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Scientific Update™

Optimizing the Care of Pulmonary Arterial Hypertension: The Importance of Functional Class and the Specific Challenges of Eisenmenger Syndrome

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Pulmonary arterial hypertension (PAH) is a chronic and progressive disease that, if left untreated, eventually leads to right-heart failure and death. One prognostic variable that has a major impact on long-term outcomes in PAH is World Health Organization (WHO) functional class (FC). Patients with PAH in FC I or II at the time of diagnosis fare better than those in FC III or IV, and improvement in FC during therapy is also associated with better prognosis. Eisenmenger syndrome (ES) represents the most compromised clinical groups among patients with PAH associated with congenital heart disease (CHD). ES patients typically have a poor prognosis, particularly if they are left untreated. Improved outcomes for ES patients are being sought through intervention with PAH-specific therapies and both evidence and observational data for their utility in this setting is accumulating. In this issue of *Cardiology Scientific Update*, evidence supporting a prognostic role of FC and the benefit of a goal-directed therapy aiming at improving the FC of these patients will be reviewed. As well, the prognosis of a growing population of patients with ES and the increasingly appreciated advantage of treatment options using PAH-specific therapy in ES patients will be discussed.

Improvement of Functional Class in PAH – the Impact on Long-term Outcomes

PAH is a progressive disease associated with poor prognosis.[1,2] Employing a treat-to-target approach, as recommended in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines,[3] is a crucial strategy to improve patient outcomes. This involves setting a number of treatment goals, assessing patients' response to therapy, and making treatment decisions accordingly. For successful implementation of this strategy, it is essential that parameters with prognostic relevance are used to set treatment goals.

WHO-FC is recommended as a treatment goal,[3,4] as it is a powerful predictor of long-term outcomes in PAH.[1] Recent studies have demonstrated that patients in WHO-FC I/II at baseline have better long-term outcomes than those in FC III/IV.[5-7] These reports include the French registry data on patients with idiopathic, heritable, and anorexigen-associated PAH,[6] as well as data from a retrospective study in ES.[5] In addition to having prognostic relevance as a baseline parameter, change in FC during treatment is reflected in patients' prognosis.[7-9] Recent data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL)[10] have highlighted the impact of change in FC on long-term outcomes.[11] Of the 1082 PAH patients in FC III at enrollment, 26% (n=281) had improved to FC I/II at the first follow-up visit, 66% (n=718) had remained stable in FC III and 8% (n=83) had deteriorated to FC IV (Figure 1). The 2-year Kaplan-Meier survival estimate from the first follow-up visit was statistically significantly better for patients who improved from FC III to FC I/II (88 ± 2%) than for patients who remained in FC III (76 ± 2%) or worsened to FC IV (34 ± 6%; $P<0.001$ for all pairwise comparisons).[11] These data, therefore, demonstrate that patients who achieve FC II on therapy have better long-term outcomes and reinforce the role of FC II as an essential treatment target.

Once appropriate treatment goals have been defined, the ESC/ERS treatment algorithm should be followed with these goals in mind.[3] For FC III patients, initial monotherapy with an endothelin receptor antagonist, a phosphodiesterase-5 inhibitor or a prostanoid is recommended. To determine whether patients are meeting their therapeutic goals, regular reassessment is essential.[3] For patients considered to have an inadequate

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Figure 1: REVEAL Registry: Impact of change in functional class (FC) on prognosis[11]

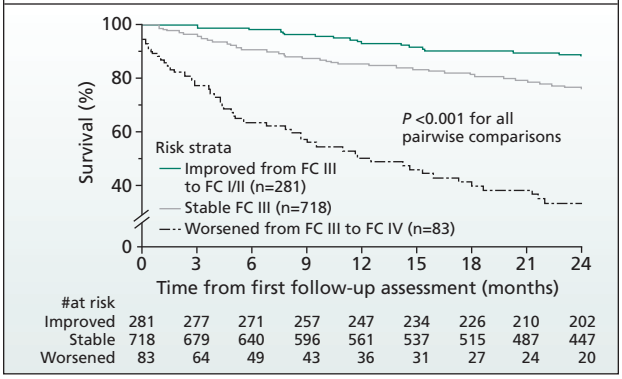

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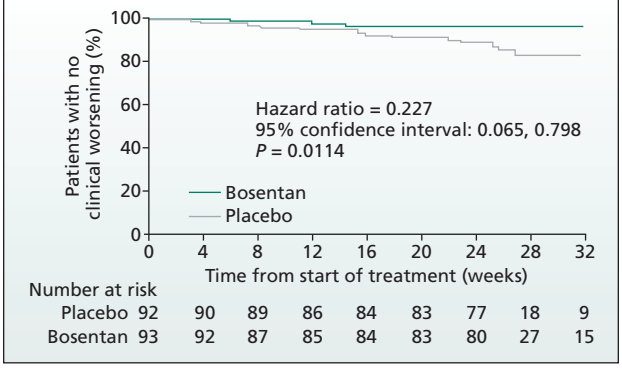
Figure 2: Early intervention with bosentan delay PAH progression



PAH = pulmonary arterial hypertension

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response to therapy, a step-up approach involving sequential combination therapy is recommended.[1] For patients in FC IV, initial treatment with intravenous epoprostenol is recommended and upfront combination therapy may be considered.[3] Improving FC is vital to improve long-term outcomes in PAH. A treat-to-target approach should include FC II as a goal.

FC II – An Achievable Target in PAH

FC is a powerful predictor of long-term outcomes in PAH.[1] Improved prognosis among patients in FC II over those in FC III/IV[2,5,6,12] provides a strong rationale for early detection and timely treatment to maintain patients in FC II. In addition, improvement to FC II during treatment is indicative of a positive outcome.[7,9] FC II is therefore an important goal of the treatment of PAH.

The value of early initiation of therapy was clearly demonstrated in the EARLY trial,[13] a study dedicated to FC II patients. The secondary endpoints of EARLY included the change from baseline in FC and time to clinical worsening as an assessment of PAH progression. Over the 6-month study period, compared with placebo, bosentan treatment was associated with a significantly lower incidence of worsening FC (P=0.0285) and a significant delay in PAH progression (relative risk reduction: 77%; P=0.0114) (Figure 2). Bosentan also significantly reduced pulmonary vascular resistance (co-primary endpoint P<0.0001). The trend towards an increase in 6-minute walk distance (6-MWD; co-primary endpoint P=0.076) possibly reflected the relatively well-preserved exercise capacity of the enrolled population, which may be difficult to improve. The EARLY study showed that FC can be maintained and PAH progression delayed in FC II patients treated with bosentan.

The open-label extension of EARLY investigated the long-term outcomes of initiating bosentan in FC II.[14] In an interim analysis of 157 patients at 3 years, the Kaplan-Meier estimate of survival associated with bosentan therapy was 89.9% (95% confidence interval [CI]: 85.3, 94.4) and 82.9% of subjects experienced no clinical worsening (95% CI: 77.2, 88.6). The mean change in 6-MWD was +7.6 m at 30 months, and WHO FC improved in 20.2% of subjects (n=26) and worsened in 11.6% (n=15).

Despite the clear benefits of early treatment, the reality remains that many patients are diagnosed in FC III/IV. For FC III patients, the goal of FC II may be achieved by treatment according to the ESC/ERS guidelines, including combination therapy where recommended.[3]

In summary, the prognostic relevance of FC II provides a strong rationale for its inclusion as a mandatory treatment target. Early detection and treatment, alongside the use of combination therapy where appropriate, represent key elements in the strategy to achieve FC II.

ES – A Growing Population with a Poor Prognosis

CHD patients are at increased risk of developing PAH.[15] PAH-CHD patients represent a heterogeneous group, classified into 4 clinical subsets,[3] and these clinical groups were reviewed in a previous issue of *Cardiology Scientific Update*.[16] The first subset is ES, the most advanced form of PAH-CHD.[15] ES is defined as CHD that initially causes systemic-to-pulmonary shunts resulting in severe pulmonary vascular changes and PAH, with subsequent reversal of the shunt and the development of cyanosis.[17] For CHD patients with a left-to-right shunt, timely surgical correction of the cardiac defect before the onset of high PVR can prevent or reverse PAH. Patients who do not have surgical repair in a timely fashion may develop ES, with certain cardiac defects carrying a greater risk for progression to ES than others.

The prevalence of CHD is increasing, and there has been a change in the demographics of this population, with a growing number of pediatric patients now surviving into adulthood.[18] As a significant proportion of CHD patients develop PAH,[15] this will translate into an increase in the number of PAH-CHD patients. ES affects approximately 4% of adult CHD patients under follow-up at major international centres.[19] Patients with certain defects are at a greater risk; for example, approximately 50% of

all patients with large unrepaired ventricular septal defects are at risk of developing ES.[20] Once ES develops, reparative surgery is contraindicated. It is crucial that patients have access to available tertiary care and pharmacological therapy, so that they are managed according to the ESC guidelines for grown-up CHD.[21]

The development of ES is associated with poor prognosis, as well as considerable morbidity and poor quality of life.[20] Recent data have shown ES patients to have a 5-year mortality rate of 23.3%,[5] and development of ES in patients with complex CHD is associated with a 10- to 12-fold increase in mortality.[20] Several factors that impact on the prognosis of ES have been identified. The outlook is especially poor for patients in WHO-FC III/IV. In a recent study, the overall 5-year mortality rate for ES was 32.2% for patients in FC III/IV versus 14.1% for patients in FC I/II (P=0.006).[5] While the mortality rate is significantly higher for patients in FC III/IV, it is important to note that it is considerable even in FC II patients.

Other predictors of increased mortality in ES include history of arrhythmia, younger age at presentation, and right-ventricular dysfunction.[19,22-24] In addition, the survival prospects of ES patients with complex anatomy are significantly poorer than for patients with simple underlying cardiac lesions. Another very important factor that influences outcomes in ES is the use of PAH-specific therapies. A recent long-term study found that cumulative mortality in ES was significantly higher in those patients who were not on PAH-specific therapies, indicating their important role in ES.[5] As the understanding of the prevalence and natural history of ES improves, it becomes increasingly clear that one must act to improve the outlook for patients with this severe condition.

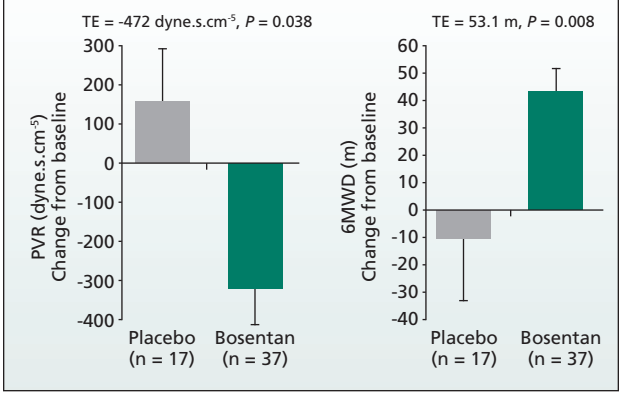
ES – Treatment Options with PAH-specific Therapies

As structural abnormalities of the pulmonary vasculature in ES are similar to those in other forms of PAH,[20] targeted PAH-specific therapies have been investigated in ES and represent an important treatment option for this population. Among PAH-specific therapies, the dual endothelin-receptor antagonist (ERA) bosentan is the only oral therapy with data derived from a randomized, placebo-controlled study in ES. In the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) study,[25] bosentan significantly reduced pulmonary vascular resistance and markedly increased 6-MWD, without compromising peripheral oxygen saturation (Figure 3). BREATHE-5 illustrated that ES patients can benefit from bosentan, and based on these data, bosentan is the only approved treatment for PAH associated with congenital systemic-to-pulmonary shunts and ES in WHO-FC III. In addition, the ESC/ERS guidelines recommend bosentan as first-line therapy for ES patients (class I, level B) (Table 1).[3]

Data from other PAH-specific therapies, such as the prostanoids, are limited to case reports and small studies.[20,26] Experience from phosphodiesterase-5 inhibitors and the ERA ambrisentan have also been gained from relatively small-scale studies.[20,27,28] Randomized, placebo-controlled trials are needed to validate these encouraging preliminary results.[3]

The long-term impact of advanced therapies (AT) in ES has recently been evaluated.[5] Patients were started on bosentan (73.5%), sildenafil (25%), or epoprostenol (1.5%); the use of AT was associated with significantly lower all-cause mortality in this population, as estimated by Cox regression analysis. Of

Figure 3: BREATHE-5: Reduced PVR and increased 6-MWD following bosentan



PVR = pulmonary vascular resistance; 6-MWD = 6-minute walk distance; TE = treatment effect

Adapted from Galiè N, et al. *Circulation*. 2006;114:48-54.

Table 1: Recommendation: PAH associated with congenital cardiac shunts

	Class	Level
The ERA bosentan is indicated in WHO-FC III patients with ES	I	B
Other ERAs, phosphodiesterase type-5 inhibitors and prostanoids should be considered in ES patients	IIa	C
In the absence of significant hemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C
The use of supplemental oxygen therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the hematocrit is >65%	IIa	C
Combination therapy may be considered in ES patients	IIb	C
The use of calcium channel blockers is not recommended in ES patients	III	C

ERA = endothelin-receptor antagonist; WHO-FC = World Health Association functional class; ES = Eisenmenger syndrome

Reprinted from Galiè N, et al. *Eur Heart J*. 2009;30:2493-2537.

52 patients who died during the study, only 2 were receiving AT, indicating that AT has long-term benefits in ES.

Conclusion

In PAH, including PAH-CHD, the use of combination therapy for patients who respond inadequately to monotherapy (ie, who do not achieve their treatment goals) is recommended in the ESC/ERS guidelines.[3] Although published data are relatively limited, there is growing evidence from expert centres that combination therapy may be beneficial. Observation of clinical practice shows that PAH-specific therapies are increasingly used in ES. The outlook for ES patients is likely to improve further as the focus for management turns to a treat-to-target approach in this population.

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