Pulmonary Arterial Hypertension: New Insights Into the Optimal Role of Current and Emerging Prostacyclin Therapies

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Pulmonary arterial hypertension (PAH), which is a subset of pulmonary hypertension, is a group of diseases distinguished by vascular remodeling of the small pulmonary arteries with associated elevated pulmonary arterial pressure and right ventricular failure. This progressive and sometimes fatal disease occurs as an idiopathic disease or as a component of other disease states. Estimates of the incidence of PAH have varied from 5 to 52 cases/1 million population. Symptoms begin with shortness of breath with exertion and progress to dyspnea with normal activities and, finally, dyspnea at rest. Untreated patients with PAH have a 1-, 3-, and 5-year survival rate of 68%, 48%, and 34%, respectively. Treated, the survival rates improve to 91% to 97% after 1 year and 84% to 91% after 2 years. The current definition of PAH consists of 3 specific hemodynamic assessments confirmed by right heart catheterization findings. One of several important pathophysiologic mechanisms involved in PAH is pulmonary vascular remodeling, which is caused by endothelial and smooth muscle cell hyperproliferation. This is coincident with overexpression of the vasoconstrictor endothelin-1 and a reduction in the vasodilators nitric oxide and prostacyclin, which further impedes proper vasomotor tone, among other effects. Prostacyclin therapies augment the decreased prostacyclin levels in patients with PAH. The currently approved prostacyclins for the treatment of PAH include epoprostenol, iloprost, and treprostinil. Among the 3 medications, the delivery options include intravenous infusion, subcutaneous infusion, and inhaled formulations. Epoprostenol has been shown to have a positive effect on survival in patients with PAH. All prostacyclins have demonstrated improvements in functional class, exercise tolerance, and hemodynamics in patients with PAH. Intravenously and subcutaneously administered formulations of prostacyclins require continuous infusion pump administration, which presents clinical challenges for both the patient and the care provider. Dosing must be individualized and also presents a clinical challenge. Inhaled formulations seem efficacious in moderately symptomatic patients with PAH and might be appropriate when combined with an oral medication. Combination therapies are commonly used in clinical practice, with the decision to do so based on randomized controlled trial data and case study evidence. The present report provides an overview of PAH, the scientific rationale for treatment with prostacyclin therapy, and the benefits and risks of prostacyclin therapy, both as monotherapy and combined with other medications approved for the treatment of PAH. **(Am J Cardiol 2013;111[suppl]:1A−16A)**

Overview of Pulmonary Arterial Hypertension

Etiology: Pulmonary arterial hypertension (PAH) is a group of diseases having in common vascular remodeling of the small pulmonary arteries with associated elevated pulmonary arterial pressure and right ventricular failure. It is a progressive and fatal disease if untreated.

PAH occurs as an idiopathic disease (formerly referred to as "primary pulmonary hypertension") or as a component of other disease states, including connective tissue diseases, congenital heart disease, human immunodeficiency virus infection, and others. PAH is also associated with familial genetic patterns, venous or capillary involvement, and persistent PAH of the newborn (Table 1). The primary pathophysiology is remodeling of the small pulmonary arteries and increased pulmonary vascular resistance. Symptoms begin as shortness of breath on exertion and progress to dyspnea with normal activities and, finally, dyspnea at rest. In advanced PAH, patients are unable to perform any activity without shortness of breath or chest pain.[1,2]

Classification: The World Health Organization (WHO) formulated a clinical classification of the various

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Table 1
Revised (2009) World Health Organization (WHO) classification of group 1 pulmonary arterial hypertension (PAH)

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 Human immunodeficiency virus 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

Data from Simonneau et al.[3]

Table 2
World Health Organization (WHO) functional classification for patients with pulmonary arterial hypertension (PAH)

Class	Description
I	Patients with pulmonary hypertension but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity; they are comfortable at rest; less-than-ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
IV	Patients with pulmonary hypertension with an inability to carry out any physical activity without symptoms; these patients manifest signs of right heart failure; dyspnea and/or fatigue can even be present at rest; discomfort is increased by any physical activity

manifestations of pulmonary hypertension, of which PAH is a subgroup, according to similarities in pathophysiologic mechanisms, clinical presentation, and therapeutic approaches. This classification system was initially adopted in 1998 and was re-examined in 2003 and 2008. The WHO pulmonary hypertension groups consist of the following[3]:

Group 1: pulmonary arterial hypertension
Group 2: pulmonary hypertension with left heart disease
Group 3: pulmonary hypertension associated with lung disease and/or hypoxemia
Group 4: pulmonary hypertension due to chronic thrombotic and/or embolic disease
Group 5: miscellaneous (sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels [adenopathy, tumor, fibrosing mediastinitis])

Patients can also be classified according to their functional abilities and symptom severity. The WHO classification of functional capacity is an adaption of the New York Heart Association (NYHA) classification system and is commonly used in both daily practice and clinical trials to describe patients (Table 2). The WHO functional class is determined from the patient's own subjective impression of ability and symptom severity.[2] The indications for Food and Drug Administration–approved treatments of PAH specify the WHO classification.

Epidemiology and survival: Estimates of the incidence of PAH have varied from 5 to 52 cases/1 million population.[4,5] The incidence of PAH associated with scleroderma is estimated at 30 to 286 cases/1 million population.[6] PAH occurs in both genders and in all age groups; although after puberty, PAH is seen approximately twice as often in females.[7] Untreated patients with PAH face an estimated mean survival of 2.8 years, with a 1-, 3-, and 5-year survival rate of 68%, 48%, and 34%, respectively.[8] Treated, the survival rates improve to 91% to 97% after 1 year and 84% to 91% after 2 years.[9] The French Network on Pulmonary Arterial Hypertension registry calculated a 1-, 2-, and 3-year survival rate of 87%, 76%, and 67%, respectively.[4] Patients with PAH associated with the scleroderma spectrum of diseases have a poorer prognosis.[10] Data from both the Registry to EValuate Early And Long-term PAH disease management (REVEAL) and the United Kingdom-connective tissue disease-associated PAH registries showed patients with systemic sclerosis-related PAH have the poorest survival of all connective tissue disease–associated PAH subgroups.[11,12]

Diagnosis: The current definition of PAH consists of 3 hemodynamic assessments[10]: mean pulmonary artery pressure >25 mm Hg; pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure ≤ 15 mm Hg; and pulmonary vascular resistance >3 Wood units.

The original National Institutes of Health registry defined PAH as a mean pulmonary artery pressure of >25 mm Hg at rest or >30 mm Hg during exercise in the absence of pulmonary venous hypertension.[13] The issue of exercise-induced PAH, in which, with exercise, the mean pulmonary artery pressure increases to >30 mm Hg and the pulmonary capillary wedge pressure remains <20 mm Hg, has generated some controversy. After the Fourth World Symposium on Pulmonary Hypertension in Dana Point, California, in early 2008, the section of the definition referring to mean pulmonary artery pressure during exercise was removed because of a lack of agreement on how to assess and define it.[14] Noninvasive methods of assessing mean pulmonary artery pressure during exercise are not reliable.[15] A 2008 study of 406 subjects used invasive maximum cardiopulmonary exercise testing to fully phonotype the patient with exercise-induced PAH. Their findings lent support to the hypothesis that exercise-induced PAH is an early form of progressive disease, which has important clinical implications.[15] The need remains for additional studies to better understand the relation of exercise-induced PAH to disease progression and its utility as a diagnostic component.

Patients suspected of PAH should undergo a thorough evaluation (history and physical examination), electrocardiogram, chest x-ray, and echocardiogram. The symptoms of PAH

are nonspecific and include breathlessness, fatigue, weakness, angina, syncope, and abdominal distension. Symptoms at rest are reported only in very advanced cases. The physical signs of PAH include a right parasternal lift and an accentuated pulmonary component of second heart sound. Fairly rare findings include a pansystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency, and a right ventricular third sound. The physical examination findings are often subtle. The electrocardiogram might suggest PAH by demonstrating a right axis deviation and right ventricular hypertrophy and strain and right atrial enlargement. Many patients with idiopathic PAH will have abnormal chest x-ray findings with central pulmonary arterial dilation and right atrial and right ventricular enlargement in more advanced cases. Echocardiography will help to evaluate the right heart structure and function and estimate the hemodynamic alterations.[16]

Patients at greater risk of PAH should be screened periodically, including patients with a known genetic mutation, those with the scleroderma spectrum of diseases, and those with portal hypertension undergoing evaluation for liver transplantation.[10] A proper diagnosis cannot be made from accurate pressure readings in the pulmonary arterial and pulmonary venous bed. These pressure readings are obtained through pulmonary artery catheterization. Echocardiography can detect patients with elevated pulmonary artery pressure, but it cannot distinguish between an elevation in pressure caused by an increase in the precapillary resistance, which indicates PAH, or an elevation of postcapillary pressure, which does not.

The diagnosis of PAH must be confirmed by right heart catheterization.[10] After the diagnosis, the patient response to therapy and disease progression are generally assessed using noninvasive tests, including transthoracic echocardiography, WHO functional class, and the 6-minute walk test. Two biomarkers, brain natriuretic peptide and N-terminal fragment-pro-brain natriuretic peptide, are used to assess disease severity, with the serum levels of brain natriuretic peptide increasing as right ventricular function fails.[2,10] Patients with a plasma brain natriuretic peptide <180 pg/ml, and especially patients whose brain natriuretic peptide levels decrease within 6 months of starting treatment, have a better prognosis.[17]

Patients considered for long-term calcium channel blocker therapy should undergo acute vasodilator testing to test the vasoreactivity. The decision of whether to start calcium channel blocker therapy should be made carefully, and some experts have recommended calcium channel blocker therapy be used only if normalization or near normalization of the mean pulmonary artery pressure and pulmonary vascular resistance occurs. True responders are uncommon, and an acute reduction in mean pulmonary artery pressure and pulmonary vascular resistance does not indicate whether the patient will have a sustained benefit from calcium channel blocker therapy or will be among the many who fail to improve.[18] Chronic use of calcium channel blocker therapy can have poor outcomes if used inappropriately. These patients can have decreased cardiac output and systemic vascular resistance without improvement in mean pulmonary artery pressure and pulmonary vascular resistance over time, thereby worsening their condition in the absence of appropriate treatment.[18] A 2005 retrospective study of 557 patients with idiopathic PAH found that 6.8% of the study sample had a sustained long-term benefit from calcium channel blocker monotherapy. During acute vasodilator testing, these patients showed significantly lower levels of both mean pulmonary artery pressure and mean pulmonary vascular resistance, which reached near-normal values.[18] Patients who start calcium channel blocker therapy should be closely monitored for both treatment safety and efficacy. Patients with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing.

Pathophysiology

Pulmonary vascular dysfunction: The pathophysiology of PAH is a complex interplay of vasoconstriction, vascular wall hypertrophy, fibrosis, and thrombosis.[19–22] Pathologic findings show intimal hyperplasia and fibrosis, medial hypertrophy, and in situ thrombi of the small pulmonary arteries and arterioles.[22] Until recently, the underlying causes of symptoms were thought to mainly be vasoconstriction and vasodilation pathology; however, it is now believed that the processes that contribute to PAH involve abnormal proliferation of the vascular smooth muscle and endothelial cells, infiltration of the inflammatory cells, and fibrosis of vascular elements. These changes are associated with increased endothelin levels, decreased nitric oxide levels, and decreased prostacyclin levels. These factors influence vasodilation, vasoconstriction, and cell proliferation, among other processes.[23]

Recent studies have also shown that PAH is a disease of abnormal cellular proliferation and apoptosis that affects the pulmonary vasculature. An important mechanism involved in pulmonary vascular remodeling is believed to be endothelial cell hyperproliferation.[10,23] This endothelial cell hyperproliferation affects all cell types within the pulmonary arterial wall, including the endothelial, smooth muscle, and fibroblast cells.[23] Endothelial cell dysfunction results in overexpression of the peptide endothelin-1, a vasoconstrictor.[24] Overexpression of endothelin-1 reduces the synthesis of the vasodilators nitric oxide and prostacyclin, which further impedes the proper vasodilatory response and affects vascular and myocardial homeostasis, metabolism, and cell survival.[23,25,26] Endothelin-1 overexpression is also thought to induce inflammatory responses[27] and induce fibrosis.[28] Pulmonary smooth muscle cell dysfunction, caused by blocked voltage-gated potassium channels in the pulmonary artery smooth muscle cells, also contributes to PAH pathology by hyperproliferation.[19] This pulmonary vascular dysfunction results in an increase in pulmonary vascular resistance and an elevation of pulmonary arterial pressure, causing increased afterload on the right ventricle and, ultimately, right heart failure.[29]

Contribution of genetic mutations and other risk factors: Three genetic mutations have been identified that might predispose persons to PAH: bone morphogenetic protein receptor type II; activin-like kinase type 1; and 5-hydroxytryptamine (serotonin) transporter.

Table 3
Food and Drug Administration–approved therapies for pulmonary arterial hypertension (PAH)

Generic Name	Brand Name	Route of Administration	Drug Class	Indication
Epoprostenol	Flolan	IV	Prostacyclin derivative	Treatment of PAH (WHO group 1) to improve exercise capacity
Epoprostenol	Veletri	IV	Prostacyclin derivative	Treatment of PAH (WHO group 1) to improve exercise capacity
Iloprost	Ventavis	Inhaled	Prostacyclin derivative	Treatment of PAH (WHO group 1) to improve composite end point of exercise tolerance, symptoms (NYHA class), and lack of deterioration
Treprostinil	Remodulin	IV or SC	Prostacyclin derivative	Treatment of PAH (WHO group 1) to diminish symptoms associated with exercise Patients requiring transition from Flolan to reduce rate of clinical deterioration
Treprostinil	Tyvaso	Inhaled	Prostacyclin derivative	Treatment of PAH (WHO group 1) to improve exercise ability
Bosentan	Tracleer	Oral	ERA	Treatment of PAH (WHO group 1) to improve exercise ability and decrease clinical worsening
Ambrisentan	Letairis	Oral	ERA	Treatment of PAH (WHO group 1) to improve exercise ability and delay clinical worsening
Sildenafil	Revatio	Oral	PDE-5 inhibitor	Treatment of PAH (WHO group I) to improve exercise ability and delay clinical worsening
Tadalafil	Adcirca	Oral	PDE-5 inhibitor	Treatment of PAH (WHO group 1) to improve exercise ability

ERA = endothelin receptor antagonist; PDE-5 = phosphodiesterase 5.

About 50% of patients with familial PAH and ≤25% of patients with idiopathic PAH have been found to have abnormal bone morphogenetic protein receptor type II genetic abnormalities.[30,31] In carriers, mutations in bone morphogenetic protein receptor type II confer a 15% to 20% lifetime risk of developing PAH.[30,32] The bone morphogenetic protein receptor type II pathway is implicated in apoptosis in some cell types, which might contribute to endothelial cell hyperproliferation in the disease.[33] Activin-like kinase type 1 mutations have been identified in patients with PAH in association with hereditary hemorrhagic telangiectasia. Activin-like kinase type 1 mutations can affect vascular dilation and the occlusion of small pulmonary arteries.[34] The 5-hydroxytryptamine (serotonin) transporter gene is related to pulmonary artery smooth muscle hypertrophy and was found in a greater percentage of patients with idiopathic PAH than in controls.[35]

In addition to genetic abnormalities, other risk factors have been associated with PAH. PAH is a known complication of patients with systemic sclerosis. Patients with congenital heart disease and systemic-to-pulmonary shunts are known to develop PAH if their conditions remain uncorrected.[10] Patients with human immunodeficiency virus infection are 6 to 12 times more likely than the general population to develop PAH.[10] The use of anorexigens for weight loss in the 1960s was associated with PAH, and these drugs were removed from the market. Structurally related compounds such as fenfluramine and dexfenfluramine were linked to PAH in the 1980s and 1990s[36,37] and were removed from the market in 1997.[38] PAH has been associated with rapeseed oil,[39] L-trypophan,[40] and illicit drugs such as methamphetamine.[41,42] PAH also has been recognized in patients with portal hypertension.[10]

PAH registry findings: Patient registry data have contributed important findings that have led to improved risk stratification and treatment and has given evidence of improved outcomes in recent years. The first National Institutes of Health registry, the Patient Registry for the Characterization of Primary Pulmonary Hypertension, was initiated in 1981. Its purpose was to broaden knowledge of the clinical characteristics and natural history of what is now known as idiopathic PAH and to provide practical benefits such as the investigation of potential causes, facilitation of early and accurate diagnoses, and development of more effective treatment strategies.[13,43] The observational nature of registries, compared with clinical trials, allows for longer follow-up periods and larger study populations and avoids selection bias. After the National Institutes of Health registry of the 1980s, a number of current PAH registries have been developed that have generated valuable data, including the Registry to EValuate Early And Long-term PAH disease management (REVEAL) registry; French, Swiss, Chinese, and United Kingdom registries; and the Mayo, Chicago, and Stanford registries. The REVEAL registry is the largest United States PAH registry to date.[43] Currently, data have been presented on 4 REVEAL objectives: (1) characterizing the demographics and clinical course of patients with WHO group 1 PAH, (2) evaluating differences in patient outcomes according to WHO group 1 classification subgroups, (3) comparing the outcomes in patients who do and do not meet prespecified traditional hemodynamic criteria for the diagnosis of PAH, and (4) identifying the clinical predictors of the short- and long-term outcomes. The REVEAL findings have also been used to generate a practical risk score calculator.[43]

Approved Therapies for PAH

The Food and Drug Administration has approved 9 medications to date for the treatment of PAH. According to their mechanism of action, these medications fall into 3 categories:

Prostacyclin derivatives—these medications augment decreased prostacyclin levels in patients with PAH

Endothelin receptor antagonists—these medications block the binding of endothelin-1 to the receptor, targeting overexpression of endothelin-1 in patients with PAH

Phosphodiesterase 5 inhibitors—these medications block the breakdown of cyclic guanosine monophosphate, which mediates the effects of nitric oxide. The accumulation of cyclic guanosine monophosphate enhances nitric oxide-mediated vasodilation. The efficacy of phosphodiesterase 5 inhibitors is dependent on the availability of nitric oxide.

PAH medications are available for oral, inhaled, subcutaneous (SC), and intravenous (IV) administration. The Food and Drug Administration−approved therapies for PAH are listed in Table 3.

Clinical utility of prostacyclin in treatment of PAH: Prostacyclin is produced in vascular endothelial cells and is found in reduced levels in patients with PAH. Prostacyclin is a powerful vasodilator that also inhibits platelet aggregation, inflammation, and vascular smooth muscle proliferation.[29] It is believed that reduced synthesis of prostacyclin is a contributing factor to the development of PAH.[1]

Epoprostenol was the first prostacyclin therapy approved for PAH. It has powerful vasodilatory effects and been shown to inhibit platelet aggregation and vascular smooth muscle proliferation.[42] Studies have shown improvements in symptoms and hemodynamic parameters, improved exercise capacity, and survival.[29,45] Epoprostenol has a very short serum half-life of ~6 minutes, which presents clinical challenges. Continuous infusion by an indwelling catheter is inconvenient to use and also carries the risks of infection and morbidity and even death in the case of pump failure and dosing interruption.[29] Other prostacyclin agents have been developed in recent years to improve administration. These agents include inhaled iloprost and treprostinil and SC- and IV-administered treprostinil. Each of these medications has different safety and efficacy profiles that must be considered.

Treatment timing with the use of prostacyclins has been an issue of discussion for some time. Typically, oral (non-prostacyclin) medications produce improved symptoms for a period of time in some, but not all, patients; however, many patients with PAH eventually experience clinical worsening and require prostacyclin therapy. A recent study has emphasized the importance of starting prostacyclin therapy in patients with PAH at the first signs of clinical worsening and has shown poor clinical outcomes for patients who are not referred for prostacyclin treatment early enough in the disease course to affect survival.[46] Other investigators have agreed that evidence also exists to suggest that early use of prostacyclins in patients with mild-to-moderate disease might slow disease progression.[47]

Identifying patient candidates for prostacyclin treatment

Risk stratification: Patients with PAH are stratified according to risk to determine the prognosis and most appropriate treatment strategy. The WHO functional class ranking, a modification of the NYHA functional class, is a tool for risk stratification. Functional classes II and III indicate patients at lower risk, and functional class IV indicates patients at greater risk of serious outcomes. Symptom progression, including dyspnea on exertion, fatigue, chest pain, syncope, palpitations, and lower extremity edema, is a factor in the risk stratification. Other factors include the hemodynamic findings, clinical evidence of right ventricular failure, 6-minute walk test results, cardiopulmonary exercise testing results, echocardiographic findings, and biomarker levels. Brain natriuretic peptide and N-terminal fragment-pro-brain natriuretic peptide are good predictors of survival. The choice of which biomarker to use varies by practice center; pro-brain natriuretic peptide is most often used because its levels appear to correlate with right ventricular enlargement and dysfunction.[10]

The underlying etiology is also a prognostic indicator. PAH associated with scleroderma has had less favorable outcomes than other PAH etiologies. Patients with human immunodeficiency virus−associated PAH have survival similar to that of patients with idiopathic PAH. Patients with coronary heart disease−associated PAH generally have better outcomes than other PAH groups, although other factors such as age and the treatment strategy for coronary heart disease can also affect the prognosis.[10]

An important prognostic tool has been generated from the REVEAL registry data. The REVEAL risk calculator, a prognostic equation, helps clinicians individualize and optimize the therapeutic strategies for patients with PAH. The calculator estimates the 1-year survival from the point of assessment, apart from the point of diagnosis; thus, it can be used at any time during the disease course. The calculator showed an ability to discriminate between lower and higher risk patients.[48] Recently, the REVEAL risk calculator was used in the French Pulmonary Hypertension Network and was shown to be accurate and appropriate for use in clinical practice.[49]

Another factor to be considered when risk-stratifying patients for appropriate therapy is the practical support issue. A patient using epoprostenol must be able to manage sterile preparation of the medication, operation of the infusion pump, and care of the central venous catheter, or the patient must have a caregiver who can provide this care. The patient must understand that such therapy will continue for an extended period.

Prostacyclin Treatment Options: A Comparison of Benefits and Risks

The currently approved prostacyclin treatment options for PAH include epoprostenol, iloprost, and treprostinil. For these 3 medications, the delivery options include IV infusion, SC infusion, and inhaled formulations (Table 3). For the purpose of the present discussion, we have organized the medications according to the route of delivery.

Continuous IV infusion

Epoprostenol: Epoprostenol is a prostacyclin derivative indicated for the treatment of PAH (WHO group 1) to improve

exercise capacity and is the most studied of the prostacyclins.[50] Two brands are available: Flolan and Veletri. This medication acts to promote vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

Epoprostenol has been shown to have a positive effect on survival. A 12-week, open, randomized, prospective study of epoprostenol by Barst et al[45] evaluated the effects on patients with NYHA functional class III or IV idiopathic PAH. Epoprostenol combined with conventional therapy was compared to conventional therapy alone in 81 patients. The study showed that epoprostenol improved the exercise capacity, symptoms, hemodynamics, quality of life, and survival.[45] Sitbon et al[51] published a longer term study in 2002 of 178 patients with NYHA functional class III or IV PAH. Survival rates improved from those of historical controls, with a survival rate at 1, 2, 3, and 5 years of 85%, 70%, 63%, and 55%, respectively. Survival was associated with disease severity at baseline and the 3-month response to therapy.[51] A 2002 study by McLaughlin et al[44] sought to evaluate the long-term effects of epoprostenol on survival in patients with idiopathic PAH and to identify the factors that might predict the outcome. The study of 162 patients with NYHA functional class III and IV PAH showed improved survival at 1, 2, and 3 years of 87.8%, 76.3%, and 62.8%, respectively, and survival was significantly greater than expected from the historical data.[44] Both studies showed improvements in functional class, exercise tolerance, and hemodynamics. Larger trials are needed to adequately assess the survival benefits.

Treprostinil: Treprostinil (Remodulin) is a prostacyclin derivative that can be administered by either an IV central catheter or an SC infusion. Because continuous IV administration places the patient at risk of serious infection, continuous SC infusion has been recommended whenever possible for patients who can tolerate this route. Treprostinil is indicated for the treatment of PAH (WHO group 1) to diminish the symptoms associated with exercise and for patients who require transition from Flolan to reduce the rate of clinical deterioration. Just as with epoprostinol, treprostinil works through vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Unlike epoprostinol, however, treprostinil has a longer terminal half-life of 4 hours.

Most studies of treprostinil used SC administration. However, a 2010, placebo-controlled, 12-week study by Hiremath et al[52] evaluated IV treprostinil in 44 treatment-naive patients with idiopathic PAH or familial PAH in NYHA class III. The study showed treprostinil improved the 6-minute walk test results, functional class, and dyspnea.[52] One recent retrospective cohort study by López-Medrano et al[53] of 55 patients with PAH who received continuous IV infusion therapy with either treprostinil or epoprostenol showed that patients administered IV treprostinil experienced a greater rate of gram-negative bacteremia. The cause of infection in that study was not determined but was suspected to have occurred during reconstitution and storage of the medication.[53]

The most common side effects include diarrhea; jaw pain; swelling of the feet, ankles, and legs; widening of the blood vessels; and nausea.[53]

Continuous SC infusion

Treprostinil: Treprostinil, which can be administered either by continuous IV catheter or continuous SC infusion, has been described in the previous section. It has a longer half-life than epoprostenol (~4 hours vs ~6 minutes), which allows for continuous SC rather than IV infusion.

Several clinical studies have shown the therapeutic benefits of continuous SC-infused treprostinil, which avoids the risk of serious infection associated with continuous IV catheter administration. Simonneau et al[54] reported the results of a 12-week, randomized, double-blind, placebo-controlled study of 470 patients with NYHA class II, III, or IV PAH who were administered treprostinil by SC infusion. The results showed a 6-minute walk test improvement of 10 m in the treprostinil-treated patients. Survival did not improve, however. The most common side effects included SC infusion site pain and reaction, headache, diarrhea, nausea, jaw pain, vasodilation, dizziness, edema, pruritus, and hypotension.[54] Eighteen patients (8%) in the treprostinil group discontinued the study treatment because of infusion site pain. No infusion site infections were reported.[54] In a longer term study of SC treprostinil, 860 patients with PAH treated with treprostinil were followed up for ≤4 years. Other medications were added as needed. Survival was 87% to 68% over 1 to 4 years for all patients and 88% to 70% over 1 to 4 years with SC treprostinil monotherapy. The safety profile was consistent with the results from short-term studies.[55]

Aerosols by nebulization

Iloprost: Inhaled prostacyclins were developed to provide the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects (risk of infection and infusion site reactions). Inhaled iloprost (Ventavis) was evaluated in 203 patients with selected forms of PAH, including scleroderma-associated and appetite-suppressant–associated PAH, in NYHA class III or IV. The results showed improvement in the 6-minute walk test results (36.4 m), hemodynamic values, NYHA class, dyspnea, and quality of life.[56] Several long-term studies of inhaled iloprost have been conducted. In 1 study of 76 patients with idiopathic PAH who were prospectively identified and treated with inhaled iloprost, only a few patients could be stabilized with inhaled iloprost monotherapy.[57] Other studies reported more positive outcomes. Another open-label, 2-year study of 63 patients with PAH suggested a long-term clinical benefit with no severe side effects.[58] The most common adverse events from inhaled iloprost include flushing, increased cough, headache, trismus, insomnia, nausea, hypotension, vomiting, increased alkaline phosphatase, flu syndrome, back pain, tongue pain,

palpitations, syncope, increased gamma-glutamyl transferase, muscle cramps, hemoptysis, and pneumonia. Finally, inhaled iloprost requires 6 to 9 inhalation sessions daily.

Treprostinil: Inhaled treprostinil (Tyvaso) has been evaluated as an add-on therapy for patients with PAH who are taking oral bosentan. A 12-week study of 12 patients who were still symptomatic after taking bosentan reported improvement in the 6-minute walk test results, hemodynamic measurements, and NYHA functional class after the addition of inhaled treprostinil.[59] The Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH) I study, a randomized, double-blind, controlled trial of 235 patients with PAH in NYHA class III or IV, evaluated the effects of inhaled treprostinil as an add-on therapy to either oral bosentan or sildenafil. The study reported an improvement in the 6-minute walk test results of 20 m at 12 weeks and improvement in quality of life and N-terminal fragment-pro-brain natriuretic peptide measures. No improvements were seen in the interval to clinical worsening, NYHA functional class, or PAH signs and symptoms. Inhaled treprostinil was safe and well tolerated. The most common side effects were cough and throat irritation; headache; gastrointestinal effects; muscle, jaw, or bone pain; flushing; and syncope.[60] Patients in both studies received 4 inhalation sessions daily. A very recent study by Perez et al[61] assessed the efficacy of inhaled treprostinil in patients transitioned from IV or SC treprostinil or IV epoprostenol. Most patients demonstrated no deterioration in the 6-minute walk test results or hemodynamic findings, but a few demonstrated worsening NYHA functional class within 7 months. Inhaled treprostinil might be an alternative medication for clinically stable patients who cannot tolerate infusion, but such conversion is not ideal for all patients, and those who do transition should be monitored for signs of clinical worsening.[61]

Practical considerations: Epoprostenol was the first drug approved by the Food and Drug Administration for the treatment of PAH and has been shown to have positive effects on exercise capacity, symptoms, hemodynamics, quality of life, and survival.[45] It is considered first-line therapy for very ill patients with PAH.[62] However, because of its short half life of ~6 minutes, epoprostenol requires continuous infusion pump administration, which presents significant clinical challenges for both patients and care providers. Dosing interruptions and IV catheter infections can be life-threatening. Because the administration of epoprostenol can be complex, centers with experience with the management and follow-up of patients taking epoprostenol should provide this therapy. Another challenge of administration is that the epoprostenol formulation Flolan is unstable at room temperature and can require ice packs during administration. Veletri is a room-temperature–stable formulation.

Epoprostenol dosing is also challenging and must be individualized. Common doses range from 25 to 40 ng/kg/min for monotherapy. A chronic overdose can result in high cardiac output failure. Dosing titration varies among treatment centers and depends on patient tolerance. The side effects common to all prostacyclins include headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain and are usually well tolerated.[10,62] Most complications from using epoprostenol result from delivery system malfunctions, which can be life-threatening, and equally serious venous line infections.[62] It is important to persevere with the challenges of administration, because epoprostenol is an effective medication and is the only prostacyclin prospectively shown to enhance survival.[45] Additionally, evidence has shown that early administration of a prostacyclin at the first signs of clinical worsening can prevent disease progression.[46,47]

Treprostinil is room temperature stable and has a longer half-life than epoprostenol (~4 hours vs ~6 minutes). This allows for SC rather than IV administration, although treprostinil is approved for both routes of administration. For some patients, SC infusion will prove to be too painful, and these patients can be considered for IV infusion with either treprostinil or epoprostenol. The longer half-life of treprostinil minimizes the risk of fatal cardiovascular repercussions in the case of infusion interruption.[62] Treprostinil can be considered as first-line therapy in place of epoprostenol because of its longer half-life, SC administration, and room temperature stability.[62] Cassettes of treprostinil are changed every other day compared to epoprostinol cassettes, which are changed daily.[62] The optimal dosing for treprostinil (both SC and IV) varies because of the wide range of effective dosing used in clinical trials.

Experts have reported effective doses of 40 to 110 ng/kg/min, greater than epoprostenol dosing, because of the difference in formulation. Patients transitioning from SC to IV treprostinil will not require a significant dose adjustment.[62] The SC sites are usually changed every 2 to 4 weeks if the patient does not experience too much discomfort.

The inhaled prostacyclin formulations, iloprost and treprostinil, have been developed to ease administration. From a pathophysiologic perspective, inhalation therapy seems logical, because the distal airspaces are in close proximity to the resistance pulmonary arterioles.[63] Using a dedicated nebulizer, iloprost has a short half-life and requires 6 to 9 daily inhalation sessions, and the frequency of sessions required makes patient adherence a challenge.[62] Treprostinil shows a relative selectivity for the pulmonary circulation compared to iloprost, and this was a driver for inhaled treprostinil development.[63] In a crossover study, iloprost and treprostinil were found to produce comparable maximal decreases in pulmonary vascular resistance; however, the peak effect of treprostinil occurs later than iloprost (18 vs 8 minutes), and the duration of effect is longer.[64] A study examining the effects of transitioning from iloprost to the longer acting treprostinil showed high patient satisfaction and a reduction of 66% in daily administration time.[65] The most common side effect for both inhaled iloprost and treprostinil is cough.[63] Inhaled formulations seem efficacious in moderately symptomatic patients with PAH and could be

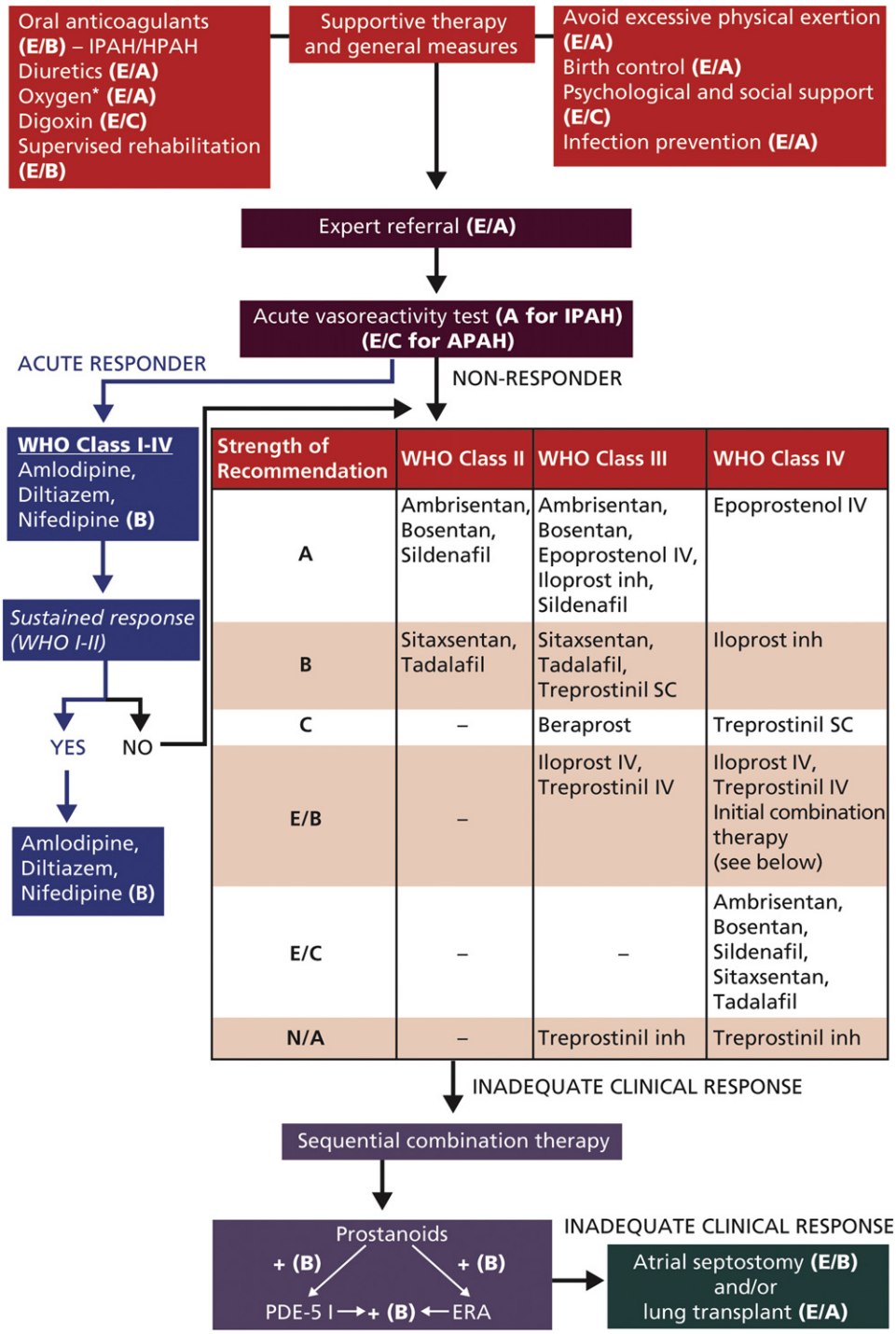

Figure 1. Dana Point 2008 PAH evidence-based treatment algorithm. Note, IV iloprost is not licensed for use in the United States. Reprinted from *J Am Coll Cardiol*, 54(Suppl 1), Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galiè N. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. S78–S84, Copyright (2009), with permission from Elsevier.[101] APAH = associated pulmonary hypertension; ERA = endothelin receptor antagonist; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; WHO = World Health Organization. *To maintain oxygen at 92%.

appropriate when used with an oral medication. The decision to replace infusion therapy with inhalation therapy might be feasible in carefully selected patients but has not been systematically studied and should only be done by a center experienced in prostacyclin use.[63]

Combination therapy: In theory, combination therapy should be the preferred method of treatment, first, because the 3 classes of drugs indicated for the treatment of PAH (endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostacyclins) work through different pathways

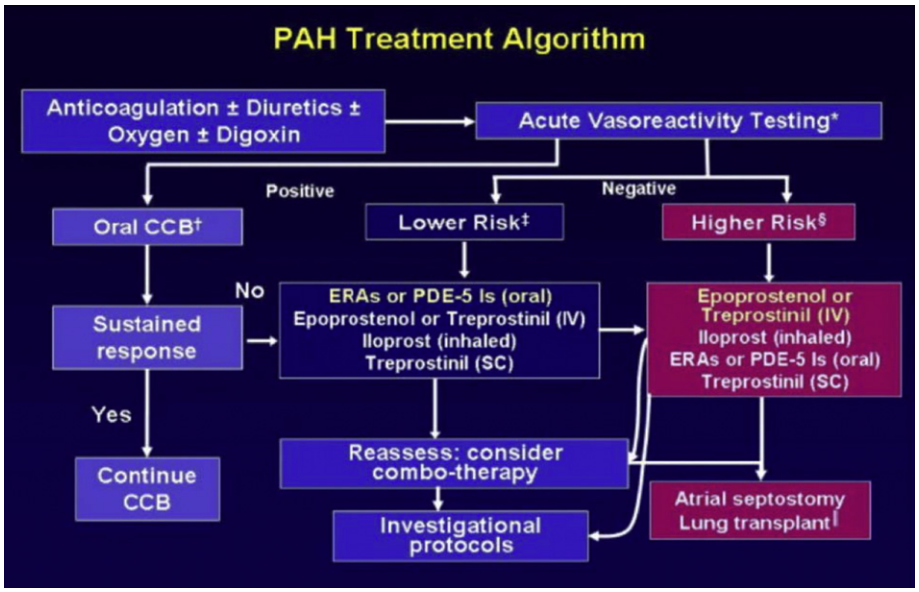

Figure 2. American College of Cardiology Foundation/American Heart Association 2009 treatment algorithm for PAH. CCB = calcium channel blocker; ERAs = endothelin receptor antagonists. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, et al. American College of Cardiology Foundation Task Force on Expert Consensus Documents, American Heart Association, American College of Chest Physicians, American Thoracic Society, Inc, Pulmonary Hypertension Association. 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.53:1573−1619.[10] *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.

and so should have both additive and synergistic effects; and second, no single medication has been found to produce completely satisfactory outcomes in very sick patients. This situation is analogous to other disease states such as systemic hypertension, diabetes, and others in which combination therapies provide better disease management than single agents.[2,66,67]

No formal recommendations have been developed for combination therapy for PAH; however, combination therapy is being used routinely in clinical practice, and data exist to support this decision. Eight randomized controlled trials[60,68−74] and numerous open-label studies[59,70,75−91] form the basis of evidence for the benefits of combination therapy in clinical practice.

A recent meta-analysis of several clinical trials of combination therapy found that combination therapy for PAH significantly reduced the incidence of clinical worsening, improved the exercise capacity, and improved the hemodynamic measurements. Combination therapy was safe and well tolerated, with no significant difference in the incidence of adverse events. However, no improvements in functional class or mortality were found.[67] The results further support the practice of using combination therapy as a reasonable strategy in patients who are not responding to therapy and to help prevent clinical worsening in less sick patients.[2]

Investigational Prostacyclin-Pathway Drugs

Oral treprostinil: An oral form of treprostinil is currently undergoing a number of clinical trials as both monotherapy and add-on therapy.[92−96] Positive outcomes from the Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension (FREEDOM-M) trial supported the initiation of the FREEDOM-C trial, which assessed the efficacy and safety of twice-daily oral sustained-release treprostinil in the treatment of PAH with a concomitant endothelin receptor antagonist and/or phosphodiesterase 5 inhibitor. Data from that study have recently been reported. The 16-week, double-blind, placebo-controlled study of 350 clinically stable patients with PAH did not achieve significance in its primary end point of 6-minute walk test improvement. It is expected that the titration and dosing knowledge gained from that trial will provide the basis for future studies.[97] Because of positive results from the FREEDOM-M trial, however, a new drug application has been filed, and future studies are planned.[98]

Selexipag: The oral drug selexipag is chemically distinct from prostacyclin and prostacyclin analogs. Selexipag is a prostacyclin IP receptor agonist that is highly selective for the human prostacyclin IP receptor. Prostacyclin analogs are not selective and activate other prostacyclin receptors. The very selective profile of selexipag causes greater vasodilatory effects than iloprost. Selexipag has a half-life of ~8 hours, making it an attractive candidate for clinical use.[29] Two phase III studies of selexipag in patients with PAH are currently enrolling patients.[99,100]

Discussion

Dr. Zamanian. I would like to start the discussion on the topic of treatment algorithms for prostacyclins. The Dana Point algorithm stratifies patients just by neoclassification (Figure 1).[101] Based on the strength of evidence of WHO class, it determines what type of treatment patients should receive. In my opinion, it never did a good enough job of risk stratifying. I think the American College of Cardiology Foundation/American Heart Association algorithm (Figure 2),[10] which stratifies according to high and low risk, is much more useful. However, the odd thing about it is, therapies in the United States carry the WHO class in the indication. In your practice, do you apply the Dana Point algorithm and stratify risk according to NYHA class, or do you use a more comprehensive risk stratification approach?

Dr. Waxman. I find that determining low risk versus high risk is usually based on common sense and clinical acumen. The issues listed in the algorithms are what we take into account as we make clinical decisions. What it ultimately comes down to is that with a sicker patient, we are going to be more aggressive. What do we mean by "aggressive" with regard to therapy? I think, as you and I have often discussed, the role of prostacyclins and that they are underused is really important. If I could treat every patient with PAH with one, I would, but certainly they are used more in the sicker patient. However, with the less sick patient—and I think this is something that the algorithms tend to overlook—there is often a role for dual therapy. We should treat patients with PAH the same that we would treat someone with systemic hypertension or any other common medical disease: by providing combination therapy to a less-sick patient so that they do not become a more-sick patient.

Dr. Zamanian. Yes, that is interesting. We are at the point at which we need to use combination therapies, but we do not have any guidelines to help us. But, intuitively, as you said, we tend to treat the more-sick patient more aggressively.

Dr. Waxman. Yes, and I think it is impossible for algorithms to cover the type of individualized approach we take in choosing first-line therapy. In our practice, we tend to use more phosphodiesterase 5 inhibitors instead of endothelin receptor antagonists as first-line agents, which I know is different from some other practices. The choice varies. A part of my own algorithm is determining the age of the patient and what comorbidities this patient might have, and this helps me decide which therapy I should start with.

A number of patients who are not so sick could benefit from prostacyclins, but they are not easy drugs to use. Certainly, the infusion pump is a barrier. I have been using inhaled prostacyclin more often, but not for any patient who is less than functional class III. Also, cost is an issue in the decision to use inhaled prostacyclin. We have been doing clinical trials with oral treprostinil, but it is not yet approved; and it will still be challenging to prescribe because of dose titration issues. The side effects can be significant if one increases the dose too quickly; thus, we do very small incremental increases in the dosage. Also, the patient must take it with a certain amount of fat calories so that it is absorbed in an even fashion. The variability is great with absorption of the oral drug. If it is not absorbed properly, it can cause abdominal side effects. Patients who are functional class II will require a smaller dose than patients who are functional class III or IV. It is a complicated drug to prescribe, which should be done by clinicians who have experience in prescribing it. This is not a drug that someone unfamiliar with it can prescribe.

However, despite the challenges, it is important to prescribe this drug to patients with PAH. It has been shown that prostacyclins are underprescribed. A recent study by Badagliacca et al[46] showed a clear effect of the late prescription of prostacyclin therapy and also data from the REVEAL registry showed that ½ of patients who die with pulmonary hypertension or PAH are dying having never been treated with a prostacyclin. However, it is the 1 drug we have with clear data that show it affects mortality. It is the best type of drug we have to treat these patients.

There is also benefit in combining prostacyclins with phosphodiesterase 5 inhibitors and, possibly, with endothelin receptor antagonists. Based on what we now know, there is no reason to hold back giving what we know are the best therapies to the sickest patients.

Dr. Zamanian. The report by Badagliacca et al[46] is very interesting. As I read it, my takeaway is that if one waits and urgently start prostacyclins, one might be too late for the beneficial effects to help patients in the very end stages of PAH. The present report and the REVEAL registry data indicate that we should not wait until the patient is very, very sick, because even the gain we might see from prostacyclin treatment will be limited at that point.

Dr. Waxman. Yes, if we wait until the patient is functional class IV or advanced functional class IV, multisystem disease is present as a result of heart failure, and it is not easy to improve functional class in such a patient. Therefore, we should not be waiting for salvage therapy; we should be using prostacyclins as standard therapy.

Dr. Zamanian. When do you start combination therapy in your patients?

Dr. Waxman. There is no clear indication, because limited clinical trials are only being done now. However, in my own practice, I generally try to combine therapies fairly

early on in the hopes of maximizing the beneficial effects of the drugs. One combination study has been published, the combination of sildenafil and epoprostenol, and this showed a positive outcome for the combined regimen versus the 2 drugs separately. Thus, our usual practice is to combine a phosphodiesterase 5 with a prostacyclin within a couple of weeks of initiating the prostacyclin. We use other drugs generally as add-on therapy when either the response is not what we think it should have been or the patient's condition is declining.

Dr. Zamanian. I could not agree with you more, Aaron, about the benefits of combination therapy for PAH. We have a small study going on now in 4 centers in which we randomize patients who take tadalafil and either no additional medication or inhaled treprostinil, with the goal of measuring right ventricular function changes in 6 months and then the interval to clinical worsening. My interpretation of the published data is that the phosphodiesterase 5−prostacyclin access is important to patients, and we need to understand its effects on long-term outcome. The question remains, how can we provide more patients with the treatment they need earlier in the disease course?

Dr. Waxman. I think we have to educate community clinicians about the importance of early referral in patients with PAH. Because of increased specialization, just as with any other specialty practice, such as kidney disease or heart failure or a specific pulmonary disease, I think it is impossible for someone who is not in the field to know all the intricacies of how to treat these patients. Also, these patients require a significant amount of work. They have comorbidities, and the specialist often takes over most of their primary care issues, similar to what an oncologist or endocrinologist might do for their patients.

Dr. Zamanian. I think it would be difficult for a community physician to manage the specifics of authorization for aggressive prostacyclin therapy and, thus, are likely to prescribe oral therapy. It is very frustrating when a patient who is very sick is referred to us after having been receiving oral therapy for perhaps 2 years instead of receiving the prostacyclin they needed right from the start. If improving the WHO functional class is the first goal of therapy, it might be impossible at that point in the disease.

Dr. Waxman. There is no question that improving the WHO functional class is the first goal of therapy. I often depend more on a patient's subjective description of how they are doing than anything objective just because objective evaluations are either hard to do or are variable. I do a 6-minute walk test on every patient every time, and it tends to help me correlate their subjective descriptors.

Dr. Zamanian. We do that also—we check the 6-minute walk test results every time a patient comes in. I think a number of the outcomes measures that can be used really relay much of the same information, and we would like to see these outcomes measures "normalize" or improve. However, we must consider these measurements in context, and that is one of the limitations. Marius Hoeper, years ago, demonstrated that patients do better when they had very specific therapy goals set. I think that, except for the NYHA class and the 6-minute walk test, the outcome measures are not standardized across different centers, and some of us have chosen them according to our own research and intuition. I think standardization of these outcomes measures is an important issue. I believe that most centers routinely use the NYHA class, the 6-minute walk test, and echocardiography.

Dr. Waxman. I agree. All these measures have their strengths and weaknesses. We measure N-terminal fragment-pro-brain natriuretic peptide, but our approach to using this has been more as a baseline for when a patient is admitted to the hospital to try to avoid performing right heart catheterization to determine whether they have volume overload. However, the N-terminal fragment-pro-brain natriuretic peptide is a very limited biomarker.

Dr. Zamanian. We also measure the N-terminal fragment-pro-brain natriuretic peptide at baseline and when we think the patient is stable. If the patient is hospitalized, we measure N-terminal fragment-pro-brain natriuretic peptide at baseline and at the end of hospitalization. However, as you said, there is limited utility in the change in N-terminal fragment-pro-brain natriuretic peptide levels, especially in the setting of other conditions such as infections and renal failure. We do not use right heart catheterization as an outcome measure, do you?

Dr. Waxman. No. The only time I will perform follow-up right heart catheterization is if a patient is not doing well, and I cannot determine the reason. I learned a while ago that the right heart catheterization findings do not change very much in even the first 2 years of therapy, and the findings do not indicate whether a patient has or has not responded to therapy. The use of right heart catheterization does help if a patient is declining and has other comorbidities and I do not know whether it is worsening right ventricular end-diastolic pressure or pulmonary vascular resistance or whether their cardiac output is decreasing. Certainly, when a patient is acutely decompensating, it can be helpful. I would like to hear more about the diffusion lung capacity output, because I think that makes sense, and I think it is underused as both a screening tool and a follow-up tool.

Dr. Zamanian. I agree. diffusion lung capacity outputs have been demonstrated to predict the prognosis long term, both within the REVEAL registry and the Chicago experience, mainly if the diffusion lung capacity output is $>80\%$ versus $<40\%$. As you know, Aaron, you and I have presented these data at a couple of conferences, and the data are currently being revised. We know that a diffusion lung capacity output in the setting of these registries had been used as a non-hemoglobin-adjusted diffusion lung capacity output, and because the patients with the most severe PAH are also anemic, the percentage of predicted diffusion lung capacity output for a nonadjusted hemoglobin might be incorrect. Therefore, we set out to ensure that we could demonstrate hemoglobin-adjusted diffusion lung capacity output. In about 250 patients with WHO group 1 PAH and patients with

chronic thromboembolic PAH, we demonstrated that the paradigm stands that a well-preserved diffusion lung capacity output at baseline adjusted for hemoglobin is predictive of the prognosis, and vice versa. However, we also hypothesized that the diffusion capacity, as a marker of vascular endothelial function, might predict whether patients would improve, worsen, or stay the same in terms of their diffusion lung capacity output over time relative to the development of interstitial lung disease. David Langleben of McGill University has data that show that the diffusion lung capacity output is a good marker of endothelial function in biochemical assays using the hydrolysis of angiotensin-converting enzyme in the lungs and, specifically, in patients with connective tissue disease. In our group, we showed that a $\geq$10% improvement in the diffusion lung capacity output predicted a substantial improvement in outcomes from the point of the second diffusion lung capacity output measurement to several years out. These data are being vetted for publication, and, in the meantime, at our center, we started using some of these parameters at the patients' annual visits.

Dr. Waxman. I think diffusion lung capacity output is an underused test, and, at the very least, it is reflective of the surface area of the lung and ventilation perfusion. Thus, it makes good sense that it should have utility in this setting.

Dr. Zamanian. I know that you lead the field with work in cardiopulmonary exercise testing. What have you found to be the best way to use this tool?

Dr. Waxman. We generally use invasive cardiopulmonary exercise testing to assess patients with unexplained dyspnea. In patients who have mild pulmonary vascular disease, we use it to try to determine why they are short of breath, to have a better sense of the physiologic basis. We are starting to combine a 6-minute walk test on a treadmill with right heart catheterization and a metabolic cart to try to explain why they are limited on the 6-minute walk test; that is, what are the features of their physiology that limit them? Is it the pulmonary vascular resistance? Is it the effect on gas exchange? Or is it more related to a peripheral limit than a hemodynamic limit? The latter is what we think is more likely and what the invasive cardiopulmonary exercise testing can indicate more clearly. The issue might be an energy metabolism problem, even at the level of the skeletal muscle, and this might be why patients feel better with medication, yet their hemodynamics do not improve for a long time.

Dr. Zamanian. Another issue I would like to discuss is taking care of patients with PAH in the critical care environment. I think prostacyclins are both underused and misused in intensive care units quite frequently. I have often had patients referred to me who have been labeled hemodynamically as having pulmonary hypertension without an additional evaluation of that patient, and this patient might be prescribed epoprostenol and then delivered to me for discharge. The patient might not even have the indication for prostacyclin. For instance, the patient might have acute respiratory distress syndrome. I also frequently see patients with low cardiac output after valve surgery. There is a need for the appropriate use of prostacyclins in the critical care unit.

There is now an initiative across the United States to nebulize epoprostenol, instead of inhaled nitric oxide, in the intensive care units. Would you like to comment on that, Aaron?

Dr. Waxman. Yes, I agree. Appropriate prostacyclin use in the critical care unit is a very important topic. These patients have some of the most complicated conditions we treat in the hospital, especially if they receive ventilation, and they have pulmonary hypertension, and they have any sort of systemic hemodynamic problem.

The issue of inhaled prostacyclins is important. We developed a number of protocols at my center for using inhaled epoprostenol and inhaled milrinone. We have used them both individually and as adjuncts to intravenous therapy in patients with severe right heart failure, and we have seen very good results. One challenge with using inhaled milrinone is dosing, because if one supersaturates the lung, systemic effects occur. However, if one can find the right dosing, it works very well.

It is also important to teach clinicians in this setting how to manage a ventilator for a patient with pulmonary hypertension in the hopes of weaning the patient off the ventilator successfully and the hemodynamic effects of that. However, that might be beyond the scope of this discussion. Certainly, I dislike seeing indiscriminate application of pulmonary vasodilators without any consideration of the true underlying diagnosis. I have seen patients administered oral agents if the physician sees an elevated pressure on the echocardiogram and that might not be the appropriate treatment.

Roham, based on our discussion today, is there a patient case that you would like to use as a teaching point?

Dr. Zamanian. Yes, I would like to discuss a patient I saw recently who did not have an unusual case at all. She was a young woman, 30 years old, who was referred by her primary care physician for dyspnea on normal exertion. She had been treated for asthma and then chronic obstructive pulmonary disease with an "as needed" albuterol inhaler and a regimen of inhaled corticosteroids. She received this treatment for upward of 6 months with no improvement. Her primary care physician ordered an echocardiogram, which showed elevated pulmonary artery pressure, and diagnosed PAH. She was prescribed bosentan with no improvement and 3 months later was switched to sildenafil. Her condition worsened, and then she was referred to me.

I ordered a chest x-ray, an electrocardiogram, and a repeat echocardiogram. The chest x-ray showed enlargement of the central pulmonary arteries with a reduction of the retrosternal air space on the lateral view. The electrocardiogram showed right ventricular strain with anterior ST- and T-wave abnormalities. The echocardiogram showed an enlarged right ventricle, a depressed left ventricle, and pulmonary hypertension. A pulmonary function test revealed a significantly decreased diffusion

lung capacity output. Right heart catheterization confirmed the diagnosis of PAH. I was not comfortable starting treatment with a central venous catheter, because I was not confident she would be able to care for it properly, and she had little support from family or friends. Thus, I started her with SC treprostinil. She tolerated the SC line well, and, after 6 months of treatment, her condition had stabilized.

The point I would like to make in describing this case is that my patient experienced unnecessary deterioration while taking the oral medications and should have been referred for more aggressive care after several weeks, not several months, of failing to improve. The diagnosis was made on the basis of the echocardiographic findings, but PAH cannot be confirmed without right heart catheterization. I believe that if I had treated this patient earlier in her disease progression, her functional class would have improved by now. As it is, she came to me as class III and is still class III, which limits her daily activities.

The information I would like to convey: if dyspnea does not improve within several weeks with asthma or chronic obstructive pulmonary disease treatments and if pulmonary hypertension or PAH is suspected, it is important to refer that patient without delay to a center with experience in treating PAH.

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