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Risk stratification strategy and assessment of disease progression in patients with pulmonary arterial hypertension: Updated Recommendations from the Cologne Consensus Conference 2018

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ABSTRACT

In the summer of 2016, delegates from the German Respiratory Society, the German Society of Cardiology and the German Society of Pediatric Cardiology met in Cologne, Germany, to define consensus-based practice recommendations for the management of patients with pulmonary arterial hypertension (PAH). These recommendations were built on the 2015 European Pulmonary Hypertension guidelines and included new evidence, where available, and were last updated in the spring of 2018. This article focusses on the proposed risk stratification and assessment of disease progression in patients with pulmonary arterial hypertension (PAH), covering 3 parts: In part 1, methods and markers that are recommended to assess severity and progression of PAH are discussed and commented. These updated comments incorporate most recent data as well as challenges arising from the variability of phenotypes of PAH patients with increasing cardiopulmonary comorbidities. In part 2, the proposed ESC/ERS risk stratification strategy is discussed, together with a review of the recent validation studies from different European registries. Finally, in part 3, the working group of the Cologne Consensus Conference provides recommendations on how risk assessment may be implemented in routine clinical practice and may serve clinical decision making.

1. Introduction

This article focusses on the proposed risk stratification and assessment of disease progression in patients with pulmonary arterial hypertension (PAH).

In the first part, methods and markers that are recommended to assess severity and progression of PAH are discussed. This part starts with text sections that are very close to the original text of the guidelines of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) on pulmonary hypertension (PH) [1], followed by comments provided by the working group of the Cologne Consensus Conference. These updated comments incorporate most recent data as well as challenges arising from the variability of phenotypes of PAH patients with increasing cardiopulmonary comorbidities.

In the second part, the newly proposed ESC/ERS risk stratification strategy is discussed, together with a review of the very recent registry

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studies from different European countries. Finally, in part 3, the working group provides recommendations on how risk assessment may be implemented in routine clinical practice.

2. Part 1: methods and markers to assess severity and progression of PAH

2.1. Clinical parameters, imaging, and hemodynamics

Clinical assessment remains a key part of the evaluation of patients with PAH, as it provides valuable information for determining disease severity, improvement, deterioration or stability. Elementary parts of history taking between follow-up visits include changes in exercise capacity, episodes of chest pain, arrhythmia, hemoptysis or syncope and changes in medications, as well as adherence to the prescribed drugs. Physical examination provides information on the presence or absence of peripheral or central cyanosis, enlarged jugular veins, edema, ascites and pleural effusions and on heart rate, rhythm and blood pressure. The World Health Organization functional class (WHO-FC), despite its inter-observer variability [2], remains one of the most powerful predictors of survival, not only at diagnosis, but also during follow-up [3–5]. A worsening WHO-FC is one of the most alarming indicators of disease progression, which should trigger further diagnostic studies to identify the causes of clinical deterioration [4,6].

Comment: *The cited WHO-FC data are obtained from PAH patient groups with a mean age of 43 and 55 years. It should be noted that these "classical" PAH patients may have severely impaired hemodynamics even if their symptoms are mild (WHO-FC II)* [7]. *On the other hand, it should be borne in mind that especially in older patients WHO-FC is less PAH-specific and rather represents an integrative parameter of PAH and comorbidities. Therefore, in these patients, special attention should be paid to determine whether the restriction in WHO-FC is caused by PAH.*

However, since functionality (WHO-FC) is linked to survival, correlates closely with quality of life (QoL) and can be regularly and easily assessed in all patients as the disease progresses, WHO-FC continues to occupy a prominent position in the functional assessment of patients with PAH. In addition, in all of the three registry studies validating the risk stratification strategy, WHO-FC was used as a key variable of functional impairment of patients with PAH [8–10].

As RV function is a key determinant of exercise capacity and outcome in patients with PAH, **echocardiography** remains an important follow-up tool. In contrast to common belief, the estimated systolic PAP (PAPs) at rest is usually not prognostic and not relevant for therapeutic decision making [3,4,11]. An increase in PAPs does not necessarily reflect disease progression and a decrease in PAPs does not necessarily signal improvement. A comprehensive echocardiographic assessment includes a description of chamber sizes, particularly of the RA and RV area, the magnitude of tricuspid regurgitation, the LV eccentricity index and RV contractility, which can be determined by several variables, including RV longitudinal systolic strain/strain rate and RV fractional area change, Tei index and tricuspid annular plane systolic excursion (TAPSE) [12–19].

Three-dimensional echocardiography may achieve a better estimation than standard two-dimensional assessment, but underestimations of volumes and ejection fractions have been reported [20]. Speckle tracking improves the quantification of RV function [21]. Given the complex geometry of the RV, none of these variables alone is sufficient to describe RV function, and the overall impression of an experienced physician is often more important than single variables. Echocardiography during exercise provides additional information on RV function. Of note, a marked increase (>30 mm Hg) of PAPs during exercise reflects better RV function and is associated with a better long-term outcome than a modest or no increase. This so-called contractile reserve has recently been shown to be an independent prognostic marker in patients with severe PH [22].

CMR imaging is more accurate for the assessment of RV morphology and function than echocardiography and also allows measurement of stroke volume and CO. A number of CMR prognostic markers have been identified, including increased RV volume, reduced LV volume, reduced RV ejection fraction, and reduced stroke volume. There is some evidence that follow-up CMR studies may have utility in the long-term management of PAH by identifying RV failure prior to the development of clinical features [23,24].

Comment: *Despite its key role as a parameter of disease severity and follow-up tool in PAH, only the Swedish registry* [10] *included data from echocardiography in their risk evaluation, using right atrial area and the presence of pericardial effusion. These data were not available in the two other registries* [8,9]. *Still, echocardiography remains an important non-invasive tool to assess RV function and overload. Its role in risk assessment and therapeutic decision-making may be underestimated by the current registry studies and needs to be further evaluated.*

Hemodynamics assessed by RHC provide important prognostic information, both at the time of diagnosis and during follow-up. RA pressure, cardiac index (CI) and mixed venous oxygen saturation (SvO_2) are the most robust indicators of RV function and prognosis, whereas PAPm provides little prognostic information (except for CCB responders) [3,4,6,11,25]. Non-invasive assessment of CO by rebreathing techniques [26] or bioreactance [27] has not yet been sufficiently validated to allow routine clinical use and therapeutic decision making.

There are still uncertainties around the optimal timing of follow-up RHC. Strategies vary between centres, from regular invasive hemodynamic assessments to a predominantly non-invasive follow-up strategy. There is no evidence that an approach involving regular RHC is associated with better outcomes than a predominantly non-invasive follow-up strategy. However, there is consensus among experts that RHC should be performed whenever therapeutic decisions can be expected from the results, which may include changes in medications and/or decisions regarding listing for transplantation.

Comment: *Since initial diagnosis of PAH mandates the presence of the complete set of invasive hemodynamic data during RHC, mRAP, CI and SvO_2 will be available at baseline. In addition, hemodynamic assessment remains essential during follow-up examinations, especially in patients who remain at intermediate or high risk despite targeted therapy. This is confirmed by current data indicating that hemodynamics assessed by RHC during follow-up, particularly stroke volume index (SVI) and RAP, are predictive of survival in PAH* [61].

2.2. Exercise capacity

The 6-min walking test (6MWT), a submaximal exercise test, remains the most widely used exercise test in PH centres. The test is easy to perform, inexpensive and familiar to patients and centres. As with all PH assessments, 6MWT results must always be interpreted in the clinical context. The 6-min walking distance (6MWD) is influenced by several factors, including sex, age, height, weight, co-morbidities, need for O_2, learning curve, and motivation. Nevertheless, test results are usually given in absolute numbers rather than percent predicted. Absolute values, but not changes in 6MWD, provide prognostic information, but there is no single threshold that is applicable for all patients [3,6,28–30]. It is recommended to use the Borg score at the end of the 6MWT to determine the level of effort. In addition, some studies suggest that adding peripheral O_2 measurements and heart rate response may improve the prognostic relevance, but these findings await independent confirmation [30,31].

Cardiopulmonary exercise testing (CPET) is usually performed as a maximal exercise test and provides important information on exercise capacity as well as on gas exchange, ventilatory efficacy and cardiac function during exercise. Most PH centres use an incremental ramp protocol, although the test has not yet been standardized for this patient population. Patients with PAH show a typical pattern with a low end-tidal partial pressure of carbon dioxide (pCO_2), high ventilator equivalents for carbon dioxide (VE/VCO_2), low oxygen pulse (VO_2/HR) and low peak oxygen uptake (peak VO_2) [32]. Several variables

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determined by CPET provide prognostic information, although peak VO_2 is most widely used for therapeutic decision making [15,33–36]. The diagnostic and prognostic information provided by CPET add to that provided by the 6MWT [33].

Comment: *The 6 MWT and CPET are influenced by different influencing factors, and interpretation has to be done in the clinical context. This seems to be especially important in patients with comorbidities or different etiologies of PAH (e.g. scleroderma). CPET may also have a value to differentiate between PH etiologies* [37,38]. *However, while no data exist about CPET parameters from the three validation registry studies, the 6MWT has been evaluated. Although the included etiologies of PAH differed in the studies, the proposed cut-off value of 440 m for the 6 MWD has been applied and proved to be of prognostic value in all three studies* [8–10].

2.3. Biochemical markers

There is still no specific marker for PAH or pulmonary vascular remodelling, although a wide variety of biomarkers have been explored in the field. These can be grouped into markers of vascular dysfunction [asymmetric dimethylarginine (ADMA), endothelin-1, angiopoeitins, von Willebrand factor] [39–44], markers of inflammation (C-reactive protein, interleukin 6, chemokines) [45–48], markers of myocardial stress (atrial natriuretic peptide, brain natriuretic peptide (BNP)/NT-proBNP, troponins) [4,30,49–52], markers of low CO and/or tissue hypoxia [pCO_2, uric acid, growth differentiation factor 15 (GDF15), osteopontin] [53–56] and markers of secondary organ damage (creatinine, bilirubin) [4,52]. This list is constantly growing, but so far **BNP** and **NT-proBNP** remain the only biomarkers that are widely used in the routine practice of PH centres as well as in clinical trials. BNP/NT-proBNP levels correlate with myocardial dysfunction and provide prognostic information at the time of diagnosis and during follow-up assessments [57]. They are not specific for PH, but can be elevated in almost any heart disease. BNP/NT-proBNP levels tend to have a high variability and should be interpreted in the clinical context. There are no clear advantages of using BNP versus NT-proBNP. BNP appears to have a slightly tighter correlation with pulmonary hemodynamics and is less affected by kidney function, whereas NT-proBNP seems to be a stronger predictor of prognosis [52].

Comment: *Cut-off values for BNP of 50 ng/l and of 300 ng/l for NT-proBNP as proposed in the ESC/ERS guidelines have been applied in the current registry studies* [8–10]. *This may be normal or near normal values for many, especially younger, patients. However, since a wide range across different ages exists for both BNP and NT-proBNP levels, individual normal values may differ from these cut-offs. Therefore, an individualization of BNP and NT-proBNP by dividing measured by individual normal values has been suggested* [58]. *Also, the etiology of PAH has to be taken into account. Since in patients with scleroderma a disproportionate increase of NT-proBNP has been shown as compared to patients with IPAH* [59]. *Similarly, adjusted values also have to be considered in patients with atrial fibrillation.*

3. Introducing a risk assessment in pulmonary arterial hypertension (Table 1) [1] (Original Table risk stratification European guidelines)

The introduction of risk stratification is an important innovation in the current European guidelines. The approach is based on the assumption that the prognosis of PAH reflects the severity of PAH itself and that the achievement of a low risk profile could serve as an adequate treatment goal.

The suggested risk stratification approach discriminates three different risk groups (low - intermediate - high) and gives estimates for the expected 1-year mortality of <5%, 5–10% and >10%, respectively. The integrated determinants of prognosis resemble parameters that are routinely used in PH centers to define hemodynamic impairment (RAP, CI, SVO_2), detect impaired right heart function via imaging modalities (echocardiography, CMR imaging) and/or measurement of BNP/NT-proBNP levels, evaluate functional capacity (WHO functional class, 6MWD, CPET) and define the clinical status (signs of right heart failure, progression of symptoms, occurrence of syncope).

However, the proposed variables and cut-off values of these parameters warranted validation and were mainly based on expert opinion [60] and from smaller outcome studies, predominantly from younger patients with idiopathic and hereditary PAH (IPAH and HPAH) or PAH associated with human immunodeficiency virus (HIV) infection or intake of anorexigens.

Table 1
Risk assessment in pulmonary arterial hypertension (from [1]).

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm² No pericardial effusion	RA area 18–26 cm² No or minimal, pericardial effusion	RA area >26 cm² Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m² SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m² SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m² SvO_2 <60%

6MWD: 6-minute walking distance; BNP: brain natriuretic peptide; CI: cardiac index; CMR: cardiac magnetic resonance; NT-proBNP: N-terminal pro-brain natriuretic peptide; pred.: predicted; RA: right atrium; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; VE/VCO_2: ventilatory equivalents for carbon dioxide; VO_2: oxygen consumption; WHO: World Health Organization.
[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.
[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity.

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4. Part 2: validation of the ESC/ERS risk assessment approach

Very recently, three independent registry-based studies from France [8], Sweden (SPAHR) [10] and COMPERA [9] (Tables 2A, 2B, 2C and 2D) evaluated the risk stratification approach (Table 3) suggested in the European guidelines (Table 1). Taken together, these registries comprise data of approximately 3000 newly diagnosed PAH patients over an inclusion period of about ten years (roughly from 2006 to end of 2016).

The **French registry** [8] included 1017 adult (≥18 years) PAH patients (IPAH in 75%, FPAH in 9% and drugs and toxins induced in 16%), but excluded associated PAH (e. g. CTD-PAH). The hemodynamic data showed a typical PAH profile with mPAP 50 mm Hg, CI 2.4 l/min/m2, mRAP 8.6 mm Hg, SvO2 63% and PVR 10.5 WU. Most patients were in WHO-FC III (61%) or IV (13%) at baseline, whereas 26% were in WHO-FC I–II. Initial PAH-targeted treatment was implemented in 90% of patients, comprising 47% of patients on monotherapy, including 7% treated with CCB. Combination therapies were implemented in 43%, including 3% with CCB.

For **risk assessment**, four variables (WHO-FC, 6MWD, RAP and cardiac index) were evaluated at the time of PAH diagnosis (baseline) and at the time of first re-evaluation, and the authors analyzed the number of variables meeting the low risk cut-off levels. On exploratory analyses, the additive value of BNP or NT-proBNP and of mixed venous oxygen saturation (SvO_2) was tested in a subset of 603 patients for whom these data were available.

In this study, the number of low-risk criteria present discriminated the risk of death or lung transplantation at baseline and at first re-evaluation (after a median follow up period of 4 months). Moreover, each of the four low-risk criteria independently predicted transplant-free survival at first re-evaluation. Notably, when BNP/NT-proBNP values were added to the equation, the invasive hemodynamics did no longer predict survival at follow-up.

Although the risk assessment performed well at baseline, the number of low-risk criteria achieved during the first year (i.e. individual response to initial management) at follow-up discriminated patients at low risk even better, and the 5-year-survival of patients meeting all three non-invasive low risk criteria at follow-up was 97%. Of note,

Table 2A
Evaluation of risk assessment strategy, data from the French, COMPERA and the Swedish cohorts [8–10]. Risk assessment at baseline.

Parameter	French cohort (3)	COMPERA cohort (4)	Swedish cohort (5)
Study population (n)	1017	1588	530
Inclusion period	Jan/2006 – March/2016	Jan/2009 – Nov/2016	Jan/2008 – Mar/2016
Incident patients	Yes	Yes	Yes
Age (years) @ baseline	57	64	
(low - intermediate - high risk)		53 - 66 - 65	57 - 68 - 66
Female (n%)	59	66 - 63 - 66	
(low - intermediate - high risk)			72 - 62 - 66
PAH subgroups			
IPAH in n (%)	762 (75)	1060 (67)	261
FPAH	94 (9)		7
Drugs, toxins PAH	161 (16)		16
CTD-PAH	Excluded	347 (22)	162
CHD-PAH		70 (4)	67
Others PAH		111 (7)	0
HIV-PAH		22 (1)	3
Portal PAH		89 (6)	14
Variables assessed			
Clinical variables (syncope etc.)	n	n	n
Functional status			
• WHO FC	y (all)	y	y
• 6 MWD	y (all)	y	y
• CPET	n	n	n
RH assessment			
• BNP and/or NT-proBNP	y ($n = 603$)	y	y
• Echo (incl. RAA, PE)	n	n	y
Hemodynamics			
• RAP	y (all)	y	y
• CI	y (all)	y	y
• SVO_2	n	y	y
Hemodynamic data @ baseline available in n (%)	1017 (100) inclusion crit.	1588 (100) inclusion crit.	530 (100) inclusion crit.
Initial variables assessed (baseline)	5 (4 variables as inclusion criterion)	6 (≥2 as inclusion criterion)	7 (6–7)
Variables assessed (n, %)	• 4 variables available (1017, 100) • 5 variables available (603, 59)	• 3 variables available (1580, 99.4) • 4 variables available (1515, 95.3) • 5 variables available (1312, 86.2) • 6 variables available (879, 55.4)	WHO FC + 6MWD + RV function (NP and/or Echo and/or RHC) in 79% (≥3 variables)
Initial treatment (within 3 months) (low - intermediate - high risk) (%)			
CCB in n%	102 (10%)	9% - 4% - 1%	6% - 5% - 4%
PAH Mono n%	480 (47%)	81% - 86% - 73%	94% - 85% - 56%
PAH Combination n%	436 (43%)	19% - 14% - 27%	6% - 15% - 44%
PAH dual n%	365 (36%)		6% - 14% - 40%
PAH triple n%	71 (7%)		0% - 1% - 4%
PCA n%	124 (12.2%) derived data	4 - 6 - 7	0% - 1% - 4%
missing data or (study drug) n%			6 (2)%- 3(3%) - 2 (2)%

IPAH = idiopathic pulmonary arterial hypertension; fPAH = familial pulmonary arterial hypertension; CTD-PAH = connective tissue disease associated PAH; CHD-PAH = congenital heart disease associated PAH; WHO FC=World Health Organization functional class; 6 MWD = 6 Minute Walking Distance; CPET = cardiopulmonary exercise testing; NP = natriuretic peptides; BNP = brain natriuretic peptide; NT-proBNP=N-terminal fragment of pro-brain natriuretic peptide; RAA = right atrial area, PE = pericardial effusion; RV = right ventricle; RAP = right atrial pressure; CI = cardiac index; SvO_2 = mixed venous oxygen saturation; CCB = calcium channel blockers; PCA = prostacyclin or analogs; LTx = lung transplantation.

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Table 2B
Evaluation of risk assessment strategy, data from the French, COMPERA and the Swedish cohorts [8–10]. Risk assessment at follow up.

Parameter	French cohort	COMPERA cohort	Swedish cohort
Variables assessed (follow up)	5 (4 in primary analysis)	6	5 (3–6)
Variables assessed (follow up)	• 4 variables available (1017, 100) • 5 variables available (603, 59)	• Pts. with 2 variables available (1230, 90.8) • Pts. with 3 variables available (720, 53.1) • Pts. with 4 variables available (379, 28) • Pts. with 5 variables available (270, 19.9) • Pts. with 6 variables available (117, 8.6)	FC + 6MWD + RV function (NP and/or Echo and/or RHC) in 80%
Reassessment in n (%)	1017 (100)	1355 (86)	383 (72)
median time to follow up (mo)	4.4	n/a	4
time period	within 12 months	within 3 to 24 months	within 12 months
Complete follow up time (mo)	34 (Median)		27 (Median)
Deaths overall in n (%)	238 (23) median FU 34 months	331 (30.3) FU 60 months	167 (31.5) median FU 27 months
Deaths attributed to PAH	n/a	38–63% SvO2 better than CI	n/a
LTx (n) during complete follow up (low - intermediate - high risk)	31 (3)	14 (<1) 1 (0.5)-10 (0.9)-3 (1.1)	13 (2.4)
Hemodynamic data @ follow up available in n (%)	1017 (100)	386 (35)	RAP in 34%, CI in 33%, SvO_2 in 26%

during the follow-up period, the ratio of patients with a low risk profile (at least three out of four variables in the low risk group) increased from 17 to 41.5%.

In summary, this study validates an abbreviated version of the ESC/ERS risk stratification strategy in a large cohort of classical PAH patients with idiopathic, familial and drug induced PAH. The used risk variables are part of the standard work-up of PAH patients at baseline and follow-up. Importantly, risk profiles were modifiable using PAH targeted treatments. This emphasizes the modifiable character of the chosen variables and the dynamic character of this risk assessment approach.

The **Swedish Pulmonary Arterial Hypertension Registry (SPAHR)** [10] reported on data of 530 patients with PAH, comprising a broad spectrum of etiologies (IPAH in 49%, FPAH in 1%, drugs- and toxin-induced in 3%, PAH-CTD in 31%, PAH-CHD in 13% and portal hypertension associated PAH in 3%). While numbers of hemodynamics and functional parameters as well as BNP/NT-proBNP levels were missing in this manuscript, data on demographics, comorbidities, treatment etc. were given for the specific risk groups.

For risk stratification, seven variables were available (WHO-FC, 6MWD, NT-proBNP, RAP, CI, SvO2, right atrial area and the presence

Table 2C
Evaluation of risk assessment strategy, data from the French, COMPERA and the Swedish cohorts [8–10]. Definition and outcome of different risk profiles.

Parameter	French cohort (3)	COMPERA cohort (4)	Swedish cohort (5)
Definition of risk categories	No initial categorization variables attributed to risk low - intermediate - high according to guidelines	Grades for risk groups low - intermediate - high (1-3) Sum of grades/variables	Grades for risk groups low - intermediate - high (1-3) Sum of grades/variables
Variables in low risk		n/a	n/a
(0 - 1 - 2 - 3 - 4) % @ baseline	25.5 - 36.5 - 21 - 11 - 6		
(0 - 1 - 2 - 3 - 4) % @ follow up	9.522 - 27 - 24.5 - 17		
Low risk[a] @ baseline			
• Patients at low risk in n (%)	17%[a]	196 (12%)[b]	23%[b]
• Outcome (1-, 3-, 5-year survival) for low risk profile at follow up	99%, 93%	97%, 84%, 76%	99%, 95%, 85%
Low risk[a] @ follow up			
• Patients at low risk in n (%)	41.5%[a]	261 (24%)[b]	29%[b]
• Outcome (1-, 3-, 5-year survival) for			
• Low risk profile at follow up	n/a	97%, 87%, 68%	99%, 97%, 92%
• Maintained or improved to low risk	99%, 93%	n/a	n/a 100%, 98%, 89% (low risk maintained) 100%, 96%, 96% (improved to low risk)
High risk[b] @ baseline			
• Patients at high risk in n (%)		276 (17%)	10%
• Outcome (1-, 3-, 5-year survival) for low risk profile at follow up		Survival 79, 53 and 32%	Survival 74, 51 and 35%
High risk** @ follow up			
Patients at high risk in n (%)	95 (8%)	183 (17%)	11%
Outcome (1-, 3-, 5-year survival) for			
• High risk profile at follow up	Survival 87%, 67% (@ 2 years)[c]	Survival 72, 44 and 23%	Survival 70, 25 and 6%
• Maintained or worsened to high risk	survival 70%, 42% (@ 2 years)[d]		
Intermediate risk @ baseline and/or follow up (%)[a]		1116 (70%), 650 (59%),	67%, 60%
1, 3 and 5 yr survival baseline risk			
1, 3 and 5 yr survival follow up risk intermediate		Survival 90, 68 and 52%	Survival 83, 67, 52%
1, 3 and 5 yr survival remain intermediate or high		Survival 92, 67 and 51%	Survival 91, 73 and 56%
1, 3 and 5 yr survival deteriorate follow up risk			Survival 90, 68 and 50% Survival 81, 60 and 43%

Legend:
[a] 3 or 4 (of 4) variables in low risk according to guidelines.
[b] Grade 1 (mean of available variables), see text for details.
[c] Zero low risk variables and one in high risk.
[d] Zero low risk variables and > one in high risk.

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Table 2D
Valuation of risk assessment strategy, data from the French, COMPERA and the Swedish cohorts [8–10]. Further insights.

Parameter	French cohort (3)	COMPERA cohort (4)	Swedish cohort (5)
Strength	Large study population with high level of follow up parameter Classical PAH cohort Significant sub analyses of 607 patients with available BNP/NTproBNP which allows prioritisation of parameters at follow up	Largest population survival data remain significant for subgroups incl. RHC (55.4%)	Data remain significant after exclusion of IPAH > 65 yr significance for subgroups
Weakness	Classical PAH cohort associated forms of PAH excluded	Age CTD-PAH n.s. @baseline for low and intermediate but high vs low/intermediate CTD-PAH $p < 0.05$ @follow up for low and intermediate but highly significant high vs low/intermediate follow up assessment low proportion of NP and RHC	Age Comorbidities higher in intermediate and high risk
	Rate of combination therapies not in accordance with guidelines	Rate of combination therapies not in accordance with guidelines Low rate of prostanoids	Rate of combination therapies not in accordance with guidelines Low rate of prostanoids
Invasive hemodynamics			
• Invasive hemodynamics	• SvO2 better than CI	• SvO2 better than CI	
• BNP < 50/NTproBNP < 300	• In subanalysis (n = 603) hemodynamics without additive prognostic value when NP are normal		

or absence of pericardial effusion). Follow-up data were available for 383 patients.

Patients were categorized as low, intermediate of high risk according to cut-off values for the above-mentioned variables defined in the ESC/ERS guidelines. Each variable was graded from 1 to 3 where 1 = low risk, 2 = intermediate risk, and 3 = high risk. Dividing the sum of all grades by the number of available variables for each patient rendered a mean grade. The mean grade was rounded to the nearest integer, which was used to define the patient's risk group.

At baseline, 23% of patients were classified as low risk, 67% as intermediate risk, and 10% as high risk. Observed 1-, 3-, and 5-year mortality rates were 1, 5, and 15% (low risk), 17, 33, and 48% (intermediate risk) and 26, 49, and 65% (high risk), respectively.

At follow-up, 29% met the low risk definition, 60% were at intermediate risk and 11% at high risk. Mortality after 1, 3, and 5 years was 1, 3, and 8% (low risk), 9, 27, and 44% (intermediate risk) and 30, 75, and 94% (high risk), respectively. Importantly, the risk profile at follow-up appeared to predict long-term outcome better than the baseline risk assessment. Patients who improved to a low-risk profile at follow-up had a similar low mortality risk (0, 4, and 4% after 1-, 3-, and 5-years) as those who presented with a low risk at baseline and remained at low risk. Patients who worsened to an intermediate or high-risk profile during follow-up had basically the same survival as those who presented with an intermediate or high risk profile at baseline and did not change risk category. Sub-analyses of the largest PAH subsets, including CTD-PAH, yielded similar results. Remarkably, although not surprising, patients with a low-risk profile were younger, indicating that lower age is associated with better outcome. However, during the multivariate analyses, adjusted for age, sex, and PAH subset, the reduced mortality risk for patients with a low-risk profile remained. This was also true for sensitivity analyses when IPAH patients >65 years at diagnosis were excluded.

In conclusion, this data supports the risk assessment approach proposed by the ESC/ERS guidelines. Although another approach was used as compared to the French registry, it further supports the notion that patients with a low risk profile at baseline and, particularly, at follow-up have an expected survival of 99% at one year. In contrast, patients who are at high risk at baseline and/or during follow-up, have an expected 1 year-survival of only 70 to 74%. Importantly, these results were true for the overall (elderly) population and PAH subgroups as well as across different ages. Looking at the contribution of the individual variables, it seems that mainly WHO-FC (available in 95%), 6MWD (available in 85%), and NT-proBNP (available in 89%) triggered these results. Follow-up data for echocardiography were available in only 37–69% of all patients. The performance of follow-up invasive hemodynamics could not be fully assessed, since only around one third of patients was reassessed by right heart catheterization during follow-up.

COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) [9] is a European registry that prospectively enrolls and follows patients with all forms of PH, including those with PAH, with ~80% of the patients coming from German PH centers. The actual analysis included data from 1588 incident PAH patients (IPAH, FPAH or drugs-, toxin induced PAH in 67%, CTD-PAH in 22%, CHD-PAH in 4%, HIV-PAH in 1%, portal hypertension associated PAH and other forms of PAH in 7%).

The hemodynamic data showed a typical PAH profile with mPAP 45 mm Hg, CI 2.3 l/min/m2, mRAP 8 mm Hg, SvO2 63% and PVR of approximately 10 WU. Most patients were in WHO-FC III (70%) or IV (15%) at baseline, 11% were in WHO-FC I–II.

Risk stratification was done at baseline and during follow-up, using three noninvasive parameters (WHO-FC, 6 MWD, BNP or NT-proBNP) and three variables derived from right heart catheterization (RAP, CI and SvO2). At baseline, three parameters were available in 99%, 4 variables in 95%, 5 in 86%, and 6 parameters were available in 55%. Using these parameters, patients were categorized as low, intermediate or high risk, according to the above-mentioned method utilized by the SPAHR registry.

Baseline evaluation and mortality - When using this approach, 12% of patients were in the low risk group, 70% and 17% in the intermediate and high risk group at baseline, respectively. Observed 1-, 3-, and 5-year mortality was 3%, 16%, and 24% for the low risk group, 10%, 32, and 48%

Table 3
Validated parameters for the risk assessment strategy in PAH [8–10].

	Low risk	Intermediate risk	High risk
WHO FC	I,II	III	IV
6 MWD (m)	>440	165–440	<165
BNP or (NT-proBNP) (ng/L)	<50 (<300)	50–300 (300–1400)	>300 (>1400)
RAP (mm Hg)	<8	8–14	>14
Cardiac Index (l/min/qm)	≥2.5	2.0–2.4	<2.0
SvO_2 (%)	>65	60–65	<60

WHO FC: World Health Organization functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; SvO2: mixed venous oxygen saturation.

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in the intermediate risk group, and 21%, 47%, and 68% in patients at high risk, respectively. Within 5 years after the diagnosis of PAH, 29% patients had died: 13.3% in the low-risk group, 28.0% in the intermediate-risk group and 43.8% in the high-risk group. Right heart failure was reported as the most likely cause of death in 38% of the patients who died in the low-risk group, in 54% of the patients who died in the intermediate-risk group and in 63% of the patients who died in the high-risk group. Importantly, in the overall PAH cohort, these results were consistent in a subanalysis of patients with all six variables available ($n = 879$; 55%), confirming a statistically significant difference between the three risk categories. Concerning the different etiologies of PAH, these observations were consistent in idiopathic/hereditary and drug-induced PAH. In patients with CTD-PAH, there was no significant survival difference between the low-risk group and the intermediate-risk group. However, the survival differences between the high-risk group and the two other groups were statistically significant.

Follow-up evaluation and mortality - Follow-up data between 3 months and 2 years after treatment initiation were available for 1355 patients. Availability of variables of interest is given in Tables 2A, 2B, 2C, and 2D. Hemodynamic follow-up data were available for only 35% of these patients. In terms of the risk stratification during follow-up, 23% out of 1073 improved their risk category, whereas 62.2% remained stable, and 14.8% deteriorated. More precisely, the ratio of low risk patients improved to 24%, whereas the fraction of intermediate risk patients dropped to 59% and the portion of high risk patients remained at 17%. The resulting mortality in the respective risk group was comparable to that at baseline. Moreover, changes in the risk category from baseline to follow-up were associated with a shift in the mortality risk.

Within 5 years of follow-up assessment, 30.3% patients had died: 14.9% in the low-risk group, 30.9% in the intermediate-risk group, and 49.7% in the high-risk group. Even for the follow-up evaluation of the risk assessment, differences between survival rates for the different risk groups were highly statistically different for the overall cohort and idiopathic/hereditary/drug-induced PAH. The survival difference in patients with CTD-PAH between the low-risk group and the intermediate-risk group was of marginal statistical significance, whereas the difference between the high-risk and the low and intermediate-risk groups were highly significant.

In **conclusion**, this study validates the risk assessment strategy proposed in the guidelines in the so far largest cohort of patients diagnosed with PAH from different etiologies. A combination of values derived from invasive (RAP, CI and SvO_2) and non-invasive (FC, 6 MWD, BNP or NT-proBNP) tests discriminated effectively between patients with different risk categories. This risk stratification strategy also proved valid for both baseline and follow-up assessments. The risk prediction proved accurate with high statistical significance in the overall PAH cohort and for idiopathic/hereditary and drug-induced PAH. A minor deviation of the consistency of survival data was observed between the low- and intermediate-risk group at baseline (lack of statistical significance), and during follow-up (marginal statistical significance) in the subgroup of CTD-PAH. Moreover, the risk estimates proposed in the European PH guidelines with annual mortality risks of <5%, 5–10%, and > 10% in patients at low, intermediate or high risk, respectively, were confirmed in the present series, both at baseline as well as at follow-up.

In this study, the likelihood of death attributed by the investigators to PAH was 38% in the low-risk group, and 63% in the high-risk group, respectively. Although assigning causes of death is often associated with uncertainties, these data underline the integrative character of some non-invasive parameters. Especially results from methods that aim at objectively assess functional capacity may have been affected by the older age of the patient population. The age of this patient cohort may have also influenced the follow-up strategy, favoring a non-invasive approach. Given the fact that follow-up hemodynamics were only available in 35% of cases, and several variables from echocardiography and CPET were not available for this analysis, further studies are needed to determine the most reliable dataset.

Nevertheless, it is important to appreciate the fact that the risk categories (arising mainly from functional assessment and BNP or NT-proBNP) were variable, comparing baseline and follow-up. Moreover, a shift (towards a lower or higher risk) between the risk categories was associated with a better or worse outcome, respectively. This dynamic character of the risk strategy supports the approach that achieving a low risk strategy can serve as a therapeutic target in patients with PAH.

5. Summary of available data

In summary, the above-mentioned studies from different European countries validated the risk assessment approach for patients with PAH, proposed by the ESC/ERS guidelines in approximately 3000 newly diagnosed PAH patients over an inclusion period of approximately ten years (from 2006 to end of 2016). These data now provide evidence that:

1) An abbreviated version of the PAH risk stratification strategy discriminates effectively between patients with a low, intermediate, or high risk of death;
   - the proposed combination of values taken from invasive (RAP, CI and SvO_2) and non-invasive (WHO-FC, 6MWD, BNP or NT-proBNP) methods for risk categorization is confirmed.
   - while all parameters are of value when the initial diagnosis is made, invasive hemodynamics did not add significantly during follow-up assessment in patients at low risk, when BNP and/or NT-proBNP values are <50 and <300 ng/l respectively (which can be designated as *normal* for many PAH patients). However, invasive hemodynamics (SVI, RAP) during follow-up proved effective in predicting survival in PAH patients in general.
   - given the fact that follow-up hemodynamics and echocardiography were only available in a minority of patients and cardiopulmonary exercise testing as well as clinical assessment with regard to syncope etc. were not evaluated in the validation studies, further studies are needed to evaluate the most reliable data set.
2) This risk stratification strategy proved valid for both baseline and follow-up assessments; and is particularly accurate in patients with "classical PAH" (idiopathic/hereditary/drug-induced).
3) Prognostication seems to be especially precise in the two extremes of the risk categories (low and high risk groups), leaving scope for interpretation of patients at intermediate risk.
4) Risk profiles are modifiable, with an impact on observed mortality. This emphasizes the dynamic character of the risk assessment approach.
5) Expected annual mortality risk for the different risk categories ranges from <5% (low risk) to 5–10% (intermediate) and >10% in patients at high risk.

6. Part 3: recommendations for the use of risk stratification and clinical decision making in routine practice

Since validation for the risk assessment strategy proposed by the European guidelines is now available, this approach is recommended by the Cologne Consensus Conference working group for patients with "classical PAH" (Fig. 1).

- Risk assessment for individual patients should be included in the initial evaluation process of patients with "classical PAH" (baseline) and during follow-up. To this end, all available parameters should be included to categorize individual annual mortality risk as low, intermediate, or high.
- A composite of invasive (RAP, CI and SvO_2) and non-invasive parameters of functional impairment (WHO-FC, 6 MWD) and right heart

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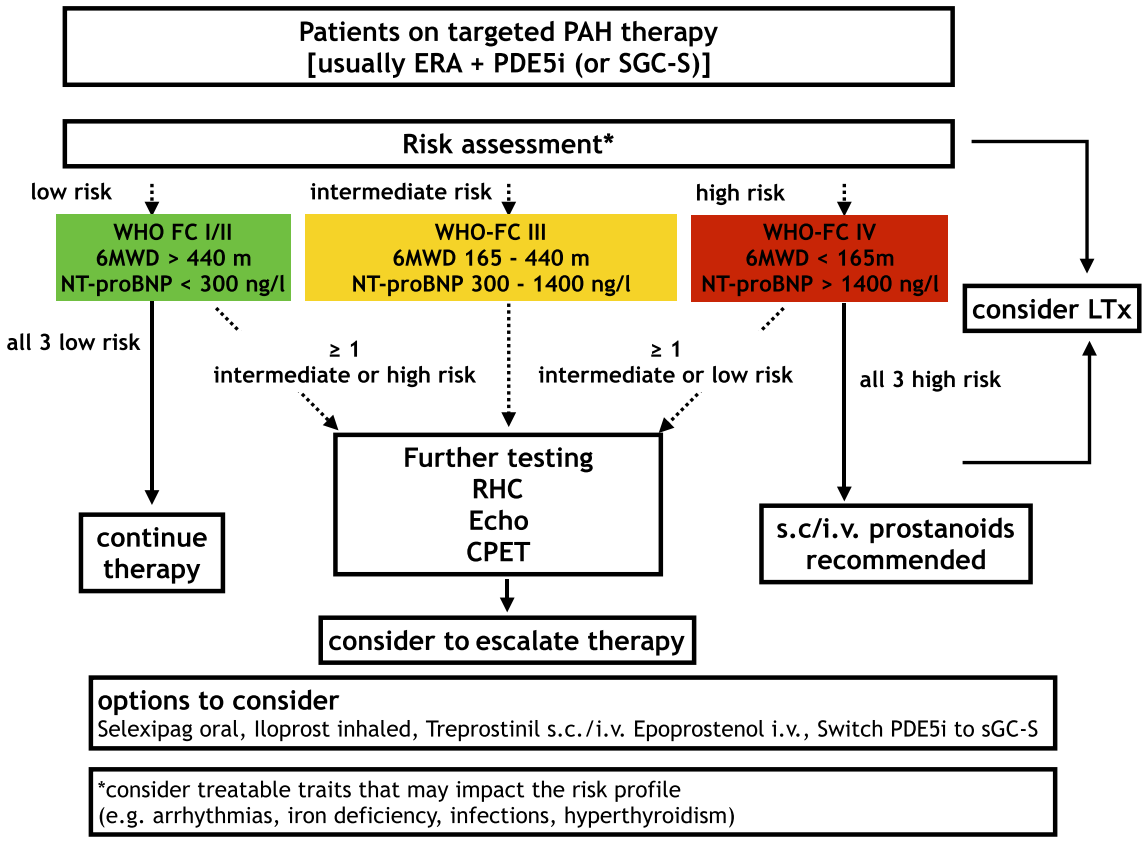

Fig. 1. Evidence based risk assessment algorithm during follow-up assessment of PAH patients. For details see recommendations.

failure (BNP or NT-proBNP) is recommended at baseline, using the cut-off values for each parameter proposed by the guidelines (see Table 1).

- During follow-up, a primarily non-invasive reevaluation is recommended, including at least a minimal set of parameters (WHO-FC, 6 MWD and BNP or NT-proBNP). From these parameters a risk category should be calculated (Fig. 1).
- ***Low risk***: all parameters meet low risk criteria → no additional testing is recommended on a routine basis, and established therapy should be continued.
- ***High risk***: all parameters meet high risk criteria → no additional testing is recommended on a routine basis, and s.c./i.v. prostanoids should be considered.
- ***Intermediate risk***: for this patient group → additional testing, in particular repeat right heart catheterization, as well as echocardiography and CPET, are recommended to guide further therapeutic decision-making. Based on additional testing, treatment escalation may be considered. This is in accordance with the current guidelines recommending follow-up right heart catheterization "… whenever therapeutic decisions can be expected from the results".
- Echocardiography and CPET have not been validated in the above mentioned registry studies, and therefore no evidence-based recommendations can be made for these modalities in terms of risk assessment. However, the broad availability of both techniques and the potential value of echocardiography and CPET in experienced hands are appreciated. Further evaluation and validation of these modalities in the context of risk assessment are warranted.

Conflicts of interest/author declarations

HHL: received fees for lectures and/or consultancy from Actelion, Bayer, GSK, Merck, and Pfizer.

HtF: received fees for lectures and/or consultancy from Actelion, Bayer, BMS, GSK, Servier.

HG: received fees for lectures and/or consultancy from Actelion, Astra, Zeneca, Bayer, BMS, GSK, Janssen Cilag, Lilly, MSD, Novartis, OMT, Pfizer, United Therapeutics.

MH: received fees for consulting and/or lectures and conference sponsorship from Actelion, AOP orphan/OMT, Bayer, Gilead, GSK, MSD, Novartis, and Pfizer.

MMH: received fees for consulting and/or lectures from Actelion, Bayer, Gilead, GSK, Merck and Pfizer.

HK: received Sponsorship/Honoraria from Actelion, Bayer Healthcare, Bristol Myers Squibb. He is Steering Board member of the COMPERA International Steering Board, and had Research grant from Deutsche Stiftung für Herzforschung and Deutsche Herzstiftung.

CK: received fees for lectures and/or consultancy from Actelion, Pfizer, GSK, Novartis, Bayer.

GR: received fees for lectures and/or consultancy from Actelion, Bayer, BMS, Celgene, GSK, Pfizer, Medac, MSD, Roche.

SU: received fees for lectures and/or consultancy from Schweizerischer Nationalfond, Zürcher Lungenliga, Actelion, Bayer, Orpha-Swiss.

MS: received fees for lectures and/or consultancy from Actelion, Bayer, GSK, Pfizer.

RE: received fees for lectures and/or consultancy from Actelion, Bayer, GSK, Merck, OMT, Pfizer, United Therapeutics.

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