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# Scientific Update™

## NYHA Functional Class II: An Achievable Goal for All Patients with Pulmonary Arterial Hypertension Receiving Treatment

Originally presented by: Simon Gibbs, MD, Jean-Luc Vachiéry, MD, Nazzareno Galiè, MD, and Vallerie McLaughlin, MD

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Discussed by: JUAN CARLOS MONGE, MD, FACC, FRCPC

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by a poor prognosis with a median survival of ~2.8 years in patients with untreated idiopathic PAH, and only 1 year for patients with untreated PAH associated with systemic sclerosis (scleroderma).<sup>1,3</sup> The prevalence of PAH ranges from 15 to 50 patients per 1 million population; for instance, in the United Kingdom the number of patients receiving treatment for PAH is 27 patients/million population. This issue of *Cardiology Scientific Update* discusses the identification of patients at an earlier functional stage and examines the concept of “treating to target,” ie, setting and achieving more aggressive goals in the management of patients with PAH, including the use of combination therapy.

PAH is more prevalent in certain populations; eg, patients with connective tissue disease are particularly at risk, with pulmonary hypertension found in ~7%-12% of patients hospitalized for scleroderma.<sup>4,6</sup> PAH is also seen in patients with human immunodeficiency virus/acquired immunodeficiency syndrome, although the prevalence is probably lower than in scleroderma, and it is an important problem for a significant proportion of patients with congenital heart disease.

In patients with World Health Organization (WHO) functional class II symptoms, which are similar to New York Heart Association (NYHA) functional class II symptoms for heart failure, there is only a relatively short delay between these symptoms and the progression to functional class III (Figure 1). Additionally, the evidence suggests that if treatment is initiated after the onset of WHO class III symptoms the prognosis may be poorer, but treatment at an improved functional class has a beneficial impact on prognosis (Figure 2).

PAH is a progressive disease that leads to right-ventricular dysfunction. Currently, there is no cure for PAH and, until very recently, only patients with class III or IV symptoms, well advanced in the hemodynamic continuum of the disease, were considered

eligible for treatment. Generally, at this point in the disease course even stabilization, which was often the most hopeful outcome, is not satisfactory. If supported by evidence, it would be reasonable to initiate treatment when the patients are in functional class II before serious right-ventricular dysfunction is present. Stabilization at, or improvement, to a better functional class would be a more satisfactory outcome and could improve overall prognosis.

In recent years, many important advances have been made in the management of PAH. There are better tools for assessment and diagnosis in this disease, and targeted screening programs have been implemented. Additionally, the field has gained an improved understanding of the pathophysiology of PAH, resulting in the development of PAH-specific therapies and leading to improved long-term outcomes.<sup>7</sup> The combination of an earlier diagnosis, a more timely intervention earlier in the disease process, and a goal-oriented treatment strategy (“treating to target”) are all important steps towards achieving the ambitious goal of improving outcomes in this serious disease.

The diagnosis of PAH at an early stage can often be a challenging diagnostic problem; however, the identification of patients in WHO/NYHA functional class II is a feasible objective. The targeted screening of high-risk groups, such as those with systemic sclerosis, may assist in early-stage diagnosis. Annual echocardiographic screening is now recommended for scleroderma patients with symptoms compatible with PAH (Grade 1 recommendation, level of evidence C). A weaker recommendation is in place for asymptomatic patients (Grade IIb recommendation, level of evidence C).<sup>8</sup> A recent report also indicated that screening HIV patients leads to an earlier diagnosis.<sup>9</sup>

After a definitive diagnosis of PAH is established, the initiation of effective and specific therapy is essential and should not be delayed. This extremely important point should be emphasized given the rapidly progressive nature of PAH and the benefits of early therapeutic intervention in NYHA functional class I or II over treatment initiated in the latter stages of the disease.<sup>10,11</sup>

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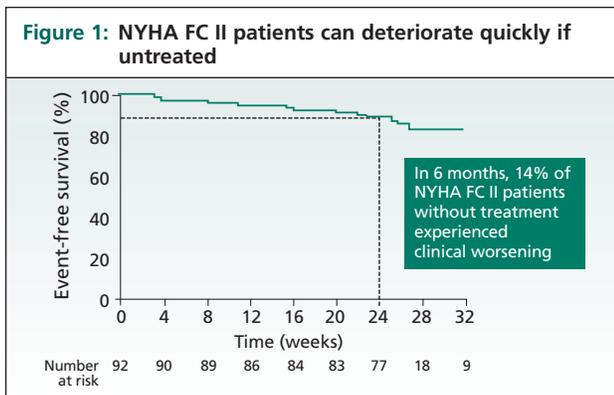
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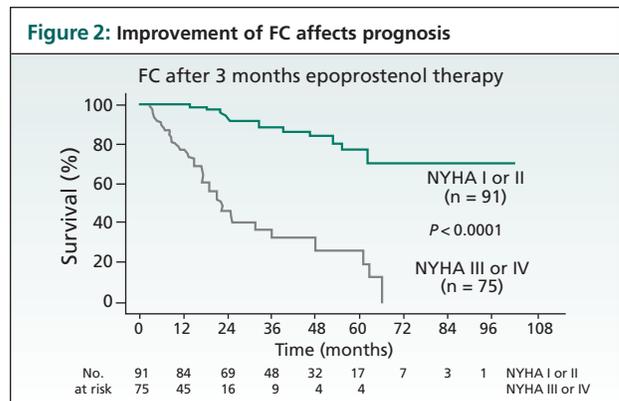
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In addition to earlier initiation of effective therapy, a goal-oriented approach is gaining acceptance for the management of PAH. This approach includes considering the use of agents with potential complementarities and synergistic mechanisms of action, not only in patients with advanced disease who are not responding to monotherapy, but also in less-stable functional class II patients. More clinical studies are needed to determine the best approach in the treat-to-target strategy. For now, it is crucially important to assess the efficacy of treatment by combinations of methods such as exercise capacity, echocardiography, cardiac biomarkers, and right heart catheterization.

### Early detection and intervention in PAH

The Endothelin Antagonist tRial in mildly symptomatic PAH patients (EARLY) study<sup>12</sup> demonstrated the value of early therapeutic intervention in PAH. EARLY is the only randomized, placebo-controlled trial to exclusively enroll a WHO functional class II patient population; it was designed to evaluate the effects of the dual endothelin receptor antagonist (ERA), bosentan, while providing insight into the natural history of PAH, specifically, at the earlier stages. EARLY involved 185 patients who received 6 months of either placebo or bosentan; 29 patients were taking sildenafil at study entry and were permitted to stay on the drug during the trial with assignment in nearly equal numbers to the placebo and bosentan groups. An analysis of baseline characteristics demonstrated that the study patient population was compatible with a functional class II population, since the mean 6-minute walk distance (6-MWD) was 436 m, consistent with data from the French National Registry.<sup>13</sup>

The EARLY trial demonstrated a highly significant reduction in pulmonary vascular resistance ( $P < 0.0001$ ), a co-primary endpoint. There was no statistically significant difference in the other co-primary endpoint, the 6-MWD ( $P = 0.076$ ), which may be a reflection of the relatively well-preserved baseline exercise capacity. However, there was a significant delay in the time to clinical worsening ( $P = 0.0114$ ) in the bosentan-treated group compared with placebo. Moreover, only 3% of the patients treated with bosentan experienced clinical worsening compared with 14% of the patients on placebo (Figure 3). The stabilization of WHO functional class in the bosentan group also supports the conclusion that a delay in disease progression is associated with this ERA treatment.



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Other significant improvements in bosentan-treated patients were found in the levels of the cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) and in the Short Form (SF)-36 Health Survey results, compared with placebo. Additionally, in the subgroup of patients who remained concomitantly on sildenafil, there were also improvements in line with the overall results of the trial. Bosentan exhibited a safety and tolerability profile that was consistent with previous placebo-controlled clinical trials.<sup>14,15</sup> Based on the results of EARLY, bosentan is now approved in Europe, the United States, and Canada for the treatment of PAH in patients with WHO/NYHA functional class II.

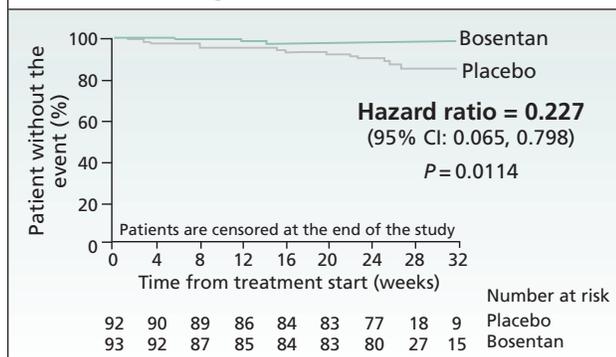
Although EARLY is the only trial to date examining a functional class II patient population exclusively, other studies have included some patients with NYHA functional class II PAH. These studies include the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study,<sup>16,17</sup> the Safety and Efficacy Study of Sitaxentan Sodium in Patients With Pulmonary Arterial Hypertension (STRIDE)-1 and STRIDE-2 with a selective ERA,<sup>18,19</sup> and the Ambrisentan in Patients With Moderate to Severe Pulmonary Arterial Hypertension (PAH), ARIES-1 and ARIES-2 studies with another selective ERA.<sup>20</sup> Unlike EARLY, however, these studies included <40% NYHA functional class II patients and the baseline 6-MWD was on average <400 m revealing that, overall, the patients were in a later disease stage than the patients enrolled in EARLY (Figure 4).

The EARLY study reinforces the importance of the early diagnosis and initiation of therapy in PAH; it is the first clinical trial to demonstrate that clinical worsening can be delayed in mildly symptomatic (NYHA II) PAH patients. Because EARLY was a placebo-controlled trial, it also provided important information about the natural history and the progressive nature of PAH even in minimally symptomatic patients, strongly endorsing early intervention and screening programs in high-risk groups. A program called ItinAIR-Sclérodémie has been implemented for screening throughout France, revealing the effectiveness of this approach.<sup>4</sup>

### Achieving treatment goals in PAH

PAH is a complex disease, but after the fruitful research of recent years, the pathophysiology is much clearer. The prostacyclin, endothelin, and nitric oxide pathways are implicated in

**Figure 3: EARLY: Effect of bosentan on time to clinical worsening<sup>12</sup>**



Reproduced from Galie N et al. *Lancet*. 2008;371(9630):2093-2100, copyright © 2008, with permission from Elsevier. PVR = pulmonary vascular resistance; CI = confidence interval.

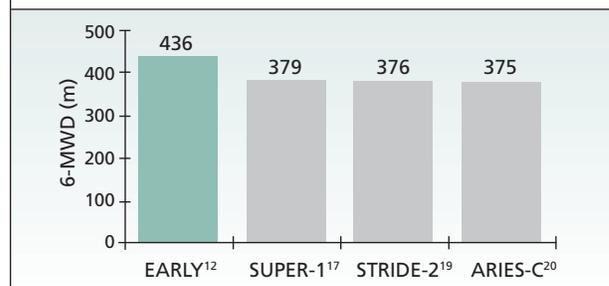
the pathogenesis of PAH and therapies specifically targeting these aspects are the usual first-line treatments for this condition. The dual ERA, bosentan, is indicated as a first-line therapy for NYHA functional class III patients and, following the EARLY trial, the indication was extended to functional class II patients.<sup>8</sup> Other approved PAH therapies in Canada include the ERAs, ambrisentan and sitaxsentan, the phosphodiesterase (PDE)-5 inhibitor, sildenafil, and the prostanoids, epoprostenol, and treprostinil.

The aggressive and unrelenting nature of PAH and the involvement of multiple pathways in its pathogenesis provide a strong rationale for the use of combination therapy involving agents with complementary and synergistic mechanisms of action.<sup>21</sup> Escalating therapy by combining agents is now considered an appropriate option in most patients who continue to exhibit disease progression on monotherapy. The selection of a drug combination must take into account the evidence for the individual agents, including their safety and efficacy. Although combination therapy data are now reported more frequently, further clinical trials are necessary to evaluate the most effective combinations in specific patient populations and to address important issues such as the use of drugs simultaneously or sequentially.<sup>22</sup>

In the management of PAH, a treat-to-target approach for combination therapy is effective and used in many specialized PAH centres. These centres apply goal-oriented algorithms with predefined follow-up parameters to evaluate patient response to therapy and to determine the most appropriate treatment. With an improved understanding of PAH natural history, the impact of functional capacity on survival, and the possible prognostic improvements with current therapies, treatment goals have become more ambitious. Previously, step-up therapy was considered only in PAH patients with evident clinical deterioration, but now the focus is shifting towards achieving and maintaining functional class II.

One example, among several others, of a centre utilizing a goal-oriented treatment algorithm is the Pulmonary Vascular Disease Center at the University of Bologna, Italy. In this centre, patients are assessed prior to the initiation of a new treatment and 3 to 4 months later, using such parameters as predefined goals for functional capacity, exercise tolerance, and hemo-

**Figure 4: Pivotal RCTs in PAH with oral drugs: 6-MWD in NYHA FC II**



RCT = randomized, controlled trial; 6-MWD = 6-minute walking distance.

dynamics. Combination therapy is initiated if the patient does not meet the following criteria: improvement or maintenance of functional capacity to NYHA II, 6-MWD >500 m in patients <55 years of age, cardiac index >2.4 L/min/m<sup>2</sup>, and mean right-atrial pressure <10 mm Hg. Based on this strategy, >40% of the patients treated at this centre are receiving combination therapy. A German centre found that therapy with combinations of bosentan, sildenafil, and iloprost reduced the need for intravenous prostanoids and lung transplantation in NYHA functional class III and IV patients.<sup>23</sup>

### Exploring the evidence for combination therapy

Data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) indicate that bosentan and sildenafil are the most commonly used combination regimen for PAH management.<sup>24</sup> Both drugs are administered orally, avoiding the obvious problems and limitations of intravenous drugs. Additionally, both agents are generally well tolerated and target different pathways. A recent retrospective analysis<sup>25</sup> of PAH patients, who were deteriorating on monotherapy, demonstrated that sequential dual therapy (bosentan + sildenafil in 74%) led to improvements in the 6-MWD, the NYHA functional class, and cardiac hemodynamics after the addition of the second agent. Moreover, these beneficial effects were maintained for 12 months.

The Combination Therapy in Pulmonary Arterial Hypertension (COMPASS) program is a series of studies initiated in 2006 that was designed to specifically evaluate the safety and efficacy of bosentan in combination with sildenafil. COMPASS-1<sup>26</sup> was a multicentre, open-label, prospective study demonstrating that a single dose of sildenafil in PAH patients receiving long-term bosentan led to significant improvements in pulmonary vascular resistance (PVR; 15.2% reduction observed 60 minutes after a 25-mg dose) and total pulmonary resistance (13.3% reduction). COMPASS-2 is a double-blind, placebo-controlled study evaluating the effect on morbidity and mortality of adding bosentan to sildenafil compared with sildenafil alone. This study is the first event-driven trial in PAH with morbidity and mortality as the primary endpoint; recruitment for COMPASS-2 is ongoing worldwide.

COMPASS-3 is an open-label Phase IV study designed to assess whether treatment with bosentan, either as monotherapy or with the addition of sildenafil, improves the 6-MWD after

28 weeks of therapy. This study is also evaluating the utility of magnetic-resonance imaging to assess cardiac remodeling in PAH patients and correlating any improved functional capacity with other parameters. Interestingly, in the subgroup of patients in the EARLY trial who received bosentan in combination with sildenafil there were improvements in PVR similar to those seen in COMPASS-1,<sup>12</sup> in addition, time to clinical worsening exhibited a trend towards improvement compared with patients on sildenafil plus placebo.

Part of another trial, the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST)<sup>27</sup> investigated the effects of combining bosentan with the PDE-5 inhibitor, tadalafil, over 16 weeks. In patients receiving first-line bosentan, the addition of tadalafil 40 mg resulted in a 23 m increase in the 6-minute walk distance compared with the addition of placebo, although this failed to achieve statistical significance.

The combination of bosentan<sup>28-31</sup> or sildenafil<sup>31,32</sup> with prostanoids has also been evaluated. In the placebo-controlled Safety and Pilot Efficacy Trial of Iloprost Inhaled Solution as Add-On Therapy With Bosentan in Subjects With PAH (STEP) trial,<sup>30</sup> the combination resulted in significant improvements in NYHA functional class, mean pulmonary arterial pressure, PVR, and time to clinical worsening. In an open-label extension of STEP, the combination continued to be well tolerated and survival was 97.2% after 1 year.<sup>28</sup>

## Conclusion

It is clear that increasing evidence from clinical trials, registries, and clinical practice in specialized centres support the use of combination therapy in PAH; as a result, it will probably play an increasingly important role in the management of this serious disease and is likely to be reflected in future international treatment recommendations. A goal-driven approach (treating to target) and the use of combination therapy will also increase the likelihood that reaching or maintaining NYHA functional class II becomes an achievable goal for many patients with PAH.

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