



ORIGINAL CLINICAL SCIENCE

REVEAL risk scores applied to riociguat-treated patients in PATENT-2: Impact of changes in risk score on survival

Raymond L. Benza, MD,^a Harrison W. Farber, MD,^b Adaani Frost, MD,^c Hossein-Ardeschir Ghofrani, MD,^{d,e} Miguel A. Gómez-Sánchez, MD,^f David Langleben, MD,^g Stephan Rosenkranz, MD,^h Dennis Busse, Dipl Stat,ⁱ Christian Meier, MD,^j Sylvia Nikkho, MD,^k and Marius M. Hoeper, MD^l

From the ^aCardiovascular Institute, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA; ^bPulmonary Center, Boston University School of Medicine, Boston, Massachusetts, USA; ^cHouston Methodist Hospital & Weill Cornell Medical College, Houston, Texas, USA; ^dUniversity of Giessen and Marburg Lung Center, member of the German Center of Lung Research, Giessen, Germany; ^eDepartment of Medicine, Imperial College London, London, UK; ^fHospital General Nuestra Señora del Prado, Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Talavera de la Reina, Spain; ^gCenter for Pulmonary Vascular Disease and Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; ^hDepartment of Cardiology and Cardiovascular Research Center Cologne, Heart Centre, University Hospital of Cologne, Cologne, Germany; ⁱChrestos Concept GmbH & Co. KG, Essen, Germany; ^jGlobal Medical Affairs, Bayer AG, Berlin, Germany; ^kGlobal Clinical Development, Bayer AG, Berlin, Germany; and the ^lClinic for Respiratory Medicine, Hannover Medical School, member of the German Center of Lung Research, Hannover, Germany.

KEYWORDS:

pulmonary arterial hypertension;
risk assessment;
soluble guanylate cyclase stimulator;
right heart failure;
survival;
clinical worsening

BACKGROUND: The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk score (RRS) calculator was developed using data derived from the REVEAL registry, and predicts survival in patients with pulmonary arterial hypertension (PAH) based on multiple patient characteristics. Herein we applied the RRS to a pivotal PAH trial database, the 12-week PATENT-1 and open-label PATENT-2 extension studies of riociguat. We examined the effect of riociguat vs placebo on RRS in PATENT-1, and investigated the prognostic implications of change in RRS during PATENT-1 on long-term outcomes in PATENT-2.

METHODS: RRS was calculated post hoc for baseline and Week 12 of PATENT-1, and Week 12 of PATENT-2. Patients were grouped into risk strata by RRS. Kaplan–Meier estimates were made for survival and clinical worsening-free survival in PATENT-2 to evaluate the relationship between RRS in PATENT-1 and long-term outcomes in PATENT-2.

RESULTS: A total of 396 patients completed PATENT-1 and participated in PATENT-2. In PATENT-1, riociguat significantly improved RRS ($p = 0.031$) and risk stratum ($p = 0.018$) between baseline and Week 12 compared with placebo. RRS at baseline, and at PATENT-1 Week 12, and change in RRS during PATENT-1 were significantly associated with survival (hazard ratios for a 1-point reduction in RRS: 0.675, 0.705 and 0.804, respectively) and clinical worsening-free survival (hazard ratios of 0.736, 0.716 and 0.753, respectively) over 2 years in PATENT-2.

Reprint requests: Raymond L. Benza, MD, Cardiovascular Institute, Allegheny General Hospital, 320 E North Ave, Pittsburgh, PA 15212.
Telephone: +412 359 3584. Fax: +412 359 6334.
E-mail address: rbenza@wpahs.org

CONCLUSIONS: RRS at baseline and Week 12, and change in RRS, were significant predictors of both survival and clinical worsening-free survival. These data support the long-term predictive value of the RRS in a controlled study population.

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Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance (PVR) due to progressive remodeling of the pulmonary vasculature, leading to right ventricular failure and eventual death.¹ Despite recent advances in the treatment of PAH, mortality remains high,^{2,3} with 1- and 5-year survival rates in newly diagnosed patients estimated at 86% and 61%, respectively.³

PAH is a rare condition, with an estimated prevalence of 6.6 to 26.0 cases per million individuals.^{4,5} Much of our knowledge about long-term outcomes in PAH is derived from multi-institutional patient registries.^{6–8} REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) is a large, United States-based registry of patients with PAH, initiated in 2006 to evaluate the clinical course and management of PAH.⁴ Analysis of data from REVEAL has provided valuable insights into predictors of survival in PAH, which has enabled development of a risk score calculator to predict 1-year survival in patients with PAH.^{8,9} The REVEAL risk score (RRS) calculator is a composite, weighted risk algorithm incorporating 12 evaluable elements considered important for outcome (e.g., 6-minute walking distance [6MWD], hemodynamic parameters, renal function and *N*-terminal pro-hormone of brain natriuretic peptide [NT-proBNP]). Although the RRS calculator was initially developed and validated for point-in-time assessment of risk, it also has prognostic value when used for serial risk assessment, enabling clinicians to reassess patients' risk and monitor their response to treatment.¹⁰

Riociguat is a soluble guanylate cyclase (sGC) stimulator approved for the treatment of PAH and inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension. In the 12-week, placebo-controlled PATENT-1 study, riociguat significantly improved 6MWD (the primary end-point) compared with placebo in patients with PAH, and was associated with significant improvements in a range of secondary end-points, including PVR, NT-proBNP, World Health Organization functional class (WHO FC), time to clinical worsening and Borg dyspnea score.¹¹ The improvements in 6MWD and WHO FC seen in PATENT-1 were sustained at 2-year follow-up in the long-term, open-label extension study, PATENT-2.¹²

Herein we report the results of a post-hoc exploratory analysis of PATENT-1 and -2 to assess the effect of riociguat on RRS, and to investigate the relationship between short-term change in RRS and long-term outcomes. The study population assessed did not contribute to the derivation of the RRS calculator.

Methods

All patients who completed PATENT-1 (NCT00810693) and enrolled in PATENT-2 (NCT00863681) were included in this analysis. The methodology for these studies has been described in detail previously.^{11,13} Pertinent details of the studies are included in the [Supplementary Material](#) available online at www.jhltonline.org/.

This post-hoc analysis used the RRS calculator as described elsewhere.^{8,9} The algorithm incorporated 10 evaluable elements, which were used to calculate RRS scores ([Table 1](#)). Data for 2 parameters typically included in the RRS calculation, pericardial effusion and diffusing capacity of the lung for carbon monoxide, were not available for the PATENT-1 and -2 cohorts; however, the RRS only requires 7 evaluable elements to maintain significant predictive power and calibration.^{8,9} In this algorithm, calculated risk score could range from 1 (lowest risk) to 20 (highest risk).

RRS was calculated for all patients at PATENT-1 baseline (referred to as baseline throughout), PATENT-1 Week 12 and PATENT-2 Week 12. Based on their RRS, patients were stratified at baseline and again at PATENT-1 Week 12 into 1 of 5 previously defined⁹ risk strata: low (score 1 to 7); average (8); moderately high (9); high (10 or 11); and very high (≥ 12). For analysis of risk strata, the moderately high, high and very high strata were grouped into a single "higher" stratum (i.e., score ≥ 9), due to the small number of patients in these strata. Changes in RRS and risk strata were calculated from baseline to PATENT-1 Week 12, and from baseline to PATENT-2 Week 12. Survival and clinical worsening-free survival in PATENT-2 were determined using Kaplan–Meier estimates. The relationships between RRS at baseline, at PATENT-1 Week 12, and the change from baseline to PATENT-1 Week 12 and both survival and clinical worsening-free survival in PATENT-2 were assessed to determine the predictive value of RRS and change in RRS. The statistical analysis methodology is described in the [Supplementary Material](#) online.

Results

Patients' characteristics

Of 443 patients included in PATENT-1, 396 patients entered PATENT-2. Patients' characteristics of this cohort have been published previously.¹³ The disease characteristics used to calculate RRS are shown in [Table 1](#). At baseline, RRS was 6.9 ± 2.0 (mean \pm standard deviation) for the riociguat 2.5 mg group and 6.8 ± 1.8 for the placebo group. The majority of patients (233 [59%]) were in the low-risk stratum at baseline, 84 (21%) were in the average-risk stratum, and 79 (20%) were in the 3 higher risk strata.

Table 1 Disease Characteristics Used to Calculate RRS and Baseline Demographics for PATENT-1

	Riociguat 2.5 mg (<i>n</i> = 231)	Placebo (<i>n</i> = 109)	Total (<i>n</i> = 396)
WHO Group I subgroup (PAH classification)			
Idiopathic	136 (60)	74 (68)	245 (62)
Familial	7 (3)	1 (1)	9 (2)
Associated with connective tissue disease	63 (27)	18 (17)	94 (24)
Associated with congenital heart disease	14 (6)	12 (11)	33 (8)
Associated with portopulmonary hypertension	10 (4)	2 (2)	12 (3)
Associated with anorexigen or amphetamine	1 (<0.5)	2 (2)	3 (1)
Renal sufficiency			
Renal insufficiency ^a	7 (3)	1 (1)	10 (3)
No renal insufficiency	215 (93)	103 (95)	368 (93)
Missing information	9 (4)	5 (5)	18 (5)
Age and gender			
Male, >60 years	16 (7)	10 (9)	29 (7)
Female or male, ≤60 years	215 (93)	99 (91)	367 (93)
WHO functional class			
I	5 (2)	3 (3)	12 (3)
II	98 (42)	54 (50)	169 (43)
III	128 (55)	49 (45)	212 (54)
IV	0	2 (2)	2 (1)
Missing information	0	1 (1)	1 (<0.5)
Systolic blood pressure (mm Hg)			
<110	96 (42)	37 (34)	158 (40)
≥110	135 (58)	72 (66)	238 (60)
Heart rate (bpm)			
>92	16 (7)	15 (14)	36 (9)
≤92	215 (93)	94 (86)	360 (91)
6MWD (m)			
≥440	37 (16)	16 (15)	57 (14)
<440 to ≥165	191 (83)	93 (85)	335 (85)
<165	3 (1)	0	4 (1)
NT-proBNP (pg/ml)			
<300	94 (41)	32 (29)	148 (37)
≥300 to 1,500	70 (30)	41 (38)	119 (30)
>1,500	46 (20)	24 (22)	87 (22)
Missing information	21 (9)	12 (11)	42 (11)
RAP (mm Hg)			
>20 / ≤20	6 (3) / 225 (97)	2 (2) / 107 (98)	8 (2) / 388 (98)
PVR (mm Hg/min/liter)			
>2,560 / ≤2,560	1 (<0.5) / 230 (100)	1 (1) / 108 (99)	3 (1) / 393 (99)

Data are presented as number (%). 6MWD, 6-minute walking distance; bpm, beats per minute; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RRS, REVEAL risk score; WHO, World Health Organization.

^aRenal insufficiency was defined as a creatinine level >1.4 mg/dl at PATENT-1 baseline, and ≥1.6 mg/dl during the study (significant renal insufficiency precluded enrollment in PATENT-1).

RRS and relationship with long-term outcomes

Riociguat treatment significantly improved RRS from baseline to PATENT-1 Week 12, compared with placebo (Table 2a and Figure 1). In the first 12 weeks of PATENT-2, this improvement continued in patients who received riociguat in PATENT-1. Patients who received placebo in PATENT-1 and went on to receive riociguat in PATENT-2 (referred to hereafter as “former placebo”) demonstrated improvement similar to riociguat patients in PATENT-1 (Table 2b and Figure 1).

A univariate Cox proportional hazards model adjusted by main study treatment showed that RRS at baseline and at PATENT-1 Week 12 were both significant predictors of

survival ($p < 0.0001$) (Table 3); a 1-point difference in RRS at baseline or PATENT-1 Week 12 was associated with an approximate 30% reduction in the relative risk of death in PATENT-2. A bivariate Cox proportional hazards analysis adjusted by main study treatment, where baseline and change from baseline were adjusted for each other, showed a significant relationship between baseline or change from baseline and survival in PATENT-2 ($p = 0.0346$), and a 1-point reduction in RRS from baseline to PATENT-1 Week 12 was associated with a 20% reduction in relative risk of death in PATENT-2 over 2 years (Table 3). Consistent with the survival results, similar patterns were observed for the relationship between RRS and clinical worsening-free survival (Table 3).

Table 2a Change in RRS From Baseline to PATENT-1 Week 12

	Riociguat 2.5 mg (<i>n</i> = 231)			Placebo (<i>n</i> = 109)			LS mean difference (95% CI)	Riociguat vs placebo <i>p</i> -value
	Baseline	PATENT-1 Week 12	Change from baseline	Baseline	PATENT-1 Week 12	Change from baseline		
RRS	6.9 ± 2.0	6.3 ± 2.1	−0.6 ± 1.4	6.8 ± 1.8	6.7 ± 2.2	−0.1 ± 1.6	−0.44 (−0.76 to −0.11)	0.031

CI, confidence interval; LS, least squares; RRS, REVEAL risk score.

Risk stratum and relationship with long-term outcomes

Riociguat treatment improved risk stratum in PATENT-1 ($p = 0.0181$ compared with placebo at PATENT-1 Week 12) (see [Table S1](#) and [Figure S1](#) in the [Supplementary Material](#) online). The improvement in risk stratum observed with riociguat treatment during PATENT-1 continued to PATENT-2 Week 12 for former riociguat patients, whereas former placebo patients demonstrated improvements in risk stratum after initiation of riociguat (see [Figure S1](#) online).

Survival was significantly different across risk strata assessed at baseline ($p = 0.0012$) and at PATENT-1 Week 12 ($p = 0.0011$; [Figure 2](#)). Clinical worsening-free survival was also significantly different across risk strata at baseline and at PATENT-1 Week 12 ($p < 0.0001$ and $p < 0.0001$, respectively; [Figure 3](#)), and change in risk stratum from baseline to PATENT-1 Week 12 was a significant predictor of survival and clinical worsening-free survival ($p = 0.0298$ and $p = 0.0008$, respectively; [Figure 4](#)) in Kaplan–Meier analyses. The highest survival and clinical worsening-free survival rates were seen in patients who remained stable in their risk stratum, possibly due to the large number of patients who were in the low-risk stratum at baseline. Estimated survival and clinical worsening-free survival rates are shown in [Table S2](#) online.

Discussion

The RRS calculator is a validated, easily applied tool for predicting survival in patients with PAH, and serial

calculation of the RRS can be used to monitor changes in a patient's mortality risk over time.^{10,14} Herein we applied the RRS to a clinical trial group not involved in the derivation of the score. We performed a post-hoc exploratory analysis of PATENT-1 and -2 to assess the effect of riociguat on the RRS, and to examine the potential predictive value of change in RRS over time for long-term outcomes. The data presented herein reinforce existing evidence demonstrating the benefits of riociguat in PAH and, importantly, show that change in RRS predicts both long-term survival and clinical worsening in patients treated with riociguat.

Treatment with riociguat significantly improved RRS and risk stratum across all baseline risk strata over the 12 weeks of PATENT-1, with sustained improvements in PATENT-2. These results are consistent with the efficacy results of PATENT-1 and -2, of which the primary and secondary end-points are also variables used to calculate the RRS.^{12–14}

Cox proportional hazards analyses showed that RRS at baseline and at PATENT-1 Week 12, and change in RRS from baseline to PATENT-1 Week 12 were significantly associated with both survival and clinical worsening-free survival over 2 years, with worsening RRS predicting poorer long-term outcomes. Similarly, risk stratum at baseline and at PATENT-1 Week 12, and change in risk stratum from baseline to PATENT-1 Week 12 were also associated with survival and clinical worsening-free survival in PATENT-2.

This study has confirmed the utility of the RRS for predicting long-term outcomes from short-term response to treatment in a clinical trial cohort, and shows that the RRS is useful in predicting clinical worsening. This is an important finding considering that contemporary treatment practices are increasingly focused on preventing morbidity due to the improved short-term survival observed with modern therapeutics.^{15–18} Moreover, clinical worsening has been used as an outcome measure in recent clinical trials in PAH,¹⁹ either as part of a composite primary end-point^{15,17,18} or as a secondary end-point.^{11,20} Clinical worsening events such as hospitalization, rather than survival, have been shown to be the main factors driving significance in the composite primary end-point trials SERAPHIN, AMBITION and GRIPHON.^{15,17,18} Thus, the ability to predict which patients may have morbid events should help facilitate recruitment strategies for future trials. Risk assessment using criteria similar to those that comprise the RRS were introduced in the 2015 European Respiratory Society/European Society of Cardiology guidelines for the treatment of pulmonary

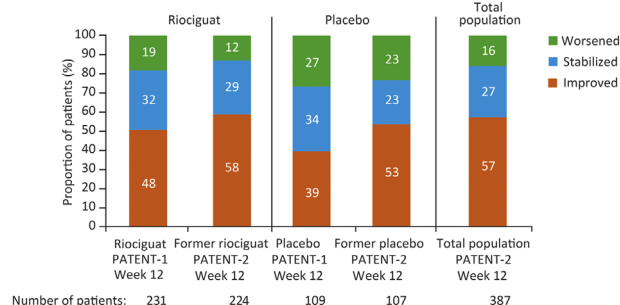


Figure 1 The proportion of patients with improved, stabilized, or worsened REVEAL risk score at PATENT-1 Week 12 and PATENT-2 Week 12. Former riociguat refers to patients who received riociguat in both PATENT-1 and PATENT-2; former placebo refers to patients who received placebo in PATENT-1 and riociguat in PATENT-2. Percentages may not add up to 100% due to rounding.

Table 2b Change in RRS From Baseline to PATENT-2 Week 12

	Riociguat 2.5 mg (<i>n</i> = 231)		Former placebo ^a (<i>n</i> = 109)	
	PATENT-2 Week 12	Change from baseline to PATENT-2 Week 12	PATENT-2 Week 12	Change from baseline to PATENT-2 Week 12
RRS	5.9 ± 2.2	-1.0 ± 1.6	6.2 ± 2.1	-0.6 ± 1.8

Data are presented as mean ± standard deviation. CI, confidence interval; RRS, REVEAL risk score.

^aRefers to patients randomized to placebo in PATENT-1, and receiving riociguat in PATENT-2.

hypertension, stratifying patients by 1-year mortality risk using generalized risk profiles.¹ In contrast to these suggested risk profiles, the RRS is a “weighted” score, which may offer a more accurate assessment of overall risk. The observed association between RRS and clinical worsening-free survival in PATENT-2 suggests that the RRS may be a useful clinical tool to help guide treatment decisions and planning of future clinical trials.

The RRS of the PATENT-2 cohort indicated that the majority of patients in the study were low risk, with a mean RRS of 6.9 at baseline, despite over half of the population being classified in WHO FC III at baseline. It is now widely accepted that risk assessment of patients with PAH should be based not on a single parameter alone, but rather on several different criteria, and a weighted composite measure may be even better suited to identifying patient risk groups. As risk prediction is an essential component of clinical trial design, this observation suggests the potential utility of the RRS in assessing patients for clinical trials.

In our analysis, the RRS was calculated using 10 of the standard 12 variables for RRS calculation. As noted earlier, the RRS incorporates a “missing data indicator” and only requires 7 evaluable elements to maintain significant predictive power and calibration^{8,9}; therefore, the non-inclusion of these 3 variables should not have affected the direction of the results. A small, single-center study investigating simplified models of the RRS found no statistical difference in the ability to predict 1-year survival between the full RRS, simple (15 variables; all except for pulmonary function test and hemodynamic data) and clinical (5 variables, including PAH type, WHO FC, BNP,

glomerular filtration rate and right atrial pressure by echocardiography) models of the RRS.²¹

There are several limitations to this study. First, this was a post-hoc exploratory analysis, rather than a pre-planned analysis. As such, the proportion of patients in the 3 higher risk strata was very low, necessitating the pooling of these strata, and the high proportion of low-risk patients in PATENT-1 and -2 meant that a large proportion of the study population could not improve their risk strata. Second, as the RRS is a weighted, composite instrument, it is not possible to use the risk score to identify which of the parameters modified by riociguat treatment has the greatest impact on long-term outcome. This issue was addressed by Ghofrani and colleagues in their analysis of predictors of long-term outcomes in the PATENT-2 study.¹⁶

In conclusion, these data support the utility of the RRS in predicting long-term survival and clinical worsening-free survival in patients receiving treatment with riociguat for PAH.

Disclosure statement

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Table 3 Cox Proportional Hazards Analysis of Survival and Clinical Worsening-free Survival by RRS at Baseline and at PATENT-1 Week 12

	Survival			Clinical worsening-free survival		
	Hazard ratio ^a	95% CI	<i>p</i> -value	Hazard ratio ^a	95% CI	<i>p</i> -value
Univariate model						
Risk score at baseline	0.675	0.573 to 0.796	<0.0001	0.736	0.661 to 0.821	<0.0001
Risk score at PATENT-1 Week 12	0.705	0.613 to 0.810	<0.0001	0.716	0.651 to 0.787	<0.0001
Bivariate model ^b						
Risk score at baseline	0.653	0.554 to 0.770	<0.0001	0.695	0.622 to 0.776	<0.0001
Change from baseline to PATENT-1 Week 12 in risk score	0.804	0.657 to 0.984	0.0346	0.753	0.658 to 0.861	<0.0001

CI, confidence interval; RRS, REVEAL risk score.

^aHazard ratio describes the risk of dying or experiencing a clinical worsening event at any time for a patient with a given risk score compared with a patient whose risk score differs by 1 point.

^bModel includes baseline and change from baseline risk score as covariates.

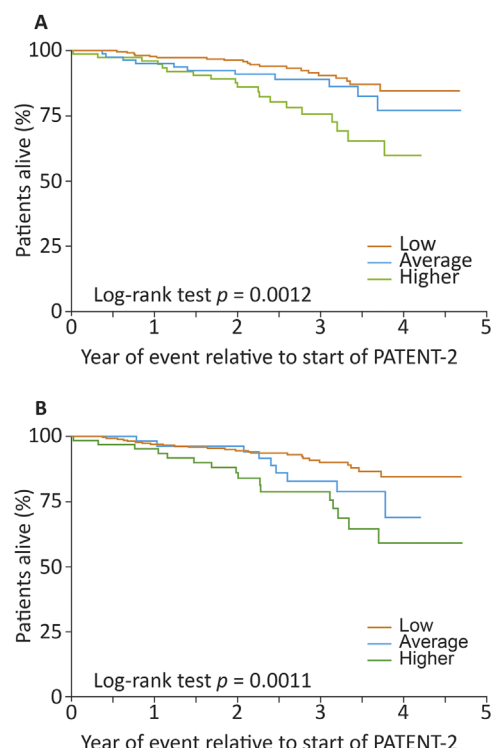


Figure 2 Kaplan-Meier analyses for survival by risk stratum at (A) PATENT-1 baseline and (B) PATENT-1 Week 12.

Actelion, Bayer, Ergonex, Gilead, GSK, Novartis and Pfizer; consultancy fees from AbbVie, Actelion, Bayer, Bellerophon Pulse Technologies, Ergonex, Gilead, GSK, Medscape, MSD Sharpe & Dohme, Novartis, OMT, Pfizer and Web MD Global; and

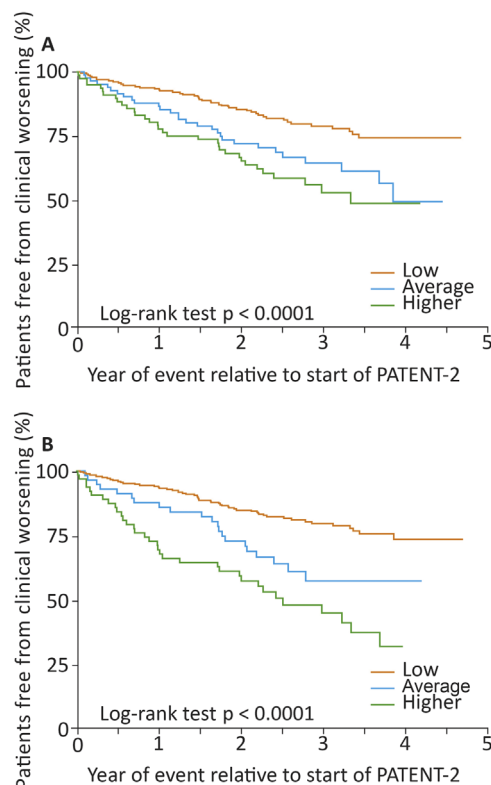


Figure 3 Kaplan-Meier analyses for clinical worsening-free survival by risk stratum at (A) baseline and (B) PATENT-1 Week 12.

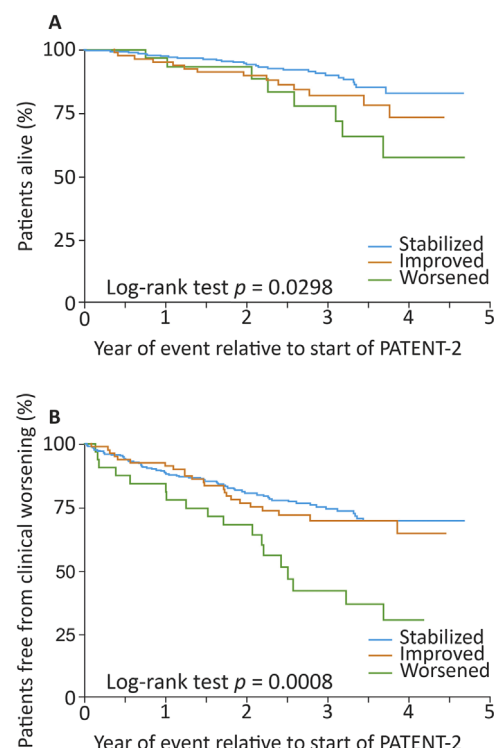


Figure 4 Kaplan-Meier analyses by change in risk stratum from baseline to PATENT-1 Week 12 for (A) survival and (B) clinical worsening-free survival in PATENT-2.

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Appendix A. Supporting information

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

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