The study of rare diseases is limited by just that, their infrequency. Pulmonary arterial hypertension (PAH), for example, has a prevalence of 15 cases per million.1 Although there has been an explosion in knowledge of and therapies for this life-threatening disease over the past decade, most of our insight is based on small studies. The first therapy that was approved by the Food and Drug Administration in 1995, intravenous epoprostenol, was based on the results of an 81-patient trial.2 The most recently approved therapy, inhaled treprostinil, in 2009, was based on the results of a 235-patient trial.3 Similarly, our understanding of the natural history of this disease is based on small observational series.

To further our comprehension of rare diseases, we often turn to “registries,” constructed as multicenter cohorts of patients who have the disease with longitudinal follow-up. Despite the inherent limitations of their observational and uncontrolled nature, which also represent strengths, these cohorts are useful to describe and compare patient characteristics, practice patterns, and outcomes. Observations from such registries can generate hypotheses that subsequently form the basis of further studies. Lastly, such cohorts facilitate the study of the prognostic profile of the disease via the derivation and validation of clinical prediction tools.

In this issue of Circulation, data from the 2 of the most important present-day registries in PAH give us the opportunity to better understand the prognosis of PAH, its determinants, and outcomes in the current treatment era. Humbert and colleagues4 share data from the French National Registry, in which 354 consecutive idiopathic, heritable, and anorexigen-associated patients with PAH were enrolled from October 2002 to October 2003. They report 1-, 2-, and 3-year survival rates of 82.9%, 67.1%, and 58.2%, respectively. Sadly, despite the many advances in therapy that we have seen since the National Institutes of Health Registry, this study suggests that current-day survival has improved just modestly. Univariate analyses suggested that the factors associated with a better prognosis were female sex, functional class I or II symptoms, greater 6-minute walk distance, lower right atrial pressure, and higher cardiac output. The multivariate analysis reduced this list to 3 independent factors, namely, sex, 6-minute walk distance, and cardiac output at diagnosis, thus generating a simple and novel risk-prediction equation.5

Outcomes from the REVEAL Registry (the Registry to Evaluate Early and Long-Term PAH Disease Management), a 54-center collaborative US effort, are also reported by Benza and coworkers6 in this issue of Circulation. In this analysis of 2716 patients with PAH, 1-year survival was 91% from the date of enrollment, whereas the 1- and 3-year survival rates from the time of PAH diagnosis were 87.7% and 72.1%, respectively. As was found in the French Registry, sex, functional class, and 6-minute walk distance were predictive of outcome. Additional prognostic variables included origin of PAH, age, pulmonary vascular resistance, right atrial pressure, renal insufficiency, resting systolic blood pressure and heart rate, brain natriuretic peptide, presence of a peri-cardial effusion, and diffusion capacity of the lung for carbon monoxide. A prognostic equation using all of these factors was generated that allowed the patient to be placed in a “risk stratum” predictive of 1-year survival. This equation, based on measurements taken at the time of enrollment and not necessarily initial diagnosis, is intended to be used with data available at any point in time in the disease course.

There are remarkable similarities in the French and REVEAL studies. First, despite the subjectivity and interobserver and intraobserver variabilities, the prognostic ability of a simple assessment such as functional class remains powerful. As shown in many previous publications and as demonstrated in both of the present observations, patients with functional class I or II symptoms enjoy a better prognosis than those with more advanced symptoms. Similarly, despite the often criticized limitations of an exercise assessment as crude as the 6-minute walk distance, the important prognostic implications of this measure are also confirmed in both of these studies. Although assessed somewhat differently, both registries also acknowledge the importance of hemodynamic parameters that reflect right ventricular function, namely, right atrial pressure and cardiac output.

Despite these similarities, the approaches taken by the authors differed on some fronts. To achieve a homogeneous population, the French study limited the present analysis to idiopathic, heritable, and anorexigen-associated PAH, whereas the vision of the REVEAL study was to develop an equation that was applicable to all types of PAH. Of clinical significance, one of the important differences between the 2 studies involved the timing of the prognostic factors. Whereas the French study based its analysis of prognosis strictly on...
factors measured at the time of initial diagnosis, the REVEAL study used prognostic factors measured at the point in time in the disease course defined by the date of enrollment into the registry. As a result, the trajectory of the disease course is not taken into consideration in the REVEAL equation. The REVEAL study used the time from diagnosis to enrollment as one of the predictors of mortality and found that it was not independently associated with survival. Although this result is certainly pertinent, another useful analysis would be to assess the interaction between this time delay from diagnosis to enrollment and the predictors. Such an analysis would address the pragmatic question of whether the prediction equation, or some of its prognostic components, changes as the patient advances in the disease course. Additionally, the REVEAL study considered a 1-year mortality horizon for its prognostic tool, whereas the French study was based on a longer 3-year term.

A major methodological issue in these studies lies in the approach used to deal with the patients who were enrolled well into their disease (prevalent subjects) in contrast to those who entered the study at the time of initial diagnosis (incident subjects). This may have led to an underestimation of mortality by both studies. The use of prevalent subjects in a cohort study will generally not matter if the mortality rate is constant over time, but this does not appear to be the case for PAH. Indeed, the recently presented incident cohort of 398 newly diagnosed patients with PAH used for validation of the REVEAL prognostic equation suggests that there is an early high rate of death, with >10% of patients in the high-risk and very-high-risk score strata dying in the first 2 months after diagnosis. The French cohort also found this early mortality pattern in the patients in New York Heart Association class IV, although the number of such patients was limited. Thus, estimation of the survival function starting with the time of enrollment will produce a distorted picture by the inclusion of prevalent patients who in fact represent the “survivors” of this early risk period. In the REVEAL cohort of 2716 patients, 86.5% were enrolled >3 years on average after their initial diagnosis. As a result, the survival function for this mixed population, dominated by the prevalent “survivors,” found very low mortality in the first 2 months. The French study, which included 56 incident patients and 134 prevalent patients, was careful to estimate the survival function starting with the time of initial diagnosis, with the prevalent patients contributing to this estimation only at the enrollment point in the disease course. This difference in approach may explain in part the lower 83% 1-year survival from PAH diagnosis in the French study compared with 91% for the REVEAL study from enrollment. However, the REVEAL study also used the same approach as the French study as a sensitivity analysis. It therefore appears puzzling that with the same statistical technique, the 3-year survival from PAH diagnosis is so much lower at 58% in the French study compared with 72% in the REVEAL study. Although this statistical approach is valid, it does assume that the left truncation in the prevalent patients is random; this assumption, however, is highly improbable, because the patients who were most likely to have been excluded by this left truncation were those who had more severe disease and those who died early after initial diagnosis. As a result, the reported survival rates from both studies are likely somewhat optimistic. With a disease like PAH, registries will need to develop mechanisms that ensure the identification and inclusion of all such severe case subjects who die early after diagnosis. Only then will we be in a better position to compare the survival profile of patients with PAH and to assess whether newer treatments lead to improvements in outcomes.

Another methodological issue raised by these studies involves the definition used to classify patients as “incident.” In the French study, incident cases were defined as patients who received a diagnosis of PAH during the 1-year recruitment phase of the study, whereas the REVEAL registry defined incident subjects as patients newly diagnosed within the 90 days prior to enrollment. This latter definition can introduce “immortal time,” which refers to a time period during which no deaths could have occurred. In this case, the time between the initial diagnosis of PAH and the date of enrollment during this 90-day span could be immortal. In the presence of such immortal time, the analysis of survival from the diagnosis until death will inherently include a period of “guaranteed” survival, which can lead to immortal time bias when survival comparisons are made. It is particularly noteworthy that both studies were alert to this problem by properly analyzing survival at the appropriate time points. Other studies, by following this example of careful survival analysis, will avoid this unfortunate frequent mistake in observational studies, particularly those that assess drug effectiveness.

Several conclusions are drawn from these data, and many more questions remain. Despite the advances recently made in medical therapy for PAH, the mortality remains unacceptably high. We must continue the quest to find effective approaches to therapy for this devastating disease. Earlier recognition, more aggressive treatment strategies, and the continued development of novel therapies all have the potential to improve outcomes. Furthermore, both studies demonstrate that simple measures of functional class, 6-minute walk distance, and hemodynamic parameters that reflect right ventricular function are important determinants of outcome. However, the potential implications of these findings in clinical practice have yet to be delineated. Exactly how do we interpret a calculated predicted survival for a patient as we are discussing their individual case? How do we change therapy on the basis of these data? How might the predicted survival change as the patient does or does not respond to therapy? Given the high mortality noted in the initial months after diagnosis in both studies, should we employ a more aggressive approach to therapy early? How might this information be used to determine the most appropriate approach to lung transplantation listing?

One hypothesis generated from these registries is the notion of a “treat to target” or “goal-oriented” approach to therapy. Both registries have defined variables that are associated with a better or worse prognosis. Some of these variables (for example, functional class, 6-minute walk distance, and hemodynamics) might be improved with therapy. Indeed, previous observations with epoprostenol demonstrated that patients who improved to functional class I or II
and achieved a 6-minute walk distance >380 m experienced a much better survival rate than those who did not.\textsuperscript{9,10} Optimization of treatment and achievement of specific targets or goals might improve longer-term outcomes in PAH. On the basis of previous observations, and now more solid data from these 2 registries, reasonable goals of therapy would include achievement of functional class I or II status, good 6-minute walk hall (>380 to 440 m, considering underlying patient characteristics), normal right atrial pressure, and normal cardiac output. A normal brain natriuretic peptide level may also be considered a reasonable treatment goal. To achieve such goals, patients with PAH must be monitored closely, and response to therapy should be reassessed regularly, as advocated in recent guidelines and consensus statements.\textsuperscript{11,12} Consideration should be given to a change in or escalation of therapy should the patient not meet these treatment goals. This may include the use of targeted therapy with some combination of endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclins. Although the use of combination therapy is frequent in clinical practice, many patients are not given prostacyclins, one of the most effective therapies in PAH. Previous data from the REVEAL registry demonstrated that fewer than 50% of patients with functional class III symptoms and fewer than 60% of patients with functional class IV symptoms were undergoing prostacyclin therapy.\textsuperscript{13} Despite the complicated nature of prostacyclin delivery, perhaps more aggressive treatment of these patients will improve outcomes. Additionally, it is clear that our outcomes are far from optimal. This observation is the impetus to continue the development of novel therapies for PAH.

Both the French and REVEAL investigators are to be congratulated on their valuable contributions to our understanding of PAH. Although exciting, enthusiasm for the clinical prediction rules generated by registries must be tempered until further analysis and investigation have been completed. Such tools need to undergo both narrow and broad validation to determine their accuracy. Lastly, an impact analysis is required. This provides evidence that the tool changes physician behavior and improves patient outcomes and/or reduces costs.

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References


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