CHEST

Original Research

PULMONARY VASCULAR DISEASE

# An Evaluation of Long-term Survival From Time of Diagnosis in Pulmonary Arterial Hypertension From the REVEAL Registry

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***Background:*** **The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) was established to characterize the clinical course, treatment, and predictors of outcomes in patients with pulmonary arterial hypertension (PAH) in the United States. To date, estimated survival based on time of patient enrollment has been established and reported. To determine whether the survival of patients with PAH has improved over recent decades, we assessed survival from time of diagnosis for the REVEAL Registry cohort and compared these results to the estimated survival using the National Institutes of Health (NIH) prognostic equation.**

***Methods:*** **Newly or previously diagnosed patients (aged ≥ 3 months at diagnosis) with PAH enrolled from March 2006 to December 2009 at 55 US centers were included in the current analysis.**

***Results:*** **A total of 2,635 patients qualified for this analysis. One-, 3-, 5-, and 7-year survival rates from time of diagnostic right-sided heart catheterization were 85%, 68%, 57%, and 49%, respectively. For patients with idiopathic/familial PAH, survival rates were 91% ± 2%, 74% ± 2%, 65% ± 3%, and 59% ± 3% compared with estimated survival rates of 68%, 47%, 36%, and 32%, respectively, using the NIH equation.**

***Conclusions:*** **Comprehensive analysis of survival from time of diagnosis in a large cohort of patients with PAH suggests considerable improvements in survival in the past 2 decades since the establishment of the NIH registry, the effects of which most likely reflect a combination of changes in treatments, improved patient support strategies, and possibly a PAH population at variance with other cohorts.**

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

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**Abbreviations:** APAH = pulmonary arterial hypertension associated with other conditions; CHD = congenital heart disease; CTD = connective tissue disease; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PoPH = portopulmonary hypertension; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; RHC = right-sided heart catheterization

Pulmonary arterial hypertension (PAH) is a progressive, fatal disease characterized by increased pulmonary vascular resistance due to vascular proliferation and remodeling of the pulmonary arterioles that lead to right-sided ventricular failure and, ultimately, death.[1,2] Natural history estimates of survival in patients with idiopathic PAH (IPAH) or familial PAH (FPAH) were derived from the first PAH registry established by the National Institutes of Health (NIH) in the 1980s.[3,4] Based on the 194 patients with IPAH or FPAH enrolled at 32 US centers, the estimated median survival was 2.8 years after diagnosis.[3] Since then, significant advances have been made in treatment options and management, including the approval of several drugs in the United States for the treatment of adult PAH.[2]

Recent PAH registries provide a more current perspective on patient outcomes by using matched populations to facilitate historical comparison with the NIH registry. The prospective, observational, national,

French PAH registry (the French Network on Pulmonary Arterial Hypertension at 17 university hospitals) enrolled 674 newly and previously diagnosed patients over a 1-year period commencing in October 2002.[5] The estimated 1- and 3-year survival rates of the subgroup of patients with IPAH/FPAH/anorexigen-associated PAH for whom 3-year follow-up results were reported were 82.9% and 58.2%, respectively.[6] This was significantly better than the survival rate observed in newly diagnosed patients in the NIH registry. Consistent with these findings, reports from other contemporary registries of patients with PAH have also documented an improvement in survival rates compared with that predicted using the NIH prognostic equation, which was developed before the advent of modern PAH therapeutics.[6-9]

Unlike the NIH registry, the 55-center, observational Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) (initiated in 2006) was designed to provide information about demographics, longitudinal clinical course, and management of patients with group 1 pulmonary hypertension (PH) in the current treatment era from a US perspective.[10] We previously reported an estimated 91% 1-year survival rate in the REVEAL Registry from the time of enrollment of 2,716 consecutively enrolled patients with group 1 PH, which was higher than that originally reported by the NIH study (68%).[11] Key predictors of survival were identified, and a prognostic model was developed to predict 1-year survival from any time point in the course of a patient's disease.

To provide an estimate of survival in newly diagnosed patients with PAH (group 1 PH) using current treatment modalities, we analyzed survival from time of diagnostic right-sided heart catheterization (RHC) in patients enrolled in the REVEAL Registry and investigated risk according to PAH classification. Furthermore, we compared survival in the subgroup of patients with IPAH/FPAH who met the NIH registry hemodynamic inclusion criteria with that predicted by the NIH survival equation, to elucidate (1) whether survival has truly improved in the current treatment era, and (2) whether this component is related to improvements in current management or to a change in patient phenotypes.

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## Materials and Methods

### *Study Design and Participants*

The observational, prospective REVEAL Registry study was conducted at 55 sites in the United States (see e-Appendix 1 for a list of the REVEAL Registry sites and corresponding institutional review board numbers). The design and inclusion criteria for the REVEAL Registry have been described previously.[10] The protocol was reviewed by the institutional review board of each participating center, and all participants or their legal guardians provided written informed consent (and assent in the cases of pediatric patients) before study entry.

Patients aged ≥ 3 months at diagnosis who met the modified definition for group 1 PH[12] were enrolled consecutively beginning in March 2006. Enrollment of previously diagnosed patients ended in September 2007, whereas enrollment of newly diagnosed patients continued through December 2009. Patients who were diagnosed before November 2001 were excluded from the analysis so that all analyzed patients were diagnosed within the contemporary treatment era, in which multiple approved classes of therapy were available (the first PAH therapy, continuous IV administration, was approved in the United States in 1995 and the first oral PAH therapy was approved in the United States in November 2001).

All patients who met the following hemodynamic RHC criteria for PAH were included in the current analysis: mean pulmonary artery pressure (mPAP) > 25 mm Hg at rest, pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure ≤ 15 mm Hg, and pulmonary vascular resistance ≥ 3 Wood units (240 dynes/s/cm$^{-5}$). Patients were to be followed up for a minimum of 5 years from enrollment. Newly diagnosed patients had their diagnosis confirmed by RHC within the 3 months before enrollment, whereas previously diagnosed patients had their diagnosis confirmed by RHC > 3 months before enrollment.

### *Statistical Analyses*

Survival was estimated from the time of diagnostic RHC using the Kaplan-Meier method, accounting for both right censoring and left truncation, with all-cause mortality as the end point in the full REVEAL Registry cohort and stratified by group 1 PH subgroup[12] (ie, IPAH, FPAH, or PAH associated with other conditions [APAH]). Transplantation is considered neither an event nor a form of censoring, because survival follow-up continues post-transplant. Patients with multiple causes were categorized based on a hierarchy used previously in the REVEAL Registry.[13]

To avoid immortal time bias,[14] time-to-event analyses were restricted to the time during which patients were followed prospectively. This was accomplished by evaluating survival measured from the time of diagnostic RHC, using a delayed-entry variant of the standard product-limit estimator, which accounts for data that are not only right censored but also left truncated.[15] Right censoring occurs because all patients have not been followed through to the time of death as of the last follow-up; in contrast, left truncation occurs because patients who died between time of diagnosis and initiation of the REVEAL Registry were not included in the study.[16] All survival analyses were restricted to

7-year survival from time of diagnostic RHC, which was after November 2001 for all patients included in the current analysis, as explained previously.

Survival was also determined in a subgroup of the full REVEAL Registry cohort, which, for purposes of comparison, was composed of patients who met the same criteria as the original NIH study[3] with survival predicted by the NIH equation. This was the REVEAL Registry unweighted NIH cohort, and it included patients with IPAH/FPAH meeting the hemodynamic criteria used in the NIH survival analysis (PCWP ≤ 12 mm Hg).[3] A second comparison with survival predicted by the NIH equation was conducted, but in addition to using the same NIH enrollment criteria, inverse-propensity weighting[17] was used to increase the weighting of male patients, younger patients, and patients with a higher mPAP to match the distribution of these variables reported in the NIH registry (REVEAL Registry NIH weighted cohort). In addition, to explore the effect of modern treatment options on survival, only those patients who initiated therapy with endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and/or prostacyclin/prostacyclin analogues within 6 months of diagnostic RHC were included in the subgroup because none of these three treatment options was available at the time of the NIH study. These cohorts were compared on a survival basis with that derived from the NIH survival equation.[3]

## Results

### *Patient Demographic, Hemodynamic, and Functional Characteristics*

A total of 3,517 patients meeting all inclusion criteria were enrolled consecutively in the REVEAL Registry; 612 were excluded from this analysis because of diagnostic RHC before November 2001. Patient disposition and inclusion in each of the analyses are shown in Figure 1. The overall survival analysis included 2,635 patients, including 1,267 patients with IPAH/FPAH, of whom 985 met the NIH PCWP criteria (≤ 12 mm Hg), 755 of whom, unlike the NIH patients, were treated within 6 months of diagnosis with PAH-specific therapies. Selected demographics and hemodynamics of the cohorts included in the current analysis, the full cohort (N = 2,635), the NIH cohort (n = 187), and the unweighted and weighted REVEAL Registry NIH cohorts (both n = 755) are presented in Table 1. The mean age of the full REVEAL Registry cohort in the current study was greater than that of the NIH cohort; furthermore, there were more female patients in the REVEAL Registry.[13,18] In the overall cohort, the mean time from diagnosis to enrollment was 17.4 months, and the median time was 11.5 months (range, 0-67.8 months). Among newly and previously diagnosed patients, the mean and median times from diagnosis to enrollment were 0.9 and 0.5 months (range, 0-3 months) and 25.6 and 23.2 months (range, 3-67.8 months), respectively. The mean time from initial symptoms to diagnosis in the overall cohort (N = 2,635) was 31 months, and the median time was 12.8 months (range, −5.5 to 654.9 months).

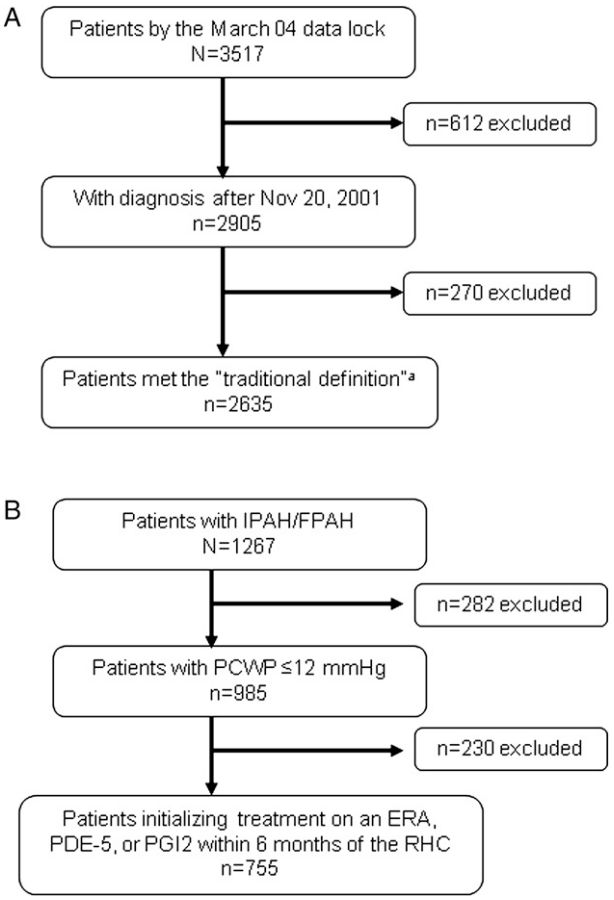


Figure 1. Flowchart depicting patients included/excluded from each analysis. A, Full Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) cohort. B, REVEAL Registry National Institutes of Health cohort. In the current analysis, the full REVEAL Registry cohort was defined as all patients who met the inclusion criteria (ie, who met the traditional definition of pulmonary arterial hypertension [PAH] within the defined enrollment period) but excluded patients who were diagnosed after November 2001, patients with a PCWP > 15 mm Hg, and patients who met the entry criteria during exercise. [a]Traditional definition excludes patients with a wedge pressure of 16-18 mm Hg, as well as patients that met the entry criteria during exercise. ERA = endothelin receptor antagonist; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE-5 = phosphodiesterase-5 inhibitor; PGI2 = prostacyclin analogue; RHC = right-sided heart catheterization.

### *Survival*

The mean duration of follow-up (after enrollment) among survivors was 1,155 days (range, 0-1,735 days); three patients (0.2%) had no follow-up and 85.2% of survivors were followed-up for ≥ 24 months. There were 716 deaths, and 67 patients underwent lung or heart-lung transplant. Kaplan-Meier survival estimates (± SE) for the full REVEAL Registry cohort diagnosed after November 2001 were 85% ± 1%, 68% ± 1%, 57% ± 1%, and 49% ± 1% at 1, 3, 5, and 7 years from diagnosis, respectively (Fig 2).

**Table 1—*Distribution of Sex, Age, mPAP, mRAP, and Cardiac Index at Diagnosis in the REVEAL Registry, NIH, and REVEAL Registry NIH Cohorts After Matching***

| Characteristic | REVEAL Registry Patients "Traditional Definition" Diagnosed After November 2001(N = 2,635) | NIH Cohort (N = 187) | Unweighted Comparison Cohort[a] (n = 755) | Weighted Comparison Cohort[b] (n = 755) |
|---|---|---|---|---|
| Female sex, % | 77 | 63 | 77 | 62 |
| Age, y | 50 ± 17 | 36 ± 15 | 47 ± 18 | 34 ± 16 |
| mPAP, mm Hg | 50 ± 14 | 60 ± 18 | 53 ± 13 | 60 ± 15 |
| mRAP, mm Hg | 9.4 ± 6.0 | 9.7 ± 6.0 | 9.8 ± 6.0 | 9.9 ± 5.0 |
| Cardiac index, L/min/m² | 2.3 ± 0.9 | 2.3 ± 0.9 | 2.2 ± 0.9 | 2.3 ± 1.1 |

Data are presented as mean ± SD unless indicated otherwise. NIH = National Institutes of Health; mPAP = mean pulmonary artery pressure; mRAP = mean right artery pressure; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management.

[a]REVEAL Registry unweighted comparison cohort includes all "traditional" patients with idiopathic PAH or familial PAH and pulmonary capillary wedge pressure ≤ 12 mm Hg at diagnosis, and those who initiated treatment with an endothelin receptor antagonist, phosphodiesterase-5 inhibitor, or prostacyclin/prostacyclin analogue within 6 mo of diagnostic right-sided heart catheterization. These patients meet the same criteria as the original NIH study.[3]

[b]In addition to subsetting on the NIH cohort enrollment criteria, inverse-propensity weighting[17] was used to increase the weighting of male patients, younger patients, and patients with higher than average mPAP to match the distributions of these variables reported in the NIH registry.

Separation of the Kaplan-Meier curves is observed when the subgroup survival estimates are plotted together (Fig 3), with the highest 7-year survival estimate in the subgroups of PAH associated with congenital heart disease (APAH-CHD) (67% ± 5%, $P = .017$ vs IPAH) (Fig 3A) and HIV (APAH-HIV) (64% ± 9%, $P = .74$ vs IPAH) (Fig 3B), and the lowest in the subgroups of PAH associated with connective tissue disease (APAH-CTD) (35% ± 2%, $P < .001$ vs IPAH) (Fig 3A) and portopulmonary hypertension (PoPH) (29% ± 5%, $P < .001$ vs IPAH) (Fig 3A, Table 2). The APAH-HIV, APAH-other, and FPAH subgroups all had survival similar to the IPAH subgroup, although FPAH demonstrated a tendency toward reduced survival compared with IPAH (Fig 3B, Table 2).

In the subgroup of REVEAL Registry patients who initiated PAH-specific therapy within 6 months of diagnosis and met the enrollment criteria from the NIH registry, markedly better survival over 7 years (by 22%-29%) was observed compared with the estimated survival based on the NIH equation (Fig 4). Applying age, sex, and mPAP distribution weighting to match the NIH cohort (REVEAL Registry NIH weighted cohort) did not significantly alter this result (Fig 5); the Kaplan-Meier estimated survival of the REVEAL Registry NIH weighted cohort was also better than the survival predicted by the NIH equation over 7 years (by 26%-35%). We did not attempt to directly investigate the effect of therapy on survival because the REVEAL Registry includes only a small and nonrepresentative cohort of untreated patients. The REVEAL Registry NIH cohort comprised 113 of 755 patients (15%) who were formally diagnosed (confirmatory RHC) after initiating therapy, 574 of 755 (76%) who were diagnosed before initiating therapy, and 68 of 755 (9%) who were diagnosed on the date of therapy initiation. Among newly and previously diagnosed patients, 44 of 279 (16%) and 69 of 476 (15%) were formally diagnosed after initiating therapy, 203 of 279 (73%) and 371 of 476 (78%) were

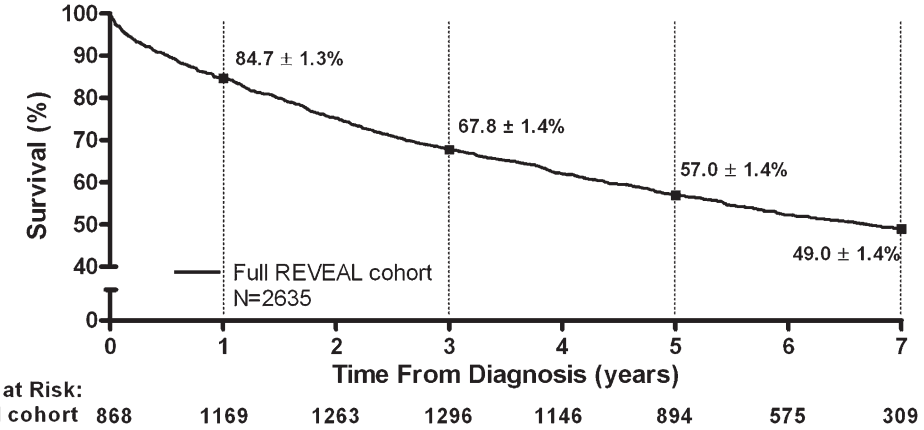


FIGURE 2. Seven-year survival from time of diagnostic right-sided heart catheterization for full REVEAL Registry cohort, using left truncation methods. ■ = estimated survival estimate ± SE at each particular time point. See Figure 1 legend for expansion of abbreviation.

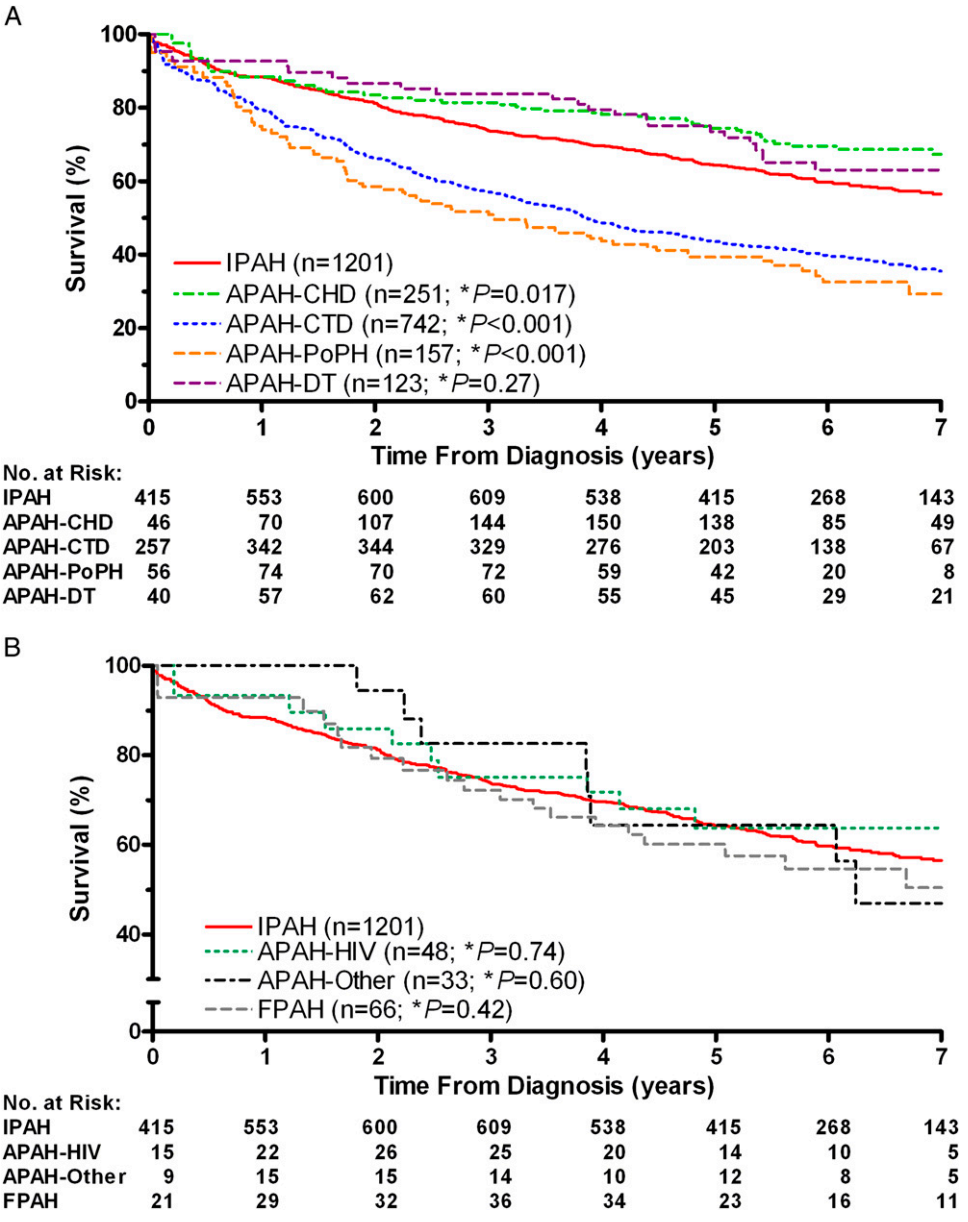


FIGURE 3. Kaplan-Meier estimates of 7-year survival from time of diagnostic right-sided heart catheterization stratified by group 1 pulmonary hypertension subgroup. A, IPAH, APAH-CTD, APAH-CHD, APAH-PoPH, and APAH-DT. B, IPAH, APAH-HIV, APAH-other, and FPAH. *P values from Cox regression model vs IPAH. APAH = pulmonary arterial hypertension associated with other conditions; CHD = congenital heart disease; CTD = connective tissue disease; DT = drugs and toxins; PoPH = portopulmonary hypertension. See Figure 1 legend for expansion of other abbreviations.

diagnosed before initiating therapy, and 32 of 279 (11%) and 36 of 476 (8%) were diagnosed on the date of therapy initiation. Of the entire cohort of 2,635 patients, 133 had never received a PAH-specific therapy, among whom 73 of 113 had never received a calcium channel blocker for the treatment of PAH.

## DISCUSSION

Our evaluation of survival from the time of diagnostic RHC in 2,635 patients with PAH enrolled in the REVEAL Registry confirms that although mortality in PAH remains unacceptably high, current survival rates have improved markedly since those reported by the NIH registry for patients diagnosed from 1981 to 1984.[3] Furthermore, a substantial improvement in survival is observed in the subgroup of REVEAL Registry patients who initiated therapy within 6 months of diagnosis and met the hemodynamic criteria from the NIH registry compared with that predicted by the NIH equation. This observation is most consistent with improvements in therapeutic options and

**Table 2—*Survival Estimates of PAH Subgroups at Years 1, 3, 5, and 7***

| PAH Subgroup | No. | Years From Diagnosis | | | |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | 7 |
| IPAH | 1,201 | 88.4 ± 1.9 | 73.7 ± 2.0 | 64.3 ± 2.1 | 56.5 ± 2.2 |
| APAH-CHD | 251 | 88.3 ± 4.5 | 81.4 ± 4.8 | 74.4 ± 4.7 | 67.3 ± 4.8 |
| APAH-CTD | 742 | 79.5 ± 2.6 | 57.1 ± 2.6 | 43.7 ± 2.4 | 35.5 ± 2.5 |
| APAH-PoPH | 157 | 74.9 ± 5.8 | 51.6 ± 5.5 | 39.4 ± 4.9 | 29.3 ± 5.3 |
| APAH-DT | 123 | 92.7 ± 5.1 | 83.7 ± 5.7 | 73.5 ± 6.2 | 63.0 ± 6.6 |
| APAH-HIV | 48 | 93.3 ± 6.2 | 75.1 ± 8.8 | 63.8 ± 9.5 | 63.8 ± 9.5 |
| APAH-other[a] | 33 | 100.0 | 82.6 ± 8.8 | 64.4 ± 11.3 | 47.0 ± 12.8 |
| FPAH | 66 | 92.9 ± 6.6 | 72.2 ± 8.2 | 60.1 ± 8.1 | 50.5 ± 8.5 |

Data are presented as estimate ± SE, %. APAH = pulmonary arterial hypertension associated with other conditions; CHD = congenital heart disease; CTD = connective tissue disease; DT = drugs and toxins; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PoPH = portopulmonary hypertension. See Table 1 for expansion of other abbreviation.

[a]APAH-other included eight patients with sickle cell disease; five with hereditary hemorrhagic telangiectasia; four with hemoglobinopathy; three each with Gaucher disease, splenectomy, or sarcoidosis; two each with polycythemia vera or chronic myeloproliferative disorder; and one each with thyroid disorder, hereditary spherocytosis, or myelofibrosis.

in the overall management of PAH. Although the contribution of patient demographics and the type(s) of clinical practices included in the analysis cannot be excluded, the statistical methodology and weighting used should have minimized or negated these variables. The difference between observed and predicted long-term survival was perhaps even more pronounced when the analysis was restricted to patients weighted similarly to those characteristics common in the original NIH cohort.

Several recent studies,[6,9,19] in addition to ours,[11] have examined survival in patients with PAH. Similar to these other studies, the 1-year survival rate in the REVEAL Registry from diagnostic RHC in a broad PAH population (ie, full REVEAL Registry cohort) was 85%, compared with 86% in the Pulmonary Hypertension Connection registry,[9] 81% in the Mayo Clinic single-center cohort analysis,[19] and 88.4% in the French registry (incident patients [defined as newly diagnosed patients for whom diagnosis was made during recruitment]).[5] Of these studies, the French registry also focused on studying survival in the modern treatment era.[6] In the 3-year survival analysis of 190 incident and prevalent patients (prevalent patients had been diagnosed within 3 years of study entry) with IPAH/FPAH/anorexigen-induced APAH in the French registry, 1- and 3-year survival rates were 82.9% (95% CI, 72.4%-95.0%) and 58.2% (95% CI, 49.0%-69.3%), respectively.[6] One-year survival from diagnostic RHC in a similar subgroup of patients from the REVEAL Registry, the REVEAL Registry NIH cohort, was comparable to the French results, with a 1-year survival rate of 91% ± 2%; however, the 3-year survival rate in this cohort was much higher

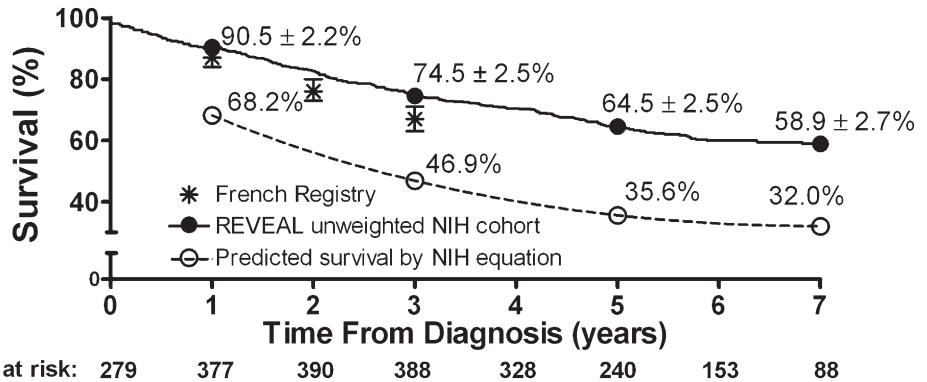


FIGURE 4. Kaplan-Meier estimates of 7-year survival from time of diagnostic right-sided heart catheterization for REVEAL Registry patients who initiated PAH-specific therapy within 6 months of diagnosis and met the NIH inclusion criteria vs survival predicted by the NIH equation. This cohort consisted of patients who met the NIH criteria (ie, had IPAH or FPAH and a PCWP of ≤ 12 mm Hg). The 1-, 2-, and 3-year survival estimates for the French registry are included for comparison (87% [95% CI, 84-90]; 76% [95% CI, 73-80]; and 67% [95% CI, 63-71], respectively).[20] NIH = National Institutes of Health. See Figure 1 legend for expansion of other abbreviations.

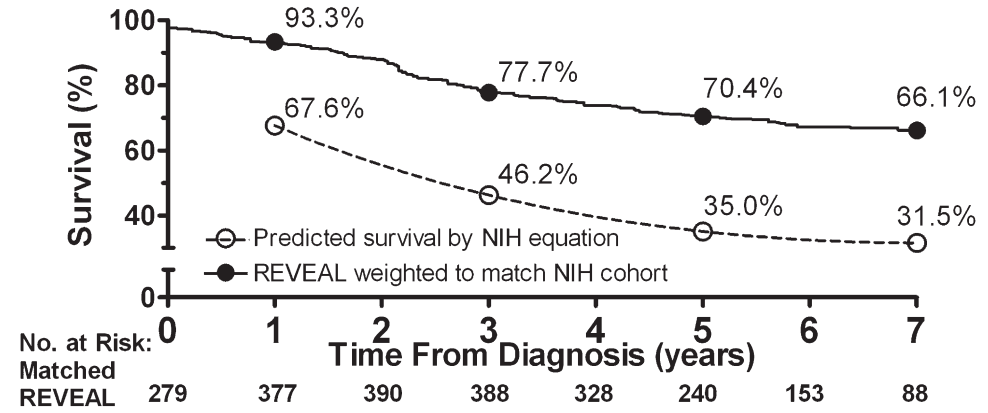


FIGURE 5. Seven-year survival from time of diagnostic RHC of REVEAL Registry cohort weighted to match age, sex, and mean pulmonary artery pressure distribution of NIH cohort. This cohort consisted of patients who met the NIH criteria (ie, had IPAH or FPAH and a pulmonary capillary wedge pressure of ≤ 12 mm Hg), and initiated an endothelin receptor antagonist, phosphodiesterase-5 inhibitor, or prostacyclin analogue within 6 months of diagnostic RHC. See Figure 1 and 4 legends for expansion of abbreviations.

(74% ± 2%) than that in the French registry (54.9%) or the Pulmonary Hypertension Connection (69%) registry.[6,9,13,18]

Several factors may have influenced this interstudy difference in 3-year survival. Patients in the French registry were enrolled between October 2002 and October 2003, when therapeutic options for PAH were limited to IV epoprostenol and oral bosentan, with the latter launched in France only in late 2002. Approximately one-third of the patients in the French study were receiving "conventional therapy" for PAH (which included oxygen, diuretics, digoxin, calcium channel blockers, and warfarin at the time of the registry). PAH therapies that became available during the 3-year follow-up of patients in the French registry were inhaled iloprost (late 2003/early 2004) and oral sildenafil (late 2005/early 2006). Additional factors that may have contributed to the later survival differences observed among the current registries include the use of specialty vs community practices, definitions used to discriminate prevalent/previously diagnosed (in the French registry, diagnosis made before enrollment; in the REVEAL Registry, diagnosis made > 90 days from enrollment) and incident/newly diagnosed patients (in the French registry, diagnosis made during enrollment; in the REVEAL Registry, diagnosis made ≤ 90 days before enrollment), and health-care access (mixed private/public funding in France vs majority private funding in the United States).

Our study results were more consistent with those of the US-based single-center Pulmonary Hypertension Connection registry, which was initiated in 2004 (but retrospectively included patients diagnosed after 1991) and enrolled a broad population of patients with PAH until 2007 (n = 576).[9] In addition to similar 1-year survival rates (discussed previously), 3- and 5-year survival rates were similar between their registry and our full REVEAL Registry cohort (69% vs 69% and 61% vs 58%, respectively).[9] Likewise, survival of the cohort of patients on PAH-specific therapy from our study who met the NIH criteria (Fig 4) was comparable to that of the IPAH, FPAH, or anorexigen-induced APAH group from the Pulmonary Hypertension Connection registry (1-, 3-, and 5-year survival of 91%, 75%, and 65%, respectively).[9] Updated prognostic equations derived from these larger sample sizes in the current era of approved therapies (as determined from the REVEAL Registry,[11] the French Registry,[6] and the single-center US study[9]) indicate that the survival estimates from the NIH registry are likely applicable only to patients who are not receiving any current approved therapies.

We previously reported 1-year survival from the time of enrollment in the REVEAL Registry to be 91.0% (95% CI, 89.9%-92.1%) and identified key predictors of survival presented in a weighted prognostic equation.[11] That analysis was not an attempt to provide an estimate of survival for the overall population, but to provide an accurate composite risk profile for survival, and it demonstrated that survival in patients with PAH was based on a weighted stratification of multiple risk factors.[11] The current analysis shows that the risk is greatest in the first year after diagnosis, leveling off moderately thereafter. Because most patients in a typical clinical practice are not new diagnoses, the shape of the latter part of the curve is consistent with those are weighted in favor of the latter portion of the time from diagnosis curve, after which the risk is somewhat diminished. The overall survival estimates are better for monitoring temporal population-level patterns in PAH as opposed to projecting the likely prognosis for an individual patient. Notably,

although we previously showed a survival disadvantage for those with a family history of PAH,[11] in the current analysis, there was no appreciable difference in unadjusted survival for those with FPAH compared with the IPAH, APAH-HIV, and APAH-other subgroups. FPAH had been identified previously in a multivariable analysis as a risk factor because the overall risk profile for patients with FPAH suggests they should have better than average outcomes, but they do not.[11] We also reported previously that CHD was not a favorable prognostic indicator.[11] In contrast, in this analysis, estimated survival appeared better for patients with APAH-CHD than for those with IPAH, APAH-CTD, or APAH-PoPH, and it was comparable to that of patients with APAH-drugs and toxins; however, we did not conduct multivariate analyses and thus such conclusions need to be interpreted with caution.

In addition to the inherent limitations of uncontrolled, observational studies for data acquisition and interpretation, the results of this analysis of the REVEAL Registry are most likely sensitive to the definition of the initiating date for survival curves. Survival can be determined from the time of symptom onset, from the time of diagnosis (as is used in this REVEAL Registry analysis), or from the time of enrollment (as was used in our previous analysis[11]). Events that occur during the temporal lapse between symptom onset and diagnosis may affect significantly overall survival. We did not define a prognostic equation for survival in the present analysis because we had previously done so from both time of enrollment and from time of diagnosis.[11] Despite the potential for a longer-term assessment, we favor serial assessments over shorter periods of time because risk is not a static condition. Patients who died between symptom onset and initial presentation or between initial presentation and diagnostic RHC were effectively invisible to us; thus, if we had attempted to estimate survival from symptom onset, this time period would have represented "immortal time."[14] Patients who died between diagnosis and initiation of the REVEAL Registry were not eligible for inclusion in the analysis, and thus, left truncation of the data was performed.[15] However, this "immortal time" bias is an inherent limitation in all registries that attempt to define survival from a time point prior to the date of consent.

Although the REVEAL Registry protocol defines patients enrolled within 90 days of diagnostic RHC as being "newly diagnosed," it is important to note that the statistical analysis used in this study accounts for each patient's delayed entry into the cohort in days. Thus, a newly diagnosed patient who enrolled 10 days after diagnosis is considered to be at risk only from day 10 forward, and not during the first 9 days after diagnosis. In contrast, in the French registry, incident and prevalent cases were defined as follows: incident cases were patients who received a diagnosis of PAH confirmed by RHC during the recruitment phase of the study (October 2002-October 2003) and prevalent cases were patients who were diagnosed before the start of the study.[6]

All REVEAL Registry patients were enrolled at PAH specialty care centers. Thus, these results are most applicable to patients treated at these centers and may not be generalizable to patients diagnosed and treated outside of a PAH center. For example, a patient may be well managed and not require referral to a center; conversely, PAH may progress too rapidly for a patient to be referred to a center.

## Conclusions

In comparison with the US-based NIH registry, which predates therapies that are specific for patients with PAH, survival analyses from time of diagnostic RHC in the REVEAL Registry demonstrate a significant improvement in outcome in the current era. A median survival of 2.8 years for patients with primary PH was documented in the NIH registry, whereas the data from the REVEAL Registry suggest that patients with PAH with a profile similar to those in the NIH registry in the United States can expect a median survival time of $>7$ years.

Although the median survival time is beyond the time frame of the period studied in this analysis, the curve would reach 50% survival at approximately 9 years, translating to a threefold improvement in median survival compared with that determined using the NIH equation. This result is consistent with those reported for other modern registries that investigated survival in patients with PAH.[6,9,19] We hypothesize that the improvements in survival reflect changes in treatments, patient support strategies, and possibly a PAH population at variance with other cohorts.


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*Dr Benza:* contributed to the study design; collection, analysis, and interpretation of the data; drafting and critical review of the manuscript; and approval of the final version.

*Mr Miller*: contributed to the study design; collection, analysis, and interpretation of the data; drafting and critical review of the manuscript; and approval of the final version.

*Dr Barst:* contributed to the study design; collection, analysis, and interpretation of the data; drafting and critical review of the manuscript; and approval of the final version.

*Dr Badesch:* contributed to the study design; collection, analysis, and interpretation of the data; drafting and critical review of the manuscript; and approval of the final version.

*Dr Frost:* contributed to the study design; collection, analysis, and interpretation of the data; drafting and critical review of the manuscript; and approval of the final version.

*Dr McGoon:* contributed to the study design; collection, analysis, and interpretation of the data; drafting and critical review of the manuscript; and approval of the final version.

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**Additional information:** The e-Appendixes can be found in the "Supplemental Materials" area of the online article.

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