

## ASSOCIATION OF BETA BLOCKER USE AND COPD MORTALITY : A SYSTEMATIC REVIEW

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### ABSTRACT

**Background:** Chronic obstructive pulmonary disease (COPD) it is currently the third greatest cause of mortality worldwide and one of the main causes of morbidity

**Aims :** This systematic review is to review the association of beta blocker use and COPD mortality.

**Methods:** This study demonstrated compliance with all requirements by means of a comparison with the standards established by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. Thus, the specialists were able to guarantee that the research was as current as feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.

**Result:** In the PubMed database, the results of our search brought up 249 articles, whereas the results of our search on SCIENCE DIRECT brought up 18.876 articles, our search on SAGEPUB brought up 4.844 articles. The results of the search conducted for the last year of 2014 yielded a total 131 articles for PubMed, 6.875 articles for SCIENCE DIRECT and 1.840 articles for SAGEPUB. In the end, we compiled a total of 8 papers, 5 of which came from PubMed, 2 of which came from SCIENCE DIRECT and 1 of which came from SAGEPUB. We included eight research that met the criteria.

**Conclusion:** In summary, beta blockers showed the effect to reduce the exacerbation or exacerbation related mortality of COPD in some cases. More studies needed in the future for more evidence of the use of beta blockers as the treatments in patients with COPD.

**Keyword:** Beta blockers, COPD, Mortality

## INTRODUCTION

The co-occurrence of COPD and cardiovascular disease (CVD) is common, and is attributed to intricate molecular pathways as well as risk factors including smoking. Because beta-blockers have been shown to reduce mortality in patients with heart failure (HF), myocardial infarction (MI), angina, or hypertension, they are advised in therapy regimens for these patients.<sup>1,2</sup>

Contrary to popular belief, coexisting HF and COPD are more common. Approximately thirty out of every 100 patients with HF also have COPD, and approximately thirty out of every 100 patients with COPD also have HF. Numerous studies have found that COPD raises a person's risk of heart failure, ischemic heart disease, or cardiovascular illness in general by two to five times. Furthermore, subclinical coronary events—which are defined by sporadic increases in troponin and occasionally by abrupt cardiac death—are more common in people with COPD.<sup>3-5</sup>

The co-occurrence of COPD and cardiovascular disorders, particularly heart failure (HF), in a large number of individuals is most likely due to a number of shared pathogenic variables, such as air pollution, smoking cigarettes, aging, chronic inflammation, and maybe being overweight or obese.<sup>6,7</sup>

Regrettably, the coexistence of COPD and HF in the same patient has a significant negative prognostic impact, raising the long-term risk of hospitalization and death by at least 30% as compared to when they do not coexist. When HF and COPD coexist, the chance of atrial flutter or fibrillation rises by approximately 50% as opposed to when they are separate conditions.<sup>8,9</sup>

The first comprehensive meta-analysis showing that beta-blockers do not worsen lung function in COPD patients was published seventeen years ago. Even now, among those who have a valid reason for therapy, the prescription rates for these drugs are still lower than for those without the disease. Despite mounting evidence to the contrary, worries about unfavorable respiratory consequences (e.g., reduction in lung function) are considered to contribute to this treatment gap. Concomitant CVD increases the clinical burden and complexity of treatment paths for COPD patients by having an independent impact on hospitalization and death.<sup>10,11</sup>

Based on information acquired in a Cochrane study, COPD guidelines support the use of cardioselective beta-blockers when appropriate. The majority of the information about the relationship between beta-blocker treatment and mortality and acute exacerbations of COPD (AECOPD) comes from observational data, and earlier reviews have included data for both cardio and non-cardioselective drugs. Though the results on mortality and FEV1 were not conclusive, a recent single RCT found that patients treated with metoprolol had a higher number of hospitalizations owing to AECOPD when compared to placebo.<sup>12-14</sup>

## METHODS

### Protocol

The author of this study ensured that it complied with the standards by adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This is done to guarantee the accuracy of the results that are derived from the investigation. Thus, the specialists were able to guarantee that the research was as current as feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.

## CRITERIA FOR ELIGIBILITY

In order to complete this literature evaluation, we looked at published research that discusses the association of beta blocker use and the mortality of COPD. This is done to enhance the patient's therapy management and to offer an explanation. This paper's primary goal is to demonstrate the applicability of the issues that have been noted overall.

To be eligible to participate in the study, researchers had to meet the following requirements: 1) English must be used to write the paper. The manuscript must fulfill both of these conditions in order to be considered for publication. 2) A few of the examined studies were released after 2013 but prior to the time frame considered relevant by this systematic review. Editorials, submissions without a DOI, already published review articles, and entries that are nearly exact replicas of journal papers that have already been published are a few examples of research that are prohibited.

## SEARCH STRATEGY

We used "beta blocker" and "copd" out using the PubMed and SAGEPUB databases by inputting the words: (("adrenergic beta antagonists"[Pharmacological Action] OR "adrenergic beta antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta antagonists"[All Fields]) OR "adrenergic beta antagonists"[All Fields] OR ("beta"[All Fields] AND "blocker"[All Fields]) OR "beta blocker"[All Fields]) AND ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR

"chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]) AND ("associate"[All Fields] OR "associated"[All Fields] OR "associates"[All Fields] OR "associating"[All Fields] OR "association"[MeSH Terms] OR "association"[All Fields] OR "associations"[All Fields])) AND ((clinicalstudy[Filter] OR clinicaltrial[Filter] OR controlledclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (2014:2024[pdat])) used in searching the literature.

**DATA RETRIEVAL**

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

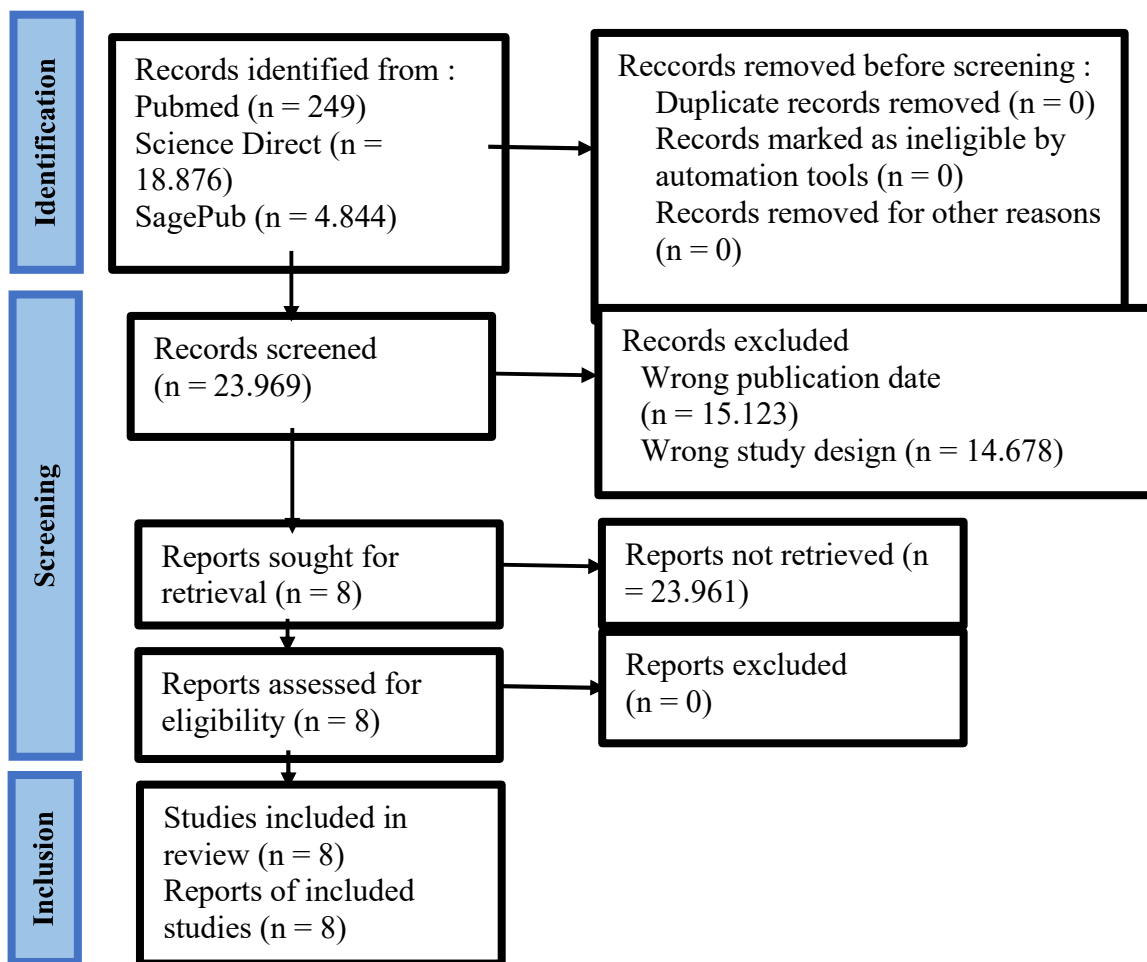


Figure 1. Prisma Flow Diagram

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**QUALITY ASSESSMENT AND DATA SYNTHESIS**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

In the PubMed database, the results of our search brought up 249 articles, whereas the results of our search on SCIENCE DIRECT brought up 18.876 articles, our search on SAGEPUB brought up 4.844 articles. The results of the search conducted for the last year of 2014 yielded a total 131 articles for PubMed, 6.875 articles for SCIENCE DIRECT and 1.840 articles for SAGEPUB. In the end, we compiled a total of 8 papers, 5 of which came from PubMed, 2 of which came from SCIENCE DIRECT and 1 of which came from SAGEPUB. We included eight research that met the criteria.

Wang, et al<sup>15</sup> (2019) showed that in most stratified studies, the use of  $\beta$ -blockers was linked to a lower risk of death; this association was evident especially in patients 65 years of age and older, in men, and in those with a variety of comorbidities. These results imply that  $\beta$ -blockers enhance COPD patients' overall survival following their initial AMI.

Cotton, et al<sup>16</sup> (2022) showed that the number of participant-reported COPD exacerbations that required oral corticosteroids and/or antibiotics during the course of the 52-week treatment period is the main outcome. Participants in a substudy will be risk-stratified for heart failure based on blood biomarker measurements and echocardiography results. The proof that bisoprolol lowers the frequency of exacerbations would be helpful to physicians, patients, and other healthcare professionals.

Dransfield, et al<sup>14</sup> (2018) showed that in patients with chronic obstructive pulmonary disease and elevated cardiovascular risk, there is no evidence to suggest that baseline  $\beta$ -blocker medication diminishes the respiratory benefits or raises the cardiovascular risk of inhaled long-acting  $\beta$ -agonists.

Parekh, et al<sup>17</sup> (2022) showed that early in the course of the therapy, metoprolol was linked to a little reduction in lung function, but these effects did not last. Baseline FVC bronchodilator responsiveness was linked to a 60% greater probability of severe or very severe exacerbations, although early lung function decline and baseline bronchodilator responsiveness did not interact with the treatment arm to predict exacerbations.

Chapman, et al<sup>18</sup> (2021) showed that when used with concurrent beta-blockers, long-acting anti-muscarinic therapy is recommended for patients with moderate-to-very severe COPD who also have cardiovascular comorbidities.

**Table 1. The literature include in this study**

Author	Origin	Method	Sample	Result
Wang et al, 2019 <sup>15</sup>	Taiwan	Retrospective study	23.116 patients	15,507 individuals did not receive a prescription for $\beta$ -blockers, out of 7609 patients (32.92%). The patients on $\beta$ -blockers were divided into two groups: those with selective and non-selective $\beta$ -blockers. A 95% confidence interval (95% CI) was obtained for the adjusted hazard ratio (HR) estimate using multivariate Cox proportional hazards models. When compared to patients without $\beta$ -blockers, patients who used selective $\beta$ -blockers had a lower risk of death (HR 0.93; 95% CI 0.89-0.98; $p < 0.01$ ), but non-selective $\beta$ -blocker groups did not raise the risk of death (HR 0.98; 95% CI 0.94-1.02; $p = 0.38$ ).
Cotton et al, 2022 <sup>16</sup>	United Kingdom	Randomized controlled trial	1.574 patients	Bisoprolol (1.25 mg tablets) or a similar placebo is the intervention. Depending on tolerance to an increase in bisoprolol/placebo dosage, the dosage is titrated up to a maximum of 4 tablets per day (5 mg bisoprolol) over a period

				of 4–7 weeks. These titration evaluations are conducted by phone or video chat. Participants take the final titrated dose of 1, 2, 3, and 4 pills for the full 52-week treatment period. During this time, they are contacted by phone or video call at 26 and 52 weeks. The number of participant-reported COPD exacerbations that required oral corticosteroids and/or antibiotics during the course of the 52-week treatment period is the main outcome. Participants in a substudy will be risk-stratified for heart failure based on blood biomarker measurements and echocardiography results.
<b>Dransfield et al, 2018<sup>14</sup></b>	Multiple countries	Randomized controlled trial	16.485 patients	At three months, in the vilanterol-alone group, the placebo-adjusted mean differences in post-bronchodilator forced expiratory volume in 1 second were 51 ml (95% confidence interval, 38-65) in those who were not receiving baseline $\beta$ -blocker therapy and 58 ml (95% confidence interval, 38-78) in those who were. In the combination fluticasone furoate/vilanterol group, the placebo-adjusted mean differences in post-bronchodilator forced expiratory volume in 1 second at 3 months were 85 ml for those receiving baseline $\beta$ -blocker therapy and 68 ml for those not receiving baseline $\beta$ -blocker medication. Overall, for exacerbations of chronic obstructive pulmonary disease, cardiovascular composite events, and all-cause mortality, there was no indication of interaction by randomized therapy, including vilanterol alone or in combination with fluticasone furoate.
<b>Parekh et al, 2022<sup>17</sup></b>	USA	Randomized controlled study		Compared to those in the placebo group, those in the metoprolol group saw a substantially larger decline in FVC from baseline to visits on Days 14 and 28, as well as a considerably bigger fall in logarithmic FVC from baseline to visits on Days 42 and 112.

				Early decrease of lung function and its interactions with treatment assignment, time to any or very severe exacerbations, or both were not associated with any of these outcomes. Regarding risk of exacerbation rate, there were no interactions found between the treatment arm and baseline bronchodilator responsiveness parameters. The risk of severe or very severe exacerbations was greater in individuals with baseline FVC bronchodilator responsiveness (adjusted rate ratio, 1.62; 95% confidence range, 1.04-2.48).
<b>Chapman et al, 2021<sup>18</sup></b>	USA	Randomized controlled study	3.589 patients	In patients taking beta-blockers, acclidinium did not statistically increase the risk of all-cause mortality (beta-blocker user: 1.13 [0.78-1.64]; non-user: 0.89 [0.62-1.26]; interaction P = 0.35) or MACE (hazard ratio 1.01 [95% CI 0.62-1.64]; non-user: 0.80 [0.51-1.24]; interaction P = 0.48). In comparison to placebo, acclidinium improved lung function and decreased the annualized rate of moderate-to-severe COPD exacerbation (beta-blocker user: rate ratio 0.75 [95% CI 0.60-0.94, P = 0.013]; non-user: 0.79 [0.67-0.93, P = 0.005]). It also delayed the time to first exacerbation. According to the least squares mean difference after 52 weeks, beta-blocker users had a higher trough FEV1 benefit than non-users (69 mL [42 mL-97 mL] versus 111 mL [95% CI 74 mL-147 mL]; interaction P = 0.041).
<b>Su et al, 2019<sup>19</sup></b>	Taiwan	Cohort study	28.097 patients	Those who were given both $\beta$ -blockers and NDCCBs (n = 302) were not included in the study, leaving 23,754 individuals. Patients were categorized into three groups according to their outpatient prescription within the exposure window: $\beta$ -blocker (n = 10,638, 44.8%), NDCCB (n = 1,747, 7.4%), and control (n = 11,369, 47.9%). While the risk of major adverse cardiac events within a year was not significantly different, the

				patients in the $\beta$ -blocker group had decreased overall mortality risks (adjusted hazard ratio [95% confidence interval]: 0.91 [0.83-0.99] compared the NDCCB group; 0.88 [0.84-0.93] versus the control group). $\beta$ -blockers reduced re-hospitalization rates by 12–32% for COPD and other respiratory conditions.
<b>Maltais et al, 2018<sup>20</sup></b>	Multiple countries	Cohort study	5.162 patients	At baseline, the group receiving $\beta$ -blocker had a greater postbronchodilator FEV1 (1.470 L) than the group not receiving $\beta$ -blocker (1.362 L). Anticipatedly, those on $\beta$ -blockers had a higher frequency of cardiovascular comorbidities and prescription histories. Patients receiving or not receiving $\beta$ -blocker medication had improvements in their lung function from baseline, and at 24 or 52 weeks, there were no significant differences between the groups in terms of trough FEV1 or trough FVC. Regarding the St. George's Respiratory Questionnaire and Transition Dyspnea Index, there were no noteworthy distinctions found between patients with and without $\beta$ -blockers. The groups' safety results were similar.
<b>Puente-Maestu et al, 2014<sup>21</sup></b>	Spain	Cohort study	256 patients	97% of individuals without COPD and 58% (95%CI, 52–64%) of patients with indication were on BB ( $p < 0.001$ ). A number of factors, including the use of BB (adjusted OR = 0.27 (95% CI 0.15–0.50), GOLD stage D (OR = 2.52 (1.40–4.53), baseline heart rate $>70$ (OR = 2.19 (1.24–3.86), use of long-acting beta2-agonists (OR = 2.18 (1.29–3.68), prior episodes of left ventricular failure (OR = 2.27 (1.19–4.33), and diabetes (OR = 1.82 (1.08–3.38) were independently associated with at least one ER visit in the preceding year among patients with COPD.

Su, et al<sup>19</sup> (2019) showed that in COPD patients, the administration of  $\beta$ -blockers after AMI was linked to a lower risk of death.  $\beta$ -blockers reduced the risk of re-hospitalization for COPD and other respiratory disorders by 12-32%, and they did not raise the risk of COPD exacerbations.

Maltais, et al<sup>20</sup> (2018) showed that in individuals with moderate to very severe COPD, baseline  $\beta$ -blocker medication had no effect on lung function, overall respiratory status, or safety of tiotropium/olodaterol. The outcomes of this sizable patient group provide credence to the prudent and suitable use of  $\beta$ -blockers in individuals with COPD and cardiovascular disease.

Puente-Maestu, et al<sup>21</sup> (2014) showed that current recommendations still propose that BB be underprescribed in patients with COPD. Patients with COPD who use BB and have CHF or CAD get fewer ER visits and exacerbations. In this cohort, other risk factors for exacerbations include GOLD stage, comorbidities, baseline heart rate, and use of long-acting beta2-agonists.

## DISCUSSION

With 3 million fatalities from chronic obstructive pulmonary disease (COPD) in 2010, it is currently the third greatest cause of mortality worldwide and one of the main causes of morbidity. Up to 75 percent of COPD-related expenses are linked to flare-ups, with a total cost of about USD 30 billion. The hypothesized effects of beta-blockers on the cardiovascular load and its related influence on mortality were notably mentioned in a recent COPD task force statement that highlighted an unmet need for medications to address common comorbidities. Patients with COPD who smoke are more likely to experience cardiovascular comorbidity in addition to other prevalent factors such as aging, systemic inflammation, and genetic predisposition.<sup>22-25</sup>

Because  $\beta$ -blockers have improved short- and long-term results, they are a routine treatment for acute myocardial infarction (AMI). Nevertheless, as  $\beta$ -blockers are believed to be connected to bronchospasm, they are frequently provided insufficiently to patients with AMI who have chronic obstructive pulmonary disease (COPD). Wang et al. discovered that the usage of  $\beta$ -blockers was linked to a lower risk of death in the majority of stratified analyses. This association was especially evident in patients 65 years of age and older, male patients, and people with a variety of comorbidities.<sup>15</sup>

The BICS research examines the potential clinical and financial advantages of including bisoprolol into standard COPD therapy. Participants in a follow-up research will be risk-stratified for heart failure in order to explore if bisoprolol's potential benefits are limited to people with undiagnosed heart disease. Cotton, et al in their study used 1574 participants divided into group used bisoprolol (1.25 mg tabs) or placebo. The results in this study showing that bisoprolol can decreased the cases of COPD exacerbations.<sup>16</sup>

Patients who have chronic obstructive lung disease frequently also have cardiovascular problems. While individuals with chronic obstructive pulmonary disease can safely utilize  $\beta$ -blockers, questions still exist about the safety and potential interactions between  $\beta$ -blockers and long-acting inhaled  $\beta$ -agonists. The 16,485 participants by Dransfield, et al was examined with 31% of the participants used the beta blocker. From this study, no enough evidence that beta blocker can decreased the exacerbations of COPD or increased the cardiovascular risk of ingaled long acting beta agonist.<sup>14</sup>

Metoprolol was linked to an increased risk of severe exacerbation, according to the BLOCK COPD ( $\beta$ -Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) research. Parekh, et al compared the changed of lung function from the treatments grous using the linear mixed effect. The beta blockers was found associated in reducing the lung function during the early time of treatment but it was not persistant.<sup>17</sup>

Patients with chronic obstructive pulmonary disease (COPD) frequently do not get beta-blocker medications for cardiovascular comorbidities because of the possibility of negative effects on airway obstruction. The 3,589 of participants with 1269 of them used the beta blockers in study by Chapman, et al. When used with concurrent beta-blockers, long-acting anti-muscarinic therapy is recommended for patients with moderate-to-very severe COPD who also have cardiovascular comorbidities.<sup>18</sup>

After an acute myocardial infarction (AMI), patients with chronic obstructive pulmonary disease (COPD) are less likely to be prescribed  $\beta$ -blockers. This might affect how they fare following AMI. Su, et al with their cohort study on 28,097 patients with COPD that hospitalized from January 2004 to December 2013 divided into group of beta blocker, non0dihydropyridine calcium channel blockers (NDCCBs) group, and control group. This study showed that beta blockers overall had lower mortality risk.<sup>19</sup>

For people with COPD, cardiovascular illness is a common comorbidity. Despite being shown to be successful in reducing cardiovascular events, many doctors, especially pulmonologists, are reluctant to employ  $\beta$ -adrenoceptor blocking medications ( $\beta$ -blockers) in patients with COPD. Maltais, et al in their large studies of 5,162 patients from moderate to very severe COPD showed that overall there is appropriate use of beta blockers in patients with COPD and cardiovascular comorbidity.<sup>20</sup>



Heart failure (CHF) or coronary artery disease (CAD) are often linked to chronic obstructive pulmonary disease (COPD). Although beta-blockers (BB) are advised, individuals with co-occurring cardiac and COPD disorders are probably not receiving enough of them. Pulmonary doctors from 14 hospitals in 7 regions of Spain sequentially recruited 256 COPD patients in their outpatient offices to determine the prevalence of BB use. The patients had to meet certain criteria, such as having CHF or CAD, not being on long-term oxygen therapy, and being diagnosed with COPD. Current recommendations still propose that BB be underprescribed in patients with COPD. Patients with COPD who use BB and have CHF or CAD get fewer ER visits and exacerbations. In this cohort, other risk factors for exacerbations include GOLD stage, comorbidities, baseline heart rate, and use of long-acting beta2-agonists.<sup>21</sup>

## CONCLUSION

In summary, beta blockers showed the effect to reduce the exacerbation or exacerbation related mortality of COPD in some cases. More studies needed in the future for more evidence of the use of beta blockers as the treatments in patients with COPD.

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