Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.023

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,

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D51–9

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.

Manuscript received October 10, 2013; accepted October 22, 2013.