

Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance



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KEYWORDS:

6-minute walk distance;
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BACKGROUND: Clinical studies of pulmonary arterial hypertension have used the change in the 6-minute walk distance (6MWD) as a clinical end point; however, its association with survival outcomes has not been well established. In this analysis, we examined the prognostic value of the baseline 6MWD, absolute thresholds of the 6MWD, and change in the 6MWD.

METHODS: Patients in the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) with 6MWD at enrollment, with or without a follow-up assessment within the first year of observation, were included. Kaplan-Meier survival estimates were computed for sub-sets with baseline 6MWD results that were above or below all possible thresholds and for sub-sets with a change in the 6MWD that was 10 percentage points above or below all possible thresholds, including improvement thresholds and worsening thresholds. Multivariable Cox regression models assessed the effect of improvement and worsening in the 6MWD on 1-year survival, adjusted for baseline factors.

RESULTS: One-year survival estimates were higher for patients with a baseline 6MWD above vs below a threshold, although no specific threshold was more prognostic than another. In a model adjusted for the baseline 6MWD and risk score, worsening of the 6MWD over time significantly predicted decreased survival, but improvement in the 6MWD did not affect survival.

CONCLUSIONS: No 6MWD improvement threshold carries particular prognostic value. Improvement in the 6MWD was not associated with survival, but worsening of the 6MWD was strongly and significantly associated with poor prognosis.

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The 6-minute walk test measures exercise tolerance.¹ The distance covered during a 6-minute walk (6MWD) is an indicator of the ability to perform activities of daily life. This, along with observations that exercise tolerance

predicts treatment effect in clinical studies of cardiovascular disease,² has led to the acceptance of the 6MWD as an unvalidated surrogate of survival outcomes in studies of pulmonary arterial hypertension (PAH). Similarly, a 15% decrease in the 6MWD coupled with other clinical markers or biomarkers suggesting deterioration has been included in definitions of “time to clinical worsening” end points.³ Improvement in the 6MWD has also been equated with improved quality of life.⁴ Although the use of the 6MWD as

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a surrogate end point has allowed shorter, smaller clinical studies in PAH,⁵ the use of the 6MWD as a surrogate of survival outcomes has not been fully validated.

Most studies of the 6MWD in PAH have found a relationship between the baseline 6MWD and mortality and survival^{6–10}; other studies have not.¹¹ Some studies have found a specific 6MWD threshold (e.g., 380 or 440 m) to predict survival, but these were not randomized, controlled studies, and the numeric value of the walk was actually the mean walk achieved in the open-label patients that were studied.^{6,12} Evaluation of the percentage-predicted 6MWD¹³ found it was no more predictive than the absolute 6MWD.¹⁴ Change in the 6MWD has not been shown to predict survival,¹⁵ largely because individual clinical studies have not been designed to evaluate mortality and survival. Improvement in the 6MWD of ≥ 41.8 m was recently found to correlate with lowered odds of a clinical event at 12 weeks, but this accounted for only 22% of the treatment effect, suggesting that change in the 6MWD alone is at best a modestly valid surrogate end point for clinical events.¹⁶ Thus, current data suggest that the 6MWD has prognostic value at baseline but that the value of this parameter alone as a marker of clinical status beyond baseline may be limited.

Currently available studies that have examined change in the 6MWD have focused primarily on mean change and not on absolute increases or decreases in the 6MWD; that is, the relative value of improving or worsening. Nevertheless, clinicians continue—without substantiation—to rely on this parameter as a surrogate for survival in patients with PAH.¹⁵ Furthermore, studies have historically emphasized improvement in the 6MWD as the primary end point, whereas deterioration of the 6MWD has had only limited use as a component of a composite worsening end point.³

The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) is the largest multicenter, observational United States–based registry of patients with PAH established to date.¹⁷ A primary objective of REVEAL is to characterize the clinical features and outcomes of patients with PAH currently under care at PAH centers. In this report, data from REVEAL were used to evaluate the prognostic value of baseline 6MWD values and change in the 6MWD over time to gain insight into the clinical significance of absolute increase vs decrease in the 6MWD. Specifically, we examined the prognostic value of the baseline 6MWD, absolute thresholds of the 6MWD, and change in the 6MWD.

Methods

Study design and patients

The design of REVEAL, including inclusion and exclusion criteria, has been described previously.¹⁷ Briefly, REVEAL is an observational, prospective registry involving 55 university-affiliated and community hospital–based PAH centers in the United States. Patients who met the modified World Health Organization (WHO) definition for Group 1 pulmonary hypertension¹⁸ and expanded hemodynamic criteria (mean pulmonary arterial pressure [PAP] > 25 mm Hg at rest or > 30 mm Hg with exercise; mean pulmonary capillary wedge pressure [PCWP] or left

ventricular end-diastolic pressure of ≤ 18 mm Hg, measured contemporaneously with PAP; pulmonary vascular resistance of ≥ 240 dyn \cdot s \cdot cm⁻⁵) were enrolled consecutively from March 2006 through December 2009.

The Institutional Review Board of each participating center reviewed the protocol, and all participants or their legal guardians provided written informed consent before study entry. The data download for this analysis occurred on February 4, 2013, and included patients meeting expanded as well as traditional, hemodynamic criteria.

Data collection

Demographics, medical history, PAH-specific and concomitant medications, diagnostic procedures, pulmonary function tests, the 6MWD, and hemodynamics were collected at the baseline assessment. Data collected retrospectively included time of diagnosis and symptom onset, specialty of evaluating physicians, tests used to diagnose PAH, WHO Group I classification, and use of PAH-specific medications. After meeting enrollment criteria, no tests or study visits were required, but data were collected prospectively every 90 days, including PAH treatments, concomitant treatments, diagnostic procedures, and outcomes.

Analytic cohort

For this analysis, REVEAL patients were included if they had WHO Group I PAH, were aged ≥ 18 years at enrollment, had PCWP of ≤ 15 mm Hg, and met the right heart catheterization criteria at rest. Further selection criteria included an available 6MWD measure at enrollment (also referred to as “baseline 6MWD”), and for analyses examining change in the 6MWD, a follow-up 6MWD measure within 12 months of enrollment. As a sensitivity analysis, the population was further restricted to newly diagnosed patients for the evaluation of the prognostic importance of change in the 6MWD.

Statistical analysis

Baseline demographic and clinical characteristics are summarized using percentages for categorical variables and means \pm standard deviation for continuous variables and summarized for patients with the baseline 6MWD only and patients with baseline and follow-up 6MWD results. Pearson’s correlation was used to evaluate associations between the 6MWD and other variables at enrollment.

Kaplan-Meier estimates were computed for patient sub-sets with 6MWD results that were above, below, or at specified 6MWD thresholds (< 165 m; 165–440 m; > 440 m), which have shown prognostic value in the 19-variable REVEAL Risk Score, an algorithm that predicts 1-year survival in PAH patients.¹⁹ All possible above and below thresholds were considered, such that the 1-year Kaplan-Meier estimate at a given threshold could be plotted against the threshold. The above and below estimates are similar to the points that would be plotted on a receiver operating characteristic (ROC) curve, except that a time-to-event outcome is used instead of a simple binary outcome. Unlike an ROC analysis, this approach could be extended for specific bandwidths of interest (e.g., ± 10 percentage points for change in the 6MWD), where all possible midpoints are considered. The resulting plots are similar to moving averages, except that the value on the y-axis is a Kaplan-Meier estimate instead of a simple average (this is also similar to a kernel smoother where a uniform distribution is used as the kernel instead of a more complex function). In this way, each point on the

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