A USA-based registry for pulmonary arterial hypertension: 1982–2006

T. Thenappan, S.J. Shah, S. Rich and M. Gomberg-Maitland

ABSTRACT: The aim of this study was to define the epidemiology of World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH) in a large referral centre in the USA.

The Pulmonary Hypertension Connection registry, initiated in 2004, evaluated all patients in a single USA practice from 1982–2006. For comparison, the authors divided the group by incident *versus* prevalent cohorts, aetiology and by treatment era.

In total, 578 patients (77% female) aged 48±14 yrs were entered. Of these, 80% had class III or IV symptoms. Over time, connective tissue disease-associated PAH increased, while referrals for HIV remained low. One-third of patients were referred on calcium channel blocker therapy even though only 4.6% had an acute response to vasodilator challenge. When compared by treatment era, there were no differences in the severity of PAH. However, survival had improved over time, with a 1-yr survival of 85% in the incident cohort.

In the USA, pulmonary arterial hypertension patients are still referred to tertiary centres too late. Referral of connective tissue disease is increasing, while referral of HIV remains low. Inappropriate calcium channel blocker treatment is common. Survival rates have increased but remain low suggesting that prognosis is improving but PAH is still a progressive, fatal disease.

KEYWORDS: Aetiology, epidemiology, medications, pulmonary arterial hypertension, survival

Pulmonary arterial hypertension (PAH) is a debilitating, progressive disease of the pulmonary vasculature resulting in right heart failure and death. Idiopathic and familial forms of PAH (IPAH and FPAH, respectively, formerly known as primary pulmonary hypertension) occur more often in females than in males, with a mean age at diagnosis of 35 yrs and a median survival of 2.8 yrs if untreated [1, 2]. Under the most recent World Health Organization (WHO) guidelines, diverse aetiologies of PAH are grouped together based on similar pulmonary arterial pathological changes. Group I PAH now includes IPAH, FPAH and PAH associated with connective tissue diseases, congenital heart disease, portal hypertension, anorexigens or HIV [3]. Approved therapies for PAH, such as prostacyclins (epoprostenol, treprostinil and iloprost) [4–7], endothelin receptor antagonists (bosentan, ambrisentan) [8, 9] and phosphodiesterase-5 inhibitors (sildenafil) [10] all produce modest functional improvement with minimal change in haemodynamic measurements at cardiac catheterisation.

Despite an increased understanding of the pathophysiology of PAH and development of new treatments, basic information about the epidemiology and prognosis of PAH in the current era is lacking. Most of the current knowledge of the natural history of PAH is derived from the landmark National Institutes of Health (NIH) registry that followed patients with only primary pulmonary hypertension [1]. More recently, the French Network on Pulmonary Arterial Hypertension initiated a national prospective registry to study current epidemiological trends in PAH [11]. The French registry illustrated that PAH is still detected late in the course of the disease with severe functional and haemodynamic compromise. In addition, PEACOCK et al. [12] examined the incidence and prevalence of PAH in Scotland from two perspectives. 1) Scotland population-based hospitalisation records from 1986–2001 (Scottish Morbidity Report; SMR); and 2) from a specialised tertiary centre, the Scottish Pulmonary Vascular Unit (SPVU), from 1997–2005. The authors found a higher prevalence of PAH in the generalised cohort (SMR) than in the incident SPVU cohort. This illustrates the differences in disease among different populations and that the burden of disease is likely to be underestimated, requiring more global epidemiological investigation [13].

In light of treatment advances in PAH and in the absence of a contemporary USA-based registry,

the current authors initiated a registry to include all patients with pulmonary hypertension referred to a large USA-based tertiary referral practice. The aim of the present study was to define the clinical characteristics and prognosis of patients with WHO Group I PAH in the registry, and to compare groups by aetiology and treatment era.

METHODS

Data collection

The Pulmonary Hypertension Connection (PHC) database was initiated in March 2004. All patients evaluated at a single USA practice over time at three different university hospitals (University of Illinois, Rush University Medical Center and University of Chicago, all Chicago, IL, USA) between 1982 and 2006 were entered into the registry. Over this time-period, four physicians acquired all the clinical data. Data were collected by chart review and entered using an internet-based electronic data-capture system. Patients were entered retrospectively from 1982–2004, and consecutively thereafter.

Since initiation, two individuals with expertise in data management and clinical care of pulmonary hypertension patients have entered the data. The PHC registry is based on patients seen as an initial referral to the current authors' outpatient clinic. Consent was obtained during initial outpatient office evaluation for new patients, but was not necessary (IRB approved) for existing patients. Data entry on incident cases occurred after the complete initial evaluation. The database was approved by the respective Institutional Review Boards based on the location of the practice, and all actively seen patients gave informed consent to be entered into the registry.

Study population

A total of 1,360 patients referred to the present authors' practice from 1982–2006 were entered into the registry (812 patients were entered retrospectively and 548 patients were entered prospectively). Baseline demographics, clinical phenotype, medication, echocardiography, exercise test and cardiac catheterisation data was collected on all patients seen in the practice. From the registry, all adult patients ($\geqslant$18 yrs of age at time of referral) with Group I PAH (n=578) were identified. As per the WHO clinical classification [14], patients were excluded if they had: pulmonary venous hypertension diagnosed by pulmonary capillary wedge pressure >15 mmHg; obstructive lung disease diagnosed by reduced expiratory flow rates (forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <70% predicted); more than mild interstitial lung disease diagnosed by typical appearance on computed tomography (CT); chronic pulmonary thromboembolic disease diagnosed by ventilation perfusion (V/Q) scan (other than normal or low probability), contrast-enhanced chest CT or pulmonary angiography if necessary; and pulmonary hypertension associated with sarcoidosis and other infiltrative diseases.

Variables collected

The following baseline variables were analysed at the time of referral for characterisation of clinical phenotype: demographic data including age and sex; coexisting illnesses; WHO functional class; PAH-specific medications (prostacyclins, endothelin antagonists, phosphodiesterase inhibitors, warfarin

and calcium channel blockers (CCBs)); other concomitant medications; electrocardiogram; baseline laboratory tests including antinuclear antibody (ANA); pulmonary function testing; V/Q scan; chest CT; exercise treadmill testing using the Naughton–Balke protocol [15]; 6-minute walk test [16]; echocardiography; and baseline haemodynamic variables including mean right atrial pressure, pulmonary artery systolic, diastolic and mean pressures, cardiac index (CI), pulmonary artery oxygen saturation and peripheral vascular resistance. Cardiac output was determined by thermodilution unless an intracardiac shunt was present, in which case cardiac output was determined by the Fick principle. All patients had left heart catheterisation to determine left ventricular end diastolic pressure (LVEDP). Acute vasodilator challenge was performed during right heart catheterisation with adenosine [17]. A positive vasodilator response was defined as a >10 mmHg reduction of mean pulmonary artery pressure (mPAP) down to an mPAP of <40 mmHg, with an unchanged or improved CI [18]. All tests recorded were carried out by the current authors' practice, except for a minority of cases (<5%) in which cardiac catheterisation was performed by the referring facility in the 3 months prior to referral. Exercise testing, cardiac catheterisation and/or vasodilator testing were not performed if considered clinically unsafe. Vital statistics were collected for all patients by chart review and by query of the Social Security Death Index.

Statistical analysis

The patients were compared by incident (2004–2006) *versus* prevalent (1982–2004) cohorts, aetiology and by treatment era based on the availability of various PAH-specific medications: pre-1996 (before approved therapies); 1996–2002 (only *i.v.* epoprostenol); and post-2002 (*i.v.*, subcutaneous or inhalational prostacyclins, endothelin blockers and phosphodiesterase inhibitors). Continuous variables were compared using unpaired t-tests and ANOVA, or by equivalent nonparametric test (when appropriate). Categorical variables were compared using the Chi-squared test or Fisher's exact test.

Survival analysis was performed using the Kaplan–Meier survival analysis, with the date of entry into the study defined as the date of the patient's first cardiac catheterisation by the current authors' practice identifying PAH, or (for those patients who did not undergo cardiac catheterisation) date of referral to the practice. The primary end-point was death. The authors determined a 1-, 3- and 5-yr survival rate for the entire cohort, and a 1-yr survival was determined for the incident cohort.

RESULTS

Overall WHO Group I cohort

A total of 578 patients with WHO Group I PAH were entered into the authors' registry. Clinical, exercise and haemodynamic data for the entire cohort (and for incident and prevalent subgroups) are summarised in table 1 and the percentage of patients on various medications at the time of referral is shown in table 2. The mean age of patients enrolled in the total cohort was 48$\pm$14 yrs and 77% were females. The female/male ratio varied by age, as shown in figure 1. While the highest frequency was in the fourth decade for males and the fifth decade for females, 8.5% were >70 yrs of age at the time of

TABLE 1	Clinical and haemodynamic data at the time of diagnosis of pulmonary arterial hypertension			
Clinical data	**All cases**	**Incident cases**	**Prevalent cases**	**p-value[#]**
Subjects n	578	82	496	
Female	77	76	77	0.75
Age yrs	48 ± 14 (21–83)	51 ± 14 (21–79)	48 ± 14 (21–83)	0.063
WHO functional class III–IV	80	83	76	0.19
Exercise capacity METs	3.5 ± 3	3.6 ± 1.8	3.5 ± 2.0	0.87
Haemodynamic data				
mRAP mmHg	11 ± 7	10 ± 7	11 ± 7	0.037
mPAP mmHg	52 ± 14	51 ± 12	52 ± 14	0.30
PCWP mmHg	10 ± 4	10 ± 4	10 ± 4	0.89
Cardiac index L·min^{-1}·m^{-2}	2.3 ± 0.9	2.4 ± 0.8	2.2 ± 0.9	0.07
P_{A,O_2} saturation	58 ± 12	61 ± 10	57 ± 12	0.015
PVR Woods unit	12.5 ± 7.3	11 ± 5	13 ± 7	0.027
Acute vasodilator responders	4.6	4.5	4.6	0.99
Aetiology				0.12
Idiopathic/familial	48	34	50	
Connective tissue disease	30	40	28	
Congenital heart disease	11	13	10	
Portal hypertension	7	9	7	
Anorexigens	3	2	3	
HIV	1	1	1	

Data are presented as %, mean $\pm$ SD or mean $\pm$ SD (range), unless otherwise stated. WHO: World Health Organization; METs: metabolic equivalents; mRAP: mean right atrial pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; P_{A,O_2}: alveolar oxygen partial pressure; PVR: pulmonary vascular resistance. [#]: comparisons are for incident *versus* prevalent cases of pulmonary arterial hypertension.

diagnosis. At presentation, most of the patients (80%) had WHO functional class III or IV symptoms.

Medications at time of referral

Only a small percentage of patients were receiving PAH-specific medications at the time of referral to the outpatient clinic (2.4% prostacyclins, 3.1% endothelin blockers, 0.8% phosphodiesterase inhibitors) while 28% were receiving warfarin, 18% digoxin and 31% were on CCBs. The percentage of IPAH/FPAH referred on PAH-specific therapy was 5.4%.
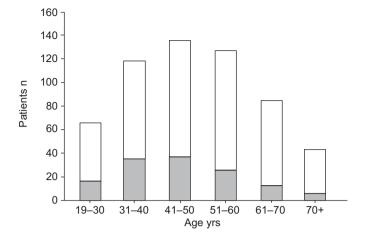
TABLE 2	Medications at the time of referral
Medication	**n (%)**
Calcium channel blockers	182 (32)
Digoxin	102 (18)
Warfarin	164 (28)
Prostacyclins	14 (2)
Endothelin antagonists	18 (3)
Phosphodiesterase inhibitors	5 (1)
Aspirin	77 (13)
Angiotensin-converting enzyme inhibitors	70 (12)
Angiotensin receptor blockers	23 (4)
β-blockers	50 (9)
Diuretics	272 (47)
Selective serotonin re-uptake inhibitors	16 (6)

ANA testing

In total, 380 patients underwent ANA testing and 202 had a positive (>1:80) result. The patterns observed were speckled (34%), centromere (20%), nucleolar (19%) and homogenous (27%). A positive ANA was detected in 33% of IPAH/FPAH patients, 34% of congenital heart disease patients, 94% of connective tissue disease patients, 40% of patients with anorexigen use and 35% of portal hypertension patients. If there were no clinical manifestations of connective tissue disease other than positive ANA, the patients were classified according to the primary cause of their PAH: if there was no apparent cause of PAH, patients were classified as IPAH.

Pulmonary diagnostic testing

On pulmonary function testing, there was no demonstrable airway obstruction, but diffusion capacity of the lung for carbon monoxide ($D_{L,CO}$) and total lung capacity (TLC) were reduced: mean $D_{L,CO}$ $55 \pm 23\%$ pred, mean TLC $88 \pm 20\%$ pred. FEV1 ($75 \pm 19\%$ pred) and FVC ($78 \pm 19\%$ pred) were relatively preserved. In total, 290 patients had a CT scan of the chest, of these 69% had a normal CT, 22% had mild interstitial lung disease (of which 84% had connective tissue disease) and 1.4% had evidence of pulmonary embolism. Other findings (all <1%) included mild emphysema, bronchiectasis, ground-glass opacities, pulmonary nodule, pneumonia, mild emphysema and pulmonary oedema. Results of V/Q scan (n=417) included: 76% normal, 20% mottled perfusion and 4% with an intermediate or high probability result. In the patients with a positive scan, the treating physician determined that these

FIGURE 1. Distribution of World Health Organization functional class I pulmonary arterial hypertension patients by age and sex. □: female; ■: male.

patients did not have chronic thromboembolic pulmonary hypertension by clinical history and diagnostic testing.

Electrocardiography and echocardiography
The electrocardiogram showed right ventricular hypertrophy with strain pattern and right atrial enlargement in 55 and 22% of patients, respectively. The echocardiogram showed moderate-to-severely decreased right ventricular systolic function in 57% and normal left ventricular function in 93% of patients, with a mean ejection fraction of $59 \pm 11\%$. Right ventricular hypertrophy was identified in 43% and 92% had tricuspid regurgitation with a mean velocity of 4.1 ± 0.9 m·s^{-1}. Data on the presence and size of pericardial effusion was not available.

Exercise capacity
Exercise tolerance was evaluated with exercise treadmill testing in 330 (57%) patients; the mean exercise capacity was 3.5 ± 3 metabolic equivalents (METs), with a mean exercise time of 305 ± 237 s. A total of 59 (10%) patients had a baseline 6-minute walk test performed with a mean walk distance of 289 ± 186 m.

Haemodynamics
Right heart catheterisation was available at baseline in 521 (90%) patients. For the total cohort, patients had moderate-to-severe PAH with an increase in mPAP (52 ± 14 mmHg), moderate elevation of mean right atrial pressure (11 ± 7 mmHg), and mildly decreased CI (2.3 ± 0.9 L·min^{-1}·m^{-2}). Acute vasodilator response was tested with adenosine in 437 (76%) patients with 20 (4.6%) patients demonstrating a positive response based on the current criteria [18]. As shown in table 1, haemodynamics were similar between the incident and prevalent cohorts except for a statistically significant difference in mean right atrial pressure (p=0.037), pulmonary artery oxygen saturation (p=0.015) and the calculated pulmonary vascular resistance (p=0.027), all indicating slightly less severe disease in the incident cohort.

Subgroups of WHO Group I PAH
Table 1 shows the proportion of patients in each subgroup of Group I PAH by aetiology. For the total cohort, nearly half of

the patients (48%) had IPAH (44%) or FPAH (4%) and the remainder had associated conditions: connective tissue disease (30%); congenital heart disease (11%); portal hypertension (7%); anorexigens (3%); and HIV (1%).

Of the congenital heart disease patients, defects were as follows: atrial septal defect (70%); ventricular septal defect (8%); repaired patent ductus arteriosus (4%); partial anomalous venous drainage (2%); and complex lesions (tetralogy of fallot or D-transposition of the great vessels; 1%). Combined defects included one patient with an atrial septal defect and anomalous pulmonary venous drainage and two patients with repaired ventricular septal defects and patent ductus arteriosus.

Although the overall differences in aetiology between incident and prevalent cohorts was not statistically different, the incident cohort had a larger percentage of connective tissue disease (40 versus 28%), and fewer IPAH/FPAH (34 versus 50%) patients compared with the prevalent cohort. The clinical characteristics and haemodynamic parameters of patients in various subgroups of PAH are displayed in tables 3 and 4, respectively. In all subgroups except for HIV, there was a greater than 2:1 female predominance and all patients were older than previous epidemiological studies of PAH.

Compared with other subgroups, patients with connective tissue disease had more severe disease with a lower exercise capacity, a worse functional class (with more referred at functional class IV), a higher mPAP and pulmonary vascular resistance, and lower CI (tables 3 and 4). Patients with portal hypertension and congenital heart disease-associated PAH were less ill with a higher functional class and exercise capacity, lower mPAP and pulmonary vascular resistance, and higher CI (table 4). A positive acute vasodilator response to adenosine only occurred in patients with IPAH/ FPAH (4.5%), connective tissue disease (2.3%) and congenital heart disease (12.5%).

Comparison of different eras of treatment
Table 5 compares the clinical and haemodynamic characteristics of patients diagnosed with PAH in different treatment eras. Of the 10% of total patients who did not undergo catheterisation at time of referral, 3% were in era I, 13% in era II and 8% in era III. In the current era (2002–2006), patients were older and had similar functional class to era I, but improved compared with era II. The percentage of patients with IPAH/ FPAH decreased over time, while the percentage of patients with connective tissue disease increased. Of the current era, 15% of patients were referred on approved therapy for PAH, although none were on prostacyclin. There were no differences in the severity of PAH based on exercise capacity or haemodynamics. The proportion of total PAH patients with an acute vasodilator response to adenosine was not different between the three eras, nor was the difference between the proportion of patients with IPAH/FPAH who responded to adenosine: 5.0, 5.7 and 5.0% in the three treatment eras, respectively (p=0.98).

Survival
Of the total 578 patients, nine were lost for follow-up and 326 of the remaining 569 patients died. For the total cohort, the median survival time was 3.6 (interquartile range 1.4–7.4) yrs.

TABLE 3	Baseline clinical characteristics of patients by aetiology of pulmonary arterial hypertension (PAH)						
Clinical Data	IPAH/FPAH	CTD	Congenital heart disease	Anorexigen	HIV	Portal hypertension	p-value
Age yrs	45 ± 14	55 ± 15	42 ± 12	52 ± 11	40 ± 4	49 ± 9	<0.0001
Female	75	87	68	100	13	70	<0.0001
WHO functional class							
Mean	3.0 ± 0.9	3.2 ± 0.7	2.8 ± 0.9	3.1 ± 0.7	2.7 ± 0.8	2.9 ± 0.9	<0.007
Class I	7	3	10	0	0	7	
Class II	13	9	21	19	43	22	
Class III	49	49	45	56	43	49	
Class IV	31	39	24	25	14	22	
Exercise capacity METs	3.7 ± 3.1	3.1 ± 2.7	3.9 ± 2.9	3.6 ± 3.2	3.3 ± 3.7	3.5 ± 3.0	0.199

Data are presented as mean $\pm$ SD or %, unless otherwise stated. IPAH: idiopathic PAH; FPAH: familial PAH; CTD: connective tissue disease; WHO: World Health Organization; METs: metabolic equivalents.

Figure 2 shows the Kaplan–Meier survival curve for the entire cohort. The actual 1-, 3- and 5-yr survival rates were 84, 67 and 58%. The 1-yr survival for the incident cohort of 82 patients was 85% (12 deaths). In the incident cohort, 1-yr survival was better than the NIH registry that was carried out in the 1980s but similar to the French registry (88% 1-yr survival) [11].

DISCUSSION
Since publication of the epidemiology of primary pulmonary hypertension in the NIH registry in the mid 1980s [1] there has been significant progress in the understanding of the pathophysiology and treatment of PAH [14, 19]. Despite these significant advances, the epidemiology and clinical characteristics of USA-based patients with WHO Group I PAH have not been well defined. The current authors' registry, the PHC database, is the first and largest USA-based registry for WHO Group I PAH. Current knowledge about PAH in the USA is based on industry-sponsored studies with limited patients. The large number of patients in the present study allows better characterisation of the clinical features, haemodynamic parameters and survival of PAH.

Data from the PHC database confirmed the female predominance of IPAH, which was even higher than previous reports of 2:1, and illustrated that the female predominance exists in all aetiologies of Group I PAH except HIV. Although similar to French findings [11, 20], this may have been due to the small HIV cohort evaluated by the present authors. All patient subtypes were older than previously reported by the NIH registry, for example mean age of IPAH/FPAH patients was 45 yrs compared with a mean age of 36 yrs in the NIH registry [1]. Similar to recent data [11, 21], the current registry demonstrated that PAH can manifest even at a relatively later age, with 8.5% of patients diagnosed after 70 yrs of age. The severely diminished exercise capacity of 3.5 METs correlated with the patients' diminished functional class, right ventricular dysfunction and severely diminished haemodynamics.

More than half of the study patients had conditions associated with PAH (non-IPAH/FPAH) and, over time, referrals increased substantially for patients with connective tissue disease, slightly for congenital heart disease and portal hypertension, and less for patients with IPAH/FPAH. These findings may reflect the increased number of PAH centres in the USA, increased use of noninvasive screening diagnostics and increased awareness of the subtypes of the disease. The current authors hypothesise that increased referral for connective tissue disease is most likely to be due to the increased awareness of PAH by rheumatologists. It is unclear if these are true differences between the rates of connective tissue disease PAH at the current authors' institution compared with those observed by the French group, if there are differences in referral patterns between the USA and Europe, or if this is a referral bias to a single tertiary centre. Patients with connective tissue disease had worse clinical status, consistent with recent reports [22–25], while those with congenital heart disease and portal hypertension had better functional class and haemodynamics than the other subtypes.

The number of patients referred with PAH associated with HIV were much lower than observed by the French group. The low numbers of HIV patients referred to the current authors' clinic is an important finding highlighting the possible underappreciation of PAH in HIV. Another possibility is that patients with HIV have comorbidities which may outweigh PAH in clinical importance, thereby also limiting referral. HIV-associated PAH in the USA, therefore, merits further study to determine whether these patients could benefit from more frequent referral to PAH specialists.

Only a small percentage of patients in the registry were receiving PAH specific medications at the time of referral, emphasising that PAH is still a disease managed mainly in tertiary centres and that patients are still referred to these centres late in the disease. As a cardiology practice, the present authors' group believed that data collection on antihypertensive medications would be informative as it is unknown if these agents are beneficial or harmful in this population and it will be difficult to perform a randomised study to assess their effects. It is reported that the withdrawal of β-blockers in portal hypertension patients is harmful [26]. However, as this registry is modelled after the NIH registry, collecting only baseline data, the authors do not have data on the effects of medication changes. The use of selective serotonin re-uptake inhibitors for

TABLE 4	Haemodynamics at the time of diagnosis for patients in each subtype of pulmonary arterial hypertension (PAH)						
	IPAH/FPAH	CTD	Congenital heart disease	Anorexigen	HIV	Portal hypertension	p-value
mRAP mmHg	11±7	11±6	10±7	13±5	14±5	12±7	0.17
mPAP mmHg	56±13	48±11	54±22	52±12	50±5	46±14	<0.0001
PCWP mmHg	10±4	10±4	13±8	9±3	10±2	12±5	<0.0001
Cardiac index L·min^{-1}·m^{-2}	2±0.7	2.3±0.8	2.8±0.7	1.9±0.7	2.3±0.8	3.2±1.5	<0.0001
P_{A,O_2} saturation	57±11	57±11	66±14	54±13	54±9	62±13	<0.0001
PVR Woods unit	14±6.8	11.1±5.9	13.2±11.4	13.5±7.1	10.3±3.3	7.4±5.3	<0.0001
Acute vasodilator responders	5.4	2.3	12.5	0	0	0	0.12

Data are presented as mean±SD or %, unless otherwise stated. IPAH: idiopathic PAH; FPAH: familial PAH; CTD: connective tissue disease; mRAP: mean right atrial pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; P_{A,O_2}: alveolar oxygen partial pressure; PVR: pulmonary vascular resistance.

TABLE 5	Comparison of clinical and haemodynamic data for patients diagnosed in three different treatment eras		
	Year		p-value
	1982–1996	1996–2002	2002–2006	
Subjects n	103	328	147	
Age yr	41±12	49±14	52±14	<0.0001
Female	77 (75)	253 (77)	115 (78)	0.81
WHO functional class	3.2±0.9	2.9±0.8	3.2±0.8	0.003
Exercise capacity METs	3.6±3.05	3.6±3.05	3.4±2.9	0.81
Prostacyclins[#]	3 (2.9)	11 (3.4)	0	0.44
Endothelin antagonists[#]	0	1 (0.3)	17 (11.6)	<0.001
Phosphodiesterase inhibitors[#]	0	0	5 (3.4)	<0.001
Idiopathic/familial PAH	77 (75)	150 (46)	49 (33)	<0.0001
CTD	12 (11)	100 (30)	61 (42)	<0.0001
Congenital heart disease	10 (10)	34 (10)	18 (12)	0.78
Portal hypertension	4 (4)	25 (8)	14 (10)	0.241
Anorexigens	0	13 (4)	3 (2)	0.065
HIV	0	6 (2)	2 (1)	0.164
RAP mmHg	12±7	11±6	10±6	0.10
mPAP mmHg	56±14	51±14	51±12	0.005
PCWP mmHg	10±4	10±4	10±5	0.40
Cardiac index L^{-1}·min·m^{-2}	2.1±0.8	2.3±0.9	2.3±0.8	0.37
P_{A,O_2} saturation	56	58	60	0.07
PVR Wood units	13.4±6.4	12.7±7.9	11.5±6.1	0.15
Acute vasodilator responders	3.7	4.2	5.8	0.78

Data are presented as mean±SD, % or n (%), unless otherwise stated. WHO: World Health Organization; METs: metabolic equivalents; PAH: pulmonary arterial hypertension; CTD: connective tissue disease; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; P_{A,O_2}: alveolar oxygen partial pressure; PVR: pulmonary vascular resistance. [#]: PAH-specific medications taken by patients at the time of referral to the authors' centre.

depression in 6% of the cohort is interesting since recent animal data suggests that it may be a potential target for treatment in PAH [27, 28], and the effect of these medications on PAH requires further evaluation.

Few patients throughout the eras responded to vasodilator testing based on the new criteria for "true responders" [18]. The consistent low response in IPAH/FPAH demonstrates the stability in referral patterns and likely a more accurate reflection of persistent response [29]. The data also substantiates the new definition compared with a previous definition, defined from the current authors' earlier IPAH/FPAH cohort, which may have overestimated rates of response [30]. Interestingly, a high percentage of the responders had congenital heart disease, a finding that requires further study. Of greater importance is the large number of patients referred to the authors' clinic receiving CCB therapy without proper evaluation in all three treatment eras. After comprehensive evaluation, CCBs were discontinued in all nonresponders due
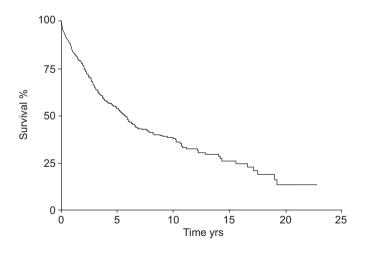

FIGURE 2. Kaplan–Meier survival curve for World Health Organization functional class I pulmonary arterial hypertension patients. The number of patients at risk at 0, 5, 10, 15 and 20 yrs was 568, 240, 71, 19 and 3, respectively.

to the possible harmful effects of CCBs in these patients. However, there may be many more PAH patients in the community who are not rigorously evaluated for vasodilator response and who are receiving potentially harmful therapy with CCBs.

The 1-yr survival in the PHC incident cohort was similar to the French registry. The PHC included all patients evaluated between 1982 and 2006 and, unlike the NIH and French registries, the PHC is a single academic centre registry, with only four physicians acquiring all the clinical data for the entire cohort of 578 patients. The NIH registry included patients with untreated IPAH/FPAH and anorexigens only, but the PHC, similar to the French registry, included patients from all subgroups of WHO Group I. For the entire present study cohort, the 1-, 3- and 5-yr survival rates were 84, 67 and 58%, respectively, and the median survival time was 3.6 yrs. Although patients continue to present with advanced disease, there appears to be improved survival of IPAH/FPAH patients (85%) compared with the NIH registry. Since there is currently no survival equation for the subgroups of WHO Group I PAH, and the present incident cohort is small, it is difficult to accurately compare subgroup survival with previous survival data.

Several limitations should be considered when interpreting data from the current authors' registry. The present authors acknowledge that standard of care practice of diagnostics, such as exercise treadmill testing, adenosine to evaluate vasodilator reserve during cardiac catheterisation and measurement of LVEDP before and after vasodilator testing, are used at their site and are not universal procedures in the pulmonary hypertension community. The authors prefer the treadmill test because it avoids many of the ambiguities associated with the 6-minute walk test, and because determination of METs is a reliable measure of exercise capacity in PAH patients, predicts outcome in patients on epoprostenol and correlates well with the 6-minute walk distance [31, 32]. The current authors' group has demonstrated the ability of adenosine to predict response to CCBs and to predict outcome on epoprostenol [1, 17, 32, 33]. With its ease of administration, short half-life and the authors' experience, they continue to use adenosine as the agent of choice for vasodilator testing. The authors found differences in the LVEDP and wedge pressure measurements in some patients, and are currently investigating these differences prospectively. Anecdotally, the LVEDP has been useful in connective tissue disease patients who frequently have diastolic dysfunction. In these patients, a rise in the LVEDP after vasodilator challenge secondary to the increased cardiac output was observed, halting the use of prostacyclin. However, this clinical practice requires further investigation.

This is an observational study with a large number of patients entered retrospectively; this can lead to lost data or inconclusive data for analysis. As a longstanding cardiology practice with consistent practice patterns, much of the data for diagnostic evaluation were obtained at the site in order to standardise results. Anorexigen use was lower than expected, which may have been due to the retrospective nature of the study. A few patients may have been misclassified as IPAH during their initial visit to the clinic (from which data for the registry was gathered), and later diagnosed with anorexigen-associated

PAH when the treating physician uncovered prior anorexigen use. However, in the incident cohort (in whom full charts are available and have been reviewed) the number of patients with prior anorexigen use is truly quite low.

The present authors' registry included patients from a single USA practice, and may not reflect national trends. The REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) registry is a multicentre, observational, industry sponsored USA-based study currently enrolling PAH patients and may provide more insight in to the national trends. The current registry was based on patients referred to a tertiary medical centre and the results may not generalise to undiagnosed patients in the community. An echocardiography was used for diagnosing PAH in 57 (10%) patients since they were too ill to undergo cardiac catheterisation at the time of referral. Since none of these patients had risk factors or evidence of diastolic dysfunction (including left ventricular hypertrophy) the authors did not believe that these patients were misclassified. Finally, there were only a limited number of patients with HIV associated PAH in the registry, as discussed previously.

In conclusion, the Pulmonary Hypertension Connection registry provides insights into the clinical characteristics of a large number of USA-based patients with pulmonary arterial hypertension referred to a single practice over time. Specifically, the current authors have found the following. 1) The percentage of patients with connective tissue disease-associated pulmonary arterial hypertension appears to be increasing. 2) The number of HIV patients referred for pulmonary arterial hypertension remains low. 3) Many patients with pulmonary arterial hypertension are still being referred on potentially harmful calcium channel blockers therapy without an adequate prior evaluation for true pulmonary vasoreactivity. 4) Patients with pulmonary arterial hypertension are still referred late in the disease process at a time when haemodynamic abnormalities are at an advanced stage. Fortunately, survival rates, although still low, appear to have improved despite similar clinical status, suggesting that overall health and treatment may be improving due to practice guidelines, improved diagnostics and new therapies.

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