



Selective Beta-Blockers on Chronic Obstructive Pulmonary Disease: A Literature Review

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Abstract

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are usually coexisting. While beta-blockers are the indispensable management of an array of cardiovascular diseases, inhaled beta-receptor agonists are the central treatment for COPD patients. This review aims to assess the effect of beta-blockers on exacerbation rate, mortality, and quality of life among the COPD population. After the search on Cochrane Library, Pubmed, and Scopus, 15 relevant full-text articles published between 2012 and 2022 were included. We compared selective beta-blockers versus either non-users or non-selective agents. The results showed that selective beta-blockers did not increase the mortality and exacerbation rate in the COPD population and evidence on health-related quality of life is still sparse. However, more RCTs should be carried out for more precise information.

Keywords: beta-blockers, COPD, COPD exacerbation, mortality, quality of life

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are usually coexisting. While beta-blockers are the indispensable management of an array of cardiovascular diseases, inhaled beta-receptor agonists are the central treatment for COPD patients.¹ Hence, many physicians worry that the administration of beta-blocker may devastate the stable condition of COPD and

this misconception may prevent patients from guideline-recommended treatment.

COPD, a progressive chronic obstructive pulmonary condition, is suspected in over-35-year-old heavy smokers who have chronic dyspnea, progressive limitation of physical activities, and chronic cough. COPD is diagnosed given the post-bronchodilator FEV₁/FVC of under 0.7.²

The main risk factor of COPD is protracted smoking or other inhaled toxic substance exposure. The acute worsening

episodes of COPD symptoms are called exacerbations, which have negative repercussions on patients' quality of life and the disease prognosis.²

In 2019, 3.23 million patients died from COPD and the majority of them were under 70. Additionally, COPD results in a remarkable financial encumbrance due to reduced productivity, everyday management expenses, and costs for acute flare-ups.³ According to the EPIC survey performed in nine countries in the Asia-Pacific region, when 112,330 households were screened, 4289 individuals had the diagnosis of COPD. The estimated prevalence was 6.2%, with 19.1% of severe disease. 50% of patients in this survey reported acute events during the previous year.⁴

Both COPD and its acute exacerbations cause great encumbrance for not only individual patients but also the community. Hence, the control of COPD including interfering with acute events, reducing mortality, protecting the residual lung function, and improving daily symptoms and quality of life is important.⁵

CVDs are the common comorbid condition of COPD.⁶ COPD patients have a considerably higher risk of ischemic heart disease, heart failure, cardiac dysrhythmia, pulmonary hypertension, and peripheral arterial diseases compared to healthy individuals.⁷

The assumed mechanisms of the relationship between these two conditions are multifaceted. The first element is the common risk factors including cigarette consumption, sedentary lifestyle,

unhealthy diet, and exposure to pollution.⁸ Secondly, emphysema in COPD patients also plays an important role. Hyperinflation increases the pressure on the cardiac system, causes dysfunction of the right ventricle, reduces the left ventricular filling, and then decreases the cardiac output.^{8,9}

Furthermore, hypoxemia, resulting from pulmonary hyperinflation, leads to vasoconstriction, vascular remodeling, and cardiac repolarization alteration. The consequences are arrhythmias and sudden cardiac death. Chronic pulmonary inflammation increases the inflammatory factors such as surfactant protein D, C-reactive protein, fibrinogen, IL-6, IL-8, and TNF- α in the systemic circulation. These factors result in arterial stiffness and CVD.^{8,9}

CVD harms COPD progression and outcomes. CVD increases the rate of hospitalization, hospital length of stay, in-hospital death, and readmission rate among COPD patients.⁸ COPD, in turn, worsens the stability of CVD. In the SUMMIT randomized clinical trial with 16,485 COPD patients, the risk of CVD acute events was remarkably higher 30 days after a COPD flare-up and stayed high for up to 1 year.¹⁰ Due to the vicious cycle between these two conditions, the treatment of both diseases must be optimized.

There are two types of beta-blockers, non-selective and selective agents. Selective beta-blockers affect predominantly the beta-1 receptors in cardiac and kidney tissue to hinder the effect of epinephrine and norepinephrine.

Selective beta-blockers include Atenolol, Bisoprolol, Metoprolol, Nebivolol, Betaxolol, Esmolol, and Acebutolol.¹¹ Selective beta-blockers are central to the management of many CVDs such as heart failure, atrial fibrillation, or ischemic heart diseases.^{12–14}

Regarding COPD, inhaled beta-receptor agonists affect beta-2 receptors, which are located predominantly in the airway smooth muscle, to reverse the contraction of these muscles in COPD individuals.¹⁵ While selective beta-blockers and beta-2 receptor agonists affect different receptors in the heart and the lungs, medical staff are still afraid that the co-administration of selective beta-blockers may devastate the stable situation in COPD patients. Here, we retrieve and synthesize the evidence of the safety profile of selective beta-blockers on COPD patients during the previous decade.

METHOD

Open-access full-text English articles of randomized control trials, non-randomized control trials, and observational studies published in peer-reviewed journals from 2012 to 2022 were searched in Cochrane Library, PubMed, and Scopus with the searching string of ("Cardio-selective beta-blockers OR Selective beta-1-blockers OR Atenolol OR Bisoprolol OR Metoprolol OR Nebivolol OR Betaxolol OR Esmolol OR Acebutolol) AND ("chronic obstructive pulmonary disease" OR "obstructive lung disease" OR "COPD"). The primary inclusion criteria were COPD

patients who had exposure to selective beta-blockers compared to either no beta-blocker therapy or non-selective agents. The outcomes of interest were the rate of acute exacerbations, mortality, and quality of life.

Firstly, we screened the titles and abstracts for relevant studies and appropriate information. Then, the articles without open access were excluded. The open-access full-text versions were analyzed by a single investigator for appropriate methodology and eligibility criteria. The reference list of all studies was rechecked to eliminate duplications.

After the search and screening process, 15 articles were included. For each study, data were extracted on the name of authors, year of publication, country of origin, design, study period, sample size, age, type of beta-blockers, and outcomes. Trends of outcomes were summarized and highlighted to build the report and identify evidence gaps.

RESULTS

The electronic search identified 107 records. After removing 11 duplications, 1 research protocol, and 80 papers with inappropriate research questions, design, and language, or no free full text, 15 articles were included. Of over 15 publications, 11 studies reported the mortality rate, 7 studies gave information about the rate of acute exacerbations and only 2 papers informed the quality of life.

Table 1. Study characteristics

Author	Design and time range	Country and time range	Age range (years)	Population	Number of subjects	Intervention	Comparison	Outcome
Dransfield et al (2019)	<ul style="list-style-type: none"> Prospective, doubled blinded RCT[†] May 2016 – March 2019 	The United States	<ul style="list-style-type: none"> Range: 40–85 Mean: 65.0±7.8 	COPD* patients/ moderate airflow limitation + increased AECOPD [§] risk	<ul style="list-style-type: none"> Treatment group: 268 Control group: 246 	Extended-release Metoprolol	Placebo	The time until the first exacerbation
Ke et al (2016)	<ul style="list-style-type: none"> RCT[†] Jan 2012 – Jan 2015 	China	Range: 48-74	Inhospital patients with HF [‡] + COPD*	<ul style="list-style-type: none"> Treatment group: 60 Control group: 60 	Bisoprolol fumarate + trimetazidine	<ul style="list-style-type: none"> Standard therapy: HF[‡]: Low flow oxygen inhalation + inotropic agents + reduced cardiac stress COPD*: antibiotics, doxofylline and ambroxol 	Health-related quality of life
He et al (2017)	<ul style="list-style-type: none"> RCT[†] Jul 2013 – Jul 2014 	China	Range: 44-85	AECOPD [§] patients complicated with right HF [‡]	<ul style="list-style-type: none"> Treatment group: 50 Control group: 50 	Metoprolol tartrate oral	COPD* standard treatment following GOLD 2013	AECOPD [§] Mortality rate
Angeloni et al (2013)	<ul style="list-style-type: none"> Prospective Cohort study Apr 2004 – Apr 2009 	Italy	<ul style="list-style-type: none"> Mean: Treatment group: 70±8 Control group: 70±9 	COPD* patients undergoing coronary artery bypass grafting	<ul style="list-style-type: none"> Treatment group: 104 Control group: 104 	Selective beta-blockers (Atenolol, Bisoprolol, Metoprolol, Nebivolol)	No beta-blockers	AECOPD [§] Overall mortality

Author	Design and time range	Country and time range	Age range (years)	Population	Number of subjects	Intervention	Comparison	Outcome
Zvizdic et al (2019)	<ul style="list-style-type: none"> Prospective cohort study 12-month follow-up 	Bosnia and Herzegovina	---	COPD* patients	<ul style="list-style-type: none"> Treatment group: 24 Control group: 44 	Selective beta-blockers (Bisoprolol, Metoprolol, Nebivolol)	Verapamil and Digoxin	AECOPD [§]
Karimi et al (2020)	<ul style="list-style-type: none"> Prospective population-based cohort study Jan 1991 – Jan 2011 	Netherlands	Mean: 69.7±9.2	COPD* patients with cardiovascular indication of beta-blockers	Total population: 1312	Selective beta-blockers	No beta-blockers	AECOPD [§]
Dong et al (2016)	<ul style="list-style-type: none"> Retrospective cohort study 1994 - 2013 	The United States, Italy, Taiwan	Mean: 71	COPD* patients who hospitalized for acute coronary syndrome	<ul style="list-style-type: none"> Treatment group: 18406 Control group: 4579 	Selective beta-blockers	Non-dihydropyridine calcium channel blocker	All-cause mortality
Su et al (2016)	<ul style="list-style-type: none"> Retrospective population-based cohort study Jan 2000 – Dec 2009 	Taiwan	Median: 70 (20–101)	HF ⁺ and COPD* patients	Total population: 11558	Bisoprolol, Metoprolol, Carvedilol	No beta-blocker	Mortality
Mentz et al (2013)	<ul style="list-style-type: none"> Retrospective analysis with data from OPTIMIZE-HF 2003 - 2004 	The United States	Mean age of COPD* population: 73 (63–80)	COPD* patients with LVSD	COPD* population: 722 patients	Selective beta-blockers	No beta-blockers & non-selective beta-blockers	Mortality

Author	Design and time range	Country and time range	Age range (years)	Population	Number of subjects	Intervention	Comparison	Outcome
Kubota et al (2021)	<ul style="list-style-type: none"> Retrospective analysis with data from the ASIAN-HF registry 2010 - 2015 	China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand	<ul style="list-style-type: none"> Treatment group: 63.3±13.6, Control group: 66.8±12.7 	HF ⁺ and COPD* patients	<ul style="list-style-type: none"> Total population: 412 Treatment group: 149 Control group: 139 	Selective beta-blockers (Bisoprolol, Metoprolol, Nebivolol)	No beta-blocker	All-cause mortality Cardiovascular mortality
Huang et al (2017)	<ul style="list-style-type: none"> Population-based nested case-control study 1998 - 2010 	Taiwan	<ul style="list-style-type: none"> Case group: 72.12±8.25 Control group: 72.50±9.01 	COPD* patients	<ul style="list-style-type: none"> Treatment group: 16067 Control group: 55970 	Selective beta-blocker	No beta-blocker	AECOPD [§]
Mentz et al (2013)	<ul style="list-style-type: none"> Analysis with data from HF-ACTION 2003 - 2007 	The United States, Canada, France	Median: 64 (56–71)	HF ⁺ and COPD* patients with ejection fraction ≤35%	249	Selective beta-blocker	Non-selective beta-blocker	Mortality
Chung et al (2022)	<ul style="list-style-type: none"> Retrospective cohort study Jan 2001 – Dec 2013 	Taiwan	<ul style="list-style-type: none"> Treatment group: 70.7±11.8 Control group: 70.7±22.7 	COPD* patients with myocardial infarction	<ul style="list-style-type: none"> Treatment group: 7247 Control group: 7542 	Selective beta-blocker	Non-selective beta-blocker	All-cause mortality

Author	Design and time range	Country and time range	Age range (years)	Population	Number of subjects	Intervention	Comparison	Outcome
Stefan et al (2012)	<ul style="list-style-type: none"> Retrospective cohort study Jan 2006 – Dec 2007 	The United States	Median: 72 (64–94)	Ischemic heart disease, congestive HF [‡] and hypertension patients hospitalized for AECOPD [§]	<ul style="list-style-type: none"> Treatment group: 7639 Control group: 2431 	Selective beta-blocker	Non-selective beta-blocker	In-hospital mortality
Kubota et al (2015)	<ul style="list-style-type: none"> Retrospective, non-randomized single center trial Jan 2009 – Dec 2012 	Japan	<ul style="list-style-type: none"> Treatment group: 78.2±8.2 Control group: 79.1±6.5 	COPD* patients hospitalized for acute decompensated HF [‡]	<ul style="list-style-type: none"> Bisoprolol group: 34 Carvedilol group: 52 No beta-blocker: 46 	Bisoprolol	Carvedilol	All-cause mortality

Note: *: Chronic obstructive pulmonary disease; †: randomized controlled trial; ‡: heart failure, §: acute exacerbation of COPD; ||: global obstructive lung disease

The main characteristics of these studies are shown in Table 1. In this article, we compare the effect and safety of selective beta-blockers versus no beta-blocker therapy and non-selective agents.

Among 15 included studies, 11 compared selective beta-blockers with non-users. 7 citations reported the mortality rate, 6 conveyed the rate of acute events and only 2 discussed the quality of life.

The beta-blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease (BLOCK COPD trial) is a double-blind RCT, which assessed the risk exacerbations and mortality rate of Metoprolol in 532 COPD patients aged between 40 and 85 years who had moderate airflow limitation with increased risk of acute events at 26 medical centers in the United States from May 2016 to March 2019.¹⁶

In the intervention group, Metoprolol was prescribed with the initial dose of 50 mg per day for 42 days before being titrated to 25, 50, and 100 mg per day based on the heart rate, systolic blood pressure, FEV₁ and side effects of Metoprolol.¹⁶

After 336 days, patients in both arms were weaned off either Metoprolol or a placebo and followed until 378 days for any symptoms of Metoprolol withdrawal. As a result, 11 and 5 individuals died in Metoprolol and control groups, respectively, with unadjusted HR of 2.18 (95% CI=0.76–6.29) and adjusted HR of 2.13 (95% CI=0.69–6.42; P=0.14).¹⁶

Another double-blind RCT in China assessed the safety of Metoprolol Tartrate

prescribed for 100 heart failure patients who were hospitalized for acute exacerbation of COPD. As many as 100 patients aged 44 to 95 years were randomly assigned to Metoprolol and standard treatment arms. The dose of Metoprolol was sequentially adjusted to 6.25 mg, 12.5 mg, and 25 mg twice a day. Although no value of P was demonstrated, the mortality rate in the Metoprolol arm (0.0%) was lower than the control one (4.3%).¹⁷

Angeloni et al assessed the prescription of beta-blockers in 104 COPD patients who underwent coronary artery bypass grafting compared with 104 patients receiving no beta-blocker therapy at one institute from April 2004 to April 2009.¹⁸

Beta-blockers included Atenolol, Bisoprolol, Metoprolol, or Nebivolol. While the 30-day and in-hospital mortality were similar in both groups, the overall mortality after 3 years of follow-up in the beta-blocker group (7.7%) was lower than the control group (18.3%) with the value of P=0.03. The death incidence of the intervention group was 3.02 deaths per 100 patient-year, half of the control one, 7.03 deaths per 100 patient-year, with a relative risk reduction of 57% (P=0.004).¹⁸

By retrieving five databases in the United States, Taiwan, and Italy, Dong et al recruited 22985 COPD patients hospitalized for acute coronary syndrome to evaluate the safety of selective beta-blockers (22985 patients) compared to non-dihydropyridine calcium channel blockers (4579 patients).¹⁹ The all-cause

mortality crude HRs for selective agents compared to the control one were 0.73 (95% CI=0.65-0.83). Using the high-dimensional propensity score matching technique, the treatment group included 11497 patients and the control group comprised 3588 people with adjusted HRs were 0.90 (95% CI=0.78-1.02).

A nationwide retrospective population-based cohort study in Taiwan recruited 11558 COPD individuals who had concomitant heart failure from the Taiwan National Health Insurance Research Database between January 2000 and December 2009 to assess the survival effect of Bisoprolol, Metoprolol, and Carvedilol compared with no beta-blocker therapy. The defined daily doses of Carvedilol, Bisoprolol, and Metoprolol were 6.25 mg, 1.25 mg, and 25 mg in that order. The patient population was divided into two groups, heart failure with and without concomitant COPD.²⁰

In the COPD subgroup, only Bisoprolol showed an association regarding survival effect compared with nonuse while no association between Carvedilol and Metoprolol was observed. The effect of low and high posology was also analyzed. Additionally, this effect was dependent on bisoprolol posology. Low-dose with HR=0.76 (95% CI=0.59–0.97; P=0.030) and high-dose with HR=0.40 (95% CI=0.26–0.63; P<0.001).²⁰

Using data from the large national registry and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) in the United States, Mentz

et al performed a retrospective analysis of 722 COPD patients who had an ejection fraction of less than 40% to evaluate the safety of selective beta-blockers versus non-users in COPD population. The HR for 60-day mortality when comparing cardio-selective and no beta-blocker therapy was 0.53 (95% CI=0.25–1.13).²¹

Extracting data from the ASIAN-HF registry, a prospective observational multinational study performed in 11 Asian countries from 2010 to 2015, Kubota et al recruited 412 heart failure who had concomitant COPD and divided these patients into 3 groups regarding the type of beta-blocker: non-users (n=139), selective (n=149), and non-selective agents (n=124).²²

Hence, all-cause mortality, cardiovascular mortality, and heart-failure-related rehospitalization were measured. Concerning all-cause mortality, the adjusted HR of selective beta-blockers compared with non-users was 0.58 (95% CI=0.34–0.99; P=0.044) while no association was observed before the adjustment (P=0.139). Furthermore, no association between cardio-selective agents and cardiovascular mortality.

In the previously mentioned BLOCK COPD trial, which compared Metoprolol and placebo on 532 COPD patients, no significant difference in the median time until the first exacerbation between the intervention and control groups with the unadjusted HR=1.05 (95% CI=0.84–1.32; P=0.66) and adjusted HR=1.12 (95% CI=0.88–1.42). While there was no difference in the overall rates of

exacerbations between the two groups with a rate ratio of 1.05 (95% CI=0.85–1.28), the rate of severe exacerbation and very severe exacerbation was higher in the Metoprolol group compared to the control arm, with the rate ratio of 1.51 (95% CI=1.00–2.29) and 3.71 (95% CI=1.10–16.98) respectively.¹⁶

The previously mentioned RCT in China by He et al also studied the effect of Metoprolol Tartrate on the frequency of acute COPD exacerbations among 100 heart failure patients hospitalized due to acute exacerbation of COPD between July 2013 and July 2014.¹⁷ The exacerbation frequency of the Metoprolol arm (1.64±0.94 times/year) was significantly higher than the control arm (2.04±0.82 times/year; $t = -2.215$; $P = 0.029$).

The prospective cohort study by Angeloni et al outlined in the previous part also reported the results on COPD exacerbations. As demonstrated in this study, the COPD exacerbation rate of the intervention group (Atenolol, Bisoprolol, Metoprolol, or Nebivolol) was similar to the control one (44.2% vs 43.3%; $P = 0.99$).¹⁸ The person-time incidence of the beta-blocker group was 17.4 events/100 patient-years versus 16.7 events/100 patients-years for the control population (4% relative risk increase; $P = 0.47$).

In another prospective cohort study, Zvidic et al recruited 68 GOLD II-III COPD patients with a left ventricular ejection fraction of more than 35% and divided them into 2 groups of moderate (GOLD II) and severe (GOLD III) airflow obstruction given the spirometry results.²³

In each group, the intervention arm was treated with Metoprolol, Bisoprolol, and Nebivolol while the control arm received Verapamil along with Digoxin. The follow-up period was 12 months and the endpoint was the frequency of exacerbations. As a result, the number of exacerbations of the experimental arm (0.600±0.632) was remarkably inferior to the control group (1.333±0.963) with the value of $P = 0.007$ in the moderate airflow obstruction group while no statistical difference between the two arms was found in the severe airflow obstruction group.²³

From the Rotterdam study, which is a prospective population-based cohort study in the Netherlands on 15000 participants, Karimi et al followed 1312 COPD subjects from January 1991 to January 2011 intending to evaluate the association between beta-blocker and COPD exacerbations in patients with and without cardiovascular indications for beta-blockers.²⁴

In the total population of 1312 patients, the current use of selective agents decreases the risk of flare-ups compared with non-users ($HR = 0.69$; 95% CI=0.58–0.83; $P = 0.00005$). With subgroup analysis in patients with cardiovascular indication for beta-blockers, the current use of selective agent also reduced the number of COPD acute events compared to non-users ($HR = 0.69$; 95% CI=0.57–0.85; $P = 0.0004$) while this association was not proved in the group without cardiovascular indication for beta-blocker ($HR = 0.94$; 95% CI=0.55–1.62; $P = 0.835$).²⁴

From 1998 to 2010, a population-based nested case-control study retrieved 16067 COPD patients with severe exacerbations and 55970 stable COPD patients from the Taiwan National Health Insurance Research Database as the case and the control groups to assess the safety of beta-blockers on COPD patients. The age, gender, COPD diagnosis period, and beta-blocker use duration were matched in both groups.²⁵

What was observed, is that there was a lower risk of acute exacerbations in the current selective beta-blocker users compared with the non-users (OR=0.90; 95% CI=0.85–0.96). Among Acebutolol, Atenolol, Betaxolol, Bisoprolol, and Metoprolol, Betaxolol showed a significant reduction of acute exacerbation risk (OR=0.75; 95% CI=0.60–0.95).²⁵

Two studies reported the health-related quality of life and both studies used St. George's Respiratory Questionnaire. An RCT performed between January 2012 and January 2015 randomly recruited 120 patients aged 48 to 74 years to compare the combination of Bisoprolol and Trimetazidine with the standard treatment in grade II-III heart failure with comorbid COPD.²⁶

The standard treatment included low-flow oxygen, inotropic agents, antibiotics, Doxofylline, and reduced cardiac stress therapy. Trimetazidine was given orally at 20 mg 3 times per day. The posology of Bisoprolol was increased gradually depending on the patient's tolerance.²⁶

The results showed no statistical differences between the 2 groups with St. George's Respiratory Questionnaire total scores before treatment of 55±13 and 54±12 for the control and treatment groups respectively (P>0.05). However, after the treatment administration, the score of the treatment group (40±11) was significantly lower than the control group (54±12) with the value of P<0.05.²⁶

Once again, the previously mentioned BLOCK COPD trial also showed no difference between the Metoprolol and placebo groups. However, no specific data were shown.¹⁶

Among 15 articles, 5 publications compared cardioselective versus non-selective agents. All 5 studies conveyed the mortality rate and only 1 study discussed the COPD exacerbation rate. No study gave information on the quality of life.

With the data from the OPTIMIZE-HF trial as mentioned above, Mentz et al performed a retrospective analysis in 722 COPD patients who had an ejection fraction of less than 40% to compare not only the selective beta-blockers versus non-users but also the selective versus non-selective agents. What is concluded, is that no significant difference was found regarding 60-day mortality with HR=1.14 (95% CI=0.57–1.56).²¹

With the data from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), which was a multicenter RCT in the United States, Canada, and France to evaluate the effect and safety of physical activity training in heart failure patients, Mentz et al identified

249 COPD patients aged 56 to 71 and performed an analysis to investigate the risk of mortality/hospitalization of beta-blocker use.²⁷ In this COPD cohort, no evidence for the association of beta-blocker types and risk of mortality/hospitalization was found with an adjusted HR=0.91 (95% CI=0.64–1.29; P=0.58).

More recently, a retrospective nationwide population-based cohort study enrolled 7247 patients using selective beta-blockers and 7542 patients on non-selective agents from the Taiwan National Health Insurance Research Database to compare 2 types of beta-blockers on COPD patients who had a comorbid myocardial infarction. Patients were followed every 3 months until withdrawal, death, or December 2013.²⁸

All-cause mortality and major adverse cardiac and cerebrovascular events were the outcomes of interest. In terms of mortality, the results showed that the selective agents showed a superior safety profile than the non-selective one after the inverse probability of treatment weighting (8.9 vs 9.6 events per 100 person-years; HR=0.93; 95% CI=0.89–0.96). With subgroup analysis, Bisoprolol was better than Carvedilol (9.3 vs 10.3 events per 100 person-years, HR=0.90; 95% CI=0.86–0.94).²⁸

As many as 7639 and 2431 COPD patients receiving selective and non-selective beta-blockers for ischemic heart disease, congestive heart failure, and hypertension were retrieved from the Perspective inpatient administrative database and included in a retrospective

cohort study from 1 January 2016 to 1 December 2017.²⁹

The outcomes included in-hospital mortality, late mechanical ventilation, hospital length of stay, and 30-day readmission. Metoprolol (74%) and Atenolol (23.5%) were the most common selective agents prescribed while Carvedilol (85%) and Propranolol (7.2%) were most indicated as non-selective medications. After matching by propensity score adjustment, there was no association between the selectivity of beta-blockers and in-hospital mortality with OR=0.88 (95% CI=0.71–1.09).²⁹

Kubota et al conducted a retrospective, non-randomized, single-center trial from 1 January 2009, to 31 December 2012 on 132 COPD patients hospitalized for acute decompensated heart failure.²²

At discharge, 46 patients received no beta-blockers, 52 patients received Carvedilol, 34 patients received Bisoprolol, and all of them were followed every 1-2 months. When comparing Carvedilol and Bisoprolol, no difference in all-cause mortality rate was found (11.5% and 8.8%, correspondingly).²²

Also, in the retrospective, non-randomized, single-center trial by Kubota et al in 2015 on 132 COPD and heart failure patients, Carvedilol, a non-selective agent, demonstrated a higher rate of acute exacerbations of either heart failure or COPD than Bisoprolol (55.8% vs 17.6% respectively; P=0.033).²² It concluded that Bisoprolol was safer than Carvedilol.

DISCUSSION

COPD, which results from bronchitis with/without emphysema, is diagnosed given the exposure to risk factors, appropriate clinical findings, and spirometry results.² It is well established that CVDs are a prevalent comorbid disease in COPD patients.^{6,7} While inhaled beta-agonists are the main medication for COPD patients,² beta-blockers are the hallmark of the treatment for many CVDs.¹

Medical staff worldwide are concerned that the treatment of beta-blockers may devastate the stable condition of COPD. Hence, we aim to summarize the evidence available during the last decade about the safety of selective beta-blockers on COPD patients focusing on 3 outcomes including mortality, acute exacerbation, and quality of life. Primarily, we intended to include only RCTs but after the preliminary database search, only 3 RCTs during the previous decade were found. Hence, we included all study types including randomized control trials, non-randomized control trials, and different types of observational studies. As a result, 15 studies were identified and most were cohort studies.

Firstly, we aim to compare selective beta-blocker versus no beta-blocker therapy. Among 7 studies that compared the mortality rate between the 2 groups, 3 studies concluded that the mortality rate was similar, and 4 studies reported that selective agents decrease the risk of death in COPD patients. In other words, selective beta-blockers did not increase the mortality

rate in COPD patients. Among 6 studies that gave information on COPD acute exacerbation, 2 showed similar results between groups, 3 indicated that selective agents could reduce the risk of exacerbations and 1 reported that the risk of exacerbation was related to the severity of airflow limitation. To clarify, the risk of COPD acute events does not increase when patients are prescribed selective beta-blockers.

The mortality and acute exacerbation safety of beta-blockers in COPD patients have been proven in some previous systematic reviews and meta-analyses. A systematic review and meta-analysis by Etminan et al included 9 retrospective cohort studies from 1961 to 2012 to clarify this safety.³⁰

Although there were biases and heterogeneity between studies, the protective effect on all-cause mortality was demonstrated with a pooled relative risk of 0.69 (95% CI=0.62–0.78; I²=82%). This study is different from ours because there was no selectivity of beta-blockers. Another meta-analysis by Du et al with 15 cohort studies published between 1966 and 2013 showed the reduction of overall mortality (relative risk of 0.72 with 95% CI=0.63–0.83) and COPD exacerbation (relative risk of 0.63 with 95% CI of 0.57 – 0.71) in the beta-blocker group.³¹

However, like the previous one, this meta-analysis included both selective and non-selective medications in the intervention group, which is different from our review. More recently, Gulea et al included 23 observational studies and 14

RCTs. In terms of COPD exacerbation, only 1 RCT and 5 observational studies were identified and included.³²

The result is that the risk of COPD flare-up is reduced with the presence of beta-blockers (HR=0.78; 95% CI=0.74–0.82). With respect to mortality, the narrative syntheses showed the adjusted risk estimates between beta-blocker versus no beta-blocker therapy were from HR was 0.46 (95% CI=0.19–1.11) to 1.19 (95% CI=1.04–1.37). Hence, beta-blockers did not have a detrimental effect on the COPD population. Again, this meta-analysis assessed both selective and non-selective agents.

Therefore, we further our review and compare selective and non-selective agents. In terms of mortality, 4 studies showed no difference between 2 agents and only 1 paper reported the superior effect of selective medication. Regarding exacerbation rate, only one publication was available and the sample size was relatively small (132 patients). In most of these studies, the superior effect of selective beta-blockers in the COPD population was not concluded but the number of studies was relatively small and there was a lack of RCTs, which are the best design in the hierarchy of evidence.

Additionally, we identify some gaps that can be filled by further research. Firstly, an array of observational studies concerning the utilization of beta-blockers in the COPD population were published but high-quality RCTs and related systematic reviews and meta-analyses are still sparse. Secondly, the evidence on quality of life

was still limited. There were only 2 RCTs that compared the St. George's Respiratory Questionnaire between selective beta-blockers and non-users during the last 10 years and the results were contradictory. Hence, more well-designed research should be conducted to fill in these gaps.

CONCLUSION

This review shows that the use of selective beta-blockers among COPD patients is safe because these medications do not increase death and COPD exacerbation. However, there should be more double-blind RCTs with appropriate sample sizes to critically examine this safety. Furthermore, we are unable to establish the superior safety of selective beta-blockers compared with non-selective agents because the evidence with high-quality methodological design on this question is still sparse. Ultimately, the evidence on health-related quality of life is limited and more research is needed to shed light on this problem.

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