ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Comparison of hemodynamic parameters in treatment-naïve and pre-treated patients with pulmonary arterial hypertension in the randomized phase III PATENT-1 study

Nazzareno Galiè, MD,[a] Friedrich Grimminger, MD, PhD,[b] Ekkehard Grünig, MD,[c] Marius M. Hoeper, MD,[d] Marc Humbert, MD, PhD,[e] Zhi-Cheng Jing, MD,[f] Anne M. Keogh, PhD,[g] David Langleben, MD,[h] Lewis J. Rubin, MD,[i] Arno Fritsch, PhD,[j] Neil Davie, PhD,[j] and Hossein-Ardeschir Ghofrani, MD[b,k]

From the [a]Department of Experimental, Diagnostic, and Specialty Medicine–DIMES, Bologna University Hospital, Bologna, Italy; [b]University of Giessen and Marburg Lung Center, member of German Center for Lung Research, Giessen, Germany; [c]Centre for Pulmonary Hypertension, Thoraxclinic, University Hospital Heidelberg, Heidelberg, Germany; [d]Clinic for Respiratory Medicine, Hannover Medical School, member of German Center for Lung Research, Hannover, Germany; [e]Assistance Publique–Hôpitaux de Paris, Service de Pneumologie, Hôpital Bicêtre, Université Paris-Sud, Laboratoire d'Excellence en Recherche sur le Médicament et Innovation Thérapeutique, and Institut National de la Santé et de la Recherche Médicale Unité 999, Le Kremlin–Bicêtre, France; [f]State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China; [g]Heart Transplant Unit, St. Vincent's Hospital, Sydney, New South Wales, Australia; [h]Center for Pulmonary Vascular Disease and Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [i]Pulmonary and Critical Care Division, University of California, San Diego, La Jolla, California; [j]Global Clinical Development, Bayer Pharma AG, Wuppertal, Germany; and the [k]Department of Medicine, Imperial College London, London, United Kingdom.

KEYWORDS:
pulmonary arterial hypertension;
clinical trial;
pulmonary;
riociguat;
soluble guanylate cyclase stimulator

BACKGROUND: Detailed hemodynamic data from the phase III PATENT-1 study of riociguat in patients with pulmonary arterial hypertension (PAH) were investigated.

METHODS: Patients with PAH who were treatment naïve or pre-treated with endothelin receptor antagonists or non-intravenous prostanoids were randomly assigned to riociguat up to 2.5 mg 3 times a day or placebo. Hemodynamic parameters were assessed at baseline and week 12.

RESULTS: Riociguat significantly decreased pulmonary vascular resistance in treatment-naïve ($n = 221$; least squares [LS] mean difference −266 dyne•sec•cm^{-5} [95% confidence interval (CI) −357 to −175; $p < 0.0001$]) and pre-treated ($n = 222$; LS mean difference −186 dyne•sec •cm^{-5} [95% CI −252 to −120; $p < 0.0001$]) patients and significantly increased cardiac index (LS mean difference +0.7 [95% CI 0.5 to 0.8] and +0.5 [95% CI 0.3 to 0.7], respectively [both $p < 0.0001$]). Mean pulmonary artery pressure ($p = 0.0056$ and $p = 0.0019$ for treatment-naïve and pre-treated patients, respectively), mean arterial pressure (both $p < 0.0001$), and systemic vascular

Reprint requests: Nazzareno Galiè, MD, Institute of Cardiology, University of Bologna, via Massarenti 9, Bologna 40138, Italy. Telephone: 39 051 349 858. Fax: 39 051 344 859.

E-mail address: nazzareno.galie@unibo.it

http://dx.doi.org/10.1016/j.healun.2016.12.012

resistance (both $p < 0.0001$) were significantly reduced, and there was an increase in mixed venous oxygen saturation ($p < 0.0001$ and $p = 0.0004$, respectively). Results were similar in patients pre-treated with endothelin receptor antagonists and patients pre-treated with non-intravenous prostanoids. Improvements in 6-minute walking distance correlated very weakly with improvements in pulmonary vascular resistance ($r = -0.21$ [95% CI −0.30 to −0.11; $p < 0.0001$]) and cardiac index ($r = 0.16$ [95% CI 0.06 to 0.25; $p < 0.0016$]).

CONCLUSIONS: Riociguat significantly improved hemodynamic parameters in pre-treated and treatment-naïve patients with PAH.

J Heart Lung Transplant 2017;36:509–519

Pulmonary arterial hypertension (PAH) is a chronic and life-threatening disease characterized by increased pulmonary vascular resistance (PVR) secondary to progressive vascular remodeling that can ultimately lead to right heart failure and death.[1,2] Despite advances in current therapies for PAH, mortality of patients with PAH remains high. Data from 3 national registries (US REVEAL, French, and Chinese) show mortality ranges from 15% to 32% at 1 year and from 32% to 61% at 3 years.[3–6]

Right heart catheterization (RHC) is considered the gold standard for hemodynamic assessment of pulmonary hypertension and is required to exclude left heart disease, confirm diagnosis, assess disease severity, and guide treatment decisions.[2,7] PAH is defined by a mean pulmonary artery pressure (mPAP) $\geq$25 mm Hg, pulmonary artery wedge pressure $\leq$15 mm Hg, and PVR $>$3 Wood units and, in advanced cases, by an increase in right atrial pressure (RAP) and a reduction in cardiac output (CO).[2,7] Current PAH treatment guidelines recommend that patients should be reassessed after the initiation of therapy to verify the achievement of a "low risk" status, based on clinical and hemodynamic parameters and exercise capacity.[2,7] Hemodynamic parameters, such as PVR, RAP, and cardiac index, are predictive of mortality at diagnosis and during follow-up.[8–11]

PAH is associated with endothelial dysfunction, impaired synthesis of nitric oxide (NO), and insufficient stimulation of the NO–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway.[12–14] Riociguat is the first member of the sGC stimulator class of therapeutic agents.[13–16] It has a dual mode of action, sensitizing sGC to endogenous NO by stabilizing NO–sGC binding and directly stimulating sGC independently of NO, increasing generation of cGMP.[13,14,17] In the phase III PATENT-1 study, riociguat significantly improved 6-minute walking distance (6MWD) and a range of secondary end-points, including PVR, *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) plasma levels, World Health Organization (WHO) functional class (FC), time to clinical worsening, and Borg dyspnea score in patients with PAH.[18] Riociguat is currently approved for treatment of PAH[2,19] by the European Medicines Agency and the US Food and Drug Administration. We present the hemodynamic findings from PATENT-1 in subgroups of patients who were treatment naïve or pre-treated with endothelin receptor antagonists (ERAs) or non-intravenous prostanoids and describe their correlation with changes in exercise capacity. In contrast to some previous studies that investigated pulmonary hemodynamics only in a subset of the trial population, all patients in PATENT-1 underwent RHC at baseline and at the end of the randomized period; therefore, data were collected from the entire study population.[18,20,21]

Methods

Study population

The PATENT-1 study methodology has been published previously.[18] Patients with symptomatic PAH who were receiving no other treatment for PAH and patients who were receiving treatment with ERAs or non-intravenous prostanoids were eligible. Oral anticoagulants as well as diuretics and supplemental oxygen at stable doses were permitted. Patients receiving phosphodiesterase-5 inhibitors were excluded. Local ethics committees approved the research protocol, and written informed consent was obtained from patients in accordance with the Declaration of Helsinki. The study is registered at ClinicalTrials.gov (identifier NCT00810693).

Study design

PATENT-1 was a 12-week, double-blind, randomized, placebo-controlled trial conducted in 124 centers across 30 countries between December 2008 and May 2012. Patients were randomly assigned using an interactive voice-response system and a computer-generated random code provided by Bayer Randomization Management to 1 of 3 regimens in a 2:4:1 ratio: placebo, oral riociguat administered at doses individually adjusted up to 2.5 mg 3 times daily, or riociguat at individually adjusted doses capped at an exploratory dose of 1.5 mg 3 times daily.[18] During weeks 1–8, the dose was adjusted from a starting dose of 1 mg 3 times daily every 2 weeks according to an individual plan based on the patient's systolic blood pressure and signs or symptoms of hypotension. Patients in the placebo group underwent sham dose adjustment. The dose reached at the end of

week 8 was considered to be the optimal dose for the individual patient and was continued for another 4 weeks. Randomly assigned patients were assessed at baseline and at weeks 2, 4, 6, 8, and 12. Hemodynamic parameters were assessed by RHC (Swan–Ganz catheterization and thermodilution methodology) at baseline and week 12.

Outcome measures

The primary outcome of the PATENT-1 study was change from baseline in 6MWD at week 12.[18] Secondary outcomes included change from baseline at week 12 in PVR, NT-proBNP, WHO FC, and time to clinical worsening. Additional exploratory hemodynamic parameters included RAP, pulmonary artery wedge pressure, CO, and mixed venous oxygen saturation (SvO_2). Calculated parameters, determined using standard formulas, included mean arterial pressure (MAP), mPAP, PVR, systemic vascular resistance (SVR), and cardiac index. Adverse events (AEs) and laboratory variables were assessed throughout the study and during the safety follow-up period.

Statistical analysis

The statistical analysis plan for PATENT-1 has been published previously.[18] The pre-defined efficacy analyses compared the riociguat 2.5 mg 3 times daily–maximum and placebo groups. Changes from baseline to week 12 in hemodynamic parameters were analyzed by analysis of covariance, followed by a test of normality of the residuals and a non-parametric stratified Wilcoxon test on rejection. Post hoc analysis of the changes in hemodynamic parameters in the pre-treated and treatment-naïve subgroups was undertaken using the same methods. Pearson's correlation coefficient was used to determine correlation between change in 6MWD and change in PVR and cardiac index.

Missing values, where the patient died or withdrew from the study, were imputed by the last observation carried forward method according to the last post-baseline measurement for hemodynamic parameters and NT-proBNP (both taken during the termination visit in the case of patients who withdrew). In the case of withdrawal with no post-baseline measurements or death, the baseline value was used. In the case of 6MWD, the last observed value was taken except in cases of death or clinical worsening without a termination visit, where worst values were imputed (0 m). AEs during the study period included all AEs that started or worsened from the time of administration of the first dose of the study drug until 2 days after the administration of the last dose.

Results

Baseline demographics and hemodynamics (2.5 mg 3 times daily–maximum group)

Baseline characteristics were well balanced between the groups (Table 1 and Table S1, available in the online version of this article at www.jhltonline.org). At baseline in the overall population, 221 patients (50%) were treatment naïve and 222 patients (50%) were pre-treated. Of the pre-treated patients, 194 (44%) were receiving ERAs (primarily bosentan [28%] and ambrisentan [11%]) and 31 (7%) were receiving non-intravenous prostanoids (primarily inhaled iloprost [5%], oral beraprost [3%], and non-intravenous treprostinil [2%]). Three patients were pre-treated with both an ERA and non-intravenous prostanoids and were included in both subgroups for the purposes of this analysis. Most patients were classified as WHO FC II or III. More patients in the pre-treated subgroup were in WHO FC III and fewer patients were in WHO FC II

Table 1 Baseline Demographic Characteristics for Overall Group and Treatment-Naïve and Pre-treated Subgroups (Riociguat 2.5 mg 3 Times Daily–Maximum Group vs Placebo)

	Treatment naïve		Pre-treated overall		All patients	
Characteristic	Riociguat ($n = 123$)	Placebo ($n = 66$)	Riociguat ($n = 131$)	Placebo ($n = 60$)	Riociguat ($n = 254$)	Placebo ($n = 126$)
Female sex, *n* (%)	94 (76)	52 (79)	109 (83)	46 (77)	203 (80)	98 (78)
Race, *n* (%)						
White	60 (49)	30 (46)	101 (77)	48 (80)	161 (63)	78 (62)
Black	1 (1)	0	3 (2)	1 (2)	4 (2)	1 (1)
Asian	56 (46)	29 (44)	23 (18)	9 (15)	79 (31)	38 (30)
Mixed	0	0	1 (1)	1 (2)	1 (0.4)	1 (1)
Not reported	6 (5)	7 (11)	3 (2)	1 (2)	9 (4)	8 (6)
Age, years, mean (SD)	48 (17)	48 (18)	54 (15)	53 (15)	51 (17)	51 (17)
BMI, kg/m^2, mean (SD)	25 (5)	26 (6)	27 (6)	27 (6)	26 (5)	26 (6)
WHO FC, *n* (%)[a]						
I	3 (2)	4 (6)	2 (2)	0[b]	5 (2)	4 (3)
II	65 (53)	35 (53)	43 (33)	25 (42)[b]	108 (43)	60 (48)
III	55 (45)	25 (38)	85 (65)	33 (56)[b]	140 (55)	58 (46)
IV	0	2 (3)	1 (1)	1 (2)[b]	1 (0.4)	3 (2)
Missing	0	0	0	0	0	1 (1)
6MWD, m, mean (SD)	370 (66)	360 (80)	353 (69)	376 (68)	361 (68)	368 (75)

6MWD, 6-minute walking distance; BMI, body mass index; WHO FC, World Health Organization functional class.
[a]Data may not add up to 100% owing to rounding.
[b]$n = 59$.

Table 2 Baseline and Change From Baseline in Hemodynamic Parameters in Treatment-Naïve and Pre-treated Subgroups (Riociguat 2.5 mg 3 Times Daily–Maximum Group vs Placebo)

	Treatment naïve								Pre-treated overall							
	Riociguat			Placebo					Riociguat			Placebo				
Parameter	*n*	BL[a]	Change from BL at week 12[a]	*n*	BL[a]	Change from BL at week 12[a]	LS mean difference (95% CI)	Riociguat vs placebo *p*-value	*n*	BL[a]	Change from BL at week 12[a]	*n*	BL[a]	Change from BL at week 12[a]	LS mean difference (95% CI)	Riociguat vs placebo *p*-value
PVR, dyne•sec •cm^{-5}	115	888 (505)	−259 (296)	55	855 (477)	+17 (361)	−266 (−357 to −175)	<0.0001	117	695 (373)	−188 (215)	52	812 (480)	−36 (263)	−186 (−252 to −120)	<0.0001
SVR, dyne•sec •cm^{-5}	112	1,793 (622)	−525 (464)	54	1,772 (610)	−56 (597)	−457 (−584 to −330)	<0.0001	115	1,535 (475)	−374 (383)	52	1,619 (460)	−79 (410)	−343 (−437 to −249)	<0.0001
mPAP, mm Hg	116	49.3 (15)	−4.4 (8)	56	48.9 (16)	−0.3 (12)	−4.0 (−6.9 to −1.2)	0.0056	119	45.0 (14)	−3.5 (8)	53	49.0 (14)	−0.7 (6)	−3.5 (−5.7 to −1.3)	0.0019
MAP, mm Hg	113	92.2 (13)	−10 (10)	57	90.6 (13)	−1.3 (13)	−7.7 (−11.0 to −4.3)	<0.0001	116	88.6 (12)	−7.6 (12)	52	90.5 (12)	−1.5 (12)	−7.0 (−10.3 to −3.6)	<0.0001
RAP, mm Hg	116	7.4 (5.2)	−0.2 (7.0)	55	6.9 (4.6)	+1.7 (5.7)	−1.5 (−3.4 to 0.4)	0.11	119	7.8 (5.6)	−0.2 (4.3)	53	7.4 (4.6)	+0.2 (3.8)	−0.3 (−1.6 to 0.9)	0.60
Cardiac output, liters/min	115	4.2 (1.3)	+1.0 (1.0)	55	4.2 (1.4)	−0.1 (1.2)	+1.1 (0.7 to 1.4)	<0.0001	118	4.5 (1.1)	+0.9 (1.0)	53	4.4 (1.2)	+0.1 (0.9)	+0.8 (0.5 to 1.1)	<0.0001
Cardiac index, liters/min/m^2	115	2.5 (0.7)	+0.6 (0.6)	55	2.5 (0.9)	−0.1 (0.7)	+0.7 (0.5 to 0.8)	<0.0001	118	2.6 (0.6)	+0.5 (0.6)	53	2.5 (0.6)	+0.04 (0.5)	+0.5 (0.3 to 0.7)	<0.0001
SvO_2, %	103	65.0 (11)	+4.1 (9.5)	51	67.0 (9)	−2.5 (9.6)	+5.6 (2.9 to 8.3)	<0.0001	107	64.7 (9)	+2.3 (7.3)	49	65.0 (8)	−2.1 (7.7)	+4.3 (2.0 to 6.7)	0.0004

BL, baseline; CI, confidence interval; LS, least squares; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance.

[a]Data shown are mean (SD).

Table 3 Baseline and Change From Baseline in Hemodynamic Parameters in Subgroups Pre-treated With ERAs and Non-intravenous Prostanoids (Riociguat 2.5 mg 3 Times a Day–Maximum Group vs Placebo)

	Pretreated non-intravenous prostanoids								Pretreated ERAs							
	Riociguat			Placebo					Riociguat			Placebo				
Parameter	*n*	BL[a]	Change from BL at week 12[a]	*n*	BL[a]	Change from BL at week 12[a]	LS mean difference (95% CI)	Riociguat vs placebo *p*-value	*n*	BL[a]	Change from BL at week 12[a]	*n*	BL[a]	Change from BL at week 12[a]	LS mean difference (95% CI)	Riociguat vs placebo *p*-value
PVR, dyne•sec •cm^{-5}	19	860 (348)	−259 (260)	5	840 (263)	+61 (198)	−309 (−488 to −129)	0.0018	100	665 (367)	−174 (202)	48	816 (496)	−46 (266)	−168 (−237 to −98)	<0.0001
SVR, dyne•sec •cm^{-5}	20	1,594 (529)	−402 (364)	6	1,645 (359)	−56 (305)	−373 (−605 to −141)	0.0029	97	1,524 (461)	−368 (386)	47	1,612 (470)	−81 (420)	−339 (−442 to −237)	<0.0001
mPAP, mm Hg	20	49 (14)	−3 (10)	6	54 (6)	+3 (4)	−7.9 (−14.7 to −1.1)	0.025	101	44 (14)	−4 (7)	48	49 (15)	−1 (6)	−3.2 (−5.4 to −0.9)	0.0059
MAP, mm Hg	20	85 (13)	−6 (10)	6	92 (11)	−1 (8)	−7.0 (−15.9 to 1.9)	0.12	98	89 (12)	−8 (12)	47	90 (12)	−1 (12)	−7.0 (−10.6 to −3.4)	0.0002
RAP, mm Hg	20	11.5 (9.7)	−0.2 (5.7)	6	8.2 (3.1)	+1.8 (2.4)	−1.4 (−6.4 to 3.6)	0.57	101	7.2 (4.1)	−0.3 (3.9)	48	7.4 (4.8)	0 (3.9)	−0.3 (−1.6 to 0.9)	0.58
Cardiac output, liters/min	20	3.9 (0.9)	+0.8 (0.8)	6	4.3 (1.2)	−0.1 (0.9)	0.7 (−0.03 to 1.4)	0.060	100	4.6 (1.1)	+0.9 (1.0)	48	4.4 (1.2)	+0.1 (0.9)	0.8 (0.5 to 1.1)	<0.0001
Cardiac index, liters/min/m^2	20	2.4 (0.5)	+0.5 (0.5)	6	2.5 (0.6)	−0.02 (0.5)	0.5 (0.0 to 1.0)	0.052	100	2.6 (0.6)	+0.5 (0.6)	48	2.5 (0.6)	+0.05 (0.5)	0.5 (0.3 to 0.7)	<0.0001
SvO_2, %	20	59 (10)	+2.4 (6.8)	6	64 (4)	−4.3 (7.9)	5.8 (−1.0 to 12.7)	0.092	89	65 (8)	+2.5 (7.6)	44	65 (9)	−1.7 (7.7)	4.4 (1.8 to 6.9)	0.0009

BL, baseline; CI, confidence interval; ERA, endothelin receptor antagonist; LS, least squares; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance.

[a]Data shown are mean (SD).

compared with the treatment-naïve subgroup. Patient disposition in PATENT-1 has been reported previously.[18]

The baseline hemodynamic values for the overall population have been published previously[18] and were characteristic of patients with PAH, with PVR and mPAP elevated above normal values.[2,7,18] Baseline hemodynamic parameters were comparable between the treatment-naïve and pre-treated subgroups (although PVR was lower in pre-treated patients) (Table 2) and between the subgroups pre-treated with ERAs and with non-intravenous prostanoids (Table 3).

Dosing

In the riociguat arm, 75% of patients were receiving the maximum 2.5 mg 3 times daily dose at week 12, 15% were receiving 2 mg 3 times daily, 6% were receiving 1.5 mg 3 times daily, 3% were receiving 1 mg 3 times daily, and 2% were receiving 0.5 mg 3 times daily.

Hemodynamic parameters

In the overall population, riociguat significantly improved a range of hemodynamic parameters at week 12 compared with placebo.[18] PVR was significantly decreased in the riociguat group (−28%) vs placebo (−1%) by a least squares (LS) mean difference of −226 dyne•sec•cm^{-5} (95% confidence interval [CI] −281 to −170; $p < 0.0001$) (Figure 1A). Cardiac index was significantly increased in the riociguat group (+21%) compared with placebo (−1%) by an LS mean difference of +0.6 liters/min/m^2 (95% CI 0.4 to 0.7; $p < 0.0001$) (Figure 1B), and SVR was significantly decreased in the riociguat group compared with placebo by an LS mean difference of −395 dyne•sec•cm^{-5} (95% CI −473 to −316; $p < 0.0001$). Significant changes were also observed in mPAP ($p = 0.0002$), CO ($p < 0.0001$), SvO_2 ($p < 0.0001$), and MAP ($p < 0.0001$).[18]

RAP was increased at baseline (mean 7.6 mm Hg [SD 5.4 mm Hg]) and was unchanged at week 12 (LS mean difference −1 mm Hg [95% CI –2 to 0.1; $p = 0.0734$]). There was a marked decrease in mean ± SD systolic blood pressure in the riociguat 2.5 mg–maximum arm by −10 mm Hg ± 14 (from 115 mm Hg ± 15 at baseline to 105 mm Hg ± 13 at week 12; $n = 253$), whereas in the placebo group, mean ± SD systolic blood pressure decreased by −3 mm Hg ± 14 (from 114 mm Hg ± 14 at baseline to 111 mm Hg ± 15 at week 12; $n = 126$). No clinically relevant changes in heart rate were observed during the study. In the riociguat group, mean ± SD heart rate was 76 beats/min ± 11 at baseline compared with 77 beats/min ± 12 at week 12; the corresponding values in the placebo group were 78 beats/min ± 13 and 78 beats/min ± 13. Mean ± SD arterial oxygen saturation decreased from baseline to week 12 by −1.5% ± 5.0 in the riociguat group ($n = 228$) and by −0.6% ± 4.1 in the placebo group ($n = 109$).

The hemodynamic improvements seen in the overall riociguat population were consistent across the treatment-naïve and pre-treated subgroups, including the subgroups pre-treated with ERAs and non-intravenous prostanoids (Tables 2 and 3 and Figures 1 and 2). Improvements in PVR, mPAP, CO, cardiac index, and SvO_2 were numeri-

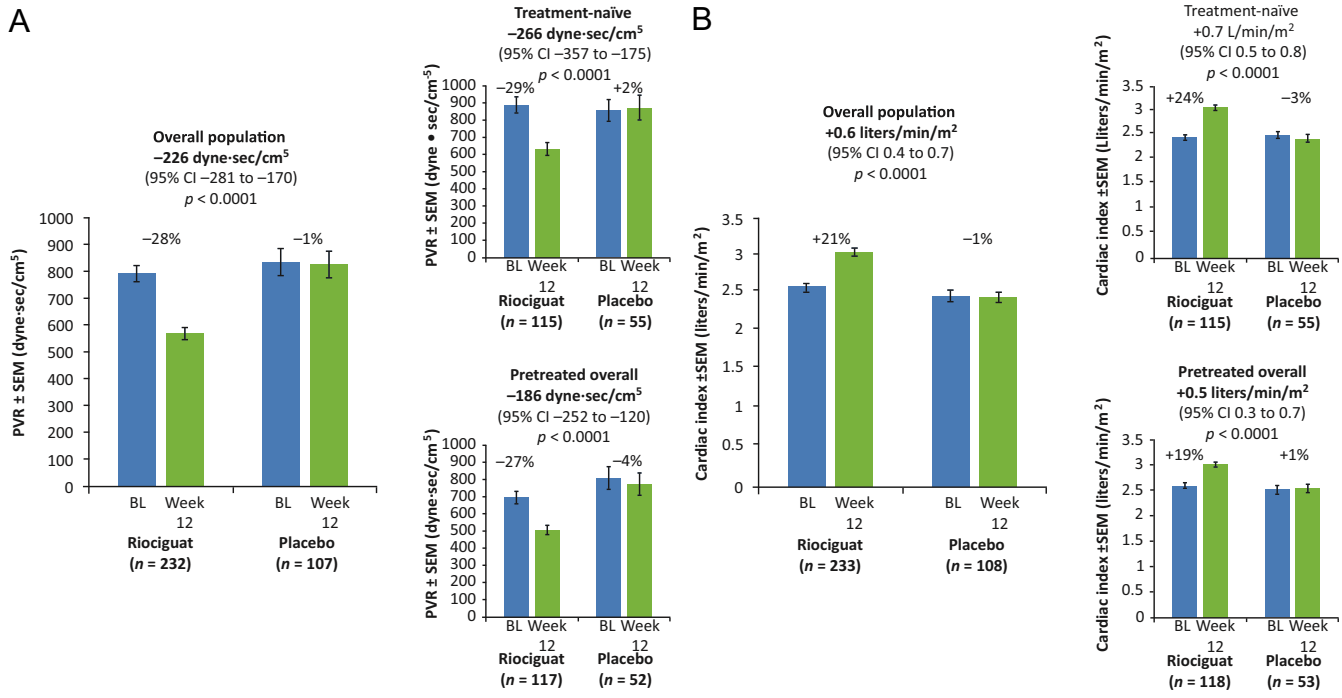

Figure 1 (A) PVR at baseline (BL) and week 12 and (B) cardiac index at BL and week 12 for the overall population and treatment-naïve and pre-treated subgroups (riociguat 2.5 mg 3 times daily–maximum group vs placebo). LS mean treatment effect (95% CI) was determined using analysis of covariance. Missing values, where the patient withdrew or died, were imputed at week 12.

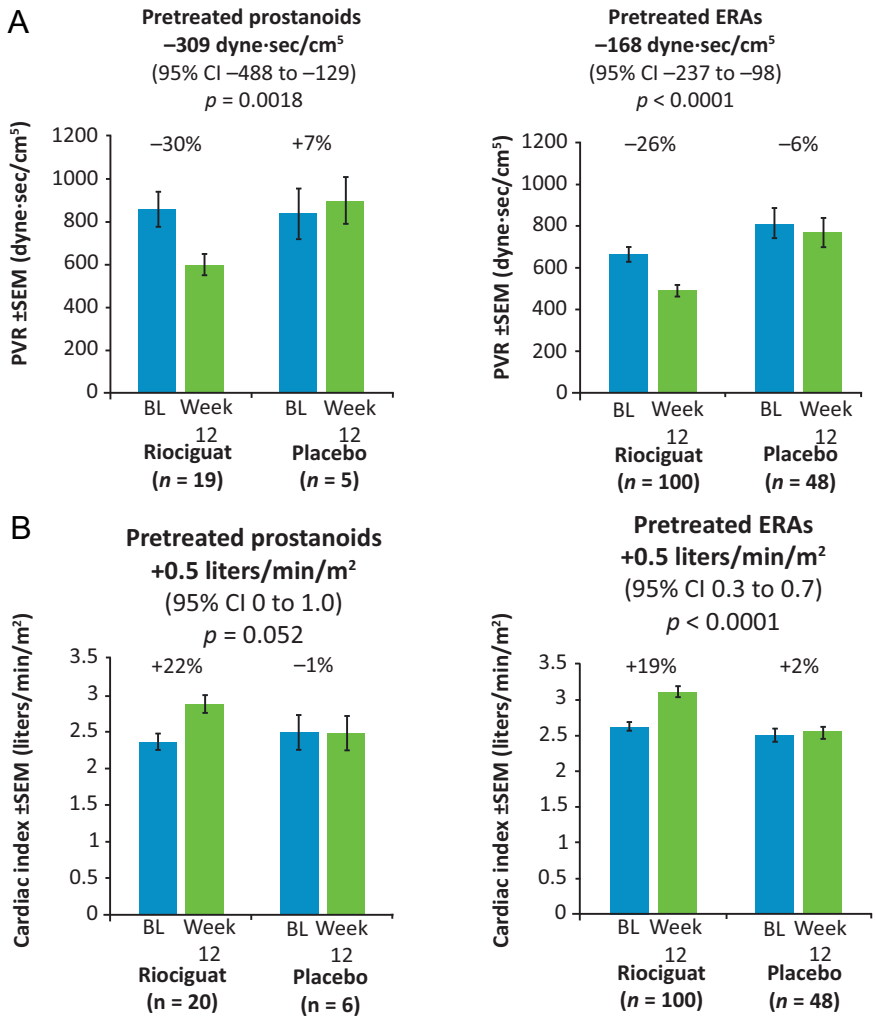

Figure 2 (A) PVR at baseline (BL) and week 12 and (B) cardiac index at BL and week 12 for subgroups pre-treated with ERAs and non-intravenous prostanoids (2.5 mg 3 times daily–maximum group). LS mean treatment effect (95% CI) was determined using analysis of covariance. Missing values, where the patient withdrew or died, were imputed at week 12.

cally greater in the treatment-naïve subgroup compared with the pre-treated subgroup (Table 2 and Figure 1). However, the relative changes in PVR (treatment-naïve vs pre-treated group: −29% vs −27%), mPAP (−9% vs −8%), CO (+24% vs +20%), cardiac index (+24% vs +19%), and SvO_2 (+6% vs +4%) were similar between the subgroups.

Effect on other end-points

Riociguat increased 6MWD at week 12 (primary end-point) in the treatment-naïve (LS mean difference: +38 m; 95% CI 14 to 62 m) and pre-treated subgroups (LS mean difference: +36 m; 95% CI 15 to 56 m) (Figure 3).[18] In the overall population, although statistically significant, the correlation between improvements in 6MWD and hemodynamic parameters was too weak to clearly suggest a relationship. The correlation coefficient (r) between change in 6MWD and PVR was −0.21 (95% CI −0.30 to −0.11; $p < 0.0001$) and between change in 6MWD and cardiac index was 0.16 (95% CI 0.06 to 0.25; $p = 0.0016$) (Figure 4). The correlation coefficients between 6MWD and PVR at baseline and between 6MWD and cardiac index at baseline were −0.079 (95% CI −0.171 to 0.014; $p = 0.097$) and 0.156 (95% CI 0.063 to −0.245; $p = 0.0010$), respectively. At week 12, the correlation coefficients between 6MWD and PVR and between 6MWD and cardiac index were −0.097 (95% CI −0.195 to 0.003; $p = 0.056$) and 0.132 (95% CI 0.033 to 0.228; $p = 0.0091$), respectively.

Safety

Detailed safety data from the PATENT-1 study have been published previously.[18] There were no differences in AEs between the treatment-naïve and pre-treated subgroups (Table 4). In the overall population, 8 patients experienced an AE of hemoptysis (6 [2%] in the riociguat 2.5 mg 3 times daily–maximum group and 2 [2%] in the placebo group). Two (1%) patients in the riociguat 2.5 mg 3 times daily–maximum group experienced serious AEs of hemoptysis, but this was judged not to be related to the study drug in both patients by the investigators. AEs specific to the RHC procedure were infrequent. In the overall population,

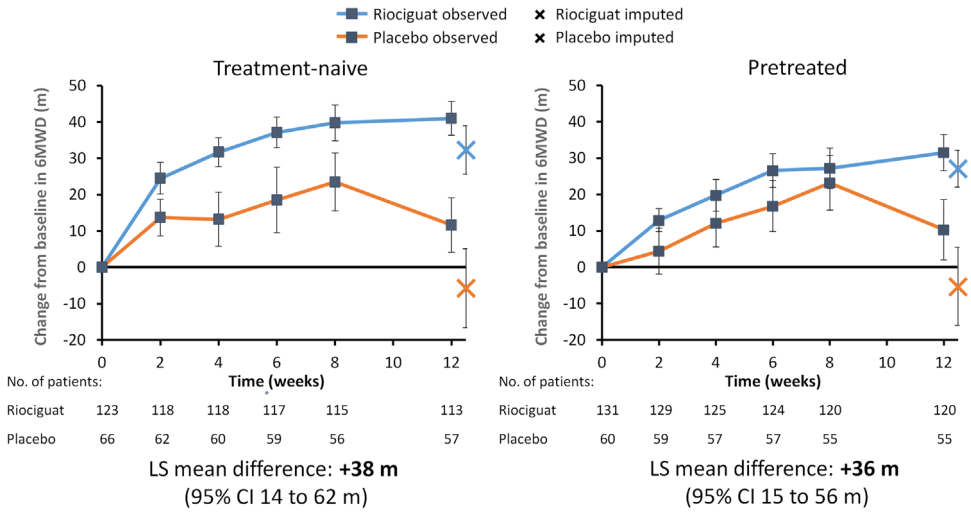

Figure 3 The 6MWD over time in treatment-naïve and pre-treated subgroups in PATENT-1 (riociguat 2.5 mg 3 times daily–maximum group vs placebo). Missing values, where the patient withdrew or died, were imputed at week 12 according to the last observed value except in cases of death or clinical worsening without termination visit, when worst value (0 m) was imputed. Graphs show mean ± SEM.

1 patient (1%) in the placebo group experienced an AE of catheter-site hemorrhage, whereas 1 patient (<1%) in the riociguat 2.5 mg 3 times daily–maximum group experienced catheter-site pain.

Discussion

In PATENT-1, riociguat significantly improved a range of hemodynamic parameters in patients with PAH, including PVR, mPAP, SvO_2, and cardiac index. These improvements were consistent in treatment-naïve patients and patients who were pre-treated with ERAs or non-intravenous prostanoids. In the overall population, the improvements in PVR and cardiac index correlated weakly with improvement in 6MWD. Hemodynamic data were available at baseline and week 12 for most patients enrolled in the study, in contrast to several previous studies in which hemodynamic data were available only for subsets of patients.[20,21]

The hemodynamic improvements with riociguat were consistent in treatment-naïve patients and patients who were pre-treated. In accordance with previous studies that included treatment-naïve and pre-treated patients,[20,21] hemodynamic impairments were generally more pronounced at baseline, and improvements at week 12 were greater in the treatment-naïve subgroup. The relative changes in PVR, mPAP, cardiac index, and SvO_2 were similar in the treatment-naïve and pre-treated subgroups. Furthermore, these improvements were consistent when riociguat was combined with ERAs or non-intravenous prostanoids.

Reductions in MAP and SVR were observed in the riociguat 2.5 mg 3 times daily–maximum group (Tables 2 and 3) compared with no substantial changes in the placebo groups. This is concordant with the prevalence of hypotension as an AE in both treatment-naïve and pre-treated groups (Table 4) and outlines the importance of progressive, individualized dose adjustment of riociguat when used as monotherapy or in combination with ERAs or non-intravenous prostanoids.

Hemodynamic parameters have been shown to correlate with prognosis in patients with PAH,[11,22–24] and registry data suggest that baseline mPAP, RAP, cardiac index, PVR, and SvO_2 may be predictive of survival in patients with

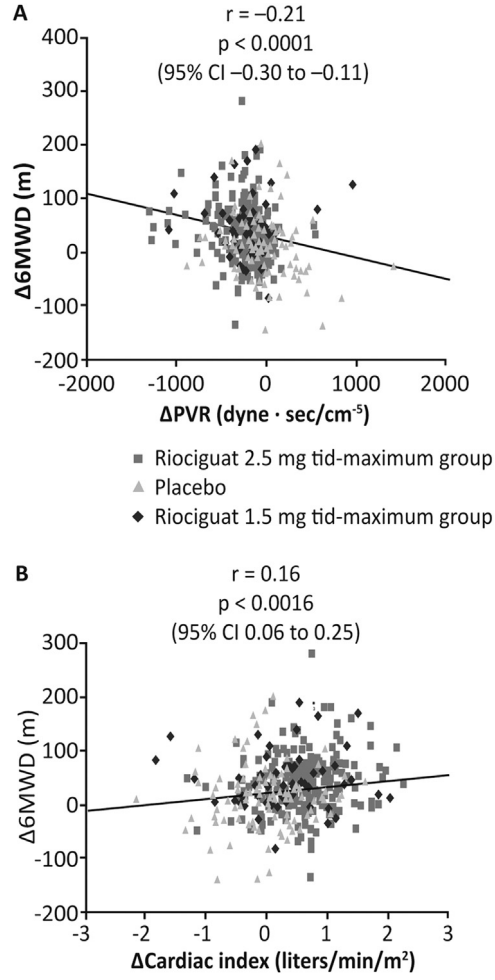

Figure 4 Correlation scatterplots showing change from baseline to week 12 in (A) 6MWD vs PVR and (B) 6MWD vs cardiac index. tid, 3 times daily.

Table 4 AEs Occurring in >5% of Patients in Any Group

	Treatment naïve		Pre-treated	
AE, *n* (%)	Riociguat 2.5 mg 3 times daily–maximum (*n* = 123)	Placebo (*n* = 66)	Riociguat 2.5 mg 3 times daily–maximum (*n* = 131)	Placebo (*n* = 60)
Any	107 (87)	56 (85)	120 (92)	52 (87)
Headache	27 (22)	6 (9)	42 (32)	19 (32)
Dyspepsia	25 (20)	5 (8)	23 (18)	5 (8)
Peripheral edema	22 (18)	8 (12)	22 (17)	6 (10)
Dizziness	16 (13)	7 (11)	24 (18)	8 (13)
Nausea	16 (13)	6 (9)	24 (18)	10 (17)
Diarrhea	14 (11)	5 (8)	21 (16)	8 (13)
Hypotension	14 (11)	0	11 (8)	3 (5)
Vomiting	12 (10)	4 (6)	14 (11)	7 (12)
Nasopharyngitis	10 (8)	6 (9)	16 (12)	8 (13)
Anemia	7 (6)	0	14 (11)	3 (5)
Palpitations	7 (6)	3 (5)	13 (10)	3 (5)
Epistaxis	7 (6)	0	4 (3)	1 (2)
Extremity pain	7 (6)	2 (3)	4 (3)	4 (7)
Chest pain	6 (5)	5 (8)	12 (9)	6 (10)
Gastroesophageal reflux disease	6 (5)	2 (3)	8 (6)	2 (3)
Constipation	5 (4)	1 (2)	4 (3)	1 (2)
Upper abdominal pain	5 (4)	1 (2)	4 (3)	4 (7)
Pyrexia	5 (4)	2 (3)	3 (2)	2 (3)
Chest discomfort	5 (4)	8 (12)	1 (1)	3 (5)
Cough	4 (3)	6 (9)	8 (6)	7 (12)
Hypokalemia	4 (3)	1 (2)	8 (6)	5 (8)
Tachycardia	4 (3)	5 (8)	5 (4)	2 (3)
Asthenia	4 (3)	1 (2)	3 (2)	2 (3)
Upper respiratory tract infection	4 (3)	3 (5)	3 (2)	2 (3)
Nasal congestion	3 (2)	1 (2)	8 (6)	2 (3)
Back pain	3 (2)	1 (2)	6 (5)	3 (5)
Abdominal distention	3 (2)	1 (2)	3 (2)	0
Erythema	3 (2)	0	0	0
Abdominal pain	2 (2)	0	8 (6)	3 (5)
Bronchitis	2 (2)	1 (2)	7 (5)	2 (3)
Respiratory tract infection	2 (2)	3 (5)	5 (4)	2 (3)
RV failure	2 (2)	0	1 (1)	1 (2)
Dyspnea	1 (1)	9 (14)	15 (12)	5 (8)
Fatigue	1 (1)	4 (6)	6 (5)	4 (7)
Gastritis	1 (1)	0	3 (2)	0
Urinary tract infection	1 (1)	0	2 (2)	4 (7)
Pneumonia	1 (1)	1 (2)	1 (1)	0
Syncope	1 (1)	4 (6)	2 (2)	1 (2)
Hot flush	1 (1)	2 (3)	0	4 (7)
Flushing	0	2 (3)	5 (4)	5 (8)
Worsening PAH	0	0	1 (1)	2 (3)
Decreased hemoglobin	0	0	0	0
Gastric polyps	0	0	0	0
Other AEs of interest				
Hemoptysis	4 (3)	2 (3)	2 (2)	0

AE, adverse event; PAH, pulmonary arterial hypertension; RV, right ventricular.

PAH.[5,8,9,25,26] More importantly, parameters identified as predictive of survival at baseline can provide prognostic information during follow-up.[11,22–24] Significant improvements in PVR, mPAP, SvO_2, and cardiac index were observed in the present study. These were accompanied, as expected, by a significant decrease in NT-proBNP levels in the primary analysis of PATENT-1.[18] The mechanisms underlying the hemodynamic improvements observed with riociguat have yet to be elucidated. Whether potentially disease-modifying effects of riociguat, such as the anti-fibrotic, anti-proliferative, and anti-inflammatory effects observed in pre-clinical studies, play a role is unknown and requires further characterization.[13] Although the improvement in 6MWD at the end of PATENT-1 was significantly correlated with improvements in both PVR and cardiac index, the correlations were small. These small

correlations underscore the need to assess different areas, including clinical, functional, exercise, and hemodynamic parameters in individual patients, as reported in recent guidelines to fully evaluate disease severity and treatment effect.[2] This need has been reported before, and several composite risk factor formulas have been developed using registry data to better predict patient survival and prognosis.[4,25,27] The limitations of this predictive approach are demonstrated by observations that some compounds may improve exercise capacity and hemodynamic parameters in patients with PAH, without modifying long-term outcome.[28,29] Therefore, the concordance between predictive parameters and long-term outcome should be verified for each individual compound and for each treatment strategy.

Limitations

Analysis of the treatment-naïve and pre-treated subgroups was pre-specified; however, statistical testing of hemodynamic data in these subgroups was performed post hoc, using the same statistical methods as the pre-specified subgroup analyses of 6MWD. Furthermore, PATENT-1 assessed the effect of riociguat on hemodynamic parameters at baseline and after 12 weeks of therapy, and long-term hemodynamic measurements were not planned. Therefore, future studies will need to determine whether the hemodynamic changes at week 12 correlate with long-term clinical outcome. Although a dose response was observed in cardiac index, a concomitant dose response in SvO_2 was not observed. This may be due to limitations in SvO_2 assessment in this study, as hemodynamic parameters were assessed by a single method (i.e., thermodilution RHC), and oximetry-based calculations of CO were not collected. Only a small number of patients pre-treated with non-intravenous prostanoids were included in the study, and patients with PAH resulting from other etiologies, such as human immunodeficiency virus, were excluded.

Conclusions

In the PATENT-1 study, 12 weeks of treatment with riociguat provided improvements in PVR, mPAP, SvO_2, and cardiac index in the absence of significant changes in heart rate. Reductions in MAP and SVR were also observed. The changes in hemodynamic parameters seen in the overall group were consistent in the treatment-naïve and pre-treated subgroups, including patients pre-treated with ERAs and non-intravenous prostanoids, and were accompanied by significant improvements in 6MWD. For patients with PAH, riociguat offers an additional treatment option, either as monotherapy or in combination with ERAs and non-intravenous prostanoids.

Disclosure statement

N.G. reports grants, personal fees, and non-financial support from Bayer; grants and personal fees from Actelion and Pfizer; and personal fees from Eli Lilly and Company, GlaxoSmithKline, and Novartis. F.G. reports grants, personal fees, and non-financial support from Bayer and personal fees from Actelion, Eli Lilly and Company, Novartis, and Pfizer. E.G. reports grants, personal fees, and non-financial support from Bayer; grants and personal fees from Actelion, GlaxoSmithKline, Eli Lilly and Company, and Pfizer; non-financial support from Alexion Pharmaceuticals; and personal fees from Miltenyi Biotec, Novartis, and United Therapeutics. M.M.H. reports grants, personal fees, and non-financial support from Bayer HealthCare Pharmaceuticals and personal fees from Actelion, GlaxoSmithKline, Eli Lilly and Company, Novartis, and Pfizer. M.H. reports personal fees from Actelion, Bayer, GlaxoSmithKline, Novartis, Pfizer, and Aires. Z.-C.J. reports personal fees from Bayer, Actelion, Pfizer, and United Therapeutics. A.M.K. reports grants and personal fees from Bayer, Actelion, GlaxoSmithKline, and United Therapeutics. D.L. reports grants, personal fees, and non-financial support from Bayer. L.J.R. reports personal fees and non-financial support from Bayer; personal fees and stock options from GeNO; and personal and other fees from Actelion, Pfizer, United Therapeutics, Lung Biotechnology, Gilead Sciences, GlaxoSmithKline, National Heart, Lung, and Blood Institute, US Food and Drug Administration, mondoBIOTECH, Arena Pharmaceuticals, Liquidia Technologies, and Regeneron, although many of these consultancies are not currently viable. A.F. is an employee of Bayer Pharma AG. N.D. is an employee of Bayer Pharma AG. H.-A.G. reports grants from Actelion, Bayer, Ergonex, and Pfizer and personal fees from Actelion, Bayer, Ergonex, Gilead, GlaxoSmithKline, Merck, Novartis, and Pfizer.

This study was funded by Bayer Pharma AG (Berlin, Germany). Editorial support was provided by Adelphi Communications Ltd (Bollington, United Kingdom), funded by Bayer Pharma AG.

Supplementary data

Supplementary data are available online at jhltonline.org.

References

1. McLaughlin VV, Archer SL, Badesch DB, et al. 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.
2. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016; 37:67-119.
3. Jing ZC, Xu XQ, Han ZY, et al. Registry and survival study in Chinese patients with idiopathic and familial pulmonary arterial hypertension. Chest 2007;132:373-9.
4. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 2010;36:549-55.
5. 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 REVEAL. Chest 2012;142:448-56.

6. Keogh A, Strange G, McNeil K, et al. The Bosentan Patient Registry: long-term survival in pulmonary arterial hypertension. Intern Med J 2011;41:227-34.
7. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42-50.
8. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343-9.
9. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156-63.
10. Benza RL, Miller DP, Gomberg-Maitland M, et al. 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.
11. Tiede H, Sommer N, Milger K, et al. Short-term improvement in pulmonary hemodynamics is strongly predictive of long-term survival in patients with pulmonary arterial hypertension. Pulm Circ 2013;3:523-32.
12. Klinger JR, Abman SH, Gladwin MT. Nitric oxide deficiency and endothelial dysfunction in pulmonary arterial hypertension. Am J Respir Crit Care Med 2013;188:639-46.
13. Stasch JP, Evgenov OV. Soluble guanylate cyclase stimulators in pulmonary hypertension. Handb Exp Pharmacol 2013;218:279-313.
14. Stasch JP, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation 2011;123:2263-73.
15. Schermuly RT, Stasch JP, Pullamsetti SS, et al. Expression and function of soluble guanylate cyclase in pulmonary arterial hypertension. Eur Respir J 2008;32:881-91.
16. Follmann M, Griebenow N, Hahn MG, et al. The chemistry and biology of soluble guanylate cyclase stimulators and activators. Angew Chem Int Ed Engl 2013;52:9442-62.
17. Stasch JP, Hobbs AJ. NO-independent, haem-dependent soluble guanylate cyclase stimulators. Handb Exp Pharmacol 2009:277-308.
18. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013; 369:330-40.
19. Conole D, Scott LJ. Riociguat: first global approval. Drugs 2013; 73:1967-75.
20. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009;119:2894-903.
21. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809-18.
22. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002; 106:1477-82.
23. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2012;39:589-96.
24. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780-8.
25. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL risk score calculator in newly diagnosed patients with pulmonary arterial hypertension. Chest 2012;141:354-62.
26. Agarwal R, Gomberg-Maitland M. Prognostication in pulmonary arterial hypertension. Heart Fail Clin 2012;8:373-83.
27. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J 2010;35: 1079-87.
28. Frost AE, Barst RJ, Hoeper MM, et al. Long-term safety and efficacy of imatinib in pulmonary arterial hypertension. J Heart Lung Transplant 2015;34:1366-75.
29. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 2013;127:1128-38.