EXPERT CONSENSUS DOCUMENT

ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension

A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association

Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association

Writing Committee Members

Vallerie V. McLaughlin, MD, FACC, FAHA, FCCP, *Chair**

Stephen L. Archer, MD, FACC, FAHA†
David B. Badesch, MD, FCCP‡
Robyn J. Barst, MD, FACC, FAHA, FCCP†
Harrison W. Farber, MD, FAHA, FCCP†
Jonathan R. Lindner, MD, FACC
Michael A. Mathier, MD, FACC*
Michael D. McGoon, MD, FACC, FCCP§

Myung H. Park, MD, FACC*
Robert S. Rosenson, MD, FACC, FAHA*
Lewis J. Rubin, MD, FAHA, FCCP‖
Victor F. Tapson, MD*
John Varga, MD, FACR¶

*American College of Cardiology Foundation Representative, †American Heart Association Representative, ‡American Thoracic Society Representative, §Pulmonary Hypertension Association Representative, ‖American College of Chest Physicians Representative, ¶American College of Rheumatology Representative

ACCF Task Force Members

Robert A. Harrington, MD, FACC, FAHA, *Chair*

Jeffrey L. Anderson, MD, FACC, FAHA#
Eric R. Bates, MD, FACC
Charles R. Bridges, MD, MPH, FACC, FAHA
Mark J. Eisenberg, MD, MPH, FACC, FAHA
Victor A. Ferrari, MD, FACC, FAHA
Cindy L. Grines, MD, FACC#
Mark A. Hlatky, MD, FACC, FAHA
Alice K. Jacobs, MD, FACC, FAHA
Sanjay Kaul, MD, MBBS, FACC, FAHA

Robert C. Lichtenberg, MD, FACC#
Jonathan R. Lindner, MD, FACC#
David J. Moliterno, MD, FACC
Debabrata Mukherjee, MD, FACC
Gerald M. Pohost, MD, FACC, FAHA#
Robert S. Rosenson, MD, FACC, FAHA
Richard S. Schofield, MD, FACC, FAHA#
Samuel J. Shubrooks, Jr, MD, FACC, FAHA#
James H. Stein, MD, FACC, FAHA
Cynthia M. Tracy, MD, FACC, FAHA#
Howard H. Weitz, MD, FACC
Deborah J. Wesley, RN, BSN, CCA

#Former Task Force member during the writing effort

TABLE OF CONTENTS

Preamble

This document has been developed by the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents (ECDs), and was cosponsored by the American Heart Association (AHA). Expert Consensus Documents are intended to inform practitioners and other interested parties of the opinion of the ACCF and cosponsors concerning evolving areas of clinical practice and/or technologies that are widely available or new to the practice community. Topics chosen for coverage by expert consensus documents are so designed because the evidence base, the experience with technology, and/or the clinical practice are not considered sufficiently well developed to be evaluated by the formal ACCF/AHA practice guidelines process. Often the topic is the subject of ongoing investigation. Thus, the reader should view the ECD as the best attempt of the ACCF and the cosponsors to inform and guide clinical practice in areas where rigorous evidence may not be available or the evidence to date is not widely accepted. When feasible, ECDs include indications or contraindications. Some topics covered by ECDs will be addressed subsequently by the ACCF/AHA Practice Guidelines Committee.

Because the development of expert consensus documents depends on the knowledge and experience of experts and investigators in the field, many of whom have relationships with industry (RWI), the policy addressing writing committee members' RWI must be realistic, workable, and implemented in a way that protects the integrity of the process while allowing an open and honest exchange of the most up-to-date information. Every possible effort is made to formulate a writing committee with a reasonable balance of RWI. Specifically, all members of the writing panel are asked to provide disclosure statements of all relationships that might be perceived as real or potential conflicts of interest. Participation in the writing committee is dependent on a review of all relevant RWI by the task force to ensure balance so that fair and unbiased consensus can be reached. In addition, statements of RWI are reported orally and in writing to all members of the writing panel at every meeting and conference call and are updated as changes occur.

In the case of pulmonary hypertension, because of the relatively small number of experts engaged in clinical care and research in this area, identifying experts without RWI in this disease area was a challenge. To mitigate this concern and reduce the risk of bias, extensive peer review was completed in addition to review and approval by the AHA's Scientific Advisory Coordinating Committee (SACC) and the ACCF's Board of Trustees. SACC members only participate in the review and approval process if they have no relevant RWI themselves. To provide complete transparency, the RWI information for writing committee members and peer reviewers are published in the appendixes of the document.

Robert A. Harrington, MD, FACC
Chair, ACCF Task Force on
Expert Consensus Documents

1. Executive Summary

Pulmonary hypertension (PH) is a complex, multidisciplinary disorder. Recent advances have led to increased recognition and new therapies. While some data exist to form treatment guidelines, other areas have been inadequately explored.

1.1. Pathology and Pathogenesis

Pulmonary arterial hypertension (PAH) is a syndrome resulting from restricted flow through the pulmonary arterial circulation resulting in increased pulmonary vascular resistance and ultimately in right heart failure. Multiple pathogenic pathways have been implicated in the development of PAH, including those at the molecular and genetic levels and in the smooth muscle and endothelial cells and adventitia. The imbalance in the vasoconstrictor/vasodilator milieu has served as the basis for current medical therapies, although increasingly it is recognized that PAH also involves an imbalance of proliferation and apoptosis (favoring the former).

1.2. Classification and Epidemiology

While previously considered a rare disease, the most recent evidence from a French registry suggests that the prevalence of PAH is about 15 per million (1). Idiopathic pulmonary arterial hypertension (IPAH) is more prevalent in women and was the most common type of PAH in the French registry. Familial PAH often results from a mutation in the bone morphogenic protein receptor-2 (BMPR2) and is inherited as an autosomal dominant disease with incomplete penetrance and genetic anticipation. PAH is also associated with congenital heart disease (CHD), connective tissue diseases, drugs and toxins, human immunodeficiency virus (HIV), portal hypertension, hemoglobinopathies, and myeloproliferative disorders. Primary PH formerly encompassed idiopathic, familial, and anorexigen induced PAH. These groups together comprise World Health Organization (WHO) Group I PAH. Other WHO categories

Table 1. Revised WHO Classification of PH

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
       1.3.1. Connective tissue disorder
       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 hemorrhagic telangiectasia, hemoglobinopathies, chronic 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 hemangiomatosis (PCH)
   1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   2.1. Left-sided atrial or ventricular heart disease
   2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   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 (CTEPH)
   4.1. Thromboembolic obstruction of proximal pulmonary arteries
   4.2. Thromboembolic obstruction of distal pulmonary arteries
   4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Reprinted from Simonneau et al. (32).

include Group II, PH with left heart disease, Group III, PH associated with lung diseases and/or hypoxemia, Group IV, PH due to chronic thrombotic and/or embolic disease, and Group V, miscellaneous causes of PH (Table 1).

1.3. Natural History and Survival

The prognosis of PAH is poor, with an approximately 15% mortality within 1 year on modern therapy (2). Predictors of a poor prognosis include: advanced functional class, poor exercise capacity as measured by 6-minute walk (6MW) test or cardiopulmonary exercise test, high right atrial (RA) pressure, significant right ventricular (RV) dysfunction, evidence of RV failure, low cardiac index, elevated brain natriuretic peptide (BNP), and underlying diagnosis of scleroderma spectrum of diseases.

1.4. Screening and Diagnostic Assessment

Patients at sufficient risk for the development of PAH to warrant periodic screening include those with a known BMPR2 mutation, scleroderma spectrum of diseases, and portal hypertension who are undergoing evaluation for liver transplantation. The most appropriate study to obtain in patients suspected of having PH based on history, physical examination, chest x-ray (CXR), and electrocardiogram

(ECG) is an echocardiogram. Evaluation for other potential etiologies, such as thromboembolic disease, is appropriate in all patients suspected of having PAH. The diagnosis of PAH requires confirmation with a complete right heart catheterization (RHC). The current hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units (3). Acute vasodilator testing, which involves the administration of pharmacologic agents to test the presence of pulmonary vasoreactivity, has prognositic value and should be performed in all IPAH patients who might be considered potential candidates for long-term calcium-channel blocker therapy. Those with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing. The definition of an acute responder is a reduction in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output. Vasodilator testing should be performed by centers with experience in the administration of these agents and the interpretation of the results.

1.5. Evidenced-Based Treatment Algorithm

Goals of treatment include improvement in the patient's symptoms, quality of life, and survival. Objective assessments to measure treatment response include improvement in exercise capacity (6MW test, cardiopulmonary exercise test, treadmill test), hemodynamics, and survival. General measures that should be addressed include diet, exercise, appropriate vaccinations, and avoidance of pregnancy. Warfarin anticoagulation is recommended in all patients with IPAH based on 1 prospective and 2 retrospective observational, uncontrolled trials. Diuretics are used for symptomatic management of RV volume overload. Oxygen is recommended to maintain oxygen saturation greater than 90%. Calcium channel blockers are indicated only for patients who have a positive acute vasodilator response as described in the preceding text. Patients treated with calcium channel blockers should be followed closely for both the safety and the efficacy of this therapy. Continuous intravenous epoprostenol improves exercise capacity, hemodynamics, and survival in IPAH and is the preferred treatment option for the most critically ill patients. Although expensive and cumbersome to administer, epoprostenol is the only therapy for PAH that has been shown to prolong survival. Treprostinil, a prostanoid, may be delivered via either continuous intravenous or subcutaneous infusion. Iloprost is a prostanoid delivered by an adaptive aerosolized device 6 times daily. The delivery system and side effects of the prostanoids should be carefully considered when assessing patients for prostanoid therapy. The endothelin receptor antagonists are oral therapies that improve exercise capacity in PAH. Liver function tests must be monitored indefinitely on a monthly basis. Phosphodiesterase (PDE)-5 inhibitors also improve

exercise capacity and hemodynamics in PAH. In general, patients with poor prognostic indexes should be initiated on parenteral therapy, while patients with class II or early III symptoms commonly commence therapy with either endothelin receptor antagonists or PDE-5 inhibitors. Given the multiple mechanisms of action, there is scientific rationale for the use of combination therapy for PAH, which is an area of active investigation. Initial results are encouraging and more combination therapy trials are underway. Lung transplantation is an option for selected patients who progress despite optimal medical management.

1.6. Reassessing Patients Over Time: How to Follow Patients on Treatment

Due to the complex nature of the disease and its treatments, PAH patients must be closely followed. In general, office visits should be more frequent for patients with advanced symptoms, right heart failure, and advanced hemodynamics and those on parenteral or combination therapy. Such patients generally should be seen every 3 months (or more frequently). Less ill patients on oral therapy generally should be seen every 3 to 6 months. Most experts obtain an assessment of functional class and exercise capacity, such as a 6MW or graded treadmill test, with each office visit. Nurse clinicians experienced in the care of PAH patients should be an integral part of chronic outpatient management.

1.7. Non-Pulmonary Arterial Hypertension Pulmonary Hypertension Populations

Most cardiologists and pulmonologists will see PH associated with elevated left heart filling pressures much more frequently than PAH. Any disorder that elevates left heart filling pressures, including systolic dysfunction, diastolic dysfunction, and valvular heart disease, can result in elevated pulmonary artery pressures. Treatment should be directed at the underlying left heart disease. In rare instances, PAH-specific therapy may be considered if the underlying cause has been optimally treated, the PCWP is normal or minimally elevated, the transpulmonary gradient and pulmonary vascular resistance are significantly elevated, and the patient's symptoms suggest that PAH-specific therapy may yield clinical benefit. This subset of patients may be described as those with "disproportionate" PH (greater than expected on the basis of their elevated left heart pressure or lung disease). Experts caution against widespread treatment for non-PAH PH until clinical trial data indicate whether such patients benefit from them. The potential adverse effects of PAH-specific therapies in such patients include worsening fluid retention, pulmonary edema, and ventilation perfusion mismatch.

1.8. Pulmonary Arterial Hypertension in Congenital Heart Disease

The incidence of CHD is approximately 8 per 1,000 live births (4), and approximately 30% of children who do not undergo surgical repair will develop pulmonary vascular

disease. Patients with PAH related to CHD who are not candidates for surgical correction are treated similar to IPAH patients. The natural history of such patients tends to be better than those with other types of PAH.

1.9. Pediatric Pulmonary Arterial Hypertension

Persistent PH of the newborn is a syndrome characterized by increased pulmonary vascular resistance, right to left shunting, and severe hypoxemia. Treatment options include inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation. Pediatric IPAH is treated similar to that in adults. A higher percentage of children are acute responders and candidates for calcium channel blockers.

2. Introduction

The field of PH has evolved substantially over the past decade. While there are some data from which evidence based guidelines for PAH have been generated, other aspects of the assessment and management of PH have been largely unexplored.

The writing committee consisted of acknowledged experts in the field of PH. In addition to members designated by the ACCF and AHA, the Writing Committee included representation from the American College of Chest Physicians (ACCP); the American College of Rheumatology; the American Thoracic Society, Inc. (ATS); and the Pulmonary Hypertension Association (PHA). This diverse representation reflects the multidisciplinary nature of PH. Representation by an outside organization does not necessarily imply endorsement. This document was reviewed by 4 official representatives from the ACCF and AHA; organizational review by the ACCP, ATS, and PHA; as well as by 13 content reviewers. This document was approved for publication by the governing bodies of the ACCF in November 2008 and AHA in February 2009. In addition, the governing boards of the ACCP, ATS, and PHA formally endorsed this document. This document will be considered current until the Task Force on ECDs revises it or withdraws it from publication.

This statement is the first ACCF/AHA Clinical Expert Consensus Document on PH. At its first meeting, each member of this ACCF/AHA Writing Committee indicated any relationships with industry, and these relationships were reiterated at each subsequent meeting and on each conference call. Relevant conflicts of the writing committee and peer reviewers are reported in Appendixes 1 and 2, respectively. At the first meeting the writing committee discussed the topics to be covered in the document and assigned lead authors for each section. The entire writing group reviewed each section and discussed important issues for further drafts. The committee met again to come to a consensus on outstanding issues, and further meetings and teleconferences occurred between the chairman and writing group members who were not present at the meetings to ensure consensus on important points. In instances where there was not consensus amongst the writing group, a majority opinion and a minority opinion is presented. Each writing group member has read and approved the entire document. Outside peer review was also undertaken before the document was finalized.

3. Pathology and Pathogenesis

PAH is a syndrome resulting from restricted flow through the pulmonary arterial circulation, which leads to pathological increases in PVR and ultimately to right heart failure (5). The predominant cause of increased PVR is loss of vascular luminal cross section due to vascular remodeling produced by excessive cell proliferation and reduced rates of apoptosis, although excessive vasoconstriction plays a significant role in approximately 20% of patients (6,7).

Improved understanding of the disease pathways in PAH, even if a single primary cause remains elusive, has led to therapeutic strategies, including the administration of prostanoids, the antagonism of endothelin receptors, and inhibition of PDE-5. Future therapeutic options identified by basic studies include inhibiting pyruvate dehydrogenase kinase (PDK), the serotonin transporter (5-HTT), the antiapoptotic protein survivin, several transcription factors (notably hypoxia inducible factor-1 alpha [HIF-1 alpha] nuclear factor activating T lymphocytes [NFAT]), and augmenting voltage-gated potassium channel channels (e.g., Kv1.5). Additional therapies in early clinical development include vasoactive intestinal peptide and tyrosine kinase inhibitors. Administration of angiogenic factors and stem cells and agents targeting mitochondrial dysfunction may also have therapeutic promise.

3.1. Histology

PAH is a panvasculopathy predominantly affecting small pulmonary arteries (also called "resistance arteries" because they regulate regional blood flow in the lung) (8). PAH is characterized by a variety of arterial abnormalities, including intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation, and plexiform arteriopathy. An individual patient may manifest all of these lesions, and the distribution of lesions may be diffuse or focal. Our understanding of the natural history of the evolution of vascular lesions in PAH, except for patients with CHD, is limited because biopsies are rarely obtained in adult patients. However, it is believed that medial hypertrophy is an earlier and more reversible lesion than intimal fibrosis or plexogenic arteriopathy.

3.2. The Right Ventricle

RV function is a major determinant of functional capacity and prognosis in PAH (5). While RV hypertrophy and dilatation are initiated by increased afterload (i.e., elevated PVR), the adequacy of the RV's compensatory response (preservation of stroke volume) is quite variable amongst

individuals. It remains unclear why some RVs compensate while others decompensate, manifest as thinning and dilatation of the wall, and reduce the RV ejection fraction. The neonatal RV is much more tolerant of increased PVR, partially explaining the better survival in children with PAH associated with CHD. RV function could potentially be improved by effective therapies to regress pulmonary vascular obstruction or by directly improving RV contractile function.

3.3. Molecular Abnormalities in Pulmonary Arterial Hypertension

The pathobiological mechanisms of PAH have recently been reviewed (9). The PAH "phenotype" is characterized by endothelial dysfunction, a decreased ratio of apoptosis/proliferation in pulmonary artery smooth muscle cells (PASMCs), and a thickened, disordered adventitia in which there is excessive activation of adventitial metalloproteases. Like cancer and atherosclerosis, PAH does not have a single cause: a "multi-hit model" is more likely.

3.4. Genetics of Pulmonary Arterial Hypertension

PAH is inherited in less than 10% of cases (1,10). Mutations in 2 genes in the transforming growth factor beta receptor pathway, BMPR2, and activin-like kinase 1 have been implicated in the pathogenesis of familial PAH. BMPR2 modulates vascular cell growth by activating the intracellular pathways of SMAD and LIM kinase (11–13) Many different BMPR2 mutations occur in familial PAH. These mutations, which lead to loss of function in the SMAD signaling pathway, are prevalent in familial PAH (prevalence ~75%) (11,12). Activin-like kinase 1 mutations, detected in a group of patients with hereditary hemorrhagic telangiectasia and PAH (13), are also thought to result in growth-promoting alterations of SMAD-dependent signaling. Overexpression of a dominant negative form of BMPR2 in PASMC leads to PAH and Kv1.5 downregulation in transgenic mice (14,15).

3.5. Abnormalities in the Blood and Endothelium in Pulmonary Arterial Hypertension

In the vascular lumen, PAH is characterized by platelets that are depleted of serotonin and elevation of plasma serotonin (16). Endothelial dysfunction is common in PAH. The PAH endothelium is characterized by increased production of vasoconstrictor/mitogenic compounds, such as endothelin and thromboxane, and deficient production of vasodilators, such as prostacyclin (17–19). Elevated levels of fibrinopeptide A and plasminogen activator inhibitor-1 and reduced levels of tissue plasminogen activator contribute to the procoagulant state. Endothelial injury may also expose the underlying smooth muscle cells to circulating mitogens and growth factors that stimulate cell proliferation.

3.6. Prostacyclin and Thromboxane A_2

The prostanoids prostacyclin and thromboxane A_2 are major arachidonic acid metabolites. Prostacyclin is a potent vasodilator, inhibits platelet activation, and has antiproliferative properties, whereas thromboxane A_2 is a potent vasoconstrictor and promotes proliferation platelet activation. In PAH, the balance between these 2 molecules is shifted toward thromboxane A_2 (17), favoring thrombosis, proliferation, and vasoconstriction. Additionally, prostacyclin synthase is decreased in the small- and medium-sized pulmonary arteries in PAH (20).

3.7. Endothelin-1

Endothelin-1 (ET-1) is a potent vasoconstrictor and stimulates PASMC proliferation. Plasma levels of ET-1 are increased in PAH and correlate with severity of PAH and prognosis (21). Moreover, clearance of ET-1 in the pulmonary vasculature is reduced in PAH (19).

3.8. Nitric Oxide

Nitric oxide (NO) is a vasodilator and inhibitor of platelet activation and vascular smooth-muscle cell proliferation. NO is produced by 3 isoforms of nitric oxide synthases (NOS). Decreased endothelial NOS (NOS3) has been observed in PAH patients (18). Once formed, the effects of NO are largely mediated by cyclic guanosine monophosphate (cGMP) which is rapidly inactivated by PDE, especially the PDE-5 isoenzymes. eNOS knockout mice display PH and even more profound systemic hypertension (22). PDE-5 is present in large amounts in the lung, giving rationale for the use of PDE-5 inhibitors in PAH.

3.9. Additional Vasoactive Substances

Serotonin (5-hydroxytryptamine) is a vasoconstrictor and promotes PASMC hypertrophy and hyperplasia. Allelic variation in serotonin transporter (5-HTT) and the 5-hydroxytryptamine 2B receptor (5-HT2B), have been described in platelets and lung tissue from patients with PAH (23). Transgenic mice overexpressing the serotonin transporter have PAH and decreased Kv1.5 expression (14). Despite these observations, the level of serotonin alone is not likely a determinant of PAH, since serotonin-reuptake inhibitors are in widespread clinical use but are not associated with an increased incidence of PAH and may, in fact, be a potential PAH therapy (24). Vasoactive intestinal peptide (VIP) is a member of the glucagon-growth hormone-releasing superfamily and has a pharmacologic profile similar to prostacyclins. Serum and lung tissue VIP levels are decreased in PAH patients, and exogenous VIP may decrease pulmonary artery pressure (PAP) and PVR, inhibit platelet activation, and reduce PASMC proliferation (25).

3.10. Inflammation

Autoantibodies, proinflammatory cytokines, and inflammatory infiltrates have been observed in some cases of PAH, suggesting that inflammation may contribute to the development of some forms of PAH (26).

3.11. Pulmonary Artery Smooth Muscle Cells in Pulmonary Arterial Hypertension

In PAH, PASMCs have a collection of abnormalities that favor a decreased apoptosis/proliferation ratio. These abnormalities include inappropriate activation of transcription factors (HIF-1 alpha and NFAT), decreased expression of certain K+ channels (e.g., Kv1.5 and Kv2.1), and de novo expression of the antiapoptotic protein survivin. Several abnormalities are observed in human PAH and in rodent models of PAH (notably loss of Kv1.5, activation of survivin, and nuclear translocation of HIF-1 alpha) (27,28). The PASMCs in PAH also display excessive proliferation in response to transforming growth factor beta, and this propensity to accumulate unwanted cells is exacerbated by impaired smooth muscle cell apoptosis. The impaired apoptosis appears to be multifactorial, related to abnormal mitochondrial hyperpolarization, activation of transcription factors (such as HIF-1 alpha and NFAT), and de novo expression of the antiapoptotic protein survivin (27). This occurs in both the PASMCs and endothelial cells (29). Another factor that promotes calcium overload and PASMC proliferation is increased expression of transient receptor potential channels, which promotes calcium overload (30).

In PAH the adventitia is fragmented, permitting cell migration and creating mitogenic peptides, such as tenascin (31). It is conceivable that inhibition of metalloproteases may have therapeutic potential in PAH.

While great strides have been made in understanding the basic mechanisms of the pathobiology and the pathogenesis of PAH over the past 2 decades, our understanding is far from complete. Ongoing investigation into many novel pathways will potentially lead to more therapeutic options in the decades to come. Figure 1 (31a) summarizes many of the relevant cellular pathways in the pathogenesis of PAH.

4. Classification and Epidemiology of Pulmonary Arterial Hypertension (WHO Group I)

The current classification of PH is depicted in Table 1 (32).

4.1. Idiopathic Pulmonary Arterial Hypertension

IPAH is a rare disease, with a female/male ratio of 1.7:1 and a mean age at diagnosis of 37 years (10). Most recent epidemiologic data suggest that the prevalence of PAH may be up to 15 per million, with a prevalence of IPAH of about 6 per million (1). Interestingly, recent studies suggest the age range of affected individuals may be increasing, as cases of IPAH have been reported in many patients greater than 70 years old (33).

4.2. Familial Pulmonary Arterial Hypertension

Hereditary transmission of PAH has been reported in approximately 6% to 10% of patients with PAH; in 50% to 90% of these individuals, mutations in BMPR2 have been identified (34,35). Mutations in BMPR2 have been found in up to 25% of patients with IPAH (36), in 15% of PAH related to fenfluramine use, and rarely in patients with other forms of associated PAH (37,38). The mutations in BMPR2 in familial pulmonary arterial hypertension (FPAH) are characterized by genetic anticipation and incomplete penetrance. The phenotype is not expressed in all generations, but when expressed, occurs at an earlier age and is associated with more severe and rapidly progressive disease (39,40).

4.3. Pulmonary Arterial Hypertension Associated With Congenital Heart Disease

PAH is a well-recognized complication of uncorrected increased pulmonary blood flow associated with CHD and systemic-to-pulmonary shunts. The development of PAH and subsequent reversal of shunt flow (Eisenmenger syndrome) occurs more frequently when blood flow is extremely high and the shunt exposes the pulmonary vasculature to systemic level pressures, such as occurs with a ventricular septal defect, patent ductus arteriosus, or truncus arteriosus. However, PAH may also occur with low pressure-high flow abnormalities, such as with atrial septal defects.

4.4. Pulmonary Arterial Hypertension Associated With Connective Tissue Diseases

A primary pulmonary arteriopathy occurs most commonly in patients with the limited cutaneous form of systemic sclerosis, formerly referred to as the CREST (calcinosis, Raynaud's, esophageal dysfunction, sclerodactaly, telangectasias) variant. Although at autopsy, 65% to 80% of individuals have histopathological changes consistent with PAH, less than 10% develop clinically apparent disease (41). Surveillance echocardiography suggests that there is a substantial prevalence of mild to moderate PH in connective tissue disease patients (41,42). However, the management and natural history of such patients has not been well studied. Histology consistent with PAH has also been observed in systemic lupus erythematosus, mixed connective tissue disease, and rheumatoid arthritis.

4.5. Pulmonary Arterial Hypertension Associated With Human Immunodeficiency Virus Infection

Population studies of individuals infected with HIV suggest that the incidence of PAH is approximately 0.5%, or 6 to 12 times that of the general population, and has not declined significantly with aggressive antiretroviral therapy (43–45). The occurrence of PAH is independent of the CD4 count or previous opportunistic infections, but appears related to the duration of HIV infection (46). Although PAH occurs
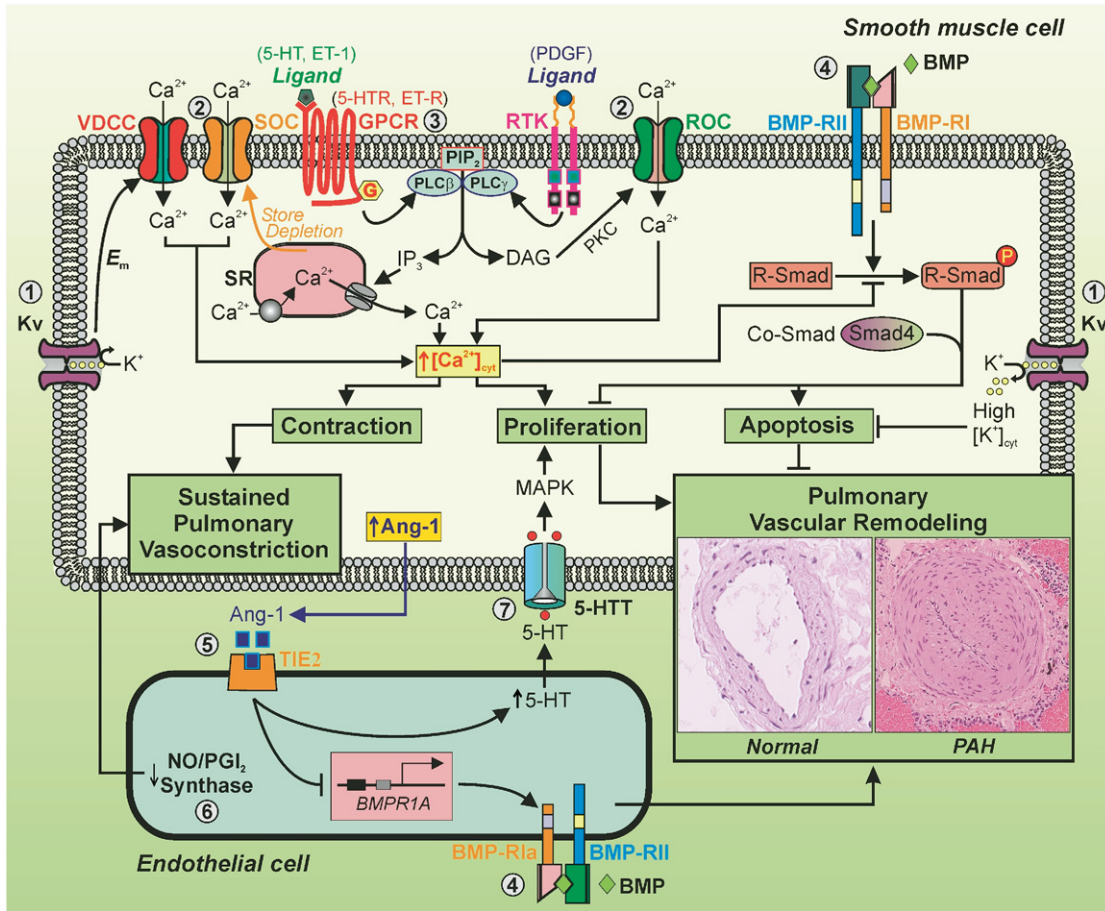
Figure 1. Relevant Pathways in the Pathogenesis of Pulmonary Arterial Hypertension

Schematic depicting the potential "hits" involved in the development of PAH. A rise in $[Ca^{2+}]$cyt in PASMCs (due to increased Kv channel activity ① and membrane depolarization, which opens VDCCs; upregulated TRPC channels that participate in forming receptor- and store-operated Ca^{2+} channels ②; and upregulated membrane receptors [e.g., serotonin, endothelin, or leukotriene receptors] ③ and their downstream signaling cascades) causes pulmonary vasoconstriction, stimulates PASMC proliferation, and inhibits the BMP-signaling pathway that leads to antiproliferative and proapoptotic effects on PASMCs. Dysfunction of BMP signaling due to BMP-RII mutation and BMP-RII/ BMP-RI downregulation ④ and inhibition of Kv channel function and expression ① attenuate PASMC apoptosis and promote PASMC proliferation. Increased Ang-1 synthesis and release ⑤ from PASMCs enhance 5-HT production and downregulate BMP-RIA in PAECs and further enhance PASMC contraction and proliferation, whereas inhibited nitric oxide and prostacyclin synthesis ⑥ in PAECs would attenuate the endothelium-derived relaxing effect on pulmonary arteries and promote sustained vasoconstriction and PASMC proliferation. Increased activity and expression of the 5-HTT ⑦ would serve as an additional pathway to stimulate PASMC growth via the MAPK pathway. In addition, a variety of splicing factors, transcription factors, protein kinases, extracellular metalloproteinases, and circulating growth factors would serve as the "hits" to mediate the phenotypical transition of normal cells to contractive or hypertrophied cells and to maintain the progression of PAH.

5-HT indicates 5-hydroxytryptamine; 5-HTT, 5-HT transporter; 5-HTR, 5-hydroxytryptophan; Ang-1, angiopoietin; AVD, apoptotic volume decrease; BMP, bone morphogenetic protein; BMP-RI, BMP type I receptor; BMP-RII, BMP type II receptor; BMPR-IA, BMP receptor IA; Ca^{2+}, calcium ion; Co-Smad, common smad; cyt, cytosine; DAG, diacylglycerol; E_m, membrane potential; ET-1, endothelin-1; ET-R, endothelin receptor; GPCR, G protein-coupled receptor; IP_3, inositol 1,4,5-trisphosphate; K, potassium; Kv, voltage-gated potassium channel; MAPK, mitogen-activated protein kinase; NO/PGI_2, nitric oxide/prostacyclin; PAEC, pulmonary arterial endothelial cell; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle; PDGF, platelet-derived growth factor; PIP_2, phosphatidylinositol biphosphate; PLC, phospholipase C; PLCβ, PLC-beta; PLCγ, PLC gamma; PKC, protein kinase C; ROC, receptor-operated calcium channel; R-Smad, receptor-activated smad signaling pathway; RTK, receptor tyrosine kinase; SOC, store-operated channel; SR, sarcoplasmic reticulum; TIE2, tyrosine-protein kinase receptor; TRPC, transient receptor potential channel; and VDCC, voltage-dependent calcium channel. Reprinted from Yuan and Rubin (31a).

with greater frequency in individuals who have used intravenous drugs, no clear etiological link has been established with foreign body emboli or the portal hypertension frequently observed in these same individuals because of concomitant infection with hepatitis B or C. Because HIV does not directly infect vascular endothelial cells or smooth muscle cells, the mechanism of PAH in HIV infection remains unclear. Routine screening for PAH in HIV is not recommended due to the relatively low disease prevalence in HIV patients.

4.6. Pulmonary Arterial Hypertension Associated With Portal Hypertension

In a large autopsy series, histological changes consistent with PAH occurred in 0.73% of individuals with cirrhosis, 6 times the prevalence in all autopsies (47). Hemodynamic studies have estimated the prevalence of PAH in these individuals at 2% to 6%; however, the prevalence may be higher in patients referred for liver transplantation (48). The risk of developing PAH increases with the duration of portal hypertension. The mechanism of this association is

unclear, but cirrhosis without the presence of portal hypertension appears insufficient for the development of PAH. Portal hypertension patients may also develop PH related to high flow states and left ventricular (LV) diastolic dysfunction, which are important to distinguish from PAH.

4.7. Pulmonary Arterial Hypertension Associated With Drugs and Toxins

Association between anorexigens (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) and PAH was initially observed in the 1960s when an epidemic of IPAH (then termed PPH) was noted in Europe following the introduction of aminorex fumarate (49). Upon withdrawal of this medication, the incidence of PAH decreased to background; however, structurally related compounds, such as fenfluramine and dexfenfluramine, were subsequently developed in the 1980s. Exposure to these agents for as little as 3 months also has been associated with an increased incidence of IPAH (50). Epidemiologic studies have also linked the development of PAH to rapeseed oil (51), L-tryptophan (52), and illicit drugs such as methamphetamine and cocaine (53,54).

4.8. Pulmonary Arterial Hypertension Associated With Hemoglobinopathies

PH is increasingly recognized in patients with sickle cell disease, with a prevalence reported as high as 30% in echocardiography-based studies (55,56). A more recent report suggests that the proportion of patients with sickle cell disease who have PAH is much lower, less than 10% (57). It also highlights other factors that may contribute to PH in sickle cell disease patients including thromboembolic disease, restrictive lung disease, and left heart disease. Whether the PH is the cause of the increased mortality or is a surrogate marker remains unclear; however, the 2-year mortality rate in these patients is approximately 50% (55,56). The pathobiology of PH in sickle cell disease is likely multifactorial: sickle cell related pulmonary vasculopathy, asplenia, pulmonary parenchymal and vascular injury from acute chest syndrome, and systemic loss of bioavailable NO by hemoglobin released during hemolysis and increased oxidant burden (58). Plasma levels of endothelin-1 are elevated in patients with sickle cell disease (59). Despite the relatively mild nature of the PH in many of these patients, the histopathology is often quite similar to PAH, including plexiform lesions. Hemodynamic parameters in PH associated with sickle cell disease are often different from those in other forms of PAH. PAP and PVR are often lower than that observed in IPAH, yet patients with sickle cell disease and PH are often very symptomatic. In contrast to patients with other forms of PAH, who by definition have normal LV systolic and diastolic function, sickle cell disease-PH patients often have elevated left heart filling pressures suggesting impaired LV diastolic function. They also have decreased hemoglobin and a high cardiac output but have limited systemic oxygen transport. Other anemias, including

homozygous beta-thalassemia and hereditary spherocytosis have also been associated with the development of PH (60,61).

4.9. Pulmonary Arterial Hypertension Associated With Other Etiologies

PH clinically and histologically indistinguishable from IPAH has been observed in approximately 15% of individuals with hereditary hemorrhagic telangiectasia, an autosomal dominant vascular dysplasia (13,62). There is also an association between thrombocytosis, chronic myelodysplastic syndrome, and the development of PAH (63). Lastly, a high incidence of asplenia and thyroid disease have been reported in patients with PAH (64,65).

4.10. Pulmonary Arterial Hypertension Associated With Pulmonary Venous or Capillary Abnormalities

In rare instances, the typical histological findings of PAH are associated with an occlusive venopathy (pulmonary veno-occlusive disease) or a microvasculopathy (pulmonary capillary hemangiomatosis). In addition to the histology of PAH, these entities also exhibit the findings of pulmonary venous hypertension, including pulmonary hemosiderosis, interstitial edema, and lymphatic dilation (66). Although the clinical presentation is usually indistinguishable from PAH, rapid development of pulmonary edema after administration of vasodilators such as epoprostenol has been reported in both entities (67,68) and is often a clue to the appropriate diagnosis.

5. Natural History and Survival

The prognosis of PAH and variables influencing the prognosis have recently been reviewed (69). The natural history of IPAH has been well characterized. The National Institutes of Health (NIH) Registry followed 194 patients with IPAH enrolled at 32 clinical centers from 1981 to 1985 (70). The estimated median survival was 2.8 years, with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively. Studies from Japan, India, and Mexico have suggested similar results, with a median survival in the range of 2 to 3 years.

Prognosis is also influenced by underlying etiology (Figure 2). The prognosis in patients with PAH associated with the scleroderma spectrum of diseases appears to be worse than for IPAH, and the untreated 2-year survival rate may be as low as 40% (71). Even with epoprostenol therapy, patients with PAH related to the scleroderma spectrum of diseases have a less favorable outcome (72), although recent data suggest that in the era of expanding PAH therapy, prognosis may be improving (73). Data from 2 studies (prospective and retrospective) suggest that patients with HIV-associated PAH appear to have similar survival as those with IPAH (43,74), and deaths in this setting are most commonly related to PAH. It is clear that patients with CHD have a better prognosis than those with IPAH,
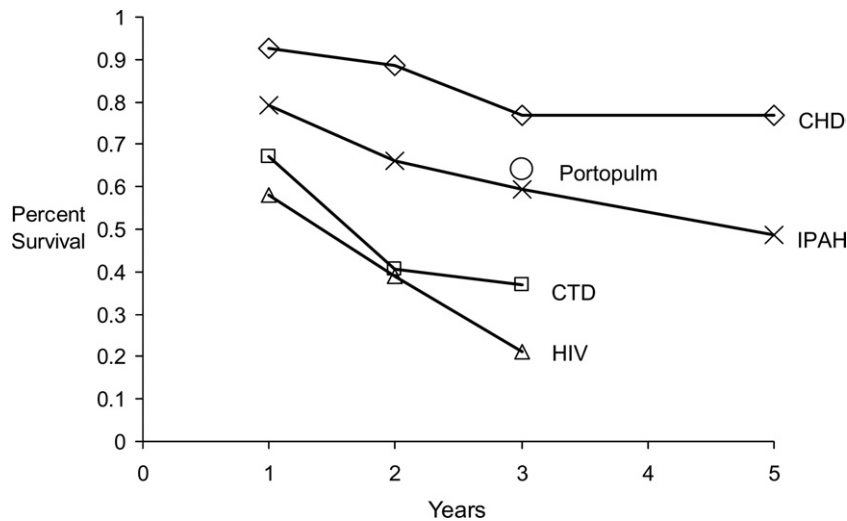
Figure 2. Mean Survival of Patients With PAH Based on Etiology

CHD indicates congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus related;
IPAH, idiopathic pulmonary arterial hypertension; and Portopulm, portopulmonary hypertension. Adapted from McLaughlin et al. (69).

although it is uncertain whether this reflects the relative youth of these patients, their better adapted right ventricles, or the potential advantages of a residual shunt. In a study evaluating 100 adults with severe PAH, 37 of whom had Eisenmenger syndrome and 6 of whom had previously repaired congenital heart defects, actuarial survival of non-transplanted patients was 97%, 89%, and 77% at 1, 2, and 3 years, respectively, compared with 77%, 69%, and 35% at 1, 2, and 3 years, respectively, for patients with IPAH (75). In a cohort of epoprostenol-treated PAH patients, survival was greater for those with CHD than for IPAH (72).

5.1. Medical Therapy for Pulmonary Arterial Hypertension: Impact Upon Survival

The positive impact of epoprostenol on survival in IPAH has been well described in 1 randomized controlled trial and 2 single center, observational, uncontrolled trials (76–78). Long-term epoprostenol therapy appears to improve hemo-dynamics and quality of life in patients with PAH and CHD who fail conventional therapy (79), and improvement has been demonstrated in the scleroderma spectrum of diseases population (80), but trials large enough to ade-quately assess survival benefit are not available.

Long-term observational studies with first line bosentan and treprostinil have also suggested an improved survival in PAH, although controlled clinical trial data are not available (81,82). Calcium channel blockers may favorably influence survival in the small proportion of patients with IPAH who demonstrate a significant vasodilator response at RHC (83,84). Anticoagulation therapy has been associated with improved survival in IPAH (83) as well as in diet drug-induced PAH (85) in open label, uncontrolled series. However, a large, prospective randomized trial with the specific purpose of looking at this end point has not been conducted. Recent registry data indicate an 85% survival

rate at 1 year for patients with PAH observed at a single center from 1982 to 2006 (2).

5.2. Factors Impacting Survival and Facilitating Assessment of Prognosis

Important prognostic factors have recently been reviewed (69) and will be briefly summarized.

5.3. Functional Class

The NIH cohort study showed that among 194 patients who received a diagnosis of IPAH between 1981 and 1985, the risk of death was higher among patients in New York Heart Association (NYHA) functional class III or IV than among those in NYHA functional class I or II. In the NIH registry, the median survival among patients presenting with NYHA functional class I and II symptoms was nearly 6 years versus 2.5 years for patients with functional class III symptoms and just 6 months for patients who presented with functional class IV symptoms (70). Other series have confirmed the importance of functional class as a prognostic variable, even during treatment (77,78). Mortality is higher in both treated and untreated functional class III but particularly in functional class IV IPAH patients. Patients who improved to functional class I or II status with epoprostenol had a better prognosis than patients who remained in functional class III or IV (77,78).

5.4. Exercise Tolerance

In the pivotal epoprostenol IPAH trial, performance in the unencouraged 6MW test was found to be an independent predictor of survival, leading to use of this test as the primary end point for many prospective trials (76). Other studies have suggested the prognostic value of this test; in patients on epoprostenol, unencouraged 6MW distance at

baseline and after 3 months of therapy was associated with survival by univariate analysis (78,86).

Maximal oxygen consumption (peak VO$_2$) determined by progressive, exercise testing with cycle ergometry has been found to be an independent predictor of survival in 1 study in patients with IPAH (87); Kaplan-Meier analysis in this study revealed that patients with a peak VO$_2$ greater than 10.4 mL/kg/min had significantly better 1-year survival than patients with lower peak VO$_2$ values. Patients with a peak systemic blood pressure greater than 120 mm Hg also had a better 1-year survival than those patients who did not achieve this systemic blood pressure. In IPAH patients treated with epoprostenol, treadmill exercise time has also been shown to be predictive of survival (77). Cardiopulmonary exercise testing is used less frequently in PAH clinical trials due to lack of methodologic consistency among different centers. The Naughton-Balke treadmill test reported in exercise metabolic equivalents is a useful means of assessing functional capacity in PAH patients (88).

5.5. Hemodynamics

All large published evaluations implicate hemodynamics as an important predictor of survival (70,77,78). In the NIH registry, 3 hemodynamic variables were associated with an increased risk of death by univariate analysis: increased mPAP (odds ratio [OR]: 1.16; 95% confidence interval: 1.05 to 1.28), increased mean right atrial pressure (mRAP) (OR: 1.99; 95% confidence interval: 1.47 to 2.69), and decreased cardiac index (CI) (OR: 0.62; 95% confidence interval: 0.46 to 0.82). These 3 variables were also predictive in a multivariate analysis. Data from the NIH registry were used to formulate a regression equation in which these 3 variables were used to estimate survival. Data from Mexico in the pre-epoprostenol era support the validity of the NIH equation, and suggest the importance of other predictors such as decreased mixed venous oxygen (MVO$_2$) and increased heart rate (89). Interestingly, mPAP was not a predictor based upon these data, and this is likely due to the eventual decrease in mPAP as the right ventricle fails. Baseline hemodynamic variables appear to have less prognostic value in patients with IPAH who are treated with epoprostenol (78). Based upon available data, it is agreed that mRAP, CI, and mPAP are predictive of survival, with the understanding that as RV function worsens, mPAP may actually decrease. Experienced clinicians use mRAP and CI together with other clinical parameters to prognosticate.

True vasodilator responders have an excellent prognosis, with up to a 95% survival at 5 years (83,84). Although the main purpose of acute vasodilator testing is to identify patients that might respond to oral calcium channel blockers, the results of vasodilator testing also have prognostic implications. The issue of whether degree of vasodilator responsiveness has prognostic implications in patients who are treated with medical therapies other than calcium channel blockers is controversial. However, calcium channel blockers should not be considered as PAH-specific therapy

if there is not an acute response to a short acting vasodilator. In a large series of patients with IPAH receiving long-term intravenous epoprostenol, the change in PVR acutely with adenosine was predictive of survival by a univariate analysis (77).

5.6. Echocardiography

While echocardiography has been a pivotal screening test in PAH, studies evaluating the prognostic value of echocardiographic parameters have been limited to relatively small series. RA and RV enlargement, reduced RV function, displacement of the intraventricular septum, tricuspid regurgitation (TR), the Tei index, and pericardial effusion have been evaluated. The presence of any degree of pericardial effusion has proven a consistent predictor of mortality (90). The Doppler echocardiographic index ("Tei index" or myocardial performance index), an index of combined RV systolic and diastolic function obtained by dividing the sum of both isovolumetric contraction and relaxation intervals by the ejection time, appears to be predictive of an adverse outcome on univariate analysis and by multivariate regression analysis (91,92). Clinicians often rely on the subjective appearance of the RA and RV to make clinical decisions, even without formal size measurements.

5.7. Magnetic Resonance Imaging

Cardiac magnetic resonance (MR) imaging accurately assesses size and function of the RV with a high degree of reproducibility. RV function is an important prognositic indicator in PAH and cardiac MR imaging of poor RV function, including stroke volume less than or equal to 25 mL/m^2, RV end-diastolic volume greater than or equal to 84 mL/m^2, and LV end-diastolic volume less than or equal to 40 mL/m^2, were found to be independent predictors of mortality and treatment failure in a study of 64 patients (93). Additionally, pulmonary artery stiffness, as measured by relative cross-sectional area change was predictive of survival in a cohort of 86 PAH patients studied with MR imaging (94). Those with a relative cross-sectional area change of less than 16% had a greater mortality than those with value greater than 16%.

5.8. Biomarkers

Both atrial natriuretic peptide and BNP have been shown to correlate with survival in IPAH and to correlate with other predictors of survival. BNP and NT-proBNP appear to be better independent predictors (95,96). Increased uric acid levels, which may reflect impaired oxidative metabolism, have been shown to be increased with severity of functional class and hemodynamics in IPAH, and among the noninvasive tests studied, independently correlated with mortality (97). Detectable cardiac troponin T also confers a poor prognosis, potentially due to the effect of RV ischemia (98). Of the above biomarkers, proBNP levels are increasingly being used and appear to correlate with RV enlargement and dysfunction.

Table 2. PAH*: Determinants of Prognosis

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO_2 greater than 10.4 mL/kg/min	Peak VO_2 less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m²	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m²
BNP§	Minimally elevated	Significantly elevated

Reprinted from McLaughlin and McGoon (99). *Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions. †WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class. ‡6MW distance is also influenced by age, gender, and height. §As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.

6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO_2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.

5.9. Summary of Recommendations

Successful prognostication of survival is crucial in planning appropriate therapeutic measures including aggressive medical therapy and transplantation, and should encompass multiple variables. The most conclusive data are available for IPAH, and limited data are available for associated forms of PAH. Important prognostic variables are summarized in Table 2 (PAH: Determinants of Prognosis) (99). While this table is meant to provide guidance, in many instances, the same patient may have a high-risk finding, a low-risk finding, and/or a finding between the 2. This scheme allows for latitude in the composite assessment of an individual patient by the experienced physician.

6. Screening and Diagnostic and Hemodynamic Assessment

6.1. Definition of Pulmonary Hypertension

The term PH refers to the presence of abnormally high pulmonary vascular pressure. PAH is a category of PH (Venice Group 1) (Table 1) (32); the 2 terms are not synonymous. The conventional definition of PAH used in clinical studies includes an mPAP of greater than 25 mm Hg at rest in the setting of a normal pulmonary arterial wedge pressure of 15 mm Hg or less with a PVR greater than 3 Wood units. Patients enrolled in the NIH registry of primary PH (now IPAH) in the 1980s had the following hemodynamic characteristics: an mPAP of 60 plus or minus 18 mm Hg, cardiac index of 2.3 plus or minus 0.9 L/min/m², and pulmonary arterial wedge pressure of 8 plus or minus 4 mm Hg (10). This hemodynamic definition has subsequently been applied in enrollment requirements in virtually every randomized clinical treatment trial along with additional criteria including functional classification and 6MW test to ensure that a relatively advanced stage of disease was studied.

6.2. Diagnostic Strategy

The diagnostic strategy for PH depends on the context in which it is employed: 1) detection of a substrate in which the likelihood of a pulmonary vasculopathy may be heightened; 2) discovery of the presence of PH; 3) classification of the type of PH; 4) confirmation of the presence of suspected PH; and 5) determination of an appropriate treatment category. The approach to diagnosis has been previously outlined (3). The general strategy for assessment is shown in Figure 3.

SUBSTRATE RECOGNITION

Certain medical conditions and genetic susceptibilities are recognized as predisposing a person to the development of PAH, and were reviewed in Section 4 of this document. Risk factors for PAH and consensus screening guidelines are displayed in Table 3.

DISCOVERY OF PULMONARY HYPERTENSION

A discovery strategy is required for patients who are at risk of having PH, including those with genetic substrates, risk factors, or suggestive symptoms or physical examination findings. The most common presenting symptoms of PH include dyspnea on exertion, fatigue, chest pain, syncope, palpitations, and lower extremity edema. Common physical examination findings are displayed in Table 4 (100). The CXR and ECG may display markers suggestive of PH that bear further evaluation (Figure 4).

6.3. Echocardiography

If PH is suspected based on the history, risk factor assessment, and physical examination, an echocardiogram is the next appropriate study. The Doppler echocardiogram can simultaneously provide an estimate of RV systolic pressure, functional and morphologic cardiac sequelae of PH, and identification of possible cardiac causes of PH. Common echocardiographic findings of PAH are featured in Figure 5. In the absence of other potential etiologies of PH, such as left heart disease or advanced lung disease, an estimated RV
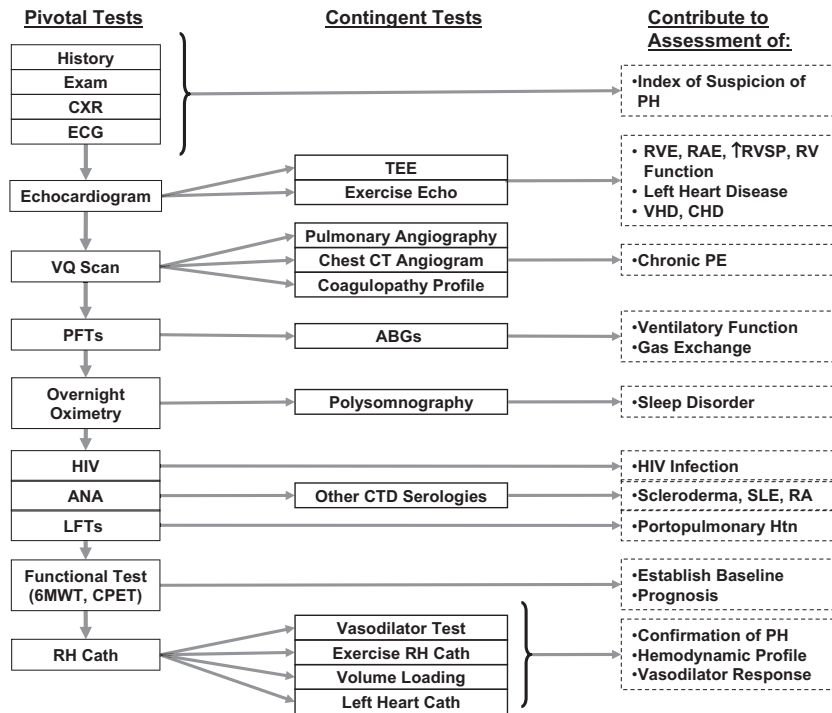
Figure 3. Diagnostic Approach to PAH

General guidelines for the evaluation of pulmonary hypertension. Since the suspicion of PH may arise in various ways, the sequence of tests may vary. However, the diagnosis of PAH requires that certain data support a specific diagnosis. In addition, the diagnosis of idiopathic pulmonary arterial hypertension is one of excluding all other reasonable possibilities. Pivotal tests are those that are essential to establishing a diagnosis of any type of PAH either by identification of criteria of associated disease or exclusion of diagnoses other than IPAH. All pivotal tests are required for a definitive diagnosis and baseline characterization. An abnormality of one assessment (such as obstructive pulmonary disease on PFTs), does not preclude that another abnormality (chronic thromboembolic disease on VQ scan and pulmonary angiogram) is contributing or predominant. Contingent tests are recommended to elucidate or confirm results of the pivotal tests, and need only be performed in the appropriate clinical context. The combination of pivotal and appropriate contingent tests contribute to assessment of the differential diagnoses in the right-hand column. It should be recognized that definitive diagnosis may require additional specific evaluations not necessarily included in this general guideline. 6MWT indicates 6-minute walk test; ABGs, arterial blood gases; ANA, antinuclear antibody serology; CHD, congenital heart disease; CPET, cardiopulmonary exercise test; CT, computerized tomography; CTD, connective tissue disease; CXR, chest X-ray; ECG, electrocardiogram; HIV, human immunodeficiency virus screening; Htn, hypertension; LFT, liver function test; PE, pulmonary embolism; PFT, pulmonary function test; PH, pulmonary hypertension; RA, rheumatoid arthritis; RAE, right atrial enlargement; RH Cath, right heart catheterization; RVE, right ventricular enlargement; RVSP, right ventricular systolic pressure; SLE, systemic lupus erythematosus; TEE, transesophageal echocardiography; VHD, valvular heart disease; and VQ Scan, ventilation-perfusion scintigram.

systolic pressure of greater than 40 mm Hg generally warrants further evaluation in the patient with unexplained dyspnea. Additionally, other echocardiographic findings, including RA or RV enlargement or intraventricular septal flattening, may also trigger further evaluation. Echocardiography can also identify coexistent abnormalities that do not themselves cause PAH but support a specific diagnosis (Table 5), although many of these findings lack specificity.

The spectral Doppler profile of TR is too weak or insufficient to measure the RV to RA pressure gradient in approximately 10% to 25% of patients with PH referred for evaluation (101,102). When this problem is encountered, the spectral TR signal can be enhanced by intravenous bolus administration of a small amount of agitated saline contrast, or with commercially available encapsulated microbubble contrast agents that are indicated for use to enhance the LV endocardial borders. Very small amounts of these agents are required for Doppler enhancement, and encapsulated agents should be used with caution in patients with severe pulmonary vascular disease (102a). In these instances, the presence

of right heart chamber enlargement or septal flattening suggests elevated right heart pressures.

6.4. Exercise Echocardiography

While hemodynamics are most often measured at rest, patients usually experience dyspnea with exercise, leading to an interest in the utility of exercise echocardiography to detect "exercise-induced PH." Exercise echocardiography is challenging both to perform and interpret and is generally used in a research setting. It may not be possible to discern by echocardiography alone to what extent elevated left heart filling pressure might contribute to "exercise-induced PH" in an individual patient. The consensus is that no treatment decisions can be made on the basis of exercise-induced PH alone.

6.5. Newer Imaging Techniques in the Diagnostic Assessment of Pulmonary Hypertension

There is considerable interest in the utilization of newer imaging techniques in the assessment of patients with PH. Computed tomography (CT) and MR imaging techniques

Table 3. Approach Following Substrate Recognition

Substrate	Further Assessment	Rationale
BMPR2 mutation	Echocardiogram yearly; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	Early detection of PAH; 20% chance of developing PAH
1st degree relative of patient with BMPR2 mutation or within pedigree of 2 or more patients with a diagnosis of PAH	Genetic counseling and recommendation for BMPR2 genotyping; proceed as above if positive	Autosomal dominant transmission
Systemic sclerosis	Echocardiogram yearly; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	About 8% (by RHC) −27% (by echocardiogram screening) prevalence of PAH in systemic sclerosis (27,78)
HIV infection	Echocardiogram if symptoms or signs suggestive of PAH; RHC if echo demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	0.5% prevalence of PAH
Portal hypertension	Echocardiogram if OLT considered; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	4% prevalence of PAH in candidates for OLT; PAH is predictive of poor OLT outcome
Prior appetite suppressant use (fenfluramine)	Echocardiogram only if symptomatic	Incidence of PAH is approximately 0.005% if agent used greater than 3 months
Congenital heart disease with shunt	Echocardiogram and RHC at time of diagnosis; consider repair of defect if significant L-R shunt present	High probability of PAH developing in unrepaired shunt (Eisenmenger syndrome)
Recent acute pulmonary embolism	Ventilation-perfusion (V/Q) scintigraphy 3 months after event if symptomatic; pulmonary angiogram if positive	3% risk of chronic thromboembolic PH; negative VQ scan excludes chronic thromboembolism
Sickle cell disease	Echocardiogram yearly; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	Increased mortality if PH present, early detection of PH, 30% develop PH, about 10% develop PAH

BMPR2 indicates bone morphogenic protein receptor 2; HIV, human immunodeficiency virus; L-R, left to right; OLT, orthotopic liver transplantation; PAH, pulmonary arterial hypertension; and RHC, right heart catheterization.

are being explored to assess RV mass, volumes, and function, and in the area of chronic thromboembolic pulmonary hypertension (CTEPH). Promising MR markers of PAH include change in the ratio of septal curvature, RV ejection fraction, RV volume, noninvasively measured cardiac index, and delayed hyperenhancement (measured using gadolinium-enhanced MR imaging) (93).

CLASSIFICATION

In most cases, PH is discovered during evaluation for symptoms (dyspnea, fatigue, chest pain, syncope, or edema). Once suspected, based on echocardiographic criteria, a search for a potential underlying association or cause must be undertaken in order to treat the PH appropriately and advise regarding prognosis and adjunctive therapy. At the outset, all causes of PAH (Group 1) and non-PAH (Groups 2 to 5) PH must be considered. The algorithm in Figure 3 reflects the fact that both appropriate assessment for underlying cause (Table 1) as well as the hemodynamic pattern (see the following text) are required.

It is important to exclude other disorders that cause PH during the diagnostic evaluation, as etiology of PH dictates treatment. While much of the evaluation is self evident in Figure 3, special emphasis on excluding CTEPH is appropriate. Approximately 3% to 4% of those who experience an acute pulmonary embolus (PE) do not fully resolve the thrombus burden, despite anticoagulation, and go on to develop CTEPH (103). On the other hand, one half of those patients who are ultimately diagnosed with CTEPH do not give a history of an acute PE. CTEPH has recently been reviewed (104). The screening test of choice to exclude CTEPH in the patient with otherwise unexplained dyspnea and PH is the radionuclide perfusion scan. A normal or very low probability essentially excludes CTEPH, and a high probability scan warrants further evaluation with a pulmonary angiogram. Clinical judgment is required for those with a nondiagnostic scan, and based on the clinical suspicion and presence of underlying parenchymal lung disease, further evaluation may be warranted. At the current time, spiral or PE protocol CT, while excellent for excluding an acute PE in the appropriate clinical setting, is less sensitive than the perfusion scan to exclude CTEPH. It is important to rule out CTEPH even in those with an underlying risk factor for PAH, such as the scleroderma spectrum of diseases population, as the therapeutic implications of the diagnosis are substantial. In some patients, such as those with parenchymal lung disease and a low likelihood of CTEPH, the perfusion scan may be difficult to interpret and a PE protocol CT may be useful. CT is also useful to determine the extent of parenchymal lung disease. With advances in technol-

Table 4. Features of the Physical Examination Pertinent to the Evaluation of PH

Sign	Implication
Physical Signs That Reflect Severity of PH	
Accentuated pulmonary component of S_2 (audible at apex in over 90%)	High pulmonary pressure increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of pulmonary valve into high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S_4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular "a" wave	Poor right ventricular compliance
Physical Signs That Suggest Moderate to Severe PH	
Moderate to severe PH	
Holosystolic murmur that increases with inspiration	Tricuspid regurgitation
Increased jugular v waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced PH with right ventricular failure	
Right ventricular S_3 (in 23%)	Right ventricular dysfunction
Distention of jugular veins	Right ventricular dysfunction or tricuspid regurgitation or both
Hepatomegaly	Right ventricular dysfunction or tricuspid regurgitation or both
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction
Physical Signs That Suggest Possible Underlying Cause or Associations of PH	
Central cyanosis	Abnormal V/Q, intra-pulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venopathy
Cardiac auscultatory findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Rales, dullness, or decreased breath sounds	Pulmonary congestion or effusion or both
Fine rales, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils	Possible substrate for disordered ventilation
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic PH
Splenomegaly, spider angiomata, palmary erythema, icterus, caput medusa, ascites	Portal hypertension

PH indicates pulmonary hypertension.

ogy, PE protocol CT may replace perfusion scanning to screen for CTEPH in the future.

CONFIRMATION

Although Doppler echocardiography and associated findings may suggest the presence of PH, RHC (with an accurate assessment of PVR) is required to confirm the diagnosis and to define the hemodynamic profile in greater detail and accuracy.

6.6. Invasive Hemodynamic Assessment

Careful invasive assessment of pulmonary hemodynamics is pivotal in the evaluation of any patient with suspected PAH. The utility of RHC is dependent on the accuracy and completeness of the data obtained. Essential components of the RHC are summarized in Table 6.

Many of the causes of elevated PA pressure (PH) are not caused by pulmonary vascular pathology. For example, PH commonly occurs with high transpulmonary flow in the setting of exercise, anemia, pregnancy, sepsis, portopulmonary syndrome, or thyrotoxicosis. In these conditions, the pulmonary vascular bed is anatomically normal and the PH resolves when the cardiac output returns to normal levels. The transpulmonary gradient (PAP mean-wedge) is significantly elevated in PAH patients, but not in patients whose PH is due to increased cardiac output, left heart myocardial, or valvular disease. There is a small subset of the patients with diseases causing passive PH who have a disproportionate elevation of PVR (identified somewhat arbitrarily by PVR greater than 3 Wood units and a transpulmonary gradient greater than 20 mm Hg) (see Section 9, Non-Pulmonary Arterial Hypertension Pulmonary Hypertension Populations).

It was the committee's majority opinion that diagnostic criteria for PAH stated in several recent guidelines should

A

B
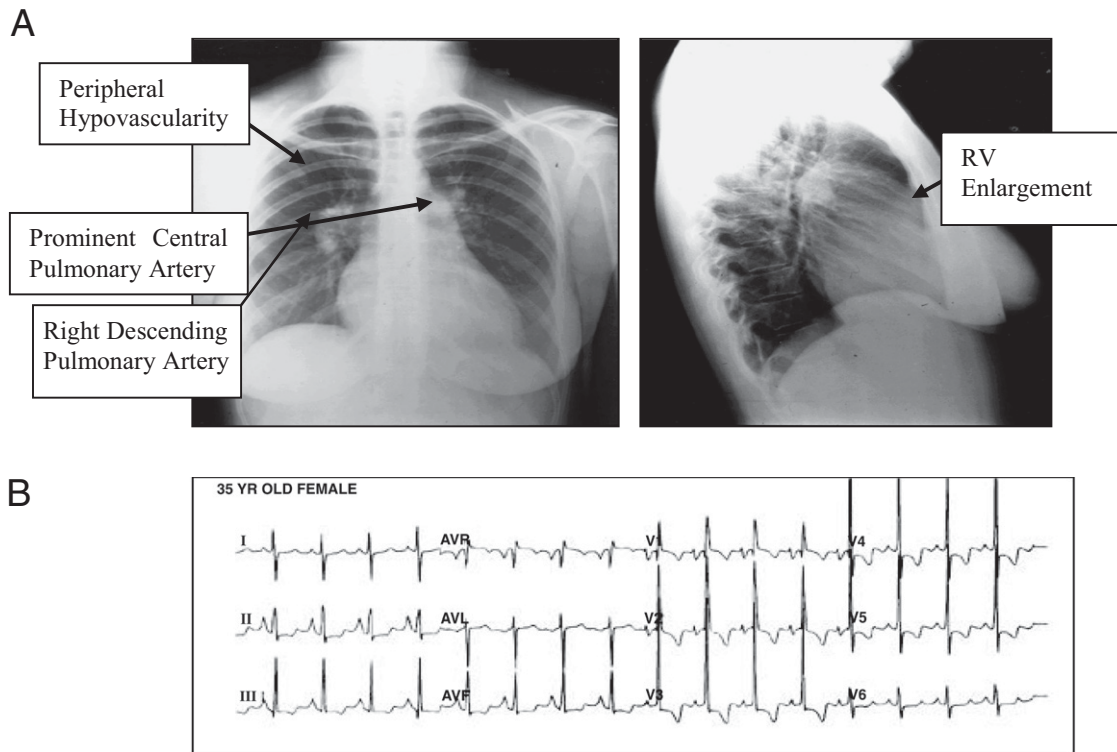
Figure 4. Chest X-Ray and ECG in PAH

Postero-anterior and lateral chest X-ray (top) shows decreased peripheral lung vascular markings, hilar pulmonary artery prominence, and right ventricular enlargement of a patient with idiopathic PAH. ECG (bottom) of the same patient reveals right atrial enlargement, right ventricular hypertrophy and strain, and right axis deviation of the QRS complex. ECG indicates electrocardiogram; and PAH, pulmonary arterial hypertension.

be clarified as requiring elevated PVR as opposed to simply an elevated mPAP in the setting of a normal left heart filling pressure (105,106). PVR is a more robust diagnostic criterion for PAH because it reflects the influence of transpulmonary gradient and cardiac output and is only elevated if the vascular obstruction occurs within the precapillary pulmonary circulation. PVR is a useful measure to apply to patients with increased mPAP. PVR distinguishes passive PH (elevated mPAP, normal PVR) from PH caused by pulmonary vascular disease (elevated mPAP, elevated PVR). By definition, PVR and mPAP are both elevated in PAH. However, PVR can also be elevated in patients with valve disease or LV disease (some of whom have an element of pulmonary artery disease, in addition to passive PH). PAH remains a diagnosis of exclusion. After excluding lung disease, thromboembolic disease, LV disease, or valve disease, the diagnostic criteria for PAH requires both a mPAP greater than 25 mm Hg and a PVR greater than 3 Wood units. In such a setting, PAH is the most likely cause of the PH. Invasive hemodynamic studies are essential to establish a correct diagnosis: therefore, the committee cautions against over-reliance on noninvasive, echocardiographically derived estimates of PAP. If one considers a general cardiology population, PAP will be elevated much more often due to left heart diseases (systolic or diastolic dysfunction) or valvular disease than by true pulmonary vascular disease. It was the minority opinion that the requirement for

an elevation in PVR greater than 3 Wood units not be included as a component of the hemodynamic definition of PAH. These committee members cited primarily high flow conditions as potential exceptions to this definition, including uncorrected CHD, sickle cell disease, and portopulmonary hypertension. At certain stages of these disorders, some patients might have elevated mPAP, but a normal PVR due to a high cardiac output, yet have pulmonary vascular disease histologically. Ultimately, it may be proposed that elevated PAP alone is sufficient to diagnosis PH, whereas PVR must be included to diagnose PAH.

6.7. Right Heart Catheterization

Some patients initially suspected of having PAH will not require catheterization, having had an alternative diagnosis established by noninvasive testing. However, all patients that are still suspected of having PAH after noninvasive evaluation should undergo RHC prior to initiation of therapy. The utility of RHC is dependent on the accuracy and completeness of the data obtained. The sequence in this diagnostic algorithm, with the RHC reserved for those who after noninvasive screening are considered "probable PAH patients," allows the procedure to be focused on measuring PAP, calculating PVR, and performing vasodilator testing. While RHC remains the gold standard assessment of hemodynamics in PH, most often, measurements are made with the patient at rest, and may not reflect the true extent
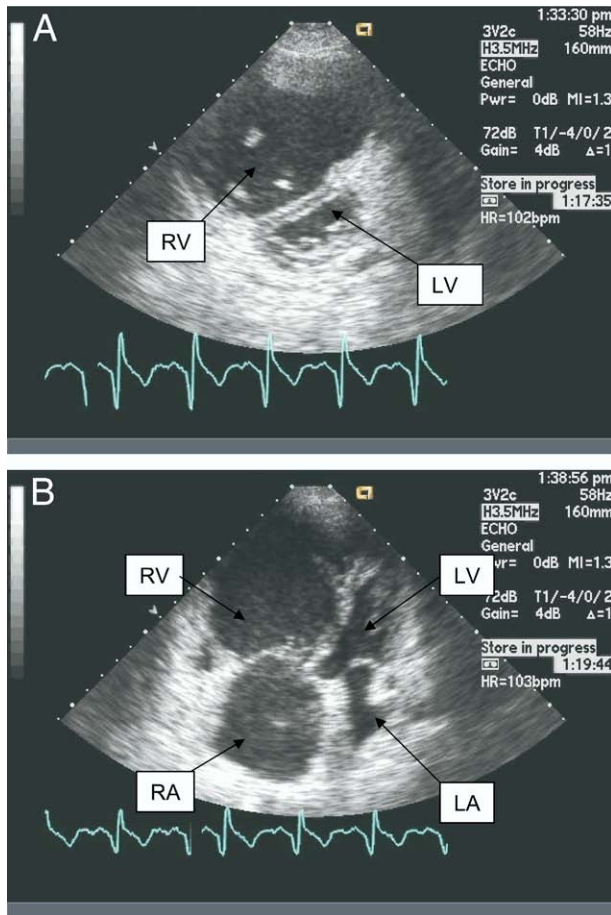
Figure 5. Echocardiographic Features of PAH

(A) Parasternal short axis view. (B) Apical 4 chamber view. Common echocardiographic findings in PAH include: right atrial enlargement; right ventricular enlargement; abnormal contour, flattening, or reverse curvature of the interventricular septum; and underfilled left heart chambers. LA indicates left atrial; LV, left ventricular; RA, right atrial; and RV, right ventricular. Reprinted with permission from the University of Michigan.

of hemodynamic compromise. Exercise RHC is technically difficult, both to perform and interpret, and while not used routinely in most clinical settings, is an area of active investigation.

6.8. Components of an Optimal Invasive Evaluation

The rigorous diagnosis of PAH in the catheterization laboratory should include wedging a balloon flotation catheter in several segments of the pulmonary vasculature. Measurement of the wedge pressure, a surrogate for left atrial pressure in the absence of pulmonary vein obstruction, is useful to exclude PH due to left heart diseases; the wedge pressure may be normal in some segments in pulmonary veno-occlusive disease. The wedge pressure should be measured at end-expiration of a spontaneous respiratory cycle. If an optimal wedge pressure tracing cannot be obtained, or if there is any question about the accuracy of the wedge pressure tracing, a measurement of LV end-diastolic pressure should be obtained. As PCWP measurements are

Table 5. Causes for PH Identified by Echocardiography

Conditions That Predispose to Pulmonary Hypertension
- Congenital or acquired valvular disease (MR, MS, AS, prosthetic valve dysfunction)
- Left ventricular systolic dysfunction
- Impaired left ventricular diastolic function (hypertensive heart disease, HCM, Fabry's disease, infiltrative cardiomyopathies)
- Other obstructive lesions (coarctation, supravalvular AS, subaortic membrane, cor triatriatum)
- Congenital disease with shunt (ASD, VSD, coronary fistula, patent ductus arteriosus, anomalous pulmonary venous return)
- Pulmonary embolus (thrombus in IVC, right-sided cardiac chamber, or PA; tricuspid or pulmonic valve vegetation)
- Pulmonary vein thrombosis/stenosis

Findings That Suggest Specific Disease Entity
- Left-sided valve changes (SLE, anorexigen use)
- Intra-pulmonary shunts (hereditary hemorrhagic telangiectasia)
- Pericardial effusion (IPAH, SLE, systemic sclerosis)

AS indicates aortic stenosis; ASD, atrial septal defect; HCM, hypertrophic cardiomyopathy; IPAH, idiopathic pulmonary arterial hypertension; IVC, inferior vena cava; MR, mitral regurgitation; MS, mitral stenosis; PA, pulmonary artery; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

sometimes inaccurate, a direct measurement of LVEDP is recommended in patients in whom left heart disease is the likely etiology, such as those with symptoms of orthopnea or associated risk factors. Thermodilution cardiac output, if results are consistent when measured in triplicate, can be adequate in PAH patients, provided there is not severe tricuspid regurgitation or an intracardiac shunt. Indeed, there are data suggesting that even in the presence of low cardiac output and significant tricuspid regurgitation the thermodilution technique correlates well with the Fick technique in patients with PH (107). However, because severe tricuspid regurgitation is not uncommon in PAH, a Fick determination of cardiac output may be required. Potential errors related to the Fick measurement include assumptions and inaccurate measurements of oxygen consumption. Without a reliable measure of cardiac output, the ability to calculate PVR and to interpret acute vasodilator testing is compromised.

Table 6. Essential Components of Invasive Hemodynamic Assessment

Oxygen saturations (SVC, IVC, RV, PA, SA)

Right atrial pressure

Right ventricular pressure

Pulmonary artery pressure, systolic, diastolic, mean

Pulmonary arterial wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure

Cardiac output/index

Pulmonary vascular resistance

Systemic blood pressure

Heart rate

Response to acute vasodilator

IVC indicates inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SA, systemic artery; and SVC, superior vena cava.

Table 7. Agents for Acute Vasodilator Testing

	Epoprostenol	Adenosine	Nitric Oxide
Route of Administration	Intravenous infusion	Intravenous infusion	Inhaled
Dose Titration	2 ng/kg/min every 10 to 15 min	50 mcg/kg/min every 2 min	None
Dose Range	2 to 10 ng/kg/min	50 to 250 mcg/kg/min	10 to 80 ppm
Side Effects	Headache, nausea, lightheadedness	Dyspnea, chest pain, AV block	Increased left heart filling pressure in susceptible patients

AV indicates atrioventricular.

6.9. Safety of Heart Catheterization

Although RHC and pulmonary angiography are invasive, they can be performed safely by experienced operators even in patients with severe PH and right heart failure. A recent study retrospectively reviewed over 5,000 RHC procedures and prospectively collected an additional 1,500 procedures, for a total of 7,218 RHC procedures performed at 20 major pulmonary vascular centers over a 5-year period (108). The results from the retrospective and the prospective analyses were almost identical. Overall, 76 (1.1%) serious events were reported. The most frequent complications were related to venous access (e.g., hematoma, pneumothorax), followed by arrhythmias and hypotensive episodes related to vagal reactions or pulmonary vasoreactivity testing. The vast majority of these complications were mild to moderate in intensity and resolved either spontaneously or after appropriate intervention. Four fatal events were recorded in association with any of the catheter procedures, only 1 of which was directly related to the performance of the procedure, resulting in an overall procedure-related mortality of 0.05%.

6.10. Spontaneous Variability in Pulmonary Artery Pressure

Vascular pressure measurements obtained during RHC may be influenced by ventilation in 2 ways that must be considered in the interpretation of hemodynamic variables: 1) normal fluctuations in PAP and flow that occur as a function of phasic, dynamic changes during breathing; and 2) larger, partly artifactual swings in pressure that may occur during exercise, hyperventilation, valsalva, or in the setting of chronic lung disease. The normal decrease in intrathoracic pressure that is caused by inspiration slightly reduces PAP relative to atmospheric pressure and increases venous return to the right heart, resulting in an increase in pulmonary blood flow. With passive exhalation, intrathoracic pressure approaches atmospheric pressure. These effects in normal individuals are small, but become accentuated during assisted ventilation or in patients with lung disease. Our consensus was that physicians can reduce variability by consistently measuring pressures over 2 to 3 respiratory cycles at end-exhalation when intrathoracic pressure is closest to atmospheric.

6.11. Ambulatory Measurement of Pulmonary Hemodynamics

Despite the "definitive" role of RHC, the procedure is carried out under artificial conditions that may not reflect pulmonary hemodynamic conditions during the patients' daily lives. Thus, using a single value for a hemodynamic parameter as a baseline assessment of disease that is known to progress or against which to judge the effects of therapy risks mistaking spontaneous variability for a meaningful difference (or lack of difference). Ongoing investigation of an implantable monitor that provides continuous RV and PA hemodynamics (109,110) may provide a more reliable means of assessing the course of selected patients (111).

6.12. Acute Vasodilator Testing

The rationale for vasodilator testing in the diagnostic evaluation of PAH patients is based on 2 factors: 1) acute vasodilator responsiveness identifies patients with a better prognosis; and 2) responders are more likely to have a sustained beneficial response to oral calcium channel blockers than nonresponders and could be treated with these less expensive drugs (84,112).

6.13. Agents for Acute Vasodilator Testing

Acute vasodilator testing is usually performed during the same procedure as the diagnostic catheterization. The ideal vasodilator agent for PAH is selective for the pulmonary circulation and has rapid onset and offset of effect. Acute vasodilator testing is most commonly performed using iNO (113), intravenous epoprostenol (114), or intravenous adenosine (115) (Table 7). Although there is no evidence-based guideline for selection of vasodilators, it is our consensus that iNO is the preferred vasodilator, while intravenous epoprostenol and intravenous adenosine are acceptable alternatives. The optimal dose of iNO has not been established by a clinical trial. However, in clinical practice, it is common to use doses of 20 to 40 ppm for 5 minutes. Repeat hemodynamics should be obtained while on iNO and it may then be discontinued, without weaning, after the hemodynamic data are obtained. The choice of vasodilator remains one of operator preference; however, one should not use calcium channel blockers, sodium nitroprusside, or nitrates for acute vasodilator testing as the safety and efficacy of these agents for acute vasodilator testing has not been established in PAH patients.

6.14. Definition of Responders to Acute Vasodilator Testing in Pulmonary Arterial Hypertension

The definition of a "positive" response is controversial. Using the definition of a positive response as a 20% fall in both PAP and PVR with either intravenous epoprostenol or

iNO, Sitbon et al. (84) found only 70 responders out of 557 patients with IPAH (12.6%), a rate lower than that reported by Rich et al. (83) in 64 IPAH patients (26.6%) or by Weir et al. (116) in the NIH registry (55%) (83,84,116). More importantly, Sitbon et al. (81) observed that only 38 of the 70 acute responders (6.8% of the total IPAH study population) displayed long-term improvement with calcium channel blocker therapy. Logistic regression analysis identified the following variables achieved during acute vasodilator administration that were associated with long-term calcium channel blocker therapy success: a reduction in mPAP to less than 37 mm Hg, a fall in mPAP greater than 31%, a reduction in PVR to less than 6.7 Wood units, and a fall in PVR greater than 45%. These authors noted, however, that 6 long-term responders to calcium channel blockers failed to meet these a posteriori criteria of acute response.

Based largely on the data from the Sitbon series, the European Society of Cardiology and the ACCP guidelines proposed that an acute response to acute vasodilator testing be defined as a decrease in mPAP by at least 10 mm Hg to an absolute level of less than 40 mm Hg without a decrease in cardiac output (105,117). While the sensitivity of these criteria are insufficient to capture all patients who may be responsive to long-term calcium channel blocker therapy, they are sufficiently specific to identify patients who are unlikely to benefit from this form of therapy and for whom other treatments are appropriate. There are little data on which to make recommendations in the patient with an mPAP less than 40 mm Hg at baseline. In the event that such a patient had a substantial (less than 20%) reduction in mPAP in the setting of a normal cardiac output, it would be reasonable to administer a trial of calcium channel blockers and assess the clinical response.

6.15. Vasodilator Testing in Pulmonary Arterial Hypertension Subsets

The best data supporting the use of acute vasodilator testing to determine prognosis comes from IPAH patients. Limited data exist, but suggest that responders to vasodilators are rare among other groups, including those with the BMPR2 genotype (118) anorexigen induced PAH (119), and those with scleroderma spectrum of diseases (120). Caution is required in testing patients with concomitant LV disease, as pulmonary edema in response to iNO or epoprostenol has been reported in patients with stable heart failure due to left heart disease (121) or with pulmonary venoocclusive disease, possibly relating to vasodilatation and flooding of the capillary bed in response to a highly selective arterial vasodilator.

DETERMINING TREATMENT

In general, distinguishing optimal treatment strategies broadly depends on the diagnostic categories, hemodynamics, severity of the disease, and associated findings. (See Section 6.15.)

6.16. Summary

We recommend the following, with respect to diagnostic assessment for PH:

1. Certain individuals with predisposing risk factors warrant periodic screening for PAH (Table 3).
2. Patients in whom there is an index of suspicion of PH based on history, risk factor assessment, physical examination, CXR, and ECG warrant further evaluation.
3. The most appropriate initial study to evaluate patients in whom PH is suspected is a Doppler echocardiogram.
4. Evaluation for other etiologies of PH, for example, CTEPH, is appropriate in all instances (Figure 3).
5. The diagnosis of PAH requires confirmation by a complete RHC. The hemodynamic definition of PAH is an mPAP greater than 25 mm Hg, a PCWP/LAP/LVEDP less than or equal to 15 mm Hg, and a PVR greater than 3 Wood units.
6. Acute vasodilator testing should be performed in all IPAH patients who might be considered potential candidates for long-term therapy with oral calcium channel blockers. IPAH patients in whom chronic calcium channel blocker therapy would not be considered, such as those with overt right heart failure or hemodynamic instability, need not undergo acute vasodilator testing.
7. Acute vasodilator testing should be performed at centers experienced in the administration of these agents and in the interpretation of the results.
8. The definition of an acute response that may warrant initiation of long-term therapy with oral calcium channel blockers is a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output. Although this stringent definition may misclassify a few patients who could be treated effectively with long-term oral calcium channel blockers, it will reliably identify those who are least likely to benefit from oral calcium channel blocker therapy and, therefore, provides the greatest degree of safety.
9. Patients with PAH due to conditions other than IPAH have a very low rate of long-term responsiveness to oral calcium channel blocker therapy. Accordingly, the decision to proceed with acute testing in such patients should be individualized.
10. Acute vasodilator testing is not indicated, and may be harmful, in patients with significantly elevated left heart filling pressures.

7. Evidence-Based Treatment Algorithm

Treatment of PAH has evolved considerably over the past decade due in part to advances in knowledge of the basic pathobiology of the disease and the availability of agents that target known derangements in the pathobiologic pro-

cess. Treatment algorithms have been formulated by the ACCP, the European Society of Cardiology, and a panel of experts who convened at the Third World Symposium on Pulmonary Hypertension held in Venice, Italy, in 2003 (105,117,122). Notably, the clinical data on which these algorithms are based were conducted primarily in patients with IPAH and PAH related to connective tissue disease and anorexigens. A smaller number of trials have also included PAH related to CHD and HIV. These clinical trial data cannot necessarily be extrapolated to those with other types of PH, including those related to left heart disease and hypoxemic lung disease, or other types of WHO Group I PAH.

Treatment goals in PAH patients are numerous. Improving the patients symptoms, which commonly include dyspnea, is paramount. Enhancing functional capacity, measured objectively by an assessment of exercise endurance such as the 6MW or a cardiopulmonary exercise test, is also a treatment objective. Given the severe hemodynamic derangements in PAH, lowering PAP and normalizing cardiac output are important treatment goals. Another important goal is to reverse or at least prevent progression of the disease, that is, prevent the need for more therapies, hospitalization, and lung transplantation. Last, we strive to improve survival, which, while important, is rarely an end point in clinical trials of PAH treatment due to the small number of patients and limited duration of the trials.

7.1. General Measures

While limited data exist on which to base recommendations regarding exercise, we encourage low level graded aerobic exercise, such as walking, as tolerated. Intensive exercise training was studied in a randomized fashion in 30 patients who were stable on disease-targeted medical therapy. After 15 weeks, those who received exercise training demonstrated improvements in 6MW test, quality of life, functional class, and peak oxygen consumption (123). Patients are advised to avoid heavy physical exertion or isometric exercise (straining against a fixed resistance) as this may evoke exertional syncope. Exposure to high altitudes may contribute to hypoxic pulmonary vasoconstriction and may not be well tolerated. Similarly, some patients may require oxygen on commercial aircraft. While there are no data from controlled trials, we recommend that patients with a preflight pulse oximetry saturation of less than 92% should receive supplemental oxygen (124). A sodium restricted diet (less than 2,400 mg per day) is advised and is particularly important to manage volume status in patients with RV failure. Routine immunizations, such as those against influenza and pneumococcal pneumonia, are advised.

The hemodynamic fluctuations of pregnancy, labor, delivery, and the postpartum period are potentially devastating in PAH patients. Some series have demonstrated a 30% to 50% maternal mortality rate (125). Current guidelines recommend that pregnancy be avoided or terminated early in women with PAH (117). It is important to discuss effective methods of birth control with women with PAH of child-bearing potential, although the preferred method is not clear. While estrogen-containing contraceptives may increase risk of venous thromboembolism, currently available lower-dose preparations with concurrent warfarin anticoagulation are a reasonable option. Surgical sterilization and barrier methods are also alternatives.

7.2. Background Therapy

Several agents are commonly used in the treatment of PAH despite relatively little controlled trial data. Anticoagulants have been studied in 3 noncontrolled observational series in patients with primarily IPAH, 1 prospective and 2 retrospective (83,85,126). An improvement in survival with warfarin anticoagulation has been observed. Per our committee's consensus, we recommend warfarin anticoagulation in IPAH patients titrated to an international normalized ratio of 1.5 to 2.5. Few data exist to guide recommendations for patients with associated forms of PAH. We recommend anticoagulation in such patients with more advanced disease, such as those on continuous intravenous therapy, in the absence of contraindications. Diuretics are indicated to manage RV volume overload, which is commonly manifest as elevated jugular venous pressure, lower extremity edema, and abdominal distention. In some cases, intravenous diuretics are required. Serum electrolytes and renal function should be closely monitored. As hypoxemia is a potent pulmonary vasoconstrictor, most experts recommend oxygen supplementation to maintain oxygen saturation above 90%. There are few data pertaining to the use of digoxin in PAH. One acute study demonstrated that the administration of intravenous digoxin in IPAH patients produced a modest increase in cardiac output and a reduction in circulating norepinephrine levels, although longer-term data are not available (127). Digoxin is sometimes used in those patients with right heart failure and a low cardiac output and in patients with atrial arrhythmias.

7.3. Calcium Channel Blockers

The enthusiasm for the use of calcium channel blockers in IPAH dates back to 1992 with the publication of a study that demonstrated 95% 5-year survival in a very select group of patients with IPAH who exhibited an acute vasodilator response to calcium channel blockers (83). More recent data regarding vasodilator testing were discussed previously (Section 6). The current consensus definition of a response is now defined as a fall in mPAP of greater than or equal to 10 mm Hg, to an mPAP less than or equal to 40 mm Hg, with an unchanged or increased cardiac output. While many experts also perform vasodilator testing on patients with associated forms of PAH, true responders are very uncommon. Patients who meet these criteria may be treated with calcium channel blockers and should be followed closely for both safety and efficacy of calcium channel blocker therapy. If a patient who meets the definition of an acute response does not improve to functional class I or II on calcium

channel blocker therapy, the patient should not be considered a chronic responder, and alternative or additional PAH therapy should be instituted. Long acting nifedipine, diltiazem, or amlodipine are the most commonly used calcium channel blockers. Due to its potential negative inotropic effects, verapamil should be avoided.

7.4. Prostanoids

As previously discussed, prostacyclin synthase is reduced in PAH patients, resulting in inadequate production of prostacyclin I$_2$, a vasodilator with antiproliferative effects. Administering prostanoids has been a mainstay of PAH therapy for more than a decade. There are currently 3 commercially available prostanoids: epoprostenol, treprostinil, and iloprost.

7.5. Epoprostenol

Intravenous epoprostenol improves functional class, exercise tolerance, hemodynamics, and survival in IPAH. An open label, randomized trial of 81 functional class III and IV IPAH patients demonstrated significant improvements in the primary end point of 6MW test (32 m increase with epoprostenol versus 15 m decrease with conventional therapy alone, placebo-corrected change of 47 m) and in secondary end points including hemodynamics and quality of life (76). Eight patients, all of whom were randomized to conventional therapy alone, died over the course of the 12-week trial, suggesting a survival benefit of the drug (p= 0.003). Longer-term observational studies have confirmed the chronic benefits of intravenous epoprostenol in IPAH patients. In a series of 178 functional class III and IV IPAH patients, Sitbon et al. (78) reported improved survival with intravenous epoprostenol compared to historical controls with 1-, 2-, 3-, and 5-year survival rates of 85%, 70%, 63%, and 55%, respectively. Similarly, in a series of 162 functional class III and IV patients, intravenous epoprostenol resulted in improved survival as compared with the predicted survival based on the NIH equation with 1-, 2-, 3-, and 5-year survival rates of 88%, 76%, 63%, and 56%, respectively (77). Improvements in functional class, exercise endurance, and hemodynamics were noted in both of these observational studies.

Intravenous epoprostenol has also been evaluated in PAH associated with the scleroderma spectrum of diseases. A multicenter, open label, randomized trial demonstrated marked improvements in exercise endurance (median change +46 m with epoprostenol, −48 m with conventional therapy alone) and hemodynamics, but no effect on mortality after 12 weeks of therapy (80). Observational series have also reported favorable effects of intravenous epoprostenol in patients with numerous forms of associated PAH (72,79,128–131).

Epoprostenol must be delivered by continuous intravenous infusion. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. Intravenous epoprostenol is commonly started in the hospital at a dose of 2 ng/kg/min and the dose is further adjusted up based on symptoms of PAH and side effects of the drug. While the dosing must be highly individualized, most experts believe that the optimal dose range for chronic therapy is between 25 and 40 ng/kg/min for most adult patients, when used as monotherapy. Chronic overdose sometimes results in high cardiac output failure, and the long-term consequences of this are unknown and may be detrimental (132). Common side effects include headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions can be life-threatening. Given its considerable complexity, epoprostenol use should be limited to centers experienced with its administration and with systematic follow-up of patients.

7.6. Treprostinil

Treprostinil is a stable prostanoid with an elimination half life of about 4.5 hours that was first studied using subcutaneous administration during a 12-week, placebo controlled, multicenter, randomized trial of 470 patients with functional class II, III, or IV PAH (IPAH, connective tissue disease of CHD related) (133,134). Subcutaneous treprostinil resulted in a modest but statistically significant between treatment group median increase of 16 m of the 6MW test, which was dose related. The change in 6MW test was a result of improvement in the group receiving treprostinil, and there was no change in 6MW test in the placebo group. Adverse effects included pain or erythema at the site of the subcutaneous infusion in 85% of patients. Other common side effects include headache, diarrhea, rash, and nausea. The Food and Drug Administration (FDA) approved subcutaneous treprostinil in 2002 for use in functional class II, III, and IV PAH.

More recently, intravenous treprostinil has been studied in an open label, uncontrolled fashion. Tapson et al. (135) reported an 82 m improvement (from 319 plus or minus 22 m to 400 plus or minus 26 m, p=0.001) of 6MW test in 16 functional class III or IV PAH patients treated with intravenous treprostinil as monotherapy. In a similar open label trial, Gomberg-Maitland et al. (136) transitioned 31 functional class II and III PAH patients from intravenous epoprostenol to intravenous treprostinil. Twenty-seven patients completed the transition, and 4 were transitioned back to epoprostenol. Exercise endurance as measured by the 6MW test was maintained among the patients completing the transition (438 plus or minus 16 m at baseline, 439 plus or minus 16 m at week 12), although there was a modest increase in PAP and decrease in CI. Notably, the dose of intravenous treprostinil at the end of 12 weeks was more than twice the dose of intravenous epoprostenol at the start of the study (83 ng/kg/min versus 40 ng/kg/min). In 2004, the FDA approved the use of intravenous treprostinil in functional class II, III, and IV PAH patients in whom subcutaneous infusion is not tolerated. Intravenous treprostinil has a side effect profile similar to intravenous epopro-

stenol. A Centers for Disease Control and Prevention report recently raised the concern for an increased risk of blood-stream infections, particularly with gram-negative organisms, in patients receiving intravenous treprostinil (137). Catheter infections can be life threatening. The overall infection rate with treprostinil was significantly greater than that of epoprostenol (incidence ratio 2.57, 95% confidence interval: 1.81 to 3.64), with a higher rate of gram-negative bacteremia. There was considerable variability from one site to another. Inclusion of the index site that made the initial observation, the retrospective nature of the study, and site to site variation, with some just including treprostinil patients as opposed to both epoprostenol and treprostinil, are among the limitations of this observation. This finding has led to revised recommendations regarding catheter care (138). Clinically, it also highlights the importance in the choice of empiric antibiotics in those suspected of having a blood-stream infection. Investigational trials with both inhaled and oral formulations of treprostinil are ongoing. Given the complexity of administration of both intravenous and sub-cutaneous treprostinil, administration should be limited to centers with experience with this agent.

7.7. Iloprost

Iloprost is a prostanoid that can be delivered by an adaptive aerosol device that has been studied in a 12-week, multi-center, placebo-controlled, randomized trial of 207 func-tional class III and IV patients with either IPAH, PAH associated with scleroderma spectrum of diseases or appetite suppressants, or PH related to inoperable chronic throm-boembolic disease (139). This study utilized a novel com-posite end point of improvement in functional class by at least 1 level and improvement in 6MW test by at least 10% in the absence of clinical deterioration. The combined clinical end point was met by 16.8% of those receiving inhaled iloprost compared to 4.9% of those receiving pla-cebo (p=0.007). The treatment effect on the 6MW test was a mean increase of 36 m in favor of iloprost (p=0.004). This was attributable to both an improvement in the iloprost group and a deterioration in the placebo group. Longer-term outcomes with iloprost monotherapy are conflicting. In a study of 24 iloprost-treated IPAH patients, Hoeper et al. (140) reported sustained benefits in exercise capacity and hemodynamics at 1 year. More recently, Opitz et al. (141) reported event-free survival rates of 53%, 29%, and 20% at 1, 2, and 3 years, respectively, in IPAH patients treated with iloprost monotherapy. Common side effects of inhaled iloprost include cough, headache, flushing, and jaw pain. Iloprost was approved by the FDA in 2004 for functional class III and IV PAH.

7.8. Endothelin Receptor Antagonists

Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the development of PAH. Attempting to treat PAH by endothelin receptor blockade is a promising approach supported by evidence of the pathogenic role of endothelin-1 in PAH, as discussed in Section 3.

7.9. Bosentan

In an initial effort to evaluate bosentan in PAH, a relatively small, randomized, double-blind, placebo-controlled, mul-ticenter study of 32 functional classes III or IV IPAH or scleroderma spectrum of diseases associated patients PAH were randomized to receive bosentan versus placebo (2:1 ratio) (142). After 12 weeks, the 6MW test improved by 70 m (from 360 plus or minus 19 m at baseline to 430 plus or minus 14 m at week 12; p<0.05) in the bosentan arm, whereas no improvement was seen with placebo (355 plus or minus 25 m at baseline and 349 plus or minus 44 m at week 12). The median change from baseline was 51 m with bosentan versus −6 m with placebo. The mean difference between treatment arms in the 6MW test was 76 plus or minus 31 m (mean plus or minus SEM) in favor of bosentan (95% confidence interval: 12 to 139; p=0.021). Bosentan improved cardiac index and reduced mPAP and PVR. Functional class improved in patients treated with bosentan.

A second double-blind, placebo-controlled study evalu-ated bosentan in 213 patients with WHO functional classes III to IV PAH (either idiopathic or associated with con-nective tissue disease) who were randomized to placebo or bosentan 125 or 250 mg twice daily for a minimum of 16 weeks (62.5 mg twice daily for 4 weeks, then target dose) (143). The primary end point was change in exercise capacity (assessed by 6MW test), and secondary end points included changes in Borg dyspnea index, WHO functional class, and time from randomization to clinical worsening. After 16 weeks, bosentan improved the 6MW test by 36 m, whereas deterioration (−8 m) was seen with placebo, and the difference between treatment groups in the mean change in 6MW test was 44 m in favor of bosentan (95% confi-dence interval: 21 to 67 m, p=0.0002). No dose response for efficacy could be ascertained, although the placebo-corrected improvement in 6MW test for the currently FDA-approved dose of 125 mg twice daily was 35 m. This study was the first to assess time to clinical worsening, a composite morbidity and mortality end point. Time to clinical worsening was defined in this study as time to death, lung transplantation, hospitalization for PH, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy. The risk of clinical worsening was reduced by bosentan compared with placebo (p=0.0015). Abnormal hepatic function (as indi-cated by elevated levels of alanine aminotransferase and/or aspartate aminotransferase), syncope, and flushing occurred more frequently in the bosentan group. Abnormal hepatic function was dose-dependent, being more frequently re-ported as an adverse event in the high dosage bosentan group (250 mg twice daily) than in the low dosage group (125 mg twice daily) (14% versus 5%, respectively).

Longer-term data regarding bosentan therapy have been more recently published. McLaughlin et al. (82) reported

that open label, first-line therapy with bosentan, with the addition or transition to other therapy as needed, resulted in Kaplan-Meier survival estimates of 96% at 12 months and 89% at 24 months. At the end of 12 and 24 months, 85% and 70% of patients, respectively, remained alive and on bosentan monotherapy. Similar survival rates of 90% and 87% at 1 and 2 years were reported in a single center retrospective analysis (144). However, based on predefined clinical criteria, 44% of patients required prostanoid therapy during follow up. Sitbon et al. (145) compared open label survival in functional class III IPAH treated with bosentan with historical data from similar patients treated with epoprostenol. Baseline characteristics for the 139 patients treated with bosentan and the 346 patients treated with epoprostenol suggested that the epoprostenol cohort had more severe disease. Kaplan-Meier survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated cohort and 91% and 84% in the epoprostenol cohort.

Bosentan therapy has also been evaluated by Galie et al. (146) in a multicenter, double-blind, randomized, and placebo-controlled study in patients with functional class III Eisenmenger syndrome (the BREATHE-5 [Tracleer (Bosentan) in Patients With Pulmonary Arterial Hypertension Related to Eisenmenger Physiology] study). Fifty-four patients were randomized 2:1 to bosentan versus placebo for 16 weeks. Bosentan did not worsen oxygen saturation, and compared with placebo, bosentan reduced pulmonary vascular resistance index, decreased mPAP, and increased exercise capacity. Four patients discontinued due to adverse events, 2 (5%) in the bosentan arm and 2 (12%) in the placebo arm. Open label data with bosentan suggest clinical improvements in HIV patients with PAH, while preliminary data suggest benefits in those with inoperable CTEPH and early stage disease (147,148). Bosentan has also recently been evaluated in a mildly symptomatic or functional class II population (149). In this study, 168 PAH patients (IPAH, FPAH, PAH associated with connective tissue disease, anorexigen use, HIV, CHD) with a mean baseline 6MW test of 435 m were randomized to receive bosentan or placebo for 26 weeks. There was a significant improvement in one coprimary end point, change in PVR, but not the other, change in 6MW test. There was an improvement in the secondary end point of time to clinical worsening. The adverse event profile with bosentan was similar to previous studies.

Bosentan is currently widely used in patients with PAH. Close follow-up over time, of both efficacy and safety, is encouraged. The FDA requires that liver function tests be checked monthly, and that the hematocrit should be checked every 3 months. In addition to potential hepatotoxicity, other side effects include anemia and the development of edema. Hormonal methods of birth control may be less effective with concurrent administration of bosentan, and barrier techniques of contraception are recommended. This is particularly important because bosentan is poten-

tially teratogenic. 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 counseled regarding this possibility prior to taking these drugs.

7.10. Sitaxsentan

Sitaxsentan is more selective for the ET_A receptor. In a randomized, double-blind, placebo-controlled trial (the STRIDE-1 [Sitaxsentan to Relieve Impaired Exercise] trial) 178 NYHA functional class II, III, and IV patients with either IPAH, PAH related to connective tissue disease, or PAH related to congenital systemic to pulmonary shunts, were equally randomized to receive placebo, sitaxsentan 100 mg, or sitaxsentan 300 mg orally once daily. Sitaxsentan improved exercise capacity, as assessed by 6MW test, and functional class after 12 weeks of treatment. The incidence of liver function abnormalities was more favorable for the 100 mg dose, that is, the incidence of elevated aminotransferase values (greater than $3\times$ normal), which reversed in all cases, was 3% for the placebo group, 0% for the 100-mg group, and 10% for the 300-mg group. In an earlier pilot study, sitaxsentan was associated with fatal hepatitis when used at higher doses (150). The most frequently reported laboratory adverse event was increased international normalized ratio or prothrombin time, related to sitaxsentan's inhibitory effect on the CYP2C9 P450 enzyme, the principal hepatic enzyme involved in the metabolism of warfarin.

The STRIDE-2 study randomized 247 PAH patients (245 were treated) with IPAH or PAH associated with connective tissue disease or CHD to blinded placebo (n=62), blinded sitaxsentan 50 mg (n=62) or 100 mg (n=61), or open-label bosentan (n=60) (151). At week 18, patients treated with sitaxsentan 100 mg had an increased 6MW test compared with the placebo group (31.4 m, p=0.03), and improved functional class (p=0.04). The placebo-subtracted treatment effect for sitaxsentan 50 mg was 24.2 m (p=0.07) and for open-label bosentan, 29.5 m (p=0.05). The incidence of elevated hepatic transaminases (greater than 3 times the upper limit of normal) was 6% for placebo, 5% for sitaxsentan 50 mg, 3% for sitaxsentan 100 mg, and 11% for bosentan. Sitaxsentan is currently approved in the European Union, Canada, and Australia, but not in the United States.

7.11. Ambrisentan

Ambrisentan is a relatively selective antagonist of the ETA receptor. A phase 2 dose-ranging study evaluated the efficacy and safety of 4 doses of ambrisentan in patients with PAH (152). In this double-blind study, 64 patients with IPAH or PAH associated with connective tissue disease, anorexigen use, or HIV infection were randomized to receive various doses of ambrisentan (1, 2.5, 5, or 10 mg) once daily for 12 weeks. The 6MW test (plus 36.1 m, p <0.0001) improved from baseline with ambrisentan, with similar increases for each dose group (range plus 33.9 to plus

38.1 m). Adverse events were generally unrelated to dose, including the incidence of elevated serum aminotransferase concentrations greater than 3 times the upper limit of normal (incidence of 3.1%). Two pivotal phase III clinical trials of ambrisentan in PAH have been completed and randomized 202 and 192 patients with PAH respectively to placebo or ambrisentan. Doses of 5 and 10 mg of ambrisentan were compared with placebo in ARIES (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study)-1, and doses of 2.5 and 5 mg of ambrisentan were compared with placebo in ARIES-2 (153). After 12 weeks, there were improvements in the primary end point of 6MW test in both studies. The change in mean 6MW test in ARIES-1 was plus 22.8 m and plus 43.6 m for the 5- and 10-mg doses, respectively, and minus 7.8 m in the placebo group. In ARIES-2 it was plus 22.2 m and plus 49.4 m for the 2.5- and 5-mg doses, respectively, and minus 10.1 m in the placebo group. The secondary end point of time to clinical worsening was improved with active therapy in ARIES-2. Ambrisentan was FDA approved in June 2007 for PAH patients with functional class II and III symptoms. As a class, endothelin receptor antagonists have the potential for liver injury and teratogenicity. The incidence of transaminases elevations at 1 year was 2.8% in the clinical trials. Monthly monitoring of liver function tests, a monthly pregnancy test in women of child-bearing potential, and periodic hemoglobin measurements are required. Other potential side effects include lower extremity edema, which is more frequent (29%) and severe in patients over 65 years of age, and nasal congestion (154). Precautions regarding contraception and testicular atrophy are similar to bosentan.

7.12. Phosphodiesterase Inhibitors

As discussed in Section 3, the vasodilatory effects of NO depend upon its ability to augment and sustain cGMP content in vascular smooth muscle. NO activates guanylate cyclase, which increases cGMP production. Cyclic GMP causes vasorelaxation, but its effects are short-lived due to the rapid degradation of cGMP by PDEs. PDE-5 hydrolyzes cAMP and cGMP, limiting their intracellular signaling. PDE-5 inhibitors, such as sildenafil and tadalafil, might therefore be expected to enhance or prolong the effects of these vasodilating (and perhaps antiproliferative) cyclic nucleotides.

7.13. Sildenafil

Sildenafil is a specific PDE5 inhibitor that has been utilized previously for treatment of erectile dysfunction. The SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) study was a randomized, double-blind, placebo-controlled trial that assigned 278 patients with PAH (either IPAH or PAH associated with connective tissue disease or with repaired congenital systemic-to-pulmonary shunts) to placebo or sildenafil (20, 40, or 80 mg) orally 3 times daily for 12 weeks (155). The 6MW test increased from baseline in all sildenafil groups, with mean placebo-corrected treat-

ment effects of 45, 46, and 50 m for 20-, 40-, and 80-mg doses of sildenafil, respectively ($p<0.001$ for all comparisons). This appeared to be entirely related to improvements with active therapy, as there was little change in 6MW test in the placebo group. All sildenafil doses reduced the mPAP and improved functional class. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil versus placebo. Long-term data (available only at a dose of 80 mg 3 times daily) in 222 patients completing 1 year of treatment with sildenafil monotherapy showed sustained improvement from baseline at 1 year in the 6MW test (51 m). The FDA-approved dose of sildenafil in patients with PAH is 20 mg administered orally 3 times daily. Side effects include headache, flushing, dyspepsia, and epistaxis. There has been considerable discussion as to whether or not higher doses might confer additional hemodynamic benefit, but such doses continue to be "off-label" (156).

7.14. Tadalafil

Another longer-acting PDE inhibitor, tadalafil, is currently undergoing clinical study. Like sildenafil, tadalafil has been approved previously by the FDA for treatment of erectile dysfunction. However, it remains investigational in patients with PAH.

7.15. Combination Therapy

Given the availability of medications that target different pathologic processes, combination therapy is an attractive theoretical option in PAH, just as in LV systolic dysfunction. The goal of combination therapy should be to maximize efficacy, while minimizing toxicity. The safety and efficacy of combination therapy in PAH is a subject of active investigation. To date, there are 3 small, placebo-controlled, combination therapy trials. One studied functional class III or IV patients with either IPAH or PAH related to connective tissue disease starting on intravenous epoprostenol and randomized them to receive bosentan or placebo (157). This small, underpowered study failed to demonstrate the benefits of combination therapy. More recently, inhaled iloprost has been studied in patients who remained symptomatic (NYHA functional class III or IV) while on stable bosentan therapy for at least 3 months (158). In this multicenter, placebo-controlled, randomized trial, 67 patients with PAH (94% NYHA functional class III, mean baseline 6MW test 355 m) were randomized to receive inhaled iloprost, (5 mcg, 6 to 9 times per day) or placebo. After 12 weeks, the primary efficacy measure, post inhalation 6MW test, improved by 30 m in the iloprost group and 4 m in the placebo group, for a placebo-adjusted difference of plus 26 m ($p=0.051$). There were also improvements in NYHA functional class ($p=0.002$), time to clinical worsening ($p=0.022$) and postinhalation mPAP ($p<0.001$) and PVR ($p<0.001$). However, a study with a similar design was terminated early due to a futility analysis (159). The primary end point, change in 6MW test, improved by 1 m in the

placebo group but declined by 9 m in the iloprost group. None of the secondary end points, including functional class, peak oxygen uptake, and time to clinical worsening, differed between the groups. Most recently, the addition of sildenafil (target dose 80 mg 3 times daily) or placebo was evaluated in 267 PAH patients who remained symptomatic with a 6MW test of 100 to 450 m while on a stable dose of intravenous epoprostenol for at least 3 months (160). Patients treated with sildenafil experienced a placebo-adjusted improvement in 6MW test of 28.8 m (p=0.0002) at 16 weeks, as well as improvements in mPAP, cardiac output, and time to clinical worsening. Several smaller, open label observational studies have suggested benefit of combination therapy. Multiple randomized controlled trials of combination therapy are currently ongoing, and to adequately study the safety and efficacy of combination therapy, we encourage enrollment into randomized controlled trials.

7.16. Limitations of Clinical Trials in Pulmonary Arterial Hypertension

While the medications studied in the clinical trials reviewed in the preceding text represent, in our view, advancements in the care of PAH patients, many patients still remain symptomatic, with a suboptimal quality of life and impaired hemodynamics despite treatment. With the exception of calcium channel blockers in a robust responder, most therapies reduce PAP by 10% to 20%. A recent meta-analysis of 16 randomized trials in PAH found the following: 1) a nonsignificant reduction in all-cause mortality (relative risk 0.70, 95% confidence interval: 0.41 to 1.22); 2) a significant improvement in exercise capacity as assessed by the 6MW test of 42.6 m (95% confidence interval: 27.8 to 57.8 m); and 3) an improved dyspnea status by at least 1 functional class (relative risk 1.83, 95% confidence interval: 1.26 to 2.66) (161). Notably, with one exception, these trials were all 8 to 16 weeks in duration. None were powered to detect a survival benefit. More recently, a meta-analysis performed on 21 randomized controlled trials (3140 patients) in PAH patients published through October 2008 reported improvements in the 6MW distance and a 43% decrease in mortality in patients treated with PAH-specific therapies versus patients randomized to placebo (161a). Additionally, the role of PAH-specific therapy in certain subgroups has not been adequately studied. For example, a meta-analysis of the scleroderma spectrum of diseases related PAH patients included in 10 randomized controlled trials of oral therapy failed to demonstrate an improvement in exercise capacity in this subgroup (162). Interestingly, this is contrary to the study of epoprostenol performed specifically in the scleroderma spectrum of diseases population, which demonstrated the greatest improvement in 6MW test ever reported in a clinical trial in PAH (117).

7.17. Cost Considerations

Clinical trials in PAH have not included analysis regarding cost/benefit ratio, quality-adjusted life years saved, or number needed to treat. The PAH-specific therapies are expensive. The approximate annual cost for sildenafil is $12 761,

for bosentan is $55 890, for ambrisentan is $56 736, and for iloprost is $92 146. Because dosing is individualized and a patient's weight factors into the amount of drug used, there is considerable variation in the cost of epoprostenol and treprostinil from patient to patient. Based on a 70-kg patient at the lower end of the dosing spectrum, the annual cost for epoprostenol is $33 153 and for treprostinil is $97 615. These costs may be much higher for larger patients and at higher doses (163).

7.18. Invasive Therapies

Despite advances in the medical treatment for PAH, many patients experience progressive functional decline, largely related to worsening right heart failure. It is in these patients that interventional and surgical therapeutic options should be considered, including atrial septostomy and lung or combined heart and lung transplantation. In patients with PH caused by chronic pulmonary thromboembolism, surgical thromboendarterectomy may be beneficial. A body of clinical data has emerged to help guide the utilization of these strategies, and reviews of their role in the therapy of patients with PAH have recently been published (164–166). Other surgical approaches, such as RV mechanical assistance, are under investigation.

7.19. Atrial Septostomy

As right heart function worsens in response to ongoing severe PAH, patients experience progressive dyspnea, ascites, edema, and may have presyncope or syncope. Atrial septostomy creates a right to left inter-atrial shunt, decreasing right heart filling pressures and improving right heart function and left heart filling. While the created shunt decreases systemic arterial oxygen saturation, it is anticipated that the improved cardiac output will result in overall augmentation of systemic oxygen delivery.

Several case series have reported hemodynamic and clinical improvement following the procedure (167–169). Improved cardiac output appears to be the principal hemodynamic benefit; the magnitude of the improvement has ranged from 15% to nearly 60%. Improvements in NYHA functional class and 6MW test have also been reported (169). Reported success rates for bridging patients to transplantation with septostomy range from 30% to 40% (167,168). Procedural mortality is high, however, with an estimate of 15% based on published series (though this has ranged from 5% to 50% in the different centers). This mortality is undoubtedly driven by the severity of PAH and right heart failure of the patients undergoing the procedure. At the same time, however, this mortality clearly contributes to the practice of reserving the procedure for critically ill patients. Within this group, those with advanced age, renal dysfunction, and the most severe derangements in hemodynamics and systemic oxygenation face the greatest procedural risk.

Atrial septostomy may be performed by either blade or graded balloon dilation techniques, both of which have been described previously. Recently, the utility of a customized

septostomy device (170) and the use of intracardiac echocardiographic imaging to guide the location and extent of septostomy creation (171) have been reported. Ongoing advances may yield improved outcomes in the future.

Currently, atrial septostomy is recommended for patients with severe PAH and intractable right heart failure despite maximal medical therapy, including optimized PAH-specific agents and inotropes. Indeed, this represents a very narrow window and identification of appropriate patients requires experience and judgment. The goals of the procedure are palliation and restoration and maintenance of clinical stability until a transplant can be performed. Atrial septostomy should be performed only by experienced operators in centers with the resources to care for such critically ill patients. The procedure should be considered before hemodynamic compromise and end-organ dysfunction is too far advanced.

7.20. Lung and Combined Heart and Lung Transplantation

Lung transplantation has been an option for the therapy for select patients with end-stage pulmonary disease for the past 25 years. Currently, approximately 4% of the approximately 1,700 single lung (SLTx), double lung (DLTx), and combined heart and lung (HLTx) transplants annually performed worldwide in adults are for the primary indication of PAH (172). While patients with PAH undergoing transplantation face an increase in operative mortality, their long term outcomes are comparable with patients with other primary indications (172). The International Society for Heart and Lung Transplant registry reports 1-, 3-, 5-, and 10-year survivals of 66%, 57%, 47%, and 27%, respectively, in PAH patients undergoing transplant. By way of comparison, survival rates for all patients transplanted were 78%, 61%, 49%, and 25% at these respective time points (172,173).

There is no agreement on the optimal type of transplantation for patients with PAH. While acceptable outcomes have been demonstrated with SLTx, many centers prefer DLTx to limit the reperfusion injury that has been reported in the donor lung of PAH patients undergoing SLTx (174). The decision to perform HLTx in PAH patients is based on the severity of cardiac decompensation. The combined procedure is generally reserved for patients with intractable right heart failure, especially when a patient has become dependent on inotropic support. Combined heart and lung transplant is also often required in patients with PAH in the setting of complex CHD, although in some instances combining SLTx or DLTx with simultaneous repair of the congenital cardiac abnormality may be feasible (175). Also, patients with PH and concomitant advanced left heart disease may be considered for HLTx. Finally, when PAH is not the primary indication for lung transplantation, the presence of secondary PH and its sequelae may similarly impact the choice of transplant type. Choice of procedure is therefore dependent on the patient characteristics, as well as the desire to optimally use scarce donor organs, the ease (or difficulty) of each surgical procedure, and a given center's preference.

Transplantation as a potential therapeutic option should be discussed with PAH patients at the time of diagnosis. Timing of referral is challenging, and local practices and organ availability must be considered. Patients who are otherwise good transplant candidates should be referred when they have an unacceptable response to PAH therapies. In the current patient prioritization scheme used by the United Network for Organ Sharing, patients with PAH may be assigned a lung allocation score below that of patients with other common diagnoses, such as pulmonary fibrosis. In addition, a determination that a patient is functional class IV paradoxically lowers the patient's score (a recognition of the worsened peri- and posttransplant outcomes observed in these patients). The thoracic committee of the United Network for Organ Sharing is constantly reviewing and revising this process. Application for an exception based on certain hemodynamic criteria is now possible for PAH patients. Revisions to the scoring system to include changes in bilirubin and creatinine are being discussed. Once a patient has been evaluated and considered a candidate for transplantation, aggressive follow up and therapy are required to maintain cardiac function and improve the likelihood that a combined heart and lung transplant will not be required.

7.21. Pulmonary Thromboendarterectomy

Patients with suspected PAH should undergo evaluation for CTEPH. As discussed in the preceding text, the screening tool of choice for CTEPH is perfusion scanning. If indicative of CTEPH, a pulmonary angiogram should be performed. Patients are considered to be candidates for pulmonary thromboendarterectomy (PTE) if they have surgically accessible disease and present acceptable surgical risk. The goal of PTE is to remove sufficient material from the pulmonary arteries to substantially lower PVR and improve cardiac output. The diagnostic evaluation of patients with CTEPH, surgical technique, and outcomes have been reviewed recently (104). This complex and life-saving therapy is best performed at high-volume centers as the learning curve and required support systems are prohibitive for most hospitals.

7.22. Right Ventricular Assist Device

The development of refractory right heart failure portends a grave prognosis in patients with PAH. Left- and biventricular assist devices have proven effective in supporting patients with severe left- and biventricular failure. Preclinical studies have suggested the usefulness of right ventricular assist device (RVAD) support in a model of PH (176). While a growing body of literature has emerged demonstrating the utility of RVAD support in patients with acute postoperative RV failure, often in the presence of PH, its utility in patients with PAH has not as yet been tested.

7.23. Treatment Algorithm

The optimal therapy for a patient is a highly individualized decision, taking into account many factors including: severity of illness, route of administration, side effects, comorbid
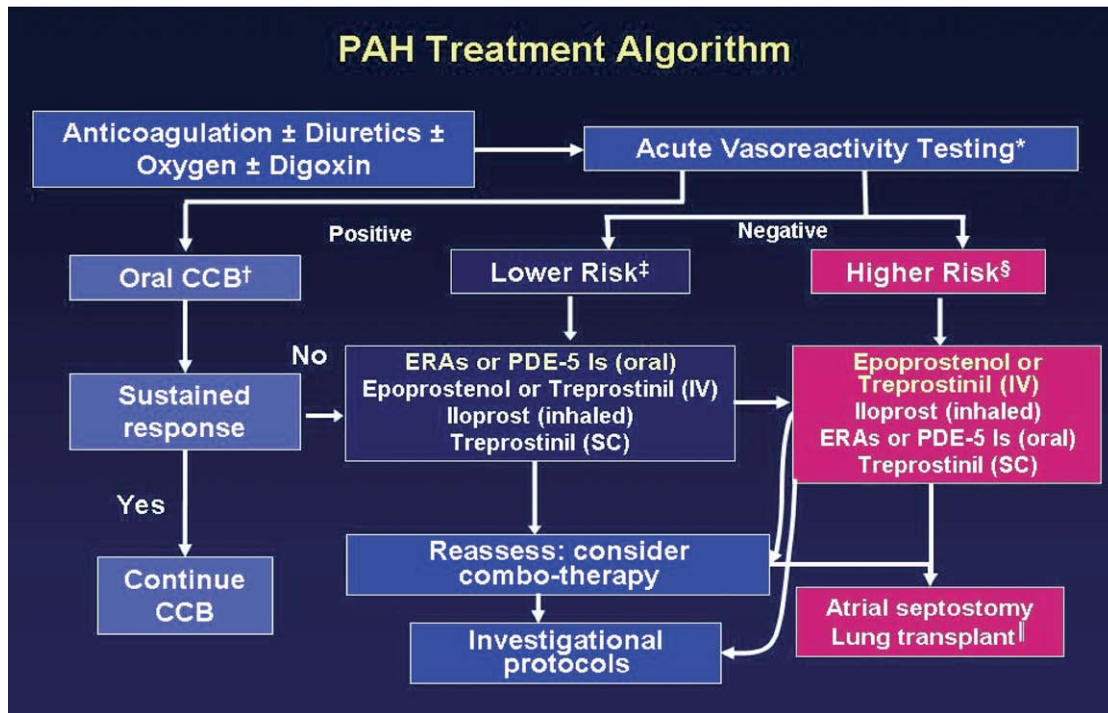
Figure 6. Treatment Algorithm for PAH

Background therapies include warfarin anticoagulation, which is recommended in all patients with IPAH without contraindication. Diuretics are used for management of right heart failure. Oxygen is recommended to maintain oxygen saturation greater than 90%. *Acute vasodilator testing should be performed in all IPAH patients who may be potential candidates for long-term therapy with calcium channel blockers (CCBs). Patients with PAH due to conditions other than IPAH have a very low rate of long-term responsiveness to oral CCBs, and the value of acute vasodilator testing in such patients needs to be individualized. IPAH patients in whom CCB therapy would not be considered, such as those with right heart failure or hemodynamic instability, should not undergo acute vasodilator testing. †CCBs are indicated only for patients who have a positive acute vasodilator response, and such patients need to be followed closely both for safety and efficacy. ‡For patients who did not have a positive acute vasodilator testing and are considered lower risk based on clinical assessment (Table 2), oral therapy with ERA or PDE-5I would be the first line of therapy recommended. If an oral regimen is not appropriate, the other treatments would need to be considered based on patient's profile and side effects and risk of each therapy. §For patients who are considered high risk based on clinical assessment (Table 2), continuous treatment with intravenous (IV) prostacyclin (epoprostenol or treprostinil) would be the first line of therapy recommended. If a patient is not a candidate for continuous IV treatment, the other therapies would have to be considered based on patient's profile and side effects and risk of each treatment. Epoprostenol improves exercise capacity, hemodynamics, and survival in IPAH and is the preferred treatment option for the most critically ill patients. Although expensive and difficult to administer, epoprostenol is the only therapy for PAH that has been shown to prolong survival. Treprostinil may be delivered via either continuous IV or subcutaneous (SC) infusion. Iloprost is a prostacyclin analogue delivered by an adaptive aerosolized device 6 times daily. The endothelin receptor antagonists are oral therapies that improve exercise capacity in PAH. Liver function tests must be monitored indefinitely on a monthly basis. Phosphodiesterase inhibitors also improve exercise capacity. Combination therapy should be considered when patients are not responding adequately to initial monotherapy (Table 8). ‖Timing for lung transplantation and/or atrial septostomy is challenging and is reserved for patients who progress despite optimal medical treatment.

illness, treatment goals, and clinician preference. An algorithm for therapy of PAH is depicted in Figure 6 (99).

8. Reassessing Patients Over Time: How to Follow Patients on Treatment

While guidelines for the diagnosis and initial treatment have been developed recently, a guideline focusing on how to reassess patients over time has been lacking. Almost all of the randomized clinical trials studying PAH therapies to date have been short-term studies, usually 12 to 16 weeks in duration. Furthermore, the long-term experiences published thus far usually detail single center experiences, without placebo or control groups, making it difficult to infer generalized practice patterns. Most importantly, treatment of PAH is a rapidly evolving field with emergence of new information and development of novel therapies, which have further hampered creation of a coherent guideline outlining ongoing evaluation.

The complexity of the disease and the rapid advances occurring in PAH mandate a guideline outlining long-term management recommendations. Although the therapies that have been approved thus far have been effective in improving quality of life and outcome to varying degree, clinical experience has demonstrated that some patients progress despite treatment while others decline after initial improvement. Furthermore, long-term experiences with epoprostenol have demonstrated the importance of vigilant early follow-up, since patients who remain in functional class III or IV despite therapy have poor outcomes and should be considered for lung transplant (77,78).

Important prognostic indicators, both at baseline and on treatment, were reviewed in Section 5 of this document. These include WHO functional class, exercise endurance (6MW test or CPET), and echocardiographic and hemodynamic parameters. There are emerging data regarding the prognostic implications of BNP. Consensus recommenda-

Table 8. Longitudinal Evaluation of the PAH Patient*

Clinical Course	Stable; no increase in symptoms and/or decompensation	Unstable; increase in symptoms and/or decompensation
Physical Examination	No evidence of right heart failure	Signs of right heart failure
Functional Class	I/II	IV†
6MWD	Greater than 400 m	Less than 300 m
Echocardiogram	RV size/function normal	RV enlargement/dysfunction
Hemodynamics	RAP normal	RAP high
	CI normal	CI low
BNP	Near normal/remaining stable or decreasing	Elevated/increasing
Treatment	Oral therapy	Intravenous prostacyclin and/or combination treatment
Frequency of Evaluation	Q 3 to 6 months‡	Q 1 to 3 months
FC Assessment	Every clinic visit	Every clinic visit
6MWT	Every clinic visit	Every clinic visit
Echocardiogram§	Q 12 months or center dependent	Q 6 to 12 months or center dependent
BNP‖	Center dependent	Center dependent
RHC	Clinical deterioration and center dependent	Q 6 to 12 months or clinical deterioration

*For patients in the high-risk category, consider referral to a PH specialty center for consideration for advanced therapies, clinical trials, and/or lung transplantation. †The frequency of follow-up evaluation for patients in FC III and/or 6MWD between 300 to 400 m would depend on composite of detailed assessments on other clinical and objective characteristics listed. ‡For patients who remain stable on established therapy, follow-up assessments can be performed by referring physician(s) or PH specialty centers. §Echocardiographic measurement of PASP is estimation only and it is strongly advised not to rely on its evaluation as the sole parameter to make therapeutic decisions. ‖The utility of serial BNP levels to guide management in individual patients has not been established.

BNP indicates brain natriuretic peptide; CI, cardiac index; FC, functional class; MWD, molecular weight distribution; MWT, minute walk test; PAH, pulmonary arterial hypertension; Q, every; RAP, right atrial pressure; RHC, right heart catheterization; and RV, right ventricle.

tions on the frequency and extent of longitudinal follow up of the PAH patient are displayed in Table 8.

Combining agents of different classes for the treatment of PAH patients who remain symptomatic and do not achieve treatment goals is an area of active research. Limited data from randomized controlled trials suggest that outcomes are better when multiple agents are used in such patients, and larger randomized controlled trials to address this issue are underway. Addition of an endothelin receptor antagonist, PDE-5 inhibitor, or a prostanoid could also be considered outside of a trial setting. If a patient improves with the additional agent, it is unclear whether the initial agent should be continued or discontinued.

8.1. Role of Nurses in Managing Pulmonary Arterial Hypertension Patients at Specialty Centers

It is our opinion that nurses provide a crucial link between the physician(s) and patient in all PAH specialty centers. First, competent nursing education of the patient, triage, and medical assessment are necessary to manage PAH patients who not only have complex disease but also need complex therapies, such as intravenous or subcutaneous prostanoids. Frequent telephone calls are necessary during initiation, after an episode of decompensation, and for periodic evaluation with these treatments. It is also crucial for patients to be proactive in the management of their disease and to be instructed to communicate with the nurses in the event of clinical problems. This is best accomplished when patients are given specific instructions, access to the nursing staff, and a shared sense of responsibility for managing their disease and treatment plan.

Nurses also provide emotional support to patients and their families, especially during the initial period of accepting the diagnosis or with acute illness. They spend time educating patients on the disease process and answering questions regarding different therapies or issues on how PAH impacts activities of daily living. Also, nurses are often the ones patients and their families turn to for assistance for help in navigating through insurance companies and dealing with realities associated with financial aspects of PAH therapies. Indeed, one of the distinguishing features that marks a group as a PAH specialty center is the availability of competent and caring nursing staff dedicated to meeting the unique challenges of patients with PAH (Table 9). Additionally, specialty pharmacies that dispense many of the PAH therapies employ nurses and pharmacists who play a key role in educating patients about the therapies.

9. Non-Pulmonary Arterial Hypertension Pulmonary Hypertension Populations

While recent evidence points to an increase in the number of patients with WHO Group 1 PAH (1), the number of

Table 9. The Role of Nurses in Managing PAH Patients at Specialty Centers

Clinical Indication	Frequency of Phone Triage/Management
After initiation of IV prostacyclin	1 to 2×/week to weekly until dose titration/ symptoms stable
Chronic IV prostacyclin	Q 1 to 2 months and prn
After initiation of combination therapy	Q 2 to 4 weeks and/or prn
After initiation of oral regimen	Q 1 to 2 months and/or prn
After discharge from hospital for PAH decompensation	Q days to 1 week for 1 to 2 weeks

IV indicates intravenous; PAH, pulmonary arterial hypertension; prn, as needed; and Q, every.

patients with PH related to chronic left heart disease (WHO Group 2) or chronic hypoxic states (WHO Group 3) is far greater. It is universally agreed that such patients require optimization of therapies targeting their underlying disease state (tailored heart failure interventions for patients with congestive heart failure, for example). However, it is not uncommon that even with such optimization, clinically meaningful PH remains. A subset of patients may be described as having PH "out of proportion" to their underlying disease state. Examples would include patients with a modest degree of obstructive lung disease or left heart disease that nonetheless manifest severe PH. Some have speculated that these patients have a form of PAH that may merit therapy with PAH-specific agents. Unfortunately, there are relatively few data available to guide decision making regarding the use of PAH-specific therapies for these patients. Other populations in which the use of these therapies is controversial include those with CTEPH and those with PH following a variety of cardiac surgical procedures. This section explores the diagnostic and therapeutic approach to these patient populations.

9.1. WHO Group 2: Pulmonary Venous Hypertension

9.1.1. Systolic Heart Failure and Pulmonary Hypertension

Despite significant advances in the treatment of patients with systolic heart failure with neurohormonal modulators including angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone, the morbidity and mortality among patients with advanced heart failure remains high (177). Development of PH, which usually progresses to affect RV function, signals progression of disease and poor outcome (5). PH in association with left heart failure usually occurs initially as pulmonary venous hypertension. Over a period of time, partly as an adaptive mechanism against pulmonary edema, an increase in pulmonary artery resistance may ensue.

Although optimizing neurohormonal antagonists remains the mainstay in treating patients with systolic heart failure, efforts to target PAH by applying similar principles used in treating idiopathic PAH have been pursued. The FIRST (Flolan International Randomized Survival Trial) study enrolled 471 patients with advanced heart failure to receive continuous epoprostenol infusion plus standard care or standard care alone (178). Although a hemodynamic improvement was seen among patients receiving epoprostenol with an increase in CI and a decrease in PCWP and PVR, the study was terminated early due to a strong trend toward increased mortality rates in patients receiving epoprostenol. Several explanations given included the long-term detrimental effects observed with systemic vasodilatation in systolic heart failure and possible hazardous effects of epoprostenol among patients with ischemia. Based on the findings of this study, chronic use of epoprostenol in patients with systolic heart failure is contraindicated. The only other prostanoid-based agent tested in patients with

chronic heart failure is inhaled iloprost (179). Investigators have reported hemodynamic benefits of short-term use of iloprost in heart transplant candidates with increased PAP. Significant decreases in mPAP and PVR was demonstrated.

Similar to increase in activation of several other neurohormonal systems, the level of endothelin (ET)-1 is also increased in chronic heart failure (180). Studies investigating the short-term hemodynamic effect of endothelin receptor antagonists (ERAs) in patients with chronic heart failure were initially encouraging. A 2-week therapy with nonselective ERA bosentan in 36 patients with symptomatic heart failure despite treatment with standard regimen resulted in a reduction of both systemic and pulmonary pressures and increase in cardiac output (181). These initial encouraging results prompted long-term randomized trials. In the REACH-1 (Research on Endothelin Antagonists in Chronic Heart Failure) study, 370 patients with advanced heart failure (NYHA functional class IIIB/IV) received bosentan or placebo. However, this trial was stopped prematurely due to safety issues, namely elevated liver transaminases, and the question of possible long-term benefit using lower doses was raised based on observing a trend towards reduction in heart failure-related morbidity and mortality among patients who received therapy (182). The ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trial enrolled over 1600 patients and studied lowered doses of bosentan versus placebo (183). However, no improvement in outcome was demonstrated between patients treated with bosentan and conventional treatment versus conventional treatment alone. There was an increased risk of early heart failure exacerbations due to fluid retention in patients treated with bosentan.

Several hypotheses have been raised regarding the lack of improvement seen with the addition of ERAs in heart failure patients. One reason may lie in patient selection. Endothelin receptor blockers reduce PAP and increase cardiac output in patients with IPAH (142). It is possible that adding ERAs may prove to be beneficial only for patients with chronic heart failure and PH. Indeed, a recent report described 5 patients who were deemed ineligible for heart transplantation due to severe irreversible PH (184). A 6-week trial of bosentan resulted in decreased PVR, making the patients eligible for heart transplantation, which they all underwent successfully. Another case report illustrates a patient who was considered for heart and lung transplantation secondary to biventricular dysfunction and severe PH (185). After 3 months of therapy on bosentan, improvement in LV function and PAP made him eligible for double lung transplantation. Larger studies are needed to determine the safety and benefit of adding ERAs to currently used neurohormonal antagonists among patients with chronic heart failure and PH.

Two small reports have demonstrated safety and hemodynamic effects of short-term use of sildenafil in patients with congestive heart failure and PH (186,187). An acute study has shown that sildenafil administration improved

peak VO$_2$, reduced VE/VCO$_2$ slope, and produced pulmonary vasodilatation during rest and exercise in patients with heart failure and PH (188). In addition, sildenafil treatment for 12 weeks improved exercise capacity and quality of life in patients with systolic heart failure and PH, compared with placebo-treated patients (189). Longer-term use of PDE-5 inhibitors in heart failure patients has not been investigated to date.

9.1.2. Diastolic Heart Failure and Pulmonary Hypertension

Diastolic heart failure refers to clinical syndromes in which patients present with heart failure symptoms with preserved LV systolic function. The predominant underlying structural abnormalities in diastolic heart failure are concentric hypertrophy and/or remodeling. This is often caused by chronic pressure overload, usually due to hypertension. The other characteristics associated include normal or reduced LV volume, abnormal diastolic function, and left atrial enlargement (190). These abnormalities impair the filling process of the left ventricle, especially under conditions that increase the heart rate (i.e., exercise or arrhythmia), resulting in inadequate cardiac performance and clinical symptoms.

Treatment strategies for diastolic heart failure include treating hypertension and preventing or aiming for regression of hypertrophy, accomplished mainly by using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Strict volume control is necessary, obtained through diuretics and sodium restriction. Prevention of tachyarrhythmia and controlling the heart rate to optimize diastolic filling time are most often achieved using beta-blockers and calcium channel blockers. Furthermore, improving lusitropy and preventing ischemia are also imperative when considering treatment strategy.

There are no established guidelines for treatment of diastolic heart failure. Many patients with this syndrome share similar risk profiles such as hypertension, diabetes mellitus, LV hypertrophy, atrial fibrillation, sleep disordered breathing (SDB), and atherosclerotic disease. Therefore, some of the general principles used in treating systolic heart failure patients have been applied. A few small studies have shown that angiotensin receptor blockers improve exercise tolerance. The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity)-Preserved trial suggested that treatment with candesartan reduces hospitalization related to diastolic heart failure, though mortality benefit was not seen (191).

When patients present with both diastolic heart failure and elevated PAP, measures to optimally treat systemic hypertension and normalize volume status must be in place. Performing RHC with careful attention paid to obtaining accurate PCWP, and in most cases LVEDP, is important in placing the correct diagnosis. Paradoxically, it is possible that the PCWP or LVEDP might be normal in such a patient with severe RV failure and low cardiac output. If PAP remains elevated despite normalizing systemic blood pressure and attaining euvolemic status, it is unclear if consideration should be given to targeted therapy for PAH. Furthermore, in the presence of hypertrophy and/or echocardiographic evidence of abnormal relaxation, it is unknown what PAP should be considered "out of proportion" to the presence of left heart changes. No studies are available to guide this therapeutic decision.

9.1.3. Valvular Dysfunction and Pulmonary Hypertension

Development of PH in association with valvular dysfunction has been shown to be a marker of advanced disease. Rosenhek et al. (192) reported their findings from prospectively following 132 consecutive patients with severe degenerative mitral regurgitation for 62 plus or minus 26 months. This group used criteria consisting of development of symptoms, LV enlargement or dysfunction, recurrent atrial fibrillation, or PH. Evaluation of event-free survival demonstrated the presence of symptoms to be correlated with worst outcome; however, among this cohort, only 5 patients developed new onset of atrial fibrillation or PH. This study is in accordance with the U.S. and European practice guidelines recommendation for surgery in asymptomatic patients with MR with regards to presence of PH. The guideline recommends systolic PAP exceeding 50 mm Hg to be a IIa indication for surgery (193).

Elevated estimated RV systolic pressure on echocardiography has multiple potential etiologies. When an etiology such as left heart disease or pulmonary disease is found, the underlying disorder should be treated aggressively. In many instances the PAP will decline with appropriate management of the underlying disorder. If the estimated PAP remains elevated, and the patient remains symptomatic, further evaluation, including an RHC, may be appropriate.

9.2. WHO Group 3: Hypoxia-Associated Pulmonary Hypertension

The respiratory diseases most frequently associated with PH are chronic obstructive pulmonary disease, interstitial lung disease, and SDB. Less common pulmonary abnormalities, such as chronic hypoventilation syndromes and high altitude exposure, can also produce PH, but will not be discussed here. These are categorized as WHO Group III PH. The topic of pulmonary diseases and the heart has recently been reviewed (194).

9.2.1. Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension

Chronic obstructive pulmonary disease (COPD) is a highly prevalent lung disorder of the lung parenchyma, including airways, resulting in a ventilatory limitation to exertion, recurring respiratory infections, and often chronic hypoxia and hypercapnea. COPD, predominantly caused by smoking, is associated with pulmonary vascular changes including intimal thickening, which decreases luminal cross-sectional area (195,196). While PH is thought to be common in patients with COPD, its exact prevalence is uncertain and is heavily influenced by disease severity: two thirds of patients

with advanced COPD have been reported to have PH detected echocardiographically (197). More recently, the cardiopulmonary hemodynamics of a retrospective series of 998 patients with COPD has been published (198). Twenty-seven patients (3%) had severe PH, defined as an mPAP greater than 40 mm Hg. Interestingly, 16 of these 27 had another possible cause of PH, such as anorexigen exposure, connective tissue disease, thromboembolic disease, or LV disease. In only 11 patients, or 1.1%, was COPD the only potential etiology of the PH. The median PAP in these 11 patients was 48 mm Hg. These patients had an unusual pattern of cardiopulmonary abnormalities with mild to moderate airway obstruction, severe hypoxemia, hypocapnea, and a very low diffusing capacity for carbon monoxide.

In a similar series, among 215 patients with severe COPD who underwent RHC to evaluate candidacy for either lung transplantation or lung volume reduction surgery, PH, defined as an mPAP greater than 25 mm Hg, was present in 50.2% of patients (199). The PH was characterized as moderate (mPAP 35 to 45 mm Hg) in 9.8% and severe (mPAP greater than 45 mm Hg) in 3.7%. A cluster analysis identified a subgroup of atypical patients characterized by moderate impairment of the pulmonary mechanics with moderate to severe PH and severe hypoxemia. Observations suggest that a different biological mechanism results in changes in the pulmonary vascular bed in susceptible patients and that severe PH occurs in the presence of lung disease rather than as a result of the lung disease. For example, a genetic predisposition to PH in COPD patients, as a result of a 5-HTT polymorphism, has been described, which may predispose to more severe PH in hypoxemic patients with COPD (200).

In the vast majority of COPD patients, PH is mild and treatment should be directed at the underlying COPD. This should include bronchodilator and anti-inflammatory therapy, and most importantly, oxygen. Patients who present with severe PH should be evaluated for another disease process that is responsible for the high PAP before it is attributed to the COPD. Specific treatment of PH in the setting of COPD has not been adequately studied. Open label, uncontrolled observations with both bosentan and sildenafil have suggested benefit, although adequately designed trials are lacking (201–203). Worsening V/Q mismatch, resulting in further hypoxemia due to nonselective vasodilatation is a potential risk.

9.2.2. Interstitial Lung Disease and Pulmonary Hypertension

Interstitial lung disease (ILD) is a heterogeneous group of disorders generally featuring inflammatory and/or fibrotic destruction of the pulmonary parenchyma, and commonly associated with PH (204). Idiopathic pulmonary fibrosis (IPF) is a relatively common form of ILD. The prevalence of PH as determined by echocardiogram in patients with IPF is uncertain, but has been reported to be as high as 40% in a general IPF population (205) and 60% in patients with

IPF referred for lung transplant evaluation (206). As with COPD, the magnitude of PH in patients with IPF is often modest, though a sizeable minority may have more marked pressure (207). Recent data have shown a lack of correlation between lung function variables and PAP in patients with IPF, suggesting mechanisms other than the degree of fibrosis underlying the PH seen in this disease (205). The treatment of PH associated with ILD should begin with optimal treatment of the ILD, potentially including immunomodulatory therapies and supplemental oxygen. The role of PAH-specific therapies in the treatment of PH associated with ILD has not been adequately investigated.

Sarcoidosis is a disease of unknown etiology, often grouped among the ILDs and commonly associated with PH. According to the 2003 classification, PH associated with sarcoidosis falls into Group V or "miscellaneous" PH. As in COPD, the frequency with which PH complicates sarcoidosis appears to increase with disease severity (208). A small, uncontrolled study reported clinical improvement in patients with severe PH associated with sarcoidosis treated chronically with intravenous epoprostenol (209). A controlled trial of bosentan in this population is scheduled to begin in the near future.

9.2.3. Sleep Disordered Breathing

SDB, especially when accompanied by frequent and severe hypoxemia, can produce PH. Generally, the magnitude of the pressure elevation is modest even in severe cases of sleep apnea. Accordingly, if a patient with SDB is found to have severe PH, a complete diagnostic evaluation should be undertaken to assess for other possible etiologies of the PH. At the same time, all patients with PH should be evaluated and treated (if indicated) for SDB to limit the adverse pulmonary vascular effects of the SDB (210).

Therapy of PH associated with SDB centers on prevention of episodic hypoxia by the provision of continuous positive airway pressure (with or without supplemental oxygen) or, less commonly, with surgery or the use of an oral prosthesis. PAH-specific agents have not been studied in patients with PH associated with SDB, although they may be used when PH persists despite adequate therapy of the SDB.

9.3. WHO Group 4: Thromboembolic Pulmonary Hypertension

CTEPH is defined as PH associated with an elevated mPAP (greater than 25 mm Hg) caused by thromboemboli in the pulmonary arterial system. A recent prospective, longitudinal study following patients presenting with acute PE but with no other history of venous thromboembolism estimated the cumulative incidence of CTEPH to be 1.0% 6 months after acute PE, 3.1% after 1 year, and 3.8% after 2 years (103), suggesting that the disease may be much more common than previously believed. Hoeper et al. (104) have recently reviewed CTEPH in detail. The current model of CTEPH pathogenesis is based upon gradual formation of organized thromboemboli after deep venous thrombosis and

PE. No abnormality of the coagulation or fibrinolytic pathway or of the pulmonary endothelium has been consistently identified except for anticardiolipin antibody (approximately 10% of patients) and elevated levels of factor VIII. Splenectomy, ventriculo-atrial shunt, infected intravenous lines, and chronic inflammatory states appear to be independent risk factors for CTEPH (212).

Pulmonary microvascular changes manifesting as pulmonary hypertensive arteriopathy likely contribute to disease progression (211). Mechanisms for significant distal disease may involve: 1) obstructions of "small" subsegmental elastic pulmonary arteries; 2) classic pulmonary arteriopathy of small muscular arteries and arterioles distal to nonobstructed vessels; and 3) pulmonary arteriopathy of small muscular arteries and arterioles distal to totally or partially obstructed vessels. Distal pulmonary vasculopathy of both occluded and nonoccluded pulmonary vasculature is characterized by lesions considered typical for IPAH, including plexiform lesions.

CT findings of CTEPH may be minimal and a ventilation-perfusion scan should always be considered in the setting of possible CTEPH. A normal perfusion study or the presence of multiple, small, subsegmental defects make IPAH or another form of small-vessel PH more likely, and one or more mismatched segmental or larger defects generally indicates CTEPH. Occasionally, multiple mismatched defects are seen in pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, fibrosing mediastinitis, pulmonary vasculitis, or pulmonary artery sarcoma. CT or angiographic evidence of CTEPH includes pouching, webs, or bands with or without poststenotic dilatation, intimal irregularities, abrupt narrowing, or total occlusion. Pulmonary angiography has been the cornerstone of managing patients with CTEPH for many years and confirms the diagnosis and gives an indication of operability.

9.3.1. Surgical and Invasive Therapy

PTE is potentially curative, although it cannot be performed in a substantial proportion of patients (104,165,213,214) and surgical success is dependent on careful patient selection and operator experience. Invasive therapeutic approaches other than PTE are currently limited. Possible alternatives include lung transplantation and balloon pulmonary dilation (angioplasty) (164,215). The latter technique may be beneficial, but it is not, at present, routinely applied (215). While there are little clinical data to support the practice, inferior vena cava filter placement prior to PTE is standard at most large centers.

9.3.2. Medical Therapy

As in PAH, diuretics and oxygen are used as indicated. Lifelong anticoagulation therapy is prescribed. Pharmacologic therapies approved for use in treating IPAH are being studied in CTEPH in view of the potential for nonocclusive small vessel vasculopathy. Most clinical evidence is currently limited to small, uncontrolled trials. There has been 1 placebo-controlled trial for CTEPH, which evaluated bosentan in patients with either inoperable disease or persistent PH following PTE (147). Patients treated with bosentan demonstrated a reduction in PVR, but no change in 6MW test, compared with placebo.

Pharmacotherapy may be beneficial in 4 settings (216). First, when PTE is not possible due to significant distal disease, medical therapy may be the only possibility, with transplant considered for the most severely ill individuals. Second, in high-risk patients with extremely poor hemodynamics, intravenous epoprostenol may be considered as a therapeutic bridge to PTE (217). Such individuals include those with functional class IV symptoms, mPAP greater than 50 mm Hg, CI less than 2.0 L/min/m^2, and PVR greater than 1,000 dyn·s·cm^{-5} (216). While this approach may improve surgical success, medical therapy should not significantly delay PTE. Third, patients with persistent PH after PTE (about 10% to 15%), and who often have significant residual distal pathology, should be considered for medical therapy. Finally, when surgery is contraindicated due to significant comorbidity, medical therapy can be considered. Data from open label observations of medical therapy in CTEPH have been recently reviewed and are promising but do not permit derivation of a strong evidence base (104).

9.3.3. Pulmonary Hypertension in the Cardiac Surgical Patient

As the spectrum of cardiac surgical procedures—coronary revascularization, valve repair and replacement, mechanical assist device implantation, and cardiac transplantation—has been offered to an increasingly complex population of patients, the importance of peri- and postoperative PH and right heart failure has become apparent. Often, PH is noted preoperatively and appropriate therapy may be initiated prior to surgery. Less commonly, it develops perioperatively without antecedent evidence of pulmonary vascular disease or right heart failure. Outcomes are significantly worse in patients with perioperative PH and RV failure (218–220), prompting interest in the utility of newer therapies for this situation, including PAH-specific therapies. Little information has emerged thus far regarding the utility of these therapies in this setting, and concern exists regarding potential adverse effects should left-sided cardiac filling pressures not be normalized following surgery.

9.3.4. Preoperative Pulmonary Hypertension

Significant PH has been reported in several patient populations in which cardiac surgery may be required, and it is particularly common in patients with chronic mitral or aortic valvular disease and in those with chronic severe left heart failure (218–220). In the latter group, the presence of significant PH with a high PVR may disqualify a patient from receiving an orthotopic cardiac transplantation. Reversibility of the high PVR is often assessed by the administration of short acting pulmonary and systemic arterial

vasodilators (221). Several reports describe the use of chronic vasodilator agents or mechanical LV assistance to lower PVR in patients with chronic left heart failure and initially fixed PH. Specific PAH therapies are rarely used in patients with PH resulting from chronic valvular disease or left heart failure; the persistently elevated left-sided cardiac filling pressures generally seen in these patients puts them at risk for pulmonary edema when challenged with a selective pulmonary vasodilator. Furthermore, studies have indicated that despite the adverse impact of PH on survival, surgical aortic or mitral valve replacement and percutaneous mitral valvuloplasty all have acceptable outcomes and frequently result in regression of PH (218,222,223).

9.3.5. Postoperative Pulmonary Hypertension

PH may persist following cardiac surgery despite successful reduction of left-sided cardiac filling pressures to normal or near-normal levels. In this circumstance, initiation of PAH-specific therapy may be considered. It is advisable to perform full RHC to ensure normalization of left-sided cardiac filling pressures prior to beginning such treatment. De novo PH following cardiac surgery is quite unusual.

Studies suggest that some patients with mitral stenosis have a significant rate of residual PH following successful percutaneous balloon valvuloplasty (223) or surgical commissurotomy or valve replacement (222). The incidence appears highest in patients with the greatest elevation of PVR preoperatively, and may be as high as 25% (223). PH may complicate aortic stenosis as well, and may also persist following surgical valve replacement (218). The incidence of PH following LV assist device implantation for chronic severe heart failure is uncertain. One study suggested that nearly 50% of such patients will have evidence of at least mild PH acutely upon weaning from cardiopulmonary bypass (224). PH is fairly common following cardiac transplantation; the estimated incidence of at least mild PH has been in excess of 60% (225). Severe PH following cardiac transplantation is rare, likely owing to aggressive preoperative screening for fixed PH in transplant candidates.

A number of therapeutic strategies have been employed for patients with PH with or without RV failure during and following cardiac surgery. In a population undergoing a variety of surgical interventions including coronary revascularization, valve repair and replacement, mechanical assist device implantation, and cardiac transplantation, inhaled NO, given at a dose of 20 ppm for a mean of 36 hours, improved pulmonary and systemic arterial pressures and cardiac index (226). Other studies have shown similar benefits of NO in more homogenous populations with PH following valve surgery (227), ventricular assist device implantation (224), and cardiac transplantation (228). On balance, inhaled NO is an effective short-term strategy for the management of PH following cardiac surgery. Inhaled prostacyclin has also been used in patients with PH following valve surgery (229). A head-to-head comparison of inhaled prostacyclin and NO in this population found both

to be effective and to have better tolerability than intravenous nitroprusside (230). Inhaled iloprost has been used successfully in patients with PH and acute RV failure during and following cardiac transplantation (231). Sildenafil has been reported to have beneficial hemodynamic effects when administered by nasogastric tube in patients undergoing cardiac surgery who develop intraoperative PH (232).

For more persistent PH following cardiac surgery, oral PAH therapy may be considered. A small case series suggested that oral sildenafil may be helpful in weaning patients from intravenous or inhaled PAH therapy for PH following cardiac surgery (233). No clinical reports exist of bosentan used for this indication; however, a preclinical study demonstrated its ability to prevent PH associated with cardiopulmonary bypass (234).

9.4. Summary of Recommendations

1. **Patients with PH require a thorough diagnostic evaluation to elucidate the roles of pulmonary venous hypertension, chronic lung disease with hypoxemia, and/or pulmonary thromboembolism to the pathogenesis of their disease.**

   Accordingly, RHC, lung function and imaging studies, determination of arterial oxygen saturation (at rest, with activity, and overnight), and ventilation-perfusion scanning are all mandatory elements of the assessment of these patients.

2. **Patients with PH related to pulmonary venous hypertension may be considered for PAH-specific therapy provided:**
   a. **the cause of the pulmonary venous hypertension is first optimally treated; and**
   b. **the PCWP is normal or only minimally elevated; and**
   c. **the transpulmonary gradient (TPG) and PVR are significantly elevated; and**
   d. **the patient's symptoms suggest that PAH-specific therapy may yield clinical benefit.**

   Treatment of such patients with PAH-specific therapy should be undertaken with great care, as these treatments may result in an increase in fluid retention, left-sided cardiac filling pressures, and pulmonary edema, and result in clinical deterioration. Decisions about whether and how to treat such patients should be made on a case by case basis by experienced PH caregivers.

3. **Patients with PH related to chronic lung disease and hypoxemia may be considered for PAH-specific therapy provided:**
   a. **the chronic lung disease and hypoxemia are first optimally treated; and**
   b. **the TPG and PVR are significantly elevated; and**
   c. **the patient's symptoms suggest that PAH-specific therapy may yield clinical benefit.**

   Treatment of such patients with PAH-specific therapy should be undertaken with great care, as these treatments may result in worsened hypoxemia and clinical deteriora-

tion. Decisions about whether and how to treat such patients should be made on a case by case basis by experienced PH caregivers.

4. **Patients with chronic thromboembolic PH may be considered for PAH-specific therapy provided:**
   a. **appropriate secondary preventative measures, including anticoagulation, has been instituted; and**
   b. **PTE has been performed or is not indicated; and**
   c. **the TPG and PVR are significantly elevated; and**
   d. **the patient's symptoms suggest that PAH-specific therapy may yield clinical benefit.**

Decisions about whether and how to treat such patients should be made on a case by case basis by experienced PH caregivers.

5. **Patients with PH following cardiac surgery may be considered for PAH-specific therapy provided:**
   a. **the surgery and concomitant medical therapy provide optimal treatment of the underlying cardiac disease; and**
   b. **the surgery and concomitant medical therapy result in a normal or only minimally elevated PCWP; and**
   c. **the TPG and PVR remain significantly elevated; and**
   d. **the patient's clinical condition suggests that PAH-specific therapy may yield clinical benefit.**

Decisions about whether and how to treat such patients should be made on a case by case basis by experienced PH caregivers.

10. Congenital Heart Disease-Related Pulmonary Arterial Hypertension

Overall, the incidence of CHD is approximately 8 per 1,000 live births (235).

Many different forms of CHD are associated with an increased risk for the development of pulmonary vascular disease (PVD). In patients with systemic-to-pulmonary shunts, the type and size of the defect, as well as the magnitude of the shunt, are risk factors for the development of PAH. Shear stress due to increased pulmonary blood flow and/or increased pulmonary artery pressure appears to play a major role in the development of PVD related to CHD. Based on natural history studies, approximately 30% of all children born with CHD who do not undergo surgical repair will develop PVD (235).

However, to date we have limited ability to determine which patients develop early irreversible PVD. There appears to be a difference between the pre- and post-tricuspid shunt lesions. The laminar shear stress induced by the increase in pulmonary blood flow alone may not be the same as the laminar and circumferential pressure shear stress induced by post-tricuspid shunt lesions, for example, a ventricular septal defect. Patients with small- to moderate-sized ventricular septal defects develop PVD in only approximately 3% of cases; in contrast, almost all patients with an unrepaired truncus arteriosus develop PVD, while approx-

imately 50% with a large ventricular septal defect and 10% with an atrial septal defect develop PVD. In addition, there is significant biologic variability in the clinical presentation and prognosis. While some children with the same underlying CHD develop irreversible PVD in the first year of life, others with the same CHD may maintain acceptable levels of pulmonary vascular resistance for many years. A recent study demonstrated BMPR2 mutations in patients with PAH in CHD. Mutations in BMPR2 occur in patients with FPAH and IPAH. These data raise the possibility that the presence of a genetic predisposition in some patients with CHD may contribute to the observed biologic variability (236). Further investigation into the role of genetic mutations may offer insight into which children with CHD should undergo surgical repair during early infancy. However, whether early therapeutic interventions halt or reverse the progression of the PVD remains unclear.

Over the past several decades, advances in pediatric cardiology/cardiac surgery have increased the number of patients with CHD surviving into adulthood. However, despite surgical correction of large systemic-to-pulmonary shunts in infancy, surgical repair does not guarantee that patients will not develop PVD postoperatively, and thus although early diagnosis and improved cardiac surgery have significantly decreased the number of patients overall with Eisenmenger syndrome, some of these patients, for reasons that remain unclear, develop progressive PVD following surgical repair. In addition to the symptoms and complications associated with PAH without Eisenmenger syndrome, patients with Eisenmenger syndrome have additional comorbid conditions due to right-to-left shunting and hypoxemia resulting in hematologic, hemostatic, cerebrovascular, renal, rheumatologic, and cardiac complications.

With respect to therapeutic interventions, whether medical or surgical, risk:benefit considerations need to be carefully evaluated based on the natural history of the condition as well as on an individual basis. The survival and long term outcome for patients with classic Eisenmenger syndrome is quite different than for patients with other forms of PAH, such as IPAH/FPAH or PAH related to connective tissue disease (72). Untreated, survival rates are 80% at 5 years and approximately 40% at 25 years. Despite the differences in etiology and prognosis, PAH associated with CHD shares similarities with IPAH, for example, pulmonary vascular histopathology. Based on these similarities, therapeutic modalities demonstrated to be efficacious in patients with IPAH are beginning to be evaluated in patients with PAH associated with CHD based on presumed similar pathobiology. As opposed to patients with IPAH, in whom the likelihood of acute pulmonary vasoreactivity with effective long-term calcium channel blockade therapy is less than 10%, this is virtually nonexistent in patients with PAH related to CHD. To date, the only disease-specific targeted PAH therapy that has been demonstrated to be efficacious in patients with PAH related to CHD is the ETA/ETB receptor antagonist bosentan. Although this trial was only

16 weeks in duration, a relatively short period of time for patients with Eisenmenger syndrome in whom the natural history is significantly more protracted than for IPAH, bosentan improved exercise capacity and decreased pulmonary vascular resistance without worsening systemic arterial oxygen saturation; the safety and tolerability profile was comparable to that observed with previous PAH bosentan trials (146). In addition, although not randomized controlled trials, several open label uncontrolled studies have reported improved exercise capacity and hemodynamics (including improvement in systemic arterial oxygen saturation) with chronic intravenous epoprostenol (79,130). The risk of complications with chronic intravenous epoprostenol, such as paradoxical emboli, needs to be carefully weighed in patients with unrepaired or residual congenital heart defects. Whether nonparenterally administered prostanoids such as inhaled or oral prostanoids will prove to be efficacious remains to be determined. In addition, whether PDE-5 inhibitors such as sildenafil will be efficacious in patients with PAH/CHD will require further study.

11. Pediatric Pulmonary Arterial Hypertension

11.1. Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by increased pulmonary vascular resistance, right-to-left shunting, and severe hypoxemia. PPHN is frequently associated with pulmonary parenchymal abnormalities, including meconium aspiration, pneumonia, sepsis, lung hypoplasia, and alveolar capillary dysplasia. In some instances there is no evidence of pulmonary parenchymal disease, and the etiology is unknown. Thus, although PPHN is multifactorial in origin, the nature of the underlying defect(s) causing failure to adapt to extrauterine life is uncertain. This is not surprising, since the mechanisms responsible for achieving a normal fall in PVR at birth are poorly understood. In the mature pulmonary circulation, the interaction between healthy endothelial and smooth muscle cells produces a balance between relaxation and contraction favoring relaxation due to release of endothelium-derived NO. Whether failure to achieve the normal reduction in PAP at birth is due to failure of endothelium-dependent and/or independent relaxation, a primary structural abnormality of the pulmonary vascular smooth muscle cells, or an excess of vasoconstrictor agents such as endothelin or thromboxane remains unclear. Increased circulating endothelin-1 levels have been reported after birth in these neonates. However, the primary abnormality most likely varies with various risk factors similar to what is postulated for various other forms of PAH. The rationale for treating with inhaled NO and possibly a PDE-5 inhibitor such as sildenafil is due to an absolute or relative lack of endogenous NO. Lung recruitment strategies facilitated by high frequency ventilation may be particularly useful in enhancing the efficacy of inhaled NO. Extracorporeal membrane oxygenation has improved survival for neonates with refractory hypoxemia, although it may be associated with significant morbidity (i.e., hemorrhagic, neurologic, and other complications). The efficacy of inhaled NO has also been demonstrated in multicenter randomized clinical trials, (i.e., improved oxygenation and reduction in the need for extracorporeal membrane oxygenation). However, despite the significant advances in treatment strategies for PPHN, this condition continues to have an unacceptably high morbidity and mortality rate of approximately 10% to 20%.

11.2. Pediatric Pulmonary Arterial Hypertension

Without treatment, the natural history for children with IPAH is worse than in adults; however, with treatment, the outcome appears better in children than in adults. Unfortunately, due to limited data in children with PAH, management decisions are often extrapolated from adult studies. The selection of optimal therapy is complex, as there are no consistently successful treatments, and some agents may involve complicated delivery systems, specific dosing regimens, side effects, and potential complications. Furthermore, if the disease progresses, the treatment may have to be revised based on risk:benefit considerations.

In the absence of studies specifically reporting the clinical response of children to PAH therapy, similar clinical strategies have been suggested for the management of PAH in children; however, without evidence-based data, these guidelines must be used with caution. It should also be highlighted that children not infrequently have a very high PAP but remain in functional class II due to the absence of RV failure during childhood. Those with syncope or near syncope, despite their functional class based on their level of dyspnea, should be treated aggressively, as one would treat a functional class IV patient. Based on expert consensus, the initial approach following the diagnosis of PAH in a child is, in the absence of a contraindication, to treat the child with digitalis and diuretics, anticoagulation with warfarin, and supplemental oxygen if clinically indicated. Patients who are responders to acute vasoreactivity testing are also treated with high-dose calcium channel blockade; nonresponders and responders who remain functional class III are considered for treatment with either an endothelin receptor antagonist, for example, bosentan, a PDE-5 inhibitor, for example, sildenafil, or a prostanoid, for example, inhaled iloprost. Functional class IV children and class III patients who do not improve with an endothelin receptor antagonist, PDE-5 inhibitor, or inhaled prostanoid should be considered for treatment with an intravenous prostanoid, for example, epoprostenol/treprostinil. Due to differences in metabolic activity in children versus adults, acute and chronic pharmacokinetic studies are helpful to determine optimal dosing in children. With the advent of new drugs with targeted mechanisms of action, combination therapy may become an attractive option for children who fail to improve or deteriorate with a single agent; however, clinical data are

currently limited. Finally, atrial septostomy and lung or heart-lung transplantation can be considered for refractory PAH.

Based on similar pathobiology and pathophysiology in children and adults with various forms of PAH, the consensus amongst the PH community is that the diseases are the same in children and in adults. The increased understanding of FPAH further supports this, with genetic anticipation highlighting the biologic variability that exists in many forms of PAH. However, in IPAH, a significantly greater percentage of children (up to 40%) are acute responders compared with adults, and the younger the child is at the time of diagnosis, the greater the likelihood of acute pulmonary vasoreactivity with acute vasodilator testing. Uncontrolled trials have reported that long-term administration of high-dose calcium channel blockade prolongs survival in children, similar to that reported in adults (237). However, despite continued calcium channel blockade therapy, the benefit observed in IPAH children who are responders (97% 5-year survival) is not always preserved long term (10-year survival 81%) and treatment success at 10 years in children who are acute responders is less than 50% (238). Consequently, children who are acutely responsive at diagnosis still have a significant risk for treatment failure long term on calcium channel blockade and need close follow-up. Serial reevaluation, including repeat acute vasodilator testing, is necessary in these children to maintain an optimal therapeutic regimen.

Open label, uncontrolled studies with intravenous epoprostenol in IPAH children have demonstrated sustained clinical and hemodynamic benefits for over 10 years. Long-term intravenous epoprostenol has also been used successfully in children with PAH associated with CHD, improving hemodynamics and quality of life parameters. Data on bosentan therapy for PAH in children remain limited. A retrospective analysis of 86 children with IPAH or PAH-CHD demonstrated beneficial long-term effects of bosentan (alone or in combination with intravenous epoprostenol) on functional capacity, hemodynamics, and survival in children with PAH (239). Subsequent analysis of the subgroup with PAH and CHD also demonstrated clinical and hemodynamic improvement similar to the experience with adult Eisenmenger patients.

Assessing safety and efficacy, particularly in young pediatric patients, is problematic, that is, accurate assessment of exercise capacity even in children old enough to exercise is fraught with difficulty. In addition, due to the biologic variability of PAH with the progressive nature more often more severe in the pediatric patients compared with adults, ethical issues become more problematic when considering long observational periods to assess overall morbidity and mortality. Long-term safety issues are equally problematic when initiating therapy with unknown long-term safety effects in children. Thus, although clinical investigation with children with PAH is more difficult and often approached without enthusiasm, the potential rewards for having a significant impact on overall quality of life as well as long-term survival should far outweigh the difficulties and impediments in developing improved therapeutic modalities for children.

12. Pulmonary Hypertension Centers of Excellence

PAH is a rare disease with a high mortality. Given the complex nature of this disease, if at all possible, most patients should be managed at or in conjunction with a PAH Center of Excellence. Centers that specialize in PAH offer physicians with expertise and experience in this complicated disease, nursing staff specially trained to assist in the management of PAH patients and the complex therapies for this disease, and often clinical trials of investigational agents. Multidisciplinary programs enlist the expertise of both cardiologists and pulmonologists, and commonly rheumatologists, hepatologists, infectious disease specialists, hematologists, transplant physicians, psychologists, and social workers.

Staff

American College of Cardiology Foundation
John C. Lewin, MD, Chief Executive Officer
Charlene May, Senior Director, Science and Clinical Policy
Tanja Kharlamova, Associate Director, Science and Clinical Policy
Fareen Pourhamidi, MS, MPH, Senior Specialist, Evidence-Based Medicine
María Velásquez, Specialist, Science and Clinical Policy
Erin A. Barrett, Senior Specialist, Science and Clinical Policy

American Heart Association
Nancy Brown, Chief Executive Officer
Rose Marie Robertson, MD, FAHA, FESC, Chief Science Officer
Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations

REFERENCES

1. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173:1023–30.
2. Thenappan T, Shah SJ, Rich S, et al. A USA-based registry for pulmonary arterial hypertension: 1982–2006. Eur Respir J. 2007;30:1103–10.
3. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:14S–34S.
4. Friedman WF. Proceedings of National Heart, Lung, and Blood Institute pediatric cardiology workshop: pulmonary hypertension. Pediatr Res. 1986;20:811–24.
5. Voelkel NF, Quaife RA, Leinwand LA, et al. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. Circulation. 2006;114:1883–91.
6. 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.

7. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111:3105–11.

8. Archer S, Rich S. Primary pulmonary hypertension: a vascular biology and translational research "Work in progress." Circulation. 2000;102:2781–91.

9. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med. 2004;351:1655–65.

10. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987;107:216–23.

11. Deng Z, Morse JH, Slager SL, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet. 2000;67:737–44.

12. Lane KB, Machado RD, Pauciulo MW, et al. Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. The International PPH Consortium. Nat Genet. 2000;26:81–4.

13. Trembath RC, Thomson JR, Machado RD, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med. 2001;345:325–34.

14. Guignabert C, Izikki M, Tu LI, et al. Transgenic mice overexpressing the 5-hydroxytryptamine transporter gene in smooth muscle develop pulmonary hypertension. Circ Res. 2006;98:1323–30.

15. West J, Fagan K, Steudel W, et al. Pulmonary hypertension in transgenic mice expressing a dominant-negative BMPRII gene in smooth muscle. Circ Res. 2004;94:1109–14.

16. Herve P, Launay JM, Scrobohaci ML, et al. Increased plasma serotonin in primary pulmonary hypertension. Am J Med. 1995;99:249–54.

17. Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med. 1992;327:70–5.

18. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med. 1993;328:1732–9.

19. Stewart DJ, Levy RD, Cernacek P, et al. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med. 1991;114:464–9.

20. Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med. 1999;159:1925–32.

21. Rubens C, Ewert R, Halank M, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. Chest. 2001;120:1562–9.

22. Steudel W, Ichinose F, Huang PL, et al. Pulmonary vasoconstriction and hypertension in mice with targeted disruption of the endothelial nitric oxide synthase (NOS 3) gene. Circ Res. 1997;81:34–41.

23. Eddahibi S, Humbert M, Fadel E, et al. Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. J Clin Invest. 2001;108:1141–50.

24. Marcos E, Adnot S, Pham MH, et al. Serotonin transporter inhibitors protect against hypoxic pulmonary hypertension. Am J Respir Crit Care Med. 2003;168:487–93.

25. Petkov V, Mosgoeller W, Ziesche R, et al. Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. J Clin Invest. 2003;111:1339–46.

26. Eddahibi S, Morrell N, d'Ortho MP, et al. Pathobiology of pulmonary arterial hypertension. Eur Respir J. 2002;20:1559–72.

27. Bonnet S, Michelakis ED, Porter CJ, et al. An abnormal mitochondrial-hypoxia inducible factor-1alpha-Kv channel pathway disrupts oxygen sensing and triggers pulmonary arterial hypertension in fawn hooded rats: similarities to human pulmonary arterial hypertension. Circulation. 2006;113:2630–41.

28. Yuan XJ, Wang J, Juhaszova M, et al. Attenuated K+ channel gene transcription in primary pulmonary hypertension. Lancet. 1998;351:726–7.

29. Bonnet S, Rochefort G, Sutendra G, et al. The nuclear factor of activated T cells in pulmonary arterial hypertension can be therapeutically targeted. Proc Natl Acad Sci U S A. 2007;104:11418–23.

30. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43:13S–24S.

31. Cowan KN, Jones PL, Rabinovitch M. Elastase and matrix metalloproteinase inhibitors induce regression, and tenascin-C antisense prevents progression, of vascular disease. J Clin Invest. 2000;105:21–34.

31a.Yuan JX, Rubin LJ. Pathogenesis of pulmonary arterial hypertension: the need for multiple hits. Circulation. 2005;111:534–8.

32. Simonneau G, Galie N, Rubin L, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43 Suppl 1:S5–12.

33. Yigla M, Kramer MR, Bendayan D, et al. Unexplained severe pulmonary hypertension in the elderly: report on 14 patients. Isr Med Assoc J. 2004;6:78–81.

34. Cogan JD, Vnencak-Jones CL, Phillips JA III, et al. Gross BMPR2 gene rearrangements constitute a new cause for primary pulmonary hypertension. Genet Med. 2005;7:169–74.

35. Machado RD, Pauciulo MW, Thomson JR, et al. BMPR2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. Am J Hum Genet. 2001;68:92–102.

36. Thomson JR, Machado RD, Pauciulo MW, et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-beta family. J Med Genet. 2000;37:741–5.

37. Humbert M, Labrune P, Sitbon O, et al. Pulmonary arterial hypertension and type-I glycogen-storage disease: the serotonin hypothesis. Eur Respir J. 2002;20:59–65.

38. Koehler R, Grunig E, Pauciulo MW, et al. Low frequency of BMPR2 mutations in a German cohort of patients with sporadic idiopathic pulmonary arterial hypertension. J Med Genet. 2004;41:e127.

39. Loyd JE, Butler MG, Foroud TM, et al. Genetic anticipation and abnormal gender ratio at birth in familial primary pulmonary hypertension. Am J Respir Crit Care Med. 1995;152:93–7.

40. Sztrymf B, Coulet F, Girerd B, et al. Clinical outcomes of pulmonary arterial hypertension in carriers of BMPR2 mutation. Am J Respir Crit Care Med. 2008;177:1377–83.

41. Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum. 2005;52:3792–800.

42. Mukerjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis. 2003;62:1088–93.

43. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV Cohort Study. Am J Respir Crit Care Med. 1997;155:990–5.

44. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med. 2008;177:108–13.

45. Speich R, Jenni R, Opravil M, et al. Primary pulmonary hypertension in HIV infection. Chest. 1991;100:1268–71.

46. Mehta NJ, Khan IA, Mehta RN, et al. HIV-Related pulmonary hypertension: analytic review of 131 cases. Chest. 2000;118:1133–41.

47. McDonnell PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? Am Rev Respir Dis. 1983;127:437–41.

48. Castro M, Krowka MJ, Schroeder DR, et al. Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients. Mayo Clin Proc. 1996;71:543–51.

49. Gurtner HP. Aminorex and pulmonary hypertension. A review. Cor Vasa. 1985;27:160–71.

50. Abenhaim L, Moride Y, Brenot F, 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.

51. Gomez-Sanchez MA, Saenz de la Calzada C, Gomez-Pajuelo C, et al. Clinical and pathologic manifestations of pulmonary vascular disease in the toxic oil syndrome. J Am Coll Cardiol. 1991;18:1539–45.

52. Sack KE, Criswell LA. Eosinophilia-myalgia syndrome: the aftermath. South Med J. 1992;85:878–82.

53. Albertson TE, Walby WF, Derlet RW. Stimulant-induced pulmonary toxicity. Chest. 1995;108:1140–9.

54. Chin KM, Channick RN, Rubin LJ. Is methamphetamine use associated with idiopathic pulmonary arterial hypertension? Chest. 2006;130:1657–63.

55. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. Blood. 2003; 101:1257–61.
56. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004;350:886–95.
57. Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J Respir Crit Care Med. 2007;175:1272–9.
58. Klings ES, Farber HW. Role of free radicals in the pathogenesis of acute chest syndrome in sickle cell disease. Respir Res. 2001;2:280–5.
59. Rybicki AC, Benjamin LJ. Increased levels of endothelin-1 in plasma of sickle cell anemia patients. Blood. 1998;92:2594–6.
60. Aessopos A, Farmakis D, Karagiorga M, et al. Cardiac involvement in thalassemia intermedia: a multicenter study. Blood. 2001;97: 3411–6.
61. Hayag-Barin JE, Smith RE, Tucker FC, Jr. Hereditary spherocytosis, thrombocytosis, and chronic pulmonary emboli: a case report and review of the literature. Am J Hematol. 1998;57:82–4.
62. Abdalla SA, Gallione CJ, Barst RJ, et al. Primary pulmonary hypertension in families with hereditary haemorrhagic telangiectasia. Eur Respir J. 2004;23:373–7.
63. Dingli D, Utz JP, Krowka MJ, et al. Unexplained pulmonary hypertension in chronic myeloproliferative disorders. Chest. 2001; 120:801–8.
64. Chu JW, Kao PN, Faul JL, et al. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. Chest. 2002;122: 1668–73.
65. Peacock AJ. Pulmonary hypertension after splenectomy: a consequence of loss of the splenic filter or is there something more? Thorax. 2005;60:983–4.
66. Pietra GG, Capron F, Stewart S, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol. 2004;43:25S–32S.
67. Holcomb BW Jr., Loyd JE, Ely EW, et al. Pulmonary veno-occlusive disease: a case series and new observations. Chest. 2000;118:1671–9.
68. Okumura H, Nagaya N, Kyotani S, et al. Effects of continuous IV prostacyclin in a patient with pulmonary veno-occlusive disease. Chest. 2002;122:1096–8.
69. McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:78S–92S.
70. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115:343–9.
71. Stupi AM, Steen VD, Owens GR, et al. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. Arthritis Rheum. 1986;29:515–24.
72. Kuhn KP, Byrne DW, Arbogast PG, et al. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. Am J Respir Crit Care Med. 2003;167:580–6.
73. Williams MH, Das C, Handler CE, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart. 2006;92:926–32.
74. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. Circulation. 1994;89:2722–7.
75. Hopkins WE, Ochoa LL, Richardson GW, et al. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant. 1996;15:100–5.
76. Barst RJ, Rubin LJ, Long WA, 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.
77. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002;106:1477–82.
78. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002;40:780–8.
79. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation. 1999;99:1858–65.
80. Badesch DB, Tapson VF, McGoon MD, 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.
81. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;28:1195–203.
82. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J. 2005;25:244–9.
83. 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.
84. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111:3105–11.
85. Frank H, Mlczoch J, Huber K, et al. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest. 1997;112:714–21.
86. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2000;161:487–92.
87. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation. 2002;106:319–24.
88. Gomberg-Maitland M, Huo D, Benza RL, et al. Creation of a model comparing 6-minute walk test to metabolic equivalent in evaluating treatment effects in pulmonary arterial hypertension. J Heart Lung Transplant. 2007;26:732–8.
89. Sandoval J, Bauerle O, Palomar A, et al. Survival in primary pulmonary hypertension. Validation of a prognostic equation. Circulation. 1994;89:1733–44.
90. Eysmann SB, Palevsky HI, Reichek N, et al. Two-dimensional and Doppler-echocardiographic and cardiac catheterization correlates of survival in primary pulmonary hypertension. Circulation. 1989;80: 353–60.
91. Tei C, Dujardin KS, Hodge DO, et al. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr. 1996;9:838–47.
92. Yeo TC, Dujardin KS, Tei C, et al. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol. 1998;81:1157–61.
93. van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J. 2007;28:1250–7.
94. Gan CT, Lankhaar JW, Westerhof N, et al. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. Chest. 2007;132:1906–12.
95. Fijalkowska A, Kurzyna M, Torbicki A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest. 2006;129:1313–21.
96. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation. 2000;102:865–70.
97. Nagaya N, Uematsu M, Satoh T, et al. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. Am J Respir Crit Care Med. 1999;160:487–92.
98. Torbicki A, Kurzyna M, Kuca P, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. Circulation. 2003;108: 844–8.
99. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation. 2006;114:1417–31.
100. McGoon M, Fuster V, Freeman W, Edwards W, Scott J. Pulmonary hypertension. In: Giuliani E, Gersh B, McGoon M, et al., editors. Mayo Clinic practice of cardiology. St. Louis, MO: Mosby, 1996: 1815–36.
101. Currie PJ, Seward JB, Chan KL, et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol. 1985;6: 750–6.

102. Hinderliter AL, Willis PW, Long WA, et al. Frequency and severity of tricuspid regurgitation determined by Doppler echocardiography in primary pulmonary hypertension. Am J Cardiol. 2003;91:1033–7, A9.

102a. Lantheus Medical Imaging. Definity prescribing information. 2008. Available at: http://www.definityimaging.com/prescribing_info.html. Accessed February 11, 2009.

103. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257–64.

104. Hoeper MM, Mayer E, Simonneau G, et al. Chronic thromboembolic pulmonary hypertension. Circulation. 2006;113:2011–20.

105. Galie N, Torbicki A, Barst R, et al. 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. Eur Heart J. 2004;25:2243–78.

106. Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:7S–10S.

107. Hoeper MM, Maier R, Tongers J, et al. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. Am J Respir Crit Care Med. 1999;160:535–41.

108. Hoeper MM, Lee SH, Voswinckel R, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol. 2006;48:2546–52.

109. Fruhwald FM, Kjellstrom B, Perthold W, et al. Hemodynamic observations in two pulmonary hypertensive patients changing treatment from inhaled iloprost to the oral endothelin-antagonist bosentan. J Heart Lung Transplant. 2005;24:631–4.

110. Wonisch M, Fruhwald FM, Maier R, et al. Continuous haemodynamic monitoring during exercise in patients with pulmonary hypertension. Int J Cardiol. 2005;101:415–20.

111. Karamanoglu M, McGoon M, Frantz RP, et al. Right ventricular pressure waveform and wave reflection analysis in patients with pulmonary arterial hypertension. Chest. 2007;132:37–43.

112. Morales-Blanhir J, Santos S, de Jover L, et al. Clinical value of vasodilator test with inhaled nitric oxide for predicting long-term response to oral vasodilators in pulmonary hypertension. Respir Med. 2004;98:225–34.

113. Pepke-Zaba J, Higenbottam TW, Dinh'Xuan AT, et al. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet. 1991;338:1173–4.

114. Rubin LJ, Groves BM, Reeves JT, et al. Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. Circulation. 1982;66:334–8.

115. Schrader BJ, Inbar S, Kaufmann L, et al. Comparison of the effects of adenosine and nifedipine in pulmonary hypertension. J Am Coll Cardiol. 1992;19:1060–4.

116. Weir EK, Rubin LJ, Ayres SM, et al. The acute administration of vasodilators in primary pulmonary hypertension. Experience from the National Institutes of Health Registry on Primary Pulmonary Hypertension. Am Rev Respir Dis. 1989;140:1623–30.

117. Badesch DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest. 2007;131:1917–28.

118. Elliott CG, Glissmeyer EW, Havlena GT, et al. Relationship of BMPR2 mutations to vasoreactivity in pulmonary arterial hypertension. Circulation. 2006;113:2509–15.

119. Simonneau G, Fartoukh M, Sitbon O, et al. Primary pulmonary hypertension associated with the use of fenfluramine derivatives. Chest. 1998;114:195S–9S.

120. Klings ES, Hill NS, Ieong MH, et al. Systemic sclerosis-associated pulmonary hypertension: short- and long-term effects of epoprostenol (prostacyclin). Arthritis Rheum. 1999;42:2638–45.

121. Bocchi EA, Bacal F, Auler Junior JO, et al. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. Am J Cardiol. 1994;74:70–2.

122. Galie N, Seeger W, Naeije R, et al. Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43:81S–8S.

123. Mereles D, Ehlken N, Kreuscher S, 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.

124. Mohr LC. Hypoxia during air travel in adults with pulmonary disease. Am J Med Sci. 2008;335:71–9.

125. Weiss BM, Zemp L, Seifert B, et al. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol. 1998;31:1650–7.

126. Fuster V, Steele PM, Edwards WD, et al. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation. 1984;70:580–7.

127. Rich S, Seidlitz M, Dodin E, et al. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest. 1998;114:787–92.

128. Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. Am J Respir Crit Care Med. 2000;162:1846–50.

129. Kuo PC, Johnson LB, Plotkin JS, et al. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. Transplantation. 1997;63:604–6.

130. McLaughlin VV, Genthner DE, Panella MM, et al. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. Ann Intern Med. 1999;130:740–3.

131. Nunes H, Humbert M, Sitbon O, et al. Prognostic factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med. 2003;167:1433–9.

132. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. J Am Coll Cardiol. 1999;34:1184–7.

133. Laliberte K, Arneson C, Jeffs R, et al. Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and subcutaneous route to normal volunteers. J Cardiovasc Pharmacol. 2004;44:209–14.

134. Simonneau G, Barst RJ, Galie N, 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.

135. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12–week trial. Chest. 2006;129:683–8.

136. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med. 2005;172:1586–9.

137. Centers for Disease Control and Prevention. Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension—seven sites, United States, 2003–2006. MMWR Morb Mortal Wkly Rep. 2007;56:170–2.

138. Doran A, Ivy D, Barst RJ, et al. Guidelines for the prevention of central venous catheter-related bloodstream infections with prostanoid therapy for pulmonary arterial hypertension. Adv Pulm Hypertens. 2008; 7:245–248.

139. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347:322–9.

140. Hoeper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med. 2000;342:1866–70.

141. Opitz CF, Wensel R, Winkler J, et al. Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. Eur Heart J. 2005;26:1895–902.

142. Channick RN, Simonneau G, Sitbon O, 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.

143. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346:896–903.

144. Provencher S, Sitbon O, Humbert M, et al. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J. 2006;27:589–95.

145. Sitbon O, McLaughlin VV, Badesch DB, 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.

146. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114:48–54.

147. Jais X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BEN-EFit (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 2008;52:2127–34.

148. Sitbon O, Gressin V, Speich R, et al. Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004;170:1212–7.

149. Galie N, Rubin L, Hoeper M, 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.

150. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004;169:441–7.

151. Barst RJ, Rich S, Widlitz A, et al. Clinical efficacy of sitaxsentan, an endothelin-A receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. Chest. 2002;121:1860–8.

152. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46:529–35.

153. Galie N, Olschewski H, Oudiz RJ, 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 (abstr). Circulation. 2008;117:3010–9.

154. Gilead. Letairis full prescribing information. 2008. Available at: http://www.letairis.com/full_prescribing_information.html. Accessed February 11, 2009.

155. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353:2148–57.

156. Hoeper MM, Welte T. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2006;354:1091–3.

157. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. Eur Respir J. 2004;24:353–9.

158. McLaughlin VV, Oudiz RJ, Frost A, 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.

159. Hoeper MM, Leuchte H, Halank M, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2006;28:691–4.

160. Simonneau G, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med. 2008;149:521–30.

161. Macchia A, Marchioli R, Marfisi R, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J. 2007;153:1037–47.

161a. Galie N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J. 2009;30:394–403.

162. Avouac J, Wipff J, Kahan A, et al. Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: a meta-analysis of randomised controlled trials. Ann Rheum Dis. 2008;67:808–14.

163. Ambrisentan (Letairis) for pulmonary arterial hypertension. Med Lett Drugs Ther. 2007;49:87–8.

164. Doyle RL, McCrory D, Channick RN, et al. Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:63S–71S.

165. Klepetko W, Mayer E, Sandoval J, et al. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43:73S–80S.

166. Olsson JK, Zamanian RT, Feinstein JA, et al. Surgical and interventional therapies for pulmonary arterial hypertension. Semin Respir Crit Care Med. 2005;26:417–28.

167. Reichenberger F, Pepke-Zaba J, McNeil K, et al. Atrial septostomy in the treatment of severe pulmonary arterial hypertension. Thorax. 2003;58:797–800.

168. Rothman A, Sklansky MS, Lucas VW, et al. Atrial septostomy as a bridge to lung transplantation in patients with severe pulmonary hypertension. Am J Cardiol. 1999;84:682–6.

169. Sandoval J, Gaspar J, Pulido T, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol. 1998;32:297–304.

170. O'Loughlin AJ, Keogh A, Muller DW. Insertion of a fenestrated Amplatzer atrial septostomy device for severe pulmonary hypertension. Heart Lung Circ. 2006;15:275–7.

171. Moscucci M, Dairywala IT, Chetcuti S, et al. Balloon atrial septostomy in end-stage pulmonary hypertension guided by a novel intracardiac echocardiographic transducer. Catheter Cardiovasc Interv. 2001;52:530–4.

172. Trulock EP, Edwards LB, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-third official adult lung and heart-lung transplantation report—2006. J Heart Lung Transplant. 2006;25:880–92.

173. Deleted in proof.

174. Cottini SR, Lerch N, de Perrot M, et al. Risk factors for reperfusion injury after lung transplantation. Intensive Care Med. 2006;32:557–63.

175. Choong CK, Sweet SC, Guthrie TJ, et al. Repair of congenital heart lesions combined with lung transplantation for the treatment of severe pulmonary hypertension: a 13–year experience. J Thorac Cardiovasc Surg. 2005;129:661–9.

176. Kindo M, Radovancevic B, Gregoric ID, et al. Biventricular support with the Jarvik 2000 ventricular assist device in a calf model of pulmonary hypertension. ASAIO J. 2004;50:444–50.

177. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003;348:2007–18.

178. Califf RM, Adams KF, McKenna WJ, 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.

179. Sablotzki A, Czeslick E, Gruenig E, et al. First experiences with the stable prostacyclin analog iloprost in the evaluation of heart transplant candidates with increased pulmonary vascular resistance. J Thorac Cardiovasc Surg. 2003;125:960–2.

180. Konstam MA, DeNofrio D. Endothelin expression and the progression of heart failure: exemplifying the vagaries of therapeutic development. Circulation. 2004;109:143–5.

181. Sutsch G, Kiowski W, Yan XW, et al. Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. Circulation. 1998;98:2262–8.

182. Mylona P, Cleland JG. Update of REACH-1 and MERIT-HF clinical trials in heart failure. Cardio.net Editorial Team. Eur J Heart Fail. 1999;1:197–200.

183. Teerlink JR. Recent heart failure trials of neurohormonal modulation (OVERTURE and ENABLE): approaching the asymptote of efficacy? J Card Fail. 2002;8:124–7.

184. Perez-Villa F, Cuppoletti A, Rossel V, et al. Initial experience with bosentan therapy in patients considered ineligible for heart transplantation because of severe pulmonary hypertension. Clin Transplant. 2006;20:239–44.

185. Brauchlin AE, Soccal PM, Rochat T, et al. Severe left ventricular dysfunction secondary to primary pulmonary hypertension: bridging therapy with bosentan before lung transplantation. J Heart Lung Transplant. 2005;24:777–80.

186. Alaeddini J, Uber PA, Park MH, et al. Efficacy and safety of sildenafil in the evaluation of pulmonary hypertension in severe heart failure. Am J Cardiol. 2004;94:1475–7.

187. Lepore JJ, Maroo A, Bigatello LM, et al. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. Chest. 2005;127:1647–53.

188. Lewis GD, Lachmann J, Camuso J, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation. 2007;115:59–66.

189. Lewis GD, Shah R, Shahzad K, 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.

190. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 2004;350:1953–9.

191. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777–81.

192. Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation. 2006;113:2238–44.

193. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48:e1–149.

194. Han MK, McLaughlin VV, Criner GJ, et al. Pulmonary diseases and the heart. Circulation. 2007;116:2992–3005.

195. Higenbottam T. Pulmonary hypertension and chronic obstructive pulmonary disease: a case for treatment. Proc Am Thorac Soc. 2005;2:12–9.

196. Naeije R. Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2:20–2.

197. Scharf SM, Iqbal M, Keller C, et al. Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med. 2002;166:314–22.

198. Chaouat A, Bugnet AS, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172:189–94.

199. Thabut G, Dauriat G, Stern JB, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest. 2005;127:1531–6.

200. Eddahibi S, Chaouat A, Morrell N, et al. Polymorphism of the serotonin transporter gene and pulmonary hypertension in chronic obstructive pulmonary disease. Circulation. 2003;108:1839–44.

201. Alp S, Skrygan M, Schmidt WE, et al. Sildenafil improves hemodynamic parameters in COPD—an investigation of six patients. Pulm Pharmacol Ther. 2006;19:386–90.

202. Madden BP, Allenby M, Loke TK, et al. A potential role for sildenafil in the management of pulmonary hypertension in patients with parenchymal lung disease. Vascul Pharmacol. 2006;44:372–6.

203. Maloney JP. Advances in the treatment of secondary pulmonary hypertension. Curr Opin Pulm Med. 2003;9:139–43.

204. Ryu JH, Krowka MJ, Pellikka PA, et al. Pulmonary hypertension in patients with interstitial lung diseases. Mayo Clin Proc. 2007;82:342–50.

205. Nathan SD, Shlobin OA, Ahmad S, et al. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest. 2007;131:657–63.

206. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med. 2003;167:735–40.

207. Leuchte HH, Neurohr C, Baumgartner R, et al. Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. Am J Respir Crit Care Med. 2004;170:360–5.

208. Shorr AF, Helman DL, Davies DB, et al. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. Eur Respir J. 2005;25:783–8.

209. Fisher KA, Serlin DM, Wilson KC, et al. Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. Chest. 2006;130:1481–8.

210. Atwood CW Jr., McCrory D, Garcia JG, et al. Pulmonary artery hypertension and sleep-disordered breathing: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:72S–7S.

211. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest. 1993;103:685–92.

212. Bonderman D, Jakowitsch J, Adlbrecht C, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost. 2005;93:512–6.

213. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg. 2003;76:1457–62.

214. Kim NH. Assessment of operability in chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc. 2006;3:584–8.

215. Feinstein JA, Goldhaber SZ, Lock JE, et al. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation. 2001;103:10–3.

216. Bresser P, Pepke-Zaba J, Jais X, et al. Medical therapies for chronic thromboembolic pulmonary hypertension: an evolving treatment paradigm. Proc Am Thorac Soc. 2006;3:594–600.

217. Kerr KM, Rubin LJ. Epoprostenol therapy as a bridge to pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Chest. 2003;123:319–20.

218. Malouf JF, Enriquez-Sarano M, Pellikka PA, et al. Severe pulmonary hypertension in patients with severe aortic valve stenosis: clinical profile and prognostic implications. J Am Coll Cardiol. 2002;40:789–95.

219. Vincens JJ, Temizer D, Post JR, et al. Long-term outcome of cardiac surgery in patients with mitral stenosis and severe pulmonary hypertension. Circulation. 1995;92:II137–42.

220. Yang H, Davidson WR Jr., Chambers CE, et al. Preoperative pulmonary hypertension is associated with postoperative left ventricular dysfunction in chronic organic mitral regurgitation: an echocardiographic and hemodynamic study. J Am Soc Echocardiogr. 2006;19:1051–5.

221. Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol. 1992;19:48–54.

222. Aris A, Camara ML. As originally published in 1988: long-term results of mitral valve surgery in patients with severe pulmonary hypertension. Updated in 1996. Ann Thorac Surg. 1996;61:1583–4.

223. Umesan CV, Kapoor A, Sinha N, et al. Effect of Inoue balloon mitral valvotomy on severe pulmonary arterial hypertension in 315 patients with rheumatic mitral stenosis: immediate and long-term results. J Heart Valve Dis. 2000;9:609–15.

224. Argenziano M, Choudhri AF, Moazami N, et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg. 1998;65:340–5.

225. Chang PP, Longenecker JC, Wang NY, et al. Mild vs severe pulmonary hypertension before heart transplantation: different effects on posttransplantation pulmonary hypertension and mortality. J Heart Lung Transplant. 2005;24:998–1007.

226. Beck JR, Mongero LB, Kroslowitz RM, et al. Inhaled nitric oxide improves hemodynamics in patients with acute pulmonary hypertension after high-risk cardiac surgery. Perfusion. 1999;14:37–42.

227. Santini F, Casali G, Franchi G, et al. Hemodynamic effects of inhaled nitric oxide and phosphodiesterase inhibitor (dipyridamole) on secondary pulmonary hypertension following heart valve surgery in adults. Int J Cardiol. 2005;103:156–63.

228. Rea RS, Ansani NT, Seybert AL. Role of inhaled nitric oxide in adult heart or lung transplant recipients. Ann Pharmacother. 2005;39:913–7.

229. Lowson SM, Doctor A, Walsh BK, et al. Inhaled prostacyclin for the treatment of pulmonary hypertension after cardiac surgery. Crit Care Med. 2002;30:2762–4.

230. Fattouch K, Sbraga F, Bianco G, et al. Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. J Card Surg. 2005;20:171–6.

231. Theodoraki K, Tsiapras D, Tsourelis L, et al. Inhaled iloprost in eight heart transplant recipients presenting with post-bypass acute right ventricular dysfunction. Acta Anaesthesiol Scand. 2006;50:1213–7.

232. Madden BP, Sheth A, Ho TB, et al. Potential role for sildenafil in the management of perioperative pulmonary hypertension and right ventricular dysfunction after cardiac surgery. Br J Anaesth. 2004;93:155–6.

233. Trachte AL, Lobato EB, Urdaneta F, et al. Oral sildenafil reduces pulmonary hypertension after cardiac surgery. Ann Thorac Surg. 2005;79:194–7.

234. Carteaux JP, Roux S, Siaghy M, et al. Acute pulmonary hypertension after cardiopulmonary bypass in pig: the role of endogenous endothelin. Eur J Cardiothorac Surg. 1999;15:346–52.

235. Friedman WF. Proceedings of National Heart, Lung, and Blood Institute pediatric cardiology workshop: pulmonary hypertension. Pediatr Res. 1986;20:811–24.
236. Roberts KE, McElroy JJ, Wong WP, et al. BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur Respir J. 2004;24:371–4.
237. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99:1197–208.
238. Yung D, Widlitz AC, Rosenzweig EB, et al. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004; 110:660–5.

239. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46:697–704.

Key Words: ACCF/AHA Expert Consensus Document ■ pulmonary hypertension ■ pulmonary arterial hypertension ■ hemodynamics ■ prostacyclin ■ endothelin receptor antagonists ■ phosphodiesterase inhibitors.

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—ACCF/AHA 2009 EXPERT CONSENSUS DOCUMENT ON PULMONARY HYPERTENSION

Committee Member	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grant	Board of Directors	Expert Witness or Consultant
Dr. Vallerie V. McLaughlin (Chair)	• Actelion* • CoTherix* • Gilead/Myogen* • Pfizer	• Actelion* • CoTherix • Gilead/Myogen • Pfizer	None	• Actelion* • CoTherix* • Encysive* • Lung Rx* • Pfizer* • United Therapeutics*	None	No
Dr. Stephen L. Archer	None	None	None	None	None	No
Dr. David Badesch	• Actelion* • Amgen • CoTherix* • Encysive* • Gilead/Myogen* • GlaxoSmithKline • InterMune • Mondo Biotech • Pfizer* • PR Pharmaceuticals • Scios • United Therapeutics/ Lung Rx	None	None	• Actelion* • CoTherix* • Encysive* • Gilead/Myogen* • Lilly/ICOS* • Pfizer* • United Therapeutics/ Lung Rx	• Pulmonary Hypertension Association	Yes. Diet drug litigation.
Dr. Robyn J. Barst	• Actelion* • CoTherix* • Encysive* • Generamedix • Gilead/Myogen • GlaxoSmithKline • INO Therapeutics* • Lung Rx • Medtronic • MondoBIOTECH • Pfizer* • Novartis • United Therapeutics*	• Actelion* • CoTherix* • Encysive* • Gilead • INO Therapeutics • Pfizer*	None	• Actelion* • CoTherix* • Encysive* • Gilead/Myogen • INO Therapeutics* • Lung Rx • Medtronic • MondoBIOTECH • Novartis • Pfizer* • United Therapeutics*	None	Yes. Diet drug litigation.
Dr. Harrison W. Farber	• Actelion • Gilead/Myogen • United Therapeutics	• Actelion • Encysive • Gilead/Myogen • Pfizer	None	• Actelion • Epix • Gilead • Scios*	None	No
Dr. Jonathan R. Lindner	None	None	None	None	None	No

Committee Member	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grant	Board of Directors	Expert Witness or Consultant
Dr. Michael A. Mathier	• Actelion* • Gilead/Myogen	• Actelion* • CoTherix • Encysive • GlaxoSmithKline • Scios	None	• Actelion*	None	No
Dr. Michael D. McGoon	• Actelion • CoTherix* • Medtronic • United Therapeurtics	None	None	• Actelion* • CoTherix* • Encysive • Gilead/Myogen* • Medtronic* • Pfizer* • United Therapeutics	None	No
Dr. Myung H. Park	• Actelion* • CoTherix • Encysive • Pfizer • United Therapeutics	• Actelion* • CoTherix • Encysive • Pfizer • United Therapeutics	None	• Actelion* • CoTherix	None	No
Dr. Robert S. Rosenson	• Abbott • Anthera • AstraZeneca* • Daiichi Sankyo • LipoScience • Roche	None	• LipoScience*	None	• Grain Board	No
Dr. Lewis J. Rubin	• Actelion* • Aires • CoTherix* • Encysive* • Gilead/Myogen* • Mondo Biotech • Pfizer • United Therapeutics*	None	• Aires • United Therapeutics*	• Actelion* • CoTherix* • Gilead/Myogen* • Pfizer* • United Therapeutics*	None	Yes. Diet drug litigation (plaintiff).
Dr. Victor F. Tapson	• Actelion* • CoTherix* • Encysive • Gilead/Myogen* • Lungs Rx* • Pfizer • United Therapeutics	• Actelion* • Gilead/Myogen*	None	• Actelion* • CoTherix* • Encysive* • Gilead/Myogen* • Lungs Rx* • Pfizer* • United Therapeutics*	None	Yes. Diet drug litigation.
Dr. John Varga	• Actelion*	None	None	None	None	No

This table represents the relevant relationships of committee members with industry and other entities that were reported orally at the initial writing committee meeting and updated in conjunction with all meetings and conference calls of the writing committee during the document development process. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships noted in this table are modest unless otherwise noted. *Significant (greater than $10 000) relationship.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—ACCF/AHA 2009 EXPERT CONSENSUS DOCUMENT ON PULMONARY HYPERTENSION

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Robert S. Rosenson	Official Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	• Abbott • Anthera • AstraZeneca* • Daiichi Sankyo • LipoScience • Roche	None	• LipoScience*	None	• Grain Board	No
Dr. Vincent F. Carr	Official Reviewer— ACCF Board of Governors	None	None	None	None	None	No
Dr. Patrick T. O'Gara	Official Reviewer— ACCF Board of Trustees	None	None	None	None	None	No
Dr. Karen A. Fagan	Official Reviewer— AHA	• Gilead/Myogen	• Gilead/Myogen	None	None	None	No
Dr. Stuart Rich	Official Reviewer— AHA	None	None	None	None	None	No
Dr. Kamal K. Mubarak	Organizational Reviewer— American College of Chest Physicians	• Actelion • Encysive • Gilead/Myogen • United Therapeutics	• Actelion • Encysive • Gilead/Myogen	None	• Actelion • Encysive • Gilead/Myogen • Lilly/ICOS	None	No
Dr. Francisco Soto	Organizational Reviewer— American College of Chest Physicians	• Actelion* • Gilead/Myogen	• Actelion*	None	None	• Actelion* • Encysive* • Pfizer*	No
Dr. Nicholas S. Hill	Organizational Reviewer— American Thoracic Society	• Actelion • Gilead/Myogen • United Therapeutics	• Actelion • Gilead/Myogen	None	• Actelion* • Epix • Gilead/Myogen* • Lilly* • Lung RX* • Pfizer* • United Therapeutics*	None	No
Dr. Ronald J. Oudiz	Organizational Reviewer— Pulmonary Hypertension Association	• Actelion • Gilead/Myogen • GlaxoSmithKline • Lilly/ICOS • Lung RX • Pfizer • United Therapeutics	• Actelion • Gilead/Myogen • Pfizer • United Therapeutics	None	• Actelion • Gilead/Myogen • GlaxoSmithKline • Lilly/ICOS • Lung RX • Pfizer • United Therapeutics	None	No
Dr. Ivan Robbins	Organizational Reviewer— Pulmonary Hypertension Association	• Actelion • Gilead/Myogen	None	• Actelion • Gilead/Myogen	• Actelion • BioMarin • Gilead/Myogen • Pfizer • United Therapeutics	None	2006, 2007; Represented plaintiffs in cases involving the potential role of appetite suppressants in the development of pulmonary hypertension.

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Javed Butler	Content Reviewer— ACCF Heart Failure & Transplant Committee	None	• Boehringer • Ingelheim* • GlaxoSmithKline* • Novartis*	None	None	None	No
Dr. David E. Lanfear	Content Reviewer— ACCF Heart Failure & Transplant Committee	• Thoratec	None	None	None	None	No
Dr. Donna F. Petruccelli	Content Reviewer— ACCF Heart Failure & Transplant Committee	None	None	None	None	None	No
Dr. Louis Bezold	Content Reviewer— ACCF Adult Congenital & Pediatric Cardiology Council	None	None	None	None	None	No
Dr. Meryl Cohen	Content Reviewer— ACCF Adult Congenital & Pediatric Cardiology Council	None	None	None	None	None	No
Dr. Jeffrey A. Feinstein	Content Reviewer— ACCF Adult Congenital & Pediatric Cardiology Council	• Eli Lilly • United Therapeutics	None	None	• iNO Therapeutics • Pfizer	None	No
Dr. Charles R. Bridges	Content Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	None	None	None	None	None	No
Dr. Alice Jacobs	Content Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	None	None	None	None	None	No
Dr. David J. Moliterno	Content Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	• Boston Scientific • Schering-Plough	None	None	None	• Boston Scientific	No
Dr. Debabrata Mukherjee	Content Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	None	None	None	None	None	No

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Richard S. Schofield	Content Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	• Medtronic	• AtCor Medical • Novartis • Scios	None	None	None	No
Dr. James H. Stein	Content Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	• Amgen • LipoScience • Merck • Pfizer	• KOS • Pfizer* • Takeda*	• Wisconsin Alumni Research Foundation	• AstraZeneca* • Bristol-Myers Squibb* • LipoScience • PreMD • Sanofi-Aventis • Sonosite	• KOS	No
Ms. Deborah Wesley-Farrington	Content Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	None	None	None	None	None	No

This table represents the relevant relationships with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. *Significant (greater than $10 000) relationship.