Eur Respir Rev 2012; 21: 123, 8–18
DOI: 10.1183/09059180.00008211

EUROPEAN RESPIRATORY UPDATE

REVEAL: a contemporary US pulmonary arterial hypertension registry

M.D. McGoon* and D.P. Miller#

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 trials, allowing for a more accurate and generalisable assessment of demographics, comorbidities and disease severity. Additionally, observational studies often have larger sample 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

*Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, and #ICON Late Phase and Outcomes Research, San Francisco, CA, USA.

CORRESPONDENCE: M.D. McGoon, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, Minnesota, MN 55905, USA. E-mail: mmcgoon@mayo.edu

Received: Nov 28 2011; Accepted after revision: Dec 12 2011

PROVENANCE: Publication of this peer-reviewed article was supported by Actelion Pharmaceuticals Ltd, Switzerland (article sponsor, *European Respiratory Review* issue 123).

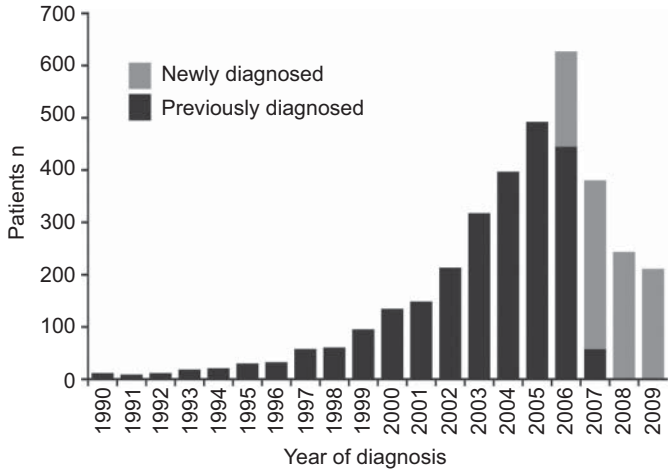


FIGURE 1. Number of previously (n=2,555) and newly (n=960) diagnosed pulmonary arterial hypertension patients enrolled in REVEAL by year of diagnosis.

provide insights not only into the characteristics of patients considered to have PAH, but also into the adherence of physicians to the published guidelines for making the diagnosis. Since all relevant test results were collected in the database, 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 ($\bar{P}_{pa}$) >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].

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} ⩽15 mmHg). The mean±SD age of this group at enrolment was 53.0±14.0 yrs (50.1±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±14.5 yrs (49.9±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±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 (⩽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 ⩽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.

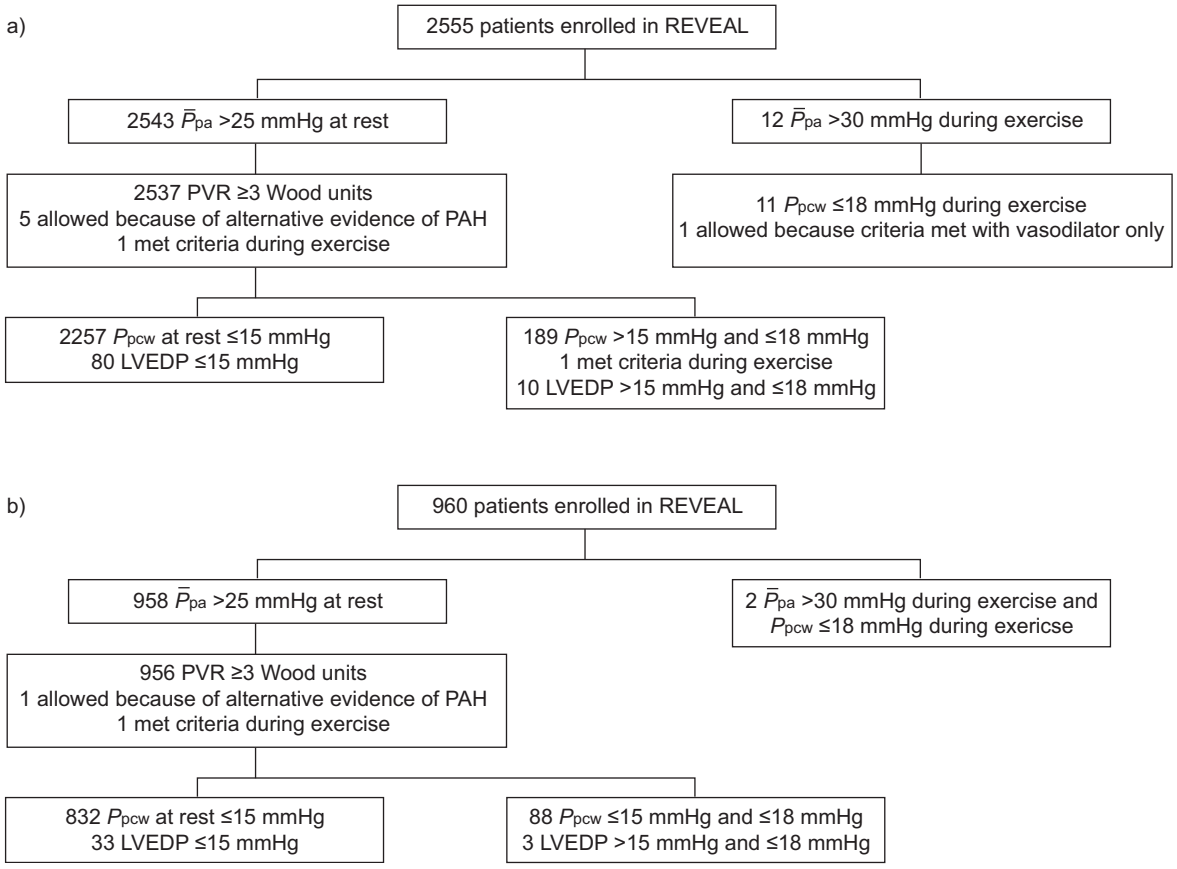


FIGURE 2. Inclusion characteristics of a) previously diagnosed and b) newly diagnosed pulmonary arterial hypertension (PAH) patients enrolled in REVEAL. PVR: pulmonary vascular resistance; $\bar{P}_{pa}$: mean pulmonary artery pressure; P_{pcw}: pulmonary capillary wedge pressure; LVEDP: left ventricular end-diastolic pressure.

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) 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 ($\bar{P}_{ra}$) <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) $\geqslant$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

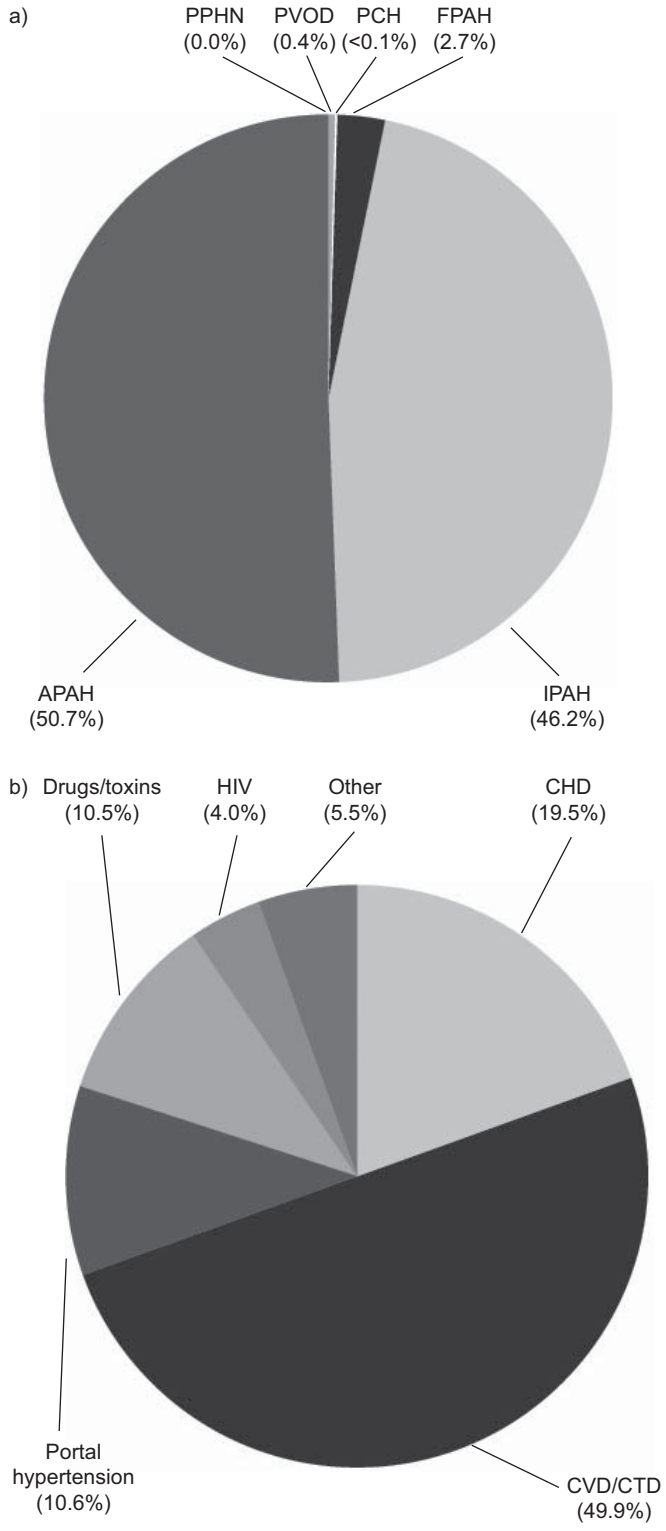


FIGURE 3. a) Pulmonary arterial hypertension (PAH) aetiological breakdown of REVEAL patients at enrolment. b) Breakdown of associated PAH subgroup. PPHN: persistent pulmonary hypertension of the newborn; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; FPAH: familial PAH; APAH: associated PAH; IPAH: idiopathic PAH; CHD: congenital heart disease; CVD/CTD: collagen vascular disease/connective tissue disease. Reproduced from [15] with permission from the publisher.

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 $\bar{P}_{pa}$, $\bar{P}_{ra}$ 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 $\bar{P}_{pa}$ 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

TABLE 1 Diagnostic right heart catheterisation parameters of patients meeting traditional haemodynamic criteria in the REVEAL registry by World Health Organization (WHO) group I diagnosis at enrolment

Characteristics	All patients[#]	IPAH	All patients with APAH[¶]	APAH subgroups[+]			
				CHD	CVD/CTD	Portal hypertension	Drugs/ toxins
Subjects n	2525	1166	1280	250	639	136	134
$\bar{P}_{pa}$ mmHg	50.7±13.6	52.1±13.0	49.1±13.8	59.5±16.9	44.9±11.2	48.5±10.6	52.2±12.2
Subjects n	2525	1166	1280	250	639	136	134
p-value		<0.001[f]					
P_{pcw} mmHg	9.1±3.5	9.2±3.5	9.0±3.5	8.9±3.6	8.9±3.5	9.3±3.6	9.2±3.6
Subjects n	2525	1166	1280	250	639	136	134
p-value		0.14					
$\bar{P}_{ra}$ mmHg	9.3±5.6	9.9±5.7	8.6±5.5	7.2±4.5	8.7±5.6	8.3±5.9	10.7±5.9
Subjects n	2298	1050	1174	229	580	131	127
p-value		<0.001[f]					
PVRI Wood units·m^2	21.1±12.5	22.9±11.4	19.0±13.0	23.7±20.9	16.9±9.1	15.7±7.2	24.2±12.7
Subjects n	1868	842	965	186	488	100	100
p-value		<0.001[f]					
Fick or thermodilution CI L·min^{-1}·m^{2}[§]	2.4±0.8	2.2±0.8	2.5±0.9	2.7±1.0	2.5±0.8	2.8±0.8	2.1±0.8
Subjects n	1868	842	965	186	488	100	100
p-value		<0.001[f]					
S_{V,O_2} %	62.9±10.0	61.8±9.8	64.2±10.1	67.3±9.5	63.3±10.0	66.6±8.5	61.1±9.7
Subjects n	1456	665	738	148	356	86	96
p-value		<0.001[f]					

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; $\bar{P}_{pa}$: mean pulmonary artery pressure; P_{pcw}: pulmonary capillary wedge pressure; $\bar{P}_{ra}$: mean right atrial pressure; PVRI: pulmonary vascular resistance index; CI: cardiac index; S_{V,O_2}: mixed venous oxygen saturation. [#]: all patients aged ⩾19 yrs at diagnosis with a P_{pcw} ⩽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-occulsive disease and persistent pulmonary hypertension of the newborn); [¶]: all 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; [f]: 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 [15] with permission from the publisher.

not have significantly better outcomes. Compared with IPAH, patients with CTD-APAH appeared to have a unique phenotype with a higher risk profile, including higher levels of brain natriuretic peptide (BNP) and lower diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$).

PoPH-APAH

Patients with PoPH-APAH have also been identified as a higher risk cohort [23]. Unlike patients with CTD-APAH, the overall risk profile for PoPH-APAH does not immediately help to explain the worse outcomes seen in this cohort. In fact, patients with PoPH-APAH have higher average cardiac index and lower average $\bar{P}_{ra}$ compared with IPAH/FPAH patients and newly diagnosed PoPH-APAH patients have higher than average 6MWD. Nonetheless, 2-yr survival from enrolment is worse for both newly diagnosed and previously diagnosed PoPH-APAH patients compared with IPAH/FPAH, as is the case with 5-yr survival from diagnosis. Practice patterns differences were also identified. In particular, PoPH-APAH patients were less likely than IPAH/FPAH patients to be on a PAH-specific therapy at enrolment [23].

CHD-APAH

To date, the most extensive evaluation of CHD-APAH patients has occurred within the paediatric cohort. Paediatric patients with CHD-APAH do not have significantly better survival than paediatric patients with IPAH/FPAH, and no survival differences were identified between paediatric patients with repaired or unrepaired 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 conventional definition of acute vasoresponders demonstrated a trend towards improved survival, although acute vasoresponders were treated with both calcium channel blockers alone and as combination therapy [17].

NON-TRADITIONAL HAEMODYNAMIC CRITERIA

Demographics and comorbidities

In the initial enrolment phase (up to September 2007), 239 adult patients had a P_{pcw} 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

TABLE 2 Pulmonary arterial hypertension-specific medications among patients meeting traditional haemodynamic criteria in the REVEAL registry at enrolment

	ERA[#]	PDE-5 inhibitor[¶]	Prostacyclin analogue		
			Intravenous epoprostenol	Inhaled iloprost	Treprostinil[+]
Overall use[§]	1147 (47.0)	1194 (49.0)	480 (19.7)	237 (9.7)	307 (12.6)
Monotherapy	452 (18.5)	417 (17.1)	188 (7.7)	23 (0.9)	84 (3.4)
Combination with one oral therapy[f]	291 (11.9)	290 (11.9)	243 (10.0)	138 (5.7)	148 (6.1)
Combination with one prostacyclin analogue	224 (9.2)	305 (12.5)	2 (0.1)	3 (0.1)	5 (0.2)
Combination with >1 other therapy	180 (7.4)	182 (7.5)	47 (1.9)	73 (3.0)	70 (2.9)
NYHA/WHO functional class I/II					
Overall use	468 (47.1)	474 (47.7)	187 (18.8)	71 (7.1)	111 (11.2)
Monotherapy	216 (21.7)	187 (18.8)	83 (8.4)	4 (0.4)	26 (2.6)
Combination with one oral therapy[f]	110 (11.1)	109 (11.0)	85 (8.6)	41 (4.1)	60 (6.0)
Combination with one prostacyclin analogue	76 (7.6)	110 (11.1)			
Combination with >1 other therapy	66 (6.6)	686 (6.8)	19 (1.9)	26 (2.6)	25 (2.5)
NYHA/WHO functional class III					
Overall use	525 (47.7)	567 (51.5)	218 (19.8)	130 (11.8)	161 (14.6)
Monotherapy	181 (16.4)	177 (16.1)	80 (7.3)	16 (1.5)	43 (3.9)
Combination with one oral therapy[f]	147 (13.4)	147 (13.4)	117 (10.6)	78 (7.1)	79 (7.2)
Combination with one prostacyclin analogue	114 (10.4)	160 (14.5)	2 (0.2)	2 (0.2)	4 (0.4)
Combination with >1 other therapy	83 (7.5)	83 (7.5)	19 (1.7)	34 (3.1)	35 (3.2)
NYHA/WHO functional class IV					
Overall use	55 (44.4)	61 (49.2)	44 (35.5)	14 (11.3)	15 (12.1)
Monotherapy	5 (4.0)	14 (11.3)	17 (13.7)	2 (16)	5 (4.0)
Combination with one oral therapy[f]	16 (12.9)	16 (12.9)	21 (16.9)	8 (6.5)	4 (3.2)
Combination with one prostacyclin analogue	18 (14.5)	15 (12.1)			
Combination with >1 other therapy	16 (12.9)	16 (12.9)	6 (4.8)	4 (3.2)	6 (4.8)

Data are presented as n (%). Combinations with one oral therapy, with one prostacyclin analogue, and with more than one oral therapy are mutually exclusive and exclude calcium channel blockers. Blinded clinical trial patients are excluded from this presentation (n=87). ERA: endothelin receptor antagonist; PDE-5: phosphodiesterase type-5; NYHA/WHO: New York Heart Association/World Health Organization. [#]: 953 on bosentan, 106 on sitaxsentan and 89 on ambrisentan; [¶]: 1,147 on sildenafil and 47 on tadalafil; [+]: treprostinil use includes 159 on intravenous, 112 on subcutaneous, 28 on inhaled and nine on oral treprostinil; [§]: n=2,435; [f]: oral therapy is defined as bosentan, sildenafil, ambrisentan, sitaxsentan and tadalafil. Reproduced from [15] 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 P_{pcw} 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 P_{pcw} >15 mmHg. Approximately half of these PAH patients with non-traditional haemodynamics had a P_{pcw} measured at ⩽15 mmHg on a subsequent RHC. Similarly, some patients who originally fell within the traditional haemodynamic criteria had higher P_{pcw} outside of the traditional range at follow-up RHC. Among patients who were diagnosed with a P_{pcw} 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 P_{pcw}, 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 patients. In both groups, patients with $\bar{P}_{ra}$ of ⩾14 mmHg and patients with 6MWD <300 m were shown to have worse survival than was predicted by the LAS. An adjustment to the

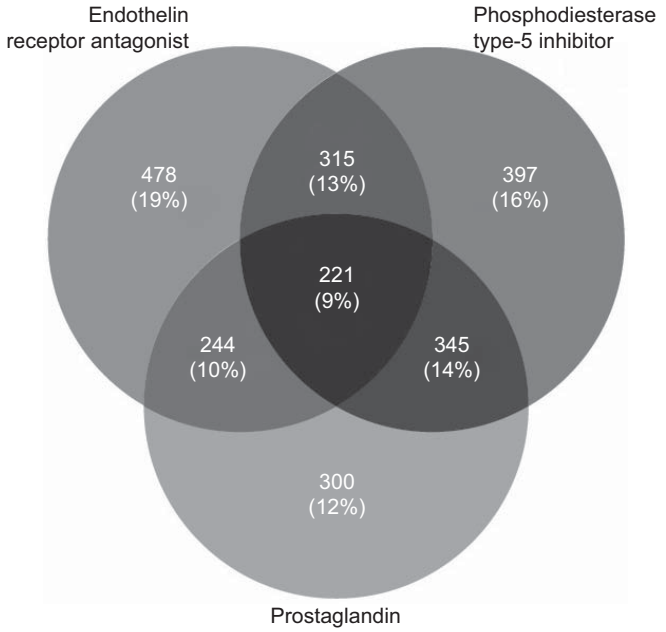


FIGURE 4. Pulmonary arterial hypertension specific medication use at enrolment among previously diagnosed patients. 184 (7%) of patients were not on a prostaglandin, phosphodiesterase type-5 inhibitor or endothelin receptor antagonist. Of these, 88 were on calcium channel blockers for the treatment of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

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

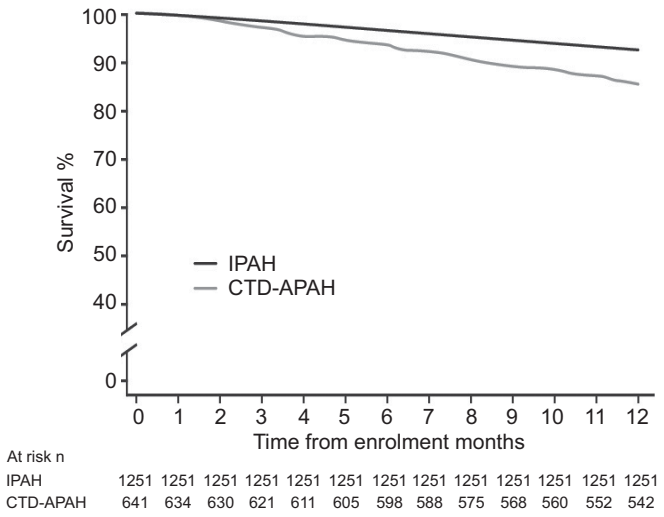


FIGURE 5. 1-yr survival estimates of 641 connective tissue disease-associated pulmonary arterial hypertension (CTD-APAH) patients compared with 1,251 idiopathic pulmonary arterial hypertension (IPAH) patients in REVEAL. Log rank $p<0.0001$. Reproduced from [22] with permission from the publisher.

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 (P_{pcw}) of 16–18 mmHg

	P_{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
$\bar{P}_{ra}$ 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
Cadiomyopathy dilated	24 (1.0)	4 (1.7)	0.286
Warfarin	1302 (53.4)	105 (45.1)	0.016
Oxygen	982 (40.3)	110 (47.2)	0.036
β-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; $\bar{P}_{ra}$: mean right atrial pressure; PVRI: pulmonary vascular resistance index. #: body mass index ⩾30 kg·m^{-2}. Reproduced from [15] with permission from the publisher.

usually) align in an individual patient in a consistent direction. A patient may have a pessimistically predictive BNP level, but an optimistic 6MWD or $\bar{P}_{ra}$. In view of this, it seems appropriate to consider the total information available about a patient in order to arrive at a reasonable conclusion about their severity of disease and outlook for future stability or deterioration [26]. As mentioned previously, a pre-specified objective of the REVEAL registry was to identify predictors of short- and long-term survival reflecting current treatment and clinical variables. Therefore, we assessed the prognostic value of multiple factors to enable more accurate risk stratification, and developed an algorithm for predicting survival in patients with PAH.

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 $\bar{P}_{ra}$ >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.

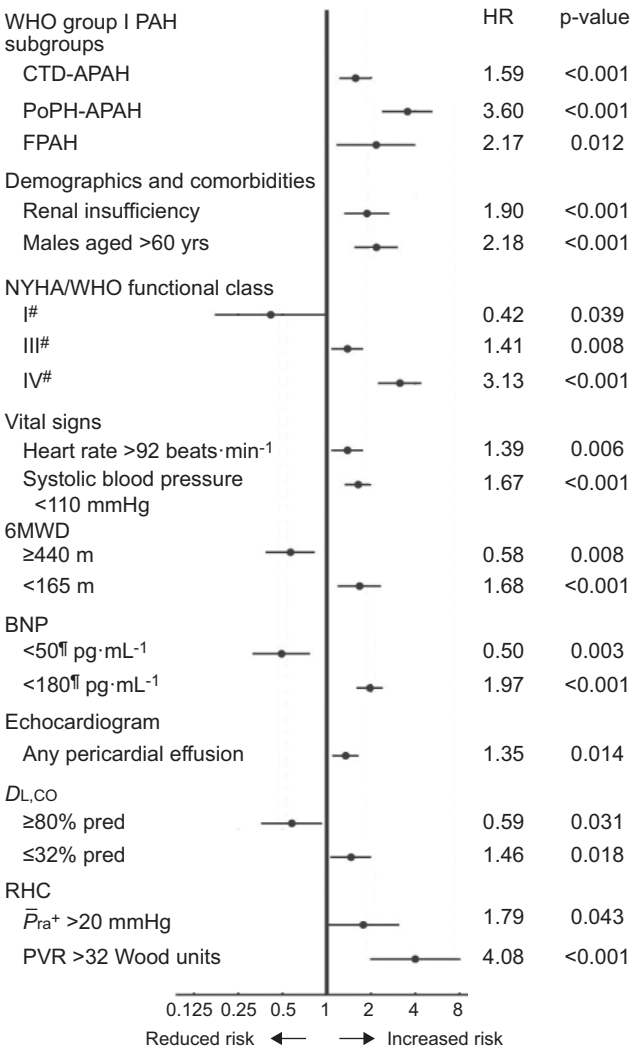
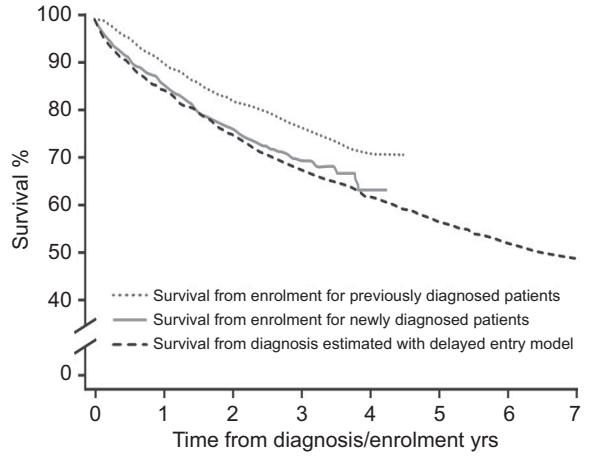


FIGURE 6. Cox proportional hazard estimates for multivariate model of survival, limited to terms included in the final stepwise model. Parameters significantly associated with 1-yr survival include the Borg dyspnoea scale, right ventricular dysfunction, pulmonary vascular resistance (PVR) index, pulmonary capillary wedge pressure, cardiac index, mean pulmonary artery pressure and total serum bilirubin. Candidate predictor variables that were not significant at the univariable level included Tei index, vasoreactivity, race, newly diagnosed pulmonary arterial hypertension (PAH) and income. Missing Borg scale and missing PVR index were both associated with lower than average observed survival and were, therefore, considered candidate predictor variables. WHO: World Health Organization; CTD: connective tissue disease; APAH: associated PAH; PoPH: portal hypertension; FPAH: familial PAH; NYHA: New York Heart Association; 6MWD; 6-min walk distance; BNP: brain natriuretic protein; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; RHC: right heart catheterisation; $\bar{P}_{ra}$: mean right atrial pressure. Data are presented as hazard ratio (HR) with 95% confidence level. #: reference category was NYHA/WHO functional class II or missing; ¶: if N-terminal proBNP is available and BNP is not, cut-off points are replaced with <300 pg·mL^{-1} and >1,500 pg·mL^{-1}; +: restricted to tests performed within 1 yr of enrolment, otherwise, the indicator is set to 0. Reproduced from [27] with permission from the publisher.

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_{pcw}, 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



At risk n

Delayed entry (all)	965	1259	1356	1371	1168	902	684	536
KM#	965	751	475	250	34	0	0	0
KM¶	2553	2289	2012	1725	365	0	0	0

FIGURE 7. Survival estimates of patients in REVEAL using Kaplan–Meier estimates stratified by newly *versus* previously diagnosed patients and survival estimated by a delayed entry model accounting for truncation. The model includes all REVEAL patients but the number of patients at risk is limited to the time period during which they were followed in the study. Therefore, the first 3 months is estimated exclusively based on newly diagnosed patients and thereafter combined data from previously diagnosed patients and long-term follow-up of newly diagnosed patients. #: newly diagnosed; ¶: previously diagnosed.

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

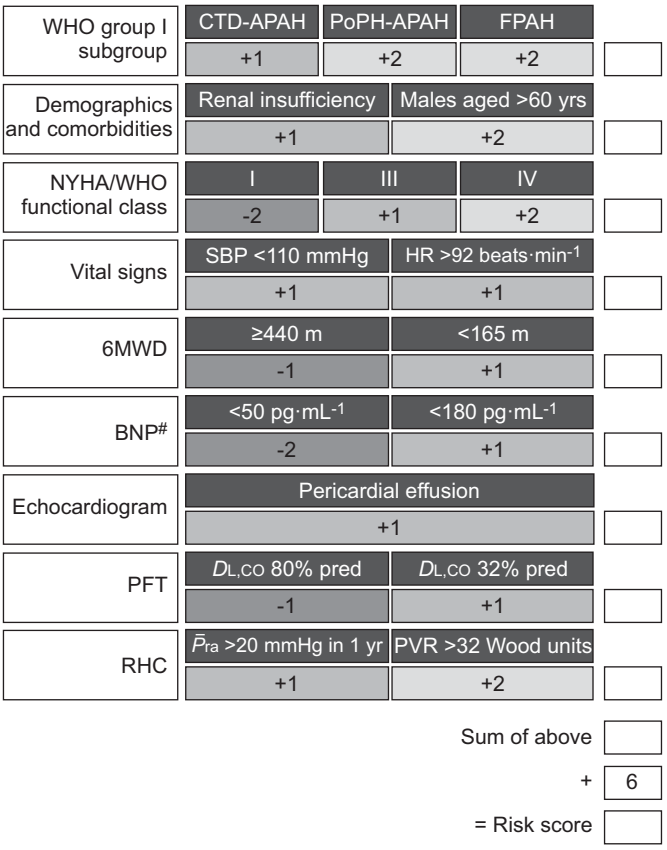


FIGURE 8. REVEAL pulmonary arterial hypertension (PAH) risk score. CTD: connective tissue disease; APAH: associated PAH; PoPH: portal hypertension; FPAH: familial PAH; WHO: World Health Organization; NYHA: New York Heart Association; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; PFT: pulmonary function test; RHC: right heart catheterisation; SBP: systolic blood pressure; HR: heart rate; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; $\bar{P}_{ra}$: mean right atrial pressure; PVR: pulmonary vascular resistance. #: if N-terminal proBNP is available and BNP is not, cut-off points are replaced with <300 pg·mL^{-1} and >1,500 pg·mL^{-1}. Reproduced from [31] with permission from the publisher.

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

M.D. McGoon's institution has received research funding from Medtronic and Gilead for studies related to pulmonary hypertension in which he was primary investigator. He has served on advisory, steering and/or endpoint/DSMB committees for Actelion, Gilead, Lung LLC, GSK and Medtronic. He has received honoraria for speaking at conferences supported by Actelion and Gilead. D.P. Miller is an employee of ICON Late Phase and Outcomes Research, a division of ICON PLC. His department receives research funding from pharmaceutical companies to conduct observational research. Funding for the statistical analysis of the REVEAL study is provided by Actelion. No funding was provided for his participation in this manuscript.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the principal investigators and their study coordinators for their participation in the REVEAL Registry: D. Badesch and C. Abbott (University of Colorado Health Sciences Center, Aurora, CO, USA); D. Ivy and K. Miller-Reed (Children's Hospital, Dept of Cardiology, Aurora, CO, USA); E. Berman-Rosenzweig and K. Lee (Columbia University, New York, NY, USA); J. White and K. Frutiger (University of Rochester Medical Center, Rochester, NY, USA); R. Sulica and R. Fenton (Beth Israel Medical Center, New York, NY, USA); A. Talwar and R. Miller (North Shore University - LIJ Medical Center, New Hyde Park, NY, USA); S. Hansdottir and P. Scovel (University of Iowa Hospitals and Clinics, Iowa City, IA, USA); M. Colvin-Adams and N. Harcourt (University of Minnesota Medical Center, Fairview, Minneapolis, MN, USA); R. Frantz and L. Durst (Mayo Clinic College of Medicine, Rochester, MN, USA); C. Daniels and J. Williamson-Mueller (Children's Research Institute at Ohio State, Columbus, OH, USA); C. Daniels and J. Holzaepfel (Ohio State University, Columbus, OH, USA); R. Dweik and J. Newman (Cleveland Clinic Foundation, Cleveland, OH, USA); R. Schilz and D. Haney (University Hospital of Cleveland, Cleveland, OH, USA); G. Elliott and N. Kitterman (Intermountain Medical Center and the University of Utah, Salt Lake City, UT, USA); H. Farber and K. Tobin Finch (Boston University School of Medicine, Boston, MA, USA); N. Hill and K. Sachetta (Tufts-New England Medical Center, Boston, MA, USA); A. Waxman and L. Lawler (Massachusetts General Hospital, Boston, MA, USA); A. Frost and H. Purl (Baylor College of Medicine, Houston, TX, USA); G. Mallory and A. Bogran (Texas Children's Hospital, Houston, TX, USA); D.J. Levine and A. Cline (University of Texas Health Science Center, San Antonio, TX, USA); C. Markin and L. Roessel (Legacy Clinic Northwest, Portland, OR, USA); M. Mathier and Y. Mallory (University of Pittsburgh School of Medicine, Pittsburgh, PA, USA); D. Taichman and M.J. Patel (University of Pennsylvania Medical Center, Philadelphia, PA, USA); S. Murali and A. Nowicki (Allegheny General Hospital, Pittsburgh, PA, USA); S. Weaver and G. Larese-Ortiz (Temple Lung Center, Philadelphia, PA, USA); D. McGlothlin and E. Kobashigawa (UCSF Medical Center, San Francisco, CA, USA); S. Shapiro and G. Traiger (VA Greater Los Angeles Health System, Los Angeles, CA, USA); V. Test and L. Santana (UCSD Medical Center, La Jolla, CA, USA); R. Zamanian and V. Scott (Stanford University Medical Center, Palo Alto, CA, USA); R. Oudiz and J. Beckman (LA Biomedical Research Institute at Harbor-UCLA, Torrance, CA, USA); D. Ross and M. Dyke (UCLA Medical Center, Los Angeles, CA, USA); D. Moore and M.B. Boyd (Children's Hospital at Vanderbilt, Nashville, TN, USA); I. Robbins and T. Oyler (Vanderbilt University Medical Center, Nashville, TN, USA); J. Tallaj and R. Culbreth (University of Alabama at Birmingham, Birmingham, AL, USA); D. Yung and A. Davis (Seattle Children's, Seattle, WA, USA); C. Burger and P. Long (Mayo Clinic, Jacksonville, FL, USA); K. Mubarak and R. Carrie (University of Florida, Gainesville, FL, USA); J. Swisher and L. Karasick (Suncoast Lung Center, Sarasota, FL, USA); M. Chakinala and M. Duncan (Washington University, St. Louis, MO, USA); M.R. Costanzo and D. Heidenreich (Midwest Heart Foundation, Naperville, IL, USA); M. Gomberg and S. Coslet (University of Chicago Hospitals, Chicago, IL, USA); J. Gossage and M. James (Medical College of Georgia, Augusta, GA, USA); D. Grinnan and A. Frayser (Virginia Commonwealth University, Richmond, VA, USA); S. Nathan and Lori Schlegel (Inova Heart and Vascular Institute, Falls Church, VA, USA); P. Hassoun and J. Miller (Johns Hopkins Medical Center, Baltimore, MD, USA); M. Park and F.E. Pa'ahana-Janowick (University of Maryland School of Medicine, Baltimore, MD, USA); K. Highland and N.L. Craft (Medical University of South Carolina, Charleston, SC, USA); J. Klinger and B. Smithson (Rhode Island Hospital, Providence, RI, USA); S. Knoper (University of Arizona, Tucson, AZ, USA); W. McConnell and K. Hobbs (Kentuckiana Pulmonary Associates, Louisville, KY, USA); G. Saydain and S. Ahmad (FCCP, Wayne State University, Detroit, MI, USA); J. Wilt and B. Van Over (Spectrum Health Hospitals, Grand Rapids, MI, USA); V. Tapson and K. Kennedy (Duke University Medical Center, Durham, NC, USA); R. Tumuluri and S. Oxborough (St. Luke's Medical Center- Aurora, Milwaukee, WI, USA); H. Ventura and B. Harris (Ochsner Clinic Foundation, New Orleans, LA, USA).

The authors received editorial assistance from L. Thomas, Elements Communications Ltd (Westerham, UK), supported by Actelion Pharmaceuticals Ltd.

REFERENCES

1 Rich S, Dantzker DR, Ayres SM, *et al.* Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1987; 107: 216–223.
2 Rich S, ed. Executive summary from the World Symposium on Primary Pulmonary Hypertension 1998. Evian, September 6–10, 1998. Co-sponsored by the World Health Organization.
3 Simonneau G, Galiè N, Rubin L, *et al.* Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, S5–S12.
4 Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S43–S54.
5 Stricker H, Domenighett G, Popov W, *et al.* Severe pulmonary hypertension: data from the Swiss Registry. *Swiss Med Wkly* 2001; 131: 346–350.
6 Jing Z-C, Xu X-Q, Han Z-Y, *et al.* Registry and survival study in Chinese patients with idiopathic and familial pulmonary arterial hypertension. *Chest* 2007; 132: 373–379.
7 Peacock AJ, Murphy NF, McMurray JJ, *et al.* An epidemiological study of pulmonary arterial hypertension. *Eur Respir J* 2007; 30: 104–109.

8 Fischler M, Speich R, Dorschner L, *et al.* Pulmonary hypertension in Switzerland: treatment and clinical course. *Swiss Med Wkly* 2008; 138: 371–378.
9 Tueller C, Stricker H, Soccal P, *et al.* Epidemiology of pulmonary hypertension: new data from the Swiss registry. *Swiss Med Wkly* 2008; 138: 379–384.
10 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
11 Thenappan T, Shah SJ, Rich S, *et al.* A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur Respir J* 2007; 30: 1103–1110.
12 Thenappan T, Shah SJ, Rich S, *et al.* Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J* 2010; 35: 1079–1087.
13 Kane GC, Maradit-Kremers H, Slusser JP, *et al.* Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. *Chest* 2011; 139: 1285–1293.
14 McGoon MD, Krichman A, Farber H, *et al.* Design of the REVEAL registry for US patients with pulmonary arterial hypertension. *Mayo Clin Proc* 2008; 83: 923–931.
15 Badesch DB, Raskob GE, Elliott CG, *et al.* Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. *Chest* 2010; 137: 376–387.
16 Shapiro S, Traiger GL, Turner M, *et al*. Gender differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term PAH disease management (REVEAL). *Chest* 2011; [Epub ahead of print DOI: 10.1378/chest.10-3114].
17 Barst RJ, McGoon MD, Elliott CG, *et al*. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term PAH disease management. *Circulation* 2011; [Epub ahead of print DOI: 10.1161/circulationaha.111.026591].
18 Brown LM, Chen H, Halpern S, *et al.* Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. *Chest* 2011; 140: 19–26.
19 Burger CD, Foreman AJ, Miller DP, *et al.* Comparison of body habitus in patients with pulmonary arterial hypertension enrolled in the Registry to EValuate Early And Long-term PAH disease management with normative values from the National Health and Nutrition Examination Survey. *Mayo Clin Proc* 2011; 86: 105–112.
20 Farber HW, Foreman AJ, Miller DP, *et al.* REVEAL registry: correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertension. *Congest Heart Fail* 2011; 17: 56–64.
21 Frost AE, Badesch DB, Barst RJ, *et al.* The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. *Chest* 2011; 139: 128–137.
22 Chung L, Liu J, Parsons L, *et al.* Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010; 138: 1383–1394.
23 Krowka MJ, Miller DP, Barst RJ, *et al*. Portopulmonary hypertension: a report from the US-based REVEAL registry. *Chest* 2011; [Epub ahead of print DOI: 10.1378/chest.11-0160].
24 Benza RL, Miller DP, Frost A, *et al.* Analysis of the lung allocation score estimation of risk of death in patients with pulmonary arterial hypertension using data from the REVEAL Registry. *Transplantation* 2010; 90: 298–305.
25 Humbert M, Sitbon O, Yaici A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.
26 Humbert M, Montani D, Souza R. Predicting survival in pulmonary arterial hypertension: time to combine markers. *Chest* 2011; 139: 1263–1264.
27 Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension. Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). *Circulation* 2010; 122: 164–172.
28 Benza RL, Miller DP, Barst RJ, *et al*. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from REVEAL. *Chest* 2011 (in press).
29 Miller DP, Foreman AJ. Estimating survival from diagnosis when study enrollment is after time of diagnosis: a left truncation case study. *Pharmacoepidemiol Drug Saf* 2011; 20: S1.
30 Humbert M, Sitbon O, Chaouat A, *et al.* Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.
31 Benza RL, Gomberg-Maitland M, Miller DP, *et al*. The REVEAL risk score calculator in newly diagnosed patients with pulmonary arterial hypertension. *Chest* 2011; [Epub ahead of print DOI: 10.1378/chest.11–0676].
32 McGoon MD, Benza RL, Fronst AE, *et al*. Validation of the French Pulmonary Hypertension Network equation to estimate survival: a REVEAL analysis. *Am J Respir Crit Care Med* 2012; (in press).