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Bosentan and ambrisentan in the treatment of idiopathic pulmonary fibrosis: a meta-analysis

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Abstract. – OBJECTIVE: The aim is to showcase the effectiveness and safety of bosentan or ambrisentan in individuals diagnosed with idiopathic pulmonary fibrosis (IPF) and offer fresh evidence for the management of this condition.

MATERIALS AND METHODS: For this research, we conducted a meta-analysis of randomized controlled trials by searching various databases, including the Cochrane Library, Excerpta Medica Database, PubMed, and Web of Science. The retrieval was conducted until November 2021. We analyzed the variances in 6-minute walk distance (6MWD), death, diffusion capacity for carbon monoxide (DLCO), forced vital capacity (FVC), hospitalization, IPF worsening, mean pulmonary arterial pressure, serious adverse events (SAEs), Short Form-36 improved, and St. George's Respiratory Questionnaire between the treatment and control groups.

RESULTS: A sum of six studies involving 1,928 participants were found to meet the inclusion criteria. The quality of evidence was high. The control group had significantly higher values for 6MWD, DLCO, and FVC compared to the ambrisentan treatment group. The rates of hospitalization and IPF worsening were considerably greater in comparison with the control group. The bosentan group exhibited significantly reduced rates of hospitalization and IPF worsening in comparison with the control group. Both drugs did not cause any raising in death or SAEs when in comparison with the control group.

CONCLUSIONS: The findings of this research validate the effectiveness and safety of bosentan for treating IPF patients. This medication can enhance the quality of life for individuals with IPF without causing any significant increase in SAEs. However, it does not have a notable influence on the long-term prognosis. The findings of this research do not endorse the utilization of ambrisentan in individuals diagnosed with IPF.

Key Words:
Bosentan, Ambrisentan, Idiopathic pulmonary fibrosis, Meta-analysis.

Abbreviations

IPF: Idiopathic pulmonary fibrosis; PH: Pulmonary hypertension; IP: Interstitial pneumonia; PAP: Pulmonary arterial pressure; ETA: Endothelin A; RCTs: Randomized controlled trials; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; PROSPERO: International Prospective Register of Systematic Reviews; Embase: Excerpta Medica Database; MeSH: Medical Subject Headings; SAEs: Serious adverse events; SF-36: Short Form-36; 6MWD: 6-minute walk distance; DLCO: Diffusion capacity for carbon monoxide; FVC: Forced vital capacity; mPAP: Mean pulmonary arterial pressure; SGRQ: St. George's Respiratory Questionnaire; SLB: Surgical lung biopsy; SD: Standard deviation; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RR: Relative risk; SMD: Standardized mean difference; SE: Standard error; ES: Effect size; I2: I-squared; CI: Confidence interval; ETRAs: Endothelin receptor antagonists.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a grievous and frequently deadly interstitial lung disease characterized by chronic progression, lacking a known cause, and typically resulting in a middle survival time of 2-4 years following diacrisis[1,2]. Nevertheless, up until now, there has been no authorization for medications to cure IPF[3].

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IPF pathogenesis involves the participation of endothelin-1, which is recognized as a profibrotic and growth factor[4,5]. The presence of endothelin receptors is elevated in lung tissue affected by IPF, and inhibiting endothelin receptor activity could potentially alleviate the extent of pulmonary fibrosis[6,7].

Multiple research studies[3,8,9] have indicated that bosentan demonstrates efficacy in ameliorating pulmonary hypertension (PH) among individuals diagnosed with IPF. The BUILD-1 and BUILD-3 trials seem to contradict the utilization of bosentan in individuals with IPF, as the combination of various risk factors for IPF might have a cumulative impact on treatment results. The BUILD-1 trial demonstrated the efficacy of bosentan in a specific group of individuals suffering from interstitial pneumonia (IP). However, it was observed that a sizable number of IPF invalids in the bosentan cohort experienced increased pulmonary arterial pressure (PAP) and IPF advancement, which was found to be linked to an unfavorable prognosis[10]. Ambrisentan is a selective endothelin A (ETA) receptor antagonist[11]. The mechanism of action of ambrisentan differs entirely from that of bosentan, which may result in varying clinical effects of these medications in IPF cases[12].

Consequently, a meta-analysis was conducted to evaluate the impacts of bosentan and ambrisentan on individuals diagnosed with IPF. The aim of this work was to estimate if bosentan or ambrisentan can alter symptoms and outcomes in patients with IPF by conducting a meta-analysis of randomized controlled trials (RCTs).

Materials and Methods

The meta-analysis followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[13] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021293091).

Literature Search Strategy

In November 2021, we conducted a search for research papers on bosentan, ambrisentan, IPF, and RCTs in the Cochrane Library, Excerpta Medica Database (Embase), PubMed, and Web of Science databases. The coming Medical Subject Headings (MeSH) terms were utilized for retrieval: "Bosentan", "4-t-Butyl-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide", "Bosentan Monohydrate", "Tracleer", "Bosentan Anhydrous", "Ro 47-0203", "Ro 47 0203", "Ro 470203", "Ro-47-0203", "Ambrisentan", "(S)-ambrisentan", "(+)-(2S)-2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenylpropanoic acid", "(+)-ambrisentan", "LU 208075", "LU-208075", "LU208075", "BSF 208075", "BSF-208075", "BSF208075", "Volibris", "ambrisentan, (-)-", "(R)-ambrisentan", "ambrisentan, (R)-", "(-)-ambrisentan", "GSK-1325760", "GSK 1325760A", "GSK1325760A", "GSK 1325760", "GSK-1325760A", "GSK1325760", "Letairis", "ambrisentan, (+-)-", "(+-)-ambrisentan", "Idiopathic Pulmonary Fibrosis", "Idiopathic Pulmonary Fibroses", "Pulmonary Fibroses, Idiopathic", "Idiopathic Fibrosing Alveolitis, Chronic Form", "Fibrosing Alveolitis, Cryptogenic", "Fibrocystic Pulmonary Dysplasia", "Dysplasia, Fibrocystic Pulmonary", "Fibrocystic Pulmonary Dysplasias", "Pulmonary Dysplasia, Fibrocystic", "Cryptogenic Fibrosing Alveolitis", "Cryptogenic Fibrosing Alveolitides", "Fibrosing Alveolitides, Cryptogenic", "Pulmonary Fibrosis, Idiopathic", "Usual Interstitial Pneumonia", "Interstitial Pneumonia, Usual", "Usual Interstitial Pneumonias", "Interstitial Pneumonitis, Usual", "Pneumonitides, Usual Interstitial", "Pneumonitis, Usual Interstitial", "Usual Interstitial Pneumonitides", "Usual Interstitial Pneumonitis", "Familial Idiopathic Pulmonary Fibrosis", and "Idiopathic Pulmonary Fibrosis, Familial". The studies were searched for references, with no limitations on the date of publication or language.

Individuals meeting the inclusion criteria included those (a) diagnosed with IPF and (b) of any gender or age. The patients in the intervention groups received treatment with (a) bosentan or ambrisentan or (b) bosentan or ambrisentan plus background therapies (e.g., additional medications), and background therapies were also administered to the control groups. The individuals in the control groups were either provided with (a) a placebo or no treatment or (b) a placebo or no treatment in conjunction with background treatments, mirroring the interventions administered to the intervention groups. Only RCTs were involved in the study. There were no limitations on the languages. The studies yielded findings on various aspects, including the (a) occurrence rate of death, hospitalization, IPF worsening, serious adverse events (SAEs), and Short Form-36 (SF-36) score improvement and (b) average difference (between the baseline and endpoint) in the 6-minute walk distance (6MWD), diffusion capacity for carbon monoxide (DLCO), forced vital capacity (FVC), mean pulmonary arterial pressure (mPAP), and St. George's Respiratory Questionnaire (SGRQ) scores.

The criteria for exclusion included (a) trials with crossover design and (b) trials that did not have available outcomes.

Data Extraction Procedure

Data was extracted by two researchers separately on the basis of the inclusion and exclusion criteria. A third researcher resolved any disagreements. The following information was extracted from the paper that met the criteria, including author, year, country, age, sex, IPF duration, sample size, treatment duration, PH, surgical lung biopsy (SLB), treatment, and various outcomes assessed (6MWD, death, DLCO, FVC, hospitalization, IPF worsening, mPAP, SAEs, SF-36 improved, SGRQ). In the consequences, the dichotomous variables were displayed as percentages, and the continuous variables were presented as the mean ± standard deviation (SD). To prevent the exclusion of relevant research, a thorough examination was conducted on the title, abstract, full text, and references of every research that was included.

Grading of Evidence

To assess the bias in RCTs, we utilized RevMan 5.4 from the Cochrane Collaboration (London, UK)[14]. Additionally, for evaluating the quality of evidence in consequences, we employed GRADEprofiler 3.6.1 from the GRADE Working Group (Rome, Italy), associated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

Data Analysis

In our study, we incorporated RCTs that compared the effectiveness and safety of bosentan or ambrisentan to alternative interventions (placebo, no treatment, other drugs) in individuals suffering from IPF. We obtained 10 results, including (a) primary results such as 6MWD, death, hospitalization, IPF worsening, and SAEs, and (b) secondary results such as DLCO, FVC, mPAP, SF-36 improved, and SGRQ. With these findings, we extensively evaluated the effects of bosentan or ambrisentan on subjects with IPF.

The relative risk (RR) was calculated by comparing the occurrence of death, hospitalization, IPF worsening, SAEs, and SF-36 improvement between the intervention persons and the control persons throughout the therapy period. The standardized mean difference (SMD) was counted by comparing the average changes in 6MWD, DLCO, FVC, mPAP, and SGRQ between the intervention persons and the control persons before and after treatment. The SD was not directly provided in certain studies, so the standard error (SE), median, and quartile were transformed into the SD[15]. The occurrences of death, hospitalization, IPF worsening, SAEs, and SF-36 improvement were represented as binary variables. The effect size (ES) was expressed as RR. Conversely, the alterations in 6MWD, DLCO, FVC, mPAP, and SGRQ were considered as continuous variables, with the ES being SMD. The I-squared (I2) test was employed to examine heterogeneity among studies, and an I2 value of 50% or higher indicated remarkable heterogeneity[16,17]. Despite the diversity, the random-effect model was utilized to merge the ES[18]. In order to minimize heterogeneity between studies, we performed subgroup analyses based on the medications used. Due to the limited research conducted, a publication bias test was not performed[19]. By displaying the impacts of every subgroup and the overall outcome, the forest plot effectively demonstrated the results of the meta-analysis. Stata 12.0 (StataCorp LP; Texas, USA) was used to analyze all the data. The 95% confidence interval (CI) of ES represents the expression of all data. Except as otherwise mentioned, we employed $p < 0.05$ to indicate that the discrepancy was statistically valid.

Results

Selection and Characteristics of Studies

A total of 370 studies were obtained from the databases, out of which 364 studies were excluded, and ultimately, six studies[8,9,20-23] (1,928 participants) were included for meta-analysis (**Supplementary Figure 1**). Between 2008 and 2017, six studies were published, with treatment durations ranging from 48 to 104 weeks (Table I). One study[23] provided the baseline PH, and one provided the baseline SLB9 (Table I). Three studies[8,9,21] compared "bosentan 250 mg/day" and "placebo", one study[23] compared "bosentan 250 mg/day" and "no treatment", and two studies[20,22] compared "ambrisentan 10 mg/day" with "placebo" (Table I). The outcomes of two studies[8,20] included 6MWD, four studies[8,9,20,23] considered death, two studies[9,20] explored DLCO, two studies examined FVC[9,20], two studies[20,23] assessed hospitalization, four studies[8,9,20,21] investigated IPF worsening, one study[22] delved into mPAP, three studies[8,9,20] explored Serious Adverse Events (SAEs), one study[8] examined SF-36, and two studies[8,20] addressed SGRQ (Table I). One study[20] recorded results at weeks 12, 24, 36, 48, 60, 72, and 84. Table II displays the findings of all research studies.

Table I. Characteristics of the included studies.

Author	Year	Country	Age (year)†	Male (n)‡	IPF duration (year)†	Participant (n)		Treatment duration (week)	Pulmonary hypertension	Surgical lung biopsy	Treatment		Outcomes
						Intervention	Control				Intervention	Control	
King Jr. et al[8]	2008	Multiple	65.2 ± 8.8	112 (72.7)	2.5 ± 1.9	71	83	52	N/A	N/A	Bosentan 250 mg/day	Placebo	6MWD, death, IPF worsening, SAEs, SF-36 improved, SGRQ
King Jr. et al[9]	2011	Multiple	63.6 ± 8.8	429 (69.6)	N/A	407	209	85	N/A	Yes	Bosentan 250 mg/day	Placebo	Death, DLCO, FVC, IPF worsening, SAEs
Raghu et al[21]	2010	USA	N/A	N/A	N/A	67	82	52	N/A	N/A	Bosentan 250 mg/day	Placebo	IPF worsening
Raghu et al[20]	2013	Multiple	65.9 ± 8.8	355 (72.2)	1.0 ± 1.3	329	163	Raghu-1: 12 Raghu-2: 24 Raghu-3: 36 Raghu-4: 48 Raghu-5: 60 Raghu-6: 72 Raghu-7: 84	N/A	N/A	Ambrisentan 10 mg/day	Placebo	6MWD, death, DLCO, FVC, hospitalization, IPF worsening, SAEs, SGRQ
Raghu et al[22]	2015	USA	66.0 ± 7.3	354 (72.5)	N/A	325	163	48	N/A	N/A	Ambrisentan 10 mg/day	Placebo	mPAP
Tanaka et al[23]	2017	Japan	68.7 ± 7.3	17 (70.8)	N/A	12	12	104	Yes	N/A	Bosentan 250 mg/day	No treatment	Death, hospitalization

†Data are presented as the mean ± standard deviation. ‡Data are presented as the number (percentage). IPF, idiopathic pulmonary fibrosis. N/A, not available. 6MWD, 6-minute walk distance. SAEs, serious adverse events. SF-36, Short Form-36. SGRQ, St. George's Respiratory Questionnaire. DLCO, diffusion capacity for carbon monoxide. FVC, forced vital capacity. mPAP, mean pulmonary arterial pressure.

Table II. Outcomes of the included studies.

Author	Groups	6MWD (m)†	Death (%)‡	DLCO (% predicted)†	FVC (% predicted)†	Hospitalization (%)‡	IPF worsening (%)‡	mPAP (mmHg)†	SAEs (%)‡	SF-36 improved (%)‡	SGRQ (score)†
King Jr. et al[18] (2008)	Bosentan	-52.0 ± 121.0	4.2	N/A	N/A	N/A	18.3	N/A	29.7	39.4	-0.7 ± 19.9
	Placebo	-34.0 ± 127.0	3.6	N/A	N/A	N/A	32.5	N/A	34.5	27.7	2.6 ± 20.5
King Jr. et al[9] (2011)	Bosentan	N/A	2.7	-0.3 ± 1.8	-0.1 ± 1.2	N/A	31.4	N/A	31.8	N/A	N/A
	Placebo	N/A	2.9	-0.5 ± 2.5	-0.2 ± 1.4	N/A	39.2	N/A	35.4	N/A	N/A
Raghu et al[121] (2010)	Bosentan	N/A	N/A	N/A	N/A	N/A	16.9	N/A	N/A	N/A	N/A
	Placebo	N/A	N/A	N/A	N/A	N/A	24.1	N/A	N/A	N/A	N/A
Raghu et al[20] (2013)	Ambrisentan	Raghu-1: -21.0 ± 95.3 Raghu-2: -14.7 ± 101.3 Raghu-3: -29.2 ± 110.6 Raghu-4: -36.3 ± 124.0 Raghu-5: -40.9 ± 150.8 Raghu-6: -70.2 ± 207.3 Raghu-7: -38.3 ± 297.5	7.9	Raghu-1: -1.2 ± 22.2 Raghu-2: -2.0 ± 23.6 Raghu-3: -4.5 ± 26.4 Raghu-4: -5.9 ± 31.5 Raghu-5: -9.7 ± 39.8 Raghu-6: -12.6 ± 57.4 Raghu-7: -6.5 ± 80.5	Raghu-1: -2.1 ± 9.3 Raghu-2: -2.7 ± 9.7 Raghu-3: -3.6 ± 11.1 Raghu-4: -4.7 ± 13.0 Raghu-5: -8.0 ± 16.2 Raghu-6: -10.8 ± 23.6 Raghu-7: -11.7 ± 33.3	13.4	30.1	N/A	22.2	N/A	4.7 ± 19.9
	Placebo	Raghu-1: -4.8 ± 94.5 Raghu-2: -12.5 ± 99.3 Raghu-3: -9.5 ± 107.2 Raghu-4: -18.1 ± 121.8 Raghu-5: -31.9 ± 147.5 Raghu-6: -52.1 ± 193.1 Raghu-7: -58.1 ± 267.1	3.7	Raghu-1: 1.2 ± 22.5 Raghu-2: 2.1 ± 23.5 Raghu-3: -0.9 ± 26.1 Raghu-4: -1.9 ± 30.6 Raghu-5: -5.7 ± 37.8 Raghu-6: -6.4 ± 53.4 Raghu-7: -1.6 ± 75.9	Raghu-1: -0.3 ± 9.8 Raghu-2: -1.3 ± 10.4 Raghu-3: -2.5 ± 11.1 Raghu-4: -3.9 ± 13.0 Raghu-5: -5.9 ± 16.0 Raghu-6: -7.6 ± 22.1 Raghu-7: -9.3 ± 31.3	5.5	17.2	N/A	15.3	N/A	3.0 ± 13.8
Raghu et al[22] (2015)	Ambrisentan	N/A	N/A	N/A	N/A	N/A	N/A	-1.1 ± 6.0	N/A	N/A	N/A
	Placebo	N/A	N/A	N/A	N/A	N/A	N/A	0.4 ± 5.9	N/A	N/A	N/A
Tanaka et al[23] (2017)	Bosentan	N/A	8.3	N/A	N/A	16.7	N/A	N/A	N/A	N/A	N/A
	No treatment	N/A	58.3	N/A	N/A	66.7	N/A	N/A	N/A	N/A	N/A

Data are presented as the mean ± standard deviation or percentage. † Data are reported as the mean change from baseline to end point. ‡ Data are reported as the incidence during the study periods. IPF, idiopathic pulmonary fibrosis. N/A, not available. 6MWD, 6-minute walk distance. SAEs, serious adverse events. SF-36, Short Form-36. SGRQ, St. George's Respiratory Questionnaire. DLCO, diffusion capacity for carbon monoxide. FVC, forced vital capacity. mPAP, mean pulmonary arterial pressure. Raghu-1: the duration of treatment is 12 weeks. Raghu-2: the duration of treatment is 24 weeks. Raghu-3: the duration of treatment is 36 weeks. Raghu-4: the duration of treatment is 48 weeks. Raghu-5: the duration of treatment is 60 weeks. Raghu-6: the duration of treatment is 72 weeks. Raghu-7: the duration of treatment is 84 weeks.

Bias of Studies

Supplementary Figure 2 shows a resume of the potential risks of bias in all the research. While some research had a low risk of bias, there was uncertainty regarding the allocation concealment risk in one study.

Outcomes

6MWD

Subgroup analyses were performed using interventions as the basis (2 studies[8,20], 646 participants). The bosentan and placebo groups did not show any notable disparities in 6MWD alterations. In a combined examination of results for various treatment regimens, the decrease in 6MWD in the ambrisentan group was notably inferior to that observed in the placebo group. The studies did not show any notable heterogeneity (Figure 1).

Death

A subgroup analysis was accomplished based on the intervention, involving 4 studies[8,9,20,23] and 1,286 participants. No notable disparity in death rates was observed between the bosentan group and the placebo or non-treatment groups. The mortality rates did not differ notably between the ambrisentan and placebo groups. Furthermore, there was no notable heterogeneity between studies (Figure 2).

DLCO

Subgroup analysis was conducted using interventions in 2 studies[9,20] involving 1,102 participants. No notable distinction in DLCO alterations was observed between the bosentan group and the placebo group. When we pooled the results for different treatment times, the ambrisentan group had significantly lower DLCO changes than the placebo group. The studies did not show any notable heterogeneity (Figure 3).

FVC

We performed a subgroup analysis by interventions (2 studies[9,20], 1,103 participants). No notable disparity in FVC alterations was observed between the bosentan group and the placebo group. After combining the outcomes for various treatment durations, it was observed that the ambrisentan group exhibited considerably reduced FVC alterations compared to the placebo group. No notable heterogeneity was observed among the studies (Figure 4).

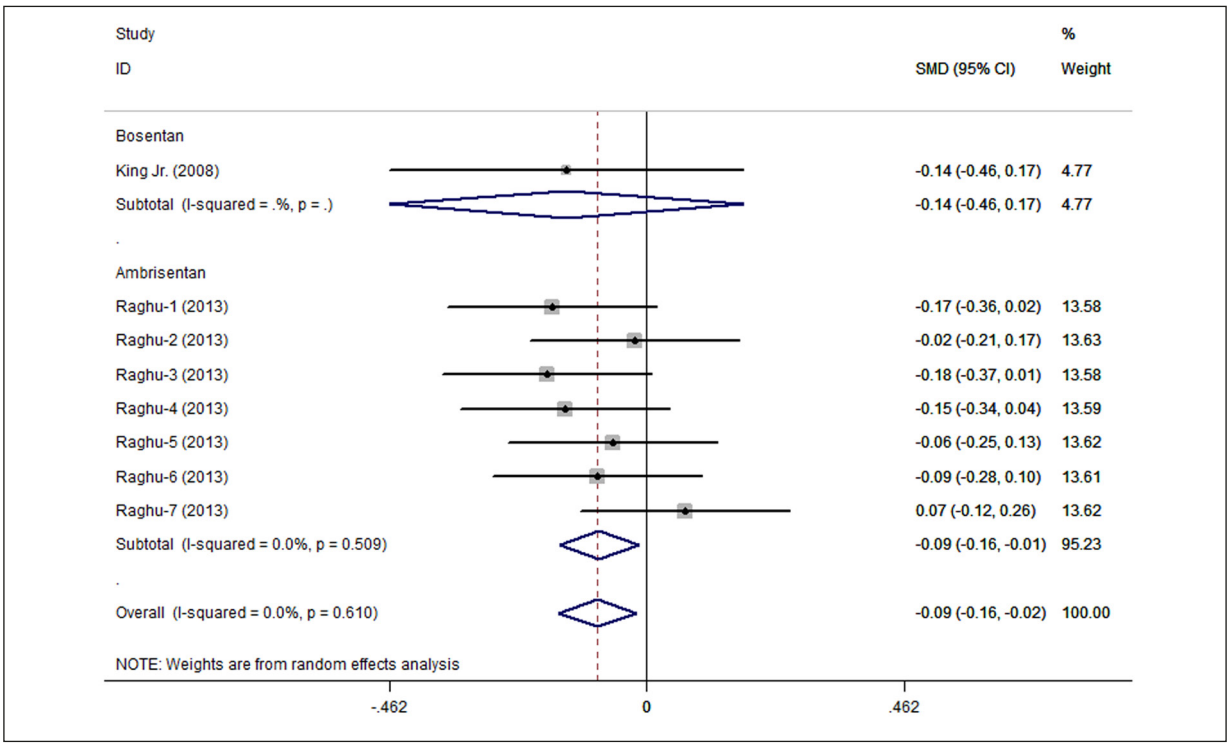

Figure 1. Forest plot comparing the 6MWD of groups treated with bosentan or ambrisentan *vs.* control. Left: favors the control. Right: favors the intervention. 6MWD, 6-minute walk distance. SMD, standardized mean difference.

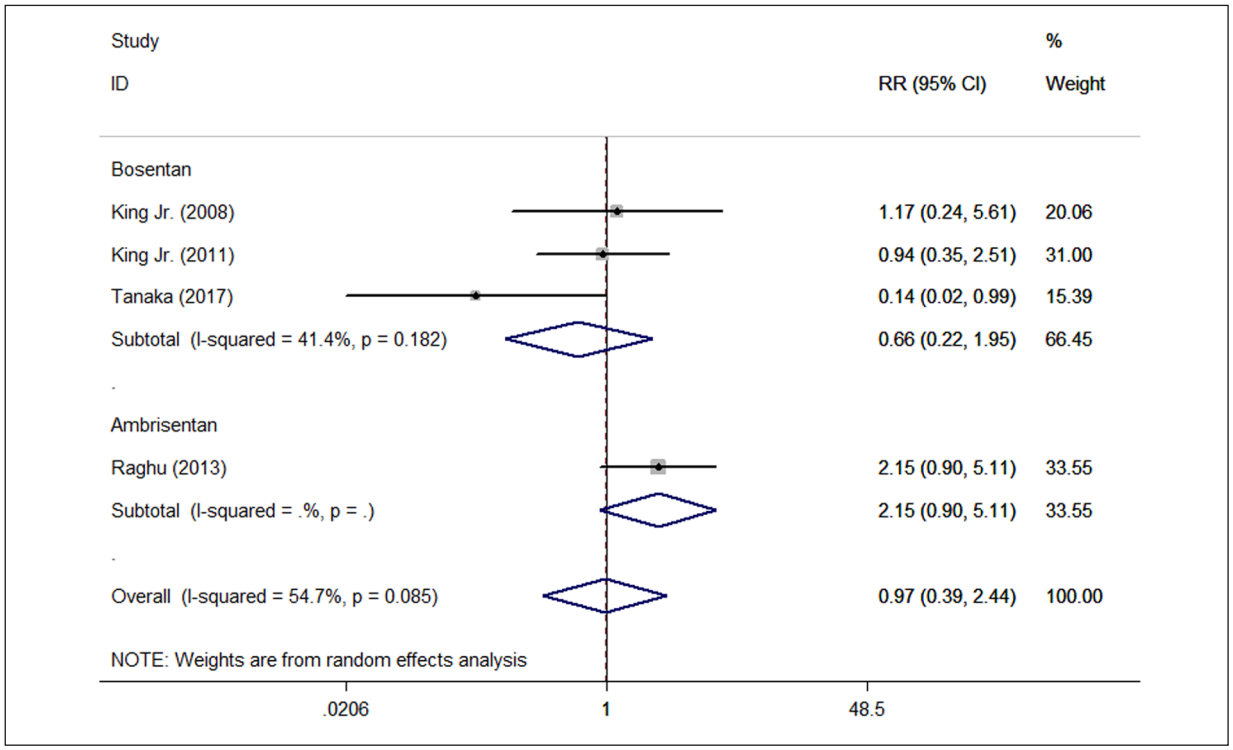

Figure 2. Forest plot comparing death of groups treated with bosentan or ambrisentan *vs*. control. Left: favors the intervention. Right: favors the control. RR, relative risk.

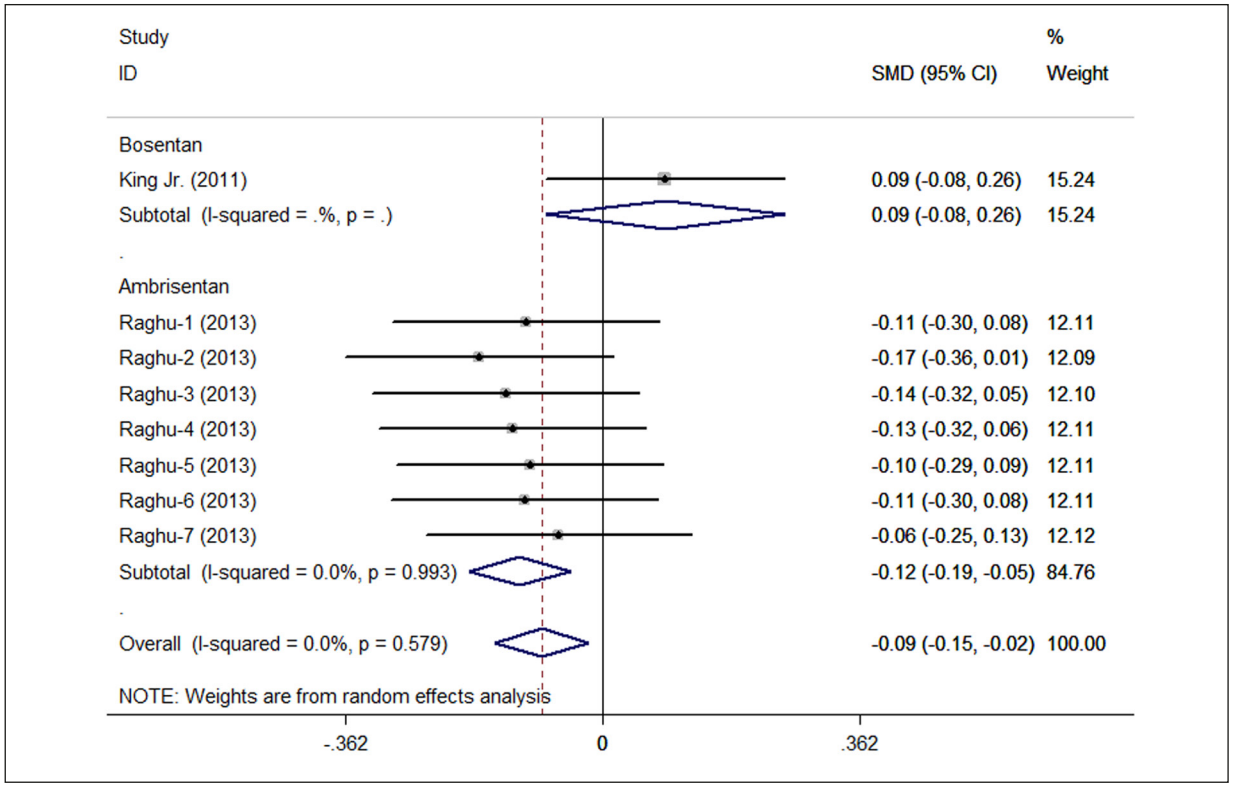

Figure 3. Forest plot comparing DLCO of groups treated with bosentan or ambrisentan *vs*. control. Left: favors the control. Right: favors the intervention. DLCO, diffusion capacity for carbon monoxide. SMD, standardized mean difference.

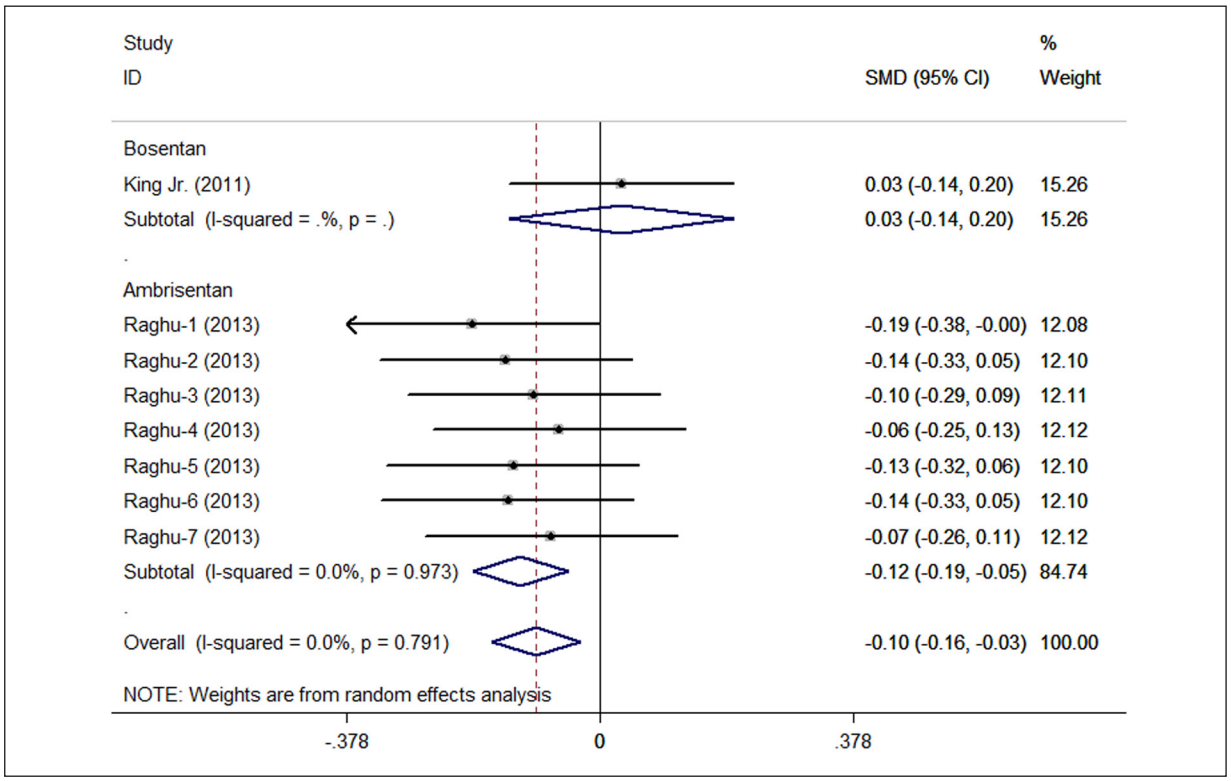

Figure 4. Forest plot comparing FVC of groups treated with bosentan or ambrisentan *vs.* control. Left: favors the control. Right: favors the intervention. FVC, forced vital capacity. SMD, standardized mean difference.

Hospitalization

A subgroup analysis was performed, taking into account the interventions used (2 studies[20,23], 516 participants). The rate of hospitalization in the bosentan group was markedly lower in comparison with the untreated group. The rate of hospitalization in the ambrisentan group was markedly greater in comparison with the placebo group (**Supplementary Figure 3**).

IPF worsening

Subgroup analysis was conducted using interventions in 4 studies[8,9,20,21] involving 1,416 participants. The occurrence of IPF worsening in the bosentan group was markedly less than in the placebo group. The rate of IPF worsening in the ambrisentan group was considerably greater in comparison with the placebo group. Moreover, there was no significant heterogeneity between studies (**Supplementary Figure 4**).

mPAP

A study[22] with 117 participants found no noteworthy difference in mPAP changes between the ambrisentan and placebo groups, as depicted in **Supplementary Figure 5**.

SAEs

A subgroup analysis was performed, taking into account the interventions used in 3 studies[8,9,20] involving 1,265 participants. The bosentan group and the placebo group showed no notable disparity in the likelihood of SAEs. The occurrence of SAEs did not differ notably between the ambrisentan group and the placebo group. Furthermore, there was no notable heterogeneity between studies (**Supplementary Figure 6**).

SF-36 improved

A study[8] involving 154 participants found no notable disparity in the rate of SF-36 improvement between patients in the ambrisentan and placebo groups (**Supplementary Figure 7**).

SGRQ

For subgroup analysis, we employed interventions in 2 studies[8,20] involving 391 participants. No notable disparity in SGRQ alterations was observed between the bosentan group and the placebo group. The ambrisentan group did not show any notable disparity in SGRQ changes when compared with the placebo group (**Supplementary Figure 8**).

Quality of Evidence

The evidence quality of all results was evaluated by the GRADE approach as shown below: 6MWD (high), death (high), DLCO (high), FVC (high), hospitalization (high), IPF worsening (high), mPAP (high), SAEs (high), SF-36 improved (high), and SGRQ (high) (**Supplementary Figure 9**).

Discussion

There is currently no effective treatment for IPF. A meta-analysis[24] found that pirfenidone significantly improved symptoms and mortality in patients with IPF compared with placebo, but significantly increased adverse reactions. Some clinical studies[3,8,9] have found that endothelin receptor antagonists (ETRAs) such as bosentan may be effective against IPF, but corresponding meta-analyses have been lacking to confirm this finding. Our study revealed that bosentan improved hospitalization rates and IPF exacerbations in patients with IPF, while ambrisentan worsened 6MWD, DLCO, FVC, hospitalization rates, and IPF exacerbations, both of which had no significant effect on SAEs and death. These results support bosentan as a treatment option to improve symptoms in patients with IPF, while ambrisentan is not recommended.

A network meta-analysis found no significant difference between 10 commonly used treatments for mortality and SAEs in patients with IPF compared with placebo. Among them, bosentan showed an improving trend in mortality and SAEs, while ambrisentan showed a worsening trend[25]. Our study included a new high-quality RCT that included patients with IPF combined with PH and compared bosentan with untreated patients[23]. Our study found that bosentan can significantly improve hospitalization rates and IPF exacerbations in patients with IPF without increasing death and SAEs, providing new evidence for the treatment of IPF. We also found that ambrisentan worsened symptoms in patients with IPF, further confirming previous findings.

We performed subgroup analyses based on intervention agents, reducing interstudy heterogeneity, and included research with a low risk of bias and high quality of evidence for outcomes, suggesting high confidence in the results. In our research, it was found that bosentan effectively enhanced symptoms in IPF patients without any SAEs; however, it did not have a positive impact on mortality rates. Hence, the clinical objective of enhancing the long-term outlook for individuals with IPF remains unchanged.

The shortcomings of this study include the following points. First, the number of studies that satisfied the inclusion criteria was small; most of them were bosentan studies[8,9,21,23], and part of the resulting data came from a single study[8,22]. Second, the bias risk of most studies[8,9,20-22] was low, and a single study[23] had an unknown risk of allocation concealment. Third, most of the studies[8,9,20-22] used a placebo as a control, while a single study[23] used no treatment as a control. Fourth, the treatment duration in the studies varied between 12 and 104 weeks, and the ideal intervention duration remained uncertain. Fifth, only one study[23] included all IPF patients with PH, and it is unclear whether bosentan and ambrisentan, as ETRAs, have better efficacy in these patients. Sixth, only one study[9] included IPF patients with SLB, and the diagnosis of IPF lacked histopathological evidence.

In spite of these limitations, our research suggests utilizing bosentan as a means to enhance clinical manifestations in individuals with IPF, while discouraging the usage of ambrisentan.

Conclusions

This research confirmed the effectiveness and safety of bosentan in improving symptoms (hospitalization and worsening of IPF) in sick persons with IPF (without increased death and SAEs) and confirmed the harmfulness of ambrisentan in such patients. The treatment of IPF requires more clinical evidence.

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Authors' Contributions

Xian-Ling Zhou conceived the idea for the study. Hua-Feng Li, Ji-Xu Wang, and Zhe-Fan Xie selected studies for inclusion and abstracted data. Lin-Hui Li, Bin Li, Fang-Fei Huang, and Jing Li performed the statistical analyses. Lin-Hui Li, Bin Li, Fang-Fei Huang, and Jing Li interpreted the data. Xian-Ling Zhou wrote the first draft. Hua-Feng Li, Ji-Xu Wang, and Zhe-Fan Xie critically revised the paper for important intellectual content. All authors approved the final draft.

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Conflict of Interest
The authors declare no conflicts of interest.

Data Availability
The data are available from the corresponding author upon reasonable request.

Informed Consent
Not applicable.

Ethics Approval
Not applicable.

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