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# Prognostic value of improvement endpoints in pulmonary arterial hypertension trials: A COMPERA analysis

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**KEYWORDS:**
pulmonary arterial hypertension;
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endpoints;
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**BACKGROUND:** The prognostic value of improvement endpoints that have been used in clinical trials of treatments for pulmonary arterial hypertension (PAH) needs to be further investigated.

**METHODS:** Using the COMPERA database, we evaluated the prognostic value of improvements in functional class (FC) and absolute or relative improvements in 6-min walking distance (6MWD) and N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP). In addition, we investigated multicomponent endpoints based on prespecified improvements in FC, 6MWD and NT-proBNP that have been used in recent PAH trials. Finally, we assessed the predictive value of improvements determined by risk stratification tools. The effects of changes from baseline to first follow-up (3-12 months after initiation of PAH therapy) on consecutive survival were determined by Kaplan-Meier analysis with Log-Rank testing and Cox proportional hazard analyses.

**RESULTS:** All analyses were based on 596 patients with newly diagnosed PAH for whom complete data were available at baseline and first follow-up. Improvements in FC were associated with improved survival, whereas absolute or relative improvements in 6MWD had no predictive value. For NT-proBNP, absolute declines conferred no prognostic information while relative declines by ≥35% were associated with better survival. Improvements in multicomponent endpoints were associated with improved survival and the same was found for risk stratification tools.

**CONCLUSION:** While sole improvements in 6MWD and NT-proBNP had minor prognostic relevance, improvements in multicomponent endpoints and risk stratification tools based on FC, 6MWD, and NT-proBNP were associated with improved survival. These tools should be further explored as outcome measures in PAH trials.

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Over the past 2 decades, the pulmonary arterial hypertension (PAH) field has witnessed an evolution not only in the availability of treatment options but also in the design of clinical trials. While most of the earlier PAH trials have used the change in 6-min walking distance (6MWD) after 3 to 6 months of therapy as primary outcome measure,[1-5] more recent trials have focused on demonstrating a delay in clinical worsening.[6-10] This shift was primarily due to the observation that improvements in 6MWD have limited prognostic value.[11-13] However, the trials aiming at demonstrating effects on clinical worsening required larger sample sizes and longer follow-up periods than the trials aiming at improving 6MWD.[7-9,14] In addition, the clinical worsening endpoint does not capture clinical improvement, which is a major drawback when compounds are being investigated that primarily aim at improving hemodynamics, right ventricular function, and exercise capacity.

Demonstrating a reduction in clinical worsening events is a particular problem in trials enrolling patients who are already receiving optimized medical therapy, many of whom tend to be stable over extended periods of time. An example was the recent *Sotatercept for Pulmonary Arterial hypertension* (PULSAR) study,[15] in which 106 patients were randomly assigned to receive sotatercept or placebo in addition to background therapy over a 24-week period. The patients had to be stable in functional class (FC) II or III at enrolment. More than half of them were receiving triple combination therapy with endothelin receptor antagonists, agents acting on the prostacyclin pathway, and phosphodiesterase-5 inhibitors (PDE5i) or soluble guanylate cyclase stimulators, respectively. While sotatercept improved hemodynamic, FC, 6MWD, and serum levels of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), there was no effect on clinical worsening with 2 events in the placebo group and one event in the active treatment group.

To overcome the limitations of established endpoints, novel outcome measures have been introduced to detect clinical improvements by combining parameters which have

Take home message: Improvements in multicomponent endpoints based on functional class, 6 min walking distance and NT-proBNP and improvements in risk have prognostic value in patients with pulmonary arterial hypertension.

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prognostic value.[15,16] This includes established risk stratification tools [17-20] as well as newly designed models looking at multicomponent improvement endpoints, that is, prespecified combined changes in FC, 6MWD and NT-proBNP. Such endpoints have recently been included as primary outcome measure in the *Riociguat replacing PDE5i therapy evaluated against continued PDE5i therapy* (REPLACE) study and as exploratory endpoint in the PULSAR trial.[15,16] In both studies, the multicomponent improvement endpoints were met. However, the duration of these trials was too short to determine whether improvements in multicomponent endpoints translated into improved long-term survival. So far, none of these tools has been sufficiently validated to be acceptable for regulatory agencies as a primary outcome measure in pivotal PAH trials.

Herein, we assessed the *Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension* (COMPERA) database to analyze the prognostic value of improvements in a variety of outcome measures including multicomponent improvement endpoints and established risk stratification tools.

## Methods

### Database

Details of COMPERA (www.COMPERA.org; registered at Clinicaltrials.gov under the identifier NCT01347216) have been previously reported.[18,21,22] Briefly, 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 prior to inclusion.

### Patients

For the present analysis, patients were selected from the COMPERA database by the following criteria: (i) treatment-naïve patients aged 18-80 years newly diagnosed with PAH between January 1st, 2009, and December 31st, 2020; (ii) hemodynamic at baseline showing mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR > 3 WU (240 dyn•s•cm$^{-5}$), and (iii) all three variables of interest (FC, 6MWD, NT-proBNP) available at baseline and at first follow-up (3-12 months after treatment initiation). Patients with other forms of pulmonary hypertension (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 hemangiomatosis.

### Evaluation of endpoints

This analysis was done in three parts: First, we assessed the prognostic value of improvements in FC, 6MWD and NT-proBNP from baseline to first follow-up looking at (i) any improvement in FC versus no improvement or worsening in FC; (ii) the subgroup of patients in FC III at baseline who improved to FC I or II; (iii) improvement in 6MWD per 10 m intervals, up to ≥80 m; (iv) improvement in 6MWD per 5% intervals, up to ≥40%; (v) improvement in NT-proBNP per 10% intervals, up to ≥80%; and (vi) improvement in NT-proBNP per 100 ng/L intervals, up to 800 ng/L.

Next, we evaluated the prognostic value of multicomponent improvement endpoints used in previous studies: (i) the REPLACE endpoint,[16] where at least 2 out of the 3 following criteria had to apply: improvement from FC III to FC I/II, 6MWD increase by ≥30 m or by ≥10%; reduction in NT-proBNP by ≥30%; (ii) a modified REPLACE endpoint using the same criteria but including patients in any FC; (iii) the PULSAR endpoint,[15] where all of the following criteria had to apply: improvement from FC III to FC I/II or maintenance of FC I/II; 6MWD increase by ≥30 m; reduction in NT-proBNP by ≥30% or maintenance of NT-proBNP <300 ng/L; (iv) a modified PULSAR endpoint using the same criteria but including patients in any FC.

Finally, we analyzed the prognostic value of risk stratification tools: (i) ESC/ERS 3-strata model:[18,20] 1, 2, or 3 points were assigned to FC I/II, III and IV, 6MWD >440 m, 165 to 440 m and <165 m, and NT-proBNP <300 ng/L, 300 to 1,400 ng/L, and >1,400 ng/L, respectively, followed by calculation of the rounded average value to determine individual risk (1 = low, 2 = intermediate, 3 = high risk); (ii) ESC/ERS 4-strata model[23,24]: 1, 2, 3, or 4 points were assigned to FC I/II (1 point), III (3 points) and IV (4 points) 6MWD >400 m, 320 to 440 m, 165 to 319 m and <165 m, and NT-proBNP <300 ng/L, 300 to 649 ng/l, 650 to 1,100 ng/L and >1,100 ng/L, respectively, followed by calculation of the rounded average value to determine individual risk; and (iii) French non-invasive model[17]: The number of variables meeting the low risk criteria (FC I/II, 6MWD >440 m, and NT-proBNP <300 ng/L) was calculated.

For all endpoints, comparisons were made between patients in whom the improvement criteria were met and patients in whom the criteria were not met.

### Statistical analyses

This was a posthoc analysis of prospectively collected data. Categorical data are presented as number and percentage, continuous data as mean ± standard deviation (SD) or as median and first and third quartile [Q1, Q3]. The data set as of September 1st, 2021, was analyzed. First follow-up was defined as first follow-up visit within 3 to 12 months after treatment initiation. 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. Survival analyses were done from first follow-up, which was set as landmark.[25] Comparisons were made according to improvements in the respective measurements from baseline to first follow-up using Kaplan-Meier analysis and log-rank test. For 6MWD increase by ≥30 m, decline in NT-proBNP by ≥30% and the multicomponent improvement endpoints, additional Cox proportional hazard analyses were performed to determine the effect size.

All statistical analyses were performed using R version 4.0.0.

## Results

### Patient characteristics, treatment, and survival of the entire cohort

Out of 2,560 patients with PAH, 596 patients had complete documentation of all required variables and were included

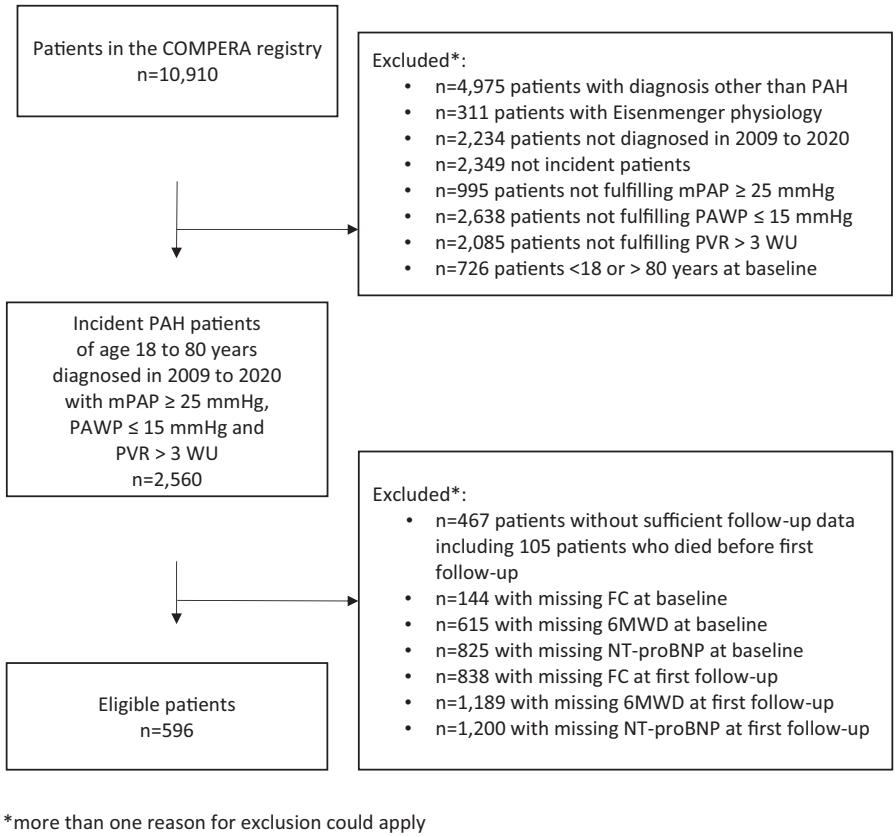


**Figure 1** STROBE diagram showing patient eligibility for analysis.

in the present analysis (Figure 1). The patient characteristics including the PAH medications used at baseline and first follow-up are shown in Table 1. A comparison of included and excluded patients is shown in Table S1 of the appendix. Compared to included patients, excluded patients were slightly older, more often male, and had more severely impaired exercise capacity; otherwise, both groups were comparable.

The first follow-up visit took place 4.1 (3.4, 5.5) months after baseline. The median observation time after the first follow-up visit was 3.0 years. During the observation period, 189 (31.7%) patients died, 8 (1.3%) underwent lung transplantation, and 34 (5.7%) were lost to follow-up. The estimated survival rates of the entire cohort were 95.0% after 1 year, 76.3% after 3 years and 65.5% after 5 years.

## Improvements in single variables from baseline to first follow-up and consecutive survival

*FC* - Improvements in FC from baseline to first follow-up were observed in 210 (35.2%) patients, and patients who improved their FC had a better long-term survival than patients who did not improve ($p = 0.0015$; Figure 2A). Similar results were obtained for patients (37.4%) presenting in FC III at baseline who improved to FC I or II ($p < 0.0001$; Figure 2B).

*6MWD* – Absolute and relative improvements in 6MWD ranging from 1 to 80 m and 1-40%, respectively, were not associated with improved survival. This included increases in 6MWD by ≥30 m or ≥10% from baseline, which both were not associated with a long-term survival benefit ($p = 0.28$ and $p = 0.88$, respectively). Detailed information on the prognostic impact of improvements in 6MWD are provided in Figures S1a and S1b of the supplementary material.

*NT-proBNP* - Absolute reductions in NT-proBNP were not associated with improved long-term survival as shown in Figure S2a of the supplementary material. In contrast, relative reductions expressed in percent of baseline values were associated with improved survival rates. No significant improvements in survival were associated with NT-proBNP reductions by 15% ($p = 0.08$), 20% ($p = 0.10$), 25% ($p = 0.069$), and 30% ($p = 0.1$), while significant survival benefits were seen with NT-proBNP improvements of 35% ($p = 0.006$) and 40% ($p = 0.037$), respectively. However, 35% and 40% reductions in NT-proBNP were achieved only in 28.3% and 19.8%, respectively, of the patients (Figure S2b in the supplementary material).

## Multicomponent improvement endpoints used in previous clinical trials

*REPLACE endpoint* – Of the 438 patients presenting in FC III at baseline, 231 (52.7%) met the REPLACE endpoint, and these patients had a better long-term survival than

**Table 1** Patient Characteristics and Treatments for Pulmonary Arterial Hypertension at Inclusion and First Follow-Up

| | Baseline (n = 596) | First follow-up (n = 596) |
|---|---|---|
| Age, years | 61.0 (15.7) | |
| Female | 397 (66.6%) | |
| BMI, kg/m$^2$ | 28.6 (6.3) | |
| Diagnosis | | |
| I/H/D-PAH | 430 (72.1%) | |
| PAH-CTD | 111 (18.6%) | |
| PAH-CHD | 19 (3.2%) | |
| PAH-HIV | 5 (0.8%) | |
| PoPH | 31 (5.2%) | |
| WHO FC | | |
| I | 5 (0.8%) | 20 (3.4%) |
| II | 113 (19.0%) | 260 (43.6%) |
| III | 438 (73.5%) | 299 (50.2%) |
| IV | 40 (6.7%) | 17 (2.9%) |
| 6MWD, m | 316.6 (130.4) | 358.3 (129.8) |
| NT-proBNP, ng/L | 1,347 [433, 3214] | 589 [203, 1664] |
| Hemodynamics | | |
| RAP, mmHg | 8.6 (4.8) | |
| mPAP, mmHg | 45.5 (13.0) | |
| PAWP, mmHg | 9.1 (3.4) | |
| CI, L/min/m$^2$ | 2.3 (0.7) | |
| PVR, WU | 9.6 (5.2) | |
| $SvO_2$, % | 63.4 (8.5) | |
| Comorbidities | | |
| Arterial hypertension | 290 (56.2%) | |
| Coronary heart disease | 116 (23.6%) | |
| Diabetes mellitus | 125 (24.4%) | |
| Obesity[a] | 221 (37.8%) | |
| Atrial fibrillation | 83 (15.0%) | |
| Therapy[b] | | |
| CCB | 28 (4.7%) | 28 (4.7%) |
| ERA | 235 (39.4%) | 321 (53.9%) |
| PDE5i/sGCs | 465 (78.0%) | 487 (81.7%) |
| PCA | 21 (3.5%) | 46 (7.7%) |
| Monotherapy | 454 (76.2%) | 326 (54.7%) |
| Combination Therapy | 142 (23.8%) | 262 (44.0%) |
| Combination therapy incl IV/SC prostacyclin analogues[c] | 8 (1.3%) | 11 (1.8%) |

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

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; CCB, calcium channel blocker; CHD, congenital heart disease; CTD, connective tissue disease; ERA endothelin receptor antagonists; HIV, human immunodeficiency virus; I/D/H-PAH, idiopathic, drug-associated or hereditary PAH; IV/SC, intravenous/subcutaneous; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitors; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial pressure; sGCs, stimulator of soluble guanylate cyclase; $SvO_2$, mixed-venous oxygen saturation; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance.

[a]BMI ≥30 kg/m$^2$.

[b]Patients could receive more than one treatment.

[c]Intravenous epoprostenol, intravenous iloprost, intravenous or subcutaneous treprostinil.

patients who did not meet this endpoint ($p$ = 0.0025; Figure 3A).

*Modified REPLACE endpoint* - The modified REPLACE endpoint was met by 60.7% of the patients, and patients who met this endpoint had a better long-term survival than patients who did not meet this endpoint ($p < 0.0001$; Figure 3B).

*PULSAR endpoint* - Of the 556 patients presenting in FC I, II or III at baseline, 134 (24.1%) met the PULSAR endpoint, and these patients had a better long-term survival than patients who did not meet this endpoint ($p$ = 0.00023; Figure 3C).

*Modified PULSAR endpoint* - The modified PULSAR endpoint was met by 26.7% of the patients, and patients who met this endpoint had a better long-term survival than patients who did not meet this endpoint ($p$ = 0.00015; Figure 3D).

## Risk assessment tools

*ESC/ERS 3-strata and 4-strata models* - With the ESC/ERS 3-strata model, 39.3% of the patients had an improvement in risk, and patients who improved risk had a better long-term survival than patients who did not ($p < 0.0001$; Figure 4A). With the 4-strata model, 51.0% of the patients had an improvement in risk, and the consecutive survival was better in patients who improved their risk category versus those who did not ($p < 0.0001$; Figure 4B).

*French model* - With the French noninvasive risk stratification model, 46.3% of the patients had an improvement in the number of variables meeting the low risk criteria, and patients who improved their risk profile had a better long-term survival than patients who did not ($p < 0.0001$; Figure 4C).

Figure 5 depicts the hazard ratios and 95% confidence intervals for the survival effects associated with meeting selected individual endpoints and the multicomponent endpoints evaluated in the present study. More than 50% reductions in the relative risk of death were observed with the PULSAR endpoints, the ESC/ERS 3-strata model and the French model.

## Discussion

Our study showed that improvements in FC were associated with improved consecutive survival, while improvements in NT-proBNP had relatively little and improvements in 6MWD no predictive value. In contrast, improvements in multicomponent endpoints and risk stratification tools were associated with better long-term survival.

The prognostic relevance of improvements in FC has been reported before.[18,19,26-28] The same is true for the lack of association between improvements in 6MWD and survival, [11-13] which have led to discussions about the usefulness of changes in 6MWD as primary endpoint in clinical trials.[14] However, 6MWD is a measurement of exercise capacity, which is relevant on its own in a disease where impaired exercise capacity is the leading symptom.

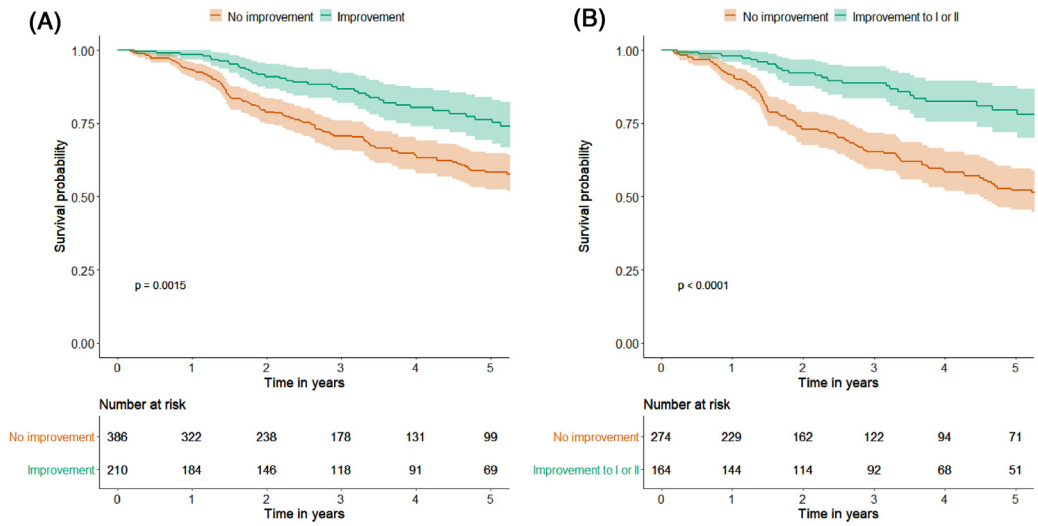


**Figure 2** Kaplan-Meier survival estimates in patients who had an improvement from baseline to first follow-up in functional class (A) or whose functional class improved from functional class III to I/II (B). Analyses were performed on all 596 patients (A) and on the 438 patients who presented in functional class III at enrolment (B). Kaplan-Meier survival estimates were done for patients who improved functional class from baseline to the first follow-up assessment and patients whose functional class did not change or deteriorate. Statistical comparisons were made with the Log-Rank test.

Improvements by ≥30 m are considered relevant to patients as they are associated with improved quality of life,[29] which justifies inclusion of this criterion in multicomponent endpoints.

NT-proBNP has been identified as independent prognostic variable in PAH.[17,18,26] Still, the prognostic significance of improvements in NT-proBNP is unclear, and previous studies have yielded conflicting results. Mauritz et al. reported that a 15% decline in NT-proBNP translated into better outcomes,[30] whereas Fritz and al. found that changes in BNP were not predictive of subsequent survival.[13] In the present study, absolute declines in NT-proBNP up to 800 ng/l were not prognostic, while relative declines by ≥35% were associated with improved survival.

Multicomponent endpoints have been introduced with the intention to detect improvements that are clinically relevant but also have prognostic value. Validation of this concept, however, is pending. In the REPLACE study, a randomized, open-label study that assessed the effects of switching from phosphodiesterase-5 inhibitors to riociguat, the multicomponent improvement endpoint was used as primary outcome measure and was met by 41% of the patients who switched therapies compared to 20% of the patients who maintained their treatment.[16] In our present study, 53% of the patients met the REPLACE improvement criteria and these patients had a survival benefit.

In the PULSAR study, a randomized, double-blind, placebo-controlled study, which investigated the effects of sotatercept in patients with PAH, the multicomponent improvement endpoint, an exploratory outcome measure, was met by 38% of the patients who received active drug compared to 3% of the patients who received placebo.[15] The main difference between the REPLACE and the PULSAR endpoints was that REPLACE required two of three criteria to be met whereas in PULSAR, all components had to be met. Hence, it is not surprising that in our analysis, fewer patients met the PULSAR criteria than the REPLACE criteria. In our present analysis, the PULSAR multicomponent improvement endpoint was met by 24% of the patients, and achieving this endpoint was associated with a more than 50% relative risk reduction in consecutive mortality.

Like the multicomponent endpoints, all risk stratification tools investigated in the present analysis proved potentially useful as 39% to 51% of patients met the improvement criteria, and meeting these criteria was associated with a relative risk reduction of death by approximately 50%. The predictive value of the ESC/ERS 3-strata model[18,20] was slightly higher than that of the 4-strata model,[23,24] but the improvement endpoint was met by more patients with the 4 strata-model. The French non-invasive model[17] was sensitive to changes in risk and had strong prognostic value.

To be useful as outcome measures in PAH trials, endpoints need to be clinically relevant and must be accepted by key stakeholders including patients, physicians, regulatory agencies, and payors. Change in 6MWD is still accepted as primary outcome measure by regulatory agencies as a measure of functional capacity, that is, one of the components of the Food and Drug Administration's *feels, functions or survives* principle.[31] However, given the lack of association between 6MWD improvement and survival, change in 6MWD alone is viewed with skepticism by patients, physicians, and payors.[14]

Time to clinical worsening is increasingly used as primary endpoint in PAH trials. Slowing disease progression is undoubtedly an important treatment objective in a progressive disease, and events of clinical worsening signal an increased mortality risk.[32] However, demonstrating effects on clinical worsening requires large study populations and long observation times. Improving hemodynamic, right

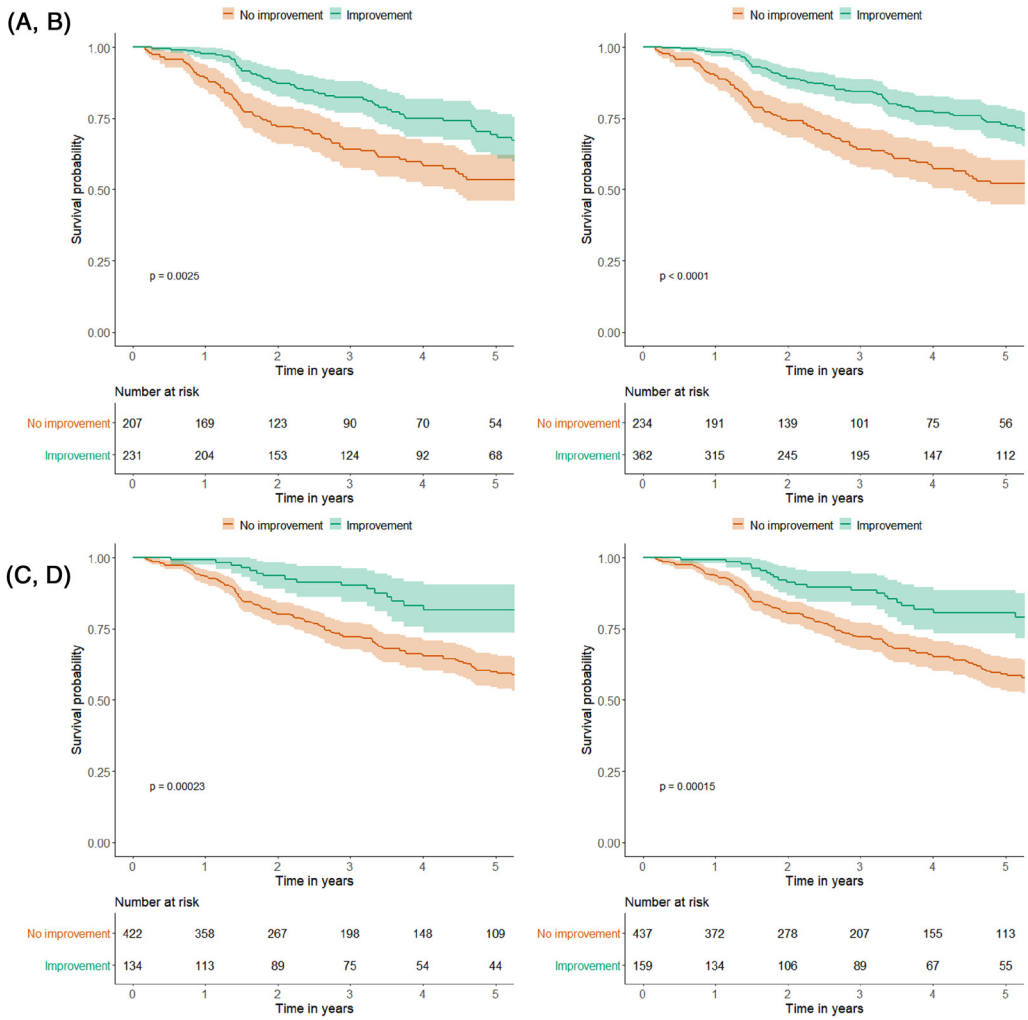


**Figure 3** Kaplan-Meier survival estimates in patients who had an improvement from baseline to first follow-up with the REPLACE endpoint (A), the modified REPLACE endpoint, (B) the PULSAR endpoint (C), and the modified PULSAR endpoint (D). Analyses were based on the multicomponent improvement endpoints that have been used in the REPLACE study and the PULSAR trial and utilized prespecified improvements in functional class, 6 min walking distance and N-terminal fragment of pro-brain natriuretic peptide. The original REPLACE endpoint was based on patients presenting at FC III at enrolment; the modified REPLACE endpoint could be used with any FC at baseline. The original PULSAR endpoint was based on FC I, II or III at enrolment, whereas any FC was allowed for the modified PULSAR endpoint.

Kaplan-Meier survival estimates were done for patients whose endpoint improved from baseline to the first follow-up assessment and patients whose endpoint did not change or deteriorate. Statistical comparisons were made with the Log-Rank test.

ventricular function and exercise capacity are key treatment objectives in a debilitating disease like PAH, and some of these components are incorporated in the composite endpoints studied in the present analysis. Still, to be acceptable for authorities, all components need to be relevant to the patients, which may be the case for improvements in FC and 6MWD but not for improvements in NT-proBNP.[31] Eventually, a multicomponent tool may become an accepted and validated surrogate endpoint, that is, a substitute for a patient relevant endpoint, by demonstrating strong and robust predictive value.[31] The present study may be a first step to validate multicomponent endpoints, but additional confirmation from prospective clinical trials is required before health authorities may consider such outcome measures as surrogate endpoints in PAH trials.[14,31]

Risk stratification tools may be better suited as surrogate endpoints than multicomponent improvement endpoints for several reasons: First, they capture clinical improvement and clinical worsening at the same time, which may be advantageous when calculating statistical power and sample sizes of clinical trials.[33,34] Second, the prognostic value of risk stratification tools has already been validated in several registry studies and posthoc analyses of clinical trials.[17,18,20,26,35] Third, our present study shows that the number of patients meeting the endpoint criteria was comparable for multicomponent endpoints and risk stratification tools, and the same was true for the prognostic value. Fourth, there will be no progress when each new trial invents its own endpoints.

Our study has strengths and limitations: Strengths include the relatively large number of well-characterized patients for whom complete data were available as well as the relatively long follow-up period. Limitations include the high number of patients who were not eligible for the present analysis because of missing values. While we cannot fully exclude a selection bias, the baseline

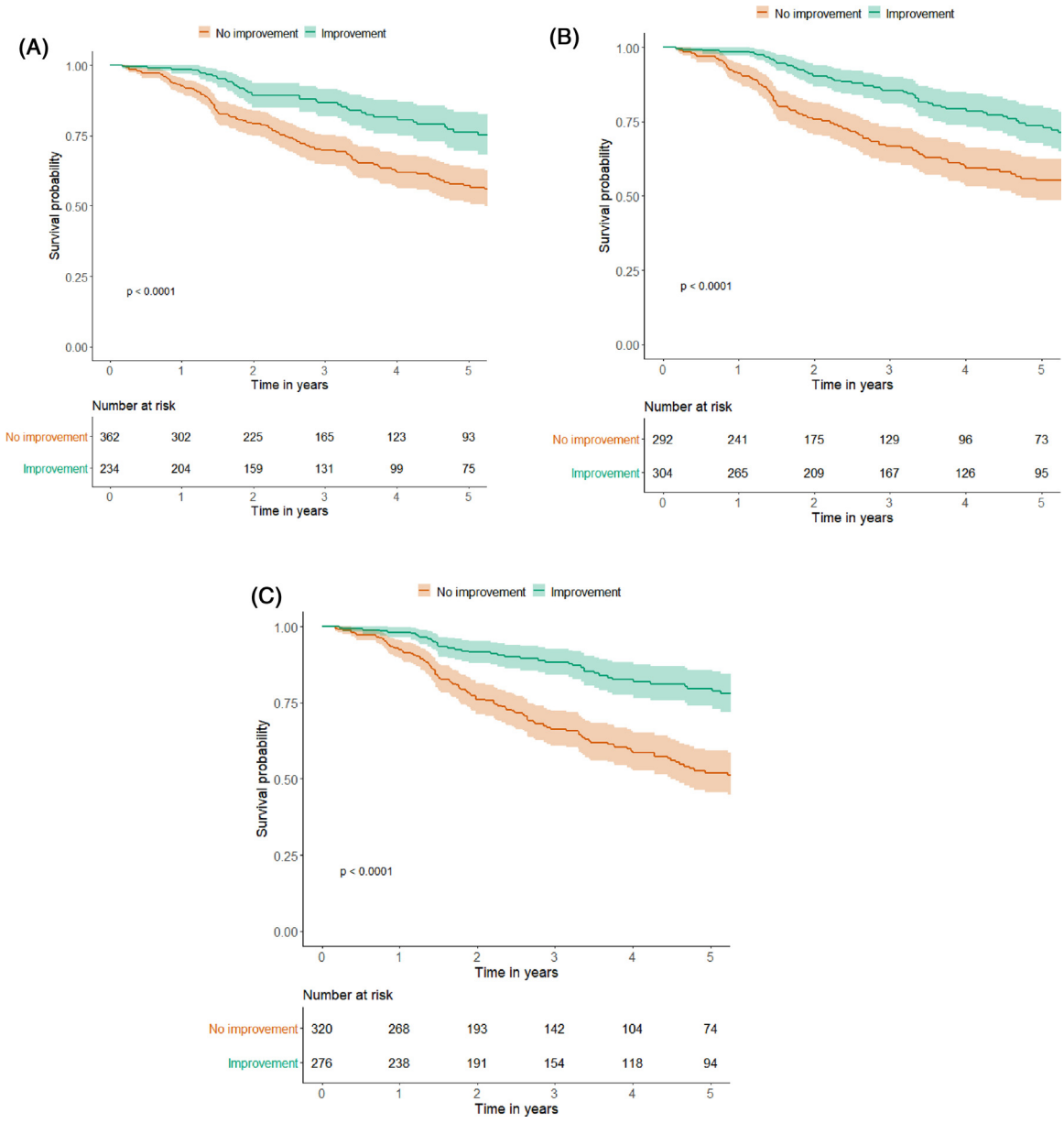


**Figure 4** Kaplan-Meier survival estimates in patients who had an improvement from baseline to first follow-up with the ESC/ERS 3-strata risk model (A), the ESC/ERS 4-strata risk model (B), and the French non-invasive risk stratification model (C). Analyses were based on improvements in risk using various established risk stratification tools, sometimes with modifications. Risk was based on pre-specified thresholds for functional class, 6 min walking distance and N-terminal fragment of pro-brain natriuretic peptide. Details on risk calculation are described in the text. Kaplan-Meier survival estimates were done for patients who improved risk from baseline to the first follow-up assessment and patients in whom risk did not change or deteriorate. Statistical comparisons were made with the Log-Rank test.

characteristics of included and excluded patients were similar, so that we assume that data were randomly missing. In addition, the observed treatment effects were obtained from treatment-naïve patients. In clinical trials, investigational treatments are given as add-on medication to established therapies, and the magnitude of effect may differ.

Our data have been collected over a long period, and treatment strategies have changed with an increasing use of combination therapy over time.[22,36] It is therefore possible that our findings may not fully apply to patients receiving contemporary treatments. In addition, the patients in the present series were older and had more co-morbidities than a typical PAH trial population. Furthermore, the median observation period of 4.1 months between baseline and first follow-up was shorter than the 24-week follow-up, which has been commonly used in more recent clinical trials. It is possible that the shorter follow-up interval may have affected our results, although FC, 6MWD and NT-proBNP usually do no change substantially between week 16 and week 24 after treatment initiation.[16,37,38] Finally, we were unable to evaluate REVEAL[19] and REVEAL lite 2,[26] which are widely used risk stratification tools, as some of the required variables were not captured in the COMPERA database.

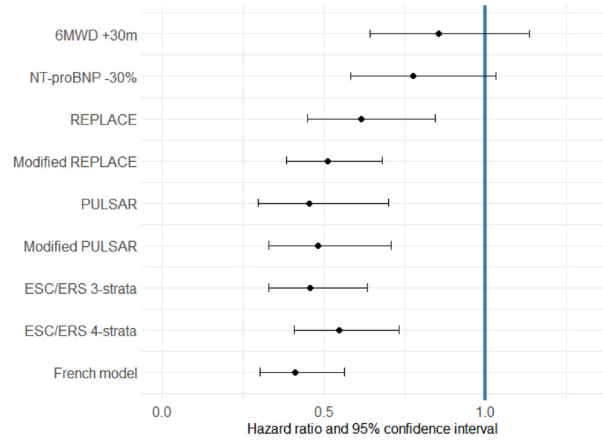


**Figure 5** Mortality risk determined by Cox proportional hazard analysis following improvements from baseline to first follow-up in selected variables. Hazard ratio (with 95% confidence intervals) as determined by Cox proportional hazard analyses depicting the relative risk of death depending on improvement versus no improvement in the respective endpoints.

Abbreviations: 6MWD, 6-min walking distance; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; the study acronyms and risk assessment tools are described in the text.

In conclusion, our data suggest that improvements in multicomponent endpoints and established risk stratification models predict survival. These tools should be further investigated as outcome measures in PAH trials to determine whether they may eventually become acceptable surrogate endpoints in the future.

## Author contributions

MMH: Study conceptualization, supervision, data collection, drafting of the manuscript and approval of the final draft for submission; CP: statistical analysis, review and editing of the manuscript draft, and approval of the final draft for submission; KMO: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; DH: statistical analysis, review and editing of the manuscript draft, and approval of the final draft for submission; DP: supervision, review and editing of the manuscript draft, and approval of the final draft for submission; EG: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; GS: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; CDV: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; HG: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; OD: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; CO: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; JSRG: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; MD: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; HAG: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; RE: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; HK: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; HJK: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; DS: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; JB: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; KM: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; MHa: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; HW: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; HJS: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; MHe: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; DD: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; IT: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; AVN: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; SU: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; HK: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; MC: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; SE: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; KHS: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; SR: data collection, review and editing of the manuscript draft, and approval of the final draft for submission; TJL: data collection, review and editing of the manuscript draft, and approval of the final draft for submission.

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## Supplementary materials

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