ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Risk stratification and response to therapy in patients with pulmonary arterial hypertension and comorbidities: A COMPERA analysis

Stephan Rosenkranz, MD,[a] Christine Pausch, PhD,[b] John G. Coghlan, MD,[c] Doerte Huscher, MD,[d] David Pittrow, MD,[b,e] Ekkehard Grünig, MD,[f] Gerd Staehler, MD,[g] Carmine Dario Vizza, MD,[h] Henning Gall, MD,[i,j] Oliver Distler, MD,[k] Marion Delcroix, MD,[l] Hossain A. Ghofrani, MD,[i,j,m] Ralf Ewert, MD,[n] Hans-Joachim Kabitz, MD,[o] Dirk Skowasch, MD,[p] Juergen Behr, MD,[q,r] Katrin Milger, MD,[r] Michael Halank, MD,[s] Heinrike Wilkens, MD,[t] Hans-Jürgen Seyfarth, MD,[u] Matthias Held, MD,[v] Laura Scelsi, MD,[w] Claus Neurohr, MD,[x] Anton Vonk-Noordegraaf, MD,[y] Silvia Ulrich, MD,[z] Hans Klose, MD,[aa] Martin Claussen, MD,[bb] Stephan Eisenmann, MD,[cc] Kai-Helge Schmidt, MD,[dd] Bjoern Andrew Remppis, MD,[ee] Andris Skride, MD,[ff] Elena Jureviciene, MD,[gg] Lina Gumbiene, MD,[gg] Skaidrius Miliauskas, MD,[hh] Judith Löffler-Ragg, MD,[ii] Tobias J. Lange, MD,[jj] Karen M. Olsson, MD,[j,kk] Marius M. Hoeper, MD,[j,kk] and Christian Opitz, MD[ll]

From the [a]Clinic III for Internal Medicine (Cardiology) and Center for Molecular Medicine (CMMC), and the Cologne Cardiovascular Research Center (CCRC), University of Cologne, Cologne, Germany; [b]GWT-TUD GmbH, Epidemiological Centre, Dresden, Germany; [c]Department of Cardiology, Royal Free Hospital, London, United Kingdom; [d]Institute of Biometry and Clinical Epidemiology, and Berlin Institute of Health, Charité-Universitätsmedizin, Berlin, Germany; [e]Institute for Clinical Pharmacology, Medical Faculty, Technical University, Dresden, Germany; [f]Center for Pulmonary Hypertension, Thoraxklinik at Heidelberg University Hospital, Translational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), Heidelberg, Germany; [g]Fachklinik Löwenstein, Löwenstein, Germany; [h]Dipartimento di Scienze Cliniche Internistiche, Anestiologiche e Cardiolohiche, Sapienza, University of Rome; Rome, Italy; [i]Department of Internal Medicine, Justus-Liebig-University Giessen, Universities of Giessen and Marburg Lung Center (UGMLC), Giessen, Germany; [j]German Center of Lung Research (DZL), Germany; [k]Department of Rheumatology, University Hospital, Zurich, Switzerland; [l]Clinical Department of Respiratory Diseases, University Hospitals of Leuven and Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven - University of Leuven, Leuven, Belgium; [m]Department of Medicine, Imperial College London, London, United Kingdom; [n]Clinic of Internal Medicine, Department of Respiratory Medicine, Universitätsmedizin Greifswald, Germany; [o]Gemeinnützige Krankenhausbetriebsgesellschaft Konstanz mbH, Medizinische Klinik II, Konstanz, Germany; [p]Universitätsklinikum Bonn, Medizinische Klinik und Poliklinik II, Innere Medizin - Kardiologie/Pneumologie, Bonn; [q]Comprehensive Pneumology Center, Lungenforschungsambulanz, Helmholtz Zentrum, München, Germany; [r]Department of Medicine V, University Hospital, LMU Munich, Comprehensive Pneumology Center Munich (CPC-M), Munich, Germany; [s]Universitätsklinikum Carl Gustav Carus der Technischen Universität Dresden, Medizinische Klinik und Poliklinik I, Dresden, Germany; [t]Klinik für Innere Medizin V, Pneumologie, Universitätsklinikum des Saarlandes, Homburg, Germany; [u]Universitätsklinikum Leipzig, Medizinische Klinik und Poliklinik II, Abteilung für Pneumologie,

https://doi.org/10.1016/j.healun.2022.10.003

Leipzig, Germany; [v]Department of Internal Medicine, Respiratory Medicine and Ventilatory Support, Medical Mission Hospital, Central Clinic Würzburg, Würzburg, Germany; [w]Fondazione IRCSS S. Matteo Pavia, Division of Cardiology Stolfo Davide, Azienda Sanitaria Universitaria Giuliano Isontina, Pavia, Italy; [x]Department of Pulmonology and Respiratory Medicine, Robert-Bosch-Krankenhaus Stuttgart, Stuttgart, Germany; [y]Amsterdam UMC, Vrije Universiteit Amsterdam, dept of Pulmonary Medicine, Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands; [z]Clinic of Pulmonology, University Hospital of Zurich, Zurich, Switzerland; [aa]Department of Respiratory Medicine, Eppendorf University Hospital, Hamburg, Germany; [bb]LungenClinic Grosshansdorf, Fachabteilung Pneumologie, Grohansdorf, Germany; [cc]Department of Respiratory Medicine, Universitätsklinikum Halle, Halle, Germany; [dd]Department of Cardiology and Center of Thrombosis and Hemostasis (CTH); University Medical Center Mainz, Germany; [ee]Herz- und Gefäzentrum Bad Bevensen, Bad Bevensen, Germany; [ff]Riga Stradiņš University, Rare Diseases Unit VSIA Pauls Stradins Clinical University Hospital, Riga, Latvia; [gg]Faculty of Medicine of Vilnius University, Competence Centre of Pulmonary Hypertension, Vilnius University Hospital Santaros klinikos, Vilnius, Lithuania; [hh]Department of Pulmonology, Lithuanian University of Health Sciences, Kaunas, Lithuania; [ii]Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria; [jj]Department of Internal Medicine II, University Medical Center Regensburg, Regensburg, Germany; [kk]Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany; and the [ll]Department of Cardiology, DRK Kliniken Berlin Westend, Berlin, Germany.

KEYWORDS:
pulmonary arterial hypertension;
*k*t;
risk;
4-strata approach;
mortality;
comorbidities

BACKGROUND: A diagnosis of idiopathic pulmonary arterial hypertension (IPAH) is frequently made in elderly patients who present with comorbidities, especially hypertension, coronary heart disease, diabetes mellitus, and obesity. It is unknown to what extent the presence of these comorbidities affects the response to PAH therapies and whether risk stratification predicts outcome in patients with comorbidities.

METHODS: We assessed the database of COMPERA, a European pulmonary hypertension registry, to determine changes after initiation of PAH therapy in WHO functional class (FC), 6-minute walking distance (6MWD), brain natriuretic peptide (BNP) or N-terminal fragment of probrain natriuretic peptide (NT-pro-BNP), and mortality risk assessed by a 4-strata model in patients with IPAH and no comorbidities, 1-2 comorbidities and 3-4 comorbidities.

RESULTS: The analysis was based on 1,120 IPAH patients (n = 208 [19%] without comorbidities, n = 641 [57%] with 1-2 comorbidities, and n = 271 [24%] with 3-4 comorbidities). Improvements in FC, 6MWD, BNP/NT-pro-BNP, and mortality risk from baseline to first follow-up were significantly larger in patients with no comorbidities than in patients with comorbidities, while they were not significantly different in patients with 1-2 and 3-4 comorbidities**.** The 4-strata risk tool predicted survival in patients without comorbidities as well as in patients with 1-2 or 3-4 comorbidities.

CONCLUSIONS: Our data suggest that patients with IPAH and comorbidities benefit from PAH medication with improvements in FC, 6MWD, BNP/NT-pro-BNP, and mortality risk, albeit to a lesser extent than patients without comorbidities. The 4-strata risk tool predicted outcome in patients with IPAH irrespective of the presence of comorbidities.

J Heart Lung Transplant 2023;42:102−114

Background

Idiopathic pulmonary arterial hypertension (IPAH) is a disease of the pulmonary vasculature characterized by progressive pulmonary vascular remodeling, which may lead to death from right heart failure. Various treatments have been introduced over the past 20 years, and estimation of the individual mortality risk has become an essential tool to guide treatment decisions.[1,2] The 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS) joint pulmonary hypertension (PH) guidelines proposed a multimodal risk assessment strategy categorizing patients in 3 risk strata (low, intermediate, or high) based on their estimated 1-year mortality risk.[1] Several validation studies have subsequently shown that risk stratification is able to predict outcome both at the time of diagnosis and during follow-up, that is, after the initiation of targeted therapy.[3-5] In addition, it has been shown consistently that simplified, noninvasive versions based on WHO functional class (FC), 6-minute walking distance (6MWD), and brain natriuretic peptide (BNP) or the NT-terminal fragment of pro-BNP (NT-pro-BNP), respectively, provide reliable prognostication in patients with IPAH.[3-5]

A limitation of the 3-strata risk model is that the proportion of patients achieving the low-risk category is small while the vast majority are categorized as an intermediate risk both at diagnosis and follow-up.[3,4] Recently, a modified risk stratification tool using a 4-strata model based on refined cut-off levels for FC, 6MWD, and BNP/NT-pro-

Reprint requests: Marius M Hoeper, MD, Department of Respiratory Medicine, Hannover Medical School, Carl-Neuberg-Str. 1, 30623 Hannover, Germany. Telephone: +49 511 532 3530. Fax: +49 511 532 161103.
E-mail addresses: hoeper.marius@mh-hannover.de, hoepermm@gmail.com

BNP has been introduced. This refined approach subdivides the intermediate risk group into intermediate-low and intermediate-high risk and is more sensitive to prognostically relevant changes in risk than the original 3-strata model.[6,7]

In addition to the risk assessment methodology, the ability of risk stratification to capture treatment response and provide prognostic information is influenced by patient phenotypes. Registry data have shown that IPAH is frequently diagnosed in elderly individuals, and such patients are more likely to present with comorbidities.[8-10] Based on criteria from the AMBITION study, a subclassification of PAH patients into those with "classical PAH" and "PAH with comorbidities" has been introduced.[11] The latter group is defined by the presence of certain comorbidities of interest that are frequently associated with left heart disease, especially heart failure with preserved ejection fraction (HFpEF), that is, arterial hypertension, diabetes mellitus, coronary heart disease, and obesity (defined by a body mass index [BMI] >30 kg/m^2). Data from the Swedish Pulmonary Arterial Hypertension Registry (SPAHR) demonstrated that in contrast to younger patients, elderly patients with comorbidities failed to show improvement of their risk status (when using the 3-strata model) upon treatment initiation, raising the question if or to what extent these patients benefit from PAH therapies.[12]

In the present analysis, we assessed the *Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension* (COMPERA) database to analyze changes in FC, 6MWD, NT-pro-BNP/BNP, and risk (based on the 4-strata model) upon initiation of PAH therapies as well as the survival of patients with IPAH with or without comorbidities.

Methods

Database

Details of COMPERA (www.COMPERA.org; registered at Clinicaltrials.gov under the identifier NCT01347216) have been previously reported.[4,7,13] In brief, COMPERA is an ongoing PH registry that prospectively collects baseline, follow-up, and outcome data of newly diagnosed patients who receive targeted therapies for any form of PH. PH centers from several European countries participate (Austria, Belgium, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Slovakia, Switzerland, United Kingdom), with about 80% of the enrolled patients coming from Germany.

COMPERA has been approved by the ethics committees of all participating centers, and all patients provided written, informed consent before inclusion.

Patients

For the present analysis, patients were selected from the COMPERA database by the following criteria: (1) treatment-naïve patients aged ≥18 years newly diagnosed with IPAH between January 1, 2009, and December 31, 2021; (2) hemodynamics available on baseline showing mPAP ≥25 mm Hg, PAWP ≤15 mm Hg, PVR > 3 WU, (3) information available on comorbidities (arterial hypertension, diabetes mellitus, coronary heart disease, obesity defined as BMI >30 kg/m^2) at baseline, and (4) at least 2 variables of interest (FC, 6MWD, BNP or NT-pro-BNP) available at baseline and at first follow-up (3-12 months after treatment initiation). Patients who did not fulfill these criteria and patients with other forms of PH or PAH were excluded.

Risk stratification

Risk was assessed by the ESC/ERS 4-strata model.[6,7] In brief, 1, 2, 3, or 4 points were assigned to FC I/II (1 point), III (3 points) and IV (4 points), 6MWD >440 m, 320-440 m, 165-319 m, and <165 m, and BNP <50 ng/liter, 50-199 ng/liter, 200-800 ng/liter, and >800 ng/liter, or NT-pro-BNP <300 ng/liter, 300-649 ng/liter, 650-1100 ng/liter, and >1100 ng/liter, respectively. The points were summed up, divided by the number of denominators, and rounded to the next integer to determine individual risk. The primary analysis was done on all included patients. A sensitivity analysis was performed for patients who had all variables available at baseline and first follow-up.

Statistical analyses

This was a posthoc analysis of prospectively collected data. Categorical data are presented as numbers and percentages, continuous data as median and first and third quartile [Q1, Q3]. Data available up to March 1, 2022, was analyzed. First, follow-up was defined as the first follow-up visit within 3 to 12 months after treatment initiation. Patients were classified into those without any comorbidity, 1-2 comorbidities, or 3-4 comorbidities at baseline out of arterial hypertension, diabetes mellitus, coronary heart disease, and obesity. For group comparisons, 2-sample Welch *t*-tests or Wilcoxon rank sum tests were used for continuous data. Categorical data were compared by Pearson's chi-square test. Vital status was ascertained by on-site visits or phone calls to the patients or their caregivers. Patients who were lost to follow-up were censored at the date of the last contact. Transplant-free survival analyses estimated by Kaplan-Meier analysis using the log-rank test for comparisons were done from baseline and from first follow-up, respectively. Cox proportional hazard analyses were performed to determine the effects of baseline characteristics on survival. A *p*-value of 0.05 or less was considered as statistically significant. No adjustment for multiple testing was done.

All statistical analyses were performed using R version 4.1.3.

Results

Patients and treatments

Out of 3,437 patients with IPAH, 1,120 patients (n = 208 [19%] without comorbidities; n = 641 [57%] with 1-2 comorbidities [328 patients with 1 comorbidity and 313 patients with 2 comorbidities], and n = 271 [24%] with 3-4 comorbidities [214 patients with 3 comorbidities and 57 patients with 4 comorbidities]) met the eligibility criteria and were included (Figure 1). The patient characteristics are shown in Table 1. The PAH medications used initially (within 3 months after diagnosis) and 1 year (9-15 months) after diagnosis are shown in Table 2. A comparison of included and excluded patients with IPAH is shown in Table S1 of the appendix.

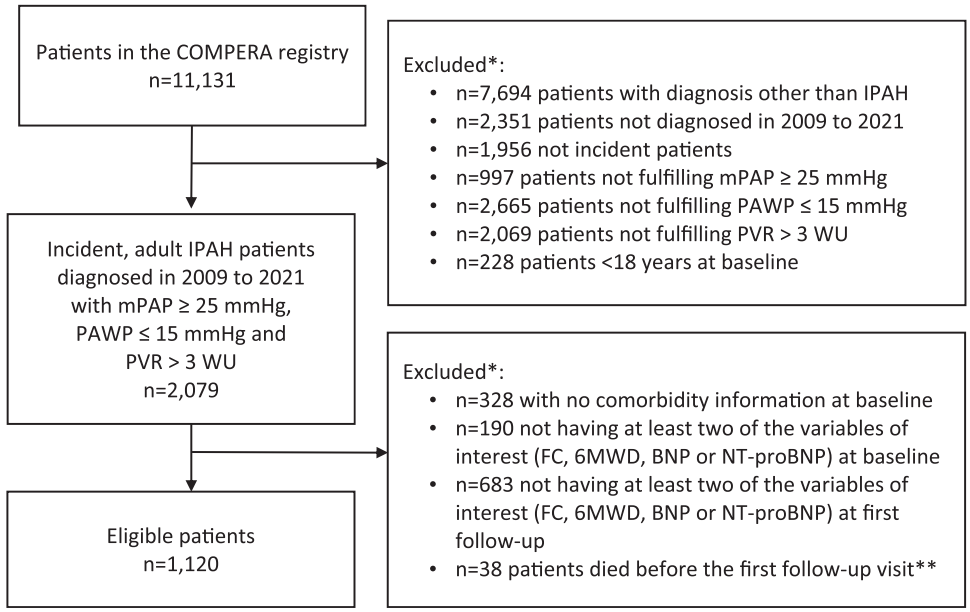

Figure 1 STROBE diagram showing patient selection for this analysis *more than 1 reason for exclusion could apply. **Of these 38 patients, 6 patients had no comorbidities, 16 patients had 1 or 2 comorbidities, and 11 patients had 3 or 4 comorbidities at baseline (5 of these patients had no comorbidity information at baseline). First follow-up is the first assessment ≥ 12 weeks after treatment initiation, up to 12 months.

Discontinuation rates of PAH treatments and reasons for discontinuations are depicted in Table 3. The drug discontinuation rate of PDE5i within the first year after diagnosis ranged from 7% to 11% with no significant differences between patients with no, 1-2, or 3-4 comorbidities. In contrast, the discontinuation rate of ERA increased from 4% in patients with no comorbidities to 13% in patients with 1-2 comorbidities and 17% with 3-4 comorbidities.

FC, 6MWD, BNP/NT-proBNP, and risk at baseline and first follow-up

The first follow-up visit took place 4.1 [3.3, 5.6] months after baseline. FC improved from baseline to first follow-up by at least 1 class in 51% of the patients without comorbidities and in 33% and 28% of the patients with 1-2 and 3-4 comorbidities, respectively. 6MWD improved by 43 [-3, 100] m, 30 [-10, 71] m, and 30 [0, 68] m. BNP/NT-proBNP changed from baseline to first follow-up by -45 [-77, 0] %, -26 [-59, 18] % and -20 [-56, 38] %, respectively. Changes in FC, 6MWD, and NT-pro-BNP contributed in a similar manner to changes in risk (Table S2). For all variables, improvements from baseline to first follow-up were significantly larger in the cohort of patients with no comorbidities than in the 2 cohorts of patients with comorbidities, while they were not significantly different in patients with 1-2 or 3-4 comorbidities (Figures 2A-C).

With the ESC/ERS 4-strata model, risk improved in 52% of the patients without comorbidities and in 33% and 34% of the patients with 1-2 and 3-4 comorbidities, respectively. In patients with comorbidities improvements in risk were largely driven by improvements from the intermediate-high-risk category to the intermediate-low-risk category (Figure 3A). WHO FC, 6MWD, and NT-pro-BNP at baseline and first follow-up by number of comorbidities in relation to risk categories are schematically shown in Figure 3B.

Comparable findings were obtained by a sensitivity analysis including only patients for whom all variables were available at baseline and first follow-up ($n = 498$) (Figure S1).

Survival

The median observation time was 3.6 [1.9, 6.0] years for patients with no comorbidities, 3.0 [1.5, 5.3] years for patients with 1-2 comorbidities, and 2.6 [1.5, 4.7] years for patients with 3-4 comorbidities. In the cohort of 208 patients with no comorbidities, 54 (26%) patients died, 9 (4%) underwent lung transplantation, and 15 (7%) were lost to follow-up. The corresponding numbers for the 641 patients with 1-2 comorbidities were 234 (37%), 3 (0%), and 27 (4%). Among the 271 patients with 3-4 comorbidities, 123 (45%) died, 0 (0%) underwent lung transplantation, and 12 (4%) were lost to follow-up. The Kaplan-Meier estimated transplant-free survival rates at 1, 3, and 5 years for patients with no comorbidities were 99%, 81%, and 73%, respectively. In patients with 1-2 comorbidities, the corresponding numbers were 96%, 75%, and 60%. In patients with 3-4 comorbidities, the respective survival rates were 95%, 67%, and 46%. Pulmonary hypertension and/or right heart failure were attributed by the investigators as the main cause of death in 36 (67%) patients with no comorbidities and in 140 (60%) and 66 (54%) patients with 1-2 and 3-4 comorbidities ($p = 0.247$), respectively.

Cox proportional hazard analysis showed that higher age, male sex, high risk at baseline, number of comorbidities, and a low lung diffusion capacity for carbon monoxide (DLCO) were associated with an increased mortality

Table 1 Baseline Characteristics

	No comorb *n* = 208	No vs 1-2 comorb (*p*-value)	1-2 comorb *n* = 641	1-2 vs 3-4 comorb (*p*-value)	3-4 comorb *n* = 271	No vs 3-4 comorb (*p*-value)	All *n* = 1120
Age (years)	51 [36, 70]	<0.0001	73 [63, 79]	0.0003	74 [67, 79]	<0.0001	72 [59, 78]
Female	141 (67.8%)	0.2145	402 (62.7%)	0.0206	147 (54.2%)	0.0037	690 (61.6%)
BMI (kg/m^2)	24 [22, 27]	<0.0001	28 [25, 32]	<0.0001	33 [29, 36]	<0.0001	28 [25, 33]
WHO FC, N = 1,100 (98.2%) I, *n* (%) II, *n* (%) III, *n* (%) IV, *n* (%)	3 (1.5%) 41 (19.9%) 135 (65.5%) 27 (13.1%)	0.0034	2 (0.3%) 71 (11.3%) 462 (73.4%) 94 (14.9%)	0.2173	0 (0%) 19 (7.2%) 206 (77.7%) 40 (15.1%)	<0.0001	5 (0.5%) 131 (11.9%) 803 (73.0%) 161 (14.6%)
6MWD (m), N = 937 (83.7%)	373 [250, 458]	<0.0001	300 [210, 380]	<0.0001	240 [170, 310]	<0.0001	300 [200, 378]
NT-pro-BNP (ng/liter), N = 878 (78.4%)	1162 [354, 2236]	0.0001	1668 [638, 3842]	0.2619	1596 [539, 3293]	0.0187	1560 [563, 3452]
BNP (ng/liter) N = 166 (14.8%)	286 [108, 451]	0.7478	249 [81, 514]	0.4194	156 [106, 346]	0.2030	223 [90, 406]
RAP (mm Hg) N = 1,062 (94.8%)	6 [4, 9]	0.0056	8 [5, 11]	0.3566	8 [6, 11]	0.0018	7 [5, 11]
PAPm (mm Hg) N = 1,120 (100%)	45 [37, 54]	<0.0001	41 [34, 49]	0.8016	41 [35, 49]	<0.0001	42 [34, 50]
PAWP (mm Hg) N = 1,120 (100%)	8 [6, 11]	<0.0001	10 [7, 12]	0.4465	10 [7, 13]	<0.0001	10 [7, 12]
CI (l/min/m^2) N = 1,047 (93.5%)	2.1 [1.6, 2.7]	0.2604	2.0 [1.6, 2.5]	0.3146	2.1 [1.7, 2.6]	0.8326	2.0 [1.6, 2.6]
PVR (WU N = 1,120 (100%)	9.9 [6.9, 14.2]	<0.0001	8.2 [6.0, 11.5]	0.0060	7.5 [5.7, 10.3]	<0.0001	8.4 [6.0, 11,7]
SvO_2 (%) N = 988 (88.2%)	64 [59, 70]	0.1836	64 [58, 67]	0.9875	63 [58, 67]	0.2346	64 [58, 68]
Atrial fibrillation N = 1,075 (96.0%)	16 (8.2%)	<0.0001	167 (27.0%)	0.4036	63 (24.0%)	<0.0001	246 (22.9%)
DLCO (% pred) N = 881 (78.7%)	59 [39, 74]	0.1795	51 [36, 71]	0.2093	49 [34, 67]	0.0319	52 [35, 71]
DLCO <45% pred	54 (34.8%)	0.2937	201 (40.0%)	0.4167	97 (43.5%)	0.1132	352 (40.0%)
Smoking history N = 896 (80%)	66 (43.7%)	0.9610	232 (44.4%)	0.2225	110 (49.5%)	0.3156	408 (45.5%)
Pack years (ever smokers only)	20 [10, 48]	0.3088	30 [15, 40]	0.3402	30 [15, 50]	0.0948	30 [15, 40]
	0 (0%)	<0.0001	478 (74.6%)	<0.0001	268 (98.9%)	<0.0001	746 (66.6%)

(*continued on next page*)

Table 1 (*Continued*)

	No comorb n = 208	No vs 1-2 comorb (p-value)	1-2 comorb n = 641	1-2 vs 3-4 comorb (p-value)	3-4 comorb n = 271	No vs 3-4 comorb (p-value)	All n = 1120
Hypertension N = 1,120 (100%)							
Coronary heart disease N =1.120 (100%)	0 (0%)	<0.0001	132 (20.6%)	<0.0001	175 (64.6%)	<0.0001	307 (27.4%)
Diabetes mellitus N = 1,120 (100%)	0 (0%)	<0.0001	116 (18.1%)	<0.0001	227 (83.8%)	<0.0001	343 (30.6%)
BMI ≥30 kg/m^2 N = 1,120 (100%)	0 (0%)	<0.0001	228 (35.6%)	<0.0001	200 (73.8%)	<0.0001	428 (38.2%)

Abbreviations: 6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; Comorb, comorbidities; DLCO, diffusion capacity of the lung for carbon monoxide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO_2, mixed-venous oxygen saturation; WHO FC, World Health Organization Functional Class.

Categorical data are shown as n (%) of the respective population. Continuous data are depicted as median [Q1, Q3].

risk (Table S3). When all 4 comorbidities were included in the Cox proportional hazard model instead of the number of comorbidities, only coronary heart disease (hazard ratio 1.35, 95% confidence interval 1.05-1.74, p = 0.0186) and diabetes (hazard ratio 1.28, 95% confidence interval 1.01-1.63, p = 0.0444) were associated with an increased mortality risk.

The unadjusted survival differences between the 3 cohorts were statistically significant ($p < 0.0001$; Figure 4). However, when adjusted for age and sex, the survival differences were no longer statistically significant for patients with 1-2 and 3-4 comorbidities compared to patients without comorbidities.

Survival according to risk assessed by the ESC/ERS 4-strata model is shown in Figure 5A-C. In all cohorts, there was good discrimination of survival according to risk at baseline and − even more so − at follow-up. However, in patients with comorbidities, especially in those with 3-4 comorbidities, the proportion of patients with a low-risk profile was small both at baseline and at follow-up, and the survival estimates of patients meeting low-risk or intermediate low-risk criteria were comparable.

Discussion

In the present analysis, 42% of the IPAH patients without comorbidities reached a low risk profile with PAH treatment, while only 12% of the patients with 1-2 comorbidities and 3% of the patients with 3-4 comorbidities met the low risk criteria at first follow-up. Nevertheless, improvements in risk assessed by the ESC/ERS 4-strata model were observed in patients with comorbidities, mostly from the intermediate-high to the intermediate-low category. These patients showed improvements in FC, 6MWD, and BNP/NT-pro-BNP when treated with PAH medications, although to a lesser extent than patients with IPAH who had none of these comorbidities. Moreover, the ESC/ERS 4-strata risk stratification tool predicted mortality in patients with IPAH irrespective of the presence and number of certain comorbidities of interest, that is, hypertension, coronary heart disease, diabetes, and obesity.

A mitigated response to PAH medications in patients with IPAH and comorbidities has already been suggested by previous studies.[14,15] In an analysis from the AMBITION study, patients who were excluded from the primary analysis because they had a left heart phenotype with ≥3 comorbidities had lesser improvements in 6MWD and NT-pro-BNP after initiation of PAH therapy than patients who were included in the primary analysis.[15] In an earlier report from COMPERA, Opitz and coworkers also showed that patients with IPAH and ≥3 comorbidities showed less improvement in FC, 6MWD, and NT-proBNP than patients with IPAH without comorbidities.[16] In a posthoc analysis from the GRIPHON study, there were no differences in the (overall modest) effects of selexipag, a prostacyclin receptor agonist, on 6MWD and NT-pro-BNP in patients with ≥3 comorbidities and in patients with fewer or no comorbidities. However, selexipag reduced the risk of a clinical worsening event irrespective of the comorbidity status.[17]

Table 2 PAH Therapies at Baseline and 1 Year After Diagnosis

	No comorb *n* = 208	No vs 1-2 comorb (*p*-value)	1-2 comorb *n* = 641	1-2 vs 3-4 comorb (*p*-value)	3-4 comorb *n* = 271	No vs 3-4 comorb (*p*-value)	All *n*=1,120
Initial treatment (Up to 3 months after diagnosis), *N* = 1,068 (95.4%)							
CCB, *n* (%)	29 (14.8%)	<0.0001	24 (3.9%)	0.3083	6 (2.3%)	<0.0001	59 (5.5%)
ERA, *n* (%)	72 (36.7%)	0.0008	147 (24.1%)	0.0409	46 (17.6%)	<0.0001	265 (24.8%)
PDE5i, *n* (%)	142 (72.4%)	0.0006	511 (83.8%)	0.7987	222 (84.7%)	0.0019	875 (81.9%)
sGCs, *n* (%)	9 (4.6%)	0.8439	24 (3.9%)	0.7997	12 (4.6%)	1.0000	45 (4.2%)
PCA/PRA, *n* (%)	10 (5.1%)	0.0365	12 (2.0%)	0.9620	6 (2.3%)	0.1724	28 (2.6%)
Combination therapy	55 (28.1%)	0.0002	97 (15.9%)	0.0791	29 (11.1%)	<0.0001	181 (16.9%)
ERA + PDE5i/sGSc	41 (20.9%)	0.0109	80 (13.1%)	0.0171	19 (7.3%)	<0.0001	140 (13.1%)
ERA + PDE5i/sGSc + PCA/PRA	9 (4.6%)	0.0067	7 (1.1%)	0.4839	1 (0.4%)	0.0064	17 (1.6%)
At 1 year (9-15 months) after diagnosis, *N* = 929 (82.9%)							
CCB, *n* (%)	27 (15.1%)	<0.0001	17 (3.2%)	0.8864	6 (2.7%)	<0.0001	50 (5.4%)
ERA, *n* (%)	113 (63.1%)	<0.0001	220 (41.7%)	0.2610	82 (36.9%)	<0.0001	415 (44.7%)
PDE5i, *n* (%)	136 (76.0%)	0.0585	437 (82.8%)	0.9243	185 (83.3%)	0.0879	758 (81.6%)
sGCs, *n* (%)	13 (7.3%)	0.8439	27 (5.1%)	0.8674	10 (4.5%)	0.3347	50 (5.4%)
PCA/PRA, *n* (%)	23 (12.8%)	0.1426	46 (8.7%)	0.4545	15 (6.8%)	0.0575	84 (9.0%)
Combination therapy	112 (62.6%)	<0.0001	197 (37.3%)	0.7727	77 (34.7%)	<0.0001	386 (41.6%)
ERA + PDE5i/sGSc + PCA/PRA	75 (41.9%)	0.0005	146 (27.7%)	0.5528	56 (25.2%)	0.0006	277 (29.8%)
ERA + PDE5i/sGSc + PCA/PRA	22 (12.3%)	0.0247	35 (6.6%)	0.0862	7 (3.2%)	0.0009	64 (6.9%)

Abbreviations: CCB, calcium channel blocker; ERA, endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; PCA, prostacyclin analoges; PRA, prostacyclin receptor agonists; sGCs, stimulator of soluble guanylate cyclase.

Data are shown as *n* (%) of the respective population.

Table 3 Discontinuations of PAH Therapies Initiated Within the First Year After Diagnosis

	No comorb (*n* = 208)	No vs 1-2 comorb (*p*-value)	1-2 comorb (*n* = 641)	1-2 vs 3-4 comorb (*p*-value)	3-4 comorb (*n* = 271)	No vs 3-4 comorb (*p*-value)	All patients (*n* = 1,120)
PDE5i /sGCs	181 (87%)		594 (92.7%)		253 (93.4%)		1028 (91.8%)
Discontinuations	13 (7.2%)	0.516	54 (9.1%)	0.556	27 (10.7%)	0.284	94 (9.1%)
- Lack of tolerability[a]	3 (23.1%)		18 (33.3%)		12 (44.4%)		33 (35.1%)
Edema	1 (33.3%)		3 (16.7%)		2 (16.7%)		6 (18.2%)
Gastrointestinal	0 (0%)		4 (22.2%)		2 (16.7%)		6 (18.2%)
Liver abnormalities	0 (0%)		0 (0%)		0 (0%)		0 (0%)
Other	3 (100.0%)		17 (94.4%)		9 (75.0%)		29 (87.9%)
- Efficacy failure	2 (15.4%)		14 (25.9%)		5 (18.5%)		21 (22.3%)
- Other[b]	8 (61.5%)		22 (40.7%)		10 (37.0%)		40 (42.6%)
ERA	133 (63.9%)		299 (46.6%)		110 (40.6%)		542 (48.4%)
Discontinuations	5 (3.8%)	0.007	38 (12.7%)	0.307	19 (17.3%)	<0.001	62 (11.4%)
- Lack of tolerability[a]	2 (40.0%)		22 (57.9%)		13 (68.4%)		37 (59.7%)
Edema	2 (100.0%)		13 (59.1%)		5 (38.5%)		20 (54.1%)
Gastrointestinal	0 (0%)		1 (4.5%)		5 (38.5%)		6 (16.2%)
Liver abnormalities	0 (0%)		1 (4.5%)		0 (0%)		1 (2.7%)
Other	2 (100.0%)		18 (81.8%)		11 (84.6%)		31 (83.8%)
- Efficacy failure	1 (20.0%)		3 (7.9%)		2 (10.5%)		6 (9.7%)
- Other[c]	2 (40.0%)		13 (34.2%)		4 (21.1%)		19 (30.6%)
PCA/PRA	28 (13.5%)		58 (9.0%)		19 (7.0%)		105 (9.4%)
Discontinuations	2 (7.1%)	1.000	5 (8.6%)	1.000	2 (10.5%)	1.000	9 (8.6%)
- Lack of tolerability[a]	1 (50%)		3 (60%)		1 (50.0%)		5 (55.6%)
Edema	0 (0%)		1 (33.3%)		0 (0%)		1 (20.0%)
Gastrointestinal	0 (0%)		1 (33.3%)		0 (0%)		1 (20.0%)
Liver abnormalities	0 (0%)		0 (0%)		0 (0%)		0 (0%)
Other	1 (100.0%)		2 (66.7%)		1 (100.0%)		4 (80.0%)
- Efficacy failure	0 (0%)		0 (0%)		0 (0%)		0 (0%)
- Other	1 (50%)		2 (40%)		1 (50%)		4 (44.4%)

Abbreviations: Comorb, comorbidities; ERA endothelin receptor antagonists; PCA, prostacyclin analoges; PDE5i, phosphodiesterase-5 inhibitors; PRA, prostacyclin receptor agonists; sGCs, soluble guanylate stimulators.

Data represent *n* (%).

[a]multiple reasons were possible

[b]includes switch from PDE5i to riociguat (*n* = 16)

[c]includes withdrawal of sitaxentan (*n* = 1)

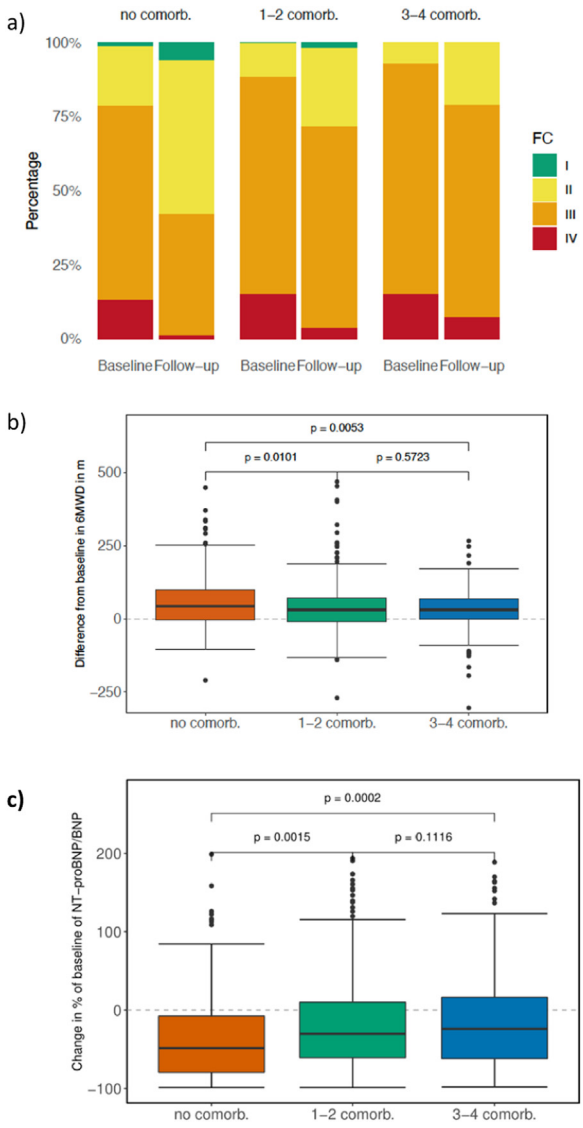

Figure 2 WHO functional class at baseline and first follow-up (A), and changes from baseline to first follow-up in 6-minute walking distance (B), and BNP/NT-pro-BNP (C) according to the number of comorbidities. First follow-up was defined as the first follow-up at least 3 months after the start of therapy. For improvement by at least 1 functional class, the *p*-value of the chi-square test for no vs 1-2 comorbidities considering improvement by at least 1 FC was <0.0001; for 1-2 vs 3-4 comorbidities, the *p*-value was 0.1469, and for no vs 3-4 comorbidities, the *p*-value was <0.0001.

It is important to note that in our series, the majority of the patients with comorbidities were treated with PDE5i monotherapy, while only about 33% of the patients received combination therapy within 1 year after diagnosis. Prostacyclin pathway agents were used in less than 10%. It is unknown if these patients would have had a better treatment response with a broader use of combination therapies.

Besides efficacy, safety and tolerability of PAH medications may also be a matter of concern in patients with IPAH and comorbidities. In the present analysis, drug discontinuation rates ranged from 7% to 11% for PDE5 inhibitors, with no statistically significant differences between patients with or without comorbidities. In contrast, the drug discontinuation rate of ERAs increased with the number of comorbidities from 4% in patients without comorbidities to 17% in patients with 3-4 comorbidities, along with a remarkably higher proportion of patients who discontinued due to side effects (40% and 68%, respectively). A high rate of PAH drug discontinuation due to adverse events, mainly edema, was also found in the abovementioned analysis from the AMBITION study where discontinuation rates in patients receiving initial combination therapy were 33% in patients who had ≥3 comorbidities compared to 14% in patients who had fewer or no comorbidities. The corresponding numbers were 38% vs 19% for ERA monotherapy and 23% vs 15% for PDE5 inhibitor monotherapy.[15] In the GRIPHON study, there was an increased risk of selexipag discontinuation due to adverse events in patients with ≥3 comorbidities compared to patients with fewer or no comorbidities (21% vs 13%).[17] Overall, these findings suggest that PDE5 inhibitors may be better tolerated than ERA and prostacyclin receptor agonists by patients with PAH and comorbidities, which might be one of the reasons why most patients with comorbidities in the present series were treated with PDE5 inhibitor monotherapy rather than combination therapy.

Risk stratification has become an important tool to guide treatment decisions in patients with PAH, but the role of risk stratification in patients with IPAH and comorbidities is unclear. The predictive value of the ESC/ERS risk 3-strata model in patients with IPAH and comorbidities has been questioned.[18] In a recent cluster analysis from COMPERA, risk assessed by the ESC/ERS 3-strata model did not improve after initiation of PAH therapy in patients with a left heart phenotype.[13] These observations were in line with an earlier analysis from the Swedish PAH registry, where Hjalmarsson and coworkers showed that patients with IPAH ≥65 years of age did not improve risk assessed by the ESC/ERS 3-strata model after initiation of PAH medications.[12]

Compared to the ESC/ERS 3-strata model, the ESC/ERS 4-strata model has been found to be more sensitive to changes in risk and more predictive for consecutive mortality.[6,7] In the present study, the 4-strata model predicted outcomes in patients with or without comorbidities. The dispersion of survival curves in patients with comorbidities was not as large as in patients without comorbidities. This finding is not surprising as our analyses were based on all-cause mortality, while PAH was considered the leading cause of death in 67% of the patients without comorbidities compared to 60% and 54% in patients with 1-2 or 3-4 comorbidities, respectively. Nevertheless, PH was the leading cause of death in all 3 cohorts, even in patients with 3-4 comorbidities.

As in previous studies,[12,13] few patients with comorbidities from the present series reached a low-risk profile with PAH therapies. However, the survival of patients with comorbidities and a low-risk profile was similar to the survival of patients with comorbidities who reached an intermediate-low-risk profile after initiation of PAH therapies. In contrast, patients without comorbidities had a better long-term survival when they reached a low-risk profile

rather than an intermediate-low-risk profile with PAH therapies. Hence, reaching a low or intermediate-low-risk profile might be a reasonable treatment goal in patients with PAH and comorbidities while a low-risk profile should remain the goal of PAH therapy in patients with PAH and no comorbidities.

Our study has several limitations. Information on key variables which were used as inclusion or exclusion criteria was complete but there were missing values for other variables, including those required for risk stratification, which is important to note as the ESC/ERS 4-strata model has not been validated for missing values. Furthermore, a small but nonnegligible number of patients were lost to follow-up. A small number (1.8%) of the patients potentially eligible for this analysis died within 3 months of treatment initiation, which may have introduced an immortal time bias as the study included only patients for whom follow-up information on risk variables was available. In addition, the diagnostic classification of IPAH was made by the investigators based on current guidelines. While all patients had a PAWP ≤15 mm Hg at inclusion, misclassification of some patients cannot be excluded, and it should be noted that, despite having precapillary PH, many of the patients with comorbidities had a left heart phenotype. Finally, we focused on a set of comorbidities that have gained interest in the PAH community because they characterize a distinct patient phenotype. Still, we acknowledge that many other comorbid conditions and frailty, which are not captured in our database, may have affected treatment response and survival as well.

In conclusion, we found that in patients with IPAH and comorbidities, PAH treatments resulted in improvements in FC, 6MWD, BNP/NT-pro-BNP, and mortality risk assessed by the ESC/ERS 4-strata model, albeit to a lesser extent than in patients with IPAH who had no comorbidities. The ESC/ERS 4-strata model predicted outcomes in patients with IPAH irrespective of the absence or presence of comorbidities. Few patients with IPAH and comorbidities reached a low-risk profile with PAH therapy, but the survival of these patients was similar to the survival of patients with IPAH and comorbidities who reached an intermediate-low risk profile. Hence, reaching an intermediate-low-risk profile might be a reasonable treatment goal in patients with IPAH and comorbidities.

Disclosure statement

Stephan Rosenkranz has received fees for lectures and/or consultations from Abbott, Acceleron, Actelion, Bayer,

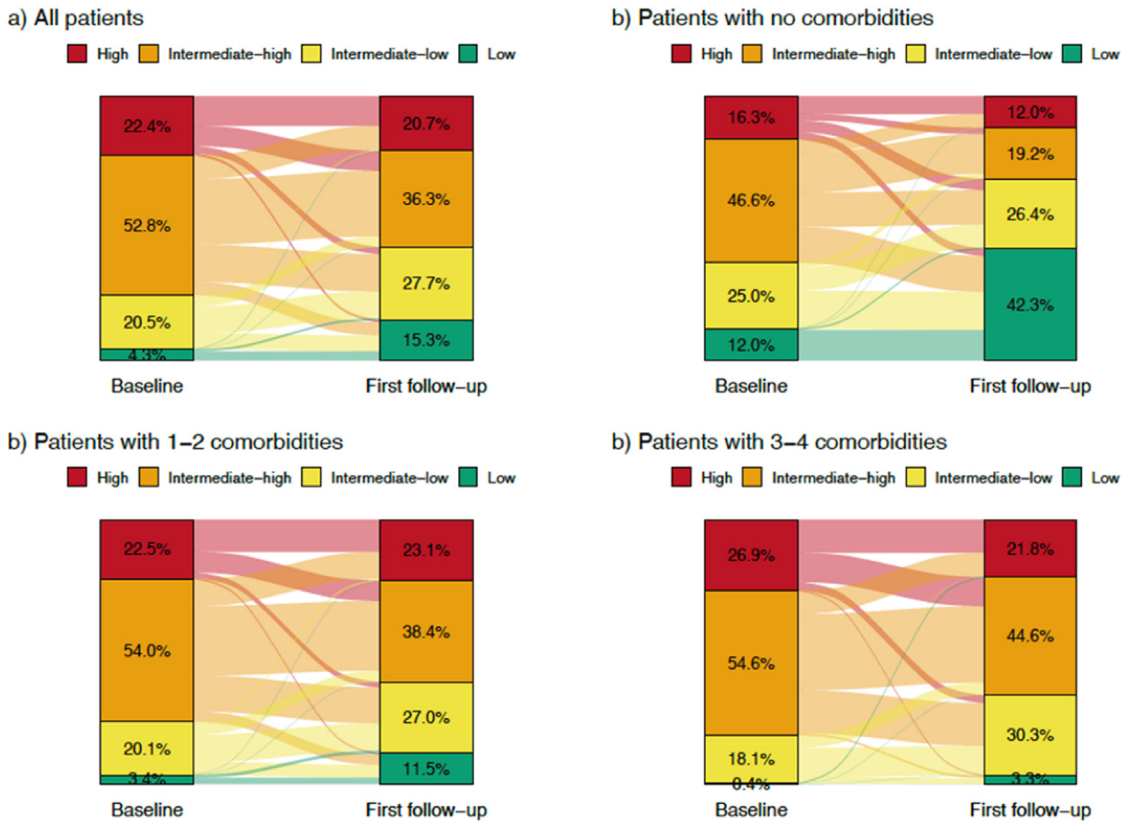

Figure 3 (A) Change in risk from baseline to first follow-up using the ESC/ERS 4-strata model according to the number of comorbidities. First follow-up was defined as the first follow-up at least 3 months after start of therapy. Box plots showing median and Q1, Q3 for 6MWD and NT-pro-BNP and mean ± standard. (B) Schematic depiction of WHO functional class (FC), 6-minute walk distance (6MWD) and NT-pro-BNP at baseline and first follow-up by numbers of comorbidities in relation to risk categories deviation for WHO FC at baseline (light gray) and first follow-up (dark gray). For 6MWD and NT-pro-BNP, the colours represent risk categories with red = high risk, orange = intermediate-high risk, yellow = intermediate-low risk and green = low risk. The respective cut-off values for 6MWD were <165 m, 165-319 m, 320-440 m, and >440 m, and for NT-proBNP >1100 ng/liter, 650-1100 ng/liter, 300-649 ng/liter and <300 ng/liter. For WHO FC, the color code is red = FC IV, orange = FC III; green = FC I/II.

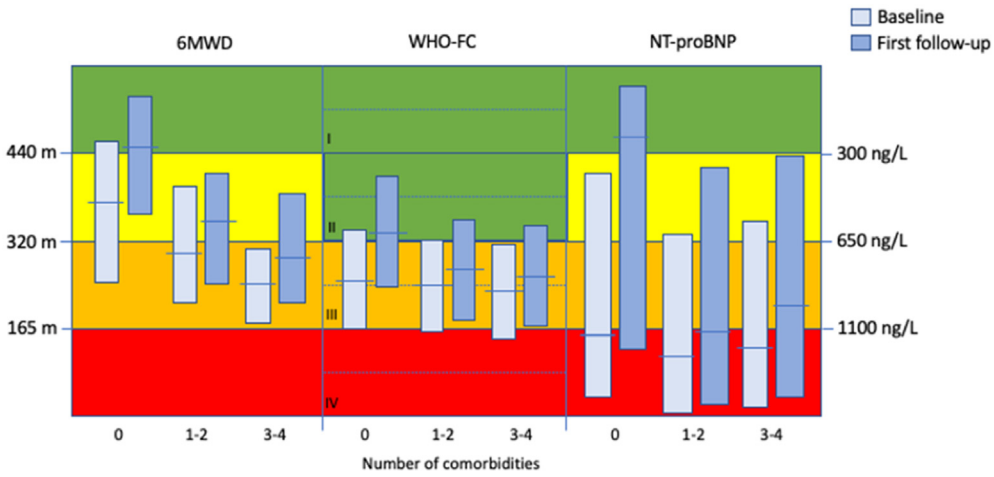

Figure 3 Continued

BMS, Gilead, GSK, Janssen, MSD, Novartis, Pfizer, United Therapeutics and Vifor; research grants to institution from AstraZeneca, Actelion, Bayer Janssen and Novartis. C.P. has no disclosures. J.G.C. has received fees for lectures and/or consultations from Bayer, Janssen, MSD, and United Therapeutics. D.H. has received travel compensation from Shire. D.P. has received fees for consultations from Actelion, Amgen, Aspen, Bayer, Biogen, Boehringer Ingelheim, Daiichi Sankyo, MSD, Novartis, Sanofi-Genzyme, Takeda and Viatris. E.G. has received fees for lectures and/or consultations from Actelion, Bayer, Ferrer, GSK, Janssen, MSD, and Orpha Care. G.S. has received honoraria for lectures and/or consultancy for Actelion, Bayer, GSK, Novartis, and Pfizer. C.D.V. has received fees for lectures and/or consultations from Acceleron, Actelion, Bayer, GSK, Janssen, MSD, Pfizer, and United Therapeutics. H.G. reports personal fees from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer

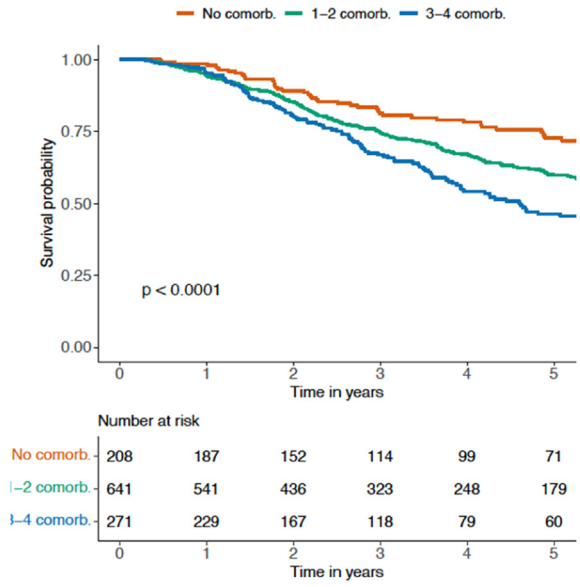

Figure 4 Kaplan-Meier survival estimates of patients with idiopathic pulmonary arterial hypertension according to the number of comorbidities.

and United Therapeutics. O.D. has/had consultancy relationship and/or has received research funding from 4 D Science, Actelion, Active Biotec, Bayer, Biogen Idec, Boehringer Ingelheim Pharma, BMS, ChemoAb, EpiPharm, Ergonex, espeRare foundation, GSK, Genentech/Roche, Inventiva, Janssen, Lilly, medac, MedImmune, Mitsubishi Tanabe, Pharmacyclics, Pfizer, Sanofi, Serodapharm and Sinoxa in the area of potential treatments of scleroderma and its complications including PAH. In addition, Prof Distler has a patent mir-29 for the treatment of systemic sclerosis licensed. M.D. reports research grants from Actelion/J&J, speaker and consultant fees from Bayer, MSD, Acceleron, AOP, Daiichi Sankyo, outside the submitted work. Marion Delcroix is holder of the Janssen Chair for Pulmonary Hypertension at the KU Leuven. H.A.G. has received honorariums for consultations and/or speaking at conferences from Bayer HealthCare AG, Actelion, Encysive, Pfizer, Ergonex, Lilly, and Novartis. He is a member of advisory boards for Acceleron, Bayer HealthCare AG, Pfizer, GSK, Actelion, Lilly, Merck, Encysive, and Ergonex. He has also received governmental grants from the German Research Foundation (DFG), Excellence Cluster Cardiopulmonary Research (ECCPS), State Government of Hessen (LOEWE), and the German Ministry for Education and Research (BMBF). R.E. has received speaker fees and honoraria for consultations from Actelion, Bayer, GSK, Janssen, Lilly, MSD, Novartis, Pfizer, and United Therapeutics. H.-J.K. has received fees from Löwenstein Medical, Weinmann, Philips Respironics, ResMed, Vivisol, Sapio Life and Sanofi-Genzyme. D.S. received fees for lectures and/or consulting and/or research support to institution from Actelion, Bayer, GSK, Janssen, MSD and Pfizer. J.B. received grants from Actelion, AstraZeneca, Bayer, Biogen, Boehringer-Ingelheim, Galapagos, Novartis, Roche, and Sanofi/Genzyme. K.M. has received fees from Actelion, AstraZeneca, GSK, Janssen, MSD, Novartis and Sanofi-Aventis. M.H. has received speaker fees and honoraria for consultations from Acceleron, Actelion, AstraZeneca, Bayer, BerlinChemie, GSK, Janssen and Novartis. H. W. received fees for lectures and/or consultations from Actelion, Bayer, Biotest, Boehringer, GSK, Janssen, Pfizer

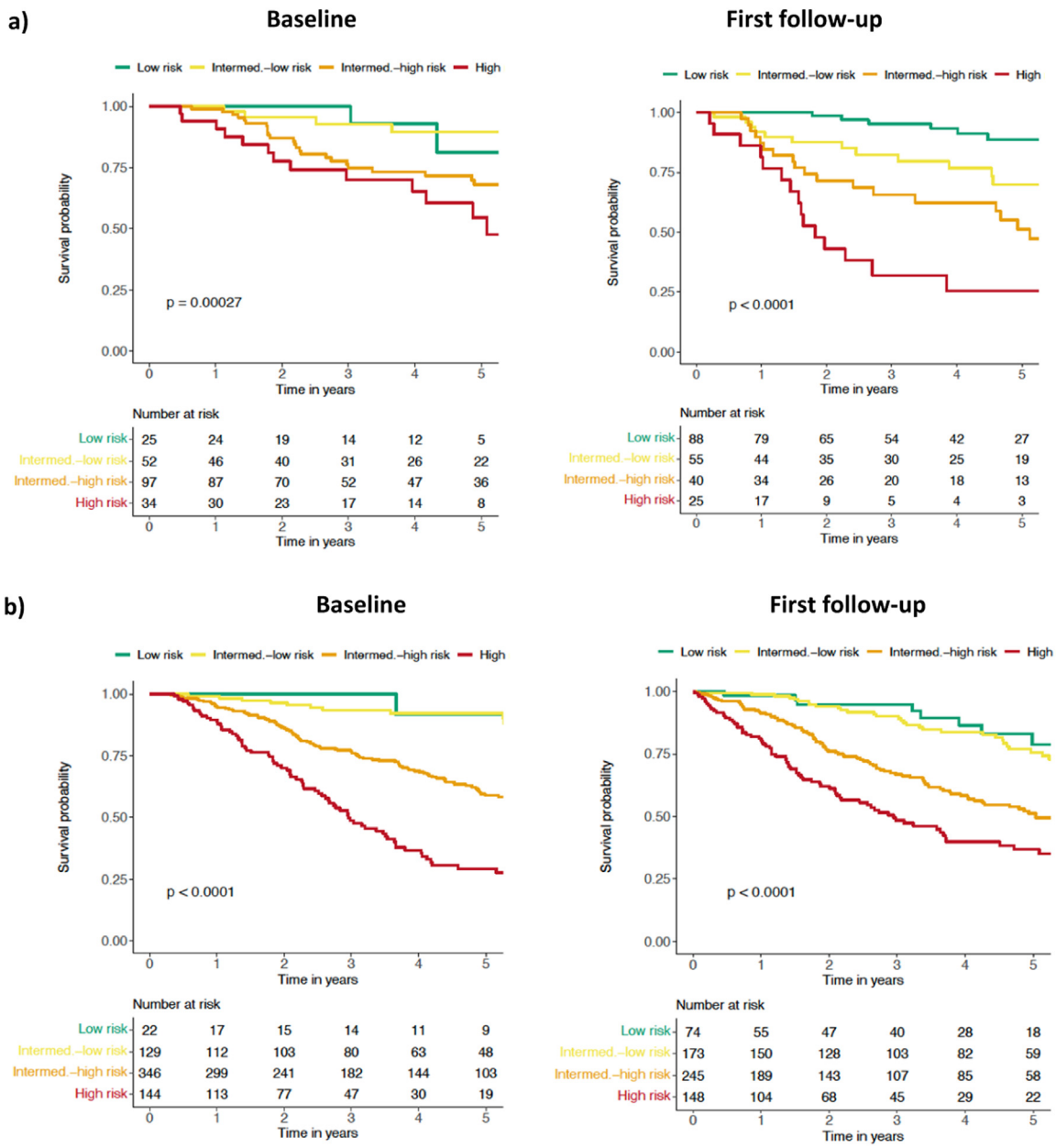

Figure 5 Mortality risk assessed by the ESC/ERS 4-strata model at baseline and first follow-up and consecutive survival patients with idiopathic pulmonary arterial hypertension with (A) no comorbidities, (B) 1-2 comorbidities, and (C) 3-4 comorbidities. First follow-up was defined as the first follow-up at least 3 months after start of therapy. In the cohort of patients with 3-4 comorbidities, a single patient met low-risk criteria at baseline; this patient died at 3 years (not shown).

and Roche. H.-J.S. has received speaker fees and honoraria for consultations from Actelion, Bayer, GSK, Janssen and MSD. Matthias Held has received speaker fees and honoraria for consultations from Actelion, Bayer, Boehringer Ingelheim Pharma, Glaxo Smith Kline, Janssen, MSD, Novartis, Pfizer, Nycomed, Roche and Servier. L.S. has no disclosures. C.N. has received fees for lectures and/or consultations from Actelion, AstraZeneca, GSK, MSD, Novartis and Sanofi-Aventis. A.V.-N. reports receiving fees for lectures and/or consultations from Actelion, Bayer, GlaxoSmithKline, Janssen, MSD and Pfizer. S.U. reports grants from the Swiss National Science Foundation, Zurich and Swiss Lung League, Actelion/Janssen SA, Orpha Swiss and MSD such as personal fees for congresses, advisory and lectures from Actelion/Janssen, MSD, Orpha Swiss and Novartis outside the submitted work. H.K. has received speaker fees and honoraria for consultations from Actelion, Bayer, GSK, Janssen, MSD, Novartis, Pfizer, and United Therapeutics. M.C. reports honoraria for lectures from Boehringer Ingelheim Pharma GmbH and Roche Pharma, and for serving on advisory boards from Boehringer Ingelheim. S.E. has received honoraria for lectures and/or consultations from Actelion, MSD, Bayer, Acceleron, Gilead, AstraZeneca, Pulmox, Boston Scientific, Boehringer Ingelheim. K.H.S. has received fees for lectures and educational events from Abbott, Janssen and MSD. B.A.R. has received honoraria from Novartis, ImpulseDynamic, AstraZenneca, Bayer, RenalGuard, and Vifor. A.S. reports no conflicts of

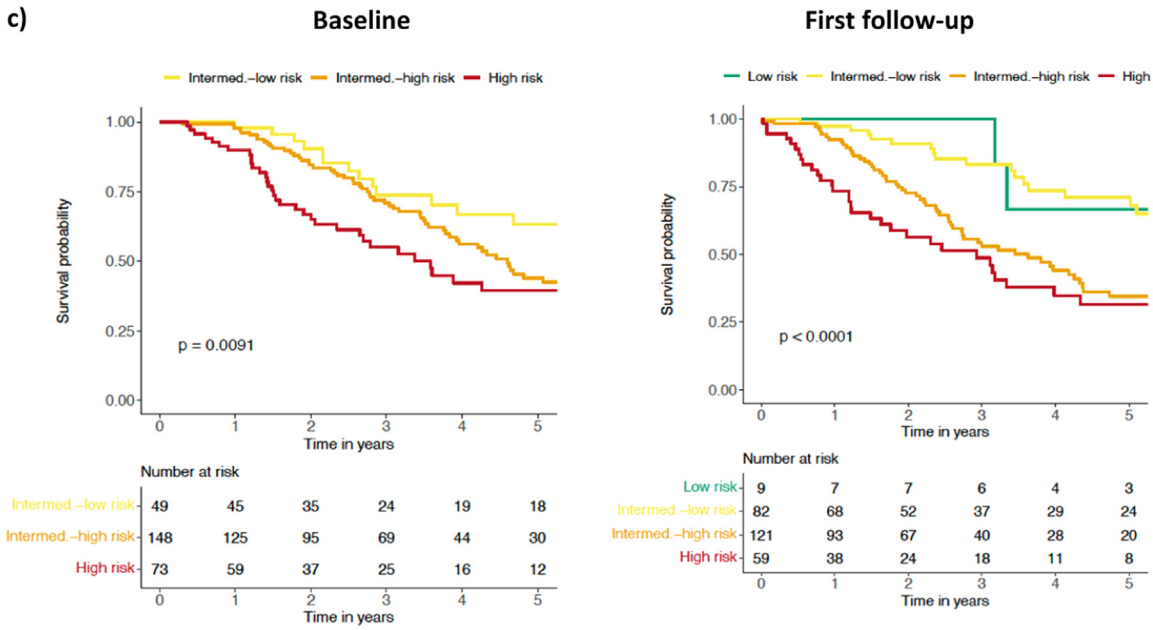

Figure 5 Continued

interest. E.J reports no conflicts of interest. L.G. has received speaker's fees from Actelion, Janssen, and Medis. S.M. has no disclosures. J.L.-R. has no disclosures. T.J.L. has received speaker fees and honoraria for consultation from Acceleron, Actelion, Bayer, GSK, Janssen-Cilag, MSD, Pfizer, and United Therapeutics. K.M.O has received fees for lectures and/or consultations from Acceleron, Actelion, AOP Health, Bayer, Ferrer, Janssen, and MSD. M.M. H has received fees for lectures and/or consultations from Acceleron, Actelion, Bayer, GSK, Janssen, MSD, and Pfizer. C.O. has no disclosures.

This work was supported by the German Centre of Lung Research (DZL). COMPERA is funded by unrestricted grants from Acceleron, Bayer, Ferrer, Janssen, and OMT. These companies were not involved in data analysis or the writing of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2022.10.003.

References

1. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75. https://doi.org/10.1183/13993003.01032-2015.
2. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respirat J 2019;53:1801889. https://doi.org/10.1183/13993003.01889-2018. In eng.
3. Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 2018;39:4175-81. https://doi.org/10.1093/eurheartj/ehx257.
4. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J 2017;50. https://doi.org/10.1183/13993003.00740-2017.
5. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J 2017;50. https://doi.org/10.1183/13993003.00889-2017.
6. Boucly A, Weatherald J, Savale L, et al. External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry. Eur Respir J 2022;59. https://doi.org/10.1183/13993003.02419-2021.
7. Hoeper MM, Pausch C, Olsson KM, et al. COMPERA 2.0: a refined 4-strata risk assessment model for pulmonary arterial hypertension. Eur Respir J 2021. https://doi.org/10.1183/13993003.02311-2021.
8. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol 2013;168:871-80. https://doi.org/10.1016/j.ijcard.2012.10.026. In Eng.
9. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest 2011;139:128-37. https://doi.org/10.1378/chest.10-0075. In eng.
10. Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012;186:790-6. https://doi.org/10.1164/rccm.201203-0383OC. In eng.
11. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44. https://doi.org/10.1056/NEJMoa1413687.
12. Hjalmarsson C, Radegran G, Kylhammar D, et al. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. Eur Respir J 2018;51:1702310. https://doi.org/10.1183/13993003.02310-2017. In eng.
13. Hoeper MM, Pausch C, Grunig E, et al. Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. J Heart Lung Transplant 2020;39:1435-44. https://doi.org/10.1016/j.healun.2020.09.011. In eng.
14. Kianzad A, van Wezenbeek J, Celant LR, et al. Idiopathic pulmonary arterial hypertension patients with a high H2FPEF-score: insights from the Amsterdam UMC PAH-cohort. J Heart Lung Transplant 2022. https://doi.org/10.1016/j.healun.2022.05.007.

15. McLaughlin VV, Vachiery JL, Oudiz RJ, et al. Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: results from the AMBITION trial. J Heart Lung Transplant 2019;38:1286-95. https://doi.org/10.1016/j.healun.2019.09.010. In eng.
16. Opitz CF, Hoeper MM, Gibbs JS, et al. Pre-capillary, combined, and post-capillary pulmonary hypertension: a pathophysiological continuum. J Am Coll Cardiol 2016;68:368-78. https://doi.org/10.1016/j.jacc.2016.05.047.
17. Rosenkranz S, Channick R, Chin KM, et al. The impact of comorbidities on selexipag treatment effect in patients with pulmonary arterial hypertension: insights from the GRIPHON study. Eur J Heart Fail 2021. https://doi.org/10.1002/ejhf.2369.
18. Xanthouli P, Koegler M, Marra AM, et al. Risk stratification and prognostic factors in patients with pulmonary arterial hypertension and comorbidities a cross-sectional cohort study with survival follow-up. Respir Res 2020;21:127. https://doi.org/10.1186/s12931-020-01393-1.