Change in REVEAL Lite 2 risk score predicts outcomes in patients with pulmonary arterial hypertension in the PATENT study

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BACKGROUND: Risk assessment is essential in pulmonary arterial hypertension (PAH) management. We investigated the effect of riociguat on REVEAL Lite 2 score, an abridged version of the REVEAL risk score, and its association with long-term outcomes in PATENT.

METHODS: PATENT-1 was a randomized, double-blind study of riociguat vs placebo in patients with PAH. In the PATENT-2 open-label extension, all patients received riociguat up to 2.5 mg three times daily (n = 396). REVEAL Lite 2 scores were calculated at baseline, PATENT-1 Week 12, and PATENT-2 Week 12, with patients stratified as low- (1-5), intermediate- (6-7), or high-risk (≥8). Kaplan-Meier and Cox proportional hazards analyses assessed association of riociguat with survival and clinical worsening-free survival (CWFS).

RESULTS: REVEAL Lite 2 score improved with riociguat 2.5 mg at PATENT-1 Week 12 (least-squares mean difference vs placebo: −0.8; p = 0.0004). More patients receiving riociguat 2.5 mg stabilized or improved risk stratum at PATENT-1 Week 12 vs placebo (p = 0.0005) and achieved low-risk status. REVEAL Lite 2 score at baseline and PATENT-1 Week 12 were associated with survival and CWFS (all p < 0.0001), as was change in score from baseline to Week 12 (p = 0.0002 and p < 0.0001, respectively). Survival and CWFS differed between risk strata at baseline (p < 0.0001) and PATENT-1 Week 12 (p < 0.0001).

CONCLUSIONS: This analysis confirms the risk-reduction benefits of riociguat in patients with PAH and further contributes to the validation of REVEAL Lite 2 in facilitating PAH risk assessment.

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Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance leading to right ventricular failure and death.1 Regular risk assessment of patients with PAH using a multidimensional approach is recommended and can aid clinicians in determining individual clinical management plans and optimizing patient outcomes to attain the overall treatment goal of achieving a low-risk status.1-3 Several risk assessment strategies or tools assessing a range of different variables have been developed, including risk equations from the French Pulmonary Hypertension Registry (FPHN),4 the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA),5 the Swedish PAH risk score,6 and the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL).7,8

The REVEAL risk score (RRS) has been shown to predict survival in patients with PAH and to have prognostic value in serial risk assessments.9-11 Recently, an updated version (RRS 2.0) was developed to further refine risk prediction.8 In real-life clinical practice, time, data availability, and assessment constraints can have a limiting effect on the use of invasive risk assessment tools. To improve the usability of the RRS in everyday clinical settings, an abridged version, REVEAL Lite, was developed, reducing the number of variables from the 12 used in RRS, to eight non-invasive variables and excluding some non-modifiable variables. This has been further refined to six variables in the REVEAL Lite 2 score, with exclusion of the World Health Organization (WHO) Group 1 etiological subgroup (i.e., PAH subtypes), demographics (sex/age), all-cause hospitalization within the previous 6 months, diffusing capacity of the lungs for carbon monoxide, mean right atrial pressure, and pulmonary vascular resistance.12

Riociguat is a soluble guanylate cyclase stimulator approved for the treatment of PAH and inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension.13-16 In the PATENT-1 and PATENT-2 studies of riociguat in patients with PAH, 12 weeks of riociguat decreased RRS10 and RRS 2.0.17 Additionally, lower RRS and RRS 2.0 were associated with an improvement in survival and clinical worsening-free survival (CWFS) in the long-term extension, PATENT-2. This post hoc analysis of the PATENT studies aimed to investigate the effect of riociguat on REVEAL Lite 2 score and the association of REVEAL Lite 2 and long-term outcomes in patients with PAH.

Materials and methods

Study design and patients

PATENT-1 was a randomized, double-blind, 12-week, placebo-controlled study of riociguat in patients with PAH. Patients received riociguat up to 2.5 mg-maximum three times daily (2.5 mg-max three times daily [three times a day]) or an exploratory dose capped at 1.5 mg-max three times a day, or placebo. PATENT-2 was an open-label extension in which all patients received riociguat (up to 2.5 mg-max three times a day). The methodologies for PATENT-1 (NCT0081063) and PATENT-2 (NCT00863681) have been described previously.16,18 All patients who completed PATENT-1 and enrolled in PATENT-2 were included in this analysis.

The PATENT studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The institutional review board at each participating center approved the study protocol and all patients gave written informed consent.

REVEAL Lite 2 risk assessment

REVEAL Lite 2 was developed using data from the REVEAL registry of patients consisting of all WHO Group I PAH subgroups except for pulmonary hypertension (PH) of the newborn.7 The six parameters used in REVEAL Lite 2 are: 1) renal insufficiency (score +1 if estimated glomerular filtration rate [eGFR] is <60 mL/min/1.73 m² or renal insufficiency is present in the judgment of the clinician if eGFR is not available); 2) WHO/New York Heart Association functional class (FC) (score –1 if FC I; +1 if FC III; +2 if FC IV); 3) systolic blood pressure (score +1 if <110 mm Hg); 4) heart rate (score +1 if >96 bpm); 5) 6-minute walking distance (6MWD) (score –2 if ≥440 m; –1 if 320–<440 m; +1 if <165 m); and 6) N-terminal prohormone of brain natriuretic peptide (score –2 if <300 pg/mL; +2 if ≥1100 pg/mL).12

In the present analysis, REVEAL Lite 2 scores were calculated using the variables listed in Table 1 at baseline (i.e., PATENT-1 baseline), PATENT-1 Week 12, and PATENT-2 Week 12. Missing values of score components for the later visits (i.e., PATENT-1 Week 12 and PATENT-2 Week 12) were imputed using the last observation carried forward. The number of imputed values for REVEAL Lite 2 score are shown in Table S1.

Patients were stratified into three risk strata based on their REVEAL Lite 2 score at baseline and PATENT-1 Week 12: low (score 1-5), intermediate (score 6-7), and high (score ≥8). REVEAL Lite 2 risk strata were based on REVEAL 2.0 risk scores using a subpopulation of patients in REVEAL who had survived for ≥1 year after enrollment.12 Change in REVEAL Lite 2 scores and risk strata for the riociguat 2.5 mg-max and placebo groups in PATENT-1 were assessed as previously described for the RRS.10

Assessment of long-term outcomes

Kaplan-Meier estimates were used to calculate survival and CWFS measured from the start of PATENT-2 and included pooled data from patients receiving riociguat 2.5 mg-max, those receiving riociguat 1.5 mg, and those receiving placebo, in PATENT-1. Clinical worsening was defined as first occurrence of any of the following events: death, heart/lung transplantation, atrial septostomy, hospitalization due to worsening of PH, start of new specific PH treatment, persistent decrease of >15% from baseline in 6 MWD, and persistent worsening of WHO FC. Overall, in the
PATENT-2 2014 data cut, 108 (27%) of 396 patients experienced clinical worsening events, including 50 (13%) patient deaths. The associations between REVEAL Lite 2 score at baseline and PATENT-1 Week 12 with survival and CWFS were assessed using a Cox proportional hazards model, including the REVEAL Lite 2 score at baseline or PATENT-1 Week 12 and study treatment as covariates. The relationship between change in score from baseline to PATENT-1 Week 12 and survival and CWFS was assessed using a Cox proportional hazards model, including baseline, change from baseline in REVEAL Lite 2 score, and study treatment as covariates. Concordance indices (C-indices) were calculated for prediction of survival or CWFS within 1 year after the start of PATENT-2 based on the original RRS and on REVEAL Lite 2 at baseline and Week 12.

### Results

#### PATENT-2 patient baseline characteristics

A total of 443 patients were treated in PATENT-1: 254 patients in the riociguat 2.5 mg-max group, 63 patients in the 1.5 mg-max group, and 126 patients in the placebo group. The majority of these patients (396 [89%]) entered PATENT-2 and were included in the analysis. Of these, 231 received riociguat 2.5 mg-max in PATENT-1, 56 patients received 1.5 mg-max, and 109 patients received placebo. Baseline characteristics of patients entering PATENT-2 were similar to those who entered PATENT-1. The characteristics used to calculate the REVEAL Lite 2 score for patients in PATENT-1 who entered PATENT-2 are shown in Table 1.

#### REVEAL Lite 2: Short-term effects

**REVEAL Lite 2 score:** REVEAL Lite 2 score significantly improved with riociguat 2.5 mg-max three times a day at PATENT-1 Week 12, compared with placebo (Table 2A, Figure 2), with a least-squares mean difference (95% confidence interval) of -1.50 (p < 0.001).
At PATENT-2 Week 12, further improvements were observed with riociguat 2.5 mg-max three times a day (Table 2B); the percentage of riociguat-treated patients who had improved their risk score increased from 51% at PATENT-1 Week 12 to 60% at PATENT-2 Week 12 (Figure 2). Former placebo patients showed improvements in the REVEAL Lite 2 score, similar to those observed with riociguat 2.5 mg-max three times a day at PATENT-1 Week 12 (Table 2, Figure 2).

**REVEAL Lite 2 risk strata:** Riociguat 2.5 mg-max three times a day significantly improved the risk stratum at PATENT-1 Week 12 compared with placebo using a stratified Wilcoxon test \( (p = 0.0005) \) (Figure 1). When assessing patients achieving low-risk status, more patients receiving riociguat 2.5 mg-max three times a day were in the low-risk stratum at PATENT-1 Week 12 (59%) compared with baseline (43%) while there was very little change in the proportion of placebo patients in the low-risk stratum at PATENT-1 Week 12 (45%) vs baseline (43%). At PATENT-2 Week 12, further improvements were observed with 65% of patients receiving riociguat 2.5 mg-max three times a day in the low-risk stratum; the proportion of former placebo patients in the low-risk stratum increased to 60%.

In each risk stratum, a higher proportion of patients receiving riociguat 2.5 mg-max three times a day either stabilized or improved risk stratum from baseline to PATENT-1 Week 12, compared with placebo (Figure 3A). At PATENT-2 Week 12, further improvements in risk strata were observed in patients receiving riociguat 2.5 mg-max three times a day. Former placebo patients experienced improvements in risk strata that were similar to those observed in riociguat 2.5 mg-max three times a day patients at PATENT-1 Week 12 (Figure 3B).

### REVEAL Lite 2: Long-term outcomes

**REVEAL Lite 2 score:** A Cox proportional hazards model adjusted for main study treatment showed that REVEAL Lite 2 scores at baseline \( (p < 0.0001) \) and PATENT-1 Week 12 \( (p < 0.0001) \) were significantly associated with survival (Table 3). A 1-point difference in REVEAL Lite 2 score at PATENT-1 baseline or Week 12 was associated with 21% and 24% reductions in the relative risk of death in PATENT-2, respectively. A Cox proportional hazards model including baseline, change from baseline at PATENT-1 Week 12, and main study treatment as covariates, showed that change in REVEAL Lite 2 score from baseline to PATENT-1 Week 12 was significantly associated with survival \( (p = 0.0002) \) (Table 3). A 1-point change in REVEAL Lite 2 score from baseline to PATENT-1 Week 12 was associated with a 23% reduction in the relative risk of death in PATENT-2. The C-indices for prediction of survival within 1 year after the start of PATENT-2 based on REVEAL Lite 2 at baseline and Week 12 were 0.57 (95% CI 0.41-0.72) and 0.67 (0.54-0.80), respectively, and were consistent with those of the original RRS applied
to the PATENT studies (Table S2). Similar to survival, the Cox proportional hazards models showed that REVEAL Lite 2 score at baseline and PATENT-1 Week 12, and change in REVEAL Lite 2 score from baseline to PATENT-1 Week 12, were also significantly associated with CWFS (all \( p < 0.0001 \)) (Table 3). The C-indices for prediction of CWFS within 1 year after the start of PATENT-2 based on REVEAL Lite 2 at baseline and Week 12 were 0.67 (95% CI 0.58-0.76) and 0.74 (0.66-0.82), respectively, and were again consistent with the original RRS (Table S2).

**REVEAL Lite 2 risk strata:** Kaplan-Meier curves for survival were significantly different between risk strata at baseline \(( p < 0.0001 \)) and PATENT-1 Week 12 \(( p < 0.0001 \)) (Figure 4), and for change in risk stratum from baseline at PATENT-1 Week 12 \(( p = 0.0062 \)) (Figure S1A). Similarly, CWFS was significantly different across REVEAL Lite 2 risk strata when risk was assessed at baseline \(( p < 0.0001 \)) and at PATENT-1 Week 12 \(( p < 0.0001 \)) (Figure 5). Here, a more distinct separation of the curves can be observed compared to the survival outcome. There was, however, no significant difference in CWFS across categories of change from baseline in risk stratum at PATENT-1 Week 12 \(( p = 0.0062 \)) (Figure S1B). Estimated survival and CWFS rates are shown in Table S3.

**Figure 1** Proportion of patients in the low, intermediate, and high REVEAL Lite 2 risk strata at baseline, PATENT-1 Week 12, and PATENT-2 Week 12.

**Figure 2** Proportion of patients with improved, stable, and worsened REVEAL Lite 2 risk score from baseline to PATENT-1 Week 12 and PATENT-2 Week 12 compared with baseline.

Improved, stable, or worsened REVEAL Lite 2 score determined by a 1-point change threshold. Percentages may not add up to 100% due to rounding.
In this analysis of REVEAL Lite 2 score in patients from the PATENT studies, riociguat significantly improved REVEAL Lite 2 score and risk stratum in patients with PAH, with more patients achieving low-risk status, as has been previously demonstrated with the original RRS and RRS 2.0 risk calculators. In addition, REVEAL Lite 2 and original RRS scores at baseline and Week 12 were significantly associated with survival and CWFS in patients with PAH receiving riociguat, with C-indices >0.5. The C-indices should, however, be interpreted with caution as there were only small numbers of patients in the intermediate- and high-risk categories, and a low number of events overall. This may explain the overlap between the survival curves over the long term, particularly the curves based on risk category at baseline, and the relatively low C-indices for survival (0.57-0.67). Separation of the intermediate-
high-risk groups was generally better based on risk at Week 12, probably as a result of factors such as improved management and addition of therapies, and this is consistent with data from other registries such as COMPERA and the FPHN registry. In addition, the use of a condensed, three-category model may have reduced the distinction between the intermediate- and high-risk groups. Greater separation may be seen if individual risk scores were plotted rather than grouped into risk categories, although a far larger study population would be needed for this. Similar findings in the PATENT study population were shown in previous analyses of RRS and RRS 2.0, as well as of the European Society of Cardiology/European Respiratory Society risk stratification methods. Similar in concept to the French non-invasive risk stratification, REVEAL Lite 2 uses fewer risk variables than RRS and RRS 2.0 and supports the notion that this may be a viable methodology for accurate risk prediction in patients with PAH.

The PAH treatment guidelines recommend regular risk assessment using a multidimensional approach including a range of clinical, hemodynamic, and functional parameters. The RRS and RRS 2.0 risk assessment tools include several of these parameters and have been validated in both real-world registry and clinical study populations of patients with PAH. In routine management of PAH, however, any tool used for risk assessment must be feasible within the time and practical constraints of real-life clinical practice. Interestingly, a recent international survey of disease progression risk assessment in PAH showed that while multifactorial risk assessment (in accordance with ESC/ERS guidelines) was performed in clinical practice, not all parameters were likely to be measured, and that hemodynamic parameters were among those least likely to be assessed at follow-up. Even though the RRS and RRS 2.0 tools are valid without the hemodynamic data, REVEAL Lite 2 was developed to completely focus on six core non-invasive, modifiable elements and was internally validated against the REVEAL population. A separate validation study of REVEAL Lite 2 in the REVEAL registry showed that the REVEAL Lite 2 risk assessment retains good discrimination (C-Index >0.7) compared to the original RRS and RRS 2.0. Before the present study, however, no external validation of REVEAL Lite 2 had been reported. Similar to REVEAL Lite 2, the FPHN non-invasive risk assessment has shown clinical utility and discrimination between risk strata, particularly at 5 years. Structurally, REVEAL Lite 2 is similar to the FPHN non-invasive risk assessment strategy, as both utilized cut points from the original RRS that were then incorporated into the ESC/ERS guidelines. However, similar to the RRS and RRS 2.0, REVEAL Lite 2 differs from the FPHN non-invasive risk assessment strategy by retaining statistical weighting of variables. Due to the small number of patients and events in PATENT, a direct comparison between REVEAL Lite and the FPHN non-invasive approach in PATENT is not statistically viable. However, thoughtful comparisons should be considered in larger clinical studies and perhaps by cross-validation of the two scores in the FPHN registry and the REVEAL registry, as has been done previously.

Further study limitations exist for this work, including the post hoc nature of the analyses, the high proportion of patients in the low-risk stratum at baseline, the potential for survivor bias in PATENT-2, and the small number of patients in the intermediate- and high-risk categories. Further studies should better investigate risk stratification instruments using time-dependent covariates in dedicated prospective cohorts (NCT01185730) and using alternative modeling methodology. It is also important to further externally validate REVEAL Lite 2 in patient populations other than the REVEAL registry and to define the impact of risk stratification using this instrument.

In conclusion, this post hoc analysis of the REVEAL Lite 2 risk assessment applied to the PATENT population confirmed the benefit of riociguat in terms of risk reduction in patients with PAH. The results reinforce previous analyses of PATENT data with earlier RRS calculators and further contribute to the validity of the REVEAL Lite 2 score, which is intended to facilitate accurate and regular risk assessment of patients with PAH in everyday clinical practice.
Author contributions

RLB was responsible for study design; all authors were responsible for the interpretation and writing of the report and the decision to submit the article. Bayer AG, Berlin, Germany and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA participated in the study design; in the collection, analysis, and interpretation of data; in the decision to submit the report for publication. Medical writing assistance was provided by Robyn Bradbury, PhD and Rachael Powis, PhD at Adelphi Communications Ltd (Bollington, UK), funded by Bayer AG (Berlin, Germany) in accordance with Good Publications practice.

Figure 4 Kaplan-Meier analysis for survival by stratified REVEAL Lite 2 risk strata at A, baseline and B, PATENT-1 Week 12. Day 0 of survival time considered in this analysis was the start of PATENT-2.
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Supplementary materials

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