ERJ Express. Published on September 5, 2007 as doi: 10.1183/09031936.00042107

A UNITED STATES-BASED REGISTRY FOR PULMONARY ARTERIAL HYPERTENSION: 1982-2006

Thenappan Thenappan, MD, Sanjiv J. Shah, MD, Stuart Rich, MD,

and Mardi Gomberg-Maitland, MD, MSc

Section of Cardiology, Department of Medicine, University of Chicago, Chicago, IL

Short Title: A US Registry for PAH: 1982-2006

Address for correspondence:

Mardi Gomberg-Maitland, MD, MSc

Director of Pulmonary Hypertension

5841 S Maryland Ave, MC 2016

Chicago, IL 60637

E-mail: mgomberg@medicine.bsd.uchicago.edu

Phone: 773-702-5589

Fax: 773-834-1764

Word count: 4180

Tables: 5

Figures: 2

ABSTRACT

Background: We aimed to define the epidemiology of World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH) in a large referral center in the United States (US).

Methods: The Pulmonary Hypertension Connection registry, initiated in 2004, evaluated all patients in a single US practice from 1982-2006. For comparison, we divided the group by incident vs. prevalent cohorts, by etiology, and by treatment era.

Results: 578 patients, age 48±14 years, 77% female, and 80% with class III or IV symptoms were entered. Over time, connective tissue disease (CTD)-associated PAH increased, while referrals for human immunodeficiency virus (HIV) remained low. One-third of patients were referred on calcium channel blocker (CCB) 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 has improved over time, with a 1-year survival of 85% in the incident cohort.

Conclusion: In the US, PAH patients are still referred to tertiary centers late. Referral of CTD is increasing, while referral of HIV remains low. Inappropriate CCB treatment is common. Survival rates have increased but remain low suggesting that prognosis is improving but PAH is still a progressive, fatal disease.

Key Words: epidemiology, pulmonary arterial hypertension, etiology, medications, survival

Pulmonary arterial hypertension (PAH) is a debilitating, progressive disease of the pulmonary vasculature resulting in right heart failure and death. Idiopathic (IPAH) and familial (FPAH) forms of PAH (formerly known as primary pulmonary hypertension) occur more often in women than in men, with a mean age at diagnosis of 35 years and a median survival of 2.8 years if untreated.(1, 2) Under the most recent World Health Organization (WHO) guidelines, diverse etiologies of PAH are grouped together based on similar pulmonary arterial pathologic changes. Group I PAH now includes IPAH, FPAH, and PAH associated with connective tissue diseases, congenital heart disease, portal hypertension, anorexigens, or human immunodeficiency virus (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 hemodynamic measurements at cardiac catheterization.

Despite increasing 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 our 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 epidemiologic trends in PAH.(11) The French registry illustrated that PAH is still detected late in the course of the disease with severe functional and hemodynamic compromise. In addition, Peacock et al. examined the incidence and prevalence of PAH in Scotland from two perspectives: Scotland population-based hospitalization records from 1986-2001 (Scottish Morbidity Report [SMR]), and from a specialized tertiary center, the Scottish Pulmonary Vascular Unit (SPVU), from 1997-2005.(12)

The authors found a higher prevalence of PAH in the generalized 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 underestimated, requiring more global epidemiologic investigation.(13)

In light of treatment advances in PAH and in the absence of a contemporary United States (US)-based registry, we initiated a registry to include all patients with pulmonary hypertension referred to a large US-based tertiary referral practice. The aim of our study was to define the clinical characteristics and prognosis of patients with WHO Group I PAH in our registry, and to compare groups by etiology and by treatment era.

METHODS

Data Collection

Our registry, the Pulmonary Hypertension Connection (PHC) database, was initiated in March 2004. All patients evaluated at a single US practice over time at three different university hospitals (University of Illinois at Chicago, Rush University Medical Center, and University of Chicago) 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 initiated, 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 our outpatient clinic. Consents were obtained during initial outpatient office evaluation for new patients, and during routine office visits for existing patients.

Data entry on incident cases occurs 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 our practice from 1982-2006 were entered into the registry (812 patients were entered retrospectively and 548 patients were entered prospectively). We collected baseline demographic, clinical phenotype, medication, echocardiography, exercise test, and cardiac catheterization data on all patients seen by our practice. From our registry, we identified all adult patients (≥ 18 years of age at time of referral) with Group I PAH (N=578). As per the WHO clinical classification (14), patients were excluded if they had pulmonary venous hypertension diagnosed by pulmonary capillary wedge pressure > 15 mm Hg; obstructive lung disease diagnosed by reduced expiratory flow rates (forced expiratory volume in 1 second/forced vital capacity < 70% of 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

We analyzed the following baseline variables at the time of referral for characterization 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; other concomitant medications; electrocardiogram; baseline laboratory tests including antinuclear antibody (ANA); pulmonary function testing; V/Q scan; chest CT; exercise treadmill testing using Naughton-Balke protocol (15); six minute walk test (16); echocardiography; and baseline hemodynamic variables including mean right atrial pressure, pulmonary artery systolic, diastolic and mean pressures, cardiac index, 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 catheterization to determine left ventricular end diastolic pressure (LVEDP). Acute vasodilator challenge was performed during right heart catheterization with adenosine.(17) A positive vasodilator response was defined as a > 10 mmHg reduction of mean pulmonary artery pressure (down to a mean pulmonary artery pressure < 40 mm Hg), with a normal or high cardiac index. (18) All tests recorded were those done by our practice except for a minority of cases (< 5%) in which cardiac catheterization was performed by the referring facility in the 3 months prior to referral. Exercise testing, cardiac catheterization, and/or vasodilator testing were not performed if clinically considered unsafe. Vital statistics were collected for all patients by chart review and by query of the Social Security Death Index.

Statistical Analysis

We compared patients by incident (2004-2006) vs. prevalent (1982-2004) cohorts, by etiology, and by treatment era based on the availability of various PAH-specific medications: pre-1996 (before approved therapies), 1996-2002 (only intravenous epoprostenol), and post-2002 (intravenous, subcutaneous, or inhalational prostacyclins, endothelin blockers, and

phosphodiesterase inhibitors). Continuous variables were compared using t-tests and analysis of variance, or by equivalent non-parametric test (when appropriate). Categorical variables were compared using chi-square 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 patient's first cardiac catheterization by our practice identifying PAH, or (for those patients who did not undergo cardiac catheterization) date of referral to our practice. The primary end point was death. We determined 1-, 3-, and 5-year survival rates for the entire cohort, and we determined 1-year survival for the incident cohort. All statistical analyses were performed using Stata (version 9, StataCorp LP, College Station, TX).

RESULTS

Overall WHO Group I Cohort

A total of 578 patients with WHO Group I PAH were entered in to our registry. Clinical, exercise, and hemodynamic data for the entire cohort (and for incident and prevalent subgroups) are summarized in Table I and the percentage of patients on various medications at the time of referral is shown in Table II. The mean age of patients enrolled in the total cohort was 48 ± 14 years and 77% were females. The female-to-male ratio varied by age, as shown in Figure 1. While the highest frequency of patients was in the fourth decade for males and in the fifth decade for females, 8.5% were above the age of 70 years at the time of 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 on PAH-specific medications at the time of referral to our outpatient clinic (2.4% were on prostacyclins,

3.1% were on endothelin blockers, 0.8% were on phosphodiesterase inhibitors) while 28% were on warfarin, 18% were on digoxin, and 31% were on calcium channel blockers. The percentage of IPAH/FPAH referred on PAH-specific therapy was 5.4%.

Anti-nuclear antibody testing: 380 patients underwent antinuclear antibody testing, and 202 had a positive (>1:80) results. The patterns observed were speckled (34%), centromere (20%), nucleolar (19%), and homogenous (27%). Thirty-three percent of IPAH/FPAH patients, 34% of congenital heart disease patients, 94% of connective tissue disease patients, 40% of anorexigen use, and 35% of portal hypertension patients had a positive ANA. 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 for carbon monoxide (DL_{CO}) and total lung capacity (TLC) were reduced: mean DL_{CO} 55± 23% of predicted; mean TLC 88± 20% of predicted. FEV_1 (75 ± 19% predicted) and FVC (78 ± 19% predicted) were relatively preserved. Two hundred and ninety patients had a CT scan of the chest: 69% had a normal CT, 22% had mild interstitial lung disease (of which 84% had connective tissue disease), 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 edema. Results of V/Q scan (N=417) included: 76% normal, 20% mottled perfusion, and 4% had an intermediate or high probability result. In the patients with a positive scan, the treating physician determined by clinical history and diagnostic testing that these patients did not have chronic thromboembolic pulmonary hypertension.

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±11%. Forty-three percent had right ventricular hypertrophy and 92% had tricuspid regurgitation with a mean velocity of 4.1±0.9 m/sec. Data on 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 seconds. Fifty-nine patients (10%) had a baseline six-minute walk test performed with a mean walk distance of 289±186 meters.

Hemodynamics: Right heart catheterization was available at baseline in 521 (90%) patients. For the total cohort, patients had moderate-to-severe PAH with an increase in mean pulmonary artery pressure (52 ± 14 mm Hg), moderate elevation of mean right atrial pressure (11 ± 7 mm Hg), and mildly decreased cardiac index (2.3 ± 0.9 L/min/m^2). Acute vasodilator response was tested with adenosine in 437 (76%) patients with 20 patients (4.6%) demonstrating a positive response based on the current criteria.(18) As shown in Table I, hemodynamics 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 I shows the proportion of patients in each subgroup of Group I PAH by etiology. For the total cohort, nearly one 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: 70% had an atrial septal defect, 8% had a ventricular septal defect, 4% had a repaired patent ductus arteriosus, 2% had partial anomalous venous drainage, and 1% had complex lesions (tetralogy of fallot or D-transposition of the great vessels). 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 etiology between incident and prevalent cohorts was not statistically different, the incident cohort had a larger percentage of connective tissue disease (40 vs. 28%), and less IPAH/FPAH (34% vs. 50%) patients compared with the prevalent cohort. The clinical characteristics and hemodynamic parameters of patients in various subgroups of PAH are displayed in Tables III-IV, respectively. In all subgroups except for HIV there was a greater than 2:1 female predominance and all patients were older than previous epidemiologic 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 mean pulmonary artery pressure and pulmonary vascular resistance, and lower cardiac index (Tables III-IV). Patients with portal hypertension and congenital heart disease-associated PAH were less sick with a higher functional class and exercise capacity, lower

mean pulmonary artery pressure and pulmonary vascular resistance, and higher cardiac index (Table IV). A positive acute vasodilator response to adenosine occurred only 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 V compares the clinical and hemodynamic characteristics of patients diagnosed with PAH in different treatment eras. Of the 10% of total patients who did not undergo catheterization 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. Fifteen percent of current era 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 hemodynamics. 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 3 treatment eras, respectively; p=0.98.

Survival

Of the total 578 patients, 9 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) years. Figure 2 shows the Kaplan Meier survival curve for the entire cohort. The 1-, 3-, and 5-year actual survival rates were 84%, 67%, and 58%. The 1-year survival for the incident cohort of 82

patients was 85% (12 deaths). One-year survival in the incident cohort was better than the NIH registry done in the 1980's but similar to the French registry (88% 1-year survival).(11)

DISCUSSION

Since publication of the epidemiology of primary pulmonary hypertension in the NIH registry, the last two decades has witnessed significant progress in the understanding of the pathophysiology and treatment of PAH. (14, 19) Despite these significant advances, the epidemiology and clinical characteristics of US-based patients with WHO Group I PAH have not been well defined. Our registry, the Pulmonary Hypertension Connection (PHC) database, is the first and largest US-based registry for WHO Group I PAH. Current knowledge about PAH in the US is based on industry-sponsored studies with limited patients. The large number of patients in our study allows better characterization of the clinical features, hemodynamic parameters, and survival of PAH.

Data from our 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 etiologies of Group I PAH except HIV. Although similar to our French colleagues' findings, (11, 20) this may have been due to the small HIV cohort evaluated by our group. All patient subtypes were older than previously reported by the NIH registry; for example mean age of IPAH/FPAH patients was 45 years compared to a mean age of 36 years in the NIH registry.(1) Similar to recent data, (11, 21) our registry demonstrated that PAH can manifest even at a relatively later age, with 8.5% of patients diagnosed after 70 years of age. The severely diminished exercise capacity of 3.5 METs correlated with the patients' diminished functional class, right ventricular dysfunction, and severely diminished hemodynamics.

More than half of our patients had conditions associated with PAH (non-IPAH/FPAH) and over time, our 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 centers in the US, increased use of non-invasive screening diagnostics, and increased awareness of the subtypes of the disease. We hypothesize that increased referral for connective tissue disease is most likely due to the increased awareness of PAH by the rheumatologists. It is unclear if these are true differences between the rates of connective tissue disease PAH at our institution compared with those observed by the French group, if there are differences in referral patterns between the US and Europe, or if this is a referral bias to a single tertiary center. 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 hemodynamics 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 our clinic is an important finding highlighting the possible under-appreciation 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 US 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 on PAH specific medications at the time of referral, emphasizing that PAH is still a disease managed mainly in tertiary centers and that patients are still referred to these centers late in the disease. As a cardiology practice,

our 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 do a randomized study to assess their effects. It is reported that the withdrawal of beta-blockers in portal hypertension patients is harmful. (26) However, as this registry is modeled after the NIH registry, collecting only baseline data, we do not have data on the effects of medication changes. The use of selective serotonin reuptake inhibitors for 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 previous, a definition defined from our practice's 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 our clinic on calcium channel blocker therapy without proper evaluation in all 3 treatment eras. After our comprehensive evaluation, calcium channel blockers were discontinued in all non-responders due to the possible harmful effects of calcium channel blockers 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 calcium channel blockers.

The 1-year 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 center's 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 our entire cohort, the 1-, 3-, and 5-year survival rates were 84%, 67%, and 58% respectively, and the median survival time was 3.6 years. 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 our 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 our registry. We acknowledge that standard of care practice of diagnostics such as exercise treadmill testing, adenosine to evaluate vasodilator reserve during cardiac catheterization, and measurement of LVEDP before and after vasodilator testing are used at our site, and are not universal procedures in the pulmonary hypertension community. We 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 six-minute walk distance. (31, 32)Our group has demonstrated adenosine's ability to predict response to calcium channel blockers and to predict outcome on epoprostenol. (1, 17, 32, 33) With its ease of administration, short half-life, and our experience, we continue to use adenosine as our agent of choice for vasodilator testing. Our group has found differences in the LVEDP and wedge pressure measurements in some patients, and we are currently investigating these differences prospectively. Anecdotally, the LVEDP has

been useful in the connective tissue disease patients who frequently have diastolic dysfunction. In these patients, we observe a rise in the LVEDP after vasodilator challenge secondary to the increased cardiac output, halting our 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 all obtained at the site to standardize 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 our clinic (from which data for our 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.

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

In conclusion, the PHC registry provides insights into the clinical characteristics of a large number of US-based patients with PAH referred to a single practice over time. Specifically, we have found the following: (1) The percentage of patients with connective tissue disease-associated PAH appears to be increasing; (2) The number of HIV patients referred for PAH remains low; (3) Many patients with PAH are still being referred on potentially harmful calcium channel blockers therapy without an adequate prior evaluation for true pulmonary vasoreactivity; and (4) Patients with PAH are still referred late in the disease process at a time when hemodynamic 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.

Acknowledgements: We would like to acknowledge Dr. Vallerie V. McLaughlin for her expert evaluation and care for many of the patients included in the Pulmonary Hypertension Connection. We would also like to acknowledge Jill Svenvold for her dedication to data entry and all of our nurses and support staff over the years for their hard work and support of the practice.

REFERENCES

1. Rich S, Dantzker R, Ayres S, Bergofsky E, Brundage B, Detre K, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med. 1987;107:216-223.

2. D'Alonzo G, Barst R, Ayres S, Stephen M.; Bergofsky EHB, Bruce H.; Detre, Katherine M.; Fishman, Alfred P.; Goldring, Roberta M.; Groves, Berton M.; Kernis, Janet T.; Levy, Paul S.; Pietra, Giuseppe G.; Reid, Lynne M.; Reeves, John T.; Rich, Stuart; Vreim, Carol E.; Williams, George W.; Wu, Margaret. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med. 1991;115:343-349.

3. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004 Sep 30;351(14):1425-1436.

4. Barst R, Rubin L, Long W, McGoon M, Rich S, Badesch D, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334:296-301.

5. Gomberg-Maitland M, Tapson VF, Benza RL, McLaughlin VV, Krichman A, Widlitz AC, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med. 2005 Dec 15;172(12):1586-1589.

6. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin L, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347(5):322-329.

7. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002 Mar 15;165(6):800-804.

8. Galie N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2005 Aug 2;46(3):529-535.

9. Rubin L, Badesch D, Barst R, Galie N, Black C, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Eng J Med. 2002;346(12):896-903.

10. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005 Nov 17;353(20):2148-2157.

11. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in france: results from a national registry. Am J Respir Crit Care Med. 2006 May 1;173(9):1023-1030.

12. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. Eur Respir J. 2007 Jul;30(1):1390-1395.

13. Humbert M. The burden of pulmonary hypertension. Eur Respir J. 2007 Jul;30(1):1287-1288.

14. Rubin LJ. Executive Summary. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004 Jul;126(1 Suppl):4S-6S.

15. Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. Am J Cardiol. 1972 Nov;30(7):757-762.

16. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-117.

17. Nootens M, Schrader B, Kaufman E, et.al. Comparative acute effects of adenosine and prostacyclin in primary pulmonary hypertension. Chest. 1995;107:54.

18. Barst RJ. Evaluation and treatment for angina in pulmonary arterial hypertension. Am J Med. 2004 Mar 15;116(6):427-428.

19. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med. 2004 Oct 14;351(16):1655-1665.

20. Nunes H, Humbert M, Sitbon O, Morse J, Deng Z, Knowles J, et al. Prognositc factors for survival in human immunodeficiency virus--associated pulmonary arterial hypertension. Am J Respir Crit Care Med. 2003;167:1433-1439.

21. Shapiro BP, McGoon MD, Redfield MM. Unexplained pulmonary hypertension in elderly patients. Chest. 2007 Jan;131(1):94-100.

22. Fisher MR, Mathai SC, Champion HC, Girgis RE, Housten-Harris T, Hummers L, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum. 2006 Sep;54(9):3043-3050.

23. Alkotob ML, Soltani P, Sheatt MA, Katsetos MC, Rothfield N, Hager WD, et al. Reduced exercise capacity and stress-induced pulmonary hypertension in patients with scleroderma. Chest. 2006 Jul;130(1):176-181.

24. Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. Chest. 2003 Feb;123(2):344-350.

25. Badesch D, Tapson V, McGoon M, Brundage B, Rubin L, Wigley F, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. Ann Intern Med. 2000;132:425-434.

26. Provencher S, Herve P, Jais X, Lebrec D, Humbert M, Simonneau G, et al. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. Gastroenterology. 2006 Jan;130(1):120-126.

27. Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, et al. Hyperplasia of pulmonary artery smooth muscle cells is causally related to overexpression of the serotonin transporter in primary pulmonary hypertension. CHEST. 2002;121:97S-8S.

28. MacLean M. Endothelin-1 and serotonin: Mediators of primary and secondary pulmonary hypertension. J Lab Clin Med. 1999;134:105-114.

29. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-3111.

30. Rich S, Kaufman E, Levy P. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med. 1992;327:76.

31. Gomberg-Maitland M, Huo D, Benza RL, McLaughlin VV, Tapson VF, Barst RJ. Creation of a model comparing 6-minute walk test to metabolic equivalent in evaluating treatment effects in pulmonary arterial hypertension. J Heart Lung Transplant. 2007 Jul;26(7):732-738.

32. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002 Sep 17;106(12):1477-1482.

33. Schrader BJ, Inbar S, Kaufmann L, Vestal RE, Rich S. Comparison of the effects of adenosine and nifedipine in pulmonary hypertension. J Am Coll Cardiol. 1992 Apr;19(5):1060.

FIGURE LEGENDS

Figure 1:

Title: Distribution of WHO Group I Pulmonary Arterial Hypertension Patients by Age and Gender

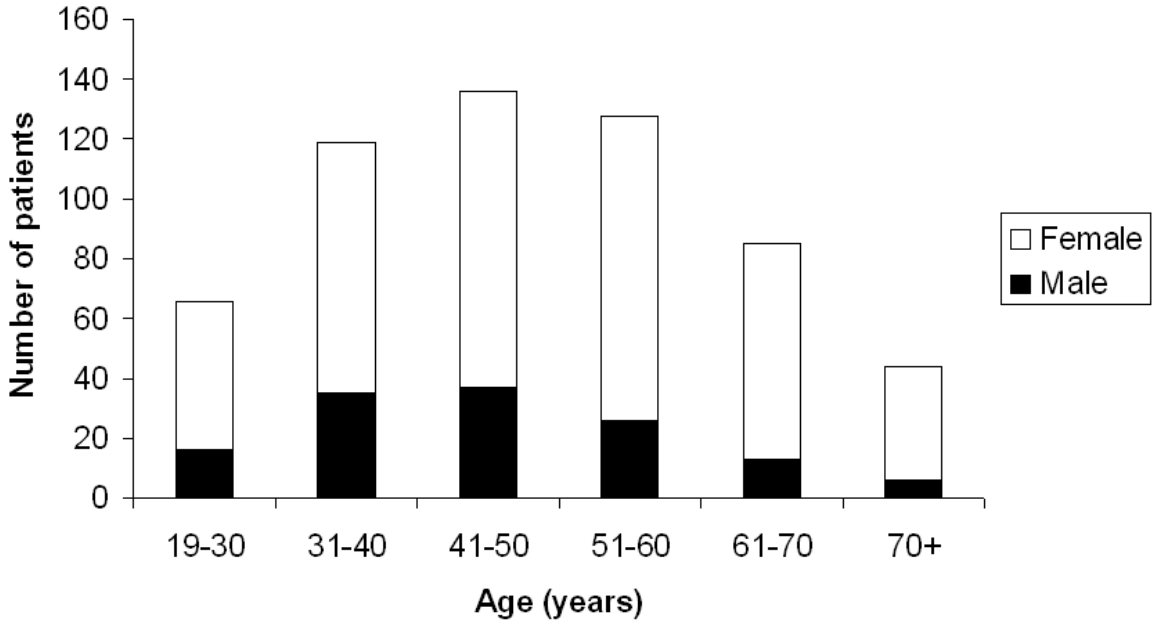
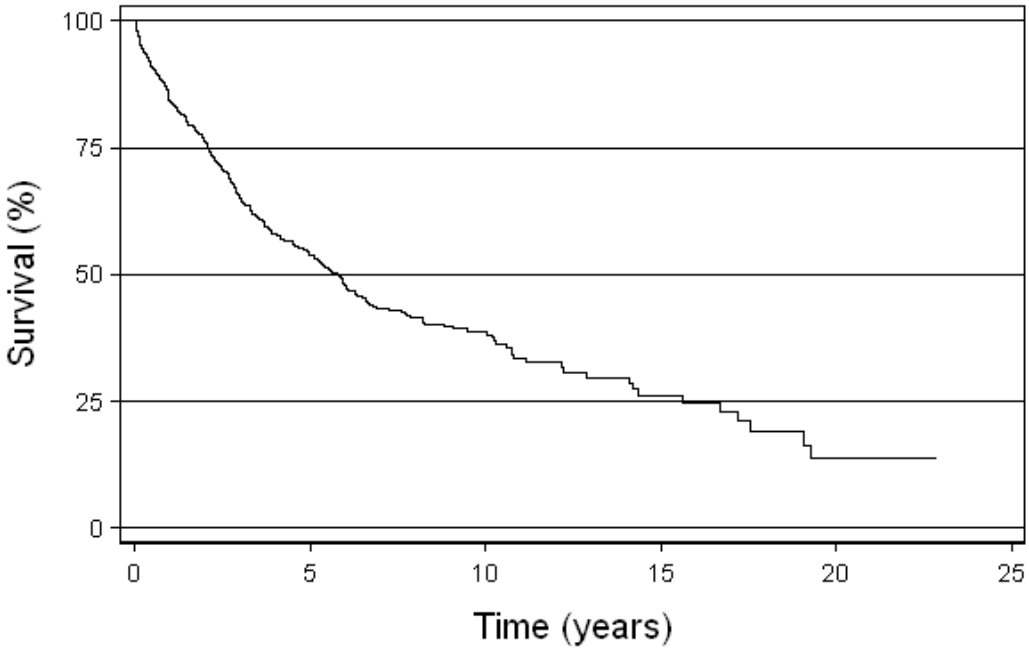


Figure 2:

Title: Kaplan-Meier Survival Curve for WHO Group I Pulmonary Arterial Hypertension Patients



No. at risk:	568	240	71	19	3

Table 1: Clinical and Hemodynamic Data at the Time of Diagnosis of Pulmonary Arterial Hypertension

Clinical Data	**All cases** (N=578)	**Incident cases** (N=82)	**Prevalent cases** (N=496)	**P-value***
Female, %	77	76	77	0.75
Age, yr (range)	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
Hemodynamic Data				
mRAP, mm Hg	11±7	10±7	11±7	0.037
mPAP, mm Hg	52±14	51±12	52±14	0.30
PCWP, mm Hg	10±4	10±4	10±4	0.89
Cardiac index, L/min/m2	2.3±0.9	2.4±0.8	2.2±0.9	0.07
PAO_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

Etiology, %				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	

WHO = World Health Organization functional class, METs = metabolic equivalents, mRAP = mean right atrial pressure, mPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PAO_2 = pulmonary arterial oxygen saturation, PVR = pulmonary vascular resistance

Data expressed as mean ± standard deviation unless otherwise indicated.

*Comparisons are for incident versus prevalent cases of pulmonary arterial hypertension.

Table II: 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)
Beta-blockers	50 (9)
Diuretics	272 (47)
Selective serotonin reuptake inhibitors	16 (6)

Table III: Baseline Clinical Characteristics of Patients by Etiology of Pulmonary Arterial Hypertension

Clinical Data	IPAH/FPAH	CTD	Congenital	Anorexigen	HIV	Portal Hypertension	P-value
Age, years	45 ± 14	55 ± 15	42 ± 12	52 ± 11	40 ± 4	49 ± 9	<0.0001
Female, %	75	87	68	100	13	70	<0.0001
Mean WHO functional class	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
WHO functional class I, %	7	3	10	0	0	7	
WHO functional class II, %	13	9	21	19	43	22	
WHO functional class III, %	49	49	45	56	43	49	
WHO functional 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

WHO = World Health Organization functional class, METs = metabolic equivalents, IPAH = idiopathic PAH, FPAH = familial PAH, CTD = connective tissue disease, congenital = congenital heart disease, HIV = human immunodeficiency virus

Table IV: Hemodynamics at the Time of Diagnosis for Patients in Each Subtype of Pulmonary Arterial Hypertension

	IPAH/FPAH	CTD	Congenital	Anorexigen	HIV	Portal Hypertension	P-value
mRAP, mm Hg	11±7	11±6	10±7	13±5	14±5	12±7	0.17
mPAP, mm Hg	56±13	48±11	54±22	52±12	50±5	46±14	<0.0001
PCWP, mm Hg	10±4	10±4	13±8	9±3	10±2	12±5	<0.0001
Cardiac index, L/min/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
PAO_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

mRAP = mean right atrial pressure, mPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PAO_2 = pulmonary artery oxygen saturation, PVR = pulmonary vascular resistance, IPAH = idiopathic pulmonary arterial hypertension, FPAH = familial pulmonary arterial hypertension, CTD = connective tissue disease, congenital = congenital heart disease, HIV = human immunodeficiency virus. Data expressed as mean ± standard deviation unless otherwise indicated.

Table V: Comparison of Clinical and Hemodynamic Data for Patients Diagnosed in Three Different Treatment Eras

	1982-1996 (N = 103)	1996-2002 (N = 328)	2002-2006 (N = 147)	P- Value
Clinical Data				
Age, yr	41 ± 12	49 ± 14	52 ± 14	<0.0001
Female, n (%)	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, n (%) †	3 (2.9)	11 (3.4)	0	0.44
Endothelin antagonists, n (%) †	0	1(0.3)	17 (11.6)	<0.001
Phosphodiesterase inhibitors, n (%) †	0	0	5 (3.4)	<0.001
Group I Subtypes, n (%)				
Idiopathic/familial pulmonary arterial hypertension	77 (75)	150 (46)	49 (33)	<0.0001
Connective tissue disease	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
Human immunodeficiency virus	0	6 (2)	2 (1)	0.164
Hemodynamic Data				
Right atrial pressure, mm Hg	12 ± 7	11 ± 6	10 ± 6	0.10

Mean pulmonary artery pressure, mm Hg	56 ± 14	51 ± 14	51 ± 12	0.005
Pulmonary capillary wedge pressure, mm Hg	10 ± 4	10 ± 4	10 ± 5	0.40
Cardiac index, L/min/m^2	2.1 ± 0.8	2.3 ± 0.9	2.3 ± 0.8	0.37
Pulmonary artery oxygen saturation, %	56	58	60	0.07
Pulmonary vascular resistance, 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

WHO = World Health Organization, METs = metabolic equivalents

Data expressed as mean ± standard deviation unless otherwise indicated

† Pulmonary arterial hypertension-specific medications taken by patients at the time of referral to our center