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Risk assessment in pulmonary arterial hypertension: Insights from the GRIPHON study

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low-risk profile;
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BACKGROUND: Approaches to risk assessment in pulmonary arterial hypertension (PAH) include the noninvasive French risk assessment approach (number of low-risk criteria based on the European Society of Cardiology and European Respiratory Society guidelines) and Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) 2.0 risk calculator. The prognostic and predictive value of these methods for morbidity/mortality was evaluated in the predominantly prevalent population of GRIPHON, the largest randomized controlled trial in PAH.

METHODS: GRIPHON randomized 1,156 patients with PAH to selexipag or placebo. Post-hoc analyses were performed on the primary composite end-point of morbidity/mortality by the number of low-risk criteria (World Health Organization functional class I-II; 6-minute walk distance >440 m; N-terminal pro-brain natriuretic peptide <300 ng/liter) and REVEAL 2.0 risk category. Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazard models.

RESULTS: Both the number of low-risk criteria and the REVEAL 2.0 risk category were prognostic for morbidity/mortality at baseline and any time-point during the study. Patients with 3 low-risk criteria at baseline had a 94% reduced risk of morbidity/mortality compared to patients with 0 low-risk criteria and were all categorized as low-risk by REVEAL 2.0. The treatment effect of selexipag on morbidity/mortality was consistent irrespective of the number of low-risk criteria or the REVEAL 2.0 risk category at any time-point during the study. Selexipag-treated patients were more likely to increase their number of low-risk criteria from baseline to week 26 than placebo-treated patients (odds ratio 1.69, $p = 0.0002$); similar results were observed for REVEAL 2.0 risk score.

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CONCLUSIONS: These results support the association between risk profile and long-term outcome and suggest that selexipag treatment may improve risk profile.
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With the availability of numerous treatment options, risk assessment in pulmonary arterial hypertension (PAH) has become essential in informing treatment decisions based on patient prognosis.[1−4] The 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines recommend (1) classifying patients as at low, intermediate, or high risk of 1-year mortality using several prognostic determinants, and (2) achieving a low-risk status as a treatment goal.[1,2] The prognostic value of ESC/ERS guidelines-based approach to assessing individual risk was recently demonstrated in analyses of newly diagnosed patients from several European registries.[5−8] The noninvasive French risk assessment method aims to identify patients maintaining or achieving a very low-risk status[5] based on the presence of 3 low-risk criteria: World Health Organization functional class (WHO FC) I-II, 6-minute walk distance (6MWD) >440 m, and N-terminal pro-brain natriuretic peptide (NT-proBNP) <300 ng/liter or brain natriuretic peptide <50 ng/liter. The number of low-risk criteria accurately predicted transplant-free survival and identified a population at very low-risk (i.e., 3 low-risk criteria) in a cohort of patients with PAH enrolled in the French registry,[5] and in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry.[8]

The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk calculator can be used to classify patients into low, intermediate, or high-risk categories based on a score derived from multiple, clinically relevant prognostic variables[9−11] and has been externally validated.[12] Additions to and adjustment of certain variables led to the development of REVEAL 2.0,[13] which was also validated.[14]

The phase III GRIPHON study,[15] the largest event-driven outcome trial to date in PAH, allows evaluation of the ability of these risk assessment approaches to predict long-term morbidity/mortality outcomes in the context of a randomized, controlled trial and in a predominantly prevalent population. GRIPHON evaluated the efficacy and safety of selexipag, an oral, selective prostacyclin receptor (IP) agonist, in 1,156 patients. Selexipag reduced the risk of the primary composite outcome of independently adjudicated morbidity/mortality events by 40% ($p < 0.001$) vs placebo.[15] The present post-hoc analyses aimed to evaluate the relationship between risk profile and long-term morbidity/mortality outcome in the large GRIPHON population using the noninvasive French approach and REVEAL 2.0, and to gain insight into the role that these risk assessment methods may have in clinical practice. The study also aimed to assess the treatment effect of selexipag vs placebo on the outcome according to risk and to evaluate whether treatment with selexipag improved risk profile.

Methods

Study design

GRIPHON (NCT01106014) was a global, double-blind, randomized, placebo-controlled, event-driven phase III study.[15] The study was conducted in accordance with the amended Declaration of Helsinki, and the protocol was reviewed by local institutional review boards. Patients were randomized (1:1) to receive selexipag or placebo, and selexipag was titrated to the highest tolerated dose or the maximum dose of 1,600 μg twice daily. Double-blind treatment continued until the occurrence of a primary end-point event, premature discontinuation of double-blind treatment, or end of the study.

Participants

GRIPHON included adult patients (aged 18−75 years) with a confirmed diagnosis of idiopathic PAH, heritable PAH, or PAH associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, drug use, or toxin exposure. Patients were required to have a pulmonary vascular resistance of ≥400 dyn × sec·cm^{-5} and a 6MWD from 50 m to 450 m. Treatment-naive patients and patients receiving a stable dose of an endothelin receptor antagonist, a phosphodiesterase-5 inhibitor, or both were eligible. Written informed consent was obtained from all patients.

Outcomes

The primary composite end-point was time from randomization to first morbidity/mortality event up to the end of double-blind treatment (defined as 7 days after the last intake of selexipag or placebo). All events were adjudicated by a blinded independent critical event committee. Criteria for morbidity events have been described (refer to Supplementary Methods available online at www.jhltonline.org). Time to death from any cause up to the end of the study was a secondary end-point.

Risk assessment

Patients were classified into subgroups according to 2 risk assessment methods: (1) Noninvasive French risk assessment approach (number of the following low-risk criteria: WHO FC I-II, 6MWD >440 m, and NT-proBNP <300 ng/liter)[5]; and (2) REVEAL 2.0 category based on REVEAL 2.0 score (low: ≤6, intermediate: 7−8, high: ≥9) (see Supplementary Methods online).[13]

Statistical analysis

All randomized patients were included in these post-hoc analyses. Kaplan-Meier estimates for the composite primary end-point (morbidity/mortality event up to end of treatment) and for all-cause mortality up to end of the study were calculated for patients grouped according to risk at baseline. Cox proportional hazard models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI) for the primary end-point according to baseline risk. The association between risk at any time during the study and the primary end-point was evaluated using time-dependent Cox proportional hazard models. Cox proportional hazard models included treatment and risk group as covariates and were either adjusted or unadjusted for other baseline covariates (see Supplementary methods online). The consistency of treatment effects across risk subgroups was assessed using interaction tests, using a significance level of 0.01 to account for the increased risk of a type 1 error associated with multiple subgroup analyses.[16] The 2 risk assessment methods were descriptively compared by assessing the baseline distribution of patients between risk categories. The proportion of patients with improvement, deterioration, or no change in risk subgroup from baseline to week 26 was determined in both treatment arms. Cochran-Mantel-Haenszel tests, adjusted for risk at baseline, were used to examine the difference in the proportions of patients with an improvement in risk between the 2 treatment arms. The treatment effect for selexipag vs placebo was expressed via a common odds ratio (OR) with corresponding 95%CI and *p*-value. For REVEAL 2.0, the test assessed improvement in REVEAL 2.0 risk score.

Imputation rules for missing data are described in the Supplementary methods (see online). All statistical analyses used SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

Of the 1,156 patients included in GRIPHON, at baseline 442 (38.2%) had 0 low-risk criteria, 419 (36.2%) had 1 low-risk criterion, 254 (22.0%) had 2 low-risk criteria and 41 (3.5%) had 3 low-risk criteria (Supplementary Figure S1A online). When stratified by REVEAL 2.0 risk category, there were 552 (47.8%), 285 (24.7%), and 319 (27.6%) patients in the low, intermediate, and high categories, respectively (Supplementary Figure S1B online). Aside from the parameters used to classify risk, baseline characteristics were generally balanced between the subgroups (Supplementary Tables S1 and S2 online); patients with more low-risk criteria and those in REVEAL 2.0 low-risk category tended to be younger than higher-risk patients.

Association between risk profile and long-term outcome

Patients with a greater number of low-risk criteria at baseline had a lower risk of experiencing a morbidity/mortality event, irrespective of assigned treatment (Figure 1) (Supplementary Figure S2A and Supplementary Table S3A online). Based on the Cox model adjusted for baseline covariates, the number of low-risk criteria present at baseline was prognostic for morbidity/mortality ($p = 0.0398$) (Supplementary Table S4A online), and this was not influenced by age. Compared with patients with 0 low-risk criteria, patients with 1, 2, or 3 low-risk criteria at baseline had a 56% (HR 0.44, 95% CI 0.35−0.56), 80% (HR 0.20, 95% CI 0.14−0.30), and 94% (HR 0.06, 95% CI 0.01−0.31) reduced risk, respectively, of experiencing a morbidity/mortality event (Supplementary Table S4A online). The number of low-risk criteria was also prognostic when risk was assessed in a time-dependent Cox model ($p < 0.0001$). The number of low-risk criteria at baseline was also prognostic for all-cause death (Supplementary Figure S3A online). Patients with 3 low-risk criteria had excellent long-term prognosis.

When risk was assessed using REVEAL 2.0, similar findings were observed (Figure 1) (Supplementary Figure S2B and Supplementary Table S3B online). The risk category at baseline was prognostic for morbidity/mortality ($p = 0.0074$) (Supplementary Table S4B online) and was not influenced by age. The risk category was also prognostic for all-cause death (Supplementary Figure S3B online). Compared with high-risk patients, a low or intermediate-risk status at baseline conferred a 78% (HR 0.22, 95% CI 0.17−0.28) or 49% (HR 0.51, 95% CI 0.40−0.66) reduced risk of experiencing a morbidity/mortality event (Supplementary Table S4B online). REVEAL 2.0 risk category was also prognostic for morbidity/mortality when risk was assessed in a time-dependent Cox model ($p < 0.0001$).

Consistent results were observed in sensitivity analyses that were not adjusted for baseline covariates other than treatment and risk group (Supplementary Table S4 online) and in analyses performed to assess the impact of missing data for the number of low-risk criteria only (data not shown).

Comparison of risk assignment between the noninvasive French risk assessment approach and REVEAL 2.0

The distribution of patients between risk groups at baseline was compared descriptively between the 2 risk assessment approaches (Table 1). All 41 patients with 3 low-risk criteria were also at low-risk according to REVEAL 2.0. Most (94.5%) patients with 2 low-risk criteria and 55.4% of those with 1 low-risk criterion were low-risk according to REVEAL 2.0. Conversely, the majority (60.6%) of patients with 0 low-risk criteria were in the high-risk REVEAL 2.0 category.

Association between risk profile and treatment response to selexipag

Selexipag reduced the risk of a morbidity/mortality event by 41% (HR 0.59; 95% CI 0.45−0.78), 35% (HR 0.65; 95% CI 0.45−0.93), and 42% (HR 0.58; 95% CI 0.31−1.08) in the subgroup of patients with 0, 1, and 2 low-risk criteria, respectively (Figure 2A), compared with placebo. The treatment effect was consistent across the subgroups (interaction *p*-value 0.931). When considering the number of low-risk criteria at any time-point during the study, the treatment effect (HR, [95% CI]) was 0.82 (0.65−1.03),

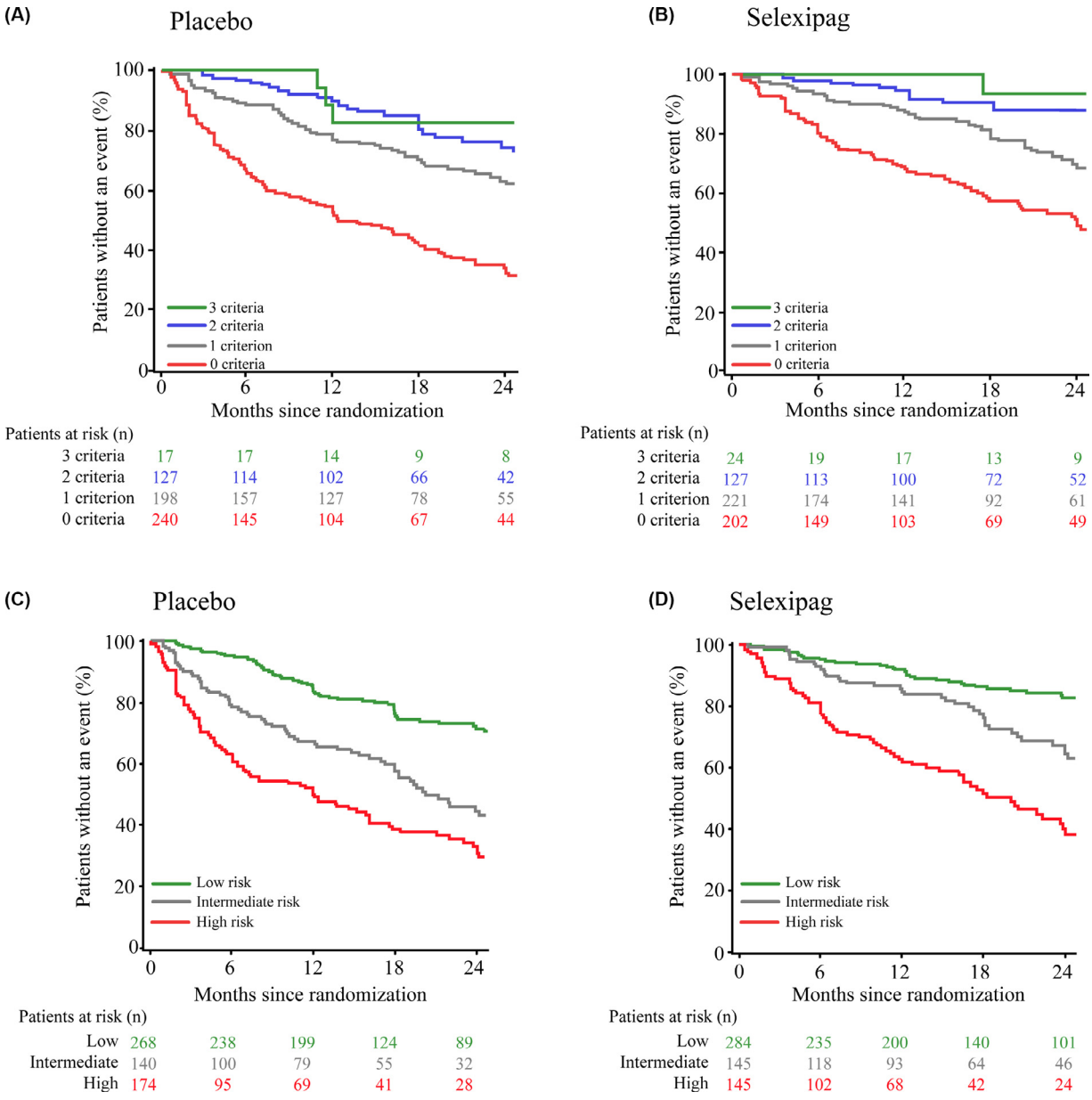

Figure 1 Time from randomization to first morbidity/mortality event based on (A, B) the number of low-risk criteria at baseline according to the noninvasive French risk assessment approach or (C, D) REVEAL 2.0 risk category at baseline. Kaplan-Meier estimates of time to first morbidity/mortality event are shown for the placebo and selexipag arms for subgroups defined according to risk at baseline. (A, B) Risk determined by the number of low-risk criteria defined according to the noninvasive French risk assessment approach (WHO FC I-II, 6MWD >440 m, and NT-proBNP <300 ng/liter). At baseline, data were missing for 1 risk criterion (NT-proBNP) in 14 patients (1.2%; 6 selexipag patients and 8 placebo patients) and were imputed as not low-risk. (C,D) Risk category determined by REVEAL 2.0 risk score at baseline: low (≤6), intermediate (7-8), high (≥9). At baseline, data were missing for 3 risk parameters in 2 patients (0.2%), 4 risk parameters in 364 patients (31.5%), 5 risk parameters in 77 patients (6.7%), 6 risk parameters in 701 patients (60.6%), 7 risk parameters in 10 patients (0.9%), and 8 risk parameters in 2 patients (0.2%). For both risk assessment methods, Kaplan-Meier curves are truncated to the point at which the number of patients at risk falls below 10% of the number of randomized patients in any of the subgroups in either treatment arm. 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; WHO FC, World Health Organization functional class.

0.59 (0.36−0.96), and 0.80 (0.26−2.50) for the subgroups of patients with 0, 1, and 2 low-risk criteria, respectively (Figure 2B). This treatment effect was also consistent across the subgroups (interaction *p*-value 0.702). HR could not be calculated in the subgroups of patients with 3 low-risk criteria because too few morbidity/mortality events occurred. For the 3 low-risk criteria subgroup, morbidity/mortality events were reported for 1 of 24 (4.2%) patients in the selexipag arm compared with 3 of 17 (17.6%) in the placebo arm (Supplementary Table S3A online).

When patients were stratified by REVEAL 2.0 risk category, the treatment effect of selexipag vs placebo on

Table 1 Distribution of Patients between Risk Groups at Baseline Categorized Using the Noninvasive French Approach and REVEAL 2.0

	Number of low-risk criteria (noninvasive French approach)[a]				
REVEAL 2.0 risk category[b]	3	2	1	0	Total
Low	41 (100.0)	240 (94.5)	232 (55.4)	39 (8.8)	552 (47.8)
Intermediate	0	12 (4.7)	138 (32.9)	135 (30.5)	285 (24.7)
High	0	2 (0.8)	49 (11.7)	268 (60.6)	319 (27.6)
Total	41 (3.5)	254 (22.0)	419 (36.2)	442 (38.2)	1,156 (100.0)

6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; WHO FC, World Health Organization functional class.

Data are number (%).

[a]Low-risk criteria defined as WHO FC I-II, 6MWD >440 m, and NT-proBNP <300 ng/liter.

[b]Defined by REVEAL 2.0 risk score at baseline: low (≤6), intermediate (7-8), high (≥9).

morbidity/mortality was consistent across subgroups defined by risk at baseline (interaction *p*-value 0.276) (Figure 3A) and in the time-dependent analysis, although in the latter the treatment effect was more pronounced in the low and intermediate-risk subgroups compared with the high-risk subgroup (interaction *p*-value 0.034) (Figure 3B).

Consistent results were reported in sensitivity analyses that were not adjusted for baseline covariates other than

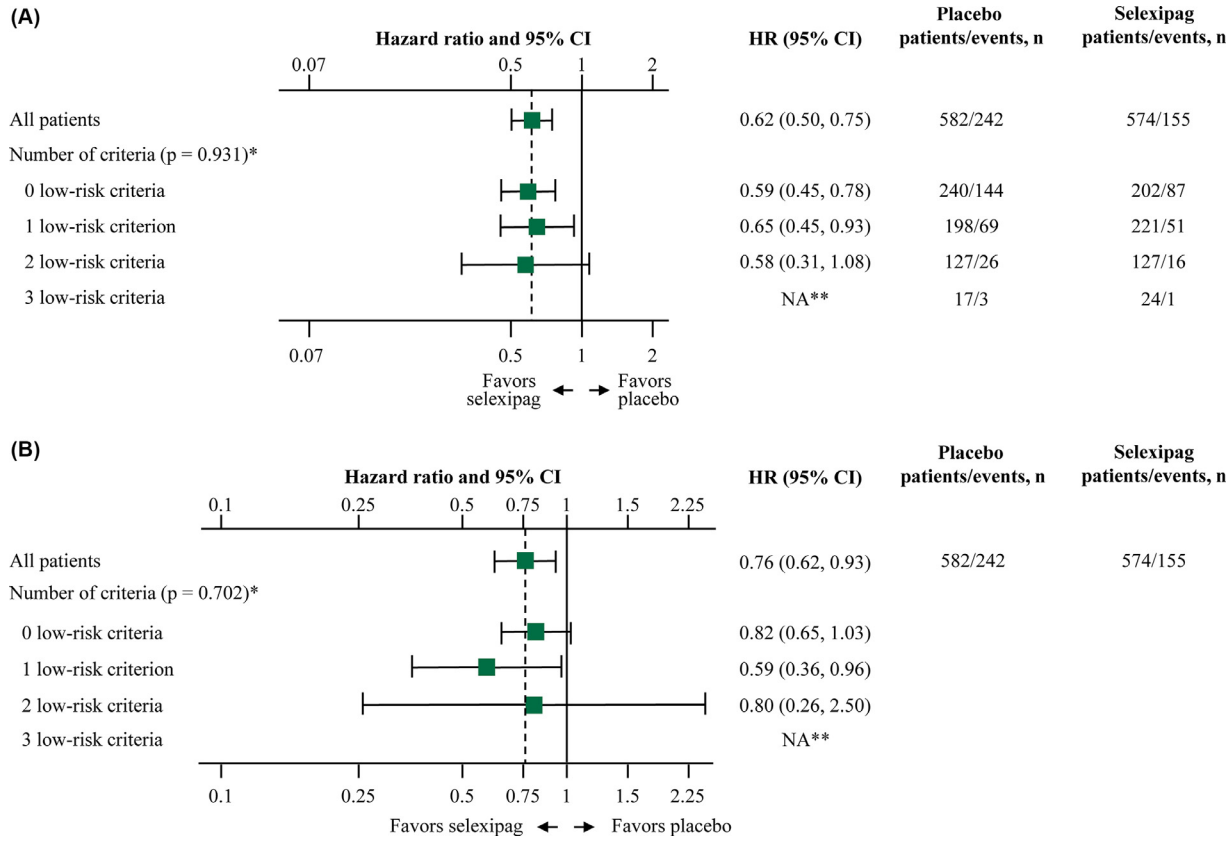

Figure 2 Effect of selexipag on the primary composite end-point of morbidity/mortality by number of low-risk criteria assessed using the noninvasive French risk assessment approach. Cox proportional hazard models adjusted for (A) number of low-risk criteria at baseline and (B) number of low-risk criteria as a time-dependent covariate were used to calculate HR and 95% CI for selexipag vs placebo. Both models were also adjusted for treatment group, background PAH therapy, race, geographic region, sex, etiology, and age at baseline, and included the interaction between treatment group and risk, and age and risk. The consistency of treatment effects across risk subgroups was assessed using interaction tests. **p*-value for interaction. ***HRs could not be calculated in the subgroups of patients with 3 low-risk criteria because of the low numbers of morbidity/mortality events that occurred. At baseline, data were missing for 1 risk criterion (NT-proBNP) in 14 patients (1.2%; 6 selexipag patients and 8 placebo patients) and were imputed as not low-risk. Low-risk criteria defined as WHO FC I-II, 6MWD >440 m, and NT-proBNP <300 ng/liter. 6MWD, 6-minute walk distance; CI, confidence interval; HR, hazard ratio; NA, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; WHO FC, World Health Organization functional class.

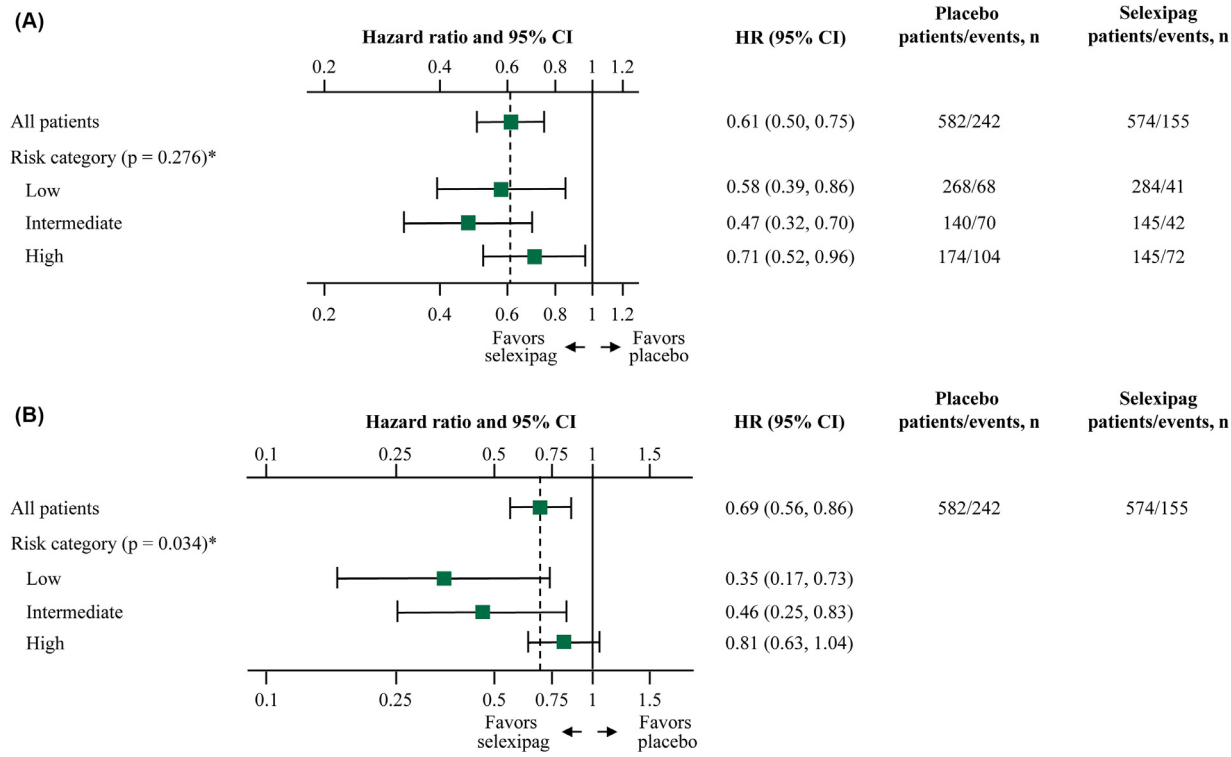

Figure 3 Effect of selexipag on the primary composite end-point of morbidity/mortality by REVEAL 2.0 risk category. Cox proportional hazard models adjusted for (A) REVEAL 2.0 category at baseline and (B) REVEAL 2.0 category as a time-dependent covariate were used to calculate HR and 95% CI for selexipag versus placebo. Both models were adjusted for treatment group, background PAH therapy, race, geographic region, sex, etiology, and age at baseline and included the interaction between treatment group and risk, and age and risk. The consistency of treatment effects across risk subgroups was assessed using interaction tests. Missing data were not imputed. **p*-value for interaction. Risk category determined by REVEAL 2.0 risk score: low (≤6), intermediate (7-8), high (≥9). At baseline, data were missing for 3 risk parameters in 2 patients (0.2%), 4 risk parameters in 364 patients (31.5%), 5 risk parameters in 77 patients (6.7%), 6 risk parameters in 701 patients (60.6%), 7 risk parameters in 10 patients (0.9%) and 8 risk parameters in 2 patients (0.2%). Missing data at baseline were not imputed and 0 points were assigned to the parameter for calculation of the REVEAL 2.0 score. CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management.

treatment and risk group (Supplementary Table S5 online) and in analyses performed to assess the impact of missing data for the number of low-risk criteria only (data not shown)

Change in risk profile over time

The number of low-risk criteria from baseline to week 26 increased by 18.6% and 27.5% of patients receiving placebo or selexipag, respectively (Figure 4A). Patients taking selexipag were more likely to increase their number of low-risk criteria from baseline to week 26 compared with patients receiving placebo (OR 1.69, 95% CI 1.28−2.24, $p = 0.0002$).

When patients were stratified by REVEAL 2.0 risk category, 8.2% of patients receiving placebo and 14.6% of patients receiving selexipag improved their risk category from baseline to week 26 (Figure 4B). Patients receiving selexipag were more likely to improve their REVEAL 2.0 risk score from baseline to week 26 compared with patients receiving placebo (OR 1.84, 95% CI 1.41−2.40, $p < 0.0001$).

Discussion

Our study evaluated the relationship between risk profile and long-term outcomes in the GRIPHON trial using the noninvasive French risk assessment approach,[5] and REVEAL 2.0.[13] We have demonstrated that both the number of low-risk criteria (i.e., WHO FC I-II, 6MWD >440 m, and NT-proBNP <300 ng/liter) and the REVEAL 2.0 risk category are prognostic of morbidity/mortality. Furthermore, we illustrate that treatment with selexipag had a beneficial effect on outcome, irrespective of the number of low-risk criteria or REVEAL 2.0 category. For both risk assessment approaches, patients treated with selexipag were more likely to improve their risk profile from baseline to week 26 compared with placebo.

The prognostic value of the noninvasive French approach for transplant-free survival has been demonstrated in registry analyses of newly diagnosed patients,[5,8] demonstrating the ability of this approach to identify patients at very low risk. The prognostic value of REVEAL 2.0 has been validated in a registry of predominantly prevalent patients.[14] The association between risk and outcome has also been investigated using clinical trial data. A recent post-hoc analysis of data from 340 patients in the open-label extension trial PAH: a long-term

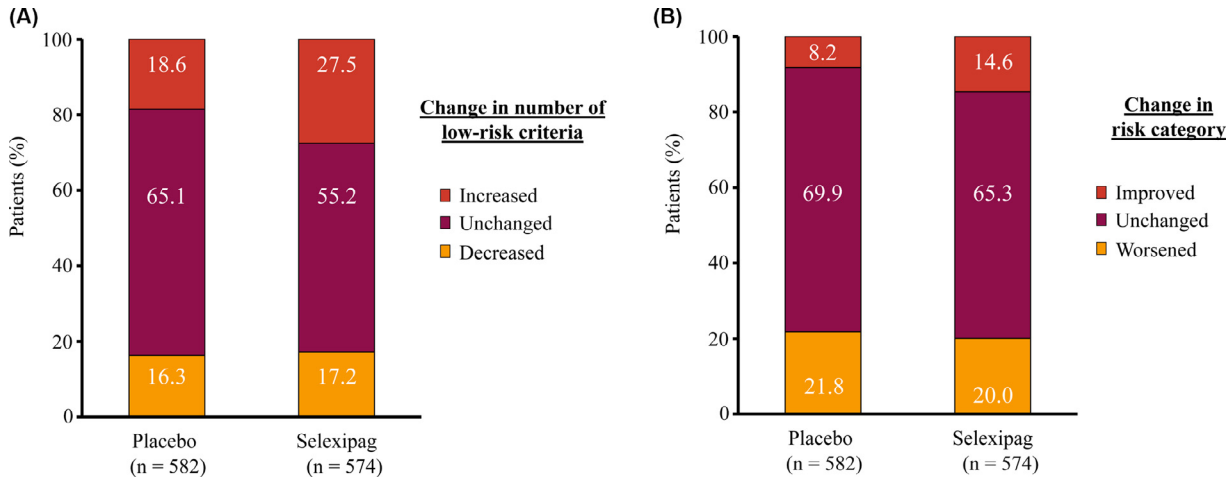

Figure 4 Change in risk from baseline to week 26 by treatment arm. (A) Change in the number of low-risk criteria according to the noninvasive French risk assessment approach. In the placebo group, assessments at baseline were missing for 8 patients for NT-proBNP; at week 26, assessments were missing for 118 patients for WHO FC, 136 patients for 6MWD and 130 patients for NT-proBNP. At week 26, 117 placebo patients were missing assessments for all 3 parameters, 75 (64%) of these because of a primary end-point event. In the selexipag group, assessments at baseline were missing for 6 patients for NT-proBNP; at week 26, assessments were missing for 96 patients for WHO FC, 114 patients for 6MWD and 109 patients for NT-proBNP. At week 26, 95 selexipag patients were missing assessments for all 3 parameters, 32 (34%) of these because of a primary end-point event. Missing assessments were imputed as not low-risk. Low-risk criteria defined as WHO FC I-II, 6MWD >440 m, and NT-proBNP <300 ng/L. (B) Change in REVEAL 2.0 risk category. Risk category determined by REVEAL 2.0 risk score at baseline or week 26: low (≤6), intermediate (7-8), high (≥9). At baseline, data were missing for 3 risk parameters in 2 patients (0.2%), 4 risk parameters in 364 patients (31.5%), 5 risk parameters in 77 patients (6.7%), 6 risk parameters in 701 patients (60.6%), 7 risk parameters in 10 patients (0.9%) and 8 risk parameters in 2 patients (0.2%). Missing data at baseline were not imputed and 0 points were assigned to the parameter for calculation of the REVEAL 2.0 score. At week 26, imputations were performed for 124 placebo patients and 103 selexipag patients for parameters that were present at baseline but missing at week 26. If a patient had experienced a primary end-point event before week 26, missing data were imputed using the worst-case scenario (highest risk category). If a patient had not experienced a primary end-point event before week 26, missing data were imputed with the last observation carried forward. 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; WHO FC, World Health Organization functional class.

extension study 2 (PATENT-2),[17] demonstrated that the noninvasive French risk assessment approach discriminated for clinical worsening-free survival and overall survival in a mostly prevalent PAH population.[17] In a post-hoc analysis of patients with newly-diagnosed PAH in the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) study, time to clinical failure correlated with the baseline risk category determined using the original REVEAL score.[11]

Our results add to these previous studies by demonstrating that counting the number of low-risk criteria using the noninvasive French risk assessment strategy has prognostic value for long-term outcomes in a large randomized controlled trial, as measured by the primary composite morbidity/mortality end-point, allowing the identification of a patient population with excellent long-term prognosis. In addition, our data confirm that this risk assessment strategy has relevance in a large population of prevalent patients and not only in newly diagnosed patients. Furthermore, this is the first time that REVEAL 2.0 has been validated as prognostic for morbidity/mortality in a mostly prevalent clinical trial population. As GRIPHON included a large proportion of prevalent patients, with a mean (SD) time from diagnosis of 2.4 (3.6) years before enrollment in the study,[15] the baseline time-point in these analyses may be considered as a follow-up assessment, rather than a true baseline assessment (i.e., at the time of diagnosis). Therefore, our results underline the relevance of these approaches to risk assessment at follow-up. This finding is important as it reiterates the relevance of regular risk monitoring during the follow-up of patients in clinical practice.

Overall, for every gain in the number of low-risk criteria at baseline or improvement in REVEAL 2.0 risk category, the risk of a morbidity/mortality event approximately halved. The risk subgroup was prognostic for the outcome, regardless of whether assessed at baseline or at any time-point during the study. This finding emphasizes the importance of achieving and/or maintaining a low-risk profile as recommended in the ESC/ERS guidelines[1,2] and supports the concept of early intensification of PAH therapy to achieve this goal.

The 2 approaches were not formally compared because of their fundamentally different objectives. The noninvasive French approach identifies patients at very low risk (i.e., those meeting treatment goals) while REVEAL 2.0 stratifies patients as low, intermediate, or high-risk. All patients with 3 low-risk criteria (i.e., at very low-risk) were also categorized as low-risk by REVEAL 2.0. In addition, as the number of low-risk criteria decreased, the proportion of patients in the REVEAL 2.0 high-risk category increased. These insights are important as they support the potentially complementary roles of these approaches in

clinical practice. For example, patients may benefit from a comprehensive risk assessment using REVEAL 2.0 at diagnosis. At follow-up, initial assessment with the noninvasive French approach may be useful to differentiate patients who meet the treatment goals and have an excellent long-term prognosis from those who need further assessment and closer monitoring. Those patients can then be more extensively examined and stratified into low, intermediate, and high 1-year mortality risk categories according to REVEAL 2.0.

As well as confirming the prognostic value of risk assessment, our study investigated the association between risk profile, as determined by the noninvasive French approach or by REVEAL 2.0, and response to selexipag treatment. Our analysis found that the addition of selexipag to the treatment regimen had a beneficial effect on long-term outcome, irrespective of the number of low-risk criteria at baseline or at any time-point during the study. When risk was assessed using REVEAL 2.0, the treatment effect of selexipag was also beneficial across all risk categories, albeit more pronounced in the low and intermediate-risk groups. The benefit seen in the subgroup of patients with 2 low-risk criteria or the REVEAL 2.0 low-risk category has clinical implications as it supports a proactive approach to treatment in patients with less severe disease. Patients with 0 low-risk criteria or categorized as high-risk using REVEAL 2.0 may benefit from selexipag; however, given their poor prognosis, they should be carefully and frequently monitored, allowing treatment escalation, including initiation of parenteral prostacyclin, as soon as clinically indicated.

Our findings also suggest an impact of selexipag on risk profile. Compared with placebo, patients taking selexipag were more likely to improve their risk profile from baseline to week 26, whether the risk was assessed by the number of low-risk criteria or using REVEAL 2.0. These analyses suggest that the initiation of selexipag treatment may help patients reach or maintain a low-risk profile.

These analyses are post-hoc and, therefore subject to limitations. GRIPHON was not powered to assess treatment effects and interactions in subgroups defined by risk status and as a result, the CIs are relatively wide. Treatment comparisons were not possible in the subgroup of patients with 3 low-risk criteria because too few morbidity/mortality events were observed in these low-risk patients. In addition, the number of patients in this subgroup was somewhat limited, in part because patients with 6MWD >450 m were excluded from entry into the study.[15] As the study was not designed to assess REVEAL 2.0 risk score, data were missing for some parameters.

In conclusion, our analyses show that assessing risk at baseline and at any time-point after that, using either the noninvasive French risk assessment method or REVEAL 2.0, identifies patient subgroups with distinct prognoses for morbidity/mortality in a generally prevalent population. These methods of assessing risk can be viewed as complementary. The French noninvasive approach can be used to identify patients at very low-risk at follow-up and REVEAL 2.0 can be used to assess risk for patients with fewer than 3 low-risk criteria at follow-up. Furthermore, we showed that all subgroups benefited from selexipag regardless of risk and that selexipag may improve risk profile in patients with PAH. Overall, these analyses support the importance of regular risk assessment and achieving and/or maintaining a low-risk profile, as recommended by the ESC/ERS guidelines and detailed in the Proceedings of the Sixth World Symposium on Pulmonary Hypertension.[1–3]

Disclosure statement

O.S. has served as a steering committee member for Actelion Pharmaceuticals Ltd; has served as an advisory board member for and received research grants from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; has received consultancy fees from Actelion Pharmaceuticals Ltd, Arena, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; has received speaker fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; has served on a scientific advisory board for Arena Pharmaceuticals and Gossamer Bio, and has received writing assistance from Actelion Pharmaceuticals Ltd and GlaxoSmithKline. K.C. has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received research grants from Actelion Pharmaceuticals Ltd, Ironwood Pharmaceuticals, National Institutes of Health, and SoniVie; has served on an advisory board for Bayer Healthcare (through University of California San Diego) and Flowonix; has served as an adjudication committee member for Arena Pharmaceuticals; is Circulation Associate Editor for American Heart Association, and has received consultancy fees from Actelion Pharmaceuticals Ltd. R.C. has served as a steering committee member for Actelion Pharmaceuticals Ltd; has served on an advisory board for Actelion Pharmaceuticals Ltd and Bayer; has received consultancy fees from Bayer and Arena Pharmaceuticals, and has received research grants from Actelion Pharmaceuticals Ltd and United Therapeutics. R.B. has received writing assistance from Actelion Pharmaceuticals Ltd and research grants from Actelion Pharmaceuticals Ltd, United Therapeutics, the American Heart Association, Bayer, the National Institutes of Health/National Heart, Lung, and Blood Institute, PhaseBio, Liquidia, and Abbott. L.D. is an employee of Actelion Pharmaceuticals Ltd and in the past held stock and/or stock options for Actelion Pharmaceuticals Ltd and currently holds stock and/or stock options in the parent company Johnson & Johnson. S.G. has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received speaker fees from Actelion Pharmaceuticals Ltd; has received advisory board fees from Actelion Pharmaceuticals Ltd, and Daiichi-Sankyo; and has served on a data and safety monitoring board for United Therapeutics. H.A.G. has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received advisory board and speaker fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, Novartis, and Pfizer; has received consultancy fees from Actelion Pharmaceuticals Ltd, Bayer,

Bellerophon Pulse Technologies, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Pfizer; and has received research grants from Actelion Pharmaceuticals Ltd and Deutsche Forschungsgemeinschaft. I.L. has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received speaker fees from Actelion Pharmaceuticals Ltd, Merck Sharp & Dohme, and AOP Orphan Pharmaceuticals; and has received research grants from Actelion Pharmaceuticals Ltd and AOP Orphan Pharmaceuticals. V.M. reports grants, personal fees and non-financial support from Actelion Pharmaceuticals Ltd and Bayer; grants from Eiger and SoniVie; and personal fees from United Therapeutics, Arena, Caremark, Medtronic and Merck Sharp & Dohme. R.P. is an employee of Actelion Pharmaceuticals Ltd and in the past held stock and/or stock options for Actelion Pharmaceuticals Ltd and currently holds stock and/or stock options in the parent company Johnson & Johnson. L.R. has served as a steering committee member for Actelion Pharmaceuticals Ltd; and has received consultancy fees from Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, GeNO Pharmaceuticals, Gilead, Karos Pharmaceuticals, Pfizer, and SoniVie Ltd. G. Simonneau has served as a steering committee member for and received research grants from Actelion Pharmaceuticals Ltd and Bayer; and has received speaker and consultancy fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer. V.T. has served as a steering committee member for Actelion Pharmaceuticals Ltd, Bayer, and United Therapeutics; has received consultancy fees from Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, Bayer, Daiichi-Sankyo, EKOS/BTG, Gilead Sciences, Janssen, Reata, and United Therapeutics; has received research grants from Arena Pharmaceuticals, Arena, Bayer, EKOS/BTG, and Riata; has received speaker fees from Bayer, Gilead Sciences, and Janssen. N.G. is a steering committee member for Actelion Pharmaceuticals; has received grant support, personal fees and non-financial support from Actelion Pharmaceuticals; and has received grant support and personal fees from Bayer Healthcare, Pfizer and GlaxoSmithKline. M.H. has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received speaker and consultancy fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer; and has received research grants from Actelion Pharmaceuticals Ltd.

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Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org/.

Supplementary materials

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