



Early View

Original research article

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COMPERA 2.0: A refined 4-strata risk assessment model for pulmonary arterial hypertension

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Take home message: COMPERA 2.0, a 4-strata risk assessment model based on refined cut-off levels for FC, 6MWD and BNP/NT-proBNP was more sensitive to prognostically significant changes in risk than the original 3-strata model.

Abstract

Background Risk stratification plays an essential role in the management of patients with pulmonary arterial hypertension (PAH). The current European guidelines propose a 3-strata model to categorize risk as low, intermediate, or high, based on the expected 1-year mortality. However, with this model, most patients are categorized as intermediate risk. We investigated a modified approach based on 4 risk categories with intermediate risk subdivided into intermediate-low and intermediate-high risk.

Methods We analysed data from COMPERA, a European pulmonary hypertension registry, and calculated risk at diagnosis and first follow-up based on functional class (FC), 6 min walking distance (6MWD) and serum levels of brain natriuretic peptide (BNP) or N-terminal fragment of pro-BNP (NT-proBNP), using refined cut-off values. Survival was assessed with Kaplan-Meier analyses, log-rank testing, and Cox proportional hazards models.

Results Data from 1,655 patients with PAH were analysed. Using the 3-strata model, most patients were classified as intermediate risk (76.0% at baseline and 63.9% at first follow-up). The refined 4-strata risk model yielded a more nuanced separation and predicted long-term survival, especially at follow-up assessment. Changes in risk from baseline to follow-up were observed in 31.1% of the patients with the 3-strata model and in 49.2% with the 4-strata model. These changes, including those between the intermediate-low and intermediate-high strata, were associated with changes in long-term mortality risk.

Conclusions Modified risk stratification using a 4-strata model based on refined cut-off levels for FC, 6MWD and BNP/NT-proBNP was more sensitive to prognostically relevant changes in risk than the original 3-strata model.

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Key words: pulmonary hypertension, pulmonary arterial hypertension, treatment, survival, mortality, risk, prognosis, long-term, observational

Introduction

Risk stratification has become an integral part of the management of patients with pulmonary arterial hypertension (PAH). The 2015 joint pulmonary hypertension (PH) guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) proposed a multidimensional risk stratification model based on 14 variables derived from 9 assessments [1, 2]. Based on this model, risk is divided into 3 strata as low, intermediate, or high with estimated 1-year mortality rates <5%, 5-10% and >10%, respectively. Achieving and maintaining a low risk profile is recommended as treatment goal in patients with PAH [1-3].

Since publication of these guidelines, several registry-based studies showed that simplified versions of the ESC/ERS tool provided reliable prognostication. In particular, a combination of functional class (FC), 6-minute walking testing (6MWT), and brain natriuretic peptide (BNP) or N-terminal fragment of pro-BNP (NT-proBNP) was found to have strong prognostic value, both at the time of diagnosis and – even more so – at follow-up, i.e., after initiation of targeted therapies [4-6]. These variables were also the most reliable predictive parameters in the Lite-2 version of the REVEAL risk calculator, a risk stratification tool developed in the US [7-9].

Several modalities have been developed to calculate individual risk. French investigators used a panel of non-invasive (FC, 6MWD, BNP/NT-proBNP) and invasive (right atrial pressure, cardiac index) variables and summed up the number of variables meeting low risk criteria. They found that combined assessment of FC, 6MWD, and BNP/NT-proBNP had the highest prognostic value [4]. This strategy was confirmed by the *Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension* (COMPERA) investigators [10]. In both series, patients who met low risk criteria for all 3 variables (FC I or II, 6MWD >440 m, BNP <50 ng/l or NT-proBNP <300 ng/l) while on therapy had 5-year survival rates >90%. However, these criteria were met only by 9-19% of the patients [4, 10].

The Swedish Pulmonary Arterial Hypertension Registry (SPAHR) group and the COMPERA group used an alternative approach: Based on the cut-off levels proposed in the ESC/ERS guidelines, each variable was graded from 1 to 3, where 1 defined low, 2 intermediate and 3 high risk. The mean value was calculated by dividing the sum of all grades by the number of variables [5, 6]. As the French group, the SPAHR and COMPERA groups included

haemodynamics (right atrial pressure, cardiac index, mixed-venous oxygen saturation) in addition to FC, 6MWD, and BNP/NT-proBNP. In line with the French observations, the COMPERA investigators found that the non-invasive variables had a higher predictive value than the haemodynamic variables and showed that risk assessment based on the non-invasive variables alone provided good discrimination demonstrating significant survival differences between the risk groups [6].

Based on these studies, FC, 6MWD, and BNP/NT-proBNP have been established as key elements of current risk assessment tools in PAH. However, it was noted in the SPAHR and COMPERA analyses that most patients did not meet the low risk criteria while receiving PAH treatment. In fact, the majority of patients met intermediate risk criteria (approximately 70% at baseline and 60% at follow-up) [5, 6]. In these patients, a more granular risk prediction is required, in particular for far-reaching therapeutic decisions including the need for parenteral prostanoid therapy and evaluation for lung transplantation. Several investigators have shown that the use of additional variables derived from echocardiography, right heart catheterization or blood gas analysis improved risk prediction [11-14]. As an alternative model, the SPAHR group recently proposed a modification of their original approach defining a calculated score of 1.5-1.99 as intermediate-low risk and a score of 2.0-2.4 as intermediate-high risk [15]. This approach showed promising results with further discrimination within the intermediate-risk group, albeit based on a relatively small sample size.

We hypothesized that a 4-risk strata subdivision (low, intermediate-low, intermediate-high, and high) based on more granularity within the cut-off levels of 6MWD, FC and BNP/NT-proBNP might improve risk stratification. Here, we used the COMPERA database to investigate a refined risk stratification model (COMPERA 2.0) using modified cut-off levels, some of which have been proposed recently by the REVEAL group [7].

Methods

Database

Details of COMPERA (www.COMPERA.org; registered at [Clinicaltrials.gov](https://clinicaltrials.gov) under the identifier NCT01347216) have been reported in previous communications [16, 17]. In summary, COMPERA is an ongoing PH registry launched in 2007 that prospectively collects baseline, follow-up, and outcome data of patients who receive targeted therapies for any form of PH. Patients are enrolled within 6 months after the PH diagnosis to ensure inclusion of newly diagnosed patients only. PH centres 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 prior to inclusion.

Patients

For the present analysis, patients were selected from the COMPERA database by the following criteria: (i) treatment-naïve patients ≥ 18 years newly diagnosed with any form of PAH between January 1st, 2009 and December 31st, 2020, (ii) at least one follow-up available, (iii) baseline haemodynamics showing mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 WU ($240 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$), and (iv) all three variables of interest (FC, 6MWD, BNP or NT-proBNP) available at baseline. Patients with other forms of PH were excluded from this analysis as were patients with Eisenmenger syndrome and patients with confirmed or suspected pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis.

Refined risk stratification

The cut-off levels for FC, 6MWD and NT-proBNP for the COMPERA 2.0 risk stratification model were modified from the ESC/ERS guidelines and from our previous analysis [2, 6] as follows: The refined cut-off values for 6MWD and BNP were adopted from REVEAL [8, 9]. As no NT-proBNP cut-off value to distinguish between intermediate-low risk and intermediate-high risk was available from REVEAL Lite 2, we determined the optimal cut-off from the

present data base by selecting the value with the highest predictive value, i.e., the lowest p-value of the log-rank test, for mortality in the group of patients with NT-proBNP levels between 300 ng/l and 1,100 ng/l at baseline, using 50-ng/l intervals.

For FC, we considered distinguishing between FC I and II. However, as very few patients in the present data set were classified as FC I (n=7 at baseline), and as FC II has repeatedly been shown to be associated with good long-term survival, we continued grouping FC I and II as a single (low risk) group.

Based on the criteria shown in **Table 1**, each variable was graded from 1 to 4, and the mean was calculated by dividing the sum of all grades by the number of variables and rounding to the next integer. For the 3-strata model, we defined a score of 1 as low risk, 2 as intermediate risk and 3 as high risk. For the 4-strata model, we used the following definitions: 1 = low, 2 = intermediate-low, 3 = intermediate-high, and 4 = high risk. Risk stratification was performed at baseline, i.e., before initiation of PAH medications, and at first follow-up between 3 and 12 months after treatment initiation.

Statistical analyses

This was a post-hoc analysis of prospectively collected data. Continuous data are presented as mean \pm standard deviation (SD) or as median and first and third quartile [Q1, Q3], categorical data as number and percentage. The data set as of June 30th, 2021, was analysed. Vital status was ascertained by on-site visits or phone calls to the patients or their caregivers. Patients who underwent lung transplantation and patients who were lost to follow-up were censored at the date of the last contact. No imputations were made for missing data. Survival was evaluated using Kaplan-Meier analysis and log-rank test. Survival analyses were done for the entire group and for subgroups of patients with I/H/D-PAH and CTD-PAH according to risk at baseline and first follow-up (with survival time starting at first follow-up for the latter analysis). The effects of changes in risk from baseline to first follow-up on consecutive survival were evaluated using the Cox regression model. The associated hazard ratios (HR) and 95% confidence intervals (CIs) were calculated.

All statistical analyses were performed using R version 4.0.0.

Results

Baseline characteristics and survival of the entire cohort

Of 10,825 patients enrolled into COMPERA, 9,710 were excluded for the reasons shown in Figure 1, including 136 patients who fulfilled all inclusion criteria but who had no follow-up information or were lost to follow-up without any information. A total of 1,655 patients were finally included in this analysis. The characteristics of these patients at baseline are shown in **Table 2**.

The median [Q1, Q3] observation time was 2.6 [1.2, 4.9] years. During follow-up, 640 (38.7%) patients died, 21 (1.3%) underwent lung transplantation, and 90 (5.4%) were lost to follow-up. For the entire cohort, the Kaplan-Meier estimated survival rates 1, 3 and 5 years after diagnosis were 91.1%, 70.7% and 55.2% respectively.

Determination of NT-proBNP cut-off level to distinguish between intermediate-low and intermediate-high risk

To determine the NT-proBNP cut-off level for the discrimination between intermediate-low and intermediate-high risk, we calculated the log-rank test for patients whose baseline NT-proBNP levels were between 300 ng/l and 1,100 ng/l (n=374), using 50 ng/l steps to split these patients in two groups. As shown in **Supplementary Figure S1**, the lowest p-value ($p=0.091$) was found for an NT-proBNP value of 650 ng/l. As this number was also close to this group's median, we used it as cut-off to distinguish between the two intermediate risk groups in all further analyses.

Risk at baseline and survival

At baseline, using the 3-strata model, 142 (8.6%) patients were classified as low risk, 1,257 (76.0%) patients as intermediate risk, and 256 (15.5%) patients as high risk.

With the 4-strata, model, 92 (5.6%) patients were classified as low risk, 401 (24.2%) patients as intermediate-low risk, 910 (55.0%) patients as intermediate-high risk, and 252 (15.2%) as high risk (**Table 2**).

The Kaplan-Meier estimated survival rates 1, 3 and 5 years after diagnosis for the low risk group were 100%, 89.0% and 82.9%, respectively; for the intermediate-low risk group, 97.9%, 85.6% and 78.6%, respectively; for the intermediate-high risk group, 90.9%, 62.2% and 50.3%, respectively; and for the high risk group, 78.1%, 46.5% and 28.2%, respectively ($p < 0.001$ for between-group comparisons; **Figure 2a**). The survival estimates of the I/H/D-PAH and CTD-PAH subgroups in the 4-risk strata were consistent with the overall group as shown in supplementary Figures S2 and S3.

Risk at follow-up and survival

Information on risk variables at first follow-up after treatment initiation (median, 4.1 months) was available for 1,414 patients (**Supplementary Table S1**). At that time, 64.1% of the patients were receiving monotherapy, 33.2% oral combination therapy, and 1.3% combination therapy including intravenous or subcutaneous prostacyclin analogues (**Supplementary Table S2**).

At first follow-up, with the 3-strata model, 282 (19.9%) patients were classified as low risk, 903 (63.9%) patients as intermediate risk, and 229 (16.2%) as high risk.

With the 4-strata model, 240 (17%) patients were classified as low risk, 395 patients (27.9%) as intermediate-low risk, 534 (37.8%) as intermediate-high risk, and 245 (17.3%) as high risk.

The Kaplan-Meier estimated survival rates 1, 3 and 5 years after diagnosis for the low risk at first follow-up group were 98.5%, 91.2% and 82.8%, respectively; for the intermediate-low risk group, 97.2%, 81.8% and 66.8%, respectively; for the intermediate-high risk group, 91.3%, 63.0% and 46.5%, respectively; and for the high risk group, 78.0%, 48.0% and 33.3%, respectively ($p < 0.001$ for between-group comparisons; **Figure 2b**).

Changes in risk from baseline to first follow-up and survival

Overall, risk improved from baseline to first follow-up (**Figure 3**). When the 3-strata approach was applied to the current data set, 440 (31.1%) patients changed their risk category (**Figure 3a and Supplementary Table S3**). Changes in risk from baseline to follow-up were associated with changes in long-term mortality risk as shown in **Figure 4a and b**.

Using the refined 4-strata approach, 695 (49.2%) patients changed their risk category from baseline to first follow-up including 263 (18.6%) patients who changed between the intermediate-low and intermediate-high strata (**Figure 3b and Supplementary Table S4**).

Changes in risk observed with the 4-strata model including those between intermediate-low and intermediate-high risk were associated with changes in long-term mortality risk (**Figures 5a-d**). In patients who started at intermediate-low risk at baseline, the likelihood of death increased by 60.3% in those who deteriorated to intermediate-high risk at follow-up (n=65), compared to patients who remained at intermediate-low risk (HR 1.603, 95% CI 0.921-2.792); if these patients improved to low risk (n=102), the likelihood of death decreased by 35.5% (HR 0.645, 95% CI 0.343-1.214; **Figure 5a**).

In patients coming from intermediate-high risk at baseline, the likelihood of death decreased by 20.1% in those who improved to intermediate-low risk at follow-up (n=198) compared to patients who remained at intermediate-high risk (HR 0.799, 95% CI 0.611-1.046; **Figure 5b**). If these patients deteriorated to high risk at follow-up (n=139), they had a 49.2% increased likelihood of death compared to patients who remained at intermediate-high risk (HR 1.492, 95% CI 1.122-1.983; **Figure 5b**). Conversely, in patients coming from high risk at baseline, only a slightly decreased likelihood of death was seen when improving to intermediate-high risk at follow-up (n=80) compared to patients who remained at high risk (HR 0.895, 95% CI 0.608-1.317; **Figure 5c**).

Of note, of 995 patients who were classified as high or intermediate-high risk at baseline, only 75 (7.5%) improved to low risk at follow-up, but n=216 (21.7%) improved to intermediate-low risk (**Supplementary Table S4**). In this group of patients, reaching an intermediate-low risk profile at follow up was associated with a 41.3% reduction in the likelihood of death compared to patients who did not improve their risk category (HR 0.587, 95% CI 0.459-0.749; **Figure 5d**).

Discussion

In the present study, we evaluated a modified risk assessment strategy termed COMPERA 2.0 using 4 instead of 3 risk strata and refined cut-off levels for 6MWD and BNP/NT-proBNP. The main findings were that (i) very few patients (5.6%) were at low risk at the time of diagnosis; (ii) with the 3-strata model, most patients presented with an intermediate risk profile at the time of diagnosis and at follow-up, and this group was further divided into an intermediate-low and an intermediate-high risk group with the 4-strata model; (iii) the long-term survival of patients presenting with low or intermediate-low risk at the time of diagnosis was almost identical; (iv) at follow-up, all four risk strata were of reasonable size (17-38% of the patients) showing significant differences in long-term survival; (v) with the 4-strata model, changes in risk from baseline to first follow-up were documented in 49.2% of the patients, compared to 31.1% with the 3-strata model; (vi) changes in risk from baseline to first follow-up observed with the 4-strata model, including changes between intermediate-low and intermediate-high risk, were associated with changes in long-term mortality risk; and (vii) patients classified as high or intermediate-high risk at baseline had a very low likelihood of reaching a low risk profile, but a higher likelihood of reaching an intermediate-low risk profile, which was associated with a decreased mortality risk over time.

It was not surprising to find a very low number of patients presenting with a low risk profile at the time of diagnosis. This is in line with previous data from SPAHR and COMPERA [5, 6] as well as findings from the French registry [4]. At baseline, the 4-strata model did not show a survival difference in patients classified as low or intermediate-low risk. However, risk assessment at the time of diagnosis is particularly important for identifying high risk patients, for whom initial combination therapy including intravenous or subcutaneous prostacyclin analogues is recommended, whereas for all other patients, initial oral combination therapy is currently the preferred treatment [2, 3]. Hence the absence of a survival difference between patients presenting with low or intermediate-low risk at baseline is not considered a shortcoming of the proposed model. At the same time, an intermediate-high risk status at baseline may prompt physicians to initiate a more aggressive therapeutic approach, especially when keeping in mind a recent publication from France on the effects of initial treatment strategies on long-term survival [18].

Compared to risk assessment at the time of diagnosis, risk stratification after treatment initiation provides more reliable prognostic information as it incorporates the individual response to therapy [19]. It has already been shown by several groups that changes in risk translate into changes in long-term survival [4, 6, 9]. However, a substantial limitation of the 3-strata model is that most patients present at intermediate risk at baseline and during follow-up while the number of patients who change their risk category is relatively low. Applying the original 3-strata model to the present series, 76.0% of the patients were at intermediate risk at baseline and 63.9% at follow-up, and only 31.1% changed their risk category between baseline and first follow-up. Thus, the 3-strata model may not be sufficiently sensitive to prognostically relevant changes. With the refined 4-strata model, changes from baseline to first follow-up were observed in 49.2% of the patients. Changes between the intermediate-low and intermediate-high strata occurred in 18.6% of the patients, and these changes had an impact on consecutive survival. Hence, there was more between-group penetrability with the 4-strata model, which may be of relevance not only in clinical settings but also when risk stratification tools are considered as endpoints in clinical trials, where it will have a substantial impact on sample size calculations if changes can be expected to occur in about 30% or in almost 50% of the participants.

According to current guidelines, achieving and maintaining a low risk profile is a major treatment objective in PAH [1-3], but it has been shown that this goal is not reached in most patients [4, 6, 20]. In the present series, only 7.5% of the patients who were classified as high or intermediate-high risk at baseline reached the low risk category at follow-up, while 21.7% reached the intermediate-low risk category, which was associated with a decreased mortality risk, albeit less so than with reaching the low risk category. Thus, while improving from high or intermediate-high to intermediate low risk can be considered a partial treatment success, our data confirm that a low risk profile is an essential treatment goal in patients with PAH. At the same time, an intermediate-high risk category at follow-up was associated with a high mortality risk and should trigger treatment escalation whenever reasonably possible. Hence, the distinction between intermediate-low and intermediate-high risk can support clinical decision-making.

In the present analysis, we used several cut-off values that have originally been proposed by the REVEAL group [7-9], and one may ask why not use REVEAL Lite 2 instead of COMPERA 2.0? REVEAL Lite 2 is a well validated and established tool, but we believe that our model has

potential advantages. Firstly, REVEAL Lite 2 has no NT-proBNP cut-off to distinguish between intermediate-low and intermediate-high risk, which is a major drawback as today, NT-proBNP is used more frequently than BNP as cardiac biomarker. Secondly, REVEAL Lite 2 includes heart rate and systolic blood pressure, i.e., two highly variable parameters, which were not obtained in a standardized manner in the original REVEAL registry [8]. The prognostic value of these parameters awaits independent confirmation, especially when added to FC, 6MWD and BNP/NT-proBNP. Thirdly, REVEAL Lite 2 incorporates renal dysfunction, defined as estimated glomerular filtration rate <60 ml/min/1.73m² or renal insufficiency deemed present by the investigator. While there is little doubt that kidney function is prognostically important in patients with PAH [21], we believe that this variable needs to be better defined and validated before being included in risk stratification models. The COMPERA 2.0 model is based only on parameters that have been thoroughly validated, and future studies are needed to determine whether the use of additional parameters increases the predictive value of this tool.

The limitations of the present study are those inherent to registry analyses, including lack of standardized visit schedules and missing values. The number of patients lost to follow-up was small, but not negligible. Although the sample size was relatively large, the numbers became small for the subgroup analyses. This was particularly relevant for the number of patients who changed their risk category between baseline and follow-up, which became relatively small in some subsets, so that statistical significance could not be claimed for all possible changes in risk and their impact on consecutive survival. Furthermore, the NT-proBNP cut-off value was derived and validated in the same cohort, so that independent confirmation is necessary. In addition, we did not attempt to further calibrate and weigh the variables in our model.

As a general limitation, all available simplified models provide a basic risk assessment, while individual risk is determined by numerous other factors including age [22, 23], sex [24], type of PAH [25], symptoms, signs, disease trajectories [26], and co-morbidities [16]. In addition, risk stratification can be modified by variables derived from cardiac imaging [27-30], cardiopulmonary exercise testing [31] and right heart catheterization [13, 32]. Hence, while combining FC, 6MWD and NT-proBNP has proven useful for a primary risk assessment, all available information should be considered for individual treatment decisions.

In summary, our data show that a 4-strata risk model based on refined cut-off levels for FC, 6MWD and BNP/NT-proBNP was more sensitive than the 3-strata model to prognostically relevant changes in risk. Thus, it is possible that the 4-strata model may be more useful both in clinical practice and as research tool in clinical trials. If these findings can be confirmed by other groups, the 4-strata model may replace the current 3-strata model as risk stratification tool in PAH.

Table 1 Criteria for refined risk stratification in the 3-strata model and the 4-strata-model based on functional class, 6 min walking distance and BNP/NT-proBNP

3-strata model

| Points assigned | 1 | 2 | 3 |
|----------------------|-----------------------|------------------------------|-------------------------|
| FC | I or II | III | IV |
| 6MWD | >440 m | 440-165 m | <165 m |
| BNP or NT-proBNP* | <50 ng/l <300 ng/l | 50-800 ng/l 300-1100 ng/l | >800 ng/l >1100 ng/l |

4-strata model

| Points assigned | 1 | 2 | 3 | 4 |
|----------------------|-----------------------|-----------------------------|-------------------------------|-------------------------|
| FC | I or II | - | III | IV |
| 6MWD | >440 m | 440-320 m | 319-165 m | <165 m |
| BNP or NT-proBNP* | <50 ng/l <300 ng/l | 50-199 ng/l 300-649 ng/l | 200-800 ng/l 650-1100 ng/l | >800 ng/l >1100 ng/l |

FC, functional class; 6MWD, 6 min walking distance, BNP, brain natriuretic peptide, NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide

*The cut-off values for 6MWD and BNP were obtained from REVEAL Lite 2 [9], while the cut-off values for NT-proBNP were derived from ROC analysis of all patients from the present analysis with baseline NT-proBNP values between 300 and 1100 ng/l. When both BNP and NT-proBNP were available, NT-proBNP was used.

Table 2 Baseline characteristics

| | Low risk n=92 (5.6%) | Intermediate low risk n=401 (24.2%) | Intermediate high risk n=910 (55.0%) | High risk n=252 (15.2%) | All n=1655 (100%) | Available data |
|---------------------------|-------------------------|--|---|-------------------------------|-------------------------|--------------------------|
| Age, years | 49.9 (17.0) | 61.5 (15.1) | 67.5 (14.7) | 71.4 (12.8) | 65.7 (15.5) | 1655 (100.0%) |
| Female | 58 (63.0%) | 259 (64.6%) | 573 (63.0%) | 174 (69.0%) | 1064 (64.3%) | 1655 (100.0%) |
| BMI, kg/m ² | 26.7 (5.2) | 28.7 (6.3) | 28.0 (5.9) | 28.6 (6.4) | 28.2 (6.0) | 1604 (96.9%) |
| Diagnosis | | | | | | 1655 (100.0%) |
| I/H/D PAH | 59 (64.1%) | 282 (70.3%) | 659 (72.4%) | 182 (72.2%) | 1182 (71.4%) | |
| CTD-PAH | 18 (19.6%) | 68 (17.0%) | 184 (20.2%) | 60 (23.8%) | 330 (19.9%) | |
| CHD-PAH | 5 (5.4%) | 21 (5.2%) | 20 (2.2%) | 0 (0.0%) | 46 (2.8%) | |
| HIV-PAH | 3 (3.3%) | 4 (1.0%) | 6 (0.7%) | 1 (0.4%) | 14 (0.8%) | |
| PoPH | 7 (7.6%) | 26 (6.5%) | 41 (4.5%) | 9 (3.6%) | 83 (5.0%) | |
| WHO FC | | | | | | 1655 (100.0%) |
| I | 2 (2.2%) | 5 (1.2%) | 0 (0.0%) | 0 (0.0%) | 7 (0.4%) | |
| II | 90 (97.8%) | 111 (27.7%) | 36 (4.0%) | 0 (0.0%) | 237 (14.3%) | |
| III | 0 (0.0%) | 281 (70.1%) | 813 (89.3%) | 115 (45.6%) | 1209 (73.1%) | |
| IV | 0 (0.0%) | 4 (1.0%) | 61 (6.7%) | 137 (54.4%) | 202 (12.2%) | |
| 6MWD, m | 488.7 (84.5) | 380.7 (92.2) | 279.0 (92.8) | 132.7 (63.9) | 293.0 (125.8) | 1655 (100.0%) |
| NT-proBNP, ng/L | 130 [68, 252] | 398 [194, 642] | 1930 [1022, 3468] | 4192 [2255, 7122] | 1499 [512, 3330] | 1389 (83.9%) |
| BNP, ng/L | 99 [58, 131] | 82 [34, 147] | 280 [134, 543] | 543 [373, 1035] | 214 [94, 432] | 271 (16.4%) ¹ |
| RAP, mmHg | 6.2 (3.6) | 6.8 (4.3) | 8.3 (4.7) | 10.3 (5.2) | 8.2 (4.8) | 1538 (92.9%) |
| PAPm, mmHg | 42.8 (13.5) | 41.2 (13.0) | 43.5 (11.9) | 46.1 (10.8) | 43.3 (12.2) | 1655 (100.0%) |
| PAWP, mmHg | 8.4 (3.2) | 9.1 (3.4) | 9.6 (3.3) | 9.5 (3.4) | 9.4 (3.3) | 1655 (100.0%) |
| CI, L/min/m ² | 2.8 (0.8) | 2.4 (0.8) | 2.1 (0.7) | 1.9 (0.7) | 2.2 (0.7) | 1566 (94.6%) |
| PVR, WU | 7.7 (4.4) | 7.6 (4.2) | 9.6 (4.7) | 11.7 (5.7) | 9.3 (4.9) | 1655 (100.0%) |
| SvO ₂ , % | 70.0 (6.4) | 67.3 (6.1) | 62.0 (7.7) | 59.2 (7.9) | 63.2 (8.0) | 1450 (87.6%) |
| DLCO, % pred | 60.7 (18.1) | 58.5 (21.8) | 50.3 (20.9) | 42.4 (20.5) | 51.5 (21.6) | 1168 (70.6%) |
| Comorbidities | 0.9 (0.9) | 1.5 (1.1) | 1.8 (1.3) | 2.0 (1.3) | 1.7 (1.2) | 1300 (78.5%) |
| Arterial hypertension | 31 (43.7%) | 201 (59.3%) | 514 (64.2%) | 143 (70.1%) | 889 (62.9%) | 1414 (85.4%) |
| Coronary heart disease | 7 (10.4%) | 66 (19.9%) | 209 (27.0%) | 61 (29.5%) | 343 (24.9%) | 1379 (83.3%) |
| Diabetes mellitus | 6 (8.7%) | 77 (23.1%) | 215 (27.2%) | 70 (33.5%) | 368 (26.2%) | 1402 (84.7%) |
| BMI ≥30 kg/m ² | 19 (21.8%) | 150 (38.2%) | 294 (33.0%) | 90 (37.0%) | 553 (34.2%) | 1615 (97.6%) |

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

Abbreviations: BMI, body mass index; PAH, pulmonary arterial hypertension; I/D/H-PAH, idiopathic, drug-associated or hereditary PAH; CTD, connective tissue disease; HIV, human immunodeficiency virus; PoPH, portopulmonary hypertension; CHD, congenital heart disease; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO₂, mixed-venous oxygen saturation; DLCO, diffusion capacity of the lung for carbon monoxide

Figure legends

Figure 1 STROBE diagram showing patient eligibility for analysis

Figure 2a Kaplan-Meier survival curves based on the 4 risk strata obtained at baseline

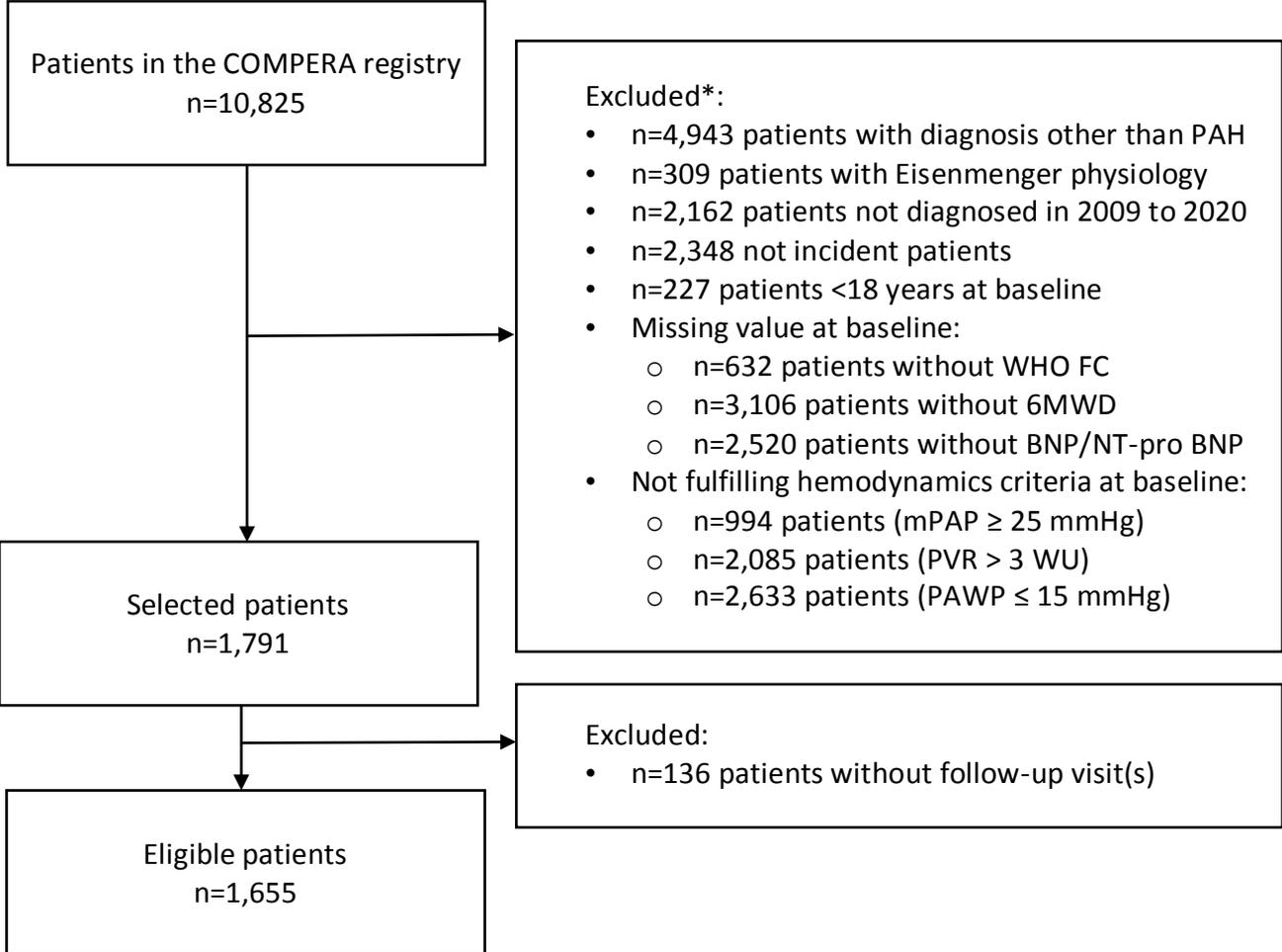
Figure 2b Kaplan-Meier survival curves based on the 4 risk strata obtained at first follow-up

Figure 3 Change in risk from baseline to first follow-up

Figure 4 Mortality risk of patients who changed their risk category from baseline to follow-up with the 3-strata model

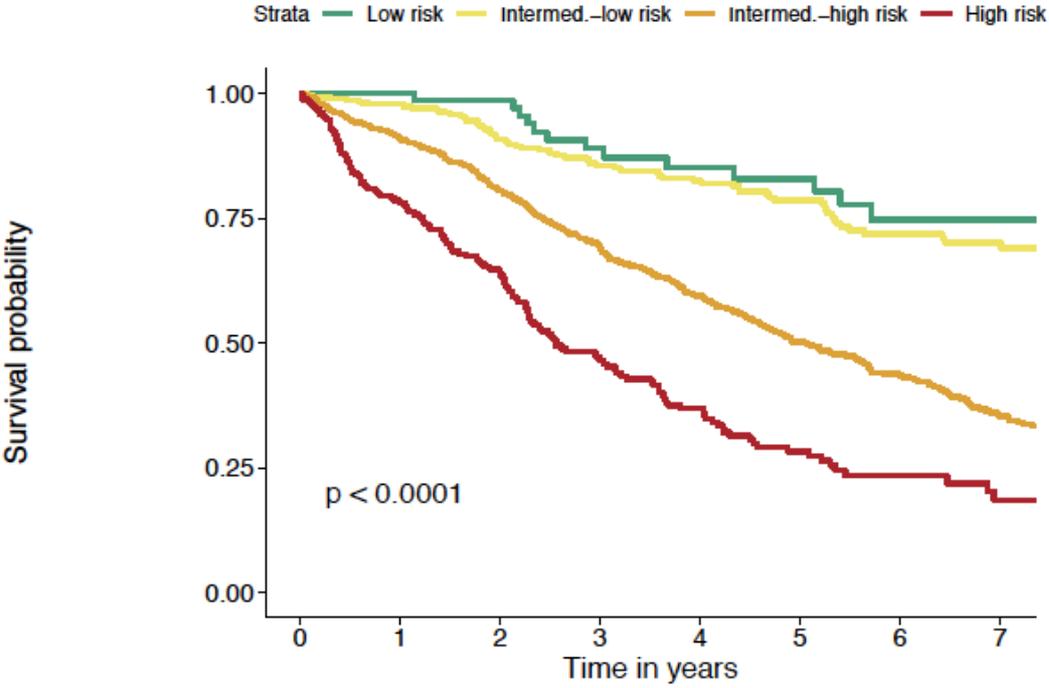
Figure 5 Mortality risk of patients who changed their risk category from baseline to follow-up with the 4-strata model

Figure 1 STROBE diagram showing patient eligibility for analysis



*more than one reason for exclusion could apply

Figure 2a: Kaplan-Meier survival curves based on the 4 risk strata obtained at baseline



Number at risk

| Strata | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---------------------|-----|-----|-----|-----|-----|-----|-----|----|
| Low risk | 92 | 76 | 65 | 49 | 40 | 34 | 24 | 17 |
| Intermed.-low risk | 401 | 335 | 270 | 213 | 166 | 125 | 88 | 71 |
| Intermed.-high risk | 910 | 726 | 540 | 406 | 299 | 205 | 143 | 92 |
| High risk | 252 | 167 | 119 | 77 | 56 | 32 | 20 | 11 |

Time in years

Figure 2b: Kaplan-Meier survival curves based on the 4 risk strata obtained at first follow-up

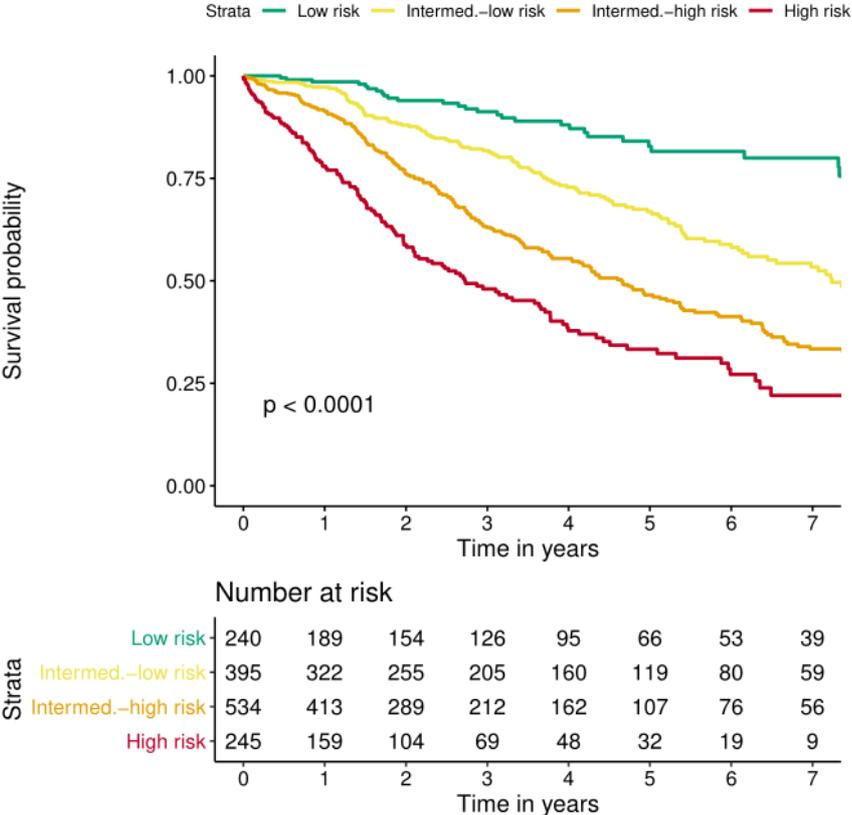
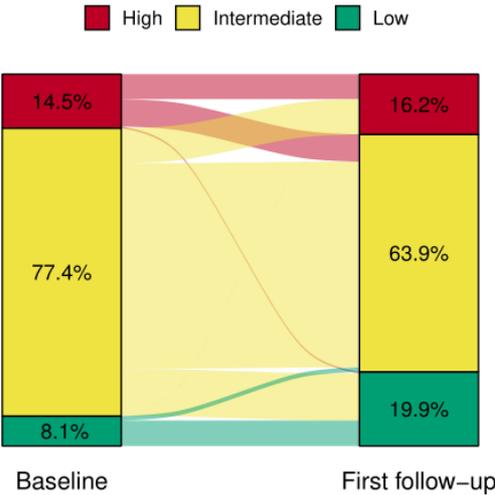
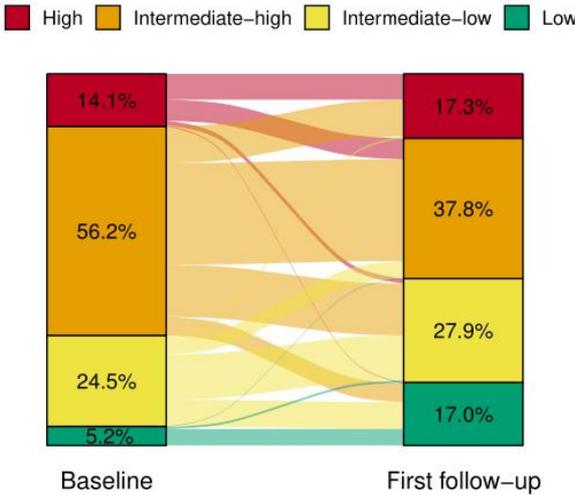


Figure 3: Change in risk from baseline to first follow-up

a)

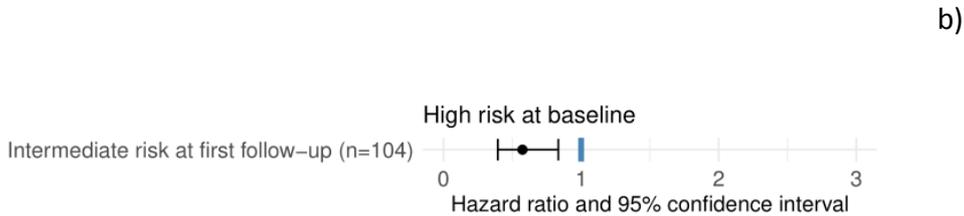
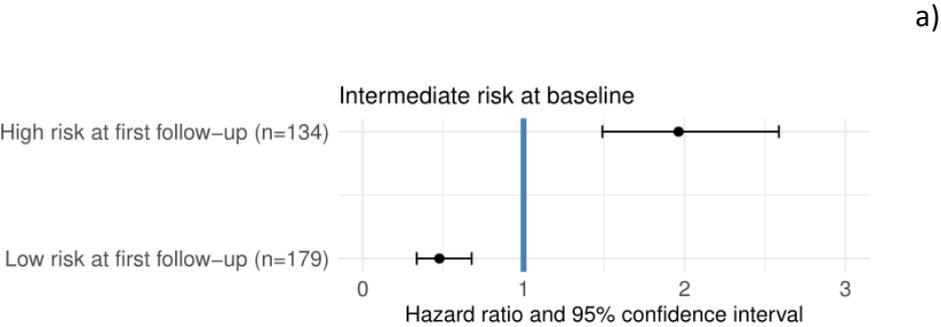


b)



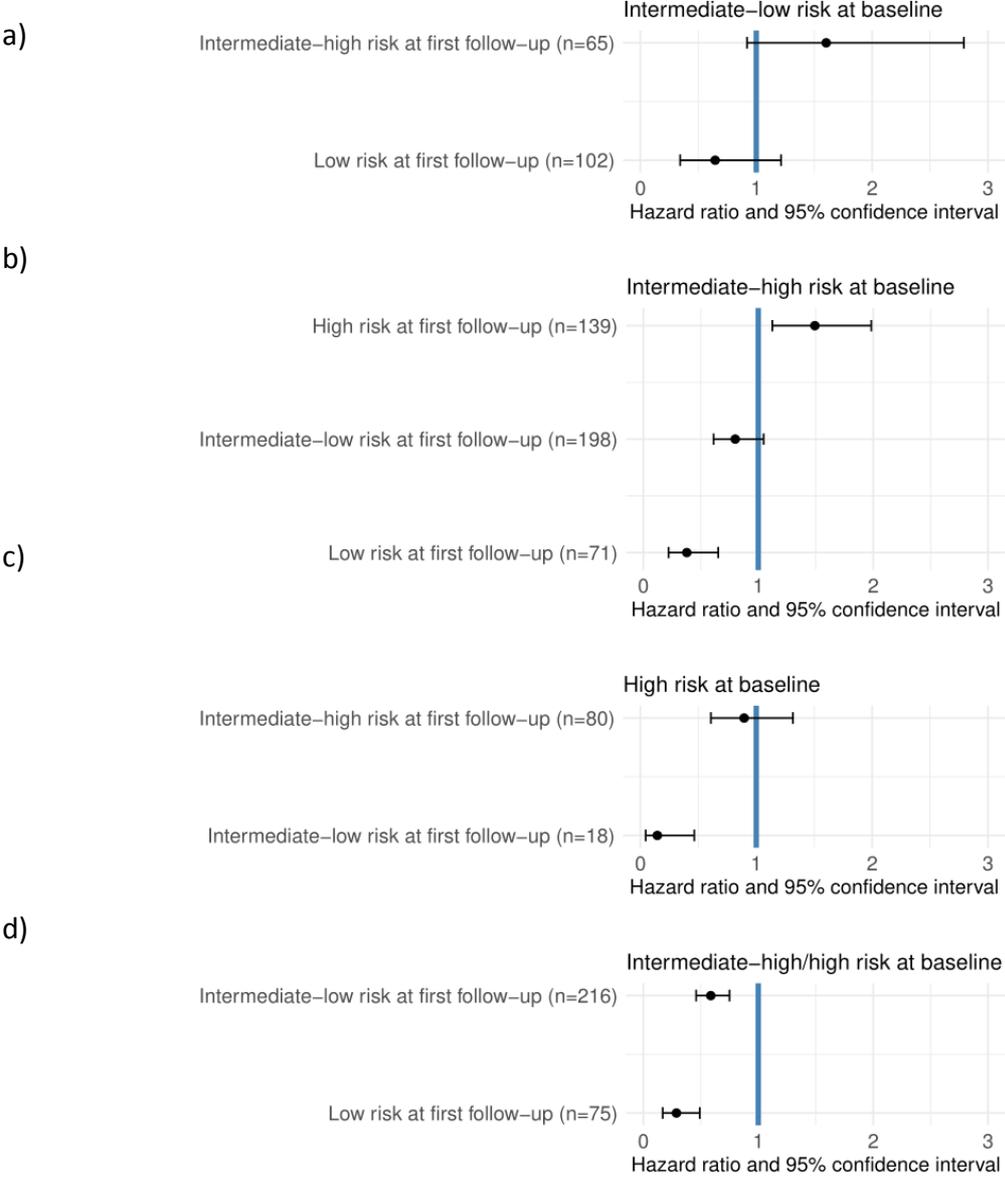
Risk at baseline and at first follow-up and changes in risk are shown for the (a) 3-strata model and (b) the 4-strata model

Figure 4: Mortality risk of patients who changed their risk category from baseline to follow-up with the 3-strata model



Mortality risk of patients who changed from baseline to follow-up with the 3-strata model from (a) intermediate risk to other risk categories and (b), from high risk to intermediate risk. Data for patients coming from low risk at baseline and those from patients coming from high risk and improving to low risk are not shown due to small numbers. All comparisons were made against patients who remained in their original risk category. Analyses were done with Cox proportional hazard models and depicted as hazard ratio and 95% confidence intervals.

Figure 5: Mortality risk of patients who changed their risk category from baseline to follow-up with the 4-strata model



Survival of patients who changed from baseline to follow-up with the 4-strata model from (a) intermediate low risk to other risk categories, (b) intermediate-high risk to other risk categories, (c) high risk to other risk categories, and (d) from intermediate-high or high risk combined to intermediate-low or low risk. Data for patients coming from low risk at baseline and those from patients coming from high risk and improving to low risk are not shown due to small numbers.

All comparisons were made against patients who remained in their original risk category.
Analyses were done with Cox proportional hazard models and depicted as hazard ratio and 95% confidence intervals

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Refined simplified risk stratification (Risk 2.0) in patients with PAH:

Results from COMPERA

Supplementary material

Table S1 Characteristics of the patients at follow-up (first assessment ≥ 12 weeks after treatment initiation, up to 12 months)

| | Low risk n=240 (17.0%) | Intermediate low risk n=395 (27.9%) | Intermediate high risk n=534 (37.8%) | High risk n=245 (17.3%) | All n=1414 (100%) | Available data |
|---------------------------------|------------------------------|--|---|-------------------------------|-------------------------|----------------|
| Age, years | 51.1 (15.7) | 63.8 (14.4) | 70.1 (12.9) | 75.0 (10.1) | 66.0 (15.5) | 1414 (100.0%) |
| Female | 148 (61.7%) | 257 (65.1%) | 361 (67.6%) | 157 (64.1%) | 923 (65.3%) | 1414 (100.0%) |
| BMI, kg/m ² | 26.8 (5.2) | 29.1 (7.0) | 28.6 (6.4) | 28.1 (5.7) | 28.3 (6.3) | 1123 (79.4%) |
| Diagnosis | | | | | | 1414 (100.0%) |
| I/H/D PAH | 164 (68.3%) | 276 (69.9%) | 391 (73.2%) | 188 (76.7%) | 1019 (72.1%) | |
| CTD-PAH | 44 (18.3%) | 73 (18.5%) | 107 (20.0%) | 45 (18.4%) | 269 (19.0%) | |
| CHD-PAH | 5 (2.1%) | 18 (4.6%) | 13 (2.4%) | 6 (2.4%) | 42 (3.0%) | |
| HIV-PAH | 3 (1.3%) | 4 (1.0%) | 5 (0.9%) | 1 (0.4%) | 13 (0.9%) | |
| PoPH | 24 (10.0%) | 24 (6.1%) | 18 (3.4%) | 5 (2.0%) | 71 (5.0%) | |
| WHO FC | | | | | | 1242 (87.8%) |
| I | 23 (10.5%) | 10 (2.8%) | 1 (0.2%) | 0 (0.0%) | 34 (2.6%) | |
| II | 196 (89.5%) | 172 (48.2%) | 49 (9.7%) | 0 (0.0%) | 417 (32.2%) | |
| III | 0 (0.0%) | 175 (49.0%) | 445 (88.3%) | 169 (77.9%) | 789 (60.8%) | |
| IV | 0 (0.0%) | 0 (0.0%) | 9 (1.8%) | 48 (22.1%) | 57 (4.4%) | |
| 6MWD, m | 490.9 (74.8) | 382.3 (88.0) | 279.2 (83.9) | 145.0 (71.2) | 345.4 (128.7) | 975 (69.0%) |
| NT-proBNP, ng/L | 139 [68, 223] | 372 [207, 711] | 1462 [757, 2620] | 3137 [1753, 5410] | 839 [259, 2168] | 1040 (73.6%) |
| BNP, ng/L | 25 [18, 42] | 100 [58, 153] | 254 [124, 358] | 523 [350, 915] | 149 [73, 330] | 186 (13.2%) |
| Comorbidities | 0.9 (1.0) | 1.7 (1.2) | 1.9 (1.2) | 2.1 (1.1) | 1.7 (1.2) | 1127 (79.7%) |
| Arterial hypertension | 74 (36.1%) | 207 (61.4%) | 333 (72.4%) | 156 (72.6%) | 770 (63.3%) | 1217 (86.1%) |
| Coronary heart disease | 18 (9.1%) | 73 (22.8%) | 128 (28.4%) | 68 (31.3%) | 287 (24.2%) | 1185 (83.8%) |
| Diabetes mellitus | 26 (12.8%) | 91 (27.6%) | 129 (27.9%) | 66 (30.4%) | 312 (25.7%) | 1212 (85.7%) |
| BMI ≥ 30 kg/m ² | 57 (24.5%) | 152 (39.2%) | 199 (38.4%) | 68 (28.3%) | 476 (34.5%) | 1379 (97.5%) |

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

Abbreviations: BMI, body mass index; PAH, pulmonary arterial hypertension; I/D/H-PAH, idiopathic, drug-associated or hereditary PAH; CTD, connective tissue disease; HIV, human immunodeficiency virus; PoPH, portopulmonary hypertension; CHD, congenital heart disease; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain

natriuretic peptide; RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO₂, mixed-venous oxygen saturation; DLCO, diffusion capacity of the lung for carbon monoxide; CCB, calcium channel blocker; ERA endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; PCA, prostacyclin analogues

Table S2: PAH medications used at the time of the first follow-up visit

| | Low risk n=240 (17.0%) | Intermediate low risk n=395 (27.9%) | Intermediate high risk n=534 (37.8%) | High risk n=245 (17.3%) | All n=1414 (100%) |
|--|------------------------------|--|---|-------------------------------|-------------------------|
| Therapy (n=1,414) | | | | | |
| CCB | 28 (11.7%) | 13 (3.3%) | 16 (3.0%) | 2 (0.8%) | 59 (4.2%) |
| ERA | 139 (57.9%) | 183 (46.3%) | 239 (44.8%) | 66 (26.9%) | 627 (44.3%) |
| PDE5i/sGCs | 183 (76.2%) | 328 (83.0%) | 425 (79.6%) | 205 (83.7%) | 1141 (80.7%) |
| PCA | 10 (4.2%) | 20 (5.1%) | 26 (4.9%) | 14 (5.7%) | 70 (5.0%) |
| Monotherapy | 122 (50.8%) | 249 (63.0%) | 346 (64.8%) | 189 (77.1%) | 906 (64.1%) |
| Combination therapy | 114 (47.5%) | 139 (35.2%) | 172 (32.2%) | 45 (18.4%) | 470 (33.2%) |
| Combination therapy incl. IV/SC PCA | 2 (0.8%) | 7 (1.8%) | 6 (1.1%) | 3 (1.2%) | 18 (1.3%) |

CCB, calcium channel blocker; ERA endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; IV, intravenous; SC, subcutaneous; PCA, prostacyclin analogues

Table S3: Change in risk strata from baseline to follow-up by risk at baseline with the 3-strata model

| Risk | Low at follow-up | Intermediate at follow-up | High at follow-up | Sum |
|---------------------------------|-------------------------|----------------------------------|--------------------------|------------|
| Low at baseline | 97 | 17 | 0 | 114 |
| Intermediate at baseline | 179 | 782 | 134 | 1095 |
| High at baseline | 6 | 104 | 95 | 205 |
| Sum | 282 | 903 | 229 | 1414 |

Table S4: Change in risk strata from baseline to follow-up by risk at baseline with the 4-strata model

| Risk | Low at follow-up | Intermediate-low at follow-up | Intermediate-high at follow-up | High at follow-up | Sum |
|--------------------------------------|-------------------------|--------------------------------------|---------------------------------------|--------------------------|------------|
| Low at baseline | 63 | 8 | 2 | 0 | 73 |
| Intermediate-low at baseline | 102 | 171 | 65 | 8 | 346 |
| Intermediate-high at baseline | 71 | 198 | 387 | 139 | 795 |
| High at baseline | 4 | 18 | 80 | 98 | 200 |
| Sum | 240 | 395 | 534 | 245 | 1414 |

Figure S1: Scatterplot of different NT-proBNP cut-off values and the corresponding p-values of the long-rank test for the 369 patients with an NT-proBNP value of 300-1100 ng/l

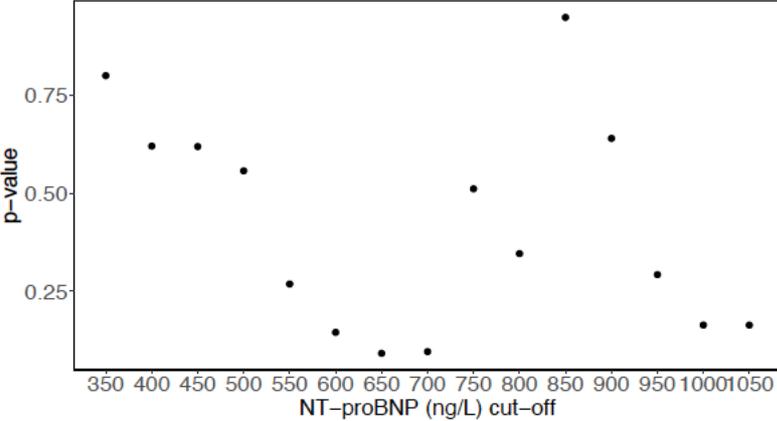
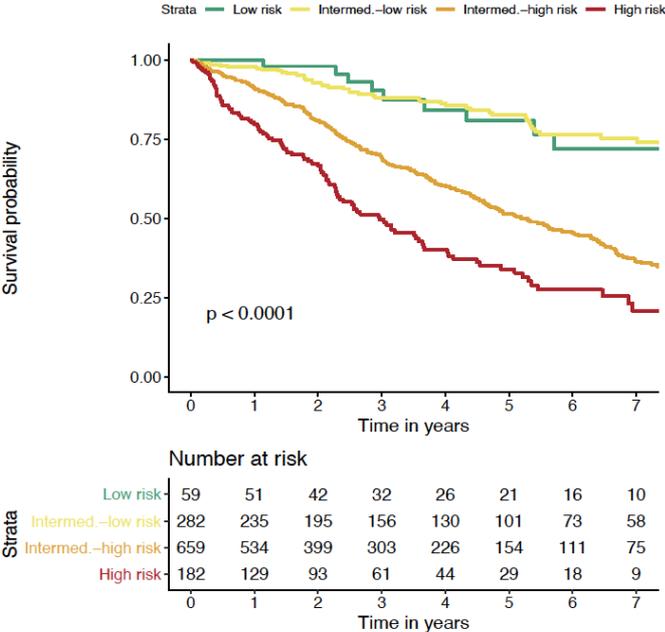


Figure S2 Kaplan-Meier survival curves based on the 4 risk strata obtained at (a) baseline and (b) at first follow-up for the subgroup of patients with idiopathic, heritable and drug-associated PAH

(a)



(b)

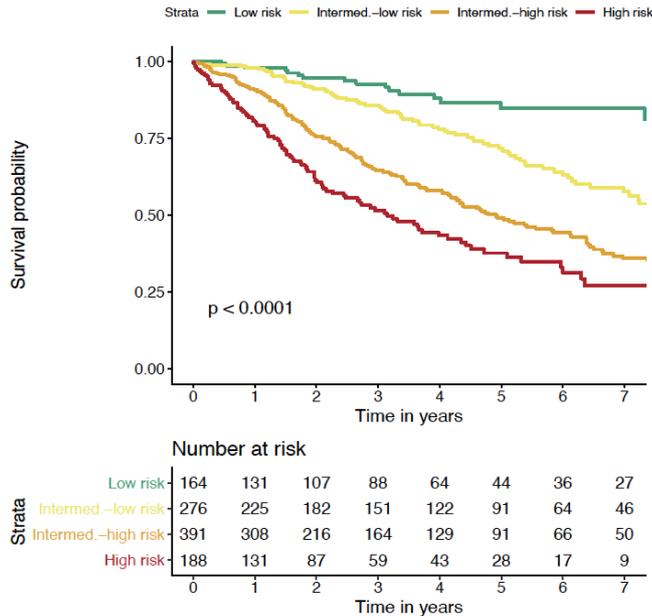
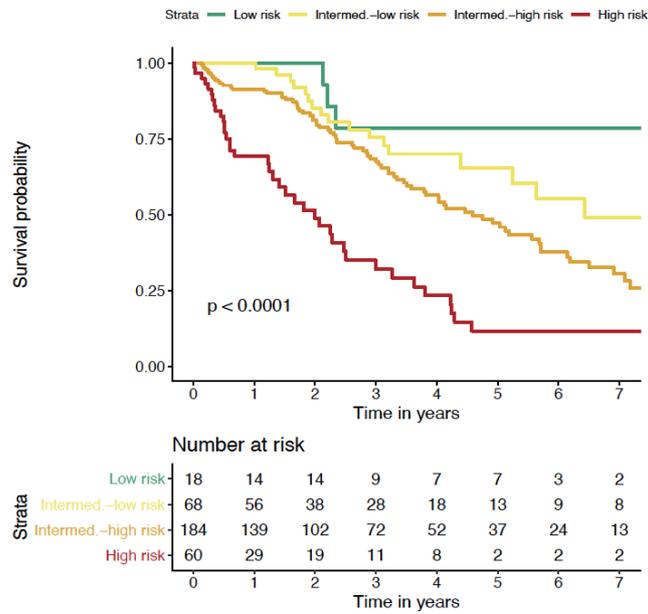


Figure S3 Kaplan-Meier survival curves based on the 4 risk strata obtained at baseline and at first follow-up for the subgroup of patients with connective tissue disease-associated PAH

(a)



(b)

