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In this issue of *Advances*, section editors Oksana Shlobin, MD, and Jonathan Rich, MD, review findings from 2 recently published studies focused on outcomes and implications of the REVEAL registry.

Farber HW, Miller DP, Poms AD, et al. Five-year Outcomes of Patients Enrolled in the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension (PAH) Disease Management (REVEAL). *Chest*. 2015 Jun 11. [Epub ahead of print]

Benza RL, Miller DP, Foreman AJ, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease (REVEAL) analysis. *J Heart Lung Transplant*. 2015;34(3):356-361.

With advances in pulmonary hypertension (PH)-specific therapy, the prognosis of pulmonary arterial hypertension (PAH) patients has improved significantly. The National Institutes of Health (NIH) database provided the majority of the data on natural disease progression. The REVEAL database was the second prospective longitudinal observational registry of 55 US sites that compiled data on both incidental and prevalent PAH patients, and provided important information on disease progression, prognostic factors, and survival in the new era of PAH therapy. In 2015, 2 articles analyzing the REVEAL database were published: one on 5-year outcomes of patients enrolled in the database and another on prognostic implications of serial risk score assessment.

The REVEAL registry enrolled hemodynamically diagnosed PAH Group 1 patients consecutively from March 2006 to December 2009. Demographics, disease characteristics, hemodynamic data, and management practices data were collected. Prior REVEAL analysis demonstrated that a change in functional class (FC) correlated with survival. For example, worsening from FC III to FC IV predicts worsened survival, and improvement from FC III to FC I/II correlated with improved outcomes. The most recent paper analyzed 5-year survival of both incident and prevalent patients with idiopathic, familial, congenital heart disease, and connective tissue disease–associated PAH, stratified by baseline FC status. Primary survival analysis was conducted for the entire patient cohort (2039 prevalent and 710 incident patients) and the secondary analysis for subgroups (incident vs prevalent patients, age, gender, race, etiology, comorbidities, and baseline clinical characteristics).

The study described the survival rates for the overall patient cohort (with 1-, 3-, and 5-year survival of 90.4%, 76.2%, and 65.4% for prevalent patients vs 86.3%, 69.3%, and 61.2% for 1, 3, and 5 years for incident patients). The poorest outcomes were observed in FC III and IV patients, with incident patients doing better (5-year survival rates of 60.0% and 43.8% vs 57.0% and 27.2% for prevalent patients, respectively). To compare, the NIH database 5-year survival rate was 34% in largely untreated patients, indicating that despite therapy, prevalent patients presenting with FC IV symptoms continue to have a very poor prognosis and probably have a phenotype of the disease less responsive to therapy. In contrast, newly diagnosed FC IV patients represent a mostly treatment-naïve population with greater opportunity for improvement with PAH-specific therapy. Interestingly, FC I and II survival rates were numerically lower in the incident patient cohort (72.0% vs 77.7% in the pooled FC I and II group). This finding is probably due to a better risk profile of prevalent patients in lower FC groups and survivor bias inherent to analysis of pooled incident and prevalent populations. A significant number (30%) of incident FC III patients improved to FC I/II, likely due to administration of PAH-specific therapy within 3 months of diagnosis. This suggests that treatment should be initiated as early as possible in the treatment-naïve patients, as they appear to be at greatest risk of disease progression and probably have the greatest opportunity to experience functional improvement.

When analyzed by etiology, FC at presentation was also strongly associated with 5-year survival in specific etiological subgroups in both incident and prevalent populations, with former subgroups doing better across the subgroups. The study also examined the effect of changes in FC in a subgroup of 1866 prevalent and 614 incident patients within 12 months of enrollment, confirming the results of the previously published data that improvement in FC has a positive impact on outcomes. Another subgroup analysis examined the patients with missing follow-up FC data to determine the effect of other factors on survival and found that white patients has a relatively worse survival, and pulmonary vascular resistance $\leq$5 Wood units and body mass index $>$30 provided protective benefit. The authors concluded that single point-in-time FC measurement at enrollment remains an important predictor of outcomes in PAH patients.

To better predict patients' 1-year survival, the data from REVEAL was used to develop prognostic equation and a simplified risk score calculator and then validated in several studies. The risk score calculator uses 19 clinical variables, widely available in clinical practices, thus making it a useful and simple clinical tool. The authors used the data from the

REVEAL database to assess the prognostic implications of changes in the risk score (increased by at least 1 [or prognosis worsened], unchanged, or decreased by at least 1 [or prognosis improved]), including the contributions of the modifiable variables (such as hemodynamic and vital signs parameters, renal function, 6-minute walk distance [6MWD], brain natriuretic peptide [BNP] level, pericardial effusion status, diffusion lung capacity for carbon monoxide, age, and New York Heart Association [NYHA] FC) during a 12-month period in 2529 patients.

Sixty-seven percent of incident patients started a new PAH therapy, with 35% of patients receiving combination treatment and 25% a prostanoid during the first year. In prevalent patients, new medication was started in 36% of patients, with 54% receiving combination therapy and 34% prostanoids. Numerically, more incident patients had therapy escalation in comparison to their baseline therapy.

At 12 months' assessment when the risk score was recalculated, 38% had no change, 32% had a decrease, and 30% an increase in the score. The incident or newly diagnosed patients were more likely to improve (or have decreased scores [44%]), in comparison to prevalent patients (28%). Six individual variables improved and/or worsened sufficiently to results in score change: NYHA FC, systolic blood pressure, heart rate, 6MWD, BNP, and presence of pericardial effusion. When patients were stratified by change in risk score, the 1-year survival was 93.7% in patients whose score improved, 90.3% in patients whose score was unchanged, and 84.6% in patients whose score worsened. The findings were similar in both prevalent and incident groups.

The authors examined the effect of risk score at baseline, its change, and the risk score at 12 months' reassessment as predictors of subsequent 1-year survival in 2 different multivariable Cox models. One analysis demonstrated that the change in risk score significantly predicted subsequent survival (hazard ratio [HR] of 1.67 [95% confidence interval (CI) 1.41–1.99] for worsened score and HR of 0.57 [95% CI 0.47–0.69] for improved score), and another showed that both the enrollment and follow-up risk scores predicted survival with the latter being a stronger predictor of survival (HR 1.40 [95% CI 1.33–1.47] vs HR 1.10 [95% CI 1.04–1.15]), thus underscoring the importance of ongoing risk assessment and aggressive therapy to change modifiable factors. The authors concluded that in addition to clinical assessment, the REVEAL risk score calculator can be used as a prognostic tool serially and help individualize therapy in patients to meet their specific treatment needs.