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REVIEW

Challenges in the diagnosis and treatment of pulmonary arterial hypertension

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ABSTRACT: Advances in the diagnosis and management of pulmonary arterial hypertension (PAH) have resulted in significant improvements in outcomes for patients with this devastating and progressive disease. However, because of the non-specific nature of its symptoms, and the low level of suspicion among clinicians, prompt and accurate diagnosis of PAH as a rare disease remains a challenge. This article explains some of the issues that need to be addressed when faced with a patient with suspected PAH and describes how noninvasive and invasive techniques can be used effectively to ensure an accurate diagnosis.

The availability of PAH-specific therapy means that once diagnosed, patients have a much greater chance of survival than they would have had in the past. However, despite improved survival, mortality is still high and, therefore, there is still room for improvement. It is currently recommended that patients with an inadequate clinical response to treatment receive sequential combination therapy; however, supportive data are still scarce. Although there is no clear explanation, these findings may be explained by the design and end-points chosen in clinical trials, the changing population of PAH and a need to improve the management strategy in this disease. Indeed, there is a clear need for randomised controlled studies that investigate whether adopting individualised treatment strategies, including upfront combination therapy, could help to optimise long-term management of patients with PAH.

KEYWORDS: Combination therapy, diagnostic algorithms, pulmonary arterial hypertension-specific therapy, screening

The past two decades have seen major progress in the field of pulmonary hypertension (PH). In the 1990s, PH was classified as either primary pulmonary hypertension (PPH) or secondary PH and treatment options were limited to intravenous prostacyclin only for PPH [1]. Since then, advances in our understanding of the disease have led to an evolution in the classification of PH and the development of new and effective therapies, most particularly for pulmonary arterial hypertension (PAH). The current classification of PH groups together a range of different manifestations that share similarities not only in pathophysiological mechanisms, but also in terms of clinical presentation and therapeutic approaches (table 1) [2]. Grouping diagnoses/diseases according to their pathophysiology has also led to the development of diagnostic algorithms that aim to facilitate the prompt diagnosis and accurate classification of PH, which is essential if a patient is to receive optimal management. In addition, it is important that patients with suspected PH are referred rapidly to expert centres in order to avoid delays in final diagnosis and treatment. New algorithms and guidelines have undoubtedly improved the diagnosis of PAH and, together with the development of disease-specific therapies, have contributed towards significant improvements in outcome for these patients in the modern treatment era [3–5]. However, despite these improvements, the management of patients with PAH remains challenging at all stages; from initial diagnosis to treatment. This article examines some of the potential issues faced when diagnosing and treating a patient with PAH, and discusses a number of areas in which further evidence is needed to guide optimal therapy.

THE CHALLENGE OF DIAGNOSIS IN PAH

Prompt and accurate diagnosis and classification of PAH is a pivotal step. Failure to make the correct diagnosis could have direct consequences. For example, a therapy that may be effective in

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TABLE 1 Clinical classification of pulmonary hypertension (PH)

Classification	Sub-classification
1. Pulmonary arterial hypertension	1.1 Idiopathic
	1.2 Heritable
	1.3 Drugs and toxins induced
	1.4 Associated with (APAH)
	1.4.1 Connective tissue diseases
	1.4.2 HIV infection
	1.4.3 Portal hypertension
	1.4.4 Congenital heart disease
	1.4.5 Schistosomiasis
	1.4.6 Chronic haemolytic anaemia
	1.5 Persistent PH of the newborn
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	
2. PH due to left heart disease	2.1 Systolic dysfunction
	2.2 Diastolic dysfunction
	2.3 Valvular disease
3. PH due to lung diseases and/or hypoxaemia	3.1 Chronic obstructive pulmonary disease
	3.2 Interstitial lung disease
	3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
	3.4 Sleep-disordered breathing
	3.5 Alveolar hypoventilation disorders
	3.6 Chronic exposure to high altitude
	3.7 Developmental abnormalities
4. Chronic thromboembolic PH	
5. PH with unclear and/or multifactorial mechanisms	5.1 Haematological disorders: myeloproliferative disorders and splenectomy
	5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangioleiomyomatosis neurofibromatosis and vasculitis
	5.3 Metabolic disorders: glycogen storage disease, Gaucher disease and thyroid disorders
	5.4 Others: tumoural obstruction, fibrosing mediastinitis and chronic renal failure on dialysis

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one form of PH may be ineffective or potentially detrimental in PH due to other causes. Conversely, without a correct diagnosis patients may not receive beneficial, or even life-saving, treatment [6]. A major problem that has yet to be overcome is late diagnosis of PAH. Analysis of data from a number of contemporary registry studies has shown that 70–80% of patients are in World Health Organization functional class (WHO-FC) III/IV at diagnosis. Noticeably, this is similar to the 70% reported in the 1980s (fig. 1) [7]. In the 1987 National Institutes of Health registry, the mean time between symptom onset and diagnosis was 24 months [8]; almost 20 yrs later there was no improvement, with a mean time to diagnosis of 27 months in a contemporary French registry [9] and ~33 months in the US Registry to Evaluate Early And Long-term PAH disease management (REVEAL) [10]. This delay in diagnosis remains unacceptably high. The reasons behind the late identification of PAH probably result, at least in part, from the insidious nature of the disease itself. The symptoms of PAH, particularly in the early stages, can be subtle. Symptoms such as breathlessness, fatigue and weakness are non-specific and overlap with other more common disorders such as asthma, left heart disease (LHD) and chronic obstructive pulmonary disease [2]. This could result in a delay in diagnosis, or even misdiagnosis in the early stages of the disease. In REVEAL, for example, a history of common respiratory disorders was independently associated with delayed PAH recognition [11]. The challenge PAH specialists face is encouraging earlier recognition and referral of patients at a time when they have less severe disease and will potentially respond better to treatment. There is clearly a need to raise the index of suspicion, to enable medical professionals to consider the possibility of PAH in patients with such non-specific symptoms or unexplained dyspnoea and to appropriately refer them for further assessment.

The initial noninvasive assessment of a patient with PAH includes a number of routine, widely available tests that are, nevertheless, valuable steps in the diagnostic algorithm (fig. 2) [2]. Although chest radiographs may be normal in the early stages of PAH, they will be abnormal in the vast majority of patients by the time of diagnosis. Indeed, enlargement of the pulmonary artery in the absence of obvious lung disease or signs of LHD, for example, may support a suspicion of PAH. Similarly, although normal in early PAH, electrocardiography (ECG) can also be suggestive of, or provide supportive evidence for, PAH with a significant number of affected patients showing right-axis

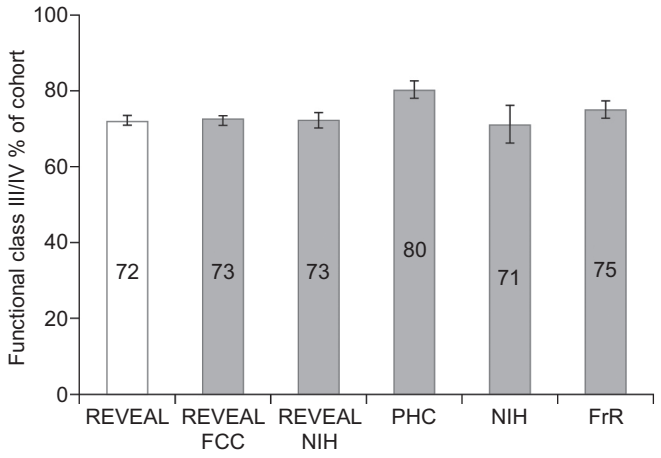

FIGURE 1. Patients in World Health Organization functional class III/IV in various registries. REVEAL: Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; REVEAL FCC: REVEAL French Comparison Cohort; NIH: National Institutes of Health; PHC: Pulmonary Hypertension Connection; FrR: French registry. REVEAL NIH: REVEAL NIH comparison cohort. Reproduced from [7] with permission from the publisher.

deviation and/or right ventricular strain. However, ECG does not have sufficient sensitivity or specificity to act as a screening tool on its own [2]. Echocardiography can be seen as the ''gatekeeper'' of the diagnosis as it is used to identify structural anomalies indicative of PAH, such as right ventricular hypertrophy, to obtain noninvasive estimates of a number of right heart haemodynamic variables and to exclude other causes of PH (for example, LHD, although this diagnosis is also difficult outside specialist centres). Tricuspid regurgitation velocity (TRV) is routinely used to estimate right ventricular systolic pressure (RVSP), which, in the absence of pulmonary stenosis, is almost identical to systolic pulmonary artery pressure ($P_{pa,sys}$). The estimate is based on the Bernoulli equation in which RVSP = $(4 \times TRV^2)$ + right atrial pressure. The latter is best estimated by the size and collapsibility of the inferior vena cava. A diagnosis of PH is unlikely in patients with a TRV of $\leqslant 2.8$ m·s^{-1} (estimated $P_{pa,sys} \leqslant 36$ mmHg) in the absence of other signs, while a TRV >3.4 m·s^{-1} (estimated $P_{pa,sys} > 50$ mmHg) is highly suggestive of PH and should lead to a confirmation by right heart catheterisation (RHC) [2]. However, this leaves a ''grey area'' occupied by patients with a TRV of 2.9–3.4 m·s^{-1} and an estimated $P_{pa,sys}$ of 37–50 mmHg where the diagnosis is uncertain. In general, there is a good overall correlation between Doppler-derived estimates of $P_{pa,sys}$ and those measured directly by RHC, with acceptable sensitivity and specificity [12, 13]. In individual patients, however, echocardiographic estimates of $P_{pa,sys}$ can be inaccurate and commonly vary by ± 10 mmHg compared with RHC values. This discrepancy occurs, at least in part, because the echocardiographic estimate of right atrial pressure lacks accuracy. In addition, echocardiography-derived $P_{pa,sys}$ does not provide a good assessment of mean pulmonary artery pressure (mP_{pa}), which is the basis of the definition of PH, although mP_{pa} can be calculated from the estimate of $P_{pa,sys}$. Overall echocardiography is unsuitable as a method of diagnosis, but provides the most effective screening tool in patients with a suspicion of PH [2] or in high-risk patients such as those with systemic sclerosis (SSc) [14] or with congenital heart disease [15], who are recognised as being predisposed to developing PAH. However, care should still be taken when working in these high-risk groups of patients to ensure an appropriate diagnosis. For example, a patient with an unrestricted shunt may have high $P_{pa,sys}$ mainly driven by a high pulmonary blood flow, in the absence of significant increase of pulmonary vascular resistance.

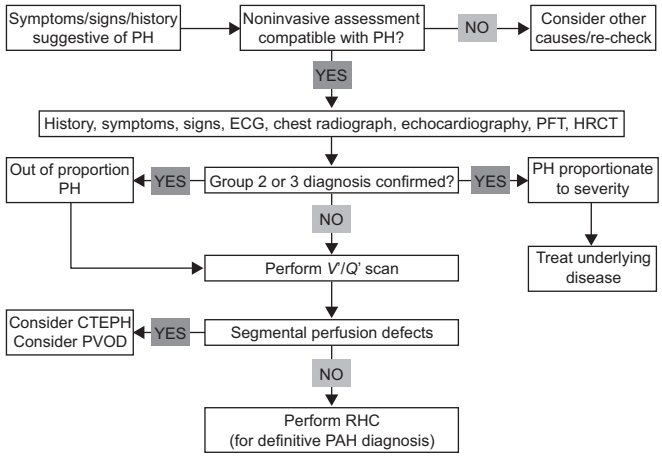

FIGURE 2. Diagnostic algorithm. PH: pulmonary hypertension; ECG: electrocardiogram; PFT: pulmonary function tests; HRCT: high-resolution computed tomography; *V'/Q'*: ventilation/perfusion; CTEPH: chronic thromboembolic PH; PVOD: pulmonary veno-occlusive disease; RHC: right heart catheterisation; PAH: pulmonary arterial hypertension. Reproduced from [2] with permission from the publisher.

An important step in the differential diagnosis is the exclusion of other causes of PH, such as respiratory disorders (Group 3) and chronic thromboembolic PH (CTEPH). For this purpose, high-resolution computed tomography (HRCT) scanning is extremely useful, in addition to pulmonary function tests and arterial blood gas analysis, to rule out the presence of significant lung parenchymal disease and is also important in distinguishing PAH from pulmonary veno-occlusive disease. Ventilation/perfusion scintigraphy is the standard test to raise a suspicion of CTEPH and may prompt the requirement for an angiocomputed tomography scan and/or a pulmonary angiography, to determine the presence of operable disease.

Despite advances in noninvasive imaging techniques such as echocardiography and cardiac magnetic resonance imaging [16, 17], RHC remains the diagnostic gold standard for PAH. As well as providing a definitive PAH diagnosis, RHC is used to determine disease severity, to test for vasoreactivity and to monitor patients for treatment effects. Despite concerns about the safety of the technique, the overall procedure-related mortality is very low (0.055%) in experienced centres [18]. The haemodynamic definition of PH is a mP_{pa} $\geqslant 25$ mmHg together with a pulmonary capillary wedge pressure (P_{pcw}) of $\leqslant 15$ mmHg, which defines pre-capillary PH, while a P_{pcw} of >15 mmHg defines the presence of pulmonary venous (or post-capillary) hypertension as a result of LHD (PH-LHD; WHO Group 2 PH) [2]. This differentiation is based on the assumption that P_{pcw} is a surrogate marker for left ventricular end-diastolic pressure (LVEDP). However, in a recent retrospective study, ~50% of patients with PH and a $P_{pcw} < 15$ mmHg (diagnostic of PAH) were subsequently found to have LVEDP >15 mmHg on

left heart catheterisation (diagnostic of PH-LHD) [19]. The results of this study should encourage PAH specialists to ensure that measurements of P_{pcw} are performed thoroughly at end-expiration and to perform direct LVEDP measurements (preferably simultaneous to P_{pcw}) in case of doubt. Although RHC is considered diagnostic, it is therefore important not to rely on any single haemodynamic parameter, but rather to ensure that the finding fits with the clinical picture and, if suspicious, to perform other tests (*e.g.* left heart catheterisation) to ensure an accurate diagnosis.

Although recent diagnostic algorithms have certainly improved the process of diagnosis, there are many situations faced in the clinic in which their application is challenging. As described previously, a particular diagnostic challenge can be distinguishing between patients with PAH and those with PH-LHD. There are a number of clinical factors that may particularly point to PH-LHD, such as older age, obesity, diabetes, coronary heart disease and atrial fibrillation [2]. Echocardiography in these patients may show changes including left atrial enlargement, left ventricular hypertrophy and indicators of elevated left ventricle filling pressures. Among patients with left heart failure, up to 44% have a normal ejection fraction despite obvious signs of left heart problems and diastolic dysfunction (heart failure with preserved ejection fraction (HFpEF)) [20]. Approximately 50% of patients with HFpEF will develop PH that can be severe, suggesting that pulmonary vascular disease may be a contributing factor. Importantly, in terms of diagnosis, P_{pcw} may be normal in patients with HFpEF; where there are suspicions that this might be the case, left heart catheterisation must be used to measure LVEDP. The role of exercise haemodynamics or fluid challenge to uncover diastolic dysfunction as a cause of PH remains to be established. It is important for all such complex patient groups that a correct diagnosis is made prior to the initiation of PAH-specific therapies that, at best, will not benefit them and, at worst, may be detrimental.

Another diagnostic challenge is the group of patients with combined pulmonary fibrosis and emphysema syndrome (CPFE), which is characterised by dyspnoea, upper-lobe emphysema, lower-lobe fibrosis and abnormalities of gas exchange [21]. In approximately half of these patients, CPFE is complicated by the presence of PH, and the development of PH worsens the already significant mortality associated with this syndrome. The presence of near normal airflow and lung volumes in these patients, together with the fact that characteristic upper-lobe emphysema and lower-lobe fibrosis may not be visible on chest radiographs in earlier stages, may lead to an assumption that the patient has PAH. However, the presence of severely reduced diffusing capacity of the lung for carbon monoxide indicates that PAH is unlikely and further tests such as HRCT scanning should be undertaken.

A further complication affecting the diagnosis of PAH reflects the changing demographics of patients with the disease. Comparison of data from the 1980s National Institutes of Health registry with contemporary registries shows an ageing PAH population, both at diagnosis and during treatment (table 2); although, interestingly, haemodynamic parameters at the time of diagnostic RHC have not changed substantially since the 1980s despite older age at diagnosis [7]. Advancing age tends to be associated with an increase in health problems and patients in contemporary registries present with high rates of comorbidities, many of which could affect the diagnosis and management of PAH. In the REVEAL registry, for example, around 40% of patients had systemic hypertension, 33% were obese (body mass index (BMI) $\geqslant$30 kg·m^{-2}), 21% had sleep apnoea and 12% had diabetes [10]. Interestingly, the upper limit of P_{pcw} to include patients in the registry has been set at 18 mmHg, which might have led to the inclusion of patients with PH-LHD. Nevertheless, in the modern era, clinicians are faced with a more challenging patient population in terms of both diagnosis and treatment.

TABLE 2 Patient's age at diagnosis or during treatment in registry studies

Registry	Year	Subjects	Age yrs
NIH [7]	1985	187	36.4±1.1; age at diagnosis
REVEAL[#] [7]	2011	1072	44.9±0.6; age at diagnosis
French registry [9]	2006	674	50±15; age at diagnosis
REVEAL [10]	2010	2525	50.1±14.4; age at diagnosis
UK National Audit[¶] [22]	2011	3163	55.3; age of cohort

Data are presented as n, mean±SD or mean. REVEAL: Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management. [#]: REVEAL patients matched to National Institute of Health (NIH) registry patients; [¶]: patients being treated with pulmonary arterial hypertension-specific therapies.

CHALLENGES IN THE TREATMENT OF PAH

Without treatment, PAH is a relentlessly progressive disease. This is the case even for patients who are mildly symptomatic. Data from the placebo arm of the EARLY study of bosentan in PAH patients in WHO-FC II demonstrated that 14% showed signs of clinical worsening during the 6-month study [23]. In recent years, the availability of PAH-specific therapy means that there have been significant improvements in the management of PAH and this is reflected in improved survival in the modern treatment era [3–5]. However, despite improvements in management and treatment, for the majority of patients with PAH, disease progression is inevitable and long-term survival remains poor. For example, in REVEAL the 1-, 3-, 5- and 7-yr survival rates from time of diagnostic RHC were 85%, 68%, 57% and 49%, respectively, in patients with all-cause PAH [5]. Similarly, in the French registry the 3-yr survival was 58.2% for patients with idiopathic PAH, heritable PAH or drug-induced PAH [3]. In some groups of patients with PAH, prognosis is particularly poor. Risk of death in patients with PAH associated with SSc (PAH-SSc) has been shown to be significantly higher compared with patients with idiopathic PAH [24], and in a recent study, 3-yr survival was found to be significantly lower in patients with PAH-SSc compared with those with idiopathic PAH (60% *versus* 77%, respectively) [25]. Importantly, the results from these registries are fairly consistent and provide confirmation of the rapidly progressive nature of the disease.

It seems clear that the ultimate goals of PAH therapy are no functional impairment, normalisation of haemodynamics and improved outcome. How to achieve this improvement remains a major challenge for clinicians today and, although treatment has advanced towards these goals, there is clearly much room

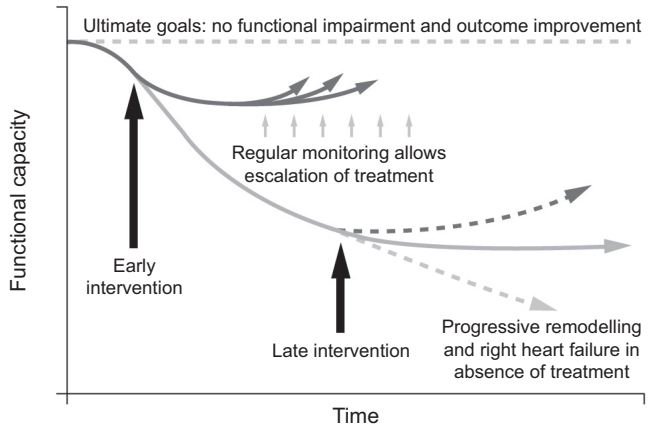

FIGURE 3. Schematic diagram showing the ideal approach to pulmonary arterial hypertension management, which involves regular monitoring and early intervention. Reproduced from [26] with permission from the publisher.

for improvement. In addition, haemodynamic normalisation can only be achieved in the very limited subgroup of acute responders to vasoreactivity challenge who achieve a long-term response to calcium channel blockers [2]. In general terms, a ''combination'' strategy of early intervention before functional impairment becomes more severe, together with regular monitoring and timely escalation of therapy is required (fig. 3) [26]. The problem of delayed diagnosis in PAH, as discussed previously, has obvious implications for early intervention, and clearly needs to be addressed. Once patients start treatment, current PAH treatment guidelines recommend a sequential add-on approach to combination therapy, with the timing of treatment escalation being determined by a patient's response; measured using variables known to be prognostic indicators (goal-oriented therapy) [2, 27]. Patients should be assessed at baseline and regularly every 3–6 months thereafter, or 3–4 months after initiation or change of therapy or in the case of clinical worsening. In general, tools and variables used to monitor PAH reflect three main aspects of the disease: 1) clinical aspects including symptoms and WHO-FC; 2) exercise capacity measured by the 6-min walk distance (6MWD) and cardiopulmonary exercise testing; and 3) right ventricular function using RHC, echocardiography and biomarkers [28]. In fact, overall, most of the parameters measured reflect right ventricular function, either directly or indirectly. As no single variable is capable of fully evaluating prognosis when used alone, assessment of patients during treatment requires monitoring of a combination of prognostic indicators. Current guidelines recommend patients are evaluated using a range of invasive and noninvasive variables, with the overall clinical condition of a patient being defined by the presence of measures associated with either ''worse prognosis'' or ''better prognosis'' (table 3) [2]. Based on these assessments, patients can be defined as stable and satisfactory (*i.e.* meeting the majority of criteria associated with ''better prognosis''), stable but not satisfactory (*i.e.* have not met some of the criteria associated with ''better prognosis'') or unstable and deteriorating (*i.e.* meeting the majority of criteria associated with ''worse prognosis'').

Patients who have an inadequate clinical response to therapy require re-evaluation and consideration for escalation of treatment [2]. This group of patients includes those initially in WHO-FC II or III who are either stable and not satisfactory, or unstable and deteriorating or those initially in WHO-FC IV who have not shown rapid improvement to WHO-FC II or better, or who are stable but not satisfactory. This goal-oriented strategy is recommended by treatment guidelines with a Class I level of recommendation and associated level of evidence C (*i.e.* based on expert opinion rather than clinical data). Overall, the majority of parameters used to assess patients have been evaluated as risk predictors at time of diagnosis, rather than during treatment, and therefore their validity in this setting has not been established. Variables with the potential to help monitor response to therapy are currently being investigated. In a recent study, NICKEL *et al.* [29] followed 109 patients with idiopathic PAH being treated with PAH-specific therapies. Patients were monitored every 3–12 months for a median of 38 months after initiation of therapy using a range of haemodynamic, functional and biochemical markers [29]. Standard baseline parameters including 6MWD, right atrial pressure, cardiac index, mixed venous oxygen saturation (S_{v,O_2}) and N-terminal pro-brain

TABLE 3 Variables with established importance for assessing disease severity, stability and prognosis in pulmonary arterial hypertension

Determinants of prognosis	Better prognosis	Worse prognosis
Clinical evidence of RVF	No	Yes
Rate of progression of symptoms	Slow	Rapid
Syncope	No	Yes
WHO-FC	I, II	IV
6MWT	Longer (>500 m)	Shorter (<300 m)
Cardiopulmonary exercise testing	Peak O_2 consumption >15 mL·min^{-1}·kg^{-1}	Peak O_2 consumption <12 mL·min^{-1}·kg^{-1}
BNP/NT-proBNP plasma levels	Normal or near normal	Very elevated and rising
Echocardiographic findings	No pericardial effusion	Pericardial effusion
	TAPSE >2.0 cm	TAPSE <1.5 cm
Haemodynamics	P_{ra} <8 mmHg and CI ⩾2.5 L·min^{-1}·m^{-2}	P_{ra} >15 mmHg or CI ⩽2.0 L·min^{-1}·m^{-2}

RVF: right ventricle failure; WHO-FC: World Health Organization functional class; 6MWT: 6-min walk test; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; TAPSE: tricuspid annular plane systolic excursion; P_{ra}: right atrial pressure; CI: cardiac index. Reproduced from [2] with permission from the publisher.

natriuretic peptide (NT-proBNP) were found to be independent predictors of survival. Furthermore, changes in WHO-FC, cardiac index, S_{v,O_2} and NT-proBNP during treatment were significant predictors of outcome with a higher predictive value than variables obtained at baseline, and improvements as well as deteriorations in these parameters after initiation of PAH-specific therapy had a strong impact on survival.

For those patients who have an inadequate clinical response on follow-up, treatment escalation in the form of sequential combination therapy is recommended; however, it is unclear whether this is the best strategy, or whether upfront combination therapy may be more successful. The vast majority of clinical trial data supporting the use of combination therapy in PAH have come from trials using sequential therapy [23, 30–37]. However, most of these trials failed to show a significant improvement in their primary end-point (usually 6MWD) associated with the use of combination therapy when compared with monotherapy, and the effects on time to clinical worsening have been variable (table 4). When interpreting these apparently disappointing data it should be borne in mind that although 6MWD is a proven prognostic indicator in PAH, in general its correlation with other end-points is poor and there is no linear relationship between change from baseline in 6MWD and morbidity/mortality [38]. Its suitability as a stand-alone end-point in clinical trials of PAH therapies is, therefore, questionable and increasingly controversial. Time to clinical worsening (TTCW) may represent a more suitable end-point because it is very relevant to clinical outcome in patients, which may be of particular importance in demonstrating the efficacy of combination therapy [38, 39]. However, TTCW has usually been included as a secondary or exploratory end-point in clinical trials and the definition of TTCW has been varied and unspecific with assessments being performed over relatively short time periods. These factors may, at least in part, account for the lack of benefit of combination therapy in terms of TTCW in the majority of clinical trials. In terms of trial end-points, time to first morbidity/mortality event may be more clinically relevant than TTCW and the time to the first morbidity/mortality event has recently been applied in the long-term event-driven SERAPHIN (Study with an endothelin receptor antagonist in pulmonary arterial hypertension to improve clinical outcome) trial of the dual endothelin receptor antagonist macitentan (Clinicaltrials.gov NCT00660179). In SERAPHIN the primary end-point of time to the first morbidity or mortality event (a composite end-point that included a range of outcome measures) aimed to provide a more comprehensive and relevant reflection of the true progression of PAH. It consists of: 1) worsening of PAH (defined by a pre-specified decline in 6MWD, worsening of symptoms and need for new PAH treatments); 2) initiation of intravenous or subcutaneous prostanoids; 3) atrial septostomy; 4) lung transplantation; and 5) death.

As previously mentioned, the vast majority of data on combination therapy in PAH concerns sequential therapy. However, it is unclear whether this is the optimal strategy and it is possible that upfront combination therapy may be more beneficial. The ongoing AMBITION (Ambrisentan and tadalafil in subjects with pulmonary arterial hypertension) study (Clinicaltrials.gov NCT01178073) aims to compare first-line combination therapy (ambrisentan and tadalafil) with first-line monotherapy in patients in WHO-FC II or III on the time to clinical failure. This novel end-point consists of morbidity and

TABLE 4 Clinical trials of combination therapy in pulmonary arterial hypertension (PAH)

Trial [ref.]	Background therapy/study drug	Design	Patients	Subjects n	Duration weeks	Primary end-point	Efficacy	
							Primary end-point	TTCW
BREATHE-2 [30]	Epoprostenol/bosentan	Upfront RCT	IPAH, SSc, SLE	33	16	TPR	-	ND
STEP [31]	Bosentan/iloprost (inhaled)	Sequential RCT	PAH	67	12	6MWD	-	+
COMBI [32]	Bosentan/iloprost (inhaled)	Sequential open label	IPAH	40	12	6MWD	-	-
PACES [33]	Epoprostenol/sildenafil	Sequential RCT	IPAH, CTD, CHD	277	12	6MWD	+	+
TRIUMPH-1 [34]	Sildenafil, bosentan or both/treprostinil (inhaled)	Sequential RCT	PAH	235	12	6MWD	+	-
FREEDOM-C [35]	Sildenafil, ERA or both/treprostinil (oral)	Sequential RCT	PAH	354	16	6MWD	-	-
IMPRES [36]	⩾2 PAH-specific therapies/imatinib	Sequential RCT	IPAH, HPAH, CTD, CHD	202	24	6MWD	+	-
PHIRST [37]	Bosentan/tadalafil	Sequential RCT	PAH	216[#]	16	6MWD	-	ND
EARLY [23]	Sildenafil/bosentan	Sequential RCT	PAH	28[¶]	24	PVR	+	ND

TTCW: time to clinical worsening; ERA: endothelin receptor antagonist; RCT: randomised controlled trial; IPAH: idiopathic PAH; SSc: systemic sclerosis; SLE: systemic lupus erythematosis; CTD: connective tissue disease; CHD: congenital heart disease; HPAH: heritable PAH; TPR: total pulmonary resistance; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; ND: not determined; +: met end-point; -: did not meet end-point. [#]: only patients included in the subgroup analysis of patients who were receiving concomitant bosentan at baseline were included; [¶]: only patients included in the subgroup analysis of patients who were receiving concomitant sildenafil at baseline were included.

mortality outcome measures including: 1) death; 2) hospitalisation for PAH; 3) atrial septostomy; 4) lung transplantation; and 5) absence of clinical improvement (defined by a decline in 6MWD by 15%, associated with progression or no improvement in symptoms and the need for treatment escalation) after at least 6 months. The results from this trial, the first event-driven study in naïve patients, are eagerly anticipated as they should provide valuable insight into the potential of an upfront combination therapy strategy in PAH. Certainly, lessons from other chronic and progressive diseases such as heart failure, where upfront combination treatment is the standard, would support this approach. As there is currently no cure for PAH and the prospect of drugs targeting new pathways is uncertain, we need to know how best to use our current armamentarium to optimise management. Therefore, in future trials, the paradigm needs to move from the current dogma of a two-drug regimen with a sequential approach (as seen in approval trials) to one of strategic trials aimed at improving management, possibly by utilising upfront therapy using combinations of drugs targeting different disease pathways.

As well as the question of sequential *versus* upfront combination therapy, a number of other aspects of management strategy are in need of clarification. It is clear that a range of factors affects progression and response to therapy in patients with PAH. While the ultimate goal of therapy is broadly applicable for all, it is probable that individual treatment goals should be tailored to the patients' individual risk profile and reflect factors such as patient age, BMI and comorbidities, as well as underlying aetiology. Data concerning how best to tailor management on an individual basis are currently lacking. Several questions remain to be answered, such as whether a goal-oriented strategy is actually the best treatment approach and the optimal treatment choice still needs to be established. For example, some experts question whether intravenous prostacyclin is underused in this setting in light of evidence of improved survival and its potential beneficial effects on disease progression [40].

The focus for several years has been effective pharmacological management of PAH and consequently the optimal role and timing of surgical intervention in PAH also remains to be fully defined. Despite early post-operative risks, recent transplant outcomes for PAH are encouraging. However, there is a need for information regarding the optimal timing for referral, listing and transplantation, and for the identification of more discriminatory markers of PAH prognosis to identify patients at risk and to optimise survival post transplantation [41]. Atrial septostomy is a palliative measure that may be of benefit in patients with severe, treatment-refractory PAH [42], both as a treatment option and as a bridge to transplantation [43]. In patients with severe PAH, atrial septostomy appears to improve symptoms, quality of life and survival [44], and may be particularly effective when used in combination with PAH-specific therapy [45]. However, data are sparse and there are a number of factors which require clarification, including the effects on exercise capacity and long-term haemodynamics, the benefits of a combination of atrial septostomy and drug therapy, and how early in the course of PAH atrial septostomy may be useful [44].

CONCLUSIONS

Developments in the classification, diagnosis and management of PAH and the availability of disease-targeted therapies have been associated with recent significant improvements in outcome for patients with PAH. Despite this, however, there remains much room for improvement. The diagnosis of PAH is still delayed and remains a significant challenge due to a range of factors, these include: 1) the subtlety of its symptoms and a low level of suspicion among clinicians; 2) the challenges associated with the use of diagnostic algorithms in the complex clinical conditions often encountered in ''real life''; and 3) the changing demographics and associated comorbidities of PAH patients. It is to be hoped that further evolution of diagnostic guidelines, and increased understanding of how risk scores identified in clinical registries such as REVEAL could be used in clinical practice, may considerably improve this situation and ensure patients are more rapidly and accurately diagnosed for treatment in the future. It is important to appreciate that PAH is a severe and progressive condition that requires close follow-up and regular monitoring to allow timely intervention, even in patients with mild symptoms. There is a need for new drugs targeting different pathways in PAH, but in the meantime there is also a need to better define the use of currently available therapies and treatment options. A more focused approach that takes into account individualised treatment goals may improve outcomes, while upfront rather than sequential combination therapy may prove more beneficial, particularly in patients at higher risk who may benefit from a more intensive approach. Overall, however, data to support such strategies are currently lacking.

STATEMENT OF INTEREST

J-L. Vachiéry has served as a consultant and advisory board member for Actelion, GSK and United Therapeutics. He has received speaker fees from Actelion, Bayer Shering, GSK, Eli Lilly, Pfizer and United Therapeutics. S. Gaine has served as a consultant, advisory board member and has received speaker fees from Actelion, GSK, Pfizer and United Therapeutics.

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