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CHEST

Original Research

PULMONARY HYPERTENSION

Pulmonary Arterial Hypertension

Baseline Characteristics From the REVEAL Registry

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Background: **The Registry to EValuate Early And Long-term pulmonary arterial hypertension disease management (REVEAL Registry) was established to provide updated characteristics of patients with pulmonary arterial hypertension (PAH) and to improve diagnosis, treatment, and management.**

Methods: **Fifty-four US centers enrolled consecutively screened patients with World Health Organization group I PAH who met expanded hemodynamic criteria of mean pulmonary arterial pressure (PAP) > 25 mm Hg at rest (30 mm Hg with exercise), pulmonary capillary wedge pressure (PCWP) ≤ 18 mm Hg, and pulmonary vascular resistance ≥ 240 dynes · s · cm^{-5}. Patients meeting the traditional hemodynamic definition (PCWP ≤ 15 mm Hg) were compared with those with a PCWP of 16 to 18 mm Hg.**

Results: **Between March 2006 and September 2007, 2,967 patients enrolled. Among 2,525 adults meeting traditional hemodynamic criteria, the mean age was 53 ± 14 years, and 2,007 (79.5%) were women. The mean duration between symptom onset and diagnostic catheterization was 2.8 years, and 1,008 (41.3%) patients were treated with more than one pulmonary vascular-targeted medication. Compared with patients meeting the traditional hemodynamic definition of PAH, patients with a PCWP of 16 to 18 mm Hg were older, more obese, had a lower 6-min walk distance, and had a higher incidence of systemic hypertension, sleep apnea, renal insufficiency, and diabetes.**

Conclusions: **Patients in the REVEAL Registry are older and more often female than in previous descriptions. Delays between symptom onset and diagnostic catheterization persist. Many treatment regimens are fundamentally empirical, and data will be required to determine outcomes, improve risk stratification, and develop and validate more precise prognostic tools. Patients with PCWP of 16 to 18 mm Hg differ in a number of important respects from those meeting the traditional hemodynamic definition of PAH.** ***CHEST 2010; 137(2):376–387***

Abbreviations: 6MWD = 6-min walk distance; APAH = associated pulmonary arterial hypertension; eDC = electronic data capture; IPAH = idiopathic pulmonary arterial hypertension; FPAH = familial pulmonary arterial hypertension; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; REVEAL = Registry to EValuate Early And Long-term PAH disease management; RHC = right heart catheterization; SE = standard error; WHO = World Health Organization

Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance (PVR) and arterial pressure that can lead to right heart failure and death.[1-4] The diagnosis and management of PAH has undergone significant change since the National Institutes of Health (NIH) conducted the first registry of primary pulmonary hypertension (idiopathic PAH [IPAH]) in the early 1980s.[5,6] Although clinical trials have led to advances in therapy for PAH,[7-19] the disease remains progressive and often fatal. Although clinical trials remain the standard[1] for evaluating potential new therapies, further progress will require better understanding of the patient population and outcomes of treatment as

applied in current clinical practice. Recent reviews have emphasized the need for prospective studies of the clinical course and management of PAH.[20-22]

Registries conducted since the NIH study have enhanced our understanding of select aspects of PAH. A network of 17 French university hospitals reported observations from a registry of 674 adults with PAH and described the minimum prevalence and incidence, as well as the clinical and hemodynamic characteristics, of this group.[23] The Surveillance of North American Pulmonary Hypertension[24] and Surveillance of Pulmonary Hypertension in America[25] registries focused on evaluating the association of environmental factors, particularly anorexigens, with PAH.

A large prospective study of current US practice is needed to provide a foundation for new clinical and scientific advances. The Registry to EValuate Early And Long-term PAH disease management (REVEAL Registry) was initiated to characterize the demographics, clinical course, hemodynamic features, and disease management of a US patient population with World Health Organization (WHO) group I PAH. In order to be relevant to clinical practice, this study purposefully included geographically distributed patients with a broad definition of WHO group I PAH on any current treatment. Patients with pulmonary hypertension and a mildly increased pulmonary capillary wedge pressure (PCWP) (16-18 mm Hg) were included in the REVEAL Registry, and were compared with those meeting the traditional hemodynamic definition (PCWP $\leq$ 15 mm Hg). In addition, children were included, making this the first registry to include a substantial number of pediatric patients. Longitudinal objectives are to evaluate differences in outcome according to WHO group I PAH subgroups, functional status, and hemodynamic criteria; to identify predictors of short- and long-term outcomes; and to assess the relationship between PAH medications and outcomes. In this report, we describe baseline demographics and treatment in 2,967 adult and pediatric patients diagnosed with WHO group I PAH.

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Materials and Methods

Design Overview

The REVEAL Registry was designed by an independent Steering Committee, which oversaw study execution, data analysis, and reporting of the results. The design of the registry has been described in detail.[26] The registry uses a multicenter prospective cohort design involving 54 centers in the United States (including 21 sites enrolling pediatric patients). The centers include diverse university-affiliated and community hospitals. Each of the four US Census Regions was represented.

Between March 2006 and September 2007, consecutive patients with suspected or confirmed WHO group I PAH were screened. Patients were offered participation in the study if they met inclusion criteria described below. Since the goal was to describe current practice and outcomes, the registry is entirely observational and, although a right heart catheterization (RHC) was necessary to meet the study inclusion criteria, the protocol did not direct patient management or require a prescribed visit schedule. All patients will be prospectively tracked through December 2012, with a minimum follow-up of 5 years. The protocol was reviewed and approved by the institutional review board of each participating center.

Setting and Participants

Patients with newly or previously diagnosed PAH were eligible for enrollment if they met the modified definition of WHO group I PAH[27] and prespecified hemodynamic criteria by RHC. The definition of WHO group I[27] includes patients with PAH that is idiopathic, familial, or associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, drugs or toxins, HIV infection, and miscellaneous conditions (such as splenectomy or hemoglobinopathies). Classification into these subgroups of WHO group I was assigned by the investigator enrolling the subject into the registry, based upon their impression of the most likely cause of the patient's PAH. Patients participating in clinical trials were eligible for enrollment. Patients were ineligible if they were younger than 3 months at the time of enrollment. Eligible patients were asked to provide written informed consent (and assent when appropriate) and the Health Insurance Portability and Accountability Act authorization according to International Conference on Harmonization guidance for good clinical practice. Patients were classified with newly diagnosed PAH if the diagnostic RHC occurred within the previous 90 days.

Table 1—*Demographic and Baseline Characteristics of Patients Meeting Traditional Hemodynamic Criteria in the REVEAL Registry by World Health Organization Group I Diagnosis at Enrollment*

Characteristic	All Patients[a]	IPAH	All Patients With APAH[b]	APAH Subgroup[c]			
				CHD	CVD/ CTD	Portal HT	Drugs/Toxins
Patients, No. (%)	2,525 (100)	1,166 (46.2)	1,280 (50.7)	250 (19.5)	639 (49.9)	136 (10.6)	134 (10.5)
Age at enrollment, mean ± SD, y	53.0 ± 14.0	53.1 ± 14.5	53.4 ± 13.4	45.5 ± 13.1	57.7 ± 13.0	53.3 ± 9.6	49.5 ± 10.6
Age at diagnosis, mean ± SD, y	50.1 ± 14.4	49.9 ± 14.8	50.7 ± 13.8	41.6 ± 13.3	55.5 ± 13.4	51.0 ± 9.5	46.0 ± 10.0
19-64, No. (%)	2,098 (83.1)	971 (83.3)	1,054 (82.3)	236 (94.4)	467 (73.1)	124 (91.2)	129 (96.3)
65-74, No. (%)	324 (12.8)	138 (11.8)	181 (14.1)	11 (4.4)	135 (21.1)	11 (8.1)	5 (3.7)
75 +, No. (%)	103 (4.1)	57 (4.9)	45 (3.5)	3 (1.2)	37 (5.8)	1 (0.7)	0 (0.0)
Female, No. (%)	2,007 (79.5)	936 (80.3)	1,014 (79.2)	184 (73.6)	576 (90.1)	68 (50.0)	113 (84.3)
Time from diagnosis to enrollment, mo							
Mean ± SD	35.6 ± 37.9	38.0 ± 40.4	32.7 ± 34.9	46.6 ± 50.3	26.9 ± 27.3	27.5 ± 31.1	42.6 ± 32.7
Median	24.9	26.7	23.1	33.8	18.1	17.1	39.5
(IQR)	(8.0, 50.9)	(8.3, 53.8)	(7.8, 46.7)	(16.2, 59.8)	(6.4, 40.2)	(5.7, 36.7)	(12.9, 65.7)
Newly diagnosed, No. (%)	357 (14.1)	177 (15.2)	170 (13.3)	20 (8.0)	94 (14.7)	22 (16.2)	15 (11.2)
Previously diagnosed, No. (%)	2,168 (85.9)	989 (84.8)	1,110 (86.7)	230 (92.0)	545 (85.3)	114 (83.8)	119 (88.8)
Functional class at enrollment,[d] No. (%)							
I	175 (7.6)	89 (8.3)	80 (6.9)	13 (5.7)	32 (5.7)	14 (11.4)	10 (7.8)
II	846 (36.7)	391 (36.4)	423 (36.6)	87 (38.3)	182 (32.2)	50 (40.7)	60 (46.5)
III	1,153 (50.0)	534 (49.7)	584 (50.5)	117 (51.5)	311 (54.9)	54 (43.9)	55 (42.6)
IV	130 (5.6)	60 (5.6)	69 (6.0)	10 (4.4)	41 (7.2)	5 (4.1)	4 (3.1)
6MWD at enrollment,[e] mean ± SD, m	366 ± 126	374 ± 129	356 ± 123	382 ± 121	322 ± 120	397 ± 115	410 ± 95
No.	2,034	921	1,050	210	518	105	122
		P value[f] < .001					

6MWD = 6-min walk distance; APAH = associated PAH; CHD = congenital heart disease; CVD/CTD = collagen vascular disease/connective tissue disease; FPAH = familial PAH; IPAH = idiopathic PAH; IQR = interquartile range; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; portal HT = portal hypertension; PPHN = pulmonary hypertension of the newborn; PVOD = pulmonary venoocclusive disease; REVEAL = Registry EValuate Early And Long-term PAH disease management; WHO = World Health Organization.

[a]This column reflects all patients aged ≥ 19 y at diagnosis with a PCWP ≤ 15 mm Hg enrolled during the consecutive screening of newly and previously diagnosed patients, including those with WHO group I diagnoses other than IPAH or APAH (ie, FPAH, PVOD, and PPHN).

[b]This column reflects all patients with APAH, including those with APAH subgroups other than CHD, CVD/CTD, portal HT, and drugs/toxins (ie, HIV and other).

[c]APAH subgroups are mutually exclusive according to the following hierarchy for patients with multiple associate PAH diagnoses: CHD, CVD/CTD, portal HT, drugs/toxins, HIV, and other.

[d]Modified New York Heart Association/WHO Functional Classification for Pulmonary Hypertension.

[e]This is the most recent 6MWD (closest to enrollment, including 6MWD recorded on previous forms, and excludes 87 patients in a blinded clinical trial).

[f]The *P* value for 6MWD is obtained from the two-sample *t* test examining the difference in the distribution of the characteristic among patients diagnosed with IPAH vs all patients with APAH.

RHC Criteria

To be eligible, RHC had to have been performed before study entry and after the development of symptoms associated with PAH. Eligible patients were required to meet the following qualifying catheterization criteria:

- Mean pulmonary arterial pressure (PAP) > 25 mm Hg at rest or > 30 mm Hg with exercise
- PCWP or left ventricular end-diastolic pressure ≤ 18 mm Hg
- PVR ≥ 240 dynes · sec · cm^{-5}

Although clinical trials often include only WHO group I patients with a PCWP of ≤ 15 mm Hg, this registry used a less restrictive PCWP criterion of ≤ 18 mm Hg to include patients seen in clinical practice. Patients who met catheterization criteria only with exercise were not required to meet the PVR criteria.

Data Collection

Data were collected using electronic data capture (eDC), beginning with the initial screening visit. The baseline assessment included medical history. Data collected retrospectively included time of diagnosis and symptom onset, specialty of evaluating physicians, tests used to diagnose PAH, WHO group I classification, and use of PAH-specific medications. After meeting enrollment criteria, no tests or study visits were required, but data were collected prospectively every 90 days, including PAH treatments, concomitant treatments, outcomes, and diagnostic procedures. Patients in open-label clinical trials had data collected; however, data collection was temporarily suspended for patients in blinded trials until completing the blinded portion of the study. The eDC system prompted quarterly updates with an option to indicate that the patient was not seen since the last update. Potential data inconsistencies were identified primarily by the eDC system at the point of entry. Additional queries were generated by the data coordinating center. Sites were monitored for adherence to the protocol and resolution of data queries.

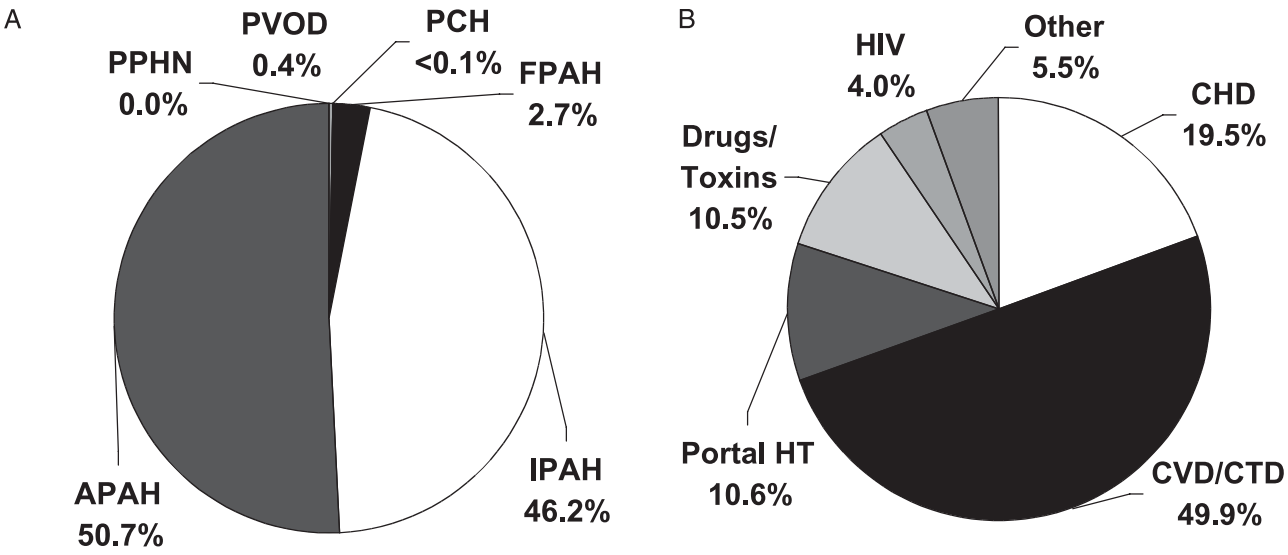

Figure 1. World Health Organization (WHO) Group I pulmonary arterial hypertension classification of REVEAL patients at enrollment. *(A)* WHO Group I PAH classification. *(B)* Breakdown of associated pulmonary arterial hypertension subgroup. APAH = associated PAH; CHD = congenital heart disease; CVD/CTD = collagen vascular disease/connective tissuedisease; FPAH = familial PAH; HT = hypertension; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatosis; PPHN = pulmonary hypertension of the newborn; PVOD = pulmonary venoocclusive disease; REVEAL = Registry to EValuate Early And Long-term PAH disease management.

Statistical Analysis

The target sample size for the study was 3,000 patients so that the study would have 80% power to detect a 20% survival difference in moderately sized subgroups of interest (eg, subgroups each representing 15%-25% of the total cohort). The cohort was designed to be sufficiently large to address potential biases through stratification and statistical models. Per protocol, as enrollment progressed, the proportions of newly and previously diagnosed patients were monitored to ensure that sufficient numbers of newly diagnosed patients were enrolled. To achieve objectives related to newly diagnosed patients, the protocol was amended in mid-2007 to extend enrollment to include 500 additional newly diagnosed patients over 2 years who are not included in this analysis. Thus, this report describes a population that is representative of the patient demographics seen routinely at enrolling centers.

Percentages and means or medians are used to summarize categorical and continuous variables, respectively. The denominator for percentages is based on those patients with non-missing data. For percentages, standard errors (SEs) for the overall sample are less than 1 percentage point and SEs for small subgroups (ie, representing 10% of the full sample) are less than 2.5 percentage points.

Results

Demographics

A total of 3,052 patients with clinically suspected WHO group I PAH were screened. Of these, 2,977 patients (97.2%) were enrolled. Ten patients were subsequently determined to have had inadvertent duplication of data; the duplicate entries were discarded, thereby yielding a final total of 2,967 patients. A total of 2,864 patients met the study entry criteria based on mean PAP, PCWP, and PVR at rest. Another 83 patients met the criteria at rest, substituting left ventricular end-diastolic pressure for PCWP. Finally, 13 patients met the criteria during exercise. The remaining seven patients received a waiver.

Characteristics of Patients Within Traditional Hemodynamic Range for PAH

After excluding 200 patients diagnosed in the pediatric age range, 239 patients with wedge pressures of 16 to 18 mm Hg, and three patients with no recorded wedge pressure, 2,525 adult patients remained who met traditional hemodynamic criteria. The patients were well distributed geographically: Midwest, 551 (21.8%); Northeast, 564 (22.3%); South, 730 (28.9%); West, 680 (26.9%). The mean ± SE time from symptom onset to diagnostic RHC was 34.1 ± 1.2 months (median 13.6). The mean ± SE time from diagnosis to enrollment in the registry was 35.6 ± 0.8 months (median 24.9). The distribution of WHO group I diagnostic classifications and characteristics at enrollment are shown in Table 1 and Figure 1. A total of 441 patients were participating in clinical trials at the time of enrollment; of these, 87 were in blinded clinical trials. A variety of specialists evaluated the patients at first presentation of initial symptoms (Table 1). The specialist that directed PAH therapy was a pulmonologist in 1,707 (67.6%) patients or a cardiologist in 811 (32.1%) patients. At the time of diagnostic RHC, 1,123 of 1,831 (61.3%) patients were functional class III and 225 (12.3%) were functional class IV. At the time of enrollment, a median of 25 months later, 1,153 of 2,304 (50.0%) patients were functional class III and 130 (5.6%) were functional class IV.

RHC: The results of the RHC qualifying the patients for enrollment are shown in Table 2. There were significant differences ($P < .001$) between patients with IPAH and patients with associated PAH (APAH) for all hemodynamic criteria except for PCWP.

Comorbid Conditions: Comorbid conditions of patients meeting traditional hemodynamic criteria at enrollment are summarized in Table 3. Among patients classified by the enrolling investigator as drugs and toxins associated with PAH, a history of using fenfluramines or fenfluramine derivatives was noted for 57 of 78 patients for whom the suspected primary agent was an anorexigen and also for 74 of 1,166 (6%) and 2 of 69 (3%) of patients with IPAH and familial PAH (FPAH), respectively. A history of amphetamine use was noted for 53 of 55 (96%) patients for whom the suspected primary agent was a drug and also for 39 of 1,166 (3%) and 1 of 69 (1%) of patients with IPAH and FPAH, respectively. The transpulmonary pressure gradient (mean PAP minus mean PCWP) was slightly lower in patients with BMI $\geq$ 30 kg/m^2 (40.7 $\pm$ 13.1 mm Hg) compared with those with BMI $<$ 30 kg/m^2 (42.1 $\pm$ 13.8 mm Hg); with systemic hypertension (40.0 $\pm$ 13.4 mm Hg) compared with those without hypertension (42.8 $\pm$ 13.8 mm Hg); or with sleep apnea (41.0 $\pm$ 12.7 mm Hg) compared with those without a diagnosis of sleep apnea (41.8 $\pm$ 13.8 mm Hg). However, the transpulmonary pressure gradient in these patients was consistent with the definition of WHO group I PAH and indicated that markedly elevated precapillary resistance, rather than elevated pulmonary venous pressure, was the predominant cause of their PAH. The results were similar in the IPAH and APAH subgroups (data not shown).

Medications at Enrollment: The PAH-specific treatments at the time of enrollment among patients meeting traditional hemodynamic criteria are shown in Table 4. The concomitant medications taken by these patients at the time of enrollment are shown in Table 5. Excluding calcium channel blockers, 266 patients were on no PAH therapies, 1,008 were on two or more drugs, and 183 were on three or more drugs. Of the 2,438 patients on any PAH treatment, 624 were taking calcium channel blockers. Of these, 212 (34.0%) were on calcium channel blockers specifically for PAH. Among 1,335 for whom results of a vasodilator challenge were known at enrollment, 136 patients were vasodilator responders and 55 of the responders (40.4%) were on calcium channel blockers for PAH. At enrollment, 16 of 124 (13%) functional class IV patients were not on any PAH-specific medications (excluding calcium channel blockers). Of these, 12 (75%) were newly diagnosed.

Among patients on endothelin receptor antagonists at enrollment, 953 were on bosentan, 89 on ambrisentan, and 106 on sitaxsentan. Among patients on phosphodiesterase-5 inhibitors, 1,147 were on sildenafil and 47 were on tadalafil. A total of 1,012 patients were treated with a prostacyclin analog: treprostinil was given intravenously, subcutaneously, in inhaled form, and orally for 159, 112, 28, and 9 patients, respectively; 237 patients received inhaled iloprost; and 480 were treated with intravenous epoprostenol sodium.

Functional Class: Mean 6-min walk distance (6MWD) correlated well with functional class. The mean $\pm$ SE 6MWD (in meters [m]) for functional classes I through IV were 475.5 $\pm$ 9.3, 419.2 $\pm$ 3.7, 323.1 $\pm$ 3.8, and 214.1 $\pm$ 13.7, respectively. There was, however, substantial overlap in walk distances for patients in the various functional classes. RHC parameters (eg, PVR [in Wood units]) were much less correlated with functional class (11.0 $\pm$ 0.5, 11.5 $\pm$ 0.3, 11.2 $\pm$ 0.2, and 11.8 $\pm$ 0.6 for functional classes I through IV, respectively).

Characteristics of Patients Outside of Traditional Hemodynamic Range for PAH

Adult patients meeting the traditional criterion of PCWP $\leq$ 15 mm Hg were compared with the 239 adult patients with PCWP of 16 to 18 mm Hg at diagnosis (Table 6). Patients with a PCWP of 16 to 18 mm Hg were older, more obese, had a lower 6MWD, and were more likely to have systemic hypertension, sleep apnea, renal insufficiency, and diabetes than adult patients meeting the traditional definition. Interestingly, they did not differ with respect to functional class or PAH treatments at enrollment. All statistically significant differences between the two groups are shown in Table 6.

Pediatric Patients

There were 200 pediatric patients enrolled whose age at diagnosis was $\leq$ 18 years, with a mean age at diagnosis of 8.0 years and a mean age at enrollment of 15.1 years (interquartile range = 8.6 to 20.0). One hundred thirty-four (67%) patients were female, and the majority saw a cardiologist at first presentation. At the time of enrollment, 38 (21%) were in functional class I, 93 (52%) were in functional class II, 43 (24%) were in functional class III, and five (3%) were in functional class IV. The mean 6MWD at enrollment was 429 $\pm$ 134 m. As compared with adult patients with traditional hemodynamics (PCWP $\leq$ 15 mm Hg), pediatric patients with traditional hemodynamics were less predominantly female, had a higher 6MWD, better functional

Table 2—*Diagnostic Right Heart Catheterization Parameters of Patients Meeting Traditional Hemodynamic Criteria in the REVEAL Registry by WHO Group I Diagnosis at Enrollment*

Characteristic	All Patients[a]	IPAH	All Patients With APAH[b]	APAH Subgroup[c]			
				CHD	CVD/ CTD	Portal HT	Drugs/ Toxins
Patients, No.	2,525	1,166	1,280	250	639	136	134
mPAP, mm Hg	50.7 ± 13.6	52.1 ± 13.0	49.1 ± 13.8	59.4 ± 16.9	44.9 ± 11.2	48.5 ± 10.6	52.2 ± 12.2
No.	2,525	1,166	1,280	250	639	136	134
		P value[d] < .001					
PCWP, mm Hg	9.1 ± 3.5	9.2 ± 3.5	9.0 ± 3.5	8.9 ± 3.6	8.9 ± 3.5	9.3 ± 3.6	9.2 ± 3.6
No.	2,525	1,166	1,280	250	639	136	134
		P value[d] = .14					
Mean RAP, mm Hg	9.3 ± 5.6	9.9 ± 5.7	8.6 ± 5.5	7.2 ± 4.5	8.7 ± 5.6	8.3 ± 5.9	10.7 ± 5.9
No.	2,298	1,050	1,174	229	580	131	127
		P value[d] < .001					
PVRI, Wood units · m^2	21.1 ± 12.5	22.9 ± 11.4	19.0 ± 13.0	23.7 ± 20.9	16.9 ± 9.1	15.7 ± 7.2	24.2 ± 12.7
No.	1,868	842	965	186	488	100	100
		P value[d] < .001					
Fick or thermodilution CI,[e] L/min × m^2	2.4 ± 0.8	2.2 ± 0.8	2.5 ± 0.9	2.7 ± 1.0	2.5 ± 0.8	2.8 ± 0.8	2.1 ± 0.8
No.	1,868	842	965	186	488	100	100
		P value[d] < .001					
SVO_2, %	62.9 ± 10.0	61.8 ± 9.8	64.2 ± 10.1	67.3 ± 9.5	63.3 ± 10.0	66.5 ± 8.5	61.1 ± 9.7
No.	1,456	665	738	148	356	86	96
		P value[d] < .001					

Values are mean ± SD unless otherwise indicated. Hemodynamics at diagnostic RHC (baseline, at rest). CI = cardiac index; mPAP = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; RAP = right arterial pressure; RHC = right heart catheterization; SVO_2 = mixed venous oxygen saturation. See Table 1 for expansion of other abbreviations.

[a]This column reflects all patients aged ≥ 19 y at diagnosis with a PCWP ≤ 15 mm Hg enrolled during the consecutive screening of newly and previously diagnosed patients, including those with WHO group I diagnoses other than IPAH or APAH (ie, FPAH, PVOD, and PPHN).

[b]This column reflects all APAH patients, including those with associated PAH subgroups other than CHD, CVD/CTD, portal HT, and drugs/toxins (ie, HIV and other).

[c]APAH subgroups are mutually exclusive according to the following hierarchy for patients with multiple associate PAH diagnoses: CHD, CVD/CTD, portal HT, drugs/toxins, HIV, and other.

[d]The *P* value for all hemodynamic parameters is obtained from the two-sample *t* test examining the difference in the distribution of the characteristic among patients diagnosed with IPAH vs all patients with APAH.

[e]Fick cardiac index is used unless it is missing, in which case thermodilution cardiac index is used.

class, higher cardiac index, and fewer comorbidities, such as systemic hypertension, obesity, and sleep apnea.

Discussion

The REVEAL Registry is the largest and most comprehensive registry of WHO group I PAH reported to date. The size of the study (2,967 patients), the number of referral sites and community practices, and geographical distribution make the results generalizable to clinical practice. No center enrolled more than 10% of the population. Importantly, by using a less-restrictive PCWP criterion of ≤ 18 mm Hg (as compared with the usual criterion of ≤ 15 mm Hg), the registry intentionally included patients more typical of those currently seen in actual practice. Roughly half of the patients had idiopathic disease, and the other half had APAH. The most common underlying associated conditions were connective tissue disease and congenital heart disease.

One striking finding is the marked female preponderance, which has increased over time in the United States. The NIH registry of primary pulmonary hypertension (or IPAH),[5] conducted in the mid-1980s, reported a 1.7:1 female-to-male ratio in the total cohort and a 4.3:1 ratio among blacks. The Surveillance of Pulmonary Hypertension in America registry,[25] conducted from 1998 to 2001 in the United States, reported a 4.3:1 ratio. The REVEAL Registry demonstrates a 4.1:1 female-to-male ratio among patients with IPAH, and a 3.8:1 ratio among those with APAH. A 5.4:1 ratio among 312 (12%) blacks supports the previous finding of higher female predominance. However, the French Registry,[23] conducted from October 2002 to October 2003, reported a 1.9:1 ratio. The reason for this demographic variability over time and between countries is unclear. A role for hormonal influences (particularly estrogens) in the pathogenesis of PAH has been considered. Estrogens may promote cellular proliferation; another disease involving the proliferation of smooth muscle cells within the lung, lymphangioleiomyomatosis,

Table 3—*Comorbid Conditions of Patients Meeting Traditional Hemodynamic Criteria in the REVEAL Registry by WHO Group I Diagnosis at Enrollment*

Comorbid Condition	All Patients[a]	IPAH	All Patients With APAH[b]	APAH Subgroup[c]			
				CHD	CVD/CTD	Portal HT	Drugs/Toxins
No.	2,438	1,114	1,247	243	617	136	132
Hypertension[d]	980 (40.2)	466 (41.8)	485 (38.9)	55 (22.6)	285 (46.2)	52 (38.2)	54 (40.9)
Obese (BMI ≥ 30 kg/m^2)[e]	697 (33.3)	365 (38.4)	307 (28.6)	44 (21.0)	136 (24.8)	35 (32.7)	62 (54.9)
CVD/CTD	705 (28.9)	64 (5.7)	637 (51.1)	7 (2.9)	617 (100.0)	4 (2.9)	3 (2.3)
Scleroderma	415 (17.0)	16 (1.4)	399 (32.0)	1 (0.4)	398 (64.5)	0 (0.0)	0 (0.0)
Other	273 (11.2)	23 (2.1)	249 (20.0)	3 (1.2)	239 (38.7)	2 (1.5)	2 (1.5)
Lupus	155 (6.4)	13 (1.2)	142 (11.4)	1 (0.4)	138 (22.4)	0 (0.0)	1 (0.8)
Rheumatoid arthritis	86 (3.5)	21 (1.9)	62 (5.0)	2 (0.8)	55 (8.9)	2 (1.5)	0 (0.0)
Clinical depression[f]	615 (25.2)	283 (25.4)	315 (25.3)	48 (19.8)	159 (25.8)	30 (22.1)	46 (34.8)
Obstructive airway disease[g]	533 (21.9)	258 (23.2)	263 (21.1)	54 (22.2)	141 (22.9)	20 (14.7)	25 (18.9)
Sleep apnea	484 (21.0)	279 (26.6)	188 (15.9)	28 (12.2)	81 (13.8)	23 (17.4)	36 (28.8)
Thyroid disease[h]	527 (21.6)	227 (20.4)	289 (23.2)	39 (16.0)	178 (28.8)	22 (16.2)	29 (22.0)
Diabetes, overall	293 (12.0)	158 (14.2)	127 (10.2)	18 (7.4)	41 (6.6)	37 (27.2)	17 (12.9)
Type 1	34 (1.4)	20 (1.8)	14 (1.1)	2 (0.8)	5 (0.8)	5 (3.7)	1 (0.8)
Type 2	259 (10.6)	138 (12.4)	113 (9.1)	16 (6.6)	36 (5.8)	32 (23.5)	16 (12.1)
Ischemic cardiovascular event	227 (9.3)	114 (10.2)	111 (8.9)	21 (8.6)	64 (10.4)	10 (7.4)	5 (3.8)
Non-skin cancer	148 (6.1)	69 (6.2)	74 (5.9)	9 (3.7)	35 (5.7)	16 (11.8)	7 (5.3)
Valvular heart disease	116 (4.8)	42 (3.8)	74 (5.9)	38 (15.6)	20 (3.2)	8 (5.9)	5 (3.8)
Cirrhosis	151 (6.2)	20 (1.8)	131 (10.5)	2 (0.8)	11 (1.8)	106 (77.9)	3 (2.3)
Renal insufficiency	109 (4.5)	48 (4.3)	60 (4.8)	4 (1.6)	43 (7.0)	5 (3.7)	2 (1.5)
History of pulmonary embolism	168 (6.9)	96 (8.6)	71 (5.7)	14 (5.8)	33 (5.3)	5 (3.7)	7 (5.3)
History of past deep vein thrombosis	145 (5.9)	68 (6.1)	77 (6.2)	6 (2.5)	51 (8.3)	6 (4.4)	6 (4.5)
Cardiomyopathy[i] (dilated)	24 (1.0)	16 (1.4)	6 (0.5)	2 (0.8)	2 (0.3)	0 (0.0)	0 (0.0)

Values presented as No. (%) unless otherwise noted. See Table 1 for expansion of abbreviations.

[a]This column reflects all patients age ≥ 19 y at diagnosis with a PCWP ≤ 15 mm Hg during the consecutive screening of newly and previously diagnosed patients, including those with WHO group I diagnoses other than IPAH or APAH (ie, FPAH, PVOD, and PPHN) with the exception of blinded clinical trial patients (N = 87).

[b]This column reflects all APAH patients, including those with associated PAH subgroups other than CHD, CVD/CTD, portal HT, and drugs/toxins (ie, HIV and other) with the exception of blinded trial patients.

[c]APAH subgroups are mutually exclusive according to the following hierarchy for patients with multiple associated PAH diagnoses: CHD, CVD/CTD, portal HT, drugs/toxins, HIV, and other.

[d]Includes patients with the comorbid condition hypertension and/or patients with a reported use of β-blockers as a concomitant medication.

[e]Obesity defined for patients aged ≥ 18 y using the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report. National Heart Lung and Blood Institute (NHLBI), June 1998.

[f]Includes patients with the comorbid condition clinical depression and/or patients with the reported use of selective serotonin reuptake inhibitors as a concomitant medication.

[g]Obstructive airway disease is defined as obstructive lung disease, reactive airways disease, and COPD.

[h]Includes patients with the comorbid condition hypothyroidism and/or patients with the reported use of "synthetic thyroid replacement treatment for hypothyroidism" as a concomitant medication.

[i]Four types of cardiomyopathy are distinguished: dilated (n = 24), hypertrophic (n = 12), ischemic (n = 11), restrictive (n = 6), and one was unspecified.

afflicts women exclusively. Although speculative, increased use of hormonal replacement therapy by women in the United States between the time of the NIH registry and the present[28,29] might have played a role in this apparent demographic shift.

The most common age of patients with PAH is between 45 and 54 years, perhaps reflecting improved survival on treatment. The population tends to be overweight, with a BMI of 29 kg/m^2; hence, obesity may be a risk factor for the development of PAH. The prevalence of recreational drug use, particularly cocaine and amphetamines, highlights emerging risk factors for the development of PAH and provides an opportunity for prevention.

Despite intensive educational efforts, a substantial delay in the referral of patients to a pulmonary hypertension center persists. The median 1-year interval from symptom onset to RHC is due in part to the nonspecific manifestations of the disease; the registry confirms the fact that dyspnea on exertion is the most common presenting symptom. Continued efforts to increase awareness among the public and clinicians are warranted.

The relationship between the mean 6MWD and functional class provides internal validation of the functional data obtained. However, there is variability in the 6MWD within each functional class, resulting in substantial overlap and supporting criticism that functional classification is subjective and observer-dependent. This is important in light of the fact that the current approach to therapy, based on Food and Drug Administration approvals and existing

Table 4—*PAH-Specific Medications Among Patients Meeting Traditional Hemodynamic Criteria in the REVEAL Registry at Enrollment*

			Prostacyclin Analog		
	ETRA[a]	PDE-5 Inhibitor[b]	IV Epoprostenol	Inhaled Iloprost	Treprostinil[c]
Overall use, N = 2,438	1,147 (47.0)	1,194 (49.0)	480 (19.7)	237 (9.7)	307 (12.6)
Monotherapy	452 (18.5)	417 (17.1)	188 (7.7)	23 (0.9)	84 (3.4)
Combination with one oral therapy[d]	291 (11.9)	290 (11.9)	243 (10.0)	138 (5.7)	148 (6.1)
Combination with one prostacyclin analog	224 (9.2)	305 (12.5)	2 (0.1)	3 (0.1)	5 (0.2)
Combination with more than one other therapy	180 (7.4)	182 (7.5)	47 (1.9)	73 (3.0)	70 (2.9)
NYHA functional class I/II					
Overall use	468 (47.1)	474 (47.7)	187 (18.8)	71 (7.1)	111 (11.2)
Monotherapy	216 (21.7)	187 (18.8)	83 (8.4)	4 (0.4)	26 (2.6)
Combination with one oral therapy[d]	110 (11.1)	109 (11.0)	85 (8.6)	41 (4.1)	60 (6.0)
Combination with one prostacyclin analog	76 (7.6)	110 (11.1)	…	…	…
Combination with more than one other therapy	66 (6.6)	68 (6.8)	19 (1.9)	26 (2.6)	25 (2.5)
NYHA functional class III					
Overall use	525 (47.7)	567 (51.5)	218 (19.8)	130 (11.8)	161 (14.6)
Monotherapy	181 (16.4)	177 (16.1)	80 (7.3)	16 (1.5)	43 (3.9)
Combination with one oral therapy[d]	147 (13.4)	147 (13.4)	117 (10.6)	78 (7.1)	79 (7.2)
Combination with one prostacyclin analog	114 (10.4)	160 (14.5)	2 (0.2)	2 (0.2)	4 (0.4)
Combination with more than one other therapy	83 (7.5)	83 (7.5)	19 (1.7)	34 (3.1)	35 (3.2)
NYHA functional class IV					
Overall use	55 (44.4)	61 (49.2)	44 (35.5)	14 (11.3)	15 (12.1)
Monotherapy	5 (4.0)	14 (11.3)	17 (13.7)	2 (1.6)	5 (4.0)
Combination with one oral therapy[d]	16 (12.9)	16 (12.9)	21 (16.9)	8 (6.5)	4 (3.2)
Combination with one prostacyclin analog	18 (14.5)	15 (12.1)	…	…	…
Combination with more than one other therapy	16 (12.9)	16 (12.9)	6 (4.8)	4 (3.2)	6 (4.8)

Values are expressed as n (%). Combinations with one oral therapy, with one prostacyclin analog, and with more than one oral therapy are mutually exclusive and exclude calcium channel blockers. Blinded clinical trial patients are excluded from this presentation (No. = 87). ETRA = endothelin receptor antagonist; NYHA = New York Heart Association; PDE-5 Inhibitor = phosphodiesterase inhibitor; SC = subcutaneous. See Table 1 for expansion of other abbreviations.

[a]n = 953 on bosentan, n = 106 on sitaxsentan, and n = 89 on ambrisentan.

[b]n = 1,147 on sildenafil and n = 47 on tadalafil.

[c]Treprostinil use includes n = 159 on IV, n = 112 on SC, n = 28 on inhaled, and n = 9 on oral treprostinil.

[d]Oral therapy is defined as bosentan, sildenafil, ambrisentan, sitaxsentan, and tadalafil.

treatment guidelines,[7-9] stratifies patients based on functional class. There was not a tight association between functional class and severity of PAP elevation.

Cardiopulmonary hemodynamics were similar for IPAH and APAH. However, subgroup analysis demonstrated that patients with congenital heart disease had higher PAP but better cardiac output and exercise capacity than those with connective tissue disease. This finding supports the relative prognostic importance of right ventricular function and cardiac output as compared with PAP alone.

A variety of comorbid conditions were identified, including systemic hypertension, obstructive lung disease, sleep apnea, and prior venous thromboembolism, which were not believed to represent the principal cause for the patients' pulmonary hypertension. Patients with PAH due to an underlying condition were classified as having APAH or were excluded as being outside the diagnostic category of PAH. Systemic hypertension was the most commonly reported comorbid condition (40.2% of patients), perhaps reflecting either a generalized vasculopathy or common substrate affecting both the pulmonary and systemic circulations, such as sleep apnea or diastolic dysfunction. Thyroid disease, as noted in prior reports,[30-35] was seen relatively frequently and may signal an underlying autoimmune process.

As compared with patients meeting the traditional hemodynamic definition of PAH, patients with a PCWP of 16 to 18 mm Hg were older, more obese, had a lower 6MWD, and had a higher incidence of systemic hypertension, sleep apnea, renal insufficiency, and diabetes. These observations are consistent with patients who met this expanded hemodynamic definition having a higher incidence of systemic vascular and left heart disease. It is likely important to direct initial therapeutic efforts in this population toward these underlying comorbidities. Because these patients have typically been excluded from clinical trials, it remains to be determined whether such patients will respond favorably to PAH-specific therapies.

As compared with adult patients with traditional hemodynamics, pediatric patients were less predominantly female, had a higher 6MWD, better functional class, higher cardiac index, and fewer comorbidities, such as systemic hypertension, obesity, and sleep apnea. The absence of these underlying conditions suggests a primary pulmonary vasculopathy. Further comparisons

Table 5—*Concomitant Medications Taken by Patients Meeting Traditional Hemodynamic Criteria in the REVEAL Registry by WHO Group I Diagnosis at Enrollment*

	All Patients[a]	IPAH	All Patients With APAH[b]	APAH Subgroup[c]			
				CHD	CVD/CTD	Portal HT	Drugs/Toxins
Patients, No.	2,438	1,114	1,247	243	617	136	132
Diuretic	1,689 (69.3)	788 (70.7)	852 (68.3)	139 (57.2)	431 (69.9)	98 (72.1)	118 (89.4)
Warfarin	1,302 (53.4)	713 (64.0)	529 (42.4)	124 (51.0)	263 (42.6)	15 (11.0)	76 (57.6)
Oxygen	982 (40.3)	454 (40.8)	498 (39.9)	109 (44.9)	280 (45.4)	23 (16.9)	54 (40.9)
Digoxin	643 (26.4)	305 (27.4)	311 (24.9)	99 (40.7)	118 (19.1)	19 (14.0)	49 (37.1)
Synthetic thyroid replacement	502 (20.6)	216 (19.4)	278 (22.3)	37 (15.2)	177 (28.7)	22 (16.2)	23 (17.4)
Calcium channel blocker[d]	624 (25.6)	287 (25.8)	324 (26.0)	39 (16.0)	210 (34.0)	18 (13.2)	36 (27.3)
SSRI	473 (19.4)	212 (19.0)	245 (19.6)	41 (16.9)	126 (20.4)	18 (13.2)	33 (25.0)
Other antidepressants	201 (8.2)	79 (7.1)	119 (9.5)	20 (8.2)	59 (9.6)	15 (11.0)	16 (12.1)
Aspirin	382 (15.7)	153 (13.7)	227 (18.2)	58 (23.9)	133 (21.6)	10 (7.4)	10 (7.6)
Other antiinflammatory	124 (5.1)	48 (4.3)	75 (6.0)	4 (1.6)	63 (10.2)	3 (2.2)	2 (1.5)
Statin	393 (16.1)	191 (17.1)	193 (15.5)	33 (13.6)	119 (19.3)	1 (0.7)	21 (15.9)
β-Blocker	296 (12.1)	122 (11.0)	169 (13.6)	26 (10.7)	86 (13.9)	33 (24.3)	8 (6.1)
Psychotropic drugs	252 (10.3)	115 (10.3)	130 (10.4)	28 (11.5)	56 (9.1)	16 (11.8)	16 (12.1)
Corticosteroids	296 (12.1)	86 (7.7)	204 (16.4)	8 (3.3)	166 (26.9)	12 (8.8)	5 (3.8)
ACE inhibitor	276 (11.3)	118 (10.6)	153 (12.3)	25 (10.3)	93 (15.1)	12 (8.8)	10 (7.6)
Clopidogrel	48 (2.0)	17 (1.5)	31 (2.5)	5 (2.1)	20 (3.2)	2 (1.5)	1 (0.8)
None of the above	51 (2.1)	21 (1.9)	27 (2.2)	10 (4.1)	7 (1.1)	6 (4.4)	1 (0.8)

Values are expressed as n (%) unless otherwise noted. ACE = angiotensin-converting enzyme; SSRI = selective serotonin reuptake inhibitor. See Table 1 for expansion of other abbreviations.

[a]This column reflects all patients aged ≥ 19 y at diagnosis with a PCWP ≤ 15 mm Hg during the consecutive screening of newly and previously diagnosed patients, including those with WHO group I diagnoses other than IPAH or APAH (ie, FPAH, PVOD, and PPHN), with the exception of blinded clinical trial patients (No. = 87).

[b]This column reflects all patients with APAH, including those with associated PAH subgroups other than CHD, CVD/CTD, portal HT, and drugs/toxins (ie, HIV and other), with the exception of blinded trial patients.

[c]APAH subgroups are mutually exclusive according to the following hierarchy for patients with multiple associated PAH diagnoses: CHD, CVD/CTD, portal HT, drugs/toxins, HIV, and other.

[d]Includes use related to PAH and/or other conditions.

of adult and pediatric patients will require more detailed analysis.

The registry provides important insights into current treatment patterns. Only a small proportion of the patients enrolled were participating in randomized and controlled clinical trials, with a slightly larger number participating in open-label extension studies. Treatment with prostacyclin analogs increased with disease severity, as assessed by functional class. The most commonly used analog was intravenous epoprostenol, with smaller numbers of patients receiving inhaled iloprost or intravenously or subcutaneously administered treprostinil. Patients in functional classes II and III were commonly treated with oral agents, likely due to the simplicity and safety of this administration route.

The prevalence of combination therapy was high despite the paucity of randomized and controlled clinical trials evaluating the safety and efficacy of such practice. The most commonly used combination, sildenafil and bosentan, has not undergone validation in appropriately designed trials, although such a study is currently underway. The second most commonly used combination, epoprostenol and sildenafil, has recently been studied; addition of sildenafil to epoprostenol therapy was associated with further improvement in the 6MWD.[36] A trend toward increased benefit with the addition of inhaled iloprost to bosentan therapy has been reported.[37] The widespread empirical use of combination therapy documented here emphasizes the importance of assessing the outcome of different treatment subgroups within the registry and supports the need for additional clinical trials to determine its value.

Limitations of the registry include the small number of newly diagnosed cases compared with previously diagnosed cases. Although this somewhat compromises the interpretation of treatment data for new patients, this is being addressed by amendment of the protocol to permit the enrollment of another 500 newly diagnosed cases. Direct comparison of the baseline demographics of the REVEAL population to previous registries is complicated by the changing definition of PAH, the retrospective nature of enrollment, and the exclusion of pediatric patients from the analyses. These limitations are being addressed in subsequent analyses.[38-41] Interpretation of therapeutic data is also limited by the uncontrolled nature of an observational study. Nevertheless, the large sample size, broad representation, and longitudinal follow-up help to ensure that the data obtained will complement those from clinical trials.

Table 6—*Comparison of Characteristics of Patients Aged ≥ 19 Years at Diagnosis Meeting Traditional Hemodynamic Characteristics of PAH With Those Having a PCWP of 16 to 18 mm Hg*

	PCWP at Diagnosis		
	≤ 15 mm Hg No. = 2525	16-18 mm Hg No. = 239	*P* Value
Age at enrollment, mean ± SD, y	53.0 ± 14.0	56.1 ± 14.5	.001
Age at diagnosis, mean ± SD, y	50.1 ± 14.4	53.6 ± 14.9	< .001
Female	2007 (79.5)	174 (72.8)	.016
Time from diagnosis, median (IQR)	24.9 (8.0, 50.9)	20.2 (5.5, 44.6)	.038
6MWD, mean ± SD, m	366 ± 126	339 ± 117	.004
mRAP, mean ± SD, mm Hg	9.3 ± 5.6	12.8 ± 5.6	< .001
PVRI, mean ± SD, Wood units · m^2	21.1 ± 12.5	19.1 ± 13.0	.052
Hypertension	980 (40.2)	111 (47.6)	.023
Obese (BMI ≥ 30 kg/m^2)	697 (33.3)	85 (41.9)	.014
Sleep apnea	484 (21.0)	85 (39.9)	< .001
Diabetes, overall	293 (12.0)	47 (20.2)	< .001
Renal insufficiency	109 (4.5)	25 (10.7)	< .001
Cardiomyopathy (dilated)	24 (1.0)	4 (1.7)	.286
Warfarin	1302 (53.4)	105 (45.1)	.016
Oxygen	982 (40.3)	110 (47.2)	.036
β-Blocker	296 (12.1)	51 (21.9)	< .001

Values are expressed as No. (%) unless otherwise noted. mRAP = mean right arterial pressure. See Tables 1 and 2 for expansion of other abbreviations.

In summary, baseline data from the REVEAL Registry provide important insight into the demographics, diagnosis, and treatment of PAH. Findings such as the unexpectedly long time from initial presentation to confirmation of the diagnosis and referral to a center, increasing female predominance in the United States, the prevalence of various comorbidities (sleep apnea, systemic hypertension, and thyroid disease) and recreational drug use (amphetamines and cocaine), and the widespread empirical use of expensive and complicated drug combinations, all have important implications for future educational, therapeutic, and research efforts. Comparison of adult patients with a traditional hemodynamic profile to those with a mildly elevated PCWP reveals important differences that need to be further explored. These differences may have therapeutic implications. Similarly, pediatric patients differ from adults in many important respects and will require more detailed characterization. Information obtained from the registry is applicable to the practice of providers in many areas of medicine, including pulmonary medicine, cardiology, rheumatology, general medicine, and pediatrics. Increased awareness should facilitate prompt recognition and earlier referral to centers experienced in the care of these complicated patients. Follow-up data collected over 5 years will provide invaluable information about outcomes and track changes in diagnostic strategies and treatment patterns. The registry has great potential to address several of the pressing needs in the field, including better risk stratification and the development and validation of more sophisticated prognostic tools. This will undoubtedly contribute to better targeting of medical therapy going forward.

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Pulmonary Arterial Hypertension : Baseline Characteristics From the REVEAL Registry

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