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Ethnicity in Pulmonary Arterial Hypertension

Possibilities for Novel Phenotypes in the Age of Personalized Medicine

Sarah K. Medrek, MD; and Sandeep Sahay, MD

In the past decade and a half, the introduction of new therapeutic agents has revolutionized the management of pulmonary arterial hypertension (PAH). These new treatment options have improved the quality of life and survival in PAH. With an armamentarium of options available, the identification of unique phenotypes can help practitioners choose tailored treatment regimens. Experts in other cardiovascular diseases, such as congestive heart failure and hypertension, have recommended race-specific treatments in their fields based on data highlighting variations in response to therapies. With this perspective, we review evidence supporting the hypothesis that ethnicity or race plays an important role in the management of PAH. Preliminary research suggests that races/ethnicities have differences in the presentation and outcome of PAH and could respond to PAH-specific medications with varying efficacy. Genetic, physiological, and anatomic differences exist between races, particularly regarding the structure and function of the right ventricle. Unfortunately, clinical trials have not adequately included minorities, and registry data often omit inclusion of this demographic information. Further studies are needed to characterize the role that ethnicity plays in the prevalence, presentation, outcomes, and optimal treatment of PAH. CHEST 2018; 153(2):310-320

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Pulmonary hypertension (PH) is a chronic and progressive disease. If untreated, it leads to right-sided heart failure and death. The current World Health Organization classification places PAH into group 1 disease,[1] and patients with this condition have distinct treatment recommendations.[2] With the establishment of effective therapies for PAH, research has started to focus on how to best customize treatment. Identifying phenotypes of the disease and understanding different patterns of pathophysiological derangements will be critical in advancing the treatment of PAH.[3]

ABBREVIATIONS: CTD-PAH = connective tissue disease-associated pulmonary arterial hypertension; ERA = endothelin-receptor antagonist; HPAH = hereditary pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricular; MESA = Multi-Ethnic Study of Atherosclerosis; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PoPH = portopulmonary hypertension; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; RV = right ventricular; RVEF = right ventricular ejection fraction; Scl-APAH = scleroderma-associated pulmonary arterial hypertension; SLE = systemic lupus erythematosus

AFFILIATIONS: From the Division of Pulmonary, Critical Care, and Sleep Medicine (Dr Medrek), Baylor College of Medicine, Houston, TX; and Department of Medicine (Dr Sahay), Weill Cornell Medical College and Institute of Academic Medicine, Houston Methodist Hospital, Houston, TX.

CORRESPONDENCE TO: Sandeep Sahay, MD, Institute of Academic Medicine, Houston Methodist Hospital, Ste 1001, Smith Tower, 6550 Fannin St, Houston, TX 77030; e-mail: ssahay@houstonmethodist.org

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One characteristic that could help guide PAH therapies is ethnicity or race. Historically, the term race emerged in the 16th to 17th centuries to describe differences in physical characteristics between people. With scientific developments of the 19th century, it was used to refer to possible evolutionary differences between humans. Unfortunately, arguments that certain races were biologically inferior became a justification for the eugenics movement, and "ethnicity" was introduced in the 20th century as an alternative term and referred to the cultural, religious, and socioeconomic characteristics of groups.[4] These connotations persist today: MEDLINE defines race as a "major living subspecies of man differentiated by genetic and physical characteristics" and ethnicity as "a group of people with common cultural heritage that sets them apart from others in a variety of social relationships."[5] Although the US Office of Management and Budget does not offer definitions for the two terms, in 1997 they established five categories of race (including white, Asian, black, American Indian/Alaska Native, and Native Hawaiian or other Pacific Islander) and two categories of ethnicities (Hispanic or Latino and not Hispanic or Latino) to use for statistical and census purposes. This classification is also required for patients enrolled in National Institutes of Health (NIH)-sponsored clinical trials.[6,7] However, in modern use, "race" and "ethnicity" are often used interchangeably, in part because culturally defined groups often also have a common ancestral heritage. Some authors suggest using the term ethnicity in lieu of race to encompass both genetic and cultural attributes of groups of humans, but this is not universally accepted.[8]

The impact of PAH therapies in different races or ethnicities is still largely unknown. In other cardiovascular diseases, treatment guidelines specify different therapeutic strategies based on race. For systemic hypertension, guidelines recommend different first-line therapies for black vs nonblack patients.[9] Large trials in heart failure have also shown differential treatment effects for US patients self-identified as black compared with those self-identified as white.[10]

Currently, guidelines for PAH do not have any specific recommendations for targeting therapy based on race or ethnicity.[2] Extrapolating from other cardiovascular diseases, with this perspective we discuss research suggesting that PAH could also benefit from phenotyping based on this characteristic. Certain studies done in PAH support this hypothesis, as will be discussed. Research performed to date has shown differences between races/ethnicities in disease prevalence, outcomes, and response to therapy. Various biochemical, genetic, molecular, and physiological mechanisms could help explain these differences.

Prevalence of PAH by Race/Ethnicity

PAH can develop in all ethnicities, but it is less certain whether the disease differentially affects varying ethnicities or races. To begin to answer questions regarding this topic, results from national registries can provide insight. These registries provide information on demographics, disease subtype, and outcomes in addition to prevalence.[11] It is difficult to compare registries directly due to methodologic differences and confounding factors such as regional differences, including exposures, access to health care, and population-based disease comorbidities.[12] Unfortunately, few registries have reported data on race/ethnicity in their own populations. Table 1 highlights available race/ethnicity information provided by registries.

Registries from the United States provide the most information regarding race/ethnicity in PAH. The NIH registry enrolled 12.3% black patients and 2.3% Hispanic patients.[13] The Surveillance of Pulmonary Hypertension in America Registry reported a similar racial breakdown, enrolling 72.8% white patients and 18.5% nonwhite patients.[14]

The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) enrolled patients prospectively between 2006 and 2009 and included 72.8% non-Hispanic white, 12.2% black, 8.9% Hispanic, 3.3% Asian, and 2.8% other categories.[15] It showed a higher prevalence of Hispanic patients compared with earlier registries, a finding attributed to changes in population demographics.[13,15] One analysis of REVEAL compared the demographics of the registry to the concurrent general population. Results showed that blacks were relatively overrepresented in the registry compared with the general population, with a prevalence of 12.2% and an expected prevalence of 10.9%. There was underrepresentation of Hispanic patients, with the prevalence of 8.9% lower than the expected prevalence of 11.5%. There was also a relative underrepresentation of the Asian/Pacific Islander population. Whether these differences were due to disease pathophysiology, access to care, or variable ways of encoding race/ethnicity in census data vs medical charts was unknown.[15] REVEAL also showed that nonmajority racial/ethnic groups had a

TABLE 1] Registries That Have Reported a Breakdown of Their Participants by Race/Ethnicity

Registry	Cohort	Year/Type	No.	Ethnicity	%
Pulmonary Hypertension Registry of the United Kingdom and Ireland[16]	IPAH, HPAH, anorexigen-associated PAH	2001-2009/prospective	482	White Nonwhite	87.7 12.3
Chinese Registry[27]	IPAH, HPAH	1999-2004/prospective	72	Han nationality others	93.1 6.9
US NIH Registry[13]	IPAH, HPAH	1981-1985/prospective	578	White Black Hispanic	85.4 12.3 2.3
Surveillance of Pulmonary Hypertension in America Registry[14]	Primary pulmonary hypertension	1998-2001/prospective	321	White Nonwhite	81.5 18.5
US REVEAL Registry[15]	Group 1 PAH	2006-2009/prospective	2,955	White Black Hispanic Asian/Pacific Islander Other/unknown	72.8 12.2 8.9 3.3 2.8

HPAH = hereditary pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension.

higher female predominance. The female to male ratio was lowest in the white population, at 3.2:1; it was 5.5:1 in the black population, 4.7:1 in the Hispanic population, and 3.9:1 in other races.[15]

The UK registry reported race within its population and found that 12.3% of their patients were nonwhite. Like the REVEAL registry, it also found that patients of nonwhite race had a greater female predominance (84.6% female in nonwhite vs 68.3% female in white). Nonwhite patients were younger and less likely to have a history of smoking than white patients.[16]

Effect of Race/Ethnicity on Outcomes

Epidemiologic data from the United States, although limited because it is based on diagnostic coding, shows some consistent trends regarding outcomes by race/ethnicity. Data on primary pulmonary hypertension from 1979 to 1996 showed increased mortality in black patients, in particular black women.[17] Data from 1980 to 2002 evaluating primary and secondary pulmonary hypertension together showed increased age-specific death rates in black patients aged < 75 years.[18] Similar methodology evaluating 2001 to 2010 also showed a higher death rate for non-Hispanic blacks. In Asians and Hispanics, mortality was lower or similar to that in non-Hispanic whites.[19]

Despite the trend toward increased mortality in minority patients based on epidemiologic data, analysis of REVEAL data showed opposite findings. Five-year follow-up of the registry suggested that white patients had increased mortality. For white patients with previously diagnosed and newly diagnosed disease, the 5-year survival estimate was 63.5% and 57.4%, respectively, and in black patients it was 67.7% and 66%, respectively. Survival in Hispanics and other races was similar to survival in black patients.[20] The authors did not extensively analyze the topic of race/ethnicity with multivariate analysis, and it is unclear if this difference would persist after adjusting for disease severity, subtype, and other confounders. It is possible that different subgroups of PAH occur at varying rates in different backgrounds. Preliminary data obtained from analysis of 1,732 patients enrolled in the NIH-sponsored PAH Biobank supports this hypothesis. It suggested that black patients were more likely to have connective tissue-associated PAH and less likely to have portopulmonary hypertension (PoPH). Hispanic patients were more likely to have congenital heart disease.[21]

Kawut et al[22] performed a retrospective single-center cohort study from 1994 to 2002 in 82 patients with newly diagnosed PAH. Unlike REVEAL, which included all group 1 subtypes, this study included only patients with idiopathic, familial, or anorexigen-induced PAH. Multivariate survival analysis showed an association between black or Asian race and increased risk of death.[22] However, some concerns exist with this study pertaining to the socioeconomic status of the patient population. Racial status could be associated with lower socioeconomic status and decreased access to care.[23]

In the United States, the relationship between race/ethnicity and disease presentation remains an active area of investigation. Preliminary results from two studies,

TABLE 2] A Summary of Possible Explanations for Ethnic or Racial Variation in PAH

Possible Mechanism	Evidence
Genetic differences conferring increased risk to patients of different ethnicities	Variations in mitochondrial haplotypes[48] Differences in response to hypoxia[44] Polymorphisms in the gene *CYP1B1* association with reduced RVEF in black women[50]
Structural cardiovascular differences	Decreased right ventricular mass in black patients[49] Decreased pulmonary vascular distensibility in black sub-Saharan African patients[51]
Pharmacogenetic differences	Variations in endothelin-1 levels between black and white patients[52,53] Reduced efficacy of endothelin-receptor antagonists in black patients[54] Reduced nitric oxide-mediated vasodilatory response in black patients[56] Ethnic variation in cytochrome P450 enzymes[58]
Socioeconomic factors	Low socioeconomic status correlated with increased mortality in PAH in China[61] In the US, low socioeconomic status correlated with poorer functional status at the time of initial PAH diagnosis[62]

RVEF = right ventricular ejection fraction. See Table 1 legend for expansion of other abbreviations.

one involving a single center in Chicago and one evaluating the Pulmonary Hypertension Association Registry, suggest that black and Hispanics have more severe disease at the time of presentation.[24,25]

A Chinese study evaluated 55 patients with IPAH and compared them to US registry data. Despite presenting with a better functional class than the Western patients, Chinese patients had comparable hemodynamics. There was discordance between symptomatology and physiological parameters in the Chinese population.[26] This pattern, however, did not emerge in another study comparing the Chinese registries to Western registries, which showed increased Chinese mortality. Based on this information, it is difficult to draw unifying conclusions about the severity or outcomes of idiopathic pulmonary arterial hypertension (IPAH) in a Chinese vs Western population.[27]

PAH Subtypes and Race/Ethnicity

Connective tissue disease-associated PAH (CTD-PAH) is one subgroup that shows clear differences in presentation between races/ethnicities. A registry of cases of CTD-PAH in the United Kingdom showed that 76% of patients had scleroderma, 8% had mixed connective tissue disease, and 8% had systemic lupus erythematosus (SLE). Patients with scleroderma-associated PAH (Scl-APAH) without respiratory disease, meaning that they had scleroderma and met hemodynamic criteria for PH but also had an FVC > 60% and no significant pulmonary fibrosis on CT scanning, were 96% white. In comparison, patients who did have spirometric or radiographic findings suggestive of interstitial lung disease were considered as having respiratory disease-associated, scleroderma-associated PH, and were only 80% white. Survival was worse in the patients with respiratory disease-associated Scl-PH, a group with a higher nonwhite makeup.[28] Unfortunately, no specific analysis was performed comparing mortality between white and nonwhite patients in this paper. Data from China showed a pattern of CTD-PAH that was different from that in the UK cohort: 49% of patients had SLE and only 6% had scleroderma.[29]

In the United States, researchers have observed racial variation in Scl-APAH. An early study suggested that black patients with Scl-APAH presented at a younger age when compared with white patients.[30] A more recent study showed that black patients had significantly worse disease when evaluated by functional, hemodynamic, and serologic parameters. Although not statistically significant, survival in blacks was lower than in whites.[31] Other research from the United States suggests that CTD-PAH is more prevalent in black than in other races.[21]

Although other subtypes of PAH have received less attention regarding racial/ethnic variation in presentation or outcomes, some notable observations exist. There was a difference in the distribution of race/ethnicity in REVEAL between the patients with PoPH and the patients with IPAH/hereditary pulmonary arterial hypertension (HPAH). In the PoPH group, 12% of patients were Hispanic and 6% were black. In contrast, in the IPAH/HPAH group, 8% were Hispanic and 12% were black. The analysis did not adjust for possible confounders such as alcohol use or hepatitis C prevalence.[32] In HPAH, a number of genetic mutations are implicated in the pathogenesis of PAH.[33] Although there are no notable data regarding distribution of

mutations by race, it seems logical that certain mutations have different prevalence based on differing genetic backgrounds. Ongoing projects searching for novel mutations present in patients with PAH could provide increased insight on this topic.[34] Little information exists about toxin-induced PAH and race/ethnicity. However, toxins could have different manifestations based on physiological variations. For example, methamphetamine accumulates to a higher concentration in the lung in blacks than in other races.[35]

Reasons for Variations in Other Cardiovascular Diseases

Other cardiovascular diseases have shown variations in epidemiology and outcomes based on race or ethnicity. For example, in the United States, the age-adjusted rate for heart failure-related deaths for non-Hispanic blacks is higher than in the white population, and there are higher rates of hypertension and congestive heart failure in the black population.[36,37] Although this paper does not address this topic extensively, a brief description of some proposed pathogenic mechanisms in these diseases is mentioned to help provide a framework for the subsequent discussion of PAH.

Some structural cardiovascular variations could explain differences in outcomes between races/ethnicities. The Multi-Ethnic Study of Atherosclerosis (MESA) found that the left ventricular (LV) mass is lowest in Asian Americans and highest in blacks.[38] A different study evaluating differences in LV size in a prospective cohort of young adults showed that black men had increased LV mass.[39] Changes in the vascular endothelium between races offer another mechanism for differences: for example, one study suggested that impaired nitric oxide balance in black patients could predispose them to vasculopathy.[40] A number of genetic polymorphisms related to cardiovascular drug response are suggested to exist between ethnicities.[41] Variations in the aldosterone synthetase promoter gene in black patients have been linked to heart failure outcomes.[42] Finally, differences in neurohormonal signaling could also explain some of the variations in outcome between different races.[43] As we will show subsequently regarding PAH, certain of these concepts, including structural cardiovascular differences, intrinsic vascular differences, and genetic polymorphisms affecting drug metabolism or efficacy could help explain racial or ethnic variation in this disease process.

Pathophysiological Differences Between Races in PAH

With some data suggesting that there are differences in presentation and outcome between different races or ethnicities in PAH, understanding the mechanisms responsible for these discrepancies is important. Refer to Table 2 for a summary of possible explanations of variations.

There are differences between humans in the response to hypoxia, notably in groups native to high altitudes, such as Tibetans, although there is work to be done to understand the interplay between genetics and phenotypes in different populations.[44] Work evaluating the pathobiology of people living at high altitude provides insight into the role of genetic variation and response to hypoxia.[45] Novel research suggests that adverse perinatal events, including pre-eclampsia or periods of fetal hypoxia, could trigger a cascade of epigenetic events conferring a risk of subsequent pulmonary vascular disease.[46] This line of research is interesting and relevant, because there are known racial disparities in neonatal and perinatal mortality.[47]

Variations in mitochondrial haplotypes could offer another mechanism to explain racial variations. Mitochondrial function is important in PAH, because these organelles modulate the cellular response to hypoxia. A recent study suggests that certain mitochondrial haplogroups, whose distribution varies by race, could confer an increased risk of PAH.[48]

Structural cardiac differences and variations in pulmonary vasculature have been noted between different races. The most important source of data regarding variations in cardiac structure and function is MESA.[49] This investigation recruited patients without known cardiac disease at multiple centers in the United States and performed cardiac MRI. Results showed that right ventricular (RV) mass was lower in black than in white patients. This difference persisted after adjusting for differences in LV mass between the races. On initial assessment, Hispanic and Asian patients had a higher RV mass than did white patients, but this difference did not persist after adjusting for LV mass. Minorities including Hispanic, Asian, and black patients showed an increase in RV ejection fraction (RVEF) with age, possibly implying greater age-related stiffening. Black patients showed a trend toward lower baseline RVEF at baseline, although this did not meet statistical significance.[49]

Subsequent work performed in the MESA cohort has provided insight into the possible underpinnings of these cardiac differences. Work by Ventetuolo et al[50] published in 2016 evaluated 463 single nucleotide polymorphisms in 10 candidate genes in 2,761 genotyped participants and correlated them with measures of RV function. Polymorphisms in the gene *CYP1B1* were associated with differences in RVEF in black women. The study also found race-specific differences in the relationship between urinary estrogen metabolites and RVEF: although in the black and Chinese American populations there was no relationship, in white patients there was a positive correlation between estrogen metabolites and RVEF. In Hispanic patients, the correlation was negative.[50]

In addition to the differences noted between races in cardiac size and function, some preliminary data suggest that the pulmonary vasculature itself could also be different. A small study evaluated echocardiographic parameters at rest and with exercise in 30 black sub-Saharan African patients and 30 matched white patients. The calculated distensibility coefficient in the African men was lower than in the white men.[51]

PAH-Specific Therapy and Race

Variations in response to PAH-directed therapy could also play a role in causing differences in outcomes between races. The most robust data on this topic exists for the endothelin pathway. It was observed > 30 years ago that healthy black patients had increased circulating levels of endothelin-1 compared with white patients.[52] Subsequent work showed that black patients had not only higher levels of endothelin-1 but also a greater increase in response to stress.[53] Gabler et al[54] completed a pooled analysis of six randomized controlled trials of endothelin-receptor antagonists (ERAs) comparing outcomes based on demographic factors. In white patients, treatment resulted in an increased 6-min walk distance of 41.5 m, whereas black patients had a reduction in distance by 3.5 m. The *P* value for this finding was .07. They hypothesized that the higher circulating levels of endothelin-1 in blacks could mean that ERA dosing was insufficient.[54] An alternative explanation for variations in response to ERA is due to genetic differences. A study published in 2015 found that genetic polymorphisms could affect the clinical efficacy of the ERAs. It included patients with PAH who were previously enrolled in either drug trials or disease registries and a genome-wide association study was performed. The researchers found a single nucleotide polymorphism that conferred an improved clinical response to drug administration. Although this study included only patients of European descent, its results established that genetics could play a key role in the response to ERA therapy.[55]

Another important therapeutic target in PAH, nitric oxide, could also show variations with race. Studies have shown that black patients have a reduced nitric oxide-mediated vasodilatory response.[56] This finding could have a genetic basis: polymorphisms in endothelial constitutive nitric oxide synthase display racial differences, and patients with these variants have alterations in plasma nitric oxide levels.[57]

Other pharmacogenetic rationales could also explain the varying responses to treatment by race. The cytochrome P450 enzymes, which are relevant in drug metabolism, show racial variation both in their genotypic and phenotypic expression.[58]

Recent work suggests that neurohormonal pathways, including the sympathetic nervous system and renin-angiotensin-aldosterone system, could play an important role in the pathogenesis of PAH. Although there are no proven pharmacologic interventions targeting these pathways for the treatment of PAH, research is ongoing.[59] Although speculative, given that work in heart failure suggests that genetic polymorphisms in neurohormonal pathways show racial variation, it is possible that this mechanism could also explain some racial variations in PAH.[43]

Role of Socioeconomic Factors

A final but important topic when discussing ethnicity in PAH outcomes is the role of socioeconomic factors. Minority populations often have lower socioeconomic status due to complex cultural factors. Having a reduced socioeconomic status is linked to decreased access to care, resulting in higher disease severity at presentation and limiting the availability of advanced therapeutic options.[60] Prospective data collected in China suggested that lower socioeconomic status correlated with increased mortality in PAH.[61] A recent analysis evaluated US patients with PAH using their home zip code as a surrogate for socioeconomic status. There was an inverse correlation between functional class at the time of initial assessment and household income. Although mortality was not assessed, the authors argued that functional class is validated as a predictor of outcome in PAH.[62] Of note, the REVEAL registry also recorded zip codes as a marker of socioeconomic status,

TABLE 3] Summary of the Races/Ethnicities Represented in the Major PAH Drug Trials

Approved Drug	Study/Year	Location	Race	No.	%
Calcium channel blockers	Rich et al[66]/1992	Single center in the United States	Not reported	NA	NA
Epoprostenol	Barst et al[67]/1996	Multiple centers in North America	Not reported	NA	NA
Treprostinil (subcutaneous)	SC-TRE[73]/2001	40 centers in North America, Europe, and Australia	White Black Other	396 21 52	84.6 4.5 11.1
Bosentan	Study 351[74]/2001	5 centers in the United States and 1 in France	White Black Other	25 5 2	78.1 15.6 6.3
	BREATHE[75]/2002	27 centers in Europe, North America, Israel, and Australia	White Other	170 43	79.8 20.1
Iloprost	AIR[70]/2002	37 European centers	Not reported	NA	NA
Sildenafil	SUPER[76]/2005	53 centers in the United States, Mexico, South America, Europe, Asia, Australia, South Africa, and Israel	White Black Asian Other	236 6 19 16	85.2 2.1 6.9 5.8
Ambrisentan	ARIES-1[77]/2008	46 centers in the United States, Mexico, South America, Australia, and Europe	White Black Asian Hispanic Other	139 11 6 41 4	69.1 5.5 3.0 20.4 2.9
	ARIES-2[77]/2008	41 centers in Europe, Israel, and South America	White Black Asian Hispanic Other	163 0 3 26 0	84.9 0 1.6 1.3 0
Tadalafil	PHIRST[78]/2009	84 centers in Canada, the United States, Europe, and Japan	White Asian African Other	326 34 34 11	80.5 8.4 8.4 2.7
Treprostinil (inhaled)	TRIUMPH[69]/2010	Multiple centers in the United States and Europe	Not reported	NA	NA
Treprostinil (orally)	FREEDOM-C[71]/2012	Multiple centers in North America, Europe, and Australia	Not reported	NA	NA
Treprostinil (orally)	FREEDOM-C2[72]/2013	Multiple centers in North America, Europe, and China	Not reported	NA	NA
Treprostinil (orally)	FREEDOM-M[80]/2013	Multiple centers in the United States, Canada, Europe, India, China, Mexico, and Israel	Asian White Black Native American Not reported	165 143 11 28 2	47.2 41.0 3.2 8.0 0.6
Macitentan	SERAPHIN[81]/2013	39 countries including representation from Europe, Asia, South America, North America, South Africa, and Australia	White Black Asian Hispanic Other	403 19 205 109 3	54.5 2.3 27.7 14.7 0.4
Riociguat	PATENT[82]/2013	124 centers in 30 countries including representation from Europe, Asia, Australia, South America, North America, and New Zealand	White Black Asian Mixed Not available	271 6 139 2 24	61 1.4 31.4 0.5 5.4

(Continued)

TABLE 3] *(Continued)*

Approved Drug	Study/Year	Location	Race	No.	%
Selexipag	GRIPHON[68]/2015	181 centers in 39 countries including representation from Australia, South America, North America, Europe, and Asia	Not reported	NA	NA
Ambrisentan plus tadalafil	AMBITION[79]/2015	120 centers in 14 countries including representation from Australia, Europe, and North America	White Nonwhite	446 54	89.2 10.8

but this factor was not significantly predictive of mortality in an analysis performed in 2010.[63] A recent cross-sectional analysis performed at the Pulmonary Hypertension Association annual meeting evaluated the response of attendees with PAH to the Cambridge Pulmonary Hypertension Outcome Review questionnaire, which measures quality of life measures in three domains. Income did not significantly correlate with quality of life, symptoms, or activity scores. However, patients with Medicare or self-purchased health care had worse symptom scores compared with patients with private health insurance.[64]

A question therefore arises about whether poorer outcomes in various ethnicities might be due to lower socioeconomic status and not to any intrinsic physiological differences. In other diseases, apparent differences between outcomes have not persisted after adjusting for patient factors, including socioeconomic status and comorbidities.[65] Future studies of PAH should pay close attention to the role of socioeconomic status as a possible confounder. Increased inclusion of underrepresented races/ethnicities in clinical trials could help address these issues.

Enrollment of Races/Ethnicities in Trials

Inclusion of different races/ethnicities in clinical trials of PAH has been variable but overall has been insufficient. Major landmark clinical trials regarding treatment of PAH did not report race-related information.[66,67] Other trials over the years have also failed to provide this information, as recently as Prostacyclin (PGI2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) in 2015.[68-72] Most trials have recruited at least 78% white patients.[73-79] The percentage of white patients was as high as 89.2% in Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION), 85.2% in Sildenafil Use in Pulmonary Arterial Hypertension (SUPER), 84.9% in Ambrisentan in Patients with Moderate to Severe Pulmonary Arterial Hypertension (ARIES-2), and 83.6% in Subcutaneous Infusion of Treprostinil (SC-TRE).[73,76,77,79] A few studies have included a significant Asian cohort. The prevalence in Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) was 27.7%; in Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial (PATENT), it was 31.4%; and in Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension (FREEDOM-M), it was 47.2%.[80-82] Representation of black patients is poor, ranging from 0% in the ARIES-2 arm of the ambrisentan trials to a maximum of 15.6% in a trial for bosentan.[74,77] Increasing the enrollment of racial/ethnic minorities in clinical trials will increase the sample size of these populations and allow for more detailed subgroup analyses. Table 3 highlights race/ethnicity information from clinical trials.

Certain factors can complicate enrollment of racial/ethnic minorities in clinical trials. Historically in the United States, certain groups, such as blacks, have shown a reluctance to participate in clinical research. In some cases, this is due to distrust of the scientific establishment.[83] A 2008 study showed that blacks had a significantly reduced willingness to participate in cardiovascular prevention trials compared with whites.[84] Underrepresented patients have other reasons for not participating in trials, including lack of access to trials, restrictive inclusion criteria, no availability of consent forms in the native language, and a lack of education about the purpose of clinical trials.[85]

Conclusions

Although the role of race/ethnicity in PAH is complex, understanding its impact on this disease could develop increased importance as we move into the realm of personalized medicine. Work done to date trying to understand the interplay between race or ethnicity and

PAH has shown conflicting findings. Although some analyses suggest that minorities are at risk for worsened outcomes in PAH, other studies do not support this conclusion. Data from Europe and the United States show that minorities could have a higher female predominance and suggest differences in the prevalence of CTD-PAH between races/ethnicities. The role of socioeconomic factors confounds analysis and merits further investigation.

We find the information learned to date regarding pathophysiological differences between races in the realm of PAH to be thought provoking and hypothesis generating. Multiple factors affecting variations in cardiovascular function, neurohormonal signaling, and response to pharmacologic intervention between races have been identified and could play important roles in the development of PAH.

Going forward, understanding the interactions between race/ethnicity and PAH could yield important developments in tailoring therapeutic interventions to individuals. In part, this can be accomplished by continuing the important work that has already begun evaluating the genetics of this disease. Increased inclusion of minorities in clinical trials will be critical to see if therapeutic interventions have similar efficacy in different patient groups. Furthermore, analysis of existing registries, such as REVEAL, to determine racial/ethnic differences in prevalence and outcomes by PAH subtype could yield important insights. Future work should focus on these topics to enhance our ability to treat this deadly disease.

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