ORIGINAL RESEARCH

Mortality in Pulmonary Arterial Hypertension in the Modern Era: Early Insights From the Pulmonary Hypertension Association Registry

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BACKGROUND: Current mortality data for pulmonary arterial hypertension (PAH) in the United States are based on registries that enrolled patients prior to 2010. We sought to determine mortality in PAH in the modern era using the PHAR (Pulmonary Hypertension Association Registry).

METHODS AND RESULTS: We identified all adult patients with PAH enrolled in the PHAR between September 2015 and September 2020 (N=935). We used Kaplan-Meier survival analysis and Cox proportional hazards models to assess mortality at 1, 2, and 3 years. Patients were stratified based on disease severity by 3 validated risk scores. In treatment-naïve patients, we compared survival based on initial treatment strategy. The median age was 56 years (44–68 years), and 76% were women. Of the 935 patients, 483 (52%) were ≤6 months from PAH diagnosis. There were 121 deaths (12.9%) during a median follow-up time of 489 days (281–812 days). The 1-, 2-, and 3-year mortality was 8% (95% CI, 6%–10%), 16% (95% CI, 13%–19%), and 21% (95% CI, 17%–25%), respectively. When stratified into low-, intermediate-, and high-risk PAH, the mortality at 1, 2, and 3 years was 1%, 4% to 6%, and 7% to 11% for low risk; 7% to 8%, 11% to 16%, and 18% to 20% for intermediate risk; and 12% to 19%, 22% to 38%, and 28% to 55% for high risk, respectively. In treatment-naïve patients, initial combination therapy was associated with better 1-year survival (adjusted hazard ratio, 0.43 [95% CI, 0.19–0.95]; *P*=0.037).

CONCLUSIONS: Mortality in the intermediate- and high-risk patients with PAH remains unacceptably high in the PHAR, suggesting the importance for early diagnosis, aggressive use of available therapies, and the need for better therapeutics.

Key Words: pulmonary hypertension ■ right ventricle ■ survival ■ United States ■ vasodilators

Pulmonary arterial hypertension (PAH) is a progressive and devastating disease, characterized by obstructive remodeling of the distal pulmonary vasculature, leading to right ventricular failure and ultimately death.[1] Current mortality data for patients with PAH in the United States are based on registries that enrolled patients prior to 2010. The REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) enrolled patients with PAH from 55 centers in the United States between 2006 and 2009.[2–4] The 1-, 2-, and 3-year mortality rate for patients with PAH in the REVEAL was 10%, 19%, and 25%, respectively.[2,3] Similar results were reported by large single-center US registries.[5,6]

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CLINICAL PERSPECTIVE

What Is New?

- We report contemporary mortality rates for patients with pulmonary arterial hypertension in the United States. The 1-, 2-, and 3-year mortality rates are 8% (95% CI, 6%–10%), 16% (95% CI, 13%–19%), and 21% (95% CI, 17%–25%), respectively.
- When stratified into low-, intermediate-, and high-risk pulmonary arterial hypertension by validated risk scores, the mortality rates at 1 , 2, and 3 years are 1%, 4% to 6%, and 7% to 11% for low-risk; 7% to 8%, 11% to 16%, and 18% to 20% for intermediate-risk; and 12% to 19%, 22% to 38%, and 28% to 55% for high-risk patients, respectively.
- In treatment-naïve patients, initial combination therapy is associated with 57% improvement in 1-year survival when compared with initial monotherapy.

What Are the Clinical Implications?

- Mortality in intermediate- and high-risk pulmonary arterial hypertension patients in the United States remains unacceptably high, suggesting the importance for early diagnosis, aggressive use of available therapies, and the need for better therapeutics.

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Nonstandard Abbreviations and Acronyms

6MWD	6-minute walk distance
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
ERA	endothelin receptor antagonist
FC	functional class
FPHR	French Pulmonary Hypertension Registry
mRAP	mean right atrial pressure
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
PAWP	pulmonary arterial wedge pressure
PDE5i	phosphodiesterase type 5 inhibitor
PHAR	Pulmonary Hypertension Association Registry
REVEAL	The Registry to Evaluate Early and Long-Term PAH Disease Management
sGC	soluble guanylate cyclase
SPHAR	The Swedish Pulmonary Arterial Hypertension Registry
US-PHC	United States Pulmonary Hypertension Connections

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Since then, there have been many advancements and paradigm shifts in the management of patients with PAH. First, 4 new drugs, riociguat, selexipag, oral treprostinil, and macitentan, have been approved by the Food and Drug Administration in the past decade for the treatment of PAH.[7–10] Second, more importantly, after the landmark AMBITION (The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial in 2015, initial upfront dual combination therapy has become the standard of care for newly diagnosed patients with PAH who are at low or intermediate risk for mortality.[11] Finally, although anticoagulation with warfarin was previously recommended to treat all patients with PAH, currently it is recommended only in patients with idiopathic or heritable PAH.[12–14] Recent registry-based studies from Europe suggest an improvement in survival in patients with PAH in the current era.[15–17] Thus, there is a need to assess contemporary mortality rates for patients with PAH in the United States to make informed treatment decisions.

Accordingly, we aimed to determine mortality in PAH in the modern era in the United States using the PHAR (Pulmonary Hypertension Association Registry), an ongoing prospective, multicenter pulmonary hypertension registry that has been enrolling patients since 2015.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The PHAR has been previously described.[18,19] In brief, the PHAR is a prospective, multicenter registry of patients with either newly diagnosed or established PAH, pediatric pulmonary hypertension caused by developmental lung disease or chronic thromboembolic pulmonary hypertension, enrolled within 6 months of their first outpatient visit at one of the participating pulmonary hypertension care centers in the United States.[18] It was launched by the Pulmonary Hypertension Association in 2015 and currently consists of 54 participating pulmonary hypertension care centers across the United States.

For this study, we evaluated all adult patients (aged ≥18 years at the time of enrollment) with PAH who were enrolled between September 2015 and September 2020 and had at least 1 follow-up clinic visit after their baseline visit. We excluded patients with chronic thromboembolic pulmonary hypertension (Figure 1). The University of Pennsylvania Institutional Review Board approved the PHAR protocols and study-related activities (Federalwide Assurance number FWA00004028). Informed consent was obtained from each patient prior to enrollment.
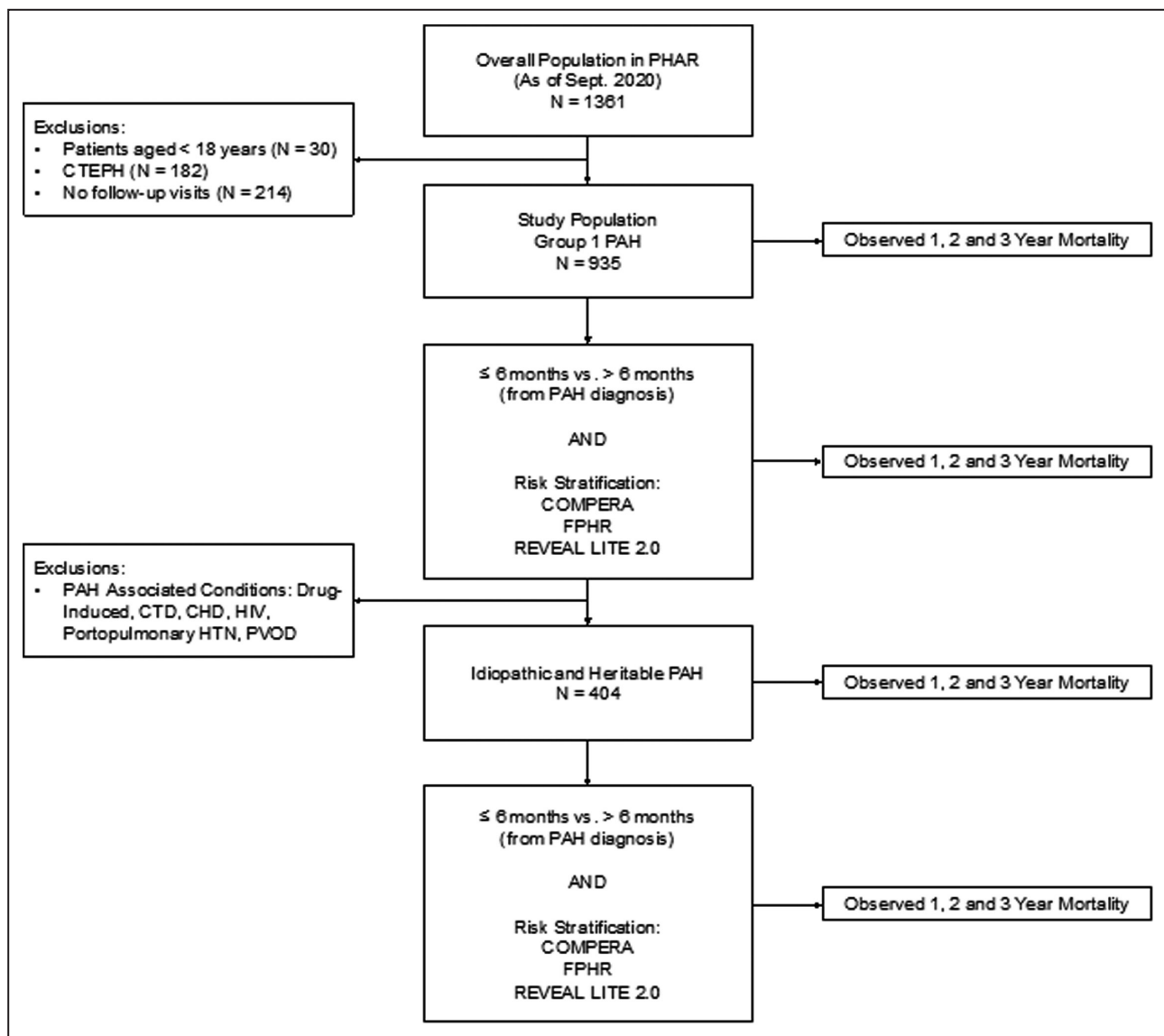
Figure 1. Study flow diagram.
CHD indicates congenital heart disease; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; FPHR, French Pulmonary Hypertension Registry; HTN, hypertension; PAH, pulmonary arterial hypertension; PHAR, Pulmonary Hypertension Association Registry; PVOD, pulmonary veno-occlusive disease; and REVEAL, The Registry to Evaluate Early and Long-Term PAH Disease Management.

Clinical Variables

The PHAR collects baseline demographics, clinical characteristics, and hemodynamics from the initial diagnostic right heart catheterization at the time of enrollment.[18] Subsequently, patients are followed up approximately every 3 to 6 months as clinically indicated. Clinical and medication data are collected at each follow-up visit. For this study, we analyzed the following baseline demographic and clinical characteristics: age, sex, race, body mass index, cause of PAH, New York Heart Association (NYHA) functional class (FC), 6-minute walk distance (6MWD), smoking status defined as smoked >100 cigarettes in his or her lifetime, blood chemistries, and hemodynamics from right heart catheterization. Blood chemistries consist of serum BNP (brain natriuretic peptide) levels, serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, and estimated glomerular filtration rate. Hemodynamic measurements from right heart catheterization include the following: mean right atrial pressure (mRAP), mean pulmonary artery pressure, pulmonary arterial wedge pressure, mixed venous oxygen saturation, cardiac index, cardiac output, and pulmonary vascular resistance (PVR). We also evaluated PAH therapies that were prescribed to a patient at enrollment, at last

follow-up visit, and at any time during the course of the disease. Monotherapy is defined as being on a medication from 1 of the following classes: (1) phosphodiesterase type 5 inhibitor (PDE5i), (2) endothelin receptor antagonist (ERA), (3) soluble guanylate cyclase (sGC) stimulators, and (4) prostacyclin pathway drugs (prostanoids or selexipag). Combination therapy is defined as being on 2 or more classes of these PAH therapies concurrently. Patients who were not on any medications from these classes of PAH therapies were defined as no therapy.

Vital Statistics

Date of death, cause of death, and lung transplantation were tracked and entered by the research coordinator at each participating site.

Stratification Based on the Time of PAH Diagnosis (≤6 Months Versus >6 Months)

In the PHAR, a study participant is defined as incident when he or she has been diagnosed with pulmonary hypertension for no more than 6 months and has not been treated with a medication for pulmonary hypertension for more than 6 months at the time of enrollment. If 1 of these 2 criteria is not met, an individual is regarded as a prevalent case. Because these definitions do not truly represent incident versus prevalent cases, we will refer to them as ≤6 months from time of diagnosis and >6 months from time of diagnosis, respectively, throughout the rest of this article.

Risk Stratification

To determine survival based on baseline risk status, patients were categorized as low risk, intermediate risk, and high risk of mortality at baseline (time of enrollment) using 3 validated risk scores: COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension),[15] FPHR (French Pulmonary Hypertension Registry),[17] and REVEAL Lite 2.0.[20]

The COMPERA risk score comprises 6 variables (NYHA FC, 6MWD, BNP or NT-proBNP, mRAP, cardiac index, and mixed venous oxygen saturation), with each variable scored as 1 (lowest risk), 2 (intermediate risk), or 3 (highest risk), according to criteria specified in Hoeper et al.[15] For each patient, the overall risk category was calculated as the mean of the available scores, rounded to the nearest integer.

The FPHR risk score was calculated from the sum of 4 low-risk criteria (NYHA FC, 6MWD, mRAP, and cardiac index).[17] Missing covariates were imputed as high risk, as previously described.[17] Patients were categorized as high risk if no low-risk criteria were met, intermediate risk if 1 or 2 low-risk criteria were met, and low risk if 3 or 4 low-risk criteria were met.

The most recent risk score, REVEAL LITE 2.0, comprises 6 variables (NYHA FC, 6MWD, BNP or NT-proBNP, systolic blood pressure, heart rate, and estimated glomerular filtration rate).[20] This score is a simplified version of the REVEAL 2.0 risk assessment calculator and allocates a score to each of the 6 variables as in the 13 variable REVEAL 2.0 score.[21] To calculate the REVEAL LITE 2.0 score, we included only patients who had a minimum of 3 variables available, with 2 of them including serum BNP/NT-pro-BNP levels, NYHA FC, or 6MWD, as previously described.[20] The total score was then categorized as low risk (0–5), intermediate risk (6–7), and high risk (≥8). We used REVEAL Lite 2.0, because the PHAR did not collect many of the variables needed to calculate full REVEAL 2.0.

Statistical Analysis

Continuous variables are reported as mean and SD or median and interquartile range (IQR), as appropriate. Categorical data are reported as frequency and percentage. Comparisons between means were performed using t tests, and tests of trend from linear regression models were used for the comparisons between levels of risk. For categorical variables, χ^2 tests were used to compare percentages and Fisher exact test when expected cell counts were <5. For nonnormally distributed variables, medians were compared using Kruskal-Wallis tests or nonparametric tests of trend. Kaplan-Meier methods were used to visualize unadjusted mortality over a 3-year period in the whole cohort and in the subcohort with idiopathic or heritable PAH. Log-rank tests were used to compare unadjusted survival. Plots were also stratified by patients who were ≤6 months from diagnosis or >6 months from diagnosis of PAH and risk status. Sensitivity analyses were performed in those patients with all variables available to calculate the 3 risk scores. To assess whether there was a difference in survival based on initial treatment strategy, we compared survival based on initial monotherapy versus combination therapy in treatment-naïve patients ≤6 months from PAH diagnosis. For comparing 1-, 2-, and 3-year survival between treatment groups, we truncated the follow-up time at 1, 2, and 3 years and calculated the P values from the log-rank test for each time-period (0–1, 0–2, 0–3 years, respectively). We used the date of enrollment in the PHAR as the date of entry into the study. The primary end point was all-cause mortality. Those who underwent lung transplantation were censored at the date of transplant, and those who had not died or were lost to follow-up were censored at their last recorded visit up to September 22, 2020. We also calculated transplant-free survival as a secondary end point. We further examined age- and sex-adjusted mortality using Cox proportional hazards regression models in the whole cohort and in the subcohort with

idiopathic or heritable PAH. We also used Cox proportional hazards model to adjust for differences in baseline characteristics (age, sex, and PVR) between initial monotherapy versus combination therapy patients. All tests were 2-sided, and statistical significance was taken to be *P*<0.05. Statistical analyses were performed using Stata Version 16.1 (StataCorp, College Station, TX).

RESULTS
All PAH
Baseline Characteristics

A total of 935 patients with PAH met study inclusion criteria (Figure 1). Table 1 describes the baseline demographics, clinical characteristics, and hemodynamics

Table 1. Baseline Characteristics of All Patients With Pulmonary Arterial Hypertension ≤6 Months Versus >6 Months From Diagnosis

Characteristic	All	≤6 mo	>6 mo	*P* value
N	935	483 (52%)	452 (48%)	
Women	710 (76%)	369 (76%)	341 (76%)	0.82
Age, y	56 (44–68)	57 (44–68)	55 (44–68)	0.89
Race				0.091
White	680 (77%)	363 (80%)	317 (74%)	
Black	124 (14%)	57 (13%)	67 (16%)	
Other[*]	77 (9.0%)	33 (7.0%)	44 (10%)	
Ethnicity				0.95
Hispanic	102 (12%)	53 (11%)	49 (12%)	
Non-Hispanic	786 (89%)	411 (89%)	375 (88%)	
BMI, kg/m^2	29.5±7.3	29.9±7.5	29.0±7.1	0.092
Smoking	430 (46%)	221 (46%)	209 (46%)	0.88
Cause				0.54
Idiopathic	379 (41%)	193 (40%)	186 (41%)	
Heritable	25 (2.7%)	15 (3.1%)	10 (2.2%)	
Drug induced	105 (11%)	51 (11%)	54 (12%)	
Connective tissue disease	299 (32%)	160 (33%)	139 (31%)	
HIV related	15 (1.6%)	5 (1.0%)	10 (2.2%)	
Portopulmonary hypertension	63 (6.7%)	35 (7.3%)	28 (6.2%)	
Congenital heart disease	44 (4.7%)	20 (4.1%)	24 (5.3%)	
PVOD/PCH	5 (0.53%)	4 (0.83%)	1 (0.22%)	
NYHA				0.26
I	68 (7.7%)	35 (7.6%)	33 (7.8%)	
II	312 (35%)	149 (32%)	163 (39%)	
III	440 (50%)	242 (53%)	198 (47%)	
IV	62 (7.0%)	34 (7.4%)	28 (6.6%)	
Six-minute walk distance, m	335±127	332±123	338±131	0.50
Right heart catheterization				
Right atrial pressure, mm Hg	10.0±6.0	10.0±5.9	9.9±6.1	0.72
Mean PA pressure, mm Hg	49.5±13.9	49.4±13.6	49.5±14.2	0.97
PA wedge pressure, mm Hg	11.2±5.7	11.3±5.9	11.0±5.4	0.49
Mixed venous oxygen saturation, %	62.0±9.7	61.4±10.2	62.8±9.1	0.12
Cardiac index, L/min per m^2	2.28±0.76	2.25±0.78	2.31±0.73	0.24
Cardiac output	4.28±1.47	4.23±1.54	4.33±1.40	0.30
Pulmonary vascular resistance, Wood units	9.1 (6.1–12.9)	9.3 (6.2–13.2)	9.0 (6.1–12.5)	0.36
Positive vasoreactivity test, n=377	56 (15%)	25 (13%)	31 (17%)	0.20
BNP, pg/mL, n=514	122 (46–366)	124 (48–323)	118 (41–419)	0.77
NT-proBNP, pg/mL, n=426	603 (223–1969)	585 (196–1685)	652 (22–2401)	0.32
Estimated GFR	77.4±27.4	79.2±26.8	75.5±27.9	0.040

Values are n (%), mean±SD, or median (25th–75th percentile). BMI indicates body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PCH, pulmonary capillary hemangiomatosis; and PVOD, pulmonary veno-occlusive disease.

*Other includes the following: Chinese, Filipino, Japanese, Korea, Vietnamese, Other Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian Indian, Mixed Race or Unknown/not reported.

of the study cohort at the time of enrollment. The median age upon enrollment into the registry was 56 years (IQR, 44–68 years), and 76% of patients were women. The breakdown by cause of PAH was as follows: idiopathic (41%), heritable (3%), connective tissue disease (32%), drug induced (11%), portopulmonary hypertension (7%), congenital heart disease (5%), HIV (2%), and pulmonary veno-occlusive disease (1%) (Figure S1). The majority of subjects were categorized as NYHA FC II (35%) or FC III (50%). The mean 6MWD was 335±127 m. The study cohort had a mRAP of 10±6 mm Hg, mean pulmonary artery pressure of 50±14 mm Hg, PVR of 9.1 Wood units (6.1–12.9 Wood units), and cardiac index of 2.3±0.8 L/min per m^2. A vasoreactivity test was performed on 377 individuals, and 56 (15%) were positive.

Of the 935 patients, there were 452 who were enrolled >6 months after PAH diagnosis, whereas 483 were enrolled ≤6 months. No significant differences were observed between the 2 groups at the time of enrollment except for lower renal function in patients >6 months after PAH diagnosis (estimated glomerular filtration rate, 75.5±27.9 versus 79.2±26.8; P=0.04).

When stratified into risk groups, 18%, 14%, and 38% of patients were categorized as low-risk; 73%, 57%, and 29% as intermediate-risk; and 9%, 29%, and 34% as high-risk group by COMPERA, FPHR, and REVEAL LITE 2.0, respectively. Tables S1 through S3 compare the demographic, clinical, and hemodynamic characteristics of patients at the time of enrollment by risk categorization. High-risk patients were older (P<0.05 for 3/3 risk scores), had higher body mass index (P<0.05 for 2/3 risk scores), and were more often smokers (P<0.05 for 3/3 risk scores) than intermediate-risk and low-risk groups. Patients with portopulmonary hypertension (P<0.05 for 3/3 risk scores) and congenital heart disease (P<0.05 for 2/3 risk scores) were more likely to portend lower risk stratification at baseline. When compared with low-risk and intermediate-risk groups, as expected, patients at high risk tended to have higher mRAP, higher mean pulmonary artery pressure, higher pulmonary arterial wedge pressure, lower mixed venous oxygen saturation, lower cardiac output, higher PVR, and lower percentage of positive vasoreactivity test. Patients in the high-risk group also had worse renal function (Tables S1 through S3).

Treatment

Table 2 describes the medications at the time of enrollment, last follow-up visit, and at any time during the course of the disease. At the time of enrollment, 30% of patients with PAH were on monotherapy, 56% were on combination therapy (43% dual and 13% triple), and 14% were not on any therapy. Compared with patients diagnosed with PAH ≤6 months from enrollment, those

who were diagnosed >6 months were more often treated with PAH therapies (oral and inhaled), combination PAH therapy, digoxin, and supplemental oxygen (Table S2). However, at their last follow-up visit, there was no difference except for increased use of selexipag and sGC in those who were >6 months from diagnosis versus ≤6 months from diagnosis (Table 2). High-risk patients were more often treated with parenteral prostacyclin (P<0.05 for 3/3 risk scores), supplemental oxygen (P<0.05 for 3/3 risk scores), and warfarin (P<0.05 for 2/3 risk scores) during the course of their disease (Tables S1 through S3).

Mortality

The median duration of follow-up was 489 days (IQR, 281–812). Of the 935 study patients, 121 (12.9%) died during follow-up. Twelve patients (1.3%) underwent lung transplantation, and 154 patients (16.5%) were either lost to follow-up, refused to continue in the registry, or transferred care to a different clinic. The observed 1-, 2-, and 3-year mortality for the total PAH cohort was 8% (95% CI, 6%–10%), 16% (95% CI, 13%–19%), and 21% (95% CI, 17%–25%), respectively (Figure 2A). Eighty-seven patients of the 121 deceased (72%) had a known cause of death, with 68 out of the 87 (78%) having died from cardiopulmonary- and pulmonary hypertension–related complications. Furthermore, of the 121 patients who died in this study cohort, 73 patients (60%) were never treated with parenteral prostacyclin (Figure S2A).

There was no difference in 1-, 2-, and 3-year mortality between those who were enrolled ≤6 months after PAH diagnosis compared with those who were enrolled >6 months from diagnosis. In patients who were >6 months from diagnosis, the 1-, 2-, and 3-year mortality rates were 6% (95% CI, 4%–9%), 15% (95% CI, 11%–20%), and 23% (95% CI, 17%–30%), as compared with 9% (95% CI, 7%–13%), 16% (95% CI, 13%–21%), and 19% (95% CI, 15%–25%) in those who were ≤6 months from diagnosis (P=0.59) (Figure S3).

When stratified into low, intermediate, and high risk by validated risk scores, the range of mortality rates at 1, 2, and 3 years were 1%, 4% to 6%, and 7% to 11% for low risk; 7% to 8%, 11% to 16%, and 18% to 20% for intermediate risk; and 12% to 19%, 22% to 38%, and 28% to 55% for high risk, respectively (Figure 3). Although the mortality rates for low- and intermediate-risk PAH were similar regardless of the risk tools used, differences among the mortality rates for high-risk subjects with PAH were much more substantial (12% versus 19% at 1 year and 28% versus 55% at 3 years between FPHR versus COMPERA, respectively) (Figure 3). We obtained similar results on sensitivity analysis restricted to patients with all variables available for risk score assessment (Data S1).

Table 2. Medications at the Time of Enrollment, Last Follow-Up Visit, and During the Course of Disease Stratified by Time From Diagnosis in All Patients With PAH

Medications	All PAH			
	All	≤6 mo	>6 mo	P value
Enrollment				
PDE5I	649 (69%)	320 (66%)	329 (73%)	0.030
ERA	469 (50%)	205 (42%)	264 (58%)	<0.001
sGCS	29 (3.1%)	10 (2.1%)	19 (4.2%)	0.060
Parenteral prostacyclin	201 (22%)	112 (23%)	89 (20%)	0.19
Oral treprostinil	17 (1.8%)	3 (0.6%)	14 (3.1%)	0.006
Selexipag	44 (4.7%)	9 (1.9%)	35 (7.7%)	<0.001
Inhaled treprostinil	41 (4.4%)	12 (2.5%)	29 (6.4%)	0.003
CCB	66 (7.1%)	27 (5.6%)	39 (8.6%)	0.070
Digoxin	61 (6.5%)	22 (4.6%)	39 (8.6%)	0.012
Warfarin	171 (18%)	74 (15%)	97 (21%)	0.015
Supplemental oxygen	359 (38%)	167 (35%)	192 (42%)	0.013
Monotherapy	283 (30%)	155 (32%)	128 (28%)	0.210
Combination therapy	522 (56%)	242 (50%)	280 (62%)	<0.001
Dual	401 (43%)	210 (43%)	191 (42%)	
Triple	121 (13%)	32 (6.6%)	89 (20%)	
No therapy	130 (14%)	86 (18%)	44 (9.7%)	<0.001
Last follow-up visit				
PDE5I	715 (76%)	366 (76%)	349 (77%)	0.61
ERA	597 (64%)	295 (61%)	302 (67%)	0.068
sGCS	55 (5.9%)	21 (4.4%)	34 (7.5%)	0.039
Parenteral prostacyclin	215 (23%)	113 (23%)	102 (23%)	0.76
Oral treprostinil	21 (2.3%)	9 (1.9%)	12 (2.7%)	0.41
Selexipag	102 (11%)	37 (7.7%)	65 (14%)	0.001
Inhaled treprostinil	63 (6.7%)	32 (6.6%)	31 (6.9%)	0.89
CCB	53 (5.7%)	23 (4.8%)	30 (6.6%)	0.22
Digoxin	63 (6.7%)	25 (5.2%)	38 (8.4%)	0.049
Warfarin	198 (21%)	91 (19%)	107 (24%)	0.071
Supplemental oxygen	435 (47%)	207 (43%)	228 (50%)	0.020
Monotherapy	187 (20%)	99 (21%)	88 (19%)	0.700
Combination therapy	676 (72%)	339 (70%)	337 (75%)	0.140
Dual	453 (48%)	246 (51%)	207 (46%)	
Triple	221 (24%)	93 (19%)	128 (28%)	
No therapy	72 (7.7%)	45 (9.3%)	27 (6.0%)	0.055
During disease course				
PDE5I	822 (88%)	414 (86%)	408 (90%)	0.033
ERA	710 (76%)	353 (73%)	357 (79%)	0.035
sGCS	76 (8.1%)	28 (5.8%)	48 (11%)	0.007

(Continued)

Table 2. Continued

Medications	All PAH			
	All	≤6 mo	>6 mo	P value
Parenteral prostacyclin	278 (30%)	147 (30%)	131 (29%)	0.63
Oral treprostinil	47 (5.0%)	16 (3.3%)	31 (6.9%)	0.013
Selexipag	147 (16%)	52 (11%)	95 (21%)	<0.001
Inhaled treprostinil	114 (12%)	45 (9.3%)	69 (15%)	0.005
CCB	107 (11%)	46 (9.5%)	61 (14%)	0.057
Digoxin	95 (10%)	36 (7.5%)	59 (13%)	0.005
Warfarin	283 (30%)	135 (28%)	148 (33%)	0.11
Supplemental oxygen	522 (56%)	247 (51%)	275 (61%)	0.003

CCB indicates calcium channel blockers; ERA, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE5I, phosphodiesterase-5-inhibitors; and sGCS, soluble guanylate cyclase stimulator.

Age- and sex-adjusted hazard ratios for mortality in patients with PAH are reported in Table 3. Transplant-free survival is reported in Figure S4 and Table S4.

Mortality Based on Initial Treatment Strategy in Patients Diagnosed With PAH ≤6 Months

Of the 483 patients who were treatment naïve and diagnosed with PAH ≤6 months, 156 patients (32%) were started on monotherapy, 241 patients (50%) were started on combination therapy, and 86 patients (18%) were not started on any therapy at the time of enrollment. In the monotherapy group, 62% received PDE5i, 21% received ERA, 15% received prostacyclin pathway drugs, and 2% received sGC stimulators. In the combination therapy group, 87% received dual therapy (53% PDE5i+ERA, 27% PDE5i+prostacyclin pathway drug, 5% ERA+prostacyclin pathway drug, 1% sGC+prostacyclin pathway drug, and 1% ERA+sGC), and 13% received triple combination therapy (12% PDE5i+ERA+prostacyclin pathway drug and 1% ERA+sGC+prostacyclin pathway drug).

Compared with the monotherapy group, patients started on combination therapy were more likely to be younger, had idiopathic PAH, had better exercise capacity, higher PVR, and lower cardiac output (Table 4). On unadjusted analysis, compared with initial monotherapy, patients treated with initial combination therapy had lower 1-year mortality (7% [95% CI, 5%–12%] versus 13% [95% CI, 8%–20%], P=0.046), but there was no difference in 2-year (17% [95% CI, 11%–24%] versus 20% [95% CI, 14%–29%], P=0.13) and 3-year (19% [95% CI, 13%–27%] versus 23% [95% CI, 15%–33%], P=0.17) mortality (Figure 4). When adjusted for age, sex, and PVR, the difference in 1-year mortality between initial monotherapy and combination therapy
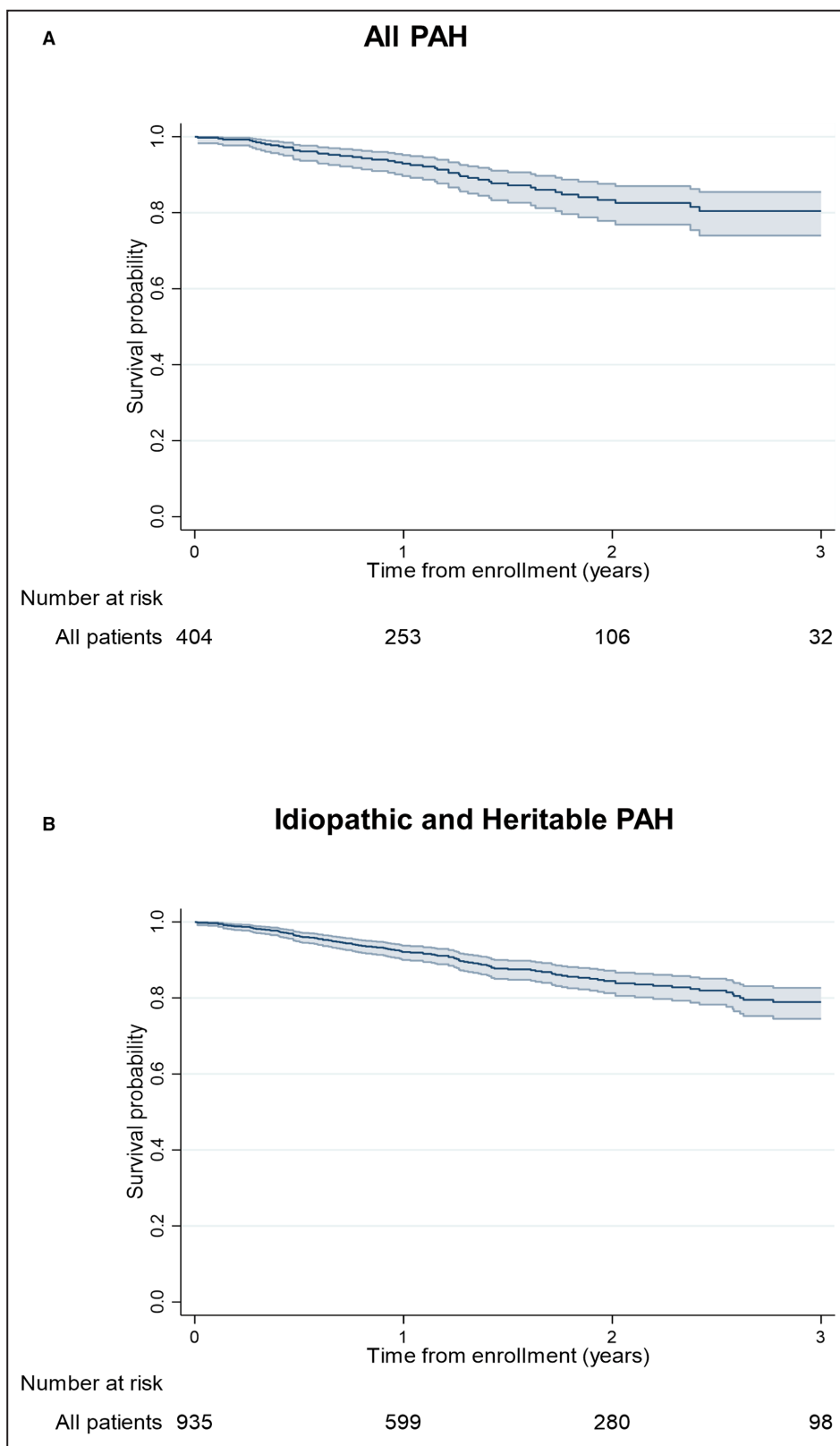
Figure 2.   Kaplan-Meier survival estimates in all PAH and idiopathic and heritable patients with PAH.
A, Mortality in all patients with PAH. **B**, Mortality in idiopathic and heritable patients with PAH. PAH indicates pulmonary arterial hypertension.
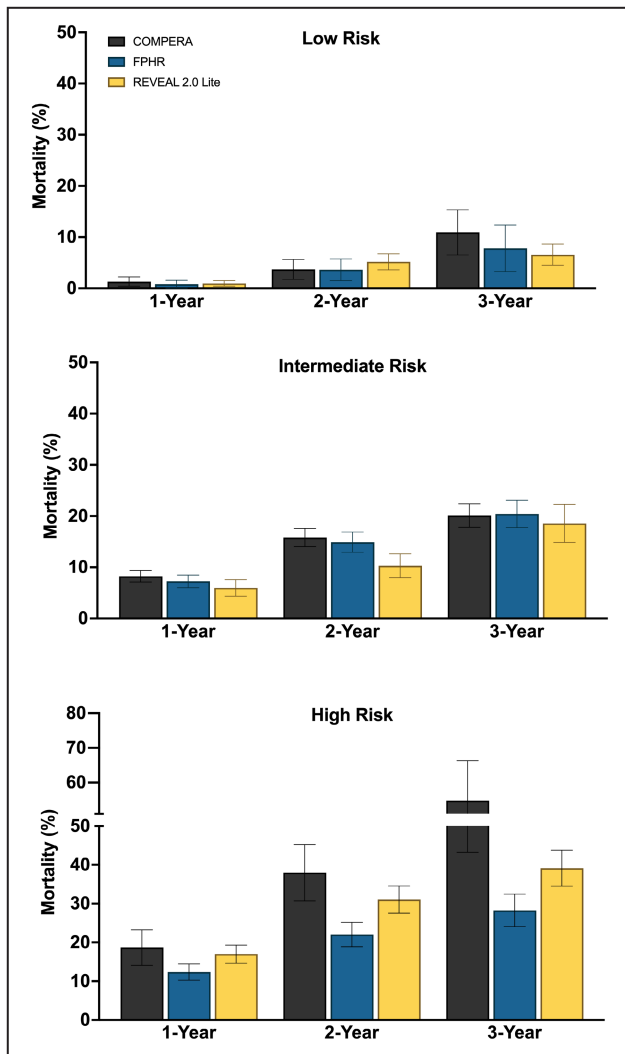
Figure 3. Mortality in all patients with PAH by risk categorization at baseline using Kaplan-Meier survival analysis.
Data are presented as mean±SE measurement. COMPERA indicates Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR, French Pulmonary Hypertension Registry; PAH, pulmonary arterial hypertension; and REVEAL, The Registry to Evaluate Early and Long-Term PAH Disease Management.

remained significant (adjusted hazard ratio, 0.43 [95% CI, 0.19–0.95]; *P*=0.037).

Idiopathic and Heritable PAH
Baseline Characteristics

For the subgroup analyses of idiopathic and heritable PAH, 404 patients were included (Figure 1). Table 5 describes the baseline demographics, clinical characteristics, and hemodynamics of patients with idiopathic or heritable PAH at the time of enrollment. The median age was 55 years (IQR, 41–68 years),

and 76% were women. Similar to the primary cohort of all PAH, the majority of patients with idiopathic and heritable PAH were White, with predominantly NYHA FC II (35%) or FC III (49%). The mean 6MWD was 344±139 m. Patients had mRAP of 10±6 mm Hg, mean pulmonary artery pressure of 52±14 mm Hg, PVR of 9.7 Wood units (6.7–13.7 Wood units), and cardiac index of 2.2±0.7 L/min per m². A vasoreactivity test was performed on 180 patients, and 30 (17%) were positive.

Compared with patients with idiopathic and heritable PAH who were ≤6 months from diagnosis, those who were >6 months from diagnosis had higher mixed venous oxygen saturation (*P*=0.0032) at the time of enrollment in the registry (Table 5).

When stratified into risk groups using the COMPERA, FPHR, and REVEAL LITE 2.0 risk tools (Tables S5 through S7), the baseline characteristics of idiopathic and heritable PAH demonstrated similar trends to those observed in the primary cohort of all patients with PAH. Notably, high-risk patients were more likely to be older (*P*<0.05 for 2/3 risk scores) and have higher body mass index (*P*<0.05 for 2/3 risk scores). Differences in hemodynamic data and biochemical studies among risk groups at the time of enrollment are also shown in Tables S5 through S7.

Mortality

During a median follow-up of 470 days (IQR, 272–752 days), a total of 47 patients (11.6%) died. Six patients (1.5%) had lung transplantation and 52 patients (12.9%) were either lost to follow-up, refused to continue in the registry, or transferred to a different clinic. The observed 1-, 2-, and 3-year mortality rates in patients with idiopathic and heritable PAH was 7% (95% CI, 5%–10%), 17% (95% CI, 12%–22%), and 20% (95% CI, 15%–26%), respectively (Figure 2B).

No difference in mortality was observed between patients with idiopathic and heritable PAH who were >6 months from diagnosis and those who were ≤6 months from diagnosis. In patients with idiopathic and heritable PAH, who were >6 months from diagnosis, the 1-, 2-, and 3-year mortality rates were 3% (95% CI, 2%–8%), 16% (95% CI, 10%–25%), and 22% (95% CI, 14%–33%) as compared with 11% (95% CI, 7%–16%), 18% (95% CI, 12%–25%), and 18% (95% CI, 12%–25%) in the patients who were ≤6 months from diagnosis, respectively (*P*=0.46) (Figure S3).

When stratified into low, intermediate, and high risk by validated risk scores, the range of mortality rates at 1, 2, and 3 years were 0%, 5% to 6%, and 6% to 16% for low-risk; 5% to 7%, 12% to 16%, and 17% to 19% for intermediate risk; and 13% to 23%, 28% to 56%, and 28% to 56% for high risk, respectively (Figure 5). Similar to the primary cohort of all patients with PAH,

Table 3.   Age- and Sex-Adjusted Hazard Ratios for Mortality in PAH

	Unadjusted	Age adjusted	Age and sex adjusted
All PAH			
≤6 mo vs >6 mo	1.10 (0.77–1.58)	1.06 (0.74–1.52)	1.05 (0.74–1.51)
COMPERA			
Low risk	Reference	Reference	Reference
Intermediate risk	3.36 (1.56–7.27)	2.77 (1.28–5.98)	2.80 (1.29–6.06)
High risk	9.79 (4.25–22.59)	7.59 (3.29–17.54)	7.93 (3.43–18.36)
FPHR			
Low risk	Reference	Reference	Reference
Intermediate risk	3.84 (1.40–10.55)	3.18 (1.16–8.75)	3.12 (1.13–8.57)
High risk	6.37 (2.31–17.60)	5.18 (1.87–14.32)	5.35 (1.94–14.80)
REVEAL LITE 2.0			
Low risk	Reference	Reference	Reference
Intermediate risk	3.03 (1.54–5.96)	2.25 (1.13–4.46)	2.40 (1.21–4.76)
High risk	8.62 (4.69–15.86)	5.62 (3.00–10.54)	6.23 (3.31–11.73)
Idiopathic/heritable			
≤6 mo vs >6 mo	1.24 (0.70–2.21)	1.22 (0.68–2.16)	1.16 (0.65–2.07)
COMPERA			
Low risk	Reference	Reference	Reference
Intermediate risk	2.15 (0.76–6.08)	1.54 (0.54–4.38)	1.60 (0.56–4.57)
High risk	9.33 (2.94–29.58)	6.64 (2.09–21.14)	7.05 (2.22–22.40)
FPHR			
Low risk	Reference	Reference	Reference
Intermediate risk	3.06 (0.72–13.00)	2.31 (0.54–9.83)	1.95 (0.46–8.33)
High risk	6.27 (1.47–26.67)	4.58 (1.07–19.51)	4.76 (1.12–20.30)
REVEAL LITE 2.0			
Low risk	Reference	Reference	Reference
Intermediate risk	2.77 (1.04–7.37)	1.95 (0.73–5.21)	2.14 (0.80–5.72)
High risk	6.63 (2.72–16.19)	3.34 (1.32–8.46)	4.17 (1.64–10.57)

COMPERA indicates Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR, French Pulmonary Hypertension Registry; PAH, pulmonary arterial hypertension; and REVEAL, The Registry to Evaluate Early and Long-Term PAH Disease Management.

the mortality rates for low- and intermediate-risk patients with idiopathic and heritable PAH were generally more congruent among the 3 risk tools than the high-risk group (13% versus 23% at 1 year and 28% versus 56% at 3 years between FPHR and COMPERA, respectively) (Figure 5).

Age- and sex-adjusted hazard ratios for mortality in patients with idiopathic and heritable PAH are reported in Table 3. Transplant-free survival is reported in Figure S4 and Table S4.

DISCUSSION

Since the conclusion of enrollment by the REVEAL registry in 2009,[4] the PHAR is the first prospective, multicenter, US-based registry to enroll patients with PAH, with a goal to improve the overall quality of care and outcomes in patients with this incurable disease.[18] In an early analysis of this large observational registry,

we found that the mortality at 1, 2, and 3 years among intermediate- and high-risk patients with PAH in general, as well as those specifically with idiopathic or heritable PAH, remains unacceptably high.

Similar to other registries, our cohort has a median age of 56 years (IQR, 44–68 years), are predominantly women (76%), White (77%), and idiopathic (41%) in cause. When compared with the observed mortality rates from other registries, such as the US-PHC (US Pulmonary Hypertension Connections),[5] the Scottish registry,[22] FPHR,[17,23] the REVEAL,[2,3] the SPAHR (Swedish Pulmonary Arterial Hypertension Registry)[16] and the COMPERA,[15] patients with PAH in the PHAR demonstrated overall lower mortality at 1, 2, and 3 years.[3,5,15,16,23,24] Lower mortality was also observed in the PHAR in patients with idiopathic and heritable PAH when compared with those in the National Institutes of Health registry,[25] the US-PHC,[5] the REVEAL,[2] the FPHR,[17] and the COMPERA.[15]

Table 4. Baseline Characteristics by Initial Treatment Strategy in Patients Diagnosed With Pulmonary Arterial Hypertension ≤6 Months

Characteristic	All	Mono	Combination
N	397	156 (39%)	241 (61%)
Women	304 (77%)	124 (79%)	180 (75%)
Age, y	57 (44–69)	60 (50–71)	55 (40–67)
Race, n=371			
White	301 (81%)	119 (81%)	182 (81%)
Black	45 (12%)	19 (13%)	26 (12%)
Other*	25 (6.7%)	9 (6.1%)	16 (7.1%)
Ethnicity, n=383			
Hispanic	41 (11%)	15 (9.9%)	26 (11%)
Non-Hispanic	342 (89%)	136 (90%)	206 (89%)
BMI, kg/m²	30.1±7.6	29.9±7.4	30.2±7.7
Smoking	185 (47%)	73 (47%)	112 (46%)
Cause			
Idiopathic	155 (39%)	55 (35%)	100 (41%)
Heritable	14 (3.5%)	2 (1.3%)	12 (5.0%)
Drug induced	38 (9.6%)	18 (12%)	20 (8.3%)
Connective tissue disease	137 (35%)	57 (37%)	80 (33%)
HIV related	4 (1.0%)	1 (0.64%)	3 (1.2%)
Portopulmonary hypertension	28 (7.1%)	14 (9.0%)	14 (5.8%)
Congenital heart disease	18 (4.5%)	7 (4.5%)	11 (4.6%)
PVOD/PCH	3 (0.76%)	2 (1.3%)	1 (0.41%)
NYHA, n=380			
I	27 (7.1%)	9 (6.0%)	18 (7.8%)
II	133 (35%)	52 (35%)	81 (35%)
III	194 (51%)	74 (49%)	120 (52%)
IV	26 (6.8%)	15 (10%)	11 (4.8%)
Six-minute walk distance, m, n=344	329±122	307±121	343±122
Right heart catheterization			
Right atrial pressure, mm Hg	10.1±5.9	9.1±5.5	10.8±6.1
Mean PA pressure, mm Hg	49.9±13.3	45.4±13.5	52.8±12.4
PA wedge pressure, mm Hg	11.4±5.8	11.3±5.9	11.5±5.8
Mixed venous oxygen saturation, %	60.7±10.3	63.3±9.5	59.1±10.5
Cardiac index, L/min per m²	2.20±0.68	2.41±0.71	2.06±0.62
Cardiac output	4.12±1.38	4.46±1.52	3.91±1.25
Pulmonary vascular resistance, Wood units	9.6 (6.2–13.4)	7.8 (4.5–11.6)	10.4 (7.9–15.2)
Positive vasoreactivity test, n=156	20 (13%)	13 (21%)	7 (7.4%)

(*Continued*)

Table 4. Continued

Characteristic	All	Mono	Combination
BNP, pg/mL, n=222	112 (47–297)	142 (62–307)	87 (42–297)
NT-proBNP, pg/mL, n=189	584 (202–1538)	744 (233–1998)	454 (191–1282)
Estimated GFR	78.5±27.0	76.1±28.2	80.1±26.1

Values are n (%), mean±SD, or median (25th–75th percentile). BMI indicates body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PCH, pulmonary capillary hemangiomatosis; and PVOD, pulmonary veno-occlusive disease.

*Other includes the following: Chinese, Filipino, Japanese, Korea, Vietnamese, Other Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian Indian, Mixed Race or Unknown/not reported.

We believe that multiple factors may have possibly contributed to these observations, because there are several ways the PHAR cohort is different from those of other registries, which could have impacted survival estimates. First, the mean age of patients in PHAR was relatively lower when compared with the COMPERA and the Swedish registry. Older age has been associated with poor survival in PAH. Secondly, PHAR included a hybrid of both incident (enrolled ≤6 months from diagnosis, 52%) and prevalent (enrolled >6 months from diagnosis, 48%) patients. In contrast, the SPAHR and the COMPERA consisted of only incident patients,[15,16] the US-PHC, REVEAL, and the FPHR had predominantly prevalent patients.[5,23,26] The fraction of incident to prevalent patients has been well known to impact survival estimates, as prevalent patients have a better survival than incident patients because of survivor bias.[27] However, interestingly, we did not observe a mortality difference in the PHAR cohort between those who were enrolled ≤6 months
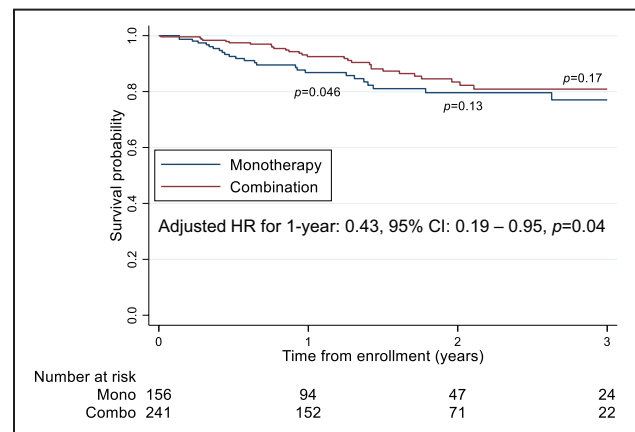

Figure 4. Kaplan-Meier survival estimates based on initial treatment strategy in patients diagnosed with PAH ≤6 months.
Combo indicates initial combination therapy (dual and triple); HR, hazard ratio; Mono, initial monotherapy; and PAH, pulmonary arterial hypertension.

Table 5. Baseline Characteristics of Idiopathic and Heritable Pulmonary Arterial Hypertension ≤6 Months Versus >6 Months From Diagnosis

Characteristic	Idiopathic/heritable	≤6 mo	>6 mo	P value
N	404	208 (51%)	196 (49%)	
Women	307 (76%)	156 (75%)	151 (77%)	0.57
Age, y	55 (41–68)	56 (41–69)	54 (41–68)	0.53
Race				0.039
White	310 (82%)	167 (87%)	143 (76%)	
Black	47 (12%)	18 (9.3%)	29 (16%)	
Other*	23 (6.1%)	8 (4.2%)	15 (8.0%)	
Ethnicity				0.70
Hispanic	42 (11%)	23 (12%)	19 (10%)	
Non-Hispanic	341 (89%)	176 (88%)	165 (90%)	
BMI, kg/m^2	30.8±7.6	31.3±7.5	30.3±7.6	0.17
Smoking	191 (47%)	97 (47%)	94 (48%)	0.79
NYHA				0.20
I	39 (10%)	19 (9.7%)	20 (11%)	
II	131 (35%)	60 (31%)	71 (39%)	
III	184 (49%)	102 (52%)	82 (46%)	
IV	21 (5.6%)	14 (7.2%)	7 (3.9%)	
Six-minute walk distance, m	344±139	347±133	342±145	0.76
Right heart catheterization				
Right atrial pressure, mm Hg	10.2±6.0	10.3±5.6	10.0±6.4	0.55
Mean PA pressure, mm Hg	51.5±13.9	52.0±14.4	51.0±13.4	0.49
PA wedge pressure, mm Hg	11.5±5.7	11.9±5.6	11.0±5.9	0.12
Mixed venous oxygen saturation, %	60.8±9.4	59.2±9.4	63.1±9.0	0.0032
Cardiac index, L/min per m^2	2.18±0.67	2.13±0.65	2.23±0.69	0.17
Cardiac output	4.17±1.34	4.05±1.34	4.30±1.33	0.076
Pulmonary vascular resistance, Wood units	9.7 (6.7–13.7)	10.0 (6.6–15.8)	9.3 (6.7–12.5)	0.053
Positive vasoreactivity test, n=180	30 (17%)	16 (16%)	14 (18%)	0.13
BNP, pg/mL	115 (43–323)	113 (47–263)	117 (34–391)	0.67
NT-proBNP, pg/mL	545 (230–1827)	592 (208–1830)	535 (233–1824)	0.96
Estimated GFR	77.4±26.4	78.2±25.5	76.4±27.4	0.49

Values are n (%), mean±SD, or median (25th–75th percentile). BMI indicates body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and PA, pulmonary artery.

*Other includes the following: Chinese, Filipino, Japanese, Korea, Vietnamese, Other Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian Indian, Mixed Race or Unknown/not reported.

from PAH diagnosis and those who were diagnosed >6 months prior to enrollment. Although the exact reason for better survival in those who were enrolled ≤6 months from diagnosis is unclear, it is possible that this may be attributable to the fact that PHAR does not enroll consecutive patients, thereby the sickest patients (1) may not have been approached for enrollment or (2) may have died within the first 6 months and did not have a chance to enroll, because the greatest survival hazard is within the first several months after diagnosis.

When stratified into risk groups by validated risk tools (COMPERA, FPHR, and REVEAL LITE 2.0), we observed that the distribution of patients among the 3 risk categories differed depending on the risk tool used. REVEAL LITE 2.0 stratified the greatest number of our subjects with PAH into the high-risk group, whereas COMPERA had the least (Tables S1 through S3). We believe that this marked difference in percentage of patients stratified into each risk group highlights the inherent bias and differences among the various risk tools. However, regardless of the risk score used, the high-risk group demonstrated higher mortality than intermediate- and low-risk groups (Table 3), which is consistent with recent findings from 3 European registries.[15–17,20] The 3-year mortality rate in the high-risk group ranged between 28% and 55%, depending on the risk score. To our surprise, only 30% of all patients
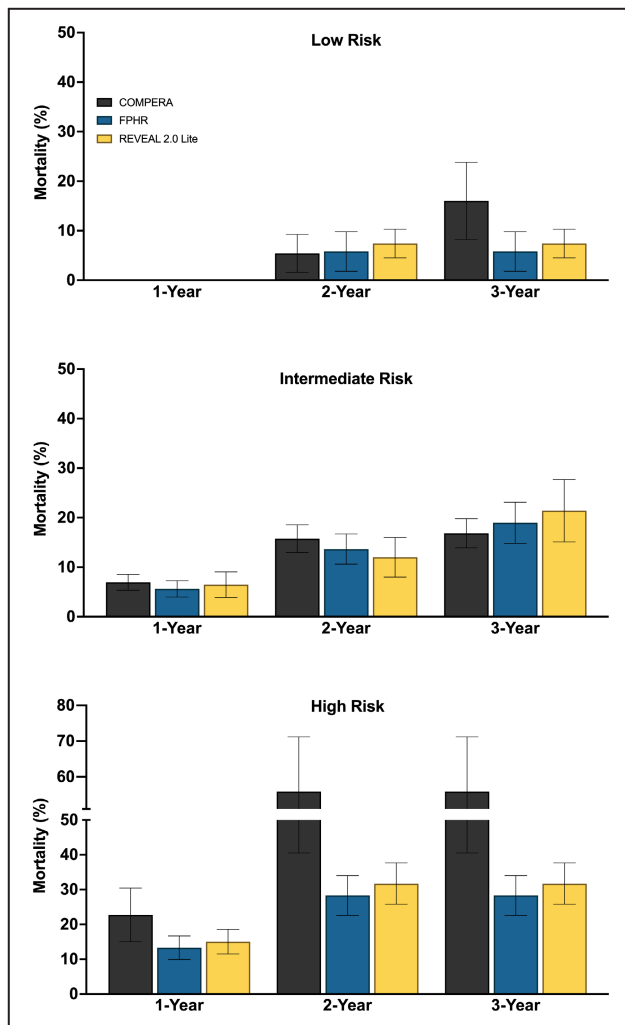
Figure 5. Mortality in idiopathic and heritable patients with PAH by risk categorization at baseline using Kaplan-Meier survival analysis.

Data are presented as mean±SE measurement. COMPERA indicates Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR, French Pulmonary Hypertension Registry; PAH, pulmonary arterial hypertension; and REVEAL, The Registry to Evaluate Early and Long-Term PAH Disease Management.

with PAH, and more importantly <50% of high-risk patients with PAH, were ever treated with parenteral prostacyclin during their disease (Figure S2B and S2C). Even in high-risk patients with idiopathic and heritable PAH, the use of parenteral prostacyclin was low (36%–56%). Alarmingly, the majority of patients who died in this study cohort (60%) did not receive parenteral prostacyclin therapy at any time during their disease (Figure S2A). This suggests that even among PHA-accredited pulmonary hypertension care centers, parenteral prostacyclin continues to be underused in the treatment of severe PAH. Although the survival benefit seen with intravenous epoprostenol was based on a single short-term study when no other treatment was

available,[28] no other PAH-specific therapies have been shown to clearly improve survival in randomized controlled trials. Recent retrospective studies from Europe suggest that combination therapy, including a parenteral prostacyclin therapy, is associated with better right ventricular function and survival compared with monotherapy or any other combination therapy.[29,30] Finally, high-risk patients in the PHAR were relatively older, more obese, and had higher pulmonary capillary wedge pressure when compared with low-risk and intermediate-risk patients, raising a question of whether there was a misclassification of pulmonary hypertension because of heart failure with preserved ejection fraction as PAH.[1,31] Alternatively, it is possible that these are patients with true PAH who have coexisting heart failure with preserved ejection fraction.

As far as management of patients with PAH, there is a growing shift toward initial combination therapy based on risk stratification. Guidelines recommend combination therapy including a parenteral prostacyclin for high-risk patients and oral monotherapy or double combination therapy for low- and intermediate-risk patients. A recent multicenter retrospective analysis from Canada showed no difference in mortality between initial monotherapy versus combination therapy in patients with PAH.[32] Moreover, a large retrospective analysis from the FPHR showed no mortality difference between initial monotherapy versus double combination therapy specifically in patients with idiopathic, heritable, and anorexigen-associated PAH; however, triple combination therapy including a parenteral prostacyclin improved 5-year mortality.[29] In our analysis, initial combination therapy (both dual and triple combination) is associated with a lower 1-year mortality, but there is no difference in 2- or 3-year mortality. However, the confidence intervals for these hazards ratios are wide; hence, these results should be interpreted with caution.

This study has several limitations including but not limited to inherent biases, quality of data collection, and missing data. Because the PHAR does not enroll consecutive patients who present to each participating center, survivor bias may have impacted the mortality rates, because the sickest patients either may not have been approached or may have died prior to a chance to enroll in the registry. Because of the ongoing recruitment in PHAR, 214 patients (18.6%) had only an initial visit recorded and were not yet due for their follow-up visit at the time of the current analysis. During the study period, 16.5% of patients were lost to follow-up. Patients who were lost to follow-up were more likely to have drug-associated PAH and were less often on pulmonary vasodilator therapies and supplemental oxygen therapy (Table S8). Because patients with drug-associated PAH have worse outcomes, this could have underestimated mortality rates in this cohort.[33] Additionally, we were unable to estimate

survival based on risk stratification at follow-up visits because of lack of hemodynamic and other pertinent data needed for risk stratification. However, follow-up risk assessment is more important in newly diagnosed and treatment-naïve patients. In the PHAR cohort, only 14% (Table 2) of patients were on no therapy at the time of enrollment; thus, this registry's design minimizes the differential predictive value of the follow-up visit as opposed to the baseline risk assessment. Furthermore, the relatively short duration of follow-up is another limitation of this study. Lastly, given the observational nature of this database, we are unable to make conclusions as to causality.

To conclude, mortality among patients with PAH with intermediate- and high-risk characteristics in the PHAR registry remain unacceptably high, highlighting the importance for early diagnosis, aggressive use of available therapies to delay disease progression, and the continued need for better therapeutics.

APPENDIX

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Acknowledgments

Sources of Funding

Disclosures

Dr Badesch has the following disclosures: Actelion (Advisory Board, Consultant, Research Support), Janssen (Research Support), Johnson and Johnson (Advisory Board, Consultant, Research Support, Stockholder), Acceleron (Advisory Board, Consultant, Research Support), Arena/United Therapeutics (Advisory Board, Consultant, Research Support), United Therapeutics/Lung LLC (Advisory Board, Consultant, Research Support), Complexa (Advisory Board, Consultant, Research Support), Altavant (Research Support), Belleraphone (Advisory Board, Consultant, Research Support), Liquidia (Advisory Board, Consultant, Research Support), Reata (Research Support), Merck (Advisory Board, Consultant, Research Support), USPHSR (Advisory Board, Consultant, Research Support), Bayer (Advisory Board, Consultant), Pfizer (Advisory Board, Consultant). Dr Chakinala has the following disclosures: Altavant (Advisory Board, Consultant, Research Support), Bayer (Advisory Board, Consultant, Research Support), Complexa (Research Support), Express Scripts (Advisory Board, Consultant), Gossamer Bio (Advisory Board, Consultant), Janssen (Advisory Board, Consultant, Research Support), Liquidia (Advisory Board, Consultant, Research Support), Medtronic (Research Support), National Institutes of Health (Research Support), Phase Bio (Advisory Board, Consultant, Research Support), Reata (Research Support), Trio Health Analytics (Research Support), United Therapeutics (Advisory Board, Consultant, Research Support), V-Wave (Advisory Board, Consultant), Vaderis Therapeutics (Advisory Board, Consultant). Dr De Marco has the following disclosures: Janssen (Advisory Board, Consultant), SCOPE/Bial (Data Safety and Monitoring Committee for Multicenter Trial), United Therapeutics (Advisory Board, Adjudication Committee for Multicenter Trial), Altevant (Advisory Board), Acceleron/Merck (Data Safety and Monitoring Committee for Multicenter Trial). Liquidia (Advisory Board). Dr Frantz has the following disclosures Bayer (Grant Submission Reviewer), Janssen (Advisory Board, Consultant), Gossamer Bio (Advisory Board, Consultant), Liquidia (Advisory Board, Consultant), United Therapeutics (Advisory Board, Presentations), Acceleron (Advisory Board, Consultant). Dr Hemnes has the following disclosures: Bayer (Consultant), Actelion (Consultant), United Therapeutics (Consultant), Complexa (Consultant), PHPrecisionMed (Shareholder). Dr Mathai has the following disclosures: Actelion (Consultant), Liquidia (Consultant), and United Therapeutics (Consultant). Dr Ryan has the following disclosures: Bayer (Speaker Honorarium, Consultant), Janssen (Speaker Honorarium, Consultant). Dr Ryan's work is funded by Stephen and Marilee Gordon. Dr Thenappan has the following disclosures: Actelion (Advisory Board, Consultant), Gilead (Advisory Board, Consultant), United Therapeutics (Advisory Board, Consultant), and Altavant (Advisory Board, Consultant). The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Tables S1–S8
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Data S1.

Sensitivity Analyses in Patients with All Variables Available to Calculate Risk Score

We performed sensitivity analyses restricting to only patients with all clinical variables available to calculate risk scores. Of the 935 patients, 466 patients had all six variables needed to calculate COMPERA risk score [70 patients were low risk (16%), 312 patients were intermediate risk (70%), and 64 patients were high risk (14%)], 684 patients had all four variables to calculate FPHR risk score [116 patients were low risk (17%), 395 patients were intermediate risk (58%), 173 patients were high risk (25%)] and 441 patients had all six variables required to calculate REVEAL 2.0 lite risk score [174 were low risk (39%), 135 were intermediate risk (31%), and 132 were high risk (30%)].

When stratified into low-, intermediate- and high-risk by validated risk scores, the range of mortality rates at 1-, 2- and 3-year were 1-2%, 2-6% and 8-10% for low-risk, 6-8%, 12-15% and 19-21% for intermediate-risk, and 9-17%, 18-36% and 21-36% for high-risk, respectively (Figure). While the mortality rates for low- and intermediate-risk PAH were similar regardless of the risk tools used, differences among the mortality rates for high-risk PAH subjects were much more substantial (9% vs. 17% at 1-year, 18% vs. 36% at 2-year, and 21% vs. 36% at 3-year between FPHR vs. COMPERA, respectively). Age and sex adjusted hazard ratio for mortality in PAH patients is reported in (Table).

Figure: Mortality in PAH Patients with All Variables Available for Risk Score Calculation by Risk Categorization
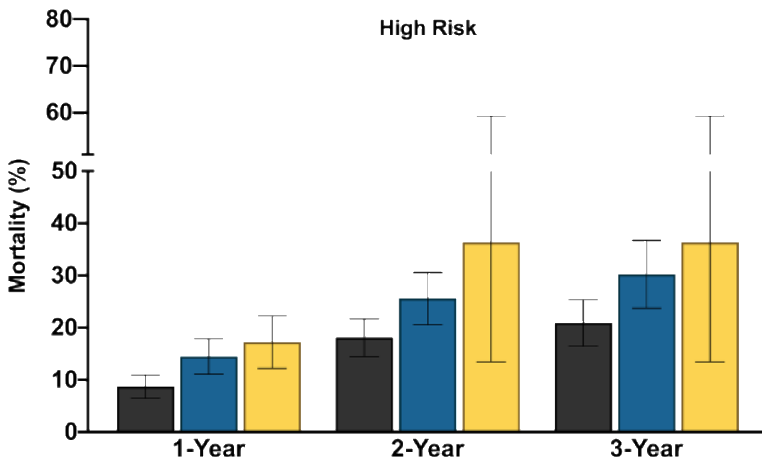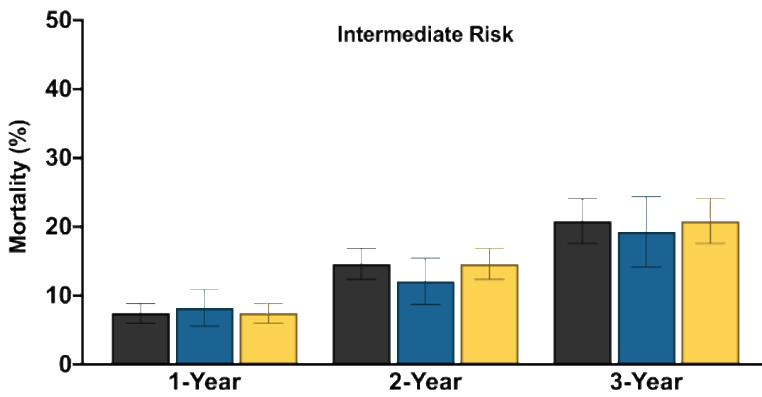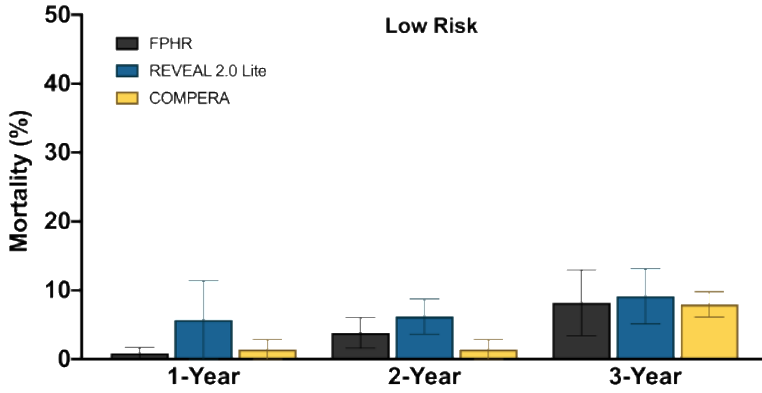
Table: Age and Sex Adjusted Mortality in PAH Patients with All Variables

Available for Risk Score Calculation

Risk Score	n	Unadjusted	Age-adjusted	Age and Sex-adjusted
COMPERA	446			
Low risk	70	Reference	Reference	Reference
Intermediate risk	312	3.77 (0.91, 15.69)	2.68 (0.64, 11.21)	2.84 (0.68, 11.93)
High risk	64	10.47 (2.43, 45.14)	7.07 (1.63, 30.74)	8.38 (1.92, 36.48)
FPHR	684			
Low risk	116	Reference	Reference	Reference
Intermediate risk	395	3.83 (1.38, 10.64)	3.39 (1.22, 9.40)	3.33 (1.20, 9.24)
High risk	173	4.62 (1.62, 13.17)	3.64 (1.27, 10.40)	3.65 (1.28, 10.43)
REVEAL LITE 2.0	441			
Low risk	174	Reference	Reference	Reference
Intermediate risk	135	3.05 (1.26, 7.35)	2.48 (1.02, 5.99)	2.77 (1.14, 6.73)
High risk	132	5.90 (2.56, 13.61)	3.67 (1.55, 8.73)	4.68 (1.95, 11.25)

FPHR – French Pulmonary Hypertension Registry, REVEAL – The Registry to Evaluate Early and Long-term PAH Disease Management, and COMPERA - Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension

Table S1. Baseline Characteristics of All PAH Patients Stratified by COMPERA Risk Score.

Characteristic	Low	Intermediate	High	p-trend
n	169 (18%)	684 (73%)	82 (9.0%)	
Women	125 (74%)	520 (76%)	65 (79%)	0.35
Age	54 (38-63)	57 (45-68)	58 (44-71)	0.0045
Race				
White	122 (76%)	500 (78%)	58 (72%)	0.73
Black	21 (13%)	85 (13%)	18 (22%)	0.12
Other	18 (11%)	54 (8.5%)	5 (6.2%)	0.17
Ethnicity				0.72
Hispanic	15 (9.3%)	80 (12%)	7 (9.1%)	
Non-Hispanic	147 (91%)	569 (88%)	70 (91%)	
BMI (kg/m^2)	28 ± 8	30 ± 7	32 ± 10	<0.001
Smoking	64 (38%)	323 (47%)	43 (52%)	0.015
Etiology				
Idiopathic	63 (37%)	283 (41%)	33 (40%)	0.49
Heritable	4 (2.4%)	20 (2.9%)	1 (1.2%)	0.79
Drug-Induced	12 (7.1%)	82 (12%)	11 (13%)	0.075
Connective Tissue Disease	57 (34%)	210 (31%)	32 (39%)	0.70
HIV-related	1 (0.59%)	12 (1.8%)	2 (2.4%)	0.22
Portopulmonary Hypertension	18 (11%)	43 (6.3%)	2 (2.4%)	0.010
Congenital Heart Disease	14 (8.3%)	29 (4.2%)	1 (1.2%)	0.007
PVOD/PCH	0 (0.0%)	5 (0.73%)	0 (0.0%)	0.68
NYHA				NA
I	32 (21%)	36 (5.5%)	0 (0.0%)	
II	94 (60%)	212 (33%)	6 (8.1%)	

III	29 (19%)	366 (56%)	45 (61%)	
IV	1 (0.64%)	38 (5.8%)	23 (31%)	
Six Minute Walk Distance (m)	436 ± 116	325 ± 112	214 ± 118	NA
Medications (Anytime during the Disease Course)				
PDE-5 Inhibitors	144 (85%)	601 (88%)	77 (94%)	0.062
Endothelium Receptor Antagonists	124 (73%)	529 (77%)	57 (70%)	0.89
Soluble Guanylate Cyclase Stimulators	12 (7.1%)	57 (8.3%)	7 (8.5%)	0.63
Parenteral Prostacyclin	31 (18%)	208 (30%)	39 (48%)	<0.001
Oral Treprostinil	8 (4.7%)	34 (5.0%)	5 (6.1%)	0.69
Selexipag	17 (10%)	117 (17%)	13 (16%)	0.088
Inhaled Prostacyclin	13 (7.7%)	89 (13%)	12 (15%)	0.060
Calcium Channel Blocker	28 (17%)	71 (10%)	8 (9.8%)	0.043
Digoxin	12 (7.1%)	71 (10%)	12 (15%)	0.061
Warfarin	46 (27%)	205 (30%)	32 (39%)	0.086
Supplemental Oxygen	84 (50%)	383 (56%)	55 (67%)	0.012
Right Heart Catheterization				
Right Atrial Pressure (mmHg)	5.4 ± 2.9	10.2 ± 5.7	17.1 ± 5.8	NA
Mean PA Pressure (mmHg)	41.9 ± 14.6	50.6 ± 13.2	55.0 ± 12.2	<0.001
PA Wedge Pressure (mmHg)	8.7 ± 3.7	11.6 ± 5.9	13.1 ± 5.7	<0.001
Mixed Venous Oxygen Saturation (%)	71.1 ± 4.5	61.4 ± 8.6	50.0 ± 8.8	NA
Cardiac Index (L/min/m^2)	2.99 ± 0.90	2.18 ± 0.62	1.61 ± 0.29	NA
Cardiac Output	5.39 ± 1.64	4.14 ± 1.33	3.12 ± 0.71	<0.001
Pulmonary Vascular Resistance (Wood)	5.8 (4.2-8.7)	9.6 (6.7-12.9)	14.2 (10.3-17.7)	<0.001

Positive vasoreactivity test (n=384)	20 (27%)	31 (11%)	5 (14%)	0.006
BNP (pg/mL) (n=514)	34 (19-72)	139 (62-363)	746 (354-1166)	NA
NT-proBNP (pg/mL) (n=426)	152 (83-280)	681 (267-2242)	2842 (1524-6317)	NA
Estimated GFR	88.0 ± 26.7	75.9 ± 26.8	68.7 ± 27.9	<0.001

Values are n (%), mean ± SD or median (25th-75th percentile)

BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery/arterial; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PDE, phosphodiesterase-5; PVOD, pulmonary veno-occlusive disease, and NA – not applicable as this variable is included in the risk calculation.

Table S2. Baseline Characteristics of All PAH Patients Stratified by FPHR Risk Score.

Characteristic	Low	Intermediate	High	*p*-trend
n	127 (14%)	534 (57%)	274 (29%)	
Women	98 (77%)	396 (74%)	216 (79%)	0.41
Age	54 (39-65)	57 (45-68)	58 (45-69)	0.016
Race				
White	91 (76%)	388 (77%)	201 (77%)	0.81
Black	15 (13%)	69 (14%)	40 (15%)	0.42
Other	14 (12%)	44 (8.8%)	19 (7.3%)	0.18
Ethnicity				0.79
Hispanic	15 (12%)	58 (12%)	29 (11%)	
Non-Hispanic	110 (88%)	444 (88%)	232 (89%)	
BMI (kg/m^2)	27.1 ± 6.4	29.1 ± 7.0	31.3 ± 7.9	<0.001
Smoking	42 (33%)	243 (46%)	145 (53%)	<0.001
Etiology				
Idiopathic	55 (43%)	209 (39%)	115 (42%)	0.97
Heritable	1 (0.79%)	21 (3.9%)	3 (1.1%)	0.54
Drug-Induced	9 (7.1%)	54 (10%)	42 (15%)	0.008
Connective Tissue Disease	39 (31%)	171 (32%)	89 (32%)	0.74
HIV-related	2 (1.6%)	10 (1.9%)	3 (1.1%)	0.58
Portopulmonary Hypertension	13 (10%)	39 (7.3%)	11 (4.0%)	0.015
Congenital Heart Disease	8 (6.3%)	26 (4.9%)	10 (3.7%)	0.23
PVOD/PCH	0 (0.0%)	4 (0.75%)	1 (0.36%)	0.88
NYHA				NA
I	29 (23%)	39 (7.7%)	0 (0.0%)	
II	89 (71%)	223 (44%)	0 (0.0%)	

III	7 (5.6%)	225 (44%)	208 (84%)	
IV	1 (0.79%)	22 (4.3%)	39 (16%)	
Six Minute Walk Distance (m)	447 ± 117	343 ± 114	254 ± 102	NA
Medications (Anytime during the Disease Course)				
PDE-5 Inhibitors	112 (88%)	467 (88%)	243 (89%)	0.78
Endothelium Receptor Antagonists	91 (72%)	418 (78%)	201 (73%)	0.85
Soluble Guanylate Cyclase Stimulators	8 (6.3%)	43 (8.1%)	25 (9.1%)	0.34
Parenteral Prostacyclin	18 (14%)	149 (28%)	111 (41%)	<0.001
Oral Treprostinil	4 (3.2%)	23 (4.3%)	20 (7.3%)	0.044
Selexipag	10 (7.9%)	92 (17%)	45 (16%)	0.093
Inhaled Prostacyclin	11 (8.7%)	67 (13%)	36 (13%)	0.27
Calcium Channel Blocker	22 (17%)	55 (10%)	30 (11%)	0.16
Digoxin	6 (4.7%)	51 (9.6%)	38 (14%)	0.004
Warfarin	33 (26%)	151 (28%)	99 (36%)	0.016
Supplemental Oxygen	60 (47%)	283 (53%)	179 (65%)	<0.001
Right Heart Catheterization				
Right Atrial Pressure (mmHg)	5.0 ± 2.5	9.1 ± 5.7	14.1 ± 5.3	NA
Mean PA Pressure (mmHg)	41.6 ± 13.4	49.3 ± 14.2	53.5 ± 11.5	<0.001
PA Wedge Pressure (mmHg)	8.2 ± 3.5	10.9 ± 5.2	13.1 ± 6.8	<0.001
Mixed Venous Oxygen Saturation (%)	69.8 ± 5.6	62.0 ± 9.0	57.9 ± 10.4	<0.001
Cardiac Index (L/min/m^2)	2.96 ± 0.95	2.30 ± 0.71	1.85 ± 0.37	NA
Cardiac Output	5.17 ± 1.68	4.38 ± 1.48	3.62 ± 0.99	<0.001
Pulmonary Vascular Resistance (Wood)	5.9 (4.3-8.7)	9.0 (6.0-12.6)	11.1 (8.3-15.2)	<0.001
Positive vasoreactivity test (n=384)	16 (33%)	25 (11%)	15 (14%)	0.017

BNP (pg/mL) (n=514)	50 (20-145)	106 (42-294)	232 (92-610)	<0.001
NT-proBNP (pg/mL) (n=426)	217 (83-468)	584 (202-2039)	1229 (405-2893)	<0.001
Estimated GFR	85.7 ± 27.7	78.2 ± 27.1	72.1 ± 26.9	<0.001

Values are n (%), mean ± SD or median (25th-75th percentile)

BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery/arterial; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PDE, phosphodiesterase-5; PVOD, pulmonary veno-occlusive disease, and NA – not applicable as this variable is included in the risk calculation.

Table S3. Baseline Characteristics of All PAH Patients Stratified by REVEAL 2.0 Lite Risk Score.

Characteristic	Low	Intermediate	High	*p*-trend
N	343 (38%)	260 (29%)	310 (34%)	
Women	246 (72%)	202 (78%)	244 (79%)	0.029
Age	50 (38-62)	57 (47-69)	64 (49-72)	<0.001
Race				
White	251 (78%)	191 (79%)	224 (76%)	0.51
Black	36 (11%)	28 (12%)	55 (19%)	0.009
Other	35 (11%)	23 (9.5%)	17 (5.7%)	0.026
Ethnicity				0.28
Hispanic	41 (13%)	31 (12%)	28 (9.7%)	
Non-Hispanic	287 (88%)	218 (88%)	261 (90%)	
BMI (kg/m^2)	29 ± 7	29 ± 7	29 ± 8	0.52
Smoking	141 (41%)	123 (47%)	154 (50%)	0.027
Etiology				
Idiopathic	138 (40%)	111 (43%)	118 (38%)	0.59
Heritable	16 (4.7%)	6 (2.3%)	3 (0.97%)	0.006
Drug-Induced	44 (13%)	24 (9.2%)	34 (11%)	0.43
Connective Tissue Disease	84 (24%)	84 (32%)	125 (40%)	<0.001
HIV-related	6 (1.8%)	4 (1.5%)	5 (1.6%)	0.89
Portopulmonary Hypertension	32 (9.3%)	16 (6.2%)	15 (4.8%)	0.024
Congenital Heart Disease	22 (6.4%)	13 (5.0%)	8 (2.6%)	0.024
PVOD/PCH	1 (0.29%)	2 (0.77%)	2 (0.65%)	0.54
NYHA				NA
I	52 (16%)	12 (4.8%)	4 (1.3%)	
II	181 (56%)	98 (39%)	32 (11%)	

III	90 (28%)	134 (53%)	216 (72%)	
IV	3 (0.92%)	8 (3.2%)	50 (17%)	
Six Minute Walk Distance (m)	417 ± 105	335 ± 93	227 ± 97	NA
Medications (Anytime during the Disease Course)				
PDE-5 Inhibitors	304 (89%)	234 (90%)	264 (85%)	0.19
Endothelium Receptor Antagonists	266 (78%)	205 (79%)	224 (72%)	0.12
Soluble Guanylate Cyclase stimulators	25 (7.3%)	19 (7.3%)	32 (10%)	0.17
Parenteral Prostacyclin	84 (25%	81 (31%)	106 (34%)	0.007
Oral Treprostinil	13 (3.8%)	13 (5.0%)	19 (6.1%)	0.17
Selexipag	53 (16%)	38 (15%)	54 (17%)	0.50
Inhaled Prostacyclin	38 (11%)	31 (12%)	41 (13%)	0.40
Calcium Channel Blocker	43 (13%)	31 (12%)	32 (10%)	0.38
Digoxin	29 (8.5%)	23 (8.9%)	39 (13%)	0.083
Warfarin	87 (25%)	83 (32%)	104 (34%)	0.022
Supplemental Oxygen	155 (45%)	140 (54%)	213 (69%)	<0.001
Right Heart Catheterization				
Right Atrial Pressure (mmHg)	8.7 ± 5.5	9.7 ± 5.4	11.3 ± 6.5	NA
Mean PA Pressure (mmHg)	48.7 ± 15.5	49.0 ± 13.6	50.6 ± 12.2	0.092
PA Wedge Pressure (mmHg)	10.6 ± 5.3	11.5 ± 5.8	11.5 ± 6.0	0.044
Mixed Venous Oxygen Saturation (%)	64.4 ± 9.1	62.2 ± 8.9	59.4 ± 10.3	<0.001
Cardiac Index (L/min/m^2)	2.42 ± 0.79	2.28 ± 0.85	2.12 ± 0.60	<0.001
Cardiac Output	4.57 ± 1.54	4.35 ± 1.64	3.91 ± 1.18	<0.001
Pulmonary Vascular Resistance (Wood)	8.5 (5.3-12.5)	9.0 (5.8-12.4)	10 (7.3-13.6)	<0.001
Positive Vasoreactivity Test (n=384)	26 (17%)	7 (6.9%)	22 (18%)	0.90

BNP (pg/mL) (n=508)	33 (18-63)	130 (78-280)	396 (212-808)	NA
NT-proBNP (pg/mL) (n=418)	189 (94-283)	790 (394-1477)	2289 (1165-4896)	NA
Estimated GFR	89.0 ± 22.9	76.2 ± 25.7	66.1 ± 28.6	NA

Values are n (%), mean ± SD or median (25th-75th percentile)

BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery/arterial; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PDE, phosphodiesterase-5; PVOD, pulmonary veno-occlusive disease, and NA – not applicable as this variable is included in the risk calculation.

Table S4. Transplant Free Survival.

	Death or Transplant Rate (95% CI)	≤ 6 months	> 6 months
All PAH			
1-Year	8.6% (6.8% - 10.7%)	9.9 % (7.3% - 13.2%)	7.2% (5.0% - 10.2%)
2-Year	16.9% (14.1% - 20.2%)	17.7 % (13.8% - 22.3%)	16.2% (12.3% - 21.2%)
3-Year	23.1% (19.4% - 27.7%)	20.6% (16.1% - 26.2%)	26% (19.6% - 33.8%)
Idiopathic and Heritable			
1-Year	7.7% (5.3% - 11%)	10.7% (6.9% - 16.3%)	4.6% (2.3% - 9.0%)
2-Year	18.6 % (14.1% - 24.3%)	18.5% (12.8% - 26.3%)	18.9% (12.5% - 28%)
3-Year	23.6% (17.4% – 31.5%)	18.5% (12.8% - 26.3%)	29.2% (18.8% - 43.6%)

Table S5. Baseline Characteristics of Idiopathic and Heritable PAH Patients Stratified by COMPERA Risk Score.

Characteristic	Low	Intermediate	High	p-trend
N	67 (17%)	303 (75%)	34 (8.4%)	
Women	48 (72%)	234 (78%)	25 (74%)	0.61
Age	51 (34-63)	56 (43-69)	57 (42-68)	0.043
Race				
White	50 (79%)	236 (83%)	24 (73%)	0.68
Black	9 (14%)	31 (11%)	7 (21%)	0.59
Other	4 (6.4%)	17 (6.0%)	2 (6.1%)	0.94
Ethnicity				0.82
Hispanic	6 (9.4%)	34 (12%)	2 (5.9%)	
Non-Hispanic	58 (91%)	251 (88%)	32 (94%)	
BMI (kg/m^2)	27 ± 6	31 ± 7	37 ± 10	<0.001
Smoking	29 (43%)	142 (47%)	20 (59%)	0.18
NYHA				NA
I	19 (31%)	20 (7.0%)	0 (0.0%)	
II	30 (48%)	97 (34%)	4 (14%)	
III	12 (19%)	154 (54%)	18 (62%)	
IV	1 (1.6%)	13 (4.6%)	7 (24%)	
Six minute walk distance (m)	484 ± 126	332 ± 120	207 ± 128	NA
Medications(Anytime during the Disease Course)				
PDE inhibitors	58 (87%)	254 (84%)	31 (92%)	0.48
Endothelium receptor antagonists	55 (82%)	238 (79%)	23 (68%)	0.24

Soluble Guanylate Cyclase stimulators	7 (11%)	31 (10%)	1 (2.9%)	0.38
Parenteral prostacyclin	18 (27%)	105 (35%)	19 (56%)	0.015
Oral Treprostinil	4 (6.0%)	16 (5.3%)	1 (2.9%)	0.80
Selexipag	5 (7.5%)	47 (16%)	8 (24%)	0.081
Inhaled Prostacyclin	6 (9.0%)	45 (15%)	3 (8.8%)	0.32
Calcium Channel Blocker	19 (28%)	28 (9.2%)	4 (12%)	<0.001
Digoxin	6 (9.0%)	30 (9.9%)	4 (12%)	0.91
Warfarin	23 (34%)	100 (33%)	19 (56%)	0.03
Supplemental Oxygen	39 (58%)	188 (62%)	23 (68%)	0.65
Right Heart Catheterization				
Right atrial pressure (mmHg)	5.1 ± 2.9	10.5 ± 5.5	17.6 ± 5.5	NA
Mean PA pressure (mmHg)	45.0 ± 16.5	52.2 ± 13.2	58.0 ± 10.0	<0.001
PA wedge pressure (mmHg)	8.3 ± 4.3	11.9 ± 5.8	13.8 ± 5.6	<0.001
Mixed Venous Oxygen Saturation (%)	70.1 ± 4.1	60.8 ± 8.5	50.3 ± 8.3	NA
Cardiac index (L/min/m^2)	2.72 ± 0.56	2.13 ± 0.65	1.61 ± 0.29	NA
Cardiac Output	4.95 ± 1.20	4.09 ± 1.35	3.38 ± 0.68	<0.001
Pulmonary vascular resistance (Wood)	7.1 (5.0-10.2)	9.8 (7.0-13.4)	15.2 (11.0-18.0)	<0.001
Positive vasoreactivity test (n=185)	13 (39%)	15 (11%)	2 (12%)	<0.001
BNP (pg/mL) (n=227)	28 (15-57)	136 (57-323)	674 (312-1701)	NA
NT-proBNP (pg/mL) (n=172)	131 (90-270)	584 (268-1830)	2277 (1074-5963)	<0.001
Estimated GFR	89.2 ± 27.0	75.6 ± 25.3	69.5 ± 28.7	<0.001

Values are n (%), mean ± SD or median (25th-75th percentile). BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide;

NYHA, New York Heart Association; PA, pulmonary artery/arterial; PAH, pulmonary arterial hypertension;

PDE, phosphodiesterase-5, and NA – not applicable as this variable is included in the risk calculation.

Table S6. Baseline Characteristics of Idiopathic and Heritable PAH Patients Stratified by FPHR Risk Score.

Characteristic	Low	Intermediate	High	p-trend
N	56 (14%)	230 (57%)	118 (29%)	
Women	46 (82%)	162 (71%)	99 (84%)	0.29
Age	51 (37-64)	55 (42-68)	58 (43-70)	0.070
Race				
White	41 (80%)	176 (80%)	93 (85%)	0.42
Black	6 (12%)	29 (13%)	12 (11%)	0.75
Other	4 (7.8%)	14 (6.4%)	5 (4.6%)	0.38
Ethnicity				0.87
Hispanic	7 (13%)	21 (9.8%)	14 (12%)	
Non-Hispanic	48 (87%)	194 (90%)	99 (88%)	
BMI (kg/m^2)	27.4 ± 7.0	30.1 ± 7.0	33.9 ± 7.8	<0.001
Smoking	20 (36%)	113 (49%)	58 (49%)	0.18
NYHA				NA
I	18 (33%)	21 (10%)	0 (0.0%)	
II	33 (60%)	98 (45%)	0 (0.0%)	
III	3 (5.5%)	93 (43%)	88 (86%)	
IV	1 (1.8%)	6 (2.8%)	14 (14%)	
Six Minute Walk Distance (m)	475 ± 129	351 ± 122	254 ± 112	NA
Medications(Anytime during the Disease Course)				
PDE inhibitors	49 (88%)	195 (85%)	99 (84%)	0.82
Endothelium receptor antagonists	45 (80%)	185 (80%)	86 (73%)	0.25
Soluble Guanylate Cyclase stimulators	4 (7.1%)	23 (10%)	12 (10%)	0.79

Parenteral prostacyclin	9 (16%)	74 (32%)	59 (50%)	<0.001
Oral Treprostinil	2 (3.6%)	10 (4.4%)	9 (7.6%)	0.36
Selexipag	5 (8.9%)	38 (17%)	17 (14%)	0.35
Inhaled Prostacyclin	7 (13%)	33 (14%)	14 (12%)	0.80
Calcium Channel Blocker	15 (27%)	23 (10%)	13 (11%)	0.003
Digoxin	4 (7.1%)	17 (7.4%)	19 (16%)	0.027
Warfarin	18 (32%)	70 (30%)	54 (46%)	0.016
Supplemental Oxygen	30 (54%)	140 (61%)	80 (68%)	0.18
Right Heart Catheterization				
Right atrial pressure (mmHg)	4.7 ± 2.3	9.6 ± 5.7	14.0 ± 5.3	NA
Mean PA pressure (mmHg)	43.7 ± 12.5	51.5 ± 14.9	55.4 ± 10.6	<0.001
PA wedge pressure (mmHg)	7.7 ± 3.8	11.4 ± 5.4	13.3 ± 6.3	<0.001
Mixed Venous Oxygen Saturation (%)	68.5 ± 5.8	61.0 ± 8.8	56.9 ± 9.6	<0.001
Cardiac index (L/min/m^2)	2.76 ± 0.66	2.19 ± 0.68	1.84 ± 0.39	NA
Cardiac Output	4.79 ± 1.22	4.25 ± 1.41	3.70 ± 1.08	<0.001
Pulmonary vascular resistance (Wood)	7.2 (5.0-9.7)	9.6 (6.6-13.0)	11.2 (7.9-16.2)	<0.001
Positive Vasoreactivity Test (n=185)	11 (48%)	15 (14%)	4 (8%)	<0.001
BNP (pg/mL) (n=231)	46 (19-153)	111 (35-294)	204 (87-564)	<0.001
NT-proBNP (pg/mL) (n=176)	209 (90-664)	521 (236-2250)	1054 (386-1824)	0.001
Estimated GFR	86 ± 25	78 ± 27	72 ± 25	0.003

Values are n (%), mean ± SD or median (25th-75th percentile)

BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-

terminal pro hormone B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary

artery/arterial; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase-5, and NA – not applicable as this variable is included in the risk calculation.

Table S7. Baseline Characteristics of Idiopathic and Heritable PAH Patients Stratified by REVEAL 2.0 Lite Risk Score.

Characteristic	Low	Intermediate	High	p-trend
n	154 (39%)	117 (30%)	121 (31%)	
Women	113 (73%)	89 (77%)	95 (79%)	0.32
Age	48 (35-62)	55 (45-69)	65 (49-73)	<0.001
Race				
White	123 (85%)	86 (80%)	92 (79%)	0.24
Black	13 (9.0%)	13 (12%)	19 (16%)	0.072
Other	9 (6.2%)	9 (8.3%)	5 (4.3%)	0.57
Ethnicity				0.86
Hispanic	16 (11%)	14 (13%)	11 (9.8%)	
Non-Hispanic	133 (89%)	96 (87%)	101 (90%)	
BMI (kg/m^2)	30 ± 7	31 ± 8	32 ± 8	0.067
Smoking	57 (37%)	62 (53%)	66 (55%)	0.0030
NYHA				NA
I	29 (20%)	9 (7.9%)	1 (0.87%)	
II	75 (52%)	43 (38%)	13 (11%)	
III	39 (27%)	60 (53%)	85 (74%)	
IV	2 (1.4%)	2 (1.8%)	16 (14%)	
Six Minute Walk Distance (m)	430 ± 117	344 ± 96	212 ± 102	NA
Medications(Anytime during the Disease Course)				
PDE inhibitors	133 (86%)	103 (88%)	95 (79%)	0.09
Endothelium receptor antagonists	129 (84%)	90 (77%)	89 (74%)	0.11

Soluble Guanylate Cyclase stimulators	18 (12%)	9 (7.7%)	12 (9.9%)	0.55
Parenteral prostacyclin	49 (31%)	44 (38%)	43 (36%)	0.60
Oral Treprostinil	7 (4.6%)	6 (5.1%)	6 (5.0%)	0.97
Selexipag	24 (16%)	10 (8.6%)	26 (22%)	0.021
Inhaled Prostacyclin	22 (14%)	18 (15%)	12 (9.9%)	0.41
Calcium Channel Blocker	22 (14%)	12 (10%)	16 (13%)	0.61
Digoxin	11 (7.1%)	13 (11%)	13 (11%)	0.46
Warfarin	50 (33%)	37 (32%)	49 (41%)	0.27
Supplemental Oxygen	84 (55%)	67 (57%)	89 (74%)	0.003
Right Heart Catheterization				
Right atrial pressure (mmHg)	8.7 ± 5.4	10.4 ± 6.0	11.4 ± 6.2	NA
Mean PA pressure (mmHg)	52.4 ± 15.7	50.6 ± 13.6	51.4 ± 11.9	0.54
PA wedge pressure (mmHg)	10.6 ± 5.7	11.9 ± 6.0	12.1 ± 5.3	0.037
Mixed Venous Oxygen Saturation (%)	63.5 ± 8.0	60.2 ± 9.9	58.7 ± 9.7	0.002
Cardiac index (L/min/m^2)	2.22 ± 0.67	2.19 ± 0.75	2.13 ± 0.60	0.28
Cardiac Output	4.3 ± 1.3	4.2 ± 1.5	4.0 ± 1.2	0.092
Pulmonary vascular resistance (Wood)	9.7 (6.6-13.8)	9.8 (6.3-12.9)	10 (6.7-13.7)	0.17
Positive Vasoreactivity Test (n=185)	17 (23%)	3 (6.0%)	9 (16%)	0.28
BNP (pg/mL) (n=227)	32 (19-75)	134 (75-294)	349 (189-728)	NA
NT-proBNP (pg/mL) (n=172)	202 (100-297)	930 (527-2689)	1750 (1079-3589)	NA
Estimated GFR	87 ± 23.3	77.4 ± 24.2	65.6 ± 27.7	NA

Values are n (%), mean ± SD or median (25th-75th percentile)

BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery/arterial; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase-5, and NA – not applicable as this variable is included in the risk calculation.

Table S8. Baseline Characteristics of All PAH: Lost to Follow Up (LTFU) vs. No Loss to Follow Up.

Characteristic	All	Not LTFU	LTFU	*p*-value
n	935	781 (84%)	154 (16%)	
Women	710 (76%)	603 (77%)	107 (70%)	0.051
Age	56 (44-68)	57 (45-68)	53 (40-67)	0.084
Race				0.10
White	680 (77%)	575 (78%)	105 (71%)	
Black	124 (14%)	101 (14%)	23 (16%)	
Other	77 (8.7%)	58 (7.9%)	19 (13%)	
Ethnicity				0.42
Hispanic	102 (11%)	82 (11%)	20 (13%)	
Non-Hispanic	786 (89%)	657 (89%)	129 (87%)	
BMI (kg/m^2)	29.5 ± 7.3	29.6 ± 7.4	29.0 ± 7.0	0.35
Smoking	430 (46%)	357 (46%)	73 (47%)	0.70
Etiology				<0.001
Idiopathic	379 (41%)	330 (42%)	49 (32%)	
Heritable	25 (2.7%)	22 (2.8%)	3 (2.0%)	
Drug-Induced	105 (11%)	69 (8.8%)	36 (23%)	
Connective Tissue Disease	299 (32%)	256 (33%)	43 (28%)	
HIV-related	15 (1.6%)	13 (1.7%)	2 (1.3%)	
Portopulmonary Hypertension	63 (6.7%)	53 (6.8%)	10 (6.5%)	
Congenital Heart Disease	44 (4.7%)	33 (4.2%)	11 (7.1%)	
PVOD/PCH	5 (0.53%)	5 (0.64%)	0 (0.0%)	
NYHA				0.68
I	68 (7.7%)	56 (7.6%)	12 (8.4%)	
II	312 (35%)	263 (36%)	49 (34%)	

III	440 (50%)	365 (49%)	75 (52%)	
IV	62 (7.0%)	55 (7.4%)	7 (4.9%)	
Six Minute Walk Distance (m)	335 ± 127	334 ± 128	342 ± 122	0.52
Medications (Anytime during the Disease Course)				
PDE-5 Inhibitors	822 (88%)	689 (88%)	133 (86%)	0.52
Endothelium Receptor Antagonists	710 (76%)	610 (78%)	100 (65%)	<0.001
Soluble Guanylate Cyclase Stimulators	76 (8.1%)	67 (8.6%)	9 (5.8%)	0.26
Parenteral Prostacyclin	278 (30%)	246 (32%)	32 (21%)	0.008
Oral Treprostinil	47 (5.0%)	45 (5.8%)	2 (1.3%)	0.015
Selexipag	147 (16%)	125 (16%)	22 (14%)	0.59
Inhaled Prostacyclin	114 (12%)	95 (12%)	19 (12%)	0.95
Calcium Channel Blocker	107 (11%)	94 (12%)	13 (8.4%)	0.20
Digoxin	95 (10%)	74 (9.5%)	21 (14%)	0.12
Warfarin	283 (30%)	237 (30%)	46 (30%)	0.91
Supplemental Oxygen	522 (56%)	451 (58%)	71 (46%)	0.008
Right Heart Catheterization				
Right Atrial Pressure (mmHg)	10.0 ± 6.0	10.1 ± 6.0	9.4 ± 6.3	0.23
Mean PA Pressure (mmHg)	49.5 ± 13.9	50.0 ± 14.0	46.7 ± 12.8	0.0078
PA Wedge Pressure (mmHg)	11.2 ± 5.7	11.2 ± 5.7	11.1 ± 5.5	0.94
Mixed Venous Oxygen Saturation (%)	62.0 ± 9.7	61.7 ± 9.8	64.0 ± 9.1	0.052
Cardiac Index (L/min/m^2)	2.28 ± 0.76	2.27 ± 0.76	2.30 ± 0.78	0.71
Cardiac Output	4.28 ± 1.47	4.26 ± 1.44	4.35 ± 1.63	0.53
Pulmonary Vascular Resistance (Wood)	9.1 (6.1-12.9)	9.3 (6.1-12.9)	8.8 (6.0-12.7)	0.35

Positive Vasoreactivity Test (n=384)	56 (15%)	52 (16%)	4 (7.4%)	0.15
BNP (pg/mL) (n=514)	122 (46-366)	126 (48-374)	114 (33-335)	0.29
NT-proBNP (pg/mL) (n=426)	603 (223-1969)	592 (228-1996)	644 (189-1685)	0.58
Estimated GFR	77.4 ± 27.4	77.4 ± 27.4	77.6 ± 27.1	0.93

Values are n (%), mean ± SD or median (25th-75th percentile)

BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery/arterial; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase-5

Figure S1. Etiology of PAH in the PHAR.
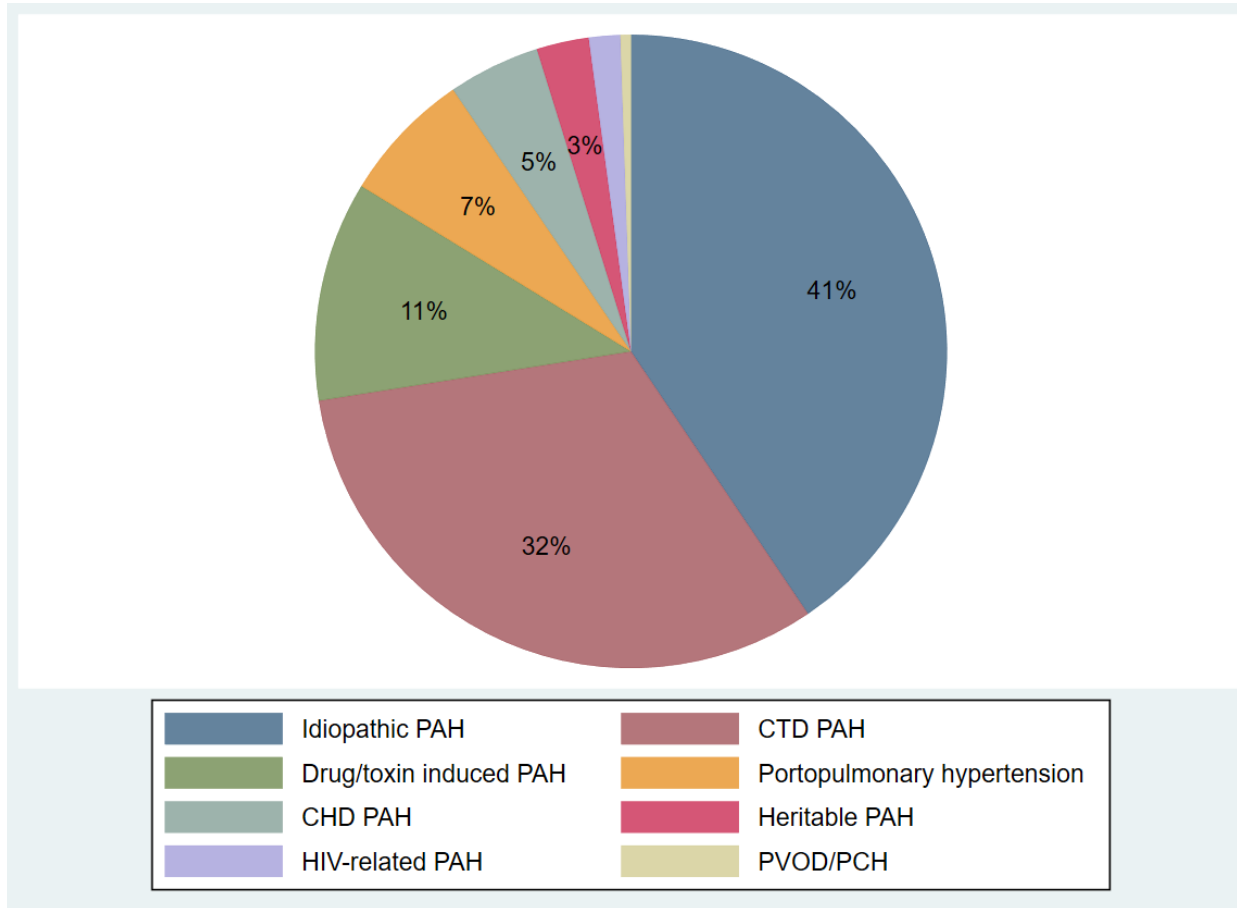
PAH – pulmonary arterial hypertension, CTD – connective tissues disease, CHD – congenital heart disease, HIV – human immunodeficiency virus, PVOD – pulmonary veno-occlusive disease, and PCH – pulmonary capillary hemangiomatosis

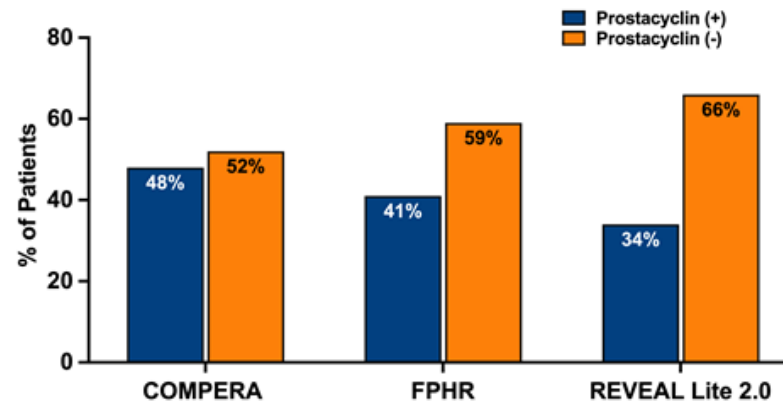**Figure S2. Parenteral Prostacyclin Use in PHAR Cohort.**

(A) Parenteral Prostacyclin Use Among Deceased

- 40.00% Prostacyclin (+)
- 60.00% Prostacylcin (-)
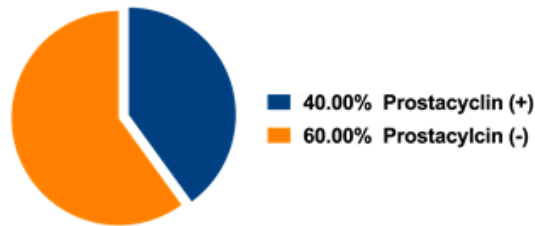
(B) Parenteral Prostacyclin Use in All PAH

- 30.00% Prostacylcin (+)
- 70.00% Prostacylcin (-)

(C) Parenteral Prostacylcin Use in High Risk PAH

FPHR – French Pulmonary Hypertension Registry, REVEAL – The Registry to Evaluate Early and Long-term PAH
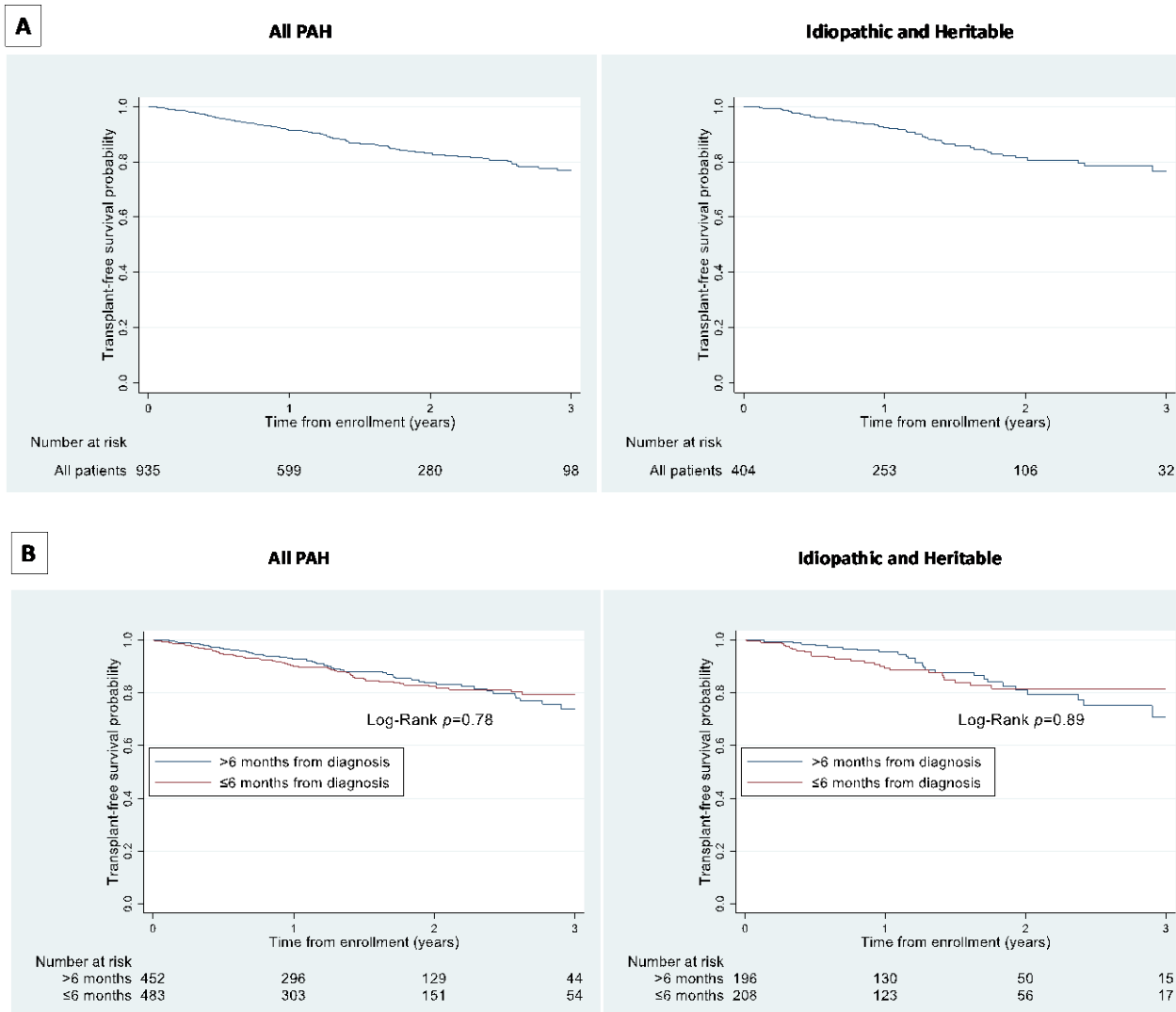
Disease Management, and HTN – hypertension, and COMPERA - Comparative, Prospective Registry of Newly Initiated

Therapies for Pulmonary Hypertension

Figure S3. Kaplan-Meier Survival Estimates in All PAH (Top) and Idiopathic and Heritable PAH (Bottom) Patients Stratified by Time from Diagnosis.

All
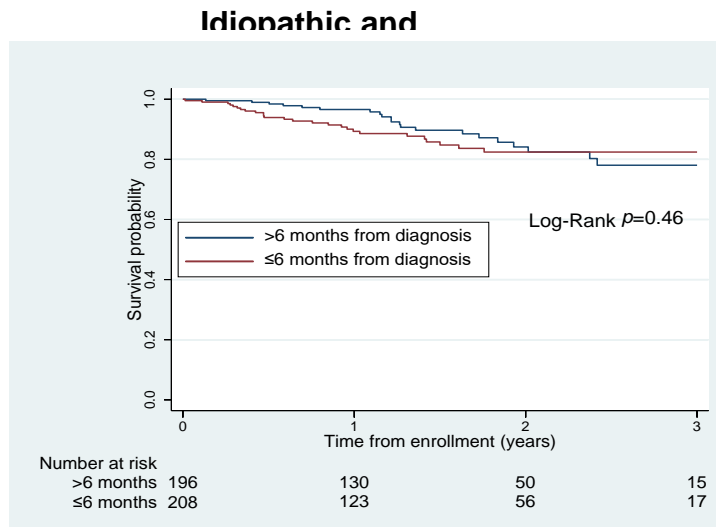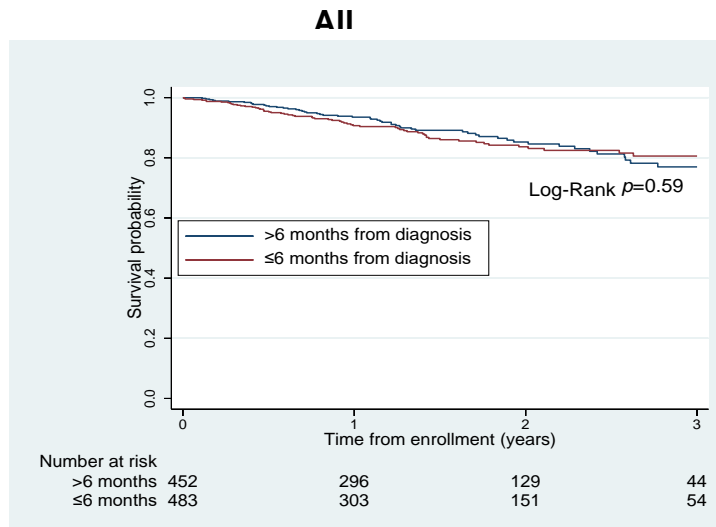
Idiopathic and

A – Mortality in All PAH categorized by ≤ 6months from diagnosis vs. > 6 months from diagnosis and B – Mortality in idiopathic and heritable PAH categorized by ≤ 6 months from diagnosis vs. > 6 months from diagnosis.

Figure S4. Transplant-Free Survival in All PAH and Idiopathic and Heritable PAH Patients (A) and Stratified by Time from Diagnosis (B).

PAH – pulmonary arterial hypertension