



Pulmonary Arterial Hypertension
Kelly M. Chin, and Lewis J. Rubin
J. Am. Coll. Cardiol. 2008;51;1527-1538
doi:10.1016/j.jacc.2008.01.024

This information is current as of July 1, 2008

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://content.onlinejacc.org/cgi/content/full/51/16/1527>



STATE-OF-THE-ART PAPER

Pulmonary Arterial Hypertension

Kelly M. Chin, MD,* Lewis J. Rubin, MD†

Dallas, Texas; and San Diego, California

Significant advances in the treatment of pulmonary arterial hypertension (PAH) have occurred over the last 10 years, starting with the approval of epoprostenol in 1998. Subsequently, multiple additional medications have received approval, including a subcutaneous prostacyclin, an inhaled prostacyclin, and oral medications in 2 separate classes. Over this same period, the classification of pulmonary hypertension has been revised with changes including the substitution of the term *idiopathic* for *primary* PAH and an expanded list of conditions felt to be associated with the development of PAH. Long-term follow-up studies have provided better information on prognosis and expected outcomes with treatment, with particularly valuable data on reassessment of prognosis after treatment with epoprostenol. Combination therapy is more frequently being used, and limited data on novel therapies such as stem cell transplantation have been published. The purpose of this review is to describe the current state of evidence for the diagnosis, prognosis, and treatment of the patient with PAH. (J Am Coll Cardiol 2008;51:1527–38) © 2008 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a progressive condition characterized by elevated pulmonary arterial pressures leading to right ventricular (RV) failure. The pulmonary vascular injury underlying PAH occurs in an idiopathic form or in association with other disease states or exposures and is probably a final common response to environmental or disease-related inciting factors coupled with genetically determined susceptibilities. Treatment options have expanded over the last decade and now include 6 U.S. Food and Drug Administration–approved medications; with these advances, prognosis is improving. This review describes the current classification system for PAH, new insights into its pathogenesis and prognosis, a recent treatment algorithm, and potential future therapeutic targets.

Classification of PAH

The pulmonary hypertension nomenclature has been revised several times, most recently in 2003. The current classification system groups together forms of pulmonary hypertension based on similarities in their pathophysiologies and responses to treatment. Five major categories of pulmonary hypertension are recognized (Table 1) (1). Group 1, PAH, is composed of diseases in which the primary abnormality is

localized to the small pulmonary arteries. This includes idiopathic (formerly primary) PAH as well as PAH associated with other medical conditions and exposures such as connective tissue disease and congenital heart disease. By definition, patients with PAH do not have significant left heart disease, lung disease, or chronic thromboembolic disease and meet specific hemodynamic criteria including a mean pulmonary arterial pressure >25 mm Hg, pulmonary capillary wedge or left ventricular end-diastolic pressure <15 mm Hg, and pulmonary vascular resistance >3 Wood units.

The characteristic pathological abnormalities in the small pulmonary arteries, ranging from intimal, medial, and adventitial proliferation to plexogenic changes consisting of masses of proliferating endothelial cells mixed with occasional myofibroblasts and necrotizing arteritis, underscore the notion that PAH is a vasoproliferative disease invoked by mitogenic stimuli.

PAH Subgroups

Familial PAH and hereditary hemorrhagic telangiectasia. Mutations in the gene encoding the bone morphogenetic protein receptor type 2 (BMPR2) have been identified as the main cause of inherited PAH, accounting for at least 60% of familial cases. Mutations have also been identified in 10% to 25% of patients with sporadic PAH and 9% of patients with PAH associated with fenfluramine use (2). Familial PAH is inherited as an autosomal dominant trait with variable penetrance and reported genetic anticipation (3). Asymptomatic carriers of the BMPR2 mutation have an abnormal increase in pulmonary arterial pressure with exercise

From the *Department of Internal Medicine, Division of Pulmonary and Critical Care, University of Texas Southwestern Medical Center, Dallas, Texas; and the †Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of California, San Diego, California. Dr. Chin is an investigator, a consultant, and a member of the Speakers' Bureau for Actelion, Encysive, Gilead, and United Therapeutics. Dr. Rubin is an investigator and consultant for Actelion, Encysive, Gilead, United Therapeutics, Pfizer, Mondogen, and Bayer-Schering.

Manuscript received November 29, 2007; revised manuscript received December 28, 2007, accepted January 6, 2008.

Abbreviations and Acronyms

- BMPR** = bone morphogenetic protein receptor
- CHF** = congestive heart failure
- HIV** = human immunodeficiency virus
- NO** = nitric oxide
- PAH** = pulmonary arterial hypertension
- RV** = right ventricle/ventricular

(4), and it is thought that additional environmental or inherited factors determine whether overt disease occurs.

The BMPR2 is a transforming growth factor-beta family receptor involved in the regulation of apoptosis and growth. Although the exact mechanism through which a decrease in BMPR2 signaling leads to PAH is unknown, complete post-natal loss of BMPR2 signaling in animal models is sufficient to cause pulmonary hypertension (5). Reduced BMPR2 expression has also been reported in the monocrotaline animal model of acquired pulmonary hypertension (6), and reduced expression of a required BMPR2 co-receptor has been described in patients with idiopathic

PAH and other forms of acquired pulmonary hypertension (7).

Another autosomal dominant genetic disorder that at times leads to PAH is hereditary hemorrhagic telangiectasia (or Osler-Weber-Rendu syndrome). This disorder is characterized by the development of mucocutaneous telangiectasias and arteriovenous malformations in the brain, lungs, liver, and gastrointestinal tract, with wide variability in organs affected, even within individual families (3,8).

Drugs and toxins: anorexigens, cocaine, amphetamine, and methamphetamine. There is an increased risk of developing PAH among patients who have taken aminorex-, dexfenfluramine-, or fenfluramine-containing appetite-suppressant medications (9,10) and among patients with exposure to stimulant medications. The precise mechanism is unknown, but it is probably related to interactions between these drugs and the serotonin transporter present in both the central nervous system and pulmonary vasculature (11). Appetite suppressants increase local levels of serotonin, a known promoter of pulmonary vascular growth and vasoconstriction (12), by acting on this transporter through “substrate mediated exchange.”

The interaction with and uptake of drugs into the pulmonary artery smooth muscle cell by the serotonin transporter may be important, as medications that simply block reuptake of serotonin (selective serotonin reuptake inhibitors) increase local levels of serotonin but have not been associated with PAH in adults (10), do not increase mortality in patients with established PAH (13), and unlike the appetite-suppressant medications, do not promote smooth muscle cell growth in vitro (14). In contrast, maternal use of selective serotonin reuptake inhibitors has been linked to persistent pulmonary hypertension of the newborn; the cause for this discrepancy remains unclear (15). The majority of patients exposed to appetite suppressant medications do not develop disease and additional genetic or environmental susceptibilities likely contribute.

Stimulants such as amphetamine, methamphetamine, and cocaine can also interact with the serotonin transporter and are also thought to lead to PAH. These drugs all have much stronger affinity for the dopamine and norepinephrine transporters, and the overall link between stimulants, the serotonin transporter, and PAH is less well established (16).

Conditions associated with PAH. Patients with connective tissue disease, congenital heart disease, portal hypertension, and human immunodeficiency virus (HIV) are at increased risk of developing PAH. Risk of PAH varies, with the highest overall risk seen among patients with certain forms of congenital heart disease, such as a large ventricular septal defect or patent ductus arteriosus. Congenital heart disease PAH patients often have higher pulmonary arterial pressures and better cardiac output at diagnosis than patients with idiopathic PAH and, subsequently, longer survival times (17). Once overt cardiac dysfunction develops, prognosis is much more guarded (18). Strong markers of poor prognosis are similar to those reported in idiopathic

Table 1 Classification of Pulmonary Hypertension Based on the 2003 World Symposium

Group 1: PAH
Idiopathic
Familial
Associated with
Collagen vascular disease
Congenital systemic-to-pulmonic shunt
Portal hypertension
HIV infection
Drugs and toxins
Other: thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomas
Persistent pulmonary hypertension of the newborn
Group 2: Pulmonary hypertension with left heart disease
Left-sided ventricular or atrial disease
Left-sided valvular disease
Group 3: Pulmonary hypertension associated with lung disease and/or hypoxemia
Chronic obstructive lung disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Group 5: Miscellaneous
Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Adapted, with permission, from Simonneau et al. (1).

HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

PAH and include high right atrial pressure and low systemic cardiac output.

Patients with scleroderma also have very high rates of developing PAH but have lower survival rates than other PAH subgroups (19). Incidence rates of approximately 30% (20) have been reported, with rates of isolated PAH highest in patients with otherwise limited scleroderma including those with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome, while those with systemic scleroderma may have significant interstitial lung disease and/or significant PAH. Other connective tissue disease patients at significantly increased risk include those with lupus and mixed connective tissue disease (21).

Rates of PAH in portal hypertension patients undergoing liver transplantation work-ups have been reported at 1% to 6% (portopulmonary hypertension), and severe untreated PAH is a contraindication to transplantation (22–24). Pathological changes in the pulmonary arteries appear identical to idiopathic PAH and are thought to relate to an imbalance in vasoactive substances due to liver disease. Careful hemodynamic evaluation is particularly important in these patients, as cardiac output and, at times, pulmonary capillary wedge pressures may be elevated leading to high pulmonary arterial pressures with normal or borderline pulmonary vascular resistance.

Finally, PAH has been reported in approximately 0.5% of patients infected with HIV (25). There has been no apparent association with cluster of differentiation 4 count or viral load (26), and although highly active antiretroviral therapy has resulted in modest improvement in pulmonary pressures in several series (27), HIV-associated PAH, as with other forms of PAH, generally requires treatment with medications targeting the pulmonary vasculature.

Pulmonary Hypertension Groups II to IV

Pulmonary hypertension due to left heart disease. Patients with left heart disease may develop pulmonary hypertension “out of proportion” to their underlying condition and at times show some of the same pathological abnormalities as patients with PAH do. These patients are classified as having “pulmonary venous hypertension,” and pulmonary artery pathological changes are generally less severe. Recommendations for treatment focus on the underlying condition, with the best example of success with this strategy coming from mitral stenosis patients undergoing successful balloon valvotomy. Although pulmonary pressures immediately after the procedure often remained elevated, pulmonary pressures normalized over 6 to 12 months time as long as an acceptable improvement in left atrial pressure was achieved. This was seen even among patients with baseline pulmonary arterial pressures >80 mm Hg, presumably due to regression of a secondary pulmonary vasculopathy (28).

Pulmonary hypertension may occur in any setting where left-sided filling pressures are elevated, with the

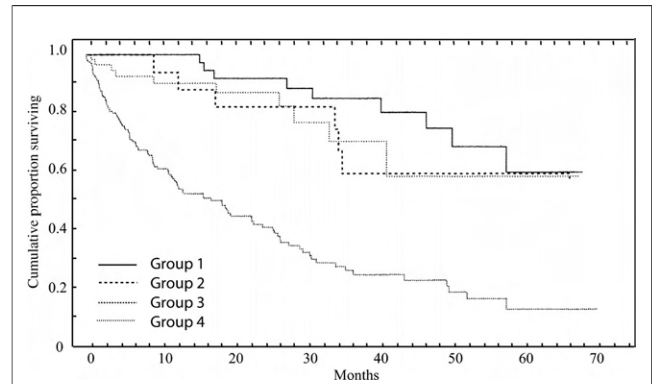


Figure 1 Survival Rates Among Patients With CHF With Systolic Dysfunction

Survival rates without urgent heart transplantation among patients with congestive heart failure (CHF) and left ventricular ejection fraction less than 35% are lower among patients with high pulmonary arterial pressures (PAPs) and low right ventricular ejection fraction (RVEF). Group 1: normal PAP/preserved RVEF (n = 73). Group 2: normal PAP/low RVEF (n = 68). Group 3: high PAP/preserved RVEF (n = 21). Group 4: high PAP/low RVEF (n = 215). Reproduced, with permission, from Ghio et al. (29).

degree of elevation usually proportional to the pulmonary capillary wedge pressure. Unfortunately, some patients go on to develop right heart failure; when this occurs survival is poor and is more closely associated with pulmonary artery pressure and *right* rather than left ventricular ejection fraction (Fig. 1) (29). In some cases, normalization of the left-sided filling pressures is impossible, and it is tempting to use medications approved for PAH. In most cases, this should be discouraged given the potential to worsen pulmonary vascular congestion and the lack of clinical trial data. Epoprostenol, in particular, should be avoided given the apparent increase in mortality seen in congestive heart failure (CHF) patients without pulmonary hypertension (30). However, small studies enrolling patients with CHF with reduced ejection fraction *plus* pulmonary hypertension have recently been published. One study found no difference in echocardiographically-determined RV systolic pressure (a questionable choice of end point) after 20 weeks of bosentan treatment (31); another study utilizing more typical end points found improved exercise capacity and hemodynamics after 12 weeks of sildenafil treatment (32).

Patients with pulmonary hypertension and CHF with preserved ejection fraction have not been studied in randomized clinical trials and are increasingly recognized as a cause of elevation in pulmonary pressures (33). Diagnosis is based on symptoms, echocardiogram, and, where necessary, right heart catheterization (34). Treatment of diastolic CHF in general focuses on optimization of hypertension, rate control of atrial fibrillation, and treatment of pulmonary congestion with diuretics (35). However, once elevation in pulmonary pressures occurs, patients often have advanced disease where diuresis leads to lower cardiac output and yet failure to control the left-sided filling pressures leads to worsening pulmonary hy-

pertension and right heart failure. These patients require close monitoring and careful control of fluid balance; whether PAH medications may be beneficial will likely be the subject of future clinical investigation.

Pulmonary hypertension associated with lung disease and/or hypoxemia. Pulmonary hypertension is common in patients with obstructive or restrictive lung disease, but in most cases, it is relatively mild. Pulmonary arterial pressures correlate better with oxygen saturation than with spirometry, and for patients who are hypoxemic at rest ($\text{PaO}_2 < 55$ to 59 mm Hg), treatment with continuous oxygen therapy improves survival (36). Some patients develop more severe pulmonary hypertension despite oxygen therapy, and a randomized clinical trial investigating inhaled iloprost among patients with pulmonary fibrosis with pulmonary hypertension is underway (37). These patients with lung disease plus pulmonary hypertension have low survival rates; whether iloprost or other PAH medications will improve symptoms or outcomes is unknown.

Pulmonary hypertension due to chronic thrombotic and/or embolic disease. Chronic thromboembolic pulmonary hypertension is due to incomplete resolution of pulmonary emboli leading to elevated pulmonary pressures and RV failure. Treatment of proximal thromboembolic disease is surgical, with perioperative mortality rates at the most experienced centers in the 4% to 5% range. Medical therapy is considered in patients with distal thromboembolic disease who are not operative candidates; it is also considered in patients who are poor surgical candidates due to comorbidities or occasionally in patients with severe right heart failure as a “bridge” to surgery. Limited case series and clinical trial data suggest that medical therapy with PAH medications is better than no therapy, but improvement is modest and should not be considered a substitute for surgical treatment (38).

Diagnosis

Clinical presentation. Most patients with PAH present with exertional dyspnea that progresses over months or even years. Exertional chest pain, syncope, and lower extremity edema are indicative of more severe pulmonary hypertension with impaired right heart function. Women are affected more commonly than men, and patients of all ages may develop the disease. The mean age at diagnosis has been reported at 36 to 50 years, with more recent series and series including associated PAH (particularly scleroderma) reporting older mean ages at diagnosis (39–41). Diagnosis is often delayed due to the subtle findings on physical examination and the nonspecific symptoms experienced by most patients.

Diagnostic evaluation. Establishing the diagnosis and etiology of PAH requires a comprehensive evaluation that includes pulmonary function testing, connective tissue disease serology, echocardiography, cardiac catheterization, and tests to exclude chronic thromboembolic disease.

Echocardiography is often the first diagnostic test to suggest the possibility of pulmonary hypertension. The pulmonary artery systolic pressure can be estimated nonin-

vasively using Doppler techniques, and when an acceptable tricuspid regurgitant jet is obtained, these estimates show excellent overall correlation with invasively determined pulmonary artery systolic pressures. However, the standard error of the estimate is relatively large (5 to 8 mm Hg) (42,43), and results for any individual patient should be viewed as only an *estimate* of the actual pulmonary arterial pressure and should be confirmed by right heart catheterization. Other common echocardiographic findings include right heart chamber enlargement, paradoxical motion of the interventricular septum, and tricuspid insufficiency. Pericardial effusions may also be visualized and, in the absence of connective tissue diseases, correlate with elevations in right atrial pressure (44).

Chest radiographs show enlarged central pulmonary arteries and right heart dilation, and the electrocardiogram may show right axis deviation, RV hypertrophy, and strain. Pulmonary function testing shows either normal lung volumes or mild restriction, and the diffusing capacity for carbon monoxide is typically reduced (45).

Ventilation perfusion testing should be performed in patients with suspected PAH to exclude surgically treatable chronic thromboembolic pulmonary hypertension; computed tomography angiography is less sensitive than ventilation perfusion scanning for *chronic* clots and should not be used for this purpose (46). A normal or low probability ventilation perfusion scan is typically seen in PAH, although a mottled appearance may be found. Specificity of ventilation perfusion scanning is lower than its sensitivity, and thus, confirmatory pulmonary arteriography is required in those with an abnormal scan (47).

Once the diagnostic evaluation has suggested PAH, right heart catheterization is required to confirm the presence and to determine the severity of pulmonary hypertension, to exclude left-sided heart disease or potentially correctable intracardiac left-to-right shunting, and to perform acute vasodilator testing.

Pulmonary veno-occlusive disease, an unusual form of pulmonary hypertension, may also be considered on clinical grounds when severe PAH accompanied by normal pulmonary capillary wedge and left ventricular diastolic pressures is associated with evidence of venous congestion on chest radiograph and a patchy appearance of tracer activity on a perfusion scan.

Screening. American College of Chest Physicians guidelines recommend screening of patient groups at very high risk of disease (expert-opinion level of evidence), based on possibly more successful outcomes among patients treated earlier in the disease process (48). Risk groups thought to warrant screening include patients with known genetic mutations predisposing to pulmonary hypertension, first-degree relatives in a familial PAH family, patients with scleroderma, patients with portal hypertension prior to liver transplantation, and patients with congenital systemic to pulmonary shunts. Doppler echocardiography is the most commonly used screening modality; in scleroderma, serial

pulmonary function testing with measurement of the diffusing capacity of the lung for carbon monoxide may also be a sensitive (though not specific) indicator of pulmonary vascular disease.

Therapy

Pharmacologic agents used in the treatment of PAH include calcium-channel blockers, prostanoids, endothelin antagonists, and phosphodiesterase type 5 inhibitors (Table 2). These agents all have pulmonary vasodilatory effects and all except calcium-channel blockers also have antiproliferative properties. This lack of an antiproliferative effect may explain why only a small subset of patients benefit from long-term calcium-channel blocker use.

Clinical trials have included mainly patients with idiopathic, fenfluramine-associated, and connective tissue disease-associated PAH, but data from other PAH patient populations is increasing. Epoprostenol remains the treatment of choice for most functional class IV patients, but oral therapy is now usually used as initial therapy for functional class II and III patients (Fig. 2) (49). Decisions are generally made based on functional class as well as hemodynamics and exercise capacity. Combination therapy is an area of growing research and is being used clinically either as an initial treatment strategy or more commonly as add-on therapy when the response to a single medication is inadequate.

Calcium-channel blockers. Calcium channel-blockers remain a treatment option only for patients with a positive vasodilator challenge, as defined in Table 3. This pattern of response is present in fewer than 10% of those with idiopathic PAH and even less frequently in patients with other forms of PAH (50). Patients whose mean pulmonary arterial pressure remains above 40 mm Hg during a vasodilator challenge despite a greater than 20% decrease are no longer considered “responders” due to excessively high

long-term failure rates. Empiric therapy without vasodilator testing is also not recommended because most patients will fail therapy.

Among vasodilator responders, calcium-channel blocker therapy can be initiated with nifedipine (30 mg/day) or diltiazem (120 mg/day) and then increased to the maximal tolerated dose. Close follow-up for continued benefit is required, because only 50% of patients maintain long-term responses.

Endothelin antagonists. Endothelin-1 is a potent vasoconstrictor and mitogen acting on both the systemic and pulmonary vasculature through 2 receptors. Although it is produced and acts predominately locally, circulating levels of endothelin-1 are increased in PAH and correlate with disease severity (51). Two endothelin antagonists, bosentan (Tracleer, Actelion, Allschwil, Switzerland) and ambrisentan (Letairis, Gilead, Forest City, California) are approved for use in the U.S., and a third drug, sitaxsentan (Thelin, Encysive, Houston, Texas) is approved in Europe and Canada. Bosentan is a nonspecific endothelin antagonist, blocking both the endothelin-A receptor and the endothelin-B receptor, while sitaxsentan and ambrisentan are specific for the endothelin-A receptor. All 3 are oral agents that led to improvement in exercise capacity and hemodynamics in 12- to 16-week clinical trials (52-55). Bosentan also led to improved survival versus “expected” survival in open label studies (56,57); long-term survival data from ambrisentan and sitaxsentan have been presented and appear to be favorable as well. The open-label extension study for sitaxsentan also included a randomized but unblinded bosentan arm; results for 6-min walk distance were similar between the 2 groups but time to clinical worsening favored sitaxsentan (58).

Bosentan has been associated with increases in liver function tests in approximately 11% of patients, while abnormalities with other endothelin antagonists are lower. Monthly liver function testing is required for patients on any endothelin antagonist, and increases in transaminases greater than 3 times normal require reduction in dose or treatment interruption, as described in the package inserts.

Phosphodiesterase-5 inhibitors. Sildenafil (Viagra, Revatio, Pfizer, New York, New York) is a phosphodiesterase-5 inhibitor initially approved for erectile dysfunction but subsequently shown to have effects on the pulmonary vasculature. Sildenafil increases the effects of locally produced nitric oxide (NO) by inhibiting the breakdown of NO’s second messenger, cyclic guanosine monophosphate. This results in pulmonary vasodilation and inhibition of smooth muscle cell growth. Because this occurs only in vascular beds with significant production of NO, sildenafil results in less ventilation-perfusion mismatch than epoprostenol. Benefits with treatment include improved symptoms, increased 6-min walk distance, improvement in hemodynamics, and in the open label follow-up study, 95% survival at 1 year (59). The approved dose is 20 mg 3 times daily, but doses up to 80 mg 3 times daily were studied and

Table 2 Medical Therapy for PAH

Medication	Dose
Bosentan (Tracleer)	Start 62.5 mg by mouth twice daily Increase to 125 mg twice daily after 4 weeks
Ambrisentan (Letairis)	Start 5 mg by mouth daily; consider increasing to 10 mg daily if 5 mg is tolerated
Sitaxsentan (Thelin)*	100 mg by mouth daily
Sildenafil (Revatio)	20 mg by mouth 3 times daily
Beraprost*	Start 20 µg by mouth 4 times a day; increase in increments of 20 µg 4 times a day if tolerated
Iloprost (Ventavis)	2.5 µg inhaled 6 to 9 times daily; if tolerated increase to 5 µg 6 to 9 times daily
Epoprostenol (Flolan)	Initiate at 2 ng/kg/min and increase every 15 min until dose-limiting side effects occur†
Treprostinil (Remodulin)	Initiate at 1.25 ng/kg/min and increase by no more than 1.25 ng/kg/min weekly for 4 weeks and after that by no more than 2.5 ng/kg/min weekly

*Not approved in the U.S. †Intravenous epoprostenol and treprostinil dosing vary; the epoprostenol package insert goes on to say that more commonly a slower titration schedule is used. Typically dose increases of 0.5 ng/kg/min to 1 ng/kg/min are performed initially daily and then approximately weekly until the target dose is achieved, limited by side effects.

PAH = pulmonary arterial hypertension.

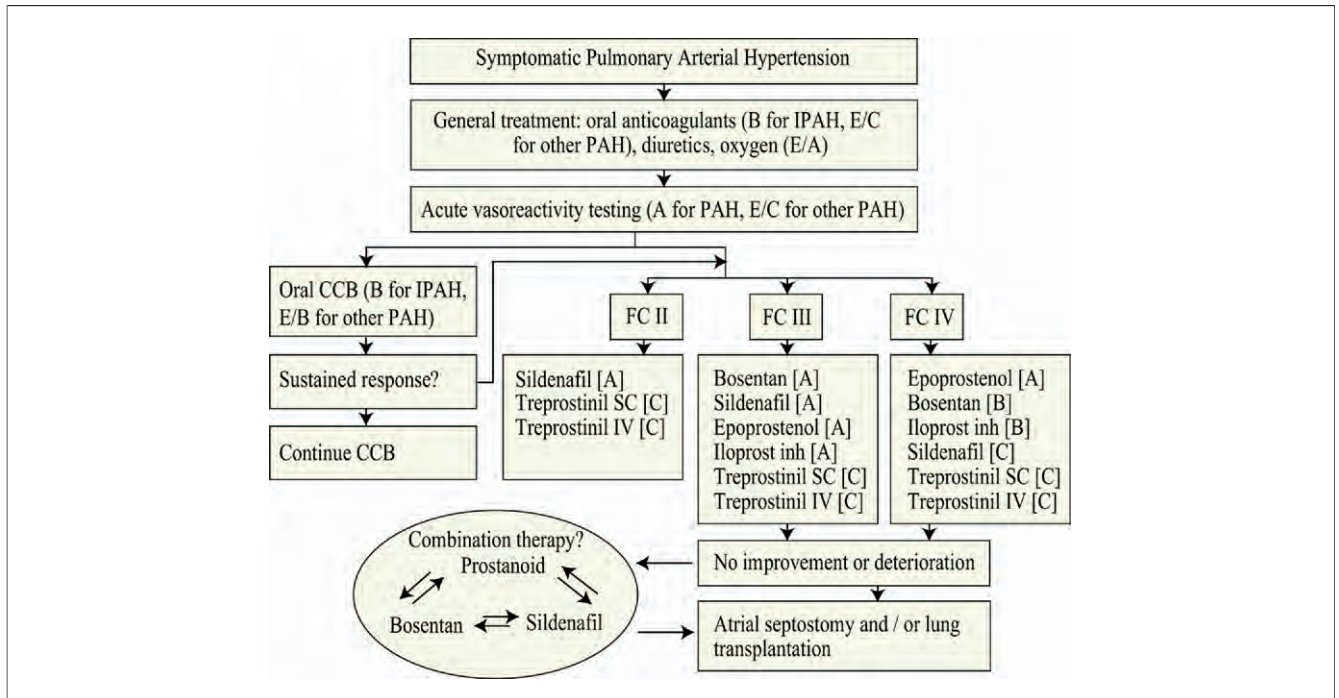


Figure 2 Treatment Algorithm for PAH Adapted From 2007 ACCP Guidelines

Letters following recommendations are based on a combination of level of evidence and perceived benefit: A = strong recommendation; B = moderate recommendation; C = weak recommendation. Recommendations with an E are based on expert opinion rather than clinical trial evidence. Ambrisentan was approved for functional class II and III pulmonary arterial hypertension (PAH) after these guidelines were published. ACCP = American College of Chest Physicians; CCB = calcium-channel blocker; FC = functional class; INH = inhaled; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; SC = subcutaneous. Reproduced, with permission, from Badesch et al. (49).

are sometimes considered when the initial response is inadequate.

Prostacyclins. The PAH patients exhibit an underproduction of prostacyclin (PGI₂) (60), a product of the arachidonic acid cascade that promotes vasodilation and inhibits vascular proliferation and platelet aggregation. Epoprostenol (synthetic prostacyclin, Flolan, Gilead) was the first Food and Drug Administration–approved therapy for PAH. Due to its short half-life, it requires delivery through a continuous portable infusion pump and an indwelling central venous catheter. Epoprostenol remains the treat-

ment of choice for patients with the most advanced disease and leads to improvements in exercise capacity, hemodynamics, and quality of life. It also appears to improve survival based on a 12-week randomized but unblinded study (61) and 2 longer-term open-label studies (62,63).

Longer-acting prostacyclin analogs have also been developed for intravenous, inhaled, and oral use, with variable effectiveness and tolerability. This includes treprostinil (Remodulin, United Therapeutics, Silver Spring, Maryland), approved for subcutaneous and intravenous use in the U.S.; iloprost (Ventavis, Actelion), approved for inhaled use in the U.S. and for intravenous and inhaled use in Europe; and beraprost (Toray Industries, New York, New York), an oral medication approved in Japan (64). Additional studies of oral and inhaled treprostinil are underway with results expected in 2008. The inhaled route provides several benefits including fewer systemic side effects and less ventilation-perfusion mismatch, though with potentially lower efficacy.

Epoprostenol or treprostinil may be initiated at 1 to 2 ng/kg/min and titrated over several days to 5 to 10 ng/kg/min, limited by side effects and systemic hypotension. Subsequent dose increases are usually made every 3 to 7 days until the initial target dose is reached. Treprostinil appears to require up to 2 times higher overall doses than epoprostenol to achieve similar effects. Excessively low doses of prostacyclins may be ineffective, but the earlier idea that all

Table 3 Vasoreactivity Testing

Responders:
Fall in mean pulmonary artery pressure of >10 mm Hg to a value <40 mm Hg
Increased or unchanged cardiac output
Commonly used agents in vasoreactivity testing
Epoprostenol: infused starting at 1 to 2 ng/kg/min and increased by 2 ng/kg/min every 5 to 10 min until a clinically significant fall in blood pressure, increase in heart rate, or adverse symptoms (e.g., nausea, vomiting) develop.
Adenosine: infused at 50 μg/kg/min and increased every 2 min until adverse symptoms or hypotension develop or until a dose of 200 to 250 μg/kg/min is reached.
Nitric oxide: inhaled nitric oxide is administered at 10 to 20 parts per million for 5 min.

Patients classified as vasoresponders may be considered for therapy with calcium-channel blockers.

patients require continuous up-titration of epoprostenol regardless of clinical status has also been questioned as this may lead to excessively high cardiac output and even high output heart failure. Instead, frequent reassessment of symptoms, exercise capacity, and, in many centers, periodic hemodynamic evaluations are used to titrate to the most effective dose. Side effects common to all prostacyclins include flushing, jaw pain, and body aches, and these may also limit the achievable dose.

PAH subgroups. Patients with idiopathic PAH and PAH associated with scleroderma (65) account for the majority of patients enrolled in clinical trials with good evidence of benefit in both groups. Small numbers of patients with repaired or unrepaired congenital heart disease have also been included in the pivotal PAH clinical trials (sitaxsentan, sildenafil, treprostinil) and in other studies (66–68) that showed improvement in hemodynamics, exercise capacity, and functional class. For HIV and portal hypertension, mainly case-series level of evidence is available; these studies showed improvement in hemodynamics, exercise capacity, and symptoms relative to baseline (69–73). Treatment has also allowed portopulmonary hypertension patients to undergo successful liver transplantation. Current treatment guidelines do not differentiate between PAH subgroups in their recommendations for initial therapy, but additional studies are needed.

Combination therapy. Combination therapy has been advocated based on the potential for additive or synergistic effects. Improvement in hemodynamics, exercise capacity, and symptoms over 12- to 16-week study periods has now been reported (Table 4) (74–77), and additional studies including 1 long-term study with a morbidity/mortality end point are ongoing. The typical improvement in walk distance (20 to 26 m) is less than that of studies comparing

monotherapy to placebo, but given improvement in symptoms, time to clinical worsening, and hemodynamics, these changes appear to be clinically significant. Additionally, a large uncontrolled study investigating protocol-driven combination therapy for patients failing to achieve certain exercise test goals while on monotherapy reported very good overall survival rates (93%, 83%, and 80% at 1, 2, and 3 years), with 43% of patients requiring combination therapy (78). Combination therapy has been suggested for patients with signs of right heart failure, 6-min walk distance <380 m and persistent functional class III or IV symptoms despite treatment with 1 medication.

Adjunctive therapies: anticoagulation, digoxin, and diuretics. Anticoagulation with warfarin has been shown in observational studies to improve survival, and it is recommended for patients with idiopathic PAH (79). Anticoagulation may prevent both in situ thrombosis and pulmonary embolism; these events may be more common and more serious in PAH due to abnormalities in platelet function and in the activated clotting system. Consideration of anticoagulation in other PAH groups has also been suggested, although this is based on expert opinion only with some patient groups (portopulmonary hypertension, congenital heart disease) at higher risk of bleeding complications. A goal international normalized ratio of either 1.5 to 2.5 (80) or at some centers 2.0 to 3.0 has generally been recommended. Anticoagulation is also recommended for all patients with chronic thromboembolic pulmonary hypertension; it has not been studied in patients with pulmonary hypertension associated with left heart disease or pulmonary hypertension associated with lung disease.

Digoxin has been used as an adjunctive treatment for right heart failure but with inconclusive benefits. It is also frequently used in the treatment of supraventricular arrhythm-

Table 4 Combination Therapy in PAH

Combination	6MWD Improvement* (m)	Other Evaluations
Bosentan ± inhaled iloprost		
STEP trial (n = 67)	Peak†: 26 m (p = 0.05) Trough: no difference	Improved functional class, time to clinical worsening, post-inhalation hemodynamics (p < 0.05)
COMBI trial (n = 40): unblinded randomized	No difference	No difference functional class, time to clinical worsening
IV epoprostenol ± oral therapy		
BREATHE-2 trial (n = 33) epoprostenol ± bosentan	No difference	Trend toward greater improvement in PVR (p = 0.08)
PACES trial (n = 267) epoprostenol ± sildenafil	26 m (p < 0.05)	Improved hemodynamics, time to clinical worsening (p < 0.05)
Oral therapy ± inhaled treprostinil		
TRIUMPH-1 trial (n = 235)	Walk improvement reported as positive (press release); results expected 2008	

In adequately powered studies, combination therapy has led to improvement in functional class, hemodynamics, and exercise capacity. *Improvement is placebo corrected. †Peak refers to post-inhalation, while trough was pre-inhalation.

BREATHE-2 = Bosentan Randomized Trial of Endothelin Antagonist Therapy; COMBI = Combination Therapy of Bosentan and Aerosolized Iloprost in Idiopathic Pulmonary Arterial Hypertension; IV = Intravenous; PACES = The Efficacy and Safety of Sildenafil Citrate Used in Combination With Intravenous Epoprostenol in PAH; PVR = pulmonary vascular resistance; STEP = Iloprost Inhalation Solution Safety and Pilot Efficacy Trial in Combination with Bosentan for Evaluation in Pulmonary Arterial Hypertension; TRIUMPH-1 = Clinical Investigation Into Inhaled Treprostinil Sodium in Patients With Severe PAH; 6MWD = 6-min walk distance; other abbreviations as in Table 1.

mias as it is better tolerated than calcium-channel blockers or beta-blockers in patients with reduced RV function.

Diuretics are often required to minimize symptoms of dyspnea and right heart failure. The excessive afterload from pulmonary hypertension often leads to marked right ventricular dilation along with compression of the left ventricle. In this setting, fluid overload may actually reduce cardiac output, and patients with severe PAH and right heart failure may require significant doses of diuretics.

Prognosis, Monitoring Response to Therapy and Lung Transplantation

Prognosis. Median survival among patients diagnosed with PAH in the U.S. between 1981 and 1985 was 2.8 years (81). Since that time, survival has improved to the point that patients are usually not referred for lung transplantation at the time of diagnosis. Instead, most patients begin medical therapy and are reassessed after at least several months of treatment. Five-year survival among epoprostenol-treated patients is now 47% to 55% with >70% 5-year survival among those improving to functional class I or II (Fig. 3) (62,63).

Although some hemodynamic improvement may be seen immediately after starting PAH medications, many patients do not have a significant acute pulmonary vasodilatory response. These patients usually still show improvement in hemodynamics when reassessed after several months, potentially due to treatment effects on growth and remodeling in the pulmonary vasculature. Increases in walk distance and reduced symptoms begin within a few weeks of treatment initiation and then may plateau around 12 to 16 weeks.

Improvement is often maintained over years, but there is significant variability and subsequent deterioration is not uncommon.

Patients who have developed signs or symptoms of right heart failure have much lower survival rates than those with only elevations in pulmonary artery pressures, and most prognostic markers measure some aspect of RV function either at rest or with exercise. Post-treatment markers of poor prognosis include elevated right atrial pressure, low cardiac index, low mixed venous oxygen saturation, continued functional class III/IV symptoms, poor exercise capacity, pericardial effusion, and elevated B-type natriuretic peptide level (56,63,82,83). The degree of elevation in pulmonary arterial pressures can also be predictive, but this is most important only while RV function is still relatively normal. Failure to show some improvement between baseline and follow-up in symptoms, hemodynamics, and exercise capacity are also poor prognostic signs.

Monitoring and lung transplantation. Frequent evaluations are required to identify patients failing therapy as well as to allow timely referral for lung transplantation. Routine follow-up should include assessment of symptoms, functional class and exercise capacity at approximately 3-month intervals, and a more detailed evaluation of pulmonary pressures and RV function on an approximately annual basis.

The 6-min walk distance is the most commonly used test to assess exercise capacity; it is performed using a long hallway and a pulse oximeter. Post-treatment distances <380 m are associated with a worse prognosis. Formal cardiopulmonary exercise testing can also be used, but appears to be less reliable in the PAH patient population unless performed in very experienced centers.

Assessment of RV function can be performed through a combination of echocardiogram, cardiac catheterization, and, potentially, B-type natriuretic peptide level or cardiac magnetic resonance imaging. Echocardiography must be used cautiously in tracking PAH patients, as echocardiographic estimates of RV systolic pressure do not predict survival (19). Rather, echocardiographic markers of RV function such as right atrial size, septal shift toward the left ventricle during diastole, and tricuspid annular plane excursion (a correlate of RV ejection fraction) predict outcome (84).

Cardiac catheterization is performed in many patients on an approximately annual basis, but this requirement is debated. Catheterization is particularly important in patients receiving an intravenous or subcutaneous prostacyclin to avoid under- and overdosing of the medication. It should also be considered in most cases where add-on therapy is planned both to confirm the need for additional therapy and to acquire a new “baseline” for future comparisons.

Patients with persistent functional class III or IV symptoms, right atrial pressure >15 mm Hg, or cardiac index <2 l/min/m² should be considered for lung transplantation; combination therapy and atrial septostomy may be consid-

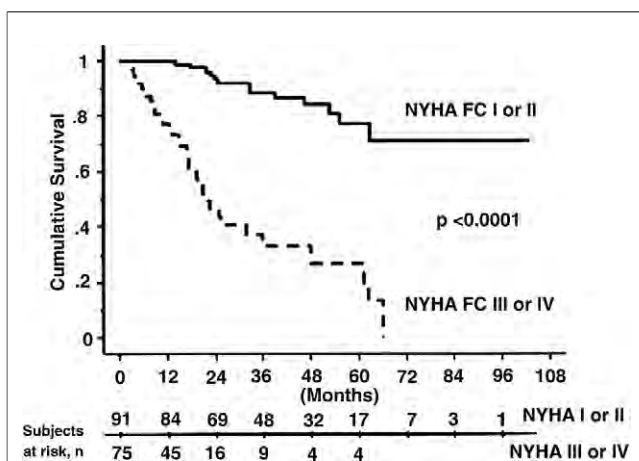


Figure 3 Survival in Patients With Idiopathic PAH After Treatment With Epoprostenol

Among patients who were FC III or IV prior to treatment with epoprostenol, survival among patients improving to FC I or II (solid line) was substantially better than patients who were FC III or IV (dashed line) after treatment; $p < 0.001$. NYHA = New York Heart Association; other abbreviations as in Figure 2. Reproduced, with permission, from Sitbon et al. (63).

ered simultaneously. For most patients, either single- or double-lung transplantation are options, but many centers prefer double-lung transplantation owing to concerns about post-operative reperfusion injury after single-lung transplantation and slightly higher ($p = 0.05$) long-term survival rates with double-lung transplantation. Survival in the early post-operative period is lower for PAH patients than for other patients undergoing lung transplantation, but 5- and 10-year survival rates are similar (85). Heart-lung transplantation is still sometimes performed, but more often is reserved for patients with pulmonary hypertension associated with complex congenital heart disease that cannot be corrected at the time of surgery.

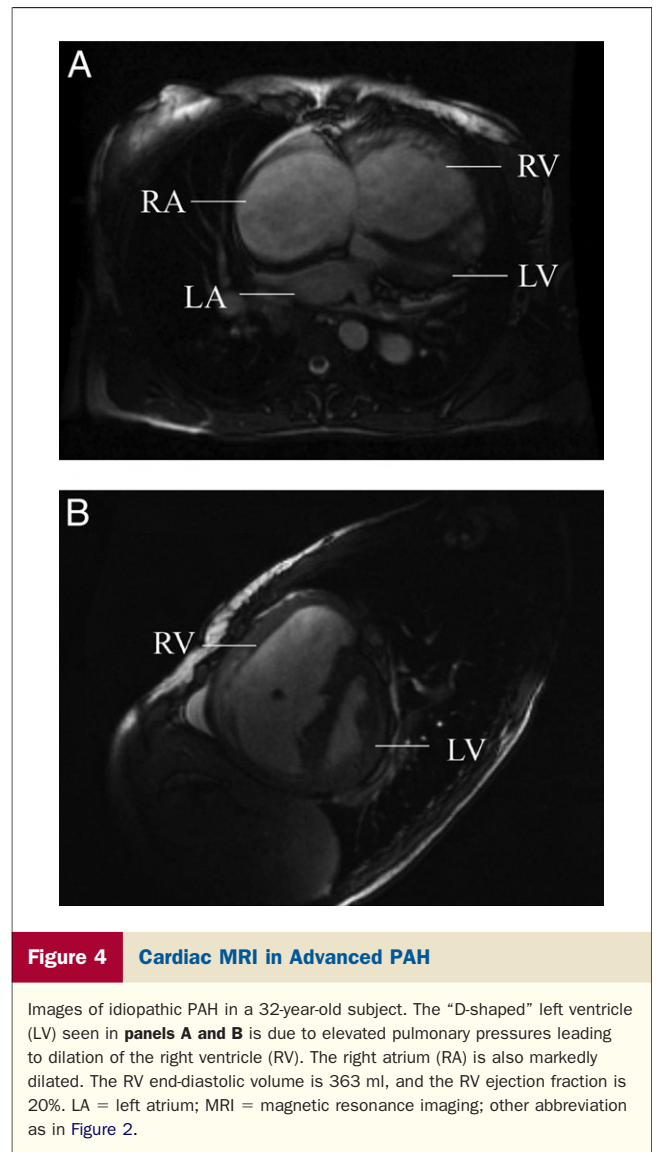
Acute Presentations: RV Failure and PAH

Patients with advanced PAH may present acutely with volume overload, marginal blood pressure, and, at times, elevated creatinine, related either to an acute process or simply worsening RV failure. Although the “preload-dependent RV” may respond poorly to significant volume depletion, aggressive volume loading of the already dilated and overloaded RV may worsen hypotension and cardiac output.

This probably relates to ventricular interdependence rather than a lack of validity of the Frank-Starling mechanism. In the decompensated patient, elevated RV volume leads to septal shift (Fig. 4), with reduced left ventricular end-diastolic volume and low cardiac output. The poor response to volume has been shown in animal models of acute RV failure, where fluid administration leads to lower cardiac output, worsening septal shift, and a progressive downward spiral in hemodynamics (86,87).

This ventricular interdependence also explains the improved cardiac output seen with atrial septostomy and may partially explain the higher survival of PAH patients with a patent foramen ovale or with congenital heart disease. In this situation, the lower systemic arterial oxygen saturation owing to right-to-left shunting is partially offset by an increase in cardiac output and, in most cases, an overall increase in oxygen delivery (88).

Treatment of the acutely ill patient with PAH should include careful evaluation for secondary causes of decompensation such as a low-grade line infection (for those on an intravenous therapy) or pulmonary thromboembolism. Many patients are volume overloaded at presentation, and diuresis, even in the setting of marginal cardiac output and low blood pressure, may be required. In some cases, support with inotropes or pressors is necessary: animal data suggest a better hemodynamic response with sympathomimetic agents such as dobutamine, norepinephrine, and dopamine rather than vasopressin or phenylephrine; milrinone also has favorable effects on cardiac output but may lead to excessive hypotension (89–92).



Future Therapeutic Targets

Novel pathways of potential importance in PAH. A variety of other substances may play roles as mediators through a final common pathway of pulmonary angiogenesis and may therefore be appealing therapeutic targets. These include vasoactive intestinal polypeptide (93), platelet-derived growth factor (94), serotonin and its receptors and transporter (95), and Rho kinase inhibitors (96). Clinical trials for many of these substances are underway.

Stem cell replacement/transplant therapy: rebuilding the damaged circulation. Endothelial progenitor cells have recently been explored as a potential source for neovascularization of the diseased pulmonary circulation of PAH. Animal data in a monocrotaline model of pulmonary hypertension was positive, and a pilot study in 31 patients with PAH found improvement in 6-min walk distance and hemodynamics 12 weeks after treatment with autologous endothelial progenitor cells (97). In animals, transfection of

the endothelial progenitor cells with NO synthase appears to reduce pulmonary pressures to an even greater extent (98). Questions at this point relate to magnitude and duration of the benefits as well as continued evaluation of safety.

Conclusions

Management of PAH has evolved significantly over the past decade with now multiple effective therapies. Patients are living longer and more comfortable lives, and many are now treated with oral therapies. However, there is still no cure for PAH, and many patients remain symptomatic despite therapy. As research in this field increases, new findings regarding the pathogenesis of PAH are presenting potential new therapeutic targets. These approaches are likely to dramatically change the management algorithm for PAH over the next decade. Treatment strategies that combine medications and target multiple pathogenic pathways have now been demonstrated to be both safe and more effective than monotherapy and are emerging as the preferred approach to management of many patients.

Reprint requests and correspondence: Dr. Kelly M. Chin, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Mail Code 75390-8550, Dallas, Texas 75235. E-mail: Kelly.Chin@utsouthwestern.edu.

REFERENCES

- Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43 Suppl 1:5S-12S.
- Newman JH, Trembath RC, Morse JA, et al. Genetic basis of pulmonary arterial hypertension: current understanding and future directions. *J Am Coll Cardiol* 2004;43 Suppl 1:33S-39S.
- Austin ED, Loyd JE. Genetics and mediators in pulmonary arterial hypertension. *Clin Chest Med* 2007;28:43-57.
- Grunig E, Janssen B, Merelles D, et al. Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene. *Circulation* 2000;102:1145-50.
- Tada Y, Majka S, Carr M, et al. Molecular effects of loss of BMPR2 signaling in smooth muscle in a transgenic mouse model of PAH. *Am J Physiol Lung Cell Mol Physiol* 2007;292:L1556-63.
- Morty RE, Nejman B, Kwapiszewska G, et al. Dysregulated bone morphogenetic protein signaling in monocrotaline-induced pulmonary arterial hypertension. *Arterioscler Thromb Vasc Biol* 2007;27:1072-8.
- Du L, Sullivan CC, Chu D, et al. Signaling molecules in nonfamilial pulmonary hypertension. *N Engl J Med* 2003;348:500-9.
- Abdalla SA, Gallione CJ, Barst RJ, et al. Primary pulmonary hypertension in families with hereditary haemorrhagic telangiectasia. *Eur Respir J* 2004;23:373-7.
- Abenham L, Moride Y, Brenot F, et al., International Primary Pulmonary Hypertension Study Group. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996;335:609-16.
- Rich S, Rubin L, Walker AM, Schneeweiss S, Abenham L. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. *Chest* 2000;117:870-4.
- Rothman RB, Ayestas MA, Dersch CM, Baumann MH. Aminorex, fenfluramine, and chlorphentermine are serotonin transporter substrates. Implications for primary pulmonary hypertension. *Circulation* 1999;100:869-75.
- Marcos E, Fadel E, Sanchez O. Serotonin-induced smooth muscle hyperplasia in various forms of human pulmonary hypertension. *Circ Res* 2004;94:1263-70.
- Kawut SM, Horn EM, Berekashvili KK, et al. Selective serotonin reuptake inhibitor use and outcomes in pulmonary arterial hypertension. *Pulm Pharmacol Ther* 2006;19:370-4.
- Eddahibi S, Guignabert C, Barlier-Mur AM, et al. Cross talk between endothelial and smooth muscle cells in pulmonary hypertension: critical role for serotonin-induced smooth muscle hyperplasia. *Circulation* 2006;113:1857-64.
- Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354:579-87.
- Chin KM, Channick RN, Rubin LJ. Is methamphetamine use associated with idiopathic pulmonary arterial hypertension? *Chest* 2006;130:1657-63.
- Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant* 1996;15:100-5.
- Oya H, Nagaya N, Uematsu M, et al. Poor prognosis and related factors in adults with Eisenmenger syndrome. *Am Heart J* 2002;143:739-44.
- McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126 Suppl 1:78S-92S.
- Chang B, Schachna L, White B, Wigley FM, Wise RA. Natural history of mild-moderate pulmonary hypertension and the risk factors for severe pulmonary hypertension in scleroderma. *J Rheumatol* 2006;33:269-74.
- Magliano M, Isenberg DA, Hillson J. Pulmonary hypertension in autoimmune rheumatic diseases: where are we now? *Arthritis Rheum* 2002;46:1997-2009.
- Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology* 2003;37:401-9.
- Halank M, Ewert R, Seyfarth HJ, Hoeffken G. Portopulmonary hypertension. *J Gastroenterol* 2006;41:837-47.
- Ashfaq M, Chinnakotla S, Rogers L, et al. The impact of treatment of portopulmonary hypertension on survival following liver transplantation. *Am J Transplant* 2007;7:1258-64.
- Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary pulmonary hypertension in HIV infection. *Chest* 1991;100:1268-71.
- Mehta NJ, Khan IA, Mehta RN, Sepkowitz DA. HIV-related pulmonary hypertension: analytic review of 131 cases. *Chest* 2000;118:1133-41.
- Zuber JP, Calmy A, Evison JM, et al. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. *Clin Infect Dis* 2004;38:1178-85.
- Fawzy ME, Hassan W, Stefadouros M, Moursi M, El Shaer F, Chaudhary MA. Prevalence and fate of severe pulmonary hypertension in 559 consecutive patients with severe rheumatic mitral stenosis undergoing mitral balloon valvotomy. *J Heart Valve Dis* 2004;13:942-7.
- Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* 2001;37:183-8.
- 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.
- Kaluski E, Cotter G, Leitman M, et al. Clinical and hemodynamic effects of bosentan dose optimization in symptomatic heart failure patients with severe systolic dysfunction, associated with secondary pulmonary hypertension—a multi-center randomized study. *Cardiology* 2008;109:273-80.
- 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.
- Neuman Y, Kotliroff A, Bental T, Siegel RJ, David D, Lishner M. Pulmonary artery pressure and diastolic dysfunction in normal left ventricular systolic function. *Int J Cardiol* 2007 Jul 20;[E-pub ahead of print].

34. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539-50.
35. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;46:e1-82.
36. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;93:391-8.
37. Patel NM, Lederer DJ, Borczuk AC, Kawut SM. Pulmonary hypertension in idiopathic pulmonary fibrosis. *Chest* 2007;132:998-1006.
38. Auger WR, Kim NH, Kerr KM, Test VJ, Fedullo PF. Chronic thromboembolic pulmonary hypertension. *Clin Chest Med* 2007;28:255-69.
39. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216-23.
40. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. *Eur Respir J* 2007;30:1103-10.
41. 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.
42. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol* 1985;6:359-65.
43. 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.
44. Hinderliter AL, Willis PW 4th, Long W, et al. Frequency and prognostic significance of pericardial effusion in primary pulmonary hypertension. *PPH Study Group. Primary pulmonary hypertension. Am J Cardiol* 1999;84:481-4.
45. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Pulmonary function in primary pulmonary hypertension. *J Am Coll Cardiol* 2003;41:1028-35.
46. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med* 2007;48:680-4.
47. Worsley DF, Palevsky HI, Alavi A. Ventilation-perfusion lung scanning in the evaluation of pulmonary hypertension. *J Nucl Med* 1994;35:793-6.
48. McGoon M, Guterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126 Suppl 1:14S-34S.
49. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007;131:1917-28.
50. 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.
51. 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.
52. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
53. Channick R, Badesch DB, Tapson VF, et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary hypertension: a placebo-controlled study. *J Heart Lung Transplant* 2001;20:262-3.
54. Barst RJ, Langleben D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006;47:2049-56.
55. Olschewski H, Galie N, Kramer M, Rubin LJ. Ambrisentan improves exercise capacity and time to clinical worsening in patients with pulmonary arterial hypertension: results of the ARIES-2 study (abstr). *Proc Am Thorac Soc* 2006;3:A728.
56. 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.
57. 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.
58. Benza R, Frost A, Girgis R, et al. Chronic treatment of pulmonary arterial hypertension with sitaxsentan and bosentan (abstr). *Proc Am Thorac Soc* 2006;3:A729.
59. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148-57.
60. 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.
61. Barst RJ, Rubin LJ, Long WA, et al. The Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;334:296-302.
62. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002;106:1477-82.
63. 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.
64. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;41:2119-25.
65. 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.
66. 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.
67. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *Am Heart J* 2006;151:851-5.
68. Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S. Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. *Heart* 2007;93:350-4.
69. Hoepfer MM, Seyfarth HJ, Hoeffken G, et al. Experience with inhaled iloprost and bosentan in portopulmonary hypertension. *Eur Respir J* 2007;30:1096-102.
70. Ashfaq M, Chinnakotla S, Rogers L, et al. The impact of treatment of portopulmonary hypertension on survival following liver transplantation. *Am J Transplant* 2007;7:1258-64.
71. 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.
72. Barbaro G, Lucchini A, Pellicelli AM, Grisorio B, Giancaspro G, Barbarini G. Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. *Heart* 2006;92:1164-6.
73. 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.
74. 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.
75. Hoepfer 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.
76. 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.
77. Simonneau G, Burgess G, Collings L, et al. Safety and efficacy of combination therapy with sildenafil and epoprostenol in patients with pulmonary arterial hypertension (PAH) (abstr). *Proc Am Thorac Soc* 2006;3:A58.
78. Hoepfer MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005;26:858-63.

79. Johnson SR, Mehta S, Granton JT. Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review. *Eur Respir J* 2006;28:999–1004.
80. Badesch DB, Abman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126 Suppl 1:35S–62S.
81. 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.
82. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002;39:1214–9.
83. Nagaya N, Nishikimi T, Uematsu M. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000;102:865–70.
84. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006;174:1034–41.
85. Trulock EP, Christie JD, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart–lung transplantation report–2007. *J Heart Lung Transplant* 2007;26:782–95.
86. Belenkie I, Dani R, Smith ER, Tyberg JV. Effects of volume loading during experimental acute pulmonary embolism. *Circulation* 1989;80:178–88.
87. Molloy DW, Lee KY, Jones D, Penner B, Prewitt RM. Effects of noradrenaline and isoproterenol on cardiopulmonary function in a canine model of acute pulmonary hypertension. *Chest* 1985;88:432–5.
88. Kurzyna M, Dabrowski M, Bielecki D, et al. Atrial septostomy in treatment of end-stage right heart failure in patients with pulmonary hypertension. *Chest* 2007;131:977–83.
89. Acosta F, Sansano T, Palenciano CG, et al. Effects of dobutamine on right ventricular function and pulmonary circulation in pulmonary hypertension during liver transplantation. *Transplant Proc* 2005;37:3869–70.
90. Hirsch LJ, Rooney MW, Wat SS, Kleinmann B, Mathru M. Nor-epinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. *Chest* 1991;100:796–801.
91. Leather HA, Segers P, Berends N, Vandermeersch E, Wouters PF. Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. *Crit Care Med* 2002;30:2548–52.
92. Rich S, Gubin S, Hart K. The effects of phenylephrine on right ventricular performance in patients with pulmonary hypertension. *Chest* 1990;98:1102–6.
93. 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.
94. Schermuly RT, Dony E, Ghofrani HA, et al. Reversal of experimental pulmonary hypertension by PDGF inhibition. *J Clin Invest* 2005;115:2811–21.
95. 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.
96. Abe K, Shimokawa H, Morikawa K, et al. Long-term treatment with a Rho-kinase inhibitor improves monocrotaline-induced fatal pulmonary hypertension in rats. *Circ Res* 2004;94:385–93.
97. Wang XX, Zhang FR, Shang YP, et al. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: a pilot randomized controlled trial. *J Am Coll Cardiol* 2007;49:1566–71.
98. Zhao YD, Courtman DW, Deng Y, Kugathasan L, Zhang Q, Stewart DJ. Rescue of monocrotaline-induced pulmonary arterial hypertension using bone marrow-derived endothelial-like progenitor cells: efficacy of combined cell and eNOS gene therapy in established disease. *Circ Res* 2005;96:442–50.

Pulmonary Arterial Hypertension
Kelly M. Chin, and Lewis J. Rubin
J. Am. Coll. Cardiol. 2008;51;1527-1538
doi:10.1016/j.jacc.2008.01.024

This information is current as of July 1, 2008

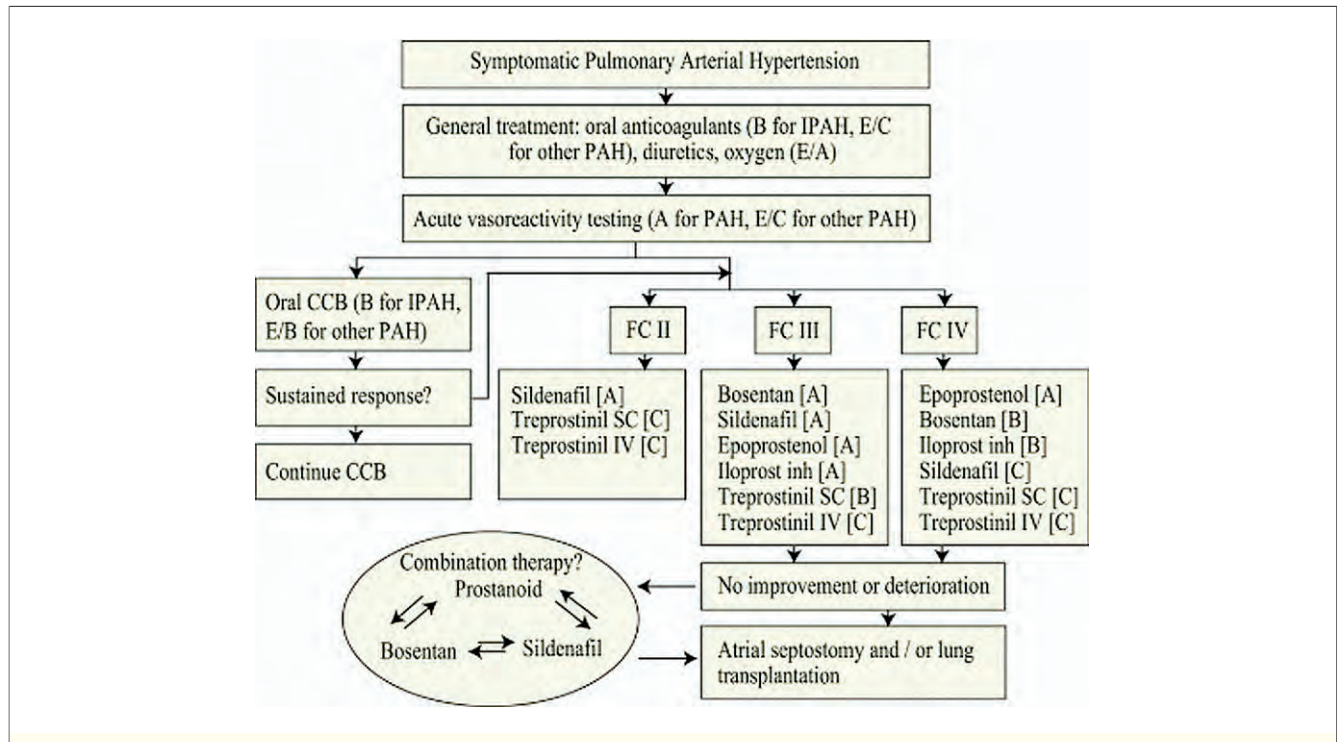
Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/51/16/1527
References	This article cites 97 articles, 55 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/51/16/1527#BIBL
Errata	An erratum has been published regarding this article. Please see next page or: http://content.onlinejacc.org/cgi/content/full/52/2/169
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl



CORRECTION

Chin KM, Rubin LJ. Pulmonary Arterial Hypertension. J Am Coll Cardiol 2008;51:1527–38.

In **Figure 2** of this article, the treatment algorithm for pulmonary arterial hypertension (PAH) adapted from the ACCP guidelines should have listed subcutaneous treprostinil for functional class III PAH as having received a level “B” rather than level “C” strength of recommendation. The corrected figure is printed below. The authors apologize for this error.



doi:10.1016/j.jacc.2008.05.005