

Systematic Review and Meta-Analysis of Pulmonary Hypertension Specific Therapy for Exercise Capacity in Chronic Obstructive Pulmonary Disease

Jinkyong Park,¹ Ju Hee Song,²
Dong-Ah Park,³ Jae Seoung Lee,²
Sang-Do Lee,² and Yeon-Mok Oh,²

¹Department of Pulmonary and Critical Care Medicine Wonkwang University, Sanbon Hospital, Gunpo; ²Department of Pulmonary and Critical Care Medicine, and Clinical Research Center for Chronic Obstructive Airway Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ³Office of Health Technology Evaluation, National Evidence-Based Healthcare Collaborating Agency, Seoul, Korea

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Address for Correspondence:

Yeon-Mok Oh, MD

Department of Pulmonary and Critical Care Medicine, and Clinical Research Center for Chronic Obstructive Airway Diseases, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea

Tel: +82.2-3010-3136, Fax: +82.2-3010-6968
E-mail: ymoh55@amc.seoul.kr

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INTRODUCTION

Pulmonary hypertension (PH) is more common among patients with severe airflow limitation. At autopsy, over forty percent of patients with chronic lung disease can display evidence of cor pulmonale (1). The exact prevalence of PH in chronic obstructive pulmonary disease (COPD) is unclear. According to some studies, the severity of PH in COPD is mild to moderate (25-35 mmHg) if the patients have no right heart failure (2). Despite the usually moderate nature of PH in COPD, it clearly has an adverse impact on survival (3). COPD patients having PH during exercise or sleep have been reportedly more prone to develop resting PH with time (4).

All the PH conditions share virtually identical pathologic features and a similar clinical picture, and are treated medically in the same way (5, 6). PH-specific therapies induce pulmonary vasodilation and have anti-proliferative effects upon the pulmonary vasculature, reducing pulmonary vascular resistance

Some patients with chronic obstructive pulmonary disease (COPD) have pulmonary hypertension (PH) that adversely affects survival. We performed a systematic review and meta-analysis to assess whether PH-specific therapies have an effect for stable COPD. Data sources were Medline, EMBASE, Cochrane Central Register of Controlled Trials, Korea med and references from relevant publications. Randomized prospective trials that compared PH specific therapy in COPD for more than 6 weeks with placebo were included. The outcomes were the exercise capacity and adverse events. Four randomized controlled trials involving 109 subjects were included in the analysis. Two trials involved bosentan, one sildenafil and one beraprost. The studies varied in duration of treatment from 3 to 18 months. In a pooled analysis of four trials, exercise-capacity was not significantly improved with PH-specific treatment for COPD (risk ratio, -5.1; 95% CI, -13.0 to 2.8). COPD with overt PH significantly improved the exercise capacity (mean difference, 111.6; 95% CI, 63.3 to 159.9) but COPD with PH unknown did not (mean difference, 26.6; 95% CI, -24.3 to 77.5). There was no significant difference in hypoxemia (mean difference, 2.6; 95% CI, -3.7 to 8.8). PH specific treatments have a significant effect in improving exercise capacity in COPD with overt PH.

Key Words: COPD; Pulmonary Hypertension; Vasodilator; Exercise

and ultimately right ventricular (RV) afterload in pulmonary arterial hypertension (PAH) (7). However, to the exclusion of correction of the hypoxemia with supplemental oxygen, PH-specific therapies in COPD have not proven effective. Current recommendations state that PH-specific therapies should be considered when PH is persistent, despite optimization of COPD management, and when PH is out of proportion to the degree of airflow obstruction. It appears rational to consider whether PH-specific treatment might decrease pulmonary pressures and improve both RV function and oxygen delivery during exercise (8), thereby increasing exercise tolerance (9) in severe COPD.

Unfortunately, published experience has consisted of only anecdotal case reports or randomized controlled clinical trials. However, almost all of these experiences showed the acute effect on the hemodynamics.

We performed a systematic review and meta-analysis to assess whether PH-specific therapies have long-lasting effects in

PH patients with COPD.

MATERIALS AND METHODS

Search methods for identification of studies

We searched Ovid-MEDLINE (1948 to October 2011), Ovid-EMBASE (1980 to October 2011), Cochrane Register of Controlled Trials (CENTRAL) of the Cochrane Library (issue 4, 2011) using the search filter in the Ovid database (SIGN; <http://www.sign.ac.uk>). The search terms were “chronic obstructive pulmonary disease” or “chronic bronchitis” or “emphysema” AND “vasodilator agent” or “phosphodiesterase v inhibitor” or “protein tyrosine kinase inhibitor” or “endothelin receptor antagonist” or “prostacyclin” “prostacyclin derivative” or “sildenafil” or “iloprost” or “tadalafil” or “udenafil” or “riociguat” or “dehydroepiandrosterone” or “epoprostenol” or “treprostinil” or “beraprost” “bosentan” or “ambrisentan” or “sitaxentan” or “imatinib” or “rho-kinase inhibitor”. We also reviewed the bibliographies of relevant review papers to identify additional publications. Finally, we also searched an international data base (<http://www.clinicaltrials.gov>) for trial registration to identify ongoing or recently completed trials. The search was performed without language restriction or years of publication. The latest date for updating the search was 20 November 2012.

Study selection

Two authors independently evaluated the eligibility of all studies to determine whether they met all of the inclusion criteria. Disagreements between two reviewers were resolved by discussion or in consultation with third authors. We included observational studies and randomized controlled trials comparing any PH-specific therapies over 6 weeks with placebo for the exercise capacity of PH in COPD. Exercise capacity was measured in a 6 min walking test or endurance time in constant work exercise test (CWET). All studies with other causes of pulmonary hypertension than COPD (including chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension) were excluded. Trials analyzed separately in the current analysis according to prospective randomized placebo-controlled design and observational design. We accepted the definitions of PH in COPD as reported in each study because we did not have access to individual patient data.

Data extraction and quality assessment

Two authors independently extracted the data of included using a standardized form developed in advance. The main pre-specified data recorded included the following: 1) year of publication; 2) patient population; 3) number of patients; 4) PH-specific agents and doses administered; 6) duration of treatment and 7) definition of PH in COPD. All reported outcome variables. We used only published data and did not contact all authors for

further information. The primary outcomes were the distance of 6-min walking of COPD with PH or endurance time in CWET. The methodological quality of trials was assessed by two reviewers with the risk of bias table for the sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias as recommended in the Cochrane Handbook of Systematic Reviews. The investigators compared their evaluations and reviewed studies together as necessary. Disagreement was solved by discussion and consensus among the authors.

Data synthesis and analysis

The mean difference (MD) and their respective 95% confidence intervals (CI) were calculated based on fixed-effect model of inverse variance estimation method. The data were inspected to see whether analysis using a random effects model would make any substantive difference. Statistical heterogeneity between trials was analyzed using Cochrane's Q statistic ($P < 0.1$ used for statistical significance) and by I^2 statistic. I^2 values greater than 25%, 50%, and 75% were considered evidence of low, moderate and high statistical heterogeneity, respectively. We pre-specified subgroup analysis by documented pulmonary hypertension given the inherent differences and explored heterogeneity between studies. Meta-analyses were conducted using Review Manager version 5.1 (RevMan; The Cochrane Collaboration, Oxford, UK). The methodological quality of the trials selected was assessed using the criteria described in the Cochrane Handbook (10).

RESULTS

Description of randomized controlled trials (RCTs)

The process of identifying eligible trials is presented in Fig. 1. We identified 4,479 citations from electronic databases and selected nine potentially relevant publications for full text assessment. Of these nine articles, five articles were excluded from this meta-analysis for the reasons presented in Fig. 1. We included four trials involving 109 subjects in the analysis (11-14). Table 1 shows the characteristics of the trials that were published between 2004 and 2011. All of the trials were randomized, double-blinded, placebo-controlled and parallel group design. Five trials published from 2005 to 2011 included subjects with COPD diagnosed by current spirometric criteria (post-bronchodilator $FEV_1/FVC < 0.7$). Among four comparisons, two involved bosentan, one involved sildenafil and one involved beraprost. Two of the four studies were diagnosed as PH by echocardiography or right heart catheterization. The duration of PH-specific treatment varied from 3 months to 18 months. All of the trials performed 6-min walking distance as the treatment outcome. Two trials performed CWET, but maximal oxygen uptake (VO_2 max) was marked as a different unit – mL/min/kg and L/min,

respectively. Only one trial investigated St. George's Respiratory Questionnaire (SGRQ). Arterial partial pressure of oxygen (PaO₂) was the secondary outcome in all trials except one.

Description of observational studies

The process of identifying eligible trials is presented in Fig. 1. We identified 5,654 citations from electronic databases and selected two potentially relevant publications for full text assess-

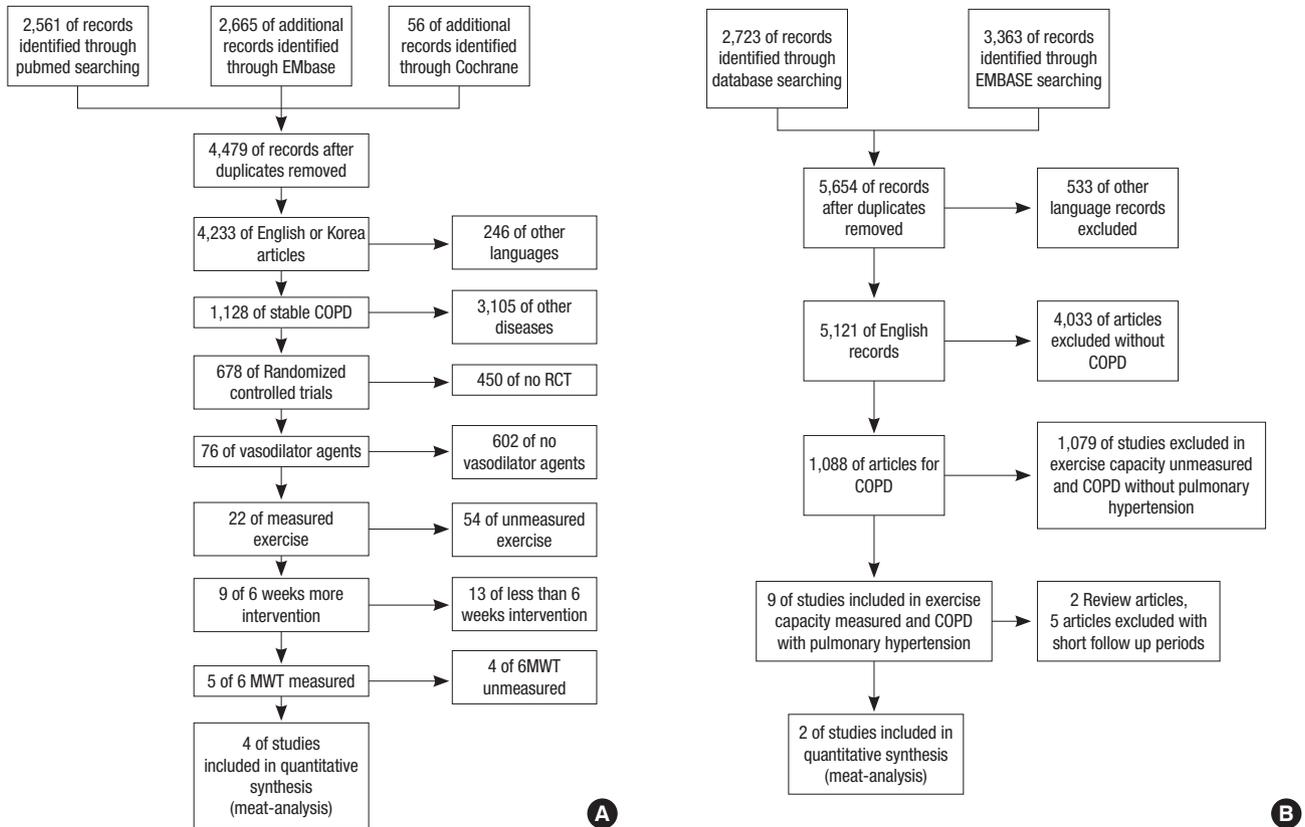


Fig. 1. Flow chart of study selection. (A) randomized controlled studies, (B) observational studies.

Table 1. Characteristics of the studies included in the meta-analysis

Study reference	Year of publication, country	Population	PH specific drug	Duration of trial	Subjects included*
Randomized controlled study					
Lee et al. (11)	2004, Korea	Aged ≥ 40 yr and had post-salbutamol FEV1/FVC ratio < 0.65 . Smokers were defined as individuals with a history of cigarette smoking for at least 10 pack-years	Beraprost 60 μ g three times daily	3 months	11/10
Rao et al. (14)	2011, India	Severe or very severe COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification were recruited if they had past history of smoking of at least 20 pack years and had pulmonary artery systolic pressure of more than 40 mmHg as measured by Doppler echocardiography	Sildenafil 20 mg three times a day	12 weeks	15/18
Stolz, et al. (12)	2008, Switzerland	Symptomatic, severe or very severe COPD and/or emphysema (in classes III–IV according to the Global Initiative for Chronic Obstructive Lung Disease classification), despite optimised therapy with short- and long-acting B ₂ -agonists, long-acting anticholinergics and inhaled steroids.	Bosentan 125 mg twice daily	12 weeks	14/9
Valerio, et al. (13)	2009, Italy	COPD using the ATS definition and classified according to the GOLD guidelines, were involved in the study. These patients were affected by pulmonary hypertension (PAPm425 mmHg, PWs15 mmHg) diagnosed using right catheterization	Bosentan 125 mg twice a day	18 months	16/16
Observational study					
Park et al. (15)	2012, Korea	Severe COPD who showed a post-bronchodilator forced expiratory volume in 1 second (FEV1) of less than 50% of the predicted value	Udenafil 50 mg once a day	8 weeks	25
Rietema et al. (16)	2008, The Netherlands	Moderate-to-severe COPD according to Global Initiative for Chronic Obstructive Lung Disease guidelines, and patients had to be without exacerbation or hospital admission in the previous 4 months	Sildenafil 50 mg three times daily	3	15

*No. of enrolled patients in intervention group/control group.

ment. We included two trials involving 76 subjects in the analysis (15, 16). Table 1 shows the characteristics of the trials that were published between 2008 and 2012. One trial was case-controlled cohort design for sildenafil and the other was a prospective single arm study for udenafil. The criteria for inclusion and exclusion were same for the Randomized controlled trials.

each included RCT study are summarized in Table 2 and are presented as percentages across all included studies in Fig. 2. All trials reported the withdrawal rate of each intervention and placebo group. There were no significant differences in the overall withdrawal rate between intervention and placebo group (17.5% vs 10.0%, $P = 0.38$) in four RCTs.

Risk of bias in included studies

The review authors' assessments of each risk of bias item for

Effects of intervention

Data regarding 6 minute walking distance for the effect of vaso-

Table 2. Risk of bias assessment for the randomized controlled studies included in the meta-analysis

Study reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Lee et al. (11)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Rao et al. (14)	Low	Low	Low	Unclear	Low	Low
Stolz et al. (12)	Low	Low	Low	Low	Low	Low
Valerio et al. (13)	Unclear	Unclear	High	High	Low	Low

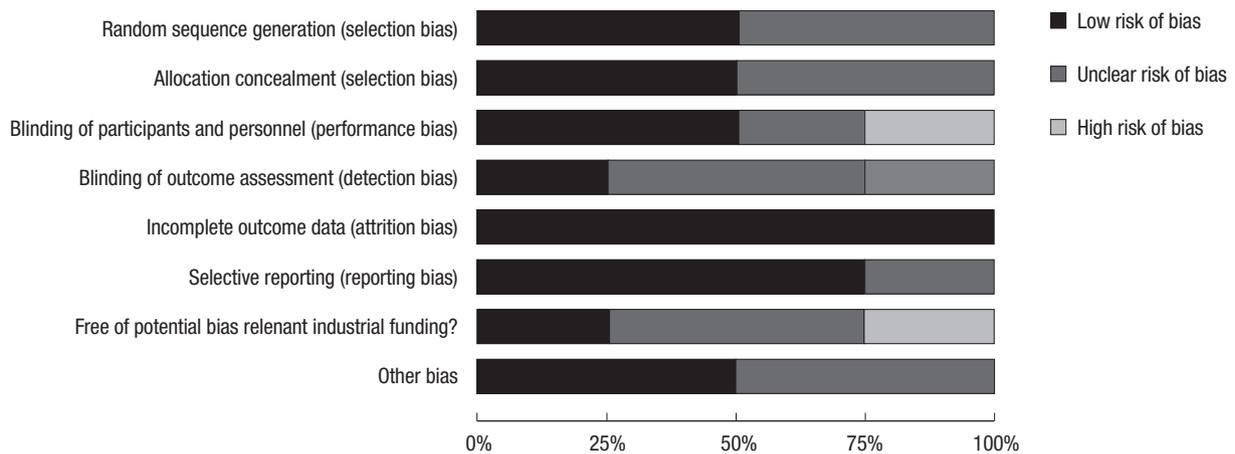


Fig. 2. Risk of bias assessment for the randomized controlled studies included in the meta-analysis.

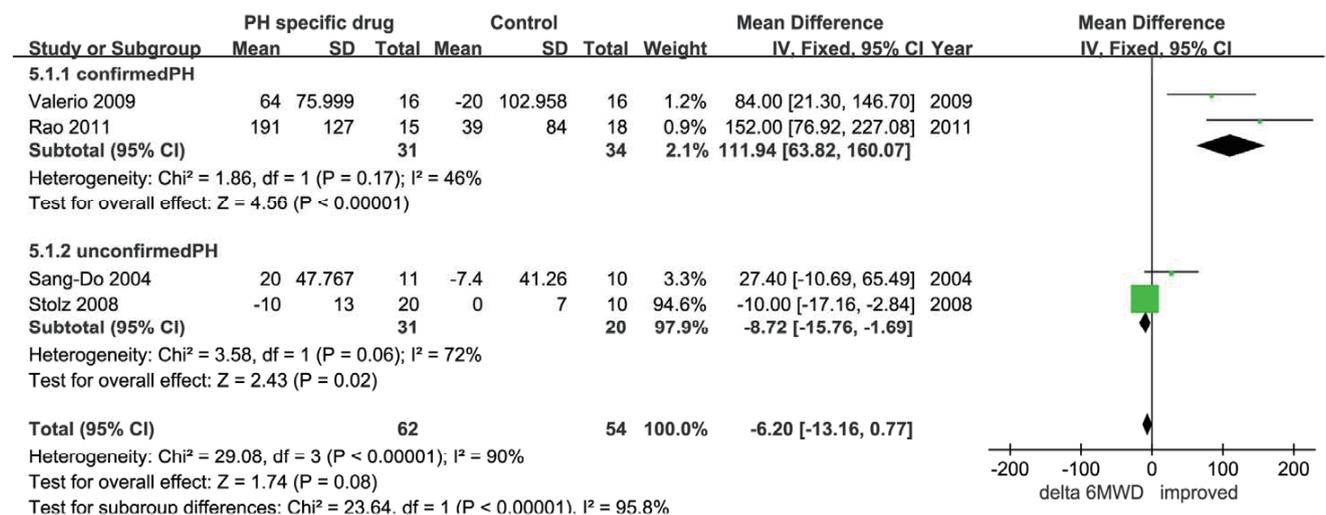


Fig. 3. Meta-analysis of randomized controlled studies of pulmonary hypertension specific treatment for COPD. SD, standard difference; IV, inverse variance; CI, confidence interval; df, degree of freedom.

dilator in the intention-to-treat population with COPD were available for four trials and were analyzed by inverse variation method, as shown in Fig. 3. There was a significant statistical heterogeneity among four trials ($I^2 = 90\%$, $P < 0.001$). In a pooled analysis of four trials, exercise-capacity was not significantly improved with PH-specific treatment for COPD (risk ratio -5.09, 95% CI -13.00 to 2.82). According to pre-specified sub-group analysis by the PH, COPD patients who were confirmed about PH significantly improved the exercise capacity (mean difference, 111.63; 95% CI 63.31 to 159.94) but COPD patients who were unconfirmed about PH did not (mean difference, 26.61;

95% CI -24.31 to 77.52). According to pre-specified sub-group analysis by the drug, there was a trend toward improving exercise capacity. There was no difference according to the drug (Fig. 4).

In observational trials, data regarding 6-min walking distance were available for two trials and were analyzed by generic inverse variation method, as shown in Fig. 5. There was no significant statistical heterogeneity among two trials ($I^2 = 0\%$, $P = 0.68$). In pooled analysis of two trials, exercise capacity had a tendency to improve.

Data regarding hypoxemia possibly related to the study drugs

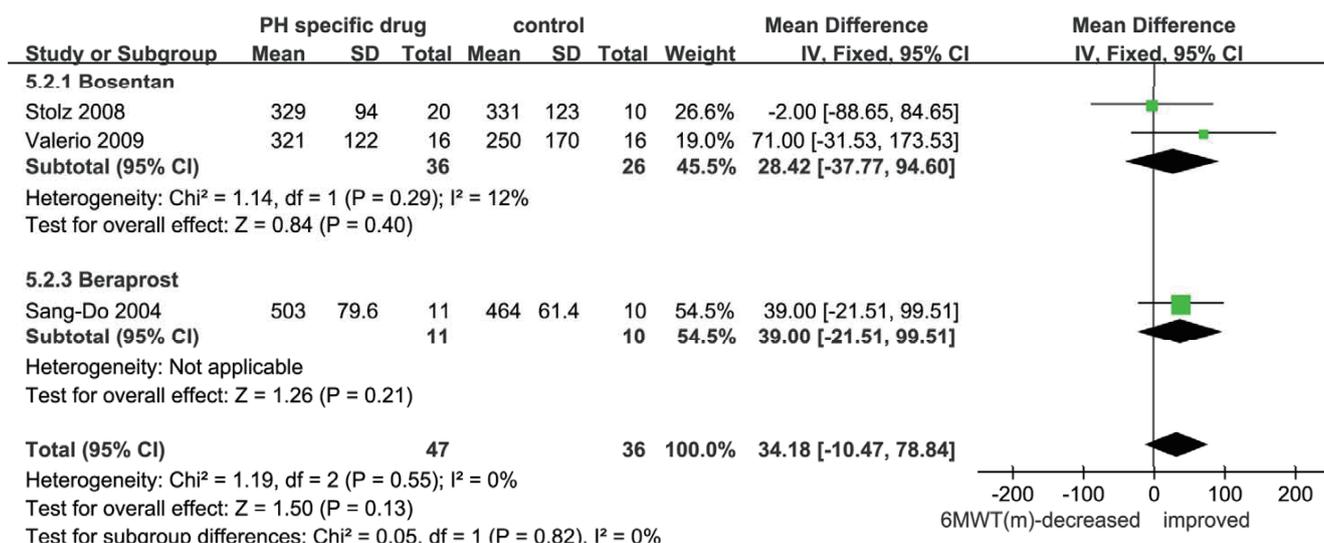


Fig. 4. Meta-analysis of randomized controlled studies about pulmonary hypertension specific treatment for COPD. SD, standard difference; IV, inverse variance; CI, confidence interval; df, degree of freedom.

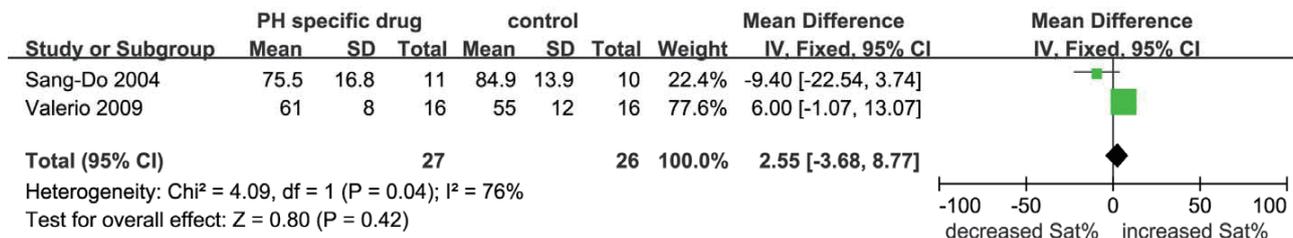


Fig. 5. Meta-analysis of hypoxemia after pulmonary hypertension specific treatment in chronic obstructive pulmonary disease in the randomized controlled studies. SD, standard difference; IV, inverse variance; CI, confidence interval; df, degree of freedom.

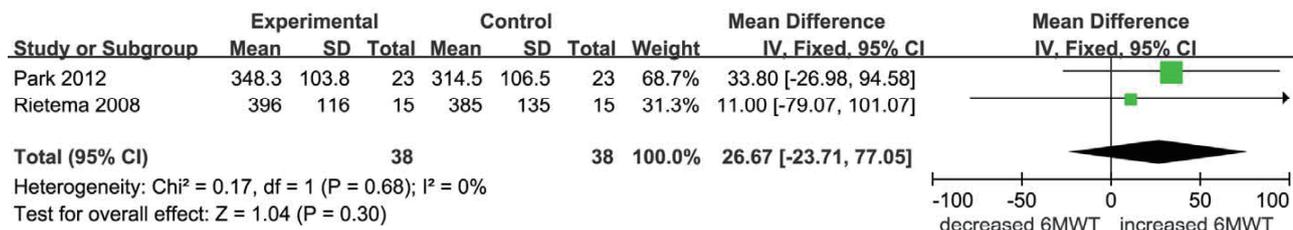


Fig. 6. Meta-analysis of observational studies about pulmonary hypertension specific treatment for COPD. SD, standard difference; IV, inverse variance; CI, confidence interval; df, degree of freedom.

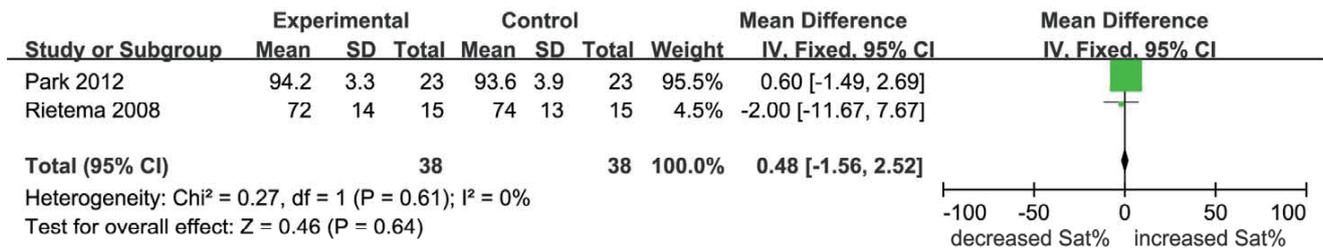


Fig. 7. Meta-analysis of hypoxemia after pulmonary hypertension specific treatment in chronic obstructive pulmonary disease in the observational studies. SD, standard difference; IV, inverse variance; CI, confidence interval; df, degree of freedom.

were available for two RCT trials (Fig. 6). There was no significant difference in hypoxemia between PH-specific treatment and placebo groups (mean difference, 2.55; 95% CI, -3.68 to 8.77). In the observational study, there was no significant difference in desaturation between pre-medication and post-medication (Fig. 7). We planned to conduct a meta-analysis for dyspnea as secondary outcome. There were two studies reported the dyspnea index. However, they used different scoring systems for dyspnea.

DISCUSSION

The pooled evidence in our systematic review showed a statistically significant increase in exercise capacity with PH-specific treatment in COPD patients with confirmed PH by right heart catheterization or echocardiography. There was no significant hypoxemia associated with PH-specific treatment that gave us pause to prescribe PH specific agents for COPD patients having PH. However, in all severe COPD patients, regardless of PH there was a question as to whether they could improve their exercise capacity.

There were some difference between PH due to COPD and other types PH. In COPD, peripheral edema may not be a sign of RV failure, because it may result from the effects of hypoxemia and hypercapnia on the renin-angiotensin-aldosterone system (17). Furthermore, concomitant left heart disease, which is commonly associated with chronic respiratory diseases, may also contribute to raise pulmonary arterial pressure (5). The diagnostic threshold for mean pulmonary arterial pressure used to diagnose PH in WHO Group 3 are perhaps reflective of the fact that these definitions were established by expert consensus rather than by objective right heart catheterization data to support an optimal diagnostic threshold (18). Previous studies have used mean pulmonary artery pressures exceeding 20 mmHg to define PH in some conditions such as COPD. The definition for PH in COPD has been debatable. Thirty five percent of all patients with severe COPD have a pulmonary artery pressure > 20 mmHg at rest (19). Pulmonary pressures during exercise are greater than predicted by the PVR equation in COPD, suggesting active pulmonary vasoconstriction on exertion (9). Hence, of those patients without PH at rest, a further

52% are estimated to develop PH during exercise (4). Like idiopathic PAH, pulmonary arteries in patients with COPD show evidence of fibromuscular intimal thickening with a diffuse increase in smooth muscle cells within the intima (20). In severe COPD, the occasional application of PH specific treatment has been used to improve RV function and exercise capacity. However, in this meta-analysis on COPD, PH-specific treatment was only effective in cases of confirmed PH at rest. It had no salience in terms of PH-specific treatment as the improvement of exercise capacity in the absence of proven PH at rest by right heart catheterization.

Concerns about worsening Ventilation/perfusion (V/Q) mismatching and hypoxia arise (21) when considering PH-specific treatment in COPD patients (22). Pulmonary vasodilators may attenuate hypoxic vasoconstriction in poorly ventilated units (23). In this meta-analysis for the secondary outcome, no worsening in oxygenation occurred significantly with PH-specific treatment, suggesting that any adverse impact on V/Q matching is minimal. In patients who have COPD, in whom hypoxemia is primarily caused by V/Q imbalance, PH-specific treatment can worsen arterial PaO_2 as a result of increased perfusion to poorly ventilated units (23). This effect can be prevented by concomitant use of supplemental oxygen.

Under the treatment guideline for PH, there is a limitation for the treatment that patients with disproportion PH due to lung diseases should be enrolled in RCTs targeting PAH-specific drugs (24). Published experience with specific PAH drug therapy is scarce and consists of the assessment of acute effects and uncontrolled studies in small series. This meta-analysis indicated that small number of randomized controlled trial is unavoidable.

Our meta-analysis was hampered by heterogeneity. We could not help converting the unit from the final value of 6 minute walking distance to the change value. We requested the additional data from the authors; some responded and others did not. Almost all patients included in meta-analysis had an optimal bronchodilator therapy except for domiciliary oxygen. There were different kind of vasodilator and diagnostic tool for PH. The meta-analysis for observational study was working together to compensate the defect. The result of meta-analysis of RCTs for the observational studies showed a similar trend of

improvement of the exercise capacity.

In conclusion, PH specific treatments have significant effect in improving the exercise capacity in COPD patients with overt PH at rest. However, our systematic review did not show a statistically significant increase in exercise capacity with PH-specific treatment in COPD patients regardless of PH at rest. From the results of this systematic review, we suggest PH-specific treatments in COPD patients with PH at rest might be as beneficial as other PH group. Future studies will be needed to determine the exact indications and risk-benefit balance of PH-specific therapy in the setting of COPD with PH at rest.

DISCLOSURE

Jinkyong Park, Ju Hee Song, Dong-Ah Park, Jae Seoung Lee have no conflicts of interest to disclose.

Yeon-Mok Oh has been an investigator in industry-sponsored studies (MSD Korea, AstraZeneca Korea, Boehringer Ingelheim Korea, Handok and GlaxoSmithKline) and in university-sponsored studies (Asan Institute for Life Science, University of Ulsan College of Medicine). Yeon-Mok Oh has participated as a speaker at scientific meetings organized and financed by pharmaceutical companies (Handok, Pfizer Korea, GlaxoSmithKline, AstraZeneca Korea, MSD Korea, and Boehringer Ingelheim Korea) and a magazine company (Korea Doctors' Weekly). Yeon-Mok Oh developed an educational presentation for a pharmaceutical company (Diachi Sankyo Korea).

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