Validation of REVEAL risk score calculator 2.0 in patients with PAH in the Phase III PATENT study

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Relevant financial relationship disclosure statement

- I will not discuss off-label use and/or investigational use of the following drugs/devices: riociguat

- The following relevant financial relationships exist related to this presentation:
- Raymond L. Benza: reports receiving grants from Actelion, Bayer AG, Bellerophon, and EIGER.
- Harrison W. Farber: reports receiving grants from Actelion, Gilead, and United Therapeutics, and receiving personal fees from Actelion, Bayer AG, Bellerophon, Gilead, and United Therapeutics.
- Adaani E. Frost: has received honoraria for consultations and/or speaking about a product or about pulmonary hypertension from Actelion, Bayer AG, Gilead, Novartis, Pfizer, and United Therapeutics/Lung LLC; grant support from Actelion, Bayer AG, Gilead, Novartis, Pfizer, and United Therapeutics/Lung LLC; and is currently on the IDMC for two studies funded by Actelion (UNISUS and MACITEPH).
- Hossein-Ardeschir Ghofrani: reports receiving grants from Actelion, Bayer AG, Ergonex, and Pfizer, and personal fees from Actelion, Bayer AG, Ergonex, Gilead, GSK, Merck, Novartis, and Pfizer.
- Paul A. Corris: reports grants and personal fees from Bayer AG, and personal fees from Actelion and GSK.
- Britta Brockmann: is an employee of Chrestos Concept GmbH & Co. KG.
- Sylvia Nikkho: is an employee of Bayer AG.
- Christian Meier: is an employee of Bayer AG.
- Marius M. Hoeper: reports receiving consultancy fees from Actelion, Bayer AG, GSK, and Pfizer, and personal fees from Actelion, Bayer AG, Gilead, GSK, MSD, and Pfizer.

Background

- The REVEAL risk score (RRS) was developed to predict 1-year mortality in patients with pulmonary arterial hypertension (PAH), based on data from the REVEAL registry[1,2]
- In PATENT-1, riociguat significantly improved RRS in patients with PAH compared with placebo.[3] In the PATENT-2 open-label extension, change in RRS was associated with survival and clinical worsening-free survival (CWFS)[3]
- The RRS 2.0 is based on the validated RRS but includes all-cause hospitalization within the previous 6 months, refines the definition of renal insufficiency, and adjusts the thresholds and values of existing variables[4]
- RRS 2.0 was developed to refine risk prediction and to assist clinicians in tailoring treatment decisions aimed at lowering a patient's risk status[4]

CWFS, clinical worsening-free survival; PAH, pulmonary arterial hypertension; RRS, REVEAL risk score.

1. Benza RL, et al. Circulation 2010;122:164–172;
2. Benza RL, et al. Chest 2012;141:354–362;
3. Benza RL, et al. J Heart Lung Transplant 2018;37:513–519;
4. Benza RL, et al. Chest 2019;156:323–337

Aim

- The aim of this post hoc exploratory analysis was to evaluate RRS 2.0 in the PATENT studies and assess the relationship between RRS 2.0 and survival and CWFS in patients with PAH

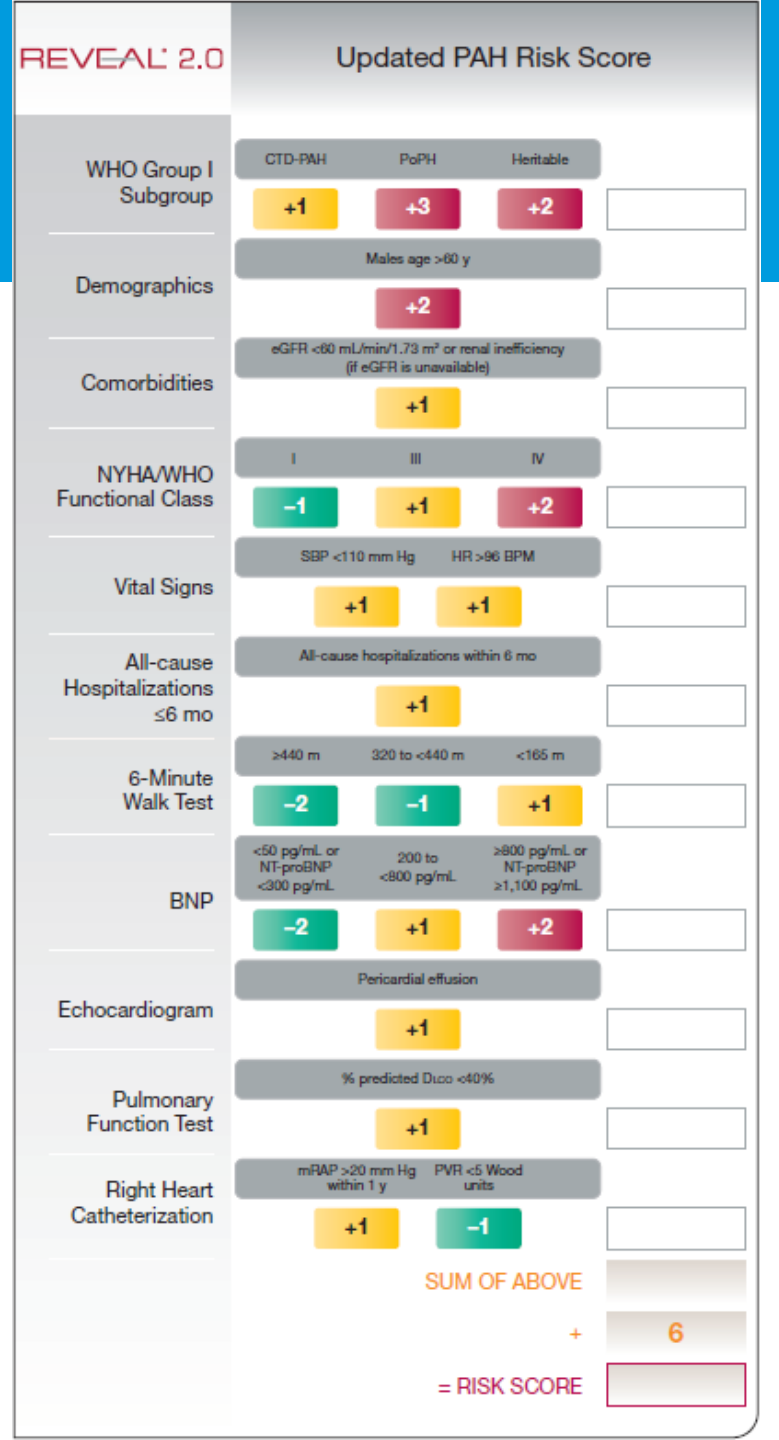


Figure from Benza RL, et al. Chest 2019;156:323–337.

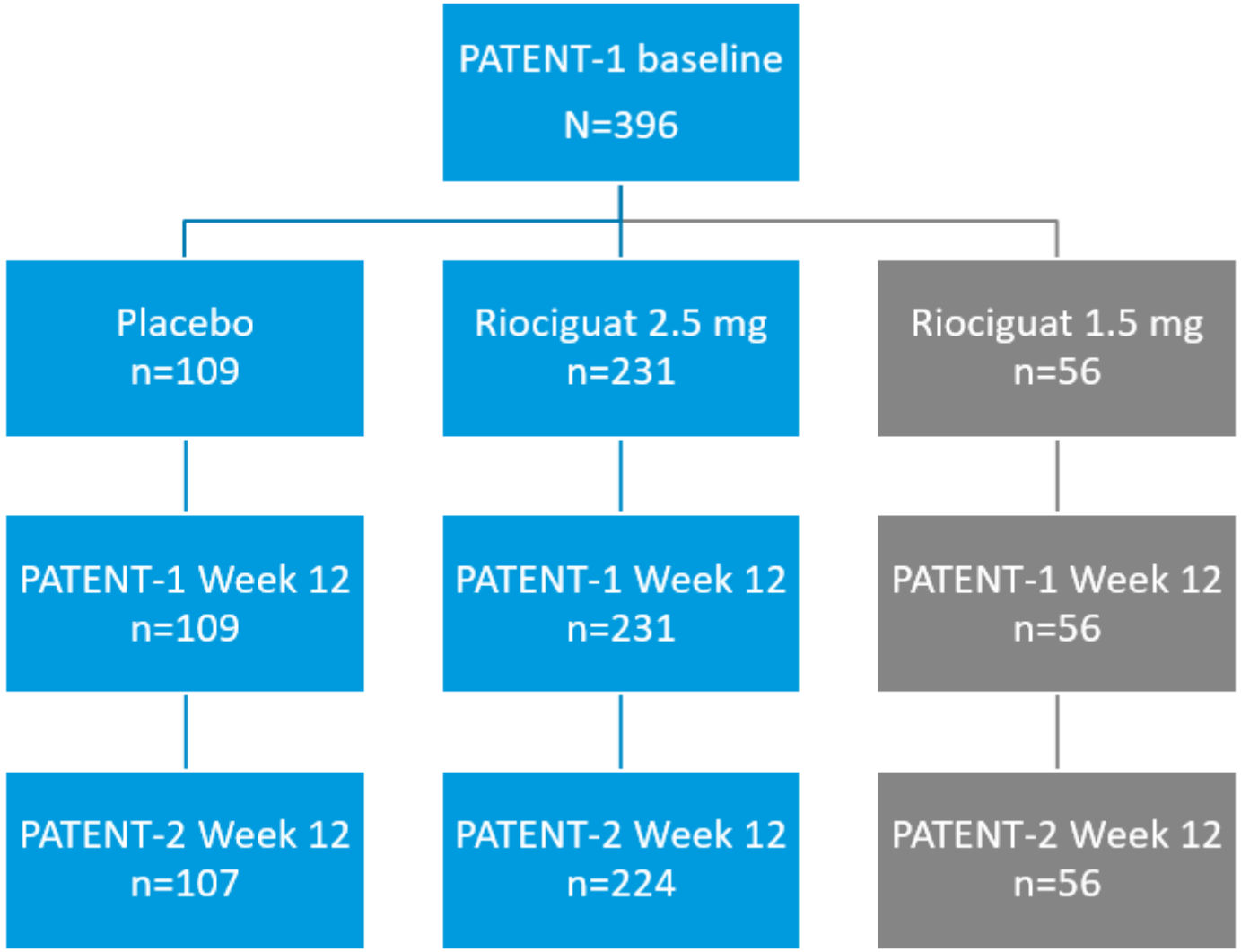
Methods

- RRS 2.0 was calculated for patients in PATENT-1 and -2 using the following parameters:
  - Venice Classification 2003 (Type 1), eGFR (or renal insufficiency if eGFR was unavailable), age/sex, WHO FC, systolic BP, heart rate, 6MWD, NT-proBNP, RAP, PVR, and all-cause hospitalization within the previous 30 days (6-month data not available)
- RRS 2.0 was calculated at PATENT-1 baseline and Week 12, and PATENT-2 Week 12
- Only patients who enrolled in PATENT-2 were included in this analysis
- Missing data were imputed using last observation carried forward
  - No imputation rule for hospitalization was applied
  - No right heart catheter was planned in PATENT-2, therefore PVR and RAP values were imputed
- Patients were stratified into three risk strata at baseline and re-stratified at PATENT-1 Week 12

Risk strata	RRS 2.0
Low	≤6
Average[a]	7–9
High[b]	≥10

[a]Average (RRS 2.0 = 7–8) and moderately high (RRS 2.0 = 9) risk strata grouped into a single average risk stratum.
[b]High (RRS 2.0 = 10–11) or very high (≥12) risk strata grouped into a single higher risk stratum.
6MWD, 6-minute walking distance; BP, blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WHO FC, World Health Organization functional class.

Patient disposition



Patient characteristics at PATENT-1 baseline

Parameter, %	Placebo (n=109)	Riociguat (2.5 mg group) (n=231)	Total (N=396)
Diagnosis			
Idiopathic PAH	68	59	62
Familial PAH	1	3	2
Connective tissue disease associated PAH	17	27	24
Congenital heart disease (operated) associated PAH	11	6	8
Portal pulmonary hypertension	2	4	3
Anorexigen or amphetamine associated PAH	2	<1	1
eGFR <60 mL/min/1.73 $m^{3,a}$/eGFR ≥60 mL/min/1.73 $m^{3,b}$	15/81	18/78	17/79
Male, aged >60 years/female and/or ≤60 years	9/91	7/93	7/93
WHO FC I/II/III/IV	3/50/45/2	2/42/55/0	3/43/54/1
Systolic BP, mmHg, <110/≥110	34/66	42/58	40/60
Heart rate, bpm, >96/≤96	10/90	4/96	5/95
6MWD, m, ≥440/320–<440/165–<320/<165	15/68/17/0	16/59/23/1	14/63/22/1
NT-proBNP, pg/mL, <300/≥300–1100/>1100	29/33/27	41/24/26	37/25/27
RAP, mmHg, >20/≤20	2/98	3/97	2/98
PVR, mmHg, <400/≥400	13/87	15/85	14/86
No/hospitalization started within 30 days before visit	91/9	90/10	90/10

Percentages may not add up to 100% due to rounding or missing information.
[a]Or renal insufficiency (if eGFR is unavailable). [b]Or no renal insufficiency (if eGFR is unavailable).
bpm, beats per minute.

RRS 2.0 status at PATENT-1 baseline

- RRS 2.0 risk stratification at baseline:
  - Low: n=194 (49%)
  - Average: n=155 (39%)
  - High: n=47 (12%)

- Mean (± standard deviation) RRS 2.0 at baseline, stratified by initial treatment assignment:
  - Placebo: 6.4 ± 2.2 (n=109)
  - Riociguat (2.5 mg–maximum group): 6.5 ± 2.6 (n=231)

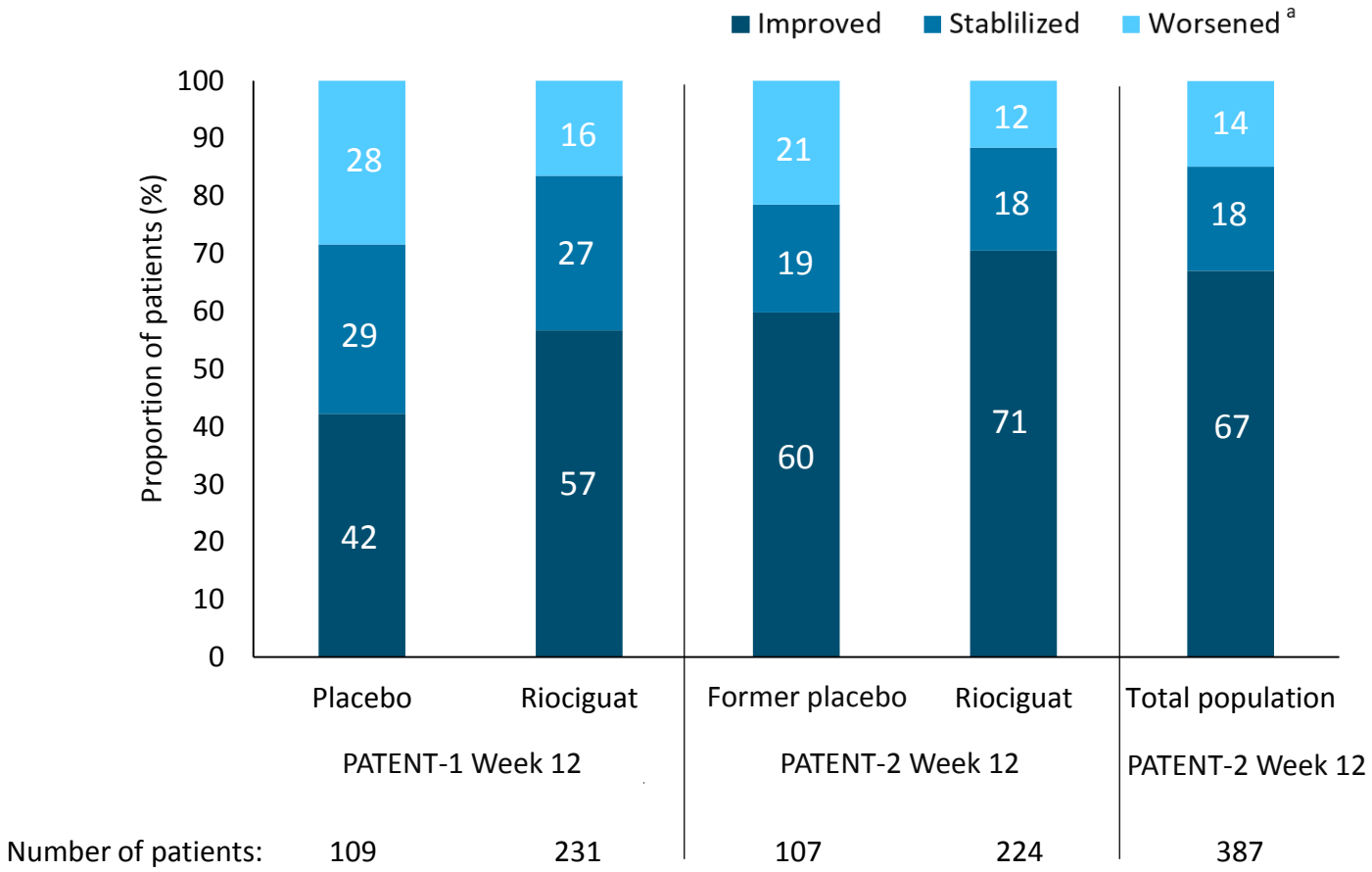
Riociguat improved RRS 2.0 in PATENT-1 and -2

	Placebo (n=109)	Riociguat (2.5 mg group) (n=231)	Total (N=396)
RRS 2.0			
Baseline	6.4 ± 2.2	6.5 ± 2.6	6.5 ± 2.5
PATENT-1 Week 12	6.4 ± 2.8	5.5 ± 2.7	5.8 ± 2.7
	Former placebo (n=107)	**Riociguat (2.5 mg group) (n=224)**	**Total (N=387)**
PATENT-2 Week 12	5.6 ± 2.7	5.1 ± 2.7	5.2 ± 2.7

- At PATENT-1 Week 12, riociguat had improved RRS 2.0 by a least-squares mean difference vs placebo of –1.0 (95% CI –1.4 to –0.6; p<0.0001)[a]

Data are mean ± standard deviation.
[a]Analysis of covariance for pairwise difference (riociguat vs placebo) for change in RRS 2.0 from baseline to PATENT-1 Week 12.
CI, confidence interval.

More patients improved risk score with riociguat compared with placebo



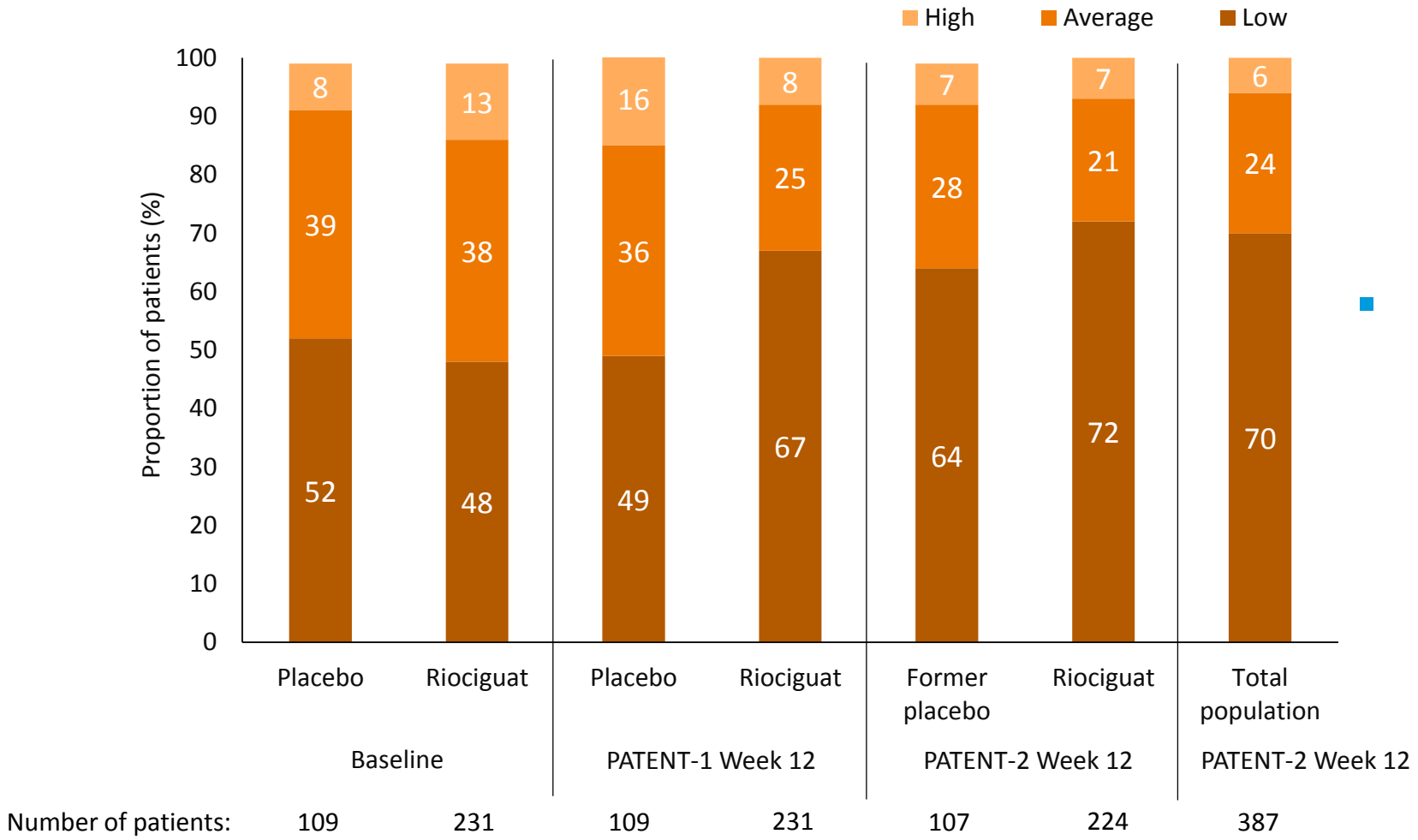
- Results were consistent with the original RRS[1]

Percentages may not add up to 100% due to rounding.

[a]Improved, stabilized, and worsened RRS 2.0 values compared with baseline values.

1. Benza RL, et al. J Heart Lung Transplant 2018;37:513–519

Proportion of patients with low, average, and high risk strata



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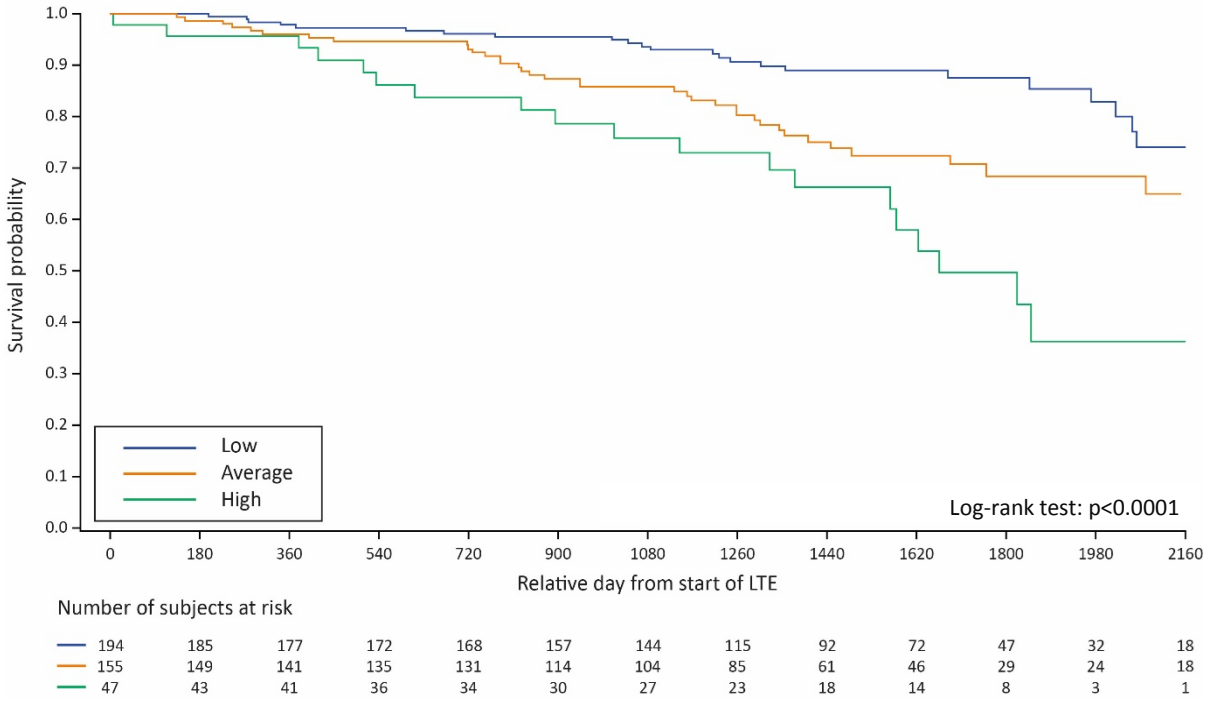
Risk stratum at baseline and Week 12 was associated with survival in PATENT-2

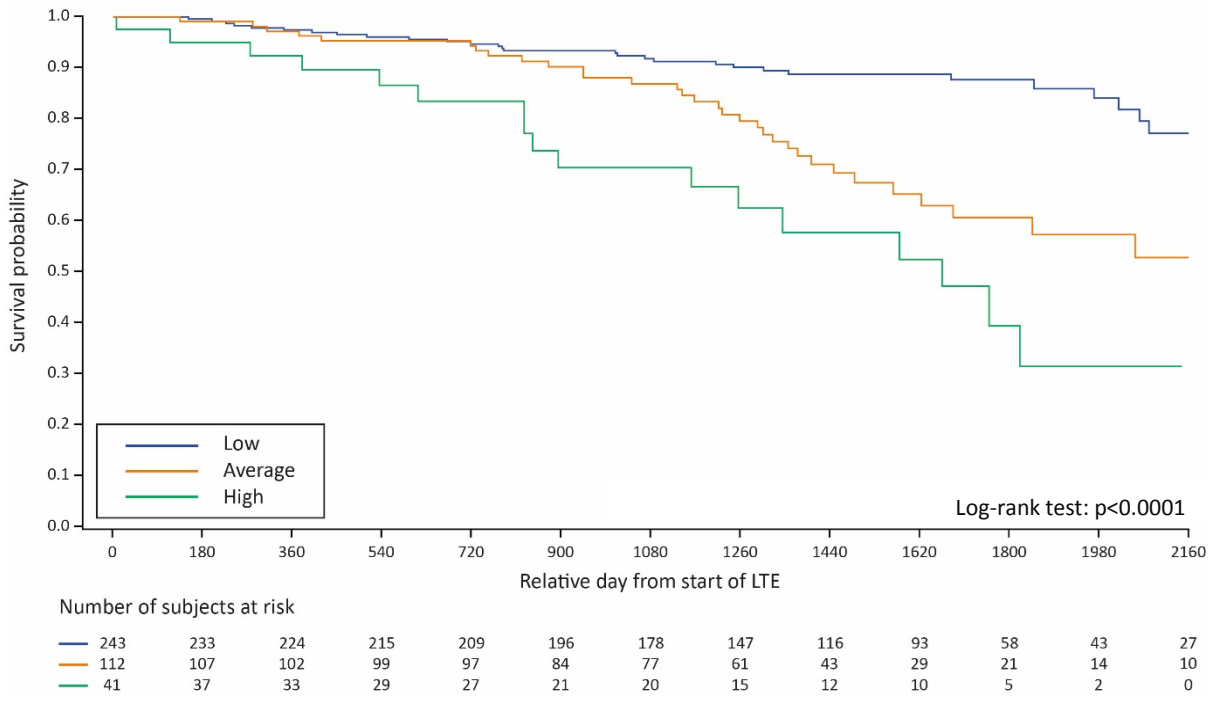
- A 1-point improvement in RRS 2.0 at baseline was associated with a 23% reduction in relative risk of a mortality event in PATENT-2

By risk stratum at baseline



Hazard ratio (95% CI) 0.77 (0.70–0.84), p<0.0001

By risk stratum at PATENT-1 Week 12



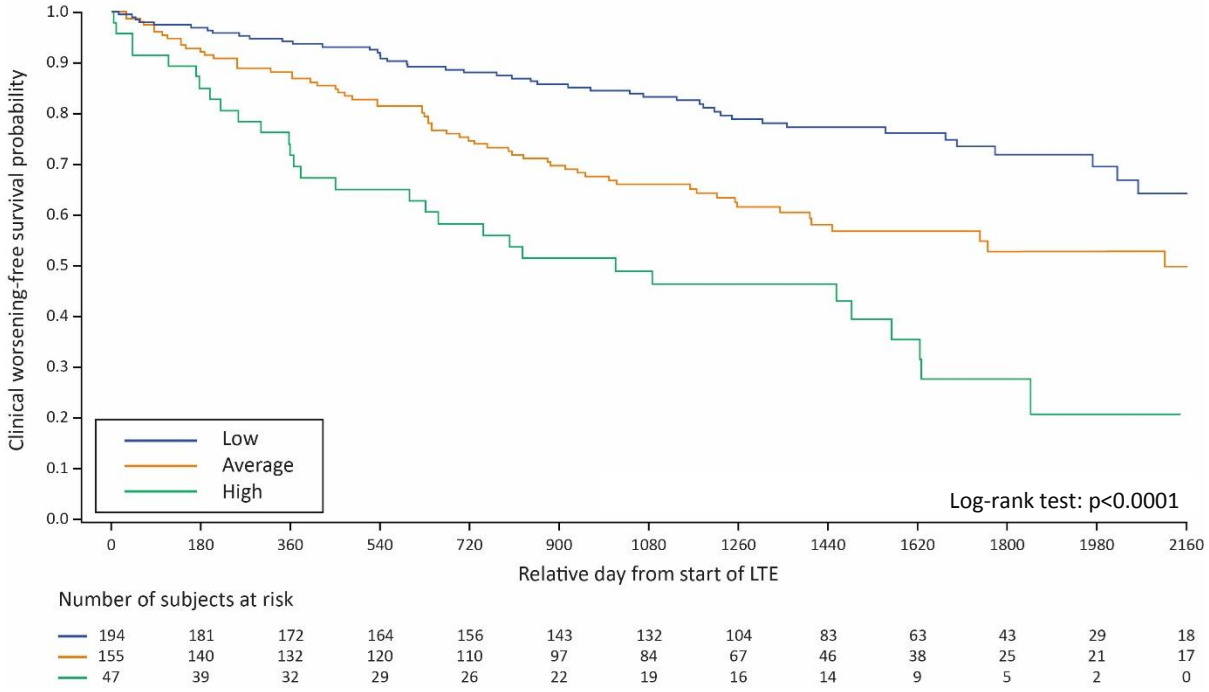
Hazard ratio (95% CI) 0.74 (0.69–0.81), p<0.0001

Day 0 refers to the start of PATENT-2.
Log-rank tests were used to determine differences between curves.
Univariate Cox proportional hazards analysis was used to predict survival by RRS 2.0 at baseline and at PATENT-1 Week 12.
A proportional hazards model including the REVEAL score 2.0 at baseline/PATENT-1 Week 12 and main study treatment as covariable was applied.

Risk stratum at baseline and Week 12 was associated with CWFS in PATENT-2

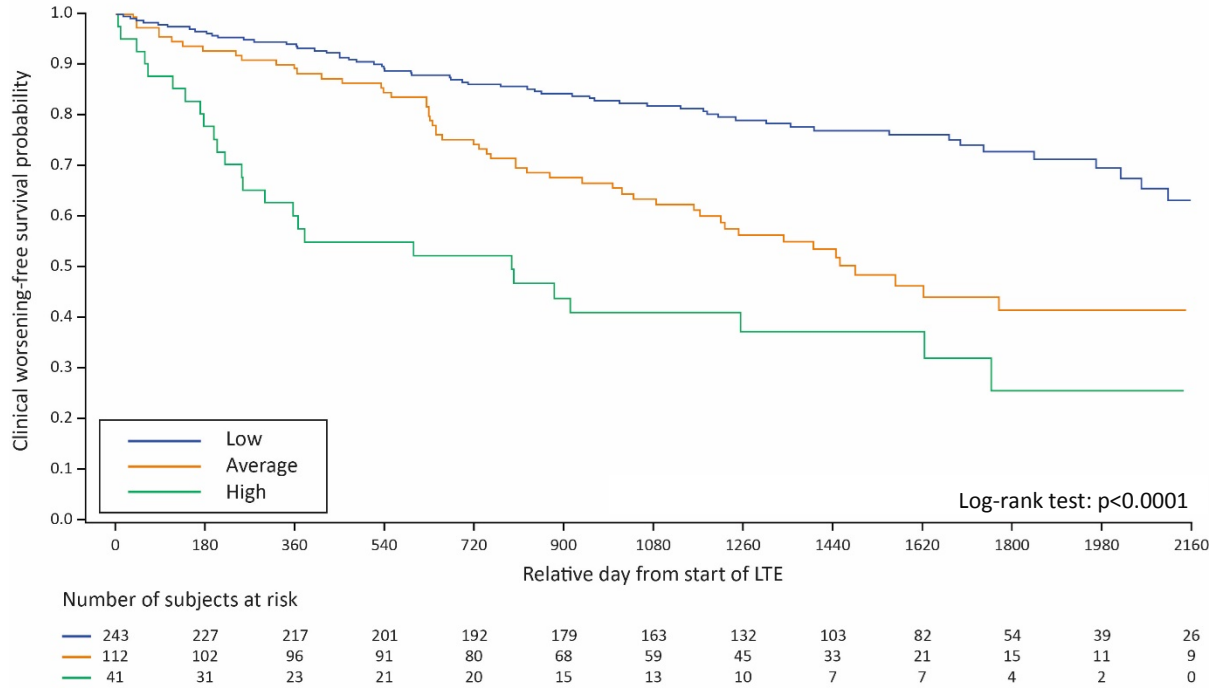
- A 1-point improvement in RRS 2.0 at baseline was associated with a 20% reduction in relative risk of a clinical worsening event in PATENT-2

By risk stratum at baseline



Hazard ratio (95% CI) 0.80 (0.74–0.86), p<0.0001

By risk stratum at PATENT-1 Week 12



Hazard ratio (95% CI) 0.77 (0.72–0.82), p<0.0001

Day 0 refers to the start of PATENT-2.
Log-rank tests were used to determine differences between curves.
Univariate Cox proportional hazards analysis was used to predict CWFS by RRS 2.0 at baseline and at PATENT-1 Week 12.
A proportional hazards model including the REVEAL score 2.0 at baseline/PATENT-1 Week 12 and main study treatment as covariable was applied.

Conclusions

- Riociguat improved RRS 2.0 and risk stratum in PATENT consistent with the original RRS
- RRS 2.0 at PATENT-1 baseline and at follow-up was predictive for survival and CWFS in patients with PAH treated with riociguat in PATENT-2
  - A 1-point improvement in RRS 2.0 at baseline was associated with a 23% reduction in relative risk of a mortality event and 20% reduction in the risk of a clinical worsening event
- RRS 2.0 is a useful tool for predicting long-term outcomes in patients with PAH and for monitoring their response to treatment

Back-up slides

Bivariate Cox proportional hazard ratio analysis: Relationship between RRS 2.0 and survival/clinical worsening

Parameter	Unit difference for HR	HR[a] (95% CI)	p-value
Survival			
Baseline RRS 2.0	–1 point	0.74 (0.67–0.81)	<0.0001
Change in RRS 2.0 from baseline to PATENT-1 Week 12	–1 point	0.76 (0.67–0.87)	<0.0001
Clinical worsening event			
Baseline RRS 2.0	–1 point	0.76 (0.71–0.82)	<0.0001
Change in RRS 2.0 from baseline to PATENT-1 Week 12	–1 point	0.79 (0.72–0.87)	<0.0001

For each parameter, baseline values and change from baseline values have been corrected for each other.
[a]Hazard 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.
HR, hazard ratio.

Estimates of survival 1 and 2 years in PATENT-2 stratified by risk at baseline, and again at PATENT-1 Week 12

Time point	Risk strata	Survival estimate by risk stratum at baseline, % (95% CI)	Survival estimate by risk stratum at PATENT-1 Week 12, % (95% CI)
Survival			
1 year	Low	98 (94–99)	97 (94–99)
	Average	96 (91–98)	97 (92–99)
	High	96 (84–99)	92 (78–97)
	Total	97 (95–98)	97 (95–98)
2 years	Low	96 (92–98)	95 (91–97)
	Average	92 (87–96)	93 (87–97)
	High	84 (69–92)	84 (67–92)

Estimates of CWFS at 1 and 2 years in PATENT-2 stratified by risk at baseline, and again at PATENT-1 Week 12

Time point	Risk strata	Survival estimate by risk stratum at baseline, % (95% CI)	Survival estimate by risk stratum at PATENT-1 Week 12, % (95% CI)
Clinical worsening-free survival			
1 year	Low	94 (89–96)	93 (89–96)
	Average	87 (80–91)	88 (81–93)
	High	72 (56–83)	60 (43–73)
	Total	88 (85–91)	88 (85–91)
2 years	Low	88 (82–92)	86 (81–90)
	Average	74 (66–80)	73 (64–81)
	High	58 (43–71)	52 (36–66)

Acknowledgments

- PATENT-1 and PATENT-2 were funded by Bayer AG, Berlin, Germany and Merck Sharp & Dohme, Kenilworth, New Jersey, USA
- Medical writing services were provided by Rachael Powis, PhD of Adelphi Communications Ltd (Macclesfield, UK) funded by Bayer AG (Berlin, Germany) in accordance with Good Publications Practice (GPP3)