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Pulmonary Arterial Hypertension

Epidemiology and Registries

Michael D. McGoon, MD,* Raymond L. Benza, MD,† Pilar Escribano-Subias, MD,‡ Xin Jiang, MD,§ Dave P. Miller, MS,‖ Andrew J. Peacock, MD,¶ Joanna Pepke-Zaba, MD,# Tomas Pulido, MD,** Stuart Rich, MD,†† Stephan Rosenkranz, MD,‡‡ Samy Suissa, PHD,§§ Marc Humbert, MD, PHD‖‖

Rochester, Minnesota; Pittsburgh, Pennsylvania; Madrid, Spain; Beijing, China; San Francisco, California; Glasgow and Cambridge, United Kingdom; Mexico City, Mexico; Chicago, Illinois; Cologne, Germany; Montreal, Quebec, Canada; and Le Kremlin Bicêtre, France

Registries of patients with pulmonary arterial hypertension (PAH) have been instrumental in characterizing the presentation and natural history of the disease and provide a basis for prognostication. Since the initial accumulation of data conducted in the 1980s, subsequent registry databases have yielded information about the demographic factors, treatment, and survival of patients and have permitted comparisons between populations in different eras and environments. Inclusion of patients with all subtypes of PAH has also allowed comparisons of these subpopulations. We describe herein the basic methodology by which PAH registries have been conducted, review key insights provided by registries, summarize issues related to interpretation and comparison of the results, and discuss the utility of data to predict survival outcomes. Potential sources of bias, particularly related to the inclusion of incident and/or prevalent patients and missing data, are addressed. A fundamental observation of current registries is that survival in the modern treatment era has improved compared with that observed previously and that outcomes among PAH subpopulations vary substantially. Continuing systematic clinical surveillance of PAH will be important as treatment evolves and as understanding of mechanisms advance. Considerations for future directions of registry studies include enrollment of a broader population of patients with pulmonary hypertension of all clinical types and severity and continued globalization and collaboration of registry databases. (J Am Coll Cardiol 2013;62:D51–9) © 2013 by the American College of Cardiology Foundation

Registries provide information about defined cohorts of patients who are intended to represent the population with similar disease characteristics. Description of patients with pulmonary hypertension (PH), or a subset of PH, and the impact of the disease (outcome) is the primary goal of clinical observational PH registries. Constellations of circumstances (risks) may be elucidated that are associated with various probabilities of outcome. Registries provide the

From the *Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; †Division of Cardiovascular Diseases, Allegheny General Hospital, Pittsburgh, Pennsylvania; ‡Cardiology Department and Spanish Cardiovascular Research Network, Hospital Universitario, Madrid, Spain; §Thrombosis Medicine Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Peking Union Medical College and Chinese Academy Medical Science, Beijing, China; ‖ICON Clinical Research, Medical Affairs Statistical Analysis, San Francisco, California; ¶Scottish Pulmonary Vascular Unit, Regional Heart and Lung Center, Glasgow, United Kingdom; #Pulmonary Vascular Diseases Unit, Papworth Hospital, Cambridge, United Kingdom; **Cardiopulmonary Department, National Heart Institute, Mexico City, Mexico; ††Section of Cardiology, University of Chicago, Chicago, Illinois; ‡‡Clinic III for Internal Medicine, Department of Cardiology, Heart Center at the University of Cologne, Cologne, Germany; §§Centre for Clinical Epidemiology, Jewish General Hospital, Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada; and the ‖‖Universite Paris-Sud, Inserm U999, LabEx LERMIT, AP-HP, DHU Thorax Innovation, Service de Pneumologie, Hôpital Bicêtre, Le Kremlin Bicêtre, France. Dr. McGoon has received institutional grants for studies in which he was the primary investigator from and Medtronic and Gilead; participated in speaking activities for Actelion, Gilead (funded conferences, not speakers' bureaus); was a consultant for Actelion; was the chair of the REVEAL Registry and on the data adjudication committees; on the Data Safety Monitoring Board of Gilead and GlaxoSmithKline; and is on the Advisory Committee of Lung LLC. Dr. Benza has contracted research for Acetlion, Bayer, Gilead, GeNO, Ikaria, and United Therapeutics; and is a consultant for Bayer and United Therapeutics. Dr. Escribano-Subias reports that the Spanish registry of PH is sponsored by a Bayer Schering Pharma educational grant; has received honoraria for sitting on advisory boards and taking at sponsored symposia from Actelion, GlaxoSmithKline, United Therapeutics, Pfizer, Bayer and Ferrer; and has received institutional grants for performing RCTs by the same companies. D. P. Miller is an employee of Icon Clinical Research, which receives research funding from pharmaceutical and biotechnology companies. Dr. Peacock has received honoraria for speaking at meetings (non-promotional) from Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics; travel assistance to conferences from Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics; research grants (educational only) from Actelion and Bayer; and has served on the advisory boards of Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, and Pfizer. Dr. Pepke-Zaba has received reimbursement of travel expenses to congresses and speakers' fees from Actelion, Pfizer, GlaxoSmithKline, Bayer; has served on the advisory boards of Actelion, Bayer, and GlaxoSmithKline; and has received funds for research and education from Actelion, Pfizer, GlaxoSmithKline, and Bayer. Dr. Pulido has received honoraria for serving as a consultant for Actelion, Bayer, and Pfizer; has received research grants (institutional) from Actelion, Bayer, Gilead, Lilly, Pfizer, and United Therapeutics; has received honoraria for serving on the advisory boards of Actelion and Bayer; and has received lecture fees from Actelion, Bayer, and Pfizer. Dr. Rosenkrantz has received speaker fees and/or renumerations for consulting from Acetelion, Bayer, GlaxoSmithKline, Lilly, Novartis, Pfizer, and United Therapeutics; and research grants from Actelion, Bayer, Novartis, Pfizer, and United Therapeutics. Dr. Suissa has participated in advisory meetings or as a conference speaker for Actelion, AstraZeneca,

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Abbreviations and Acronyms

6MWD = 6-min walk distance

CRF = case report form

CTEPH = chronic thromboembolic pulmonary hypertension

NIH = National Institutes of Health

PAH = pulmonary arterial hypertension

PH = pulmonary hypertension

PPH = primary pulmonary hypertension

foundation of knowledge upon which other important clinical research, such as clinical drug studies, may be constructed.

Methods of Registries

Definitions. The Agency for Healthcare Research and Quality in the United States defines a patient registry as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes" (1). The European Medicines Agency defines a registry as "a list of patients presenting with the same characteristic(s). This characteristic may be a disease or an outcome (disease registry) or a specific exposure (exposure or drug registry)" (2).

The European Medicines Agency defines cohort studies as involving "a population-at-risk for an event of interest followed over time for the occurrence of that event" while allowing that a registry may, itself, represent a cohort (2). The Agency for Healthcare Research and Quality defines cohort studies as a specific category of registry distinct from case-control studies. The term cohort may also be used to define a subpopulation of interest within a registry. For instance, if a registry enrolls both incident and prevalent patients, analyses may be conducted on one or both of these cohorts depending on the objective.

The term *prevalent* may be applied to patients who have previously received a diagnosis and who may enter a study when returning for follow-up visits or follow-up treatments. The term *incident* is generally used to indicate patients who have just received a diagnosis as opposed to those patients who have just experienced onset of symptoms. These patients are considered incident on the day of diagnosis and prevalent the day after.

None of the guidelines propose limiting inclusion criteria in registries to incident patients, although neither of them explicitly suggest that such a restriction would be ill-advised. The guidelines do address 3 important issues that should lead to a study-specific decision about inclusion/exclusion criteria: 1) generalizability and carefully defined target populations; 2) the need for clear objectives to define the structure and process of data collection; and 3) as noted in the GRACE (Good Research for Comparative Effectiveness) principles (3), identification of the most likely sources of bias.

Survival, bias, and missing data. Survival is one of the most common outcomes in registries. The survival curve's time frame must be clear. Survival from time of enrollment in a prevalent cohort can lead to biased results if generalized to newly diagnosed patients. Conversely, survival from diagnosis can lead to biased estimates if those results are generalized to a cohort of prevalent patients at a typical clinic. Additionally, survival estimates from one incident cohort may not be generalizable to another incident cohort if diagnosis methods or time from symptom onset to diagnosis differ between cohorts.

It is never appropriate to define an at-risk period that includes the time during which patients were not in the study. Doing so leads to immortal time bias (4) because patients are guaranteed to have survived the pre-study period. An important difference between immortal time bias and survivor bias is that there does not exist any appropriate population to whom analyses with immortal time bias may be correctly generalized. On the other hand, survivor bias, a form of selection bias, does not prevent accurate generalization so long as the results are not incautiously generalized to incident patients.

Due to the lack of randomization, confounding, rather than selection bias, is often the Achilles heel of registries, whereas generalizability to a broad cohort is often one of the greatest strengths. As a result, the guidelines do not suggest specific rules for inclusion/exclusion criteria, instead suggesting that the target population, the study objectives, and avoidance of bias should guide study design decisions.

Missing data are a common methodological problem in registries because specific clinical tests are generally not mandated. Casewise deletion of patients with missing data can lead to selection bias. If most patients in real practice do not have complete batteries of testing at regular intervals, the results of analyses using casewise deletion cannot be generalized to them. Alternative approaches include multiple imputation (5) or treating missingness as a distinct category. When outcomes data, rather than risk factor data, are missing, casewise deletion could lead to even greater biases, but imputation of outcomes is generally not desirable. Patients who are lost to follow-up should be censored at the point in time that they are lost. Care should be taken to define the time of last follow-up to ensure that it includes the time period in which an event would have been reported and excludes the time period in which an event would not have been reported.

Current pulmonary arterial hypertension registries. Pulmonary arterial hypertension (PAH) (group 1 PH) registries have used different inclusion and exclusion criteria with respect to the enrollment of newly and previously diagnosed patients. Lee et al. (6) argue in favor of restricting survival analyses to incident patients, as in the United Kingdom and

Bayer, Boehringer- Ingelheim, GlaxoSmithKline, Merck, Novartis, and Pfizer. Dr. Humbert has been a consultant for and a member of the advisory board of Actelion, Aires, Bayer, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics as well as being an investigator in trials involving these companies. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Ireland registry, whereas Miller et al. (7) argue that risk stratification or a delayed entry model accounting for left truncation is preferable to excluding prevalent patients from PAH registries. A population is said to be left truncated if patients may have been excluded from a cohort due to events that occurred before the study. Patients who die before study initiation are excluded, whereas patients who survive to study initiation are included from the point in their survival at which they were enrolled. An approach to analyzing survival from diagnosis, using both newly diagnosed and previously diagnosed patients, was used in the U.S. REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) protocol, as well as in the French Registry (8–10). Survival from time of diagnosis, using data from both incident and prevalent patients, was estimated both by Humbert et al. (9) and Benza et al. (10) and are comparable to survival estimates that are restricted to incident patients (11). Of note, inclusion of patients with nonconforming high wedge pressures (pulmonary artery pulmonary wedge pressure ranging from 16 to 18 mm Hg) has been controversial; however, these patients may be excluded or included in individual analyses and differences may be evaluated (12).

Analysis: what can be done with the data and what is not possible? Although literature on design and conduct of registries is not as extensive as the literature on clinical trials, observational researchers must begin by reviewing recent guidelines (3,13,14). Registry data are useful for describing practice patterns, characterizing populations, assessing burden of illness, and developing risk stratification tools. The use of registry data for comparative effectiveness is probably the most controversial study aim (15,16). Because aggressive treatments will generally be reserved for the sickest patients, the worst outcomes will occur frequently among these patients, thereby confounding assessment of efficacy. A variety of methods exist to adjust for confounding. Matching, multivariable risk-adjusted models of outcomes and propensity scores can be effective if all confounding variables have been identified and measured. In PAH, it is plausible that most, but not all, important potential confounders have been successfully identified due to the extensive research that has been published in the past decade on risk factors. Nonetheless, it is unlikely that all important confounders have been measured at the time of treatment selection. Variable time lags between treatment decision and treatment initiation can also increase the potential for immortal time bias to enter into a comparative effectiveness analysis.

Funding. A number of factors can make observational studies less expensive than randomized trials. Patients can generally be recruited faster due to broad inclusion criteria and few barriers to participation. There are usually no mandated treatments or tests. A risk-based site monitoring approach reduces the need for full source document verification. Some aspects of registries can also make them more expensive. These include long-term follow-up and analysis requirements associated with having multiple study objectives. Major costs include funding for site coordinators, project management, in-person meetings, data management, and statistical analysis. When studies receive industry sponsorship, the relationship of the sponsor and advisors must be clearly delineated, and it is similarly important for data ownership and data access rules to be specified contractually. Disclosing conflict of interest is critical, but there are many important scientific objectives with which the interests of industry, patients, and the scientific community are fully aligned.

Characteristics of Major Registries

Baseline. The characteristics of 11 major registries are shown in Table 1 (17–39). Six countries are represented. All registries enrolled patients with idiopathic and heritable PAH, 7 included PAH, and 1 also included chronic thromboembolic pulmonary hypertension (CTEPH) (PH Group 4). The number of patients in each registry ranged from 72 to 3,515, and the number of participating centers ranged from 1 to 55. Table 2 provides the basic presenting characteristics of patients enrolled in each registry.

Outcome. Table 3 shows survival over the duration of reported follow-up. In general, survival improved as treatment options increased. Data from the U.S. REVEAL suggests that current median survival is 7 years for patients with PAH (10) compared with 2.8 years for patients with primary pulmonary hypertension (PPH, now referred to as idiopathic/heritable PAH) in the U.S. National Institutes of Health (NIH) Registry (17).

The Changing Phenotype of PAH in the Modern Management Era

Registries have provided important information about the epidemiology and phenotype of patients with PAH. Of note, considerable changes in the PAH phenotype have been observed over the past decades. These include substantial changes in age, sex, comorbidities, and survival (Tables 2 and 4) (6,9,19,27,34,37,40). Although the mean age of patients with idiopathic PAH in the first registry created in 1981 (U.S. NIH Registry) was 36 ± 15 years (18), PAH is now more frequently diagnosed in elderly patients, resulting in a mean age at diagnosis between 50 ± 14 and 65 ± 15 years in current registries (Table 2). Furthermore, the female predominance is quite variable among registries and may not be present in elderly patients (39), and survival appears to have improved over time (Table 3). To know whether these differences reflect a change in the disease itself, one must determine all of the biases that affect PH registries and how they differ between registries before any conclusion can be made that the phenotype of PAH is actually changing (41). When looking at any registry, differences need to be identified between the target population, the accessible population, the intended population, and the population actually studied. How representative the

Table 1 General Information of PAH Registries From Different Countries and Time Periods

Registry (Ref. #)	Study Cohort	Study Design and Time Period	No. of Centers	No. of Patients	Incidence/Prevalence	Predominant Etiologies of PAH
U.S. NIH (17,18)	IPAH	Prospective, 1981–1985	32	187	NA	NA
U.S. PHC (19)	Group 1 PH, age >18 yrs	Retrospective, 1982–2004; prospective, 2004–2006	3	578	NA	IPAH, 48%; CTD-PAH, 30%; CHD-PAH, 11%
Scottish-SMR (20)	Group 1 PH (IPAH, CHD-PAH, and CTD-PAH), age 16–65 yrs	Retrospective, 1986–2001	NA	374	PAH, 7.6/26 cases/MAI; IPAH, 2.6/9 cases/MAI	IPAH, 47%; CTD-PAH, 30%; CHD-PAH, 23%
French (9,21,22)	Group 1 PH, age >18 yrs	Prospective, 2002–2003	17	674	PAH, 2.4/15 cases/MAI; IPAH, 1.0/5.9 cases/MAI	IPAH, 39%; CTD-PAH, 15% (SSc, 76%); CHD-PAH, 11%
Chinese (23)	IPAH and HPAH	Prospective, 1999–2004	1	72	NA	NA
U.S. REVEAL (8,24–33)	Group 1 PH	Prospective, 2006–2009	55	3,515 (age >3 months)	PAH, 2.0/10.6 cases/MAI IPAH, 0.9 cases/MAI	IPAH, 46%; CTD-PAH, 25% (SSc, 62%); CHD-PAH, 10%
Spanish (34)	Group 1 PH and CTEPH, age >14 yrs	Retrospective, 1998–2006; prospective, 2007–2008	31	PAH, 866; CTEPH, 162	PAH, 3.2/16 cases/MAI; IPAH, 1.2/4.6 cases/MAI	IPAH, 30%; CTD-PAH, 15% (SSc 61%); CHD-PAH, 16%
UK (6,35)	IPAH, HPAH, and anorexigen-associated PAH	Prospective, 2001–2009	8	482	1.1/6.6 cases/MI	NA
New Chinese Registry (36,37)	Group 1 PH, age >18 yrs	Prospective, 2008–2011	9	956	NA	CHD-PAH, 43%; IPAH, 35%; CTD-PAH, 19% (SLE, 51%; SSc, 9%)
Mayo (38)	Group 1 PH	Prospective, 1995–2004	1	484	NA	IPAH, HPAH 56%; CTD-PAH, 24%, other, 20%
Compera (39)	IPAH, age >18 yrs	Prospective, 2007–2011	28	587	NA	IPAH, 100%

CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; MAI = million adult inhabitants; MI = million inhabitants; NA = not available; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PHC = pulmonary hypertension connection; SMR = Scottish morbidity record; SSc = systemic sclerosis.

Table 2 Demographic, Clinical, and Hemodynamic Characteristics of PAH Registries From Different Countries and Time Periods

Registry (Ref. #)	Age, yrs		Female, %		WHO III/IV, %		6MWD, m		RAP, mm Hg		mPAP, mm Hg		PVRI, U·m^2	
	PAH	IPAH	PAH	IPAH	PAH	IPAH	PAH	IPAH	PAH	IPAH	PAH	IPAH	PAH	IPAH
U.S. NIH (17,18)	NA	36 ± 15	NA	63	NA	75	NA	NA	NA	10 ± 6	NA	60 ± 18	NA	26 ± 14
U.S. PHC (19)	48 ± 14	45 ± 14	77	75	80	80	NA	NA	11 ± 7	11 ± 7	52 ± 14	56 ± 13	NA	NA
Scottish-SMR (20)	52 ± 12	49 ± 11	70	62	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
French (9,21,22)	50 ± 15	52 ± 15	65	62	75	81	329 ± 109	328 ± 112	8 ± 5	9 ± 5	55 ± 15	56 ± 14	21 ± 10	23 ± 10
Chinese (23)	NA	36 ± 12	NA	71	NA	61	NA	NA	NA	13 ± 6	NA	69 ± 19	NA	NA
U.S. REVEAL (8,24–33)	50 ± 14	50 ± 15	80	83	56	55	366 ± 126	374 ± 129	9 ± 6	10 ± 6	51 ± 14	52 ± 13	21 ± 13	23 ± 11
Spanish (34)	45 ± 17	46 ± 18	71	73	69	70	363 ± 120	382 ± 117	9 ± 5	8 ± 5	54 ± 16	55 ± 15	NA	NA
UK (6,35)	NA	50 ± 17	NA	70	NA	84	NA	292 ± 123	NA	10 ± 6	NA	54 ± 14	NA	23 ± 10
New Chinese registry (36,37)	36 ± 13	38 ± 13	70	70	54	66	378 ± 125	353 ± 127	8 ± 5	8 ± 6	63 ± 20	63 ± 15	25 ± 14	27 ± 12
Mayo (38)	52 ± 15	52 ± 15	75	76	55	56	329 ± 125	344 ± 125	13 ± 6	13 ± 6	53 ± 13	55 ± 12	NA	NA
Compera (39)	NA	65 ± 15	NA	60	NA	91	NA	293 ± 126	NA	8 ± 5	NA	44 ± 12	NA	NA

Values are frequency (female, WHO functional class) and mean ± SD (age, 6WMD, and hemodynamic variables).
6MWD = 6-min walking distance; mPAP = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; RAP = mean right atrial pressure; SMR = Scottish morbidity record; WHO = World Health Organization; other abbreviations as in Table 1.

actual population is of the target population will determine how generalizable the registry is.

A potential explanation for the change of phenotype may be the increased awareness for PAH in the modern management era, as effective therapies are now available. Because PPH was considered a rare disease that affected young women at the time of the initial U.S.-NIH registry, it is likely that older patients and men were often not considered for the diagnosis at that time. Other factors contributing to biased enrollment include lack of awareness of this registry among nonexperts in the community and unavailability of widespread screening tools such as Doppler echocardiography. Nowadays, PAH may indeed be detected more frequently in elderly patients, as the population of most Western countries is aging. However, one should also be cautious about possible misclassifications between PAH and non-PAH PH (particularly post-capillary PH due to heart failure with preserved ejection fraction [HFpEF]), which may occur, particularly in elderly patients as a consequence of uncertainties in the current definitions and difficulties in the measurement of the pulmonary arterial wedge pressure.

Registries from China and other developing countries demonstrate demographics and characteristics similar to the early studies of the U.S. NIH Registry (23), suggesting that some differences in phenotype are related to the healthcare environment rather than to different expressions of the disease. Nonetheless, specific sources of systematic bias in PAH registries include the following: 1) changes in the classification of PH that have led to the inclusion of a varying spectrum of patients in modern registries; 2) changing interest in PH by academic physicians producing more development and dissemination of information; 3) increased awareness of PH by clinicians due to availability and marketing of effective therapy, with associated education from pharmaceutical representatives (42); 4) easier access to medical information by patients who may then influence their referral to specialized care; and 5) widespread use of noninvasive techniques (Doppler echocardiography), which allow for disease detection even in the absence of previous suspicion, thereby leading to a perception of increased disease prevalence (43). Thus, it appears that the changing phenotype of patients with PH in modern registries is potentially influenced by factors that are independent of the disease itself.

Prediction and Prognosis Based on Relevant Registry Data

The U.S. NIH Registry was the first to develop a prognostic equation. Use of this equation in the current treatment era has limitations; it provides information only on the natural history of untreated PPH rather than on group 1 PH (PAH). More recent registries (Tables 1 to 3) have identified predictors of outcome (Table 4), which show surprising homology between studies, including disease etiology, patient sex, and factors reflective of right heart function.

Table 3 Survival Data of PAH Registries From Different Countries and Time Periods

Registry (Ref. #)	Study Cohort	1 yr, %		2 yrs, %		3 yrs, %		5 yrs, %	
		PAH	IPAH	PAH	IPAH	PAH	IPAH	PAH	IPAH
U.S. NIH (17,18)	Inc	NA	68	NA	NA	NA	48	NA	34
U.S. PHC (19)	Prev and Inc	84	NA	NA	NA	67	NA	58	NA
French (9,21,22)	Prev and Inc	Ent 87 Prev 88 Inc 88	Ent 83 Prev 89 Inc 89	Ent 76 Prev 79 Inc 65	Ent 67 Prev 77 Inc 68	Ent 67 Prev 71 Inc 51	Ent 58 Prev 69 Inc 55	NA	NA
Chinese (23)	Inc	NA	68	NA	57	NA	39	NA	21
U.S. REVEAL (8,24–33)†	Prev and Inc	85	91	NA	NA	68	74	57	65
Spanish (34)	Prev and Inc	NA	89	NA	NA	NA	77	NA	68
UK (6,35)	Inc	79*	93	68*	84	57*	73	NA	61
Mayo (38)	Prev and Inc	81	NA	NA	NA	61	NA	48	NA
Compera (39)	Inc	NA	Ent 92 ≤65 yrs, 96 >65 yrs, 90	NA	Ent 83 ≤65 yrs, 91 >65 yrs, 79	NA	Ent 74 ≤65 yrs, 83 >65 yrs, 68	NA	NA

*Survival data calculated only from patients with IPAH and patients with CTD-PAH. †Data for U.S. REVEAL is from the time of diagnostic right heart catheterization.
Ent = entire study population; Inc = incident or newly diagnosed patients; Prev = prevalent or previously diagnosed patients; other abbreviations as in Table 1.

Prognostic equations and calculators. In 4 of the registries (U.S. REVEAL, U.S. Pulmonary Hypertension Connection Registry, French registry, and U.K. registry), multivariable analyses led to the development of prognostic equations (U.S. REVEAL, U.S. Pulmonary Hypertension Connection Registry, French registry) (Table 5) or calculators (U.S. REVEAL, U.K. registry). Despite the U.S. REVEAL equation's derivation in a combined incident and prevalent cohort at the time of enrollment, the equation demonstrated equal prognostic power when tested at the time of diagnosis and was validated in an entirely incident population (40) and in distinct PH populations at other institutions (38,44,45). The U.K. prognostic score was validated in a second set of incident patients taken retrospectively from the U.K. registry only (derivation was from the Scottish registry only). The French registry and U.S. REVEAL equations have shown adequate predictive power when tested in matched patients from the U.S. REVEAL and French registries, respectively (46,47). However, the French registry equation had lower calibration than the U.S. REVEAL equation when tested in respective matched populations from each registry. The U.S. REVEAL equation was also noted to have good calibration in both the U.K. and Spanish registries, whereas the French registry equation appears to slightly overestimate the risk of death in these respective registries. One explanation for this is that the French registry equation, as opposed to the U.S. REVEAL equation, was calculated in a cohort of patients recruited in the 2002/2003 period that partially preceded widespread and early use of oral therapies for PAH. It is also apparent that the earlier discussions and concerns about the relative contribution to mortality risk of newly and previously diagnosed patients is minimized and overshadowed by the overall contribution of individual risk profiles in each of these populations, respectively. In other words, a newly diagnosed patient is not "independently" at risk of dying by the mere fact of newly receiving a diagnosis, but rather because they have a larger proportion of at-risk factors than those who previously received a diagnosis (7,21).

Future Directions

Broadening to other PH groups and novel entry criteria. Although patients belonging to group 2 (PH due to left heart diseases) and group 3 (PH due to chronic lung diseases and/or hypoxia) of the PH classification represent an increasing part of the clinical practice, there is disproportionately little information about the demographic factors and clinical course of this segment of the PH population. This suggests that registry database methodology may be useful for these groups. The structure of potential registries incorporating "non-PAH" PH is problematic. A single registry could include all patients with any type of PH from which defined subgroups (i.e., PH associated with interstitial lung disease, chronic obstructive pulmonary disease, left ventricular systolic dysfunction, or left

Table 4 Multivariate Predictors of Survival

Category	Increase Risk	Decrease Risk
Demographics	Sex (male) and age interaction (>65 yrs) (9,27,33,40) Age (6,19) Male (6,9,27,34) Etiology: CTD, (6,19,27,34,37,40) PoPH, (6,34,40); HPAH, (27,40); PVOD (6,34)	
Functional capacity	Higher NYHA/WHO class (23,40,19,27,34,37) Lower 6MWD (6,9,27,40)	Lower NYHA/WHO class (19,27) Higher 6MWD (6,9,27)
Laboratory and biomarkers	Higher BNP or NT-proBNP (27,40) Higher creatinine (27,40)	Lower BNP or NT-proBNP (27)
Imaging	Echo: pericardial effusion (27,37,40)	
Lung function studies	Lower predicted DLCO (27,37,40)	Higher predicted DLCO (27,40)
Hemodynamics	Higher mRAP (6,19,27,34,40) Lower CO or CI (6,9,34) Higher PVR or PVRI (27,40)	Higher CO or CI (19)

BNP = B-type natriuretic peptide; CI = cardiac index; CO = cardiac output; DLCO = diffusing capacity of the lung for carbon monoxide; Echo = echocardiography; HPAH = heritable pulmonary arterial hypertension; mRAP = mean right atrial pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PoPH = portopulmonary hypertension; PVOD = portopulmonary hypertension; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; other abbreviations as in Tables 1 and 2.

ventricular HFpEF) could be extracted for analyses. An advantage of this model is that all patients would be enrolled from the same sites and would permit direct comparisons between cohorts with minimal adjustment for differences in enrollment patterns, location, and follow-up. Disadvantages are that many patients would need to be enrolled to provide sufficient cohort size for characterization of all groups, and a single case report form (CRF) may not be appropriate for all cohorts. The ASPIRE (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre Registry) has attempted to assess the spectrum of PH across the 5 PH groups encountered in a single specialist referral center, allowing specific descriptions of PH patients with associated diseases such as chronic obstructive pulmonary disease and other comorbidities (48,49). However, this approach describes only the subgroup of patients seen at a referral center and may differ from the characteristics of patients in the community. An alternative model would be to develop separate registries around specific disease entities of interest, using focused CRFs at a less anticipated cost. This has been successfully proposed for CTEPH (50).

Regardless of the disease area of interest, one question that should be addressed during registry design is whether the purpose is to obtain information about a precisely defined disease (option 1) or to examine a more ambiguously delineated study population to determine what defines a cohesively defined disease entity in terms of presentation and natural history (option 2). Option 1 is most appropriate for diseases in which the criteria for disease are definitive, whereas option 2 may be appropriate for circumstances in which the definition of the disease depends on multiple continuous parameters. PH fits within the second category; 1 registry (U.S. REVEAL) was constructed to examine whether there is true inhomogeneity of presentation and course between patients meeting classic definitions of disease versus those outside the definition (12). This approach has the potential for providing insight into what the clinically meaningful delimiters of the disease are.

At-risk population cohorts. Unless all patients who have PH within a population are enrolled in a registry, estimates of incidence or prevalence of disease in a pre-specified population are not possible. To understand the chances of PH developing in a population requires that the population at risk be observed systematically over time to detect the occurrence of PH. Examples of populations of interest in whom the risk of the development of PH makes systematic data collection likely to yield clinically useful information include patients with known *BMPR2* mutations, with ≥2 family members with PH, with systemic sclerosis, with cirrhosis and portal hypertension, with past or present methamphetamine use, with mean pulmonary artery pressure of 20 to 25 mm Hg, or with PH observed only during exercise.

Because not all factors that may be determinants of outcome can be anticipated, registries must be designed to

Table 5 Prognostic Equations for Probability of Survival in PAH

Registry (Ref. #)	Equation	C Index
U.S. NIH* (17)	$P(t) = H(t)A(x,y,z)$	0.588
French† (21)	$P(t;x,y,z) = H(t)A(x,y,z)$	0.57
PHC‡ (19)	$P(t) = e - A(x,y,z)t$	Not calculated
REVEAL§ (27)	$P(1\text{-year}) = S0(1)\exp(Z'\beta^{\gamma})$	0.772

*$H(t) = 0.88 - 0.14t + 0.01t^2$; $A(x,y,z) = e^{(0.007325x + 0.0526y - 0.3275z)}$, where x = mean pulmonary artery pressure; y = mean right-sided atrial pressure; and z = cardiac index. †$H(t)$ = baseline survival = $e(a + b \cdot t)$, where a and b are parameters estimated from the multivariate Cox proportional hazards model, and t is the time from diagnosis measured in years; $A(x,y,z)$ = where x is the distance walked (m) at diagnosis, $y = 1$ if female, $y = 0$ if male, and z is the cardiac output (l/min) at diagnosis; $A(x,y,z) = e^{(-(c \cdot x + d \cdot y + e \cdot z))}$, where c and d were parameters obtained from the Cox proportional hazards model. ‡$P(t)$ is the probability of survival, t is the time interval in years, $A(x,y,z) = e(-1.270 - 0.0148x + 0.0402y - 0.361z)$, x = mean pulmonary artery pressure, y = mean right atrial pressure, z = cardiac index. §$S0(1)$ is the baseline survivor function (0.9698), $Z'\beta$ is the linear component, and γ is the shrinkage coefficient (0.939).

C index = concordance index; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; other abbreviations as in Table 1.

accommodate and explore future advances in knowledge as they develop. This will require that CRFs be fluid enough to allow changes in coding variables over time, but more importantly mandates that blood and tissue of participants be collected and stored so that biomarker and genetic correlates to clinical phenotypic expression can be examined both in the present and in the future.

Globalization of registries/collaboration. The profile of PH varies throughout the world, and comparison between environments, population demographics, and healthcare delivery systems may permit the development of hypotheses about how PH is best diagnosed and managed under different conditions. Accordingly, systematic acquisition of clinical data in registries worldwide represents a desirable objective (51). This would permit insights into a broader range of PH types to identify commonalities and differences and would increase the numbers (and therefore strengthen resulting observations) of patients with any particular subclassification of PH.

Collaborative efforts among registries have been useful in creating hypotheses about these observations but have been hampered to an extent by differences in study design, patient ascertainment, entry criteria, and follow-up. More uniformly designed and orchestrated registry data acquisition and analysis will likely yield more coherent observations and conclusions.

The overriding question is not so much whether a global approach to PH registry data is desirable, but how it could be achieved. Several models can be considered: 1) a single global registry with a unified funding source under the direction of a single steering committee; 2) a variety of national or regional registries each with distinct funding sources and separate steering committees, but using a common (or overlapping) CRF and comparable enrollment principles; or 3) independently developed and operated databases using separate CRFs that can be compared using adjustments for differences to the extent possible during post hoc collaborations. Of these, model 2 seems to be the best compromise between collaboration and feasibility.

Registries have been extremely helpful in improving our understanding of PH. Important questions remain unanswered, and it is clear that more registry data will be needed to address novel questions emerging with improved knowledge of PH. Since the pioneer U.S. NIH Registry of PPH, recent information gathered from national and international registries has truly captured many changes in PAH/PH phenotypes and outcomes in the modern management era. Besides the registries discussed extensively in the present paper, others have exclusively studied specific PH subpopulations discussed in other sections of these proceedings, with more focus on CTEPH (50), pediatric PH (52–54), and PAH drug (55) registries.

Reprint requests and correspondence: Dr. Michael D. McGoon, Mayo Medical School, Mayo Clinic, E168, 200 First Street SW, Rochester, Minnesota 55905. E-mail: mmcgoon@mayo.edu.

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