Review Article
Efficacy of Riociguat on pulmonary hypertension: a systematic review and meta-analysis

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Abstract: *Aims:* Riociguat might be a promising approach to treat pulmonary hypertension. However, the results have been controversial. Therefore, we conducted a systematic review and meta-analysis to explore the efficacy of Riociguat for patients with pulmonary hypertension. *Methods:* PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of Riociguat versus placebo on pulmonary hypertension were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. The primary outcomes were the change in 6-min walking distance and EQ-5D score. Meta-analysis was performed using the random-effect model. *Results:* Five RCTs involving 627 patients were included in the meta-analysis. Overall, compared with control intervention in pulmonary hypertension, Riociguat intervention was found to significantly increase 6-min walking distance (Mean difference (MD) = 44.63; 95% CI = 25.55 - 63.71; P<0.00001), EQ-5D score (MD = 0.14; 95% CI = 0.07 - 0.21; P = 0.0002), cardiac index (MD = 0.58; 95% CI = 0.40 - 0.27; P = 0.76), and reduce PVR (MD = -281.66; 95% CI = -369.72 - -193.60; P<0.00001), NT-proBNP (MD = -447.16; 95% CI = -838.64 - -55.69; P = 0.03), with no increase in adverse events (RR = 1.03; 95% CI = 0.95 - 1.12; P = 0.43). *Conclusions:* Compared to control intervention for pulmonary hypertension, Riociguat intervention was found to significantly improve 6-min walking distance, EQ-5D score, and cardiac index, as well as reduce PVR and NT-proBNP, without an increase in adverse events.

Keywords: Riociguat, pulmonary hypertension, 6-Min walking distance, EQ-5D score, meta-analysis

Introduction

Pulmonary hypertension is known as a life-threatening condition with high morbidity and mortality and has prominent features of increased pulmonary artery pressure and elevated pulmonary vascular resistance (PVR) leading to cardiac remodeling and right heart failure [1-5]. Many factors could result in pulmonary arterial hypertension, including cardiovascular (reduced cardiac output due to high pulmonary pressures and septal deviations), pulmonary (ventilation-perfusion abnormalities) and musculo-skeletal system (altered muscle fibre properties, peripheral oxygen extraction) dysfunction [6-11].

Riociguat is the first member of the soluble guanylate cyclase (sGC) stimulator class of therapeutic agents [12-15]. It can sensitize sGC to endogenous nitric oxide (NO) by stabilizing NO-sGC binding and by directly stimulating sGC, independently of NO, via a different bind-

ing site [16, 17]. Previous studies demonstrated that Riociguat treatment is able to remarkably improve 6-min walking distance and reduce PVR and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels in patients with chronic thromboembolic pulmonary hypertension and pulmonary hypertension caused by congenital heart disease [18, 19].

In contrast to this promising finding, however, accumulating relevant RCTs showed that Riociguat treatment had no influence on Borg dyspnea score, NT-proBNP and EQ-5D score for pulmonary hypertension [18, 20]. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to investigate the influence of Riociguat treatment on pulmonary hypertension.

Materials and methods

This systematic review and meta-analysis was conducted according to the guidance of the
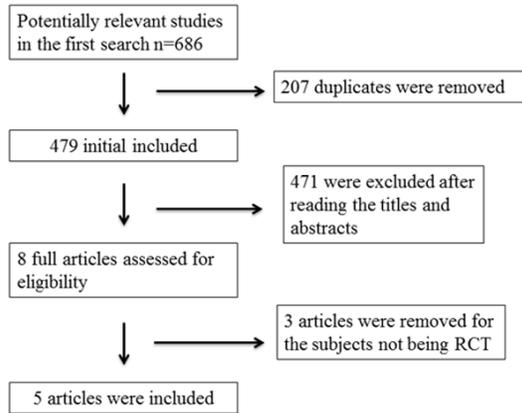
Figure 1. Flow diagram of study searching and selection process.

Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [21] and the *Cochrane Handbook for Systematic Reviews of Interventions* [22]. All analyses were based on previous published studies, thus no ethical approval and patient consent were required.

Literature search and selection criteria

PubMed, EMbase, Web of science, EBSCO, and the Cochrane library were systematically searched from inception to August 2017, with the following keywords: Riociguat, and pulmonary hypertension. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further articles were identified. Conference abstracts meeting the inclusion criteria were also included.

The inclusion criteria were as follows: study population, patients with pulmonary hypertension; intervention, Riociguat; control, placebo; outcome measure, change in 6-min walking distance and EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) score; and study design, RCT.

Data extraction and outcome measures

The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, Riociguat intervention, control, study design, change in 6-Min walking distance and EQ-5D score, PVR change, cardiac index change, change in NT-proBNP, and adverse

events. The authors were contacted to acquire the data when necessary.

The primary outcomes were represented by the changes in 6-min walking distance and EQ-5D score. Secondary outcomes included PVR change, cardiac index change, change in NT-proBNP, and adverse events.

Quality assessment in individual studies

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [23]. This scale consisted of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts, and withdrawals (0-1 points). One point would be allocated to each element if they have been mentioned in the article, and another one point would be given if the methods of randomization and/or blinding had been detailed and appropriately described. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one point was deducted. The score of Jadad Scale varied from 0 to 5 points. An article with a Jadad score ≤ 2 was considered to be of low quality. If the Jadad score ≥ 3, the study was thought to be of high quality [24].

Statistical analysis

Mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes (changes in 6-min walking distance and EQ-5D score, PVR change, cardiac index change, change in NT-proBNP and risk ratios (RRs)) with 95% CIs for dichotomous outcomes (adverse events) were used to estimate the pooled effects. All meta-analyses were performed using random-effects models with DerSimonian and Laird weights. Heterogeneity was tested using the Cochran Q statistic ($p<0.1$) and quantified with the I^2 statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An I^2 value greater than 50% indicated significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. $P<0.05$ in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Table 1. Characteristics of included studies

| NO. | Author | Riociguat group | | | | Control group | | | | Type | Jada scores |
		Number	Age (years)	Female No.	BMI, kg/m² or weight, kg	Methods	Number	Age (years)	Female No.	BMI, kg/m² or weight, kg	Methods		
1	Kim 2017	121	59±14	86	27±5 kg/m²	2.5 mg three times daily	68	60±12	45	28±5 kg/m²	Matched placebo	Chronic thrombo-embolic pulmo-nary hypertension	3
2	Rosenkranz 2015	8	41±15	6	24±5 kg/m²	1.5 mg three times daily	12	40±16	10	24±3 kg/m²	Matched placebo	Pulmonary arte-rial hypertension associated with congenital heart disease	4
3	Bonderman 2014	10	72.8 (59.0-83.0), (mean, range)	6	29.3 (23.5-33.4), (mean, range) kg/m²	Single oral 2 mg	11	75.1 (65.0-86.0), (mean, range)	31	30.2 (21.8-36.0), (mean, range) kg/m²	Matched placebo	Pulmonary hyper-tension associ-ated with diastolic heart failure	3
4	Ghofrani 2013	173	59±14	118	27±6 kg/m²	A starting dose of 1 mg three times daily, final range, 0.5 mg to 2.5 mg three times daily	88	59±13	54	28±5 kg/m²	Matched placebo	Chronic thrombo-embolic pulmo-nary hypertension	5
5	Bonderman 2013	67	59.3 (26-76), (mean, range)	12	28.9±0.6 kg/m²	2 mg three times daily	69	58.9 (25-79)	8	28.7±0.7 kg/m²	Matched placebo	Pulmonary hyper-tension caused by systolic left ventricular dys-function	4
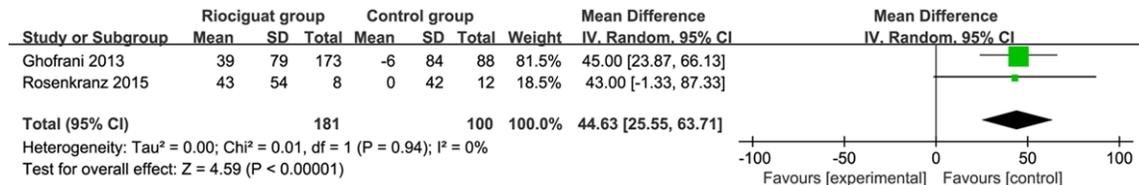
Figure 2. Forest plot for the meta-analysis of change in 6-min walking distance (m).
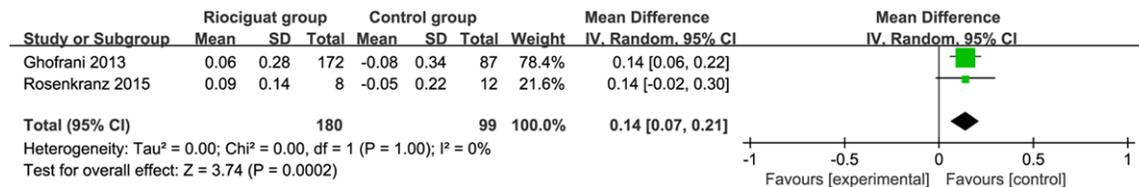

Figure 3. Forest plot for the meta-analysis of change in EQ-5D score.

Results

Literature search, study characteristics and quality assessment

The flow chart for the selection process and detailed identification is presented in **Figure 1**. 686 publications were identified through the initial search of databases. Ultimately, five RCTs were included in the meta-analysis [18-20, 25, 26].

The baseline characteristics of the five eligible RCTs in the meta-analysis were summarized in **Table 1**. The five studies were published between 2013 and 2017, and sample sizes ranged from 20 to 261 with a total of 627. Patients in the Riociguat group and control group demonstrated similar basic characteristics. The doses of Riociguat ranged from 1 mg to 2.5 mg three times daily. Three included RCTs involving patients with chronic thrombo-embolic pulmonary hypertension [18, 19], and three included RCTs involving patients with pulmonary hypertension associated with congenital heart disease [20], diastolic heart failure [25], and systolic left ventricular dysfunction [26].

Among the five RCTs, two studies reported the change in 6-min walking distance and EQ-5D score [18, 20], two studies reported the PVR change and cardiac index change [19, 20], two studies reported the change in NT-proBNP [18, 20], and five studies reported the adverse events [18-20, 25, 26]. Jadad scores of the

six included studies varied from 3 to 5, and all six studies were considered to be high-quality according to quality assessment.

Primary outcome: change in 6-Min walking distance and EQ-5D score

These two outcome data sets were analyzed with a random-effects model, the pooled estimate of the two included RCTs suggested that compared to the control group, in patients with pulmonary hypertension, Riociguat intervention was associated with a significantly higher 6-Min walking distance (MD = 44.63; 95% CI = 25.55 - 63.71; P<0.00001), with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = 0.94; **Figure 2**). Consistently, Riociguat intervention was also found to significantly improve EQ-5D score (MD = 0.14; 95% CI = 0.07 - 0.21; P = 0.0002) more than control intervention, with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = 1.00; **Figure 3**).

Sensitivity analysis

No heterogeneity was observed among the included studies for the change in 6-min walking distance and EQ-5D score. Thus, we did not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

Secondary outcomes

Compared with control intervention in patients with pulmonary hypertension, Riociguat inter-
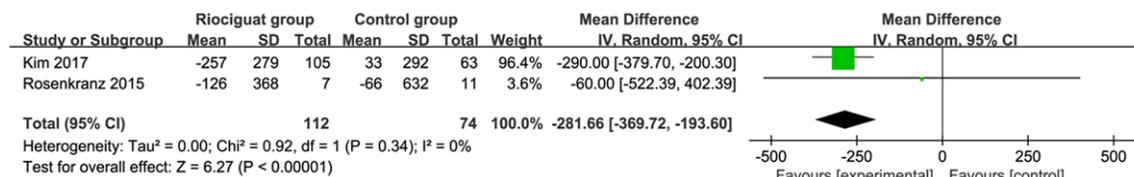
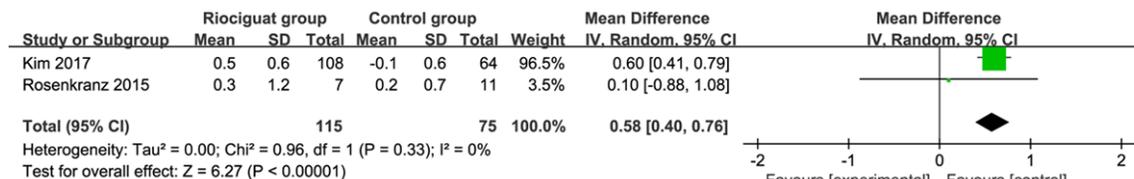**Figure 4.** Forest plot for the meta-analysis of PVR change (dyn.s/cm^5).

Figure 5. Forest plot for the meta-analysis of cardiac index change (L/min/m^2).
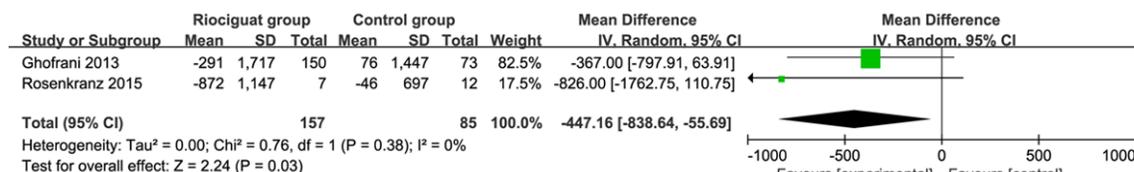

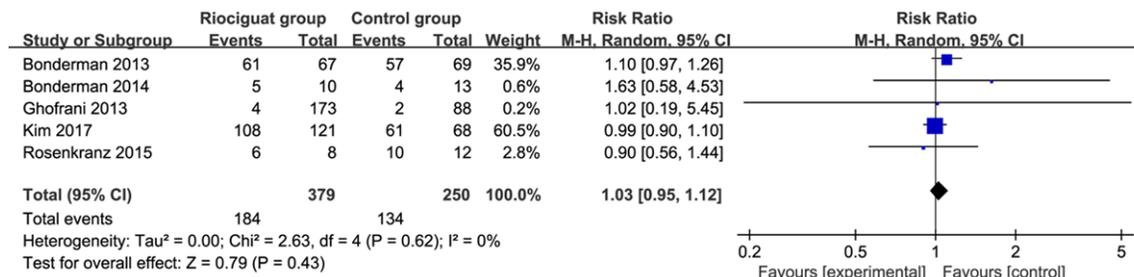**Figure 6.** Forest plot for the meta-analysis of change in NT-proBNP (pg/ml).

Figure 7. Forest plot for the meta-analysis of adverse events.

vention was associated with substantially decreased PVR change (MD = -281.66; 95% CI = -369.72 - -193.60; P<0.00001; **Figure 4**), improved cardiac index (MD = 0.58; 95% CI = 0.40 - 0.27; P = 0.76; **Figure 5**) and reduced NT-proBNP (MD = -447.16; 95% CI = -838.64 - -55.69; P = 0.03; **Figure 6**), with no increase in adverse events (RR = 1.03; 95% CI = 0.95 - 1.12; P = 0.43; **Figure 7**).

Discussion

Hemodynamic parameters were objective indicators to evaluate the status of the pulmonary circulation, including PVR, cardiac index, mean pulmonary artery pressure and right atrial pressure [27, 28]. NT-proBNP served as a biomarker of right ventricular function and an indicator of prognosis [1]. Our meta-analysis clearly suggested that compared to control intervention for pulmonary hypertension, Riociguat intervention was associated with a significantly improved 6-Min walking distance, EQ-5D score, and cardiac index, reduced PVR, and NT-proBNP. These complementary data demonstrate the value of measuring improvements across multiple parameters in order to evaluate the efficacy of Riociguat treatment on pulmonary hypertension and disease severity. To our knowledge, this is the first meta-analysis to

focus on the influence of Riociguat treatment on pulmonary hypertension.

One randomised controlled phase III study (PATENT-1) and its long-term extension study (PATENT-2) reported that Riociguat treatment could significantly improve 6-Min walking distance and WHO functional class and reduce NT-proBNP for patients with pulmonary arterial hypertension. In these studies the efficacy was sustained at 2 years [18, 20, 29]. In addition, Riociguat treatment was reported to result in improved 6-Min walking distance in patients with persistent/recurrent pulmonary arterial hypertension following complete surgical repair of congenital heart disease, which is consistent with observations in the overall PATENT-1 population (the increase of 30 m in 6-Min walking distance) [18, 20].

Riociguat application was reported to be well tolerated in patients with pulmonary arterial hypertension [30-33]. The adverse events in patients with pulmonary arterial hypertension after the treatment of Riociguat mainly included dyspepsia, dizziness, abdominal pain, headache, anaemia, epistaxis, hypotension, and nasopharyngitis etc. [18-20]. There was also no increase of adverse events following Riociguat treatment based on our meta-analysis. Hemoptysis is a serious, often life-threatening, complication of pulmonary arterial hypertension caused by congenital heart disease [34]. One RCT reported one (3%) serious adverse event of respiratory tract bleeding (pulmonary hemorrhage) for patients with pulmonary arterial hypertension caused by congenital heart disease, which was comparable to that in the overall study population [20, 29].

Several limitations should be taken into account. First, our analysis was based on only five RCTs and two of them had a relatively small sample size (n<100). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. The type of pulmonary hypertension and follow-up time in the included studies was different and it may have an influence on the pooling results. Second, the doses of Riociguat varied from 1 mg to 2.5 mg three times daily, but the optimal dose remained unknown for treating pulmonary hypertension. Finally, some unpublished and missing data might lead to bias from the pooled effect.

Riociguat intervention showed an important ability to improve quality of life and hemodynamic balance in patients with pulmonary hypertension. Riociguat treatment can now be recommended for administration in pulmonary hypertension.

Disclosure of conflict of interest

None.

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