



## REVIEW

# The study of risk in pulmonary arterial hypertension

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**ABSTRACT:** A growing body of published evidence exists on the risk factors for disease progression in pulmonary arterial hypertension (PAH). The Scientific Steering Committee for the Study of Risk in PAH was established to bring together leading clinical and statistical experts in PAH and risk modelling, for the purpose of advancing the understanding of the risk of development and progression of PAH. Herein, we discuss the impact of this information on three key areas: 1) clinical decision-making; 2) policy and reimbursement; and 3) future trials and research.

**KEYWORDS:** Economics, prognosis, pulmonary arterial hypertension, quality of life, risk, survival

### PROGNOSIS FOR SURVIVAL

Despite the limitations in comparing data across trials and from different treatment eras, survival for pulmonary arterial hypertension (PAH) does seem to have improved in the modern era [1, 2] *versus* historical survival from the National Institutes of Health (NIH) registry [3]. However, outcomes are still unacceptably low and treatment strategies need to evolve in order to improve survival.

Outcomes in PAH vary for different aetiologies, with systemic sclerosis (SSc)-associated PAH patients having among the worst survival and idiopathic PAH patients who respond to vasoreactivity testing the best survival [4–6]. Survival is also worse for incident (newly diagnosed) *versus* prevalent patients [1].

High-risk patients, such as those with SSc, may be screened for PAH. Earlier detection and earlier intervention may lead to improved outcome [7].

Age, sex, 6-min walking distance (6MWD) and cardiac output/cardiac index are commonly identified as having a strong prognostic loading. Different variables emerge as significant from different data sets, *e.g.* in the Bologna PAH experience, age and sex are important risk factors in some clinical subgroups but not all, whilst cardiac output is not identified as a risk factor, in contrast with other analyses (such as the French registry).

There are a number of considerations when analysing predictive factors from datasets, including:

1) statistical power sample size; 2) categorical (*e.g.* World Health Organization-functional class (WHO-FC)) *versus* continuous (*e.g.* 6MWD) variables; 3) subgroup-specific differences (*e.g.* age and sex); and 4) lack of variability (*e.g.* majority of subjects are WHO-FC III at baseline).

Since reduced cardiac output is frequently predictive of outcome, the Scientific Steering Committee for the Study of Risk in PAH (hereafter referred to as the group) considered the impact of heart rate, stroke volume and pulse pressure. Data from the sildenafil PAH development programme indicate that heart rate at baseline, and systemic pulse pressure at follow-up, were predictive of outcome [8]. It is of interest to perform similar analyses in other real-world, registry and clinical trial datasets.

The group noted the apparent increasing age of PAH patients, which is >50 yrs in recent registries such as the French [1], REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) [2] and CompERA [9] *versus* 35 yrs in the original NIH registry (table 1) [10]. This raises a number of questions. 1) Is PAH the same disease in elderly *versus* younger patients? 2) How do we interpret efficacy data from clinical trials, where the mean age is ~50 yrs, for older subjects? 3) Are older, often geriatric, patients as responsive to therapy (especially to vasodilators) as younger patients? 4) Is there a risk of targeted therapies

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**TABLE 1** Patient characteristics in the National Institutes of Health (NIH), French and REVEAL registries

Parameter	NIH [10]	French [1]	REVEAL [2]	CompERA [9]
<b>Year</b>	1981–1985	2002–2003	2006–2007	2007–2009 (data collection ongoing)
<b>Country</b>	USA	France	USA	6 EU countries: Germany, UK, Belgium, Netherlands, Italy and Ireland
<b>Inclusion criteria</b>	PPH	PAH	PAH	Newly initiated on PAH therapy (PAH 74%; PH 26%)
<b>Patients</b>	187	674	2716	1008
<b>Age yrs</b>	36 ± 15	50 ± 15	50 ± 17	64
<b>Time since diagnosis months</b>	24.4	27	39	Not given
<b>WHO-FC %</b>				
II	29	24	37.8	9
III/IV	71	75	53.7	91

Data are presented as n or mean ± SD, unless otherwise stated. REVEAL: Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; WHO-FC: World Health Organization-functional class; PPH: primary pulmonary hypertension (PH); PAH: pulmonary arterial hypertension; EU: European Union.

being considered “end-of-life” drugs by reimbursement bodies? 5) Is the haemodynamic definition of pulmonary hypertension (PH), using an upper limit of 15 mmHg for pulmonary capillary wedge pressure ( $P_{pcw}$ ), still valid to define pre- versus post-capillary PH, or are there differences, for example, between subjects with  $P_{pcw} < 12$  mmHg versus 12–15 mmHg?

An analysis of the impact of baseline  $P_{pcw}$  on outcome from the sildenafil clinical trial programme found that there were differences in some end-points between patients with  $P_{pcw} < 12$  mmHg versus  $> 12$  mmHg [11]. This haemodynamic classification of PAH will probably be debated at the 5th World PH Symposium in Nice, France, in February 2013.

Male sex is a risk factor for poor prognosis. In the French registry the female/male ratio is 1.7, but this increases to 4 in the REVEAL registry [1, 2]. What are the reasons for these regional differences in sex? Do these differences exist in other datasets, such as clinical trials and other registries?

## RISK ASSESSMENT

Prognostic equations have been developed from existing datasets, including the French and REVEAL registries [2, 4]. These equations describe the survival of the specific population. However, additional value could be obtained through development of a tool, e.g. risk calculator, from such predictive models to: 1) simplify the complex reality of individual PAH patients; 2) aid non-expert clinicians; 3) stimulate expert referral, especially for the most severe patients for whom complex treatment options are indicated; and 4) determine when to select a particular intervention, e.g. *i.v.* epoprostenol or listing for transplantation.

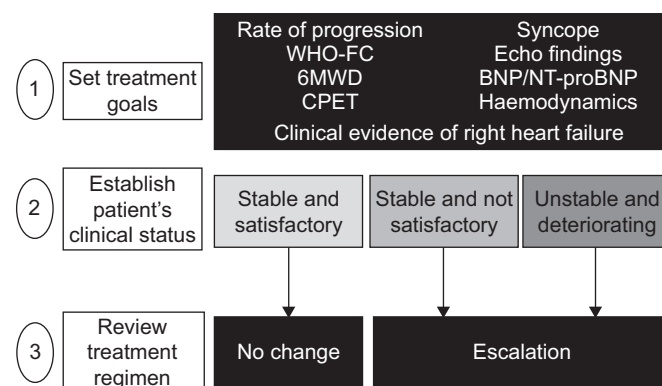
The REVEAL risk factors were given a numerical score based on severity, allowing for the creation of a risk calculator that can be used to derive a severity score and risk for poor outcome based on the presence or absence of the criteria [5]. A total of 19 parameters were included (10 from aetiology and physical examination and nine from diagnostic tests), all of which have a sound basis.

The REVEAL model and risk calculator have been successfully validated in separate US PAH populations, both incident and

prevalent [5], and further validation is planned. Similarly, the French registry equation had good reproducibility when tested in a Chinese cohort [12] and the REVEAL cohort [13].

## DYNAMIC RISK ASSESSMENT

Baseline clinical values clearly have importance in risk assessment. However, their use is limited as prognosis may change over time with interventions and as the clinical picture changes. There is a need for assessment at multiple follow-up time-points (dynamic assessment) to evaluate the impact of time-dependent variables on clinical outcomes. A single centre study from Hannover, Germany, evaluated the prognostic impact of follow-up assessment in 109 incident PAH patients [14]. After identifying prognostic factors for survival by multivariate analysis, it was feasible to stratify patients' outcomes following the European Society of Cardiology/European Respiratory Society guidelines criteria for risk assessment (fig. 1). Despite a small sample size, the study is hypothesis generating and demonstrates the need to evaluate a broad number of clinical



**FIGURE 1.** Risk assessment and treat-to-target approach for pulmonary arterial hypertension. WHO-FC: World Health Organization-functional class; 6MWD: 6-min walking distance; CPET: cardiopulmonary exercise testing; Echo: echocardiography; BNP: brain natriuretic peptide; NT-proBNP: N-terminal-pro-brain natriuretic peptide. Adapted from [15] with permission from the publisher.

factors covering all pathophysiological aspects of the disease in order to regularly re-assess treatment goals.

It may be feasible to use prospective registries to assess time-dependent prognostic variables. We can consider that there are three types of registries, all with strengths and limitations (table 2).

A novel prospective study is ongoing in France, the EFORT study (Evaluation of Prognostic FactORs and Treatment Goals in PAH) [16]. The study is enrolling newly diagnosed patients with idiopathic, heritable and anorexigen-associated PAH within the French PAH network. Regular clinical assessment and follow-up (at baseline, 3–4 months after treatment initiation or treatment change, and annually) for 3 yrs will identify prognostic factors for survival, and determine treatment strategies associated with improved outcome.

In order to increase the sample size and generalisability of the data, it was suggested to explore options to open up the study to expert centres from other countries.

From the EFORT study, it may be feasible to stratify subjects as low, medium or high risk, despite the applied treatment strategy. Subsequent research could evaluate whether changing the treatment strategy based on risk can impact patient outcome. Whilst the group acknowledges such studies may not provide the final answer, they can help to generate new questions and eventually lead to improvement in treatment guidelines and outcomes for PAH patients.

## TREATMENT STRATEGIES

Current risk equations and calculators have been developed from cohorts of subjects who have received interventions from a treating clinician. Therefore, how do we interpret the risk score for a particular patient and adjust the treatment strategy accordingly?

In patients with poor prognosis at baseline, combination therapy is an option [15]. To date, one study has demonstrated improved outcome with combination *versus* monotherapy in PAH [17]. Ongoing trials (*e.g.* AMBITION [18], COMPASS-2 [19] and A1481243 [20]) will provide additional data on how treatment strategy impacts outcome (*e.g.* goal-oriented *versus* up-front combination therapy). In a small, open-label study, up-front triple therapy with bosentan, sildenafil and *i.v.* epoprostenol in severe patients had a dramatic impact on

haemodynamics and clinical outcomes when compared with previous experience on mono- or dual therapy [21].

The outcome of the AMBITION trial is eagerly awaited; if positive, it could lead to a change in the treatment paradigm to initiate patients on oral combination therapy. However, risk assessment will remain crucial to guide treatment strategy. It is important to remember that transplantation is a therapeutic option for the most severe patients, which further highlights the importance of referral to expert centres.

## HEALTH ECONOMICS, TECHNOLOGY ASSESSMENT AND PAH

Economic evaluation is a family of methods and techniques that have been employed by health policy makers in many developed nations to assist them in making decisions concerning the adoption of new healthcare technologies. Among the most commonly employed techniques are cost-minimisation and cost-utility analysis that are designed to determine how the value created by the new treatment compares to the cost of its adoption. In cost-minimisation analyses, only the cost of treatment is concerned; therefore, the decision maker is left to assume that the treatment efficacy is equal among the therapies. In cost-utility analysis, this assumption is relaxed and efficacy is measured by its impact on quality of life measures of function [22].

However, it has not been necessary for companies developing drugs for palliative treatment to develop extensive dossiers using all of the tools of economic evaluation. Often it is only necessary for them to provide evidence of clinical efficacy and document budget impact for health authorities being petitioned. The reason for this is the special status of PAH as an orphan disease. This implies that while treatment cost per case is high, the low prevalence and high mortality result in a total monetary burden representing a relatively tiny portion of the total healthcare budget.

The group recognised that this status makes it even more important for clinicians to be aware of the balance between the efficacy of medications and their cost in choosing the optimal treatment for patients. The largest contributor to the cost of care associated with PAH is the cost of pharmaceutical treatment, and this varies dramatically ranging from more than US\$9,000 (sildenafil) to more than US\$60,000 (iloprost) annually (J.R. Edler, Center for Economic Evaluation in Medicine, Washington University School of Medicine, St. Louis, MO, USA; personal communication). When we couple this with the results of a 2009 report by CHEN *et al.* [23], which found good evidence for the cost-effectiveness of bosentan and sildenafil (at current threshold standards), clinicians in most countries can be confident that they can match treatments to their patient's needs and still make good use of societal resources.

However, this may change in the future with the advent of generic drugs, novel therapies that promise to be even more expensive than current ones, and a worsening global macroeconomic environment. In the UK and Australia, for example, there are already limitations on access to therapies for less severe patients (WHO-FC II), as well as on the use of combination therapy. The group considered including evaluation of costs into PAH clinical trials. This will probably become an increasingly important requirement for successful health technology assessment and application for reimbursement.

**TABLE 2** Types of prospective registries for analysis of time dependent prognostic variables

### Non-selective registries

Pros: epidemiology (prevalence) and clinical characteristics

Cons: survival analysis and prognosis

### Registries of newly diagnosed patients

Pros: epidemiology (incidence), survival analysis, prognosis and risk equation from baseline variables

Cons: assessment of time-dependent variables and treatment goals

### Interventional registries

Pros: assessment of time-dependent variables and treatment goals

In addition to measuring the cost of care in trials, the group acknowledged that measuring the benefit of treatments for the PAH patient using quality of life measures appropriate for economic evaluation is a challenge that remains to be addressed. Patient-reported outcomes data have been collected in PAH trials, mostly using the 36-item Short-Form Health Survey and the EuroQoL-5D. However, the responsiveness of these measures to clinically significant changes in disease status has not been well established. Establishing the validity of these measures in PAH would be a useful area for future research. If they are found to be inadequate, there may be a need for a new instrument to support decision making by health policy makers [24–26].

## CONCLUSION

PAH is rare condition, and whilst improvements in outcome have been achieved, survival remains poor. Data should be maximised, pooled where possible, and risk assessment cross-validated among patient cohorts. Risk scores are a useful research tool and can provide clinical guidance; however, they are not yet ready to replace expert clinical judgement. There is an urgent need to identify patients that fail on current therapeutic strategies and determine how to better improve outcomes.

Future research will focus on developing a dynamic risk score from prospective interventional registry studies. We should move towards collaborative, multi-national efforts to improve sample size and data generalisability. Survival remains the ultimate measure of outcome, but good surrogates should be investigated.

## STATEMENT OF INTEREST

L.J. Rubin has served on a scientific advisory committee for United Therapeutics, and has served as a consultant to NHLBI, Actelion, Pfizer, United Therapeutics, Lung LLC, Gilead, Aires Pharmaceuticals, GSK, Bayer, GeNO, Cytokinetics and Mondobiotec. G. Simonneau has received fees for speaking, educational programmes and consulting from Actelion, GSK, Pfizer, Lilly and Novartis. He has received funds for research from Actelion, GSK, Pfizer, Lilly and Novartis, and has received reimbursement for attending a symposium from Actelion, GSK, Pfizer, Lilly and Novartis. D. Badesch has received grant/research support from Glaxo Wellcome, United Therapeutics/Lung Rx, Actelion/CoTherix, Encysive, Gilead/Myogen, Pfizer, Lilly/ICOS, Bayer and Novartis. He has served as a consultant to Glaxo Wellcome/GSK, Actelion/CoTherix, Berlex, Gilead/Myogen, Encysive, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, MondoBiotech/MondoGEN/Biogen IDEC, Bayer, Arena, and Ikaria. He has also provided assistance to legal counsel for Actelion. N. Galie has been involved with steering committee activities for Eli Lilly and Co., Actelion, Pfizer, Bayer Schering, GSK and Novartis. He has been a paid lecturer, for Actelion, Eli Lilly and Co., Pfizer, Bayer Schering, and GSK. He has done contract research for Actelion, Pfizer, United Therapeutics, Bayer Schering, GSK and Novartis. M. Humbert has relationships with drug companies including Actelion, Aires, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Merck, Novartis, Nycomed, Pfizer, Stallergenes, TEVA and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. A. Keogh has received fees for speaking and clinical trials from, and been on the advisory board for Actelion, Pfizer, Bayer, Gilead, Myogen, GSK and Novartis. J. Massaro has received fees from Pfizer Inc. for statistical consulting on this project and for attending and presenting at meetings focused around this topic. The amount of fees received is US\$5,000–10,000 (approximately €4,000–8,000). M. Matucci Cerinic has received fees for speaking from Pfizer, Actelion, Bristol Myers Squibb and MSD. O. Sitbon has relationships with pharmaceuticals

companies including Actelion, Bayer HealthCare, GSK, Lilly, Pfizer and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, membership of scientific advisory boards, fees for speaking, funds for research and reimbursement for attending symposia. S. Kymes has received research support from Pfizer Inc. for work examining the economic burden of pulmonary arterial hypertension. This support has been US\$50,000–100,000. He has also received travel support and consulting fees of less than US\$10,000.

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