Haemodynamic effects of riociguat in CTEPH and PAH: a 10-year observational study

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In patients with PAH and inoperable CTEPH, riociguat improved pulmonary vascular resistance and cardiac index for 8 years, but not pulmonary arterial pressure. World Health Organization functional class may have predictive value for long-term prognosis. https://bit.ly/3dTf4ft

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Abstract

Background Long-term treatment with riociguat has been shown to enhance exercise capacity in patients with pulmonary arterial hypertension (PAH) and inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH). This study sought to evaluate the long-term haemodynamic effects of riociguat in patients with PAH and inoperable CTEPH.

Methods During this single-centre long-term observational study, riociguat was administered at a three-times-daily dose of up to 2.5 mg. The primary outcome was pulmonary vascular resistance (PVR). The secondary outcomes included mean pulmonary arterial pressure (PAP), cardiac index, mortality, clinical worsening events, 6-min walk distance (6MWD) and World Health Organization functional class (WHO FC).

Results 37 patients (CTEPH n=19; PAH n=18) were included. The median follow-up period was 96 months. The survival estimates for all the patients at 1/3/5/8 years were 0.97/0.86/0.72/0.61, without significant differences between patients with CTEPH and PAH. At the final data cut-off, PVR decreased (1232±462 dyn·s·cm^{-5} *versus* 835±348 dyn·s·cm^{-5}, p<0.001), cardiac index increased (1.7±0.4 L·min^{-1}·m^{-2} *versus* 2.4±0.5 L·min^{-1}·m^{-2}, p<0.001), 6MWD increased by 43.1±59.6 m, and WHO FC improved/stabilised/worsened in 40%/35%/25% of patients *versus* baseline. Improvement in PAP was not shown. Compared with patients in WHO FC I/II and III/IV at baseline, the 8-year clinical worsening-free survival estimates were 0.51 *versus* 0.19 (p=0.026).

Conclusions Riociguat improved PVR and cardiac index for up to 8 years, but not PAP. WHO FC may have certain predictive value for the long-term prognosis.

Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are different subtypes of pulmonary hypertension. They are characterised by increased pulmonary vascular resistance (PVR), resulting in right ventricular failure and even eventual death [1, 2]. The primary treatment for PAH is pharmacological therapy, including endothelin receptor antagonists (ERAs), prostacyclin analogues and prostacyclin receptor agonists, phosphodiesterase type 5 inhibitors (PDE-5is) and soluble guanylate cyclase (sGC) stimulators [3, 4]. For CTEPH patients, pulmonary endarterectomy (PEA) is the gold-standard therapy [1]. However, even in highly experienced pulmonary hypertension centres, PEA cannot be performed in ~50% of CTEPH patients due to the occlusion of distal vessels or

coexisting conditions or patients' refusal [5]. In addition, 17–35% of patients who undergo PEA will have residual pulmonary hypertension, which needs further treatment [6–9].

Riociguat is the first sGC stimulator showing favourable benefit–risk profile in both PAH and CTEPH patients [10, 11] with significantly improved 6-min walk distance (6MWD), PVR, N-terminal pro-brain natriuretic peptide (NT-proBNP) and World Health Organization functional class (WHO FC) in the 12-week Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (PATENT-1) study and 16-week Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (CHEST-1) study [12, 13]. The PATENT-2 and CHEST-2 open-label long-term extension (LTE) study revealed that the safety and efficacy of riociguat sustained for up to 2 years, with improvement in exercise capacity and functional capacity [14–17]. Moreover, riociguat was reported to be well tolerated for >6 years in patients with PAH and inoperable CTEPH, and improvements in 6MWD and WHO FC were maintained for ∼4 years [18].

Therefore, we hypothesised that riociguat may continue to improve the haemodynamics over the long term in patients with inoperable CTEPH and PAH. Additionally, we aimed to find predictive indicators for the long-term prognosis in patients with inoperable CTEPH and PAH. We conducted this open-label, single-centre study to evaluate the long-term safety and efficacy parameters of riociguat, in particular, effects on haemodynamics in patients with PAH and inoperable or persistent/recurrent CTEPH.

Methods

Patients

Patients completing CHEST/PATENT-1 in our centre without withdrawal or ongoing riociguat-related serious adverse events were eligible to enter the CHEST/PATENT-2 LTE study [14, 15]. Additional inclusion and exclusion criteria have been introduced previously [12, 13]. In short, PAH and inoperable or persistent/recurrent CTEPH patients aged 18–80 years with 6MWD 150–450 m, PVR >300 dyn·s·cm^{-5} and mean pulmonary arterial pressure (PAP) of ⩾25 mmHg were enrolled in this LTE study.

This study was carried out in terms of good clinical practice guidelines and the Declaration of Helsinki. The study protocol was approved by the ethics committees of Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine and Capital Medical University, Beijing, China (2009-1, 2014BJYYEC-051-02), and written informed consent was obtained from all patients.

Study design

This LTE study was a single-centre observational study conducted at Beijing Chao-Yang Hospital from 1 June 2009 to 31 December 2019. The study consisted of two phases, including an 8-week double-blind dose-adjustment phase and an open-label study phase [14, 15]. All the patients received individually adjusted dose of riociguat according to physician's discretion (up to 2.5 mg three times a day). During the open-label study phase, patients were permitted to receive ERAs and prostanoids as add-on combination treatments, but nitric oxide donors and PDE-5is were not allowed.

Baseline refers to the start of the CHEST/PATENT-1 study. Patients were followed-up at weeks 2, 4, 6, 8 and 12, and every 3 months thereafter, up to 10 years. The evaluation indicators at each follow-up included 6MWD, NT-proBNP, WHO FC and Borg dyspnoea score. At the last data collection point, right heart catheterisation (RHC) and echocardiography were also assessed. For patients who underwent balloon pulmonary angioplasty (BPA), all parameters were collected before BPA to avoid potential confounders.

Outcomes

The primary outcome of this LTE study was PVR. The secondary outcomes included mean PAP and cardiac index measured by RHC, mortality, clinical worsening events, 6MWD and WHO FC. Clinical worsening was defined as any of the following events: death, add-on other targeted drugs or hospitalisation due to disease progression. Patients were documented as censored if they withdrew without experiencing an event.

Statistical analysis

All statistical analyses were performed with STATA software version 16 and GraphPad Prism version 6.0. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. Normally distributed data were expressed as mean±SD. Data without normal distribution were expressed using median and interquartile range (IQR). Categorical data were presented as number and percentage. All variables were analysed with descriptive methods. The t-test was used to compare between two groups under the premise of normal distribution. Data without normal distribution were assessed *via* Wilcoxon rank sum

test. Cross-tabulations were checked using the Chi-squared test. Survival and clinical worsening-free survival at each time point were analysed using Kaplan–Meier curves, in which patients were censored if they had withdrawn without experiencing an event or had not reached the final follow-up. We subsequently stratified the participants by pulmonary hypertension subgroup. A p-value <0.05 was considered statistically significant.

Results

Study population

Of the 38 patients who were randomised and treated in the CHEST/PATENT-1 study, one with CTEPH was asked to withdraw from the study due to poor compliance. Thus, 37 patients (inoperable CTEPH n=19; PAH n=18) were included in the LTE study (figure 1), with a mean age of 48.8±11.7 years, of whom 24 (65%) were female. In all the cases of PAH, 14 (77.7%) were idiopathic, two (11.1%) connective tissue disease associated, one (5.6%) was congenital heart disease associated and one (5.6%) was familial. All the patients received no other treatment for PAH at the start of our study. Baseline characteristics are shown in table 1. At diagnosis, baseline haemodynamics showed patients with mean±SD PAP 52.2±11.4 mmHg, pulmonary artery wedge pressure (PAWP) 8.5±2.6 mmHg, median (IQR) cardiac index 1.7 (1.5–2.0) $L \cdot min^{-1} \cdot m^{-2}$ and mean±SD PVR 1258±415 $dyn \cdot sec \cdot cm^{-5}$. The 6MWD at baseline was 359±65 m. The majority of patients were in WHO FC I/II (CTEPH 58%; PAH 78%). Compared with the PAH patients at baseline, patients with CTEPH had a higher level of haemoglobin (p=0.049), platelets (p=0.020) and NT-proBNP (p=0.035).

Safety and survival rate

After the dose-titration phase, 35 (94.6%) patients received riociguat 2.5 mg three times a day, and two (5.4%) patients took 2 mg three times a day. Two patients with PAH withdrew from the study due to inconvenience of follow-up at 31 months and 67 months, while no CTEPH participants exited the study (figure 1). During the study period, all the CTEPH and six (33%) PAH patients received oral anticoagulant agents; eight (42%) CTEPH and four (22%) PAH patients received diuretics; and 15 (79%) CTEPH and 14 (78%) PAH patients received supplemental oxygen. Supplemental oxygen use was defined as use at any time from enrolment to the end of follow-up. One (2.7%) patient with CTEPH developed haemoptysis during the follow-up, and recovered after bronchial artery embolisation. None of the patients complained of obvious adverse drug reaction, and none withdrew for reasons related to adverse events from riociguat. After data collection at the end of our study, eight patients with CTEPH underwent BPA.

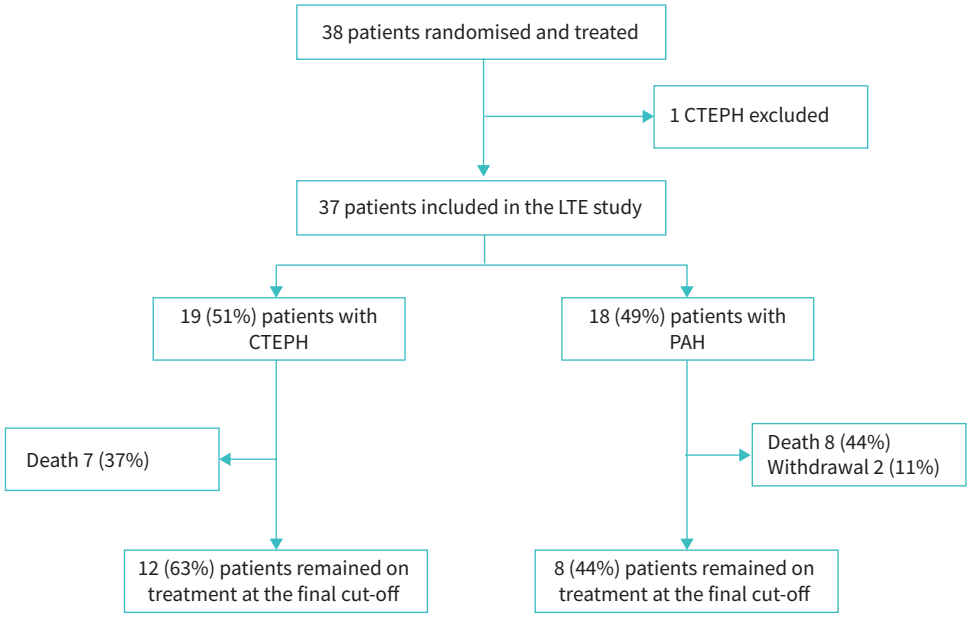


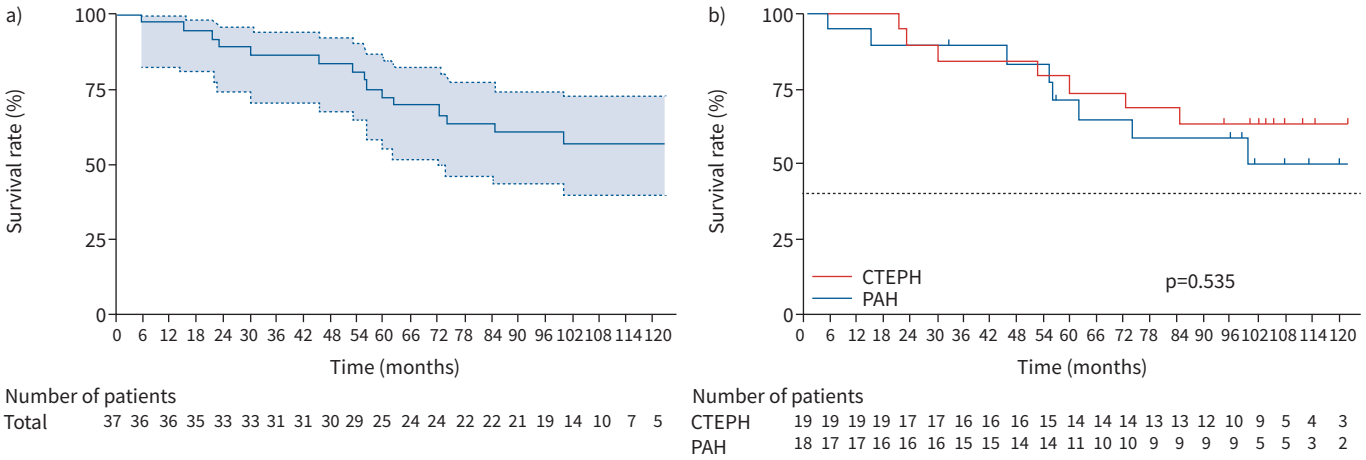
FIGURE 1 Flow diagram of the study population from the long-term extension (LTE) study. CTEPH: chronic thromboembolic pulmonary hypertension; PAH: pulmonary arterial hypertension.

TABLE 1 Baseline characteristics of the study population

	CTEPH (n=19)		PAH (n=18)		p-values
	Patients with available data	Baseline values	Patients with available data	Baseline values	
Age, years	19	50.7±10.1	18	46.7±13.2	0.305
Female	19	11 (58)	18	13 (72)	0.362
BMI, kg·m^{-2}	19	24.4±3.0	18	23.0±3.7	0.214
Laboratory tests					
Haemoglobin, g·L^{-1}	19	149 (144–163)	18	143 (128–153)	0.049
Platelets, ×10^9 cells·L^{-1}	19	207 (170–240)	18	160 (121–203)	0.020
Albumin, g·L^{-1}	19	36.5 (33.4–40.8)	18	38.6 (34.6–40.6)	0.518
AST, U·L^{-1}	19	29.6±7.5	18	30.8±9.1	0.649
ALT, U·L^{-1}	19	24.0 (15.0–35.0)	18	26.5 (20.0–37.8)	0.313
γ-GT, U·L^{-1}	19	60 (40–108)	18	57.5 (32.5–100)	0.461
Total bilirubin, µmol·L^{-1}	19	21.0±10.8	18	15.9±6.5	0.094
Creatinine, µmol·L^{-1}	19	82.3±20.3	18	72.8±19.3	0.642
NT-proBNP, pg·mL^{-1}	15	1505 (643–3430)	9	472 (155–1106)	0.035
6MWD, m	19	355±83	18	363±41	0.719
WHO FC I/II/III/IV	19	2/9/8/0	18	1/13/4/0	0.641
Echocardiography					
RV transverse diameter, mm	15	48.2±9.2	14	45.9±6.8	0.462
LV transverse diameter, mm	11	28.8 (23.0–39.0)	11	29.3 (24.1–30.1)	0.949
RV/LV	11	1.8±0.7	11	1.7±0.5	0.512
RA transverse diameter, mm	15	59.0 (45.5–60.6)	14	50.1 (41.2–56.7)	0.354
LA transverse diameter, mm	15	30.2 (25.3–35.5)	14	27.2 (26.8–31.4)	0.451
Thickness of RVAW, mm	14	6.0 (5.3–7.2)	14	5.8 (4.9–8.4)	0.734
Amplitude of RVAW motion, mm	13	1.0 (1.0–5.0)	14	3.5 (2.8–5.4)	0.068
MPA diameter, mm	14	31.7 (28.6–34.7)	14	31.8 (28.4–35.0)	0.874
TRV, m·s^{-1}	15	4.7±0.4	14	4.3±0.5	0.046
Estimated systolic PAP, mmHg	15	99.5±16.0	14	87.3±17.0	0.056
Haemodynamic parameters					
CVP, mmHg	19	9.4±6.0	18	7.1±6.1	0.251
Systolic PAP, mmHg	19	88.8±15.1	18	85.0±22.0	0.543
Diastolic PAP, mmHg	19	32 (26–38)	18	35 (28–40)	0.391
Mean PAP, mmHg	19	54 (45–59)	18	51 (42–63)	0.869
PAWP, mmHg	19	8.5±2.0	18	8.6±3.1	0.872
Cardiac output, L·min^{-1}	19	3.0±0.9	18	2.9±0.5	0.703
Cardiac index, L·min^{-1}·m^{-2}	19	1.7 (1.3–2.0)	18	1.8 (1.5–2.1)	0.425
PVR, dyn·s·cm^{-5}	19	1245±396	18	1272±446	0.847
S_{vO_2}, %	13	61.3±11.3	13	68.1±10.1	0.124

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. CTEPH: chronic thromboembolic pulmonary hypertension; PAH: pulmonary arterial hypertension; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine amino transferase; γ-GT: γ-glutamyl transferase; NT-proBNP: N-terminal pro-brain natriuretic peptide; 6MWD: 6-min walk distance; WHO FC: World Health Organization functional class; RV: right ventricle; LV: left ventricle; RV/LV: the ratio of right ventricle to left ventricle dimension; RA: right atrium; LA: left atrium; RVAW: right ventricular anterior wall; MPA: main pulmonary artery; TRV: tricuspid regurgitation velocity; PAP: pulmonary artery pressure; CVP: central venous pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation.

The median (IQR) treatment duration was 96 (56–109) months for all the patients. At the final data collection point, 15 (40.5%) out of 37 patients had died (CTEPH n=7; PAH n=8) (figure 1). 12 patients died from right-ventricular failure, one from severe pneumonia, one from massive haemoptysis and one died at home from unknown cause. Kaplan–Meier estimates of 1-year, 3-year, 5-year and 8-year survival for all the patients were 0.97 (95% CI 0.82–1.00), 0.86 (95% CI 0.71–0.94), 0.72 (95% CI 0.55–0.84) and 0.61 (95% CI 0.43–0.75), respectively (figure 2a). 1-year, 3-year, 5-year and 8-year survival estimates for CTEPH and PAH patients were 1.0, 0.84, 0.74 and 0.63 and 0.94, 0.89, 0.71 and 0.58, respectively. There was no significant difference in the survival between the CTEPH and PAH patients (p=0.535; figure 2b). Survival curves of the CTEPH and PAH patients crossed over several times, indicating that there might be some confounders. The pre-determined covariates were sex and body mass index (<24 kg·m^{-2} *versus* ⩾24 kg·m^{-2}) [19]. In addition, due to the significant differences in baseline variables between the CTEPH and PAH groups, NT-proBNP was considered to be one of the confounding factors. Subgroup analysis was performed to modify the bias, and the result showed that there was no significant difference between CTEPH and PAH groups (figure 2c).



c)

Subgroup	Patients n	p-value	Hazard ratio (95% CI)
Sex:		0.42	
Male	13		1.77 (0.47–6.61)
Female	24		2.02 (0.37–11.09)
BMI (kg·m^{-2}):		0.30	
<24	20		0.57 (0.17–1.87)
≥24	17		2.83 (0.39–20.35)
NT-pro-BNP (pg·mL^{-1}):		0.31	
<1400	15		4.18 (0.47–37.51)
≥1400	9		3.47 (0.31–38.39)
Overall	37		1.38 (0.50–3.80)

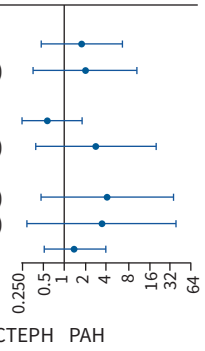


FIGURE 2 a) Kaplan–Meier survival plots for all patients (1-year, 3-year, 5-year and 8-year survival estimates for all the patients were 0.973 (95% CI 0.823–0.996), 0.865 (95% CI 0.705–0.941), 0.724 (95% CI 0.548–0.841) and 0.608 (95% CI 0.429–0.747), respectively). b) Kaplan–Meier survival plots for patients with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) showed there was no significant difference between the two groups. c) Hazard ratios for different variables showed that there was no significant difference between the CTEPH and PAH groups. BMI: body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Hospitalisation owing to disease progression was the most frequent clinical worsening event. In CTEPH patients, 11 patients were hospitalised at least once due to acute exacerbation of CTEPH; four patients started a new PAH treatment (ambrisentan n=1, bosentan n=1 and beraprost n=2). In patients with PAH, eight underwent hospitalisation due to disease progression and two added-on new targeted drugs (ambrisentan n=1 and bosentan n=1). Kaplan–Meier estimates of 1-year, 3-year, 5-year and 8-year clinical worsening-free survival for all patients were 0.92 (95% CI 0.77–0.97), 0.84 (95% CI 0.67–0.92), 0.56 (95% CI 0.38–0.70) and 0.38 (95% CI 0.23–0.54), respectively, without significant difference between the CTEPH and PAH patients (p=0.977).

Haemodynamic parameters

Haemodynamic indices by RHC at baseline were available for all 37 patients. At the final data cut-off, all 20 surviving patients underwent the haemodynamic examination, in which one patient did not complete data collection due to palpitations during RHC. Compared with baseline, PVR at the final data collection point obviously decreased (1232±462 *versus* 835±348 dyn·sec·cm^{-5}; p<0.001), cardiac output (3.0±0.9 *versus* 4.0±1.0 L·min^{-1}; p<0.001) and cardiac index (1.7±0.4 *versus* 2.4±0.5 L·min^{-1}·m^{-2}; p<0.001) were significantly increased, while mean PAP was not improved (50.2±9.8 *versus* 51.3±13.7 mmHg; p=0.677). In addition, an increase in PAWP was observed, but within 15 mmHg (table 2).

6-min walk distance

At the end-point, compared with baseline, 6MWD increased by 43.1±59.6 m (from 362.7±63.9 m to 405.8±94.9 m, p=0.004; figure 3a).

TABLE 2 Change in variables between baseline and the final data cut-off

	Patients with available data	Baseline	Final data cut-off	p-values
Haemodynamic parameters				
CVP, mmHg	19	7.8±5.2	8.9±2.7	0.400
Systolic PAP, mmHg	19	85.4±17.5	83.2±24.2	0.686
Diastolic PAP, mmHg	19	31.8±7.0	34.4±9.3	0.154
Mean PAP, mmHg	20	50.2±9.8	51.3±13.7	0.677
PAWP, mmHg	19	8 (1–10)	12 (10–15)	0.03
Cardiac output, $L \cdot min^{-1}$	19	3.0±0.9	4.0±1.0	<0.001
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	19	1.7±0.4	2.4±0.5	<0.001
PVR, $dyn \cdot s \cdot cm^{-5}$	19	1232±462	835±348	<0.001
S_{vO_2}, %	13	63.0±11.3	60.5±10.6	0.399
Echocardiography				
RV transverse diameter, mm	16	43.9±7.4	47.1±8.1	0.110
LV transverse diameter, mm	12	29 (23–32)	39 (34–44)	0.034
RV/LV	12	1.6±0.6	1.2±0.4	0.032
Thickness of RVAW, mm	9	6.3±1.4	6.8±1.6	0.377
Amplitude of RVAW motion, mm	5	3.8±2.5	3.8±1.5	0.959
MPA diameter, mm	15	30.4±3.8	37.2±9.8	0.013
TRV, $m \cdot s^{-1}$	16	4.5±0.5	4.5±0.8	0.865
Estimated systolic PAP, mmHg	15	91.6±17.6	99.4±26.0	0.306

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. CVP: central venous pressure; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; RV: right ventricle; LV: left ventricle; RV/LV: the ratio of right ventricle to left ventricle dimension; RVAW: right ventricular anterior wall; MPA: main pulmonary artery; TRV: tricuspid regurgitation velocity.

WHO FC

The comparison from baseline to the 8-year time point showed that 15 (75%) patients sustained stable or even improved WHO FC. The WHO FC improved/stabilised/worsened in 40%/35%/25% of the patients, respectively (figure 3b).

Based on the WHO FC at baseline, patients are divided into WHO FC I/II and III/IV groups. The 8-year clinical worsening-free survival estimates for WHO FC I/II and III/IV group were 0.51 (95% CI 0.30–0.69) *versus* 0.19 (95% CI 0.03–0.45; p=0.026), and the 8-year survival estimates were 0.67 (95% CI 0.45–0.82) *versus* 0.47 (95% CI 0.18–0.72; p=0.192) (figure 4).

Echocardiography

Regarding structural parameters, the transverse diameter of the left ventricle (LV) was increased (29 (23–32) mm *versus* 39 (34–44) mm; p=0.034), the ratio of right ventricle (RV) to LV dimension was significantly reduced (1.6±0.6 *versus* 1.2±0.4; p=0.032), but the transverse diameter of the RV was not significantly improved. There was a significant increase in the diameter of main pulmonary artery (30.4±3.8 mm *versus* 37.2±9.8 mm; p=0.013; table 2). At the final data cut-off, parameters such as fractional area change (29.7±10.3%), tricuspid annular plane systolic excursion (16.6±4.1 mm), right ventricular index of myocardial performance (0.6±0.1) and left ventricular eccentric index (1.5±0.4) indicated right cardiac insufficiency.

Discussion

We conducted a 10-year observational study of riociguat in patients with inoperable CTEPH and PAH, which is the longest follow-up study of riociguat reported to date. At the end of the study, RHC and echocardiography were also assessed, which is more objective and comprehensive than others have reported. We found that haemodynamic parameters such as PVR and cardiac index continued to improve for up to 8 years. Additionally, the results of this study further support the findings from CHEST/PATENT-1 and up to 2-year follow-up study of CHEST/PATENT-2 that riociguat was a well-tolerated and effective treatment for improving exercise capacity and functional capacity in patients with inoperable CTEPH and PAH [12–17].

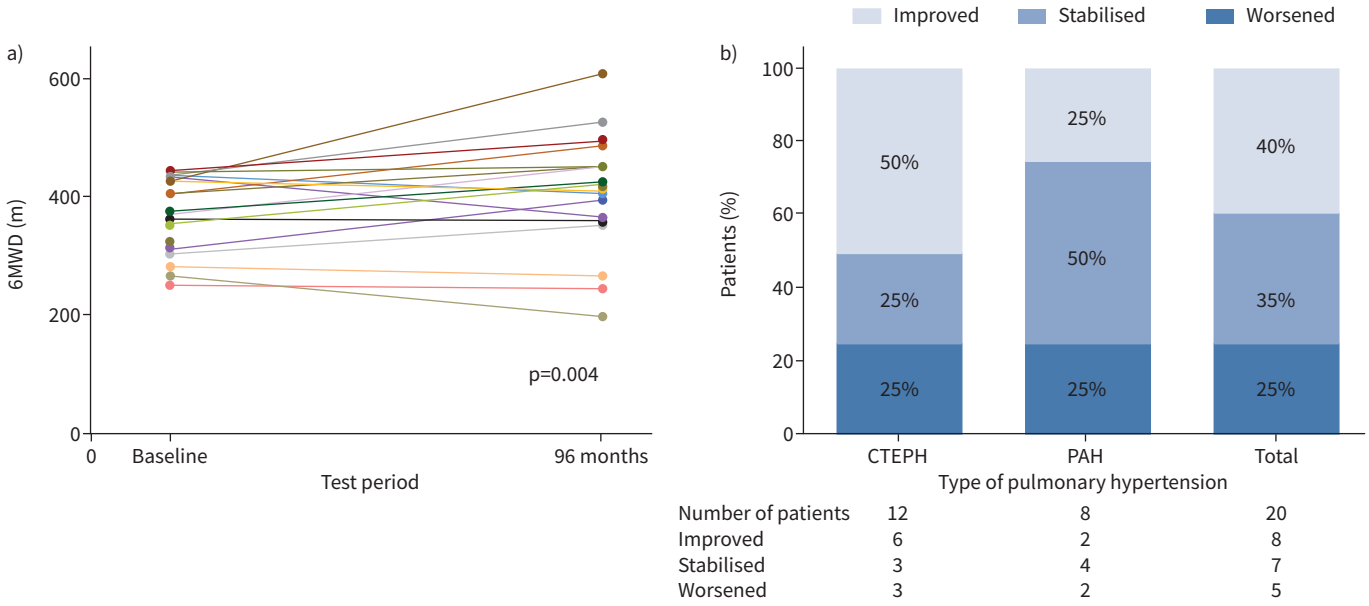


FIGURE 3 a) Increase in 6-min walk distance (6MWD) between baseline and the 96-month time point was 43.1±59.6 m (p=0.004). b) Change in World Health Organization functional class between baseline and 96-month time point. CTEPH: chronic thromboembolic pulmonary hypertension; PAH: pulmonary arterial hypertension.

Haemodynamic parameters, considered as an important end-point in studies of pulmonary hypertension, provided an objective measurement of the pulmonary circulation and were predictive of the outcome [12]. In our study, the efficacy of riociguat was underlined by the results that a range of haemodynamic parameters were significantly improved at the final data cut-off. Compared with 226 dyn·s·cm^{-5}/223 dyn·s·cm^{-5} in the CHEST/PATENT-1 studies, respectively, PVR decreased by 396 dyn·s·cm^{-5} in our LTE study [12, 13]. With respect to other secondary outcomes, the increase in cardiac index was also apparently sustained for up to 8 years. However, we observed that mean PAP had not been continuously improved during the long-term follow-up, which was inconsistent with the results of CHEST/PATENT-1 study [12, 13]. Regarding the structure of the pulmonary circulation, the results from the RIVER (Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation) study suggested that after 6 months of treatment with riociguat, patients showed significantly reduced right heart size and improved RV function in PAH and CTEPH [20]. However, in our LTE study, PAP did not decrease significantly from the baseline, and the persistent high level of PAP might lead to structural changes such as widening of the main pulmonary artery and right heart enlargement. Although RV/LV improved, this was thought to be based on the LV size tending to be normal, not due to the decrease in RV size.

In this LTE study, the majority of patients received riociguat 2.5 mg three times a day, with no serious side-effects identified during the medication period or adverse events related to riociguat contributing to withdrawal or death of patients. One patient in our study experienced haemoptysis, which accounted for 2.7% of the enrolled patients, and was comparable to 3% of patients in the CHEST/PATENT-2 study [14, 15]. In addition, there was a relatively low dropout rate during the study compared with that seen in other targeted-medication long-term studies [21–23], with two patients discontinuing treatment due to the inconvenience of follow-up. In terms of survival rate, compared with registration studies in European countries, our LTE study confirms that the survival rate of patients with PAH and inoperable CTEPH with long-term oral administration of riociguat was significantly higher [24, 25]. A national prospective study in 32 clinical centres from the United States showed that estimated survival rates of patients with primary pulmonary hypertension using conventional treatment at 1, 3 and 5 years were 68%, 48% and 34%, respectively, which were lower than that in our LTE study [26]. In patients with inoperable CTEPH, the 8-year survival rate was higher in patients treated with riociguat than in patients treated with the conventional regimen in our previous study [27]. Compared to the survival rates of PAH and inoperable CTEPH patients, although the CTEPH group showed certain advantages, there was no significant difference between the two groups. Therefore, further large-sample multicentre studies are still needed to confirm our current findings.

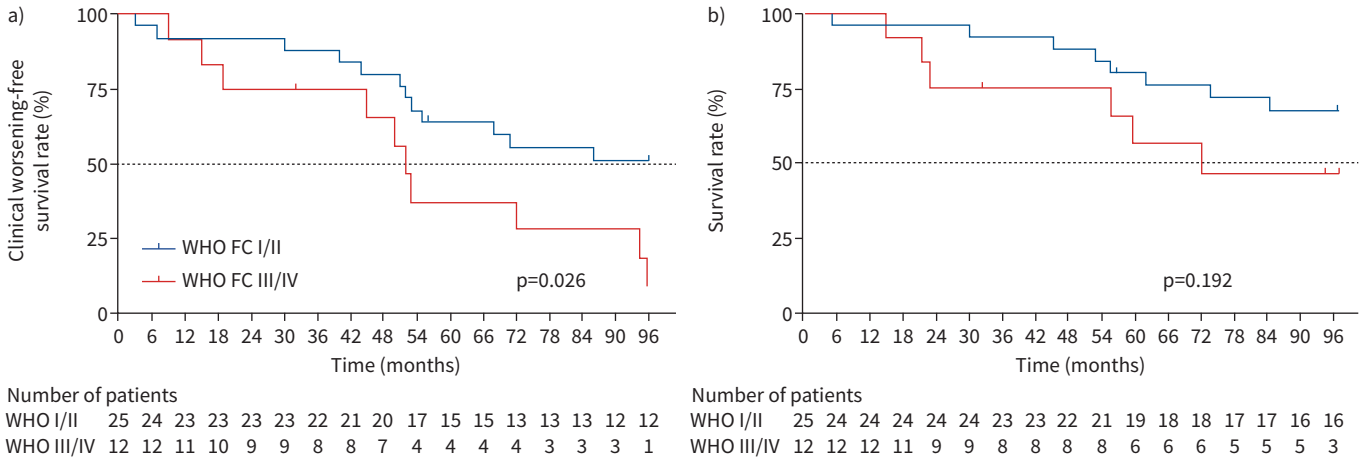


FIGURE 4 a) Kaplan–Meier estimates of 8-year clinical worsening-free survival showed significant difference between the World Health Organization functional class (WHO FC) I/II and III/IV groups at baseline (p=0.026). b) Kaplan–Meier estimates of 8-year survival showed there was no significant difference between the WHO FC I/II and III/IV groups (p=0.192).

6MWD was considered as the correlate of risk of long-term health outcomes, although it can be affected by subjective factors such as patient motivation [28, 29]. The improvement in 6MWD of riociguat was robust up to 8 years, which was apparently a continuation of the CHEST/PATENT-1 and 2-year follow-up study of CHEST/PATENT-2 [12–17]. Taking 6MWD as the observation index, the follow-up duration of our study was much longer than that of other medications for the treatment of PAH [21, 30, 31]. In a multicentre LTE study in Germany, at month 48, the 6MWD increased from baseline by 69±105 m [18]. These tend to be similar to our 8-year results: riociguat provides long-term benefits in exercise capacity for patients with PAH and inoperable CTEPH. Improvement in clinical condition with riociguat during CHEST/PATENT-1 and CHEST/PATENT-2, as measured by WHO FC, was sustained for 8 years in our study [12–15], and we found that the majority of patients remained stable or even improved in WHO FC. The 8-year clinical worsening-free survival rate of patients in WHO FC I/II at baseline was higher than that of WHO FC III/IV patients, highlighting the long-term predictive value of WHO FC for the prognosis and the importance of initiating the targeted therapy as early as possible in patients with PAH and inoperable CTEPH [14, 15]. Overall in this study, patients were treated initially with monotherapy, and other targeted drugs were added according to the physician's discretion when clinical worsening events occurred. If combined treatment was initiated at an early stage, a better prognosis might be possible. Further controlled prospective studies are still needed.

The main limitation of our study is the small population size. Although Chinese patients were among the largest subcohorts in the CHEST/PATENT-1 study, and the number of patients enrolled in our centre was the largest in the Chinese subgroups [32], the small population size caused the data to be less representative in reflecting the long-term efficacy and safety of riociguat in Chinese patients, and some potentially unmeasured confounding variables. Besides, there are several limitations, such as the different length of follow-up resulting from BPA procedure later in the study.

Conclusions

In patients with PAH and inoperable CTEPH, riociguat is a well-tolerated and effective treatment for improving PVR, cardiac index, survival rate and exercise capacity for up to 8 years. However, improvements in PAP and the structure of pulmonary circulation were not shown in our patient cohort. WHO FC may have certain predictive value for the long-term prognosis of patients with PAH and inoperable CTEPH. Further multicentre studies with larger samples are needed to verify our current findings.

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