REPORT

Considerations for Optimal Management of Patients With Pulmonary Arterial Hypertension: A Multi-Stakeholder Roundtable Discussion

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Stakeholders, including national and regional managed care decision makers and providers, met to discuss the clinical background, health economics, and management strategies for pulmonary arterial hypertension (PAH) at a roundtable meeting on December 10, 2016, in Dallas, Texas.

The goal of this meeting was to determine how to strengthen the collaboration between practitioners, health plans, and industry to optimize cost-effective treatment. The meeting was also designed to recognize the extent to which experienced practitioners should be supported in making treatment decisions for patients with PAH. To meet these objectives, strategies included: a review of the current landscape regarding treatments for PAH with patient case studies; identifying practical challenges and opportunities to achieve successful outcomes for patients with PAH; and discussing population-based PAH treatment management strategies.

Clinical Background on PAH

PAH is a rare, progressive, serious, and complex lung disease. Hemodynamically, PAH is defined as mean pulmonary arterial pressure ≥25 mm Hg, with a pulmonary arterial wedge pressure ≥15 mm Hg and pulmonary vascular resistance (PVR) >3 Wood units. These hemodynamic measurements are obtained on right heart catheterization, which is the gold standard for diagnosis of this disease.[1] Characterized by increasing PVR related to restricted flow through the pulmonary arterial circulation, PAH involves vasoconstriction, which may lead to right ventricular (RV) overload, RV failure, and premature death. Increased PVR is related to changes in pulmonary arterioles, including pulmonary vessel remodeling, inflammation, and in-situ thrombosis.[2,3]

PAH is 1 of 5 groups of pulmonary hypertension (PH) (**Table 1**[1,4]). While the most common causes of PH include left heart disease (group 2) and lung disease (group 3),[1] group 1 PAH (idiopathic) is rare, with a prevalence estimated at 12 per million to 50 per million,[5,6] and an incidence estimated at 2.4 to 7.6 new cases per

ABSTRACT

A roundtable panel of national and regional managed care decision makers and providers met to discuss pulmonary arterial hypertension (PAH) and strategies for management. As a rare, complex disease with high economic costs and potentially devastating outcomes, PAH necessitates that managed care providers balance optimal care with efficient use of healthcare resources. PAH specialists are recognized by health plans as knowledgeable experts and integral partners in managing patients and resources. The diagnosis of PAH must be confirmed by a right heart catheterization. Available therapies are indicated almost exclusively for patients with PAH (riociguat is also indicated in chronic thromboembolic pulmonary hypertension) and target 1 of 3 pathways: endothelin receptor antagonists for the endothelin pathway; phosphodiesterase type-5 inhibitors and soluble guanylate cyclase stimulators for the nitric oxide pathway; and prostanoids as well as a prostacyclin receptor agonist for the prostacyclin pathway, with combination therapy becoming more common. Even in the modern treatment era, as shown in the REVEAL and French registries, PAH is often diagnosed years after symptoms first appear, which leads to a poor prognosis and increased burden on the healthcare system. Facilitating treatment of patients with PAH through centers of excellence, and coordinating care management between health plans and providers with evidence-based approaches can lead to both better results for patients and lower healthcare costs. When PAH experts have access to the right treatments for the right patients at the right time, they can work with insurers to improve the health of patients with PAH while helping to reduce the impact on the healthcare system.

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For author information and disclosures, see end of text.

TABLE 1. Types of Pulmonary Hypertension[1,4]

Group 1. Pulmonary arterial hypertension (PAH)	
Idiopathic PAH (IPAH)	
Heritable PAH	*BMPR2, ALK-1, ENG, SMAD9, CAV1, KCNK3*
	Other mutations
Drug- and toxins-induced PAH	
Comorbidities	Connective tissue disease
	HIV infection
	Portal hypertension
	Congenital heart disease
	Schistosomiasis
Other Types of Pulmonary Hypertension (PH)	
Group 2. PH due to left heart disease	
Group 3. PH due to lung diseases and/or hypoxia	
Group 4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions	
Group 5. PH with unclear and/or multifactorial mechanisms	

BMPR2 indicates bone morphogenic protein receptor type II; ALK-1, endothelial cell-restricted TGF-β type 1 receptor; ENG, endoglin; SMAD9, decapentaplegic homolog. 9; CAV1, caveolin-1; KCNK3, potassium channel subfamily K member 3. Adapted from Galiè N, Humbert M, Vachiery JL, et al. *Eur Respir J*. 2015;46(4):903-975; and Simonneau G, Gatzoulis MA, Adatia I, et al. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41.

FIGURE 1. Delayed Diagnosis of Pulmonary Arterial Hypertension[7,11]

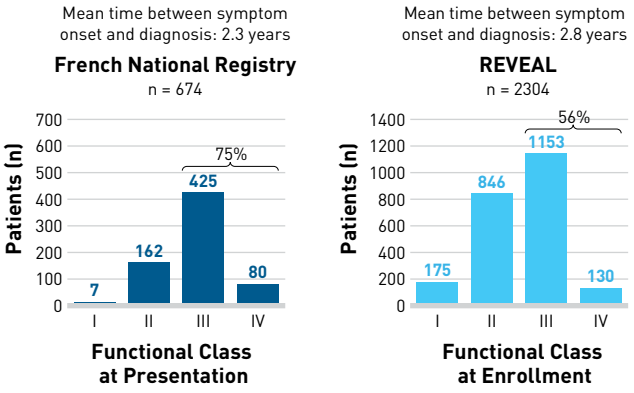
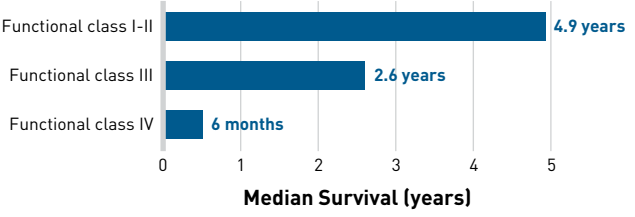


FIGURE 2. Median Survival by Functional Class Before Available Treatment[13]



million per year.[7,8] Based on the prevalence and incidence numbers, a hypothetical health plan with about 5 million patients could expect to have about 60 to 250 patients with PAH, with about 12 to 38 new cases annually.

New cases of PAH may be triggered by certain medications. The practitioner roundtable members recalled that historically, PAH came to the forefront after the introduction of the once-popular anorexigen combination of phentermine with fenfluramine or dexfenfluramine (fen-phen); fenfluramine and dexfenfluramine were withdrawn from the market in the late 1990s. The products were considered a cause of PAH in some cases.[1,9] More recently, methamphetamines have been seen as a cause of PAH for some patients.[1,10]

The mean age at diagnosis for a patient with PAH is approximately 50 years: specifically, the REVEAL registry lists a mean of 50.1 ± 14.4 SD,[11] while the French registry lists a reference center mean of 49 ± 14 SD and 53 ± 16 SD at other centers.[7] However, PAH may also be seen in newborns and in the 7th and 8th decade of life.[8,12] It is more common in women than in men.[5] The REVEAL registry lists female patients at 79.5% of those enrolled.[11]

PAH is often diagnosed long after symptoms have begun. As explained by experts at the roundtable, patients may present with vague symptoms (shortness of breath, fatigue, activity limitation) to their family practice or internal medicine physician; patients who are obese and sedentary may be told to exercise, change their diet, or stop smoking, or they may be diagnosed with asthma or chronic obstructive pulmonary disease (COPD). Unfortunately, there are no simple tests, as with diabetes or hypertension, to diagnose PAH early in the course of illness. Eventually many patients get referred to a center of excellence for PAH or a pulmonologist, cardiologist, or rheumatologist experienced with the condition. According to the REVEAL and French National registries, it may take 2.3 to 2.8 years for an accurate diagnosis, at which point patients may have progressed significantly (**Figure 1**[7]).[7] In the United States, 73.6% of patients are diagnosed after they have progressed to a later stage (World Health Organization [WHO] functional class [FC] III or IV), according to the REVEAL registry; that percentage dropped to 55.6% at the time of enrollment, which was a median of 25 months after diagnosis.[11] Similarly, in the French registry, three-fourths of patients were already at WHO FC III or IV when diagnosed.[7]

Unsurprisingly, delayed diagnosis decreases chances for survival (**Figure 2**[13]).[13] Left untreated, median survival is estimated at 2.8 years.[3,13] Based on historical data, median survival for patients at FC I and II is 4.9 years; patients at FC III, 2.6 years; and patients at FC IV, 6 months without treatment.[13]

The WHO Functional Class System is derived from the New York Heart Association (NYHA) functional class-system. Class I consists of patients with PAH who do not have a resulting limitation of

physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. Class II patients have PAH resulting in slight limitation of physical activity; they are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. Class III patients have PAH resulting in marked limitation of physical activity; they are comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. Class IV patients have an inability to carry out any physical activity without experiencing symptoms; they manifest signs of right heart failure, and dyspnea or fatigue may be present even at rest, with discomfort increased by any physical activity.[14]

PAH experts at the roundtable, including Dr Studer and Dr Kingman, explained the classification system on a practical level. The NYHA and the more detailed WHO FC systems, according to the clinical experts, are used somewhat interchangeably in practice. Although the NYHA system is used in other diseases, such as heart failure and COPD, the WHO FC system is reserved for PAH. Providers routinely assess FC, but it is often not documented in the chart.[15] The experts also agreed that categories II and III can be difficult to distinguish from each other (because there is some subjectivity in the determination); however, it is generally easy to distinguish FC I and FC IV.

A goal of treatment for the PAH patient is to achieve low-risk status, with the risk of 1-year mortality less than 5%.[1,16] Patients with a 1-year mortality rate of more than 10% are high risk—complex, very ill patients. To define low risk, parameters that are determined include absence of signs of clinical heart failure, the ability to exercise, specific biomarkers, and hemodynamics.[1] According to the roundtable experts, a goal for these low-risk patients is for them to successfully perform their job outside the household and/or function within their household.

Individuals with PAH are complicated, fragile patients who are often older, with numerous comorbidities. The most common comorbidities with PAH, according to the REVEAL registry, are hypertension, obesity, collagen vascular disease/connective tissue disease (such as scleroderma), clinical depression, obstructive lung disease, sleep apnea, thyroid disease, diabetes, and ischemic cardiac events. Other comorbidities with PAH include lupus, rheumatoid arthritis, non-skin cancer, valvular heart disease, cirrhosis, renal insufficiency, history of pulmonary embolism, history of deep vein thrombosis, and cardiomyopathy.[11] Across subsequent calendar years, the most common comorbidities among patients with PAH in the REVEAL registry were renal disease (39.4%-44.1%), diabetes (22.5%-26.1%), and coronary heart disease (23.1%-26.6%).[17]

In addition to the clinical burdens of PAH, there are economic burdens. Recently, several pharmacoeconomic studies have been published that provide valuable data and insight into the financial burden of PAH.

Expert Commentary: Diagnosing PAH

To diagnose a patient with PAH, Dr Kingman first offered this scenario: "If you have a patient who has shortness of breath, the inhaler hasn't worked, if you haven't found any other cause and its continuing to progress—or a high-risk patient, like a scleroderma patient—get an echocardiogram. That should be your first screening test." History of fen-phen use would also be a contributing factor.

Although echocardiogram pressure estimates can be unreliable, they can show, especially in more advanced cases, an enlarged right ventricle or a right ventricle not pumping normally, which are clues that someone might have PAH. On the other hand, added Dr Studer, the echocardiogram can show that a patient does not have PAH but might have something else.

Ultimately, the diagnosis of PAH should be confirmed by a right heart catheterization.

Pharmacoeconomic Research: What Is the Burden and Impact of PAH on the Healthcare System?

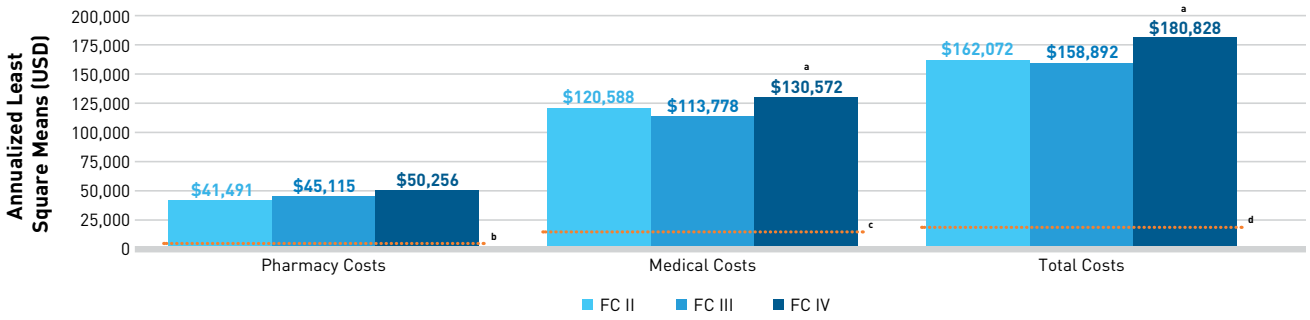
PAH has an impact on the healthcare system, but to what extent? A retrospective observational study was undertaken to determine the correlation of functional decline in PAH patients, as measured by a higher FC, with increased healthcare resource utilization (HRU) and costs.[15] Data were obtained from the Humana Research Database (Humana, Louisville, KY), which contains data from geographically dispersed US commercial and Medicare health plans providing coverage for about 19 million members. The data set included integrated medical, pharmacy, and laboratory claims. Prior authorization (PA) records for PAH therapies and medical chart abstraction were also used to obtain provider-documented FC.[15]

The FC III cohort was nearly 3 times larger than the FC II cohort, similar to the percentages found in the REVEAL registry. PAH severity, as indicated by higher FC, was associated with greater likelihood of inpatient episodes and significantly higher PAH-related costs. This pattern suggests that patients who progress to a higher FC will utilize more services; thus, preventing this progression through early treatment is desirable.[15]

Although all 3 cohorts showed high HRU, patients in FC IV had the highest pharmacy and medical costs, which supports the validity of the FC system. Further, 30% of patients in FC III and 35% of patients in FC IV were given an additional PAH-specific medication. Patients in FC IV experienced more PAH inpatient and outpatient episodes, with higher median total costs than patients in FC II or III.[15]

As further evidence of PAH disease severity, as well as the comorbidities and complexity of these patients, annual pharmacy costs for patients with PAH were 17 to 21 times higher than for average Medicare Advantage with Part D patients (**Figure 3**[15]).[15] Annual medical costs were higher than pharmacy costs and were 10

FIGURE 3. Adjusted Healthcare Costs by Type and Functional Class[15]



CY indicates calendar year; FC, functional class.
[a]*P*<.01 vs FC II or FC III using Genmod regression models.
[b]Denotes the average annual pharmacy costs for Medicare Part D ($2363; CY 2012).
[c]Denotes the average annual medical costs for Medicare ($11,392; CY 2012).
[d]Denotes the average annual total costs for Medicare ($13,755; CY 2012).

to 11 times higher for patients with PAH than for average Medicare patients (Figure 3[15]).[15] The high HRU in these patients underscores the need for accurate diagnosis and appropriate treatment by experts.

Another retrospective database study identified patients with PAH in a large US population of health-plan beneficiaries with commercial or Medicare coverage to assess timing, rates, costs, and length of stay (LOS) for hospitalizations.[18] The data source was the nationally representative Optum Research Database of medical and pharmacy claims from US health plans providing commercial and Medicare Advantage with Part D coverage, with approximately 30 million lives during the study period.[18] A total of 5566 hospitalizations were identified; 3322 of the hospitalized patients had commercial insurance, and 2244 had Medicare Advantage (**Figure 4**[18]).[18]

Averaged across all admissions for Medicare patients with PAH for any diagnosis (PAH or a comorbidity), the mean (SD) LOS was longer than for patients with commercial insurance: 12.8 (21.2) days versus 10.9 (20.4) days, respectively. Because Medicare patients are older, they have more overall comorbidities, which may contribute to the longer LOS. Patients with PAH are hospitalized often, whether for PAH or comorbid conditions; frequently, they are rehospitalized within a year. In fact, of the 2275 patients hospitalized during the study, 954 (79.3%) were readmitted 1 or more times within 1 year of the initial hospitalization; 225 (23.6%) were rehospitalized 3 or more times.[18]

Rehospitalization accounts for the majority of hospital costs. Averaged over all patients hospitalized during the study period, mean cost of readmission was $35,188 (SD = $152,006) for commercially insured patients and $19,170 (SD = $41,905) for Medicare patients. Averaged over just the 954 patients who were readmitted at least once, the 1-year readmission costs were $95,254 (SD = $238,506) for commercially insured patients and $36,543 (SD = $52,106) for Medicare patients.[18]

Number of hospitalizations and LOS are key contributors to HRU by patients with PAH. Of the rehospitalizations in the database study, 21.2% occurred within 30 days after discharge from the initial hospitalization. Retrospective claims database research studies provide evidence of the high HRU of patients with PAH and suggest that treatments that can decrease this utilization could lead to cost savings in addition to improving patient health.[19]

Expert Commentary: Practical Measures of Success

The experts agreed that treating patients early with the right medication can improve patient health and activities of daily living. "My goal is: You can walk in a grocery store, or you can walk in Walmart—or whatever activity is important for the patient to be able to resume," Dr Kingman said.

Dr Studer said the best measure of success is "preventing hospitalization"; however, he added, "We'd love to say that on a given day we've improved you to the point that you're very functional and can do your job, or whatever it is that makes you [the patient] feel productive."

Treatment for PAH

Therapies for PAH target endothelial cell dysregulation and abnormal proliferation of smooth muscle cells. Three major pathways are involved: 1) the endothelin pathway, which includes the 3 endothelin receptor antagonists; 2) the nitric oxide pathway, which includes phosphodiesterase type-5 inhibitors and soluble guanylate cyclase stimulators; and 3) the prostacyclin pathway (prostanoid and an IP receptor agonist).[20,21]

The prostacyclin pathway is the oldest and most targeted pathway. The first prostacyclin that offered specific treatment for PAH was Flolan (epoprostenol), approved in 1995.[22] Since then, other prostanoids have been developed and approved, including intravenous (IV), room temperature stable IV, subcutaneous, inhaled, and oral formulations. Additionally, a highly specific agonist for

the IP receptor—the receptor responsible for vasodilation within the lung—was recently approved.[23]

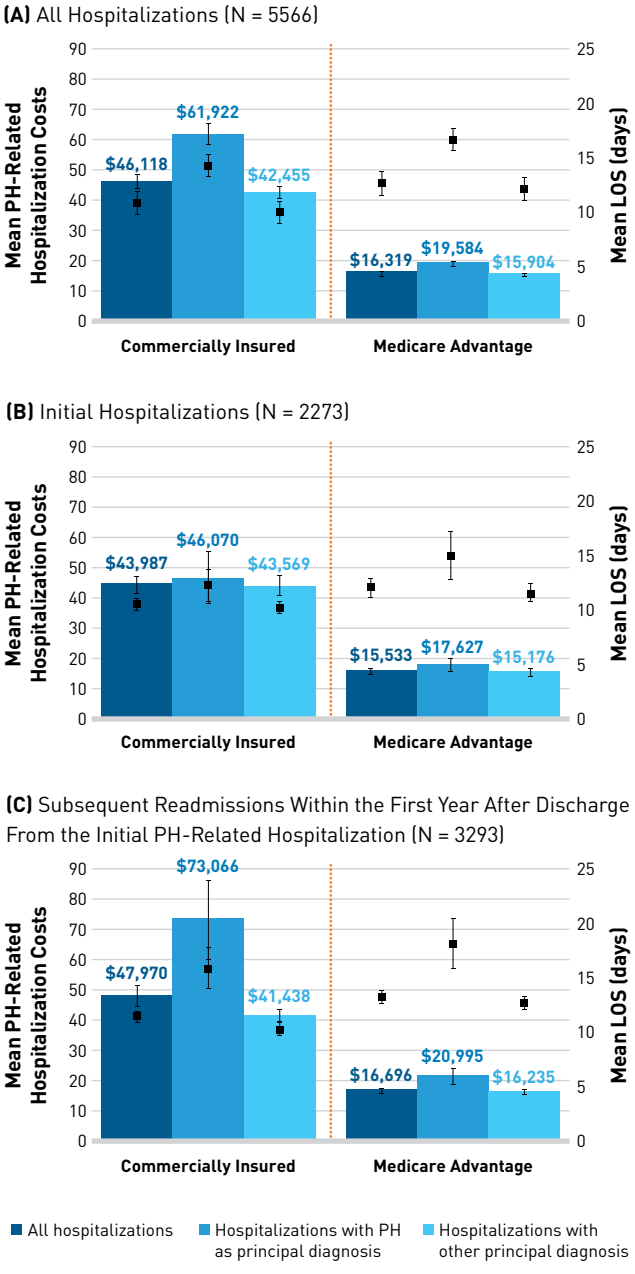
Treatment recommendations based on European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines to be considered include background therapy, general measures, and supportive therapy. (**Figure 5**[1])[1] If the patient is fortunate enough to demonstrate vasoreactivity, that patient can be on high-dose calcium channel blockers (CCBs) as long as they are monitored for continued medication response.[1] Vasoreactivity testing for CCB suitability is currently recommended for idiopathic, heritable, or drug-induced PAH, and only about 10% of these PAH patients meet the criteria.[1] The majority of cases are nonreactive, categorized as either low/intermediate risk (FC II/III) or high risk (FC IV). The ESC/ERS guidelines call for monotherapy or combination oral therapy for low- and intermediate-risk patients, and combination therapy including prostacyclin agents for high-risk patients; if the patient has inadequate clinical response, then double or triple therapy is recommended.[1]

Assessing PAH Patients for Treatment

Dr Kingman offered further perspective on determining how to treat patients with PAH. "If a patient is low risk, we're going to start with oral therapy; if they fall into a high-risk category, then those are the patients that we're going to look at putting on IV therapy quickly," she said. Generally, the slower that a patient's illness progresses, the better prognosis they will have. "If a patient was fine 2 or 3 weeks ago but is [now] having trouble walking across the room, that's going to put that patient on the worse prognosis side," she said. Another measure to consider is the 6-minute walk distance: "If it's low, less than about 380 meters, that's a higher-risk patient. Cardiopulmonary stress testing is sometimes used; if peak O_2 consumption is less than 12 mL/(kg/min), the patient is in a higher-risk category," she said. Additionally, if brain natriuretic peptide (BNP) or pro-BNP levels are very high, the patient is high risk. "Echocardiogram findings are really important," she added. "Presence of any sized pericardial effusion is a high-risk indicator, along with right ventricular enlargement or right ventricular dysfunction. When we see that, that's a higher-risk indicator. And then on hemodynamics, a right atrial pressure over 15 mm Hg or cardiac index less than 2 1/min/m^2 portends a very poor prognosis."[24,25]

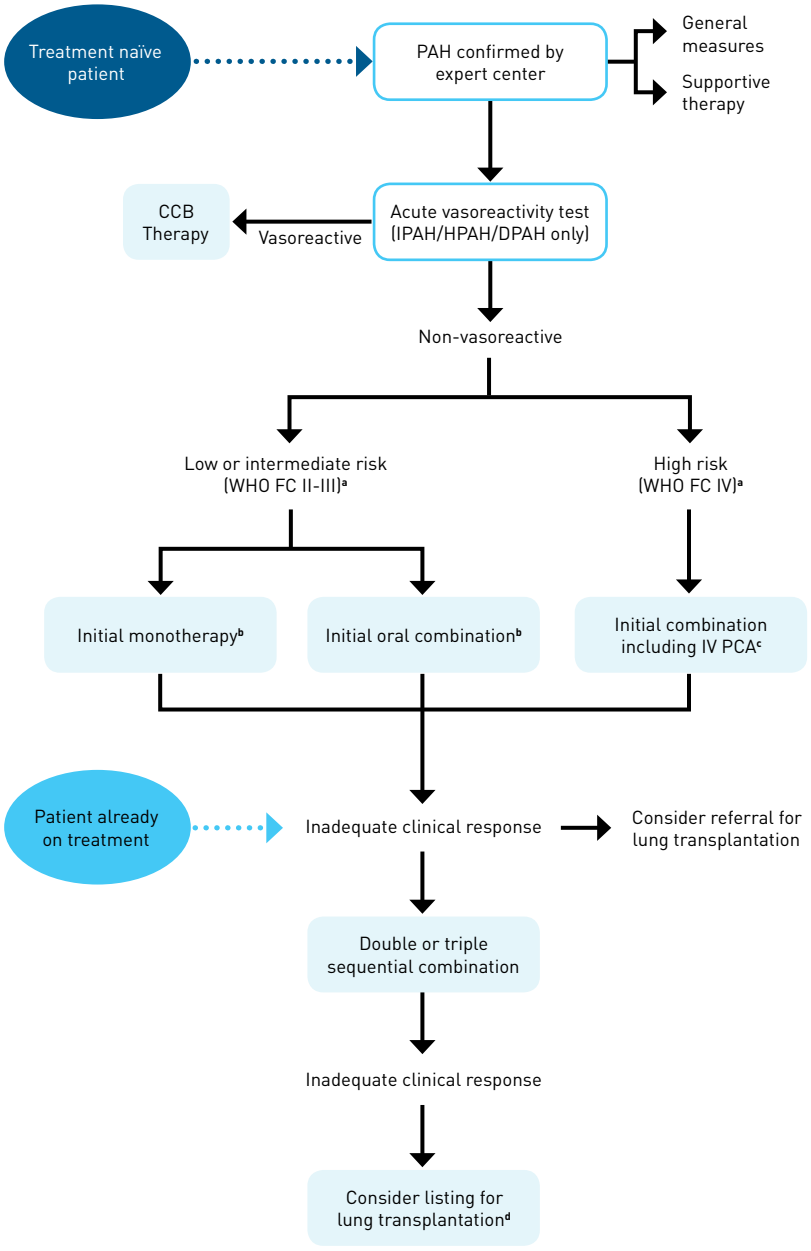
Dr Kingman also emphasized the importance of early treatment. "Studies show that the placebo group doesn't catch up," she said, referring to a meta-analysis of 21 PAH randomized, controlled clinical trials (3140 patients) reviewed for all-cause mortality.[26] The average study duration was 14 weeks,[26] and all trials were placebo-controlled.[26] Active treatment was associated with a reduction in mortality of 43% ($P = .023$).[26] The sensitivity analysis confirmed a reduction in mortality of 38% ($P = .048$).[26] The number of patients needed to be treated to prevent 1 death was 61.6.[26] Approximately 16.2 deaths were prevented in each 1000 patients treated.[26] Hospitalization rate in the actively treated group was 3.2% versus 8.03% in the placebo group; this was a 61% risk reduction for hospitalization in the treated group ($P < .001$).[26] It is important to note, however, that none of the newer agents (eg, macitentan, riociguat, oral treprostinil, and selexipag) were available at the time of this meta-analysis, and thus were not included.[26]

FIGURE 4. Total Hospitalization Costs and LOS for All Hospitalizations Associated With PAH[18]



LOS indicates length of stay; PH, pulmonary hypertension.
Bars indicate cost; squares, LOS; error bars, standard error.
Means are calculated over number of hospitalizations.

FIGURE 5. Treatment Recommendations for PAH[1,16]



CCB indicates calcium channel blocker; DPAH, drug-induced pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; WHO FC, World Health Organization Functional Class.

[a]Some WHO-FC III patients may be considered high risk.

[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.

[c]Intravenous epoprostenol should be prioritized as it has reduced the 3-month rate for mortality in high-risk PAH patients also as monotherapy.

[d]Consider also balloon atrial septostomy.

Determinants of Successful Treatment

Dr Studer said a treatment is considered successful "if you can get a patient to low risk, FC I or II—get the 6-minute walk test to be longer, get the BNP to be normal, and have normal or near-normal cardiac output and RV size and function" (**Table 2**[1,16]).[1,24] Measuring success in PAH, as opposed to in some other disease states, isn't easy, he noted: "For diabetes, you could say, if they're taking their drug and their hemoglobin A1C isn't yet normal, we would consider adding other medications; but in PAH, we just don't have that type of granularity."

Roundtable Commentary: Making Decisions in Partnership

Dr James noted the importance of social determinants of health. "Increasingly," he said, "we're using case management and other kinds of tools to help make some of these therapeutic decisions with the practitioner as to how we go about managing these individuals"—for example, determining whether the patient is capable of using intravenous therapy, which requires mixing, or whether the patient is capable of taking a medication that is dosed 3 times per day.

Dr Lewis agreed, taking the concept a step further. "The focus isn't on the managing price anymore, it's working in partnership with physicians, because we're putting much more IT infrastructure and resources into trying to develop an algorithm that will help us with outcomes," she said, referring to her company's practice of using information technology and models to "focus on best practice so we can truly pick the right drug and care combination for the right patient."

Dr Kingman offered an example of where the provider-insurer relationship can break down. Because of the new trial data from the AMBITION study, she will try to get tadalafil approved, but "9 times out of 10 the tadalafil is not approved, so we have to use sildenafil," which is "dosed 3 times a day, so it's more difficult for the patient to take. But sometimes we're at the mercy of what the insurance will allow."

Evidence-Based Treatment Approaches

The experts advised that management of PAH should incorporate evidence-based treatment. Regarding the efficacy of specific treatments, the highest level of evidence in clinical trials requires end points of time to clinical failure or clinical worsening or reduction in all-cause mortality.[1] Consequently, newer trials in PAH have had morbidity and mortality composite end points. Positive trials include SERAPHIN, which showed the broadest evidence in a wide range of patients for macitentan, and AMBITION, which studied ambrisentan in combination with tadalafil for treatment-naïve patients.[27-29] COMPASS-2 was a negative trial of bosentan and sildenafil.[30] "Look at the evidence and make decisions based on the evidence," said Dr Kingman, "and create your programs according to the clinical trial data."

"First and foremost," said Dr Studer, "make sure your diagnosis is correct—let's make sure we're treating the right patients." To illustrate, for a disease such as cystic fibrosis, "you wouldn't presume anyone had it without testing and involving a center of excellence," even just by phone or consultation, he said. "We want to make sure we have the right patient group"—which can be confirmed by right heart catheterization.

Dr Kingman agreed on the importance of a right heart catheterization to make the correct diagnosis. "All of us who are specialists in PAH have often had a patient referred who is a group II patient with heart failure, because that's much more common than PAH. I know the insurance company is acting appropriately when the outside physician has tried to get a PAH drug and the insurance company has denied it because there wasn't a right heart catheterization," she said.

Dr Studer advised insurers, "Use the evidence base, make sure you have the right diagnosis upfront, and then make the centers prove that they need additional therapy [for PAH patients]. If [the patients are] on 2 [drugs] and they want to go to the third, you say, 'Show me the data.' Show me you went through a methodical process. Prove it to me—evidence, diagnosis, guideline recommendations, and prove to me that you need more."

PAH Management Strategies

Stakeholders at the roundtable noted how they have seen the profile of PAH change over the years. One remembered that when he first joined his health plan about a decade ago, "There was a lot of discussion around PAH and what are the appropriate criteria for the health plan to have. Every single request for PAH drugs went up to medical directors, some of whom were cardiologists. And then about 5 or 6 years ago we lessened some step criteria and adjusted criteria. We have criteria that you need a right heart catheterization, but the in-depth PA review by a physician is no longer needed with more straightforward PA criteria."

Looking back 10 years, Dr Dunn remembered PAH as involving high-profile PAs that would be denied and then go through appeals. He has since seen an evolution in awareness and diagnosis: "It seemed to be a lot noisier 8 to 10 years ago," he said.

TABLE 2. Some Measurements That Determine Low Risk of 1-Year Mortality for Patients With PAH[1,16]

Determinants of Risk[a]	Measurements of Low Risk (<5%)
Clinical signs of right heart failure	Absent
Progression of symptoms	No
Syncope	No
WHO functional class	I, II
6MWD	>440 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% predicted) VE/VCO_2 slope <36
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L
Imaging (echocardiograph, CMR imaging)	RA area <18 cm^2 No pericardial effusion
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 SvO_2 >65%

6MWD indicates 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RA, right atrium; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2, oxygen consumption; WHO, World Health Organization.

[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for idiopathic pulmonary arterial hypertension (PAH) and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

Adapted from the European Society of Cardiology, Galie N, Humbert M, Vachiery JL, et al. *Eur Heart J.* 2016;37(1):67-119. http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Pulmonary-Hypertension-Guidelines-on-Diagnosis-and-Treatment-of. and European Respiratory Society, Galiè N, Humbert M, Vachiery JL, et al. *Eur Respir J.* 2015;46(4)903-975. http://erj.ersjournals.com/content/34/6/1219.short?rss=1&ssource=mfc.

Other specialty categories have become far costlier today, said Dr Cannon; PAH is no longer in the forefront. However, he said, it's important to establish appropriate criteria for PAH treatment: "Let's collaborate, and let's make sure that if we get a request, more importantly than approving it or denying it, we're funneling that person over to care management so that we can make sure that we've got enhanced coordination of care [through case managers with the health plan or specialty pharmacy]."

Dr Lewis noted another factor that has changed. "The emphasis on contracting in PAH has decreased with patent expirations and because we have more transparent partnerships with our physicians, ACOs, centers of excellence, and medical homes," she said. "PAH is not in our top 10 [in amount of expense as a specialty drug spend category]. And I think that's because we have more outcomes reimbursements with physicians."

The future of treatment for PAH could become more complicated now that PAH has gone in the direction of multiple combination

therapy, similar to cancer in its multiple-drug scenario. "I think we're going to be in a triple drug regimen," said Dr Studer, "because what disease do we really know of where there are multiple pathways known? There's been varying evidence that treating all those pathways helps, and treating it in various circumstances and combination helps, and yet we don't utilize all 3 pathways. If we had a cancer cocktail and we said, 'Well, the 4-drug regimen works well, but let's give you just 1 drug and see if the cancer gets worse,' everyone would recoil immediately from that."

Expert Commentary: Identifying Criteria for a Center of Excellence

Dr Studer described how centers of excellence in PAH are formed. "It's become an organized process through the Pulmonary Hypertension Association," he said, which is modeled somewhat on the Cystic Fibrosis Foundation; the 2 associations discussed how the system should work, he said. "There will be a 2-tier system that persists for a while, the comprehensive center—trials, multiple specialists—and then a community-type regional care center that doesn't necessarily have trials." The association will make site visits, where, he said, "they look at your records—you can't be treating in a way that's totally inconsistent. You need to go through a careful diagnostic process. You have to evidence-base your treatment—there needs to be documentation to your follow-ups."

"We want to partner with payers to get the center of excellence process to work well," Dr Studer said. "Even if you're not using the centers of excellence, you can still use centers of excellence criteria for treatment. If patients aren't near a geographic center of excellence, there could be a telemedicine consult, and patients need to have a right heart catheterization and then go through the process."

Dr Kingman noted that the Pulmonary Hypertension Association, just in the last few years, has created the centers of excellence at 2 levels. The PAH center in which she practices is characterized as a comprehensive care center, where—as opposed to the regional care centers—patients are on all therapies and research is done. "We, as the comprehensive care center, are working with the regional center to partner with them and assist them in appropriately treating these patients," she said. "It's not telemedicine, but I like that idea" for patients with travel constraints.

Right Patient, Right Drug, Right Time

"One of the views of the 'wrong treatment' right now is not treating early: Doing nothing does have a cost upfront," said Dr Studer. Going back to the meta-analysis, he said, "In trials where you had treatment versus no treatment, there was separation in function." When the untreated group was started on therapy, they might improve somewhat, "but they never made it to the functioning of the people who had even a 12- to 16-week lead time."[26]

Misdiagnosis is another problem. Dr Kingman explained, "Patients may come to us on a drug or 2 drugs, but they haven't had a right heart catheterization. So we stop their drugs and do the catheterization, and we may find that they never had PAH in the first place." "Wrong therapy is wrong diagnosis," agreed Dr Studer. "We don't want people who don't have this disease to be treated with expensive drugs. It's wrong economically, and it's very wrong, obviously, for the patients."

Dr Kingman said, "I would question why patients are on PAH drugs if they haven't had a right heart catheterization, because a lot of them are going to end up not having PAH." Added Dr Studer, "I would be very worried about a patient who went on a PAH drug for a short period—2 or 3 months as a 'therapeutic trial'; that's not always long enough to realize you're doing worse on it."

"That's where the expenses start mounting up," said Dr James. "If we only look at the drug costs for a true diagnosis, that's one thing. But mislabeling, mistreating: We have to get that out of medicine."

Roundtable Commentary: Coordination of Care Management

Dr Dunn suggested looking further into coordination of care management: "How the payers work with the provider to care-manage the patient, because there is so much hospitalization [of patients with PAH], transitions of care, and rehospitalization."

Dr James said, "What I learned with hepatitis C was that it's a big drug cost, but you've got to make sure the person takes it; otherwise they may have relapses. I have to make sure that when a patient is on an expensive drug, we have someone following along and making sure there's compliance."

But Dr Kingman and Dr Studer both said they don't have much contact with case managers. Said Dr Kingman, "Case managers are not interacting with us, but who we do interact with on a regular, daily basis are the specialty pharmacy nurses."

Dr Lewis added, "Because we own our specialty pharmacy, it's internal to us, so if you are interacting with a specialty pharmacy, that information is getting to our case managers."

"That's the issue," said Dr Dunn. "Is there appropriate care management, and who is doing it?" You don't want to have everyone talking to the patient but not in coordination, because "that's probably compromising the quality of care, and probably irritating the patient." He said his company has robust clinical programs consisting of lab data, hospitalization data, and pharmacy data, so they know what patients are doing: "We know if they're refilling their meds, we know what other conditions they have, we know when they're in the hospital." Coordinating this type of information through a case manager could be helpful to the patient.

How Can Management of PAH Be Improved?

Dr Lewis asked, "How do we look for PAH in a way that makes sense, how can we address it in a more effective way, and how can we look for patients who could be more at risk so that we could possibly treat them earlier? If you believe the premise of treating them earlier, I still would feel that, from a management perspective, we might need more data about what's going to save us money long-term. Keeping patients from transitioning from an FC III to a IV would be very vital to a health plan, but do we put our resources into trying to catch it earlier and trying to find those PAH patients earlier?"

"There are screening guidelines for patients in high-risk groups," said Dr Kingman. If PAH patients "were diagnosed sooner, theoretically they would do better and be stable for much longer, out of the hospital, and saving money."

"We are in the business of looking for methods and ways to risk stratify in certain disease states," Dr Lewis said. "We will send someone out to a patient's home to get a lab value, and we will send nurses out to see what's going on at the home so that we can keep the readmission rates lower in certain disease categories." Dr Kingman said, "If the insurance industry can direct patients to the comprehensive care centers, or at least to a regional care center, then you'll have a really high likelihood that you've got the right diagnosis. More and more centers are being accredited. Sometimes the center just does the workup and the evaluation, gets the diagnosis, and then coordinates with the local doctor so care can stay managed largely on the local level."

Dr Studer agreed on the importance of collaboration with a center, "not completely divorcing from your local care community; that [lack of collaboration] doesn't work. But there's got to be the collaboration, which could be a diagnosis, or it could be at other varying points when things get more complicated."

"We know that these drugs are all really expensive, and when you start adding 1, 2, and 3, it gets very expensive," said Dr Kingman. "As another example, there's a prostacyclin (treprostinil), now in oral formulation, that some centers use. we have chosen not to use oral treprostinil as we feel the clinical trial data does not support the cost of the medication."

TAKEAWAY COMMENTS

DR CALO: "Although there are relatively few patients with PAH, if a patient with the condition is not diagnosed until a late stage, "It's going to be bad for that person and for the healthcare system, because the costs are going to go up as the patient progresses through the levels of classification from I through IV. Therefore, it is very important that primary care physicians order the appropriate workup when confronted with a patient with the associated history and complaints."

DR. LEWIS: "I will go back to my specialty team and ask them if we're missing anything in coordination of care. If practitioners are not hearing much from our case managers, there could be something missing."

DR CANNON: "Hearing different viewpoints and understanding more of the thought process around patients reinforces the need for us to continually and openly have dialogue with the people who are providing care for the members we provide coverage for." There could be opportunity in PAH to become "more aligned with data" and have better "coordination across the system."

DR DUNN: PAH "has been off the radar screen for a while," but it seems to be coming back, so there should be preparation, including "working towards better collaboration, both in terms of formularies and care coordination." He also noted the importance of having a "clear understanding" of physician-directed prescribing or physician-directed therapeutic decisions.

DR JAMES: The concept of slowing down the progression of functional decline is "a whole wellness concept. Wellness is a concept for people with chronic conditions to make them feel better. How do we go about having the right kinds of social, pharmacologic, medical, and, to a certain extent, financial interventions that will help improve the outcome of individuals with chronic disease?"

DR KINGMAN: "I hope, moving forward, that we're all able to collaborate on a nice, even playing field," rather than being faced with "denial after denial." There is "a lot of common ground where we could work together and collaborate more and make the right decisions financially and clinically."

DR STUDER: "Better upfront dialogue makes it smoother for the individual patient down the road." For a patient who is on 1 drug and remains at FC IV, "If you were the payer, you should say [to the provider], 'What's your plan here?' You're either gaining no ground and you should consider stopping [the drug], or you may need to escalate. When the desired outcomes are clear, the treatment plan should be focused on achieving them."

The Importance of Open Access to Treatment

The health-plan participants at the roundtable meeting said they were given a deeper understanding of PAH from the expert practitioners, including details of the burden on patients living with the disease and the impact on the healthcare system, along with the importance of facilitating access to treatment options to provide appropriate care for individual patients. In turn, the practitioners gained insights into factors that health plans consider in making decisions on medications and other aspects of care. Stakeholders agreed that working together to ensure that patients with PAH are diagnosed correctly and receive appropriate treatment will result in the best outcomes for patients and optimal utilization of healthcare resources.

Conclusion

PAH is a rare, chronic, progressive, and ultimately fatal disease that affects an estimated 12 to 50 cases per million individuals. Available PAH-specific treatments include a variety of agents covering multiple mechanisms of action: prostacyclins, IP receptor agonists, endothelin-receptor antagonists, soluble guanylate cyclase stimulators, and phosphodiesterase-5 inhibitors. With the available mechanisms of action and data supporting the use of combination therapy, more attention is likely to come from managed care because of potential cost concerns. However, when treatments are used appropriately, clinical deterioration can be avoided or delayed. It is important to recognize the unique pharmacologic characteristics of agents within each class and the specific evidence supporting use of each treatment. It is also important to consider the administration characteristics of each medication and the effect of administration characteristics on patients. Because each patient with PAH has a unique set of circumstances, patients with PAH need access to individualized care. PAH specialists have the expertise to assure that the right patient gets the right drug at the right time when they have timely access to all available options. Managed care decision makers and providers can partner in the care of patients with PAH by ensuring the correct diagnosis, primarily through right heart catheterization, and facilitating the best outcomes for patients through physician-directed prescribing based on guidelines and real-world evidence. ■

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