The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension

Sean Gaine[1] and Gérald Simonneau[2]

Affiliations: [1]National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital, Dublin, Ireland. [2]Service de Pneumologie, Hôpital Universitaire de Bicêtre, Université Paris-Sud, Le Kremlin Bicêtre, France.

Correspondence: S. Gaine, National Pulmonary Hypertension Unit, Mater Misericordiae Hospital, Eccles Street, Dublin 7, Ireland. E-mail: sgaine@mater.ie

ABSTRACT Assessment of change in exercise capacity using the 6-min walk distance (6MWD) test has been the primary end-point in the majority of pulmonary arterial hypertension (PAH) clinical trials. The 6MWD has some advantages as an end-point in such studies. It is simple and inexpensive to perform, reproducible and validated. In short-term studies with small patient numbers, as is typical in a rare disease like PAH, using change from baseline in 6MWD as the primary outcome measure demonstrated statistically significant differences between placebo and study drugs, leading to their approval. However, there have been increasing calls for clinical trials to employ primary end-points that reflect long-term disease progression and morbidity. While the 6MWD was initially considered to be a potentially reliable surrogate for disease progression in PAH, there is increasing evidence that this is not necessarily the case. Given this, there is a need to re-examine the role of 6MWD in PAH trials, and to evaluate the evidence supporting whether there is a need to move from 6MWD to more robust measures of clinical outcomes, such as morbidity and mortality. However, in the clinic the 6MWD test, alongside symptoms, haemodynamics and biomarkers, remains a useful tool in the assessment and management of PAH patients.

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We need to consider more robust measures of outcomes than 6MWD in clinical trials in PAH, such as morbidity and mortality http://ow.ly/puyGI

Introduction

Over the past two decades, the treatment options for patients with pulmonary arterial hypertension (PAH) have advanced considerably with the approval of a number of effective PAH-specific drugs. In the registration trials of these agents, the most commonly used primary end-point was change in the 6-min walk distance (6MWD). The 6MWD test was employed as the primary efficacy measure in the first pivotal trial of a PAH-specific therapy, epoprostenol [1], based on the requirement of the US Food and Drug Administration (FDA) that the end-point should be a measure of either a patient's symptoms, exercise capacity or survival, rather than the original proposal of haemodynamic change [2]. As the study sponsor was unwilling to use survival as an end-point due to the required length of such a study, and they considered functional class to be too subjective a measure, exercise capacity was chosen. The 6MWD test, which had been introduced as a clinical tool for lung disease, was selected over the treadmill test by preference of the study's Steering Committee [2].

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The successful use of the change in 6MWD as a primary end-point in the first pivotal PAH trial paved the way for its use as a primary end-point and indicator of symptom change in registration trials for other PAH medications. Subsequently, change from baseline in 6MWD was used as the primary outcome measure in the short-term pivotal trials of bosentan, ambrisentan, sildenafil, tadalafil and treprostinil, and demonstrated statistically significant improvements in 6MWD in patients treated with the study drug compared with placebo [3–8]. However, as the field of PAH has advanced, the utility of 6MWD as a primary end-point in PAH trials has been challenged in recent years.

Primary end-points for clinical trials in PAH, as in any randomised controlled trial, should meet a number of criteria. They should be well defined and reliable, readily measurable and interpretable, sensitive to the effects of the intervention, and clinically meaningful [9, 10]. The FDA divides end-points into direct and surrogate categories [11]. Direct end-points are defined as clinically meaningful end-points that directly measure how a patient feels, functions or survives. Surrogate end-points are substitute measures, where changes induced by therapy on a surrogate marker reliably reflect changes in a clinically meaningful end-point and also capture the net treatment effect on the clinical outcome. The surrogate should be involved in the pathophysiological pathway that results in the clinical outcome and targeted by the intervention [12].

By measuring the distance a patient can walk, the 6MWD test can indirectly quantify shortness of breath and fatigue, two of the most common symptoms of PAH. Therefore, the change in 6MWD from baseline following an intervention indicates symptomatic improvement over that time-period. This change manifests in improvements in a patient's ability to perform day-to-day activities, and is correlated with improvements in their quality of life [13]. These improvements are naturally important to clinicians and patients and, as such, the 6MWD is a useful metric in both trials and in the clinic.

There are many advantages to using 6MWD as an end-point in clinical trials; it is a simple, inexpensive, reproducible tool that, in patients with idiopathic PAH at least, is a validated measure of exercise capacity and is accepted by the regulatory authorities for the registration of PAH drugs. Additionally, there is extensive experience with the 6MWD in idiopathic PAH and PAH associated with connective tissue disease. While 6MWD was a useful primary end-point when the study and assessment of drugs for PAH was relatively new, in today's more advanced field, disadvantages are emerging. For example, a ''ceiling effect'' in 6MWD may mask efficacy in patients with less severe symptomatic disease who have high baseline walk distances but, nevertheless, may have substantial pathology [14]. This phenomenon was observed in the bosentan trial in World Health Organization (WHO) functional class II PAH patients [15]. The specificity of 6MWD as a measure of exercise capacity can also be confounded, especially at low walk distances, by reasons not related to PAH. For example, in a patient with scleroderma, walk distance might be compromised as a result of frailty and other comorbidities. Deconditioning, *i.e.* loss of muscle tone and endurance, can also occur in chronically ill patients and affect the distance a patient is able to walk.

Furthermore, 6MWD results cannot be fully reliable if patients are already on a background therapy that may have already improved their exercise capacity to the point at which additional treatment may not provide further gains [16]. This effect was shown in a retrospective analysis of data from the Pulmonary Hypertension Response to Tadalafil (PHIRST) trial, where patients treated with tadalafil in conjunction with background therapy showed a more modest increase in 6MWD than treatment-naïve patients who received tadalafil alone [17]. This latter consideration is particularly important given that many new agents will be tested as ''add-on'' therapy in patients on background therapy with currently available PAH-specific drugs [18]. In such trials, there is a need to employ primary end-points that can measure additional treatment effects of new agents in the presence of background therapy.

Another consideration with 6MWD as a primary end-point in PAH trials is its association with long-term outcomes. It would seem a reasonable assumption that improvements in exercise capacity would be reflected in improvements in longer term outcomes, and that patients with greater improvements would have greater benefits. However, although 6MWD is undoubtedly a clinically important end-point in its own right as a measure of symptomatic improvement in PAH, its validity as a surrogate end-point for long-term outcome is less certain. This review will examine this evidence and re-examine the role of 6MWD in PAH trials in an era where there is a need to employ primary end-points that reflect long-term disease progression.

Relationship between 6MWD and long-term outcomes

There are three 6MWD parameters that have been assessed for their association with post-treatment outcomes in PAH: 1) the absolute 6MWD at baseline; 2) the absolute 6MWD at a predefined time-point post-treatment initiation; and 3) change in 6MWD from baseline to a predefined time-point post-treatment initiation. It has become clear that not all these parameters are equally valid as prognostic indicators.

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Absolute 6MWD at baseline before therapy and outcome on therapy

Early indications that the distance walked at baseline could affect outcome came from the first pivotal PAH trial of epoprostenol [1]. The eight patients, all on conventional therapy, who died during the course of the 12-week study had a significantly lower mean baseline 6MWD than the 73 patients who were alive at the end of the study (195 m *versus* 305 m; $p<0.003$). A strikingly similar result was observed many years later in the Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES) clinical trial of epoprostenol and add-on sildenafil therapy. The mean baseline 6MWD of the seven patients who died during the 16-week study was 182 m *versus* 354 m for the overall study population [19].

Analyses of survival data stratified by the median distance walked at baseline from patient cohorts in Japan and France have provided strong supportive data of an association between prognosis and baseline 6MWD [20–22]. Survival rate for patients on prostacyclin therapy from a single centre in Japan was significantly better in those whose baseline 6MWD was $\geqslant$332 m ($p<0.001$) [20]. Similarly, for patients treated with bosentan in a single centre in France, there was a significant difference in survival ($p=0.002$) based on a baseline 6MWD of >330 m *versus* <330 m [21]. Univariate analysis of data from a cohort of 178 French patients treated with epoprostenol from 1992 to 2001 put the increased risk of death at 2.2-fold in patients who had a 6MWD of $\leqslant$250 m at baseline *versus* those who could walk >250 m [22]. Data from more contemporary patients from the French PAH National Registry also demonstrated a significant association between absolute baseline 6MWD and survival in both single and multivariate analyses [23].

A visual (fig. 1) and analytical demonstration of association between baseline 6MWD and long-term outcomes has been provided by MACCHIA *et al.* [24] in their meta-analysis of 16 randomised trials in PAH including almost 2000 patients. They demonstrated a significant association between mean 6MWD at baseline and fatal events during follow-up and noted a progressively worse prognosis, particularly in patients with a baseline 6MWD <330 m.

The baseline 6MWD cut-off for stratifying groups in order to examine survival has been ~330 m in the majority of analyses and the results demonstrating an association have been consistent. The cut-off used in data analysis clearly affects the interpretation of results. Analysis of data from the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicentre, Efficacy Study (ARIES) study with ambrisentan showed that an absolute 6MWD at baseline of <250 m was associated with a mortality risk of ~50% at 2 years, while patients above this cut-off had an 8% risk of death [25]. However, 250 m is a very low threshold for 6MWD. Therefore, it is not unexpected that this group of patients had a poorer outcome. When this threshold was raised, there was very little difference in risk of death between patients with a baseline value of >288 m and those with a baseline of >415 m.

An association between a baseline threshold for 6MWD and survival may be more difficult to determine in patients with scleroderma given that their walk distance may be compromised, not due to severity of PAH but due to their age and other comorbidities.

Absolute 6MWD reached after therapy and outcome of therapy

Although there are fewer data than for baseline 6MWD, there is evidence that absolute 6MWD reached following therapy may have prognostic relevance [21, 22, 25]. In the long-term study of the 178 patient

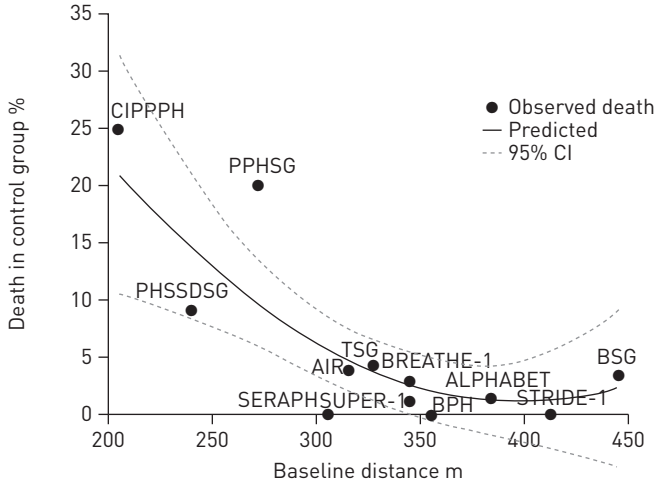

FIGURE 1 Relationship between the mean 6-min walk distance at baseline and the rate of fatal events during follow-up. Reproduced from [24] with permission from the publisher.

cohort discussed above [22], those whose 6MWD was ⩾380 m after 3 months of epoprostenol therapy had significantly better survival than patients who did not reach this threshold. Similarly, in the French single centre study by PROVENCHER *et al.* [21], patients who reached a threshold of >378 m (the median for the study) after 4 months of bosentan monotherapy had significantly better survival compared with patients who could not walk that distance (fig. 2). Survival rates for patients with a 6MWD value >378 m after 4 months were 100%, 100% and 90% at 1, 2 and 3 years, respectively, as compared with 85%, 79% and 69%, respectively, for patients with a value <378 m (p=0.005) [21]. In ARIES, patients who reached a 6MWD >323 m after 12 weeks of ambrisentan therapy had a reduced risk of death at 2 years, as evaluated in the open-label extension phase compared with those who did not reach this threshold (p<0.001). However, 6MWD after 12 weeks of therapy was no better at discriminating outcome than baseline values in this cohort [25]. In a retrospective analysis of patients included in trials of subcutaneous treprostinil, although on-treatment 6MWD did not linearly correlate with survival, a 6MWD of ⩽295 m at week 12 was associated with a marked decrease in patient survival at 3 years [26]. Although data from these studies suggest that absolute 6MWD following treatment may be prognostic, no single absolute value has been independently validated in a long-term study. Therefore, the optimal target threshold that physicians and patients need to aim for to improve long-term prognosis remains unknown.

Change in 6MWD from baseline after therapy and outcome

Although most clinical trials in PAH have used change in 6MWD to assess response to therapy over time, there appears to be little evidence to suggest it is associated with long-term outcomes. Initial indications came from the epoprostenol long-term study, where post-treatment absolute 6MWD was found to be prognostic of survival, yet patients who improved their 6MWD by ⩾112 m between baseline and after 3 months of epoprostenol therapy had no difference in survival compared with patients who did not [22]. Later studies also showed a discord between observed change in 6MWD and clinical outcome, where significant increases in 6MWD were not necessarily associated with significant improvements in measures such as time to clinical worsening [5, 6, 27]. Conversely, in the EARLY study of bosentan, a significant effect on time to clinical worsening was observed without a statistically significant change in 6MWD [14]. This may be related to the ceiling effect observed with 6MWD in patients who already have high 6MWD, as was the case in this study.

Systematic reviews and meta-analyses of randomised trials in PAH-specific therapies have shown that absolute changes from baseline in 6MWD do not predict a survival benefit [24, 28] or incidence of clinical events [29]. In their meta-analysis of data from 16 short-term (12–16 week) randomised PAH trials, MACCHIA *et al.* [24] showed that, although treatment overall was associated with a significant improvement in 6MWD, there was no association between change in 6MWD and risk of death in the short term. This was confirmed in a later meta-analysis by the same group which included an additional 10 trials published subsequent to the initial analysis. In this updated analysis it was again shown that improvements in survival during the course of the short-term studies bore no relationship to change in 6MWD [28].

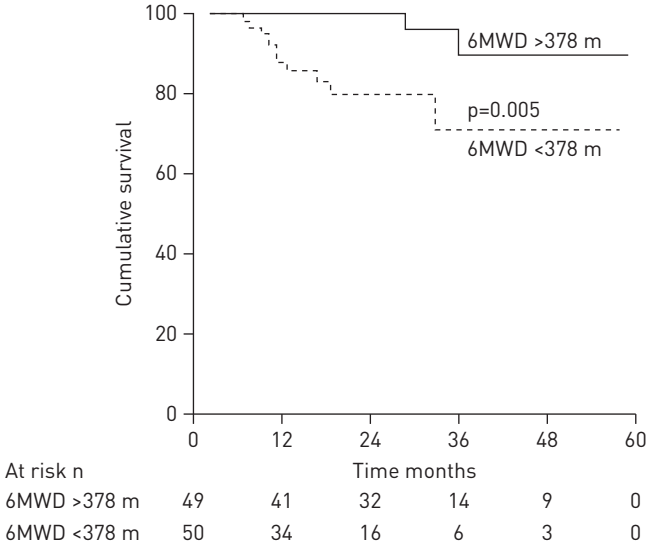

FIGURE 2 Kaplan–Meier survival estimates in patients with pulmonary arterial hypertension stratified by median 6-min walk distance (6MWD) after 4 months of bosentan monotherapy. Reproduced from [21] with permission from the publisher.

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As well as having no association with survival, change in 6MWD appears to be unrelated to clinical events. In a meta-analysis of 22 short-term randomised controlled trials including over 3000 patients, all included studies showed significant treatment-associated reductions in all-cause mortality, hospitalisation for PAH and/or lung or heart–lung transplantation, initiation of PAH rescue therapy, and in a composite outcome including all these individual parameters. However, no relationship was found between the change in 6MWD and the composite end-point or its individual components (fig. 3) [29]. In an analysis of 10 randomised controlled trials, placebo-corrected change from baseline in 6MWD was found to be related to treatment and clinical outcome, but explains only 22% of the treatment effect [30]. This latter analysis also investigated whether a threshold effect existed for change in 6MWD above which higher values reliably predict superior clinical outcomes. The authors found that 41.8 m was the minimal change in 6MWD corresponding to a statistically significant reduction in clinical events [30]. The authors also found that this threshold decreased to 25.7 m if data from the PHIRST study, which was the only study to allow concomitant background therapy, were removed from the analysis [30]. These findings suggest that trials examining new agents in the context of background therapy may need to produce larger differences in change in 6MWD to provide confidence that the results correspond to differences in clinical outcomes. However, given that 6MWD did not reflect the full effects of intervention in this analysis, the authors conclude that it has only modest validity as a surrogate end-point for clinical events, and may not be sufficient as a sole surrogate marker of outcome [30].

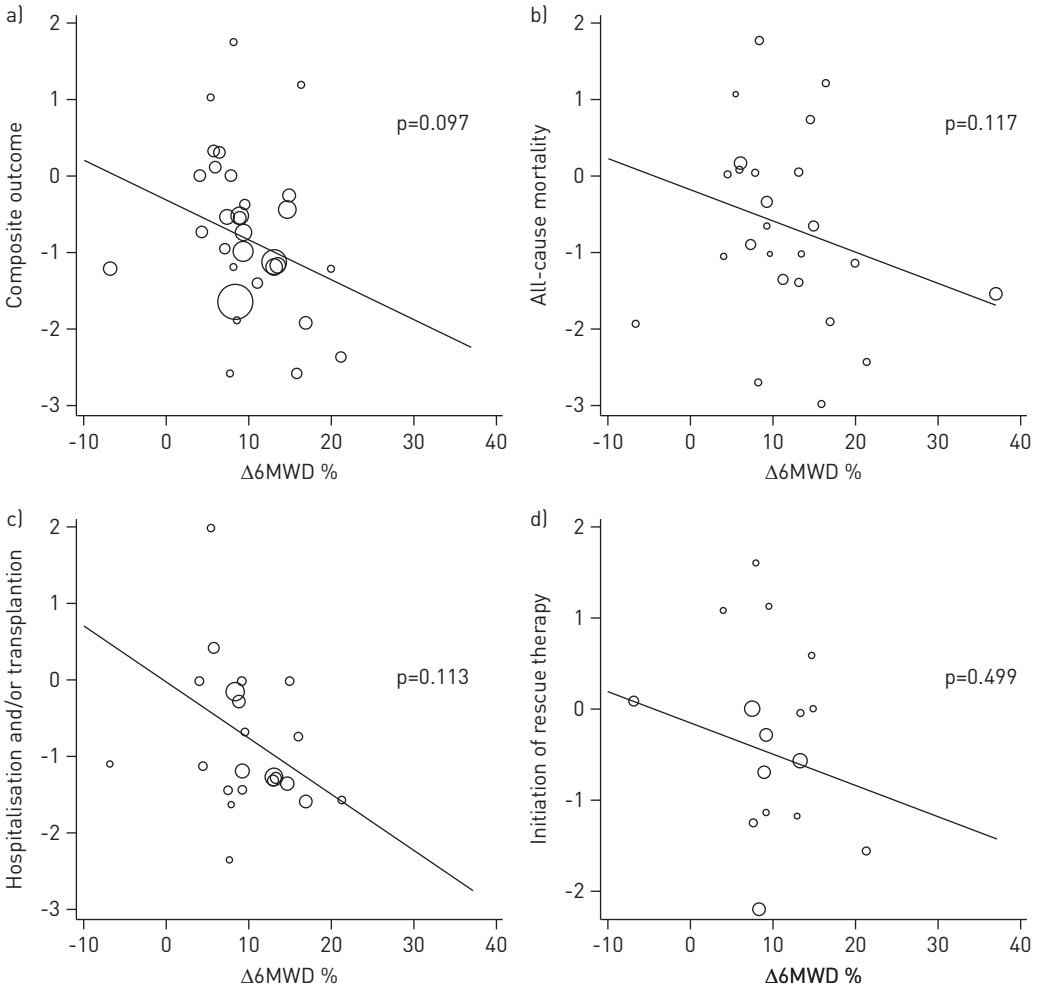
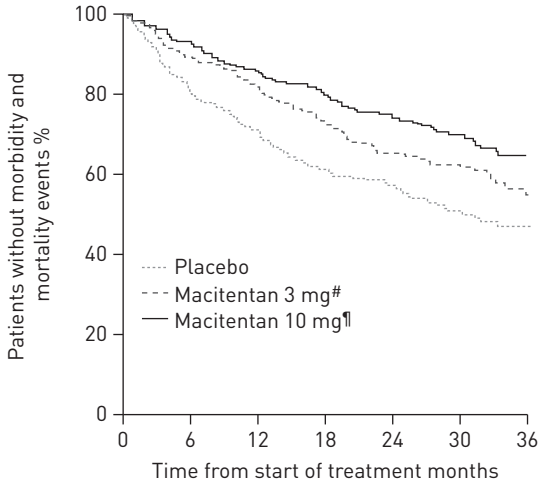


FIGURE 3 Relationship between change in 6-min walk distance (Δ6MWD) and a) composite outcome, b) all-cause mortality, c) hospitalisation for pulmonary arterial hypertension and/or lung or heart–lung transplantation, and d) initiation of pulmonary arterial hypertension rescue therapy. Reproduced from [29] with permission from the publisher.



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Placebo	250	188	160	135	122	64	23
Macitentan 3 mg	250	213	188	166	147	80	32
Macitentan 10 mg	242	208	187	171	155	91	41

FIGURE 4 Effect of macitentan on morbidity and mortality. #: risk reduction 30%, hazard ratio 0.70, p=0.01. ¶: risk reduction 45%, hazard ratio 0.55, p<0.001. Reproduced from [31] with permission from the publisher.

Use of a composite primary end-point consisting of morbidity and mortality events as an alternative to 6MWD

Recommendations have been made suggesting that new PAH drugs should be investigated in long-term trials using clinically relevant outcomes, such as morbidity and mortality events [9]. Events considered appropriate would include all-cause mortality, hospitalisation, initiation of new therapy and PAH worsening, with time to their first occurrence being assessed. As PAH worsening tends to drive treatment effect compared with stronger measures such as death or hospitalisation, which rarely occur as the first event, it should be well defined. Ideally, at least two separate criteria should be included in the definition of PAH worsening, such as decline in 6MWD from baseline and worsening WHO functional class. All events should undergo blind, independent adjudication by an expert committee to ensure robustness of the data. Furthermore, the trials should be long enough in duration and large enough to enable enough events to occur to allow adequate statistical powering of the study. Recommendations to use morbidity and mortality as a primary end-point, with the use of a uniform definition and independent adjudication, have been made previously [9]. These recommendations have been considered and implemented in the recently completed Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial of macitentan [31]. In SERAPHIN, 3 mg and 10 mg of macitentan were shown to significantly reduce the risk of morbidity and mortality events by 30% and 45%, respectively, when compared with placebo (fig. 4) [31]. Statistically significant improvements with macitentan were also observed for 6MWD after 6 months of therapy. Patients on 3 mg and 10 mg of macitentan walked an average of 16.8 m and 22 m more, respectively, than patients who received placebo. The success of this study demonstrates that such trials are feasible in PAH. Other long-term morbidity and mortality trials are also underway, including the Prostacyclin Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) trial of selexipag, an oral selective IP receptor agonist [32, 33]. It is likely that event-driven trials will become a requirement for approval of new PAH therapies, and that the use of 6MWD as the primary end-point in PAH registration trials has drawn to a close. That being said, there is still a place for 6MWD as a primary end-point in trials of subpopulations of PAH patients such as congenital heart disease, where morbidity and mortality studies are not feasible.

Conclusions

The use of the 6MWD as a primary end-point measuring symptomatic improvement has been instrumental to much of the progress that has been made over the past 20 years in PAH drug development. It has been the most commonly used primary end-point in clinical trials conducted for regulatory approval of therapies in patients with PAH. However, PAH is a chronic, progressive, functionally debilitating disease, and the prognostic relevance of 6MWD to long-term outcomes is questionable. While absolute distance walked at baseline and after therapy may have some prognostic relevance, change from baseline 6MWD does not. Consequently, data from a large number of studies show that the change from baseline in 6MWD is not a suitable predictor of clinical worsening or mortality and therefore outcome trials should be performed in

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PAH. Despite its limitations in clinical trials, it is important to remember that, in conjunction with symptom monitoring, functional class assessment, haemodynamic parameters and biomarkers, the 6MWD test plays a key role in the evaluation and management of patients with PAH.

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