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**CLINICAL RESEARCH**
*Heart failure*

# Association of β-blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis

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**Aims** The aim of this study was to clarify the effect of β-blockers (BBs) on respiratory function and survival in patients with chronic obstructive pulmonary disease with cardiovascular disease (CVD), as well as the difference between the effects of cardioselective and noncardioselective BBs.

**Methods and results** We searched for relevant literature in four electronic databases, namely, PubMed, EMBASE, Cochrane Library, and Web of Science, and compared the differences in various survival indicators between patients with chronic obstructive pulmonary disease taking BBs and those not taking BBs. Forty-nine studies were included, with a total sample size of 670 594. Among these, 12 studies were randomized controlled trials (RCTs; seven crossover and five parallel RCTs) and 37 studies were observational (including four *post hoc* analyses of data from RCTs). The hazard ratios (HRs) of chronic obstructive pulmonary disease exacerbation between patients with chronic obstructive pulmonary disease who were not treated with BBs and those who were treated with BBs, cardioselective BBs, and noncardioselective BBs were 0.77 [95% confidence interval (CI) 0.67, 0.89], 0.72 [95% CI 0.56, 0.94], and 0.98 [95% CI 0.71, 1.34, respectively] (HRs <1 indicate favouring BB therapy). The HRs of all-cause mortality between patients with chronic obstructive pulmonary disease who were not treated with BBs and those who were treated with BBs, cardioselective BBs, and noncardioselective BBs were 0.70 [95% CI 0.59, 0.83], 0.60 [95% CI 0.48, 0.76], and 0.74 [95% CI 0.60, 0.90], respectively (HRs <1 indicate favouring BB therapy). Patients with Chronic obstructive pulmonary disease treated with cardioselective BBs showed no difference in ventilation effect after the use of an agonist, in comparison with placebo. The difference in mean change in forced expiratory volume in 1 s was 0.06 [95% CI -0.02, 0.14].

**Conclusion** The use of BBs in patients with chronic obstructive pulmonary disease is not only safe but also reduces their all-cause and in-hospital mortality. Cardioselective BBs may even reduce chronic obstructive pulmonary disease exacerbations. In addition, cardioselective BBs do not affect the action of bronchodilators. Importantly, BBs reduce the heart rate acceleration caused by bronchodilators. BBs should be prescribed freely when indicated in patients with chronic obstructive pulmonary disease and heart disease.

**Keywords** Chronic obstructive pulmonary disease • Cardiovascular disease • β-Blocker • Cardioselective • Noncardioselective

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# Introduction

Chronic obstructive pulmonary disease is characterized by persistent, usually progressive airflow restriction with an increased inflammatory response. In comparison with the general population, patients with chronic obstructive pulmonary disease are more susceptible to cardiovascular disease (CVD). The risk of CVD in patients with chronic obstructive pulmonary disease is 2–5 times higher than that in the general population[1] due to two common primary risk factors: smoking and systemic inflammation. These factors contribute to the development of atherosclerosis, which, in turn, leads to endothelial dysfunction and plaque formation, and ultimately, plaque rupture and thrombosis contribute to the progression of CVD.[2] CVD is the primary cause of hospitalization in patients with chronic obstructive pulmonary disease, and the mortality rate is higher among patients who develop myocardial infarction (MI) or congestive heart failure (CHF). Therefore, coexisting chronic obstructive pulmonary disease and CVD is a cause of great concern.

Management of chronic obstructive pulmonary disease is based on long-term inhalation therapy with bronchodilators (anticholinergics or β2-agonists), corticosteroids, or combinations of these drugs. β-blockers (BBs) are standard drugs for many CVDs.[3] The opposing pharmacologic effects of BBs and β2-agonists highlight the difficulty of prescribing BBs to patients with chronic obstructive pulmonary disease with CVD.[3] Thus, the use of BBs in patients with chronic obstructive pulmonary disease and the optimal therapeutic protocol have been topics of much debate. Nevertheless, there is plenty of evidence showing that BBs may have a positive effect in patients with chronic obstructive pulmonary disease with CVD, and even in patients without CVD.[4,5] Therefore, the 2016 European Society of Cardiology guidelines recommend the use of BBs in patients with chronic obstructive pulmonary disease and CVD.[6]Although the rate of BB prescription has increased significantly since then, the problem of underutilization remains prominent in many countries,[7,8] clinicians tend not to prescribe BBs to patients with chronic obstructive pulmonary disease + CVD. We reviewed all meta-analyses and systematic reviews released after 1980 on this topic. We found that there is still no meta-analysis and systematic review that comprehensively describes the effects of BBs on patients with chronic obstructive pulmonary disease + CVD. We are still worried about the insufficient prescription of BBs, which is unfortunate for patients with chronic obstructive pulmonary disease + CVD.

On the basis of these considerations, we performed this meta-analysis to clarify the effect of BBs on respiratory function and survival in patients with chronic obstructive pulmonary disease with CVD as well as the difference between the effects of cardioselective and non-cardioselective BBs. We hope that it will influence clinicians and benefit patients with chronic obstructive pulmonary disease + CVD.

# Methods

## Protocol and guidance

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[9]

## Eligibility criteria

This study evaluated the effects of BBs on patients with chronic obstructive pulmonary disease from two perspectives. First, the differences in survivability and heart rate were compared between patients with chronic obstructive pulmonary disease who took BBs for a long time and those who did not take BBs. The inclusion criteria were as follows: patients: patients with chronic obstructive pulmonary disease with one or various CVDs; intervention: BB therapy (including cardioselective BBs, noncardioselective BBs, or both); control: patients who did not receive BB therapy; outcome: hazard ratio (HR) of survival and mean difference (MD) of heart rate; and study design: observational cohort or case–control study.

Second, BBs were compared with controls in randomized trials. The methods and results of this section are presented in Supplementary material online, Secondary outcomes.

## Information sources and search strategy

We searched for articles published before 30 September 2019, regardless of language or data, in four electronic databases: PubMed, EMBASE, Cochrane Library, and Web of Science. The articles were selected by manual screening. Our search strategy was audited by a medical librarian. The following terms were used in the searches: ("chronic obstructive lung disease" OR "COPD" OR "chronic obstructive emphysema" OR "chronic obstructive pulmonary disorder") and ("beta blocker" OR "beta adrenergic receptor blocking agent" OR "BB" OR "β adrenergic receptor blocking agent" OR "acebutolol" OR "atenolol" OR "betaxolol" OR "bisoprolol" OR "carvedilol" OR "labetalol" OR "metoprolol" OR "nadolol" OR "nebivolol" OR "penbutolol" OR "pindolol" OR "propranolol" OR "sotalol" OR "esmolol" OR "levobunolol" OR "oxprenolol").

## Study selection

We prespecified the eligibility criteria for inclusion and exclusion and the bias assessment methods and trained two reviewers. They independently screened the title and abstract to determine whether the article met the eligibility criteria. When consensus was reached, they read the full text and settled differences through discussion. The reasons for inclusion or exclusion were recorded in detail. Case reports, letters, and minutes of meetings were excluded. The PRISMA flow diagram was used to summarize study selection processes.

## Data extraction

The data extraction sheet was predefined and used by two investigators to independently extract data from each included study, including authors, publication year, study design, inclusion and exclusion criteria, population, age, BB name and dose, percentage of male subjects, sample size, grouping and number of people in the group, primary endpoint, data (including counts and effect estimates), country, treatment duration, follow-up duration, title, conclusion, and memo (for any subjective evaluation of the investigator or content that needed to be recorded). The third investigator independently reviewed the data to ensure accuracy. If no data in digital format were available, we used the free software Plot Digitizer to estimate from the graph.

## Definitions of primary outcomes

The HR of chronic obstructive pulmonary disease exacerbation and the HR of all-cause mortality and in-hospital mortality were compared between patients with chronic obstructive pulmonary disease treated with BBs and those treated without BBs to investigate whether BB treatment had an effect on patients with chronic obstructive pulmonary disease.

## Statistical analysis

Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) was used to combine the effect sizes with 95% confidence intervals (CIs) and with a two-sided $P < 0.05$ considered to be statistically significant. $I^2$ statistics were also calculated as a measure of inconsistency across studies. Heterogeneity was considered large if $I^2 > 50\%$. We evaluated the similarity across studies and came to realize that heterogeneity was inevitable due to the differences in sample size, length of intervention, and the drugs used. Therefore, we used the DerSimonian and Laird random effects model in all cases. Due to the high risk of a selection bias in observational studies, we used the matched data without exception if a match occurred in the study. (Matching requires the control to be consistent with the case in certain factors or characteristics; the purpose is to eliminate the interference of matching factors when comparing the two groups. "Matched data" refers to the effect size comparing the two groups after matching.) In addition, we extracted the full adjusted effect size to reduce the risk of bias to the minimum.

### Assessment of risk of bias in individual studies

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of case–control and cohort studies. It has three categories and eight items, including population selection, comparability, exposure evaluation, and outcome evaluation.

### Assessment of publication bias

Publication bias was assessed using the Begg rank correlation test and the Egger weighted linear regression test for implementation strategies with at least 10 studies.

## Additional analyses

A subgroup analysis of the HRs of all-cause mortality was performed among patients with chronic obstructive pulmonary disease receiving treatment with and without BBs to assess whether the all-cause mortality in patients with chronic obstructive pulmonary disease with CHF as well as in patients with chronic obstructive pulmonary disease with MI was different from that in the overall population.

# Results

## Study selection and characteristics

The initial search in four databases yielded 2059 publications. Finally, a total of 49 studies, with a combined sample of 670 594 subjects, were summarized and compared in this meta-analysis (see *Figure 1*). Among the included studies, 37 were cohort studies used to assess the HR of survival between patients with chronic obstructive pulmonary disease treated with BBs and those not treated with BBs. Almost all used various BBs daily, which included cardioselective BBs that primarily antagonize the β1 receptor, including metoprolol, bisoprolol, atenolol, and nebivolol, and noncardioselective BBs that antagonize the β1 and β2 receptors, including carvedilol, labetalol, pindolol, propranolol, nadolol, and timolol. Among these, four studies focused on comparisons between cardioselective and noncardioselective BB users, and 33 focused on comparisons between BB and no BB users (BBs refer to cardioselective or noncardioselective BBs or both) (Supplementary material online, *Table S1*).

## Risk of bias within studies

All 37 cohort or case–control studies had good overall quality. Their sample sizes were sufficiently large and basically represented the average state of the community population. Almost all studies identified and controlled important confounding factors. A few studies had insufficient follow-up durations. The NOS scores are shown in the Supplementary material online, *Table S2*.

## Synthesis of results

### Chronic obstructive pulmonary disease exacerbation

First, the pooled HR of chronic obstructive pulmonary disease exacerbation in 17 studies comparing patients with chronic obstructive pulmonary disease treated with BBs and those not treated with BBs was 0.77 [95% CI 0.67, 0.89] ($P = 0.0003$); the pooled HR of chronic obstructive pulmonary disease exacerbation in seven studies comparing patients with chronic obstructive pulmonary disease treated with cardioselective BBs and those not treated with BBs was 0.72 [95% CI 0.56, 0.94] ($P = 0.01$), suggesting that both BBs and cardioselective BBs could reduce the risk of chronic obstructive pulmonary disease exacerbation in patients with chronic obstructive pulmonary disease. Second, the pooled HR of chronic obstructive pulmonary disease exacerbation in five studies comparing patients with chronic obstructive pulmonary disease treated with noncardioselective BBs and those not treated with BBs was 0.98 [95% CI 0.71, 1.34] ($P = 0.89$), suggesting that there was no difference in chronic obstructive pulmonary disease exacerbation between those receiving noncardioselective BBs and those not receiving BBs. Third, a subgroup analysis of four studies was performed for patients with chronic obstructive pulmonary disease with CHF. The pooled HR of chronic obstructive pulmonary disease exacerbation between patients with chronic obstructive pulmonary disease with CHF who were treated with and not treated with BBs was 0.83 [95% CI 0.56, 1.23] ($P = 0.35$), suggesting that BB treatment did not affect chronic obstructive pulmonary disease exacerbation in patients with chronic obstructive pulmonary disease with CHF (*Take home figure* or Supplementary material online, *Table S3* and Supplementary material online, *Figure S1*).

### In-hospital mortality

The pooled HR of in-hospital mortality in five studies comparing patients with chronic obstructive pulmonary disease treated with BBs and those not treated with BBs was 0.67 [95% CI 0.46, 0.99] ($P = 0.04$), suggesting that the risk of in-hospital mortality in patients with chronic obstructive pulmonary disease treated with BBs was lower than that in patients not treated with BBs (*Take home figure* or Supplementary material online, *Table S3* and Supplementary material online, *Figure S2*).

### All-cause mortality

First, the pooled HR of all-cause mortality in 22 studies comparing patients with chronic obstructive pulmonary disease treated with BBs and those not treated with BBs was 0.70 [95% CI 0.59, 0.83] ($P < 0.0001$), indicating that BBs could reduce the risk of all-cause mortality in patients with chronic obstructive pulmonary disease. Second, the pooled HRs of all-cause mortality in seven studies comparing patients with chronic obstructive pulmonary disease treated

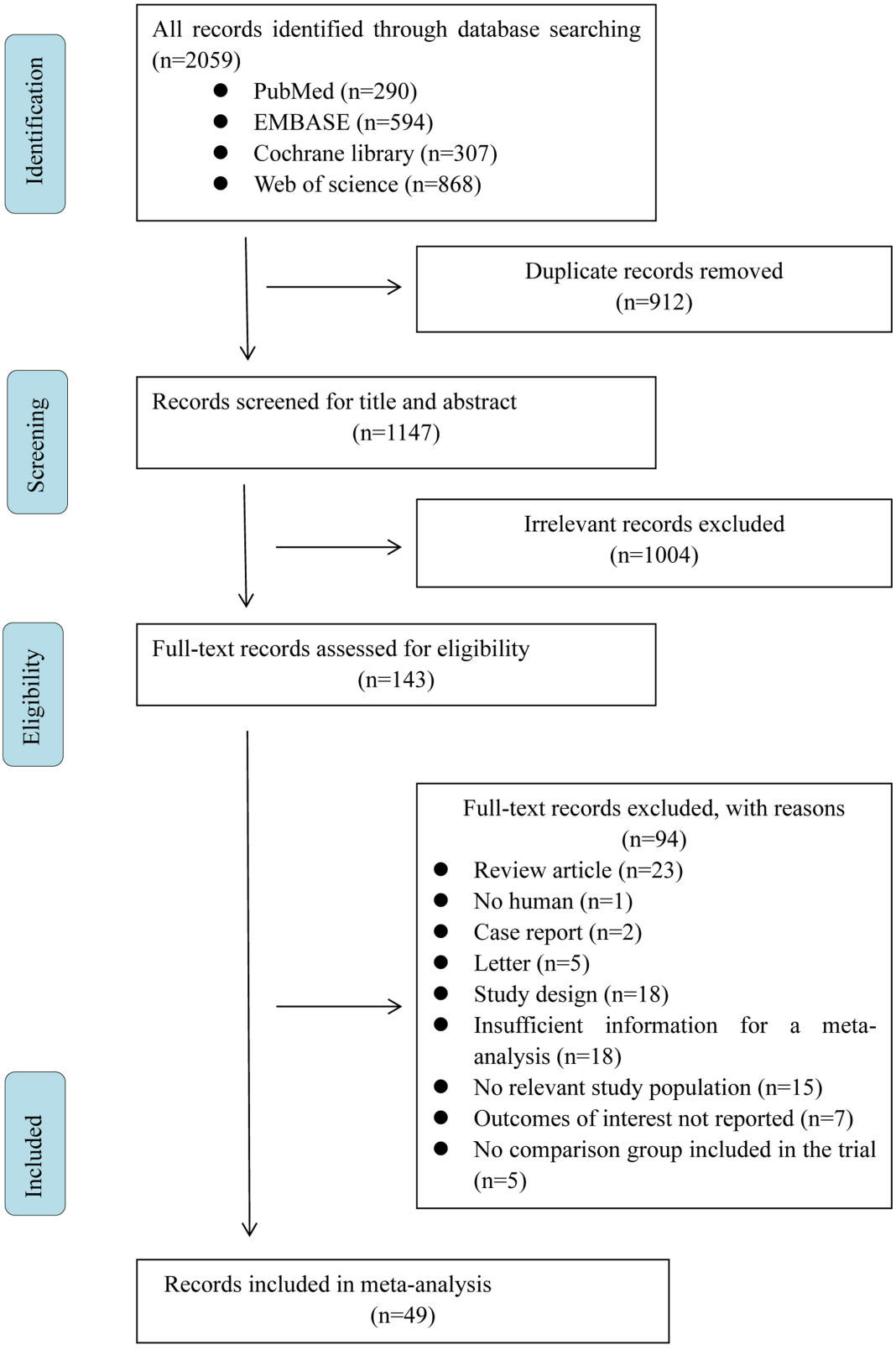
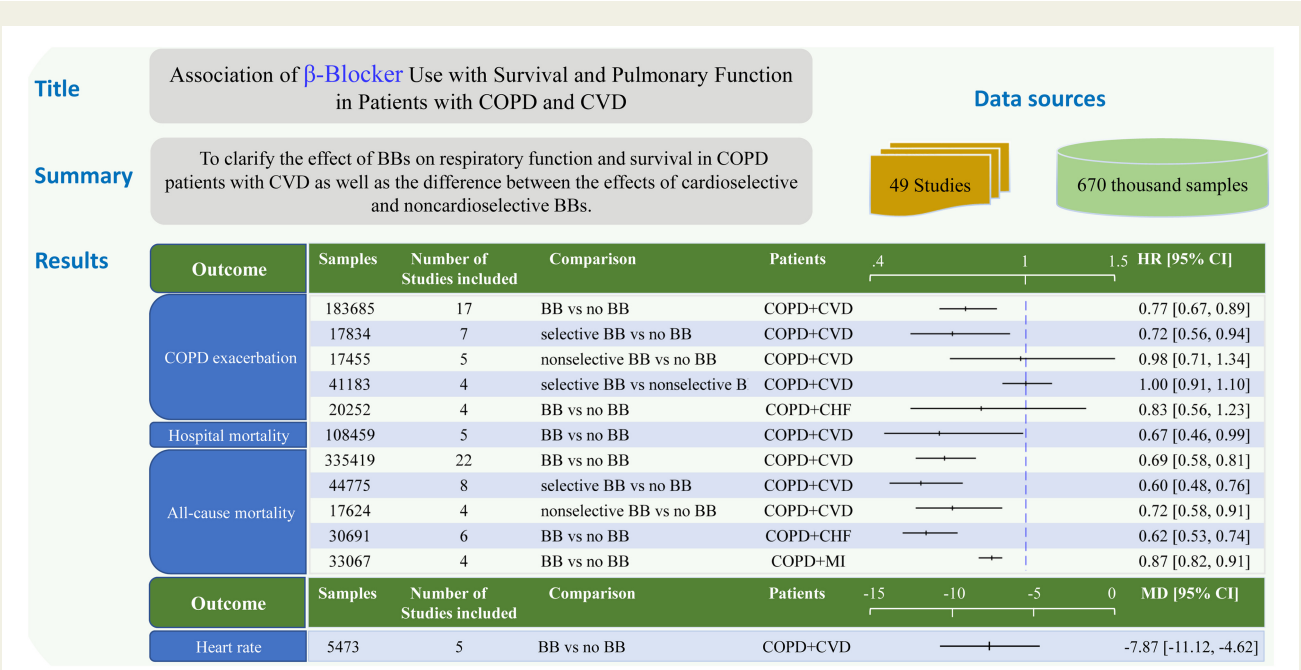



**Figure 1** Flowchart of study selection.




**Take home figure** Each line represents a combined result. Line one shows that the hazard ratios of chronic obstructive pulmonary disease exacerbation are 0.77 (95% confidence interval [0.67–0.89]) between patients with chronic obstructive pulmonary disease + cardiovascular disease who are treated with β-blockers and those who are not treated with β-blockers. A total of 17 studies, including 183 685 samples, are included in this comparison. The other results can be deduced by analogy. BBs, β-blockers; CI, confidence interval; CVD, cardiovascular disease.

with cardioselective and noncardioselective BBs and those not treated with BBs were 0.60 [95% CI 0.48, 0.76] ($P < 0.0001$) and 0.74 [95% CI 0.60, 0.90] ($P = 0.003$), respectively, indicating that both cardioselective and noncardioselective BBs could reduce the risk of all-cause mortality in patients with chronic obstructive pulmonary disease, in comparison with treatment without BBs. Third, two subgroup analyses were performed for patients with chronic obstructive pulmonary disease with CHF and patients with chronic obstructive pulmonary disease with MI. The pooled HRs of all-cause mortality between the patients with chronic obstructive pulmonary disease + CHF or chronic obstructive pulmonary disease + MI treated with BBs and those not treated with BBs were 0.67 [95% CI 0.60, 0.74] ($P < 0.00001$) and 0.87 [95% CI 0.82, 0.91] ($P < 0.00001$), respectively, indicating that BB treatment could reduce the risk of all-cause mortality in both patients with chronic obstructive pulmonary disease + CHF and chronic obstructive pulmonary disease + MI (*Take home figure* or Supplementary material online, *Table S3* and Supplementary material online, *Figure S2*). We also analysed the HR of all-cause mortality in three subgroups with follow-up periods of <1 year, 1–3 years, and >3 years. The analysis showed that there was no effect of follow-up duration on the overall pooled effect, indicating that the HR of all-cause mortality was relatively stable during the follow-up period of 6 months to 10 years (Supplementary material online, *Figures S3–S5*).

### Heart rate

We combined the baseline heart rates from five retrospective cohort studies and found that the average heart rate in patients with chronic obstructive pulmonary disease treated with BBs in combination with various daily respiratory medications was significantly lower than that in patients with chronic obstructive pulmonary disease treated without BBs (MD = -7.87 [95% CI -11.12, -4.62], $P < 0.00001$) (*Take home figure* or Supplementary material online, *Figure S6*).

### *Publication bias*

We performed Egger's test based on two comparisons of primary outcome and drew Begg funnel plots. The reason for choosing these two synthetic results was that they each included >10 studies and were of great significance to the conclusion of this meta-analysis.

There was no evidence of publication bias for the two primary outcomes (Supplementary material online, *Figures S7 and S8*).

## Discussion

In this study, we investigated the effect of BBs on chronic obstructive pulmonary disease from multiple perspectives. This meta-analysis summarized and compared 49 studies involving 670 594 patients.

### BBs do not lead to chronic obstructive pulmonary disease exacerbation in patients with chronic obstructive pulmonary disease

Our meta-analysis of respiratory function indicators suggested that BBs did reduce ventilation function when used alone, but when used

in combination with bronchodilator, cardioselective BBs did not reduce the respiratory indices or impair the effects of bronchodilators. This is probably due to the distribution of different β-adrenergic receptors (β-ARs).[10–12]

We also found that BBs did not worsen chronic obstructive pulmonary disease and even suggested that cardioselective BBs are beneficial for chronic obstructive pulmonary disease. A randomized controlled trial (RCT) involving 532 subjects with moderate and severe chronic obstructive pulmonary disease[13] showed no difference in the risk of chronic obstructive pulmonary disease exacerbation between the metoprolol and placebo groups. The majority of previous studies was observational trials; nevertheless, this RCT suggested that the use of BBs did not exacerbate chronic obstructive pulmonary disease, which was similar to our finding.

BBs may alleviate the exacerbation of chronic obstructive pulmonary disease in many ways. BBs, especially cardioselective BBs, can block the β1-AR subtype in the heart to prevent the effects of the endogenous catecholamines adrenaline and noradrenaline. BBs can reduce the heart rate as well as reduce the speed and force of myocardial contraction. Thus, BBs reduce myocardial demand and reduce mortality in heart disease.[14,15] Moreover, BBs enhance heart function, improve pulmonary hemodynamics, and relieve chronic obstructive pulmonary disease symptoms in patients with chronic obstructive pulmonary disease. At the same time, BBs not only alleviate the symptoms of chronic obstructive pulmonary disease by improving heart function but also show beneficial effects on chronic obstructive pulmonary disease itself. First, long-term administration of BBs can reduce inflammation and lung mucus secretion.[16] BBs have been reported to inhibit neutrophil chemotaxis and oxygen free radical production and reduce the release of endothelin-1 in human endothelial cells. Endothelin-1 is a bronchoconstrictor peptide, an important factor involved in chronic obstructive pulmonary disease exacerbation.[17–19] BBs can not only reduce the inflammatory cells in the bronchoalveolar lavage of antigen-challenged mice but also decrease the levels of cytokines. In addition, long-term treatment with BBs can significantly reduce the goblet cells and mucin content of airway epithelium in a time-dependent manner.[12,16] Second, BBs can reduce airway hyperresponsiveness.[12,20] Airway hyperresponsiveness itself is related to deterioration of the disease. Lin *et al.*[21] found that long-term use of BBs can also up-regulate β2-AR levels in the lungs and thus improve the effect of bronchodilators in mice. In summary, the use of BBs in the treatment of patients with chronic obstructive pulmonary disease does not exacerbate chronic obstructive pulmonary disease but may instead produce beneficial effects via anti-inflammatory activity and bronchial protection. In addition, we believe that the treatment of patients with chronic obstructive pulmonary disease with comorbid heart disease should be performed in the consideration of not only the level of a single index but also the interaction between comorbidities in a systematic manner. Although cardioselective BBs are better for reducing chronic obstructive pulmonary disease exacerbation, in some cases, more comprehensive blockade of β-AR is needed to maximize cardiac function. Our meta-analysis suggests that noncardioselective BBs are not related to the risk of chronic obstructive pulmonary disease exacerbation. This may be because although short-term respiratory indicators may decline, chronic obstructive pulmonary disease symptoms may eventually be reduced with the recovery of cardiac function in the long run. It should be emphasized that the decline in respiratory indicators does not necessarily imply exacerbation of chronic obstructive pulmonary disease and should be considered in the context of the patients' overall condition. Therefore, we believe that noncardioselective BBs should not be contraindicated in patients with chronic obstructive pulmonary disease.

## Treatment with BBs can reduce all-cause mortality in patients with chronic obstructive pulmonary disease

We conducted a meta-analysis of all-cause mortality in patients with chronic obstructive pulmonary disease who took BBs and found that the use of BBs, whether cardioselective or noncardioselective, in patients with chronic obstructive pulmonary disease had a significant effect in reducing all-cause mortality. BBs were also beneficial for patients with comorbid severe heart disease and chronic obstructive pulmonary disease.

Our meta-analysis indicated that BBs significantly reduced the heart rate in patients with chronic obstructive pulmonary disease. In many cases, elevated heart rate is associated with increased mortality and has been shown to be a modifiable risk factor. Heart rate is an important determinant of myocardial oxygen demand and coronary blood flow. A high heart rate can affect coronary blood flow and myocardial oxygen consumption, lead to diastolic dysfunction and imbalance of oxygen supply and demand, and thereby cause myocardial ischaemia. Many studies have found that lowering the heart rate offers benefits in heart failure. In addition, Omlor *et al.*[22] found that in patients with chronic obstructive pulmonary disease, elevated time-updated (most recent value before the event) resting heart rate (RHR) was related to high mortality and low forced expiratory volume in one second ($FEV_1$) and was more closely related to chronic obstructive pulmonary disease than baseline RHR. The finding that a high heart rate is associated with increased mortality provides us with an important implication that lowering the heart rate may be an effective way to reduce mortality in patients with chronic obstructive pulmonary disease. The use of BBs can effectively improve cardiac function, reduce heart rate, and reduce cardiovascular mortality in patients with chronic obstructive pulmonary disease, thereby greatly alleviating the disease as a whole and reducing all-cause mortality.

Notably, some studies reported that the use of β-AR agonists in patients with chronic obstructive pulmonary disease might accelerate the heart rate and increase the incidence of arrhythmias.[23] As many as 40% of patients developed tachycardia (even if there was no obvious heart disease),[24] which may be related to the expression of β2-AR in some parts of heart. As a result, many patients with chronic obstructive pulmonary disease with comorbid CVD had to stop taking β-AR agonists. Our meta-analysis indicated that heart rate was significantly lower in patients who took both BBs and bronchodilator than in those using bronchodilator alone and that cardioselective or noncardioselective BBs combined with β-agonist significantly reduced heart rate. Thus, patients with chronic obstructive pulmonary disease who developed tachycardia after taking β-agonists, irrespective of any history of heart disease, may take BBs to alleviate the side effects of β-agonists rather than stop taking β-agonists. For patients with chronic obstructive pulmonary disease and comorbid HF, BBs combined with β-AR agonists are a good choice.

## Limitations

The primary outcomes of this meta-analysis were based on retrospective studies. Although the data we extracted had the largest adjusted effect sizes, they were still subject to unanticipated potential biases, confounding factors, and the analysis methods used. Therefore, there were some limitations. Fortunately, some large-scale prospective trials are underway, and we are confident of a successful outcome in the near future. At present, the RCTs included were mostly crossover trials with small sample sizes and short trial periods, which can exert a certain impact on the trial outcomes. Lastly, at present, there are few studies on BBs reducing the side effects of bronchodilator, and the results need to be interpreted cautiously.

# Conclusions

The use of BBs in patients with chronic obstructive pulmonary disease is not only safe but also reduces their all-cause and in-hospital mortality. Cardioselective BBs may even reduce exacerbations in chronic obstructive pulmonary disease. In addition, cardioselective BBs do not affect the action of bronchodilators. Importantly, BBs reduce the heart rate acceleration caused by bronchodilators, which may be associated with reduced all-cause mortality. As far as insufficient prescription of BBs to patients with chronic obstructive pulmonary disease with comorbid CVD is concerned, on the one hand, clinicians do not know enough about the efficacy of BBs, and on the other hand, they may have insufficient awareness of the treatment of comorbidities; thus, they often ignore the presence of heart disease in chronic obstructive pulmonary disease. We sincerely hope that guidelines at all levels will include better interpretations of comorbidities, thereby increasing the rate of BB prescription to patients with chronic obstructive pulmonary disease.

## Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

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**Conflict of interest:** none declared.

## References

1. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015;**3**:631–639.
2. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;**107**:1514–1519.
3. Minor DS, Meyer AM, Long RC, Butler KR Jr. Beta-blockers and chronic obstructive pulmonary disease: inappropriate avoidance? *J Clin Hypertens* 2013;**15**:925–930.
4. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;Cd003566.
5. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for reversible airway disease. *Cochrane Database Syst Rev* 2002;Cd002992.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart* 2016;37:2129–2200.
7. Sessa M, Mascolo A, Mortensen RN, Andersen MP, Rosano GMC, Capuano A, Rossi F, Gislason G, Enghusen-Poulsen H, Torp-Pedersen C. Relationship between heart failure, concurrent chronic obstructive pulmonary disease and beta-blocker use: a Danish nationwide cohort study. *Eur J Heart Fail* 2018;**20**:548–556.
8. Kratzer L, Noakes P, Baumwol J, Wrobel JP. Under-utilisation of beta-blockers in patients with acute coronary syndrome and comorbid chronic obstructive pulmonary disease. *Intern Med J* 2018;**48**:931–936.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700–b2700.
10. Albouaini K, Andron M, Alahmar A, Egred M. Beta-blockers use in patients with chronic obstructive pulmonary disease and concomitant cardiovascular conditions. *Int J Chron Obstruct Pulmon Dis* 2007;**2**:535–540.
11. Ke Y, Xu D, Li M, Wu Z, Huang Y. Effects of bisoprolol in combination with trimetazidine on the treatment of heart failure and concomitant chronic obstructive pulmonary disease. *Pak J Med Sci* 2016;**32**:1208–1212.
12. Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. *PLoS One* 2014;**9**:e113048.
13. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, Cooper JAD, Criner GJ, Curtis JL, Han MK, Hatipoğlu U, Helgeson ES, Jain VV, Kalhan R, Kaminsky D, Kaner R, Kunisaki KM, Lambert AA, Lammi MR, Lindberg S, Make BJ, Martinez FJ, McEvoy C, Panos RJ, Reed RM, Scanlon PD, Sciurba FC, Smith A, Sriram PS, Stringer WW, Weingarten JA, Wells JM, Westfall E, Lazarus SC, Connett JE. Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Med* 2019;**381**:2304–2314.
14. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, Collet J-P, Kristensen SD, Aboyans V, Baumbach A, Bugiardini R, Coman IM, Delgado V, Fitzsimons D, Gaemperli O, Gershlick AH, Gielen S, Harjola V-P, Katus HA, Knuuti J, Kolh P, Leclercq C, Lip GYH, Morais J, Neskovic AN, Neumann F-J, Niessner A, Piepoli MF, Richter DJ, Shlyakhto E, Simpson IA, Steg PG, Terkelsen CJ, Thygesen K, Windecker S, Zamorano JL, Zeymer U, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Chettibi M, Hayrapetyan HG, Metzler B, Ibrahimov F, Sujayeva V, Beauloye C, Dizdarevic-Hudic L, Karamfiloff K, Skoric B, Antoniades L, Tousek P, Terkelsen PJ, Shaheen SM, Marandi T, Niemelä M, Kedev S, Gilard M, Aladashvili A, Elsaesser A, Kanakakis IG, Merkely B, Gudnason T, Iakobishvili Z, Bolognese L, Berkinbayev S, Bajraktari G, Beishenkulov M, Zake I, Lamin HB, Gustiene O, Pereira B, Xuereb RG, Ztot S, Juliebø V, Legutko J, Timóteo AT, Tatu-Chiţoiu G, Yakovlev A, Bertelli L, Nedeljkovic M, Studenčan M, Bunc M, García de Castro AM, Petursson P, Jeger R, Mourali MS, Yildirir A, Parkhomenko A, Gale CP; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
15. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
16. Nguyen LP, Omoluabi O, Parra S, Frieske JM, Clement C, Ammar-Aouchiche Z, Ho SB, Ehre C, Kesimer M, Knoll BJ, Tuvim MJ, Dickey BF, Bond RA. Chronic exposure to beta-blockers attenuates inflammation and mucin content in a murine asthma model. *Am J Respir Cell Mol Biol* 2008;**38**:256–262.

17. Lipworth B, Wedzicha J, Devereux G, Vestbo J, Dransfield MT. Beta-blockers in COPD: time for reappraisal. *Eur Respir J* 2016;**48**:880–888.
18. Dunzendorfer S, Wiedermann CJ. Modulation of neutrophil migration and superoxide anion release by metoprolol. *J Mol Cell Cardiol* 2000;**32**:915–924.
19. Roland M, Bhowmik A, Sapsford RJ, Seemungal TA, Jeffries DJ, Warner TD, Wedzicha JA. Sputum and plasma endothelin-1 levels in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2001;**56**:30–35.
20. Hanania NA, Singh S, El-Wali R, Flashner M, Franklin AE, Garner WJ, Dickey BF, Parra S, Ruoss S, Shardonofsky F, O'Connor BJ, Page C, Bond RA. The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. *Pulm Pharmacol Ther* 2008;**21**:134–141.
21. Lin R, Peng H, Nguyen LP, Dudekula NB, Shardonofsky F, Knoll BJ, Parra S, Bond RA. Changes in beta 2-adrenoceptor and other signaling proteins produced by chronic administration of 'beta-blockers' in a murine asthma model. *Pulm Pharmacol Ther* 2008;**21**:115–124.
22. Omlor AJ, Trudzinski FC, Alqudrah M, Seiler F, Biertz F, Vogelmeier CF, Welte T, Watz H, Waschki B, Brinker TJ, Andreas S, Fahndrich S, Alter P, Jorres RA, Bohm M, Bals R. Time-updated resting heart rate predicts mortality in patients with COPD. *Clin Res Cardiol* 2020;**109**:776–786.
23. Hawkins NM, Virani S, Ceconi C. Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services. *Eur Heart J* 2013;**34**:2795–2803.
24. Hanrahan JP, Grogan DR, Baumgartner RA, Wilson A, Cheng H, Zimetbaum PJ, Morganroth J. Arrhythmias in patients with chronic obstructive pulmonary disease (COPD): occurrence frequency and the effect of treatment with the inhaled long-acting beta2-agonists arformoterol and salmeterol. *Medicine* 2008;**87**:319–328.

## Corrigendum

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**Corrigendum to:** Control of blood pressure and risk of mortality in a cohort of older adults: the Berlin Initiative Study [*Eur Heart J* 2019;40:2021–2028].

The error affected the distribution of the two covariates body mass index and alcohol consumption in Table 1. Indeed, the distribution of body mass index is 69.0% (instead of the erroneous 31.0%) for $<30$ and 31.0% (instead of the erroneous 69.0%) for $\geq 30$ in the group with normalised blood pressure and 71.7% (instead of the erroneous 28.3%) for $<30$ and 28.3% (instead of the erroneous 69.0%) for $\geq 30$ in the group with non-normalised blood pressure. Moreover, the distribution of alcohol consumption is 46.7% (instead of the erroneous 17.2%) for "less than once monthly" and 17.2% (instead of the erroneous 46.7%) for "more than three times weekly" in the group with normalised blood pressure and 45.1% (instead of the erroneous 20.8%) for "less than once monthly" and 20.8% (instead of the erroneous 45.1%) for "more than three times weekly" in the group with non-normalised blood pressure. The same error also affected the distribution of the two covariates in eTable 2 and eTable 5 in the Appendix (bold denotes correction).

Importantly, the change in the distribution of the two covariates *did not affect any of the results* of our analyses on the risk of all-cause mortality. We apologise for the error.