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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FUNDING/SUPPORT: This publication was made possible by Clinical and Translational Science Awards KL2 [Grant TR000440 to A. R. T.] from the National Center for Research Resources, a component of the National Institutes of Health (NIH), NIH Roadmap for Medical Research.

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DOI: <http://dx.doi.org/10.1016/j.chest.2015.11.008>

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 population¹¹ 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.

subcutaneous treprostinil for 4 additional years.²¹ For our analyses, data from the SC-TRE (both randomized and open-label studies) and Study of Intravenous Remodulin in Patients in India with PAH (TRUST) trials were combined and reported as one trial, SC-TRE+TRUST (S+T) because of similar treatments of parenteral treprostinil and a relatively small number of patients in the TRUST trial.

Inclusion and exclusion criteria for each trial have been published previously.¹⁴⁻²⁰ Of note, all trials had as part of their exclusion criteria history of left-sided heart disease, PAWP > 15 mmHg, or pulmonary vascular resistance (PVR) < 3 Woods units. All of the trials except for Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) had an upper limit age cut-off: Oral Treprostinil in Combination With an ERA and/or PDE-5I for the Treatment of PAH (FREEDOM-C [F-C]): 70 years; SC-TRE, TRUST, Efficacy and Safety of Oral UT-15C Tablets to Treat Pulmonary Arterial Hypertension (F-C2), Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension (F-M), and Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH): 75 years. Patients from all trials were included regardless of the treatment allocation. We categorized patients into three age groups, following traditional

cutoffs used in other studies (≤ 50 , 51-64, and ≥ 65 years).^{5,6,12} For the PHIRST and S+T trials, hemodynamic parameters were measured by right heart catheterization at baseline and at completion of the trial. The effect of intervention on 6-min walk distance (6MWD) was assessed by the difference in walk distance at the end of the trial compared with baseline.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD. Normality was tested using the Shapiro-Wilk statistic. If normality did not hold, results are presented as median (interquartile range). Categorical variables are presented as n (%). Continuous and categorical variables were studied with analysis of variance and χ^2 tests. Change in 6MWD was tested against age, both as a continuous and categorical (three strata) variable. Using the general linear model procedure, these analyses were adjusted by sex, PAH etiology, race, functional class, baseline 6MWD, and when available, mean pulmonary artery pressure (mPAP) and PVR. All *P* values are two-tailed and a value of < .05 was considered statistically significant. The statistical analyses were performed using the Statistical Analysis System (SAS) 9.3, SAS Institute Inc.

Results

Patient Characteristics

Across all six studies, there were 2,627 patients comprising three age groups: ≤ 50 (n = 1,438, 54.7%), 51 to 64 (n = 780, 29.7%) and ≥ 65 years (n = 409, 15.6%) (Table 1), with an average age in each group of 36.7, 57.1, and 70.5 years, respectively (e-Table 1). In all trials there was a predominance of female patients, with men comprising between 18% and 25% across all age groups (Table 2). Only one trial had a significantly higher percentage of men in the oldest group (PHIRST: *P* = .01). There was a preponderance of white race in four of five studies that collected this variable, ranging from 41% to 89% across all age groups, and race had a strong association with age. There was a higher percentage of white race in the older patient group for all five trials (PHIRST, S+T, F-C2, F-M: *P* < .0001; F-C: *P* = .03) (Table 2).

Disease Characteristics

In all studies, there was an overall predominance of patients with idiopathic PAH (range, 53 to 74% across all age groups) (Fig 1, Table 2). There was an association between age and PAH etiology, with older patients having a significantly smaller proportion of those with idiopathic PAH in three trials (F-C, F-C2: *P* = .004; F-M: *P* = .047) and a significantly higher percentage of connective tissue disease (CTD)-associated PAH in all trials (PHIRST: *P* = .01; S+T, F-C, F-C2: *P* < .001; F-M and TRIUMPH: *P* = .002). In these clinical trials, World Health Organization (WHO) functional class was predominantly III and IV (range, 62%-100%), and the

mean 6MWD at baseline across all age groups ranged between 323 and 348 m (Fig 1, Table 3). Age was associated with worse baseline functional status, manifested by a lower proportion of patients in WHO functional classes I and II (PHIRST: *P* = .02; S+T, F-C2, F-M: *P* < .01) and lower baseline 6MWD (PHIRST, S+T, F-C, F-C2, TRIUMPH: *P* < .0001) in the oldest group. However, when comparing 6MWD percentage of predicted,²² higher values were found in older patients (PHIRST, S+T: *P* < .01; F-C2, F-M: *P* < .0001) (e-Table 2). Baseline hemodynamic parameters (collected in PHIRST and S+T only) were better in the oldest patients, with lower mPAP (PHIRST: *P* = .006; S+T: *P* < .0001) and PVR (PHIRST: *P* = .02; S+T: *P* < .0001) in both studies (Fig 2, Table 3). There were no significant differences in PAWP (Table 3).

Outcomes and Adverse Events

Overall, outcomes varied in the six trials, with a mean change in 6MWD of 13 to 34 m across all age groups. There were no differences in the percentage of patients in each treatment arm between age groups (Table 4). Outcome at end of study was associated with age, in which older patients had worse outcomes including a smaller change in 6MWD from baseline to end of study (continuous) in three trials (PHIRST: *P* = .02; F-C: *P* = .002; F-C2: *P* = .001) and a higher proportion of older patients had an overall decrease in total 6MWD (categorical) from baseline to end of study (PHIRST, F-C: *P* < .05; F-C2: *P* = .0002) (Fig 3, Table 4). An attenuated effect of age on the change in 6MWD was noted when, instead of the absolute 6MWD in meters,

the test results were expressed as a percentage of the predicted value for healthy adults²² (e-Table 2).

Sensitivity analyses demonstrated that age remained associated with change in 6MWD when considering studies that only included treatment-naïve patients (S+T and F-M) or the treatment-naïve subgroup of the PHIRST study (e-Table 3). Age differences in 6MWD

also persisted when studying only the subgroup of patients with CTD-PAH (e-Table 4).

Mortality rates were generally small in these studies and not significantly different among the age groups, except for the S+T trial ($P = .0004$). Side effects generally showed no consistent association with age, with similar rates reported for each age group. There

TABLE 2] Baseline Demographics and Disease Etiology

Variables	Clinical Trials	Age ≤ 50		50 < Age < 65		Age ≥ 65		P (Test)
		n/Mean	%/SD	n/Mean	%/SD	n/Mean	%/SD	
No. of Patients								
	PHIRST	171	42.2	122	30.1	112	27.7	...
	SC-TRE+TRUST	622	63.6	244	24.9	112	11.5	...
	FREEDOM-C	157	44.9	150	42.9	43	12.3	...
	FREEDOM-C2	150	48.4	91	29.4	69	22.3	...
	FREEDOM-M	253	72.5	77	22.1	19	5.4	...
	TRIUMPH	85	36.2	96	40.9	54	23.0	...
	Total	1,438	54.7	780	29.7	409	15.6	...
Demographics								
Sex (male)	PHIRST	30	17.5	24	19.7	34	30.4	.014
	SC-TRE +TRUST	142	22.8	62	25.4	35	31.3	.058
	FREEDOM-C	31	19.7	27	18.0	4	9.3	.163
	FREEDOM-C2	32	21.3	21	23.1	16	23.2	.729
	FREEDOM-M	66	26.1	21	27.3	0	0.0	.099
	TRIUMPH	17	20.0	18	18.8	9	16.7	.629
Race (white)	PHIRST	120	70.2	103	84.4	104	92.9	< .0001
	SC-TRE+TRUST	440	70.7	227	93.0	107	95.5	< .0001
	FREEDOM-C	134	85.4	137	91.3	41	95.3	.030
	FREEDOM-C2	67	45.0	69	75.8	62	89.9	< .0001
	FREEDOM-M	78	30.8	50	66.7	15	78.9	< .0001
	TRIUMPH	...	...	...	...	...	...	...
Disease etiology								
Idiopathic PAH	PHIRST	104	60.8	67	54.9	76	67.9	.425
	SC-TRE+TRUST	338	54.5	117	48.0	58	51.8	.248
	Freedom-C	112	71.3	101	66.9	19	44.2	.004
	Freedom-C2	112	74.7	54	59.3	37	53.6	.004
	Freedom-M	194	76.7	54	70.1	11	57.9	.047
	TRIUMPH	48	56.5	57	59.4	26	48.1	.414
CTD-associated PAH	PHIRST	26	15.2	39	32.0	30	26.8	.011
	SC-TRE+TRUST	80	12.9	64	26.2	35	31.3	< .001
	FREEDOM-C	27	17.2	44	29.1	21	48.8	< .0001
	FREEDOM-C2	29	19.3	36	39.6	32	46.4	< .0001
	FREEDOM-M	40	15.8	19	24.7	8	42.1	.002
	TRIUMPH	18	21.2	34	35.4	25	46.3	.002

P values are in bold if ≤ .05. CTD-associated PAH = connective tissue disease-associated pulmonary arterial hypertension. See Table 1 legend for expansion of other abbreviations.

Figure 1 – Etiologies of PAH and baseline 6MWD (mean $\pm$ SE) for each age group. For each of the three age groups, the percentage of patients with CTD-PAH and IPAH is shown. 6MWD = 6-min walk distance; CTD-PAH = connective tissue disease-pulmonary arterial hypertension; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; SC-TRE+TRUST = Subcutaneous Infusion of Treprostinil in Patients with PAH + Study of Intravenous Remodulin in Patients in India with PAH; TRIUMPH = Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension.

TABLE 3] Baseline Functional Capacity and Hemodynamics

Baseline Function	Clinical Trials	Age ≤ 50 y		50 < Age < 65 y		Age ≥ 65 y		P (Test)
		n/Mean	%/SD	n/Mean	%/SD	n/ Mean	%/SD	
WHO functional classes I and II	PHIRST	66	38.6%	40	32.8%	28	25.0%	.018
	SC-TRE+TRUST	99	15.9%	24	9.8%	10	8.9%	.008
	FREEDOM-C	37	23.6%	27	18.0%	11	25.6%	.764
	FREEDOM-C2	43	28.7%	26	28.6%	11	16.4%	.005
	FREEDOM-M	109	43.1%	18	24.0%	6	31.6%	.008
	TRIUMPH	...	...	...	...	...	...	...
Baseline 6MWD (m)	PHIRST	371.0	± 60.5	345.0	± 83.0	301.0	± 72.0	< .0001
	SC-TRE+TRUST	335.0	± 82.6	310.0	± 91.5	261.0	± 88.6	< .0001
	FREEDOM-C	368.0	± 62.7	333.0	± 75.1	310.0	± 80.7	< .0001
	FREEDOM-C2	354.0	± 54.1	328.0	± 68.8	295.0	± 70.2	< .0001
	FREEDOM-M	336.0	± 72.6	315.0	± 74.9	315.0	± 72.1	.068
	TRIUMPH	371.0	± 58.4	346.0	± 64.3	316.0	± 66.7	< .0001
Baseline hemodynamics								
Baseline mPAP (mmHg)	PHIRST	57.5	± 14.0	52.1	± 9.7	47.5	± 10.7	.006
	SC-TRE+TRUST	62.7	± 16.5	56.0	± 13.7	51.0	± 11.8	< .0001
Baseline PVR (Woods units)	PHIRST	12.7	± 6.2	9.4	± 2.7	9.6	± 3.9	.015
	SC-TRE+TRUST	15.0	± 7.5	12.8	± 6.6	11.9	± 5.9	< .0001
Baseline PAWP (mmHg)	PHIRST	9.0	± 5.6	10.3	± 3.8	10.2	± 4.7	.503
	SC-TRE+TRUST	9.5	± 3.5	9.4	± 3.4	10.2	± 3.9	.223

All patients on the TRIUMPH study were on WHO functional class III-IV. *P* values are in bold if ≤ .05. mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; WHO = World Health Organization. See Table 1 legend for expansion of other abbreviations.

were some adverse effects found to be associated with age, but only one was significant in more than one trial, and the relationship was inconsistent with a higher incidence of nausea in the oldest age group in FREEDOM-M (*P* = .03) but lower incidence in TRIUMPH (*P* = .02) (e-Table 1).

Multivariate Analyses

Age analyzed as a continuous variable was associated with decreased change in 6MWD, when adjusted by sex and disease etiology in four of the trials (PHIRST, F-C, F-C2, F-M) (Table 5). Age also remained associated with this outcome when adjusted by all variables significantly associated with outcome in univariate analyses: etiology, race, functional class, baseline 6MWD, mPAP, and PVR (S+T); etiology, race, functional class, and baseline 6MWD (F-C, F-C2, F-M); disease etiology and baseline 6MWD (TRIUMPH) (Table 5, e-Tables 5 and 6).

Discussion

In this study, we characterized the effects of age on PAH phenotype and outcomes by reporting the associations between age group and demographic, functional, and clinical characteristics and response to intervention. To the best of our knowledge, this is the first investigation to do so by analyzing patients enrolled in large randomized controlled trials. This analysis demonstrated that older patients participating in PAH studies do in fact differ significantly from their younger counterparts in several ways; specifically, differences in the oldest group compared with the youngest include less idiopathic and more CTD-associated PAH, worse functional class, lower 6MWD at baseline, lower mPAP and PVR at baseline, and decreased change in 6MWD from baseline to end of study. Except for one trial, no survival differences were noted among the age groups during the 3 to 4 months of follow-up used in these studies.

Figure 2 – Baseline hemodynamics (mean $\pm$ SE) for each age group. See [Figure 1](#) legend for expansion of abbreviations.

In terms of demographic factors, the most striking association with age was race as the oldest age group had a higher proportion of white patients in all five studies that recorded race. This could be influenced by several factors, such as racial disparities in life expectancy and diminished access to care for older, non-white populations.^{23,24} Sex, on the other

hand, was somewhat inconclusive; only one of the six studies showed that older patients had a higher proportion of men, but there was a trend toward greater percentage of men with older age for three trials. The European-based COMPERA registry showed a higher proportion of men in older patients⁵; another study found that male sex was significantly

TABLE 4] Treatment Groups and Outcomes

Response to Treatment	Clinical Trials	Age $\leq$ 50 y		50 < Age < 65 y		Age $\geq$ 65 y		P (Test)
		n/Mean	%/SD	n/Mean	%/SD	n/Mean	%/SD	
Active treatment arm	PHIRST	135	78.9%	101	82.8%	87	77.7%	.887
	SC-TRE+TRUST	449	72.2%	182	74.6%	89	79.5%	.105
	FREEDOM-C	71	45.2%	82	54.7%	21	48.8%	.296
	FREEDOM-C2	73	48.7%	46	50.5%	38	55.1%	.393
	FREEDOM-M	170	67.2%	53	68.8%	10	52.6%	.456
	TRIUMPH	32	37.6%	56	58.3%	27	50.0%	.081
6MWD absolute change (m)	PHIRST	43.3	$\pm$ 53.0	29.1	$\pm$ 54.1	24.4	$\pm$ 56.6	.019
	SC-TRE+TRUST	14.0	$\pm$ 73.3	13.0	$\pm$ 62.0	7.3	$\pm$ 66.5	.851
	FREEDOM-C	26.8	$\pm$ 55.5	15.3	$\pm$ 56.1	−8.4	$\pm$ 42.4	.002
	FREEDOM-C2	25.3	$\pm$ 63.3	28.3	$\pm$ 49.9	−5.6	$\pm$ 50.9	.001
	FREEDOM-M	35.9	$\pm$ 73.5	23.2	$\pm$ 50.3	9.8	$\pm$ 66.9	.169
	TRIUMPH	29.4	$\pm$ 43.9	15.9	$\pm$ 56.7	9.9	$\pm$ 51.8	.078
Decrease in 6MWD (yes)	PHIRST	52	30.4%	47	38.5%	48	42.9%	.029
	SC-TRE+TRUST	439	70.6%	173	70.9%	86	76.8%	.261
	FREEDOM-C	55	35.0%	60	40.0%	24	55.8%	.023
	FREEDOM-C2	47	31.3%	32	35.2%	41	59.4%	< .001
	FREEDOM-M	98	38.7%	32	41.6%	10	52.6%	.265
	TRIUMPH	30	35.3%	47	49.0%	22	40.7%	.379

P values are in bold if $\leq$.05. See [Table 1](#) legend for expansion of abbreviations.

Figure 3 – Change in 6MWD (mean ± SE) for each age group. See Figure 1 legend for expansion of abbreviations.

associated with increased odds of achieving a clinically relevant response to treatment in 6MWD.²⁵ However, even after adjusting for sex in our multivariate analyses, age remained associated with response to therapy.²⁵

Disease etiology was another major aspect of the discrepancy between age groups. Although registry

data have shown that idiopathic PAH is increasingly recognized in older populations, our analysis shows that idiopathic etiology was less frequent in the older group. In contrast, CTD-associated PAH accounted for a higher proportion of PAH etiology in the oldest age group, an effect noted in all six trials. Indeed, in three studies, CTD-associated PAH accounted for nearly half of patients' disease etiology in the oldest age group, a

TABLE 5] Multivariate Analyses of Association of Age as a Continuous Variable and Outcome of Change in 6MWD

Clinical Trial	Variables Included in Model	Age P Value
PHIRST	Age, sex, disease etiology	.002
	Age, race, disease etiology, functional class, baseline 6MWD, mPAP, PVR	.28
SC-TRE + TRUST	Age, sex, disease etiology	.06
	Age, race, disease etiology, functional class, baseline 6MWD, mPAP, PVR	.04
FREEDOM-C	Age, sex, disease etiology	.0006
	Age, race, disease etiology, functional class, baseline 6MWD	.0009
FREEDOM-C2	Age, sex, disease etiology	.003
	Age, race, disease etiology, functional class, baseline 6MWD	.01
FREEDOM-M	Age, sex, disease etiology	.006
	Age, race, disease etiology, functional class, baseline 6MWD	< .0001
TRIUMPH	Age, sex, disease etiology	.07
	Age, disease etiology, baseline 6MWD	.05

P values are in bold if $\leq .05$. mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance. See Table 1 legend for expansion of other abbreviations.

finding that is consistent with prior registry data.⁴ Similarly, one study evaluating PH in the elderly found CTD-associated PAH to be the major etiology of PAH.¹² The large predominance of CTD-associated PAH in the elderly suggests that there may be different pathophysiologic mechanisms in this age group, potentially driven by immunologic disturbances.^{26,27}

Age was also associated with worse baseline functional status, including a lower percentage of individuals in WHO functional class I and II and lower 6MWD at baseline in the oldest age group. When adjusting for age and anthropometric values, however, older patients actually had a higher baseline 6MWD percentage of predicted. This could represent an underestimation of distance walked in older healthy individuals by the selected formula.^{22,28,29} Hemodynamic severity was also better in older patients, with the oldest age group having lower baseline mPAP and PVR in the two trials that measured hemodynamics, a result consistent with previous registry data.⁵ Despite older patients being more likely to have some degree of left ventricular diastolic dysfunction,¹³ there were no differences in PAWP between age groups enrolled in these trials.

The difference in clinical function and hemodynamics in older patients may reflect different mechanisms of disease. Older patients may have diminished cardiopulmonary reserve, and similar degrees of hemodynamic severity manifest with a larger functional impairment. Alternatively, additional comorbidities in older patients may contribute to a larger extent, and clinical function may not be as directly related to hemodynamic severity. Understanding these concepts will require further research,¹³ but have important implications in the diagnosis and management of this growing population of PAH patients. The discrepancy between parameters of functional status and hemodynamic parameters may imply that traditional measures of disease severity and clinical function do not appropriately characterize older patients with PAH. In the future, these patients could be better characterized by adjusted measures of clinical function and hemodynamics.

Finally, age was significantly correlated with response to intervention as measured by 6MWD after conclusion of the trial. The oldest patients had a smaller change in 6MWD, with an average increase of 9 m across all trials vs 28 m for the youngest group, and increased age was inversely correlated with change in 6MWD, even after adjusting for sex, disease etiology, functional class, baseline 6MWD, and hemodynamic parameters when

available. These data are consistent with previous studies: one found that each year of age was associated with a 5-m decline in 6MWD over the following year,³⁰ and the other found that for every 10 years of age, there was a decreased likelihood of achieving the minimal important difference.²⁵ Interestingly, when analyzing the change in 6MWD, the percentage of predicted, age-related differences was attenuated. This implies that new methods of measuring response to treatment, such as using 6MWD percentage of predicted, are worth testing in future studies.

Age was associated with reduced response to treatment despite the fact that the proportions of patients on active treatment were actually higher in the oldest cohort for most of the trials. These worse outcomes also cannot be explained by duration of disease because none of the trials showed an association between age and disease duration ([e-Table 1](#)). Furthermore, the multivariate analyses demonstrate that this age-related difference in outcome is not driven by other significant differences in age groups such as sex or disease etiology. There are other potential contributors to the difference in outcomes among age groups as well that may not have been captured by this study, such as age-related changes in sex hormones or immune function.

There are many implications of these results, but in particular, clinical function and outcome measures in older patients may need to be reevaluated, perhaps to include more quality of life-based assessments, measures of disease progression such as clinical worsening or hospitalization, or use of different thresholds for minimum important difference in this group of patients. At the very least, these are factors that need to be considered when designing future trials because they may impact the outcomes of the drug approval process for new PAH therapies.

There are several limitations to this study. This was a post-hoc analysis of randomized studies. Five of the six trials included in our study had age cutoffs, therefore limiting the number of patients > 70 years old. It is possible that there could have been sampling bias toward a healthier cohort of patients, particularly in the older population, limiting the generalizability of this analysis. However, we believe that including older, less healthy patients into the patient sample would have made the differences based upon age even more drastic.

In conclusion, for the first time, this study uses a large cohort from randomized controlled trials to characterize the differences in older patients with PAH, including

dissimilar disease etiology, diminished functional status, and better hemodynamics. In addition, we showed that response to medication intervention was diminished in older patients even after adjusting for other significant variables. These differences have many implications for the management of this growing cohort of patients,

including the possibility of unique disease mechanisms, the need to reassess current outcome measures for this age group, and the importance of setting reasonable expectations for therapy goals. In addition, these data could be used to plan and design future treatment trials to best evaluate a therapy's efficacy in certain age groups.

Acknowledgments

Author contributions: J. A. R. participated in the conception and design of the study, interpretation of the results, writing, and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. J. M. C. participated in the statistical analysis, interpretation of the results, and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. O. A. M. participated in the data collection, interpretation of the results, and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. Y. R. participated in the statistical analysis, interpretation of the results, and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. A. R. T. participated in the conception and design of the study, interpretation of the results, writing and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted; and is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: J. M. C. and Y. R. are employees of United Therapeutics, the company who conducted and analyzed these clinical trials. O. A. M. is a member of the scientific advisory board of Actelion, Gilead, and Bayer, and a member of the speakers bureau of Actelion, Gilead, United Therapeutics, and Bayer. None declared (J. A. R., A. R. T.).

Role of sponsors: The sponsor had no role in the design of the study. United Therapeutics provided aggregate data and statistical support.

Other contributions: We sincerely appreciate the statistical support provided by United Therapeutics.

Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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