CHEST

# Effect of Age on Phenotype and Outcomes in Pulmonary Arterial Hypertension Trials

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**BACKGROUND:** In recent years, the population of patients with pulmonary arterial hypertension (PAH) has changed dramatically, including more advanced age at diagnosis. We hypothesized that older patients have a distinct clinical profile with different disease characteristics and response to intervention.

**METHODS:** All previously published treatment studies for PAH conducted by United Therapeutics including seven randomized, placebo-controlled trials and one extension study were included and analyzed to assess the association of age with various demographic, functional, hemodynamic, and outcome variables.

**RESULTS:** A total of 2,627 patients across three age groups were included: ≤ 50 (n = 1,438, 54.7%), 51 to 64 (n = 780, 29.7%), and ≥ 65 years (n = 409, 15.6%). In comparison with the youngest group, the oldest age group had higher proportions of connective tissue disease-associated etiology (range across the studies, 27%-49% vs 13%-21%), higher proportions of New York Heart Association Functional classes III and IV (74%-91% vs 57%-84%), shorter baseline 6-min walk distance (6MWD) (261-316 vs 335-371 m), better hemodynamic measurements including lower baseline mean pulmonary artery pressure (48-51 vs 58-63 mmHg), and smaller changes in 6MWD from baseline to endpoint (−5.6 to 24 vs 14-43 m). Age remained associated with change in 6MWD when adjusting for covariates in multivariate analyses.

**CONCLUSIONS:** For the first time, using data from large randomized controlled trials, this study characterizes the different phenotype and outcomes of older patients with PAH, which includes different disease etiology, diminished functional status, and decreased response to intervention. This may have significant implications for the management of this patient population and design of future therapy trials. CHEST 2016; 149(5):1234-1244

**KEY WORDS:** age; outcomes; pulmonary arterial hypertension; pulmonary hypertension

**ABBREVIATIONS:** 6MWD = 6-min walk distance; COMPERA = Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD = connective tissue disease; ERA = endothelin receptor antagonists; FREEDOM-C (F-C) = Oral Treprostinil in Combination With an ERA and/or PDE-5I for the Treatment of PAH; FREEDOM-C2 (F-C2) = Efficacy and Safety of Oral UT-15C Tablets to Treat Pulmonary Arterial Hypertension; FREEDOM-M (F-M) = Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PDE-5I = phosphodiesterase type 5 inhibitors; PH = pulmonary hypertension; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; PVR = pulmonary vascular resistance; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; SC-TRE = Subcutaneous Infusion of Treprostinil in Patients with PAH; S+T = SC-TRE and TRUST; TRIUMPH = Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension; TRUST = Study of Intravenous Remodulin in Patients in India with PAH; WHO = World Health Organization

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Pulmonary arterial hypertension (PAH) is a progressive pulmonary vasculopathy that can lead to right ventricle failure and death.[1] Over the past three decades, several treatments have received Food and Drug Administration approval for the treatment of PAH. Unfortunately, the prognosis remains poor for many of these patients,[1] but there is a push to understand the heterogeneity of this disease and differential responses to treatment. Since the introduction of many of these new treatments, the population of patients with PAH has changed drastically.[2,3] One of the most striking differences noted in recent patient registries is an increase in age at diagnosis,[3-6] and it remains unclear whether this increase has an impact on patient phenotypes and outcomes.

When compared with data from the National Institutes of Health (NIH) registry (1981-1985),[7] the newer US-based Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) (2006-2007) suggests that patients with PAH now receive diagnoses at an older age (45 vs 36 years).[3,4] This is also supported by the results of the European registry Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) (2007-2011)[5] and a review of 10 contemporary PAH registries, which found a mean age greater than the National Institutes of Health registry in all but one of the newer registries.[2]

Older patients with PAH may be fundamentally different than their younger counterparts. For instance, many older patients with precapillary disease may not meet traditional hemodynamic criteria for PAH,[8] mostly because of an elevated pulmonary artery wedge pressure (PAWP).[9,10] Indeed, pulmonary hypertension associated with left ventricular diastolic dysfunction is more common in the adult population[11] and is the most common cause of pulmonary hypertension in individuals ≥ 65 years old.[12] It is therefore also possible that older patients who do meet criteria for PAH may have some degree of left ventricular diastolic dysfunction and compose a unique phenotype of "mixed" pulmonary hypertension.[13]

At this point, there have been few studies assessing characteristics of patients with PAH based on their age, and none that could be found analyzing age effects on response to treatment. For the first time, we use data from large randomized, controlled PAH-specific treatment trials to evaluate patient characteristics and outcomes based on age. We hypothesized that older patients have a different phenotype, such as distinct etiologic, hemodynamic, and functional profiles, and a less favorable response to intervention.

## Materials and Methods

### *Patients and Study Design*

In the present investigation, we included all previously published treatment trials for PAH conducted by United Therapeutics including seven multicenter, randomized, double-blind, placebo-controlled, treatment trials,[14-20] and one open-label extension study.[21] Data for the seven trials are summarized in Table 1. The open-label extension study of the Subcutaneous Infusion of Treprostinil in Patients with PAH (SC-TRE) trial followed patients being treated with

**TABLE 1** ] Clinical Trials Included in Study

| Trial | Reference | Drug Studied | PH-Specific Background Therapies | Follow-up | Primary Endpoint |
|---|---|---|---|---|---|
| PHIRST | Galiè et al, 2009[14] | Tadalafil | None or bosentan | 16 wk | 6MWD |
| SC-TRE | Simonneau et al, 2002[15] | SC treprostinil | None | 12 wk | 6MWD |
| TRUST | Hiremath et al, 2010[16] | IV treprostinil | None | 12 wk | 6MWD |
| FREEDOM-C (F-C) | Tapson et al, 2012[17] | Oral treprostinil | ERA and/or PDE-5I | 16 wk | 6MWD |
| FREEDOM-C2 (F-C2) | Tapson et al, 2013[18] | Oral treprostinil | ERA and/or PDE-5I | 16 wk | 6MWD |
| FREEDOM-M (F-M) | Jing et al, 2013[19] | Oral treprostinil | None | 12 wk | 6MWD |
| TRIUMPH | McLaughlin et al, 2010[20] | Inhaled treprostinil | Bosentan or sildenafil | 12 wk | 6MWD |

6MWD = 6-min walk distance; ERA = endothelin receptor antagonists; FREEDOM-C (F-C) = Oral Treprostinil in Combination With an ERA and/or PDE-5I for the Treatment of PAH; FREEDOM-C2 (F-C2) = Oral Treprostinil in Combination With an ERA and/or PDE-5I for the Treatment of PAH 2; FREEDOM-M (F-M) = Efficacy and Safety of Oral Treprostinil Monotherapy for the Treatment of PAH; PAH = pulmonary arterial hypertension; PDE-5I = phosphodiesterase type 5 inhibitors; PH = pulmonary hypertension; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; SC-TRE = Subcutaneous Infusion of Treprostinil in Patients with PAH; TRIUMPH = Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension; TRUST = Study of Intravenous Remodulin in Patients in India with Pulmonary Arterial Hypertension.