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Five-Year Outcomes of Patients Enrolled in the REVEAL Registry

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BACKGROUND: Pulmonary arterial hypertension (PAH) is a rare, severe disease characterized by worsening right-sided heart failure, decreasing functional status, and poor survival. The present study characterizes the 5-year survival in the United States of a new and previous diagnosis of PAH in patients stratified by baseline functional class (FC). The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) is a 55-center observational US registry of the demographics, disease course, and management of patients with World Health Organization (WHO) group 1 PAH.

METHODS: The REVEAL Registry enrolled newly and previously diagnosed patients aged ≥ 3 months with WHO group 1 PAH consecutively from March 2006 to December 2009. Demographics, disease characteristics, and hemodynamic data were collected at enrollment. Survival analysis was conducted by FC and other subgroups in patients aged ≥ 18 years.

RESULTS: Survival differences between previously diagnosed and newly diagnosed patients at 1 year (90.4% vs 86.3%) were maintained to 5 years; 5-year survival for previously diagnosed patients was 65.4% compared with 61.2% for newly diagnosed patients. Previously diagnosed patients in FC I, II, III, and IV had an estimated 5-year survival rate of 88.0%, 75.6%, 57.0%, and 27.2%, respectively, compared with 72.2%, 71.7%, 60.0%, and 43.8% for newly diagnosed patients in FC I, II, III, and IV, respectively.

CONCLUSIONS: Patient survival of advanced PAH remains poor at 5 years despite treatment advances. New York Heart Association FC remains one of the most important predictors of future survival. These observations reinforce the importance of continuous monitoring of FC in patients with PAH.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00370214; URL: www.clinicaltrials.gov

CHEST 2015; 148(4):1043-1054

Manuscript received February 11, 2015; revision accepted May 14, 2015; originally published Online First June 11, 2015.

ABBREVIATIONS: 6MWD = 6-min walk distance; APAH-CHD = pulmonary arterial hypertension associated with congenital heart disease including both repaired and unrepaired; FC = functional class; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; REVEAL Registry = Registry to Evaluate Early and Long-term PAH Disease Management; WHO = World Health Organization

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Part of this article has been presented at the 2014 ATS International Conference, May 16-21, 2014, San Diego, CA.

FUNDING/SUPPORT: Actelion Pharmaceuticals US, Inc, the sponsor of the REVEAL Registry, provided funding and support for the analysis presented.

Pulmonary arterial hypertension (PAH) is a rare, severe disease characterized by worsening right-sided heart failure, decreasing functional status, and poor survival.[1] Outcome evaluation by functional class (FC) is a key variable in many predictive models of PAH. Because either improvement or decline of FC over time significantly predicts patient survival,[2] attainment of FC I or II is a critical treatment goal in practice and clinical trials.[2-4]

Although the association between FC and survival is well established, limited survival estimates exist in the literature for FC subgroups. Additionally, most available data have evaluated survival to 3 years and are based on site cohort studies.[2,5,6] Previous studies examining survival data based on FC have a small sample size and do not reflect current treatment strategies.[2,5-8] To date, there has been no multicenter, long-term analysis of survival by FC from a large cohort of patients with PAH.

The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) is an observational US disease registry providing current information about demographics, disease course, and management of patients with World Health Organization (WHO) group 1 PAH. Previous REVEAL Registry subset analyses demonstrate change in patient status, such as improvement from FC III to FC I/II or worsening from FC III to FC IV predicts significantly better or worse survival, respectively, than if the patient remained at FC III.[9] The present REVEAL Registry analysis characterizes 5-year survival of newly and previously diagnosed PAH in patients stratified by baseline FC and provides survival estimates for a range of commonly examined PAH subsets, emphasizing simple, descriptive data rather than advanced modeling. These data not only inform future clinical trial design but also increase awareness of the current burden at different stages of this illness.

Materials and Methods

The REVEAL Registry design has been described previously.[10] Briefly, the multicenter, observational, prospective registry enrolled patients aged ≥ 3 months with WHO group 1 PAH at 55 centers across the United States from March 2006 through December 2009.[10] The study was conducted in accordance with the amended Declaration of Helsinki, and the protocol was reviewed by the institutional review board of each participating center, with written informed consent obtained from all patients (e-Table 1).[10] PAH was confirmed by hemodynamic parameters using the Venice 2003 definition[11] and included mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg at rest or mPAP ≥ 30 mm Hg with exercise contemporaneously with pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure < 18 mm Hg and pulmonary vascular resistance (PVR) ≥ 240 dyn/s/cm^5.

This analysis included patients aged ≥ 18 years, previously or newly diagnosed with WHO group 1 PAH (confirmed by right-sided heart catheterization > 90 days before enrollment or within 90 days, respectively), with mPAP ≥ 25 mm Hg and PCWP ≤ 15 mm Hg measured at rest (Fig 1). Patients with elevated PCWP (> 15 mm Hg) or who met entry criteria only during exercise and patients initially included in the 2003 definition of WHO group 1 PAH[11] who are now part of group 1′[12] were excluded. Patients were classified as having idiopathic PAH (IPAH), familial PAH (FPAH), PAH associated with congenital heart disease (APAH-CHD) (repaired or, if unrepaired, with or without Eisenmenger syndrome), and/or PAH associated with connective tissue disease (without significant interstitial lung disease as defined by moderate or severe fibrosis on chest imaging or total lung capacity of 60% predicted) based on the 2003 PAH classification scheme.[11]

Data were summarized by descriptive statistics. Kaplan-Meier survival estimates ± SE were calculated from the time of enrollment. Estimates were stratified by previously and newly diagnosed PAH in patients and additional variables of interest. Kaplan-Meier curve comparisons were made on the basis of the log-rank test.

Primary survival analysis by FC was conducted for all patients with nonmissing FC data at enrollment (Fig 1). FC changes were assessed in patients with a first follow-up visit within 12 months after enrollment. The overall population was assessed based on time of enrollment. Secondary survival analysis was conducted by subgroup, including previously or newly diagnosed, age, sex, race, PAH etiology, comorbidities (COPD, diabetes, BMI > 30 kg/m^2), PAH clinical characteristics at baseline (6-min walk distance [6MWD], brain natriuretic peptide level, REVEAL Registry risk score,[13,14] hemodynamics [mPAP, mean right atrial pressure (mRAP), PVR, cardiac index], and echocardiographic findings [pericardial effusion and right ventricular dysfunction]). Patients with missing FC data at enrollment were included in secondary survival analyses of other subgroups. The final February 2013 REVEAL Registry data download was analyzed.

Results

Patient Demographics and Clinical Characteristics

The primary analysis cohort included 2,039 previously diagnosed and 710 newly diagnosed patients who were not missing FC data at enrollment (Fig 1). Demographics and clinical characteristics of each cohort according to FC are presented in Tables 1 and 2.[15] Median time from diagnosis to enrollment was 32.2 (interquartile range, 14.7-58.8) months for previously

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DOI: 10.1378/chest.15-0300