DOI: 10.1002/pul2.12274

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

The risk profile change in patients with severe chronic thromboembolic pulmonary hypertension treated with subcutaneous treprostinil

Pavel Jansa[1] | **Grzegorz Kopeć**[2] | **Adam Torbicki**[3] | **Roela Sadushi-Kolici**[4] | **Ioana-Alexandra Campean**[4] | **Michael Halank**[5] | **Iveta Simkova**[6] | **Regina Steringer-Mascherbauer**[7] | **Barbara Salobir**[8] | **Walter Klepetko**[9] | **Jaroslav Lindner**[10] | **Irene M. Lang**[4]

[1]Clinical Department of Cardiology and Angiology of the 2nd Department of Medicine, General University Hospital, Prague, Czech Republic

[2]Department of Cardiac and Vascular Diseases, Pulmonary Circulation Centre, Jagiellonian University Medical College and John Paul II Hospital in Krakow, Krakow, Poland

[3]Department of Pulmonary Circulation and Thromboembolic Diseases, European Health Center, Otwock, Poland

[4]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria

[5]Department of Internal Medicine I, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[6]Department of Cardiology and Angiology of Medical Faculty, Slovak Medical University and National Institute of Cardiovascular Diseases, Bratislava, Slovakia

[7]Department of Internal Medicine II, Ordensklinikum Linz Elisabethinen, Linz, Austria

[8]Department of Pulmonary Diseases and Allergy, Ljubljana University Medical Centre, Ljubljana, Slovenia

[9]Department of Cardiothoracic Surgery, Medical University of Vienna, Vienna, Austria

[10]2nd Department of Surgery—Department of Cardiovascular Surgery, General University Hospital, Prague, Czech Republic

Correspondence
Pavel Jansa, Clinical Department of Cardiology and Angiology of the 2nd Department of Medicine, General University Hospital, U Nemocnice 499/2, Prague 2, Prague 128 08, Czech Republic.
Email: pavel.jansa@vfn.cz

Funding information
AOP Orphan

Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is successfully treatable with pulmonary endarterectomy (PEA), balloon pulmonary angioplasty, and medical therapy. Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management risk score (RRS) is able to predict long-term outcome in inoperable patients or in patients with residual PH after surgery. We performed a post hoc analysis of RRS in patients who were enrolled in the CTREPH study (NCT01416636), a randomized, double-blind clinical trial comparing high-dose and low-dose subcutaneous (SC) treprostinil in patients with severe CTEPH that was classified by an interdisciplinary CTEPH team as nonoperable, or as persistent or recurrent pulmonary hypertension after PEA. Baseline mean RRS was similar in both treatment groups (8.7 in high-dose arm vs. 8.6 in low-dose arm), but mean RRS change from baseline to Week 24 was greater in the high-dose treprostinil

group than in the low-dose treprostinil group (−0.88 vs. −0.17). The difference in RRS change from baseline to Week 24 between high dose versus low dose was statistically significant with mean difference of −0.70 (95% confidence interval: −1.36 to −0.05, $p = 0.0352$), and was driven mainly by improvement of World Health Organization functional class and N-terminal pro-brain natriuretic peptide concentration. SC treprostinil therapy administered in standard dose had positive effect on the risk profile measured by RRS in patients with inoperable or persistent/recurrent severe CTEPH. Although our study was limited by the small sample size and post hoc nature, assessment of risk profile is of great importance to this particular patient population with very poor prognosis.

KEYWORDS
chronic thromboembolic pulmonary hypertension, REVEAL risk score, treprostinil

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) develops in approximately 2%–4% of patients who survive acute pulmonary embolism.[1] CTEPH is a vascular pulmonary disease characterized by pulmonary hypertension (PH) and increased right ventricular (RV) strain.[2] If left untreated, the prognosis for CTEPH patients is poor, with a 5-year survival rate of 30% for patients with mean pulmonary arterial pressure (mPAP) > 40 mm Hg and only 10% for patients with mPAP > 50 mm Hg.[3]

Pulmonary endarterectomy (PEA) is the first-choice treatment for operable CTEPH and potentially curative[1,4–8]; however, up to 50% of patients are considered inoperable and up to 25% develop persistent/recurrent PH after PEA.[9] Patients with inoperable CTPEH and with residual PH after PEA represent a target for medical therapies and balloon pulmonary angioplasty (BPA). Treprostinil, a subcutaneous (SC) prostacyclin analog, and riociguat, an oral guanylate cyclase stimulator, are approved for patients with inoperable CTEPH or persistent/recurrent PH after PEA; other pulmonary arterial hypertension (PAH) medications have been tested in CTEPH and are used off-label.[10]

Overall, main therapeutic effort in CTEPH is to treat mechanical vascular obstructions in vessels with a cross-sectional diameter of approximately ≥500 μm with surgery and/or BPA. With respect to medical therapy, risk stratification might aid the choice of optimal treatment. To date, there is no established scoring system for risk stratification specific for CTEPH. Observations in patients with inoperable and persistent/recurrent CTEPH have suggested a potential utility of PAH risk scores in this patient population.[11]

The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk score (RRS) calculator was developed in the US-based REVEAL to predict 1-year survival in patients with PAH,[12,13] however, it can also be used for serial risk assessment, allowing a patient's risk and response to treatment to be monitored.[14] Although the RRS calculator was initially developed and validated for PAH, several studies[15,16] confirmed that it is also applicable in inoperable CTEPH and residual PH after PEA.

Here we report the results of a post hoc analysis of RRS in patients who completed the CTREPH study, a randomized, double-blind clinical trial comparing high-dose and low-dose of SC treprostinil for 24 weeks in patients with severe CTEPH, classified as nonoperable, or with persistent or recurrent PH after PEA in the era before BPA was established across Europe.

The CTREPH study design and results have been published previously.[17] Despite a severely diseased study population in the CTREPH study (6-min walk distance less than 400 m, World Health Organization [WHO] functional class III or IV, and pulmonary vascular resistance >800 dyn s cm^{-5}), dose-dependent significant improvements of 6-min walk distance, hemodynamics, WHO functional class, and N-terminal pro-brain natriuretic peptide (NT-BNP) amounts were observed.

The safety profile of SC treprostinil in CTEPH was similar to that in patients with PAH[18] and experience gained from the use of SC treprostinil during the past decades has made adverse drug reactions manageable.

The aim of the present analysis was to investigate the possible impact of 24-week SC treprostinil on RRS and to compare the results with RRS assessment in the CHEST studies which was also performed in patients with inoperable/persistent CTEPH on medical treatment.[15]

METHODS

Patients and CTREPH study design

For the present post hoc analysis, 81 patients who completed the CTREPH study and who were without missing data for RRS calculation were included. The trial is registered at ClinicalTrialsRegister.eu, EudraCT number 2008-006441-10, and ClinicalTrials.gov, number NCT01416636. CTREPH was a 24-week, double-blind, randomized controlled phase 3 trial to investigate the efficacy and tolerability of SC treprostinil in patients with severe CTEPH, classified as nonoperable, or with persistent or recurrent PH after PEA.

Eligible patients in WHO functional class III or IV with a 6-min walk distance of 150–400 m were randomly assigned at a 1:1 allocation ratio to high-dose SC treprostinil (target dose around 30 ng/kg/min) or low-dose SC treprostinil (target dose around 3 ng/kg/min). This study was conducted in six European expert centers in Austria, Czech Republic, Germany, and Poland and enrolled 105 patients in total.

The CTREPH study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The ethics committee at each participating site approved the study protocol and all documents provided to patients before initiation of patient enrollment. All patients signed informed consent as per applicable legislation.

RRS calculation

The RRS calculator is a composite, weighted risk algorithm incorporating 12 evaluable elements considered important for outcome, including 6-min walking distance, hemodynamic parameters, renal function, and N-terminal prohormone of brain natriuretic peptide.[12] In the present analysis, we used an RRS calculation modified for CTEPH as it has been described previously by Benza et al. in 2018.[15]

Supporting Information: Table S1 shows each parameter and applicable number of points. RRS is assessed as the sum of points for each parameter, with the addition of 6. Calculated RRS can range from 0 (lowest risk) to 18 (highest risk).

Statistical methodology

All patients who completed Week 24 in the CTREPH study and who had all data available for RRS calculation were included into this post hoc analysis. Therefore, no imputation for missing values was necessary, and a full data set was used.

Analysis of covariance (ANCOVA) was performed using change in RRS from baseline to Week 24 as the dependent variable and RRS baseline and SC treprostinil treatment arm (high vs. low) as independent variables. The null hypothesis of no difference between high-dose and low-dose treatment arms in RRS change from baseline to Week 24 was tested at 0.05 level of significance.

To analyze the main driver of RRS improvement, change from baseline to Week 24 in each parameter used for RRS in each arm was calculated as mean (standard deviation [SD]) change of points and as change of total sum of points. For each RRS parameter, the difference of relevant change between high- and low-dose group was determined. Percent proportion of total RRS difference between arms calculated as percent proportion of difference in sum of points between arms for each parameter from the sum of absolute differences for all parameters to show the impact of each parameter in RRS change.

For all statistical analyses, R version 4.1.0 was used.

RESULTS

Of 81 patients from the CTREPH study, who had all data available for this post hoc analysis, there were 40 patients randomized to high-dose treprostinil and 41 patients randomized to low-dose treprostinil. Baseline characteristics of the target population including hemodynamic parameters are described in detail in Table 1.

Table 2 summarizes the number of patients by RRS score at baseline and Week 24 in each treatment arm. As shown in Table 3, the baseline mean RRS was similar in both dosing groups (8.7 in the high-dose arm vs. 8.6 in the low-dose arm), but mean RRS change from baseline to Week 24 was greater in the high-dose group than in the low-dose group (−0.88, 95% confidence interval, [95% CI]: −1.34, −0.41 vs. −0.17, 95% CI: −0.63,0.29). The difference in RRS change from baseline to Week 24 between low dose versus high dose was statistically significant with mean difference −0.70 (95% CI: −1.36 to −0.05, $p = 0.0352$). Of note, mean baseline RRS scores in both dosing groups exceeded 8 which is classifying these CTEPH patients as high risk (Figure 1).

As shown in Figure 2, over half (55%) of patients in the high-dose group improved their RRS after 24 weeks of treprostinil treatment, while RRS improvement was experienced in about one-third (34%) of patients in the low-dose group. On the opposite, worsening of the RRS was reported in 17.5% of patients in the high-dose group versus 27% of patients in the low-dose group.

A detailed analysis of RRS changes (Figure 3) shows that the extent of RRS improvement was not associated with the

TABLE 1 Baseline clinical characteristics and hemodynamics.

Characteristics	High-dose subcutaneous treprostinil ($n = 40$)	Low-dose subcutaneous treprostinil ($n = 41$)	Total ($n = 81$)
Age (years)	67 (11.7)	61 (14.4)	64 (13.4)
Distribution (years)			
≥60	30 (75%)	26 (63%)	56 (69%)
<60	10 (25%)	15 (37%)	25 (31%)
Sex			
Female	15 (38%)	20 (49%)	35 (43%)
Male	25 (63%)	21 (51%)	46 (57%)
Weight (kg)	78.6 (15.8)	82.2 (17.5)	80.4 (16.6)
Medical history			
Pulmonary embolism	19 (48%)	24 (59%)	43 (53%)
Deep venous thrombosis	11 (28%)	8 (20%)	19 (23%)
Pulmonary endarterectomy	3 (6%)	4 (10%)	7 (9%)
Concomitant medications			
Anticoagulation	40 (100%)	41 (100%)	81 (100%)
Sildenafil	5 (13%)	7 (17%)	12 (15%)
Bosentan	5 (13%)	2 (5%)	7 (9%)
Riociguat	2 (5%)	2 (5%)	4 (5%)
Bosentan, sildenafil in combination	0 (0%)	1 (2%)	1 (1%)
Riociguat, macitentan in combination	1 (3%)	0 (0%)	1 (1%)
WHO functional class			
II	2 (5%)	2 (5%)	4 (5%)
III	36 (90%)	34 (83%)	70 (86%)
IV	2 (5%)	5 (12%)	7 (9%)
6-min walk distance (m)	313.0 (63.7)	296.5 (90.1)	304.6 (78.1)
Borg Dyspnea Score	4.7 (2.1)	4.9 (2.3)	4.8 (2.2)
N-terminal prohormone of brain natriuretic peptide (pg/mL)	1850.6 (1671.2)	1998.7 (1721.9)	1925.6 (1688.1)
Hemodynamics			
Heart rate (beats/min)	77.4 (12.2)	79.2 (9.8)	78.3 (11.0)
Blood pressure systolic (mm Hg)	124.3 (16.9)	118.4 (15.1)	121.3 (16.2)
Mean right atrial pressure (mm Hg)	9.4 (6.2)	10.1 (5.5)	9.7 (5.8)
Mean pulmonary artery pressure (mm Hg)	49.7 (13.7)	49.5 (10.5)	49.6 (12.1)
Cardiac output (L/min)	4.3 (1.3)	4.3 (1.4)	4.3 (1.3)
Cardiac index (L/min/m^2)	2.3 (0.7)	2.3 (0.7)	2.3 (0.7)
Pulmonary vascular resistance (dyn s cm^{-5})	815.7 (404.8)	811.5 (312.2)	813.5 (358.6)

Note: Data are mean (SD) or *n* (%). The Borg Dyspnea score ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea.

severity of RRS at baseline because the improvement of 2 and more points was detected at the same rate in patients with high baseline RRS scores as in patients with low baseline RRS scores. Specifically, improvement in patients with baseline RRS greater or equal to 9 was experienced by 10 (25%) patients in high-dose arm and by 7 (17%) patients in low-dose arm; improvement greater or equal to 2 points was experienced by 12 (30%) patients in high-dose arm and by only 6 (14.6%) patients in the low-dose arm. Of note, no RRS worsening to Week 24 greater or equal to 3 points was detected in both treprostinil groups.

To further evaluate what was the main driver of RRS improvement, we analyzed the difference in points for each parameter used for RRS calculation between treatment arms. As shown in Table 4, 50% and 32% of the total sum of RRS difference between treatment arms was attributable to WHO functional class and NT-BNP, respectively. Furthermore, WHO functional class and NT-BNP again showed the greatest difference of the mean change of points from baseline to Week 24 between high-dose and low-dose arms, that is −0.429 and −0.273, respectively, in comparison to the other parameters (Table 4).

TABLE 2 Number (%) of patients by RRS scores in baseline and Week 24 in each treatment arm.

RRS score	High-dose arm		Low-dose arm	
	Baseline	Week 24	Baseline	Week 24
≤6	4 (10.0%)	13 (32.5%)	6 (14.6%)	6 (14.6%)
7	9 (22.5%)	5 (12.5%)	6 (14.6%)	6 (14.6%)
8	9 (22.5%)	7 (17.5%)	9 (22.0%)	9 (22.0%)
9	4 (10.0%)	5 (12.5%)	6 (14.6%)	7 (17.1%)
10	8 (20.0%)	4 (10.0%)	5 (12.2%)	6 (14.6%)
11	5 (12.5%)	4 (10.0%)	7 (17.1%)	4 (9.8%)
≥12	1 (2.5)	2 (5.0%)	2 (4.9%)	3 (7.3%)
Total	40 (100%)		41 (100%)	

Abbreviation: RRS, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management risk score.

DISCUSSION

The current post hoc analysis from the CTREPH study shows that treprostinil improved RRS in patients with severe inoperable and persistent/recurrent CTEPH after 24 weeks of treatment, although the change was

TABLE 3 Summary of RRS at baseline and RRS change from baseline to Week 24 by treatment group.

Treatment group	Mean (SD) RRS at baseline	Mean (SD) RRS change from baseline to Week 24	Mean difference (95% CI)	*p* Value
High-dose subcutaneous treprostinil ($n = 40$)	8.71 (1.76)	−0.88 (1.71)	−0.70 (−1.36 to −0.05)	0.0352
Low-dose subcutaneous treprostinil ($n = 41$)	8.58 (1.95)	−0.17 (1.18)		

Abbreviations: CI, confidence interval; RRS, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management risk score.

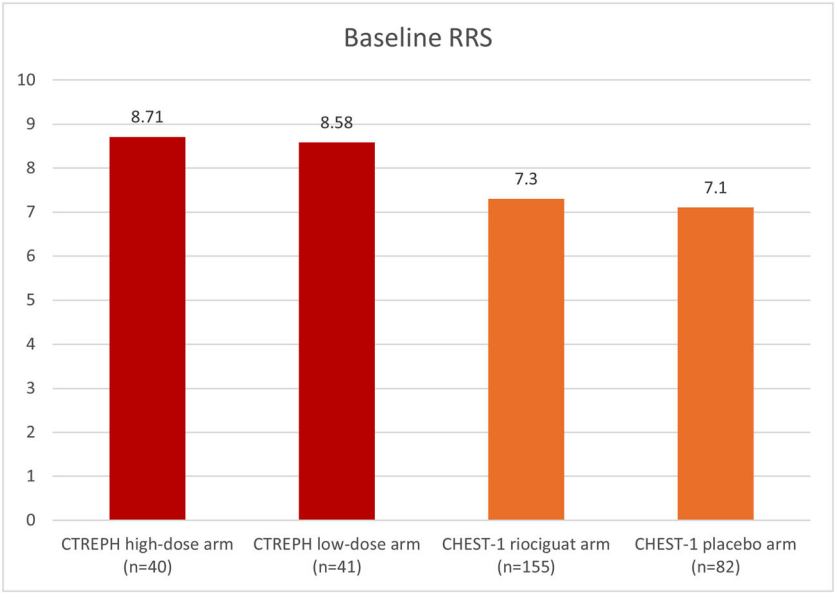

FIGURE 1 Baseline RRS score across populations in CTREPH and studies with similar target populations (CHEST-1 and CHEST-2).[15] RRS, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management risk score.

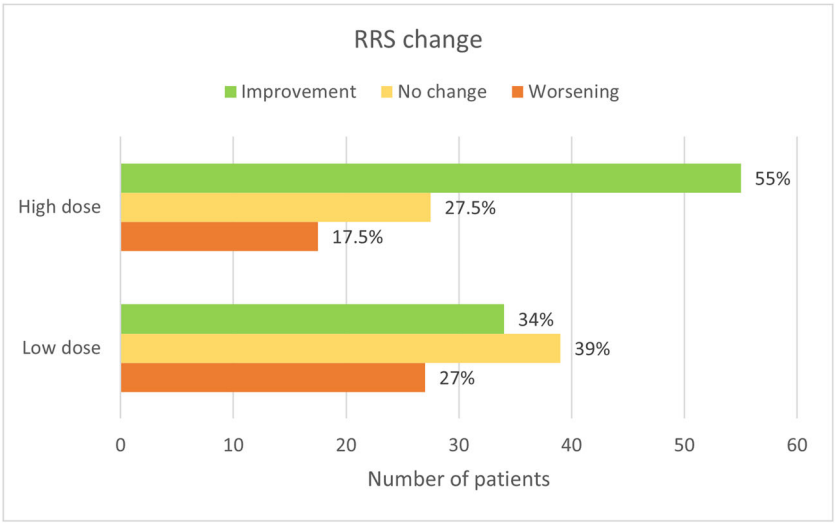

FIGURE 2 Proportion of patients by RRS change. RRS, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management risk score.

RRS change from baseline to week 24 by points

	High-dose subcutaneous treprostinil (n=40)							Low-dose subcutaneous treprostinil (n=41)						
RRS at baseline	**≥ −3**	**−2**	**−1**	**0**	**1**	**2**	**≥ +3**	**≥ −3**	**−2**	**−1**	**0**	**1**	**2**	**≥ +3**
5			1	1					1	1	1	1		
6	1		1					1					1	
7	1	2	2	3		1				1	3	2		
8	2	1	1	5						2	6	1		
9		1	1		1	1			1		2	2	1	
10	1		3	1	2	1				1	3	1		
11	1	1	1	1	1				3	1	1	1	1	
12		1								1				
Total, n (%)	**6 (15%)**	**6 (15%)**	**10 (25%)**	**11 (27.5%)**	**4 (10%)**	**3 (7.5%)**	**0**	**1 (2.4%)**	**5 (12.2%)**	**8 (19.5%)**	**16 (39%)**	**8 (19.5%)**	**3 (7.3%)**	**0**

FIGURE 3 RRS change from baseline to Week 24 by baseline RRS score. RRS, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management risk score.

statistically significant only in the high-dose group. Specifically, the estimated marginal means of the RSS change from baseline to Week 24 were −0.17 (95% CI: −0.63, 0.29) in the low-dose group and -0.88 (95% CI: −1.34, −0.41) in the high-dose group.

These results are consistent with the efficacy results of CTREPH study demonstrating that long-term SC treprostinil in patients with severe nonoperable CTEPH leads to concentration-dependent improvements of 6-min walk distance, hemodynamics, WHO functional class, and NT-BNP amounts. Those metrics are used to calculate the RRS.

Risk stratification guides treatment decisions in PAH.[2] As described above, RRS was initially developed to predict 1-year survival in patients with PAH.[12,13] Several studies[15,16] confirmed that RRS is also suitable for serial risk assessment, allowing a patient's risk and response to treatment to be monitored[13] as well as its potential applicability in patients with inoperable CTEPH or residual PH after PEA.

More specifically, RRS was designed to predict right heart failure, one of the main drivers of prognosis and causes of death in both PAH and CTEPH.[19–23] In another post hoc analysis of studies assessing riociguat treatment in patients with inoperable or persistent/recurrent CTEPH (CHEST-1) and PAH (PATENT-1), hemodynamic parameters describing RV function—stroke volume index (SVI) and right atrial pressure (RAP)—correlated significantly with RRS at baseline and at follow-up, demonstrating that the utility of RRS is intertwined with prognostication of RV function.[16] Precisely, SVI was negatively correlated with RRS, while RAP was positively correlated with RRS at baseline and follow-up in both studies. Furthermore, SVI and RAP were confirmed to be significantly associated with survival in PAH and CTEPH.[16]

TABLE 4 Change in each parameter used for RRS calculation from baseline to Week 24 by the difference in number of points and in total sum of points.

		Number of RRS points		Sum of RRS points		
Parameter	Arm	Change from baseline to Week 24 mean (SD)	High–low dose arm	Change from baseline to Week 24	High–low dose arm	Percent proportion of total RRS difference between arms (%)
Age + gender	H	0.050 (0.316)	0.001	2	0	0
	L	0.049 (0.312)		2		
Renal insufficiency	H	−0.075 (0.350)	−0.002	−3	0	0
	L	−0.073 (0.264)		−3		
Systolic blood pressure	H	0 (0.453)	−0.049	0	−2	6
	L	0.049 (0.498)		2		
Heart rate	H	0.050 (0.450)	0.005	2	2	6
	L	0 (0.224)		0		
WHO functional class	H	−0.575 (0.712)	−0.429	−23	−17	50
	L	−0.146 (0.527)		−6		
6-min walk distance	H	−0.150 (0.427)	−0.028	−6	−1	3
	L	−0.122 (0.458)		−5		
mRAP	H	0.025 (0.276)	0.025	1	1	3
	L	0 (0.316)		0		
PVR	H	0 (0)	0	0	0	0
	L	0 (0)		0		
NT-BNP	H	−0.20 (0.564)	−0.273	−8	−11	32
	L	0.073 (0.519)		3		

Abbreviations: H, high dose; L, low dose; mRAP, mean right atrial pressure; NT-BNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RRS, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management risk score; WHO, World Health Organization.

The potential of RRS change over time to be a predictive marker of long-term outcomes in patients with CTEPH was previously investigated using data collected in the randomized, double-blind, placebo-controlled, pivotal riociguat trial (CHEST-1) and its open-label extension (CHEST-2). Treatment with riociguat significantly improved RRS over 16 weeks in CHEST-1 and improvements persisted also during CHEST-2. Most importantly, RRS at baseline and at Week 16, and change in RRS from baseline to Week 16, were found to be predictors of survival and clinical event-free survival in this patient population.[15]

With respect to baseline RRS population characteristics of CTREPH study and CHEST studies in the previous paragraph, higher baseline mean (SD) RRS in CTREPH [8.71 (1.76) high-dose arm and 8.58 (1.95) in low-dose arm] in comparison to baseline RRS observed in CHEST-1 [7.3 (2.0) in riociguat arm and 7.1 (1.9) in placebo arm] and CHEST-2 [6.4 (2.5) in patients with placebo in CHEST-1][15] illustrates that the CTREPH population was at higher risk at baseline in comparison to patients enrolled in CHEST studies (Figure 1). When baseline clinical characteristics of populations again in CTREPH and CHEST studies are compared, the most prominent difference is the proportion of patients in WHO functional class III (90% in high-dose arm and 83% in low-dose arm in CTREPH vs. 63% in CHEST-1 riociguat arm and 54% in CHEST-1 placebo arm). Patients in WHO class IV were also more frequent in the CTREPH study (5% and 12% vs. 3% and 2%, respectively). On the opposite, WHO class II was rare in the CTREPH study in comparison to CHEST-1 (5% and 5% vs. 31% and 25%, respectively). Renal insufficiency was more than twice as common in the CTREPH population (23% and 24%) than in CHEST (10% and 9%). With respect to NT-BNP, NT-proBNP <300 pg/mL was less common (18% and 12% vs. 22% and 23%) in CTREPH, while NT-proBNP >1500 pg/mL was more

common (48% and 49% vs. 35% and 27%). Males >60 years of age (an important characteristic that increases RRS by 2 points) were more numerous in CTREPH, especially in the high-dose treprostinil arm (45% and 29% vs. 17% and 18%). The other clinical characteristics that are important for RRS calculation were similar in both CTREPH and CHEST-1 patient populations.[15]

Despite more severe disease in the target population of the CTREPH study, we report comparable improvements in risk profiles by a mean (SD) RRS change from baseline to Week 24 in CTREPH [−0.88 (1.71) in the high-dose arm and −0.17 (1.18) in the low-dose arm] in comparison to already published RRS changes after riociguat and placebo administration up to Week 16 [−1.1 (1.6) in the riociguat arm and −0.1 (1.4) in the placebo arm] of CHEST-1.[15] Moreover, proportions of patients by RRS improvement/stabilization/worsening indicated benefit from treprostinil treatment in comparison to placebo, although it is important to keep in mind the worse baseline condition of patients in CTREPH in comparison to CHEST-1: high-dose treprostinil 55%/27.5%/17.5% and low-dose treprostinil 34%/39%/27% up to Week 24 in CTREPH versus riociguat 65%/22%/14% and placebo 32%/37%/32% up to Week 16 in CHEST-1. Of note, our post hoc analysis confirmed RRS improvement during treprostinil treatment in all baseline risk strata as it was described for riociguat treatment.[15] Especially in the high-dose treprostinil arm, substantial improvement in RRS of ≥2 points was observed even in patients with the highest baseline RRS (Figure 3).

With respect to treprostinil dose used in CTREPH, it is important to emphasize that the target dose of 30 ng/kg/min of SC treprostinil in the high-dose arm corresponds to doses administered to patients receiving treatments for 24 weeks in real-life clinical practice, while target doses around 3 ng/kg/min of SC treprostinil in the low-dose arm were intended as control.[17] Such a low dose is not commonly used in clinical practice, but it allowed double-blinding for the drug that causes local site reactions.[24]

We identified WHO functional class and NT-BNP as the main drivers of significant RRS improvement in high-dose treprostinil treatment when 50% and 32%, respectively, of the total sum of RRS difference between treatment arms was attributable to these two parameters. WHO functional class and NT-BNP showed also the greatest difference between mean change of points used for RRS calculation between treatment arms (−0.429 and −0.273, respectively) in comparison to the other parameters. Performed analyses are very simple, but sufficient for the basic concept to plan future research. More sophisticated statistical methods would provide us with more detailed insight into main drivers of risk profile and potentially survival, but these models require higher number of patients. We also have to emphasize that there are different point ranges for individual parameters of RRS, when WHO functional class represents the broadest range of values (−2, 0, 1, and 2) followed by NT-BNP (values −2 and 1), while age and gender and pulmonary resistance have a narrower interval (0 or 2) and the other parameters are within an interval of 0 or 1. However, the extent of points assigned to each parameter reflect its importance for risk profile. Further research should be focused on main drivers of survival in patients with severe CTEPH and identification of treatment targets important for improvement of long-term outcomes.

The most important limitations of this study are its post hoc nature, relatively low number of patients and the use of risk score that was developed for PAH. We are also aware that exclusion of patients from the present post hoc analysis who did not complete CTREPH (14 patients) or all their data for RRS calculation were not available (10 patients) shifts our results toward more favorable outcome. Specifically, the following reasons for premature withdrawal from CTREPH study were recorded (number of patients from low-dose group versus number of patients from high-dose group): side effects of the treatment (3 vs. 1), clinical worsening (2 vs. 3), death (1 vs. 2), and progression of concomitant diseases (0 vs. 2).[17] Furthermore, no follow-up data were collected to investigate relationship between improvement of RRS and long-term outcome. Such detailed analysis has been performed before in CTEPH patients receiving riociguat when RRS improvement during the intervention was found to be predictor of survival and clinical worsening-free survival,[15] therefore, further validation for a more severely diseased population is warranted.

The present analysis shows statistically significant improvement of RRS after SC treprostinil therapy administered in standard dose in patients with severe inoperable or persistent/recurrent CTEPH.

AUTHOR CONTRIBUTIONS

Pavel Jansa and Irene M. Lang had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Irene M. Lang was responsible for the study concept and design, critical revision of the manuscript for important intellectual content, and study supervision; all authors were responsible for acquisition, analysis, or interpretation of data; Pavel Jansa and Irene M. Lang drafted the manuscript.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Jana Mašková, EMMES BIOPHARMA GLOBAL s. r. o.

(Prague, Czech Republic) in accordance with Good Publications practice. The present post hoc analysis was funded by AOP Orphan Pharmaceuticals.

CONFLICTS OF INTEREST STATEMENT

P. J. has received fees and grants from Actelion Pharmaceuticals Ltd., AOP Orphan, Bayer HealthCare, Merck Sharp & Dohme, and GlaxoSmithKline. He has served on advisory boards for Actelion Pharmaceuticals Ltd, Bayer HealthCare, and Merck Sharp & Dohme, outside of the Article. R. S.-K. has relationships with drug companies including Actelion, AOP Orphan Pharmaceuticals, Bayer Schering Pharma, GlaxoSmithKline, and SciPharm Sàrl; is an investigator in trials involving these companies, relationships include consultancy service, and research grants. M. H. reports personal fees (lectures) from Acceleron, Actelion, AstraZeneca, Bayer Pharma AG, Berlin Chemie, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, and Optimal Medical Therapies, nonfinancial support (travel) from Actelion, Janssen-Cilag, Novartis and Optimal Medical Therapies, and is on an advisory board of Actelion, GlaxoSmithKline, Janssen-Cilag and Merk Sharp & Dohme, outside of the Article. I. S. has relationships with Actelion, AOP Orphan Pharmaceuticals, Bayer Healthcare, Merck Sharp & Dohme, GlaxoSmithKline, and Pfizer, and is an investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards, outside of the Article. I. M. L. has relationships with Actelion-Janssen, AOP Orphan Pharmaceuticals, Bayer-Schering, Daiichi Sankyo, Ferrer, SciPharm Sàrl and MSD, and is an investigator in trials involving these companies; has relationships including consultancy service, research grants, and scientific advisory boards. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The CTREPH study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The ethics committee at each participating site approved the study protocol and all documents provided to patients before initiation of patient enrollment. All patients signed informed consent as per applicable legislation.

ORCID

Pavel Jansa http://orcid.org/0000-0002-3711-7064

REFERENCES

1. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. Eur Respir Rev. 2017; 26:160121.
2. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S, Schwerzmann M, Dinh-Xuan AT, Bush A, Abdelhamid M, Aboyans V, Arbustini E, Asteggiano R, Barberà JA, Beghetti M, Čelutkienė J, Cikes M, Condliffe R, de Man F, Falk V, Fauchier L, Gaine S, Galié N, Gin-Sing W, Granton J, Grünig E, Hassoun PM, Hellemons M, Jaarsma T, Kjellström B, Klok FA, Konradi A, Koskinas KC, Kotecha D, Lang I, Lewis BS, Linhart A, Lip GYH, Løchen ML, Mathioudakis AG, Mindham R, Moledina S, Naeije R, Nielsen JC, Olschewski H, Opitz I, Petersen SE, Prescott E, Rakisheva A, Reis A, Ristić AD, Roche N, Rodrigues R, Selton-Suty C, Souza R, Swift AJ, Touyz RM, Ulrich S, Wilkins MR, Wort SJ. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731. https://doi.org/10.1093/eurheartj/ehac237
3. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2011;183(12):1605–13.
4. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, American College of Cardiology Foundation Task Force on Expert Consensus D, American Heart A, American College of Chest P, American Thoracic Society I, Pulmonary Hypertension A. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53: 1573–619.
5. Ghofrani HA, Humbert M, Langleben D, Schermuly R, Stasch JP, Wilkins MR, Klinger JR. Riociguat: mode of action and clinical development in pulmonary hypertension. Chest. 2017;151:468–80.
6. Jenkins D. Pulmonary endarterectomy: the potentially curative treatment for patients with chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2015;24:263–71.
7. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V, Mayer E. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 suppl):D92–9.
8. de Perrot M, Gopalan D, Jenkins D, Lang IM, Fadel E, Delcroix M, Benza R, Heresi GA, Kanwar M, Granton JT, McIfnnis M, AKlok F, Kerr KM, Pepke-Zaba J, Toshner M, Bykova A, D'Armini AM, Robbins IM, Madani M, McGiffin D, Wiedenroth CB, Mafeld S, Opitz I, Mercier O, Uber PA, Frantz RP, Auger WR. Evaluation and management of patients with chronic thromboembolic pulmonary hypertension—consensus statement from the ISHLT. J Heart Lung Transplant. 2021;40(11):1301–26.
9. Hsieh WC, Jansa P, Huang WC, Nižnanský M, Omara M, Lindner J. Residual pulmonary hypertension after pulmonary

endarterectomy: a meta-analysis. J Thorac Cardiovasc Surg. 2018;156:1275–87.
10. Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, Jenkins D, Kim NH, Humbert M, Jais X, Vonk Noordegraaf A, Pepke-Zaba J, Brénot P, Dorfmuller P, Fadel E, Ghofrani HA, Hoeper MM, Jansa P, Madani M, Matsubara H, Ogo T, Grünig E, D'Armini A, Galie N, Meyer B, Corkery P, Meszaros G, Mayer E, Simonneau G. ERS statement on chronic thromboembolic pulmonary hypertension. Eur Respir J. 2021;57:2002828.
11. Delcroix M, Staehler G, Gall H, Grünig E, Held M, Halank M, Klose H, Vonk-Noordegraaf A, Rosenkranz S, Pepke-Zaba J, Opitz CF, Gibbs JSR, Lange TJ, Tsangaris I, Huscher D, Pittrow D, Olsson KM, Hoeper MM. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J. 2018;52(5):1800248.
12. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and long-term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122:164–72.
13. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL registry. Chest. 2012;142:448–56.
14. Benza RL, Miller DP, Foreman AJ, Frost AE, Badesch DB, Benton WW, McGoon MD. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) analysis. J Heart Lung Transplant. 2015;34:356–61.
15. Benza RL, Farber HW, Frost A, Grünig E, Hoeper MM, Busse D, Meier C, Nikkho S, Ghofrani HA. REVEAL risk score in patients with chronic thromboembolic pulmonary hypertension receiving riociguat. J Heart Lung Transplant. 2018;37(7):836–43.
16. Benza RL, Ghofrani HA, Grünig E, Hoeper MM, Jansa P, Jing Z-C, Kim NH, Langleben D, Simonneau G, Wang C, Busse D, Meier C, Ghio S. Effect of riociguat on right ventricular function in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant. 2021;40(10):1172–80.
17. Sadushi-Kolici R, Jansa P, Kopec G, Torbicki A, Skoro-Sajer N, Campean IA, Halank M, Simkova I, Karlocai K, Steringer-Mascherbauer R, Samarzija M, Salobir B, Klepetko W, Lindner J, Lang IM. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med. 2019;7(3):239–48.
18. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165:800–4.
19. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973–81.
20. Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, Grünig E, Staehler G, Rosenkranz S, Halank M, Held M, Lange TJ, Behr J, Klose H, Claussen M, Ewert R, Opitz CF, Vizza CD, Scelsi L, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JSR, Coghlan G, Pepke-Zaba J, Schulz U, Gorenflo M, Pittrow D, Hoeper MM. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation. 2014;129(1):57–65.
21. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jaïs X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevelle P, Mayer E, Simonneau G. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an International Prospective Registry. Circulation. 2016;133(9):859–71.
22. Gall H, Felix JF, Schneck FK, Milger K, Sommer N, Voswinckel R, Franco OH, Hofman A, Schermuly RT, Weissmann N, Grimminger F, Seeger W, Ghofrani HA. The giessen pulmonary hypertension registry: survival in pulmonary hypertension subgroups. J Heart Lung Transplant. 2017;36(9):957–67.
23. Weatherald J, Boucly A, Chemla D, Savale L, Peng M, Jevnikar M, Jaïs X, Taniguchi Y, O'Connell C, Parent F, Sattler C, Hervé P, Simonneau G, Montani D, Humbert M, Adir Y, Sitbon O. Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. Circulation. 2018;137(7):693–704.
24. Chen Y, Li F, Luo J, Chen J, Luo P, Li J. Comparative efficacy and safety of targeted therapies for chronic thromboembolic pulmonary hypertension: a systematic review and network meta-analysis. Can Respir J. 2021;2021:1626971.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jansa P, Kopeć G, Torbicki A, Sadushi-Kolici R, Campean I-A, Halank M, Simkova I, Steringer-Mascherbauer R, Salobir B, Klepetko W, Lindner J, Lang IM. The risk profile change in patients with severe chronic thromboembolic pulmonary hypertension treated with subcutaneous treprostinil. Pulm Circ. 2023;13:e12274. https://doi.org/10.1002/pul2.12274