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# Efficacy and Safety of Bisoprolol in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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**Purpose:** To evaluate the clinical efficacy and safety of bisoprolol in patients with chronic obstructive pulmonary disease (COPD).

**Research Methods:** This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statements. The primary outcome measures analyzed included: Pulmonary function(FEV1, FEV1%, FVC), 6-minute walking distance (6MWD), adverse events and inflammatory cytokines(IL-6, IL-8, CRP).

**Results:** Thirty-five studies were included with a total of 3269 study participants, including 1650 in the bisoprolol group and 1619 in the control group. The effect of bisoprolol on lung function in patients with COPD, $FEV_1$, MD (0.46 [95% CI, 0.27 to 0.65], P=0.000), $FEV_1$%, MD (−0.64 [95% CI, 0.42 to 0.86], P=0.000), FVC, MD (0.20 [95% CI, 0.05 to 0.34], P=0.008), the results all showed a statistically significant result. The effect of bisoprolol on 6MWD in COPD patients, MD (1.37 [95% CI, 1.08 to 1.66], P=0.000), which showed a statistically significant result. The occurrence of adverse events in COPD patients treated with bisoprolol, RR (0.83 [95% CI, 0.54 to 1.26], P=0.382), resulted in no statistical significance. The effect of bisoprolol on inflammatory cytokines in COPD patients, IL-6, MD (−1.16 [95% CI, −1.67 to −0.65], P=0.000), IL-8, MD (−0.94 [95% CI, −1.32 to −0.56], P=0.000), CRP, MD (−1.74 [95% CI, −2.40 to −1.09], P=0.000), the results were statistically significant. We performed a subgroup analysis of each outcome indicator according to whether the patients had heart failure or not, and the results showed that the therapeutic effect of bisoprolol on COPD did not change with the presence or absence of heart failure.

**Conclusion:** Bisoprolol is safe and effective in the treatment of COPD, improving lung function and exercise performance in patients with COPD, and also reducing inflammatory markers in patients with COPD, and this effect is independent of the presence or absence of heart failure.

**Keywords:** chronic obstructive pulmonary disease, bisoprolol, beta-blockers, meta-analysis

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic disease characterized by persistent airflow limitation.[1] Because of the exponential increase in morbidity and mortality, COPD affects approximately 384 million people worldwide and is considered the third leading cause of death worldwide.[2] The pathogenesis of COPD may be related to smoking, endothelial dysfunction, abnormalities in airway and alveolar structure and function, inflammation, and genetic factors.[3] It is well known that patients with chronic obstructive pulmonary disease (COPD) are prone to hypoxic pulmonary vasoconstriction, which may lead to pulmonary hypertension and pulmonary vascular remodeling, and ultimately right ventricular dilatation, resulting in right ventricular failure, which is the main cause of clinical deterioration and death.[4] In addition to right ventricular changes, up to 30% of patients with COPD suffer from systolic or diastolic left heart failure.[5] Notably, COPD exacerbations are now recognized as heterogeneous events with different underlying pathogenic mechanisms, including cardiac decompensation and thromboembolic events.[6,7] Up to one-third of deaths in patients with COPD can be attributed to cardiovascular disease, and it has been reported that the risk of

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cardiovascular death increases by 28% for every 10% reduction in FEV1.[8] Therefore, active prevention and treatment of exacerbations and concomitant cardiovascular disease in patients with COPD appears to be of paramount importance.

Bisoprolol is a type of selective beta-blockers (BBs) that is commonly used in the treatment of patients with cardiovascular diseases such as moderate or severe chronic stable heart failure, coronary artery disease and hypertension.[9–11] Studies have shown that the use of cardioselective beta blockers in patients with COPD has no significant adverse effects on FEV1, respiratory symptoms, or responsiveness to beta agonist inhalation therapy.[12] Several studies have shown that beta blockers reduce mortality by 28% and acute exacerbations by 37% in patients with COPD.[13–15] BBs may have a positive impact on COPD patients with cardiovascular disease (CVD) and even on those without CVD.[16,17], Additional studies suggest that selective β1-blockers, in particular bisoprolol as first choice, should be preferred in case of clinical and/or radiological signs of lung fluid accumulation.[18] Despite clear evidence of the efficiency of BBs, there is confusion due to contraindications and fear of inducing adverse effects and bronchospasm, as well as the difficulty in determining whether the benefits of the drug are related to coexisting cardiovascular disease.[19,20] There is a general hesitation to use BBs in patients with COPD,[21] but if not, they may lead to an increase in cardiovascular events in high-risk patients.[22] The results of a recent meta-analysis suggest that the use of cardioselective BBs in patients with COPD not only reduces their all-cause and in-hospital mortality rates, but even reduces the exacerbation of COPD.[23] The use of BBs and the optimal treatment regimen for BBs remains controversial despite the overwhelming evidence of their benefit in patients with COPD. And to the best of our knowledge, no review has been conducted to separately investigate the clinical efficacy and safety of bisoprolol in patients with COPD. In order to provide new evidence-based medical evidence for clinical treatment, the present study was the first to apply Meta-analysis to analyze the efficacy and safety of bisoprolol in COPD patients in combination.

# Methods

This systematic review and meta-analysis was registered at PROSPERO (http://www.crd.york.ac.uk/prospero; CRD: 42023411032).The study was designed as per the Cochrane Handbook for Systematic Reviews of Interventions[24] and reported according to the PRISMA guidelines.[25]

Search databases: PubMed, Web of science, Cochrane, CNKI and Wan Fang library databases. The date of searching the database was from the date of construction to June 10, 2023. The search combined subject and free terms: Pulmonary Disease, Chronic Obstructive, Bisoprolol. See Supplementary Data S1 for detailed search strategy.

## Literature Inclusion Exclusion Criteria

Inclusion criteria were as follows: (1) adults ≥40 years of age (2) meeting the diagnostic criteria for COPD (3) bisoprolol in the experimental group and placebo or conventional treatment in the control group (4) RCT studies (5) at least one data outcome available for extraction, (6) Chinese or English literature.

Exclusion criteria were as follows: (1) studies that researched animals or cells (2) studies that are conference abstracts, letters, editorials, reviews, and meta-analyses (3) incomplete or unavailable data for extraction.

## Data Extraction and Quality Assessment

Screening literature, We imported the retrieved literature into the ENDNOTE software, and two researchers independently reviewed the retrieved documents. Based on the inclusion and exclusion criteria, the documents were initially screened by reading the titles and abstracts, and then further screened by reading the full text. For trials that met the inclusion criteria, we extracted basic information from the articles, such as last name of the first author, year of publication, type of participant, sample size, drug dosage, control, outcome and duration of follow-up. Quality assessment was performed using the Cochrane risk of bias tool to assess the quality of the RCTs, including randomized sequence generation, allocation concealment, blinding of patients and interveners, blinding of outcome measures, incomplete outcome data, selective reporting, and other potential biases. Each item was rated as “low risk”, “high risk” or “unclear”. Any disagreements were resolved through discussion and arbitration in consultation with a third author.

## Data Analysis

Statistical analyses were performed using REVMAN 4.5 and STATA MP 17.0, binary variables were represented by risks ratio (RR), and continuous variables were represented by mean difference (MD), and all effect sizes were expressed as 95% confidence intervals (CI). Heterogeneity between the results of the included studies was analyzed using the I2 test. When the test of heterogeneity was $P \geq 0.05$ and $I2 < 50\%$, it was considered that multiple similar studies were homogeneous, and a fixed-effects model was used. Otherwise, a random-effects model was used. If the number of studies for quantitative analysis was more than 10, potential publication bias was assessed using funnel plots, Begg's test and Egger's test. Sensitivity analyses were performed by conducting each meta-analysis, excluding each study in turn. Sensitivity indicated the stability of the results.

# Results

## Study Retrieved and Characteristics

Initially, 299 related studies were examined, and after reading the titles and abstracts of the studies, they were screened according to the inclusion and exclusion criteria, and finally 35 qualified clinical studies were included,[26–60] with a total of 3269 subjects, including 1650 subjects in the bisoprolol group and 1619 subjects in the control group. The screening process is shown in Figure 1, and the basic characteristics of the included studies are shown in Table 1.

## Methodological Quality Evaluation

Of the 35 included RCT studies, 3 were in English and the rest were in Chinese.The method of generating randomized sequences was explicitly mentioned in 12 studies, of which 2 were blinded. Conventional treatment was used as the control group in 24 studies, phlegm chemotherapy tablets were given to the control group in 9 studies, placebo was given to the control group in 2 studies, and only conventional oxygen treatment was given to the control group in 1 study.No other risk of bias was identified in the results of any of the studies.Details are shown in Supplementary Figure S1.

## Primary Outcome

### $FEV_1$

Twenty-two studies[26,27,29–32,34,37–39,42,43,46,47,49,51,52,55,57–60] reported $FEV_1$, with a heterogeneity test result of I2=78.2%, P=0.000, and using a random-effects model, the results showed a statistically significant difference in MD (0.46 [95% CI, 0.27 to 0.65], P=0.000). Nine of the studies[26,29,31,38,39,47,52,59,60] included patients with COPD with heart failure, and 13 studies[27,30,32,34,37,42,43,46,49,51,55,57,58] included only patients with COPD alone, with which we performed subgroup analyses, and the results showed a statistically significant difference in MD (0.32 [95% CI, 0.07 to 0.56], P=0.011) in the COPD with heart failure group. MD in the COPD alone group (0.57 [95% CI, 0.29 to 0.85], P=0.000), a statistically significant result (Figure 2). It suggests that bisoprolol significantly improved patients' $FEV_1$ in patients with COPD, and this change was independent of the presence or absence of heart failure. Despite the large heterogeneity of the results, we performed a sensitivity analysis and excluding any of the studies, the experimental results were unchanged, suggesting that the results were stable (Supplementary Figure S2.1). Meanwhile, we analyzed the results by qualitatively analyzing the funnel plot (Figure 3) and quantitatively analyzing Begg's test (p=0.430, detailed figure in Supplementary Figure S2.2) and Egger's test (p=0.264, detailed figure in Supplementary Figure S2.3), the results showed no publication bias.

## Secondary Outcomes

### $FEV_1\%$

Fourteen studies[28,33–36,40,42–45,47–49,54] reported $FEV_1\%$, with a heterogeneity test result of I2=72.6%, P=0.000, and using a random-effects model, the results showed an MD (−0.64 [95% CI, 0.42 to 0.86], P=0.000), which showed a statistically significant difference. Nine of the studies[28,33,35,36,44,45,47,48,54] included patients with COPD with heart failure, and 5 studies[34,40,42,43,49] included only patients with COPD alone, and we used this as a subgroup, which showed a statistically significant result for the MD (−0.70 [95% CI, 0.33 to 1.06], P=0.000) in the COPD with heart failure group. MD (0.54 [95% CI, 0.37 to 0.70], P=0.000) in the COPD alone group, with a statistically significant result (Figure 4). It suggests

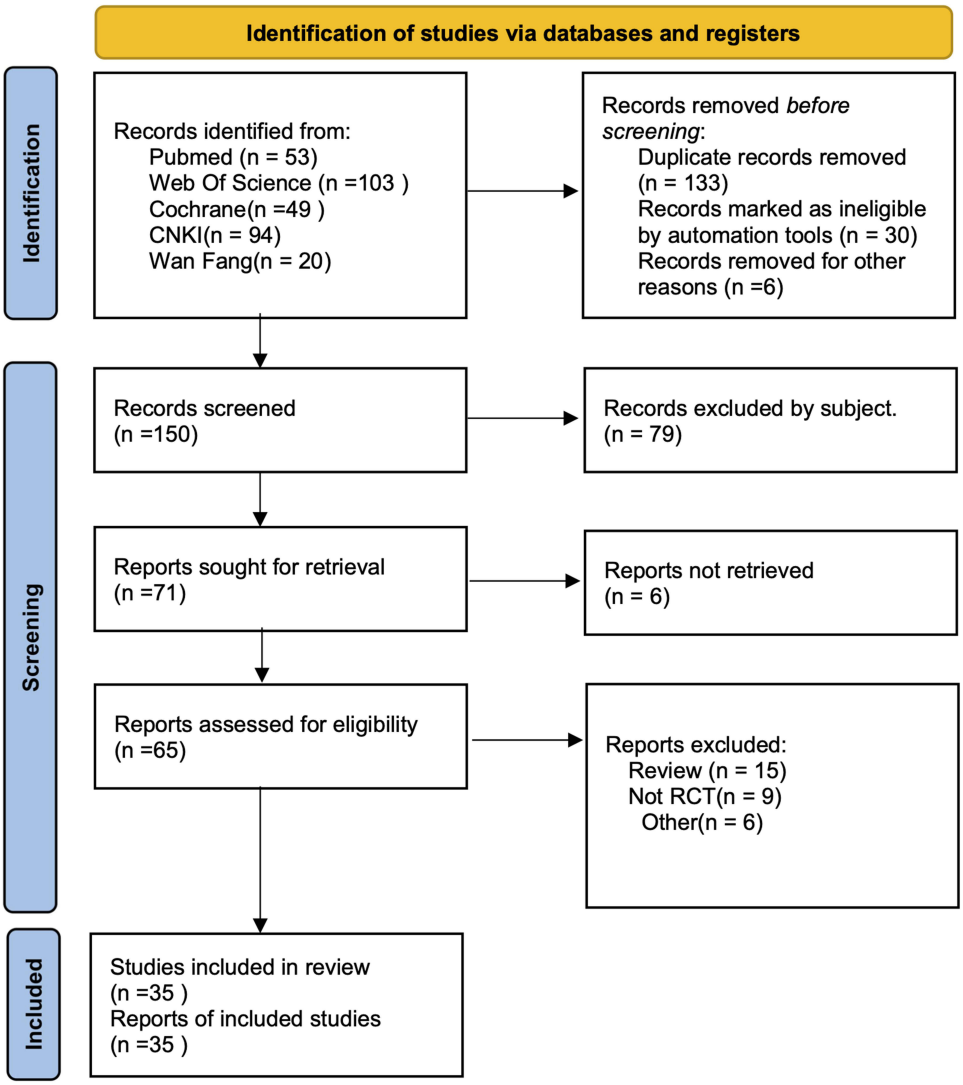


**Figure 1** PRISMA (preferred reporting items for systematic reviews and meta-analysis) flow diagram.
**Notes**: PRISMA figure adapted from Page MJ, Moher D, Bossuyt PM et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372. Creative Commons.[27]

that bisoprolol significantly improved patients' $FEV_1$% in patients with COPD, and this change was independent of the presence or absence of heart failure. However, there was a great deal of heterogeneity in the results, and according to the sensitivity analysis, excluding any of the studies, the experimental results were unchanged, suggesting that the results were stable (Supplementary Figure S3.1). Meanwhile, we analyzed the results by qualitatively analyzing the funnel plot (Figure 5) and quantitatively analyzing Begg's test (p=0.661, detailed figure in Supplementary Figure S3.2) and Egger's test (p=0.917, detailed figure in Supplementary Figure S3.3), which showed no publication bias.

## FVC

Ten studies[26,27,29–31,34,38,39,52,58] reported FVC, with a heterogeneity test result of I2=84.4%, P=0.000, and using a random-effects model, the results showed a statistically significant difference in MD (0.20 [95% CI, 0.05 to 0.34], P=0.008). Six of the studies[26,29,31,38,39,52] included patients with COPD with heart failure, and 4 studies[27,30,34,58] included only patients with COPD alone, we used this as a subgroup for our statistics, which showed a statistically significant result for the MD (0.10 [95% CI, 0.02 to 0.19], P=0.018) in the COPD with heart failure group. MD (0.46 [95% CI, 0.29 to 0.64], P=0.000) in the COPD alone group, with a statistically significant result (Figure 6). It suggests that bisoprolol improved patients' FVC in COPD patients, and the change was not related to the presence or absence of heart failure. According to the sensitivity

**Table 1** Characteristics of All Studies Included in Meta-Analysis

| Author Year | Methods | Intervention | | Sample Size | | Mean Age(Years) | | Duration | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | Treatment | Control | Treatment | Control | Treatment | Control | | |
| Lv ZY 2022[26] | RCT | Bisoprolol | Usual care | 60 | 60 | 69.65±3.35 | 70.75±3.25 | 8W | ②③④⑨ |
| Wu YM 2020[27] | RCT | Bisoprolol | Usual care | 32 | 33 | 64.25±8.26 | 64.89±9.39 | 14D | ②③④⑤⑨ |
| Liu GY 2019[28] | RCT | Bisoprolol | Usual care | 45 | 45 | 69.83±3.62 | 70.12±3.59 | 6M | ①④⑨ |
| Lv CX 2019[29] | RCT | Bisoprolol | Usual care | 44 | 44 | 62.7±2.1 | 62.3±2.6 | 6W | ②③⑤⑥⑦ |
| Zeng JW 2019[30] | RCT | Bisoprolol | Usual care | 30 | 30 | 65.68±2.71 | 65.21±2.78 | 6M | ②③⑨ |
| Yang LP 2019[31] | RCT | Bisoprolol | Usual care | 49 | 49 | 85.26±1.30 | 85.24±1.26 | 4W | ②③⑨ |
| Jin Y 2019[32] | RCT | Bisoprolol | Carbocisteine | 45 | 45 | 64.7±6.0 | 64.0±6.1 | 3M | ②④⑨ |
| Zhao MJ 2019[33] | RCT | Bisoprolol | Usual care | 35 | 35 | 72.26±5.29 | 71.98±5.47 | 3M | ①⑧ |
| Yi SP 2018[34] | RCT | Bisoprolol | Usual care | 49 | 49 | 61.89±6.74 | 61.35±6.14 | 1M | ①②③ |
| Yuan WS 2017[35] | RCT | Bisoprolol | Usual care | 25 | 25 | NA | NA | 4M | ①⑨ |
| Yang H 2017[36] | RCT | Bisoprolol | Usual care | 60 | 60 | NA | NA | 6M | ①④⑤⑥⑦⑨ |
| Wu B 2017[37] | RCT | Bisoprolol | Carbocisteine | 60 | 60 | 62.6±2.3 | 61.3±2.1 | 6M | ②⑤⑥⑦ |
| Ma L 2017[38] | RCT | Bisoprolol | Usual care | 40 | 40 | 58.7±9.6 | 59.2±9.4 | 24W | ②③④ |
| Zhou H 2017[39] | RCT | Bisoprolol | Usual care | 53 | 53 | 56±12 | 54±11 | 3M | ②③④ |
| Cai BQ 2017[40] | RCT | Bisoprolol | Carbocisteine | 49 | 49 | 56.5±7.6 | 57.0±6.9 | 3M | ①④⑧ |
| Hu ML 2016[41] | RCT | Bisoprolol | Carbocisteine | 82 | 82 | 59.4±8.8 | 60.1±8.8 | 12W | ⑤⑧ |
| Wang Y 2016[42] | RCT | Bisoprolol | Carbocisteine | 60 | 60 | 62.1±5.6 | 62.1±5.6 | 12W | ①②④⑥⑦ |
| Yang DL 2016[43] | RCT | Bisoprolol | Carbocisteine | 83 | 83 | 59.0±8.5 | 60.4±8.7 | 3M | ①②④⑤⑥⑦⑧⑨ |
| Hong SD 2016[44] | RCT | Bisoprolol | Usual care | 43 | 43 | 80.6±3.9 | 80.5±3.6 | 6M | ①⑨ |
| Zhou ZH 2016[45] | RCT | Bisoprolol | Usual care | 42 | 42 | 83.75±2.32 | 83.26±2.24 | NA | ① |
| Hu X 2016[46] | RCT | Bisoprolol | Carbocisteine | 50 | 50 | 63. 4 ± 1. 8 | 63. 2 ± 1. 6 | 6M | ②⑤ |
| Jiang X 2016[47] | RCT | Bisoprolol | Usual care | 52 | 52 | 65.8±7.4 | 65.4±7.7 | 3M | ①②④ |
| Fang Y 2015[48] | RCT | Bisoprolol | Usual care | 25 | 25 | 85.1±2.3 | 87.6±3.1 | 5M | ① |
| Xiong JM 2015[49] | RCT | Bisoprolol | Usual care | 51 | 52 | 65.2±7.5 | 67.5±7.9 | 8W | ①②④⑥⑦⑨ |
| Du JW 2015[50] | RCT | Bisoprolol | Carbocisteine | 72 | 72 | 59.7±8.7 | 60.3±8.3 | 12W | ⑤⑨ |
| Li X 2015[51] | RCT | Bisoprolol | Carbocisteine | 61 | 61 | NA | NA | 1M | ②⑤ |
| Peng HS 2015[52] | RCT | Bisoprolol | Usual care | 80 | 80 | NA | NA | 10M | ②③④⑧ |
| Zhang GF2014[53] | RCT | Bisoprolol | Usual care | 24 | 24 | 66.19±5.80 | 66.17±5.26 | 16W | ⑨ |
| Yuan WS 2012[54] | RCT | Bisoprolol | Usual care | 29 | 29 | 66.37±5.32 | 64.37±4.28 | 12W | ①④⑧ |
| Zhang LN2012[55] | RCT | Bisoprolol | Carbocisteine | 59 | 35 | 61.3±9.2 | 60.8±10.3 | 1M | ②⑤ |
| Yu Y 2011[56] | RCT | Bisoprolol | Usual care | 30 | 30 | 72.33 | 71.66 | 16W | ⑨ |
| Pei Y 2007[57] | RCT | Bisoprolol | Usual care | 30 | 22 | 53–72 | 50–70 | 1Y | ② |

(*Continued*)

**Table 1** (Continued).

| Author Year | Methods | Intervention | | Sample Size | | Mean Age(Years) | | Duration | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | Treatment | Control | Treatment | Control | Treatment | Control | | |
| Mainguy V2012[58] | RCT | Bisoprolol | Placebo | 27 | 27 | NA | NA | 14D | ②③ |
| Hawkins NM2009[59] | RCT | Bisoprolol | Placebo | 14 | 13 | 72.8 ± 7.4 | 68.7 ± 10.6 | 4M | ② |
| Ke YY 2016[60] | RCT | Bisoprolol | Usual care | 60 | 60 | 63.2(45–77) | 65.7(41–83) | 3M | ② |

**Notes**: Outcomes:①$FEV_1$%②$FEV_1$③FVC④ $FEV_1$/FVC ⑤CRP ⑥ IL-6 ⑦IL-8⑧6WMN⑨adverse events.
**Abbreviations**: RCT, randomized controlled trial; NA, not applicable; Y, year; M, month; W, week; D, day.

analysis, excluding any of the studies, the experimental results were unchanged, suggesting that the results were stable (Supplementary Figure S4.1). Meanwhile, we analyzed the results by qualitatively analyzing the funnel plot (Figure 7) and quantitatively analyzing Begg's test (p=0.721, detailed figure in Supplementary Figure S4.2)) and Egger's test (p=0.740, detailed figure in Supplementary Figure S4.3), the results indicate that there is no publication bias.

### 6MWD

Six studies[33,40,41,43,52,54] reported the results of 6MWD, with a test of heterogeneity of I2=66.0%, P=0.012, and using a random-effects model, the results showed a statistically significant result of MD (1.37 [95% CI, 1.08 to 1.66], P=0.000), the result was statistically significant. Three of the studies[33,52,54] included patients with COPD with heart failure, and three studies[40,41,43] included only patients with COPD alone, and we performed statistics with this subgroup, which showed a statistically significant result with MD (1.05 [95% CI, 0.80 to 1.30], P=0.000) in the COPD with heart failure group. MD (1.65 [95% CI, 1.43 to 1.87], P=0.000) in the COPD alone group, with statistically significant results (Figure 8). It suggests that bisoprolol significantly improves motor function in patients with COPD, and this change is independent of the presence or absence of heart failure. According to the sensitivity analysis, excluding any of the studies, the experimental results were unchanged, suggesting that the results were stable (Supplementary Figure S5).

## Adverse Events

Fourteen studies[26–28,30–32,35,36,43,44,49,50,53,56] reported adverse events, with a heterogeneity test result of I2=24.9%, P=0.207, and using a fixed-effects model, the results showed an RR (0.83 [95% CI, 0.54 to 1.26], P=0.382), which showed no statistically significant difference. Eight of the studies[26,28,31,35,36,44,53,56] included patients with COPD with heart failure, and 6 studies[27,30,32,43,49,50] included only patients with COPD alone, and we modeled this as a subgroup, which showed RR (0.77 [95% CI, 0.47 to 1.27], P=0.315) in the COPD with heart failure group, which showed no statistically significant results. RR in the COPD alone group (0.97 [95% CI, 0.44 to 2.13], P=0.944), the result was not statistically significant (Figure 9). It suggests that the use of bisoprolol to treat COPD patients is safe and reliable. Sensitivity analysis suggested that the results were stable (Supplementary Figure S6).

### IL-6

Six studies[29,36,37,42,43,49] reported results for IL-6, with a heterogeneity test result of I2=90.0%, P=0.000, and using a random-effects model, the results showed a statistically significant result for MD (−1.16 [95% CI, −1.67 to −0.65], P=0.000), results. Two of the studies[29,36] included patients with COPD with heart failure, and 4 studies[37,42,43,49] included only patients with COPD alone, and we used this as a subgroup for our statistics, which showed a statistically significant result for the MD (−1.93 [95% CI, −3.31 to −0.56], P=0.006) in the COPD with heart failure group. MD (−0.78 [95% CI, −0.96 to −0.60], P=0.000) in the COPD alone group, with statistically significant results (Figure 10). It suggests that bisoprolol significantly reduced the inflammatory marker IL-6 in COPD patients, and this change was not related to the presence or absence of heart failure. According to the sensitivity analysis, there was a large heterogeneity in the results of Yang2017, and the exclusion of that study left the experimental results unchanged, suggesting that the study might be a source of heterogeneity but had little effect on the final experimental results (Supplementary Figure S7).

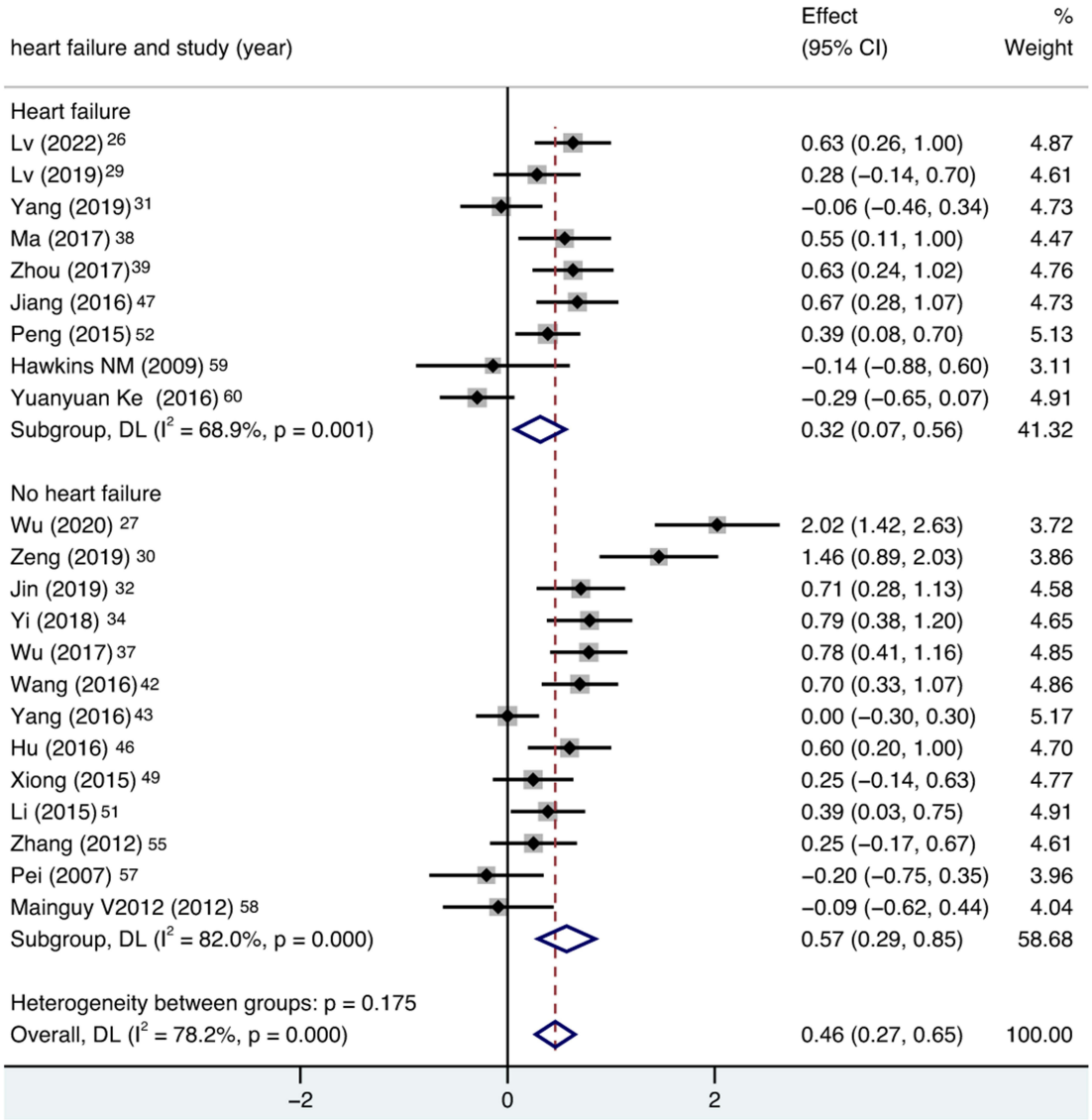


**Figure 2** Forest plot of $FEV_1$, subgroup analysis was performed according to variable of heart failure and no heart failure.

## IL-8

Six studies[29,36,37,42,43,49] reported the results of IL-8, with a heterogeneity test result of I2=83.1%, P=0.000, and using a random-effects model, the results showed a statistically significant result of MD (−0.94 [95% CI, −1.32 to −0.56], P=0.000), results. Two of the studies[29,36] included patients with COPD with heart failure, and 4 studies[37,42,43,49] included only patients with COPD alone, and we used this as a subgroup for our statistics, which showed a statistically significant result for the MD (−1.43 [95% CI, −1.74 to −1.13], P=0.000) in the COPD with heart failure group, MD (−0.71 [95% CI, −1.10 to −0.32], P=0.000) in the COPD alone group, with statistically significant results (Figure 11). It suggests that bisoprolol significantly reduced the inflammatory marker IL-8 in patients with COPD, and this change was not associated with the presence or absence of heart failure. According to the sensitivity analysis, excluding any of the studies, the experimental results were unchanged, suggesting that the results were stable (Supplementary Figure S8).

## CRP

Ten studies[27,29,36,37,41,43,46,50,51,55] reported the results of CRP, and the test of heterogeneity resulted in a statistically significant result of I2=95.5%, P=0.000, using a random-effects model, which showed an MD (−1.74 [95% CI, −2.40 to −1.09], P=0.000), result. Two of the studies[27,36] included patients with COPD with heart failure, and 8

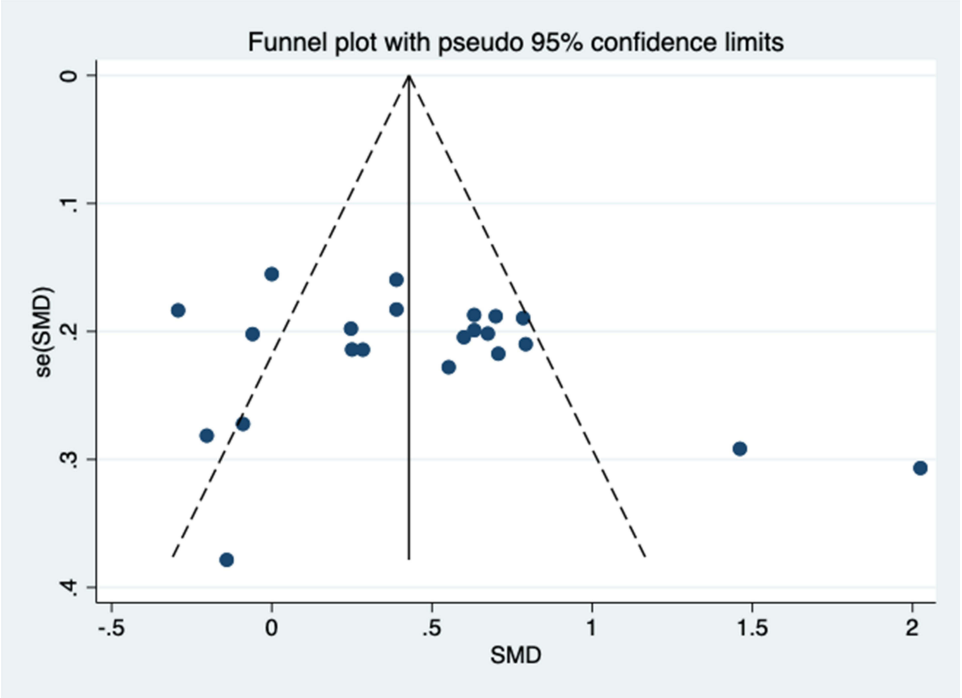


**Figure 3** Funnel plot of $FEV_1$.

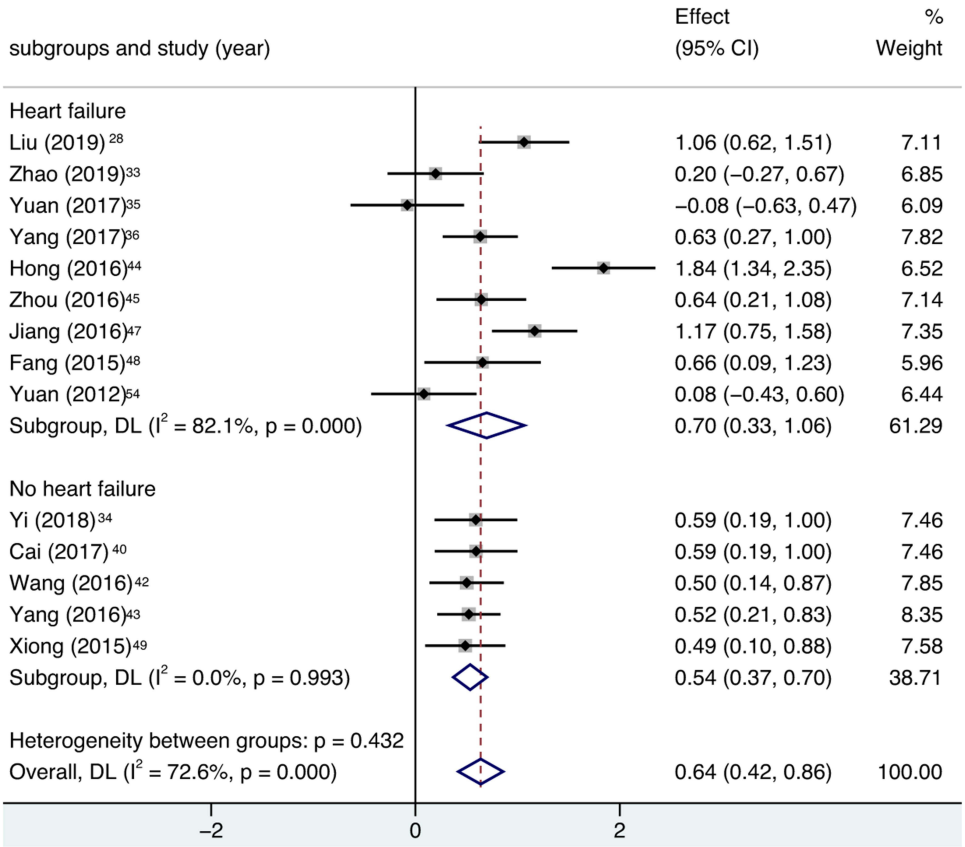


**Figure 4** Forest plot of $FEV_1$%, subgroup analysis was performed according to variable of heart failure and no heart failure.

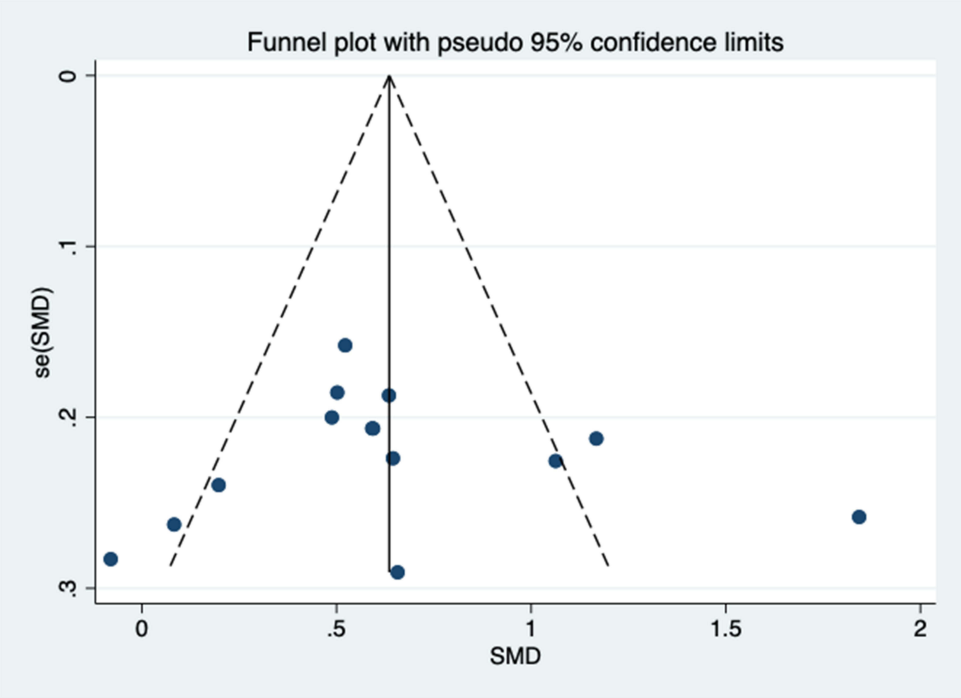


**Figure 5** Funnel plot of $FEV_1$%.

studies[27,37,41,43,46,50,51,55] included only patients with COPD alone, and we used this as a subgroup for our statistics, which showed a statistically significant result for the MD (−1.53 [95% CI, −1.84 to −1.22], P=0.000) in the COPD with heart failure group, MD (−1.80 [95% CI, −2.63 to −0.97], P=0.000) in the COPD alone group, with statistically significant results (Figure 12). It indicated that bisoprolol significantly reduced CRP, an indicator of inflammation, in patients with COPD, and this change was not related to the presence or absence of heart failure. According to the sensitivity analysis, there was a large heterogeneity in the results of Yang2016, and the experimental results were unchanged by excluding that study, suggesting that the study might be a source of heterogeneity but had little effect on the final experimental results (Supplementary Figure S9.1). Meanwhile, we analyzed the results by qualitatively analyzing the funnel plot (Figure 13) and quantitatively analyzing the Begg's test (p=0.107, see Supplementary Figure S9.2 for detailed figure)) and Egger's test (p=0.114, see Supplementary Figure S9.3), the results indicate that there is no publication bias.

## Discussion

The mechanistic link between chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) is complex, multifactorial, and not fully understood. Patients with COPD often suffer from hypoxemia and hypercapnia, and when the patient's blood carbon dioxide concentration is too high, it stimulates the chemoreceptors in the body, causing sympathetic excitation, accelerated heart rate, and increased oxygen consumption of the myocardium, which aggravates the patient's symptoms of chest tightness and shortness of breath.[61,62] COPD patients with limited motor function and reduced cardiac functional reserve significantly increase the risk of cardiovascular events in patients. It has been shown that cardiovascular mortality is reduced in COPD patients with heart rate <75 bpm compared to those with heart rate ≥75, and that elevated resting heart rate severely affects their prognosis and has emerged as an independent risk factor for their cardiovascular events.[63] Bisoprolol is a highly selective β1-AR blocker with a selectivity for β1/β2 receptors of approximately 14:1,[64] preventing the effects of the endogenous catecholamines epinephrine and norepinephrine. It can have an inhibitory effect on the sympathetic nerves of the body, which can effectively reduce the heart rate of the patients, thus improving their left ventricular compliance, decreasing myocardial contractility and cardiac afterload, decreasing myocardial oxygen consumption and preventing ventricular remodeling, which leads to an

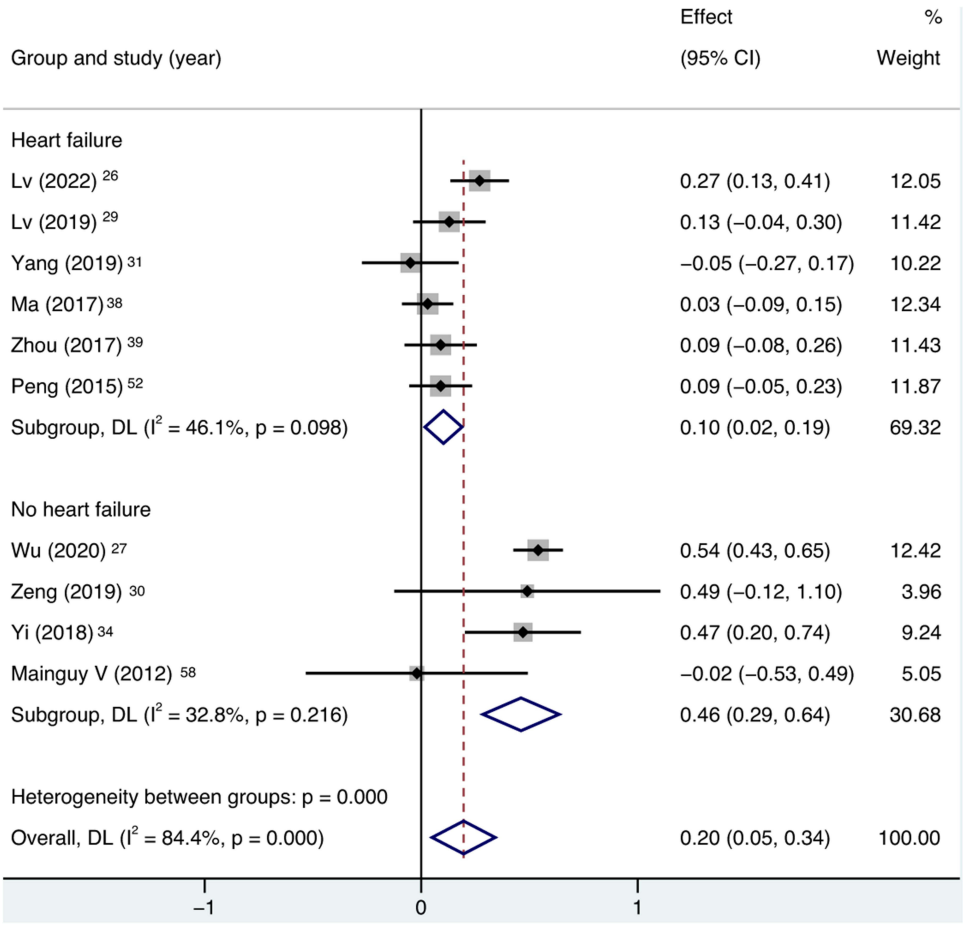


**Figure 6** Forest plot of FVC, subgroup analysis was performed according to variable of heart failure and no heart failure.

improvement in the patients' blood rheology. At the same time, the regulation of cellular immunity is enhanced, and studies have shown that long-term administration of BBs can reduce inflammation and pulmonary mucus secretion, can inhibit neutrophil chemotaxis and oxygen free radical production, reduce the cuprocyte and mucin content of airway epithelium, reduce cytokine levels, and reduce the release of endothelin-1 in human endothelial cells with bronchoconstrictor effects to slow down the deterioration of COPD.[65–68] At the same time, BBs reduce airway hyperresponsiveness, and long-term use of BBs also modulates β2-AR levels in the lungs, thereby improving the effects of bronchodilators in mice, probably because β1 blockers can play a complementary role by sensitizing β2 receptors to β2 agonists.[69,70] In conclusion, treatment of COPD patients with BBs not only benefits from improved blood rheology, but may also produce beneficial effects through anti-inflammatory activity and bronchoprotection.

Our meta-analysis showed that bisoprolol significantly improved lung function ($FEV_1$, $FEV_1$%, FVC) and exercise performance (6WMD) in patients with COPD, and the improvement was independent of whether or not there was concomitant cardiac disease, suggesting that the efficacy of bisoprolol in the treatment of patients with COPD not only benefited from the improvement in cardiac function, but also was beneficial for COPD itself. This may benefit from the multiple actions of bisoprolol, which not only improves cardiac function and reduces cardiac load and oxygen consumption in COPD patients, but also reduces airway hyperresponsiveness in COPD patients and improves the efficacy of bronchodilators, which relieves airflow obstruction. In the analysis of inflammatory factors, bisoprolol can significantly reduce IL-6, IL-8, CRP in COPD patients, and this efficacy is also independent of whether or not it is accompanied by cardiac disease, probably because bisoprolol itself has certain anti-inflammatory effects, reduces the secretion of pulmonary mucus, and can inhibit the neutrophil chemotaxis and the production of oxygen free radicals, and reduces the content of cuprocytes and mucins in the airway epithelium and lowers the level of cytokine levels.[65–68] In the

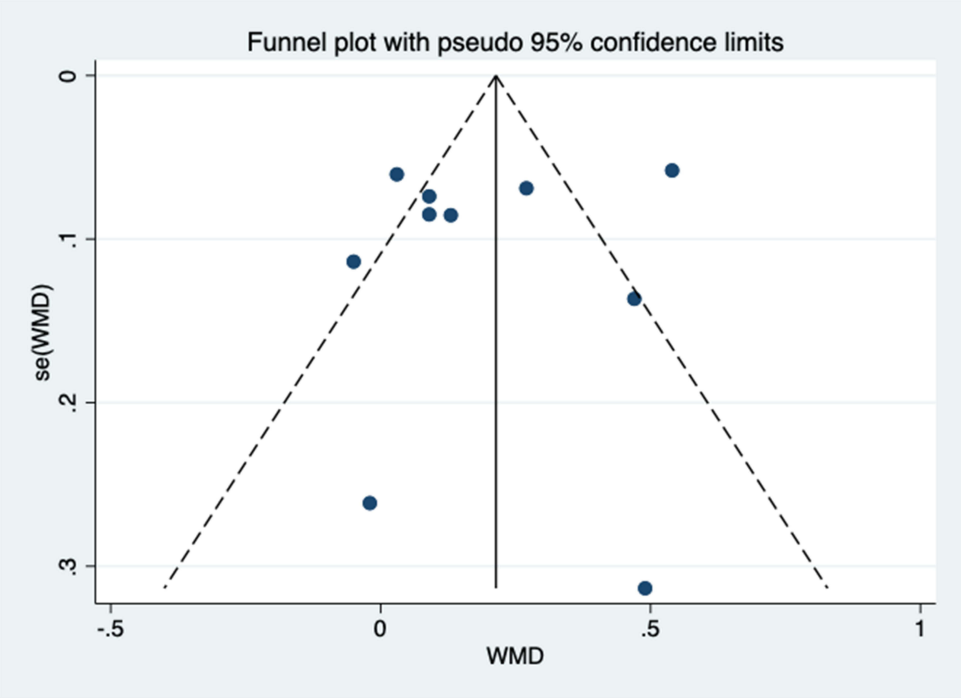


**Figure 7** Funnel plot of FVC.

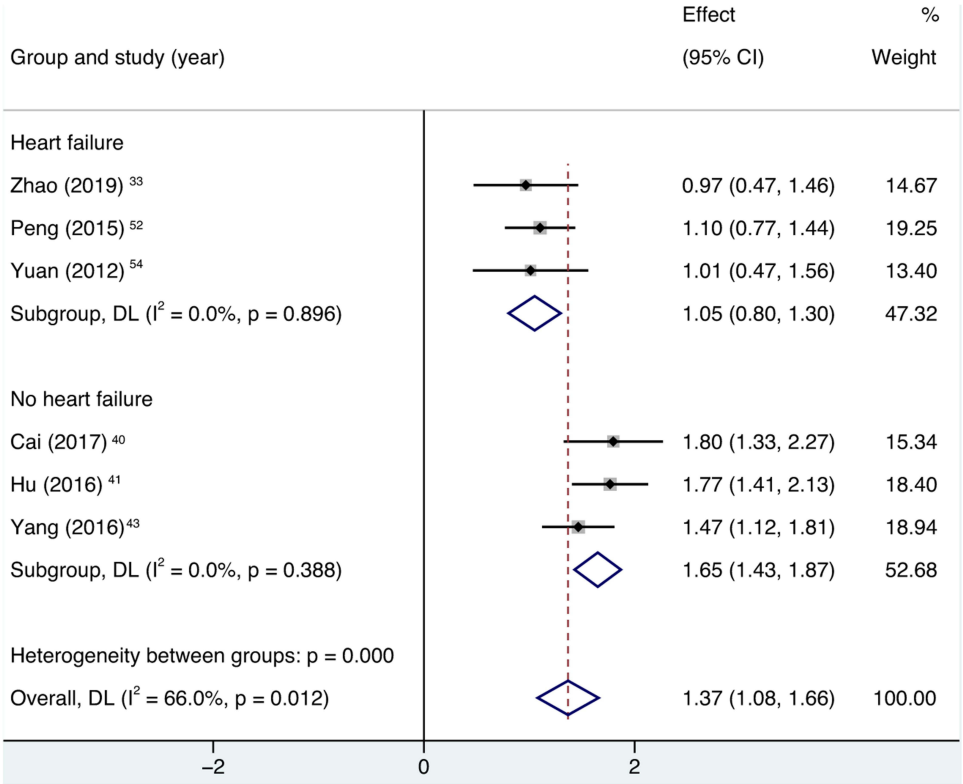


**Figure 8** Forest plot of 6-minute walking distance (6MWD), subgroup analysis was performed according to variable of heart failure and no heart failure.

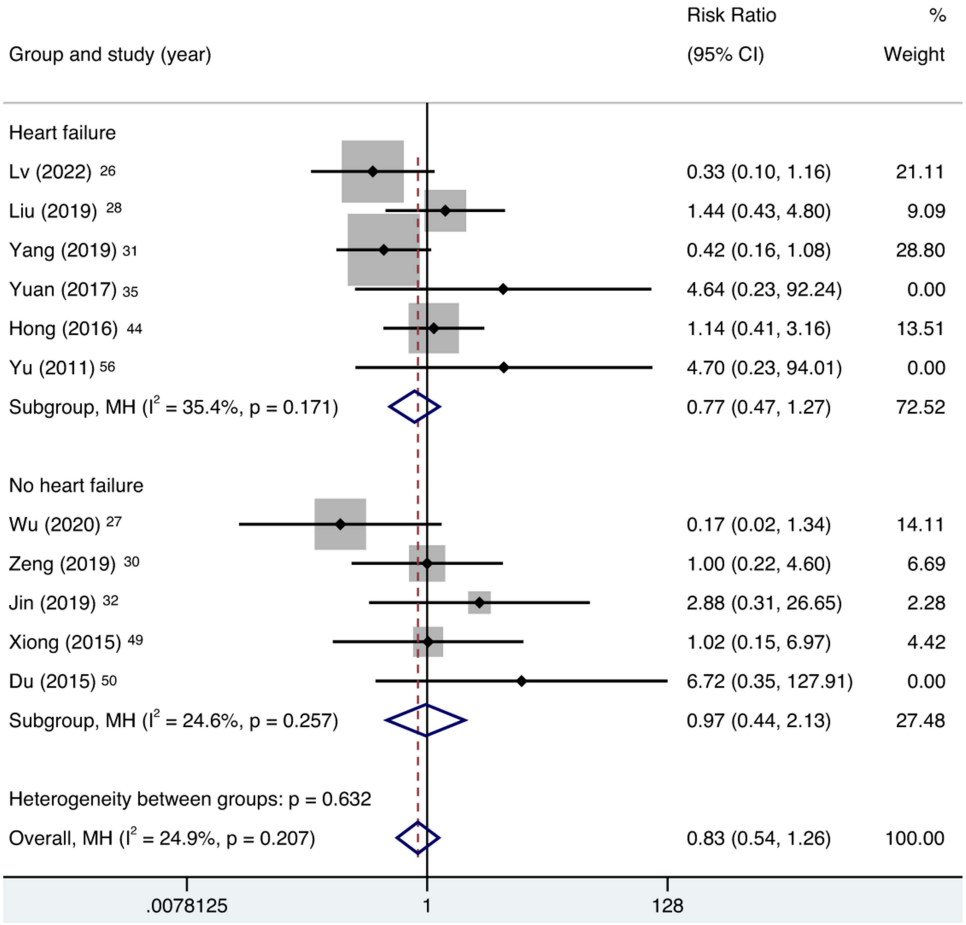


**Figure 9** Forest plot of adverse events, subgroup analysis was performed according to variable of heart failure and no heart failure.

safety analysis, there was no significant difference between the use of bisoprolol and no bisoprolol, suggesting that bisoprolol is safe and reliable for patients with COPD. Despite the great heterogeneity of most of the outcome indicators, through our analysis of the data, we still believe that the results have a certain stability and reliability. At the same time, by carefully reading and comparing the original studies and reviewing the relevant literature, we found that there are still some difficulties in the diagnosis and treatment of COPD. According to the GOLD reporting criteria, a total of 22.7% of patients hospitalized and treated for COPD had no evidence of COPD. Some studies recommend the use of the individual lower limit of normal (LLN), instead of the GOLD classification, to define COPD and prevent overdiagnosis of COPD.[71,72] Heart failure and chronic obstructive lung disease share common risk factors and pathophysiologic mechanisms, and HF itself causes a reduction in $FEV_1$ and FVC of about 20%, therefore, sometimes, it is impossible to determine whether these are COPD, HF, or both.[73] The studies we included were all conducted with the addition of bisoprolol to conventional therapy, which is administered as needed and has a great deal of heterogeneity, including treatments such as cardiotonic, diuretic, vasodilator, phlegmolytic, and bronchodilator agents, and even the use of antibiotics. And the use of these drugs and their interactions may have an unexpected impact on the experimental results.

In conclusion, the available evidence suggests that bisoprolol is safe and effective for the treatment of patients with COPD, and that this efficacy is not only effective in patients with COPD with heart failure, but also in patients without heart failure, and that the early use of bisoprolol may have a positive prognostic impact in patients with COPD. Two RCTs evaluating the effect of bisoprolol on the rate of deterioration and prevention of cardiovascular events in patients with COPD are ongoing (ISRCTN10497306, NCT03917914), and more evidence of bisoprolol for COPD will be provided in the future.

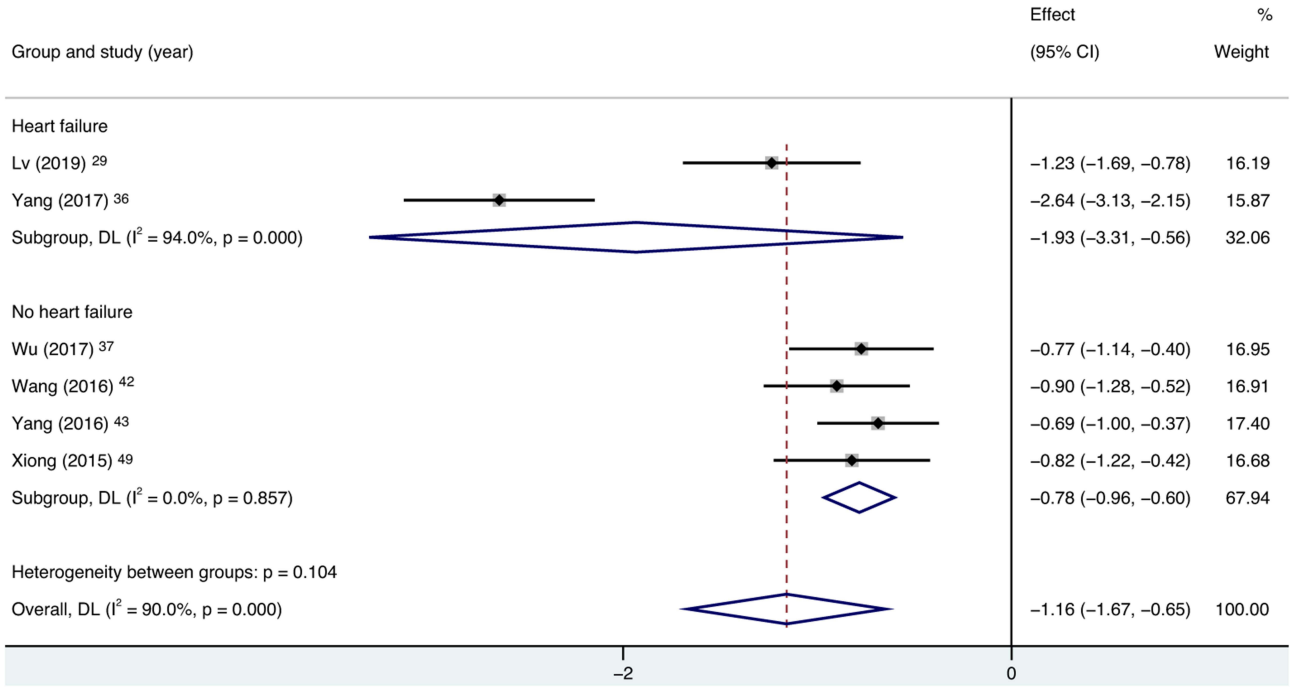


**Figure 10** Forest plot of IL-6, subgroup analysis was performed according to variable of heart failure and no heart failure.

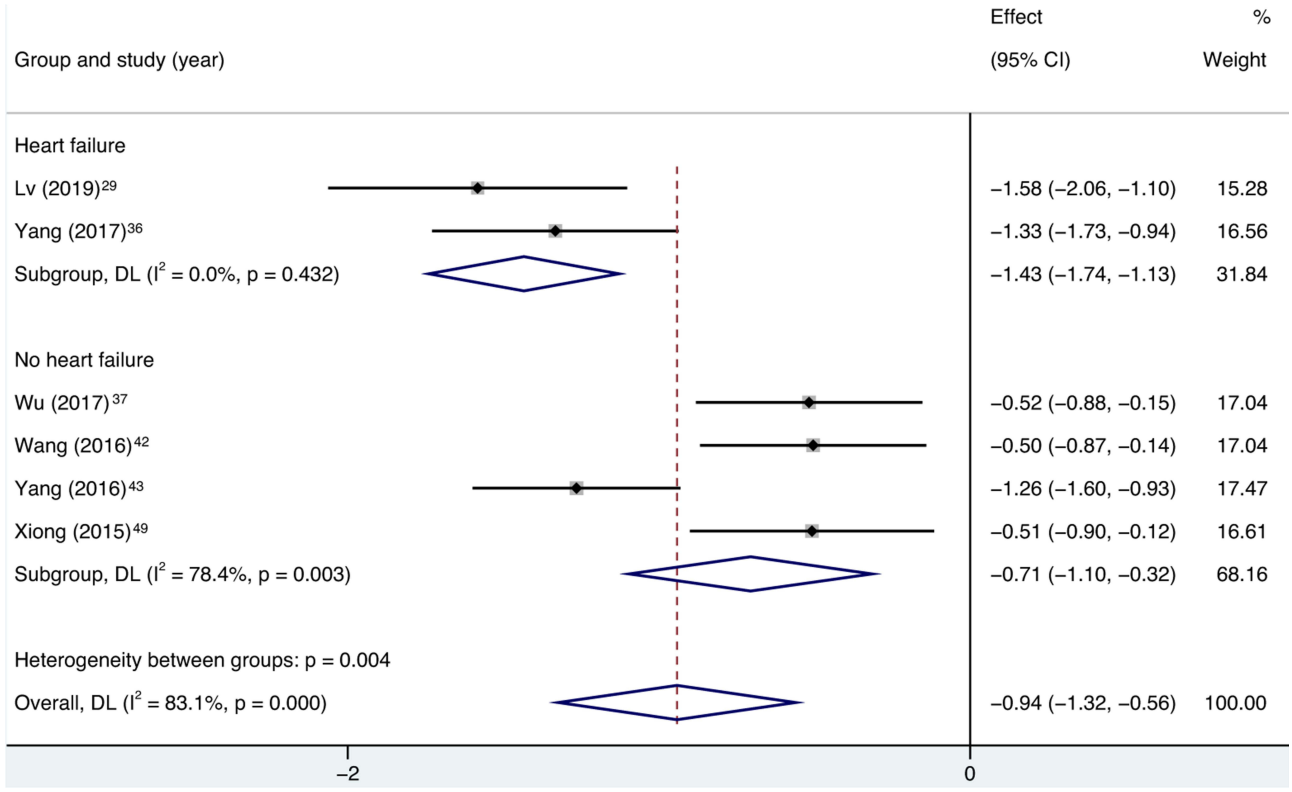


**Figure 11** Forest plot of IL-8, subgroup analysis was performed according to variable of heart failure and no heart failure.

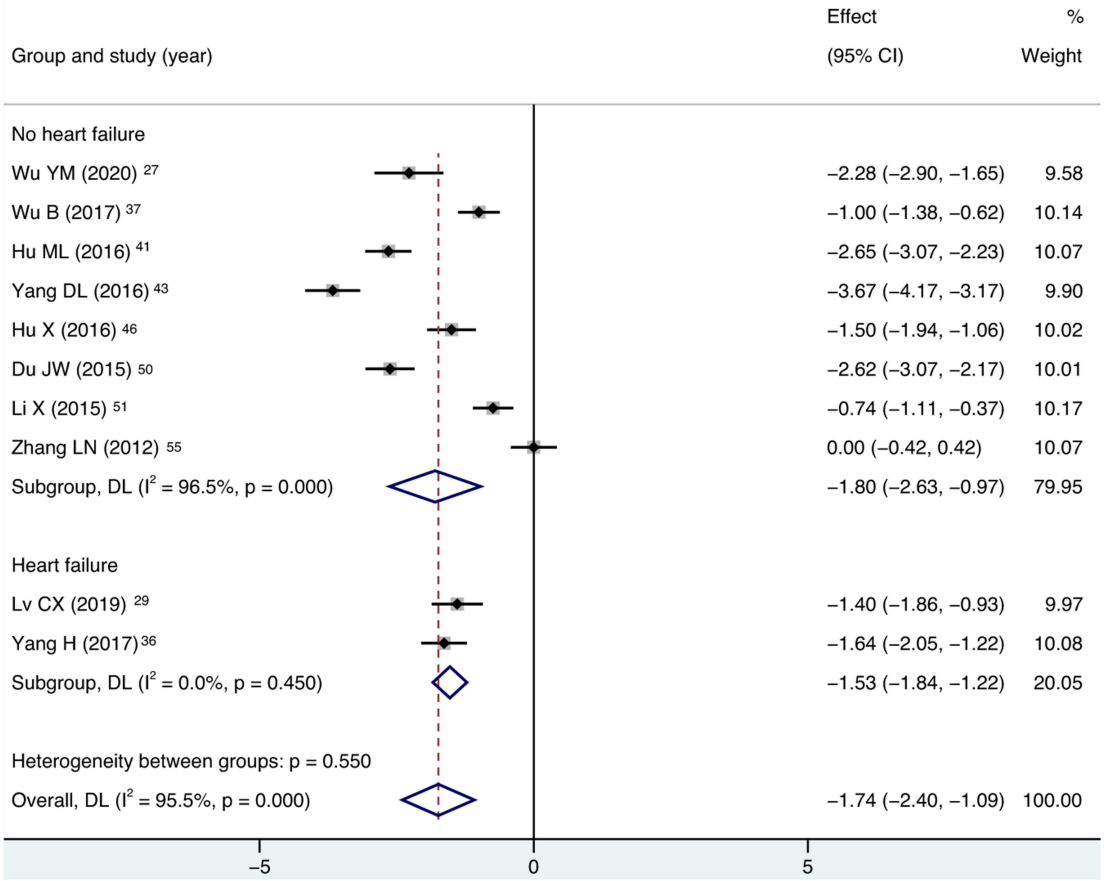


**Figure 12** Forest plot of CRP, subgroup analysis was performed according to variable of heart failure and no heart failure.

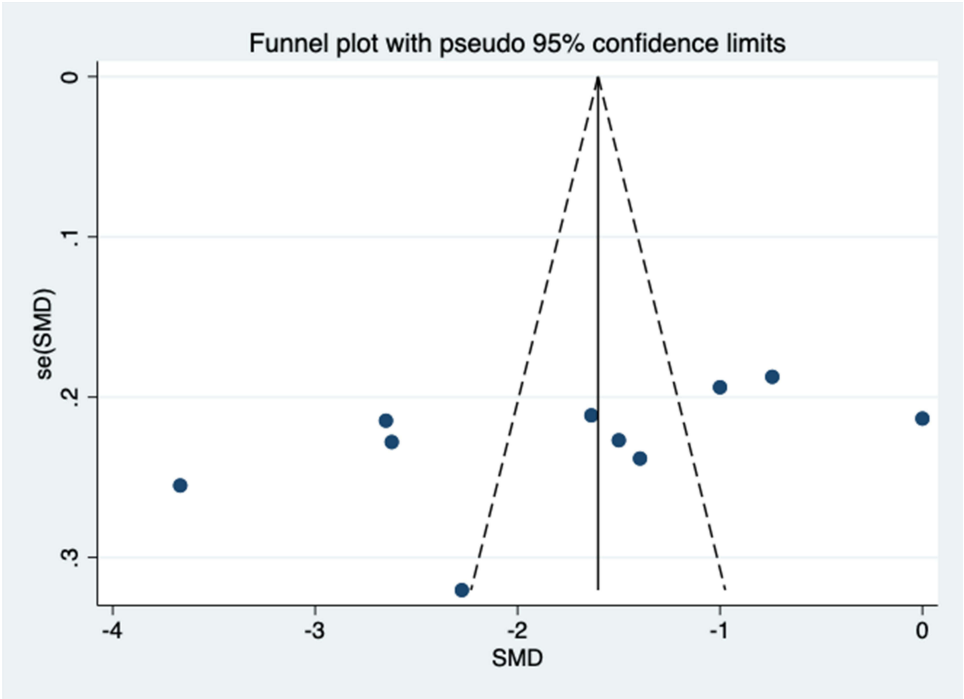


**Figure 13** Funnel plot of CRP.

## Limitations

This study provides a comprehensive meta-analysis of bisoprolol in the treatment of COPD, which is clinically instructive, but there are still some limitations, including: 1. Although we only included RCT studies, the quality of all the included literature varied, and the overall quality was not very high. 2. All the literature was not blinded, probably because the pharmacological effects of bisoprolol significantly reduced the heart rate of the patients. There is some difficulty in adopting the blinding method. 3. Most of the included literature was from China, and there may be regional differences in the population.

## Conclusion

Based on the available evidence, the results of our meta-analysis showed that bisoprolol significantly improved pulmonary function, motor function, and inflammatory factors in COPD patients, and the improvement was independent of the presence or absence of concomitant cardiac disease, suggesting that bisoprolol is effective and safe for COPD patients.

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## Disclosure

There are no other conflicts of interest in this work.

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