Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model

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The risk stratification strategy proposed by the current European PH guidelines allows accurate survival prediction http://ow.ly/KsWk30c46nK

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ABSTRACT The 2015 European pulmonary hypertension (PH) guidelines propose a risk stratification strategy for patients with pulmonary arterial hypertension (PAH). Low-, intermediate- and high-risk strata are defined by estimated 1-year mortality risks of <5%, 5–10% and >10%, respectively. This risk assessment strategy awaits validation.

We analysed data from patients with newly diagnosed PAH enrolled into COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), a European-based PH registry. An abbreviated version of the risk assessment strategy proposed by the European PH guidelines was applied, using the following variables: World Health Organization functional class, 6-min walking distance, brain natriuretic peptide or its N-terminal fragment, right atrial pressure, cardiac index and mixed venous oxygen saturation.

Data from 1588 patients were analysed. Mortality rates were significantly different between the three risk strata ($p<0.001$ for all comparisons). In the entire patient population, the observed mortality rates 1 year after diagnosis were 2.8% in the low-risk cohort (n=196), 9.9% in the intermediate-risk cohort (n=1116) and 21.2% in the high-risk cohort (n=276). In addition, the risk assessment strategy proved valid at follow-up and in major PAH subgroups.

An abbreviated version of the risk assessment strategy proposed by the current European PH guidelines provides accurate mortality estimates in patients with PAH.

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Introduction

Pulmonary arterial hypertension (PAH) has evolved from a disease with limited treatment options to one where numerous drugs targeting several pathways have become available. Hence, physicians now can choose between various therapies, modes of administration and drug combinations (recently reviewed in [1–3]). To facilitate treatment decisions, the 2015 European guidelines for pulmonary hypertension (PH) proposed a dynamic risk stratification strategy [4, 5]. This approach is based on a comprehensive assessment including clinical features, World Health Organization (WHO) functional class (FC), 6-min walking distance (6MWD), cardiopulmonary exercise testing (CPET), biomarkers (brain natriuretic peptide (BNP) and the N-terminal fragment of proBNP (NT-proBNP)) and certain variables derived from echocardiography and right heart catheterisation. Based on cut-off values gathered from the literature, three distinct risk categories have been defined: patients at low risk with an estimated 1-year mortality rate <5%; patients at intermediate risk with an estimated 1-year mortality rate of 5–10%; and patients at high risk with an estimated 1-year mortality rate >10%. This risk model is meant to be applicable in patients with newly diagnosed PAH and at any time during the course of the disease. However, the accuracy of this risk assessment strategy has not yet been established. The only validation attempt available so far came from the Swedish Pulmonary Arterial Hypertension Registry. These data suggested that the risk stratification strategy proposed by the European PH guidelines worked accurately at baseline as well as during follow-up, but were based on a relatively small number of patients (n=530 incident patients at baseline and n=383 at follow-up) [6].

In order to further validate the risk stratification strategy proposed by the European PH guidelines, we analysed data from COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), a European registry that prospectively enrols and follows patients with all forms of PH, including those with PAH.

Methods

Database

COMPERA (www.COMPERA.org; registered at Clinicaltrials.gov with identifier NCT01347216) is an ongoing web-based PH registry launched in 2007 which collects baseline, follow-up and outcome data from patients who receive targeted therapies for PH. Specialised centres in several European countries participate (Austria, Belgium, Germany, Greece, Hungary, Italy, Netherlands, Switzerland and the United Kingdom), with ∼80% of the patients coming from German PH centres.

COMPERA enrols only patients with newly diagnosed PH, *i.e.* patients must be entered into the database no later than 6 months after the date of diagnosis. COMPERA applies a series of state-of-the-art quality checks including automated queries of out-of-range data, individual queries of data that raise concerns and independent on-site source data verification. Further details of COMPERA have been published elsewhere [7–9].

The variables captured in COMPERA are prespecified. Some, but not all variables proposed for risk assessment in the European PH guidelines are regularly recorded in the database. Specifically, WHO FC, 6MWD, BNP or NT-proBNP, right atrial pressure, cardiac index and mixed venous oxygen saturation (S_{vO_2}) are recorded whenever available. These six variables were used in the present study for the validation of a truncated version of the risk assessment strategy proposed by the European PH guidelines. Variables listed in the guidelines that are not captured in COMPERA are disease progression, syncope, echocardiographic variables and CPET data.

Patients

Patients were selected from the COMPERA database according to the following criteria: 1) treatment-naïve patients newly diagnosed with PAH between January 1, 2009 and December 1, 2016 with data from

baseline and at least one follow-up visit available; 2) mean pulmonary artery pressure ⩾25 mmHg, pulmonary artery wedge pressure ⩽15 mmHg and pulmonary vascular resistance (PVR) >240 dyn·s·cm^{-5} at the time of diagnosis; and 3) at least two of the six listed variables available at baseline.

Risk stratification strategy

An abbreviated version of the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification strategy was used to categorise patients as low, intermediate or high risk (table 1). Following a validation strategy proposed by KYLHAMMAR *et al.* [6], the cut-off values proposed in the guidelines were graded 1–3 (1: low risk, 2: intermediate risk and 3: high risk). For each patient, the sum of all grades was divided by the number of available variables and rounded to the next integer to define the risk group. Calculations were made from baseline assessments and from follow-up assessments between 3 months and 2 years after the initiation of medical therapy for PAH.

Statistical analyses

The primary analysis set consisted of the entire patient population that fulfilled the inclusion criteria listed earlier. Sensitivity analyses were performed with those patients for whom all six risk score variables were available and for the subgroups of patients with idiopathic, drug-associated or hereditary PAH (I/D/H-PAH) and connective-tissue disease-associated PAH (CTD-PAH). Other subgroups were not assessed because the numbers of patients were considered too low.

Patients who underwent lung transplantation were censored at the time of surgery.

For the follow-up risk stratification, patients who underwent their first comprehensive follow-up risk assessment between 3 months and 2 years after treatment initiation were considered. Where available, we chose the first visit that included follow-up haemodynamics. If no haemodynamic follow-up was available during the first 2 years after diagnosis, we selected the follow-up visit that contained most of the data of interest. For all analyses, only patients with at least one further follow-up were included into the analysis.

Continuous data are presented as mean±SD or as median and interquartile range. In patients who died, investigators were asked to provide the most likely cause of death. There was no independent adjudication of causes of death. Survival was evaluated using Kaplan–Meier analysis and log-rank test, truncated at 5 years. Hazard ratios for the single risk-score items were estimated using Cox regression analysis, using the respective low-risk group as reference. IBM SPSS Statistics (version 19.0; Armonk, NY, USA) was used for analysis.

Results

Risk stratification at baseline and mortality

For this analysis, baseline data from a total of 1588 patients with newly diagnosed PAH fulfilling the inclusion criteria were available. Patients with I/D/H-PAH formed the largest subgroup (n=1060; 67%), followed by patients with CTD-PAH (n=347; 22%), patients with PAH associated with congenital heart disease (n=70, 4%) and patients with other forms of PAH (n=111; 7%). The characteristics of these patients are shown in table 2. Out of the six variables of interest for this study, at least two were available in all 1588 patients (primary analysis set), at least three in 1580 (99.4%) patients, at least four in 1515 (95.3%) patients, at least five in 1312 (82.6%) patients and all six variables were available in 879 (55.4%) patients.

28 (1.8%) patients were lost to follow-up: six (2.8%) in the low-risk group, 16 (1.4%) in the intermediate-risk group and six (2.3%) in the high-risk group. 14 (0.9%) patients underwent lung

TABLE 1 Variables and cut-off values used for risk stratification

	Low risk	Intermediate risk	High risk
WHO FC	I/II	III	IV
6-min walking distance m	>440	165–440	<165
BNP ng·L^{-1}	<50	50–300	>300
NT-proBNP ng·L^{-1}	<300	300–1400	>1400
Right atrial pressure mmHg	<8	8–14	>14
Cardiac index L·min^{-1}·m^{-2}	⩾2.5	2.0–2.4	<2.0
S_{vO_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; S_{vO_2}: mixed venous oxygen saturation.

TABLE 2 Characteristics of the patients included in the baseline risk stratification group

	N	Low risk	Intermediate risk	High risk	All
Subjects n		196	1116	276	1588
Age years		53±18	66±14	65±17	64±16
Female		66	63	66	64
BMI kg·m^{-2}		26±5	28±6	28±7	28±6
PAH aetiology					
I/D/H-PAH		101 (52)	760 (68)	199 (72)	1060 (67)
CTD-PAH		52 (27)	234 (21)	61 (22)	347 (22)
HIV-PAH		4 (2)	16 (1)	2 (1)	22 (1)
PoPH		20 (10)	60 (5)	9 (3)	89 (6)
CHD-PAH		19 (10)	46 (4)	5 (2)	70 (4)
WHO FC class I/II/III/IV	1530	2/47/43/0 (unknown n=8)	0/8/78/11 (unknown n=3)	0/1/53/43 (unknown n=3)	0/11/70/15 (unknown n=4)
6MWD m	1262	442±100	299±109	186±103	298±126
NT-proBNP ng·L^{-1}	1003	151 (86–351)	1404 (597–3042)	4006 (2519–6743)	1573 (526–3498)
BNP ng·L^{-1}	249	44 (25–96)	180 (93–377)	549 (418–784)	236 (101–523)
Haemodynamics					
Right atrial pressure mmHg	1506	5±3	8±4	13±5	8±5
mPAP mmHg	1588	43±13	44 ±12	50±12	45±13
PAWP mmHg	1588	8±3	9±4	10±3	9±3
Cardiac index L·min^{-1}·m^{-2}	1497	3.1±0.7	2.3±0.7	1.6±0.4	2.3±0.8
PVR dyn·s·cm^{-5}	1588	547±273	743±372	1149±522	784±431
S_{vO_2} %	1420	72±5	64±8	53±8	63±9
Initial therapy (within 3 months after diagnosis)					
CCB		9%	4%	1%	4%
ERA		43%	36%	45%	39%
PDE-5i/sGC		63%	72%	78%	72%
PCA		1%	2%	7%	3%
Monotherapy		81%	86%	73%	83%
Combination therapy		19%	14%	27%	17%
Anticoagulation		31%	44%	48%	43%

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; PAH: pulmonary arterial hypertension; I/D/H: idiopathic, drug-associated or hereditary; CTD: connective tissue disease; PoPH: portopulmonary hypertension; CHD: congenital heart disease; WHO FC: World Health Organization functional class; 6MWD: 6-min walking distance; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; BNP: brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; CCB: calcium channel blocker; ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitor; sGC: stimulator of soluble guanylate cyclase; PCA: prostacyclin analogue.

transplantation: one (0.5%) in the low-risk group, 10 (0.9%) in the intermediate-risk group and three (1.1%) in the high-risk group.

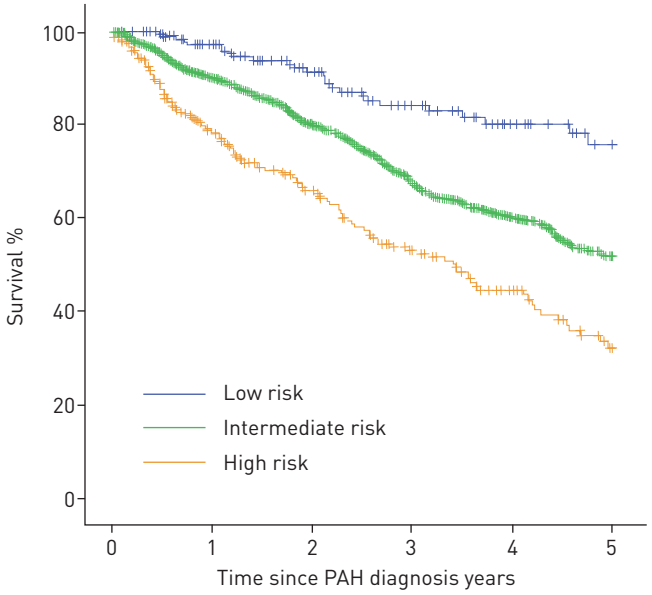
Within 5 years after the diagnosis of PAH, 459 (29%) patients had died: 26 (13.3%) in the low-risk group, 312 (28.0%) in the intermediate-risk group and 121 (43.8%) in the high-risk group. Right heart failure was reported as the most likely cause of death in 38% of the patients who died in the low-risk 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.

In the low-risk group, the survival rates at 1, 2, 3, 4 and 5 years were 97.2%, 91.5%, 84.2%, 80.2% and 75.9%, respectively. The corresponding survival rates in the intermediate-risk group were 90.1%, 80.3%, 68.1%, 60.1% and 51.9%, respectively and 78.8%, 66.0%, 53.2%, 44.7% and 32.4%, respectively, in the high-risk group ($p<0.001$ for all group comparisons; figure 1).

Almost identical results were obtained from a sensitivity analysis that included only those 879 patients for whom all six baseline variables were available. Here, the survival differences between the three risk categories were highly statistically significant, with p-values <0.001 for all comparisons (online supplementary table S1 and figure S1).

The predictive value of each variable at baseline is shown in figure 2.

The results of the analyses from the I/D/H-PAH and CTD-PAH subgroups are shown in online supplementary table S2 and figure S2 and online supplementary table S3 and figure S3, respectively. In



Years after enrolment	Survival %			Cases left n		
	Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk
0	100	100	100	196	1116	276
1	97.2	90.1	78.8	156	764	170
2	91.5	80.3	66.0	111	540	117
3	84.2	68.1	53.2	75	376	77
4	80.2	60.1	44.7	47	252	47
5	75.9	51.9	32.4	31	149	24

FIGURE 1 Kaplan–Meier survival estimates in patients with all forms of pulmonary arterial hypertension (PAH) combined per individual risk stratification at baseline.

patients with I/D/H-PAH, the survival differences between all three groups were highly statistically significant (p<0.001; online supplementary figure S2). In patients with CTD-PAH, there was no significant survival difference between the low-risk group and the intermediate-risk group at baseline (p=0.101), while the survival differences between the high-risk group and the two other groups were highly statistically significant (p<0.001; online supplementary figure S3).

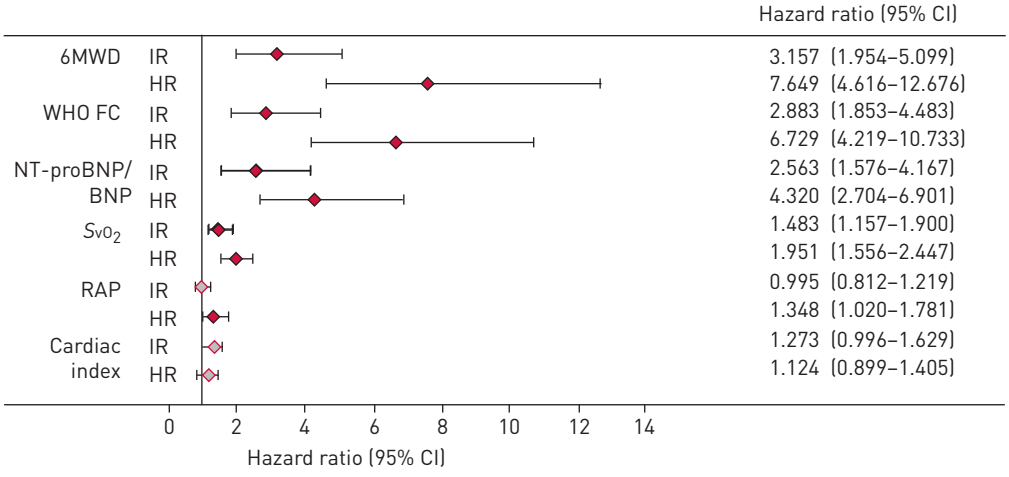


FIGURE 2 Forest plot showing the prognostic values of 6-min walking distance (6MWD), World Health Organization (WHO) functional class (FC), brain natriuretic peptide (BNP) or N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), mixed venous oxygen saturation (Sv_{O_2}), right atrial pressure (RAP) and cardiac index in the intermediate-risk (IR) and high-risk (HR) groups. Values for the parameters were obtained at baseline. The reference value is from the respective low-risk group.

TABLE 3 Variables obtained between 3 months and 2 years after treatment initiation of patients included in the follow-up risk stratification group

	N	Low risk	Intermediate risk	High risk	All
Subjects n		261	650	183	1094
Age years		52±17	66±14	73±11	64±16
Female		68	65	62	65
BMI kg·m^{-2}		26±6	29±7	29±6	28±7
PAH aetiology					
I/D/H-PAH		158 (61)	460 (71)	138 (75)	756 (69)
CTD-PAH		55 (21)	122 (19)	36 (20)	213 (20)
HIV-PAH		6 (2)	9 (1)	1 (1)	16 (2)
PoPH		25 (10)	28 (4)	2 (1)	55 (5)
CHD-PAH		17 (7)	31 (5)	6 (3)	54 (5)
WHO FC class I/II/III/IV	964	11/72/17/0	1/20/76/4	0/0/81/19	3/28/64/6
6MWD m	713	472±100	324±99	140±83	349±133
NT-proBNP ng·L^{-1}	626	145 (78–279)	900 (366–1851)	3788 (2072–5465)	887 (263–2339)
BNP ng·L^{-1}	146	27 (20–76)	136 (88–250)	457 (361–685)	190 (100–371)
Haemodynamics					
Right atrial pressure mmHg	374	5±2	8±5	15±5	8±5
mPAP mmHg	384	40±13	44±12	50±9	43±12
PAWP mmHg	378	9±3	10±4	12±5	10±4
Cardiac index L·min^{-1}·m^{-2}	360	3.2±0.8	2.3±0.7	1.7±0.4	2.6±0.8
PVR dyn·s·cm^{-5}	376	449±211	681±315	967±334	632±326
S_{vO_2} %	349	72±5	63±7	55±8	65±8
Initial therapy (within 3 months after diagnosis)					
CCB		9%	3%	1%	4%
ERA		59%	55%	48%	55%
PDE-5i/sGC		72%	75%	79%	75%
PCA		4%	6%	7%	5%
Monotherapy		51%	59%	61%	57%
Combination therapy		47%	40%	36%	41%
Anticoagulation		36%	51%	62%	49%

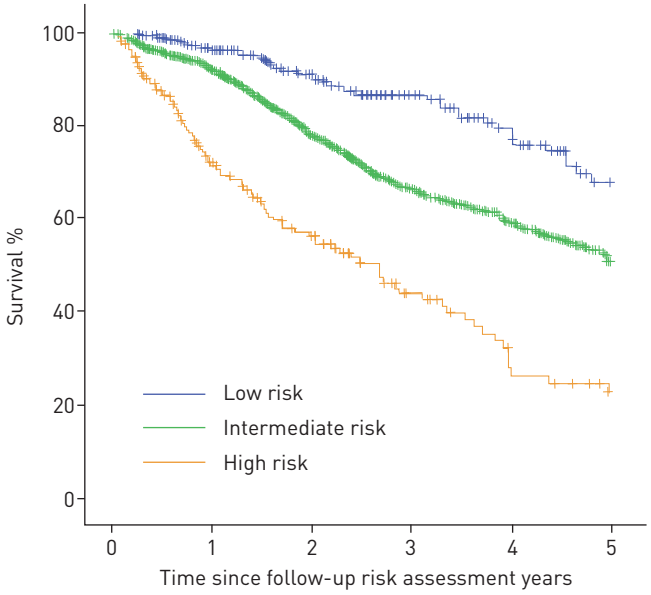
Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; PAH: pulmonary arterial hypertension; I/D/H: idiopathic, drug-associated or hereditary; CTD: connective tissue disease; PoPH: portopulmonary hypertension; CHD: congenital heart disease; WHO FC: World Health Organization functional class; 6MWD: 6-min walking distance; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; BNP: brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; CCB: calcium channel blocker; ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitor; sGCs: stimulator of soluble guanylate cyclase; PCA: prostacyclin analogue.

Risk stratification at follow-up and mortality risk

Follow-up data between 3 months and 2 years after treatment initiation were available for 1355 patients (online supplementary figure S4). Out of the six variables of interest for this study, at least two were available at the same visit in 1230 (90.8%) patients, at least three in 720 (53.1%) patients, at least four in 379 (28.0%) patients, at least five in 270 (19.9%) patients and all six variables were available in 117 (8.6%) patients. Of the patients with at least two risk score variables (assessment in median 7.2 months after baseline), data from at least one additional follow-up visit were available from 1094 patients. The characteristics of these patients are shown in table 3. Haemodynamic follow-up data were available for only 386 (35%) of these patients.

Within 5 years of follow-up assessment, 331 (30.3%) patients had died: 39 (14.9%) in the low-risk group, 201 (30.9%) in the intermediate-risk group and 91 (49.7%) in the high-risk group. In the low-risk group, the survival rates at 1, 2, 3, 4 and 5 years were 96.5%, 91.4%, 86.8%, 79.8% and 68.1%, respectively. The corresponding survival rates were 91.8%, 78.0%, 66.8%, 59.3% and 51.1%, respectively, in the intermediate-risk group, and 72.4%, 56.6%, 44.2%, 28.0% and 22.8%, respectively, in the high-risk group ($p<0.001$ for all group comparisons; figure 3).

The results of the follow-up analyses from the I/D/H-PAH and CTD-PAH subgroups are shown in online supplementary tables S2 and S3 and supplementary figures S2 and S3, respectively. In patients with I/D/H-PAH, the survival differences between all three groups were statistically significant (low-*versus* intermediate-risk group $p=0.002$; low- and intermediate-*versus* high-risk group both $p<0.001$; online supplementary figure S5). In patients with CTD-PAH, the survival difference between the low-risk group



Years after enrolment	Survival %			Cases left n		
	Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk
0	100	100	100	261	650	183
1	96.5	91.8	72.4	203	504	100
2	91.4	78.0	56.6	145	355	66
3	86.8	66.8	44.2	101	235	35
4	79.8	59.3	28.0	67	146	18
5	68.1	51.1	22.8	35	79	11

FIGURE 3 Kaplan–Meier survival estimates of patients with all forms of pulmonary arterial hypertension (PAH) combined per individual risk stratification at follow-up risk assessment between 3 months and 2 years.

and the intermediate-risk group was of marginal statistical significance (p=0.042), while the survival differences between the high-risk group and the two other groups were highly statistically significant (p<0.001; online supplementary figure S6).

The predictive value of each variable at follow-up were not calculated as BNP/NT-proBNP and follow-up haemodynamics were not available from a large proportion of the patients.

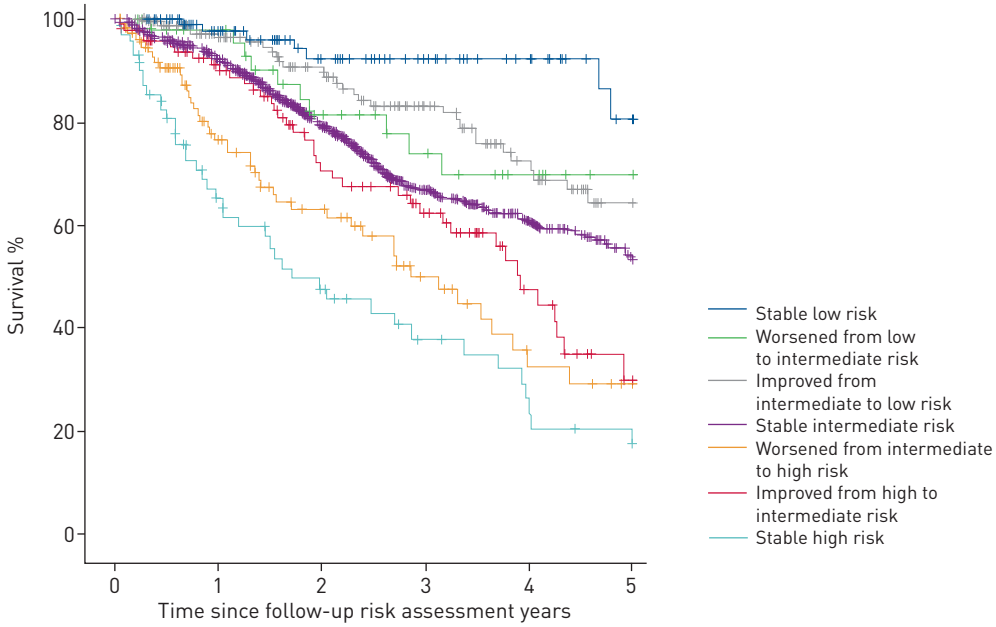
From baseline to follow-up, 247 (23.0%) out of 1073 improved their risk category; 667 (62.2%) out of 1073 remained stable and 159 (14.8%) out of 1073 deteriorated. Changes in the risk category from baseline to follow-up were associated with a shift in the mortality risk, as shown in figure 4.

Discussion

The main findings of the present study can be summarised as follows. 1) An abbreviated version of the risk stratification strategy proposed by the European PH guidelines using WHO FC, 6MWD, BNP or NT-proBNP, right atrial pressure, cardiac index and SvO_2 discriminated effectively between patients with a low, intermediate and high risk of death; 2) this risk stratification strategy was valid for baseline and follow-up assessments; 3) risk prediction proved accurate for subgroups of patients with I/D/H-PAH and CTD-PAH (except for the lack of a significant survival difference between low- and intermediate-risk CTD-PAH patients at baseline); and 4) 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 addition, among the patients who died, the likelihood of death attributed by the investigators to PAH increased from 38% in the low-risk group to 63% in the high-risk group. Although assigning causes of death is often associated with uncertainties, these findings suggest that a substantial proportion of patients, especially in the low-risk group, died from causes unrelated to PAH, which may be expected in a relatively old patient population.

Our data confirm and extend previous findings by Kylhammar *et al.* [6], who used basically the same subset of variables (plus right atrial area and the presence/absence of pericardial effusion). In that study,



	Survival %						
Years after enrolment	Stable low risk	Worsened from low to intermediate risk	Improved from intermediate to low risk	Stable intermediate risk	Worsened from intermediate to high risk	Improved from high to intermediate risk	Stable high risk
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1	97.4	97.8	96.3	91.6	76.5	89.9	65.3
2	92.2	81.4	90.7	79.1	63.1	70.4	47.7
3	92.2	73.8	83.1	67.0	49.9	62.3	38.2
4	92.2	69.7	72.4	60.5	32.6	47.5	23.5
5	80.6	69.7	64.4	53.3	29.3	30.0	17.1

	Patients at risk n						
Years after enrolment	Stable low risk	Worsened from low to intermediate risk	Improved from intermediate to low risk	Stable intermediate risk	Worsened from intermediate to high risk	Improved from high to intermediate risk	Stable high risk
0	93	49	152	504	110	95	70
1	71	39	118	391	63	74	35
2	46	26	88	282	42	47	23
3	31	19	62	181	21	34	14
4	22	12	40	117	10	16	8
5	13	7	21	68	6	4	5

FIGURE 4 Landmark analysis showing survival according to change in risk category from baseline to follow-up within 3 months and 2 years in patients with pulmonary arterial hypertension. This figure is based on n=1073 patients; those who changed from low to high risk or *vice versa* (n=23 in total) were excluded due to low numbers.

which included 530 Swedish patients with newly diagnosed PAH, the three risk groups had significantly different long-term survival rates, similar to our study. The present study was almost three times the size of the Swedish dataset. Together, these two studies comprise ~2000 patients with PAH and provide independent validation of the ESC/ERS risk stratification strategy.

Some additional findings of the present study are worthy of discussion: in our series, 12% of the patients presented in the low-risk category at the time of diagnosis. This proportion increased to 24% at follow-up. In the Swedish PH registry, the proportion of low-risk patients was 23% at baseline and 29% at follow-up. The reasons for these differences are unclear and may partly reflect the slightly different variables used for risk assessment in the two studies. Of note, the proportion of patients with a low-risk profile was small in the two cohorts, both at baseline and at follow-up. According to the current PH guidelines, the main objective of PAH therapy is achieving and maintaining a low-risk profile [4, 5]. This treatment goal was

not achieved in the majority of our patients. At the same time, our data indicate that combinations of PAH drugs were used in only 19% of all patients at baseline (*i.e.* within the first 3 months after diagnosis) and in 41% at follow-up. Even in the high-risk cohort, combination therapy was used in only 17% of the patients at baseline and in 36% at follow-up. Intravenous or subcutaneous prostacyclin analogues were virtually absent in this study (7% in high-risk patients at follow-up). Given that there is now ample evidence favouring the use of combination therapy in patients with PAH [10–13], and considering that the present ESC/ERS guidelines recommend initial combination therapy including intravenous prostacyclin for patients presenting at high risk [4, 5], it is surprising to see that monotherapy was still used in the majority of patients. One potential reason for this reluctance may be the fact that the patients in the present series were relatively old; it is possible that the presence of comorbidities may have led physicians to prefer monotherapies [7, 9]. In addition, the enrolment period for the present analysis started in 2009, when there was less evidence supporting the use of combination therapy in patients with PAH. It will be interesting to see whether the use of combination therapy increases in the future and whether this will be accompanied by better outcomes.

The 2015 ESC/ERS guidelines recommend a comprehensive risk assessment strategy based on 13 variables [4, 5]. Another widely used risk stratification tool is the REVEAL risk score, which consists of 19 variables, but has been shown to remain valid when fewer variables are used [14, 15]. The present study demonstrated that an abbreviated version of the ESC/ERS risk assessment strategy using only six or fewer selected variables provided accurate distinction between the risk groups. Variables closely linked to the mortality risk were 6MWD, WHO FC, BNP/NT-proBNP and S_{vO_2}, whereas right atrial pressure and cardiac index performed less well. These findings are only partly in line with a previous study by Nickel *et al.* [16], which showed that among various variables used for risk stratification, only WHO FC, NT-proBNP, cardiac index and S_{vO_2} provided independent prognostic information. Hence, it seems possible to use a selected number of variables for accurate discrimination of risk groups. However, given the fact that several variables from echocardiography and cardiopulmonary exercise testing were not available for our present analysis, further studies are needed to determine the most reliable dataset.

Changes in the risk category, regardless of the direction, seem to be an accurate predictor of long-term survival and may therefore be considered end-points in future clinical trials. In the present series, 48% of the patients with newly diagnosed PAH had experienced a change in the risk category from baseline to follow-up, determined mainly by changes in functional class, 6MWD and BNP/NT-proBNP. Hence, a combination of simple and noninvasive tools provides important prognostic information. Previous long-term studies have focused on clinical worsening [10, 11, 17, 18], but our data suggest that statistical tools determining the net benefit, *i.e.* the ratio of patients who improve or worsen their risk category, could increase the power of clinical trials.

Our study had several strengths and limitations. Perhaps the greatest strength was the large number of prospectively documented, newly diagnosed patients with PAH. Hence, the sample size was large enough to provide sufficient patient numbers in all three risk strata and to allow subgroup analyses, at least for patients with I/D/H-PAH and for patients with CTD-PAH. However, further research is necessary to determine whether our risk calculation approach was appropriate or whether alternative models might provide even better prognostication. One of the most important limitations of our study was the fact that not all variables included in the risk stratification strategy proposed by the European PH guidelines were available. Information on disease progression, syncope, CPET and echocardiography were missing. In addition, and perhaps most importantly, follow-up haemodynamics were available only from 386 patients within 3 months and 2 years after inclusion, *i.e.* ~35% of the patients who had follow-up data, which limits the ability of the present study to fully analyse the predictive value of invasive and noninvasive variables at follow-up. Further studies should determine whether a strategy based on a few selected parameters provides sufficient prognostic information and how much information follow-up haemodynamics add to noninvasive tools.

It may be seen as another limitation that patients enrolled in COMPERA tend to be relatively old, at least compared to other PAH registries. However, the data reflect the real-world scenario in the participating centres, particularly in Germany, and a PAH registry from Sweden has recently reported almost identical demographics [19].

In conclusion, our data show that an abbreviated version of the risk stratification strategy proposed by the current ESC/ERS PH guidelines provides an accurate prediction of mortality. The observed 1-year mortality rates are <5% in low-risk patients, between 5% and 10% in intermediate-risk patients and >10% in high-risk patients. Predictions were accurate for baseline as well as follow-up assessments. Further research is needed to determine which sets of variables have the best predictive performance and to assess the usefulness of risk categorisation strategies in clinical trials. In addition, our data show that a low-risk

profile is achieved only in a minority of patients with PAH. Improving this figure should be a major objective of future research.

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