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# The potential benefit of endothelin receptor antagonists' therapy in idiopathic pulmonary fibrosis

## A meta-analysis of results from randomized controlled trials

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**Abstract**

**Background:** Fibrotic diseases take a very heavy toll in terms of morbidity and mortality equal to or even greater than that caused by metastatic cancer. This meta-analysis aimed to evaluate the effect of endothelin receptor antagonists on idiopathic pulmonary fibrosis.

**Method:** A systematic search of the clinical trials from the Medline, Google Scholar, Cochrane Library, and PubMed electronic databases was performed. Stata version 12.0 statistical software (Stata Crop LP, College Station, TX) was adopted as statistical software.

**Result:** A total of 5 studies, which included 1500 participants. Our analysis found there is no significant difference between using the endothelin receptor antagonists' group and placebo groups regarding the lung function via estimating both the change of forced vital capacity from baseline and DLco index. Exercise capacity and serious adverse effects are taken into consideration as well; however, there is still no significant change between the 2 groups.

**Conclusion:** This meta-analysis provides insufficient evidence to support that endothelin receptor antagonists' administration provides a benefit among included participants who encounter idiopathic pulmonary fibrosis.

**Abbreviations:** 6MWD = 6-minute walk distance test, CIs = confidence intervals, DLco = diffusion capacity of the lung for carbon monoxide, ET = endothelin, FVC = forced vital capacity, ORs = Odds ratios, RCTs = randomized controlled trials, WMD = weighted mean difference.

**Keywords:** bosentan, endothelin receptor antagonists, idiopathic pulmonary fibrosis, meta-analysis.

## 1. Introduction

Interstitial lung diseases (ILDs) represent a large group of diseases that cause scarring (fibrosis) of the lungs,[1] which causes stiffness, making it difficult to breathe and get oxygen to the bloodstream.[2] Of the ILDs, idiopathic pulmonary fibrosis, also known as cryptogenic fibrosing alveolitis is the most common and fatal. It is characterized by the aberrant accumulation of epithelial and endothelial damage progressing to fibrosis in the lungs parenchyma[3] and the pathological hallmark of usual interstitial pneumonia.[4] Globally, idiopathic pulmonary fibrosis affects more than 5 million people every year.[5] Even though idiopathic pulmonary fibrosis is considered an unusual disease, it still places a severe burden on each family unfortunately getting in this kind of disease, both in economics and psychology.[6] The progression of idiopathic pulmonary fibrosis is generally manifested by a step-wise decline in pulmonary function, with worsening dyspnea and a high degree of morbidity, measured as forced vital capacity (FVC).[7,8] Endothelin receptor antagonists are a type of potent vasodilator and antimitotic substances that specifically dilate and remodel the pulmonary arterial system.[9] Bosentan, a specific dual-receptor antagonist of both endothelin (ET) receptor subtypes ($ET_A$ and $ET_B$), was firstly developed for the treatment of pulmonary arterial hypertension[10] and congestive heart failure.[11] By blocking the receptor of ET, bosentan has been shown to decrease pulmonary vascular resistance and retard the pathogenic manifestations in the bleomycin-induced pulmonary fibrosis model,[12] which reduces collagen deposition in the lungs. Despite there is emerging many medicines to cure this disease recent years with increasing knowledge about underlying mechanism of idiopathic pulmonary fibrosis, there is no therapy available to

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effectively influence this. Thus, we performed a study to evaluate the efficacy and safety of endothelin receptor antagonists in patients with idiopathic pulmonary fibrosis.

## 2. Materials and Methods

### 2.1. Ethical review

All analyses were conducted according to available published literature; thus, no ethical approval or patient consent was required.

### 2.2. Literature search strategy

We systematically performed electronic literature from Medline, Embase, Cochrane Library, and PubMed electronic databases following the recommended guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis.[13] All 4 databases were scanned from 1997 when bosentan was first indicated in the pathogenesis of pulmonary fibrosis in the rodent model until August 2021 for the keywords of endothelin receptor antagonists and idiopathic pulmonary fibrosis in combination with Boolean logic.[12] We also performed a manual search of the references cited in relevant review articles.[14] After original searching, the relevant and their references were searched manually by 2 authors.

### 2.3. Inclusion and exclusion criteria

The following predefined inclusion criteria were used: (i) population: participant with idiopathic pulmonary fibrosis; (ii) intervention: patients strictly treated with endothelin receptor antagonists; (iii) comparison intervention: use of endothelin receptor antagonists compared to placebo group; (iv) outcome measures: one or more of the clinical outcomes were reported, forced vital capacity (FVC), diffusion capacity of the lung for carbon monoxide (DLco), 6-minute walk distance test (6MWD), and serious adverse events; (v) official published studies in English prospective and retrospective studies.

The exclusion criteria were listed as follows: (i) conference or commentary articles and letters; (ii) atypical patients and outcome data; (iii) case report and case series; (iv) animal observation.

### 2.4. Data extraction and outcome measures

Two researchers independently provided a detailed record for each study for the following essential information: the first author of the study, publication year, follow-up years, study design, sampling method, endpoints, study characteristics including the number of populations, mean age, gender ratio, and country. All disagreements were discussed and reached the final decision. The outcome measurements were the following: FVC, DLco, 6-minute walk distance test, and incidence of serious adverse events.

### 2.5. Quality assessment

The Cochrane Collaboration tool was applied to evaluate the risk of bias in all involved literature. Specifically, each trial was assessed for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.[15]

### 2.6. Statistical analysis

The analysis, design, and reporting for meta-analysis were carried out using Stata version 12.0 statistical software (Stata Crop LP, College Station, TX) as statistical software. The weighted mean difference (WMD) or Odds ratios (ORs) with the corresponding 95% confidence intervals (95% CIs) were used as measures of the treatment effect of bosentan. Heterogeneity of the observed studies was accessed with the Higgins I-square ($I^2$) value. $I^2$ over 25% and 75% was considered as moderate heterogeneous or significant heterogeneity, respectively. If $I^2$ was under 25%, the endpoint item was considered to be homogeneous, then we run a meta-analysis by using a fix-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions.

## 3. Results

### 3.1. Search result

A total of 143 records were identified through the database by the search strategy, which is displayed in the following diagram (Fig. 1) in accordance with the inclusion and exclusion criteria. After removing duplicated or irrelevant articles, 49 eligible studies were enrolled in this study, of which 11 articles meeting our inclusion criteria were retrieved after evaluating the full text of the remaining articles. Finally, 5 studies[16–20] were combined in the present quantitative synthesis.

### 3.2. Characteristics of included studies

Detailed characteristics concerning the involved studies are summarized in Table 1. A total of 5 randomized controlled trials (RCTs) were published between 2008 and 2014 including 1500 participants, and the sample size varied from 60 to 616. This study enrolled 518 patients treated with bosentan, 119 patients with macitentan, and 329 with ambrisentan, which is all endothelin receptor antagonists, compared with 534 participants in the placebo group. The average ages were from 63.8 to 66.6 years, the ratios of men varied from 68.0 to 72.7%, and only Corte et al[17] reported pulmonary arterial pressure of the included participants. In each RCT, all endothelin receptor antagonists or placebo were given after the idiopathic pulmonary fibrosis. Nearly all studies (four studies) did research on forced vital capacity and diffusion capacity of the lungs for carbon monoxide. Besides, King et al,[16] Raghu et al[19] and Corte et al[17] also took 6-minute walk distance test in consideration.

### 3.3. Quality assessment

The research scores of all nonrandomized controlled trials were assessed by 2 reviewers separately evaluating the methodological quality of the included observational studies by Cochrane Collaboration tool. Most of the included RCTs were high quality. Most of them showed a low risk of bias for random sequence generation, blinding of outcome assessment, incomplete outcome data, and selective reporting. The results of the quality assessment of trials are provided in Table 2.

### 3.4. The outcome of the meta-analysis

A total of 5 RCTs were eligible for analysis, with 1500 patients undergoing idiopathic pulmonary fibrosis. The detailed results are shown in Table 3 and listed as follows.

### 3.5. Lung function

Four RCT studies (1325 patients) reported on FVC changes from baseline and at 4 to 12 months follow-up.[17–20] However, there is no difference between the using endothelin receptor antagonists and placebo group (WMD, –2.079; 95% CI, –2.079–3.471; $P$ = .463; $I^2$ = 0.0% for FVC % predicted, and WMD, 0.028; 95% CI, –0.158–0.214; $P$ = .769; $I^2$ = 0.0% for FVC L, Fig. 2).

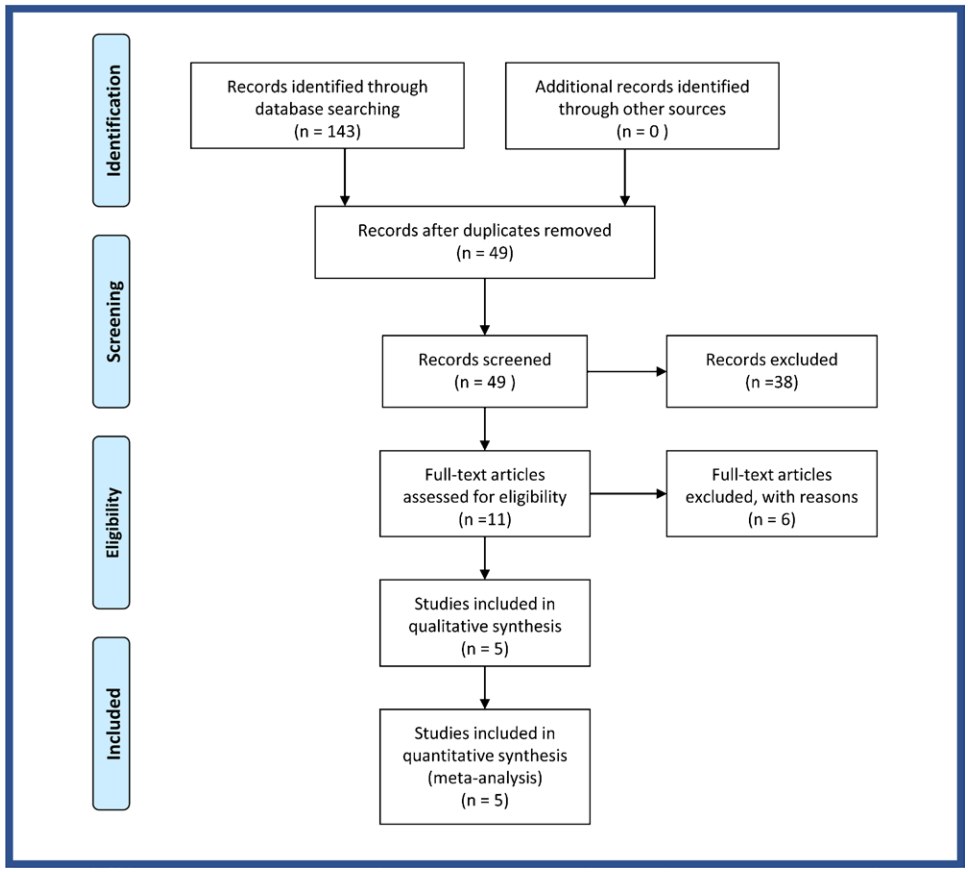


**Figure 1.** Flowchart of the study selection process.

**Table 1**

**Main characteristics of the randomized controlled trials included in the meat-analysis.**

| Study | Year | ERA | Control | Age | Men % | Duration | PAP mmHg | FVC, % predicted | DLco % predicted | 6MWDm | Intervention |
|---|---|---|---|---|---|---|---|---|---|---|---|
| King et al[1] | 2008 | 71 | 83 | 65.3 ± 8.4 | 72.7 | 12 months | NR | 65.9 ± 10.5 | 42.3 ± 9.5 | 275 ± 92 | Bosentan |
| King et al[2] | 2011 | 407 | 209 | 63.8 ± 8.4 | 69.6 | 12 months | NR | 74.9 ± 14.8 | 47.7 ± 11.9 | NR | Bosentan |
| Raghu et al[3] | 2013 | 119 | 59 | 65.1 ± 7.85 | 68.0 | 12 months | NR | 76.5 ± 15.6 | 47.8 ± 13.4 | NR | Macitentan |
| Raghu et al[4] | 2013 | 329 | 163 | 65.8 | 74.2 | 18 months | NR | 68.7 | NR | 410.4 | Ambrisentan |
| Corte et al[5] | 2014 | 40 | 20 | 66.6 ± 9.2 | 70 | 4 months | 36.0 ± 8.9 | 54.2 ± 21.2 | 21.3 | 149.3 ± 99.6 | Bosentan |

DLco = diffusion capacity of the lungs for carbon monoxide, ERA = Endothelin receptor antagonist, FVC = forced vital capacity, PAP = pulmonary arterial pressure, 6MWD = 6-minute walk distance test, NR = not reported, ± = standard deviation.

Data regarding the information of Dlco in idiopathic pulmonary fibrosis patients treated with endothelin receptor antagonists were also available in 4 trials (1325 patients).[17–20] The Dlco % predicted percentage in the endothelin receptor antagonists' group did not show a significant lower tendency than the control group (WMD, –1.334; 95% CI, –4.945–2.276; $P$ = .469; $I^2$ = 0.0%, Fig. 3) and besides, the mean change from baseline in DLco (mmol·kPa $^{-1}$·min $^{-1}$) did not differ significant between the 2 groups either (WMD, 0.124; 95% CI, –0.183–0.431; $P$ = .427; $I^2$ = 0.0%, Fig. 3).

### 3.6. Exercise capacity and serious adverse effects

Four studies were involved to measure the effectiveness of endothelin receptor antagonists in improving the exercise capacity, measured using the 6-minute walk distance.[16–19] Whereas, there was no difference in the endothelin receptor antagonists group compared with the control group (WMD, –2.160; 95% CI, –7.996–3.677; $P$ = .468). Between-trial heterogeneity was homogeneous ($I^2$ = 21.7%), similarly, serious adverse events were similar between these 2 groups (OR, 1.063; 95% CI, 0.669–1.690; $P$ = .796).

## 4. Discussion

Idiopathic pulmonary fibrosis is a kind of chronic lung fibrosing disorder with a high incidence and a worse prognosis than numerous tumors.[21] Plenty of new studies are aimed at exploring a novel treatment for suppressing the initiation and progression of pulmonary fibrosis.[22] Despite this, the optimal treatment of disease is largely unknown. Pulmonary arterial hypertension is commonly appeared with idiopathic pulmonary fibrosis, relating to a significant negative effect on survival time. Endothelin receptor antagonists, such as ambrisentan and bosentan, have been illustrated to be effective individually compared with placebo in treating pulmonary arterial hypertension.[23] Despite this, the exact effect of endothelin receptor antagonists in the treatment of idiopathic pulmonary fibrosis

**Table 2**

**Cochrane Collaboration tool for quality assessment in all included trials.**

| Trials | Year | Sequence Generation | Allocation Concealment | Blinding of Outcome Assessors | Incomplete Outcome Data | Selective Outcome Reporting | Others |
|---|---|---|---|---|---|---|---|
| King et al[1] | 2008 | Low | Unclear | Low | Low | Low | Unclear |
| King et al[2] | 2011 | Low | Unclear | Low | Low | Low | Unclear |
| Raghu et al[3] | 2013 | Low | Low | Low | Low | Low | Unclear |
| Raghu et al[4] | 2013 | Low | Low | Low | Low | Low | Low |
| Corte et al[5] | 2014 | Low | Unclear | Low | Low | Low | Unclear |

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2.King T, Brown K, Raghu G, du Bois R, Lynch D, Martinez F, et al BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2011;184(1):92–9. doi: 10.1164/rccm.201011-1874OC. PubMed PMID: 21474646.

3.Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *The European respiratory journal*. 2013;42(6):1622–32. doi: 10.1183/09031936.00104612. PubMed PMID: 23682110.

4.Raghu G, Behr J, Brown K, Egan J, Kawut S, Flaherty K, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Annals of internal medicine*. 2013;158(9):641–9. doi: 10.7326/0003-4819-158-9-201305070-00003. PubMed PMID: 23648946.

5.Corte T, Keir G, Dimopoulos K, Howard L, Corris P, Parfitt L, et al. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American journal of respiratory and critical care medicine*. 2014;190(2):208–17. doi: 10.1164/rccm.201403-0446OC. PubMed PMID: 24937643.

**Table 3**

**The outcomes of this meta-analysis.**

| Outcomes | Studies numbers | Sample size | | Overall effect | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | ERA | Placebo | Effect estimates | 95% CIs | *P* value | $I^2$ (%) | *P* value |
| FVC, % predicted | 2 | 354 | 177 | WMD (–2.079) | -2.079-3.471 | 0.463 | 0.0% | 0.773 |
| FVC, L | 2 | 526 | 268 | WMD (0.028) | -0.158-0.214 | 0.769 | 0.0% | 0.846 |
| Dlco, % predicted | 2 | 354 | 177 | WMD (–1.334) | -4.945-2.276 | 0.469 | 0.0% | 0.622 |
| DLco mmol·kPa$^{-1}$·min $^{-1}$ | 2 | 526 | 265 | WMD (0.124) | -0.183-0.431 | 0.427 | 0.0% | 0.626 |
| 6MWD | 3 | 425 | 260 | WMD (–2.160) | -7.996-3.677 | 0.468 | 21.7% | 0.279 |
| ISAE | 3 | 776 | 392 | OR (1.063) | 0.669–1.690 | 0.796 | 51.7% | 0.126 |

CIs = confidence intervals, DLco = diffusion capacity of the lung for carbon monoxide, ERA = endothelin receptor antagonist, FVC = forced vital capacity, ISAE = incidence of serious adverse events, OR = odds ratio, RD = rate difference, WMD = weighted mean difference, 6MWD = 6-minute walk distance.

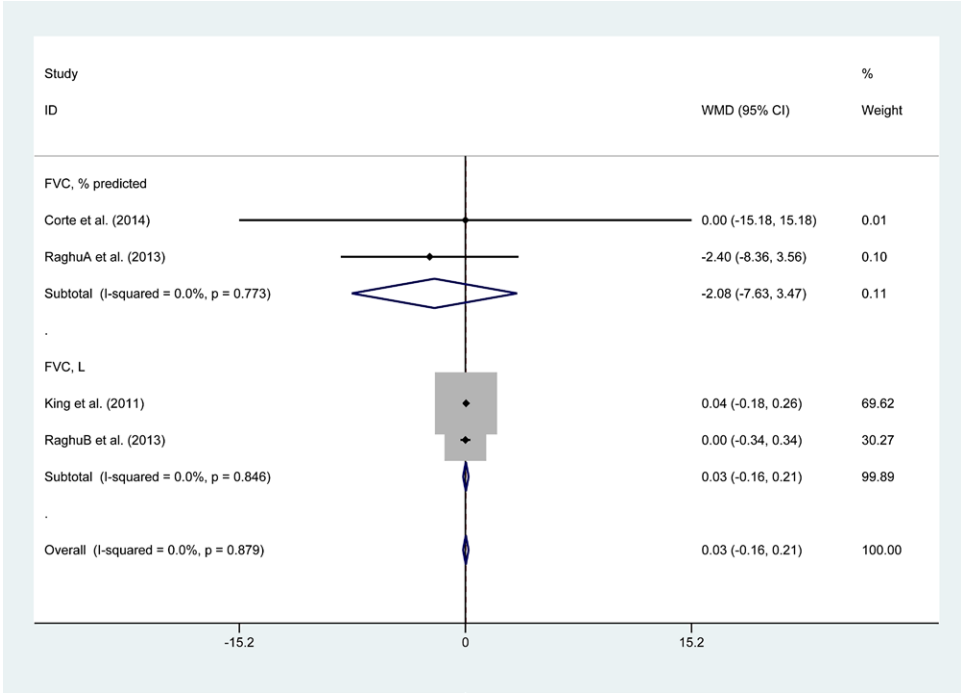


**Figure 2.** Forest plot on the assessment of the forced vital capacity.

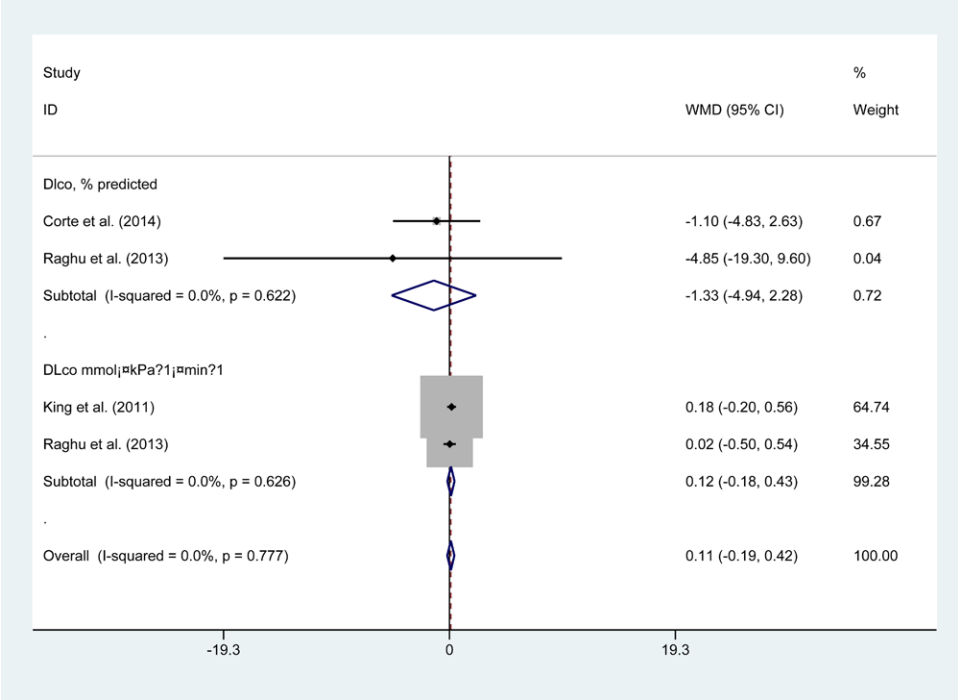


**Figure 3.** Forest plot on the assessment of the lung for carbon monoxide.

remains controversial, therefore, this study aimed to conduct a meta-analysis that evaluates current available studies to uncover the effect of endothelin receptor antagonists on the treatment of idiopathic pulmonary fibrosis.

Progress in the past several decades has been made in the widespread use of various medications to inhibit the loss of lung function in patients with idiopathic pulmonary fibrosis.[3] Gunther et al[24] conducted a study; 12 idiopathic pulmonary fibrosis patients underwent analysis of gas exchange properties on day 1 before and after the administration of 125 mg bosentan, the results showed no significant improvement in lung function within a period of 3-month treatment, even have some tendency toward deterioration of FVC (55.73 change into 52.18) and DLco (36.73 into 33.27) values. In the current study, we assess the effect of lung function by evaluating FVC and DLco in patients with idiopathic pulmonary fibrosis after endothelin receptor antagonists, demonstrating that it did not differ significantly between the experiment and the control group on changes in FVC from baseline. Similarly, Data regarding DLco changes from baseline were analyzed and revealed that no significant difference was found and the decline in percent-predicted DLco was not significantly lower in the endothelin receptor antagonists' group.

The improvement of quality of life after drug therapy is also one of the current concerns in the treatment of idiopathic pulmonary fibrosis, therefore, we evaluated the 2 items, including mean change of 6-minute walk distance (WMD, –2.160; $P = 0.468$) and incidence of serious adverse events (OR, 1.337; $P = 0.450$). This study, thus, illustrated that the endothelin receptor antagonists did not affect the improvement of idiopathic pulmonary fibrosis, which is similar to several previous publications. Raghu et al[25] revealed that bosentan did not have superiority over placebo in the improvement 6-min walking distance. Additionally, Gunther et al demonstrated that the mean value of 6-min walking distance is the same before and after the treatment of bosentan (320.9 vs 320.9). Despite Lee et al[14] performed a meta-analysis and showed that pulmonary arterial hypertension-specific agents such as PDE-5 inhibitor significantly affected the quality of life, as measured by George's Respiratory Questionnaire (SGRQ) total score. In this study, only 1 article assessed the SGRQ total score and revealed that, up to Month 6, the SGRQ total score in the bosentan group remained almost unchanged, whereas it worsened in the placebo group.[16] Therefore, more high-quality studies are necessary to uncover this issue.

Of note, several limitations were involved in this meta-analysis. First, although all the studies included in this study were RCTs, there were only 6 articles exploring the effect of endothelin receptor antagonists on idiopathic pulmonary fibrosis, and their sample size was small. Second, it is crucial to consider the heterogeneity when illustrating the results of a meta-analysis, however, this study is of a moderate-high heterogeneity of the statistical results. Third, despite we identified 2 trials that examined lung function, we had to exclude them from our pooled analyses since they reported insufficient outcomes without a value change. Finally, the follow-up period of all involved studies is not the total same. Thus, although many meaningful conclusions could be drawn about the trends in the effect of endothelin receptor antagonists, further high-quality and large sample size studies are necessary to determine the effect of endothelin receptor antagonists.

## 5. Conclusion

Despite endothelin receptor antagonists providing the better benefits for pulmonary arterial hypertension, this meta-analysis provides insufficient evidence to support that endothelin receptor antagonists' administration induces provides a benefit in idiopathic pulmonary fibrosis patients.

## Author contributions

Shuang Li and Chuanhua Yan designed and conceptualized the article. Shuang Li and Wenqiang Xin prepared the figures and tables. All authors significantly contributed to writing the paper and provided important intellectual content.

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