Sex Differences in Response to Tadalafil in Pulmonary Arterial Hypertension

Stephen C. Mathai, MD, MHS, FCCP; Paul M. Hassoun, MD, FCCP; Milo A. Puhan, MD, PhD; Yi Zhou, PhD; and Robert A. Wise, MD, FCCP

BACKGROUND: Pulmonary arterial hypertension (PAH) is a progressive disease with high rates of morbidity and mortality. Current therapies improve symptoms, functional capacity, and, in select cases, survival. Little is known about patient factors that may predict the likelihood of patient-important, clinically relevant responses to therapy such as the 6-min walk distance (6MWD) and health-related quality of life (HRQoL).

METHODS: Data from the randomized clinical trial of tadalafil in PAH were used. Adjusted logistic regression models were created to examine the relationship between baseline characteristics and odds of achieving the minimal important difference (MID) in three parameters, defined as either a >33-m increase in 6MWD, a >5-unit increase in physical component summary score of the Medical Outcomes Study Short Form-36 (SF-36), or a >5-unit increase in mental component summary score of the SF-36.

RESULTS: The study included 405 subjects. Younger age, male sex, lower baseline 6MWD, and disease etiology were associated with greater odds of achieving the MID for the 6-min walk test. Active treatment, younger age, and male sex were associated with greater odds of achieving the MID for the physical component summary score. Male sex was associated with greater odds of achieving the MID for the mental component summary score.

CONCLUSIONS: Age, sex, baseline functional capacity, and disease etiology are variably associated with the likelihood of achieving clinically relevant responses in patient-important outcomes to PAH-specific therapy such as 6MWD and HRQoL. The increased likelihood of response in men compared with women is a novel finding and may reflect pathophysiologic differences between sexes.

CHEST 2015; 147(1):188-197

Manuscript received January 31, 2014; revision accepted July 23, 2014; originally published Online First August 14, 2014.

ABBREVIATIONS: 6MWD = 6-min walk distance; 6MWT = 6-min walk test; cGMP = cyclic guanosine monophosphate; CTD = connective tissue disease; ERA = endothelin receptor antagonist; ET-1 = endothelin-1; HRQoL = health-related quality of life; MCS = mental component summary; MID = minimal important difference; NO = nitric oxide; PAH = pulmonary arterial hypertension; PCS = physical component summary; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; SF-36 = Medical Outcomes Study Short Form-36; sGC = soluble guanylate cyclase; WHO FC = World Health Organization functional class

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (Drs Mathai, Hassoun, and Wise), Johns Hopkins University School of Medicine, Baltimore, MD; Institute of Social and Preventive

Medicine (Dr Puhan), University of Zurich, Zurich, Switzerland; and United Therapeutics Corporation (Dr Zhou), Research Triangle Park, NC. This study was presented in abstract form at the American Thoracic Society International Meeting 2013, May 17-22, 2013, Philadelphia, PA.

FUNDING/SUPPORT: This study was supported by the National Heart, Lung, and Blood Institute [Grant K23 HL093387 to Dr Mathai].

CORRESPONDENCE TO: Stephen C. Mathai, MD, MHS, FCCP, Johns Hopkins University School of Medicine, Division of Pulmonary and Critical Care Medicine, 1830 E Monument St, Room 540, Baltimore, MD, 21205; e-mail: smathai4@jhmi.edu

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-0263

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease of the pulmonary vasculature that leads to right-sided heart failure and death.¹ Despite advances in our understanding of the pathogenesis and pathobiology of PAH, morbidity and mortality rates remain high. Newer therapies, directed at reducing pulmonary vascular load, have been shown to improve symptoms, quality of life, functional capacity, and, in the case of IV epoprostenol, survival.²⁻¹¹ However, PAH remains a disease without a cure in the absence of lung transplantation.

In chronic disease without cure, assessing therapeutic efficacy should be determined by improvements in clinical outcomes that are relevant to delaying or reversing the pathogenesis of the disease, to improving the patient's experience with the disease, or, ideally, both. Most clinical trials of novel therapies in PAH have used the 6-min walk test (6MWT) as the primary outcome, based upon associations with functional classification, hemodynamics, and survival demonstrated in various cohorts of patients with PAH.^{2,4-8,12-14} Accordingly, regulatory agencies have approved pharmacologic agents for PAH therapy based upon small but statistically significant changes in 6MWT in randomized clinical trials. Further, while prior studies have suggested that achievement of absolute thresholds of 6-min walk distance (6MWD) (eg, > 400 m) is associated with improved survival in PAH, incremental improvements in 6MWD and health-related quality of life (HRQoL) may also be essential components of assessing patient-important, clinically relevant treatment response.¹⁵ These parameters may represent intermediate end points (ie, true clinical end points that are not the ultimate end point of the disease) and, therefore, achievement of the minimal important difference (MID) for these parameters may be of value to the patient even in the absence of a mortality benefit.¹⁶

There are surprisingly few studies examining predictors of response to therapy in PAH. Several investigators have examined the relationship between baseline characteristics and survival, demonstrating associations between demographic, clinical, functional, and hemodynamic characteristics and survival in various cohorts of PAH.¹⁵ However, few studies have looked at the relationship between baseline characteristics and outcomes other than survival. Using pooled data from six randomized, placebo-controlled trials of endothelin receptor antagonists (ERAs), Gabler and colleagues¹⁷ found significant differences in change in 6MWT in response to therapy by sex and race, with women and white people experiencing greater increases in 6MWT than men and black people, respectively. The absence of other literature examining predictors of response to PAH therapy likely reflects the lack of validation of clinically relevant changes in surrogate end points in PAH studies (ie, clinically relevant changes in 6MWT or other patient-important measures).

Previously, our group described an estimate of the MID in the 6MWT for patients with PAH.¹⁸ The MID, defined as the smallest change or difference in an outcome measure, perceived as beneficial, that would justify a change in the patient's medical management, was determined to be around 33 m.¹⁹ Clinically relevant changes in HRQoL are also important in PAH and may predict clinical deterioration and survival.^{20,21} Identifying clinical characteristics that are associated with clinically relevant improvements in intermediate measures in response to specific PAH therapy offers the opportunity to tailor treatment strategies and to define distinct disease phenotypes. Therefore, we sought to define patient characteristics associated with patient-important, clinically relevant changes in 6MWT and HRQoL, using data from the large clinical trial of tadalafil in PAH.

Materials and Methods

The Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) trial was a double-masked, placebo-controlled, 16-week study of 405 patients with PAH, including both treatment-naïve patients and patients on background therapy with the ERA bosentan.⁵ The primary outcome was change from baseline to week 16 in 6MWD. Secondary outcome measures included HRQoL as assessed by the Medical Outcomes Study 36-item Short Form (SF-36) version 2 collected at baseline and at week 16. The 6MWT was performed according to consensus guidelines.²²

Clinically relevant changes in 6MWT and SF-36 were defined based upon the literature defining the MID for these parameters (33 m for the 6MWT and 5 units for the physical component summary [PCS] score and mental component summary [MCS] score of the SF-36).^{18,23} Analyses were conducted to assess the relationship between baseline characteristics of study subjects and achievement of MID in the

6MWT and summary components of the SF-36. First, simple, unadjusted univariable analyses using two-sample Student *t* (or Wilcoxon) tests for continuous variables and the χ^2 (or Fisher exact) test for categorical variables were performed. Then multivariable logistic regression models were created to assess the odds of achieving the MID for either parameter based upon clinical characteristics. These models included potential confounders of the relationship between demographic and clinical parameters and achieving the MID, such as age, height, BMI, sex, baseline World Health Organization functional class (WHO FC), baseline walk distance, and disease type. Since only a subset of subjects underwent baseline and end-of-study catheterization (complete data were available on 69 subjects), change in hemodynamic variables were not included in these multivariable models.

Variables selected for the multivariate models were based on both statistical and clinical significance. In addition, backward variable selection

methods were used along with a significance level of the χ^2 test result (eg, $P < .16$) for entering an effect into a separate model to explore potential differences between prediction and causal inference modeling.^{24,25} General assumptions such as linearity on logit were evaluated for the continuous variables. Collinearity, numerical stability, and influence measures were also evaluated. The potential effect modifications were assessed

by including the interactions of clinical interest (eg, sex and treatment status) in the multivariable models. The Hosmer-Lemeshow test was used to assess the overall goodness of fit for the models. The multiple imputation approach of Markov chain Monte Carlo using 1,000 imputations was implemented to impute missing data, assuming data were missing at random. All analyses were performed using SAS version 9.2 (SAS Institute Inc).

Results

As shown in Table 1, 405 subjects who completed the PHIRST trial were included in this analysis. The majority of subjects were white women who were, on average, 53 years of age. Most had idiopathic PAH, but approximately one-quarter had connective tissue disease (CTD)-related PAH. A minority had anorexigen-associated PAH or PAH related to congenital heart disease. At baseline, most subjects had WHO FC II or III disease and had a moderate degree of functional impairment based upon baseline 6MWT. Hemodynamics

at baseline revealed moderate to severe disease. When compared with population norms for the United States, four of eight domains of the SF-36 were significantly lower (Fig 1). Similarly, summary scores for the PCS, but not MCS, were significantly depressed. Overall, 48.2%, 34.6%, and 33.3% of the study subjects achieved the MID for the 6MWT, PCS, and MCS parameters, respectively, in unadjusted analyses.

Multivariable Analyses

In multivariable logistic regression models using non-imputed data, odds of achieving the MID for the 6MWT

TABLE 1 Characteristics of the Study Population

Characteristics	Placebo	Tadalafil 2.5 mg	Tadalafil 10 mg	Tadalafil 20 mg	Tadalafil 40 mg	Overall
Age, y	55 (15)	54 (16)	55 (15)	53 (16)	53 (15)	54 (15)
Female patients	65 (79)	64 (78)	68 (84)	62 (76)	59 (75)	318 (78)
White patients	72 (88)	65 (80)	64 (80)	61 (75)	64 (81)	326 (81)
PAH etiology						
Idiopathic	54 (66)	45 (55)	52 (65)	50 (61)	46 (58)	247 (61)
Collagen vascular	16 (20)	16 (20)	23 (29)	21 (26)	19 (24)	95 (24)
Anorexigen	2 (2)	5 (6)	1 (1)	4 (5)	4 (5)	16 (4)
ASD/surgical	10 (12)	16 (20)	4 (5)	7 (9)	10 (13)	47 (11)
WHO FC baseline						
I	1 (1)	1 (1)	0 (0)	0 (0)	2 (3)	4 (1)
II	23 (28)	29 (35)	24 (30)	28 (34)	26 (33)	130 (32)
III	56 (68)	49 (60)	54 (68)	54 (66)	51 (65)	264 (65)
IV	2 (2)	3 (4)	2 (3)	0 (0)	0 (0)	7 (2)
6MWT baseline, mean (SD)	343 (84)	347 (71)	338 (75)	338 (74)	352 (78)	344 (76)
Change in 6MWT, mean (SD), m	18.7 (54)	32.2 (58.9)	33.4 (63.0)	42.1 (47.5)	41.3 (49.8)	34.0 (55.5)
RAP, mean (SD), mm Hg	7 (4)	8 (4)	9 (6)	7 (4)	8 (4)	8 (4)
PAP, mean (SD), mm Hg	49 (12)	55 (14)	51 (17)	58 (12)	54 (8)	54 (13)
Cardiac index, mean (SD), L/min/m ²	2.3 (0.6)	2.4 (0.7)	2.6 (0.8)	2.7 (0.6)	2.7 (1.0)	2.5 (0.8)
PCWP, mean (SD), mm Hg	9 (3)	11 (7)	10 (5)	9 (4)	9 (4)	10 (5)
PVR, mean (SD), Wood units	11 (5)	11 (5)	11 (6)	12 (5)	11 (6)	11 (5)
Concomitant bosentan use	45 (55)	43 (52)	41 (51)	45 (55)	42 (53)	216 (53)

Data given as No. (%) unless otherwise indicated. 6MWT = 6-min walk test; ASD = atrial septal defect; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; WHO FC = World Health Organization functional class.

Figure 1 – Baseline Medical Outcomes Study Short Form-36 (SF-36) domains and summary scores compared with US population norms. Baseline values (means with SD error bars) of the eight domains and summary scores of the SF-36 for subjects in the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) trial. The dotted line represents US population normal values. BP = body pain; GH = general health; MCS = mental component summary; MH = mental health; PCS = physical component summary; PF = physical function; RE = role emotional; RP = role physical; SF = social function; VT = vitality.

were significantly associated with several baseline parameters (Table 2). Treatment status (active vs placebo) tended to be associated with odds of achieving the MID, but this relationship was not statistically significant. Older patients were less likely to achieve the 6MWT MID (OR, 0.80; 95% CI, 0.68-0.94; $P < .01$ for every 10 years of age). Men demonstrated significantly greater odds of achieving the MID than women (OR, 1.79; 95% CI, 1.04-3.08; $P = .04$); this relationship persisted when controlling for height, weight, and BMI. While race was noted in stratified analyses to be significantly associated with MID, this did not persist in multivariable analyses. However, CTD-PAH remained significantly associated with odds of achieving the MID; subjects with CTD-PAH had 50% lower odds of achieving the MID than subjects with other forms of PAH (OR, 0.51; 95% CI, 0.29-0.91; $P = .02$). Baseline 6MWD was also

associated with the MID, as subjects who had higher baseline 6MWD were less likely to achieve the MID. Multiple imputation models using the Markov chain Monte Carlo method confirmed these associations. Though the strength of the association with sex and etiology were attenuated, the point estimates, 95% CIs, and P values remained similar for both parameters (Table 3).

Similarly, we examined the odds of achieving the MID for the PCS based upon baseline characteristics in multivariable models of both the complete study data and the imputed data. Interestingly, as shown in Table 4, male sex was significantly associated with the MID (OR, 1.87; 95% CI, 1.76-3.26; $P = .03$), as were treatment status (active vs placebo; OR 2.10; 95% CI, 1.11-3.99; $P = .02$) and age (OR, 0.84; 95% CI, 0.72-1.00; $P = .05$). Odds of achieving the MID for the MCS was also

TABLE 2 Predictors of Achieving the Minimal Important Difference for the 6MWT: Nonimputed Data

Predictor	β (SE)	OR (95% CI)	P Value
Age, per 10 y	-0.22 (0.08)	0.80 (0.68-0.94)	< .01
Sex, men vs women	0.57 (0.28)	1.77 (1.03-3.06)	.04
PAH etiology, CTD vs other	-0.66 (0.29)	0.52 (0.29-0.91)	.02
WHO FC, I/II vs III/IV	0.34 (0.26)	1.40 (0.84-2.23)	.19
6MWD, baseline	-0.005 (0.002)	0.99 (0.99-0.99)	< .01
Treatment status, active vs placebo	0.37 (0.29)	1.45 (0.83-2.53)	.20
Constant	2.28	...	...

6MWD = 6-min walk distance; CTD = connective tissue disease. See Table 1 legend for expansion of other abbreviations.

TABLE 3] Predictors of Achieving the Minimal Important Difference for the 6MWT: Imputed Data

Predictor	β (SE)	OR (95% CI)	P Value
Age, per 10 y	−0.23 (0.08)	0.79 (0.68-0.93)	< .01
Sex, men vs women	0.50 (0.27)	1.65 (0.96-2.82)	.07
PAH etiology, CTD vs other	−0.49 (0.28)	0.62 (0.36-1.06)	.08
WHO FC, I/II vs III/IV	0.30 (0.25)	1.35 (0.82-2.22)	.24
6MWD, baseline	−0.005 (0.002)	0.99 (0.99-0.99)	< .01
Treatment status, active vs placebo	0.30 (0.28)	1.35 (0.78-2.33)	.29
Constant	2.47	...	...

See Table 1 and 2 legends for expansion of abbreviations.

associated with male sex, with an OR of 2.02 (95% CI, 1.16-3.52; $P = .01$) (Table 5). Treatment status trended toward significant association with achieving the MID for the MCS (OR, 1.86; 95% CI, 0.98-3.52; $P = .06$). However, unlike PCS, the odds of achieving the MID for the MCS was significantly associated with baseline walk distance, with decreasing odds of achieving the MID for the MCS with longer baseline 6MWD (OR, 0.99; 95% CI, 0.99-1.00; $P = .05$). These results were not significantly different when examined in the multiple imputation models.

Given the consistent findings of the association of male sex and increased odds of achieving the MID for each of the parameters studied, we examined the cohort stratified by sex. As shown in Table 6, men were significantly older, taller, and more likely to be white. Further, they were more likely to have idiopathic PAH. However, baseline WHO FC, 6MWD, hemodynamics, and HRQoL parameters did not differ significantly from women. As shown in Figure 2, the proportion of subjects who achieved the MID differed by sex and by treatment status. Models were created to assess potential modifiers of the relationship between sex and odds of achieving the MID. Specifically, based upon literature suggesting

age-related differences in disease severity between men and women, we examined the relationship between age and sex, dichotomizing the cohort at age 56 years.²⁶ There was no evidence of effect modification by age in the relationship between sex and odds of achieving the MID for any of the three parameters studied. However, when stratified by sex, women younger than 56 years were more likely to achieve the MID for the 6MWT (OR, 2.0; 95% CI, 1.2-3.5; $P = .01$), but no significant association with the PCS or MCS was found. There was no relationship between age and odds of achieving any of the MID parameters in men.

Discussion

In this study, we report the association between patient characteristics and treatment response in patients with PAH. To our knowledge, this is the first study to examine the relationship between baseline demographic, clinical, and functional parameters and the attainment of patient-important, clinically relevant responses to PAH-specific therapy. Our data show that immutable patient characteristics, such as age, sex, and type of disease, influence the likelihood of response to therapy. Importantly, sex was associated with significantly increased odds of clinically relevant response in all three

TABLE 4] Predictors of Achieving the Minimal Important Difference for the Physical Component Summary: Nonimputed Data

Predictor	β (SE)	OR (95% CI)	P Value
Age, per 10 y	−0.16 (0.08)	0.85 (0.72-1.00)	.05
Sex, men vs women	0.63 (0.28)	1.87 (1.07-3.26)	.03
PAH etiology, CTD vs other	−0.17 (0.31)	0.84 (0.46-1.54)	.58
WHO FC, I/II vs III/IV	−0.24 (0.28)	0.79 (0.46-1.37)	.40
6MWD, baseline	0.0004 (0.002)	1.00 (0.99-1.00)	.80
Treatment status, active vs placebo	0.74 (0.33)	2.10 (1.11-3.99)	.03
Constant	−0.59	...	...

See Table 1 and 2 legends for expansion of abbreviations.

TABLE 5] Predictors of Achieving the Minimal Important Difference for the Mental Component Summary: Nonimputed Data

Predictor	β (SE)	OR (95% CI)	P Value
Age, per 10 y	−0.05 (0.08)	0.96 (0.81-1.12)	.58
Sex, men vs women	0.70 (0.28)	2.02 (1.16-3.52)	.01
PAH etiology, CTD vs other	0.14 (0.30)	1.15 (0.64-2.08)	.64
WHO FC, I/II vs III/IV	0.34 (0.28)	1.41 (0.81-2.45)	.22
6MWD, baseline	−0.0004 (0.002)	0.99 (0.99-1.00)	.05
Treatment status, active vs placebo	0.62 (0.33)	1.86 (0.98-3.52)	.06
Constant	−0.03	...	...

See Table 1 and 2 legends for expansion of abbreviations.

outcomes assessed: 6MWD (OR, 1.7), PCS (OR, 2.1), and MCS (OR, 2.2). Further, these associations persisted when accounting for potential confounders.

The robust effect of male sex predicting response to tadalafil is at odds with previous work showing improved outcomes in women receiving ERAs.¹⁷ There are several possible explanations for this finding, including sex

differences in response to ERAs as well as sex differences in nitric oxide (NO) metabolism. In one study using patient-level data from six randomized controlled trials of ERAs, Gabler and colleagues¹⁷ found a nearly 30-m difference in 6MWD in placebo-adjusted response to ERA when comparing women to men, suggesting that women with PAH experienced greater response to

TABLE 6] Characteristics of Study Population Stratified by Sex

Characteristic	Men (n = 88)	Women (n = 317)	P Value
Age, y, No. (%)	57 (15)	53 (15)	.01
White, No. (%)	69 (79)	217 (69)	.05
Weight, kg	72 (14.3)	69.6 (21.5)	.19
Height, cm	168 (7.8)	160 (7.7)	<.01
PAH etiology, No. (%)			<.01
Idiopathic	68 (77)	179 (57)	
Collagen vascular	9 (10)	86 (27)	
Anorexigen	2 (2)	14 (4)	
ASD/surgical	9 (10)	38 (12)	
WHO FC baseline, No. (%)			.71
I	1 (1)	3 (1)	
II	25 (28)	105 (33)	
III	60 (68)	204 (64)	
IV	2 (2)	5 (2)	
6MWT baseline, m	337 (79)	348 (78)	.38
Change in 6MWT, m	45 (56)	31 (54)	<.01
RAP, mm Hg	8 (5)	8 (4)	.87
PAP, mm Hg	53 (13)	54 (13)	.69
Cardiac index, L/min/m ²	2.4 (0.6)	2.6 (0.8)	.32
PCWP, mm Hg	11 (4)	9 (4)	.47
PVR, Wood units	10 (3)	11 (6)	.38
PCS baseline	35 (7)	33 (8)	.15
MCS baseline	46 (10)	48 (10)	.10

Data given as mean (SD) unless otherwise indicated. MCS = mental component summary; PCS = physical component summary. See Table 1 legend for expansion of other abbreviations.

Figure 2 – Proportion of subjects, by sex and stratified by treatment status, who achieved the minimal important difference for the 6-min walk test.

ERA than men. The authors hypothesized that this difference in response may be related, in part, to basal differences in circulating endothelin-1 (ET-1) levels and to greater ET-1-mediated coronary vasoconstriction in men compared with women that potentially affected the magnitude of response to ET-1 antagonism.^{27–29} Still, the underlying mechanisms of this divergent functional capacity response remain largely unknown.

Another potential contributor to the divergent response in 6MWD noted in the current study may be related to sex differences in NO metabolism. NO, a signaling molecule generated in the vascular smooth muscle and endothelial cells involved in modulating vascular tone and remodeling in the pulmonary vasculature, is thought to be deficient in PAH.³⁰ Tadalafil, the agent used in the current study, is a phosphodiesterase type 5 inhibitor that enhances NO signaling by impeding the catabolism of cyclic guanosine monophosphate (cGMP), whose downstream effects lead to vasorelaxation. In a study by Chan and colleagues,³¹ NO-mediated vasodilatation in murine mesenteric arteries exhibited sex-specific responses to stimulation of the NO-soluble guanylate cyclase (sGC) pathway. Specifically, these investigators found that in male mice, NO-mediated vasodilatation was solely through the NO-sGC-cGMP pathway. However, in female mice, in addition to NO-mediated vasodilatation via the NO-sGC-cGMP pathway, blockade of endothelium-derived hyperpolarizing factor led to increases in vascular tone, suggesting that sGC-independent pathways for NO activity exist. In humans, there is also evidence to suggest that NO metabolism may differ by sex. In a study by Forte and colleagues,³² total NO biosynthesis, assessed by urinary 15-N nitrate excretion, was significantly higher in women compared with men matched on various demographic and anthropometric characteristics. Thus, it is possible that differ-

ences in response to therapy between men and women in the current study may be related to underlying differences in NO metabolism. Since men may be more NO deficient, their response to enhanced NO signaling from phosphodiesterase type V inhibitor may be more robust than that seen in women.

Interestingly, baseline treatment status (active vs placebo) was not associated with odds of achieving the MID for the 6MWT. In the PHIRST study, treatment with 40 mg tadalafil was associated with a 33-m (95% CI, 15–50 m) improvement in 6MWD compared with placebo that was highly statistically significant ($P < .01$).⁵ Our current study uses all the study data, including patients on lower doses of tadalafil in whom the treatment effect (difference in 6MWD) showed a dose-response relationship: for the 2.5-mg group, 14 m (95% CI, 6–33 m); for the 10-mg group, 20 m (95% CI, 10–39 m); and for the 20-mg group, 27 m (95% CI, 11–44 m). Therefore, subjects assigned to lower-dose active treatment in the PHIRST study would be less likely achieve the MID of 33 m. Further, studies of combination therapy in PAH have consistently shown smaller average increases in 6MWD compared with studies of treatment-naïve patients (on average, about 25 m); > 55% of the PHIRST cohort were on background therapy. However, we found that neither the treatment effect (placebo-corrected change in 6MWD: 25.5 [SD, 60.8] m vs 31.2 [SD, 54.4] m; $P = .34$) nor the calculated MID differed between those patients who were treatment naïve and those on background therapy (estimate range, 30.4–38.7 m vs 27.2–37.4 m, respectively).¹⁸ Further, change in 6MWD in response to placebo may vary by sex. The prior study by Gabler and colleagues¹⁷ showed that women receiving placebo were significantly more likely to exhibit decline in 6MWD compared with men receiving placebo.

In the current study, male sex was also associated with achieving clinically relevant responses in HRQoL, both in the PCS and MCS of the SF-36. This may be related to sex differences in the psychologic response to improvements in physical health status or may reflect the off-target effects on sexual functioning from phosphodiesterase type 5 inhibitors, which has been previously shown to improve HRQoL independent from sexual quality of life.³³ Overall, the impact of sex on HRQoL has not been examined extensively in PAH. Although several randomized clinical trials of therapeutic agents in PAH have assessed various measures of HRQoL and disease-specific measures of QoL, most commonly as a secondary outcome measure, detailed analyses of these results, other than changes in mean

values of HRQoL parameters, are not often reported.^{10,11} In one cross-sectional study of HRQoL in patients with PAH, there was no significant relationship between sex and HRQoL.³⁴ In the current study, trends toward baseline differences in HRQoL were noted between sexes (Table 6). Men tended to have better HRQoL related to the physical domains of the SF-36, but were more likely to have poorer HRQoL related to the mental domains of the SF-36. However, in multivariable analyses, men were more likely to have clinically relevant improvements in both parameters. The baseline differences noted in both domains of the SF-36 and in response to tadalafil remain novel findings that need further exploration, particularly given the recent associations noted between HRQoL and clinical deterioration and survival.^{20,21}

Other characteristics were associated with odds of achieving clinically relevant outcomes. Older age at enrollment and shorter baseline 6MWD were both associated with attainment of clinically relevant responses. Age at diagnosis of PAH has been shown to be associated with disease severity and may be modified by sex. In the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry), no differences in survival were found between men and women aged < 60 years; however, men > 60 years old had a 60% increased risk of death compared with women > 60 years old.²⁶ Interestingly, analyses of pooled data from clinical trials of PAH-specific therapies demonstrated younger men (< 45 years old) had worse baseline hemodynamics than their female counterparts, with > 5 mm Hg higher mean pulmonary artery pressure after adjustment for race, height, and weight. This difference did not persist among other age strata.³⁵ In the current study, we found no effect modification of age (when included as a continuous variable or when stratified at 56 years of age) upon the relationship between sex and odds of achieving clinically relevant changes in 6MWD. However, when compared with women > 56 years of age, women younger than age 56 years were more likely to achieve the MID for 6MWT, but not the PCS or MCS, suggesting age may modify the response to therapy in women. Overall, subjects with shorter 6MWD at baseline were more likely to attain clinically relevant responses to therapy in both 6MWD and HRQoL. These findings are distinctly different from prior studies that demonstrated shorter baseline and posttreatment 6MWD is associated with poorer survival, highlighting the complex relationship between patient-important outcomes and survival.³⁶⁻⁴⁰

Subjects with CTD-PAH were less likely to experience clinically relevant improvement in 6MWD in the cur-

rent study, a finding that has been demonstrated in prior studies.^{2,7,41,42} This lack of response in CTD-PAH is often attributed to various comorbidities in CTD that may limit the efficacy of PAH-specific agents or may reflect inadequacy of currently used outcome measures for PAH in CTD-associated disease.^{43,44} This is further supported by the lack of association with clinically relevant improvement in the PCS and MCS in this subgroup. These findings highlight the need for the development and validation of disease-specific measures in CTD-PAH.

There are several limitations to the current study. While studies in normal populations from which predictive equations for the 6MWT have demonstrated significant differences in 6MWD between men and women based solely upon sex, these differences are not pronounced in PAH.⁴⁵⁻⁴⁷ As shown by Ventetuolo and colleagues,³⁵ at baseline assessment of > 1,200 patients with PAH enrolled in clinical trials for PAH therapy, the difference in mean 6MWD between men and women was < 20 m. Thus, it is unlikely that the observed differences in odds of achieving the MID for the 6MWT are based upon baseline differences in 6MWT between men and women. Further, the same data set used to determine an estimate of the MID for the 6MWT in PAH was used in this study and, therefore, these findings may only be applicable to patients with similar baseline demographic, functional, and hemodynamic characteristics. However, the study population is similar to most large, randomized clinical trials of novel therapies in PAH and, therefore, the results are likely generalizable to larger populations. Additionally, the MID for the PCS and MCS parameters were not derived from the current study cohort and, thus, may be more widely applicable. In any case, validation of these findings in other PAH cohorts is warranted. Importantly, factors for which we did not account in our multivariable analyses may influence the relationship between sex and these outcomes of interest. As discussed earlier, it is possible that off-target effects on erectile function may influence the observed increase in odds of a clinically relevant response in HRQoL in men compared with women. However, these effects would not explain the differences noted in 6MWD.

In conclusion, our study shows that baseline patient characteristics and, in particular, male sex are significantly associated with odds of achieving clinically relevant responses in patient-important outcomes such as 6MWD and HRQoL. This sex-specific heterogeneity in treatment response may reflect differences in

the pathobiology of PAH or in the efficacy of therapies for PAH. These findings offer the opportunity to inform individual treatment decisions and provide

the basis for exploring potential differences in mechanisms of disease and response to therapy between sexes.

Acknowledgments

Author contributions: S. C. M. served as principal author, drafted the manuscript, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. S. C. M., P. M. H., M. A. P., and R. A. W. contributed to the conception and design of the study and S. C. M., P. M. H., M. A. P., Y. Z., and R. A. W. contributed to data analysis and interpretation, and revision and final approval of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Mathai has served as a consultant for Actelion Pharmaceuticals Ltd, Bayer HealthCare (Bayer AG), and United Therapeutics Corp. Dr Hassoun has served on the advisory boards of Merck & Co Inc, Bayer AG, and Gilead Sciences Inc. Dr Wise has served as a consultant for the following companies that are not related to the content of this manuscript: AstraZeneca plc, Boehringer-Ingelheim GmbH, BristolMyersSquibb Co, Forest Laboratories Inc, GlaxoSmithKline plc, Intermune Inc, Janssen Global Services LLC, Merck & Co Inc, Mylan Laboratories Inc, Pfizer Inc, Pulmonx Corp, Roche-Genentech (Genentech Inc), Spiration Inc, and Sunovion Pharmaceuticals Inc. Drs Puhon and Zhou have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

- McLaughlin VV, Archer SL, Badesch DB, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53(17):1573-1619.
- Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346(12):896-903.
- O'Callaghan DS, Dorfmueller P, Jaïs X, et al. Pulmonary veno-occlusive disease: the bête noire of pulmonary hypertension in connective tissue diseases? *Presse Med*. 2011;40(1 pt 2):e65-e78.
- Barst RJ, Rubin LJ, Long WA, et al; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996;334(5):296-301.
- Galiè N, Brundage BH, Ghofrani HA, et al; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894-2903.
- Galiè N, Olschewski H, Oudiz RJ, et al; Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008;117(23):3010-3019.
- Galiè N, Ghofrani HA, Torbicki A, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353(20):2148-2157.
- Simonneau G, Barst RJ, Galiè N, et al; Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(6):800-804.
- Chen H, Rosenzweig EB, Gatzkowski SK, Arneson C, Nelsen AC, Bourge RC. Treatment satisfaction is associated with improved quality of life in patients treated with inhaled treprostinil for pulmonary arterial hypertension. *Health Qual Life Outcomes*. 2013;11:31.
- Pepke-Zaba J, Beardsworth A, Chan M, Angalakuditi M. Tadalafil therapy and health-related quality of life in pulmonary arterial hypertension. *Curr Med Res Opin*. 2009;25(10):2479-2485.
- Pepke-Zaba J, Gilbert C, Collings L, Brown MC. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. *Chest*. 2008;133(1):183-189.
- Hooper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation*. 2013;127(10):1128-1138.
- Ghofrani HA, Galiè N, Grimminger F, et al; PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2013;369(4):330-340.
- McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915-1922.
- McLaughlin V. Managing pulmonary arterial hypertension and optimizing treatment options: prognosis of pulmonary artery hypertension. *Am J Cardiol*. 2013;111(8 Suppl):10C-15C.
- Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? *JAMA*. 1999;282(8):790-795.
- Gabler NB, French B, Strom BL, et al. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. *Chest*. 2012;141(1):20-26.
- Mathai SC, Puhon MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2012;186(5):428-433.
- Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. *Curr Opin Rheumatol*. 2002;14(2):109-114.
- McCabe C, Bennett M, Doughty N, MacKenzie Ross R, Sharples L, Pepke-Zaba J. Patient-reported outcomes assessed by the CAMPHOR questionnaire predict clinical deterioration in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest*. 2013;144(2):522-530.
- Suber T, Shao K, Bueso M, et al. Impact of health related quality of life on outcomes in pulmonary arterial hypertension differs by disease type. *Am J Respir Crit Care Med*. 2013;187:A5376.
- Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. *Am J Respir Crit Care Med*. 2003;167(9):1287.
- Ware JE, Kosinski MA, Dewey JE. *How to Score Version 2 of the SF-36 Health Survey*. Lincoln, RI: QualityMetric, Inc; 2000.
- Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. *BMJ*. 2009;338:b604.
- Sauerbrei W. The use of resampling methods to simplify regression models in medical statistics. *Appl Stat*. 1999;48(3):313-329.
- Shapiro S, Traiger GL, Turner M, McGoon MD, Wason P, Barst RJ. Sex

- differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Chest*. 2012;141(2):363-373.
27. Miyauchi T, Yanagisawa M, Iida K, et al. Age- and sex-related variation of plasma endothelin-1 concentration in normal and hypertensive subjects. *Am Heart J*. 1992;123(4 pt 1):1092-1093.
 28. Polderman KH, Stehouwer CD, van Kamp GJ, Dekker GA, Verheugt FW, Gooren LJ. Influence of sex hormones on plasma endothelin levels. *Ann Intern Med*. 1993;118(6):429-432.
 29. Stauffer BL, Westby CM, Greiner JJ, Van Guilder GP, Desouza CA. Sex differences in endothelin-1-mediated vasoconstrictor tone in middle-aged and older adults. *Am J Physiol Regul Integr Comp Physiol*. 2010;298(2):R261-R265.
 30. Klinger JR, Abman SH, Gladwin MT. Nitric oxide deficiency and endothelial dysfunction in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2013;188(6):639-646.
 31. Chan MV, Bubb KJ, Noyce A, et al. Distinct endothelial pathways underlie sexual dimorphism in vascular autoregulation. *Br J Pharmacol*. 2012;167(4):805-817.
 32. Forte P, Kneale BJ, Milne E, et al. Evidence for difference in nitric oxide biosynthesis between healthy women and men. *Hypertension*. 1998;32(4):730-734.
 33. Giuliano F, Peña BM, Mishra A, Smith MD. Efficacy results and quality-of-life measures in men receiving sildenafil citrate for the treatment of erectile dysfunction. *Qual Life Res*. 2001;10(4):359-369.
 34. Taichman DB, Shin J, Hud L, et al. Health-related quality of life in patients with pulmonary arterial hypertension. *Respir Res*. 2005;6:92.
 35. Ventetuolo CE, Praetgaard A, Palevsky HI, Klinger JR, Halpern SD, Kawut SM. Sex and haemodynamics in pulmonary arterial hypertension. *Eur Respir J*. 2014;43(2):523-530.
 36. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol*. 2002;40(4):780-788.
 37. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J*. 2006;27(5):589-595.
 38. Gabler NB, French B, Strom BL, et al. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. *Circulation*. 2012;126(3):349-356.
 39. Fritz JS, Blair C, Oudiz RJ, et al. Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension. *Chest*. 2013;143(2):315-323.
 40. Mathai SC. Solvitur ambulando...or maybe not? *Chest*. 2013;143(2):285-287.
 41. Mathai SC, Girgis RE, Fisher MR, et al. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J*. 2007;29(3):469-475.
 42. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J*. 2004;24(3):353-359.
 43. Mathai SC, Hassoun PM. Pulmonary arterial hypertension associated with systemic sclerosis. *Expert Rev Respir Med*. 2011;5(2):267-279.
 44. Denton CP, Avouac J, Behrens F, et al. Systemic sclerosis-associated pulmonary hypertension: why disease-specific composite endpoints are needed. *Arthritis Res Ther*. 2011;13(3):114.
 45. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J*. 1999;14(2):270-274.
 46. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil*. 2001;21(2):87-93.
 47. Chetta A, Zanini A, Pisi G, et al. Reference values for the 6-min walk test in healthy subjects 20-50 years old. *Respir Med*. 2006;100(9):1573-1578.