The right heart and pulmonary circulation (VI)

Current Therapeutic Approaches to Pulmonary Arterial Hypertension

Nazzareno Galiè, Massimiliano Palazzini, Enri Leci, and Alessandra Manes

Institute of Cardiology, University of Bologna, Bologna, Italy

Pulmonary hypertension is a heterogeneous hemodynamic and pathophysiological state that is observed in a number of clinical conditions, which have been divided into six diagnostic groups. Although the increase in pulmonary pressure observed in these clinical groups may be similar, underlying disease mechanisms, diagnostic methods, and prognostic and therapeutic consequences are completely different.

Pulmonary arterial hypertension is associated with several rare conditions that have comparable clinical and hemodynamic characteristics and exhibit virtually identical anatomical and pathological alterations in the lung microcirculation. These conditions include idiopathic and familial forms of the disease and disease forms associated with connective tissue disease, congenital heart defects involving systemic-to-pulmonary arterial shunts, portal hypertension, and HIV infection. It has been shown that treatment with specific drugs (e.g. prostanoids, endothelin-receptor antagonists and phosphodiesterase type-5 inhibitors) is effective in these patients and that these drugs can also be administered in various combinations. An evidence-based treatment algorithm has been developed for these patients.

In patients with pulmonary hypertension due to left heart disease or lung disease, treatment focuses on the underlying condition and there is no convincing evidence that agents approved for pulmonary arterial hypertension are effective. For patients with chronic thromboembolic pulmonary hypertension, the treatment of choice is pulmonary endarterectomy. However, drugs intended specifically for the treatment of pulmonary arterial hypertension may be considered in inoperable cases or after suboptimal surgery.

Key words: *Pulmonary hypertension. Prostanoids. Endothelin-receptor antagonists. Phosphodiesterase inhibitors.*

Estrategias terapéuticas actuales en la hipertensión arterial pulmonar

La hipertensión pulmonar es un estado hemodinámico y fisiopatológico heterogéneo que puede observarse en múltiples situaciones clínicas, que se han clasificado en seis grupos diagnósticos. A pesar de que las elevaciones de la presión pulmonar pueden ser similares en los diferentes grupos clínicos, los mecanismos subyacentes, los enfoques diagnósticos y las repercusiones pronósticas y terapéuticas son completamente diferentes.

La hipertensión arterial pulmonar incluye trastornos infrecuentes que tienen en común un cuadro clínico y hemodinámico comparable y unas alteraciones anatomopatológicas prácticamente idénticas en la microcirculación pulmonar. Comprende formas idiopáticas y familiares, así como las formas asociadas a enfermedades del tejido conjuntivo, cardiopatías congénitas con cortocircuito sistémico-pulmonar, hipertensión portal e infección por el VIH. Se ha demostrado que determinados tratamientos farmacológicos específicos (prostanoides, antagonistas de los receptores de endotelina e inhibidores de la fosfodiesterasa tipo 5) son eficaces en este grupo y pueden administrarse también de manera combinada. Existe un algoritmo de tratamiento basado en la evidencia para estos pacientes.

En los pacientes con hipertensión pulmonar debida a una cardiopatía izquierda o enfermedades pulmonares, el tratamiento se centra en el trastorno subyacente, y no se ha demostrado de manera convincente que las medicaciones autorizadas para la hipertensión arterial pulmonar sean eficaces. En los pacientes con hipertensión pulmonar tromboembólica crónica, el tratamiento de elección es la endarterectomía pulmonar, y puede considerarse el uso de fármacos específicos para la hipertensión arterial pulmonar en los casos inoperables o tras una intervención quirúrgica subóptima.

Palabras clave: *Hipertensión pulmonar. Prostanoides. Antagonistas de la endotelina. Inhibidores de la fosfodiesterasa.*

INTRODUCTION

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC).[1]

Correspondence: Prof N. Galiè,
Institute of Cardiology. University of Bologna,
Via Massarenti 9. 40138-Bologna. Italy
E-mail: nazzareno.galie@unibo.it

TABLE 1. **Haemodynamic Definitions of Pulmonary Hypertension[a]**

Definition	Characteristics	Clinical Groups[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg, PWP ≤15 mmHg, CO normal or reduced[b]	Pulmonary arterial hypertension PH due to lung diseases Chronic thromboembolic PH PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg, PWP >15 mmHg, CO normal or reduced[b]	PH due to left heart disease
	Passive	TPG ≤12 mmHg
	Reactive (out of proportion)	TPG >12 mmHg

CO indicates cardiac output; PAP, pulmonary arterial pressure; PH, pulmonary hypertension; PWP, pulmonary wedge pressure; TPG, transpulmonary pressure gradient (mean PAP—mean PWP)
[a]All values measured at rest.
[b]According to Table 2.
[c]High cardiac output can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia, hyperthyroidism, etc.

PH is heterogeneous from the pathophysiological point of view and the diversity is also reflected in the hemodynamic classification (Table 1).[2]

The different hemodynamic forms of PH can be found in multiple clinical conditions which have been classified in 6 main groups and at least 26 subgroups (Table 2). Each main clinical group shows specific pathologic changes in the lung distal arteries, capillaries and small veins. If we combine the hemodynamic and clinical heterogeneity we understand the importance of an accurate diagnosis in the individual patient, which is crucial for the prognostic assessment and the treatment strategy. In addition, the concomitant presence of different hemodynamic and clinical mechanisms cannot be excluded in individual patients.

The presence of PH as defined above is always an ominous prognostic sign even if the severity may differ according to hemodynamic changes and the underlying clinical condition.

The therapeutic approach also is markedly different according to the clinical groups and the symptomatic and hemodynamic severity.

The classifications are described in an initial common paragraph while the treatment strategies of the four more frequent clinical groups are discussed individually.

DEFINITIONS AND CLASSIFICATIONS

Hemodynamic Classification

PH has been defined as an increase in mean PAP ≥25 mmHg at rest as assessed by RHC.[3,4] Recent re-evaluation of available data have shown that the normal mean PAP at rest is 14 (3) mmHg with an upper limit of normal of approximately 20 mmHg.[5,6] The significance of mean PAP between 21 and 24 mmHg is unclear. Patients presenting with PAP in this range need further evaluation in epidemiological studies. The definition of PH on exercise as a mean PAP >30 mmHg as assessed by RHC is not supported by published data; healthy individuals can reach much higher values.[5,7] Thus no viable definition for PH on exercise as assessed by RHC can be provided at the present time.

An additional very important haemodynamic parameter which characterizes the definitions of PH is pulmonary wedge pressure (PWP). In fact, according to various combinations of values of PWP, pulmonary vascular resistance (PVR) and cardiac output (CO), different hemodynamic types of PH are shown in Table 1. Pre-capillary PH (PH with normal PWP) is found in the clinical groups 1, 3, 4, and 5 while post-capillary PH (PH with elevated PWP) is found in the clinical group 2 (Table 2).[8] The distinction between pre-capillary and post-capillary PH is extremely important because the treatment strategy may differ markedly between the two hemodynamic conditions; therapies effective in the pre-capillary form may be detrimental in the post-capillary type and vice versa.

Clinical Classification

The more updated clinical classification of PH is presented in Table 2.[9] Clinical conditions with PH are classified into six groups according to similar pathological, pathophysiological and therapeutic characteristics: pulmonary arterial hypertension (PAH - group 1), pulmonary veno-occlusive disease (group 1'), PH due to left heart disease - group 2, PH due to lung diseases (group 3), chronic thromboembolic PH (CTEPH, group 4) and PH with unclear and/or multifactorial mechanisms (group 5). Despite possible comparable elevations

TABLE 2. **Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008[2])**

1 - Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic PAH
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH):
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

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

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

3 - Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 - Chronic thromboembolic pulmonary hypertension

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

ALK-1 indicates activin receptor-like kinase 1 gene; APAH, associated pulmonary arterial hypertension; BMPR2, bone morphogenetic protein receptor, type 2; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

of PAP and PVR in the different clinical groups, the underlying mechanisms, the diagnostic approaches and the prognostic and therapeutic implications are completely different. The features of each main clinical group are discussed in the specific sections, with particular attention to PAH - group 1, in which PH represents the leading pathophysiological feature.

It is important to avoid the typical confusion between PH and PAH. In fact, while PH is a *hemodynamic* condition (Table 1), PAH is a *clinical* condition characterised by the presence of precapillary PH (Table 1) in the absence of other causes of precapillary PH such as PH due to lung diseases, CTEPH or other rare diseases (Table 2). PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation (Table 2).

Comparative epidemiological data on the prevalence of the different groups of PH are not available. In a survey performed in an echocardiography laboratory,[10] the prevalence of PH (defined as a PA systolic pressure >40 mmHg) among 4,579 patients was 10.5%. Among the 483 cases with PH 78.7% had left heart disease (Group 2), 9.7% had lung diseases and hypoxaemia (Group 3), 4.2% had PAH (Group 1), 0.6% had CTEPH (Group 4) and in 6.8% it was not possible to define a diagnosis.

PULMONARY ARTERIAL HYPERTENSION

PAH (Table 2) represents the type of PH in which the most important advances in the understanding and treatment have been achieved in the past decade. It is also the group in which PH is the "core" of the clinical problems and may be treated by specific drug therapy.

Pathobiology and Pathophysiology

PAH comprises apparently heterogeneous conditions (Table 2) that share comparable clinical and hemodynamic pictures and virtually identical pathological changes of the lung microcirculation. Pathological lesions affect the distal pulmonary arteries (<500 μm) in particular. They are characterized by medial hypertrophy, intimal proliferative and fibrotic changes (concentric, eccentric), adventitial thickening with moderate peri-vascular inflammatory infiltrates, complex lesions (plexiform, dilated lesions) and thrombotic lesions. Pulmonary veins are classically unaffected. Additional pathological changes include dilatation of the proximal elastic pulmonary arteries and of the bronchial arteries (likely due to a compensatory mechanism intended to provide supplementary blood flow to hypoperfused lung parenchyma areas). The exact processes that initiate the pathological changes seen in PAH are still unknown, even if it is recognized that PAH has a multifactorial pathobiology that involves

various biochemical pathways and cell types. The increase in PVR is related to different mechanisms, including vasoconstriction, proliferative and obstructive remodeling of the pulmonary vessel wall, inflammation and thrombosis. The PVR increase leads to right ventricular (RV) overload, hypertrophy and dilatation and eventually to RV failure and death. The importance of the progression of RV failure on the outcome of idiopatic PAH (IPAH) patients is confirmed by the prognostic impact of right atrial pressure, cardiac index (CI) and PAP,[4] the 3 main parameters of RV pump function. The depression of myocardial contractility seems to be one of the primary events in the progression of heart failure in a chronically overloaded RV. Changes in the adrenergic pathways of RV myocytes leading to reduced contractility have been shown in IPAH patients.[11] Afterload mismatch remains the leading determinant of heart failure in patients with PAH and CTEPH because its removal, as follows successful pulmonary endarterectomy or lung transplantation,[12] leads almost invariably to sustained recovery of RV function. The hemodynamic changes and the prognosis of patients with PAH are related to the complex pathophysiological interactions between the rate of progression (or regression) of the obstructive changes in the pulmonary microcirculation and the response of the overloaded RV, which may also be influenced by genetic determinants.[13]

Initial Treatment Approach

The suggested initial approach after the diagnosis of PAH is the adoption of the general measures, initiation of supportive therapy and referral to an expert centre for vasoreactivity testing. General measures are recommendations on general activities of daily living including physical activity, birth control and pregnancy, travel, psychosocial support, infection prevention, and elective surgery. Supportive therapies include oral anticoagulants, diuretics, oxygen, digoxin, and other inotropic drugs. These treatments are recommended even if no formal randomised controlled trials (RCTs) have been performed in PAH. Supportive therapies are largely used in PAH patients, as demonstrated by the baseline treatment of PAH patients included in the RCTs testing the efficacy of modern targeted treatments.[14] Calcium channel blockers agents (CCBs) are included in this chapter because they represent the first class of drugs developed for the treatment of a minority of patients with PAH, those responders to the acute vasoreactivity test. In these cases, the clear favourable response of the long-term treatment with high doses of CCBs has discouraged the performance of RCTs for ethical reasons.

General Measures

Patients with PAH require sensible advice about general activities of daily living and need to adapt to the uncertainty associated with a serious chronic life-threatening disease. The diagnosis usually confers a degree of social isolation.[15] Encouraging patients and their family members to join patient support groups can have positive effects on coping, confidence and outlook.

Physical Activity and Supervised Rehabilitation

Patients should be encouraged to be active within symptom limits. Mild breathlessness is acceptable but patients should avoid exertion that leads to severe breathlessness, exertional dizziness, or chest pain. Patients should therefore avoid excessive physical activity that leads to distressing symptoms but when physically deconditioned may undertake supervised exercise rehabilitation.[16] There is growing evidence supporting loss of peripheral muscle mass in patients with advanced PAH and this may be corrected by a defined rehabilitation program.

Pregnancy and Birth Control

Pregnancy is associated with a 30%-50% mortality in patients with PAH[17] and as a consequence PAH is a contra-indication to pregnancy.[1] Barrier contraceptive methods are safe for the patient but with an unpredictable effect. Progesterone-only preparations such as medroxyprogesterone acetate and etonogestrel are effective approaches to contraception and avoid potential issues of estrogens such as those included in the mini-pill.[18] It should be remembered that the endothelin receptor antagonist (ERA) bosentan may reduce the efficacy of oral contraceptive agents. The Mirena coil is also effective.[18] A combination of 2 methods may also be utilized. The patient who becomes pregnant should be informed of the high risk of pregnancy and termination of pregnancy discussed. Those patients who choose to continue pregnancy should be treated with disease targeted therapies, planned elective delivery and effective close collaboration between obstetricians and the PAH team.[19,20]

Travel/Altitude

Air travels are considered to be of potential harm for patients with underlying pulmonary hypertension because of the generalized pulmonary vasoconstriction at O_2 concentration <21%.[21] The known physiological effects of hypoxia suggest that in-flight O_2 administration should be considered for patients in World Health Organization (WHO)

functional class III and IV and those with arterial blood O_2 pressure consistently less than 8 kPa (60 mmHg). Similarly, such patients should avoid going to altitudes above 1500 to 2000 metres without supplemental O_2. Patients should be advised to travel with written information about their PAH and be advised how to contact local PH clinics in close proximity to where they are travelling. Prolonged air travel is considered a risk factor for deep venous thrombosis and for PAH patients who are not treated with oral anticoagulants and have potential additional risk factors such as WHO functional class III and IV or obesity, preventive measures (low-molecular-weight heparin, leg exercises) on long-haul flights over 5000 km may be considered.

Psychosocial Support

Many PAH patients develop anxiety and depression leading to impairment in quality of life. Timely referral to a psychiatrist or psychologist should be made when appropriate. Patient support groups may also play an important role in this area and patients should be advised to join such groups.

Infection Prevention

Patients with PAH are susceptible to developing pneumonia, which is the cause of death in 7% of cases.[22] Whilst there are no controlled trials, it is recommended to vaccinate against influenza and pneumococcal pneumonia.

Elective Surgery

Elective surgery is expected to have an increased risk in patients with PAH. It is not clear as to which form of anaesthesia is preferable but epidural is probably better tolerated than general anaesthesia. Patients usually maintained on oral therapy may require temporary conversion to intravenous or nebulised treatment until they are able to both swallow and absorb drugs taken orally.

Hemoglobin Level

PAH patients are highly sensitive to reduction of hemoglobin levels. Any kind of anaemia even of milder degrees should be corrected. On the other hand, especially patients with long-standing hypoxemia like those with right-to-left shunts tend to develop erythrocytosis with elevated levels of hematocrit. In these circumstances, venesections are indicated only if hematocrit is above 65% and hyperviscosity symptoms are present.[23]

Concomitant medications

Currently 3 classes of drugs are approved in PAH (ERA, phosphodiesterase type-5 inhibitors, and prostanoids) and care is needed to avoid interactions between them and with any other drug.[1] Even if non-steroid anti-inflammatory drugs seem not to be associated to PAH in a case-control study,[24] 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 compounds (eg, antidepressants) are unknown but no clear relationships with PAH have yet been demonstrated. The efficacy of current treatments for chronic "biventricular" heart failure like ACE-inhibitors and beta-blockers has not been tested in patients with PAH. In addition, the use of these compounds may favour hypotension and progression of right heart failure in PAH patients due to vasodilatation and negative inotropic effects.

Supportive Treatments

Oral Anticoagulants

There is a high prevalence of vascular thrombotic lesions at post mortem in patients with IPAH.[25,26] Abnormalities in coagulation and fibrinolytic pathways have also been reported, and mural thrombi have been shown in central elastic pulmonary arteries of patients with IPAH[26] and Eisenmenger's syndrome patients.[23,27]

All the above factors together with the non-specific increased risk for venous thromboembolism, including heart failure and immobility, may represent the rationale for oral anticoagulation in PAH.

Evidence in favor of oral anticoagulation is confined to patients with IPAH, heritable PAH and PAH due to anorexigens; it is generally retrospective and based on single centre experience.[25,28,29] In recent clinical trials, oral anticoagulant treatment was present at inclusion in a fraction of patients ranging from 50% to 80%.[30] The potential benefits of oral anticoagulation should be weighed against the risks in patients with other forms of PAH, especially when there is an increased risk of bleeding such as PAH associated with Eisenmenger's syndrome and hemoptysis, connective tissue diseases and gastro-intestinal tract abnormalities (predisposing to bleeding), portal hypertension (severe oesophageal varices, coagulation abnormalities, low platelet count) and HIV infection (low platelet count, poor compliance). Generally, patients with PAH receiving therapy with long-term intravenous

prostaglandins are anticoagulated in the absence of contra-indications, due in part to the additional risk of catheter-associated thrombosis. Advice regarding the target international normalized ratio in patients with IPAH varies from 1.5 to 2.5 in most centres of North America to 2.0 to 3.0 in European centres.

Diuretics

Decompensated right heart failure leads to fluid retention, raised central venous pressure, hepatic congestion, peripheral oedema, and ascites (in advanced cases).[31] Clinical experience shows clear symptomatic benefit in fluid overloaded patients treated with this therapy. The appropriate diuretic dose is strictly individual and theoretically should be the lowest dose that maintains an optimal fluid balance and minimizes symptoms of congestion. Proper fluid balance can be facilitated by a controlled salt and water intake. Intravenous administration of diuretics is temporarily preferred in cases of fluid retention to overcome the reduced oral bioavailability. Loop diuretics are generally used and furosemide oral doses may vary from 20-25 mg/day up to 500 mg/day.[32] The addition of aldosterone antagonists should also be considered.

Oxygen

The oxygen content of arterial blood and oxygen delivery to tissues are generally not reduced unless the PaO_2 falls <60 mmHg.[33] Most patients with lung diseases are hypoxemic because of altered ventilation-perfusion matching.[34] In contrast, most patients with PAH (except those with associated congenital heart disease) present with only mild degrees of arterial hypoxemia at rest. No consistent data are currently available on the effect of long-term O_2 treatment in patients with PAH. Guidance may be empirically based on the guidelines of parenchymal lung diseases: when arterial blood O_2 pressure is consistently less than 8 kPa (60 mmHg) patients are advised to take O_2 to achieve arterial blood O_2 pressure >8 kPa.[35] Ambulatory O_2 may be considered in patients when there is evidence of symptomatic benefit and correctable desaturation on exercise. There is little rationale to treat with long-term oxygen therapy patients with hypoxaemia predominantly due to right-to-left shunt through a patent foramen ovale, atrial or ventricular septal defects or patent ductus arteriosus. In these cases a consistent increase of oxygen saturation and symptomatic improvement on oxygen therapy should be demonstrated.

Inotropic Drugs

The effects of adrenergic inotropic drugs on the failing right ventricle have received little attention by investigators. Data on humans are available mostly for the prevalent beta 2-adrenergic receptor agonist isoproterenol[36] that was administered to IPAH patients for its supposed effects of vasodilatation on pulmonary circulation.[37,38] Dobutamine[36] is a prevalent beta 1-adrenergic receptor agonist that exerts inotropic and vasodilator effects comparable to isoproterenol but has a less pronounced chronotropic activity. Dopamine[36] is a beta-, alpha- and dopaminergic-receptor agonist and its profile of action may present some advantages over the prevalent beta-receptor agonist drugs. In fact, the alpha-adrenergic activity helps to preserve the blood pressure levels and even to increase them. The absence of systemic hypotensive effects together with the renal blood flow increase suggest the use of dopamine alone or in combination with dobutamine as the inotropic strategy of choice in PAH patients.

Although digoxin has been shown to improve cardiac output acutely in IPAH, its efficacy is unknown when administered chronically.[39] It may be given to slow ventricular rate in patients with PAH who develop atrial tachyarrhythmias.

Acute Vasoreactivity Test and Long-Term Treatment With Calcium-Channel Blockers (CCBs)

A minority of patients with PAH (in particular idiopathic PAH) respond with a meaningful reduction of pulmonary artery pressure associated to a reduction of pulmonary vascular resistance on acute vasoreactivity tests. In these cases, a favourable effect of long-term treatment with high doses of CCBs, in particular with nifedipine and diltiazem, has been demonstrated.[28,40]

In PAH, vasoreactivity testing should be performed at the time of diagnostic right heart catheterization to identify patients who may benefit from long-term therapy with CCBs.[28,41] Acute vasodilator challenge should only be performed with short-acting, safe and easy to administer drugs with no or limited systemic effects. Currently the agent most used in acute testing is nitric oxide[41]; based on previous experience[28,42,43] intravenous epoprostenol or intravenous adenosine may also be used as an alternative (but with a risk of systemic vasodilator effects). Inhaled iloprost and oral sildenafil may be associated with significant vasodilator effects. Their role in the prediction of response to CCB therapy has not yet been demonstrated. Due to the risk of potentially life-threatening complications, the use of CCB

given orally or intravenously as an acute test is discouraged. A positive acute response is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged CO.[41] Only about 10% of patients with IPAH will meet these criteria. Positive acute responders are most likely to show a sustained response to long-term treatment with high doses of CCB and they are the only patients that can safely be treated with this type of therapy. About half of IPAH positive acute responders are also positive long-term responders to CCBs[41] and only in these cases is the continuation of CCB as a single treatment warranted. The usefulness of acute vasoreactivity tests and long-term treatment with CCBs in patients with other PAH types, such as heritable PAH, connective tissues diseases, and HIV infection is less clear than in IPAH. Acute vasoreactivity studies to identify patients with a long-term favourable response to CCB is not recommended in patients with pulmonary hypertension associated with left heart disease, lung diseases, CTEPH, and PH due to multiple mechanisms..

The CCBs that have been predominantly used in reported studies are nifedipine, diltiazem and amlodipine, with particular emphasis on the first 2.[28,41] The daily doses of these drugs that have shown efficacy in IPAH are relatively high, 120-240 mg for nifedipine, 240-720 mg for diltiazem, and up to 20 mg for amlodipine. It is advisable to start with a low dose, eg, 30 mg of slow release nifedipine twice a day or 60 mg of diltiazem 3 times a day or 2.5 mg of amlodipine once a day and increase cautiously and progressively to the maximum tolerated dose. Limiting factors for dose increase are usually systemic hypotension and lower limb peripheral oedema. Patients with IPAH who meet the criteria for a positive vasodilator response and are treated with CCB should be followed closely for both safety and efficacy with an initial reassessment after 3-4 months of therapy including RHC.

If the patient does not show an adequate response (defined as being in WHO functional class I or II and with a marked hemodynamic improvement), additional PAH therapy should be instituted. Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on CCBs because of potential severe side-effects (eg, hypotension, syncope, and RV failure).

Vasodilator responsiveness does not appear to predict a favourable long-term response to CCB therapy in patients with PAH in the setting of connective tissue diseases, and high dose CCB are often not well tolerated in such patients.[44]

No clear data support the use of CCBs in patients with Eisenmenger's syndrome and the empirical use of CCB is dangerous and should be avoided.

Specific Drug Therapies

Specific therapies include those targeting the pathobiological abnormalities of PAH such as prostanoids, ERA and phosphodyesterase type-5 inhibitors.

Prostanoids

Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilatation of all vascular beds studied. This compound is the most potent endogenous inhibitor of platelet aggregation and also appears to have both cytoprotective and antiproliferative activities.[45] Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites.[46]

Epoprostenol (synthetic prostacyclin) is available as a stable freeze-dried preparation that needs to be dissolved to allow intravenous infusion. Epoprostenol has a short half-life (3–5 min) and is stable at room temperature for only 8 h; this explains why it must be administered continuously by means of infusion pumps and permanent tunnellized catheters. The efficacy of continuous intravenous administration of epoprostenol has been tested in three unblinded RCTs in patients with IPAH[47,48] and in those with PAH associated with the scleroderma spectrum of diseases.[49] Epoprostenol improves symptoms, exercise capacity and hemodynamics in both clinical conditions, and is the only treatment shown to improve survival in IPAH in a randomized study. Long-term treatment with epoprostenol is initiated at a dose of 2–4 ng/kg/min, with doses increasing at a rate limited by adverse effects (flushing, headache, diarrhea, leg pain). Optimal dose varies between individual patients, ranging from 20 to 40 ng/kg/min.[50,51] Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis. 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.

Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature.

These characteristics allow administration of the compound by the intravenous as well as the subcutaneous route. The subcutaneous administration of treprostinil can be accomplished by micro-infusion pumps and small subcutaneous catheters. The effects of treprostinil in PAH were studied in the largest worldwide randomized controlled trial performed in this condition, and showed improvements in exercise capacity, hemodynamics and symptoms.[52] The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who could tolerate upper quartile doses (>13.8 ng/kg/min). Infusion site pain was the most common adverse 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. Among the 15% of patients who continued to receive subcutaneous treprostinil alone, survival appears to be improved.[53]

In another long-term, open-label study, sustained improvement in exercise capacity and symptoms with subcutaneous treprostinil was reported in patients with IPAH or CTEPH, with a mean follow-up of 26 months.[54] Treprostinil has been recently approved in the USA for intravenous use in patients with PAH: the effects appear to be comparable with those of epoprostenol but at a dose 2 to 3 times higher. It is more convenient for the patient because the reservoir can be changed every 48 hours as compared to 12 hours with epoprostenol. A phase III randomised controlled trial of inhaled treprostinil was recently completed and preliminary data show improvements in exercise capacity. Oral treprostinil is currently being evaluated in RCT and in PAH Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral and aerosol administration. Inhaled therapy for PAH is an attractive concept that has the theoretical advantage of being selective for the pulmonary circulation. Inhaled iloprost has been evaluated in one RCT in which daily repetitive iloprost inhalations (6 to 9 times, 2.5–5 μg/inhalation, median 30 μg daily) were compared with placebo inhalation in patients with PAH and CTEPH.[55] The study showed an increase in exercise capacity and improvement in symptoms, PVR and clinical events in enrolled patients. A second RCT on 60 patients already treated with bosentan increased in exercise capacity in the subjects randomized to the addition of inhaled iloprost, compared with placebo. Overall, inhaled iloprost was well tolerated. Continuous intravenous administration of iloprost appears to be as effective as epoprostenol in a small series of patients with PAH and CTEPH.[56]

Endothelin Receptor Antagonists

Activation of the endothelin (ET)-1 system has been demonstrated in both plasma and lung tissues of PAH patients.[57] Although it is not clear if the increases in ET-1 plasma levels are a cause or a consequence of PH,[58] studies on tissue ET system expression support a prominent role for ET-1 in the pathogenesis of PAH.[59]

Bosentan is an oral active dual ET_A and ET_B receptor antagonist and was the first molecule of this class of drugs to be synthesized. Bosentan has been evaluated in PAH in five RCTs that have shown improvement in exercise capacity, functional class, haemodynamics, echocardiographic and Doppler variables, and time to clinical worsening.[60-64] Two randomised controlled trials have enrolled exclusively patients with WHO/New York Heart Association (NYHA) functional class II[63] or patients with Eisenmenger Syndrome.[64] Long-term observational studies have demonstrated the durability of the effect of bosentan over time.[9] Increases in hepatic aminotransferases occurred in 10% of the subjects but were found to be dose dependent and reversible after dose reduction or discontinuation. For these reasons liver function tests should be performed at least monthly in patients receiving bosentan.

Sitaxsentan, a selective orally active ET_A receptor antagonist, has been assessed in 2 RCTs in patients with WHO/NYHA class II/III PAH.[65,66] Aetiology included IPAH and PAH associated with connective tissue diseases or congenital heart diseases. The studies demonstrated improvements in exercise capacity and hemodynamics. A one-year, open-label observational study demonstrated the durability of the effects of sitaxsentan over time.[67] Incidence of abnormal liver function tests, which reversed in all cases, was 3%-5% for the approved dose of 100 mg (monthly monitoring is required). Interaction with warfarin requires the reduction of the anticoagulant dose by about 80% to stabilize the international normalized ratio.

Ambrisentan, a non-sulfonamide, propanoic acid-class, ERA that is selective for the ET_A receptor, has been in evaluated in a pilot study[68] and in 2 large RCT that demonstrated efficacy on symptoms, exercise capacity, hemodynamics and time to clinical worsening.[69] The open-label continuation study has demonstrated the durability of the effects of ambrisentan for at least one year.[69] Ambrisentan has been approved for the treatment of WHO/NYHA functional class II patients. The current approved is 5 mg once daily (OD), which can be increased to 10 mg OD if the drug is tolerated with the initial dose. Incidence of abnormal liver function tests ranges from 0.8%

to 3%. However even in patients treated with ambrisentan, liver function tests are required at least monthly. Caution is suggested for the co-administration of ambrisentan with ketoconazole and cyclosporine.

Phosphodiesterase Type-5 Inhibitors

Sildenafil is an orally active, potent and selective inhibitor of phosphodiesterase type-5 that exerts its pharmacological effect by increasing the intracellular concentration of cGMP. A number of uncontrolled studies have reported favourable effects of sildenafil in IPAH, PAH associated to connective tissue diseases and to congenital heart diseases, and in CTEPH.[70-72] A pivotal RCT in 278 PAH patients treated with sildenafil 20, 40, or 80 mg 3 times daily (TID) has confirmed favourable results on exercise capacity, symptoms and hemodynamics.[73] Although the approved dose is 20 mg TID, the durability of effect up to one year has been demonstrated only with the dose of 80 mg TID. In clinical practice, up-titration beyond 20 mg TID. (mainly 40 to 80 mg TID) is frequently needed. Most side effects of sildenafil were mild to moderate and mainly related to vasodilation.

Tadalafil is an OD dosing, selective phosphodyesterase-5 (PDE-5) inhibitor, currently approved for the treatment of erectile dysfunction. A pivotal RCT on 406 PAH patients treated with tadalafil 5, 10, 20, or 40 mg OD has shown favourable results on exercise capacity, symptoms, hemodynamics and time to clinical worsening for the largest dose.[74] Side effects profile was similar to sildenafil.

Combination Therapy

Combination therapy is the simultaneous use of more than one PAH-targeted class of drugs, eg, ERA, PDE-5 inhibitors, prostanoids, and novel substances. Although long-term safety and efficacy have not yet been amply explored, numerous case series have suggested that various drug combinations appear to be safe and effective. Different randomised controlled studies have shown the efficacy of the combination of bosentan and epoprostenol,[62] of the addition of inhaled iloprost to patients on background therapy with bosentan,[75] of bosentan in patients on background therapy with sildenafil,[63] of sildenafil in patients on background treatment with epoprostenol,[76] of inhaled treprostinil in patients with background treatment with either bosentan or sildenafil and of tadalafil in patients on background treatment with bosentan.[74] Additional trials with novel compounds are on going. There are many open questions regarding combination therapy, including the optimal combination and timing. Candidates to combination therapy are patients whose status is defined as stable but unsatisfactory or unstable and deteriorating.[1] Given the complexities related to combination therapy, it is recommended that candidates be referred to expert centers.

Interventional Procedures

Balloon Atrial Septostomy

The role of balloon atrial septostomy in the treatment of patients with PAH is uncertain because its efficacy has been reported only in small series and case reports.[77] In addition to symptomatic and hemodynamic improvement, increased survival compared with historical control groups has been shown. 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 of 5%–15%. In expert centers this procedure is now performed in cases of failure of available medical treatments.

Lung transplantation

Lung and heart–lung transplantation in PAH has been assessed only in prospective uncontrolled series, since formal RCTs are considered unethical in the absence of alternative treatment options.[77] The 3-year and 5-year survival after lung and heart–lung transplantation is approximately 55% and 45%, respectively.[78] Both single and bilateral lung transplantation have been performed for IPAH and these operations have been combined with repair of cardiac defects in Eisenmenger's syndrome. Recipient survival rates have been similar after single and bilateral lung transplantation and after heart–lung transplantation for PAH. However, many transplant centres currently prefer to perform bilateral lung transplantation. Lung and heart–lung transplantation are indicated in PAH patients with advanced WHO/NYHA class III and class IV symptoms that are refractory to available medical treatments. The appropriate timing of listing for transplantation is complicated by the unpredictable waiting period and the donor organ shortage.

Clinical Response to Treatment

The treatment algorithm includes the concept of adequacy of response to initial treatment. *Adequate clinical response* is defined as the achievement of *a stable and satisfactory clinical status,* including absence of clinical signs of RV failure,[51] stable WHO functional class I or II without syncope, a 6-minute

walk distance >500 meters[51,79], a peak VO_2 >15 mL/min/kg,[80,81] normal or near-normal BNP/NT-proBNP plasma levels,[82,83] no pericardial effusion,[84] tricuspid annular plane systolic excursion >2 cm,[85] right atrial pressure <8 mmHg, and a CI >2.5 L/min/m^2.[4,50,51,79,86]

Inadequate clinical response to treatment for patients initially in WHO functional class II or III is considered a *clinical status defined as stable and not satisfactory*: some of the limits described above for a stable and satisfactory condition are not fulfilled, and the patient and treating physician consider the status, although stable, to be less than desirable.

Alternatively, a *clinical state defined as unstable and deteriorating* is also an *inadequate clinical response*: the patient is characterized by evidence of progression of RV failure symptoms and signs, worsening WHO functional class, ie, from II to III or III to IV, a 6-min walk distance <300 meters,[51,79] a peak VO_2 <12 mL/min/kg,[80] rising BNP/NT-proBNP plasma levels,[82,83] evidence of pericardial effusion,[84] tricuspid annular plane systolic excursion <1.5 cm,[85] right atrial pressure >15 mmHg and rising, and a CI that is <2 L/min/m^2 and falling.[4,50,51,79,86] Clinical warning signs include increasing oedema and/or the need to escalate diuretic therapy, new onset or increasing frequency/severity of angina (which can be a sign of deteriorating RV function), and the onset or increasing frequency of syncope which is often a grim prognostic sign and requires immediate attention as it heralds low output heart failure. Supraventricular arrhythmias may be seen in this condition and contribute to clinical deterioration.

Finally, *inadequate clinical response* for patients who were initially in WHO functional class IV is considered the absence of a rapid improvement to WHO functional class III or better.

Treatment Algorithm

The treatment algorithm for PAH patients (Figure) is not appropriate for patients in other clinical groups and in particular for patients in PH associated with left heart diseases or with parenchymal lung diseases.

General measures and supportive therapy need to be initiated after PAH diagnosis.

Due to the complexity of the additional evaluation and the treatment options available, it is strongly recommended that patients with PAH be referred to a specialized center.

Acute vasoreactivity testing should be performed and high-dose CCBs therapy performed as appropriate.

Non-responders to acute vasoreactivity testing who are in WHO/NYHA functional class II should be treated with an ERA or a PDE-5 inhibitor.

Non responders to acute vasoreactivity testing, or responders who remain in (or progress to) WHO functional class III should be considered candidates for treatment either an ERA, a PDE-5 inhibitor or a prostanoid. As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatments can be proposed. In this case, the choice of therapy depends on a variety of factors, including the approval status, route of administration, the side effect profile, patient's preferences and physician's experience. Some settings still use first-line intravenous epoprostenol in WHO functional class III patients, due to its demonstrated survival benefits.

Continuous intravenous epoprostenol may be considered as first-line therapy for WHO functional class IV PAH patients because of the demonstrated survival benefit in this subset. Intravenous and subcutaneous treprostinil have also been approved for the treatment of WHO functional class IV patients in the USA. Although no randomised controlled trials have been performed with the intravenous delivery of iloprost, this PGI2 analogue has been approved in New Zealand. Both ERA and PDE-5 inhibitors are considered as a second line for severely ill patients. In WHO functional class IV patients, initial combination therapy may be considered.

In case of inadequate clinical response, sequential combination therapy can be considered. Combination therapy may include a prostanoid plus an endothelin receptor antagonist, an endothelin receptor antagonist plus a PDE-5 inhibitor, a prostanoid plus a PDE-5 inhibitor. Appropriate protocols for timing and dosing to limit possible side effects of the combination have yet to be defined.

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

PULMONARY HYPERTENSION DUE TO LEFT HEART DISEASE

PH carries a poor prognosis for patients with chronic heart failure.[87] The mechanisms responsible for the increase in PAP are multiple and include the passive backward transmission of the elevated pressure (post-capillary passive PH, Table 1). In these cases the transpulmonary pressure gradient (TPG = mean PAP minus mean PWP) and PVR are within the normal range. In other circumstances the elevation of PAP is greater than that of PWP (increased TPG) and an

increase in PVR is also observed (postcapillary reactive or "out of proportion" PH, Table 1). The elevation of PVR is due to an increase in pulmonary arteries vasomotor tone and/or to fixed structural obstructive remodelling of the pulmonary artery resistance vessels[88]: the former component of reactive PH is reversible under acute pharmacological testing while the latter, characterized by medial hypertrophy and intimal proliferation of the pulmonary arteriole, does not respond to the acute challenge.[8]

Which factors lead to reactive (out of proportion) PH and why some patients develop the acutely reversible vasoconstrictive or fixed obstructive components or both is poorly understood. Pathophysiological mechanisms may include vasoconstrictive reflexes arising from stretch receptors localized in the left atrium and pulmonary veins, and endothelial dysfunction of pulmonary arteries that may favour vasoconstriction and proliferation of vessel wall cells. The prevalence of PH in patients with chronic heart failure increases with the progression of functional class impairment. Up to 60% of patients with severe left ventricular systolic dysfunction and up to 70% of patients with isolated left ventricular diastolic dysfunction may present with PH.[89] In left-sided valvular diseases, the prevalence of PH increases with the severity of the defect and of the symptoms. PH can be found in virtually all patients with severe symptomatic mitral valve disease and up to 65% of those with symptomatic aortic stenosis.[6,8,90] Currently, there is no specific therapy for PH due to left heart diseases. A number of drugs (including diuretics, nitrates, hydralazine, angiotensin converting enzyme inhibitors, beta-adrenoceptors blockers, nesiritide, and inotropic agents) or interventions (left ventricular assist device implantation, valvular surgery, resynchronization therapy and heart transplantation) may lower PAP more or less rapidly through a drop in left-sided filling pressures.[8] Therefore, management of PH due to left heart disease should be aimed at the optimal treatment of the underlying disease. No heart failure drugs are contra-indicated because of PH.[91]

Few studies have examined the role of drugs currently recommended in PAH. The use of inhaled nitric oxide has been shown to reduce PAP but also to increase PWP, increasing the likelihood of lung oedema.[92] RCTs evaluating the effects of chronic use of epoprostenol[93] and bosentan[94,95] in advanced heart failure have been terminated early due to an increased rate of events in the investigational drug treated group compared with conventional therapy. A small study recently suggested that sildenafil may improve exercise capacity and quality of life in patients with PH due to left heart disease.[96] The history of medical therapy for heart failure is full of examples where drugs had positive effects on surrogate endpoints but eventually turned out to be detrimental, such as the phosphodiesterase type-3 inhibitors. Thus, the use of PAH-specific drugs is not recommended until robust data from long-term studies are available, in particular in "out of proportion" PH associated with left heart disease.

PULMONARY HYPERTENSION DUE TO LUNG DISEASE

PH is a poor prognostic factor in either chronic obstructive pulmonary disease (COPD) or interstitial lung diseases. The pathobiological and pathophysiological mechanisms involved in this setting are multiple and include hypoxic vasoconstriction, mechanical stress of hyperinflated lungs, loss of capillaries, inflammation and toxic effects of cigarette smoke. There are also data supporting an endothelium-derived vasoconstrictor–vasodilator imbalance. Based on published series, the incidence of significant PH in COPD patients with at least one previous hospitalization for exacerbation of respiratory failure is 20%. In advanced COPD, PH is highly prevalent (>50%),[97,98] although generably of mild severity. In interstitial lung disease, the prevalence of PH is 32%-39%.[99] The combination of lung fibrosis with emphysema is associated with a higher prevalence of PH.[100] Currently there is no specific therapy for PH associated with COPD or interstitial lung diseases. Long-term O_2 administration has been shown to partially reduce the progression of PH in COPD. Nevertheless, with this treatment PAP rarely returns to normal values and the structural abnormalities of pulmonary vessels remain unaltered.[35] In interstitial lung diseases, the role of long-term O_2 therapy on PH progression is less clear. Treatment with conventional vasodilators is not recommended because they may impair gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction[101,102] and their lack of efficacy after long-term use.[103,104] Published experience with specific PAH drug therapy is scarce and consists of the assessment of acute effects[105,106] and uncontrolled studies in small series.[107-111]

The treatment of choice for patients with COPD or interstitial lung diseases and associated PH who are hypoxemic is long-term O_2 therapy. Patients with "out of proportion" PH due to lung diseases (characterized by dyspnoea insufficiently explained by lung mechanical disturbances and mean PAP ≥40-45 mmHg) should be referred to expert centres and enrolled in clinical trials targeting PAH specific

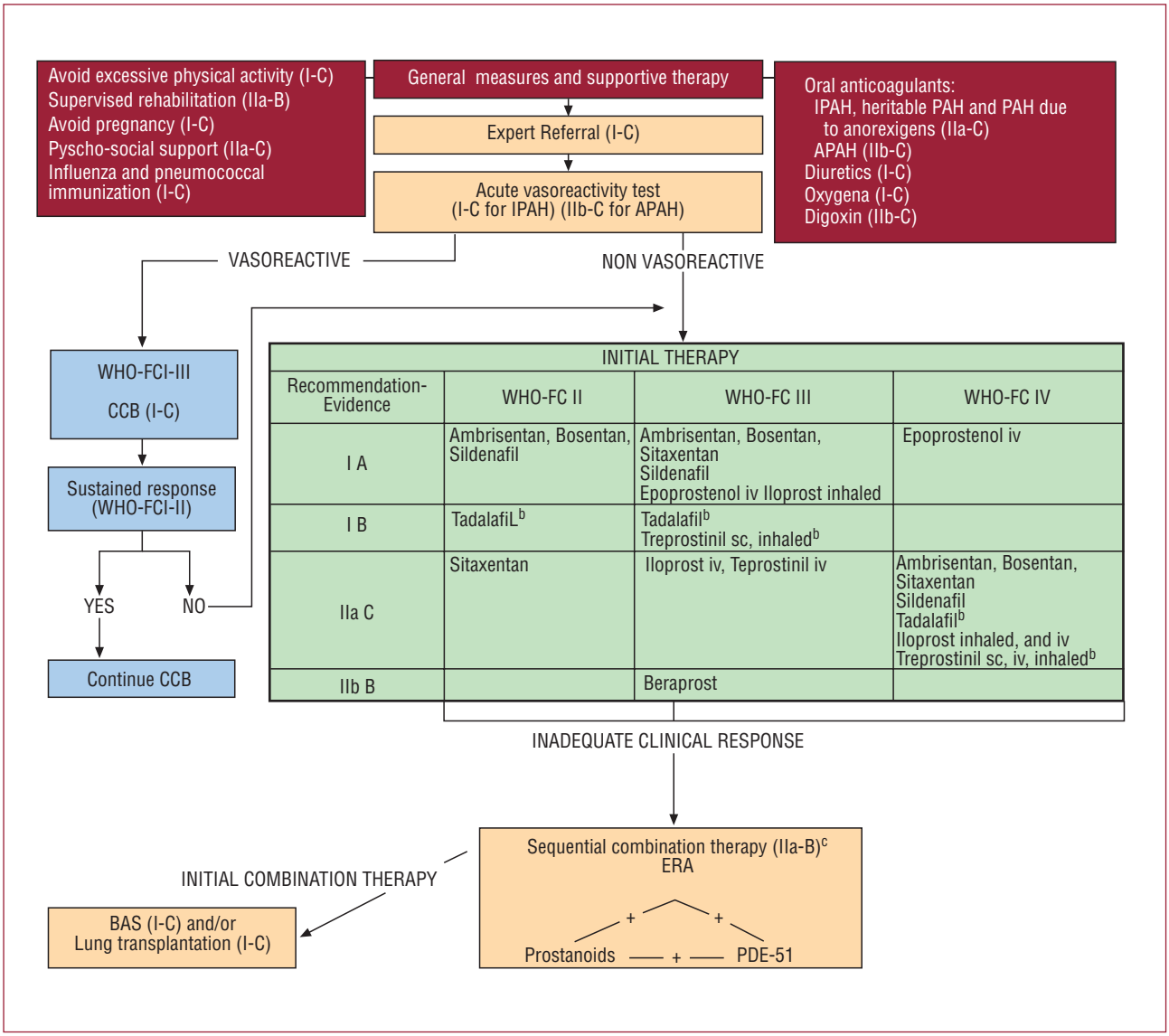

Figure 1. Evidence-based treatment algorithm for pulmonary arterial hypertension patients.
APAH indicates associated pulmonary arterial hypertension; BAS, balloon atrial septostomy; CCB, calcium channel blockers; ERA, endothelin receptor antagonists; FC, functional class; IPAH, idiopathic pulmonary arterial hypertension; PDE-5 I: phosphodyesterase-5 inhibitors; WHO/NYHA, World Health Organization/New York Heart Organization.
[a]To maintain O_2 at 92%.
[b]Under regulatory review.
[c]IIa-C for WHO-FC II.

drug therapy. The use of targeted PAH therapy in patients with COPD or interstitial lung diseases and mean PAP<40 mmHg is currently discouraged because there are no systematic data regarding its safety or efficacy.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Non-resolution of acute embolic masses which later undergo fibrosis leading to mechanical obstruction of pulmonary arteries is the most important pathobiological process in CTEPH. The obstructive lesions observed in the distal pulmonary arteries of non-obstructed areas (virtually identical to those observed in PAH) may be related to a variety of factors, such as shear stress, pressure, inflammation, and the release of cytokines and vasculotrophic mediators. Although more recent papers suggest that the prevalence of CTEPH is up to 3.8% in survivors of acute pulmonary embolism,[112] most experts

believe that the true incidence of CTEPH after acute pulmonary embolism is 0.5%-2%. CTEPH can be found in patients without any previous clinical episode of acute pulmonary embolism or deep venous thrombosis (up to 50% in different series).[113]

Patients with CTEPH should receive life long anticoagulation, usually with vitamin K antagonists adjusted to a target international normalized ratio between 2.0 and 3.0. Despite anticoagulation, CTEPH patients without additional treatments have a poor prognosis.

Therapeutic decisions concerning patients with CTEPH should be made at an expert centre based upon interdisciplinary discussion among internists, radiologists and expert surgeons. Pulmonary endarterectomy is the treatment of choice for patients with CTEPH, as it is a potentially curative option. As a rule, a patient should not be considered inoperable until the case has been reviewed by an experienced surgeon.

The general medical intensive treatment of advanced WHO functional class III or class IV CTEPH patients does not differ substantially from treatment of PAH. An urgent pulmonary endarterectomy should be planned as soon as reasonable hemodynamic conditions have been restored.

Specific PAH drug therapy may play a role in selected CTEPH patients, mainly for three different scenarios: *a)* patients are not considered candidates for surgery; *b)* preoperative treatment is deemed appropriate to improve hemodynamics; and *c)* patients present with symptomatic residual/recurrent PH after pulmonary endarterectomy surgery.

REFERENCES

1. Galiè N, Hoeper M, Humbert M, Torbicki A, Vachiery JL, Barberà JA, et al. Guidelines on diagnosis and treatment of pulmonary hypertension: The Task Force on Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and of the European Respiratory Society. Eur Heart J. 2009;30:2493-537.
2. Simonneau G, Robbins I, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54:S43-54.
3. Hatano S, Strasser T. World Health Organization 1975 Primary pulmonary hypertension. Geneva: WHO; 1975.
4. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115:343-9.
5. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects A systematic review. Eur Respir J. 2009; 34:888-94
6. Badesch BD, Champion HC, Gómez-Sánchez MA, Hoeper M, Loyd J, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54:S55-S56.
7. Naeije R, Melot C, Niset G, Delcroix M, Wagner PD. Mechanisms of improved arterial oxygenation after peripheral chemoreceptor stimulation during hypoxic exercise. J Appl Physiol. 1993;74:1666-71.
8. Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. Clin Chest Med. 2007;28:233-41.
9. Procedings of the 4th World Symposium on Pulmonary Hypertension. J Am Coll Cardiol. 2009;544:1s-103s.
10. Gabbay E, Yeow W, Playford D. Pulmonary arterial hypertension (PAH) is an uncommon cause of pulmonary Hhypertension (PH) in an unselected population: The Armadale echocardiography study. Am J Resp Crit Care Med. 2007;175:A713.
11. Bristow MR, Minobe W, Rasmussen R, Larrabee P, Skerl L, Klein JW, et al. Beta-adrenergic neuroeffector abnormalities in the failing human heart are produced by local rather than systemic mechanisms. J Clin Invest. 1992;89:803-15.
12. Keogh A, Benza RL, Corris P, Dartevelle P, Frost A, Kim NH, et al. Interventional and surgical modalities of treatment in pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54:S67-S77.
13. Abraham WT, Raynolds MV, Gottschall B, Badesch DB, Wynne KM, Groves BM, et al. Importance of angiotensin-converting enzyme in pulmonary hypertension. Cardiology. 1995;10 Supp l1:9-15.
14. Galiè N, Manes A, Negro L, Palazzini M, Bacchi Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J. 2009;30:394-403.
15. Loewe B, Graefe K, Ufer C, Kroenke K, Grünig E, Herzog W, et al. Ansiety and depression in patients with pulmonary hypertension. Psycosom Med. 2004;66:831-6.
16. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation. 2006;114: 1482-9.
17. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J. 2009;30:256-65.
18. Thorne S, Nelson-Piercy C, MacGregor AJ, Gibbs S, Crowhurst J, Panay, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. J Fam Plann Reprod Health Care. 2006;32:75-81.
19. Bendayan D, Hod M, Oron G, Sagie A, Eidelman L, Shitrit D, et al. Pregnancy outcome in patients with pulmonary arterial hypertension receiving prostacuclin therapy. Obstet Gynecol. 2005;106:1206-10.
20. Bonnin M, Mercier FJ, Sitbon O, Roger-Christoph S, Jaïs X, Humbert M, et al. Severe pulmonary hypertension during pregnancy: mode of delivery and anesthetic management of 15 consecutive cases. Anestesiology. 2005;102:1133-7.
21. Mohr LCM. Hypoxia during air travel in adults with pulmonary disease. Am J MedSci. 2008;335:71-9.
22. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987;107: 216-23.
23. Galiè N, Manes A, Palazzini M, Negro L, Marinelli A, Gambetti S, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Drugs. 2008;68:1049-66.
24. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996;335:609-16.
25. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation. 1984 ;70: 580-7.
26. Moser KM, Fedullo PF, Finkbeiner WE, Golden J. Do patients with primary pulmonary hypertension develop extensive central thrombi? Circulation. 1995;91:741-5.
27. Beghetti M, Galiè N. Eisenmenger syndrome: a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;53:733-40.
28. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med. 1992;327:76-81.
29. Frank H, Mlczoch J, Huber K, Schuster E, Gurtner HP, Kneussl M. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest. 1997;112:714-21.
30. Rich S, editor. Primary pulmonary hypertension: executive summary from the World Symposium-Primary Pulmonary Hypertension 1998. World Health Organization. Available from: http://web.archive.org/web/20020408173726/http://www.who.int/ncd/cvd/pph.html. Last accessed: March 30th 2010.
31. Cohn JN. Optimal diuretic therapy for heart failure. Am J Med. 2001;111:577.
32. Murray MD, Deer MM, Ferguson JA, Dexter PR, Bennett SJ, Perkins SM, et al. Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. Am J Med. 2001;111:513-20.
33. Hales CA. The site and mechanisms of oxygen sensing for the pulmonary vessels. Circulation. 1985;88:235s-240s.
34. West JB. Ventilation/perfusion relationships. Am Rev Respir Dis. 1977;116:919-43.
35. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1985;131:493-8.
36. Leier CV. Acute inotropic support. In: Leier CV, ed. Cardiotonic Drugs. New York: Marcel Dekker; 1986. p. 49-84.
37. Shettigar UR, Hultgren HN, Specter M, Martin R, Davies DH. Primary pulmonary hypertension favorable effect of isoproterenol. N Engl J Med. 1976;295:1414-5.
38. Pietro DA, LaBresh KA, Shulman RM, Folland ED, Parisi AF, Sasahara AA. Sustained improvement in primary

pulmonary hypertension during six years of treatment with sublingual isoproterenol. N Engl J Med. 1984;310:1032-4.
39. Rich S, Seidlitz M, Dodin E, Osimani D, Judd D, Genthner D, et al. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest. 1998;114:787-92.
40. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99:1197-208.
41. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111:3105-11.
42. Galiè N, Ussia G, Passarelli P, Parlangeli R, Branzi A, Magnani B. Role of pharmacologic tests in the treatment of primary pulmonary hypertension. Am J Cardiol. 1995;75:55A-62A.
43. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med. 1998;338:273-7.
44. Mukerjee D, St George D, Coleiro B, Knight C, Denton CP, Davar J, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis. 2003;62:1088-93.
45. Jones DA, Benjamin CW, Linseman DA. Activation of thromboxane and prostacyclin receptors elicits opposing effects on vascular smooth muscle cell growth and mitogen-activated protein kinase signaling cascades. Mol Pharmacol. 1995;48:890-6.
46. Galie N, Manes A, Branzi A. Prostanoids for pulmonary arterial hypertension. Am J Respir Med. 2003;2:123-37.
47. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med. 1990;112:485-91.
48. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996;334: 296-302.
49. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med. 2000;132:425-34.
50. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002;106:1477-82.
51. Sitbon O, Humbert M, Nunes H, Parent F, García G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002;40:780-8.
52. Simonneau G, Barst RJ, Galiè N, Naeije R, Rich S, Bourge RC, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165:800-4.
53. Barst RJ, Galiè N, Naeije R, Simonneau G, Jeffs R, Arneson C, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;28:1195-203.
54. Lang I, Gómez-Sánchez M, Kneussl M, Naeije R, Escribano P, Skoro-Sajer N, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest. 2006;129:1636-43.
55. Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, et al. Inhaled iloprost in severe pulmonary hypertension. N Engl J Med. 2002;347:322-9.
56. Higenbottam T, Butt AY, McMahon A, Westerbeck R, Sharples L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. Heart. 1998;80:151-5.
57. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med. 1993;328:1732-9.
58. Stewart DJ, Levy RD, Cernacek P, Langleben D. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med. 1991;114:464-9.
59. Galiè N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. Cardiovasc Res. 2004;61:227-37.
60. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet. 2001;358:1119-23.
61. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346:896-903.
62. Humbert M, Barst RJ, Robbins IM, Channick RN, Galiè N, Boonstra A, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. Eur Respir J. 2004;24:353-9.
63. Galiè.N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer GMB, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet. 2008;371:2093-100.
64. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114:48-54.
65. Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004;169:441-7.
66. Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol. 2006;47:2049-56.
67. Benza RL, Barst RJ, Galiè N, Frost A, Girgis RE, Highland KB, et al. Sitaxsentan for the treatment of pulmonary arterial hypertension: a one year, prospective, open label, observation of outcome and survival. Chest. 2008;134:775-82.
68. Galiè N, Badesch BD, Oudiz R, Simonneau G, McGoon M, Keogh A, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46:529-35.
69. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, et al. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008;117:3010-9.
70. Bhatia S, Frantz RP, Severson CJ, Durst LA, McGoon MD. Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy. Mayo Clin Proc. 2003;78: 1207-13.
71. Michelakis ED, Tymchak W, Noga M, Webster L, Wu XC, Lien D, et al. Long-term treatment with oral sildenafil Is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. Circulation. 2003;108:2066-9.
72. Ghofrani HA, Schermuly RT, Rose F, Wiedemann R, Kohstall MG, Kreckel A, et al. Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2003;167:1139-41.

73. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. New Engl J Med. 2005;353:2148-57.
74. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, et al. Tadalafil Therapy for Pulmonary Arterial Hypertension. Circulation. 2009;119:2894-903.
75. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2006;174: 1257-63.
76. Simonneau G, Rubin L, Galiè N, Barst RJ, Fleming T, Frost A, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension. Ann Intern Med. 2008;149:521-30.
77. Klepetko W, Mayer E, Sandoval J, Trulock EP, Vachiery JL, Dartevelle P, et al. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43 Suppl 1:S73-S80.
78. Hertz MI, Taylor DO, Trulock EP, Boucek MM, Mohacsi PJ, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: Nineteenth Official Report 2002. J Heart Lung Transplant. 2002;21:950-70.
79. Sitbon O, McLaughlin VV, Badesch DB, Barst RJ, Black C, Galiè N, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax. 2005;60: 1025-30.
80. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation. 2002;106:319-24.
81. Sun XG, Hansen JE, Oudiz R, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104:429-35.
82. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation. 2000;102:865-70.
83. Fijalkowska A, Kurzyna M, Torbicki A, Szewczyk G, Florczyk M, Pruszczyk P, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest. 2006;129:1313-21.
84. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol. 2002;39:1214-9.
85. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med. 2006;174:1034-41.
86. McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galiè N, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J. 2005;25: 244-9.
87. Grigioni F, Potena L, Galiè N, Fallani F, Bigliardi M, Coccolo F, et al. Prognostic implications of serial assessments of pulmonary hypertension in severe chronic heart failure. J Heart Lung Transplant. 2006;25:1241-6.
88. Delgado JF, Conde E, Sánchez V, López-Ríos F, Gómez-Sánchez MA, Escribano P, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail. 2005;7:1011-6.
89. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol. 2001;37:183-8.
90. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007;28:230-68.
91. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J.2008;29:2388-442.
92. Loh E, Stamler JS, Hare JM, Loscalzo J, Colucci WS. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. Circulation.1994;90:2780-5.
93. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J.1997;134:44-54.
94. Packer M, McMurray J, Massie BM, Caspi A, Charlon V, Cohen-Solal A, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail.2005;11: 12-20.
95. Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? Int J Cardiol.2002;85:195-7.
96. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007;116:1555-62.
97. Thabut G, Dauriat G, Stern JB, Logeart D, Levy A, Marrash-Chahla R, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest. 2005;127:1531-6.
98. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172:189-94.
99. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;129:746-52.
100. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26:586-93.
101. Agustí AG, Barberà JA, Roca J, Wagner PD, Guitart R, Rodríguez-Roisin R. Hypoxic pulmonary vasoconstriction and gas exchange during exercise in chronic obstructive pulmonary disease. Chest. 1990;97:268-75.
102. Barberà JA, Roger N, Roca J, Rovira I, Higenbottam TW, Rodríguez-Roisin R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. Lancet. 1996;347:436-40.
103. Morrell NW, Higham MA, Phillips PG, Shakur BH, Robinson PJ, Beddoes RJ. Pilot study of losartan for pulmonary hypertension in chronic obstructive pulmonary disease. Respir Res. 2005;6:88-95.
104. Saadjian AY, Philip-Joet FF, Vestri R, Arnaud AG. Long-term treatment of chronic obstructive lung disease by Nifedipine: an 18-month haemodynamic study. Eur Respir J. 1988;1:716-20.

105. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet. 2002;360:895-900.
106. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med. 1999;160:600-7.
107. Alp S, Skrygan M, Schmidt WE, Bastian A. Sildenafil improves hemodynamic parameters in COPD--an investigation of six patients. Pulm Pharmacol Ther. 2006;19:386-90.
108. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest. 2007;131:897-9.
109. Gunther A, Enke B, Markart P, Hammerl P, Morr H, Behr J, et al. Safety and tolerability of bosentan in idiopathic pulmonary fibrosis: an open label study. Eur Respir J. 2007;29:713-9.
110. Madden BP, Allenby M, Loke TK, Sheth A. A potential role for sildenafil in the management of pulmonary hypertension in patients with parenchymal lung disease. Vascul Pharmacol. 2006;44:372-6.
111. Rietema H, Holverda S, Bogaard HJ, Marcus JT, Smit HJ, Westerhof N, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. Eur Respir J. 2008;31:759-64.
112. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257-64.
113. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation. 2006;113:2011-20.