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

Suqiao Yang[1,2,3], Yuanhua Yang[1,2,3*], Yixiao Zhang[1,2,3], Tuguang Kuang[1,2,3], Juanni Gong[1,2,3], Jifeng Li[1,2,3], Yidan Li[4], Jianfeng Wang[5], Xiaojuan Guo[5], and Ran Miao[3,6]

[1]Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; [2]Beijing Institute of Respiratory Medicine, Beijing, China; [3]Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing, China; [4]Department of Echocardiography, Heart Center, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; [5]Department of Radiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; [6]Medical Research Center, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China;

[*]Corresponding author: Yuanhua Yang, MD, Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, No. 8 Gongtinan Road, Chaoyang District, Beijing 100020, China. Telephone: 86-10-85231437. Email: yyh1031@sina.com

Take home message: 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.

ABSTRACT

Background: Long-term treatment with riociguat has been shown to enhance exercise capacity in patients of 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 of PAH and inoperable CTEPH.

Methods: During this single-center 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 (CI), mortality, clinical worsening events, 6-minute walking 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 year were 0.97/0.86/0.72/0.61, without significant difference 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}, $p < 0.001$), CI 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/stabilized/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 CI 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 (PH). They are characterized by increased pulmonary vascular resistance (PVR), resulting in right ventricular failure even death eventually [1, 2]. The primary treatment for PAH is pharmacologic 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 PH centers, PEA cannot be performed in approximately 50% of CTEPH patients due to the occlusion of distal vessels or coexisting conditions or decline surgery [5]. In addition, 17-35% of patients who have undergone PEA will have residual PH, which needs further treatment [6-9].

Riociguat is the first sGC stimulator showing favorable benefit-risk profile in both PAH and CTEPH patients [10, 11] with significantly improved 6-minute walking 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 more than 6 years in patients with PAH and inoperable CTEPH, and improvements in 6MWD and WHO FC were maintained for about 4 years [18].

Therefore, we hypothesized that riociguat may continue to improve the hemodynamics over the long-term in patients with inoperable CTEPH and PAH. Additionally, we devoted ourselves to find predictive indicators for the long-term prognosis in patients with inoperable CTEPH and PAH. We herein conduct this open-label, single center 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 center 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 between 18-80 years with 6WMD of 150 to 450 m, PVR of more than 300 dyn·s·cm^{-5}, and mean pulmonary arterial pressure (MPAP) of at least 25 mm Hg 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, Capital Medical University, Beijing, China (the ethic ID: 2009-1, 2014BJYYEC-051-02), and written informed consents were obtained from all patients.

Study Design

This LTE study was a single-center observational study conducted at Beijing Chao-Yang Hospital from June 1, 2009 to December 31, 2019. The study consists of two phases, including an eight-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 the physician's discretion (up to 2.5 mg dosage 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 catheterization (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 MPAP and cardiac index (CI) measured by RHC, mortality, clinical worsening events, 6WMD and WHO FC. Clinical worsening was defined as any of the following events: death, add-on other targeted drugs, or hospitalization due to disease progression. Patients was 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 ± standard deviation (SD). Data without normal distribution were expressed using median and interquartile range (IQR). Categorical data were presented as number and percentage. All variables were analyzed with descriptive methods. *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 with Chi-squared test. Survival and clinical worsening-free survival at each time point were analyzed 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 randomized and treated in the CHEST/PATENT-1 study, 1 patient 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 which 24 (65%) patients were female. In all the patients with PAH, 14 (77.7%) were idiopathic, 2 (11.1%) were connective-tissue

disease-associated, 1 (5.6%) was congenital heart disease associated, and 1 (5.6%) was familial PAH. 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 MPAP 52.2 ± 11.4 mmHg, pulmonary artery wedge pressure (PAWP) 8.5 ± 2.6 mmHg, CI 1.7 $L \cdot min^{-1} \cdot m^{-2}$ (IQR 1.5-2.0 $L \cdot min^{-1} \cdot m^{-2}$) and 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 hemoglobin ($p = 0.049$), platelet ($p = 0.020$) and NT-proBNP ($p = 0.035$).

Safety and Survival Rate

After dose titration phase, 35 patients (94.6%) received riociguat 2.5 mg three times a day, and 2 patients (5.4%) 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, respectively, , while no CTEPH participants exited (Figure 1). During the study period, all the CTEPH and 6 (33%) PAH patients received oral anticoagulants agents, 8 (42%) CTEPH and 4 (22%) PAH patients received diuretics, 15 (79%) CTEPH and 14 (78%) PAH patients received supplemental oxygen. Supplemental oxygen use was defined as use at any time from enrollment to the end of follow-up. One patient (2.7%) with CTEPH developed hemoptysis during the follow-up, and recovered after bronchial artery embolization. None of the patients complained of obvious adverse drug reaction, and none withdrew for reasons related to adverse events of

riociguat. After data collection at the end of our study, 8 patients with CTEPH underwent BPA.

The median treatment duration was 96 months (IQR 56-109 months) for all the patients. At the final data collection point, 15 out of 37 (40.5%) patients died (CTEPH, n=7; PAH, n=8) (Figure 1). Twelve patients died from right-ventricular failure, 1 from severe pneumonia, 1 from massive hemoptysis, and 1 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 1.0/0.84/0.74/0.63 and 0.94/0.89/0.71/0.58, 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 predetermined covariates were sex and body mass index (BMI, < 24 $kg \cdot m^{-2}$ vs ≥24 $kg \cdot m^{-2}$) [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).

Hospitalization owing to disease progression was the most frequent clinical worsening event. In CTEPH patients, 11 patients were hospitalized at least once due to acute exacerbation of CTEPH, 4 patients started a new PAH treatment (1 ambrisentan, 1 bosentan and 2 beraprost). For patients with PAH, 8 patients underwent hospitalization due to disease

progression, and 2 patients added on new targeted drugs (1 ambrisentan and 1 bosentan). Kaplan-Meier estimates of 1-year, 3-year, 5-year and 8-year clinical worsening-free survival for all the 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 ($p = 0.977$).

Hemodynamic Parameters

Hemodynamic indices by RHC at baseline were available for all the 37 patients. At the final data cut-off, all the 20 surviving patients underwent the hemodynamic 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 vs 835 ± 348 dyn· sec·cm^{-5}, $p < 0.001$), cardiac output (CO, 3.0 ± 0.9 vs 4.0 ± 1.0 L·min^{-1}, $p < 0.001$) and CI (1.7 ± 0.4 vs 2.4 ± 0.5 L·min^{-1}·m^{-2}, $p < 0.001$) were significantly increased, while MPAP was not improved (50.2 ± 9.8 vs 51.3 ± 13.7 mmHg, $p = 0.677$). In addition, the increase in PAWP was also observed, but still within 15 mmHg (Table 2).

6MWD

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

WHO FC

The comparation from baseline to the 8-year time point showed 15 patients (75%) sustained stabled or even improved in WHO FC. The WHO FC had improved/stabilized/worsened in 40/35/25% of the patients (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 to the structure parameters, the transverse diameter of the left ventricle (LV) was increased [29 (23-32) versus 39 (34-44), $p = 0.034$], the ratio of right ventricle to left ventricle dimension (RV/LV) was significantly reduced (1.6 ± 0.6 versus 1.2 ± 0.4, $p = 0.032$), but the transverse diameter of the right ventricle (RV) was not significantly improved. And there was a significant increase in the diameter of main pulmonary artery (30.4 ± 3.8 mmHg versus 37.2 ± 9.8 mmHg, $p = 0.013$, Table 2). At the final data cut-off, the 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. And 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 the hemodynamic parameters such as PVR and CI 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].

Hemodynamic parameters, considered as an important end point in studies of PH, 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 hemodynamic parameters were significantly improved at the final data cut-off. Compared with 226 dyn·s·cm^{-5} /223 dyn·s·cm^{-5} in CHEST/PATENT-1 study, PVR decreased by 396 dyn·s·cm^{-5} in our LTE study [12, 13]. With respect to other secondary outcomes, the increase in CI was also apparently sustained for up to 8 years. However, we observed that MPAP 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 recent RIVER study suggested that patients within 6-month treatment with riociguat showed significantly reduced right heart size and improved the RV function in PAH and CTEPH [20]. However, in our LTE study, the pulmonary arterial

pressure (PAP) did not significantly decrease 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 the 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, without serious side effects identified during medication period or adverse events related to riociguat contributed to withdrawal or death of patients. One patient in our study experienced hemoptysis, which accounted for 2.7% of the enrolled patients and was comparable to 3% of patients in the CHEST/PATENT-2 study [14, 15]. There was also a relatively low drop-out rate during the study compared with that seen in other targeted medications long-term study [21-23] with 2 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 centers from the United States showed that estimated rates of patients with primary PH using conventional treatment survived at 1, 3 and 5 years were 68%, 48% and 34%, which were obviously lower than that in our LTE study [26]. In patients with inoperable CTEPH, 8-year survival rate was higher in patients treated with riociguat than in patients treated with conventional regimen in our previous study [27]. Compared to the survival rates of PAH and inoperable CTEPH patients, although CTEPH group showed certain advantages, there was no significant difference between the two groups. Therefore, further large-sample multi-center studies are still needed to confirm our current findings.

6MWD was considered as correlates 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 multicenter LTE study of Germany, at Month 48, the 6MWD increased from baseline by 69 ± 105m [18]. These tend to be similar with our 8-year results that 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]. In this study, the overall patients were initially treated with monotherapy, other targeted drugs were added according to the physician's discretion when clinical worsening events occurred. If combined treatment was initiated at early stage, there might be able to obtain a better prognosis. 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 sub-cohorts in the CHEST/PATENT-1 study, and the number of patients enrolled in our center 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, CI, survival rate and exercise capacity for up to eight 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 multicenter studies with larger sample are needed to verify our current findings.

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Table 1. Baseline characteristics of the study population

Characteristics	CTEPH (n=19)		PAH (n=18)		*P* values
	Number of patients	Baseline	Number of patients	Baseline	
Age, y	19	50.7±10.1	18	46.7±13.2	0.305
Female sex	19	11 (58)	18	13 (72)	0.362
BMI, $kg \cdot m^{-2}$	19	24.4±3.0	18	23.0±3.7	0.214
Laboratory tests					
Hemoglobin, $g \cdot L^{-1}$	19	149 (144-163)	18	143 (128-153)	0.049
Platelet, $\times 10^{9} \cdot L^{-1}$	19	207 (170-240)	18	160 (121-203)	0.020
Albumin, $g \cdot L^{-1}$	19	36.5 (33.4-40.8)	18	38.6 (34.6-40.6)	0.518
AST, $U \cdot L^{-1}$	19	29.6±7.5	18	30.8±9.1	0.649
ALT, $U \cdot L^{-1}$	19	24.0 (15.0-35.0)	18	26.5 (20.0-37.8)	0.313
γ-GT, $U \cdot L^{-1}$	19	60 (40-108)	18	57.5 (32.5-100)	0.461
Total bilirubine, $umol \cdot L^{-1}$	19	21.0±10.8	18	15.9±6.5	0.094
Creatinine, $umol \cdot L^{-1}$	19	82.3±20.3	18	72.8±19.3	0.642
NT-proBNP, $pg \cdot ml^{-1}$	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, $m \cdot s^{-1}$	15	4.7±0.4	14	4.3±0.5	0.046
Estimated SPAP, 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
SPAP, mmHg	19	88.8±15.1	18	85.0±22.0	0.543
DPAP, mmHg	19	32 (26-38)	18	35 (28-40)	0.391
MPAP, 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
CO, $L \cdot min^{-1}$	19	3.0±0.9	18	2.9±0.5	0.703
CI, $L \cdot min^{-1} \cdot m^{-2}$	19	1.7 (1.3-2.0)	18	1.8 (1.5-2.1)	0.425
PVR, $dyn \cdot sec \cdot cm^{-5}$	19	1245±396	18	1272±446	0.847
SvO_2, %	13	61.3±11.3	13	68.1±10.1	0.124

Data are mean ± standard deviation (SD) or N (%) or median (interquartile range), where number is the total number of patients with available data.

CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine amino transferase; γ-GT, gamma-glutamyl transferase; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6MWD, 6-minute 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; SPAP, systolic pulmonary artery pressure; CVP, central venous pressure; DPAP, diastolic pulmonary artery pressure; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation.

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

Variables	Number of patients	Baseline	Final data cut-off	*P* values
Haemodynamic parameters				
CVP, mmHg	19	7.8±5.2	8.9±2.7	0.400
SPAP, mmHg	19	85.4±17.5	83.2±24.2	0.686
DPAP, mmHg	19	31.8±7.0	34.4±9.3	0.154
MPAP, mmHg	20	50.2±9.8	51.3±13.7	0.677
PAWP, mmHg	19	8 (1-10)	12 (10-15)	0.03
CO, $L \cdot min^{-1}$	19	3.0±0.9	4.0±1.0	<0.001
CI, $L \cdot min^{-1} \cdot m^{-2}$	19	1.7±0.4	2.4±0.5	<0.001
PVR, $dyn \cdot sec \cdot cm^{-5}$	19	1232±462	835±348	<0.001
SvO_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 SPAP, mmHg	15	91.6±17.6	99.4±26.0	0.306

Data are mean ± standard deviation (SD) or median (interquartile range), where number is the total number of patients with available data.

CVP, central venous pressure; SPAP, systolic pulmonary artery pressure; DPAP, diastolic pulmonary artery pressure; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_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.

Figure Legends

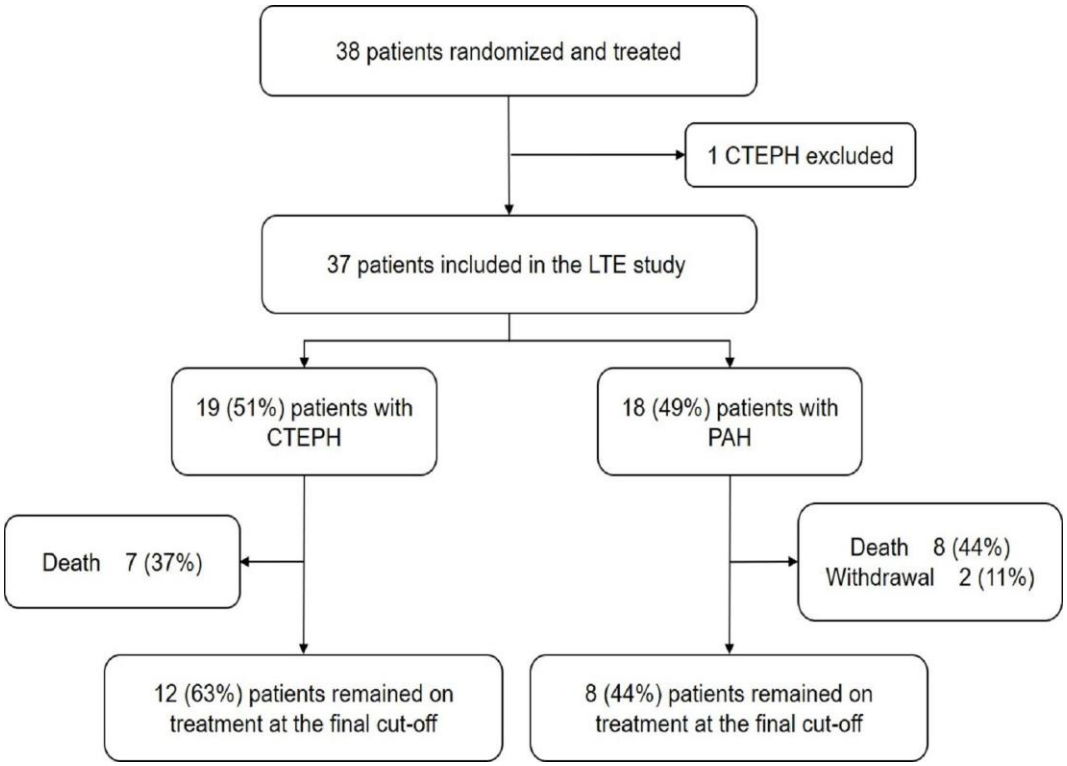
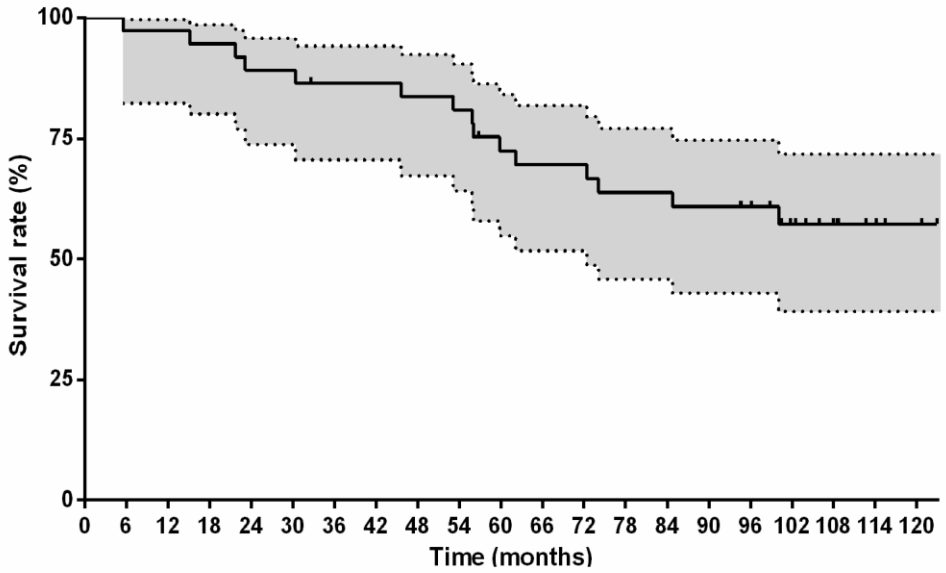


Figure 1. Flow diagram of the study population from the LTE study.

LTE, long-term extension; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension.

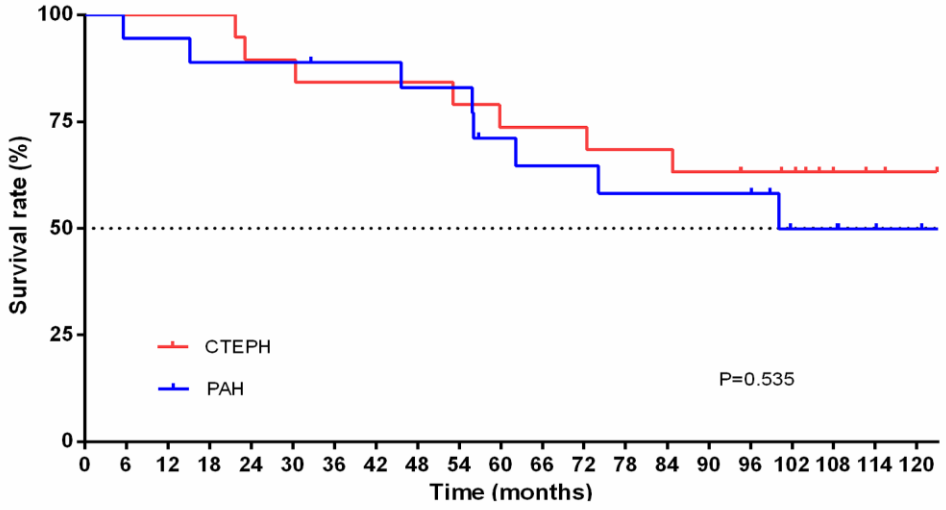
a)



Number of patients

Total	37	36	36	35	33	33	31	31	30	29	25	24	24	22	22	21	19	14	10	7	5

b)



Number of patients

CTEPH	19	19	19	19	17	17	16	16	16	15	14	14	14	13	13	12	10	9	5	4	3
PAH	18	17	17	16	16	16	15	15	14	14	11	10	10	9	9	9	9	5	5	3	2

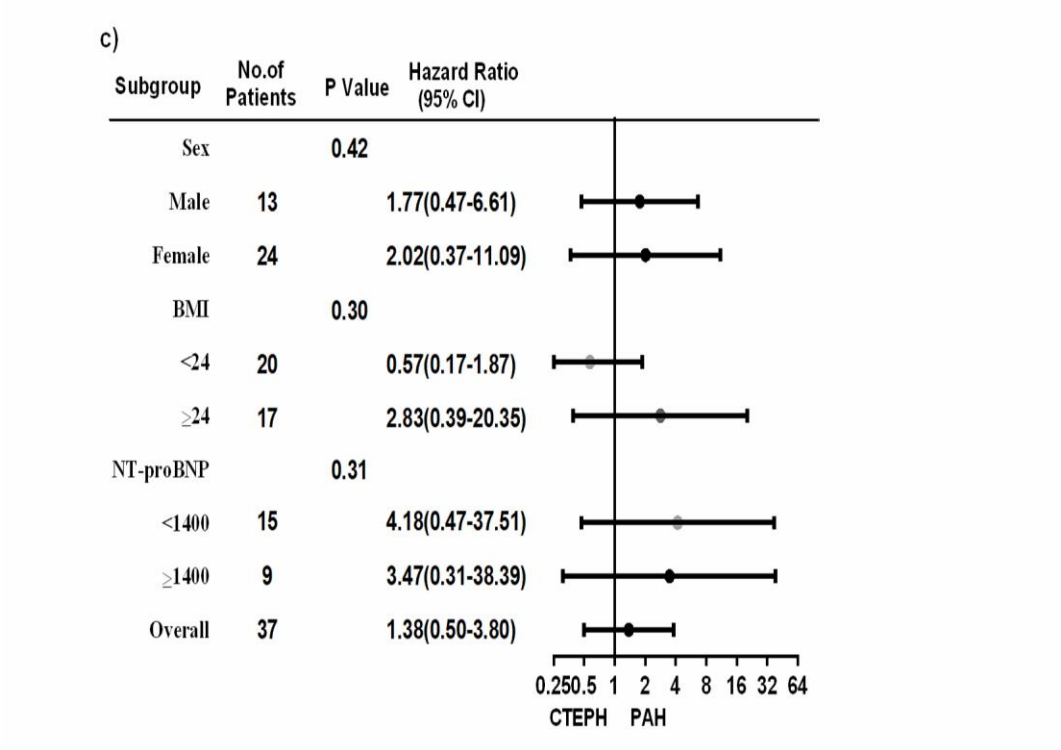
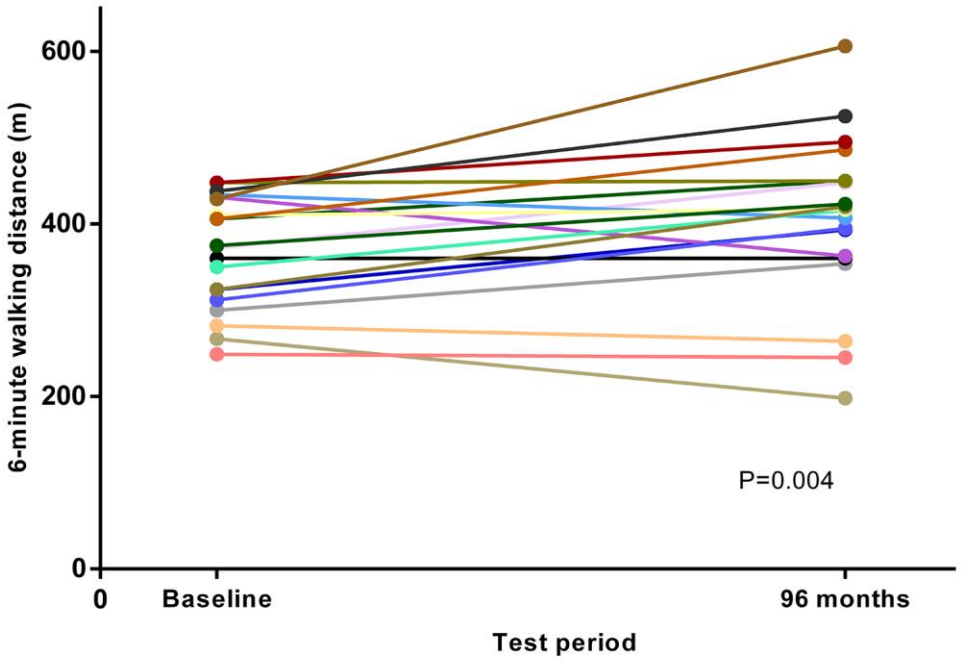


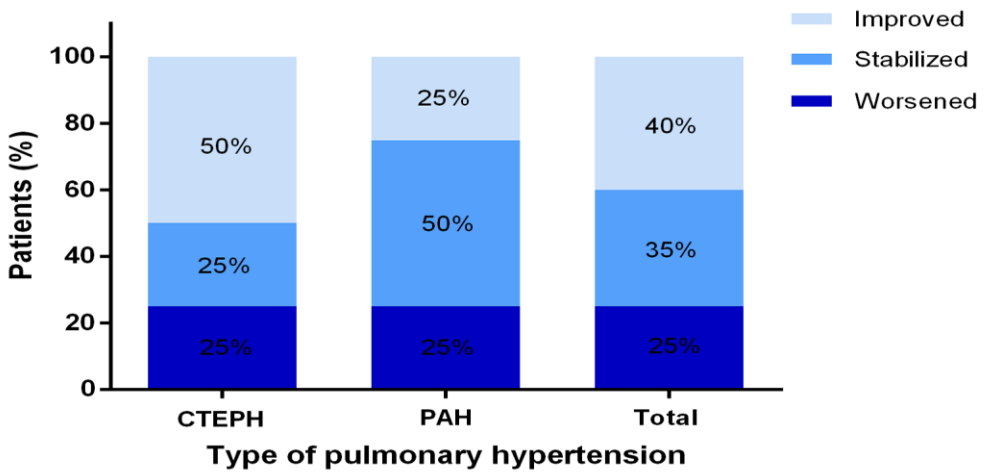
Figure 2. a) Kaplan-Meier survival plots for all the patients (1-year, 3-year, 5-year and 8-year survival estimates for all the patients were 0.973 (95% CI 0.823-0.996), 0.865 (95% CI 0.705-0.941), 0.724 (95% CI 0.548-0.841) and 0.608 (95% CI 0.429-0.747), respectively). b) Kaplan–Meier survival plots for patients with CTEPH and 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.

CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; CI, confidence interval; BMI, body mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide.

a)



b)



Number of Patients	12	8	20
Improved	6	2	8
Stabilized	3	4	7
Worsened	3	2	5

Figure 3. a) Increase in 6-minute walking distance (6MWD) between baseline and 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.

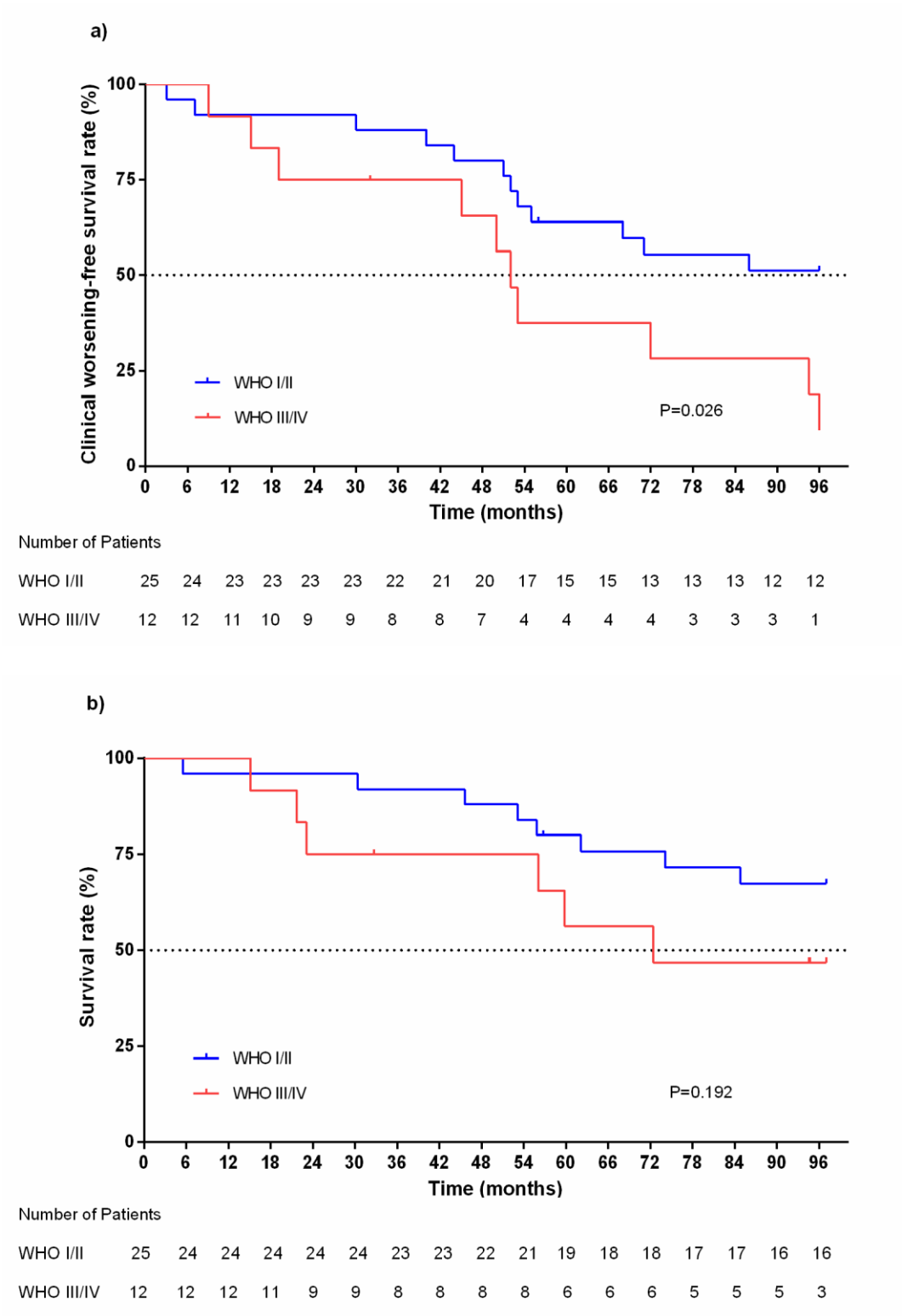


Figure 4. a) Kaplan-Meier estimates of 8-year clinical worsening-free survival showed significant difference between the WHO FC I/II and III/IV groups at baseline (P = 0.026). b)

Kaplan-Meier estimates of 8-year survival showed there was no significant difference between the WHO FC I/II and III/IV groups ($P = 0.192$).

WHO FC, World Health Organization functional class.