

# The Myth of the Stable Pulmonary Arterial Hypertension Patient

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## Introduction

Pulmonary arterial hypertension (PAH) is a rare progressive disease, with an estimated prevalence ranging from 10 to 52 cases per million.<sup>1</sup> PAH is characterized by increased pulmonary vascular resistance, increased pulmonary artery pressure, and right ventricular dysfunction, which often leads to right heart failure, morbidity, and mortality.<sup>2</sup> Over the past 2 decades, substantial progress has been made in treating patients with PAH, including multiple new pharmacologic therapies. However, patients continue to experience disease progression and high rates of healthcare resource (HCR) utilization.<sup>2-4</sup>

The awareness, knowledge of impact, and pharmacotherapeutic options have expanded, but the course of PAH remains uncertain. Although some patients can live for decades, some will die within a few months of diagnosis, and others can appear to be doing well and then abruptly decline and die.<sup>5-7</sup> Ultimately, the long-term prognosis for patients with PAH remains poor, with an unacceptable high mortality rate of almost 40% over 5 years.<sup>8</sup> Thus, the sustained clinical stability of patients with PAH cannot be assured, as even those thought to be “less severe” may progress and die. Because it is well known that PAH is a progressive disease, it is important to frequently assess patients with PAH to optimize their outcomes and escalate treatment as clinically indicated.

## Prognostic Indicators

Historically, functional class (FC), a measure of disease severity, has been considered the strongest prognostic indicator. The World Health Organization (WHO) FC system characterizes patients by classifying compromise in their functional ability (FC I-IV) according to symptoms, such as dyspnea, fatigue, chest pain, and syncope (at rest or on exertion).<sup>9</sup> FC assessment of patients with PAH was adapted from the New York Heart Association classification system and was first adopted at the second World Symposium on Pulmonary Hypertension (WSPH) (Table).<sup>9</sup> Using a simple assessment, FC can be identified at diagnosis and at follow-up to assess the impact of therapies, and it is accepted as a predictor of survival in patients with PAH.<sup>10-12</sup> The importance of this classification is appreciated in that

## ABSTRACT

Pulmonary arterial hypertension (PAH) is a rare, progressive disease that often leads to right heart failure and premature death. Despite increased awareness and an expanding treatment landscape in recent decades, long-term prognosis is poor for patients with PAH. Recently, emphasis has evolved from goal-oriented therapy to risk-assessment and achieving low-risk status. Findings from recent clinical trials suggest that functional class II patients, long assumed to be stable, are not stable. Therefore, frequent assessment of all patients with PAH is essential toward escalating treatment as indicated to optimize clinical outcomes. Lowering mortality risk, preventing disease progression, and optimizing quality of life of patients with PAH is paramount.

*Am J Manag Care.* 2019;25:S47-S52

For author information and disclosures, see end of text.

**TABLE.** PAH Classification Systems<sup>9</sup>

NYHA Functional Classification	
Class I	No symptoms with ordinary physical activity.
Class II	Symptoms with ordinary activity. Slight limitation of activity.
Class III	Symptoms with less than ordinary activity. Marked limitation of activity.
Class IV	Symptoms with any activity or even at rest.
WHO Functional Classification	
Class I	Patients with [PAH] but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with [PAH] 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.
Class III	Patients with [PAH] resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with [PAH] with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

NYHA indicates New York Heart Association; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

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all currently marketed PAH-specific therapies include FC in their indication and usage statement.<sup>9</sup> Today, after several meetings of the experts at subsequent WSPH, attainment of FC I or FC II status continues to be an important goal for PAH treatment. However, FC II patients still experience disease progression events and even death.<sup>13-15</sup> These patients cannot be considered stable. To say a patient is stable is to look at the past rather than the future. Additionally, stable is not clinically defined in current literature and we do not actually know who the stable patient is and what that patient looks like. We lack a full understanding of the predictors of decline that may enable an improved phenotyping of patients and delineation of risk. Several factors may account for the lack of stability.

Patients with PAH are a heterogeneous population, with different prognoses based on etiology. For example, patients with PAH with portal hypertension<sup>16</sup> and those with scleroderma have a higher mortality risk than do patients with idiopathic PAH.<sup>17</sup> Benza et al found that any connective tissue disease (CTD) was a contributing factor to increase the risk of mortality among patients who participated in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), a multicenter, observational, US registry designed to assess demographic, clinical, and management data on patients diagnosed with PAH.<sup>5</sup> Further, a study from van de Veerdonk et al elucidates the danger in underestimating the risk of progression for patients with FC II to FC III.<sup>18</sup> In a cohort of patients who experienced disease progression resulting in death or

lung transplantation after >5 years of clinical stability, it was noted that disease progression was preceded by changes in the right ventricle (RV) structure and function, but no change in FC, exercise capacity, and hemodynamics, suggesting that a clinically stable profile may mask development of RV failure.<sup>18</sup>

A landmark analysis demonstrated that a PAH-related morbidity event, defined in both the SERAPHIN and GRIPHON studies, was predictive of an increased risk of mortality.<sup>19</sup> Morbidity events include atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, worsening of pulmonary arterial hypertension, initiation of long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy.<sup>13,14,20</sup> In the SERAPHIN trial, compared with those patients without a morbidity event at the 3-month landmark, those with an event had an increased risk of mortality (hazard ratio [HR], 3.39; 95% CI, 1.94-5.92). Results from the GRIPHON trial demonstrated an elevated risk in mortality in patients who experienced a

prior morbidity event (HR, 4.48; 95% CI, 2.98-6.73) compared with patients who did not have a morbidity event. Analyses based on both a 6-month and 12-month landmark also showed an increased mortality risk for patients who experienced morbidity events.<sup>19</sup>

It was demonstrated in REVEAL that patients with either newly or previously diagnosed PAH, regardless of PAH etiology, and who improved from FC III to FC I/II had better survival outcomes compared with patients who remained in FC III.<sup>21</sup> It has been well documented that those patients in FC I/II compared with FC III/IV have better survival rates.<sup>4</sup>

Although FC I/II patients have better survival rates, it is understood that patients with PAH frequently have multiple comorbidities. For example, in REVEAL, the most common comorbidities among patients included hypertension, clinical depression, diabetes, obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), obstructive airway disease (OAD), sleep apnea, and thyroid disease. Patients with obesity or OAD occupied a significantly worsened FC; those with OAD or diabetes demonstrated an increased risk for mortality in comparison with the other comorbidity subgroups.<sup>22</sup> More recently, the OPsumit USers Registry (OPUS) (NCT02126943) showed that the most common comorbidities among patients (N = 1136) were hypertension, edema, diabetes mellitus, anemia, signs of right heart failure, autoimmune disease, and renal insufficiency.<sup>23</sup>

Retrospective studies have also demonstrated that patients with PAH have multiple comorbidities. In a claims database study using

the Pharmetrics Plus database that covers more than 150 million US patients, Hill et al identified 2623 patients who were treated with endothelin receptor antagonists (ERAs, n = 805) or phosphodiesterase type 5 inhibitors (PDE-5i, n = 1818) and found that among the total cohort, the most common comorbidities included renal failure/dialysis, congenital heart disease, connective tissue disease, clinical depression, liver disease, systemic hypertension, diabetes, and obesity.<sup>24</sup> Using the OPTUM research database covering more than 50 million US patients, Hull et al identified a cohort of 1637 patients with *International Classification of Diseases, Ninth Revision* codes of 416.0 and 416.8 with a claim for a PAH-specific medication. Common comorbidities included diseases of the heart; other lower respiratory disease; hypertension; diseases of arteries, arterioles and capillaries; lipid disorders; diseases of the urinary system; chronic obstructive pulmonary disease; CTD; and diabetes.<sup>25</sup>

Patients with PAH bring with them their entire medical past and often have multiple comorbidities which may contribute to their poor PAH prognoses. Further, these conditions may exacerbate minor disorders, such as upper respiratory conditions, and complicate major insults, such as pneumonia and surgery. Thus, Gaine and McLaughlin asserted that patients with PAH “can never be considered truly stable.”<sup>11</sup>

From an economic perspective, a higher FC is associated with increased healthcare resource utilization (HCRU), including more frequent inpatient stays, longer lengths of stay, more emergency department service utilization, higher all-cause medical costs, and higher total costs. Dufour et al showed that patients who declined to FC IV used more HCRs and experienced more costs compared with FC II/III patients.<sup>4</sup> Surprisingly, HCR utilization and costs were similar for FC II and FC III patients. The reasons for this are not clear, but this finding may reflect patient comorbidities or use of additional combination therapies.

### Randomized Clinical Trials

Long-term, event-driven trials have shown that FC II patients demonstrated significant improvement when additional therapy was added. In the SERAPHIN trial, 52.4% of patients were FC II and 64% were on concomitant PAH-specific therapy\*. For patients on combination therapy, there was a 38% risk reduction in the composite morbidity/mortality primary end point.<sup>14</sup> In the GRIPHON trial 46% of patients were FC II and 80% were on concomitant PAH-specific therapy. There was an overall 40% risk reduction in the composite morbidity/mortality primary end point.<sup>13</sup>

Four-year data from the open-label extension of the EARLY trial, which was conducted with PAH-targeted therapy in WHO

FC II patients, reinforced that FC II patients can have severe and often fatal progressive disease: “PAH worsening occurred at a rate of approximately 5% annually, and mortality, estimated at 15% over 4 years, remains substantial.”<sup>26</sup> Specific factors were identified as predictive of death in FC II patients, including 6-minute walking distance (6MWD) of  $\leq 437$  m, PAH diagnosis of  $< 16$  months, mixed venous oxygen saturation of  $\leq 68\%$ , high N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, and PAH-CTD. It was concluded that patients with these risk factors should prompt clinicians to employ treatment strategies such as more regular assessments and more aggressive treatments, including combination therapy. A death rate of 15% over 4 years in a mildly symptomatic PAH population<sup>26</sup> shows the need for further research and demonstrates that FC II patients may not be stable.

### Treatment Goals

Treatment goals have evolved with a desire to ensure optimal long-term outcomes. Since 2015 there has been a shift from goal-oriented therapy to a risk-assessment approach, with a treatment goal of achieving low-risk status.<sup>27</sup> The achievement of low-risk status is usually associated with FC II, good exercise capacity, good quality of life, good RV function, and a low mortality risk.<sup>27</sup> The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines recommend that patients undergo risk stratification using a multiparameter approach at diagnosis and at follow-up, based on the risk of clinical worsening and 1-year mortality. These risk categories were described as low-risk ( $< 5\%$  mortality risk), intermediate risk (5%-10% mortality risk), and high risk ( $> 10\%$  mortality risk). Multiple determinants of prognosis include clinical signs of right heart failure, progression of symptoms, syncope, WHO FC, 6MWD, cardiopulmonary exercise testing, NT-proBNP/BNP, imaging, and hemodynamics. (For further details, see ESC/ERS Guidelines 2015). Treatment is then guided by the patient’s assessed risk category. Regular assessment is “strongly recommended” to detect clinical deterioration and to rapidly escalate therapy as clinically indicated to achieve treatment goals and maintain or reestablish low-risk status.<sup>27</sup>

The goal of achieving low-risk status has been validated in studies from 3 registries: the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), the French PAH registry, and the Swedish PAH registry (SPHAR). Each of these studies used an abbreviated version of the ESC/ERS multiparameter risk assessment.

Boucly et al conducted a study in incident French PAH registry patients with idiopathic, heritable and drug-induced PAH to determine the association between long-term prognosis and the achievement

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#### FOOTNOTE

\*Stable dose (at least 3 months) of oral phosphodiesterase type 5 inhibitors, oral or inhaled prostanoids, calcium channel blockers, or L-arginine was allowed.

within 1 year of diagnosis of low-risk criteria.<sup>28</sup> The patient cohort was assessed using low risk criteria including classifications of FC I or II, 6MWD >440 m, right atrial pressure (RAP) <8 mm Hg and cardiac index (CI)  $\geq 2.5$  L/min/m<sup>2</sup>. The study included 1017 patients over a median follow-up duration of 34 months. The number of low-risk criteria presented at diagnosis and at first reevaluation were predictive of risk of death or lung transplant (both  $P < .001$ ). For the subgroup ( $n = 603$ ) of patients with BNP or NT-proBNP, 3 noninvasive criteria (FC, 6MWD, and BNP/NT-proBNP) also predicted prognostic groups ( $P < .001$ ) at first reevaluation. Thus, using this subset of parameters, the ESC/ERS low-risk criteria predicted transplant-free survival for patients with PAH.

In a second registry, Hoeper et al worked with newly diagnosed patients enrolled in the COMPERA registry, and used an abbreviated risk assessment strategy from the ESC/ERS guidelines to analyze data from 1588 patients.<sup>27,29</sup> The variables included WHO FC, 6MWD, BNP/NT-proBNP, RAP, CI, and mixed venous oxygen saturation. One year after diagnosis, mortality rates were 2.8% in the low-risk cohort, 9.9% in the intermediate-risk cohort, and 21.2% in the high-risk cohort. This risk assessment strategy proved to be effective at follow-up, as well as in major subgroups of patients with PAH. In summary, risk assessment using multiple risk factors, an abbreviated version of the European PAH guidelines, accurately predicted mortality for patients with PAH.<sup>27</sup>

Finally, Kylhammar et al used patients with PAH from the SPHAR registry to validate the benefit of reaching a low-risk profile.<sup>30</sup> Patients with PAH ( $N = 530$ ) were included, with follow-up assessments performed after a median of 4 months in 383 patients. Patients were classified into low-, intermediate-, and high-risk groups. The benefit of reaching low-risk status was estimated both at baseline and at follow-up. Survival was better ( $P < .001$ ) for patients with a higher proportion of low risk factors. When analyzed separately, the results for patients with PAH aged >65 years did not differ for patients with idiopathic or CTD-associated PAH. Patients in the low-risk group at follow-up had a reduced mortality risk (HR, 0.2; 95% CI, 0.1-0.4) in multivariable analysis (adjusted for sex, age, and subset of PAH) as compared with patients in both the intermediate- and high-risk groups. Again, these findings suggest the validity of using comprehensive multiparameter risk assessment with the aim of reaching low-risk status.<sup>30</sup>

The concept of performing risk assessment utilizing a systematic tool is not new to PAH. The REVEAL risk score calculator was developed from the REVEAL registry.<sup>5</sup> Benza et al used previously known and newly confirmed PAH prognostic findings to develop a

cohesive predictive formula, which weighs each factor in the multivariate model and determines its relevance in context with the other variables.<sup>5</sup> The multivariate model provides better risk stratification compared with that provided by individual variables. Although FC, 6MWD, and BNP had more prognostic value than the previous equation derived from the National Institutes of Health, they provide lower discriminatory power than the full prognostic equation.

Interestingly, when systematic risk assessment is utilized, FC II patients may not reveal qualities solely in 1 risk category; they may demonstrate risk parameters in multiple categories. It is imperative that all patients, including those categorized as low risk, be assessed regularly, to ensure that changes in individual parameters are detected at the earliest opportunity. Any parameters that are reclassified from low to intermediate risk should raise the practitioner's index of suspicion and prompt consideration of treatment escalation.<sup>11</sup>

## Assessment and Therapy Escalation

Since low-risk status is the accepted treatment goal, healthcare providers must not become complacent when performing frequent systematic assessments of their patients with PAH. Because mortality risk is seen in FC II patients, the goal of treatment goes beyond simply achieving FC I or II status, as was earlier thought; rather, the goal is to move the patient into a lower category. This may mean moving from intermediate to low risk or, if already low risk, achieving more parameters in the low-risk category. It is worth reiterating that, although a patient may be in the low-risk category, pathologic changes may continue in the pulmonary vasculature and RV; therefore, characterizing a patient as "stable" may be misleading. For patients in all risk categories, it is critical that frequent, regular, and systematic assessment be conducted to address changes in individual risk parameters or risk corridors, allowing for early therapy escalation for dual or even triple combination therapy.<sup>11</sup>

Combination therapy—initial or sequential—targeting multiple pathological pathways is incorporated in the ESC/ERS 2015 treatment algorithm and is often considered the standard of care.<sup>27</sup> Dual and triple combination therapies have been shown to improve long-term outcomes in randomized clinical trials.<sup>13,14,31</sup>

The most common dual therapy is an ERA and a PDE-5i. Sequential and initial dual therapy, respectively, were shown to improve long-term outcomes in the SERAPHIN and AMBITION trials. The AMBITION trial was a treatment strategy trial in which initial combination therapy with tadalafil and ambrisentan was compared with monotherapy with either drug; all were administered once daily.<sup>\*\*</sup> Initial combination therapy reduced the risk of clinical failure by

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## FOOTNOTE

\*\*AMBITION exclusion criteria: Participants must not have >3 of the following HFpEF risk factors: 1. body mass index >30 kg/m<sup>2</sup>; 2. history of essential hypertension; 3. diabetes mellitus (any type); 4. historical evidence of significance: coronary artery disease (CAD) established by any of the following: history of myocardial infarction, history of percutaneous coronary intervention, angiographic evidence of coronary artery disease (>50% stenosis in >1 vessel, positive stress test, previous coronary artery bypass graft, stable anginal).

approximately 50% in a subset of newly diagnosed, treatment-naïve patients without 3 or more comorbidities that were considered high risk for heart failure with preserved ejection fraction.<sup>31</sup> In the SERAPHIN trial, approximately 64% of patients were on background therapy at the time of randomization (of those, more than 90% were receiving a PDE-5i). For all patients, macitentan reduced the risk of a first morbidity/mortality event by 45% and for those patients on background therapy, the addition of macitentan reduced the risk of morbidity/mortality event by 38% compared with placebo.<sup>13</sup> In a post hoc evaluation of newly diagnosed, treatment-naïve patients on macitentan, monotherapy reduced the risk of a morbidity/mortality event by 60% versus placebo.<sup>20</sup>

The long-term, event-driven GRIPHON trial is the largest and only completed randomized controlled trial which allowed triple combination therapy.<sup>14</sup> Of the 1156 patients enrolled, approximately 46% were classified as FC II and nearly 53% were classified as FC III. Patients were included if they were not receiving PAH treatment or if they were on a stable dose of an ERA, PDE-5i, or both. For all selexipag patients, there was a 40% reduction in first morbidity/mortality events, compared with placebo. For patients who were not receiving PAH treatment at baseline versus those who were receiving a combination of 2 therapies and patients classified as FC II versus those classified as FC III, the effect of selexipag on the primary end point were similar.<sup>14</sup>

Because PAH is a progressive disease, the initiation of combination therapy appears inevitable. However, there is no evidence on whether initial or sequential combination therapy is more effective. Nevertheless, questions remain regarding the utility of monotherapy. The ESC/ERS algorithm allows clinicians to choose between initial monotherapy or initial combination therapy for low- or intermediate-risk patients. The SERAPHIN trial, with a 55% risk reduction for the first morbidity/mortality event for patients who were not on background therapy, supports the role of macitentan in monotherapy. Although monotherapy may have a role in the treatment of some low-risk patients, it is critical to monitor these patients closely and initiate combination therapy as soon as it becomes clinically appropriate. Most often, combination therapy will include an ERA and a PDE-5i or soluble guanylate cyclase stimulator, either as initial therapy or as sequential therapy. The ongoing TRITON trial (NCT02558231), when completed, will address the efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed PAH.<sup>32</sup>

Therapies that target the prostacyclin pathway provide an important modality to treat PAH. Initially available only as parenteral therapy, alternative routes of administration are now available, including the earlier approved inhaled and recently introduced oral formulations. Some of these drugs have been shown to be effective in studies conducted in FC II and FC III patients. For example, in a 12-week trial, oral treprostinil demonstrated an increase in exercise

capacity when used as monotherapy.<sup>33</sup> As discussed earlier, selexipag was studied in FC II and FC III patients, both as monotherapy and in dual and triple combination therapies, demonstrating a 40% decrease in the risk for the first morbidity/mortality event, with similar results for both FC II and FC III patients.<sup>14</sup>

## Conclusions

In clinical practice, it is recognized that each patient has their own unique phenotype, disease etiology, and comorbidities, which contribute to the need for individualized care. Clinical decision making must be based on frequent, systematic assessment. Regardless of the risk category into which the patient falls, vigilance in monitoring for early signs of disease progression or clinical deterioration is essential. Escalation of therapy is necessary when subtle changes in parameters are first recognized. Additional information is needed on whether initial triple combination therapy is more effective than sequentially adding a third prostacyclin pathway agent to ERA-plus-PDE-5i combination therapy. A clinical trial in process may provide definitive information on whether initial or sequential (double or triple) therapy is more effective.<sup>32</sup>

Ultimately, PAH remains a fatal disease with no cure. Our goal is to lower mortality risk, prevent disease progression, and optimize the quality of life of patients with this condition. If we assume that the FC II patient is stable, it will be to the detriment of the patient. In fact, a stable patient with PAH may not exist. Therefore, the healthcare team must maintain a healthy index of suspicion and intervene in a timely and appropriate manner. ■

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**Funding source:** Publication support provided by Janssen Pharmaceuticals.

**Author disclosures:** Dr Besinque reports no relationships or financial interests with any entity that would pose a conflict of interest with the subject matter of this supplement. Dr Lickert and Dr Pruett report to having an institutional conflict of interest with Actelion Pharmaceuticals, a Janssen Pharma company, a division of Johnson & Johnson. Dr Lickert and Dr Pruett are both employees of Actelion and own stock in Johnson & Johnson.

**Authorship information:** Analysis and interpretation of data (CAL, GMB, JAP), concept and design (CAL, JAP), critical revision of the manuscript for important intellectual content (CAL, GMB, JAP), drafting of the manuscript (CAL, JAP), supervision (CAL).

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