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Effect of riociguat on right ventricular function in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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KEYWORDS:
hypertension, pulmonary;

BACKGROUND: In the Phase III PATENT-1 (NCT00810693) and CHEST-1 (NCT00855465) studies, riociguat demonstrated efficacy vs placebo in patients with pulmonary arterial hypertension (PAH) and

[1]**Twitter information**: First/corresponding author: @OSUWexMedSummary tweet: "Post hoc analysis of the PATENT and CHEST studies suggests that riociguat improves parameters of right ventricular function, including stroke volume index and right atrial pressure, which are significantly associated with clinical outcomes"

Abbreviations: 6MWD, 6-minute walking distance; CTEPH, chronic thromboembolic pulmonary hypertension; CWFS, clinical worsening-free survival; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RRS, REVEAL Risk Score; RV, right ventricular; SD, standard deviation; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVI, stroke volume index; WHO FC, World Health Organization Functional Class.

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ventricular function, right;
PAH;
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chronic thromboembolic pulmonary hypertension (CTEPH). Clinical effects were maintained at 2 years in the long-term extension studies PATENT-2 (NCT00863681) and CHEST-2 (NCT00910429).

METHODS: This post hoc analysis of hemodynamic data from PATENT-1 and CHEST-1 assessed whether riociguat improved right ventricular (RV) function parameters including stroke volume index (SVI), stroke volume, RV work index, and cardiac efficiency. REVEAL Risk Score (RRS) was calculated for patients stratified by SVI and right atrial pressure (RAP) at baseline and follow-up. The association between RV function parameters and SVI and RAP stratification with long-term outcomes was assessed.

RESULTS: In PATENT-1 (n = 341) and CHEST-1 (n = 238), riociguat improved RV function parameters vs placebo ($p < 0.05$). At follow-up, there were significant differences in RRS between patients with favorable and unfavorable SVI and RAP, irrespective of treatment arm ($p < 0.0001$). Multiple RV function parameters at baseline and follow-up were associated with survival and clinical worsening-free survival (CWFS) in PATENT-2 (n = 396; $p < 0.05$) and CHEST-2 (n = 237). In PATENT-2, favorable SVI and RAP at follow-up only was associated with survival and CWFS ($p < 0.05$), while in CHEST-2, favorable SVI and RAP at baseline and follow-up were associated with survival and CWFS ($p < 0.05$).

CONCLUSION: This post hoc analysis of PATENT and CHEST suggests that riociguat improves RV function in patients with PAH and CTEPH.

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Mortality in patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) is generally the result of right ventricular (RV) failure.[1-3] Risk of mortality in PAH can be predicted using composite scores[4-6] such as the REVEAL Risk Score (RRS),[7-9] or risk scores based on the European Society of Cardiology/European Respiratory Society risk assessment tool.[10-12] The RRS is a validated predictor of 1-year mortality and response to treatment, based on data from the REVEAL Registry of patients with PAH and is a weighted score designed to reflect signs of RV failure based on parameters including pulmonary hemodynamics, World Health Organization Functional Class (WHO FC), and exercise capacity (6-minute walking distance [6MWD]), which are commonly used to assess the efficacy of treatments for PAH.[13] The recently updated RRS calculator, REVEAL 2.0, demonstrated greater risk discrimination in patients in REVEAL compared with other abbreviated risk scores.[14] No specific risk prediction tools for CTEPH have been developed; however, the RRS was shown to predict survival and clinical worsening-free survival (CWFS) in CHEST-2,[15] and an abbreviated version of the European Society of Cardiology/European Respiratory Society risk assessment predicted mortality in non-operated patients with CTEPH in the COMPERA registry.[16]

In the pivotal Phase III PATENT-1 and CHEST-1 studies, the soluble guanylate cyclase stimulator riociguat significantly improved 6MWD, WHO FC, and pulmonary hemodynamics vs placebo in patients with PAH and inoperable and persistent/recurrent CTEPH following pulmonary endarterectomy (PEA) after 12 and 16 weeks, respectively.[17,18] Further analysis of PATENT-1 data confirmed that riociguat significantly improved multiple hemodynamic parameters in pre-treated and treatment-naïve patients with PAH.[19] The long-term extension studies PATENT-2 and CHEST-2 showed that improvements in 6MWD and WHO FC with riociguat treatment were maintained at 2 years, supporting the long-term use of riociguat in patients with PAH and CTEPH.[20,21] Post hoc analyses of the PATENT and CHEST databases showed that riociguat improved RRS from baseline to Week 12 or 16, respectively, compared with placebo, and that RRS at baseline, Week 12 or Week 16, and change in RRS were predictors of survival and CWFS in PATENT-2 and CHEST-2, respectively.[9,15] Similar findings have been made with the French non-invasive and Swedish/COMPERA methods of risk assessment.[10] Moreover, data from the RIVER study showed that long-term treatment with riociguat significantly reduced right-heart size and improved RV function assessed by echocardiography in patients with PAH and CTEPH.[22]

A recent retrospective assessment of the prognostic value of a range of hemodynamic variables at follow-up after initial treatment of PAH in the French Pulmonary Hypertension registry showed that stroke volume index (SVI) and right atrial pressure (RAP) were independent prognostic variables for survival.[23]

We performed a post hoc analysis to determine whether riociguat improved a range of calculated parameters of RV function in the PATENT-1 and CHEST-1 studies. In addition, patients were stratified according to SVI and RAP at baseline and follow-up. Finally, we evaluated the relationship of RV function parameters and SVI/RAP subgroup with long-term outcomes in PATENT-2 and CHEST-2.

Methods

This was a post hoc analysis of data from the randomized, placebo-controlled Phase III PATENT-1 (NCT00810693) and CHEST-1 (NCT00855465) studies. The study designs and results have been published previously.[17,18] Patients underwent right-heart catheterization at baseline and at Week 12 in PATENT-1 and Week 16 in CHEST-1 (follow-up). Hemodynamic parameters

included pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), systolic pulmonary artery pressure (sPAP), RAP, cardiac output, and cardiac index.[17,18] Clinical worsening was defined as first occurrence of all-cause death, heart/lung transplantation, hospitalization due to persistent worsening of pulmonary hypertension (PH), modification of pre-existing prostanoid treatment, persistent decrease of 6MWD >15% from baseline or >30% vs the last study-related measurement due to worsening PH, or persistent worsening of WHO FC due to PH deterioration. Further criteria were specific to each trial: atrial septostomy or start of new PH-specific treatment (PATENT-1 only); or rescue PEA due to persistent worsening of PH (CHEST-1 only). Patients who completed PATENT-1 and CHEST-1 without ongoing riociguat-related adverse events were eligible to enter the PATENT-2 and CHEST-2 open-label extensions. Both studies were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and all patients provided written informed consent. The institutional review board at each participating center approved each protocol.

Parameters of cardiac function

Parameters of RV function were calculated from right-heart catheterization data as follows: stroke volume (SV) (cardiac output [in mL/min]/heart rate); SVI (cardiac index [in mL/min/m^2]/heart rate); cardiac efficiency (SV/mPAP); pulmonary artery (PA) elastance (sPAP/SV); RV work (cardiac output × mPAP × 0.0144); RV work index (cardiac index × mPAP × 0.0144); and RV power (mPAP × cardiac index).[24]

Patients were stratified into 3 subgroups based on combined thresholds for SVI (≥31 mL/beat/m^2 and <31 mL/beat/m^2) and RAP (≥10 mmHg and <10 mmHg).[23] The subgroups were classified as favorable (SVI ≥31 mL/beat/m^2 and RAP <10 mmHg), intermediate (SVI <31 mL/beat/m^2 and RAP <10 mmHg, or SVI ≥31 mL/beat/m^2 and RAP ≥10 mmHg), or unfavorable (SVI <31 mL/beat/m^2 and RAP ≥10 mmHg) combined SVI/RAP.

REVEAL risk score

RRS was evaluated using the REVEAL 2.0 calculator[14] at baseline and follow-up in subgroups of patients stratified by combined SVI/RAP. Data for 2 parameters in the RRS calculation, pericardial effusion and diffusing capacity of the lung for carbon monoxide, were not available for PATENT or CHEST, along with PAH subtype (CHEST only); however, the RRS only requires 7 evaluable elements to maintain significant predictive power and calibration.[1,8,14]

Statistical analysis

In both PATENT and CHEST, to reduce bias and include all randomized and treated patients, imputation for missing values was performed at follow-up as previously described.[17,18] Changes from baseline to follow-up in parameters of RV function were analyzed by analysis of covariance, followed by a test of normality of the residuals and a non-parametric stratified Wilcoxon test on rejection. Differences in RRS between SVI or RAP threshold subgroups were assessed using a stratified Wilcoxon test. Pearson correlation coefficients were calculated for the relationships between RRS and parameters of RV function at baseline, at follow-up, and for change from baseline at follow-up. Long-term outcomes were assessed only in patients who participated in PATENT-2 and CHEST-2, who received riociguat up to 2.5 mg 3 times daily in PATENT-1 or CHEST-1, and missing data were not imputed. A univariate Cox proportional hazards model was used to determine the relationships between RV function parameters at baseline and at follow-up with survival and CWFS in PATENT-2 or CHEST-2. Kaplan−Meier analyses were used to determine survival and CWFS, measured from the start of PATENT-2 or CHEST-2. Differences between Kaplan−Meier curves were determined using log-rank tests. Statistical significance was defined at a level of $p < 0.05$.

Results

Patients

The analysis of RV function parameters included 341 patients with PAH (riociguat, $n = 233$; placebo, $n = 108$) and 238 patients with CTEPH (riociguat, $n = 155$; placebo, $n = 83$). Patient characteristics have been published previously.[25,26]

Riociguat and right ventricular function

At follow-up in PATENT-1 (Table 1) and CHEST-1 (Table 2) there were significant improvements in all RV function parameters assessed in riociguat-treated patients vs placebo-treated patients, with a negative correlation between SVI and RAP at baseline and follow-up (Table S1).

SVI was negatively correlated with RRS, and RAP was positively correlated with RRS at baseline and follow-up in PATENT-1 and CHEST-1 (Table S2). In both studies, patients with a favorable SVI/RAP (SVI ≥31 mL/beat/m^2 and RAP <10 mmHg; green quadrant, Figure 1) at baseline had a lower mean RRS compared with those with an unfavorable SVI/RAP (SVI <31 mL/beat/m^2 and RAP ≥10 mmHg; red quadrant, Figure 1) (difference in RRS between the SVI/RAP subgroups in each treatment arm: $p < 0.0001$). At PATENT-1 follow-up, the proportion of patients in the favorable RAP/SVI subgroup increased from 51% at baseline to 65% in the riociguat arm and decreased from 40% to 35% in the placebo arm, while the percentage of patients in the unfavorable SVI/RAP subgroup decreased from 18% to 7% in the riociguat arm and increased from 17% to 24% in the placebo arm. At CHEST-1 follow-up, the proportion of patients in the favorable RAP/SVI subgroup increased from 36% at baseline to 53% in the riociguat arm and decreased from 35% to 31% in the placebo arm, while the percentage of patients in the unfavorable RAP/SVI subgroup decreased from 30% to 15% in the riociguat arm and increased marginally from 23% to 24% in the placebo arm. Similar to baseline, RRS was lower in patients with favorable SVI/RAPs vs those with unfavorable SVI/RAPs in both studies (difference between subgroups at follow-up: $p < 0.0001$).

RV function and long-term outcomes

Cox proportional hazards analyses showed that several RV function parameters at baseline and follow-up were associated with survival and CWFS in both studies (Tables S3 and S4). In particular, SVI at follow-up was associated with

Table 1 Change in Parameters of Cardiac Function from Baseline to Week 12 in PATENT-1

	Riociguat (n = 233)			Placebo (n = 108)			
Parameter, mean ± SD	Baseline	Week 12	Change from baseline	Baseline	Week 12	Change from baseline	p value comparing change[a]
SV (mL/beat)[b]	58.10 ± 18.32	68.73 ± 20.30	10.63 ± 13.68	56.64 ± 20.28	56.98 ± 20.21	0.33 ± 16.30	< 0.0001
SVI (mL/beat/m^2)[b]	33.71 ± 9.68	39.87 ± 10.26	6.16 ± 7.87	32.74 ± 11.59	32.70 ± 10.28	−0.04 ± 9.52	< 0.0001
Cardiac efficiency (mL/beat/mmHg)[b]	1.38 ± 0.65	1.82 ± 0.96	0.44 ± 0.60	1.31 ± 0.66	1.40 ± 0.87	0.09 ± 0.57	< 0.0001
PA elastance (mmHg/mL/beat)[b]	1.54 ± 0.91	1.20 ± 0.68	−0.34 ± 0.53	1.65 ± 0.96	1.67 ± 0.97	0.02 ± 0.65	< 0.0001
RV work (L/min/mmHg)	2.89 ± 1.10	3.19 ± 1.17	0.30 ± 0.78	2.99 ± 1.30	2.90 ± 1.08	−0.10 ± 0.94	0.0002
RV work index (L/min/m^2/mmHg)	1.69 ± 0.60	1.86 ± 0.63	0.17 ± 0.46	1.74 ± 0.77	1.67 ± 0.60	−0.07 ± 0.57	< 0.0001
RV power (mmHg [L/min])	0.45 ± 0.17	0.49 ± 0.18	0.05 ± 0.12	0.46 ± 0.20	0.45 ± 0.17	−0.02 ± 0.15	0.0002

SV = cardiac output (in mL/min)/heart rate; SVI = cardiac index (in mL/min/m^2)/heart rate; cardiac efficiency = SV/mPAP; PA elastance = sPAP/SV; RV work = cardiac output × mPAP × 0.0144; RV work index = cardiac index × mPAP × 0.0144; RV power = mPAP × cardiac index.

Abbreviations: mPAP, mean pulmonary artery pressure; PA, pulmonary artery; RV, right ventricular; SD, standard deviation; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVI, stroke volume index.

[a]The p value from the stratified Wilcoxon test is shown, as the normality assumption was rejected by the Shapiro–Wilk test for all parameters; stratification factors for the Wilcoxon test were treatment status (therapy-naïve, pre-treated) and region (North America, South America, Europe, China, Asia/Pacific).

[b]Riociguat, n = 227.

Table 2 Change in Parameters of Cardiac Function from Baseline to Week 16 in CHEST-1

	Riociguat (n = 155)			Placebo (n = 83)			
Parameter, mean ± SD	Baseline	Week 16	Change from baseline	Baseline	Week 16	Change from baseline	p value comparing change[a]
SV (mL/beat)[b]	54.33 ± 17.26	63.47 ± 19.07	9.14 ± 15.37	55.70 ± 19.32	53.33 ± 18.98	−2.36 ± 14.69	< 0.0001
SVI (mL/beat/m^2)[b]	30.14 ± 9.30	35.20 ± 10.27	5.07 ± 8.51	30.10 ± 9.78	29.03 ± 10.39	−1.07 ± 7.92	< 0.0001
Cardiac efficiency (mL/beat/mmHg)[b]	1.31 ± 0.59	1.72 ± 0.81	0.41 ± 0.53	1.36 ± 0.63	1.32 ± 0.71	−0.03 ± 0.53	< 0.0001
PA elastance (mmHg/mL/beat)[b]	1.66 ± 0.95	1.28 ± 0.66	−0.38 ± 0.59	1.61 ± 0.80	1.74 ± 0.91	0.13 ± 0.55	< 0.0001
RV work (L/min/mmHg)	2.62 ± 1.00	2.85 ± 1.16	0.23 ± 0.92	2.58 ± 1.06	2.55 ± 0.87	−0.02 ± 0.83	0.0317
RV work index (L/min/m^2/mmHg)	1.45 ± 0.54	1.57 ± 0.62	0.12 ± 0.50	1.39 ± 0.52	1.39 ± 0.46	−0.00 ± 0.45	0.0338
RV power (mmHg [L/min])	0.40 ± 0.15	0.44 ± 0.18	0.04 ± 0.14	0.40 ± 0.16	0.39 ± 0.13	−0.00 ± 0.13	0.0317

SV = cardiac output (in mL/min)/heart rate; SVI = cardiac index (in mL/min/m^2)/heart rate; cardiac efficiency = SV/mPAP; PA elastance = sPAP/SV; RV work = cardiac output × mPAP × 0.0144; RV work index = cardiac index × mPAP × 0.0144; RV power = mPAP × cardiac index.

Abbreviations: mPAP, mean pulmonary artery pressure; PA, pulmonary artery; RV, right ventricular; SD, standard deviation; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVI, stroke volume index.

[a]The p value from the stratified Wilcoxon test is shown, as the normality assumption was rejected by the Shapiro–Wilk test for all parameters; the stratification factor for the Wilcoxon test was region (North America, South America, Europe, China, Asia/Pacific).

[b]Riociguat, n = 154; placebo, n = 81.

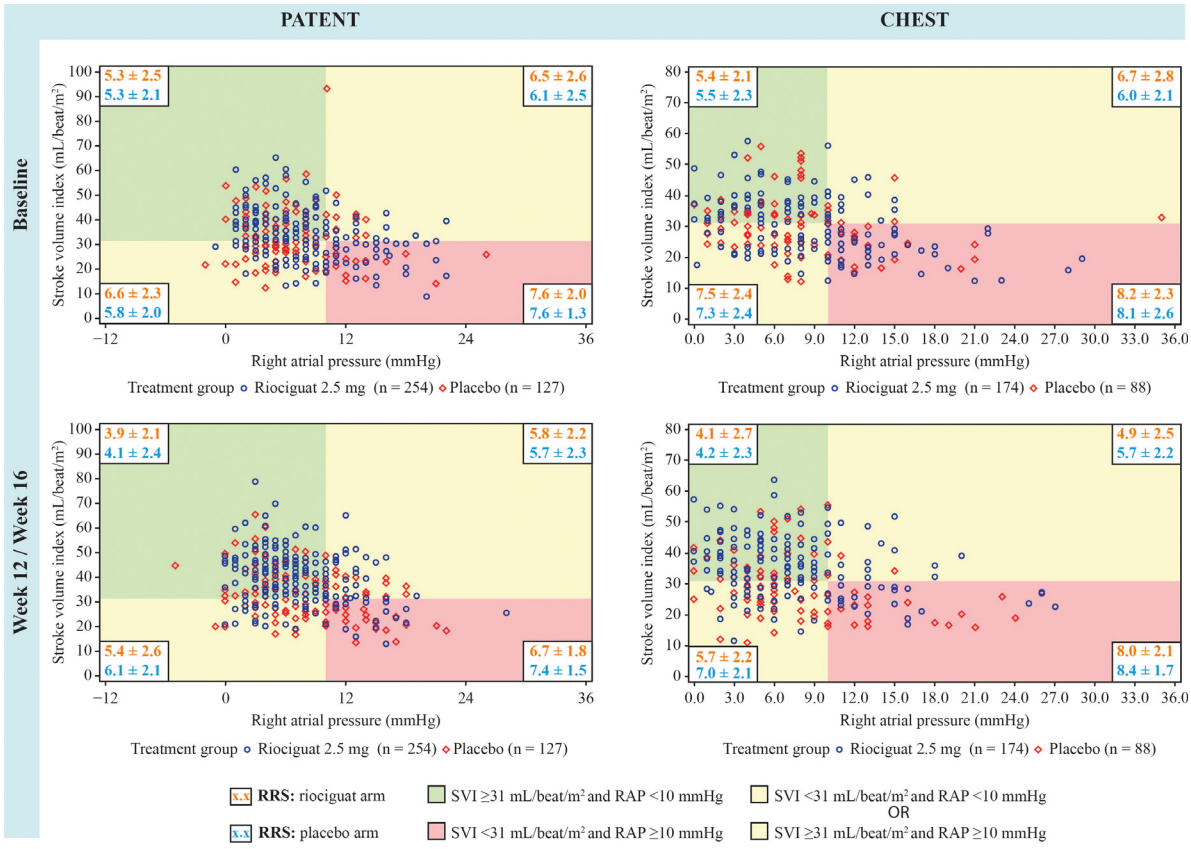

Figure 1 Scatterplots of individual patient data of SVI vs RAP stratified by SVI/RAP with mean RRS for each subgroup at baseline and Week 12 in PATENT-1, and baseline and Week 16 in CHEST-1.

Mean RRS ± SD is displayed on each quadrant for riociguat (orange text) and placebo (blue text). SVI threshold: 31 mL/beat/m^2; RAP threshold: 10 mmHg. Patients with missing SVI or RAP values were excluded. *P* value for difference between quadrants <0.0001 (stratified Wilcoxon test). RAP, right atrial pressure; RRS, REVEAL Risk Score; SD, standard deviation; SVI, stroke volume index.

survival (Table S3); for every 10 mL/beat/m^2 difference in SVI at follow-up, there was a 38% hazard reduction in survival in PATENT-2 and a 50% hazard reduction in survival in CHEST-2 (Table S3). SVI at baseline and follow-up was also significantly associated with CWFS in both studies (Table S4). Survival and CWFS were also assessed by SVI/RAP subgroup at baseline and follow-up. In PATENT-2 and CHEST-2, there were significant differences in survival between the favorable, intermediate, and unfavorable SVI/RAP subgroups at baseline and follow-up (Figure 2). In CHEST-2, but not PATENT-2, there was a significant difference in CWFS between the SVI/RAP subgroups at baseline (Figure 3). When re-stratified by SVI/RAP at follow-up, CWFS was significantly different between the subgroups in both studies (Figure 3).

Discussion

This post hoc analysis of PATENT-1 and CHEST-1 suggests that riociguat improves RV hemodynamic function in patients with PAH and inoperable or persistent/recurrent CTEPH, following 12 or 16 weeks' treatment. Furthermore, these adjunct hemodynamic parameters were significantly associated with survival.

Both SVI and RAP correlated significantly with RRS at baseline and at follow-up, demonstrating that the utility of RRS is intertwined with RV function. In both PATENT-1 and CHEST-1, more riociguat-treated patients achieved a favorable threshold of SVI ≥31 mL/beat/m^2 or RAP <10 mmHg[23] compared with placebo-treated patients. Similarly, fewer riociguat-treated patients than placebo-treated patients had an unfavorable SVI/RAP profile at follow-up, and riociguat treatment reduced RRS in all patients vs placebo. Cox proportional hazards analysis showed that several parameters of RV function were associated with survival and/or CWFS. Notably, favorable SVI and combined SVI/RAP at follow-up were associated with survival and CWFS, although in PATENT-1, there was no significant difference between the SVI/RAP groups at baseline in terms of CWFS in PATENT-2. This is not unexpected, as follow-up data take into account changes in therapy and management since baseline. Our data are consistent with the observations of Weatherald et al., whose retrospective registry study in patients with PAH showed that SVI and RAP at follow-up were independent prognostic variables.[23] In 1991, the National Institutes of Health registry identified RAP, cardiac index, and mPAP as important predictors of survival,[27] and in this study it is RAP that remains significant for prognostication.

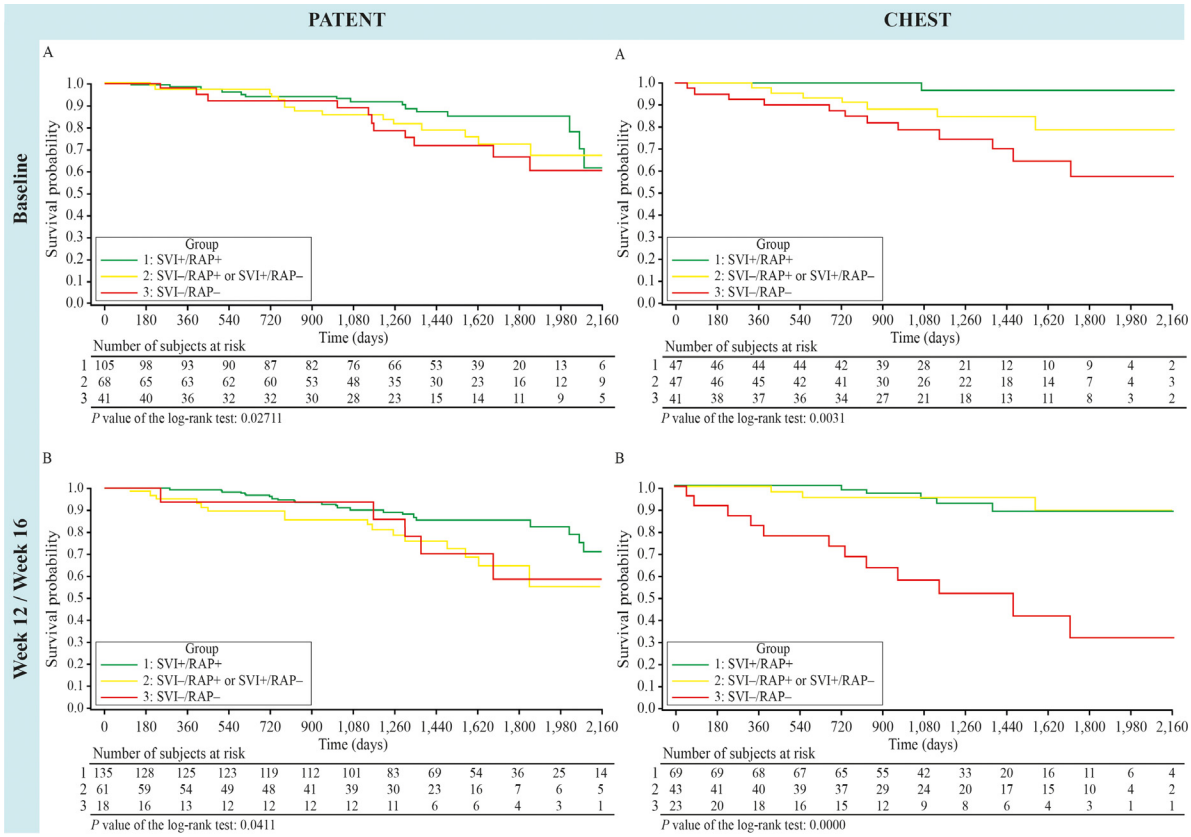

Figure 2 Kaplan–Meier plot and Cox proportional hazards analysis for survival in PATENT-2 and CHEST-2 by SVI/RAP subgroup at baseline and Week 12 in PATENT-1/Week 16 in CHEST-1. Favorable SVI/RAP: SVI ≥31 mL/beat/m^2 and RAP <10 mmHg; intermediate SVI/RAP: SVI <31 mL/beats/m^2 and RAP <10 mmHg or SVI ≥31 mL/beats/m^2 and RAP ≥10 mmHg; unfavorable SVI/RAP: SVI <31 mL/beats/m^2 and RAP ≥10 mmHg. RAP, right atrial pressure; SVI, stroke volume index.

The improvements in RV function in this analysis are consistent with the retrospective RIVER study, in which echocardiographic data from 71 German patients who participated in 1 of 5 riociguat studies (riociguat Phase II study, PATENT-1, CHEST-1, PATENT PLUS, and the CTEPH Early Access Study) were analyzed by reviewers blinded to the original clinical data.[22] In riociguat-treated patients there were significant improvements in RAP, RV area, RV thickness, and tricuspid regurgitation velocity and RV fractional area. The results from this analysis are also consistent with the RESPITE study, where riociguat improved parameters of RV function such as cardiac efficiency, SV, and SVI; at Week 24, 69% of responders (defined as free from clinical worsening, WHO FC I/II, and with an improvement in 6MWD of ≥30 m) and 48% of non-responders had achieved a favorable SVI/RAP, while 13% of responders and 23% of non-responders had not.[28]

Improvements in cardiac function have been reported in patients with PAH treated with other PAH-approved therapies. The benefits of parenteral prostanoid treatment on RV function have been observed in several small studies;[29-32] improved RV function has also been reported in small studies with bosentan[33-36] and upfront combination therapy.[37] Fewer studies evaluating RV function have been conducted in CTEPH compared with PAH; however, inhaled iloprost has demonstrated benefits on RV function in patients with persistent PH after PEA,[38,39] as have bosentan[40,41] and sildenafil.[42]

The strengths of this study include the large patient cohort with robust data derived from Phase III, randomized, placebo-controlled trials, and the use of multiple adjunct hemodynamic and paired variables to evaluate RV performance. These variables are often used to assess left ventricular performance in left-heart disease,[43-45] but are rarely utilized in PAH despite giving a more global summary of RV performance than traditional factors such as PVR and cardiac output. In addition, the novel use of paired parameters such as SVI and RAP also affords clinicians a better estimation of the balance between RV output and filling and their combined relationship to outcome. This relationship may ultimately be more important than each variable assessed in isolation. In this manner, this study has introduced a new hemodynamic vocabulary to the area of RV dysfunction in PAH. These alternative assessments may then be explored and validated later in other studies and could pave the way for their incorporation into contemporary risk assessments for this disease.

We recognize the several important limitations with this study, including its exploratory, post hoc nature. In addition, patients who did not complete PATENT-1 and CHEST-1 and patients who received placebo in PATENT-1 and CHEST-1 were not included in the analyses of long-term outcomes, which may have introduced a bias in terms

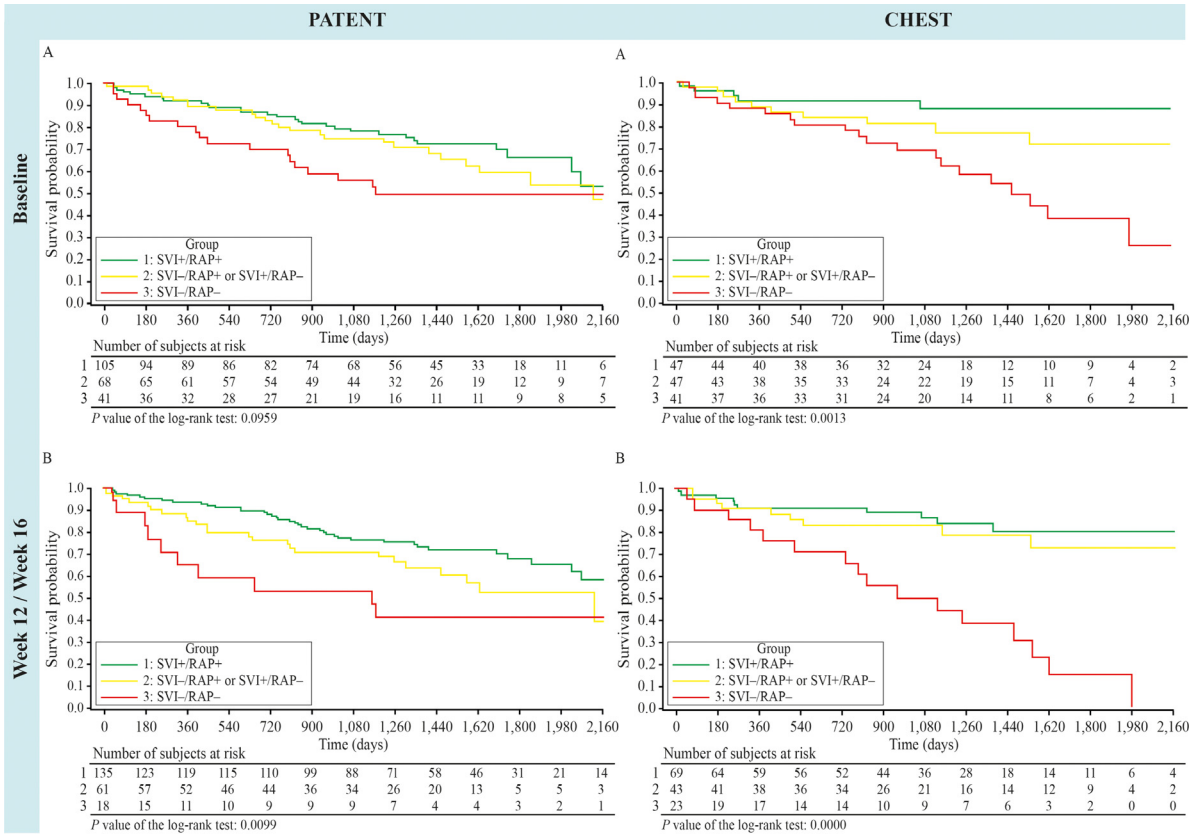

Figure 3 Kaplan–Meier plot for clinical worsening-free survival and Cox proportional hazards analysis in PATENT-2 and CHEST-2 by SVI/RAP subgroup at baseline and Week 12 in PATENT-1/Week 16 in CHEST-1.

Favorable SVI/RAP: SVI ≥31 mL/beat/m^2 and RAP <10 mmHg; intermediate SVI/RAP: SVI <31 mL/beat/m^2 and RAP <10 mmHg or SVI ≥31 mL/beat/m^2 and RAP ≥10 mmHg; unfavorable SVI/RAP: SVI <31 mL/beats/m^2 and RAP ≥10 mmHg. RAP, right atrial pressure; SVI, stroke volume index.

of survival, and, thirdly, the low mortality rates observed in PATENT-2 and CHEST-2 may have also biased the survival results, as the population who participated in the long-term extensions had already improved in response to treatment in the randomized phase. In addition, the survival curves for patients in PATENT-2 classified by SVI/RAP subgroup intersect, and therefore the proportional hazards assumption is probably not met. The survival curves for CHEST-2, however, showed more distinctive survival patterns. Finally, no imaging data were analyzed as part of the present analysis to provide insight into parameters such as RV systolic and diastolic function, and coronary perfusion/ischemia of the right ventricle. Future studies, such as the cardiac magnetic resonance imaging subgroup of the REPLACE study,[46] may provide more information on the impact of riociguat on cardiac function in patients with PAH or CTEPH.

Conclusion

These data suggest that riociguat improved RV function as measured by a variety of adjunct hemodynamic parameters in patients with PAH and CTEPH. SVI was negatively correlated with RRS, and RAP was positively correlated with RRS at baseline and follow-up in both studies. Multiple RV function parameters at baseline and follow-up were associated with survival and CWFS in PATENT-2 and CHEST-2, and a combined threshold of SVI ≥31 mL/beat/m^2 and RAP <10 mmHg at follow-up was significantly associated with survival and CWFS in PATENT-2 and CHEST-2. SVI and RAP as markers of systolic and diastolic RV function may provide additional information to follow the progress of patients with PAH or CTEPH.

Author contributions

RLB: study conceptualization, supervision and data collection, review and editing of manuscript drafts, and approval of the final draft for submission; **H-AG**: supervision and data collection, review and editing of manuscript drafts, and approval of the final draft for submission; **EG**: supervision and data collection, review and editing of manuscript drafts, and approval of the final draft for submission; **MMH**: supervision and data collection, review and editing of manuscript drafts, and approval of the final draft for submission; **PJ**: supervision and data collection, review and editing of manuscript drafts, and approval of the final draft for submission; **Z-CJ**: supervision and data collection, review and editing of manuscript drafts, and approval of the final draft for submission; **NHK**: supervision and data collection, review and editing of manuscript drafts,

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Supplementary materials

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