CHEST
Original Research
PULMONARY VASCULAR DISEASE

Race and Sex Differences in Response to Endothelin Receptor Antagonists for Pulmonary Arterial Hypertension

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Background: **Recently studied therapies for pulmonary arterial hypertension (PAH) have improved outcomes among populations of patients, but little is known about which patients are most likely to respond to specific treatments. Differences in endothelin-1 biology between sexes and between whites and blacks may lead to differences in patients' responses to treatment with endothelin receptor antagonists (ERAs).**
Methods: **We conducted pooled analyses of deidentified, patient-level data from six randomized placebo-controlled trials of ERAs submitted to the US Food and Drug Administration to elucidate heterogeneity in treatment response. We estimated the interaction between treatment assignment (ERA vs placebo) and sex and between treatment and white or black race in terms of the change in 6-min walk distance from baseline to 12 weeks.**
Results: **Trials included 1,130 participants with a mean age of 49 years; 21% were men, 74% were white, and 6% were black. The placebo-adjusted response to ERAs was 29.7 m (95% CI, 3.7-55.7 m) greater in women than in men ($P = .03$). The placebo-adjusted response was 42.2 m for whites and −1.4 m for blacks, a difference of 43.6 m (95% CI, −3.5-90.7 m) ($P = .07$). Similar results were found in sensitivity analyses and in secondary analyses using the outcome of absolute distance walked.**
Conclusions: **Women with PAH obtain greater responses to ERAs than do men, and whites may experience a greater treatment benefit than do blacks. This heterogeneity in treatment-response may reflect pathophysiologic differences between sexes and races or distinct disease phenotypes.**
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Abbreviations: 6MWD = 6-min walk distance; ERA = endothelin receptor antagonist; ET = endothelin; FDA = US Food and Drug Administration; PAH = pulmonary arterial hypertension; RCT = randomized controlled trial; RV = right ventricular

Pulmonary arterial hypertension (PAH) leads to decreased functional status, right-sided heart failure, and death.[1] Recently studied therapies have improved outcomes, yet substantial heterogeneity remains in the risk of adverse clinical outcomes and the magnitude of the treatment response.[2-4]

Plasma levels of endothelin (ET)-1 are elevated among patients with PAH, contributing to pulmonary vascular remodeling.[5-7] Endothelin receptor antagonists (ERAs) were the first oral therapies approved by the US Food and Drug Administration (FDA) for use in PAH and remain among the most commonly used drugs to treat it. Despite their effectiveness, experience has shown that certain individuals may have a dramatic clinical response to ERAs, whereas others may have no response or may worsen.

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There are known biologic differences between sexes and among different races in the production and handling of ET-1, a potent systemic and pulmonary vasoconstrictor. Men have higher concentrations of circulating ET-1 than do women,[8,9] and men exhibit greater ET-mediated coronary vasoconstriction.[10] Blacks with systemic hypertension are known

to have higher plasma levels of ET-1 than do whites and a greater increase in ET-1 in response to stress.[11] Further, blacks with systemic hypertension have a greater reduction in BP with ERAs compared with that of whites.[12] The low enrollment of men and blacks and the relatively small sizes of phase 2 and 3 trials of ERAs in PAH have until now precluded study-wide tests of heterogeneity in treatment response. We, therefore, sought to assess whether sex and race modified the effects of ERA therapy in placebo-controlled trials of ERAs.

Materials and Methods

Study Population

We obtained data on all participants included in the seven randomized placebo-controlled trials of ERAs submitted to the FDA. These seven clinical trials (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies [ARIES]-1; ARIES-2; Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy [BREATHE]-1; BREATHE-2; Sitaxsentan To Relieve Impaired Exercise [STRIDE]-1; STRIDE-2; and STRIDE-4) examined three agents (ambrisentan, bosentan, and sitaxsentan). We subsequently excluded BREATHE-2 because it included only 33 patients, did not collect data on several potential confounders, and was not a phase 3 trial. Details of the included trials are provided elsewhere.[13-17]

Deidentified individual patient data for all participants were provided by the FDA. The included trials reported similar inclusion criteria, variable collection, and outcome assessment at 12-week follow-up.

Exposure

Our primary exposure variable was treatment assignment (ERA or placebo). Across trials, different agents and doses yielded similar improvements in 6-min walk distance (6MWD) relative to placebo and were, therefore, analyzed together. Covariates included age, sex, PAH diagnosis (idiopathic, connective tissue disease, HIV infection/anorexigen use, or congenital heart disease), height, weight, baseline laboratory and hemodynamic measures, and concurrent medication use.

Outcomes

The primary outcome of interest was the change in 6MWD from baseline to 12 weeks; 6MWD was the primary end point in all but one of the trials and was selected for this reason. Baseline 6MWD was obtained at the time of, or within 2 weeks prior to, randomization.

In the primary analyses, patients who were missing a 12-week 6MWD because of study-ending clinical events (n = 43) were assigned a value of 0 m for their 12-week 6MWD assessment. This choice was made a priori based on the assumption that patients who were too sick to complete the study would also be too sick to complete a 6MWD assessment. We also performed sensitivity analyses using 50, 100, 150, or 275 m (the mean 12-week 6MWD among patients who sustained a clinical event but still completed a 12-week 6MWD assessment) as the 12-week 6MWD.

We conducted four secondary analyses. First, we explored differences between baseline and the final recorded 6MWD, accounting for the fact that some trials lasted longer than 12 weeks. These analyses produced results similar to those of the primary analyses and are not reported. Second, we examined differences in the absolute distance walked at 12 weeks, which some have considered a better predictor of clinical outcomes.[18] Third, we repeated our primary analysis in the subset of patients with idiopathic PAH. Finally, we compared the proportions of patients in each treatment-by-sex and treatment-by-race stratum who sustained clinical events (death, lung transplant, atrial septostomy, hospitalization due to worsening PAH, withdrawal for worsening right-sided heart failure, or addition of prostacyclin analogs or phosphodiesterase inhibitors for PAH). We did not consider deterioration in 6MWD in the clinical event definition because this represented our primary outcome variable.

Statistical Analysis

Participant characteristics were summarized using medians and interquartile ranges for continuous variables and percentages for categorical variables. Primary and secondary outcomes were analyzed using linear or logistic regression for continuous or binary outcomes, respectively. We restricted the sample to blacks and whites when analyzing the interaction of treatment assignment with race. Separate models including all patients were used to estimate all other effects.

For the primary outcome, our most basic model included treatment (drug or placebo), sex, race, and the treatment-by-sex or treatment-by-race interaction terms. This model also adjusted for PAH diagnosis (idiopathic, connective tissue disease, HIV/anorexigen use, or congenital heart disease, entered as indicator variables), baseline 6MWD, patient height, and study. By including sex and height in the model, we effectively modeled 6MWD % predicted without violating statistical assumptions regarding ratio values.[19] In addition, a partially adjusted model additionally included diagnostic category, age, race, and sex. All other variables were examined as potential confounders in a third model that included any variables that altered the coefficient for the interaction term by ≥ 15%. A similar approach was used to model absolute distance walked without adjustment for baseline walk distance. Achievement of a certain threshold absolute walk distance, if prognostically significant, should be independent of baseline walk distance.

Multiple imputation was used to impute 12-week 6MWD for study participants who did not have a study-ending clinical event and were missing a 12-week 6MWD value (n = 45).[20] The

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imputation model included treatment, sex, and race, in addition to variables associated with missing 12-week 6MWD: study, baseline walk distance, and diagnosis category. Twenty imputed data sets were generated to estimate the variability among imputed values. All analyses were completed in SAS, version 9.2 (SAS Institute).

The study was approved by the institutional review board of the University of Pennsylvania (Review Board No. 4, approval 811814). All coauthors had access to the study data, take responsibility for the analysis, and had authority over manuscript preparation and the decision to submit for publication.

Results

The six trials included 1,130 patients. The participants' mean age was 49 years (range, 12-82), 21% were men, 836 (74%) were white, and 65 (6%) were black (Table 1). Seven hundred seventy-three patients (68%) were randomized to an ERA and 357 (32%) to placebo. Forty-three patients (4%) experienced study-ending clinical events; an additional 10 patients (1%) sustained clinical events but completed their 12-week 6MWD assessment. Mean baseline walk distance was 349 m (SD 87.0 m). Similar hemodynamic, laboratory, and severity of illness values were observed for men and women, and for whites and blacks (e-Tables 1, 2).

Treatment Response by Sex

The placebo-adjusted treatment response (mean improvement in those who received ERAs vs placebo) was 44.1 m among women and 16.7 m among men in the base model (Table 2). Thus, treatment response was 27.4 m (95% CI, 1.3-53.5 m) greater in women than in men. Women allocated to placebo showed a decrement in 6MWD that was prevented by assignment to ERAs. Men assigned to placebo did not show a decrement in 6MWD, but also did not show the benefit observed in women with assignment to ERAs (e-Fig 1). As shown in the partially adjusted model in Table 2, adjustment for age, race, and diagnosis category did not change these results. Further adjustment for potential confounding variables, such as laboratory and hemodynamic values, did not change the results (data not shown).

Women also demonstrated greater absolute walk distances at 12 weeks, with a placebo-adjusted 6MWD that was 27.5 m (95% CI, -8.3-63.3 m) greater than that for men (Table 3). After adjustment for confounders, the placebo-adjusted improvement for women was 44.9 m (95% CI, 9.2-80.6 m) greater than that for men.

Results were similar in sensitivity analyses in which higher values were used for the 12-week 6MWD among patients experiencing interval clinical events (e-Tables 3, 4), but the magnitudes of effect sizes diminished when larger values were entered for these 12-week walk distances. Likewise, analysis of only patients with a diagnosis of idiopathic PAH yielded similar overall results (e-Table 5), making it less likely that unmeasured differences in disease subtypes between women and men explained the results. Treatment with ERAs (vs placebo) did not influence

Table 1—*Characteristics of Study Participants*

Characteristic	Active Treatment (n = 773)	Placebo (n = 357)
Age, y	50 (38-61)	49 (36-60)
Male sex, No. (%)	158 (20)	78 (22)
Race, No. (%)		
Black	45 (6)	20 (6)
White	577 (75)	259 (73)
Other[a]	151 (20)	78 (22)
Height, cm	162 (157-168)	163 (157-168)
Weight, kg	69 (59-82)	70 (59-85)
BMI, kg/m^2	25.6 (22.7-30.2)	26.2 (22.9-30.6)
PAH diagnosis, No. (%)		
Idiopathic[a]	478 (62)	229 (64)
Connective tissue disease	216 (28)	86 (24)
HIV infection/anorexigen use	23 (3)	11 (3)
Congenital heart disease	54 (7)	30 (8)
New York Heart Association functional class, No. (%)		
I-II[a]	256 (33)	114 (32)
III-IV	516 (67)	243 (68)
Baseline hemodynamics		
Mean right atrial pressure, mm Hg	7.5 (5.0-11.5)	7.5 (4.0-12.0)
Mean pulmonary arterial pressure, mm Hg	50 (40-60)	51 (42-62)
Cardiac output, L/min	4.2 (3.3-5.2)	4.2 (3.4-5.3)
Cardiac index, L/min/m^2	2.3 (1.9-2.9)	2.3 (1.9-2.8)
Pulmonary capillary wedge pressure, mm Hg	9 (7-12)	10 (7-12)
Pulmonary vascular resistance, Wood units	10.2 (6.7-14.4)	10.0 (7.0-15.0)
Baseline laboratory values		
Albumin, g/dL	4.2 (3.9-4.5)	4.2 (3.9-4.5)
Creatinine, mg/dL	0.80 (0.71-0.97)	0.80 (0.68-0.97)
Hemoglobin, g/dL	14.8 (13.4-16.0)	14.5 (13.0-15.8)
Sodium, mEq/L	140 (138-142)	140 (138-142)
Warfarin use, No. (%)	466 (60)	230 (64)
Baseline 6MWD, m	360 (289-414)	366 (288-416)
Study, No. (%)		
ARIES-1	134 (17)	67 (19)
ARIES-2	127 (16)	65 (18)
BREATHE-1	145 (19)	69 (19)
STRIDE-1	118 (15)	60 (17)
STRIDE-2	185 (24)	62 (17)
STRIDE-4[a]	64 (8)	34 (10)

Data are presented as median (interquartile range) unless indicated otherwise. 6MWD = 6-min walk distance; ARIES = Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies; BREATHE = Bosentan: Randomized Trial of Endothelin receptor Antagonist Therapy; PAH = pulmonary arterial hypertension; STRIDE = Sitaxsentan To Relieve Impaired Exercise.

[a]Reference category for analysis.

Table 2—*Change in 6MWD From Baseline to 12-wk Follow-up by Sex*

Model	Women (n = 894)	Men (n = 236)	Difference-in-Difference (95% CI)	*P* Value for Interaction
Base model[a]				
Treatment	33.4	18.8	…	…
Placebo	−10.7	2.1	…	…
Δ (treatment-placebo)	44.1	16.7	27.4 (1.3-53.5)	.04
Partially adjusted model[b]				
Treatment	35.6	20.3	…	…
Placebo	−9.7	4.7	…	…
Δ (treatment-placebo)	45.3	15.6	29.7 (3.7-55.7)	.03

See Table 1 legend for expansion of abbreviation.

[a]Adjusted for study, height, and baseline walk distance.

[b]Adjusted for study, height, baseline walk distance, age, race, and diagnosis category; additional regression output provided in e-Table 9.

the risk of clinical events among men after adjusting for study and baseline walk distance (OR = 1.28; 95% CI, 0.22-7.49), but significantly reduced the risk of clinical events among women (OR = 0.27; 95% CI, 0.14-0.55) (*P* value for interaction = .11).

Treatment Response by Race

The placebo-adjusted treatment response was 41.5 m among whites and −3.5 m among blacks in the base model (Table 4), a treatment response difference of 45.0 m (95% CI, −2.4-92.4 m) (e-Fig 2). Results were similar in the models adjusting for diagnosis category, age, and sex. Further adjustment for potential confounding variables did not change these results.

Placebo-adjusted absolute walk distances at 12 weeks were 41.6 m for whites and 11.1 m for blacks, a difference of 30.5 m (95% CI, −35.8-96.8 m) (Table 5). Similar results were found in partially adjusted models including age, sex, and diagnostic category, but an attenuation of effects was observed when including New York Heart Association class in fully adjusted models. Results were similar in sensitivity analyses (e-Tables 6, 7) and in analyses restricted to patients with idiopathic PAH (e-Table 8). There were no clinical events among blacks in the placebo groups precluding calculation of a race-by-treatment interaction.

Discussion

This study suggests that sex and race may influence the response to ERA treatment of PAH. Specifically, we found that women had significantly greater responses in terms of change in 6MWD than did men. The differences between races did not meet the criteria for significance at the 0.05 level, although they had large effect estimates and CIs that just included the null value. These findings were consistent across different parameterizations of 6MWD, and were unlikely to be due to difference in illness severity because of comparable baseline hemodynamic and laboratory measures. We also found an indication of greater reductions in clinical events with ERAs among women and whites, but these differential effects were either not statistically significant or were unable to be quantified because of the low numbers of events.

Table 3—*Absolute Distance Walked at 12-wk Follow-up by Sex*

Model	Women (n = 894)	Men (n = 236)	Difference-in-Difference (95% CI)	*P* Value for Interaction
Base model[a]				
Treatment	381.6	378.0	…	…
Placebo	337.6	361.5	…	…
Δ (treatment-placebo)	44.0	16.5	27.5 (−8.3-63.3)	.13
Partially adjusted model[b]				
Treatment	373.1	370.7	…	…
Placebo	326.0	357.5	…	…
Δ (treatment-placebo)	47.1	13.2	33.9 (−1.0-68.6)	.06
Fully adjusted model[c]				
Treatment	369.4	362.5	…	…
Placebo	319.5	357.5	…	…
Δ (treatment-placebo)	49.9	5.0	44.9 (9.2-80.6)	.01

[a]Adjusted for study and height.

[b]Adjusted for study, height, age, race, and diagnosis category.

[c]Adjusted for study, height, age, race, diagnosis category, cardiac index, and pulmonary capillary wedge pressure; additional regression output provided in e-Table 10.

Table 4—*Change in 6MWD From Baseline to 12-wk Follow-up by Race*

Model	White (n = 836)	Black (n = 65)	Difference-in-Difference (95% CI)	*P* Value for Interaction
Base model[a]				
Treatment	31.7	14.4	…	…
Placebo	−9.8	17.9	…	…
Δ (treatment-placebo)	41.5	−3.5	45.0 (−2.4-92.4)	.06
Partially adjusted model[b]				
Treatment	32.5	12.0	…	…
Placebo	−9.7	13.4	…	…
Δ (treatment-placebo)	42.2	−1.4	43.6 (−3.5-90.7)	.07

See Table 1 legend for expansion of abbreviations.
[a]Adjusted for study, height, and baseline walk distance.
[b]Adjusted for study, height, baseline walk distance, age, sex, and diagnosis category; additional regression output provided in e-Table 11.

Interestingly, women and whites experienced deteriorations in 6MWD when assigned to placebo, whereas men and blacks did not and even showed some improvement on placebo. Women experienced greater benefits from ERAs compared with men, and whites may have benefitted more than blacks. Based on these observations, future studies are needed to explore the mechanisms accounting for why women and whites may show a greater response to ERA treatment. For example, such differences might be explained, in part, by known differences in estrogen concentrations or signaling[21,22] or in right ventricular (RV) contractility[23] between men and women. Women with idiopathic PAH have a higher RV ejection fraction at baseline, independent of a variety of confounders, including pulmonary vascular resistance.[23] Indeed, studies have shown improved survival among women with PAH in long-term treated cohorts.[24] It is possible that RV adaptation could allow women to have a greater or more rapid response to PAH treatment, while having a more severe trajectory without targeted therapy. Alternatively, off-target (ie, mechanistically unpredicted) drug effects could account for some of the observed variation between sexes. Finally, it is possible that these observed differences are due to variations in disease expression on 6MWD between men and women, and whites and blacks.

Blacks have increased levels of circulating ET-1[11,25] and greater increases in ET-1 in response to stress.[12] It is possible that these higher ET-1 levels are not sufficiently inhibited by currently available ERAs. A possibly reduced treatment response in blacks is consistent with literature reporting higher mortality among blacks with idiopathic PAH,[26] and with studies suggesting that blacks with cardiovascular and pulmonary illnesses often have worse outcomes than do whites.[27-30]

The identification of treatment-response heterogeneity can improve health care. First, pinpointing patient characteristics that modify baseline risks for adverse events and/or favorable therapeutic response can inform individual treatment decisions.[2,31] Second, isolating sources of treatment-response heterogeneity can enhance knowledge of the biologic mechanisms of disease pathogenesis in PAH. Third, recognizing differences in subpopulations with PAH could maximize the efficiency of future randomized

Table 5—*Absolute Distance Walked at 12-wk Follow-up by Race*

Model	White (n = 836)	Black (n = 65)	Difference-in-Difference (95% CI)	*P* Value for Interaction
Base model[a]				
Treatment	384.1	368.0	…	…
Placebo	342.5	356.9	…	…
Δ (treatment-placebo)	41.6	11.1	30.5 (−35.8-96.8)	.37
Partially adjusted model[b]				
Treatment	387.0	360.0	…	…
Placebo	344.2	344.9	…	…
Δ (treatment-placebo)	42.8	15.1	27.7 (−36.0-91.4)	.39
Fully adjusted model[c]				
Treatment	398.7	379.5	…	…
Placebo	357.1	351.9	…	…
Δ (treatment-placebo)	41.6	27.6	14.0 (−47.8-75.8)	.66

[a]Adjusted for study and height.
[b]Adjusted for study, height, age, sex, and diagnosis category.
[c]Adjusted for study, height, age, sex, diagnosis category, and New York Heart Association class; additional regression output provided in e-Table 12.

controlled trials (RCTs) by providing metrics upon which to stratify patients at enrollment. Therefore, extrapolating the summary result of an RCT to all patients may be inappropriate because the risks of adverse events may exceed the probabilities of clinical benefits for certain patients.[2,32,33] Quantifying a treatment's risk-benefit ratio for an individual with a given baseline risk may promote safer, more rational, and cost-effective drug use.[34]

Several limitations of this analysis were also limitations of the trials in our study. These include the use of 6MWD as the primary end point, the inclusion of mostly women and whites, and the short exposure times to active drug and placebo. Whether 6MWD should be viewed as an intermediate end point of clinical import (as it is by the FDA) or as a surrogate requires further research.[35] Acceptable type 1 error rates for interaction terms are controversial and a full picture of effect modification involves more than just the interaction *P* value.[36] Our analyses showed large point estimates of the interactions between treatment assignment and both sex and race; however, the results for race were not statistically significant at the $P < .05$ level. The identification of "white" and "black" was not uniform in the RCTs included in our study, and such misclassification would tend to bias results toward the null. We were unable to control for site differences within each study because of the low number of participants at each site. Finally, although our study was limited to the trials submitted to the FDA for drug approval, these are the precise studies upon which ERA treatment recommendations are made by the FDA.

Conclusions

In conclusion, our results indicate that women with PAH derive greater treatment responses to ERAs than do men. Whites with PAH may also have better responses than do blacks. Further studies are needed to determine whether these differences are attributable to heterogeneous responses to ERAs specifically or to more generalized differences in baseline risks for clinical deterioration among groups defined by race and sex.

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