Pulmonary Vascular Diseases

Uncertainties in the Diagnosis and Treatment of Pulmonary Arterial Hypertension

Hossein A. Ghofrani, MD; Martin W. Wilkins, MD, FRCP; Stuart Rich, MD

Abstract—The availability of new treatments for patients with pulmonary arterial hypertension has increased awareness and interest in the medical community for pulmonary vascular diseases in general. Many uncertainties exist, however, regarding the diagnosis and treatment of patients with pulmonary arterial hypertension that are particularly pertinent for the management of patients with idiopathic pulmonary arterial hypertension and pulmonary hypertension associated with underlying diseases. This review highlights controversial issues around the definition and diagnosis of pulmonary hypertension, the interpretation of hemodynamic variables, and the interpretation of clinical responsiveness to chronic therapies. In addition, we propose guidelines applicable to the conduct of new therapeutic trials in pulmonary arterial hypertension, which aim to provide greater confidence in the efficacy and safety of new treatments currently under development. (Circulation. 2008;118:1195-1201.)

Key Words: catheterization ■ hypertension, pulmonary ■ hypoxia ■ trials ■ vasoconstriction

Pulmonary hypertension from any cause is more prevalent than previously believed. As reported in a Centers for Disease Control study of the prevalence of pulmonary hypertension in the United States, more than 260 000 people were discharged from the hospital with a diagnosis of pulmonary hypertension in 2002.1 It is likely that the increasing attention being paid to making a diagnosis of pulmonary hypertension is related to the fact that there are now therapies available that were not available a decade ago to treat these patients.2 Furthermore, the broad availability of Doppler echocardiography has helped with (earlier) detection of pulmonary hypertension.

A new classification of clinical pulmonary hypertension, which was revised recently,3 designated 5 categories that are distinctive because they differ in their clinical presentation, diagnostic findings, and response to treatment (Table 1).4 As we now know, a treatment that is effective for one cause of pulmonary hypertension can worsen the prognosis for pulmonary hypertension due to a different cause.5 Equally important is the fact that some treatments for pulmonary hypertension can be lifesaving, and the failure to make a correct diagnosis in a patient who is potentially curable could be catastrophic.6 It is also important to emphasize that the approved treatments for pulmonary arterial hypertension (PAH; category 1, the only category of pulmonary hypertension for which treatments are approved) have serious side effects, are exceedingly expensive, and have not been shown to be effective in patients with other forms of pulmonary hypertension. When one takes into account the mortality associated with pulmonary hypertension, as well as the risks and benefits of the different treatments, it becomes apparent that an accurate diagnosis of the cause of pulmonary hypertension is as essential as the correct diagnosis of the type of tumor in a patient with cancer.

Uncertainties With the Definition of PAH

There appear to be discrepancies in the clinical diagnosis of pulmonary hypertension made in clinical practice compared with published guidelines7 and what has been used in industry-sponsored clinical trials. The definition of PAH used in clinical trials has been a mean pulmonary arterial pressure (MPAP) >25 mm Hg at rest, a pulmonary capillary wedge pressure of <15 mm Hg, and a pulmonary vascular resistance (PVR) of >3 Wood units, which has been attributed to the criteria for idiopathic PAH established by the National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension (PPH).8 Although these were entry criteria for patients submitted to the registry, these were not the hemodynamic characteristics of patients with PPH described by that study. The NIH registry collected data on a broad spectrum of patients with elevated pulmonary arterial pressure (PAP) to better define and characterize the clinical features of PPH. The hemodynamic definition of PPH from the registry was actually an MPAP of >42 mm Hg in the face of a normal or reduced cardiac index.8 Patients with an MPAP below that level are likely to have a different cause of hypertension (see below).
Therapies,15 which is one reason they have been excluded and can also have a worsening of their hypoxemia with PAH disease (category 3). Typically, patients with PAH have impaired right-sided heart function.23 Consequently, the current recommendations for the treatment of PAH propose that the acute response of the pulmonary circulation to a pulmonary vasodilator.22 The empirical use of CCBs is discouraged because of the risks of systemic hypotension and impaired right-sided heart function.23 Consequently, the current recommendations for the treatment of PAH propose that the acute response of the pulmonary circulation to a pulmonary vasodilator should be used as the basis for selecting patients for high-dose CCB treatment; however, the

Table 1. General Classification of Pulmonary Hypertension

<table>
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<th>1. PAH</th>
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<td>2. Pulmonary hypertension with left-sided heart disease</td>
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<td>3. Pulmonary hypertension associated with lung diseases and/or hypoxemia</td>
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<tr>
<td>4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease</td>
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<tr>
<td>5. Miscellaneous</td>
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Uncertainties in the Clinical Diagnosis of Pulmonary Hypertension

Each of the categories of clinical pulmonary hypertension has its own distinguishing features. Measurement of the pulmonary capillary wedge pressure is paramount in a patient with pulmonary hypertension, because it has critical implications. Because most of the treatments for PAH increase cardiac output, they run the risk of causing acute or chronic pulmonary edema and worsening hypoxemia when given to patients with left ventricular diastolic dysfunction (category 2). Yet, the literature suggests that physicians are very poor at interpreting recordings of pulmonary capillary wedge pressure. The interobserver variability in interpreting a pulmonary capillary pressure waveform is extremely large, with variations of as much as 23 mm Hg. In addition, it has been shown that physicians consistently fail to make the determination of pulmonary wedge pressure only at end-expiration.11 The potential for clinical worsening and pulmonary edema caused by the PAH therapies is so great that, in our opinion, a direct measurement of the left ventricular end-diastolic pressure should be performed in any patient in whom an adequate pulmonary capillary wedge pressure cannot be obtained or in whom its validity is in doubt.

Doppler echocardiography has become a popular screening tool for the diagnosis of pulmonary hypertension and in some clinical trials has been the only measure of the severity of the pulmonary hypertension in response to treatment.12 In spite of the common perception that Doppler can accurately measure PAP, the data suggest that it is very imprecise. Although there is a statistically significant relationship between the right ventricular systolic pressure determined by Doppler and catheterization,13 when subjected to an analysis of precision, these measurements are often inaccurate by as much as 38 mm Hg.14 Thus, Doppler should not be used to decide when to treat patients on the basis of the magnitude of the PAP, and certainly, it should not be used as a measure of efficacy to monitor therapy. In addition, because Doppler echocardiography cannot determine pulmonary capillary wedge pressure and cardiac output, 2 critical measurements used to make an accurate diagnosis, the use of Doppler echocardiography alone to diagnose and initiate treatment of patients should be strongly discouraged.

Patients with pulmonary hypertension from interstitial lung disease (category 3) typically have impaired gas exchange and can also have a worsening of their hypoxemia with PAH therapies;15 which is one reason they have been excluded from the clinical trials of treatments of PAH. Although the diagnosis of obstructive airway disease can be made reliably from pulmonary function tests and chest CT scanning, the same cannot be said for interstitial lung disease. Reduced lung volumes on pulmonary function tests alone are too nonspecific to make the diagnosis of interstitial lung disease, because the NIH Registry on PPH showed that half of the patients with PPH had more than a 20% reduction in predicted vital capacity and FEV1 (forced expiratory volume in the first second).8 Although chest high-resolution CT scanning has high specificity for interstitial lung disease, as many as 33% of patients with new-onset interstitial lung disease will be missed.17 What is interesting to note, however, is that in published series of patients with interstitial lung disease that included hemodynamic measurements, MPAP was <40 mm Hg in 95% of the cases.17 Thus, one can be reasonably confident that the diagnosis of PAH can be made in patients who have a chest CT scan that is free of any interstitial opacities and an MPAP >40 mm Hg. Conversely, the presence of lung opacities and an MPAP of <40 mm Hg is consistent with interstitial lung disease.

Chronic thromboembolic pulmonary hypertension (category 4) is one entity that is potentially curable by pulmonary thromboendarterectomy.6 Because a large percentage of these patients will have no antecedent history of deep vein thrombosis, pulmonary embolism, or a thrombotic disorder, screening tests for the presence of pulmonary thromboembolism are absolutely necessary in all patients who present with pulmonary hypertension of unknown origin.14 Although the current trend is to use chest CT scanning with contrast to make or exclude the diagnosis, the medical literature suggests that the accuracy of both perfusion lung scanning and CT angiography is highly variable, with sensitivities ranging between 45% and 100% and specificities ranging between 78% and 100%.18,19 However, for practical reasons, a normal V/Q scan excludes thromboembolic disease. In addition, although the methodology used for perfusion lung scanning is fairly standard worldwide, the technologies used in CT scanning are quite variable from country to country and from institution to institution. We have often found both tests to be complementary, both in improving the accuracy of the diagnosis and in determining the amount of pulmonary vascularity involved with thromboemboli.

On occasion, patients have been diagnosed with PAH when they have an elevated pulmonary artery systolic pressure with a normal PVR. An elevated cardiac index (such as can occur with hyperthyroidism or severe anemia) can cause an increase in PAP in the face of a normal PVR.20,21 This is a manifestation of the linear relationship between pressure and flow in the pulmonary circulation, and thus, it would be inappropriate to characterize these patients as having PAH.

Uncertainties in Acute Vasoreactivity Testing

Treatment with high doses of calcium channel blockers (CCBs) has been shown to have a sustained beneficial effect in a very small subset of patients with severe idiopathic PAH who demonstrated an acute fall in PAP in response to a pulmonary vasodilator.25 The empirical use of CCBs is discouraged because of the risks of systemic hypotension and impaired right-sided heart function.23 Consequently, the current recommendations for the treatment of PAH propose that the acute response of the pulmonary circulation to a pulmonary vasodilator should be used as the basis for selecting patients for high-dose CCB treatment; however, the
These agents have different mechanisms of action. Moreover, the definition of a positive vasoreactive response and the preferred vasodilator remain unclear.

In a landmark report, a positive vasoreactive response was predefined as a drop in MPAP and PVR of >20%; however, in that study, MPAP in the responder patient group fell by an average of 39%, whereas PVR was reduced by 53%. More recent recommendations have suggested that the criteria for vasoreactivity should be a reduction of MPAP of >10 mm Hg, a reduction below an absolute value of 40 mm Hg, and a concomitant normalization of cardiac output on vasodilator challenge, with no mention of PVR. Support for this new definition comes from a retrospective analysis of the clinical course of 557 patients who had received high-dose CCB treatment according to prespecified responder criteria. The criteria when challenged with inhaled iloprost.

Many physicians will use the information from acute vasodilator testing to provide insight into the effects of therapies other than CCBs. Because of the many different effects these medications can have, it is important to note their impact on the interaction of precapillary and postcapillary pressures, transpulmonary blood flow, and gas exchange in every patient who undergoes vasoreactivity testing.

| Table 2. Agents Used for Determination of Acute Pulmonary Vasoreactivity |
|------------------------|-----------------|---------------------|--------------------------|------------------|---------------|
| Agent                  | Administration  | Dosage              | Advantages               | Drawbacks         | References    |
| Prostacyclin           | Intravenous     | 2 ng·kg⁻¹·min⁻¹ (stepwise increase every 10 to 15 min; maximum dose 10 ng·kg⁻¹·min⁻¹) | Affects PAP and cardiac output; can be used as a chronic therapy | Systemic hypotension; gas-exchange disturbances | 24            |
| Adenosine              | Intravenous     | 50 μg·kg⁻¹·min⁻¹ increased by 50 μg·kg⁻¹·min⁻¹ every 2 min; maximum dose of 500 μg·kg⁻¹·min⁻¹ | Affects PAP and cardiac output; rapid onset and rapid washout | Systemic hypotension; bradycardia | 26–28         |
| NO                     | Inhaled         | 5–20 ppm for 10 min | Affects PAP alone; rapid onset and washout | Rebound pulmonary hypertension in few cases | 29–31         |
| Iloprost               | Inhaled         | 2.5–5.0 μg per inhaled dose | Affects PAP selectively with minimal effects on cardiac output; can be used as chronic therapy | Potential dosing variabilities depending on investigator experience, inhalation device, and breathing pattern of the patient | 32, 33        |

By way of example, the acute vasodilator response to inhaled NO has been shown to be predictive of the long-term response to high-dose CCB therapy; however, a comparative trial of inhaled NO and inhaled iloprost in 35 patients showed that iloprost was more effective in reducing MPAP and PVR. Furthermore, aerosolized iloprost caused a significantly greater increase in cardiac output than NO (0.7 ± 0.6 versus 0.3 ± 0.4 L/min, P = 0.0002) and had a more pronounced effect on the mixed venous oxygen saturation (P = 0.003). Consequently, some patients who showed no reduction in PVR with inhaled NO fulfilled the responder criteria when challenged with inhaled iloprost.

Changes in PAP

In the absence of changes in transpulmonary blood flow and postcapillary pressure, a reduction in PAP is the direct consequence of pulmonary vasodilation. Because inhaled NO is a selective pulmonary vasodilator with no significant effects on systemic blood pressure, reductions in PAP reflect the pulmonary vasodilatory response. However, some patients with severe right-sided heart impairment may react with significant increases in cardiac output once the right ventricle is unloaded by the reduced PAP, offsetting (or “masking”) the real fall in the PAP. With the other agents used to test vasoreactivity, the response becomes even more complicated, because changes in precapillary and postcapillary pressures are regularly accompanied by changes in flow (eg, inotropic effects, reflex tachycardia), alterations in systemic blood pressure, and/or gas-exchange disturbances.
Changes in Cardiac Output
One major disadvantage of the use of echocardiography as the diagnostic tool for evaluation of pulmonary hemodynamics is the lack of adequate assessment of transpulmonary blood flow and pulmonary venous pressures. Therefore, right-sided heart catheterization remains the current gold standard for diagnosis and vasoreactivity testing. The importance of measuring cardiac output and PAP becomes obvious when the effects of inhaled NO are compared with those of intravenous prostacyclin. In addition to its desirable pulmonary vasodilatory effects, prostacyclin has an inotropic effect on the myocardium and causes systemic vasodilation, which in turn may result in reflex tachycardia, which further increases cardiac output. In a comparative trial in patients with PAH, both inhaled and infused prostacyclin had profound effects on pulmonary hemodynamics, almost equivalently reducing PVR, whereas only inhaled prostacyclin significantly reduced PAP. Whether the acute change in cardiac output alone can be used to predict response to therapies or long-term survival remains to be determined.

Changes in Pulmonary Capillary Wedge Pressure
It is essential to determine the effects of vasodilators on pulmonary capillary wedge pressure. In a study of patients with congestive heart failure and pulmonary hypertension, the pulmonary hemodynamic changes in response to inhaled NO and oral sildenafil were evaluated. Although inhalation with NO did not reduce PAP or increase cardiac index, it resulted in the largest reduction in PVR, simply as a consequence of increasing the pulmonary wedge pressure (and left ventricular end-diastolic pressure correspondingly). In contrast, oral sildenafil reduced PAP significantly and increased cardiac index, whereas the reduction in PVR was less prominent than with inhaled NO, because the wedge pressure was reduced during this intervention. Because it can be difficult to distinguish patients with idiopathic PAH from those with diastolic left ventricular dysfunction, one needs to be particularly careful when evaluating pulmonary venous or left ventricular end-diastolic pressures during drug testing.

Changes in Systemic Oxygen Saturation
Because systemic vasodilators do not exhibit regional selectivity, they cause a generalized increase in pulmonary flow without reference to alveolar ventilation. As such, vasodilators may reduce PVR, but especially in patients with pulmonary hypertension associated with underlying lung diseases (interstitial lung disease, chronic obstructive pulmonary disease), they lead to diversion of blood from well-ventilated regions to poorly ventilated regions and cause significant deterioration in gas exchange and arterial oxygenation. Several studies of adult and infant acute respiratory distress syndrome have demonstrated both the overall pulmonary and the intrapulmonary selective vasodilatory properties of inhaled NO. Inhalation of prostacyclin or its derivatives has shown similar properties in acute lung failure and in patients with chronic pulmonary hypertension. For instance, whereas inhalation of iloprost in patients with severe PH associated with lung fibrosis resulted in the same degree of reduction of PVR as intravenous prostacyclin, only inhaled iloprost preserved gas exchange. One study has suggested that sildenafil, as an oral vasodilator, has comparable pulmonary and intrapulmonary selectivity in patients with severe pulmonary hypertension associated with interstitial lung disease. Consequently, very careful consideration of potential undesirable effects on gas exchange should be undertaken when one considers therapy of pulmonary hypertension in patients with variable degrees of underlying lung diseases.

Uncertainties in Evaluating Chronic Therapy
A successful therapy for PAH is one that improves both quality of life for the patient and life expectancy. Although improvement in quality of life alone is acceptable for some conditions, this is not so for PAH. Untreated, the condition has an appalling prognosis. Experience with epoprostenol suggests that improvements in survival are possible, and this must therefore be demonstrated before any new treatment can be accepted as effective.

The difficulty with demonstrating an improvement in survival with a particular treatment is that it requires the recruitment of a sizable patient population to a clinical study and that the study be of sufficient duration. Given the profusion of novel drug targets and therapeutic strategies in recent years, the commercial pressure (and, one might add, the scientific pressure) to obtain a quick assessment of the potential value of a new treatment means that most studies use surrogate end points. The surrogate end points used in PAH studies include measures of functional status (change in 6-minute walk distance, functional class), hemodynamics (changes in PAP or PVR), and levels of biomarkers (brain natriuretic peptide or troponin). Surrogate end points are useful in that changes can be measured in every patient recruited to a study and within a reasonable timeframe.

Functional End Points
Quantitative measures of exercise capacity, such as 6-minute walk distance and cardiopulmonary exercise testing, have been used as a primary end point in clinical trials. The 6-minute walk distance test became attractive because it is easy to administer, inexpensive, and reproducible. Regulatory authorities recognize that it measures exercise capacity, which is a problem for patients with pulmonary hypertension. But 6-minute walk distance is affected by many other factors, including age, height, and general fitness, as well as susceptibility to open-label influences in unblinded studies, and what constitutes a clinically meaningful change has never been defined. In addition, substantial differences have been observed for the changes in walking distance in response to therapy between idiopathic PAH patients and those with other forms of associated PAH. Lastly, no clinical trial for PAH has ever shown that the change in 6-minute walk distance had any relationship to survival.

Hemodynamic End Points
PAP defines the condition and is a prognostic marker. Together with right atrial pressure, PVR, and cardiac output, these measures characterize the hemodynamic status of patients recruited to clinical trials and the patient population to
which the results are relevant. It should be expected that any effective treatment for PAH will reduce PAP and PVR. But again, what constitutes a clinically meaningful change must be defined.

Biochemical Biomarker End Points

The most useful biochemical biomarker available to date may be brain natriuretic peptide (and/or N-terminal prohormone brain natriuretic peptide), which can inform on the pressure load on the right ventricle and has prognostic value.\(^7\),\(^8\) A reduction in circulating brain natriuretic peptide levels should accompany the response to an effective treatment. There is increasing recognition of the importance of maintaining right ventricular function in pulmonary hypertension, but the primary goal is to retard and regress the pulmonary vascular pathology. As such, brain natriuretic peptide levels give limited information about the response of patients with pulmonary hypertension to treatment and ideally need to be coupled to a biochemical indicator, yet to be defined, of the pulmonary vascular disease process.

It is recognized that these measurements provide important information, but they must be used in context, and their limitations must be appreciated. They fail to capture the full impact of a treatment in patients with pulmonary hypertension and should not preclude the collection of definitive data on the effect of therapy on the expression and time course of the disease. One strategy that has emerged in clinical trials is the use of “time to clinical worsening.” This is an attempt to inform on the effect of a treatment on survival by using a composite of measures that might be used as a basis for management decisions in clinical practice. Typically, clinical worsening is defined by some but not necessarily all of the following parameters: death, all-cause hospitalization, deterioration in functional class, significant decrease in 6-minute walk distance, the need for intravenous prostanoid initiation, atrial septostomy, or lung transplantation. Intuitively, it should be more informative than the use of single biomarkers as surrogates, but it has never been validated against oral diuretics.

**Table 3. Criteria for Time to Clinical Worsening**

<table>
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<tr>
<th>Category</th>
<th>Definition</th>
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<tr>
<td>Death</td>
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<td>All-cause hospitalization</td>
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<tr>
<td>Need for prostacyclin rescue therapy(^*)</td>
<td></td>
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<tr>
<td>Atrial septostomy</td>
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<tr>
<td>Lung transplantation</td>
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\(^*\)Defined by 2 of the following: (1) 15% reduction in baseline 6-minute walk distance; (2) reduction in functional class; and (3) edema that has become refractory to oral diuretics.


tension with the need to obtain go/no-go decisions efficiently on the many drugs proposed for the limited pool of patients with pulmonary hypertension. We would suggest a staged approach. Hemodynamic, biochemical, and perhaps anatomic (for example, MRI of the right ventricle) data provide information about how the therapy is working, which provides important proof of concept (Table 4). Pilot studies of new treatments to identify those with the greatest potential could be powered to address these end points and thus might be achieved with a study of a small number of patients over a several-week period. If a treatment is truly effective, it should have a favorable effect on most if not all of these end points.

Those treatments that show promise would then progress to a larger study powered to compare time to clinical worsening, defined as in Table 3, coupled with a quality-of-life assessment. The Cambridge Pulmonary Hypertension Outcome Review (CAMPBOK) and Minnesota Living With Heart Failure Questionnaire have undergone limited evaluation in clinical studies and would be useful for this purpose.\(^59\),\(^60\) Such a study might require 200 or more subjects and be conducted in a 6 to 12-month period. We would propose that an improvement in time to clinical worsening and evidence of improvement in quality-of-life score, in addition to confirmation of the efficacy on the end points studied in the pilot trials, should be enough to gain limited or provisional registration of the drug. However, full registration should depend on a further, properly conducted clinical study demonstrating improvement in survival, probably over time periods of 12 to 24 months, which would enable a more robust evaluation of the risk and benefits of a new therapy. A comparison of the survival of patients undergoing new therapies with historical control subjects or data from the NIH registry is not acceptable. It is widely recognized by physicians treating patients with PAH that the availability of new treatments has led to more referrals, and the population they now treat differs from that of 10 years ago. The effect of each new therapy on
survival must be evaluated in a prospective study. Such a study would take longer but would be conducted while the pharmaceutical company was gaining some revenue for the drug and is both an ethical and scientific requirement.

Conclusions
In conclusion, a word of caution: At the present time, there are currently 7 approved drugs for the treatment of PAH worldwide, and 15 published randomized clinical trials demonstrating their effectiveness. Yet, there has never been a single randomized trial for PAH that lasted beyond 16 weeks that has demonstrated sustained clinical benefit or any reduction in mortality. The improvement in 6-minute walk distance, which has been almost predictably 30 to 40 m in every trial regardless of the drug or patient population, equates to approximately 3 steps a minute and has never been shown to equate with improved survival. In light of the reports that a 54-m improvement is the smallest change that patients can relate to actually feeling better81 and that a >90-m improvement in 6-minute walk distance is achievable with exercise training alone,54 we are left wondering whether the therapies for PAH have had any impact on the disease at all. The trivial reduction in PAP reported in those trials that measured hemodynamics amplifies this concern.

Given the extremely expensive cost of these therapies, the lack of any randomized clinical trials on the other categories of pulmonary hypertension, and the possibility that these therapies can make patients worse, we believe that with few exceptions, it is improper to treat other than PAH patients with the approved therapies. Only well-designed randomized clinical trials with appropriate end points will be able to address this question. Finally, although there is a great impulse to add therapies when a patient responds poorly or not at all to a treatment, this also carries potential risks. Although physicians usually attribute a patient’s decline to progression of their underlying disease, one needs to keep in mind that a patient who becomes worse after receiving a drug for their PAH, alone or in combination, might have been made worse by their treatment.

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