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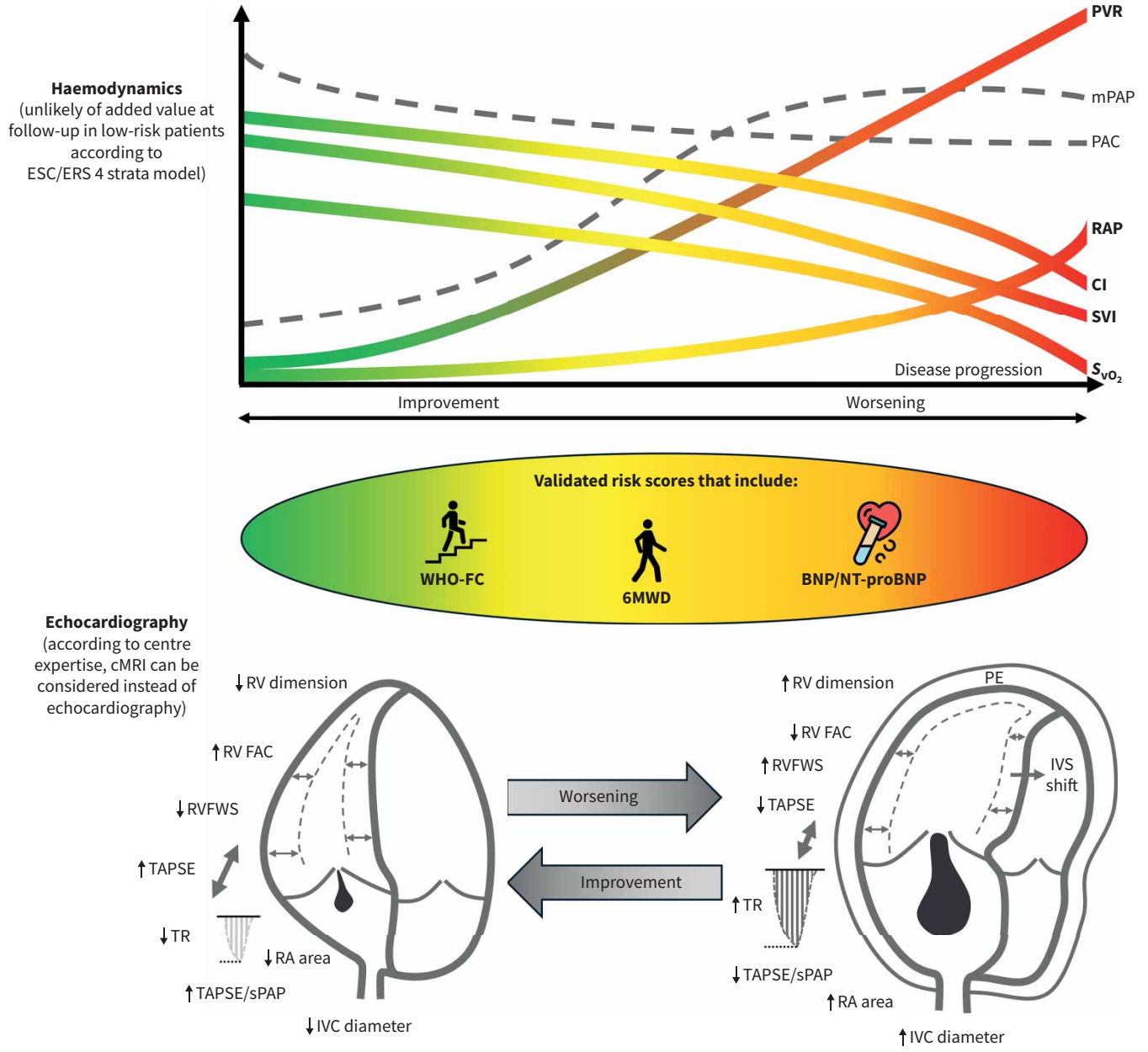

In grey: risk determinants with a less well-defined role as treatment goals

GRAPHICAL ABSTRACT Multidimensional strategy for risk stratification and treatment decisions in pulmonary arterial hypertension (PAH). ESC: European Society of Cardiology; ERS: European Respiratory Society; PVR: pulmonary vascular resistance; mPAP: mean pulmonary artery pressure; PAC: pulmonary arterial compliance; RAP: right atrial pressure; CI: cardiac index; SVI: stroke volume index; S_{vO_2}: mixed venous oxygen saturation; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; cMRI: cardiac magnetic resonance imaging; RV: right ventricle; FAC: fractional area change; RVFWS: RV free wall strain; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; IVC: inferior vena cava; TR: tricuspid regurgitation; RA: right atrium; PE: pericardial effusion; IVS: interventricular septum.

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Shareable abstract (@ERSpublications)
Risk stratification is useful in predicting outcomes and guiding treatment of patients with PAH, aiming to reach a low mortality risk; in addition to validated risk tools, PVR-associated markers are increasingly relevant in guiding treatment decisions. https://bit.ly/4cHFY6H

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Abstract

Risk stratification has gained an increasing role in predicting outcomes and guiding the treatment of patients with pulmonary arterial hypertension (PAH). The most predictive prognostic factors are three noninvasive parameters (World Health Organization functional class, 6-min walk distance and natriuretic peptides) that are included in all currently validated risk stratification tools. However, suffering from limitations mainly related to reduced specificity of PAH severity, these variables may not always be adequate in isolation for guiding individualised treatment decisions. Moreover, with effective combination treatment regimens and emerging PAH therapies, markers associated with pulmonary vascular remodelling are expected to become of increasing relevance in guiding the treatment of patients with PAH. While reaching a low mortality risk, assessed with a validated risk tool, remains an important treatment goal, preliminary data suggest that invasive haemodynamics and cardiac imaging may add incremental value in guiding treatment decisions.

Introduction

Although the first attempts to predict the survival of patients with pulmonary arterial hypertension (PAH) date back to the National Institutes of Health registry in the 1990s, it wasn't until the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) published their joint pulmonary hypertension (PH) guidelines in 2015 that risk stratification became an integral component of managing patients with PAH. While the initial recommendations on risk stratification in PAH were based on expert consensus rather than scientific evidence in this document, several tools were either further refined, newly developed and subsequently validated to predict morbidity and mortality. Most of these tools utilise noninvasive measurements of exercise tolerance (*e.g.* World Health Organization functional class (WHO-FC) and 6-min walk distance (6MWD)) and markers of right heart strain (*e.g.* natriuretic peptides). With the release of the 2022 ESC/ERS PH guidelines and other supporting documentation, risk stratification became an increasingly important tool to guide treatment decisions in patients with PAH.

Before and during the 7th World Symposium on Pulmonary Hypertension, the task force on risk stratification and treatment goals in PAH reviewed and summarised the available evidence on risk stratification, discussed the limitations of current strategies, and reviewed new data to propose future strategies to improve risk stratification in PAH, with a critical discussion on the usefulness of risk stratification for making treatment decisions and defining treatment goals.

PAH risk stratification

Clinical features and functional class

Despite being listed in the 2022 ESC/ERS PH guidelines risk table, except for WHO-FC, symptoms and signs are not consistently included in current ESC/ERS risk prediction models, while heart rate and systolic blood pressure are included in Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) risk scores. Nonetheless, clinical features play a prominent role in the management of patients with PAH. Patient feedback and clinical signs of right heart failure are often instrumental, informing physicians about disease severity and trajectories.

WHO-FC is an important component of all established prognostic scores and represents an independent predictor of prognosis [1, 2].

Exercise capacity

6-min walk test

The 6-min walk test (6MWT) is a simple, safe, inexpensive, submaximal exercise test, widely used to measure exercise capacity and accepted by global health authorities to assess "how a patient functions".

6MWD, as an absolute value, is associated with prognosis at both the time of PAH diagnosis and during follow-up [3]. Change in 6MWD, although used as the primary end-point in several clinical studies, is neither a predictor of major clinical events in short-term follow-up [4] nor a valid surrogate end-point for outcome [5]. However, changes in 6MWD are associated with changes in quality of life [6]. Studies have suggested that the minimal important difference for the change in 6MWD is 33–36 m, although this is dependent on the baseline 6MWD [6]. Deterioration in 6MWD is associated with an increased risk of morbidity and mortality events, while its improvement is not necessarily associated with better outcomes [7, 8].

While the 6MWD is correlated to PAH severity [9], it is also influenced by age and other factors, some of which have been used to develop 6MWD predictive equations; however, percentage-predicted values are no more predictive than absolute values [10].

In 2010, data from the REVEAL registry established meaningful thresholds of 165 m and 440 m as the guardrails of low and high risk [11]. These cut points were later validated in a comprehensive analysis of published 6MWD thresholds and changes and survival, confirming that a cut-off value of 165 m had the highest positive likelihood ratio for death, while the highest negative likelihood ratio, *i.e.* the best predictor of survival, was a threshold of 440 m [8, 11].

Other 6MWT parameters adding prognostic relevance to 6MWD may be heart rate recovery at 1 min [12] and exercise desaturation [13], but confirmation in large multicentric studies is needed. Additionally, preliminary results about the feasibility of remote 6MWT [14, 15] require prognostic validation before being considered for telehealth.

Cardiopulmonary exercise testing

In PAH, the highest attained oxygen uptake (peak V'_{O_2}) is associated with survival [16]. Peak V'_{O_2}, in combination with invasively measured stroke volume index (SVI), may provide incremental prognostic value in intermediate-risk PAH patients [17]. In patients with PAH, the slope of the total exhaled volume by exhaled carbon dioxide (V'_E/V'_{CO_2}-slope or the lowest ventilatory equivalent for carbon dioxide) is also associated with poor exercise capacity and survival [18].

Biomarkers

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are the most widely used prognostic biomarkers in the management of patients with PAH. In patients with PAH, natriuretic peptides reflect right heart overload or dysfunction and are correlated with haemodynamics, 6MWD and survival [19] both at baseline and at follow-up [20].

Among other prognostic and diagnostic biomarkers evaluated in PAH, there are markers associated with myocardial injury (troponin) [21], right ventricular dysfunction (growth differentiation factor 15 [22]), coagulation, inflammation and vascular remodelling such as soluble suppression of tumorigenicity 2 [23], C-reactive protein [24], interleukins [25–27], plasma stem cell factor combined with transforming growth factor-α [28], tumour necrosis factor (TNF)-α [29], insulin-like growth factor binding protein 4 [30], interferon-γ and annexin A1 [31]. In addition, biomarkers related to endothelial function such as von Willebrand factor [32] and adrenomedullin [33], extracellular matrix (matrix metalloproteinase 2) [34] and metabolism [35] as well as fibroblast growth factor-23 [36], endostatin, pentastatin [37–39] and circulating

endothelial progenitor cells [40–42] documented a prognostic role in PAH. Markers of end-organ failure such as serum creatinine, hyponatraemia and uric acid are also associated with the risk of death [11, 43, 44] as well as blood count, liver function and blood gas parameters [45–47].

At present, the challenge is to identify novel biomarkers that reflect pulmonary vascular remodelling and provide additional information to current risk stratification models. A recent study identified three biomarkers independently associated with survival in two different PAH cohorts [48]. β-nerve growth factor and CXC motif chemokine ligand 9 were predictors of death or lung transplantation, whereas high levels of TNF-related apoptosis-inducing ligand were associated with a better prognosis [48]. The prognostic value of these biomarkers was higher than the noninvasive variables WHO-FC, 6MWD and BNP/NT-proBNP [48], but independent confirmation is pending. Moreover, activin-A and follistatin-like 3 have been identified as prognostic in PAH, independent of risk stratification [49]. A proteome-wide screening in idiopathic/heritable PAH has identified a panel of nine proteins, independent of NT-proBNP, which significantly improved the risk prediction of the REVEAL risk score [50]. A more recent study identified six proteins that were associated with survival, independent of 6MWD and NT-proBNP [51].

Cardiac imaging

Echocardiography

Right heart failure is the main determinant of outcome in patients with PAH. Echocardiographic evaluation may therefore provide markers for PAH risk stratification and serial assessment. The echocardiographic variables that have been evaluated are listed in supplementary table S1.

Tricuspid annular plane systolic excursion (TAPSE), which assesses systolic displacement of the tricuspid annulus toward the right ventricular (RV) apex, is a simple and frequently used indicator of RV longitudinal systolic function. TAPSE <18 mm was independently associated with mortality in a cohort of prevalent PAH patients [52], and several smaller longitudinal studies suggest that TAPSE is useful for monitoring clinical trajectories prospectively [53, 54]. Nevertheless, TAPSE may overestimate RV function in the presence of apical longitudinal rotation, severe tricuspid regurgitation or RV dilatation [55]. Moreover, TAPSE is angle- and load-dependent, and reflects only basal longitudinal function, neglecting the contribution of apical and outflow tracts. The TAPSE/systolic pulmonary artery pressure (sPAP) ratio, a noninvasive estimate of RV–pulmonary arterial (PA) coupling [56], can be used for risk stratification when other noninvasive parameters such as 6MWD are unavailable [57] or for further risk stratification of patients who are not at low risk [58].

RV fractional area change correlates more closely with RV ejection fraction (RVEF), is more sensitive to increased afterload than TAPSE, and is associated with survival [59].

Less load-dependent RV systolic parameters may be prognostic in PAH, including RV isovolumic contraction peak velocity [60] and RV free-wall longitudinal systolic strain [61–63]. Speckle-tracking echocardiography allows the assessment of RV dyssynchrony that is associated with decreased exercise capacity, impaired haemodynamics and worse survival (values >23 ms) [64]. In addition, speckle-tracking right atrial (RA) function indices are associated with outcome in PAH [65], and RA remodelling seems to be more important than RV remodelling for prediction of clinical deterioration [62, 66].

Both RV and RA dilatation [67, 68], and RV end-systolic remodelling index [69] are associated with worse prognosis in PAH. In addition, three-dimensional echocardiography may significantly improve the accuracy and clinical utility of right heart volumetric assessments [66].

RV overload can have repercussions on morphofunctional remodelling of the left ventricle which is captured, for example, by the eccentricity index in end-diastole (volume overload) or end-systole (pressure overload), both associated with prognosis [68, 70, 71].

Despite possible limitations in the reproducibility of its severity estimate, tricuspid regurgitation represents a marker of RV remodelling that has been associated with PAH outcome [59, 72] and has been shown to be sensitive to PAH treatment [73]. Finally, parameters associated with increased RV filling pressure, such as pericardial effusion [52, 59, 68, 74] and inferior vena cava diameter [62], are predictors of prognosis.

Echocardiography is also useful for detecting the effects of PAH therapy on right heart morphology and function [73, 75] and follow-up values as well as the magnitude of right heart reverse remodelling may predict survival [53, 62, 71]. Furthermore, a comprehensive echocardiographic approach based on indicators of right heart morphology and function, RV–PA coupling, tricuspid regurgitation and signs of

systemic congestion can provide an accurate prognostic stratification in PAH [67, 71, 76–79] and can be of enhanced discriminative value as adjuncts to contemporary scoring systems [67, 77, 79].

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance imaging (cMRI) provides highly specific information on RV structure and function and is considered the gold standard for its noninvasive assessment. In PAH, increased RV afterload and insufficient adaptation of RV contractility, *e.g.* RV–PA uncoupling, cause an increase of RV end-systolic volume index (RVESVI) followed by a reduction in RVEF [80]. Initially, an increase in RV end-diastolic volume index (RVEDVI) may normalise SVI, but at the cost of increasing RV wall stress [80]. As RV dysfunction progresses, impaired left ventricular filling causes a reduction of left ventricle end-diastolic volume index (LVEDVI) [80].

RVESVI is an independent predictor of death and time to clinical worsening [81] both at baseline [82] and follow-up [82, 83] and, when used as an adjunct to contemporary scoring systems, enhanced discrimination in patients at intermediate or high risk [82]. RVEDVI is a less consistent prognostic predictor [84], but predicts both death and time to clinical worsening [81]. Increase of both RVESVI and RVEDVI is an early marker of disease progression [80]. RV hypertrophy represents adaptive remodelling, reducing wall stress due to RV dilatation. The combination of a high RV volume with a low RV mass, a pattern more frequent in the elderly, is associated with a worse outcome and a reduced likelihood of adaptive remodelling with PAH treatment [85]. Diminished LVEDVI and left ventricular SVI are also predictors of death in PAH [81, 82].

RVEF is an independent predictor of prognosis at baseline [86] and at follow-up [87], predicting both death and time to clinical worsening [81]. RVEF ⩾45% at follow-up predicts a low risk of death [83] and is correlated with a smaller baseline RVEDVI and a lower RV afterload [88]. RVEF at follow-up seems to have superior power compared to invasively assessed pulmonary vascular resistance (PVR) [89] and may detect disease progression earlier [80], since RV dysfunction can progress despite a decrease in PVR [89].

The prognostic role of cMRI parameters seems to be better at follow-up than at baseline [83]. Both volumetric (*e.g.* SVI/RVESVI ratio) and strain (*e.g.* PA global longitudinal strain) parameters describing RV–PA coupling may emerge as predictors of prognosis [81, 90]. Feature-tracking strain analysis, as well as late gadolinium enhancement, four-dimensional flow MRI, T1/T2 mapping, RA and PA cMRI parameters require further evaluation.

Invasive haemodynamics

Cardiopulmonary haemodynamics were associated with prognosis in the National Institutes of Health registry, which included young patients (average age 36 years) with untreated "primary pulmonary hypertension" with a dismal prognosis (median survival 2.8 years) [91].

Over the past two decades, the mean age of patients in registry cohorts has significantly increased [92–94], while the haemodynamic severity at diagnosis as determined by mean pulmonary artery pressure (mPAP) and PVR has decreased [94]. In most series, mPAP was not correlated with survival [92, 93, 95–99], and indeed, some studies suggested that this haemodynamic parameter was actually inversely associated with survival [100]. This is not surprising, considering that the magnitude of PA pressure elevation not only reflects the degree of pulmonary vascular obstruction, but also the systolic performance of the RV, *i.e.* patients with PAH associated with congenital heart disease may present with suprasystemic PA pressure but well-adapted RV function, while elderly patients with PAH may have impaired RV function at lower mPAP and PVR levels [101, 102]. In addition, most of the hitherto available PAH medications had only a modest effect on PA pressure, which may make it difficult to demonstrate the prognostic role of mPAP reduction in PAH patients. Nevertheless, there is emerging evidence that meaningful mPAP responses to targeted PAH therapies seem to be associated with favourable prognosis [103]. This was already described for acute responders to vasoreactivity test who receive high-dose calcium channel blockers [104], although, in this case, whether a better prognosis is related to the reduction of mPAP values or to a form of PAH with a more favourable course remains to be defined. Recently, it has been shown that, in acute responders to vasoreactivity test, improvement in pulmonary arterial compliance is associated with long-term response to calcium channel blockers and better survival [105].

The prognostic role of baseline RA pressure has been well established [93, 94, 99, 100]. Other independent baseline predictors of death described in different and relatively heterogeneous studies are cardiac index [92–94, 106, 107], SVI [97], PA compliance [97, 108, 109] and mixed venous oxygen saturation (S_{vO_2}) [68, 93, 96, 97, 107, 109]. Cardiac index, in particular, seems of additional prognostic

relevance when evaluated at peak exercise [110, 111], indicating that the haemodynamic reserves may be more prognostically relevant than the resting values.

In PAH, haemodynamics appear to have an additional independent prognostic role when assessed at follow-up (supplementary table S2) [93, 99, 112, 113]. At follow-up, parameters reflecting both RV function (RA pressure [99, 112, 114], S_{vO_2} [115, 116], cardiac index and SVI [112, 113, 116]) and, less consistently, RV afterload (PVR [11, 114, 117] and PA compliance [106]), both as absolute values and, less consistently, as changes from baseline [93, 98, 100], are independently associated with prognosis.

Although haemodynamic improvement is associated with improved exercise capacity [118, 119], it has been inconsistently linked to superior long-term outcomes, especially when considered as changes from baseline rather than absolute follow-up values [93, 100, 112, 118–121]. This inconsistency may arise from several factors: *i.e.* patients' baseline condition may have influenced these results [121], many trials that systematically re-evaluated the haemodynamic profile had short observation periods [118] and, lastly, improvement in haemodynamic parameters induced by therapies were sometimes modest and not always associated with improved RV function [89].

Current registries have highlighted little additional prognostic role of haemodynamics compared to noninvasive parameters (*i.e.* WHO-FC, 6MWD and BNP/NT-proBNP) in predicting all-cause death in the overall PAH patient population [122–125]. However, more recent data indicate that haemodynamics can improve all-cause death risk prediction in patients determined as intermediate-low or intermediate-high risk as predicted by the ESC/ERS four-stratum system [116] and can be of added value to the ESC/ERS four-stratum risk tool in predicting a combined end-point of all-cause death, nonelective hospitalisation and need for treatment escalation [99].

Patient-reported outcome measures

Patient-reported outcome measures provide a patient-centric metric regarding the impact of PAH. Health-related quality of life (HRQoL) can be described as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" [126]. HRQoL instruments can be generic (*e.g.* Medical Outcome Study 36-item short-form health survey (SF-36), EuroQol five-dimension questionnaire), or disease-specific (*e.g.* Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), emPHasis-10, Pulmonary Arterial Hypertension – Symptoms and Impact (PAH-SYMPACT) and the Living with Pulmonary Hypertension Questionnaire). Emotional/cognitive domains assess factors such as anxiety, depression, energy and social functioning. Physical functioning domains of such instruments generally correlate with metrics such as WHO-FC and 6MWD and tend to improve with therapy impacting those measures [127]. While improvement in such instruments with PAH therapy was found to be associated with survival [128], the extent to which such instruments or their components have independent predictive value for prognosis is generally under-studied. In the Pulmonary Hypertension Association Registry, patients with a higher predicted risk of mortality by Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) and REVEAL 2.0 risk scores had worse HRQoL scores as assessed by emPHasis-10 and Medical Outcome Study SF-12, with emPHasis-10 scores appearing to correlate better with risk classification [129]. The emPHasis-10 score has been shown to be an independent predictor of mortality in PAH when added to a model including age, gender, aetiology, WHO-FC, 6MWD, RA pressure and cardiac index. Improvement in the emPHasis-10 score was associated with improvement in exercise capacity [128]. The development of a PH functional classification self-report is of interest, with future work needed to determine how this metric compares to clinician-assessed WHO-FC in predicting outcomes [130].

Multiparametric risk-assessment tools

Risk tools derivation and validation methodology

Since no single variable provides sufficient prognostic information, multiparametric equations were derived from multivariate regression analyses considering haemodynamic parameters in untreated [91] and treated PAH patients [94], or combining haemodynamics, exercise capacity and clinical parameters in incident [131] and mixed incident/prevalent [11, 132] PAH populations.

The REVEAL risk score [11] developed in 2010 uses both modifiable and unmodifiable variables and was derived from a multivariate model predicting 1-year all-cause mortality in both newly (within 1 year of diagnostic right heart catheterisation (RHC)) and previously diagnosed PAH population. All PAH aetiologies were included. This score was subsequently refined including all-cause hospitalisations within 6 months and modifying cut-offs and/or weight of some variables (*i.e.* REVEAL 2.0) (table 1 and figure 1) proving to maintain significant predictive power and calibration with at least seven evaluable elements

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TABLE 1 Summary of the registries used for multiparametric risk assessment tools derivation in pulmonary arterial hypertension (PAH)

	REVEAL 2.0 [133]	REVEAL Lite 2 [125]	SPAHR [134]	COMPERA 1.0 [123]	FPHR [124]	COMPERA 2.0 [135]	Refined six-stratum score [116]
Subjects n	2529	2529	530	1588	1017	1655	1240
Mean age years	54	54	65	64	57	66	60
IPAH/HPAH/DPAH	54	54	54	67	100	71	63
CTD-PAH	24	24	31	22		20	32
CHD-PAH	12	12	12	4		3	1
PoPH	5	5	3	6		5	0
Other	5	5	<1	1		1	4
Variables							
Modifiable noninvasive	WHO-FC, 6MWD, BNP/NT-proBNP, SBP, HR, PE, D_{LCO}, hospitalisation in previous 6 months	WHO-FC, 6MWD, BNP/NT-proBNP, SBP, HR	WHO-FC, 6MWD, NT-proBNP, RA area, PE	WHO-FC, 6MWD, BNP/NT-proBNP	WHO-FC, 6MWD Exploratory: BNP/NT-proBNP	WHO-FC, 6MWD, BNP/ NT-proBNP	WHO-FC, 6MWD, BNP/NT-proBNP (for all)
Modifiable invasive	RAP, PVR		RAP, CI, S_{vO_2}	RAP, CI, S_{vO_2}	RAP, CI Exploratory: S_{vO_2}		SVI and S_{vO_2} (for intermediate-low and intermediate-high risk)
Unmodifiable	PAH subgroup, age, gender						
Comorbidities	Renal insufficiency	Renal insufficiency					
Incident patients	26.3	26.3	100	100	100	100	100
Patients at first follow-up n (%)			383 (72)	1094 (69)	1017 (100)	1414 (85)	1240 (100)
Low risk definition	Score ⩽6	Score ⩽5	<1.5 average score	<1.5 average score	3–4 out of 4 low-risk criteria	<1.5 average score	<1.5 average score
Low/intermediate/high risk patients	43/27/30	38/35/27	Baseline 23/67/10 Follow-up 29/60/11	Baseline 12.3/70.3/17.4 Follow-up 24/59/17	Baseline 17/NA/NA Follow-up 41/NA/NA	Baseline: low 5.6; intermediate-low 24.2; intermediate-high 55; high 15.2 Follow-up: low 17; intermediate-low 27.9; intermediate-high 37.8; high 17.3	Follow-up: low 31; intermediate-low 39; intermediate-high 24; high 6
1-year mortality low/ intermediate/high	1.9/6.5/25.8	2.9/7.1/25.1	Baseline 1/17/26 Follow-up 1/9/30	Baseline 2.8/9.9/21.2 Follow-up 3.5/8.2/27.6	0–1/NA/NA	Baseline: low 0; intermediate-low 2.1; intermediate-high 9.1; high 21.9 Follow-up: low 1.5; intermediate-low 2.8; intermediate-high 8.7; high 22	Follow-up: low 2; intermediate-low good haemodynamics[#] 3; intermediate-low poor haemodynamics[#] 6; intermediate-high good haemodynamics[#] 11; intermediate-high poor haemodynamics[#] 24; high 44
Missing data	7.4	8.1	Baseline 20 Follow-up 41.5	Baseline 11 Follow-up 46	0	Baseline 0 Follow-up 19	0
Initial combination therapy	25	25	12	19	43	35	44

Data are presented as % or n (%), unless otherwise stated. REVEAL: Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; SPAHR: Swedish PAH Register; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry; IPAH: idiopathic PAH; HPAH: heritable PAH; DPAH: drug-induced PAH; CTD: connective tissue disease; CHD: congenital heart disease; PoPH: portopulmonary hypertension; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; SBP: systolic blood pressure; HR: heart rate; PE: pericardial effusion; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; RA: right atrium; RAP: right atrial pressure; PVR: pulmonary vascular resistance; CI: cardiac index; S_{vO_2}: mixed venous oxygen saturation; SVI: stroke volume index; NA: not applicable. [#]: good haemodynamics defined as SVI >37 mL·m^{-2} and/or S_{vO_2} >65%.

REVEAL 2.0

	−2	−1	0	1	2	3
WHO group 1 subgroup			Other	CTD	Heritable	PoPH
Male >60 years			No		Yes	
All-cause hospitalisation ≤6 months			No	Yes		
eGFR <60 mL/min/1.73m^2 or renal insufficiency			No	Yes		
Systolic BP (mmHg)			≥110	<110		
Heart rate (bpm)			≤95	>95		
WHO-FC		I	II	III	IV	
6MWD (m)	≥440	320–440	165–320	<165		
BNP (ng·L^{-1}) or NT-proBNP (ng·L^{-1})	<50 <300		50–200 300–1100	200–800	≥800 ≥1100	
PE on echocardiogram			No	Yes		
D_{LCO} ≤40 % pred			No	Yes		
RAP >20 mmHg within 1 year			No	Yes		
PVR <5 WU		Yes	No			

Overall risk= sum of the points +6 = 0–6= Low risk; 7–8= Intermediate risk; ≥9= High risk

REVEAL Lite 2

	−2	−1	0	1	2
eGFR <60 mL/min/1.73m^2 or renal insufficiency			No	Yes	
Systolic BP (mmHg)			≥110	<110	
Heart rate (bpm)			≤95	>95	
WHO-FC		I	II	III	IV
6MWD (m)	≥440	320–440	165–320	<165	
BNP (ng·L^{-1}) or NT-proBNP (ng·L^{-1})	<50 <300		50–200 300–1100	200–800	≥800 ≥1100

Overall risk= sum of the points +6 = 0–5= Low risk; 6–7= Intermediate risk; ≥8= High risk

FIGURE 1 Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) risk tools. WHO: World Health Organization; eGFR: estimated glomerular filtration rate; BP: blood pressure; WHO-FC: WHO functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; PE: pericardial effusion; D_{LCO}: diffusing capacity of the lung for carbon monoxide; RAP: right atrial pressure; PVR: pulmonary vascular resistance; WU: Wood Units; CTD: connective tissue disease; PoPH: portopulmonary hypertension.

[133, 136]. REVEAL 2.0 predicts 1- and 5-year mortality and 1-year risk of all-cause hospitalisation or initiation of parenteral prostacyclin analogues [133, 137]. REVEAL 2.0 was internally validated at 1 year of follow-up [138] and in incident patients [133, 136] and externally validated in other registry cohorts [139–142], and randomised controlled trial (RCT) cohorts [143–148].

While the inclusion of unmodifiable parameters may be relevant to predicting overall life expectancy in PAH, the therapeutic implications are in need our further study, particularly as our knowledge genomics and age-related differences in treatment response evolve [146, 149]. REVEAL Lite 2, using only noninvasive modifiable variables, was developed (table 1 and figure 1), grouping patients according to 1-year probability of death <5% (score 1–5), 5–10% (score 6–7), >10% (score 8–14). This score provides good discrimination, although less so than the parent calculator. In addition, discrimination remained good if only WHO-FC, 6MWD and BNP/NT-proBNP were used, and all the three less predictive variables (heart rate, systolic blood pressure and renal function) were omitted, but at the expense of greater discrimination and calibration [125]. It also predicts 5-year mortality and 1-year risk of all-cause hospitalisation or initiation of parenteral prostacyclin analogues [150] and it was externally validated in other registry cohorts [141], in a cohort of patients listed for lung transplantation [151], and in RCT cohorts [145, 146].

Central to the REVEAL calculators is their use as an ordinal score and not strata, as this enhances their discrimination and allows these calculators to generate a change in risk with each incremental change in score. For example, a 1-point improvement in REVEAL 2.0 risk score at follow-up is associated with a 26% reduction in the relative risk of death and a 23% reduction in the relative risk of clinical worsening [148].

In contrast to the REVEAL approach, the ESC/ERS risk stratification method considers only modifiable variables categorised into low, intermediate or high risk according to 1-year mortality of <5%, 5–20% and >20%, respectively [152, 153]. Given the possible concomitance of parameters in different risk categories, the risk class attribution has been addressed with different approaches that were systematically tested after the publication of the 2015 ESC/ERS PH guidelines risk table in incident treatment-naïve PAH patients at baseline and after a median of 4–7 months of treatment [123, 124, 134].

In the Swedish PAH Register (SPAHR) and COMPERA registries, cut-off values of prespecified variables obtained from the literature were arbitrarily graded 1–3. To define the risk group, both at baseline and at follow-up, the average of available variables is rounded to the nearest integer (table 1, figure 2).

The SPAHR and COMPERA registries included all PAH aetiologies and considered both noninvasive and invasive parameters. However, the latter were available in no more than one-third of patients at follow-up [123, 134]. Risk stratification was repeated up to 5 years after diagnosis [154, 155]. SPAHR/COMPERA methodology was internally tested in idiopathic/heritable/drug-induced PAH and connective tissue disease (CTD)-associated PAH [123, 134], externally tested in other registry cohorts [141] including CTD-PAH patients [156–158], idiopathic PAH patients [159], and patients treated with intravenous treprostinil [160] and in RCT cohorts [161, 162].

In the French Pulmonary Hypertension Registry (FPHR), patients are stratified according to the number of low-risk criteria, considering both invasive and noninvasive parameters. Of note, the presence of three noninvasive low-risk criteria (WHO-FC, 6MWD, BNP/NT-proBNP) at follow-up was also tested (table 1, figure 2) [124]. The FPHR methodology was externally tested in other registry cohorts [141] including

ECS/ERS 3 risk-strata

Determinants of prognosis (according to 1-year estimated mortality)		Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical parameters	Signs of right HF	Absent	Absent	Present
	Symptom progression	No	Slow	Rapid
	Syncope	No	Occasional	Repeated
	WHO-FC	I, II	III	IV
Exercise tests	6MWD	>440 m	165–440 m	<165 m
	CPET			
	Peak V'_{O_2}	>15 mL·kg^{-1}·min^{-1}	11–15 mL·kg^{-1}·min^{-1}	<11 mL·kg^{-1}·min^{-1}
	V'_E/V'_{CO_2}	<36	36–44	>44
Biomarkers	BNP	<50 ng·L^{-1}	50–800 ng·L^{-1}	>800 ng·L^{-1}
	NT-proBNP	<300 ng·L^{-1}	300–1100 ng·L^{-1}	>1100 ng·L^{-1}
Imaging	Echocardiography			
	RA area	<18 cm^2	18–26 cm^2	>26 cm^2
	TAPSE/sPAP	>0.32 mm·mmHg^{-1}	0.19–0.32 mm·mmHg^{-1}	<0.19 mm·mmHg^{-1}
	PE	No	Minimal	Moderate or large
	cMRI			
	RVEF	>54%	37–54%	<37%
	SVI	>40 mL·m^{-2}	26–40 mL·m^{-2}	<26 mL·m^{-2}
	RVESVI	<42 mL·m^{-2}	42–54 mL·m^{-2}	>54 mL·m^{-2}
RHC	Haemodynamics			
	RAP	<8 mmHg	8–14 mmHg	>14 mmHg
	CI	≥2.5 L·min^{-1}·m^{-2}	2.0–2.4 L·min^{-1}·m^{-2}	<2.0 L·min^{-1}·m^{-2}
	SVI	>38 mL·m^{-2}	31–38 mL·m^{-2}	<31 mL·m^{-2}
	S_{vO_2}	>65%	60–65%	<60%

ECS/ERS 4 risk-strata

Determinants of prognosis	Low	Intermediate-low	Intermediate-high	High
WHO-FC	I, II		III	IV
6MWD	>440 m	320–440 m	165–319 m	<165 m
BNP	<50 ng·L^{-1}	50–199 ng·L^{-1}	200–800 ng·L^{-1}	>800 ng·L^{-1}
NT-proBNP	<300 ng·L^{-1}	300–649 ng·L^{-1}	650–1100 ng·L^{-1}	>1100 ng·L^{-1}

ESC/ERS risk calculation

SPAHR/COMPERA 1.0

Parameters		
Low risk 1 point	Intermediate risk 2 points	High risk 3 points

Overall risk = sum of the points / n of parameters

- 1.0–1.49= Low risk
- 1.5–2.49= Intermediate risk
- ≥2.5= High risk

FPHR invasive

Low risk parameters	
WHO-FC	I–II
6MWD	>440 m
RAP	<8 mmHg
CI	≥2.5 L·min^{-1}·m^{-2}

Low risk = 4 low risk parameters

FPHR noninvasive

Low risk parameters	
WHO-FC	I–II
6MWD	>440 m
BNP/NT-proBNP	<50/300 ng·L^{-1}

Low risk = 3 low risk parameters

COMPERA 2.0

Parameters			
Low risk 1 point	Intermediate-low risk 2 points	Intermediate-high risk 3 points	High risk 4 points

Overall risk = sum of the points / n of parameters

- 1.0–1.49= Low risk
- 1.5–2.49= Intermediate-low risk
- 2.5–3.49= Intermediate-high risk
- ≥3.5= High risk

FIGURE 2 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk tools. RHC: right heart catheterisation; HF: heart failure; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; CPET: cardiopulmonary exercise testing; V'_{O_2}: oxygen uptake; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RA: right atrium; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; PE: pericardial effusion; cMRI: cardiac magnetic resonance imaging; RVEF: right ventricular ejection fraction; SVI: stroke volume index; RVESVI: right ventricular end-systolic volume index; RAP: right atrial pressure; CI: cardiac index; S_{vO_2}: mixed venous oxygen saturation; SPAHR: Swedish Pulmonary Arterial Hypertension Registry; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry.

patients treated with parenteral prostacyclin analogues [115], CTD-PAH [113, 156] and idiopathic PAH patients [163], and in RCT cohorts [143, 146, 161].

The most prognostic modifiable parameters emerging from all registries are WHO-FC, BNP/NT-proBNP and 6MWD [123–125, 161, 164]. However, in three-risk-stratum approaches, the majority of patients meet intermediate risk criteria [123, 134]. A subdivision into four risk strata (low, intermediate-low, intermediate-high and high) using refined cut-off values from REVEAL Lite 2 for 6MWD, WHO-FC and BNP/NT-proBNP was therefore proposed from the COMPERA registry group and validated in the French registry. To define the risk group at baseline and at follow-up, cut-off values of the three variables are graded 1–4 and a weighted average of available variables is rounded to the nearest integer (figure 2). The four-stratum risk stratification score has been tested in ∼4500 patients at baseline and ∼3500 patients at follow-up, and specifically tested in CTD-PAH, systemic sclerosis-associated PAH, idiopathic/heritable/drug-induced PAH and portopulmonary hypertension [135, 165]. It is externally validated also in other registry cohorts [166], in RCT cohorts [146], in patients listed for lung transplantation [151, 167], and in patients with pulmonary veno-occlusive disease [168].

Thus, all described risk tools are externally validated, in both incident and prevalent patients and for all-cause mortality and time to clinical worsening end-points. Other methods lacking external validation have been proposed for both three-stratum [169] and four-stratum risk approaches (*e.g.* SPAHR methodology defining intermediate-low and intermediate-high with a risk score of 1.5–1.99 and 2.0–2.4, respectively [155, 166]; substratification of intermediate risk according to TAPSE [170], a combination of TAPSE/sPAP ratio with 6MWD [171], peak V'_{O_2} with SVI [17] or SVI alone [172]).

All available models have common methodological limitations, including their retrospective/*post hoc* nature of the validating analyses, a significant amount of missing data and patients lost to follow-up, the nonstandardised data collection in all registries, and the exclusion of relevant cardiac imaging and cardiopulmonary exercise testing data, genetics, PAH complications and prognostically relevant comorbidities [158, 173, 174]. Finally, the validation and comparison methodology of risk tools is essentially based on the measurement of their predictive value, identified by the concordance index (C-index). While C-index is the current gold-standard methodology, the C-index itself suffers from some limitations. C-index describes a model's ability to correctly distinguish the risk of a prespecified event between any two subjects of the study cohort (*i.e.* to assign a higher risk score to the subject experiencing an event earlier during the study period). It follows that it is dependent on the number of comparable pairs which, in turn, depends on the sample size, the number and distribution of censored subjects, the number of events, and the follow-up duration. Moreover, it does not consider the clinical relevance of the comparisons of the various pairs. Finally, the C-index is influenced by the risk profile and its distribution within the study cohort, beyond the number of risk strata attributed to the population [175].

Application of risk tools at baseline

2022 ESC/ERS PH guidelines recommended to evaluate disease severity in patients with PAH with a panel of data derived from clinical assessment, exercise tests, biochemical markers, echocardiography and haemodynamic evaluations. The use of a three-stratum model, considering all these data, including haemodynamics, is recommended at baseline in patients without cardiopulmonary comorbidities. Alternative tools such as REVEAL can be used interchangeably with the European systems. However, according to the prevailing treatment strategies and available therapies, only determining a high-risk profile has implications for the initial treatment strategy, *i.e.* triple combination therapy including a parenteral prostacyclin [152, 153]. Nevertheless, new emerging therapies and further evidence could change this approach in the future.

Many diagnostic investigations are required at baseline. REVEAL 2.0 includes much of this information as well as unmodifiable factors and, reporting as an ordinal score, allows for a granular prediction across the risk spectrum; the results derived from the global Pulmonary Vascular Research Institute GoDeep meta-registry highlighted that this may be relevant in the overall prognostic definition [176].

However, when selecting a risk score for application, it is essential to consider the intended purpose. The goal may be two-fold: to optimise prognostic predictability by encompassing various factors that could impact the patient's prognosis, both modifiable and unmodifiable, or to prioritise specificity towards the severity of PAH to the greatest extent feasible.

Application of risk tools at follow-up

The current European pulmonary hypertension guidelines recommend using a four-stratum risk stratification score at follow-up based on three noninvasive variables: WHO-FC, 6MWD and BNP or

NT-proBNP [135, 152, 153, 165]. It has been shown in two different cohorts that the ESC/ERS four-stratum risk model maintains its discriminative power when one of the three variables (WHO-FC, 6MWD and BNP/NT-proBNP) is unavailable, although the precision of absolute risk estimation is reduced [166, 177]. When applied to patients with comorbidities, the survival of low and intermediate-low risk patients is comparable [173]. Current pulmonary hypertension guidelines also suggest that additional variables should be considered as needed [152, 153]. Recently, it has been shown that haemodynamics are of no added value in predicting all-cause death in patients at low or high risk. However, a combination of SVI and S_{vO_2} is of added value in patients at intermediate-low and intermediate-high risk [116]. Other risk scores, using a similar methodology with three or four strata, but incorporating more variables including RHC, have been shown to be effective [166].

The REVEAL 2.0 score has prognostic relevance at follow-up [11, 133, 136, 178]. It takes into account a large number of prognostic variables that may be heterogeneously present in routine patient follow-up and, given its comparable level of discrimination, REVEAL can be used interchangeably with the European systems at follow-up [116, 179]. REVEAL Lite 2, based only on six noninvasive variables, may be more appropriate than REVEAL 2.0 at follow-up, particularly if invasive haemodynamics or imaging are not obtained or hospitalisations are not tracked [125, 150].

The FPHR invasive method [124], considering four criteria (figure 2), identified a 5-year transplant-free survival of 91%, 78% and 58% for patients achieving four, three or two low-risk criteria, respectively [124]. A noninvasive risk stratification model based on low-risk values for WHO-FC, 6MWD and BNP or NT-proBNP identified patients at very low risk (5-year transplant-free survival of 97%) [124], and this approach has been cross-validated in the COMPERA registry [163].

It is important to emphasise that, unlike the REVEAL scores, the French score and the ESC/ERS risk stratification scores were only assessed at baseline and first follow-up visit [124, 135, 165]. However, they have been used in subsequent follow-up visits in *post hoc* analyses or as secondary end-points of RCTs, thus demonstrating their usefulness at any time [127, 143, 155, 161]. Furthermore, the ESC/ERS four-stratum risk score has been validated at several follow-up visits in an independent cohort [166].

Risk stratification is the cornerstone of the ESC/ERS treatment algorithm [152, 153] and, when applied at baseline and at first follow-up, sets the trajectory of treatment patterns for the first year, *i.e.* the most critical time in the PAH treatment journey [123, 133, 134, 166]. Despite that, risk assessment is used only by six out of 10 clinicians and the most commonly identified barriers of utilisation are time constraints and lack of integration into electronic medical records [180–184]. To facilitate risk assessment, a comprehensive internet-based risk score calculator (www.svefph.se/risk-stratification [166, 180]; www.pahinitiative.com/hcp/risk-assessment/calculators) comprising several validated risk instruments has been developed and implemented into clinical practice. REVEAL 2.0 and REVEAL Lite 2 risk calculators are also available in the Epic electronic medical record, which is widely used, particularly in the United States of America.

Disagreement between a risk assessment strategy based on clinical gestalt or validated multiparametric risk tools has been documented [181, 185]. This highlights the importance of applying validated tools in clinical practice.

The application of risk scores at follow-up has been studied primarily in patients with idiopathic/heritable/drug-induced PAH and CTD-PAH; as in other PAH aetiologies, the prognosis can be also influenced by the underlying disease, and treatment strategies must consider factors unrelated to PAH severity that may limit tolerability and efficacy of PAH drugs and/or influence life expectancy [168, 186–188]. The latter can be true also for patients with multiple comorbidities and/or elderly patients [189].

Limitations of current risk assessment strategies and new developments

The most commonly used risk stratification tools include WHO-FC, 6MWD and BNP/NT-proBNP, as their independent prognostic value has been demonstrated repeatedly [123–125].

Despite their unquestionable prognostic value, these parameters have inherent limitations that should be considered when using these tools to guide treatment decisions, as follows.

1) WHO-FC involves a physician's subjective, nonstandardised evaluation of functional limitations in daily life. These limitations may or may not be due to PAH and are influenced by other factors, including age, comorbidities, physical fitness and behavioural aspects. Furthermore, there is no universally

accepted guidance on how to categorise patients according to WHO-FC. Notably, especially younger patients may fall into WHO-FC classes I or II despite having severe haemodynamic impairment [190].

2) Similar limitations apply to the 6MWD, which can also be influenced by factors unrelated to PAH, including age, sex, height, weight, comorbidities, physical fitness, learning curve and motivation, all variables that may significantly affect the 6MWD irrespective of haemodynamic changes [191]. Like WHO-FC, a preserved 6MWD may lead to underestimation of PAH severity, particularly in younger, otherwise healthy patients, while some patients with mild disease may walk shorter distances because of deconditioning and comorbidities.

3) BNP/NT-proBNP reflect global cardiac strain. In patients with PAH, normal or near-normal BNP/NT-proBNP values are typically associated with well-compensated right heart function. However, BNP/NT-proBNP values are affected by other factors such as age, recent physical activity, obesity, heart rhythm, kidney function and concomitant left heart disease.

Patients with PAH who meet all low-risk criteria (WHO-FC I or II, 6MWD >440 m, BNP <50 ng·L^{-1}, NT-proBNP <300 ng·L^{-1}) exhibit a favourable prognosis, particularly over the subsequent 3–5 years. This observation is not unexpected, since WHO-FC and 6MWD reflect the overall level of physical fitness, a factor known to correlate with health status and survival, not only in patients with PAH, but also in other populations [176]. Additionally, normal/near-normal BNP/NT-proBNP values generally indicate that the cardiac chambers have adapted well to their afterload.

However, as mentioned earlier, various other conditions can influence WHO-FC, 6MWD and BNP/NT-proBNP levels, especially in older patients with comorbidities. Although the existing PAH risk stratification tools can predict survival in such patients [173], their lack of disease specificity may make them less suitable for guiding PAH therapy.

One measure that has garnered recent attention is the TAPSE/sPAP ratio, an echocardiographic parameter correlated to RV–PA coupling [192]. It holds promise due to its ability to be noninvasively and repeatedly measured, its direct relevance to both PH severity and RV function adaption to afterload, and its potential to enhance the prognostic accuracy of established risk stratification tools in some studies [56–58, 193]. However, this parameter also has limitations, including the dependence on tricuspid regurgitation for its determination and a certain level of disagreement between the invasively and noninvasively derived measure, especially at higher ratios [56, 194]. Thus, researchers are also evaluating other echocardiographic and cMRI variables, biomarkers and genetic variations for this purpose [66, 67, 76, 170].

While RHC provides valuable insights into pulmonary haemodynamics and right heart function, the invasive nature may limit its applicability for routine follow-up assessments; implantable devices that continuously measure and transmit pulmonary artery pressures may partially ameliorate this problem [195]. Patients at intermediate-low or intermediate-high risk can get a more accurate all-cause death prediction with a RHC evaluation [116], and a combination of haemodynamic parameters indicative of RV preload, afterload and pump function appears to have a comparable discriminative ability and to be of incremental value to the ESC/ERS four-stratum risk tool for a combined end-point of all-cause mortality, nonelective hospitalisation and need of treatment escalation [99].

The key points can be summarised as follows:

- In patients with PAH, noninvasive risk stratification with contemporary risk scores that utilise WHO-FC, 6MWD and BNP/NT-proBNP as essential components serve as a useful basic assessment of disease severity and predicts survival. However, it is essential to recognise that none of these variables are disease-specific, which may restrict their suitability for guiding treatment decisions, particularly in patients with comorbidities.
- Parameters suitable for informing treatment decisions should consider three key criteria: 1) possess prognostic value; 2) reflect the severity of PH and/or RV dysfunction; and 3) be amenable to modification through treatment interventions.
- Selected parameters derived from invasive haemodynamics and cardiac imaging (echocardiography or cMRI) may fulfil these requirements and overcome WHO-FC, 6MWD and BNP/NT-proBNP limitations. Their incorporation in risk stratification tools warrants further evaluation.

Treatment goals in PAH

The 2022 ESC/ERS PH guidelines established a treatment goal for patients with PAH, focusing on achieving and maintaining a low risk profile (currently defined as a <5% mortality at 1 year). In this

context, low risk can be defined as meeting at least two of the following criteria: WHO-FC class I or II, 6MWD >440 m and BNP <50 ng·L^{-1} or NT-proBNP <300 ng·L^{-1}. However, this definition of a low-risk status is associated with a 5-year survival of ∼80% [135, 165] and refined classifications in which a low risk of mortality is extended to longer lengths of time may be reasonable. Notably, when all three parameters meet the low-risk criteria with medical therapy, the 5-year survival rate exceeds 90% [124, 163]. Similarly, a patient who achieves a REVEAL score of <5 has a 1- and 3-year survival >95% and a 1-year morbidity rate <5% [11, 133, 136, 178]. This indicates that striving for a low-risk status is advisable and remains a reasonable approach, although it is not always possible.

However, it is important to acknowledge the limitations of the current risk-stratification models discussed previously, as they do not consider comorbidities that may preclude achieving a low risk profile despite optimised PAH therapy. Furthermore, the extent to which treatment effects on risk correlate with treatment effects on morbidity and mortality remains uncertain. In an analysis of individual patient data from the AMBITION, SERAPHIN and GRIPHON studies, Blette *et al.* [196] recently demonstrated that the treatment effect on risk scores did not reliably predict treatment effects on clinical worsening or overall survival, despite having apparently a higher predictivity than the treatment effect on 6MWD [5] or individual haemodynamic parameters [120] on short-term outcome. However, in a *post hoc* analysis of the FREEDOM-EV trial, using change in ordinal REVEAL risk score instead of achieving a low risk, the mediation effect of risk reduction, was ∼30% and improved to 47% when only intermediate-risk patients were considered [146]. Thus, the definition of risk is critical in evaluating the utility of risk scores in mediating treatment effects. This requires further exploration in high numbers of patients in well-matched and harmonised clinical trial or registry data.

The ultimate treatment goal in PAH is sometimes described as achieving a cure, signifying complete remission of PH without the necessity for ongoing treatment. However, in a chronic condition like PAH, achieving a cure appears unrealistic. A more attainable treatment objective is partial or complete reversal of pulmonary vascular remodelling, accompanied by regression of PH, *i.e.* partial or complete disease remission. If maintained, such a treatment effect may translate into a normal life-expectancy for patients with PAH, which could become a more realistic goal in the future. Currently, we lack the tools to directly measure and quantify pulmonary vascular remodelling and the potential role of haemodynamics and right heart function as a surrogate marker of the extent of pulmonary vascular disease seems promising, even if this needs to be further investigated. The survival of patients with PAH is intricately linked to right heart function and substantial reduction of RV afterload leads to improvement of right heart function [197]. A *post hoc* analysis from the phase 3 STELLAR trial involving the activin signalling inhibitor sotatercept revealed that a mean reduction in mPAP of ∼13 mmHg from baseline was associated with improvement in RV–PA coupling, a decrease in RA pressure, RV end-diastolic and end-systolic dimensions and an amelioration in the degree of tricuspid regurgitation [73].

Haemodynamic targets associated with long-term survival are yet to be defined. Of note, in vasoresponsive patients with idiopathic PAH (vasoresponsiveness being defined as drop in mPAP by ⩾10 mmHg to <40 mmHg with an increased or unchanged cardiac index during acute vasoreactivity test), treatment with high-dose calcium channel blockers can result in superior long-term survival, even if resting haemodynamics are not entirely normalised [104]. In a multicentric series of 267 nonvasoreactive patients with idiopathic/heritable/drug-induced PAH, maintaining mPAP at or <35 mmHg during therapy was associated with a 10-year survival of ∼90% [103]. In a smaller Japanese cohort of 56 patients with idiopathic or heritable PAH, sustaining mPAP <42.5 mmHg during therapy was linked to a 100% survival rate at 10 years [198].

These observations are preliminary, and there is an ongoing debate whether PAH treatment should consider the reduction of mPAP and/or other RV afterload parameters such as PVR and PA compliance, and to what extent. While this approach may seem logical, the supporting evidence for such a strategy is limited. In fact, the prognostic role of these haemodynamic parameters in PAH patients is limited, although a PVR threshold of 5–6 Wood Units has been identified in different registries [99, 112, 133]. One important consideration is that such an approach would necessitate an invasive follow-up strategy including repeated RHC in face of only limited evidence that meeting haemodynamic thresholds yields superior long-term outcomes.

Echocardiographic indices assessing right heart function may also serve as valuable treatment targets. The current ESC/ERS PH guidelines list RA area <18 cm^2, absence of pericardial effusion, and TAPSE/sPAP ratio >0.32 mm·mmHg^{-1} as low-risk criteria [152, 153]. However, several additional echocardiographic parameters may offer potential value [67, 76]. Additionally, parameters derived from cMRI can be utilised,

although this technique is comparatively costlier, time-consuming and less widely available than echocardiography.

Taken together, the working group concluded that treatment decisions in PAH should be individualised and based on multidimensional information, incorporating clinical aspects such as WHO-FC and 6MWD, right heart strain and function determined by natriuretic peptides and cardiac imaging, and invasive haemodynamics (figure 3). Some of these indications are evidence based, while others must be the subject of research prioritisation before considering implementation in clinical practice. These methods should be considered when making decisions both on the initial therapy and on treatment adaptations during follow-up, especially during the first 3–6 months after treatment initiation when assessment of response to therapy and appropriate treatment modifications are critical.

In light of the limited available evidence, the following recommendations for treatment goals in PAH are made.

- Treatments goals need to be individualised, taking into account PAH subtype and severity, age, comorbidities, previous and current PAH medications and patient preferences.
- Reaching a low mortality risk, assessed with a validated multiparametric risk tool, remains a valid treatment objective.
- Reaching a low 1-year mortality risk does not prevent the risk of clinical deterioration in the medium- to long-term, especially if a low-risk criteria for all the three parameters (*i.e.* WHO-FC, 6MWD and

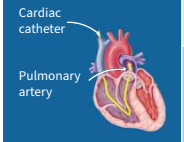
Domain	Treatment goals	Comments	Limitations
Exercise tolerance 	**6MWD >440 m** **WHO-FC I or II**	Not disease-specific, potentially affected by conditions other than PAH	Goals may not be achievable in patients with other conditions limiting exercise capacity
RV function and strain 	**BNP <50 ng·L^{-1}** **NT-proBNP <300 ng·L^{-1}**	Not disease-specific, potentially affected by conditions other than PAH	Goals may not be achievable in patients with interfering conditions
	Need for research prioritisation: RA area <18 cm^2 TR, none or trace TAPSE/sPAP >0.32 mm·mmHg^{-1}	Other imaging parameters from echocardiography and MRI are emerging	TAPSE/sPAP threshold requires further validation
Haemodynamics 	**RAP <8 mmHg** **CI ≥2.5 L·min^{-1}·m^{-2}** **SVI >37 mL·m^{-2}** **S_{vO_2} >65%** **PVR <5 WU**	Uncertain added value in low-risk patients according to ESC/ERS 4 strata model PVR <5 WU treatment goal may not apply to patients with congenital heart disease	Established prognostic value; however, not necessarily independent of noninvasive parameters
	Need for research prioritisation: mPAP <30–35 mmHg PAC ≥2.5 mL·mmHg^{-1}	With emerging therapies and effective combination treatment strategies, comprehensive haemodynamic assessment of treatment response is expected to play a prominent role in the management of patients with PAH	The proposed thresholds may be associated with long-term survival; however, this is not evidence-based and requires further validation

FIGURE 3 Comprehensive treatment goals in pulmonary arterial hypertension (PAH). RV: right ventricle; 6MWD: 6-min walk distance; WHO-FC: World Health Organization functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RA: right atrium; TR: tricuspid regurgitation; TAPSE/sPAP: tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio (estimated by echocardiography); RAP: right atrial pressure; CI: cardiac index; SVI: stroke volume index; S_{vO_2}: mixed venous oxygen saturation; PVR: pulmonary vascular resistance; WU: Wood Units; mPAP: mean pulmonary artery pressure; PAC: pulmonary arterial compliance; ESC: European Society of Cardiology; ERS: European Respiratory Society.

BNP/NT-proBNP), when using the ESC/ERS four-stratum risk tool, is not met or if a REVEAL 2.0 risk score <5/REVEAL Lite 2 risk score <4 is not reached.
- Haemodynamic parameters including RA pressure, cardiac index, S_{vO_2}, SVI and PVR should be considered when making therapeutic decisions
- According to centre expertise, cardiac imaging parameters should be considered when making therapeutic decisions
- Further research prioritisation is warranted to determine the prognostic value for long-term outcomes of haemodynamic parameters, such as mPAP, PA compliance, alongside various echocardiographic parameters, including the TAPSE/sPAP or RV free-wall longitudinal systolic strain/sPAP ratios, RA area and tricuspid regurgitation, among others.
- Normalising or nearly normalising haemodynamics and improving right heart function may become increasingly important treatment objectives, underscoring the need for continued research in these areas.

Gaps of evidence and proposals for future collaborative research programmes

Since the publication of 2015 ESC/ERS PH guidelines a low-risk-oriented treatment strategy has been advocated, defining low-risk as 1-year mortality <5%. However, this strategy has never been prospectively validated and some *post hoc* analyses of RCTs have suggested a beneficial effect of treatment escalation also in low risk patients [143, 199].

From a precision medicine perspective, treatment goals must be tailored to individual patients, taking into account factors such as age, comorbidities (especially cardiovascular and pulmonary) and PAH aetiology. However, specific individualised treatment goals have yet to be clearly identified.

Given the different pharmacological response profile of emerging treatments and the documentation of the efficacy of more aggressive combination treatment strategies, there is the need to identify markers associated with pulmonary vascular remodelling and to determine their prognostic role and/or validity as treatment goals. Future research should prioritise establishing thresholds for haemodynamic, biomarker, genomic and echocardiographic parameters associated with improved long-term survival. Utilising advanced statistical methods such as Bayesian analytic or neural networks, may enhance our ability to distinguish these thresholds given their capability to identify interactions among common predictive variables. Moreover, investigating whether a treatment strategy focussed on optimising pulmonary haemodynamics and right heart function leads to better long-term outcomes compared to a primarily risk-based approach is essential.

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