than one RCT that can be rated as A. Also regulatory agencies may grant approval to a given treatment on the basis of a single RCT with an appropriate sample size and pre specified adequate statistical requirements.

Accordingly, the *Grade of Recommendation* (Table 9) was based on the *Level of Clinical Efficacy* that is expected from the therapeutic procedure.

Finally, both components *Grade of Recommendation* and *Level of Evidence* are provided in order to give a complete profile for each treatment (Table 10). No grade of recommendation is given for drugs that are currently available only for patients enrolled in RCTs. Country-specific regulatory approval status and labelling for each compound is also provided (Table 11).

General measures

General measures include strategies devoted to limit the deleterious impact of some circumstances and external

Table 8 Levels of evidence for efficacy

Levels of Evidence	
Level of Evidence A	Data derived from multiple randomised clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomised clinical trials or multiple trials with etherogeneous results
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Table 9 Grading using classes of recommendation

Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective;
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment;
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[a]	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

[a] Use of Class III is discouraged by the ESC.

Table 10 Grading of recommendations and level of evidence for efficacy in idiopathic pulmonary arterial hypertension

Treatment	Grade of recommendations			Level of evidence
	I	IIa	IIb	
General measures		X		C
Oral anticoagulants[a]		X		C
Diuretics	X			C
Digoxin			X	C
Oxygen[b]		X		C
Calcium channel blockers[c]	X			C
Epoprostenol	X			A
Treprostinil		X		B
Iloprost (inhalation)		X		B
Iloprost (intravenous)		X		C
Beraprost			X	B
Bosentan	X[d]			A
Sitaxsentan[e]				B
Ambrisentan[e]				C
Sildenafil	X[d]			A
Combination therapy			X	C
Balloon atrial septostomy		X		C
Lung transplantation	X			C

[a] IIa for IPAH, IIb for other PAH conditions.
[b] If arterial oxygen saturation <90%.
[c] Only in patients responders to acute reactivity tests, I for IPAH, IIb for other PAH conditions.
[d] IIa B in NYHA class IV.
[e] These drugs are currently available only for patients enrolled in randomised controlled trials and no grade of recommendation is given.

Table 11 Country-specific regulatory approval and labelling for pulmonary arterial hypertension related therapeutic procedures

Treatment	Country	Labelling	
		Aetiology	NYHA/WHO FC
Oral anticoagulants	—	—	—
Diuretics	—	—	—
Digoxin	—	—	—
Oxygen	—	—	—
Calcium channel blockers	—	—	—
Epoprostenol	Europe[a]	IPAH	III—IV
	USA, Canada	IPAH and PAH-CTD	III—IV
Treprostinil	USA	PAH	II—III—IV
Iloprost (inhaled)	European Union	IPAH	III
	Australia	IPAH, PAH-CTD and CTEPH	III—IV
Iloprost (intravenous)	New Zealand	PAH	III—IV
Beraprost	Japan, Korea	IPAH	II—III—IV
Bosentan	European Union	PAH[b]	III
	USA, Canada	PAH	III—IV
Sitaxsentan	—	—	—
Ambrisentan	—	—	—
Sildenafil	—	—	—
Balloon atrial septostomy	—	—	—
Lung transplantation	—	—	—

PAH-CTD: pulmonary arterial hypertension associated with connective tissue diseases; CTEPH: non-operable chronic thromboembolic pulmonary hypertension; IPAH: idiopathic pulmonary arterial hypertension; PAH: pulmonary arterial hypertension.
[a] Epoprostenol in Europe has not been registered through the centralised procedure of the European Medecines Agency (EMEA) but it is approved in different European countries on a local basis.
[b] Efficacy has been shown in IPAH and PAH-CTD without significant interstitial pulmonary disease.

agents on patient with PAH. As for other clinical conditions, the impact of these measures has not been tested scientifically and the recommendations are based on the experts' opinion.

Grade of Recommendation = IIa; Level of Evidence = C.

Physical activity — It is unclear whether physical activity may have a negative impact on the evolution of PAH. However, potentially hazardous symptoms like

severe dyspnoea, syncope and chest pain should be clearly avoided. Exercise should be limited to a symptom-free level in order to maintain adequate skeletal muscles conditioning. Physical activity after meals or in extreme temperatures should be avoided. Appropriate adjustments of daily activities may improve quality of life and reduce the frequency of symptoms.

Travel/altitude — Hypoxia may aggravate vasoconstriction in PAH patients and it is advisable to also avoid mild degrees of hypobaric hypoxia that start at altitudes between 1500 and 2000 m. Commercial airplanes are pressurised to equivalent altitude between 1600 and 2500 m and supplemental oxygen in PAH patients should be considered. Before planning to travel, information on nearest PH clinics should be collected.

Prevention of infections — Patients with PAH are susceptible to develop pneumonia that is the cause of death in 7% of cases. Pulmonary infections are poorly tolerated and need to be promptly recognised and treated. Vaccine strategies are recommended for influenza and pneumococcus pneumonia. Any persistent fever in patients with iv catheter for continuous administration of epoprostenol should raise the suspicion of catheter infection.

Pregnancy, birth control and post-menopausal hormonal therapy[100] — Pregnancy and delivery in PAH patients are associated with an increased rate of deterioration and death.[101,102] Even if successful pregnancies have been reported in IPAH patients,[103] an appropriate method of birth control is highly recommended in women with childbearing potential. There is consensus among guidelines from the American Heart Association, and the American College of Cardiology which recommend that pregnancy be avoided or terminated in women with cyanotic congenital heart disease, PH, and Eisenmenger syndrome. The Expert consensus document of the ESC on the management of cardiovascular diseases during pregnancy outlines that severe pulmonary vascular diseases has long been known to carry a maternal mortality of 30—50%.[104] However, there is no agreement among experts on the most appropriate birth control method in these subjects. The safety of hormonal contraception is questioned for its influence on prothrombotic changes. On the other hand, the current availability of low-oestrogen dose products, and concomitant oral anticoagulant treatment may limit the risk of these agents. In addition recent studies of large numbers of patients failed to reveal any relationship between intake of hormonal contraceptive agents and PAH.[105] Some experts suggest the use of oestrogen-free products or surgical sterilisation or barrier contraceptives. It is not clear if the use of hormonal therapy in post-menopausal women with PAH is advisable or not. Probably it can be suggested only in case of intolerable menopausal symptoms and in conjunction with anticoagulation.

Haemoglobin levels — Patients with PAH are highly sensitive to reductions in haemoglobin levels. Any kind of mild anaemia should be promptly treated. On the other hand, patients with long-standing hypoxia, such as those with right-to-left shunts, tend to develop erythrocytosis with elevated levels of haematocrit. In these circumstances, phlebotomies are indicated (see section on Eisenmenger syndrome) if haematocrit is above 65% in symptomatic patients (headache, poor concentration) to reduce adverse effects of hyperviscosity.[106]

Concomitant medications — Care is needed to avoid drugs that interfere with oral anticoagulants or increase the risk of gastrointestinal bleeding. Even if non-steroid anti-inflammatory drugs seem not to be associated to PAH in a case-control study,[105] their use may further reduce glomerular filtration rate in patients with low cardiac output and pre-renal azotaemia. Anorexigens that have been linked to the development of PAH are no longer available on the market. The effects of the new generation serotonin-related anorexigens are unknown but no reports of pulmonary-related side effects are available up to now. The efficacy of current treatments for chronic ''biventricular'' heart failure like ACE-inhibitors and beta-blockers has not been confirmed in patients with PAH.[107] On the other hand, the empiric use of these treatments, even at low doses, may result in severe side effects like hypotension and right heart failure and should be discouraged.

Psychological assistance — Patients with PAH have a median age of about 40 years and exercise limitation may interfere considerably with their previous life-style. In addition, information on the severity of the disease may be obtained from many non-professional sources. Such sources may not be up-to date or may be confusing or inappropriately explicit. For this reason, many PAH patients are affected by a variable degree of anxiety and/or depression that can have a profound impact on their quality of life. The role of the PAH expert is important in supporting patients with adequate information (breaking bad news)[108] and in referring them to psychologists or psychiatrists when needed. Also support groups for patients and families coordinated or not by psychologists or psychiatrists are useful in improving the understanding and the acceptance of the disease condition.[109]

Elective surgery — Even if appropriate studies are lacking it is expected that elective surgery has an increased risk in patients with PAH. In addition, the risk should increase with the severity of NYHA functional class and in cases of thoracic and abdominal interventions. It is not clear which type of anaesthesia is advisable but probably epidural is better tolerated than general anaesthesia. The later should be performed by experienced anaesthetists with the support of PH experts for deciding the most appropriate treatment in case of complications. Patients on iv epoprostenol and subcutaneous treprostinil treatment should have fewer problems than subjects on oral or inhaled treatments. The latter may suffer from temporary obstacles to the drug administration like fasting, general anaesthesia and assisted ventilation. In case a prolonged period of withdrawal is foreseen (more than 12—24 h) it is advisable to provisionally shift to iv treatments and revert to the original therapy subsequently. Anticoagulant treatment should be interrupted for the shortest possible time and deep venous thrombosis prophylaxis should be performed.

Pharmacological treatment

Oral anticoagulant treatment

The rationale for the use of oral anticoagulant treatment in patients with PAH is based on the presence of traditional risk factors for venous thromboembolism like heart failure and sedentary lifestyle as well as on the demonstration of thrombophylic predisposition[41,42] and of thrombotic changes in the pulmonary microcirculation[5,6] and in the elastic pulmonary arteries.[110]

The evidence for favourable effects of oral anticoagulant treatment in patients with IPAH or PAH associated to anorexigens is based on retrospective analysis of single centre studies.[79,111,112] The design of these studies was not randomised and only IPAH and anorexigens-related PAH patients were included in the studies.

The target INR in patients with IPAH varies somewhat being 1.5–2.5 in most centres of North America and 2.0–3.0 in European centres.

The evidence supporting anticoagulation in patients with IPAH may be extrapolated to other patients with PAH provided that the risk/benefit ratio is carefully considered.

For example, it is generally thought that the risk of gastrointestinal bleeding may be higher in patients with PAH associated with CTD. Patients with PAH associated with congenital heart disease with intracardiac shunts are at increased risk of hemoptysis but they may be also at increased risk for paradoxical embolism in pulmonary artery and cerebral vein thrombosis.[27] Patients with porto-pulmonary hypertension may be at increased risk for gastrointestinal bleeding due to the presence of varices and low platelet counts. Patients with PAH receiving therapy with chronic iv epoprostenol are anticoagulated in the absence of contraindications, due in part to the additional risk of catheter-associated thrombosis.

In recent RCTs, oral anticoagulants were administered in 51–86% of subjects. Interestingly, the highest prevalence of oral anticoagulant treatment was seen in the trials involving mainly IPAH patients in NYHA class III and IV, while the lowest prevalence was observed in the trial that included only patients with scleroderma.[113] It should be emphasised that there is no evidence of any difference in efficacy of oral anticoagulant therapy according to functional class or other measures of severity.

Grade of Recommendation = IIa; Level of Evidence = C for IPAH. Grade of Recommendation = IIb; Level of Evidence = C for other PAH conditions.

Diuretics

Patients with decompensated right heart failure develop fluid retention that leads to increased central venous pressure, abdominal organ congestion, peripheral oedema and in advanced cases also ascites. Appropriate diuretic treatment in case of right heart failure allows clear symptomatic and clinical benefits in patients with PAH even if specific RCTs have not been performed. In the recent RCTs on new targeted treatments, 49–70% of patients were treated with diuretics. However, the lack of trials with specific classes of diuretics in PAH and the individual variability in responses leave the choice of the type and the dose of drug to be used in individual cases to the experience of the physician. Serum electrolytes and indices of renal function should be followed closely in patients receiving diuretic therapy.

Grade of Recommendation = I; Level of Evidence = C.

Oxygen

Most patients with PAH (except those with associated congenital heart disease) present with only mild degrees of arterial hypoxaemia at rest. The pathophysiological mechanisms in this case include a low mixed venous oxygen saturation caused by low cardiac output and only minimally altered ventilation perfusion matching. In some patients with profound hypoxaemia, a secondary opening of a patent foramen ovale can be found. In patients with PAH associated with congenital cardiac defects, hypoxaemia is related to reversal of left-to-right shunting and is refractory to increased inspired oxygen.

No consistent data are currently available on the effects of long-term oxygen treatment in PAH. Although improvement in PH with low-flow supplemental oxygen has been reported in some PAH patients, this has not been confirmed in controlled studies. However, it is generally considered important to maintain oxygen saturation at greater than 90% at all times. More controversial is the use of oxygen treatment in patients with PAH associated with cardiac shunts. In fact, in a controlled study on Eisenmenger syndrome patients, nocturnal oxygen therapy had no effect on haematological variables, quality of life or survival.[114] In any case, the effect of continuous oxygen administration in these cases is unknown.

Grade of Recommendation = IIa; Level of Evidence = C.

Digitalis and dobutamine

Since the depression of myocardial contractility seems to be one of the primary events in the progression of right heart failure, inotropic agents have been considered for the treatment of this condition. Short-term iv administration of digoxin in IPAH produces a modest increase in cardiac output and a significant reduction in circulating norepinephrine levels;[115] however, no data are available on the effects of long-term treatment. Accordingly, the use of digitalis in PAH patients with refractory right heart failure is based primarily on the judgment of the physician rather than on scientific evidence of efficacy. Digitalis may be used in the rare PAH patients with atrial fibrillation or atrial flutter to slow ventricular rate. Digoxin was administered in 18–53% of patients enrolled in recent RCTs in PAH. Patients with end stage PAH are treated with iv dobutamine in most expert centres.[116] This treatment often results in clinical improvement that may persist for a variable period of time, like in advanced left heart failure.

Grade of Recommendation = IIb; Level of Evidence = C.

Calcium-channel blockers

The evidence for medial hypertrophy in the small pulmonary arteries together with the reduction of PVR obtained by vasodilator drugs lead Paul Wood many years ago[34] to elaborate the ''vasoconstrictive'' hypothesis as the basis for understanding the pathogenesis and the pathophysiology of IPAH. It is now clear that only in a minority of patients with IPAH a clinically significant reduction of pulmonary artery pressure associated with long-term clinical benefits can be achieved by the use of traditional vasodilators such as CCBs.

Favourable clinical and prognostic effects of high doses of CCBs in vasoreactive patients (see in the ''Diagnosis and Assessment'' section for definition of positive acute vasoreactive response) with IPAH have been shown in single centre, non-randomised, non-controlled studies.[81,79,92,117] In these studies, the control group consisted of non-vasoreactive patients who may have a poorer prognosis ''per se'' as compared to vasoreactive individuals.[92] However, there is no clear evidence for this hypothesis and it would appear unethical to withhold a therapy with high-dose CCB from a patient with a consistent reduction of pulmonary artery pressure by acute pharmacological testing and to perform a placebo-controlled clinical trial in these subjects.[98]

The CCBs that have been predominantly used in reported studies are nifedipine and diltiazem and the choice can be based upon the patient's heart rate at baseline (relative bradycardia favouring nifedipine, and relative tachycardia favouring diltiazem). The doses of these drugs that have shown efficacy in IPAH are relatively high i.e. up to 120–240 mg/day for nifedipine and 240–720 mg/day for diltiazem.[79] It is advisable, in vasoreactive patients, to start with reduced doses (i.e. 30 mg of slow-release nifedipine bid or 60 mg of diltiazem tid) to be increased cautiously and progressively in the subsequent weeks to the maximal tolerated regimen. Limiting factors for dose increase are usually systemic hypotension and lower limb peripheral oedema. In some cases the addition of digoxin and/or diuretics can decrease the CCB side effects.[119] There are no reports on efficacy, tolerability and effective doses of new generation CCBs such as amlodipine and flodpine.

As reported above (''Diagnosis and Assessment'' section) generally, only about 10–15% of IPAH will meet the criteria for a positive acute vasoreactive response and only about half of them will also be clinical and haemodynamic long-term responders to CCB treatment. It is commonly accepted that only in these cases the continuation of CCBs as single treatment is warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with CCBs in patients with PAH associated with CTD or congenital heart disease is less clear as compared to IPAH.[81,86] However, experts suggest also in these cases to test patients for acute vasoreactivity and to treat cautiously the vasoreactive ones with oral CCB, monitoring them closely to determine both the efficacy and safety of such therapy.

Favourable results of long-term administration of high doses of calcium-channel antagonists have also been shown in children with IPAH.[118]

Grade of Recommendation = I; Level of Evidence = C for IPAH. Grade of Recommendation = IIb; Level of Evidence = C for other PAH conditions.

Synthetic prostacyclin and prostacyclin analogues

Prostacyclin is produced predominantly by endothelial cells and it induces potent vasodilatation of all vascular beds studied. This compound is the most potent endogenous inhibitor of platelet aggregation and it appears also to have both cytoprotective and antiproliferative activities.[120] A dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by a reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites.[13] Even if it is not clear if the dysregulation of the prostacyclin metabolic pathways has a causative role or is merely a consequence of PH, it represents a convincing rationale for the therapeutic use of prostacyclin in PAH patients. Initially, the clinical use of ''prostacyclin'', i.e. epoprostenol, was based on its pulmonary vasodilator properties that were shown in short term trials, and this acute effect is currently utilised in testing the vasoreactivity of pulmonary circulation. On the other hand, even patients who do not manifest acute vasodilator response to epoprostenol have shown clinical and haemodynamic improvement with chronic treatment.[121] In fact, long-term iv administration of epoprostenol lowers PVR beyond the level achieved in the acute vasoreactivity tests.[84] The hypotheses to explain these results are based on the inhibitory effects of prostacyclin on vascular growth, remodelling and obliteration that can facilitate the partial restoration of altered functions of the pulmonary microcirculation. However the precise mechanism of action of prostacyclin administration in PAH is unknown and is likely to be multifactorial. It may include relaxation of vascular smooth muscle cells (acute), inhibition of platelet aggregation, normalisation of aggregation abnormalities, dispersion of platelets aggregates, improvement of endothelial cells injury, inhibition of vascular cells migration and proliferation facilitating reverse remodelling of pulmonary vascular changes, improvement of pulmonary clearance of ET-1, direct inotropic effect, enhanced peripheral O_2 utilisation by skeletal muscles and exercise haemodynamic improvements.[13]

The clinical use of prostacyclin in patients with PAH has been extended by the synthesis of stable analogues that possess different pharmacokinetic properties but share qualitatively similar pharmacodynamic effects. Originally, the experience on humans has been collected with epoprostenol that is a synthetic salt of prostacyclin.

Epoprostenol — Epoprostenol is available as a stable, freeze-dried preparation that needs to be dissolved together with an alkaline buffer (glycine), which allows a solution to be infused intravenously. Epoprostenol has a short half-life in the circulation (3–5 min), is rapidly converted to stable breakdown products or metabolites and is stable at room temperature for only 8 h; this explains

why it needs to be administered by continuous iv route by means of infusion pumps (e.g. CADD® pump) and permanent tunnelised catheters (Hickman). The epoprostenol is kept cool by using cold packs, which allows the infusion to be changed daily. The use of subcutaneous catheters with reservoirs and transcutaneous needles (used in intermittent treatments) is discouraged.

The efficacy of continuous iv administration of epoprostenol (synthetic prostacyclin) has been tested in 3 unblinded, controlled clinical trials in IPAH[121,122] and in PAH associated with the scleroderma spectrum of diseases,[113] and is summarised in Table 12. Epoprostenol improves symptoms, exercise capacity and haemodynamics in both clinical conditions, and is the only treatment to be shown in RCTs to improve survival in IPAH.

Recently two large series of IPAH patients treated with epoprostenol have been reported.[77,87] The data showed that survival was about 65% at three years and it was related to the severity at baseline, as well as to the three-month response to therapy. The authors suggested that lung transplantation should be considered in a subset of patients who remain in NYHA functional class III or IV or in those who cannot achieve a significant exercise and haemodynamic improvement after three months of epoprostenol therapy, or both.

Long-term treatment with epoprostenol is initiated at a dose ranging from 2 to 4 ng/kg/min and increased at a rate limited by side effects (flushing, headache, diarrhoea, leg pain). Target dose for the first two to four weeks is usually around 10—15 ng/kg/min and periodic dose increases are then required to maximise efficacy and to maintain the results because of possible tolerance to the drug. Optimal dose is variable between individual patients ranging in the majority between 20 and 40 ng/kg/min but the current strategy for increases is different among centres. In two large recently published series of patients treated with epoprostenol[77,87] mean dose was 21 ± 7 and 27 ± 8 ng/kg/min, respectively.

Adverse effects with chronic epoprostenol treatment are common and include flushing, jaw pain, diarrhoea, headache, backache, foot and leg pain, abdominal cramping, nausea, and rarely hypotension. The incidence of side effects may relate to how aggressive the dose is initially up titrated. Dose reduction is required only if the intensity is moderate to severe. Recurrence of side effects may be experienced after dose increases but usually they are mild and self-limiting over time without dose changes. In some cases ascites has been reported that may be related to an increased permeability of the peritoneal membrane induced by epoprostenol. Adverse events related to the delivery system are more serious and are essentially linked to pump malfunction, local site infection, catheter obstruction and sepsis. In two large series[77,87] 0.14 and 0.19 episodes of sepsis per patients-year were reported and 8 deaths (2.8%) out of a total of 340 subjects were directly related to catheter infections. Localised infections can also occur such as small exit site reactions, tunnel infections and cellulitis. Rare events are pneumothorax and haemothorax that occur during catheter insertion. Abrupt interruption of the epoprostenol infusion should be avoided, as this may, in some patients, lead to a rebound worsening of their PH with symptomatic deterioration and even death. Management of patients on chronic epoprostenol therapy requires a considerable infrastructure, including experienced nurses and physicians.

Even if RCTs with epoprostenol have been performed only in IPAH and PAH associated with scleroderma, favourable results have also been shown in uncontrolled experiences in other subsets such as paediatric IPAH[118] systemic lupus erythematosus[123] and other CTD,[124] PAH associated with congenital heart defects with systemic to pulmonary shunts either repaired or not,[124,125] in porto-pulmonary hypertension[124,126] in PAH associated to Gaucher's disease[127] and to HIV infection.[128] There is no consensus among experienced physicians on the effectiveness of epoprostenol treatment in patients with

Table 12 Randomised controlled trials with continuous intravenous epoprostenol in patients with pulmonary arterial hypertension

Trial	IPAH[122]	IPAH[121]	PAH associated to scleroderma[113]
Patients *n*	23	81	111
Duration (months)	2	3	3
NYHA functional class (%)			
II	9	—	5
III	65	75	78
IV	26	25	17
Aetiology (%)[a]			
IPAH	100	100	—
CTD	—	—	100
CHD	—	—	—
HIV	—	—	—
Treatment effect			
Six-min walk change (m)	+45	+47	+94
Haemodynamics	Improved	Improved	Improved
Clinical events	Reduced	Reduced (improved survival)	No-change

CHD: congenital heart disease (congenital systemic to pulmonary shunts); CTD: connective tissue disease (PAH associated to scleroderma); IPAH: idiopathic pulmonary aterial hypertension.

[a] Sum of % may not be 100% for rounding to the nearest unit, 0.5 is rounded to the upper unit.

inoperable CTEPH even if some positive effects have been shown.[129]

Epoprostenol in Europe has not been registered through the centralised procedure of the European Union (EMEA) but is approved in different European countries on a local basis for IPAH in NYHA class III and IV. Epoprostenol is approved by the Food and Drug Administration (FDA) in the USA and Canada for IPAH and PAH associated with CTD in NYHA class III and IV.

Grade of Recommendation = I; Level of Evidence = A for IPAH and PAH associated with CTD.

Grade of Recommendation = IIa; Level of Evidence = C for other PAH conditions.

Four RCTs have been performed with prostacyclin analogues and are summarised in Table 13.

Treprostinil — Treprostinil is a tricyclic benzidene analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature in a physiological solution. These characteristics allow the administration of the compound by iv as well as subcutaneous route. The subcutaneous administration of treprostinil can be accomplished by micro-infusion pumps (Mini-Med pump®) and small subcutaneous catheters similar to those utilised for the administration of insulin in diabetic patients. In this case, the problems linked to a permanent central venous line, such as infections, are avoided and the management of the system is much simpler.

The effects of continuous subcutaneous administration of treprostinil in PAH were studied in the largest worldwide RCT performed in this condition, and showed improvements in exercise capacity, haemodynamics and clinical events.[130] The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who could tolerate upper quartile dose (dose > 13.8 ng/kg/min). One earlier pilot controlled study was performed with treprostinil in 26 PAH patients and showed trends in the improvement of six-minute walk distance and in the reduction of PVR.[131]

Infusion site pain was the most common side effect of treprostinil leading to discontinuation of the treatment in 8% of cases on active drug and limiting dose increase in an additional proportion of patients. Overall mortality was 3% and no difference was detected between treatment groups. Preliminary reports have shown the possibility to transition patients from iv epoprostenol to subcutaneous treprostinil.[132]

In 2002, the FDA approved the use of treprostinil in NYHA class II, III and IV patients with PAH.

Grade of Recommendation = IIa; Level of Evidence = B for PAH.

Sodium beraprost — Sodium beraprost is the first chemically stable and orally-active prostacyclin analogue. It is absorbed rapidly in fasting conditions, peak concentration is reached after 30 min and elimination half-life is 35—40 min after single oral administration.

The orally-active prostacyclin analogue beraprost has been evaluated in PAH patients in two RCTs in Europe[133] and in the United States[74] (Table 2). In the first study the drug was administered orally four times a day at the highest tolerated dose (median dose 80 μg qid) and an in-

Table 13 Randomised controlled trials with new prostacyclin analogues in patients with pulmonary arterial hypertension

Trial	Treprostinil[130]	Beraprost — EU[133]	Beraprost — USA[74]	Iloprost[135]
Patients *n*	469	130	116	203
Route	Subcutaneous	Oral	Oral	Inhaled
Duration (months)	3	3	12	3
NYHA functional class (%)				
II	11	49	53	—
III	82	51	47	59
IV	7	—	—	41
Aetiology (%)[ab]				
IPAH	58	48	74	54
CTD	19	7	10	17
CHD	24	21	16	—
CTEPH	—	—	—	28
HIV	—	7	—	—
P-PH	—	16	—	—
Treatment effect				
Peak VO_2 (% predicted)	N/A	N/A	Trend to increase	N/A
Six-min walk change (m)	16[b]	25	31[bc]	36
Haemodynamics	Improved	No change	No change	Improved[d]
Clinical events	Reduced	No-change	Reduced[d]	Reduced

CHD; congenital heart disease (congenital systemic to pulmonary shunts); CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; IPAH: idiopathic pulmonary arterial hypertension; N/A: not available; P-PH: porto-pulmonary hypertension.

[a] Sum of % may not be 100% for rounding to the nearest unit, 0.5 is rounded to the upper unit.

[b] Median change.

[c] Statistically significant at 3 and 6 months.

[d] Only pulmonary vascular resistance improved in pre-inhalation period and a more consistent improvement of other parameters is observed in post-inhalation period.

crease in exercise capacity was seen only in IPAH subjects after 3 months. In the second randomised trial that lasted 12 months, improvement in exercise capacity was observed at 3 and 6 months but not thereafter. No haemodynamic improvements were observed in the long-term study and clinical events were reduced only at the 6 month evaluation.

Beraprost sodium has been approved in Japan and South-Korea for IPAH but its development appears to have been stopped in the USA and in Europe.

Grade of Recommendation = IIb; Level of Evidence = B for IPAH.

Inhaled iloprost — Iloprost is a chemically stable prostacyclin analogue available for iv, oral and aerosol administration. Inhaled therapy for PAH is an attractive concept that has the theoretical advantage to be selective for the pulmonary circulation. In fact, since intra-acinar pulmonary arteries are closely surrounded by alveolar units, it is possible to vasodilate these vessels by an alveolar deposition of vasodilators. It is critical that aerosolised particles be small enough (diameter 3—5 μm) to ensure alveolar deposition.

After a single inhalation of iloprost a reduction of 10—20% of mean pulmonary artery pressure was observed and lasted for 45—60 min.[134] The short duration of action requires frequent inhalations (from 6 to 12 times daily) to obtain a persistent effect with long-term administration. With Jet nebulisers, the duration of each inhalation takes about 15 min; with alternative devices such as ultrasound nebulisers the inhalation time can be reduced to about 5 min.

Inhaled iloprost has been evaluated in one RCT in which daily repetitive iloprost inhalations (6—9 times 2.5—5 μg/inhalation, median 30 μg daily) were compared to placebo inhalation in patients with PAH and CTEPH[135] (Table 13). The study showed an increase in exercise capacity and improvement in symptoms, PVR and clinical events in IPAH patients only. Overall, inhaled iloprost was well tolerated: cough occurred more frequently in the iloprost group as well as flushing and headache.

A long-term, uncontrolled study on 25 patients with IPAH treated for at least one year with inhaled iloprost 100—150 μg daily has been also reported:[136] the data showed a mean increase of 85 m of the six minutes walk, a reduction of 7 mmHg in mean pulmonary artery pressure and an increase in cardiac index of 0.6 l/min/m^2. In a small study on 8 patients with PH and lung fibrosis, the acute administration of inhaled iloprost caused marked pulmonary vasodilatation with maintenance of gas exchange and systemic arterial pressure[137] showing a possible usefulness in this particular subset of patients.

Inhaled iloprost treatment has been approved by the EMEA in Europe for NYHA Class III IPAH and in Australia and New Zealand for PAH and non-operable CTEPH class III and IV.

Grade of Recommendation = IIa; Level of Evidence = B for IPAH.

Intravenous iloprost — Continuous iv administration of iloprost appears to be as effective as epoprostenol in a small series of patients with PAH and CTEPH.[138,139] Iloprost presents the advantage of being stable at room temperature and does not need to be reconstituted and refrigerated.

Continuous iv administration of iloprost has been approved in New Zealand for NYHA class III and IV PAH.

Grade of Recommendation = IIa; Level of Evidence = C for PAH.

Endothelin-1 receptor antagonists

Endothelin-1 (ET-1), a peptide produced primarily by vascular endothelial cells, is characterised as a powerful vasoconstrictor and mitogen for smooth muscle.[14] ET-1 binds to two types of receptors, ET_A and ET_B: ET_A-receptors are found in smooth muscle cells whereas ET_B-receptors are localised on both endothelial cells and in smooth muscle cells. Activation of ET_A and ET_B-receptors on smooth muscle cells mediate the vasoconstrictive and mitogenic effects of ET-1. Stimulation of endothelial ET_B-receptors promote ET-1 clearance and activation of NO and prostacyclin release.

An activation of the ET-1 system has been demonstrated in both plasma[140] and lung tissues of PAH patients.[141] Although it is not clear if the increases in ET-1 plasma levels are a cause or a consequence of PH,[140] studies on tissue ET system expression support a prominent role of ET-1 in the pathogenesis of PAH.[14]

The clear evidence of the activation of the ET system in PAH provides a sound rationale for testing ET-1 antagonists in PAH patients. The most efficient way to antagonise the ET-1 system is by the use of ET-1 receptor antagonists that can block either ET_A or both ET_A and ET_B-receptors.

Currently three RCTs with endothelin-1 receptor antagonists have been performed in PAH patients at the time of writing (Table 14):

Bosentan — Bosentan is an oral active dual ET_A and ET_B-receptor antagonist and is the first molecule of this class of drugs to be synthesised.[142] Bosentan has been evaluated in PAH in two RCTs that have shown improvement in exercise capacity, functional class, haemodynamics, echocardiographic and Doppler variables, and time to clinical worsening.[58,143,144] In the larger BREATHE-1 study, patients were randomised 1:1:1 to receive placebo or 62.5 mg of bosentan twice daily for 4 weeks followed by either bosentan 125 mg bid or 250 mg bid for a minimum of 12 weeks. Although both bosentan dosages induced a significant treatment effect, the placebo-corrected improvement tended to be more pronounced for the 250 mg bid than for the 125 mg bid dosage (+54 m and +35 m of 6MWT treatment effect, respectively). However, no formal dose response for efficacy could be ascertained. Although a similar treatment effect was achieved in patients with IPAH and in those with PAH associated with scleroderma, bosentan improved the walking distance from baseline in IPAH patients (+46 m in the bosentan group versus −5 m in the placebo group) whereas it prevented walk distance deterioration in the scleroderma patients (+3 m in the bosentan group versus −40 m in the placebo group). Increases

Table 14 Randomised controlled trials with endothelin-1 receptor antagonists in patients with pulmonary arterial hypertension

Trial	Bosentan pilot[143]	Bosentan pivotal[144]	Sitaxsentan[75]
Patients *n*	32	213	178
Route	Oral	Oral	Oral
Duration (months)	3	4	3
Primary end points	6-min walk	6-min walk	Peak-VO_2
NYHA functional class (%)			
II	—	—	33
III	100	91	66
IV	—	9	1
Aetiology (%)[a]			
IPAH	85	70	53
CTD	15	30	24
CHD	—	—	24
HIV	—	—	—
Treatment effect			
Peak VO_2 (% predicted)	N/A	N/A	+3%[b]
Six-min walk change (m)	+76	+44	+34
Hemodynamics	Improved	N/A	Improved
Clinical events	Reduced	Reduced	Reduced[c]

CHD: congenital heart disease (congenital systemic to pulmonary shunts); CTD: connective tissue disease; IPAH: idiopathic pulmonary arterial hypertension; N/A: not available.
[a] Sum of % may not be 100% for rounding to the nearest unit, 0.5 is rounded to the upper unit.
[b] Only for 300 mg dose.
[c] Only for 100 mg dose.

in hepatic aminotransferases occurred in 10% of the subjects, and were found to be dose-dependent and reversible after dose reduction or discontinuation. In fact, abnormal hepatic function was more frequent and severe in the 250 mg dose group and a decrease in transaminase concentrations was observed in all cases in which the bosentan dose was reduced. Based on these results, the recommended target therapeutic dose of bosentan was confirmed as 125 mg twice daily. The most likely mechanism for the liver enzyme changes with Bosentan treatment is a dose-dependent competition by bosentan and its metabolites with the biliary excretion of bile salts, resulting in a retention of bile salts that can be cytotoxic to hepatocytes.[145]

Twenty-nine patients received bosentan in an extension study: patients assessed at month 6 maintained the improvement in walk distance, and long-term treatment with bosentan for >1 year was associated with an improvement in haemodynamic parameters and NYHA functional class.[146]

Oral bosentan has also recently been proposed as a transition therapy in patients displaying severe and/or unbearable side effects of prostanoid therapy including sepsis with iv epoprostenol.[147]

An open-label, uncontrolled single and multiple-dose study has been performed in children 4—17 years of age with PAH (BREATHE-3) to assess pharmacokinetics, tolerability and safety of oral bosentan. In this preliminary study a significant improvement in haemodynamics was observed after 12 weeks of treatment in the 18 enrolled children either with bosentan alone or in combination with epoprostenol.[148]

Due to the potential increase in liver enzymes, the FDA requires that liver function tests be performed at least monthly in patients receiving bosentan. In addition the EMEA recommended to monitor monthly liver function tests, and currently these data are collected in an internet-based program (TRAX). Also the haemoglobin/haematocrit should be checked regularly because bosentan use may also be associated with the development of anaemia, which seems typically to be mild. Fluid retention and lower limb oedema have been also reported in patients treated with Bosentan. Careful attention must be paid to the use of adequate contraception in women of childbearing age due to the potential teratogenic effects of bosentan. In addition bosentan may decrease the efficacy of hormonal contraceptive techniques, and for this reason they should not be used alone. There is concern that the endothelin antagonists as a class may be capable of causing testicular atrophy and male infertility. Younger males who may consider conceiving should be counselled regarding this possibility prior to taking these drugs.

Bosentan has been approved for the treatment of NYHA class III and IV PAH patients in the USA and Canada. In Europe it has been approved by the EMEA for the treatment of NYHA class III patients specifying that efficacy has been demonstrated only in IPAH patients and PAH associated with scleroderma without significant lung fibrosis.

Grade of Recommendation = I; Level of Evidence = A for NYHA class III IPAH and PAH associated with scleroderma without significant lung fibrosis.

Grade of Recommendation = IIa; *Level of Evidence* = B *for NYHA class IV IPAH and PAH associated with scleroderma without significant lung fibrosis.*

Sitaxsentan — Sitaxsentan, a selective orally-active ET_A-receptor antagonist has been assessed in PAH patients in one RCT on 178 patients with NYHA class II, III

and IV PAH.[75] Aetiology included IPAH and PAH associated with CTD or congenital heart diseases. Patients were randomised 1:1:1 to placebo, sitaxsentan 100 mg, or sitaxsentan 300 mg given orally once daily for 12 weeks. The study demonstrated improvements in exercise capacity, haemodynamics and clinical events.[75] Incidence of abnormal liver function tests, which reversed in all cases, was 0% for 100 mg, and 9.5% for 300 mg. An additional pilot study with this compound in 20 PAH patients has shown similar results.[149]

Sitaxsentan may increase the international normalised ratio (INR) or prothrombin time (PT), due to the inhibition of CYP2C9 P450 enzyme, the principal hepatic enzyme involved in the metabolism of warfarin. This interaction can be managed by reducing the warfarin dose to achieve the desired INR.

A second RCT is currently ongoing with sitaxsentan to further explore both efficacy and side effects profile and to achieve approval from regulatory agencies. No grade of recommendation is given for sitaxsentan because it is currently available only for patients enrolled in RCTs.

Grade of Recommendation = currently not given; Level of Evidence = B.

Ambrisentan — Ambrisentan, a selective orally-active ET_A-receptor antagonist has thus far been evaluated in a pilot blinded dose-comparison study in 64 PAH patients. Preliminary results show improvements in exercise capacity and haemodynamics that appear similar to the results observed with the other ERAs.[150] Two RCTs are currently ongoing with ambrisentan to further explore both efficacy and side effects profile and to achieve approval from regulatory agencies. No grade of recommendation is given for ambrisentan because it is currently available only for patients enrolled in RCTs.

Grade of Recommendation = currently not given; Level of Evidence = C

Type 5 phosphodiesterase inhibitors

Sildenafil — Sildenafil is an orally-active, potent and selective inhibitor of cGMP-phosphodiesterase (PDE) type 5, that exerts its pharmacological effect by increasing the intracellular concentration of cGMP.[151] The increase of this nucleotide induces relaxation and antiproliferative effects on vascular smooth muscle cells.[152] PDE-5 is selectively abundant in the pulmonary circulation[153,154] and PDE-5 gene expression and activity are increased in chronic PH.[155,156] This suggests that sildenafil may have a prefential effect on the lung vasculature.

A number of uncontrolled studies have reported favourable effects of the orally-active type 5 phosphodiesterase inhibitor sildenafil in PAH,[157–159] CTEPH[160] and PH associated with lung fibrosis.[161] The drug at a dose ranging from 25 to 75 mg tid appears to improve both cardiopulmonary haemodynamics and exercise capacity. These studies report relatively few minor side effects (e.g., headache, nasal congestion, and visual disturbances). A RCT with a cross-over design has been recently published: sildenafil 25–100 mg tid administered in 22 NYHA II and III PAH patients improved symptoms after 6 weeks, the exercise capacity as assessed by the Naughton protocol on the treadmill (from 475 ± 168 s of exercise time at the end of placebo phase to 686 ± 224 s at the end of sildenafil phase) and the haemodynamics.[15] The results of a pivotal RCT of 278 NYHA II and III PAH patients were recently presented at the American College of Chest Physicians meeting at the end of October 2004. The data show that mean placebo-corrected treatment effects on 6MWT were around 45 m for 20, 40, and 80 mg sildenafil 3 times daily. All sildenafil doses reduced mPAP at week 12 by about 3 to 5 mmHg. At the time of writing sildenafil treatment has not yet been approved by any regulatory agency for treatment of PAH.[162] Currently, treatment with sildenafil should be considered in patients with PAH, who have failed or are not candidates for other approved therapies.

Grade of Recommendation = I; Level of Evidence = A.

Combination therapy

Combination therapy is an attractive option to address the multiple pathophysiological mechanisms that are present in PAH. Combination therapy can be pursued by the simultaneous initiation of two (or more) treatments or by the addition of a second (or third) treatment to a previous therapy that may be considered insufficient. Which of these two strategies is the best choice is currently unknown.

The efficacy and safety of the concurrent initiation of bosentan and epoprostenol were investigated in 33 NYHA class III and IV PAH randomised either to an epoprostenol+placebo group or an epoprostenol+bosentan group (BREATHE-2). Improved haemodynamics, exercise capacity and functional class were observed in both groups. Data shows that there was a trend for a greater (though non-significant) improvement in all haemodynamic parameters in the eportostenol+bosentan group.[163] However, an increase of adverse events was observed in the combination group as compared to epoprostenol alone.

Further RCT is ongoing or planned that will explore the effects of the addition of sildenafil to patients already on epoprostenol.

In patients with PAH who were deteriorating despite chronic treatment with non-parenteral prostanoids, addition of bosentan[164] or sildenafil[165] to the ongoing treatment resulted in favourable improvements in pulmonary haemodynamics and exercise capacity in uncontrolled studies.

Grade of Recommendation = IIb; Level of Evidence = C.

Interventional procedures

Balloon atrial septostomy

Several experimental[166] and clinical[167] observations have suggested that an inter-atrial defect might be of benefit in the setting of severe PH. In fact the presence of an atrial septal defect would allow right-to-left shunting to increase systemic output that, in spite of the fall in systemic arterial oxygen saturation will produce an increase in systemic oxygen transport. Furthermore, the shunt at the atrial level would allow decompression of

the right atrium and right ventricle, alleviating signs and symptoms of right heart failure.

The role of balloon atrial septostomy in the treatment of PAH patients is uncertain because its efficacy has been reported only in small series and case reports, totalling approximately 120 published cases.[168,169] In most circumstances, this intervention has been performed in severely ill patients as a palliative bridge to lung transplantation, which may explain a procedure mortality rate ranging from 5% to 15%. In addition to symptomatic and haemodynamic improvement, an increase in survival as compared with historical control groups has also been shown.[76] At present, balloon atrial septostomy is indicated for advanced NYHA class III and class IV patients with recurrent syncope and/or right heart failure despite all available medical treatments; septostomy is used either as a palliative bridge to lung transplantation or as the sole treatment modality when other options are not available.[169] Balloon atrial septostomy should be performed only in experienced centres to reduce the procedural risks.

Grade of Recommendation = IIa; Level of Evidence = C.

Lung transplantation

Lung and heart-lung transplantation in PAH have been assessed only in prospective uncontrolled series, since formal RCTs are considered unethical in the absence of alternative treatment options.[169]

The 3 and 5 year survival after lung and heart-lung transplantation is approximately 55% and 45%, respectively.[170]

Both single and bilateral lung transplantation have been performed for IPAH and these operations have been combined with repair of cardiac defects for the Eisenmenger syndrome. Recipient survival rates have been similar after single and bilateral transplantation for PAH, and if technically feasible, either of these operations is an acceptable choice for most cases of PAH. However, many transplant centres currently prefer to perform bilateral lung transplantation in part because there are generally less postoperative complications. In patients with Eisenmenger syndrome and in those with end-stage heart failure, the option of heart-lung transplantation should be carefully considered. For some complex defects, and in cases of ventricular septal defects, a survival advantage of heart-lung transplantation has been shown.

Lung and heart-lung transplantation are indicated in PAH patients with advanced NYHA class III and class IV symptoms that are refractory to available medical treatments. The unpredictability of the period on the waiting list and donor organ shortage complicate the decision-making regarding the appropriate timing of listing for transplantation.

Grade of Recommendation = I; Level of Evidence = C.

Treatment algorithm

A treatment algorithm based on the Grade of Recommendation and The Level of Evidence derived by clinical trials is reported in Fig. 3.

The algorithm is restricted to patients in *NYHA functional class III or IV* because they represent the predominant population included in RCTs.

For NYHA class I or II patients very few data are available and the most appropriate strategy has still to be determined and possibly validated by specific studies. Currently, NYHA class I and II patients should be treated with background therapy and, if vasoreactive, with CCBs. In cases with multiple favourable prognostic indicators (see the section on Assessment of Severity) a watchful-waiting strategy or inclusion in RCTs is recommended.

The different treatments have been evaluated mainly in *IPAH, and in PAH associated with scleroderma or to anorexigen use. Extrapolation of these recommendations to the other PAH subgroups should be done with caution (See the section on Specific Conditions).*

The suggested initial approach, after the diagnosis of PAH is made, is the adoption of the general measures and initiation of the background therapy that includes oral anticoagulant drugs (if no contraindications exist), diuretics in case of fluid retention, supplemental oxygen in case of hypoxaemia and digoxin in case of refractory right heart failure and/or supraventricular arrhythmias.

Due to the complexity of the additional evaluation and the treatment options available, it is strongly recommended that patients with PAH are referred to a specialised centre.

Acute vasoreactivity testing should be performed in all patients with PAH, although patients with IPAH and PAH associated to anorexigens use are the most likely to exhibit an acute positive response and to benefit from high-dose CCB therapy.

Vasoreactive patients, as defined above, should be treated with optimally tolerated doses of CCB; maintenance of the response (defined as NYHA functional class I or II with near normal haemodynamics) should be confirmed after three to six months of treatment.

Non-responders to acute vasoreactivity testing who are in NYHA functional class I and II should continue with the background therapy under close clinical follow-up.

Non-responders to acute vasoreactivity testing, or responders who remain in NYHA functional class III should be considered candidates for treatment with either an endothelin receptor antagonist (ERA) or a prostanoid. At present, the only commercially available and approved ERA is the orally-active dual receptor antagonist bosentan. Among prostanoids, treprostinil is administered subcutaneously and has been approved in the USA; Iloprost, administered by aerosol, has been approved in Europe and Australia, while beraprost is approved in Japan and South-Korea. Continuous iv administration of epoprostenol may also be used in NYHA class III patients who are refractory to ERAs or other prostanoids. Some authors still use first-line epoprostenol in NYHA class III patients, due to its demonstrated survival benefits.

The choice of the drug is dependent on a variety of factors, including the approval status, route of administration, side effect profile, patient's preferences and physician's experience.

The orally-active type 5 phosphodiesterase inhibitor sildenafil is currently not approved for the treatment of

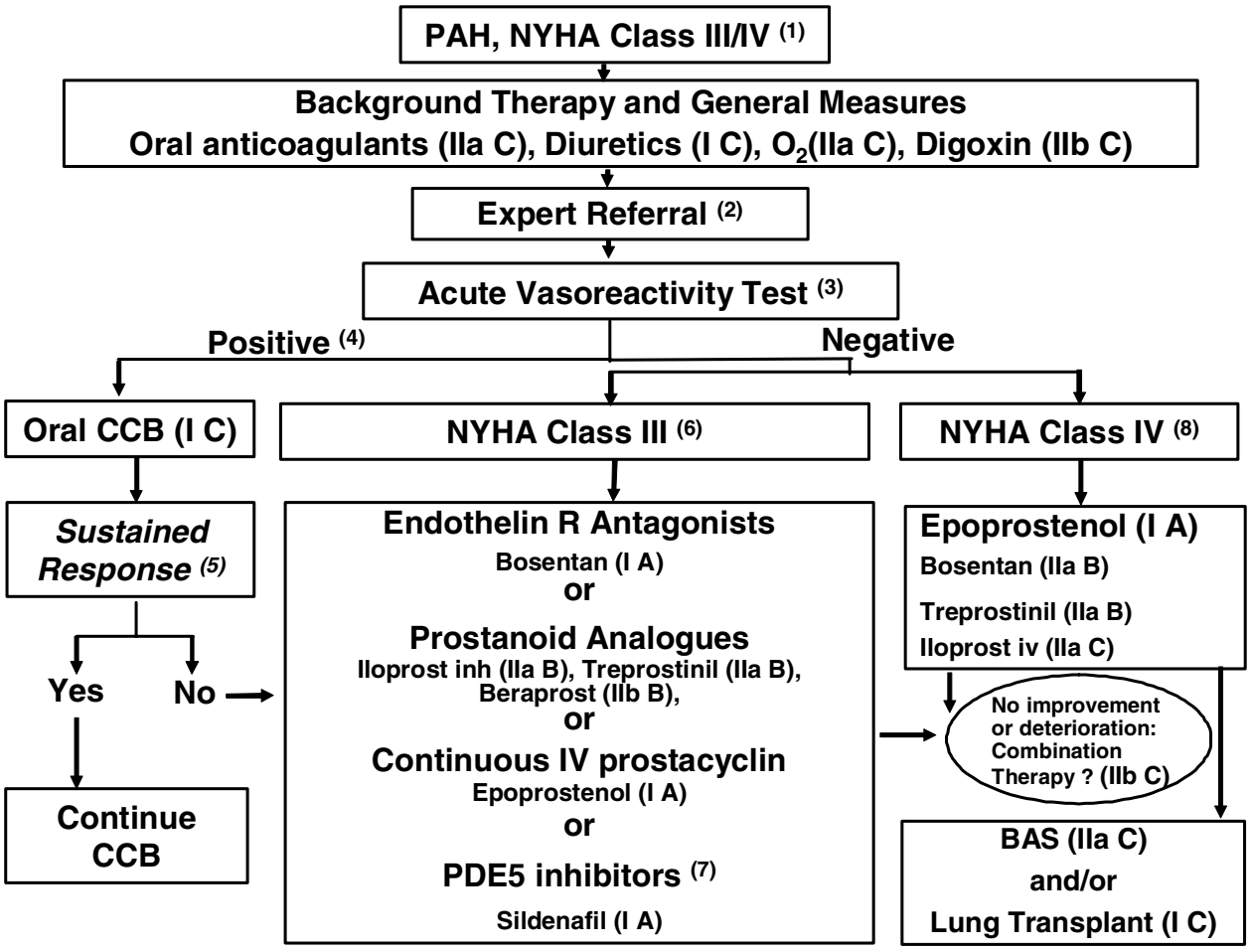

Fig. 3 Evidence-based treatment algorithm. (1) The algorithm is restricted to patients in NYHA functional class III or IV because they represent the largest population included in controlled clinical trials. For NYHA class I or II very few data are available. In addition the different treatments have been evaluated mainly in sporadic idiopathic pulmonary arterial hypertension patients (IPAH), and in PAH associated with scleroderma or to anorexigen use. Extrapolation of these recommendations to the other PAH subgroups should be done with caution. (2) Due to the complexity of the acute vasoreactivity tests, and of the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialised centre. (3) Acute vasoreactivity test should be performed in all patients with PAH even if the greater incidence of positive response is achieved in patients with IPAH and PAH associated to anorexigen use. (4) A positive acute response to vasodilators is defined as a fall in mean pulmonary artery pressure of at least 10 mmHg to less than or equal to 40 mmHg, with an increase or unchanged cardiac output during acute challenge with inhaled NO, iv epoprostenol, or iv adenosine. (5) Sustained response to calcium channel blockers (CCB) is defined as patients being in NYHA functional class I or II with near normal halemodynamics after several months of treatment. (6) In patients in NYHA functional class III, first line therapy may include oral endothelin receptor antagonists, chronic iv epoprostenol, or prostanoid analogues. (7) At the time of writing sildenafil is not approved for PAH by any regulatory agency. (8) Most experts consider that NYHA functional class IV patients in unstable condition should be treated with iv epoprostenol (survival improvement, worldwide experience and rapidity of action). A, B, C grading according to Tables 4 and 5; CCB: calcium channel blockers; inh: inhaled; iv: continuous intravenous; PDE: phophodiesterase; R: receptors.

PAH by any regulatory agency, and its use should be considered in subjects who have failed or are not candidates for other approved therapy.

The role of this drug will be better defined after the evaluation of the pivotal RCT data by regulatory agencies.

Continuous iv epoprostenol, approved in the US and Europe, may be considered as first line therapy for IPAH patients in NYHA functional class IV because of the demonstrated survival benefit in this subset.

Although both bosentan and treprostinil are approved in class IV patients, only a small number of class IV patients were included in the clinical trials of these agents. Accordingly, most experts consider these treatments as a second line for severely ill patients. Although no RCTs have been performed with the iv delivery of iloprost, this prostacyclin analogue has been approved in New Zealand.

Combination therapy (e.g. ERAs + prostanoids) may be considered for patients who fail to improve or deteriorate with first-line treatment, even though data on this specific strategy are limited and largely uncontrolled at this point. Appropriate protocols for timing and dosing to limit possible side effects of the combination have still to be implemented.

Balloon atrial septostomy and/or lung transplantation are indicated for refractory PAH or where medical treatments are unavailable. These procedures should be performed only in experienced centres.

Specific conditions

Paediatric pulmonary arterial hypertension

Incidence — The prevalence of congenital heart disease is higher amongst children than adults and great care is needed to recognise this important cause of PAH. In contrast, the prevalence of PAH related to CTD, portal hypertension, HIV infection and drugs/toxins is lower amongst children than adults. Although persistent PH of the newborn (PPHN) is also classified under PAH, its natural history and treatment are sufficiently different from those in other forms of PAH to justify its exclusion from further discussion here. PPHN is usually transient,[171,172] with infants either recovering completely without requiring chronic medical therapy or dying during the neonatal period despite maximal cardiopulmonary therapeutic interventions.[173]

Pathogenesis — No clear differences have been identified among the mechanisms involved in the development of PAH in children and in adults. However, PPHN may entail some specific pathophysiological mechanisms due to the persistence of the foetal pulmonary vascular characteristics and of the patent foramen ovale.[174] In addition, prevalence of acute vasoreactivity is higher in children with IPAH suggesting that vasoconstriction may prevail on fixed obstructive vascular changes in this subset.[79,118]

Clinical picture and investigations — Clinical, diagnostic and prognostic data on PAH have been collected predominantly in the adult population and often extrapolation of this information on the paediatric population is required.

On the basis of the NIH registry, it was raised that there is a higher mortality in children than adult patients if untreated. However, those data were collected on small numbers of paediatric cases, and preceded the availability of many of the current medical therapies. Theoretically, it might also be expected that the response to treatment would be better in children because the vasculature is still remodelling as the child grows. The new medical treatments do indeed appear to achieve greater success in children than in adults with PAH, but the course of the disease is less predictable.[175] It remains unclear as to why one child should behave differently from another when troubled by the same degree of PAH.

Despite the fact that only single centre reports are available on the diagnostic strategy, children with severe PH undergo a similar diagnostic evaluation as has been described in adults (see above).[176] Studies include arterial blood gas and oxygen saturation measurements, a chest radiograph, pulmonary function and exercise testing, echocardiogram, ventilation-perfusion scan, chest CT, abdominal ultrasound scan, serological studies for CTD, studies of hypercoagulability, and HIV testing; diagnosis needs to be confirmed by the right heart catheter study.

As in adults with severe PAH, testing of pulmonary vasoreactivity during RHC includes assessment of the acute response to a short-acting vasodilator, such as inhaled NO, iv epoprostenol or iv adenosine, to determine if there is a role for chronic therapy with an oral CCB. The prevalence of acute vasoreactivity is higher in children than adults and this permits more children than adults to be effectively treated with CCB.[79,118]

Treatment — The therapeutic algorithm for children who have PAH is similar to that used in adults, however, a few specific issues need to be addressed. For example, in children who are responsive to a specific treatment strategy, the response is often far better than that seen in adult patients. Conversely, if they fail to respond to these therapeutic modalities, their survival is often even shorter than that of adult patients with severe disease.

Since the children with PAH often have a more reactive pulmonary vascular bed than the adults, any respiratory tract infection that results in ventilation/perfusion mismatching from alveolar hypoxia can result in a catastrophic event if not aggressively treated. We recommend that children with pneumonia be hospitalised for the initiation of antibiotic therapy, with antipyretics administered for temperature elevations greater than 101 °F (38 °C) to minimise the consequences of increased metabolic demands.

Whether or not chronic anticoagulation is efficacious in children with PAH, as well as safe with a low risk/benefit profile remains to be determined. However, the current approach of experts is to anticoagulate children with right heart failure.

The safety and efficacy of CCBs is based on a patient's response to acute vasodilator testing, and the efficacy of this treatment in children is similar to that in adults. The optimal dosage regime used is usually relatively high as in adults (see above) and children tolerate and appear to need, a higher dose per kilogram than adults.

Clinical indications for chronic iv epoprostenol therapy in children are similar to adults. The optimal dose of epoprostenol remains unclear in both children and adults. In children, the starting dose is 2 ng/kg/min, as in adults, and the dose is increased as necessary. The dose usually has to be increased quite rapidly during the first months after initiating treatment. Although a mean dose at one year for an adult PAH patient is approximately 20—40 ng/kg/min, the mean dose at one year in children, particularly young children, is closer to 50—80 ng/kg/min and the ''optimal'' dose varies considerably in different patients.

Oral beraprost, inhaled iloprost and subcutaneously infused treprostinil have all been used with to treat children with PAH, with varying degrees of success. In practice, it can be difficult to dose young children effectively with inhaled iloprost, even when they are co-operative, and subcutaneous treprostinil can be too painful. Experience suggests that, as with iv epoprostenol, children need to be given a higher dose per kilogram than adults.

An open-label, uncontrolled single and multiple-dose study has been performed in children 4—17 years of age with PAH (BREATHE-3) to assess pharmacokinetics, tolerability and safety of oral bosentan. In this preliminary study a significant improvement of haemodynamics was observed after 12 weeks of Bosentan treatment in the

18 enrolled children either alone or in combination with iv epoprostenol.[177]

The use of type 5 phosphodiesterase inhibitors, such as sildenafil, has been described in children, but, data are limited to small case series.[178]

Pulmonary arterial hypertension associated to Eisenmenger syndrome

Incidence — See discussion on Eisenmenger syndrome in the Classification section on congenital systematic-to-pulmonary shunts above.

Pathogenesis — Eisenmenger syndrome is defined as a congenital heart defect that initially causes large left-to-right shunt that induces severe pulmonary vascular disease and PAH, with resultant reversal of the direction of shunting.[179] With initial left-to-right shunting, the exposure of the pulmonary vasculature to increased blood flow as well as increased pressure may result in pulmonary vascular obstructive disease and, as the PVR approaches or exceeds systemic resistance, the shunt is reversed.

Clinical picture and investigations — Most patients will have impaired exercise tolerance and exertional dyspnoea, but these symptoms may be well compensated for years. Hemoptysis may occur, as a result of rupture of dilated bronchial arteries. Since patients with reduced arterial oxygen saturation have abnormal haemostasis, they are at risk for both bleeding and thrombosis. Cerebrovascular accidents may occur as a result of paradoxical embolisation, venous thrombosis of cerebral vessels, or intracranial haemorrhage. In addition, patients with this condition are at risk for brain abscess. Patients with Eisenmenger syndrome may have syncope owing to inadequate cardiac output or, less commonly, an arrhythmia. Symptoms of heart failure, which are uncommon until the disease is far advanced, portend a poor prognosis. Survival of patients with Eisenmenger syndrome is better than that of subjects with IPAH or APAH with comparable functional class. In a series of 100 patients listed for transplantation, actuarial survival of patients who did not receive transplants was 97% at 1 year, 89% at 2 years, and 77% at 3 years for patients with Eisenmenger syndrome and 77%, 69%, and 35%, respectively, for patients with IPAH.[180]

Treatment — The recommendation given for the treatment of Eisenmenger syndrome patients are mainly based on the clinical experience of experts and not on specific RCTs.[106,181] Phlebotomy with isovolumic replacement should be performed in patients with moderate or severe symptoms of hyperviscosity (e.g. headache and poor concentration) that usually are present when haematocrit is >65%; it should not be performed in asymptomatic or mildly symptomatic patients (regardless of the haematocrit). The symptoms are usually relieved by removal of one unit of blood, always with an equal volume replacement of dextrose or saline.[106] Phlebotomies should be performed no more than 2—3 times per year to avoid depletion of the iron stores and the production of iron-deplete red cells that increase blood viscosity. Diuretics can be used in case of signs of right heart failure.

The use of supplemental oxygen therapy is controversial[182] and should be used only in cases in which it produces a consistent increase in arterial oxygen saturation and/or improved clinical well being (pulmonary restrictive component). In some centres, Eisenmenger syndrome patients are anticoagulated similarly to other subjects with PAH in the absence of contraindication. Other authors suggest to avoid this treatment that can exacerbate the haemorrhagic diathesis.[183]

Unfortunately, few RCTs evaluating the effects of the new medical regimens in PAH have included patients with the Eisenmenger syndrome.[127,130,133] One reason for this is that the natural history of the untreated Eisenmenger syndrome, despite being significantly worse than that of the normal population, is in most cases a very slowly progressive disease, making RCTs difficult. Although the natural history of IPAH and PAH associated with congenital heart disease is very different, the similarity in their histopathology suggests that a common approach to treatment may be appropriate and effective. However, the efficacy of the new treatments should be formally tested to clarify the benefit-to-risk ratio.

The use of iv epoprostenol has been shown to exert favourable effects on haemodynamics and exercise capacity[125] and the effects of subcutaneous treprostinil in Eisenmenger patients was not different from that on IPAH.[132] A RCT to assess the effects of bosentan on 65 Eisenmenger patients is currently ongoing (BREATHE-5).

Lung transplantation with repair of the cardiac defect or combined heart-lung transplantation is an option for patients with Eisenmenger syndrome who have markers of a poor prognosis (syncope, refractory right-sided heart failure, NYHA functional class III or IV, or severe hypoxemia). Because of the somewhat limited success of transplantation and the reasonably good survival among patients treated medically, careful selection of patients for transplantation is imperative.

Porto-pulmonary hypertension

Incidence — PAH is a well-recognised complication of chronic liver diseases.[184,185,186] Portal hypertension rather than the hepatic disorder itself seems to be the main determining risk factor for developing PH, leading to the concept of porto-pulmonary hypertension.[185] Initially described by Mantz and Craige in 1951, porto-pulmonary hypertension is sufficiently infrequent so that it was debated for a long time whether this association was coincidental or causally related. Several lines of evidence suggest that the existence of portal hypertension and the development of PAH is non-coincidental.[185,187] Indeed, the incidence of PAH in patients with portal hypertension is much higher than the estimated incidence of IPAH in the general population. A large retrospective autopsy study showed that PAH occurred in 0.13% of overall unselected autopsied patients, versus 0.73% of patients with cirrhosis and portal hypertension.

Two prospective haemodynamic studies showed that 2% of patients with cirrhosis and portal hypertension had significant PAH. Two recent studies carried out in patients undergoing liver transplantation found a prevalence of pulmonary hypertension of 4% and 3.5%, respectively. Finally, the IPPHS study confirmed that cirrhosis was a risk factor for PAH.[188] Portal hypertension is not a rare cause of PAH the proportion of patients with porto-pulmonary hypertension was 8% in the NIH registry. Surgical porto-systemic shunts increased the occurrence of PH in patients with portal hypertension since, in a retrospective study, approximately 65% of the patients with PAH underwent surgical shunts while 35% did not.[189] These findings strongly suggest that the development of PAH in patients with portal hypertension is related to the development of portosystemic shunts rather than portal hypertension per se. The presence of chronic parenchymal liver disease and its severity is not associated with the risk of PAH since this complication may occur in patients with extrahepatic portal hypertension.[189] Similarly, the degree of portal hypertension estimated by the hepatic venous pressure gradient and systemic haemodynamic changes are not associated with the development of PAH.[184] Only the duration of portal hypertension could increase the risk of developing PAH.

Pathogenesis — The mechanism whereby portal hypertension facilitates the development of PAH remains unknown.[185] The presence of porto-systemic shunt might allow vasoconstrictive and vasoproliferative substances, normally cleared by the liver, to reach the pulmonary circulation. Serotonin produced by the enterochromaffin cells of the intestine may be one of these substances. Histopathological findings of porto-pulmonary hypertension are indistinguishable from those commonly observed in IPAH.[190]

Clinical picture and investigations — The clinical picture of patients with porto-pulmonary hypertension may be indistinguishable from that of IPAH or may include a combination of symptoms and signs of the underlying liver disease.[185]

Echocardiographic screening for the detection of PH in patients with liver diseases is appropriate in symptomatic patients and/or in candidates for liver transplantation. A RHC should be performed in all cases with increased SPAP in order to clarify the underlying haemodynamic changes and define prognostic and therapeutic implications.

Haemodynamically, compared with patients with IPAH, patients with porto-pulmonary hypertension have a significantly higher cardiac output and significantly lower systemic vascular resistance and PVR.[191] The diagnosis of portal hypertension with a Swan Ganz catheter at the time of RHC requires the determination of a gradient between free and occluded (wedge) hepatic vein pressure or hepatic venous pressure gradient, of more than 10 mmHg (normal is <5 mmHg).[67]

In a retrospective study,[185] patients with porto-pulmonary hypertension had a better rate of survival than patients with IPAH, although there is some debate on this issue.[192]

Treatment — The treatment of porto-pulmonary hypertension can be challenging and has not been thoroughly studied. Supplemental oxygen should be used as needed to maintain arterial oxygen saturations >90%. Diuretic therapy should be utilised to control volume overload, oedema, and ascites. Anticoagulant therapy has not been carefully studied in this population, and should probably be avoided in patients with impaired hepatic function and low platelet counts, and in patients at increased risk of bleeding due to gastroesophageal varices. In the absence of a markedly increased cardiac output, and relatively low PVR, patients with mild to moderate PH should have acute vasoreactivity assessed in the catheterisation laboratory. If such patients demonstrate a favourable acute response to vasodilator, consideration should be given to the cautious introduction of a CCB. Betablockers which are normally used to treat portal hypertension and reduce the risk of variceal bleeding, may be poorly tolerated in cases of associated PAH due to the negative inotropic effect on the right ventricular myocardium.

There have been a number of case reports and small case series describing the use of iv epoprostenol for treatment of porto-pulmonary hypertension.[188,193,194] It appears as though patients with porto-pulmonary hypertension respond to chronic iv epoprostenol in a manner somewhat similar to that of patients with IPAH. However, an increased incidence of ascites and splenomegaly with this treatment has been reported.[195]

Significant PAH can substantially increase the risk associated with liver transplantation and usually PAH is a contraindication if mean PAP is $\geqslant$35 mmHg and/or PVR is $\geqslant$250 dynes s cm.[196] It is occasionally possible to reduce mPAP and PVR making a borderline candidate for liver transplantation an acceptable one through aggressive treatment of their PAH including the use of epoprostenol.[192] In cases thought to have such severe disease as to require multi-organ transplantation such as combined liver and (heart-) lung transplantation the risks are considered to be very high.[198]

Some patients seem to demonstrate improvement in their PAH following liver transplantation.[199] This may be particularly true for those with a relatively high cardiac output pre-transplantation, which then decreases following successful transplantation. Other patients may develop worsening of their PAH well after liver transplantation. Occasionally, it may be possible to wean a patient off iv epoprostenol following liver transplantation. This should probably be done very gradually, under close observation.

Due to its potential for hepatoxicity, most experts would probably recommend avoiding an oral endothelin antagonist, e.g. bosentan in this population. Despite case series from expert centres with favourable results, the risk-to-benefit ratio of endothelin receptor antagonists in patients with liver disease need to be carefully evaluated on a long-term basis.

Pulmonary arterial hypertension associated to HIV infection

Incidence — PAH is a rare but well-documented complication of HIV infection; more than 200 cases have been re-

ported in the literature.[19,200,201] Currently non-infectious cardiovascular manifestations of HIV infection such as dilated cardiomyopathy, pericardial effusion, non-bacterial thrombotic endocarditis, accelerated atherosclerosis and PAH are more commonly detected as a result of longer survival and better prophylaxis against opportunistic infections.[202] In a large case control study, 3349 HIV-infected patients over a period of 5.5 years demonstrated a cumulative incidence of PH of 0.57%, resulting in an annual incidence of 0.1%.[203]

Pathogenesis — The mechanism of the development of PAH is unknown. An indirect action of HIV through second messengers such as cytokines,[204] growth factors,[204] or ET-1[205] is strongly suspected because of the absence of viral DNA in pulmonary endothelial cells.[204,206] This hypothesis is reinforced by the presence of perivascular inflammatory cells in HIV-associated PAH.[207,208] In addition, genetic predisposition can be also invoked because this complication affects only a minority of HIV-infected patients. The absence of germline BMPR2 mutation in a subset of 30 tested patients with HIV-associated PAH suggests that other susceptibility factors are involved.[209]

Clinical picture and investigations — HIV-related PAH shows similar clinical, haemodynamic and histological findings as IPAH and it does not appear to be related to the route of HIV transmission nor to the degree of immunosuppression.[210] HIV patients may often be also infected by hepatitis B and C viruses and a concomitant liver disease may be present.

Echocardiographic screening for the detection of PH in patients with HIV infection is required in symptomatic patients. A careful exclusion of other causes of PH such as left heart and parenchymal lung and liver diseases are necessary.

RHC is recommended in all cases of suspected PAH associated with HIV infection to confirm the diagnosis, determine severity, and rule out left sided heart disease.

Mortality of patients with HIV-associated PAH is mainly related to PAH itself, rather than to other complications of HIV infection;[210] PAH is an independent predictor of mortality in these patients.[203]

Treatment — In HIV-associated PAH, therapeutic options are less well established as compared to other forms of PAH. Oral anticoagulation is often contraindicated because of frequent reduced platelet counts, difficulty with compliance and potential drug interactions between HIV medications and warfarin.

Acute vasoreactivity tests and long term beneficial effect of CCB have not been reported in this PAH subgroup.

One uncontrolled open study of 6 patients with severe HIV-associated PAH[128] suggests that continuous infusion of epoprostenol might be effective in improving functional status and haemodynamics up to 12–47 months. Lung transplantation is considered not advisable in this population.

The role of highly active antiretroviral therapy in the management of HIV-associated PAH remains to be established. A beneficial effect on pulmonary haemodynamics was observed in patients treated with nucleoside reverse transcriptase inhibitors.[203] A single case report of long-term haemodynamic improvement with this treatment, without the associated use of any vasodilator agents, has recently been published.[211] Lastly, in a large monocentric case series of 82 patients,[209] univariate analysis indicated that CD4 count (>212 cells mm^3), combination antiretroviral therapy, and the use of epoprostenol infusion, were associated with an improved survival. On multivariate analysis, only CD4 lymphocyte count was an independent predictor of survival, presumably because combination antiretroviral therapy and epoprostenol infusion were strongly linked in this study population.

Recently, clinical and haemodynamic favourable results have been shown with the use of bosentan in a series of 16 HIV-related PAH patients.[212]

In summary, uncontrolled studies suggest that patients with severe HIV-associated PAH may respond favourably to combination antiretroviral therapy, epoprostenol and possibly to bosentan. However, epoprostenol as well as endothelin receptor antagonists and PDE type 5 inhibitors should be evaluated in this patient population in controlled randomised trials.[213]

Pulmonary arterial hypertension associated to connective tissue diseases

Incidence — PH is a well-known complication of CTD such as systemic sclerosis,[214] systemic lupus erythematosus,[215] mixed CTD,[216] and to a lesser extent, rheumatoid arthritis, dermatopolymyositis, and primary Sjögren's syndrome.[217] In these patients, PAH may occur in association with interstitial fibrosis or as a result of direct proliferative vascular involvement in the absence of significant parenchymal disease or chronic hypoxia. In addition, pulmonary venous hypertension from left heart disease can be present. It is imperative to determine which mechanism is operative, as treatment may be quite different for each process.

Estimation of the prevalence of PAH in patients with CTD is difficult because of the lack of consistent epidemiological data. Estimated prevalence of PAH in these patients is highly variable, according to the definition of PAH, the method used for assessing PA pressure and potential bias concerning the study population.[4]

Systemic sclerosis, particularly in its limited variant previously defined as CREST syndrome (calcinosis, Raynaud's disease, oesophageal dysmotility, sclerodactyly, and telangiectasia), represents the main CTD associated with PAH. The recently completed registry study of PH in 722 patients with systemic sclerosis in the UK, showed the prevalence at around 12%.[214] In another series of 930 patients with systemic sclerosis the cumulative incidence of PH was 13%.[49] However, in a population-based approach the prevalence of PH was 2.6% in 3778 patients.[218] In the NIH registry, among 236 cases of unexplained PAH, 18 were associated with CTD (8%).[48] In several PAH centres, more than 10% of the patients displaying severe PAH have an associated CTD, most often the CREST variant of scleroderma.

Pathogenesis — Histopathological changes in PAH associated with CTD are generally indistinguishable from

those of classical IPAH. Moreover, the whole spectrum of pulmonary vascular pathology has been described in these patients, including PVOD disease and PCH. The pathophysiological mechanisms leading to PAH in patients with CTD diseases remain unknown. A pulmonary vasospasm, the so-called pulmonary Raynaud's phenomenon, hypothetically could play a role. The presence of antinuclear antibodies, rheumatoid factor, immunoglobulin-G, and complement fractions deposits in the wall of pulmonary vessels suggest a role for an immunological mechanism.

Clinical picture and investigations — Compared with patients with IPAH, patients with PAH associated with CTD are mainly women, are older, have a significantly lower cardiac output, and show a trend toward a shorter survival. In the UK registry, the average time between diagnosis of systemic sclerosis and PAH was 14 years, and the condition was in general found in late middle age (mean age 66 years).

Symptoms and clinical presentation are very similar to IPAH and occasionally patients can be identified as having an associated CTD by immunology screening tests. HRCT scanning is useful mainly as an exclusionary test for the presence or absence of significant fibrosis. The mortality was confirmed to be higher than that seen with IPAH (40% one-year mortality for those with advanced disease), and the predictors of outcome were the same as for IPAH (RAP, PAP and cardiac index).

Echocardiographic screening for the detection of PH has been suggested to be performed yearly in asymptomatic patients with the scleroderma spectrum of diseases[49] and only in presence of symptoms in other CTD. The rationale for screening asymptomatic patients is not clear as we do not have evidence that treatments are effective in this subset. In any case the early detection of any PAH-related symptom should prompt a complete and careful echocardiographic assessment at any time and in any patient with CTD.

As in other forms of PAH, right heart catheterisation is recommended in all cases of suspected PAH associated with CTD to confirm the diagnosis, determine severity, and rule out left sided heart disease.

Treatment — Treatment of patients with PAH associated with CTD appears more complex as compared to IPAH. Immunosuppressive therapy seems to be effective only in a minority of patients mainly suffering from conditions other than scleroderma.

The rate of acute vasoreactivity and of a long-term favourable response to CCB treatment is lower compared to IPAH. Also the risk-to-benefit ratio of oral anticoagulation is not well understood.

Continuous epoprostenol therapy has been shown to improve exercise capacity, symptoms and haemodynamics in a 3 months randomised trial of patients suffering from the scleroderma spectrum of the disease.[113] In this study, no improvement in survival was documented. Some retrospective analysis show that the effect of iv epoprostenol on survival of IPAH patients seems to be better as compared to scleroderma patients.[218,220]

Continuous subcutaneous administration of treprostinil was evaluated in a subset of 90 patients with PAH and CTD, including systemic lupus erythematosus, diffuse scleroderma, limited scleroderma and mixed CTD/overlap syndrome that were enrolled in the larger RCT on PAH.

After 12 weeks, an improvement on exercise capacity, symptoms of PAH, and haemodynamics was shown. Adverse events included infusion site pain and typical side effects related to prostaglandins.[221]

A randomised double-blind study of 12 weeks, including a subgroup of 47 patients with CTD, has shown that bosentan significantly improved exercise capacity as compared to placebo in this population. However, although a similar treatment effect was achieved in patients with IPAH and in those with PAH associated with scleroderma, bosentan improved the walking distance from baseline in IPAH patients (+46 m in the bosentan group versus −5 m in the placebo group) whereas it prevented walk distance deterioration of the scleroderma patients (+3 m in the bosentan group versus −40 m in the placebo group).[144]

In summary, in patients with PAH associated with CTD responses to treatments and long-term survival seem to be worse as compared to IPAH.

Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis

Incidence — Both PVOD and PCH are uncommon conditions, but they are increasingly recognised as causes of PAH.[222] Less than 200 cases of PVOD and PCH, combined, have been reported in the literature.

Pathogenesis — As discussed in the clinical classification and pathology sections (see above), PVOD and PCH are similar in some respects particularly in relation to the changes in the pulmonary parenchyma, i.e. pulmonary haemosiderosis, interstitial oedema and lymphatic dilatation, and to pulmonary arterial intimal fibrosis and medial hypertrophy.[6]

Of particular interest are reports of a familial occurrence in both PVOD and PCH,[223] as well as in PAH. Lastly, BMPR2 mutation, the gene associated with familial PAH and IPAH, has been documented in a patient with PVOD.[224] These findings suggest that PVOD, PCH and PAH may represent components of a spectrum of a single disease.

Clinical picture and investigations — Clinical presentation of these patients is often indistinguishable from that of patients with IPAH. However, physical examination can demonstrate findings suggestive of a diagnosis other than IPAH, such as digital clubbing and/or basilar rales on chest auscultation. Case series indicate that PVOD/PCH is associated with more severe hypoxaemia and reduction of single-breath DL_{CO}, while spirometry and lung volume measurements are generally within normal limits. The significant decrease in DL_{CO} that is often seen may be explained by chronic interstitial oedema secondary to pulmonary venous obstruction. Haemodynamic data are similar between PVOD/PCH and IPAH, although in some patients, the hypoxaemia is out of proportion to the degree of PAH and right heart dysfunction. Interestingly, PWP is often normal despite the postcapillary involvement. Indeed, the pathological changes usu-

ally occur in the venules, often without involvement of the larger veins. The static column of blood produced during the measurement of PWP is unaffected by the changes in the small pulmonary veins as long as a connection is maintained with the larger, unaffected pulmonary veins which is where the pressure will be measured in the occluded arterial segment.

Radiological data may be of great help in detecting PVOD/PCH.[62,225–227] The presence of Kerley B lines, pleural effusion and patchy irregularities on a standard chest roentgenogram may provide important clues that suggest the diagnosis. Thin-section CT of the chest has characteristic changes. The most commonly reported CT findings are a patchy centrilobular pattern of ground-glass opacities, thickened septal lines, pleural effusion, and mediastinal adenopathy. These abnormalities strongly correlate with the development of pulmonary oedema with iv infusion of epoprostenol: ground glass opacities (GGO) were significantly more frequent in PVOD/PCH than in IPAH ($p = 0.003$). In PVOD/PCH, GGO were abundant, with a random repartition. Morphologic feature of GGO was important. A centrilobular distribution (poorly defined centrilobular nodular opacities) was more frequent in PVOD/PCH ($p = 0.03$). Conversely, a panlobular distribution (geographic regions of lung attenuation with relatively well defined borders) was seen in the two groups and was not predictive. Subpleural septal lines ($p < 0.0001$), and adenopathy ($p < 0.0001$) were also significantly more frequent in PVOD/PCH than in IPAH. The association of these three findings was very specific for PVOD in cases of PH (specificity = 100%) with a 66% sensitivity. Therefore, on the initial pre-treatment chest CT, association of GGO (particularly with a centrilobular distribution), septal lines, and adenopathy are indicative of PVOD/PCH in patients displaying PAH. Caution must be taken before initiating vasodilator therapy in the presence of such radiological abnormalities.

Additional investigational methods with which to diagnose PVOD include bronchoscopy with broncho-alveolar lavage. Compared with IPAH, PVOD/PCH was characterised by significantly elevated broncho-alveolar lavage cell counts. However, the percentage of macrophages, lymphocytes and neutrophils was similar. As PVOD/PCH affects the postcapillary vasculature, it is generally associated with occult alveolar haemorrhage and haemosiderin-laden macrophages. In a recent series, the percentage of haemosiderin-laden macrophages was higher in PVOD than in IPAH ($54 \pm 37\%$ versus $3 \pm 6\%$, $p = 0.0006$). The Golde score was markedly elevated in PVOD (109 ± 97 versus 4 ± 10, $p = 0.0004$).[228] In conclusion, combined evidence of PAH, elevated numbers of haemosiderin-laden bronchoalveolar macrophages, and interstitial lung infiltrates is very suggestive of a diagnosis of PVOD/PCH.

Treatment — In the new clinical classification, PVOD and PVH are included in the category termed PAH associated with significant venous or capillary involvement. This subgroup probably requires similar management as other PAH subgroups. However, the prognosis seems worse, with a more rapid downhill course. In addition, vasodilators and especially epoprostenol have to be used with great caution because of the high risk of pulmonary oedema.[229,230] However, there are reports of sustained clinical improvement in individual patients treated with these medications. There are no data regarding the use of newer medical therapies such as endothelin receptor antagonists in the treatment of PVOD/PCH. Use of any medical therapy in these patients should be undertaken only at centres with extensive experience in the diagnosis and management of PAH, and patients must be apprised of the risks prior to treatment. Atrial septostomy may be considered but is limited by hypoxaemia, more common in PVOD/PCH than in other classes of PAH. The only curative therapy for PVOD/PCH is lung transplantation, and similar to IPAH there are no eports of recurrence of disease following transplantation.

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Appendix A. Abbreviations

Pulmonary arterial hypertension related to risk factors or associated conditions (APAH)
Bone morphogenetic protein receptor 2 (BMPR2)
Calcium channel blockers (CCB)
Cardiopulmonary exercise testing (CPET)
Computerised tomography (CT)
Chronic thromboembolic pulmonary hypertension (CTEPH)
Connective tissue disease (CTD)
Cyclic guanosine 3′-5′ monophosphate (cGMP)
Diffusion capacity for carbon monoxide (DL_{CO})
Endothelin-1 (ET-1),
European Agency for the Evaluation of Medicinal Products (EMEA)
Familial pulmonary artery hypertension (FPAH)
Food and Drug Administration (FDA)
Ground glass opacities (GGO)
High resolution computerised tomography (HRCT)
Human immunodeficiency virus (HIV)
Idiopathic pulmonary arterial hypertension (IPAH)
Interstitial lung disease (ILD)
Intravenous (iv)
New York Heart Association (NYHA)
Nitric oxide (NO)
Persistent pulmonary hypertension of the newborn (PPHN)
Phophodiesterase (PDE)
Primary pulmonary hypertension (PPH)
Pulmonary arterial hypertension (PAH)
Pulmonary hypertension (PH)
Pulmonary arterial pressure (PAP)

(*Continued on next page*)

Appendix A. Abbreviations (*Continued*)

Pulmonary artery systolic pressure (PASP)
Pulmonary capillary haemangiomatosis (PCH)
Pulmonary function tests (PFT)
Pulmonary vascular resistance (PVR)
Pulmonary veno-occlusive disease (PVOD)
Pulmonary wedge pressure (PWP)
Randomised controlled clinical trial (RCT)
Right atrial pressure (RAP)
Right heart catheterisation (RHC)
Right ventricular systolic pressure (RVSP)
Six-minute walk test (6MWT)
Transoesophageal echocardiography (TEE)
Transthoracic echocardiography (TTE)
Thromboxane A_2 (TxA_2)
Ventilation/perfusion (V/Q)
World Health Organisation (WHO)

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