The Changing Picture of Patients With Pulmonary Arterial Hypertension in the United States

How REVEAL Differs From Historic and Non-US Contemporary Registries

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**Background:** REVEAL (The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) provides current demographics of patients with group 1 pulmonary arterial hypertension (PAH) in the United States.

**Methods:** A total of 2,967 patients with PAH diagnosed based on right-sided heart catheterization were enrolled in REVEAL between March 2006 and September 2007. Demographics from the REVEAL patient cohort and REVEAL subpopulations (matched by inclusion criteria to other registries) were compared with historic US registry data and other contemporary US and non-US national PAH registries by inclusion criteria, including the National Institutes of Health (NIH) PAH registry and the French PAH registry.

**Results:** REVEAL patients matched to NIH registry patients were older at diagnosis (mean ± SE, 44.9 ± 0.6 years vs 36.4 ± 1.1 years; difference, 8.5 ± 1.4; P < .001) and more likely to be women (78.7 ± 1.2% vs 63.1 ± 3.5%; P < .001). REVEAL patients matched to French registry patients had similar age and severity at diagnosis, but REVEAL patients were more likely to be women (79.8 ± 0.8% vs 65.3 ± 1.8%; P < .001) and obese (BMI, ≥ 30 kg/m², 32.5 ± 1.0% vs 14.8 ± 1.4%; P < .001), whereas French patients were more likely to have HIV-associated PAH (6.2% vs 2.3%). The female preponderance is similar to that in other US-based contemporary registries.

**Conclusions:** At diagnosis, REVEAL patients were older than NIH registry patients and similar in age to patients enrolled in contemporary registries. Compared with NIH and contemporary European and UK registries, there was a striking preponderance of women, and REVEAL patients were more likely to be obese. These observations and the difference in HIV-associated PAH between REVEAL and other non-US contemporary registries warrant further investigation.

**Trial registry:** ClinicalTrials.gov; No.: NCT00370214; URL: clinicaltrials.gov.

Abbreviations: APAH = pulmonary arterial hypertension associated with other disorders; FC = functional class; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NHLBI = National Heart, Lung, and Blood Institute; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PHC = Pulmonary Hypertension Connection; PVR = pulmonary vascular resistance; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; REVEAL FCC = REVEAL French Comparison Cohort; REVEAL NIH = REVEAL National Institutes of Health Comparison Cohort; RHC = right-sided heart catheterization

Original Research

Pulmonary arterial hypertension (PAH) is a disease characterized by progressive fibrotic and proliferative changes in and around the small pulmonary arteries, leading to vessel obstruction, right ventricular failure, and death. The diagnosis of PAH is made after right-sided heart catheterization (RHC) confirmation of elevated pulmonary artery pressures (defined as a mean of ≥ 25 mm Hg at rest) with the absence
of other pulmonary parenchymal, hypoxic, or thrombotic lung disease or left-sided heart disease. PAH can be idiopathic, heritable, or associated with other conditions (eg, connective tissue disease). The idiopathic, heritable, and disease-associated forms of PAH share common pathology and pathophysiology. Even with increased physician awareness and relatively recent development of therapies, PAH remains frequently refractory to therapy, with death only delayed.

The ongoing, multiregister, observational, US-based REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management), sponsored by Actelion Pharmaceuticals, meets the need for information about current demographics and treatment practices for patients with group 1 PAH. Because REVEAL was initiated before publication of the fourth World Symposium on Pulmonary Hypertension, patients enrolled into the registry were classified according to the guidelines for PAH established by the third World Symposium on Pulmonary Hypertension: mean pulmonary artery pressure (mPAP) >25 mm Hg at rest or >30 mm Hg with exercise; pulmonary capillary wedge pressure (PCWP) <15 mm Hg; and pulmonary vascular resistance (PVR) >240 dyne/s/cm² (ie, >3.0 Wood units). REVEAL also included an expanded criterion for patients with PCWP ≤18 mm Hg.

The first registry for PAH, known as the Patient Registry for the Characterization of Primary Pulmonary Hypertension, began in 1981 and was sponsored by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI). It included 187 patients and provided the foundation for subsequent studies of both PAH and other pulmonary vascular diseases. More recent US registries include the large, single-center Pulmonary Hypertension Connection (PHC) registry (1982-2006) (N = 578) and the Surveillance of Pulmonary Hypertension in America registry (1998-2001) (1,180 incident enrollees with pulmonary hypertension, including 346 patients with group 1 PAH evaluated in the context of anorexigen drug exposure). National registries in Scotland and France have provided more current information on the nature of PAH in those countries. The Scottish registry used data from the Scottish Morbidity Record (1986-2001) (374 incidence cases) and the national specialist center for PAH management known as the Scottish Pulmonary Vascular Unit (1997-2005), whereas the French Network on PAH studied current epidemiologic trends (2002-2003) (N = 674).

Despite useful contributions to the PAH literature, the Surveillance of North American Pulmonary Hypertension (N = 205), a Swiss registry, and a Chinese registry were excluded from comparison in the current study because of lack of diagnostic RHC and inclusion of patients with conditions other than group 1 PAH.

The objectives of this study were to answer the following questions: Do the demographics of patients with group 1 PAH in the current era differ from the demographics of similar patients in previous US-based registries? Do the demographics of US patients with group 1 PAH differ from similar patients in non-US registries? The comparison took into account temporal and demographic trends in the United States relative to the non-US-based registries.

**Materials and Methods**

For REVEAL, investigators consecutively enrolled consenting patients with group 1 PAH at 54 US sites. The registry protocol was approved by the institutional review board of each study center. All patients provided written informed consent. To better reflect patterns of practice in the United States and to be more inclusive in analysis of treatment and outcomes over time, pediatric patients (≥18 years of age) and patients fitting a broader hemodynamic definition of PAH than usual (PCWP ≤18 mm Hg) were enrolled. Patients with a PCWP >15 mm Hg and ≤18 mm Hg were included because having a risk factor for left-sided heart dysfunction (eg, systemic hypertension, diabetes, obesity, sleep apnea) may not preclude the presence of true PAH as ventricular interdependence can produce elevations in PCWP that would otherwise exclude patients with true PAH from study enrollment. Furthermore, these patients (who often are encountered in daily practice) were included to test the validity of such inclusion in the analysis of outcomes. This expanded criterion for inclusion in a PAH registry represents a major difference between REVEAL and other contemporary and historical PAH registries. The NIH registry excluded patients with PCWP >12 mm Hg and subsequent registries and therapeutic studies have excluded patients with PCWP ≥15 mm Hg.

In addition to comparing the total REVEAL database to the different registries, enrollment criteria from other registries were applied to the REVEAL population, and the data generated from these REVEAL subpopulations were used for more tailored analyses.
comparisons with other registries. The REVEAL French Comparison Cohort (REVEAL\textsuperscript{FCC}) represented 2,355 patients from REVEAL similar to those enrolled in the French, Scottish, and PHC registries. These registries included patients aged \( \geq 18 \) years or \( \geq 16 \) years (Scottish registry) at diagnosis with PCWP \( < 15 \) mm Hg or \( \leq 15 \) mm Hg (PHC registry). The REVEAL\textsuperscript{FCC} cohort was selected to match the age and hemodynamic entry criteria of these registries. The REVEAL NIH Comparison Cohort (REVEAL\textsuperscript{NIH}) represented a subpopulation of patients \((n = 1,072)\) aged \( \geq 1 \) year at enrollment (to exclude pulmonary hypertension of the newborn) with idiopathic PAH (IPAH) or familial PAH (FPAH) and PCWP \( \leq 12 \) mm Hg (identical to the enrollment criteria for the NIH registry).\textsuperscript{5} Age, New York Heart Association and World Health Organization functional class (FC), hemodynamics at the time of diagnosis (defined as time of diagnostic RHC), and selected comorbidities were compared, when available, among the registries. The time periods and number of patients enrolled and cohort inclusion criteria for the various registries are shown in Table 1.

Lower-bound estimates of incidence and prevalence from prospective studies are underestimates because no individual study captures all patients with PAH, whether diagnosed or undiagnosed, in a national or regional population. To calculate incidence, we identified all adult patients receiving a diagnosis during a 12-month period corresponding to the latter portion of REVEAL enrollment and divided by the adult US population for the same period.\textsuperscript{13,14} The prevalence was calculated using the same denominator and included all adult REVEAL patients in the numerator. Our numerator necessarily fails to include undiagnosed and misdiagnosed patients; diagnosed patients not seen at PAH centers; patients seen at PAH centers that did not participate in REVEAL; patients seen at REVEAL sites who did not have clinic visits during the time between the site Institutional Review Board approval and the end of REVEAL enrollment; patients seen at REVEAL sites with missing data on the catheterization report, causing them to fall short of the protocol definition of PAH diagnosis; and patients seen at REVEAL sites during the enrollment period who did not consent to be included in the registry. Due to the nature of the US health-care system, it is not possible to estimate the extent to which the calculated lower bound underestimates the true incidence and prevalence.

**Results**

**Patient Cohort and Cohorts Matched to Prior Registries**

Between March 2006 and September 2007, 2,967 patients meeting study entry criteria at rest were enrolled in REVEAL. For purposes of comparison with other PAH registries, patients in REVEAL who met the definition of PAH with exercise (mPAP \( > 30 \) mm Hg) were excluded from these analyses \((n = 12)\), leaving 2,955 patients in the total REVEAL analysis cohort. The mean \( \pm SE \) duration from diagnosis to enrollment was 38.6 \( \pm 0.8 \) months (median, 26.0 months). REVEAL consisted of approximately equal numbers of patients with IPAH, FPAH (now called heritable PAH),\textsuperscript{15} and PAH associated with other disorders (APAH) (Fig 1). The NIH registry included patients with IPAH and FPAH.

**Demographics**

REVEAL demographics suggest that the modern US PAH patient population is older (mean age at diagnosis, 47 years) and has a higher female preponderance (75%; female:male ratio, 3.6:1) than in the 1980s as reported for the NIH registry (mean age, 36.4 years, female sex, 64%; female:male ratio, 1.8:1) (Fig 2). The contemporary French and Scottish registries reflect a similar female preponderance and female:male ratio to that seen in the NIH registry (65% and 66%, respectively; female:male ratio, 1.9:1). The female:male ratio for patients enrolled in REVEAL increases with survival postdiagnosis, with 3.3:1 within 1 year postdiagnosis, 3.5:1 at 1 to 5 years postdiagnosis, and 4.3:1 at \( > 5 \) years after diagnosis.

Few comorbidity data were reported in the NIH and French registries. Smoking, anorexigen exposure, contraception history, and parity data were obtained from the NIH registry participants; only anorexigen exposure history and BMI were obtained in the French registry. In contrast, robust data on comorbidities have been obtained from REVEAL. Anorexigen exposure was reported in 5% of the NIH population and 9.5% of the French population (7.3% of the French registrants reported exposure to a fenfluramine derivative). Anorexigen exposure is much higher in the REVEAL population, with 15.3% of all patients

### Table 1—Characteristics of the Registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Cohort</th>
<th>Time Period</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVEAL</td>
<td>Group 1 PAH; aged ( \geq 3 ) mo; PCWP ( \leq 18 ) mm Hg</td>
<td>2006-2014\textsuperscript{4}</td>
<td>2,955</td>
</tr>
<tr>
<td>REVEAL\textsuperscript{FCC}</td>
<td>Group 1 PAH; age (at diagnosis) ( \geq 18 ) y; PCWP ( &lt; 15 ) mm Hg</td>
<td>2006-2014\textsuperscript{4}</td>
<td>2,355</td>
</tr>
<tr>
<td>REVEAL\textsuperscript{NIH}</td>
<td>Group 1 IPAH or FPAH; age (at enrollment) ( \geq 1 ) y; PCWP ( \leq 12 ) mm Hg</td>
<td>2006-2014\textsuperscript{4}</td>
<td>1,072</td>
</tr>
<tr>
<td>PHC\textsuperscript{b}</td>
<td>Group 1 PAH; age ( \geq 18 ) y; PCWP ( \leq 15 ) mm Hg</td>
<td>1982-2006</td>
<td>578</td>
</tr>
<tr>
<td>NIH PPH</td>
<td>IPAH and FPAH with PCWP ( \leq 12 ) mm Hg</td>
<td>1981-1985</td>
<td>187</td>
</tr>
<tr>
<td>French registry\textsuperscript{a}</td>
<td>Group 1 PAH; age ( \geq 18 ) y; PCWP ( &lt; 15 ) mm Hg</td>
<td>October 2002-October 2003</td>
<td>674</td>
</tr>
<tr>
<td>Scottish\textsuperscript{a}</td>
<td>SMR data; group 1 PAH; age 16-65 y; PCWP ( &lt; 15 ) mm Hg</td>
<td>1986-2001</td>
<td>374</td>
</tr>
</tbody>
</table>

FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PHC = Pulmonary Hypertension Connection; PPH = primary pulmonary hypertension; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; REVEAL\textsuperscript{FCC} = REVEAL French Comparison Cohort; REVEAL\textsuperscript{NIH} = REVEAL NIH Comparison Cohort; SMR = Scottish Morbidity Record.

\textsuperscript{a}REVEAL enrollment was completed in December 2009. All patients will be followed for 5 years.

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Original Research

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Hispanics and Asians appear to be slightly underrepresented, and blacks are slightly overrepresented. This distribution may reflect differences in the way race is captured in medical charts vs the US Census Bureau, differences in prevalence, or differences in access to specialty care. US demographics have changed in the 2 decades since the NIH study. From 1980 to the most recent census in 2007, individuals of Hispanic origin in the United States have increased significantly from 6% to 15% of the population; the black population increased from 11.6% in 1980 to 12.8% in 2007. In the NIH registry, only 2.3% of the patients were Hispanic and 12.3% black. Demographic census reporting some appetite suppressant use, although only 3.5% reported use of a fenfluramine derivative.

Increased anorexigen exposure in REVEAL probably reflects the epidemic of obesity in the United States. Obesity (defined as BMI ≥ 30 kg/m²) occurs in 33% to 35% of adult US men and women, respectively. The overall REVEAL population reflects this demographic, with 32% classified as obese at enrollment. In contrast, only 14.8% of the French registry cohort were obese, a proportion similar to that of the adult French population.

A comparison of the actual vs expected distribution of patients in REVEAL by race (adjusted for sex and age) showed that the REVEAL distribution of whites reflect the expected profile (Table 2); Hispanics and Asians appear to be slightly underrepresented, and blacks are slightly overrepresented. This distribution may reflect differences in the way race is captured in medical charts vs the US Census Bureau, differences in prevalence, or differences in access to specialty care. US demographics have changed in the 2 decades since the NIH study. From 1980 to the most recent census in 2007, individuals of Hispanic origin in the United States have increased significantly from 6% to 15% of the population; the black population increased from 11.6% in 1980 to 12.8% in 2007. In the NIH registry, only 2.3% of the patients were Hispanic and 12.3% black. Demographic census
data in France is ethnically neutral; thus, ethnicity data are not available from the French registry. The limited data on ethnicity in Scotland suggests that < 2% of the population are nonwhite. The absence of racial or ethnic data in other contemporary national registries precludes comparisons with REVEAL data.

In the overall REVEAL cohort, the female:male ratio is 4.7:1 in the Hispanic population, 5.5:1 in the black population, 3.2:1 in the white population, and 3.9:1 in other races (Asian/Pacific Islander, Native American, other/unknown). In the REVEAL IPAH and FPAH subpopulations, the female:male ratios are 3.2, 5.2, and 5.6:1 in the white, black, and Hispanic populations, respectively, and 3.2, 6.1, and 4.2:1, respectively, in the REVEAL APAH subpopulation.

Although the increasing female preponderance reported by REVEAL affects the white population, the increase in female:male ratio (3.6:1 in the overall cohort) also may reflect the increasingly ethnically diverse US population. The marked difference in female:male ratios between different ethnic and racial groups has not been reported previously, although the original NIH registry noted that the female:male ratio was 4.3:1 in the limited black population included. The Hispanic population appears to be modestly underrepresented in the PAH population in the United States, representing only 2.3% of the NIH registry at a time when it represented 6% of the US population, and this population represented only 8.9% in REVEAL when it would be expected to represent 11.5% of an age- and sex-adjusted US population (Table 2).

There has been a substantial change in mean age at diagnosis since the NIH registry. The NIH registry excluded patients aged < 1 year, and the mean age at diagnosis was 36 years. REVEAL excluded patients with age at enrollment < 3 months, and the mean age at diagnosis was 48 years in the overall REVEAL population (three [0.1%] patients enrolled between 3 months and 1 year of age). The REVEAL subpopulations and other contemporary registries indicate a similar shift in the age demographic to older age at diagnosis since the time of the NIH registry (Fig 3).

The proportion of patients with HIV as the etiology of PAH is much lower than that in the French registry (6.2%) in both the overall REVEAL population (2.2%) and the REVEAL FCC subpopulation (2.3%). The fact that the frequency is modestly higher for REVEAL than that reported by PHC (1.0%) suggests regional HIV differences and referral differences to PAH centers within the United States.

Hemodynamic and Functional Characteristics

Hemodynamic parameters at the time of diagnostic RHC have not changed substantially since the NIH registry, despite the later age at diagnosis in contemporary registries. Although the mPAP is less in REVEAL, its subpopulations, and in contemporary registries than the mPAP reported in the original NIH registry, other hemodynamic parameters are similar across the registries. Comparisons of the hemodynamics distributions of patients from the NIH registry and the REVEAL, REVEAL FCC, and REVEAL NIH cohorts are shown in Figure 4. Little has changed in the distribution of mPAP, mean right atrial pressure, PVR index, and cardiac index from the time of the NIH study. The mPAP for the patients enrolled in the NIH registry was 60 mm Hg compared with 51 mm Hg for REVEAL and REVEAL FCC, 52 mm Hg for REVEAL NIH, 52 mm Hg for PHC, and 55 mm Hg for the French registry.

Seventy-two percent of patients in REVEAL and 73% in REVEAL FCC and REVEAL NIH were FC III/IV at diagnosis, similar to the 71% to 80% observed for the other registries (Fig 5). This similarity to the NIH study suggests little change over time in the severity of PAH at time of diagnosis.

Incidence and Prevalence Estimates

A review of incident cases in Belgium as part of a case-controlled study of IPAH with anorexigen use concluded that the annual incidence in Belgian inhabitants aged 18 to 70 years was 1.7 per million. Similarly, the estimated incidence of IPAH in Israel between 1988 and 1997 was estimated to be 1.4 cases per million population. The French Registry concluded (with caveats) that its lower-bound estimates

Table 2—Summary of Actual vs Expected Distribution of Race (Adjusted for Sex and Age)

<table>
<thead>
<tr>
<th>Race</th>
<th>REVEAL, No.</th>
<th>REVEAL, %</th>
<th>Expected, No.</th>
<th>Expected, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>2,152</td>
<td>72.8</td>
<td>2,116</td>
<td>71.6</td>
</tr>
<tr>
<td>Black</td>
<td>359</td>
<td>12.2</td>
<td>322</td>
<td>10.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>264</td>
<td>8.9</td>
<td>340</td>
<td>11.5</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>96</td>
<td>3.3</td>
<td>127</td>
<td>4.3</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>84</td>
<td>2.8</td>
<td>50</td>
<td>1.7</td>
</tr>
</tbody>
</table>

The REVEAL distribution for whites does not differ from the expected distribution (P = .14). The distribution for blacks differs slightly (P = .03), and the largest difference exists in the remaining three categories (P < .001). See Table 1 legend for expansion of abbreviation.

1Data obtained from US Census 2006 estimates. 17

2The REVEAL distribution for whites does not differ from the expected distribution (P = .14). The distribution for blacks differs slightly (P = .03), and the largest difference exists in the remaining three categories (P < .001). See Table 1 legend for expansion of abbreviation.
Figure 3. Comparison of age at diagnosis between registries restricted to patients with IPAH or FPAH by sex. Data were restricted as follows: A, REVEAL, patients aged >3 months with IPAH or FPAH and pulmonary capillary wedge pressure (PCWP) ≤18 mm Hg; mean age of population at diagnosis, 46.8 years; B, REVEAL FCC, patients aged ≥18 years at diagnosis with IPAH or FPAH and PCWP <15 mm Hg; mean age at diagnosis, 48.8 years; C, REVEAL NIH, patients aged ≥1 year at enrollment with IPAH or FPAH and PCWP ≤12 mm Hg; mean age at diagnosis, 44.9 years; D, French registry (reproduced with permission from Humbert et al26), mean age at diagnosis for patients with IPAH, 52.0 years (n = 264); mean age at diagnosis for patients with FPAH, 37.0 years (n = 26); and E, NIH registry (reprinted with permission of the American Thoracic Society5), mean age at diagnosis, 36.4 years. Dx = diagnosis. See Figure 1 legend for expansion of other abbreviations.
The comparison of REVEAL with the 1980s NIH registry shows several striking differences, regardless of whether only patients with IPAH or FPAH or the entire group 1 PAH patient cohort are examined. In particular, contemporary patients with PAH are older at diagnosis and overwhelmingly women. The older age at diagnosis in contemporary registries is of particular interest because patients have similar New York Heart Association and World Health Organization FCs at diagnosis as in the NIH registry, which suggests several possibilities. This demographic may be beneficially affected by the impact of general health and well-being of modern populations, delaying onset of PAH symptoms. However, this explanation is unlikely because Census Bureau data demonstrate that survival in the general US population has not changed greatly in the past 25 years. Alternatively, if presentation at FC III or IV was determined by incidence and prevalence of PAH was 2.4 and 15 cases per million adult inhabitants, respectively, and the low estimate for prevalence of IPAH was 5.9 cases per million inhabitants. The low estimate for incidence of adult IPAH and FPAH in the United States based on REVEAL is 1.1 cases per million. For all adult patients with group 1 PAH, the incidence is 2.3 cases per million. Matched to French registry requirements (ie, PCWP < 15 mm Hg), the incidence of adult patients with IPAH or FPAH and group 1 PAH are 0.9 and 2.0 per million, respectively. The low estimates for adult prevalence for group 1 PAH are 12.4 and 10.6 in REVEAL overall and REVEAL\textsuperscript{18}, respectively. These numbers, despite the recognition that not all patients with PAH are included in REVEAL, provide a very conservative and carefully case-ascertained baseline for future evaluations of incidence and prevalence of PAH in the United States against which future demographic studies can be compared.

![Figure 4. Distribution of hemodynamic parameters of REVEAL, REVEAL\textsuperscript{18}, and REVEAL\textsuperscript{20} cohorts compared with the NIH cohort (reproduced with permission from Rich et al\textsuperscript{5}). A, Right atrial pressure distribution at diagnosis. B, Pulmonary artery pressure distribution at diagnosis. C, Cardiac index distribution at diagnosis. D, Pulmonary vascular resistance index distribution at diagnosis. See Figure 1 legend for expansion of abbreviations.](http://journal.publications.chestnet.org/)

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**Discussion**

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a lower level of baseline function in the face of an increasingly unfit overweight population, patients should present earlier (ie, younger) with perhaps less severe hemodynamic compromise. Pulmonary artery pressures are slightly, but not significantly, lower at diagnosis than in earlier registries, which is consistent with the observation from the PHC registry that demonstrates increasing age at diagnosis for all patients by era of diagnosis (mean age from 1982-1996, 41 years; 1996-2002, 49 years; 2002-2006, 52 years). This statistically significant advancing age (P < .001) was not accompanied by any significant change in hemodynamics at diagnostic RHC and is not a function of the APAH subgroup. Explanations for the older age at diagnosis include a change in the disease itself; a change in some unrecognized intrinsic or extrinsic factor that delays disease manifestations; or a change in the patient population, with more patients in an older age group being diagnosed with a disease historically thought to target younger patients.

The female preponderance in the US PAH population is demonstrated clearly in REVEAL and is maintained in the REVEAL\textsuperscript{PCC} and REVEAL\textsuperscript{NIH} subpopulations. This female predominance, therefore, is not due to expanded criteria for enrollment (ie, higher PWCPs) or by the APAH patient population. Thus, possible explanations include increased representation of ethnic groups with a higher female: male ratio in patients with IPAH and APAH, a previously unrecognized complication of obesity, the impact of greater use of hormone therapy in the North American female population, and more rapid attrition of male patients with PAH than of female patients prior to entry into REVEAL. A survivor bias with a greater proportion of female patients among the prevalent vs the newly diagnosed patient cohort would be consistent with these possible explanations. However, the PHC database had approximately the same female: male ratio (76: 24 in incident and prevalent patients); the Surveillance of Pulmonary Hypertension in America study followed only newly diagnosed patients (ie, incident cases), with female patients representing 81% of all these new patients with IPAH. It appears, therefore, that the increasing female preponderance is not simply due to increased attrition of the male PAH population.

The observed race and ethnic distributions in REVEAL reflect current US Census Bureau data. However, in every group 1 PAH subgroup and in every REVEAL subpopulation, the female: male ratio in the nonwhite populations demonstrates an even more striking female preponderance than in whites. Interestingly, the frequency of HIV APAH was substantially higher in the French registry (6.2%) than in REVEAL (2.2%). One might attribute this finding to the socialized medicine system in France in which more patients might be recognized and treated for HIV and its complications. However, this explanation seems unlikely because the prevalence of HIV in France and the United States is similar (0.23% and 0.39%, respectively).\textsuperscript{23} IV drug abuse is a relatively infrequent cause of HIV infection in the French population (2% of cases),\textsuperscript{24} but it represents one of the greatest risk factors for HIV APAH.\textsuperscript{25} In contrast, US data demonstrate that IV drug abuse accounts for 18.5% of attributable causes of HIV, which should predict a much higher incidence of HIV APAH in the US population. These observed differences warrant further investigation.

Limitations of this review include the fact that calculation of incidence or prevalence of a disease using a registry is fraught with methodological and statistical problems. Methods such as reviews of the...
In conclusion, REVEAL, the largest registry of patients with PAH to date, has demonstrated changes in US-PAH demographics since the NIH registry from the 1980s, particularly with regard to obesity (mirroring the US Census data), older age at diagnosis, and a striking female prevalence. The female frequency in the patients with PAH in the United States also differs from demographics observed in contemporary European and UK registries, suggesting that the presence of behavioral, environmental, racial, and pharmacologic factors are more prevalent and as yet unidentified in the American populace. These factors and the other observed differences in HIV PAH populations warrant further investigation.

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Dr McGoogan: contributed to the study design; collection, analysis, and interpretation of data; and drafting, critical review, and final approval of the manuscript. Dr McGoogan: contributed to the study design; collection, analysis, and interpretation of data; and drafting, critical review, and final approval of the manuscript. Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Frost serves as a consultant for Gilead and Actelion; has received honoraria from Gilead, Actelion, and Pfizer; has provided expert testimony on diet pill litigation; has received grants from Gilead and Actelion and grants to Baylor for Institutional Review Board-approved research; and has received honoraria for her service on the REVEAL Steering Committee, which is supported by Actelion. 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