EUROPEAN RESPIRATORY UPDATE

REVEAL: a contemporary US pulmonary arterial hypertension registry

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Although a substantial amount of information about clinical pulmonary arterial hypertension (PAH) has accumulated over the past decades, there remains a need for our understanding to keep pace with the evolving milieu in which management of patients with PAH occurs. The goal of the Patient Registry for the Characterization of Primary Pulmonary Hypertension, initiated in 1981 under the sponsorship of the National Institutes of Health (NIH), was to elucidate the clinical characteristics and natural history of patients with primary pulmonary hypertension (now called idiopathic PAH; IPAH). The practical aims of the registry were to promote understanding about potential causes, facilitate early and accurate diagnosis, and develop more effective treatment strategies [1]. Analysis of the 187 patients who were enrolled from 1981 to 1985 laid a foundation of knowledge which provided the impetus for the creation of appropriate diagnostic algorithms, predictive models and the development of more effective drugs. Indeed, the importance of this undertaking has been demonstrated by its use as a basis of comparison when judging the efficacy of various treatment modalities. However, largely as a result of these advances, as well as the recognition (articulated in subsequent international symposia [2–4]) that pulmonary vascular disease is a factor in a broader spectrum of clinical contexts, the pulmonary hypertension (PH) medical community has perceived that the current understanding of this constellation of pulmonary vasculopathies requires updating and expansion.

While randomised trials remain the standard for evaluating the safety and efficacy of new drugs and treatment regimens, the structured design of clinical trials is not optimal for evaluating a range of other scientific objectives. Observational studies, when consecutive enrolment is employed, do not suffer from the selection bias that exists in almost all clinical studies, when consecutive enrolment is employed, do not evaluating a range of other scientific objectives. Observational

sizes and longer follow-up than clinical trials, such that long-term survival curves and prognostic factors can be evaluated and in-depth analyses may be pursued in subgroups of special interest. The absence of assigned treatment choices also provides greater opportunity to include patients who may not meet the standard criteria for a disease, patients for whom little is known about characteristics and outcomes.

Consequently, a number of registries have been implemented for the purpose of examining the nature of PAH in the modern era. These include databases which provide information about patients in geographically unique locations [5–10] and in individual large referral practices [11–13]. Herein, we describe the observations that have emerged to date from the largest US registry, the Registry to EValuate Early And Long-term PAH disease management (REVEAL).

PATIENT ENROLMENT INTO REVEAL

REVEAL is a multicentre, observational, US-based registry study of PAH which was designed to characterise a contemporary US PAH patient population [14]. 55 centres have contributed patient data to the REVEAL registry. All enrolled patients had to meet strict criteria of diagnosis of PAH by right heart catheterisation (RHC). Initially, patients were enrolled consecutively starting in March 2006 when they presented to the participating institutions regardless of when they had been diagnosed. Starting in September 2007, after nearly 3,000 patients had been enrolled, an additional cohort of approximately 500 newly diagnosed patients was enrolled in order to amplify this portion of the study population. Patients were designated as “newly diagnosed” if their qualifying RHC was performed within the 3 months preceding enrolment and “previously diagnosed” if their RHC was prior to the 3 months before enrolment. The enrolment date was the date of informed consent or the date of the RHC for a small number of patients who consented prior to the diagnostic RHC. Year of diagnosis for previously and newly diagnosed patients is described in figure 1. Planned patient follow-up was a minimum of 5 yrs from date of enrolment.

In addition to the participation of both newly and previously diagnosed patients, other enrolment criteria are unique and important to note. Patients could be enrolled if they met haemodynamic criteria and, in the opinion of the investigator, exhibited clinical criteria consistent with the accepted definition of PAH. No concrete clinical or laboratory test requirements were pre-specified. In this way, REVEAL intended to

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RATIONALE FOR RELAXING THE P Pulmonary Vascular Resistance (PVR)

Practice have elevated left-sided filling pressures; 2) ...

practice, the strength of evidence for making a diagnosis would be available.

The haemodynamic enrolment criteria were slightly broader than those traditionally used in previous registries or in clinical trials. Specifically, requirements were mean pulmonary artery pressure ($P_{pa}$) $>25$ mmHg at rest or $>30$ mmHg with exercise, mean pulmonary capillary wedge pressure ($P_{pcw}$) or left ventricular end-diastolic pressure $<18$ mmHg at rest, and pulmonary vascular resistance (PVR) $>3$ Wood units. The rationale for relaxing the $P_{pcw}$ was based on several considerations: 1) in reality, many patients managed as PAH in clinical practice have elevated left-sided filling pressures; 2) $P_{pcw}$ may vary from one RHC to another and may not be representative at a single determination; 3) left-sided filling pressures may be increased as a result of ventricular interaction in severe PAH; and 4) the presence of left ventricular dysfunction does not preclude the possibility of coexisting true PAH. The inclusion of such patients was considered to be important to determine whether they were similar or dissimilar to conventionally defined patients and, therefore, should or should not be candidates for PAH treatment. The only other stipulation was that patients were aged $>3$ months at the time of diagnosis.

Using these criteria, 2,555 consecutive previously diagnosed patients were enrolled between March 2006 and September 2007. A further 960 newly diagnosed patients were enrolled from March 2006 to December 2009, concurrent with the previously diagnosed patients and including the subsequent enrolment of newly diagnosed patients exclusively. The total study population as of the October 14, 2011 data lock was 3,515. A descriptive breakdown of the number of patients enrolled by inclusion criteria has previously been published for the initial cohort up to September 2007 [14]. A similar breakdown for the cohort of patients enrolled up to October 2011, stratified into previously and newly diagnosed patients, is described in figure 2.

OBJECTIVES OF REVEAL

As is common in observational studies, REVEAL has multiple objectives rather than a single primary aim [14]. To date, data have been presented on four of these stated objectives, which are to: 1) characterise the demographics and clinical course of the patient population diagnosed as having World Health Organization (WHO) group I PH (i.e. PAH); 2) evaluate differences in patient outcomes according to WHO group I classification subgroups; 3) compare outcomes in patients who do and do not meet pre-specified traditional haemodynamic criteria for the diagnosis of PAH; and 4) identify clinical predictors of short-term and long-term outcomes. Ongoing REVEAL data analysis will also fulfil the broad final objective of the study to “collect timely and relevant data that will assist in the evolving research needs of the PAH community” [14].

FIGURE 1. Number of previously (n=2,555) and newly (n=960) diagnosed pulmonary arterial hypertension patients enrolled in REVEAL by year of diagnosis.

DEMOGRAPHICS AND CLINICAL PROFILE OF THE REVEAL PATIENT POPULATION

Age and sex

Among the 2,967 consecutively enrolled patients up to September 2007 for whom baseline data have been published (data lock August 7, 2008) [15], 2,525 were adults (aged $>18$ yrs) who met traditional haemodynamic criteria ($P_{pcw}$ $\leq 15$ mmHg). The mean $\pm$ SD age of this group at enrolment was $53.0 \pm 14.0$ yrs ($50.1 \pm 14.4$ yrs at diagnosis); 2,007 (79.5%) were female [15]. For the 1,166 IPAH patients, the mean age at enrolment was $53.1 \pm 14.5$ yrs ($49.9 \pm 14.8$ yrs at diagnosis) and 936 (80.3%) were female. These patients were older than those reported in the NIH registry of the 1980s ($36 \pm 15$ yrs) and the female/male ratio of 4.07:1 overall and 3.06:1 among newly diagnosed IPAH/familial PAH (FPAH) patients represents a substantial increase over the sex ratio of 1.70:1 [1]. Female patients were more likely than male patients to have clinical depression and thyroid disease and less likely to have sleep apnoea than male patients [16].

A total of 216 paediatric patients ($\leq 18$ yrs old at data lock of November 19, 2010) were enrolled. Median age at diagnosis was 7 yrs and at enrolment was 15 yrs. 64% of the paediatric group was female [17]. The female preponderance was not present among IPAH/FPAH paediatric patients aged $\leq 12$ yrs (ratio 1.08:1).

WHO group I PAH sub-classification

The distribution among PAH diagnostic subgroups of adult patients with traditional haemodynamic criteria of PAH is shown in figure 3. Subgroups are classified according to those agreed at the 3rd World Symposium held in 2003 (Venice, Italy) as the REVEAL enrolment pre-dates the updated classifications following the 4th World Symposium in 2008 at Dana Point, CA, USA. Patients with associated PAH (APAH) comprised the largest subpopulation (50.7%), followed closely by IPAH (fig. 3a). Connective tissue disease (CTD) accounted for half of the patients within the APAH subgroup (fig 3b) [15]. Female predominance was greatest among patients with CTD-APAH (90% female) and absent only among patients with PAH associated with portal hypertension (PoPH-APAH; 50% female). The size of REVEAL allowed for accurate descriptions of these subgroups (which previously had often been pooled as “all APAH”), thereby providing greater understanding of the variation in demographics for different WHO group I subgroups.
**Functional status**

At the time of diagnostic RHC in 1,831 patients with sufficient information about contemporaneous functional status, 1,123 (61.3%) patients were WHO functional class III and 225 (12.3%) were WHO functional class IV. Thus, it is evident that the majority of patients have symptoms of advanced disease by the time a diagnosis of PAH is established by RHC. At the time of enrolment, a median of 25 months later, 1,153 (50%) out of 2,304 patients were WHO functional class III and 130 (5.6%) were WHO functional class IV [15]. The decrease in overall severity of symptoms at the later date may reflect an improvement in functional status among patients who were initiated on treatment after their diagnosis and survived to be enrolled into REVEAL.

**Timeliness of diagnosis**

In view of the presence of significant symptoms at diagnosis, it is important to determine whether the process of diagnosing PAH is perhaps unnecessarily slow. Early evaluation of the initial adult enrolment cohort with traditionally defined haemodynamics indicated that the interval between symptom onset and diagnosis was >1 yr for >50% of patients (median duration to RHC 13.6 months; mean ± SD 34.1 ± 1.2 months). Indeed, further examination of these patients disclosed that 21.1% had an interval before disease recognition of >2 yrs. To be conservative, disease recognition was defined as the earliest of: 1) the date of the diagnostic RHC; 2) the date the patient was first told they had PAH; or 3) the date of initiation of PAH-specific therapy. The patients with the highest likelihood of delayed disease recognition had symptom onset at <36 yrs of age, a history of obstructive airways disease or obstructive sleep apnoea, 6-min walk distance (6MWD) of <250 m, mean right atrial pressure (P\(_{ra}\)) <10 mmHg, or PVR <10 Wood units. Sex, race/ethnicity and geographic location were not associated with duration to diagnosis [18].

**Comorbidities**

PAH frequently occurs in patients with comorbid conditions which fall outside of the diseases considered to be APAH. The most common comorbidities not within the APAH spectrum were systemic hypertension (40%), obesity defined as a body mass index (BMI) ≥30 kg·m\(^{-2}\) (33%), clinical depression (25%), obstructive airways disease not considered to be the cause of PH (22%), sleep apnoea (21%) and diabetes mellitus (12%) [15]. An in-depth analysis of BMI in REVEAL compared with expected BMI for a population of comparable age and sex supported data from the National Health and Nutrition Examination Survey (NHANES) and showed that on average BMI in REVEAL did not differ from the general US population; however, the BMI average did mask differences of underweight and overweight in individual subgroups. Patients with IPAH and drugs and toxins APAH were slightly more likely to be overweight compared with the US population. Patients with APAH-CTD and congenital heart disease (CHD)-APAH were
more likely to be underweight with a similar trend noted in the smaller cohort with HIV-APAH [19].

**Haemodynamics**

The haemodynamic profile of the 2,525 adult patients meeting traditional haemodynamic criteria for PAH is shown in table 1. Of note, patients with IPAH had significantly higher $P_{\text{Pa}}$, $P_{\text{ra}}$ and PVR than patients with APAH, and had lower cardiac index and mixed venous oxygen saturation [15]. Mean pulmonary artery systolic pressures using data from RHC and echocardiography were compared [20] using evaluations proximate to enrolment and longitudinal data. While the enrolment data showed reasonably good correlations, changes over time were not well correlated suggesting that echocardiography alone is likely to be insufficient to monitor change in pulmonary arterial systolic pressure or progression of PAH.

**Treatment profile**

At the time of enrolment, 2,438 patients were taking PAH-specific medications, as summarised in table 2. Additional interesting observations include the fact that of the 1,335 for whom results of a vasodilator challenge at RHC were known at enrolment, 136 (10.2%) were vasodilator responders with 55 (40.4%) of these on calcium channel blockers [15]. Of the 124 WHO functional class IV patients at enrolment, 13% were not receiving any PAH-specific medications [15]. Among all previously diagnosed patients in REVEAL, 46% were on dual combination PAH-specific therapy and 9% were on triple combination PAH-specific therapy (fig. 4) on the day of enrolment. Among newly diagnosed patients, 45% were treatment naïve on the day of enrolment and 73% were treatment naïve prior to the date of RHC diagnosis. Among the newly diagnosed patients, 17% were first treated 180 days prior to the RHC diagnosis required to meet the REVEAL entry criteria. In comparison to European registries this may be unique to the US healthcare system, so it is important to note that the term “newly diagnosed” is not synonymous with “treatment naïve” or “incident”.

**COMPARISON WITH OTHER REGISTRIES**

The upward shift in the age distribution between the time of the NIH registry and today is a consistent finding of current registries in the USA and Europe, but the strong shift to greater female predominance appears to be unique to US registries [21]. Restricting the REVEAL cohort to exclude patients that would not have been included in the French National PAH registry or the NIH registry does not change these findings. Haemodynamics are also very similar between the REVEAL cohort and other studies, with the exception of a slight shift downwards in the peak of the distribution of $P_{\text{Pa}}$ in contemporary studies.

**WHO GROUP I PAH SUBGROUPS**

**CTD-APAH**

Patients with CTD-APAH have been identified as a higher risk cohort with significantly worse 1-yr survival (fig. 5) and 1-yr freedom from hospitalisation [22]. Although systemic scleroderma (SSc) comprised the largest CTD-APAH subgroup, 32% of categorised patients did not have SSc-APAH. Patients with systemic lupus erythematosus-APAH and rheumatoid arthritis-APAH had a significantly better 1-yr prognosis than patients with SSc-APAH. Patients with mixed CTD-APAH did...
PoPH-APAHP patients with PoPH-APAHP have also been identified as a higher risk profile, including higher levels of brain natriuretic peptide (BNP) and lower diffusing capacity of the lung for carbon monoxide (DLCO).

**PoPH-APAHP**

Patients with PoPH-APAHP have also been identified as a higher risk profile compared with IPAH patients with CTD-APAHP. IPAH patients with PoPH-APAHP have higher than average 6MWD. Nonetheless, 2-yr survival from enrolment is worse for both newly diagnosed and previously diagnosed PoPH-APAHP patients compared with IPAH/FPAH, as is the case with 5-yr survival from diagnosis. Practice patterns differences were also identified. In particular, PoPH-APAHP patients were less likely than IPAH/FPAH patients to be on a PAH-specific therapy at enrolment [23].

**CHD-APAHP**

To date, the most extensive evaluation of CHD-APAHP patients has occurred within the paediatric cohort. Paediatric patients with CHD-APAHP do not have significantly better outcomes than paediatric patients with IPAH/FPAH, and no survival differences were identified between paediatric patients with repaired or un repaired CHD [17]. Variables that were identified at enrolment as significantly associated with worse survival among paediatric patients were higher PVR index, lower weight-for-age z-scores and FPAH. An adaptation of the non-traditional haemodynamic parameter is obtained from the two-sample t-test examining the difference in the distribution of the characteristics among patients diagnosed with IPAH versus all patients with APAH. Reproduced from [16] with permission from the publisher.

**Non-Traditional Haemodynamic Criteria**

**Demographics and comorbidities**

In the initial enrolment phase (up to September 2007), 239 adult patients had a Ppcw of 16–18 mmHg at the time of their qualifying RHC. As shown in table 3, these patients tended to be older, more obese, walked for shorter distances on the treadmill, and had lower diffusing capacity for carbon monoxide (DLCO) compared with IPAH/FPAH patients. Reproduced from [15] with permission from the publisher.

**Table 1**

| Characteristics | All patients | IPAH | All patients with APAH | APAH subgroups |
|-----------------|-------------|------|------------------------|----------------|
| Subjects n      |             |      |                        |                |
| Ppa mmHg        |             |      |                        |                |
| Subjects n      | 2525        | 1166 | 1280                   | 250            |
| p-value         | <0.001/     |      |                        |                |
| Pcw mmHg        |             |      |                        |                |
| Subjects n      | 2525        | 1166 | 1280                   | 250            |
| p-value         | 0.14        |      |                        |                |
| Pra mmHg        |             |      |                        |                |
| Subjects n      | 2298        | 1050 | 1174                   | 229            |
| p-value         | <0.001/     |      |                        |                |
| PVRI Wood units m² |           |      |                        |                |
| Subjects n      | 1868        | 842  | 965                    | 186            |
| p-value         | <0.001/     |      |                        |                |
| Fick or thermodilution Cl / min⁻¹ m⁻² | |      |                        |                |
| Subjects n      | 1868        | 842  | 965                    | 186            |
| p-value         | <0.001/     |      |                        |                |
| SvO₂ %          |             |      |                        |                |
| Subjects n      | 1456        | 665  | 738                    | 148            |
| p-value         | <0.001/     |      |                        |                |

Data are presented as mean±SD unless otherwise stated. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; APAH: associated PAH; CHD: congenital heart disease; CVD/CTD: collagen vascular disease/connective tissue disease; Ppa: mean pulmonary artery pressure; Ppcw: pulmonary capillary wedge pressure; Pra: mean right atrial pressure; PVRI: pulmonary vascular resistance index; CI: cardiac index; SvO₂: mixed venous oxygen saturation. *: all patients aged >19 yrs at diagnosis with a Ppcw <15 mmHg enrolled during the consecutive screening of newly and previously diagnosed patients, including those with WHO group I diagnoses other than IPAH or APAH (i.e. familial PAH, pulmonary veno-occlusive disease and persistent pulmonary hypertension of the newborn); #: APAH patients, including those with associated PAH subgroups other than CHD, CVD/CTD, portal hypertension, and drugs/toxins (i.e. HIV and others); ±: APAH subgroups are mutually exclusive according to the following hierarchy for patients with multiple associated-PAH diagnoses: CHD, CVD/CTD, portal hypertension, drugs/toxins, HIV and others; *, the Fick CI is used unless it is missing, in which case thermodilution CI is used; 1: p-value for all haemodynamic parameters is obtained from the two-sample t-test examining the difference in the distribution of the characteristics among patients diagnosed with IPAH versus all patients with APAH. Reproduced from [16] with permission from the publisher.
6MWD test and had more comorbid conditions than those with traditional haemodynamics. However, patients had similar functional classifications and were on similar treatment at enrolment regardless of Ppcw status [15].

Further analysis of the complete cohort showed comparable survival for REVEAL patients with a physician diagnosis of PAH in spite of having a Ppcw >15 mmHg. Approximately half of these PAH patients with non-traditional haemodynamics had a Ppcw measured at ≤15 mmHg on a subsequent RHC. Similarly, some patients who originally fell within the traditional haemodynamic criteria had higher Ppcw outside of the traditional range at follow-up RHC. Among patients who were diagnosed with a Ppcw of ≤12 mmHg, consistent with the criteria used in the NIH registry, those with follow-up RHCs >15 mmHg had worse outcomes. Although features suggestive of metabolic syndrome were more common among patients with higher Ppcw, they were not sufficiently common to suggest that these borderline patients are not predominantly part of WHO group I PAH (A.E. Frost, Dept. of Medicine, Baylor College of Medicine, Houston, TX, USA; personal communication).

CLINICAL PREDICTORS OF OUTCOME

Lung allocation score

Before developing a PAH-specific predictive equation for survival, analysis was conducted assessing a widely used formula for a broader group of lung diseases. In the USA, transplant priority is based on a lung allocation score (LAS) that incorporates urgency and potential benefit. Urgency is based on predicted survival while on the waiting list and potential benefit is based on predicted post-transplant survival. Because PAH is a rare disease compared with other populations who are candidates for transplants, the waiting list formula does not include some variables that are known to be predictive of poor outcome in PAH. The formula does include many variables that are not proven to be prognostic for PAH patients.

Expected survival based on the waiting list component of the LAS was compared to actual survival in REVEAL among all patients and among a subset identified as potentially listable in the USA; personal communication).
A formula was proposed to correct for these critical risk factors for PAH patients, and it was demonstrated that the correction would result in higher LAS scores and greater potential for transplant for high urgency PAH cases [24]. As of October 2011, 95 transplants had been reported in REVEAL including 79 lung transplants (lung, double-lung or heart-lung), 13 liver transplants and three kidney transplants.

**1-yr survival**

Initial analysis of outcome data in REVEAL was undertaken to address the following question: what are the predictors of 1-yr survival for the population of patients typically presenting to a PH practice regardless of stage or time of disease, or whether they are already under treatment? This is a distinctly different objective than evaluating probability of survival from other “starting points”, such as the onset of symptoms, initial presumption of PAH (e.g. by Doppler echocardiography findings), confirmation of PAH by RHC or a pre-specified point in time after initiation of treatment. All of these might be expected to yield different survival curves based on specific circumstances, and all address equally interesting but distinct questions. It is well recognised that the survival curves of newly diagnosed and previously diagnosed patients with PAH (or probably any other progressive fatal disease) are not superimposable [25]. With respect to prediction, our analyses focused on the most recent assessments for all patients at the time of REVEAL enrolment, as this was the time-point with the most comprehensive and reliable data.

Numerous predictors of outcome have been identified in patients with PAH. However, it is clear from experience, as well as from evidence disclosed by registries including REVEAL, that individual predictors do not always (or even always) predict survival equally well. Therefore, an important research area is to develop a more comprehensive list of risk factors that would be useful in making treatment decisions in individual patients.

**Figure 4.** Pulmonary arterial hypertension specific medication use at enrolment among previously diagnosed patients. 184 (7%) of patients were not on a prostaglandin, phosphodiesterase type-5 inhibitor or endothelin receptor antagonist. Of these, 88 were on calcium channel blockers for the treatment of pulmonary arterial hypertension.

**Figure 5.** 1-yr survival estimates of 641 connective tissue disease-associated pulmonary arterial hypertension (CTD-APAH) patients compared with 1,251 idiopathic pulmonary arterial hypertension (IPAH) patients in REVEAL. Log rank p<0.0001. Reproduced from [22] with permission from the publisher.

**Table 3** Comparison of characteristics of patients aged ≥19 yrs at diagnosis meeting traditional haemodynamic characteristics of pulmonary arterial hypertension with those with a pulmonary capillary wedge pressure (PcW) of 16–18 mmHg

| PcW at diagnosis | ≤15 mmHg | 16–18 mmHg | p-value |
|------------------|----------|------------|--------|
| Subjects n       | 2525     | 239        |        |
| Age yrs          |          |            |        |
| At enrolment     | 53.0±14.0| 56.1±14.5  | 0.001  |
| At diagnosis     | 50.1±14.4| 53.6±14.9  | <0.001 |
| Female           |          |            |        |
| 2007 (79.5)      | 174 (72.8)|          | 0.016  |
| Time from diagnosis |      |            |        |
| 24.9 (8.0–50.9)  | 20.2 (5.5–44.6)| 0.038 |
| 6MWD m           | 366±126  | 339±117    | 0.004  |
| PRA mmHg         | 9.3±5.6  | 12.8±5.6   | <0.001 |
| PVRI Wood units·m⁻² | 21.1±12.5| 19.1±13.0  | 0.052  |
| Hypertension     | 980 (40.2)| 111 (47.6)| 0.023  |
| Obese#           | 697 (33.3)| 85 (41.9) | 0.014  |
| Sleep apnoea     | 484 (21.0)| 85 (39.9) | <0.001 |
| Diabetes overall | 293 (12.0)| 47 (20.2) | <0.001 |
| Renal insufficiency| 109 (4.5)| 25 (10.7)| <0.001 |
| Cardiomyopathy dilated | 24 (1) | 4 (1.7) | 0.286  |
| Warfarin         | 1302 (53.4)| 105 (45.1)| 0.016  |
| Oxygen           | 982 (40.3)| 110 (47.2)| 0.036  |
| α-blocker        | 296 (12.1)| 51 (21.9) | <0.001 |

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. 6MWD: 6-min walk distance; PRA: mean right atrial pressure; PVRI: pulmonary vascular resistance index. #: body mass index ≥30 kg·m⁻². Reproduced from [15] with permission from the publisher.
Predictors of survival of 2,716 adult patients meeting traditional haemodynamic criteria were analysed, and risk stratification was proposed based on a prognostic equation [27]. The equation was developed from a multivariable Cox model which identified 15 factors that were associated with increased risk and four factors that were associated with decreased risk. Adjusted for other variables, CTD-APAH, PoPH-APAH and FPAH were identified as being associated with increased risk compared with other WHO group I PAH subgroups. Other factors associated with increased risk were renal insufficiency, males aged >60 yrs, patients with a heart rate of >92 beats·min⁻¹ or systolic blood pressure <110 mmHg, and patients with pericardial effusion per echocardiography. In the multivariable model, RHC data proved to be predictive only at the extreme ends of the distributions, with higher risk associated with \( P_{ra} \) >20 mmHg for RHCs performed in the year prior to enrolment and PVR >32 Wood units. Relative to WHO functional class II, patients who were in WHO functional class III were at higher risk and, to an even greater extent were those in WHO functional class IV. Patients who were in WHO functional class I were at lower risk than the higher functional classes. BNP, \( D_{L,CO} \) % predicted and 6MWD each had higher risk and lower risk cut-off points identified. Thus, while high BNP, low 6MWD and low \( D_{L,CO} \) are associated with poor outcomes, low BNP, high 6MWD and high \( D_{L,CO} \) are associated with better than average outcomes. The hazard ratios are shown in figure 6.

**Survival from different reference points**

The observed 1-yr survival from the date of enrolment for this patient cohort was 91% (95% CI 89.9–92.1) (fig. 7) [28]; however, it is important to note that this reflects survival from REVEAL enrolment in a cohort of predominantly prevalent patients. The goal of predicting survival from any point in the patient course is quite different from the goal of estimating survival from time of diagnosis. As shown by MILLER and FOREMAN [29], a delayed entry model accounting for left truncation can reliably estimate survival from diagnosis utilising the full cohort and producing a comparable estimate to the one obtained excluding all previously diagnosed patients. The estimate of survival from enrolment among previously diagnosed patients is a biased estimate of survival from diagnosis. Similarly, the estimate of survival from diagnosis is a biased estimate of expected survival from the current time for previously diagnosed patients.

Estimates of 1-, 3-, 5- and 7-yr survival from diagnosis [28], excluding patients with non-traditional \( P_{pcoe} \), were 85%, 68%, 57% and 49%, respectively. The median survival of approximately 7 yrs was considerably better than the median survival of 3 yrs reported in the NIH registry prior to the modern treatment era. While data from the French PAH registry have shown that...
survival among IPAH patients has improved in the modern management era [30]. IPAH remains a severe, often fatal condition. Recent analysis of REVEAL confirms that IPAH patients who would have met the NIH inclusion criteria have better survival today than previously reported [28].

**Risk calculator and validation**

The >500 newly diagnosed patients enrolled after September 2007 provided a unique opportunity to validate the prognostic equation utilising data that had not been part of the model development process. Furthermore, a goal of risk stratification was to perform risk assessment at any time in the patient course. Validating a model developed in a primarily prevalent cohort in a different cohort of newly diagnosed patients allows for a robust assessment of the generalisability of the model. Additionally, a simplified version of the equation, the REVEAL risk calculator (fig. 8), was developed prior to validation, and the new patient cohort provided an opportunity to validate both the equation and the calculator [30]. The validation demonstrated excellent discrimination and calibration for both the prognostic equation and the risk calculator [31]. In addition to the new REVEAL cohort, the calculator has also been validated within a large single centre registry [13]. As some REVEAL investigators have begun using the risk calculator for serial assessment in clinical practice, further research will need to address the implications of changes in risk score over time.

**INTERIM CONCLUSIONS FROM REVEAL**

Although a remarkable depth and breadth of data remain to be analysed (and continue to be collected), REVEAL has already provided extensive information about PAH based on broad institutional, geographical, clinical, haemodynamic and demographic diversity. It has characterised features of disease and real-world management at presentation and various stages of progression in subsets of WHO group 1, sex, age, region and severity. Functional and early survival outcomes in the general PAH population and PAH subsets have been described, and predictors of outcome based on a composite of haemodynamic, clinical and functional variables have been identified. Potential practical applications of predictive capabilities in the field of transplantation have been advanced.

**Future directions**

REVEAL provides a perspective about the presentation, management and outcome of PAH in the USA. Comparison and collaboration with other large registries provide a unique opportunity to further understand differences and similarities in distinct PAH populations [32]. Notably, both REVEAL and the French Registry [10] have provided substantial updates and insights on the clinical characteristics of patients with PAH in the current era. These two robust national databases have differing but entirely complementary principles of patient
enrolment, data acquisition and analysis, which provide opportunities for further advances. Each has described the short-term outcomes of patients from various perspectives, and has elucidated variables and developed models for more accurately assessing the likelihood of survival over progressively longer periods of observation. But the two registries also differ in ways that will be of interest to explore further: a greater sex disparity in the USA compared with France (or to the USA 30 yrs ago), a more obese patient population in the USA, and a higher prevalence of HIV-related PAH in France [21].

Where do we go now?

Going forward, each registry has the potential to serve as a test population to assess the observations and conclusions of the other; this is currently being initiated to determine whether respective predictive models can be cross-validated. Perhaps more productively, ways may be found to merge some data for even more robust global conclusions about PAH and its course, including the impact of treatment strategies.

STATEMENT OF INTEREST

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