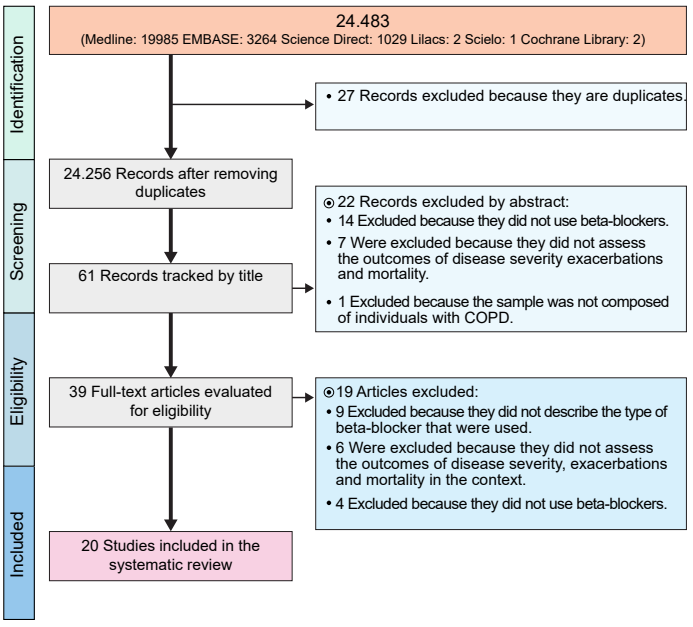
Review

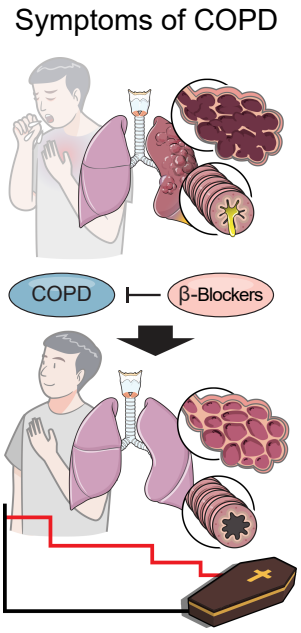
trd Tuberculosis & Respiratory Diseases

Effects of the Use of Beta-Blockers on Chronic Obstructive Pulmonary Disease Associated with Cardiovascular Comorbities: Systematic Review and Meta-analysis

Natasha Cordeiro dos Santos, M.Sc., Aquiles Assunção Camelier, Ph.D., Anne Karine Menezes, M.Sc., Victor Durier Cavalcanti de Almeida, M.Sc., Roberto Rodrigues Bandeira Tosta Maciel, Ph.D. and Fernanda Warken Rosa Camelier, Ph.D.

Department of Life Sciences, State University of Bahia, Salvador, Brazil





Abstract

Cardiovascular comorbidity is common in individuals with chronic obstructive pulmonary disease (COPD). This factor interferes with pharmacological treatment. The use of β-blockers has been proposed for their known cardioprotective effects. However, due to their adverse reactions, and the risk of causing bronchospasm, there is reluctance to use them. To summarize existing evidence on the effects of β-blocker use in COPD associated with cardiovascular comorbidities in relation to disease severity, exacerbation, and mortality outcomes. EMBASE, Medline, Lilacs, Cochrane Library, and Science Direct databases were used. Observational studies that evaluated the effects of β-blockers on individuals with COPD and cardiovascular comorbidities, and related

https://doi.org/10.4046/trd.2024.0013
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2024;87:261-281

Address for correspondence
Natasha Cordeiro dos Santos, M.Sc.
Department of Life Sciences, State University of Bahia, Silveira Martins Street, 2555, Salvador 41150-000, Brazil
E-mail natasha-cordeiro@hotmail.com

Received Jan. 27, 2024
Revised Mar. 18, 2024
Accepted Mar. 29, 2024
Published online Apr. 4, 2024

disease severity, exacerbations, or mortality outcomes were included. Studies that did not present important information about the sample and pharmacological treatment were excluded. Twenty studies were included. Relevance to patient care and clinical practice: The use of β-blockers in individuals with COPD and cardiovascular disease caused positive effects on mortality and exacerbations outcomes, compared with the results of individuals who did not use them. The severity of the disease caused a slight change in forced expiratory volume in 1 second. The odds ratio for mortality was 0.50 (95% confidence interval [CI], 0.39 to 0.63; p<0.00001), and for exacerbations, 0.76 (95% CI, 0.62 to 0.92; p=0.005), being favorable to the group that used β-blockers. Further studies are needed to study the effect of using a specific β-blocker in COPD associated with a specific cardiovascular comorbidity.

Keywords: Chronic Obstructive Pulmonary Disease; Cardiovascular Diseases; Mortality; Beta Blockers; Systematic Review

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by the chronic and persistent obstruction of small and medium airways. This disease is mainly caused by exposure to tobacco smoke, occupational exposure, and biomass combustion[1-3]. It is related to high rates of morbidity and mortality[2,4], especially when individuals have other associated concomitant diseases, such as cardiovascular ones[5].

Cardiovascular comorbidity is common in individuals with COPD due to smoking, in addition to other shared risks that include genetic susceptibility, systemic inflammation, and aging[6]. In recent years, systemic inflammation has been increasingly recognized as an important common pathway for both conditions[7]. This inflammation, expressed by increased levels of cytokines, such as tumor necrosis factor α, interleukin-1 (IL-1), and IL-6, can accelerate and perpetuate disease progression and exacerbations of both diseases[8]. Furthermore, evidence indicates that individuals with COPD and concomitant heart disease have a worse prognosis, compared to subjects with only COPD, and is associated with higher mortality[1,9].

Other factors can contribute to the occurrence of compromised cardiac function in the disease. Individuals with this disease seem to have a larger left ventricular mass, which impacts their survival[10]. The pulmonary hyperinflation characteristic of the disease can cause cardiac compression, reducing both the left ventricle and the atrium filling, even in the absence of increased pulmonary arterial pressure[11,12]. These conditions can be aggravated by the negative effects of hypoxemia on diastolic filling[13].

These factors promote a high prevalence of cardiovascular comorbidities, which interferes with the choice of therapeutic interventions, including pharmacological treatment. The use of β-blockers has been proposed for their known cardioprotective effects, in addition to reducing heart rate, and improving systolic and diastolic dysfunction. However, due to adverse reactions, and the risk of causing bronchospasm, there is reluctance to use them. One of the key issues regarding the more widespread use of β-blockers in COPD is the concern with β2 receptor antagonism and associated airway smooth muscle constriction, which can occur even with cardioselective agents that exhibit preferential β1 blockade, leading to a worsening of lung function, especially in more severe cases with compromised respiratory reserve[14].

As a result, through current scientific evidence, researchers have sought to investigate the effects of the use of these drugs in COPD, especially in terms of disease severity, exacerbations, and mortality. However, the articles that address this issue are heterogeneous, carried out in populations with specific characteristics, who use different classes and doses of β-blockers, and consequently present different results. Therefore, a current systematic review of these studies is necessary to resolve the present differences, understand the effects of these drugs on different outcomes, and finally, contribute to decision-making.

Thus, the aim of the present study is to summarize the existing evidence on the effects of the use of β-blockers in COPD associated with cardiovascular comorbidities in relation to the outcomes of disease severity, exacerbations, and mortality.

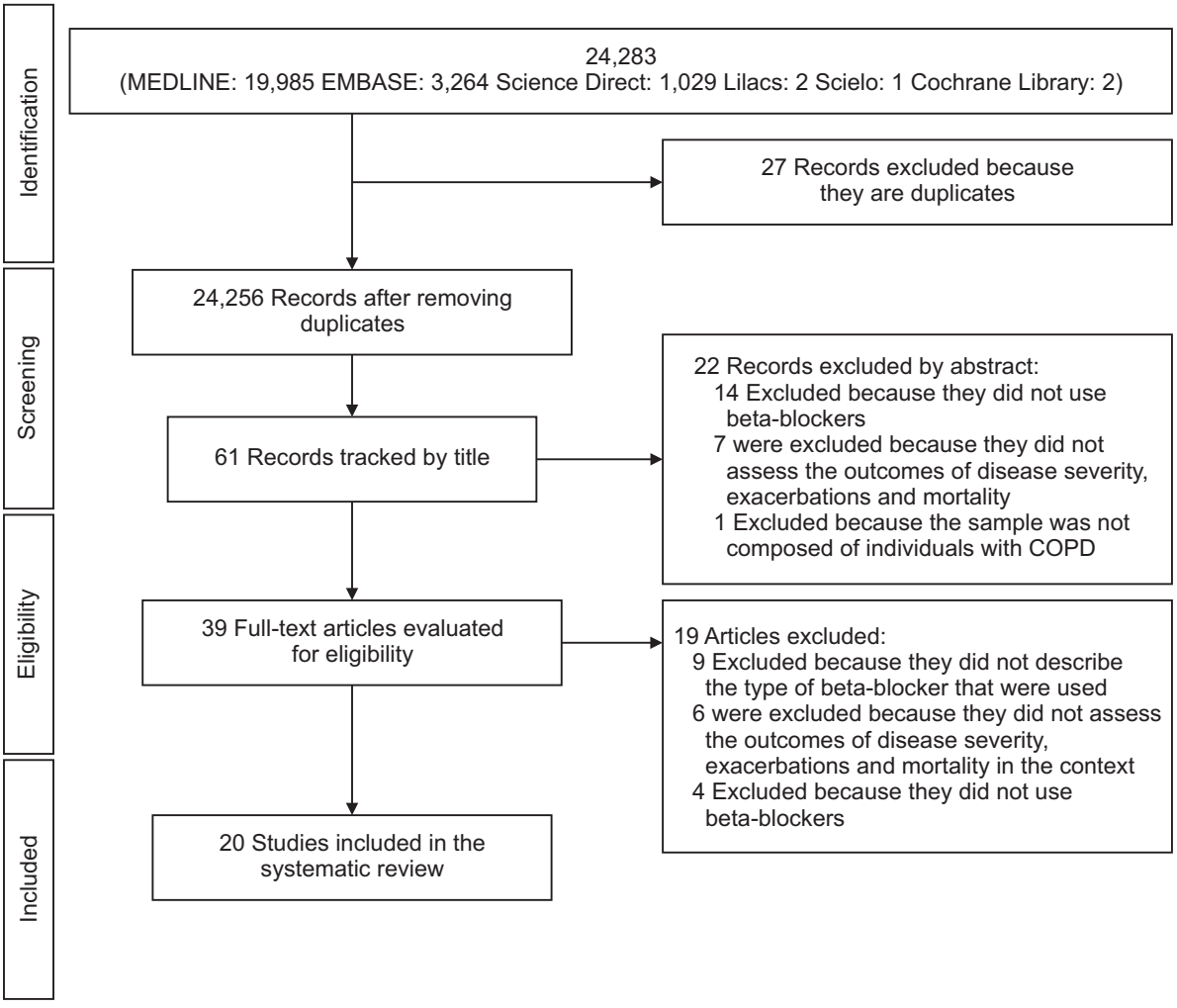
Materials and Methods

This is a systematic review and metanalysis study carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Recommendation (Main Items for Reporting Systematic Reviews and Meta-analysis)[15]. The following databases were used: EMBASE, Medical Literature Analysis and Retrieval System Online (Medline), Latin and Caribbean Literature of Sciences de la Health (Lilacs), and Scientific Electronic Library Online (Scielo), Cochrane Library, and Science Direct. The collection was carried out from June 2023 to January 2024.

The elaboration of this research was structured based on the PICOS strategy, an acronym for Population (individuals with COPD and cardiovascular diseases), Intervention—or Exposure, for observational studies (use of β-blockers), Comparison (cardioselective and non-selective), Outcomes (severity of the disease, exacerbations, and mortality), and Study design (observational studies)[16]. The keywords and synonyms were used according to the databases: "Pulmonary Disease, Chronic Obstructive; Cardiovascular Diseases; Severity of Illness; Disease exacerbation; Mortality; Adrenergic beta-antagonists," identified in the *DeCS* vocabulary system (*Descritores em Ciências da Saúde* [Health Sciences Descriptors]), the Medical Subject Headings (MeSH), and Embase Subject headings (Emtree), using the Boolean operators "AND" and "OR." The search was performed using the words found in the titles, subjects, and abstracts of the articles.

Observational studies were included in which the effects of β-blockers in individuals with a diagnosis of COPD (confirmed by spirometry) and cardiovascular comorbidities were included, and related to the outcomes of disease severity, exacerbations, or mortality. Studies should present the odds ratio (ORs) or mean and standard deviation and their corresponding confi-

Figure 1. Research flow diagram. COPD: chronic obstructive pulmonary disease.



https://doi.org/10.4046/trd.2024.0013

https://e-trd.org/

Table 1. Characteristics of the selected articles

Study	Type of study (duration of study)	Data source (country/location)	Trial sample (follow-up)	Cardiovascular comorbidity
Au et al. (2004)[18]	Retrospective cohort study (Dec. 1996 and Oct. 1999)	Data from the Outpatient Care Quality Improvement Project (ACQUIP) (USA)	1,966 Individuals with COPD and SAH who were treated with medication from a single class of antihypertensive drugs (2 years).	SAH, acute coronary syndrome, CHF
Dransfield et al. (2008)[19]	Retrospective cohort study (Oct. 1999 and Sept. 2006)	University of Alabama Hospital Administrative Data (USA)	825 Individuals with COPD who had exacerbations: Used β-blockers (n=142); Did not use β-blockers (n=683) (1 year).	AMI, CHF
Van Gestel et al. (2008)[20]	Retrospective cohort study (1990–2006)	Secondary data from Erasmus Medical Center, Rotterdam, Netherlands (Netherlands)	1,265 Individuals with COPD who underwent elective vascular surgery between 1990 and 2006: Used β-blockers (n=462); Did not use β-blockers (n=803) (5 years).	AMI, CHF transient ischemic attack
Stefan et al. (2012)[21]	Retrospective cohort study (Jan. 1, 2006–Dec. 1, 2007)	Data from 404 hospitals participating in the Perspective Base (Premier Inc., Charlotte, NC, USA) (USA)	35,082 Individuals with COPD; COPD-EA was the main diagnosis (87%); Hypertension (43%); Ischemic heart disease with or without SAH (26%); CHF with or without ischemic heart disease (31%); History of AMI (11%) (inpatient period and 30 days after hospital discharge).	CHF, SAH, ischemic heart disease, AMI
Quint et al. (2013)[22]	Retrospective cohort study (Jan. 1, 2003–Dec. 31, 2008)	Data from the National Myocardial Ischemia Audit Project (MINAP), General Practice Research (GPRD) and Cardiovascular Disease Research, Linked Bespoke studies, and the Electronic Health Records (CALIBRE) group at the University of London (England)	1,063 Individuals with COPD who suffered their first AMI. Never used β-blocker (n=586, 55.1%); Used β-blocker before AMI (n=244, 23.0%); Prescribed only due to AMI (n=233, 21.9%) (2.9 years old).	AMI, CHF, SAH, cerebrovascular disease
Mentz et al. (2013)[23]	Retrospective cohort study (2003–2004)	Data from the Intervention and Quality of Care Registry (OPTIMIZE-HF) (USA)	2,682 Individuals with CHF; With COPD (n=725); Without COPD (n=1.957) (60–90 days after hospital discharge).	CHF, SAH, arrhythmias, cerebrovascular disease
Angeloni et al. (2013)[24]	Retrospective cohort study (April 2004–April 2009)	Primary data from subjects diagnosed with COPD undergoing elective myocardial revascularization for the first time in an institution (Italy)	1,548 Individuals undergoing the first elective surgery, with CPB. 388 (25%) Diagnosed with COPD; 104 received β-blockers (group A); 104 who did not (group B) (36 months).	CAD undergoing revascularization surgery, SAH
Puente-Maestu et al. (2014)[25]	Analytical cross-sectional study (May 2012 and May 2013)	Subjects were recruited by pulmonologists at participating hospitals (Spain)	With COPD (n=256); Without COPD (n=101) (1 year)	CHF, SAH, CAD

Table 1. Continued

Study	Type of study (duration of study)	Data source (country/location)	Trial sample (follow-up)	Cardiovascular comorbidity
Lee et al. (2014)[26]	Retrospective cohort study (2004–2007)	Cohort data from the Medicare Current Beneficiary Survey, a nationally representative sample of Medicare beneficiaries (USA)	1,062 Individuals with COPD: 531 β-blocker users; 531 did not use β-blockers (3 years).	SAH, CHF, cerebrovascular disease
Kubota et al. (2015)[27]	Retrospective cohort study (Jan. 2009–Dec. 2013)	Secondary data from a large university hospital (Japan)	132 Individuals with COPD: No β-blockers (n=46); Received β-blockers before discharge (n=86) (1 year).	SAH, AF
Dong et al. (2016)[28]	Retrospective cohort study (Jan. 1, 2007–Dec. 31, 2011)	Secondary data from the Taiwan National Health Insurance Bank (China)	107,902 Individuals with COPD; Using cardioselective β-blockers (n=49,623); Using non-dihydropyridine calcium channel blockers (n=58,279) (2 years).	SAH, CHF, ischemic heart disease
Huang et al. (2017)[29]	Case-control study (1998–2010)	Taiwan National Health Insurance Research Database (NHIRD), Taiwan National Health Insurance Research Database (China)	16,067 Individuals with COPD who used β-blockers and who had severe exacerbations. Control subjects selected from the cohort of subjects with COPD using inhaled corticosteroids and β-blockers by risk sampling (n=55,970) (60 days before and 60 days after the event).	CHF, SAH, arrhythmia, cerebrovascular disease, AMI, ischemic heart disease
Oda et al. (2017)[30]	Retrospective cohort study (Jan.–Dec., 2015)	Data from Okayama University Hospital, Kama Takamatsu Hospital, Minami-Okayama Medical Center, Kobe Red Cross Hospital, Okayama Red Cross Hospital, and Okayama Saiseikai Hospital (Japan)	103 Individuals with COPD; Using β-blocker for more than 1 year (n=31); Did not use β-blockers (n=72) (1 year).	CAD, CHF, FA, SAH
Key et al. (2017)[31]	Prospective cohort study (Apr. 2012 and Aug. 2013)	Primary data collected at the Vascular Laboratory for Routine Surveillance of Abdominal Aortic Aneurysm (AAA) (England)	38 Individuals undergoing routine AAA surveillance. Without COPD (n=23); With COPD (n=15) (7 days).	Abdominal aortic aneurysm, AF
Liao et al. (2017)[32]	Retrospective cohort study (Jan. 1, 2005 and Dec. 31, 2012)	Secondary data from the Taiwan National Health Insurance Research Database (China)	1,820 Individuals diagnosed with CHF and COPD; Used β-blocker (n=589); Did not use (n=1,231) (1 year).	Ischemic heart disease, AF, AMI, arrhythmias, cerebrovascular disease
Lim et al. (2017)[33]	Retrospective cohort study (Jan. 1, 2012–Dec. 31, 2012)	Secondary data from Royal Perth Hospital (Australia)	156 Individuals who had at least one indication for the use of β-blockers. They were using β-blockers (n=53); They were not using β-blockers and had no known contraindications for its use (n=61); They were not using β-blockers and had contraindications (n=42) (1 year).	CHF, tachyarrhythmia, ischemic heart disease

https://doi.org/10.4046/trd.2024.0013

Table 1. Continued

Study	Type of study (duration of study)	Data source (country/location)	Trial sample (follow-up)	Cardiovascular comorbidity
Maltais et al. (2018)[34]	Cohort study of the TONADO research program (uninformed)	Data from the TONADO Program, multinational, with five branches (uninformed)	5,162 Individuals with COPD: Using β-blocker (n=557); They did not use β-blockers (n=4,605) (1 year).	AMI, CAD, arrhythmias, SAH, ischemic heart disease, angina, cerebrovascular disease
Rezaei et al. (2018)[35]	Prospective cohort study (Jan. 1, 2006–Dec. 31, 2007)	Data on medical services covered by health insurance funds (Austria)	COPD using β-blockers (n=875); COPD without β-blocker use (n=826); Without COPD using β-blockers (n=754); Without COPD without the use of β-blockers (n=1,064) (6 months).	CHF, CAD, arrhythmias
Zvizdic et al. (2019)[36]	Retrospective cohort study (uninformed)	Secondary data collected at the Maglaj Health Center, Tesanj General Hospital and the Clinical Center of the University of Sarajevo (Bosnia and Herzegovina)	68 Individuals with COPD. GOLD II (n=39): Verapamil and digoxin (n=24); β-blockers (n=15: 8 metoprolol, 6 bisoprolol, and 1 nebivolol); GOLD III (n=29): Verapamil and digoxin (n=20); β-blockers (n=9, 3 metoprolol, 6 bisoprolol) (12 months).	CHF
Thomas et al. (2019)[37]	Retrospective cohort study (Jan. 25, 2012–July 25, 2016)	Secondary data from a single University of Florida academic medical center (USA)	96 Individuals with COPD hospitalized for exacerbation; Individuals who used β-blockers early during hospitalization (n=55); Individuals who did not use β-blockers during hospitalization (n=41) (inpatient period and 30 days after hospital discharge).	SAH, CHF, CAD, AF

COPD: chronic obstructive pulmonary disease; SAH: systemic arterial hypertension; CHF: congestive heart failure; AMI: acute myocardial infarction; COPD-EA: exacerbations of COPD; CPB: extracorporeal circulation; CAD: coronary artery disease; AF: atrial fibrillation; AAA: abdominal aortic aneurysm; TONADO: moderate-to-very-severe COPD.

Table 2. Analysis of the articles

Study	BB type	Outcomes	Results
Au et al. (2004)[18]	Of the individuals using β-blockers, 88% were using metoprolol or atenolol (cardioselective β-blockers) at a dose of 50 mg/day for both, and 9% were using propranolol (non-selective).	Exacerbations and mortality	Individuals who used β-blockers had an unadjusted risk of exacerbation of 0.46 (95% CI, 0.21–1.04), and after adjustment to 0.65 (95% CI, 0.29–1.48). Those who used it in the previous 180 days had little effect (not aHR, 0.56; 95% CI, 0.22–1.44) (aHR, 0.68; 95% CI, 0.26–1.76). The use of β-agonists did not change mortality (without β-agonist: HR, 0.53; 95% CI, 0.26–1.12) (with β-agonist: HR, 0.67; 95% CI, 0.31–1.49). β-Blockers had a small effect on the risk of death (HR, 0.57; 95% CI, 0.33–0.89). The addition of measures of severity, comorbidity, and lung disease did not change the risk of death (HR, 0.59; 95% CI, 0.34–1.02). Compared with other antihypertensive drugs, β-blocker had a modest effect on the risk of death (HR, 0.67; 95% CI, 0.39–1.14).
Dransfield et al. (2008)[19]	Cardioselective β-blockers (mainly metoprolol and atenolol) (n=121); Non-selective β-blockers (n=24), of these 17 used carvedilol.	Exacerbations, mortality and disease severity	The use of β-blockers (OR, 0.39; 95% CI, 0.14–0.99) and short-acting β-agonists (OR, 0.08; 95% CI, 0.02–0.30) were associated with reduction mortality. An association was found between the number of daily doses of β-blocker and mortality (OR, 0.31; 95% CI, 0.12–0.80). Subjects who died also had more prior exacerbations (2.7 vs. 1.5, p<0.001) and were more likely to have cardiovascular disease (67% vs. 35%, p<0.001) and respiratory failure (58% vs. 11%, p<0.001). In the subset of individuals with spirometric data, there was no significant difference between those who received β-blockers and those who did not received, mean±SD percentage FEV_1 predicted (41%±16% vs. 40%±15%; n=44 vs. 240, p=0.67) or FEV_1/FVC ratio (0.50±0.10 vs. 0.53±0.08, p=0.61).
Van Gestel et al. (2008)[20]	Bisoprolol (cardioselective) (n=514); Atenolol (cardioselective) (n=151); Metoprolol (cardioselective) (n=325)	Mortality	Within 30 days of surgery, 16 (4%) COPD patients who were receiving β-blockers died. On the other hand, 66 (8%) patients who were not using β-blockers died within the same period of time (p=0.001). During the entire follow-up period, 184 (40%) COPD patients who were on and 532 (67%) who were not taking β-blockers died (p=0.001). Cardioselective β-blockers were independently associated with reduced 30-day mortality in patients with (OR, 0.37; 95% CI, 0.19–0.72) and without COPD (OR, 0.34; 95% CI, 0.17–0.66) (Table 2). Throughout the follow-up period, cardioselective β-blocking agents reduced long-term mortality in COPD patients (HR, 0.73; 95% CI, 0.60–0.88). A sensitivity analysis was performed using propensity score measures to adjust for various factors, including disease severity, to address the issue of confounding by indication. In this analysis, the relationship of cardioselective β-blockade with mortality in COPD patients was similar to the main analysis (OR, 0.41; 95% CI, 0.20–0.81) (HR, 0.75; 95% CI, 0.61–0.91).
Stefan et al. (2012)[21]	Cardioselective : metoprolol (74%) and atenolol (23.5%) Non-selective: carvedilol (85%) and propranolol (7.2%)	Mortality and exacerbations	The interaction between early β-blocker treatment and type of cardiovascular disease was not significant in models of mortality (p=0.9), late mechanical ventilation (p=0.7), and readmission for all causes (among survivors) (p=0.5). In the sensitivity analysis that used the in-hospital blocker prescription rate as an instrumental variable, the risk of in-hospital death was not significantly different between treated and untreated groups (OR, 0.95; 95% CI, 0.33–2.72), but treatment with β-blockers was associated with an increased risk of late mechanical ventilation (OR, 5.72; 95% CI, 1.47–22.73) and 30-day readmission (OR, 1.50; 95% CI, 0.98–2.30). Individuals treated with a non-selective β-blocker had a 25% chance of readmission within 30 days (OR, 1.25; 95% CI, 1.08–1.44).

Table 2. Continued

Study	BB type	Outcomes	Results
Quint et al. (2013)[22]	Bisolprolol (cardioselective) (n=111, 57.5%); Atenolol (cardioselective) (n=48, 24.9%); Metoprolol (cardioselective) (n=22, 11.4%); Carvedilol (n=7, 3.6%) (non-selective); Nebivolol (cardioselective) (n=2, 1.0%); Propranolol (non-selective) (n=2, 1%); Sotalol (non-selective) (n=1, 0.5%).	Mortality	β-Blockers were associated with survival benefits (adjusted RR, 0.50; 95% CI, 0.36–0.69; p<0.001). Individuals who were already using it before AMI also had a survival benefit (0.59; 95% CI, 0.44–0.79; p<0.001). With follow-up starting from hospital discharge, the effect size was slightly attenuated, but there was a similar protective effect of β-blocker treatment initiated during hospital stay for AMI (0.64; 95% CI, 0.44–0.94; p=0.02) There was a short-term survival benefit in those who used β-blockers during hospitalization (fully aHR, 0.48; 95% CI, 0.30–0.76; p=0.002) and in those who were already using it before the AMI (0.68; 95% CI, 0.46–1.0; p=0.05). Improved survival of those who received a β-blocker, compared to those who did not (RR for cardiac deaths, 0.57; 95% CI, 0.38–0.86; p=0.03) and non-cardiac deaths 0.49 (0; 95% CI, 32–0.75; p=0.01).
Mentz et al. (2013)[23]	Cardioselective (40%): metoprolol succinate was the most common in individuals with and without COPD (about 20%). Metoprolol tartrate and atenolol were the second and third most common, 12% and 5%. Non-cardioselective (60%): carvedilol was responsible for the greatest use, about 58%.	Exacerbations and mortality	The overall Kaplan-Meier 60-day mortality estimates were 6.2% and 6.0% in those with and without COPD. Without the use of β-blockers was associated with higher mortality in those with and without COPD (7.8% and 10.1%). As for mortality or readmission, 34.3% of individuals without COPD and 41.0% with COPD experienced composite end point. In the group without COPD, β-blocker use was associated with lower mortality or readmission (32%), compared with 42.6% in those who did not use it. In the COPD group, subjects who received cardioselectives had similar mortality or readmission rates (43.6%), compared to those who did not (44.1%). The COPD group that received non-selectives had a lower rate (37.7%). Non-cardioselective and cardioselective β-blockers were associated with lower risk-adjusted mortality in patients with and without COPD. There was no association between mortality or readmission between individuals with and without COPD (p>0.10).
Angeloni et al. (2013)[24]	Individuals who used non-selective β-blockers were excluded. Cardioselectives included atenolol, bisoprolol, metoprolol, and nebivolol.	Exacerbations and mortality.	AF was frequent in those who did not receive β-blockers (25% vs. 19% in group A; p=0.09). Those who had AF and used β-blockers tended to have greater conversion to sinus rhythm (75% A vs. 69% B; p=0.06). At 36 months, mortality was 12.3%. There were 7.7% in group A vs. 18.3% in group B; p=0.03; longer survival in group A; 91.8% vs. 80.6% in group B (RR, 0.38; 95% CI, χ^2–29.4; p=0.003). Heart-related deaths were 1.13/100 patient-years in A, and 3.33/100 in B (66% reduction in RR; p=0.0001). Correlation in survival between A (97.1%±1.7%) and B (91.3%±2.8%; RR, 0.40; 95% CI, χ^2–22.1; p=0.004). β-Blocker did not increase exacerbations in A (44.2%) vs. 43.3% in B (p=0.99). Exacerbations: 17.4 events/100 patient-years for A vs. 16.7 events/100 patient-years for B (4% RR increase; p=0.47). Kaplan-Meyer analysis showed exacerbation-free COPD and survival: 54.3%±4.9% in group A vs. 55.8%±4.9% in group B (RR, 1.05; 95% CI, χ^2–10.8; p=0.78).

https://doi.org/10.4046/trd.2024.0013
https://e-trd.org/

Table 2. Continued

Study	BB type	Outcomes	Results
Puente-Maestu et al. (2014)[25]	Atenolol (cardioselective): Without COPD (33%), With COPD (10%); Bisoprolol (cardioselective): Without COPD (27%), With COPD (45%); Carvedilol (non-selective): Without COPD (30%), With COPD (33%); Nevibolol (cardioselective): Without COPD (6%), With COPD (8%); Metoprolol (cardioselective): Without COPD (1%), With COPD (3%); Propanolol (non-selective): Without COPD (1%), with COPD	Exacerbations	Exacerbations (≥2) in the COPD group were associated with: use of β-blockers (OR, 0.26; 95% CI, 0.14–0.50; p=0.000); GOLD D (OR, 2.64; 95% CI, 1.43–4.93; p=0.002); diabetes (OR, 2.04; 95% CI, 1.07–3.91; p=0.031). In individuals with COPD, several factors were independently related to at least one visit to the emergency room in the previous year, such as use of β-blockers (adjusted OR, 0.27; 95% CI, 0.15–0.50); stage D GOLD (OR, 2.52; 95% CI, 1.40–4.53); baseline heart rate >70 (OR, 2.19; 95% CI, 1.24–3.86); use of long-acting β-agonists (OR, 2.18; 95% CI, 1.29–3.68); previous episodes of left ventricular failure (OR, 2.27; 95% CI, 1.19–4.33); and diabetes (OR, 1.82; 95% CI, 1.08–3.38). In COPD patients, several factors were independently related to at least one emergency room visit in the previous year, such as use of BB (adjusted OR, 0.27; 95% CI, 0.15–0.50); stage D of GOLD (OR, 2.52; 95% CI, 1.40–4.53); basal heart rate >70 (OR, 2.19; 95% CI, 1.24–3.86); use of long-acting β2-agonists (OR, 2.18; 95% CI, 1.29–3.68); previous episodes of left ventricular failure (OR, 2.27; 95% CI, 1.19–4.33); and diabetes (OR, 1.82; 95% CI, 1.08–3.38).
Lee et al. (2014)[26]	Selective β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, esmolol, nebivolol, metoprolol). Non-selective (levobunolol, metipranolol, nadolol, propranolol, sotalol, timolol) and non-selective with α-blocking properties (carvedilol and labetalol)	Mortality	During follow-up, 179 participants experienced a major cardiac event; 389 participants experienced a major pulmonary event; and 255 participants died. Each participant could have gone through one or more of these events. The HR for β-blocker use was 1.18 (95% CI, 0.85–1.62) for cardiac events, 0.91 (95% CI, 0.73–1.12) for pulmonary events, and 0.87 (95% CI, 0.67–1.13) for death.
Kubota et al. (2015)[27]	Carvedilol (non-selective) (n=52); Bisoprolol (cardioselective) (n=34)	Mortality and exacerbations	The mortality rate was higher in patients without β-blockers compared to those who received β-blockers (log-rank p=0.039), and univariate analyzes revealed that the use of β-blockers was the only factor significantly correlated with the mortality rate (HR, 0.41; 95% CI, 0.17–0.99; p=0.047). In addition, the exacerbation rate of CHF and/or COPD was higher in patients treated with carvedilol compared to bisoprolol (log-rank p=0.033). In multivariate analysis, only a past history of COPD exacerbation significantly increased the risk of re-hospitalization due to CHF and/or COPD exacerbation (aHR, 3.11; 95% CI, 1.47–6.61; p=0.003).
Dong et al. (2016)[28]	Bisoprolol (cardioselective) (63%); Atenolol (cardioselective) (31%); Metoprolol (cardioselective) (4%)	Mortality	Cardioselective BBs were associated with a lower and modest risk of overall death (HR, 0.85; 95% CI, 0.81–0.88). However, the reduced risk of overall death, was vulnerable to the distribution of COPD severity, and was easily weakened with a lower prevalence of patients with severe COPD in the cardioselective BB initiators and a higher prevalence of patients with severe COPD in the non-dihydropyridine CCB initiators. No excess benefit was detected for cardiovascular death (HR, 1.05; 95% CI, 0.97–1.13) or cardiovascular events (HR, 0.98; 95% CI, 0.94–1.03).

Table 2. Continued

Study	BB type	Outcomes	Results
Huang et al. (2017)[29]	Selectives: Acebutolol (n=954); Atenolol (n=8,372); Betaxolol (n=634); Bisoprolol (n=963); Metoprolol (n=978) Non-selective: Alprenolol (n=79); Carteolol (n=128); Carvedilol (n=3,150); Labetalol (n=1,692); Nadolol (n=194); Pindolol (n=47)	Exacerbations	β-Blocker users had a lower risk of severe exacerbations (OR, 0.90; 95% CI, 0.85–0.96). For non-selective users, current users had a higher risk (OR, 1.21; 95% CI, 1.14–1.27); this effect was not observed in previous users (OR, 1.03; 95% CI, 0.98–1.09). Betaxolol had a lower risk (OR, 0.75; 95% CI, 0.60–0.95). Labetalol and propranolol were associated with a higher risk (OR, 1.49; 95% CI, 1.32–1.67 for labetalol) (OR, 1.16; 95% CI, 1.10–1.23 for propranolol). For selective users, current users had a lower risk of exacerbations (OR, 0.90; 95% CI, 0.85–0.96), but this was not observed with previous users (OR, 0.98; 95% CI, 0.92–1.04). For acebutolol, atenolol, bisoprolol and metoprolol, lower risks of exacerbation were observed (ORs from 0.85 to 0.97), without statistical significance
Oda et al. (2017)[30]	Seletivos: Bisoprolol (n=12); Atenolol (n=6) Não seletivos: Carvedilol (n=13)	Disease severity	Individuals using β-blockers exhibited significantly lower FVC, FEV_1, and FVC%, and more advanced stage of GOLD. The mean duration of β-blocker administration was (2.8±1.7 years). There were no differences in the annual change in FEV_1 between patients who used and did not use β-blockers (−7.6±93.5 mL/year vs. −4.7±118.9 mL/year, p=0.671). After controlling for relevant confounding factors in the multivariate analyses, it was found that the use of β-blockers was not significantly associated with an annual decline in FEV_1 (β=−0.019; 95% CI, −0.073 to 0.036; p=0.503).
Key et al. (2017)[31]	Bisoprolol (cardioselective) (n=8); Atenolol (cardioselective) (n=5); Propranolol (non-selective) (n=1); Carvedilol (non-selective) (n=1); Metoprolol (cardioselective) (n=1)	Disease severity	People with COPD had airflow obstruction, increased airway resistance (Raw) and specific conductance (sGaw), static hyperinflation, and dynamic hyperinflation during exercise. Parameters measured at baseline in the COPD group: FEV_1 (L): 2.03±0.55; FEV_1 (%): 75.0±16.1; FEV_1/CVF: 0.56±0.08. In all groups, β-blocker use led to a small drop in FEV_1 (0.1 L/2.8% predicted) but did not affect gross, sGaw, static, or dynamic hyperinflation. No difference in β-blocker response was seen in those with and without COPD. Change in COPD group parameters after β-blocker use: FEV_1 (L): −0.11±0.18; FEV_1 (%): −4.2±6.5; FEV_1/FVC: −0.02±0.06.
Liao et al. (2017)[32]	Carvedilol (non-selective) (n=200); Bisoprolol (cardioselective) (n=331); Metoprolol (cardioselective) (n=10); Combinations (n=48)	Mortality and exacerbations	β-Blocker users had a significantly lower risk of death from any cause (aHR, 0.67; 95% CI, 0.47–0.96; p=0.028) and hospitalization for HF (aHR, 0.62; 95% CI, 0.39–0.98; p=0.042). However, the hospitalization rate for COPD was not significantly different between β-blocker users and non-users (aHR, 1.15; 95% CI, 0.73–1.83; p=0.549). Regarding individual β-blockers after matching the propensity score, most did not significantly reduce the risk of death from any cause or the rate of hospitalization for HF, except for high-dose bisoprolol (death from any cause: aHR, 0.51; 95% CI, 0.29–0.89; p=0.017); rate of hospitalization by CI (aHR, 0.47; 95% CI, 0.23–1.00; p=0.050). However, none of the β-blockers were associated with a reduced risk of hospitalization for COPD.
Lim et al. (2017)[33]	Metoprolol (cardioselective) (n=28); Bisoprolol (cardioselective) (n=18); Atenolol (cardioselective) (n=11); Nebivolol (cardioselective) (n=5)	Mortality	In the mortality analysis, there were fewer deaths in the adequately treated group (0 out of 53), compared to the group that was not inappropriately using BB therapy (6 out of 61), but this did not reach statistical significance (p=0.063 per test exact Fisher). There were no statistically significant differences in length of stay, or in-hospital incident tachyarrhythmia, ischemic heart disease, CHF, or stroke events.

https://doi.org/10.4046/trd.2024.0013
https://e-trd.org/

Table 2. Continued

Study	BB type	Outcomes	Results
Maltais et al. (2018)[34]	Cardioselective: Acebutolol (n=2); Atenolol (n=50); Betaxolol (n=4); Bisoprolol (n=171); Celiprolol (n=2); Metoprolol (n=170); Nebivolol (n=67) Non-cardioselective: Carteolol (n=1); Carvedilol (n=64); Labetalol (n=2); Metipranolol (n=1); Propranolol (n=19); Sotalol (n=8); Timolol (n=11)	Exacerbations	Subjects who used β-blockers at baseline experienced fewer COPD exacerbations during the study, compared to subjects without β-blockers (150 [26.9%] and 1,420 [30.8%], respectively). Time to first COPD exacerbation was not significantly different between groups (271 days vs. 236 days for patients with and without β-blocker use, respectively (aHR, 0.878; 95% CI, 0.732–1.053; p=0.1604). Moderate or severe exacerbations were observed by 145 (26.0%) and 1,339 (29.1%) in subjects with and without β-blocker use at baseline. There was no difference in time to first moderate or severe exacerbation between groups: 304 days vs. 261 days for subjects with and without β-blocker use at baseline, respectively (aHR, 0.896; 95% CI, 0.745–1.079; p=0.271).
Rezaei et al. (2018)[35]	1st Generation (non-selective: propranolol, sotalol, pindolol); 2nd Generation (β1-selective: metoprolol, atenolol, bisoprolol); 3rd Generation (selective and non-selective β1 with vasodilating effects: celiprolol, labetalol, carvedilol, nebivolol); Combined (different combinations of 1st, 2nd, and 3rd generation β-blocker)	Mortality	Among individuals with COPD, 6.9% of β-blocker users and 22.6% of non-users died. In the group without COPD, 5.4% of β-blocker users and 23.1% of non-users died. The 6-month mortality of subjects with and without COPD was 12.5% and 8.9%, respectively. Among individuals with COPD, 9.6% of β-blocker users and 21.4% of non-users died. In the group of subjects without COPD, 5.8% of β-blocker users and 17.4% of non-users died. Multivariate survival analysis revealed sex, age, co-diagnosis of diabetes and COPD as independent predictors of survival. In 2006 and 2007, being over 60 years of age and having diabetes increased the risk of death (p<0.001). In 2006, the co-diagnosis of COPD was positively associated with mortality (p<0.001) after a 30-day and 6-month observation period, but not in 2007.
Zvizdic et al. (2019)[36]	Metropolol (cardioselective) (n=11): Bisoprolol (cardioselective) (n=12); Nebivolol (cardioselective) (n=1)	Exacerbations	Within the GOLD II group, there was a trend towards a decrease in exacerbations, when compared to exacerbations in individuals using verapamil and digoxin (1.333±0.963) with those using β-blockers (0.600±0.632), p=0.007. In the GOLD III group, there was no difference in the number of exacerbations between subjects who took verapamil and digoxin (2.100±0.912) and individuals who used β-blockers (1.889±0.928), p=0.577.
Thomas et al. (2019)[37]	Cardioselective (atenolol, bisoprolol, metoprolol, acebutolol and nebivolol) Non-selective (propranolol, nadolol, carvedilol and labetalol). Metoprolol and carvedilol were the most prescribed before admission (94.4%, 96.9%) and at discharge (94.1%, 97.1%)	Exacerbations and mortality	There was no difference in the incidence of death (0 vs. 0) between cohorts. Early β-blocker continuation was not associated with increased use of corticosteroids (p=0.99) and bronchodilators, including use of β2-agonists (p=0.99). Causes within 30 days (36% vs. 27%, p=0.32) and readmissions within 30 days secondary to exacerbations (7% vs. 20%, p=0.12) with receipt of β-early blockade.

BB: β-blocker; CI: confidence interval; aHR: adjusted hazard ratio; HR: hazard ratio; OR: odds ratio; SD: standard deviation; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; RR: relative risk; AMI: acute myocardial infarction; AF: atrial fibrillation; GOLD: Global Initiative for Obstructive Lung Disease; CHF: congestive heart failure; CCB: calcium channel blocker.

dence intervals (CI), or sufficient data to calculate these parameters.

Studies that did not present important characteristics of the sample, such as age and disease severity (data that could interfere with the results), were excluded; as were articles that did not present relevant information about the pharmacological treatment, such as the medication used. The selection process, data extraction from the articles, and identification of methodological aspects was carried out by two independent reviewers. When there was disagreement between them, the reviewers read the article again for re-evaluation. If the disagreement persisted, a third independent reviewer would assess and make the final decision.

1. Statistical analysis

Subgroup analysis was performed according to the outcomes studied: disease severity, exacerbations, and mortality. For the mortality and exacerbations outcomes, a random effect model was used; while for the disease severity outcome, the mean and standard deviation were used. Data were graphically displayed using forest plot. A p-value less than 0.05 was considered statistically significant.

Statistical heterogeneity between studies was assessed using the Cochrane Q test and the I^2 inconsistency test. The following cutoff points were adopted: 0% to 25%: mild heterogeneity, acceptable; >25% to 50%: moderate heterogeneity; >50%: high heterogeneity[17]. Sensitivity analysis was evaluated using the Jackknife procedure, examining the individual influence of each study.

The quality of included studies was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute (NHLBI). The assessment of methodological quality was performed by two independent researchers. A third evaluator measured the inconsistencies, and made the final decision. Funnel charts were generated to assess publication bias. Statistical analysis were performed using Review Manager version 5.0 (Cochrane Collaboration, London, UK).

The protocol of the construction steps of this systematic review was published in the International Prospective Register of Systematic Reviews (PROSPERO), under registration CRD42020155656.

Results

The search in the databases resulted in 24,283 articles (Medline: 19,985; EMBASE: 3,264; Science Direct: 1,029; Lilacs: 2; Scielo: 1; Cochrane Library: 2), leaving 24,256 records after removing the duplicates. Of these, 61 articles were selected by title tracking; 22 were excluded due to the abstract not meeting the selection criteria, leaving 39 articles for full reading. Of these, it was found that 19 of them did not meet all the inclusion criteria, resulting in the final selection of 20 articles, as shown in Figure 1.

The 20 articles were read analytically and selectively, and organized into two tables with relevant research information, such as characteristics—author, year; type of study (duration); data source (country); sample (follow-up); and cardiovascular comorbidity (Table 1)[18-37], and the analysis of the studies—type of β-blocker used, outcomes, and results, as shown in Table 2.

Of the 20 articles, most were cohort studies, 15 being retrospective[18-23,26-28,30,32-34,36,37], and three prospective[24,31,35]. Only one article was cross-sectional observational[25], and one case-control[29]. In total, 237,709 individuals participated in the 20 surveys. For data collection, 16 articles used secondary data from medical records and multicenter research banks[18-23,26-28,30,32-35,37], while four used primary data[24,25,31,36].

Of the 20 articles, 14 studies evaluated the outcome mortality[18-24,26-28,32,33,35,37]; 14, exacerbations[18,19,21,23-25,27,29,32,34,36,37]; and four, disease severity, according to the spirometric data[19,25,30,31]. The comorbidities studied by the studies are: congestive heart failure (CHF)[18-23,25,26,28-30,33-37]; systemic arterial hypertension[18,21-30,34,37]; cerebrovascular disease[19,22,23,26,29,32,34]; arrhythmia[23,29,32-35]; ischemic heart disease[21,28,39,32-34]; atrial fibrillation[27,30-32,37]; coronary artery disease (CAD)[24,25,30,35,37]; acute coronary syndrome[18]; and abdominal aortic aneurysm[31]. Table 3 shows the β-blockers.

1. Mortality

The OR for the mortality outcome was 0.50 (95% CI, 0.39 to 0.63; p<0.00001), which was favorable to the group that used β-blockers. The results indicate a high degree of heterogeneity among the included studies (I^2=95%) (Figure 2).

2. Exacerbations

The OR for the exacerbation outcome was 0.76 (95% CI, 0.62 to 0.92; p=0.005), which was favorable for the group that used β-blockers. The results indicate a high degree of heterogeneity among the included studies (I^2=88%) (Figure 2). Data from the studies by Puente-Maestu et al.[25] and Huang et al.[29] were not included in the analysis, because they had other study designs, which interfered with the result, and led to a greater degree of heterogeneity (I^2=100%).

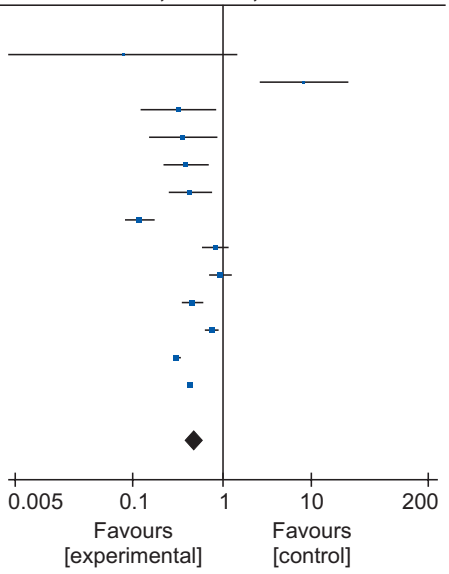
Table 3. Beta blockers used in the studies

Beta blocker	Class	Studies	Number
Metoprolol	Selective Second generation	Au et al.[18], Dransfield et al.[19], van Gestel et al.[20], Stefan et al.[21], Quint et al.[22], Mentz et al.[23], Angeloni et al.[24], Puente-Maestu et al.[25], Lee et al.[26], Dong et al.[28], Huang et al.[29], Key et al.[31], Liao et al.[32], Lim et al.[33], Maltais et al.[34], Rezaei et al.[35], Zvisdic et al.[36], Thomas et al.[37]	18
Atenolol	Selective Second generation	Au et al.[18], Dransfield et al.[19], van Gestel et al.[20], Stefan et al.[21], Quint et al.[22], Mentz et al.[23], Angeloni et al.[24], Puente-Maestu et al.[25], Lee et al.[26], Dong et al.[28], Huang et al.[29], Oda et al.[30], Key et al.[31], Lim et al.[33], Maltais et al.[34], Rezaei et al.[35], Thomas et al.[37]	17
Bisoprolol	Selective Second generation	van Gestel et al.[20], Quint et al.[22], Angeloni et al.[24], Puente-Maestu et al.[25], Lee et al.[26], Kubota et al.[27], Dong et al.[28], Huang et al.[29], Oda et al.[30], Key et al.[31], Liao et al.[32], Lim et al.[33], Maltais et al.[34], Rezaei et al.[35], Zvisdic et al.[36], Thomas et al.[37]	16
Carvedilol	Non-selective Third generation	Dransfield et al.[19], Stefan et al.[21], Quint et al.[22], Mentz et al.[23], Puente-Maestu et al.[25], Lee et al.[26], Kubota et al.[27], Huang et al.[29], Oda et al.[30], Key et al.[31], Liao et al.[32], Maltais et al.[34], Rezaei et al.[35], Thomas et al.[37]	14
Nebivolol	Selective Third generation	Quint et al.[22], Angeloni et al.[24], Puente-Maestu et al.[25], Lee et al.[26] Lim et al.[33], Maltais et al.[34], Rezaei et al.[35], Zvisdic et al.[36], Thomas et al.[37]	10
Propranolol	Non-selective First generation	Au et al.[18], Quint et al.[22], Puente-Maestu et al.[25], Lee et al.[26], Key et al.[31], Maltais et al.[34], Rezaei et al.[35], Thomas et al.[37]	8
Labetalol	Non-selective Third generation	Lee et al.[26], Huang et al.[29], Rezaei et al.[35], Maltais et al.[34], Thomas et al.[37]	5
Sotalol	Non-selective First generation	Quint et al.[22], Lee et al.[26], Maltais et al.[34], Rezaei et al.[35]	4
Acebutolol	Selective Second generation	Lee et al.[26], Huang et al.[29], Maltais et al.[34], Thomas et al.[37]	4
Betaxolol	Selective Third generation	Lee et al.[26], Huang et al.[29], Maltais et al.[34]	3
Nadolol	Non-selective First generation	Lee et al.[26], Huang et al.[29], Thomas et al.[37]	3
Pindolol	Non-selective First generation	Huang et al.[29], Rezaei et al.[35]	2
Carteolol	Non-selective Third generation	Huang et al.[29], Maltais et al.[34]	2
Celiprolol	Selective Third generation	Rezaei et al.[35], Maltais et al.[34]	2
Timolol	Non-selective First generation	Lee et al.[26], Maltais et al.[34]	2
Metipranolol	Non-selective First generation	Lee et al.[26], Maltais et al.[34]	2
Alprenolol	Non-selective Third generation	Huang et al.[29]	1
Esmolol	Selective Second generation	Lee et al.[26]	1
Levobunolol	Non-selective First generation	Lee et al.[26]	1

Figure 2. Forest plot of association between β-blockers and mortality, exacerbation, and severity. M-H: Mantel-Haenszel; CI: confidence interval; SD: standard deviation; IV: inverse variance.

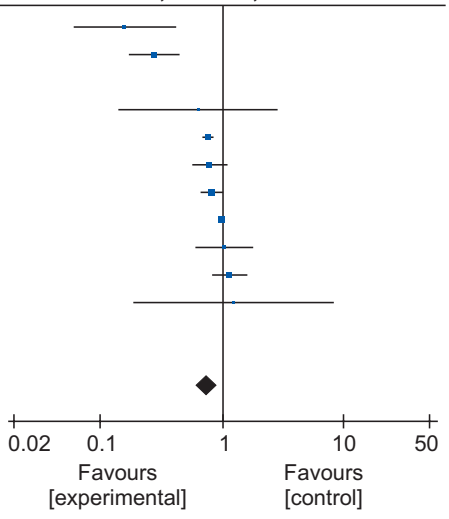
Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M−H, random, 95% CI
Thomas et al.	0	55	0	41		Not estimable
Lim et al.	0	53	6	61	0.7%	0.08 [0.00, 1.45]
Dransfield et al.	8	142	5	683	3.4%	8.10 [2.61, 25.13]
Kubota et al.	9	86	12	46	4.2%	0.33 [0.13, 0.86]
Angeloni et al.	8	104	19	104	4.7%	0.37 [0.16, 0.90]
van Gestel et al.	16	462	66	803	7.2%	0.40 [0.23, 0.70]
Au et al.	16	257	222	1,709	7.5%	0.44 [0.26, 0.75]
Liao et al.	40	577	220	577	9.2%	0.12 [0.08, 0.17]
Mentz et al.	199	506	93	216	9.5%	0.86 [0.62, 1.18]
Lee et al.	126	531	129	531	9.9%	0.97 [0.73, 1.28]
Quint et al.	153	477	294	586	10.2%	0.47 [0.36, 0.60]
Stefan et al.	197	10,070	620	25,012	10.9%	0.79 [0.67, 0.92]
Rezaei et al.	1,872	23,066	1,553	7,051	11.3%	0.31 [0.29, 0.34]
Dong et al.	5,884	49,623	13,351	58,279	11.4%	0.45 [0.44, 0.47]
Total (95% CI)		**86,009**		**95,699**	**100.0%**	**0.50 [0.39, 0.63]**
Total events	8,528		16,590			

Heterogeneity: Tau^2=0.14; Chi^2=257.82, df=12 (p<0.00001); I^2=95%
Test for overall effect: Z=5.58 (p<0.00001)



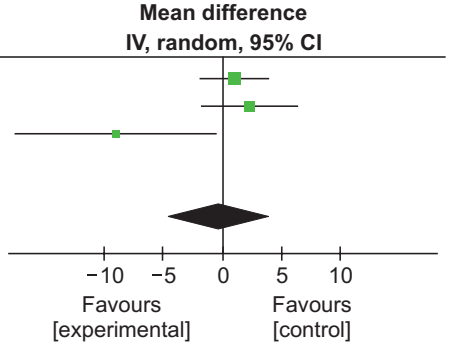
Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M−H, random, 95% CI
Thomas et al.	22	55	33	41	3.5%	0.16 [0.06, 0.41]
Lim et al.	26	577	84	577	9.2%	0.28 [0.18, 0.44]
Puente-Maestu et al.	1	149	2	107	0.0%	0.35 [0.03, 3.96]
Dransfield et al.	2	142	15	683	1.6%	0.64 [0.14, 2.81]
Stefan et al.	654	10,070	2,071	25,012	17.9%	0.77 [0.70, 0.84]
Mentz et al.	189	506	93	216	12.3%	0.79 [0.57, 1.09]
Maltais et al.	220	577	1,976	4,605	16.1%	0.82 [0.69, 0.98]
Dong et al.	12,676	33,757	12,770	33,757	18.6%	0.99 [0.96, 1.02]
Angeloni et al.	46	104	45	104	7.5%	1.04 [0.60, 1.80]
Au et al.	55	257	328	1,709	12.3%	1.15 [0.83, 1.58]
Zvizdic et al.	2	24	3	44	1.0%	1.24 [0.19, 8.00]
Huang et al.	15,084	16,067	33,952	55,970	0.0%	9.95 [9.31, 10.64]
Total (95% CI)		**46,069**		**66,748**	**100.0%**	**0.76 [0.62, 0.92]**
Total events	13,892		17,418			

Heterogeneity: Tau^2=0.05; Chi^2=74.03, df=9 (p<0.00001); I^2=88%
Test for overall effect: Z=2.79 (p=0.005)



Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI
Dransfield et al.	41	16	142	40	15	683	44.3%	1.00 [−1.86, 3.86]
Key et al.	4.2	6.5	15	1.9	5.9	23	37.3%	2.30 [−1.78, 6.38]
Oda et al.	58.9	19	31	67.9	22.4	72	18.4%	−9.00 [−17.46, -0.54]
Puente-Maestu et al.	58.7	16.9	149	52.1	18.4	107	0.0%	6.60 [2.18, 11.02]
Total (95% CI)			**188**			**778**	**100.0%**	**−0.35 [−4.81, 4.10]**

Heterogeneity: Tau^2=9.52; Chi^2=5.69, df=2 (p=0.06); I^2=65%
Test for overall effect: Z=0.15 (p=0.88)



3. Disease severity/severity of illness

Effects on disease severity were assessed using mean difference with 95% CIs using a random-effects model. The aggregated results of these studies suggest that there is no statistically significant association between the use of β-blockers and COPD severity (difference between means=−0.35; 95% CI, −4.81 to 4.10; p=0.8). The results indicate a high degree of heterogeneity among the included studies (I^2=65%) (Figure 2). Data from the study by Puente-Maestu et al.[25] were not included in

Table 4. Quality assessment of the reviewed articles

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality
Au et al. (2004)[18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Dransfield et al. (2008)[19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Van Gestel et al. (2008)[20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Stefan et al. (2012)[21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Quint et al. (2013)[22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Mentz et al. (2013)[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Angeloni et al. (2013)[24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Puente-Maestu et al. (2014)[25]	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	Y	N	NA	Y	Good
Lee et al. (2014)[26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Kubota et al. (2015)[27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Dong et al. (2016)[28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Huang et al. (2017)[29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Oda et al. (2017)[30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Key et al. (2017)[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Liao et al. (2017)[32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Lim et al. (2017)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Maltais et al. (2018)[34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good
Rezaei et al. (2018)[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Zvizdic et al. (2019)[36]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Thomas et al. (2019)[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Good

Questions:
1. Was the research question or objective in this article clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible people at least 50%?
4. Were all subjects selected or recruited from the same or similar populations (including the same duration or time period)? Are the inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?
5. Has a justification for sample size, description of potency, or variation and effect estimates been provided?
6. For the analyses in this article, were the exposure(s) of interest measured before the result(s) to be measured?
7. Was the timeframe sufficient to reasonably expect an association between exposure and outcome if it existed?
8. For exposures that may vary in amount or level, did the study examine different exposure levels as related to outcome (e.g., exposure categories or exposure measured as a continuous variable)?
9. Were exposure measures (independent all variables) clearly defined, valid, reliable, and consistently implemented across all study participants?
10. Has the exposure(s) been evaluated more than once over time?
11. Were outcome measures (dependent variables) clearly defined, valid, reliable, and consistently implemented across all study participants?
12. Were outcome assessors blinded to the exposure status of participants?
13. Was the loss to follow-up after baseline 20% or less?
14. Were the main confounding variables measured and statistically adjusted for their impact on the relationship between exposure(s) and outcome(s)?

Y: yes, N: no, NA: not applicable.

the analysis because of a different study design, which interfered with the result, and led to a greater degree of heterogeneity (I^2=73%).

All 20 articles finally selected presented the research question or objective clearly, specified the population, and showed a participation rate of eligible people of at least 50%. All study participants were selected and recruited from similar populations with pre-specified selection criteria. Only one study[36] did not provide a justification for the sample size. The article by Puente-Maestu et al.[25] was the only cross-sectional study, so it was not applicable to analyze whether the exposures of interest were evaluated before the result; whether there was enough time for an association between exposure and outcome; if exposure was evaluated more than once over time; and if there was loss to follow-up.

Across the 20 studies, different levels of exposures were examined, and exposure and outcome measures were clearly defined, valid, reliable, and consistently implemented, but only one study[34] reported blinding to the exposure status of participants. The main variables were measured and statistically adjusted for their impact on the relationship between exposure and outcome in all studies, as shown in Table 4.

Discussion

The results of the present systematic review and meta-analysis suggest that β-blockers have positive effects on mortality[18,19,22-24,35], and exacerbation[18,19,23,24,29,36], outcomes, compared to the results of individuals who did not use them. For the severity of the disease, there was a reduction in pulmonary function in subjects with COPD[30,31].

1. Mortality

Regarding the mortality outcome, studies have shown that the use of β-blockers in individuals with COPD is associated with a reduction in the number of deaths from all causes. Compared to the use of calcium channel blockers, all β-blocker dosage levels were related to lower mortality. It is supposed that the apparent benefit of these medications may be related to the reduction of cardiovascular events[18,19].

In addition to this apparent protective effect of β-blockers, according to Dransfield et al.[19], treatment with short-acting β-agonists is associated with a reduction in mortality. For the authors, it is possible that this result reflects the avoidance of administering short-acting β-agonists among subjects with a higher risk of death, such as those with tachyarrhythmia or other unstable heart disease, rather than a true beneficial effect among the recipients[19]. Other researchers found that β-agonists did not modify the effects of β-blockers on mortality[18].

In addition, Quint et al.[22] found that individuals who did not use β-blockers after myocardial infarction were more likely to use inhalers for COPD. Previous research carried out in animal models has shown that β-blockers can up-regulate β2 receptors in the lung, and thus improve the responsiveness and efficacy of inhaled bronchodilators and β2-sympathomimetics[24,38].

At first sight, this effect seems to be a counter-intuitive way through which the β-blocker can exhibit beneficial effects, but the possibility is that the up-regulation of β2 receptors by chronic β-blockade can improve the efficacy of β2-agonists[39]. This pathway is still valid regardless of selectivity, because drugs such as atenolol and bisoprolol have been shown to exert significant β2 adrenergic receptor antagonism, even at therapeutic doses, which can result in the up-regulation of β2-adrenoceptors[24,40].

Stefan et al.[21] found the β1 blocker selectivity to be associated with the risk of mortality, while non-selective β-blockers were associated with an increased risk of readmission. These findings corroborate data from previous studies that found that non-selective β-blockers increase hospital admissions in individuals with COPD, decrease forced expiratory volume in 1 second (FEV_1), and may inhibit the bronchodilator response to β2 agonists[21,41]. However, another article found no significant difference between cardioselective and non-selective β-blockers for 60-day mortality[23].

Regarding the specific type of β-blocker, Su et al.[42] demonstrated a significantly better dose-dependent survival outcome associated with the use of bisoprolol in individuals with CHF and COPD, whereas metoprolol and carvedilol showed no difference in survival. Non-selective β-blockers have been found to reduce FEV_1 and the effect of bronchodilator treatment, in addition to increasing airway hypersensitivity in individuals with COPD[42,43].

However, the use of metoprolol also showed no survival benefit. As a selective β1 blocker, metoprolol has been shown to increase airway hyperresponsiveness in subjects with COPD, whereas celiprolol, another selective β-blocker, has shown no negative pulmonary effect. These findings suggest that pulmonary influences differ between β-blockers, some of which continue to have a potential negative pulmonary effect[42,43].

2. Exacerbations

Regarding the exacerbation outcome, Su et al.[42] found

that individuals who used β-blockers had a point estimate of fewer exacerbations than those who did not use it. For the authors, potential biological and non-biological explanations may include the up-regulation of β receptors and better response to bronchodilators associated with β-blocker use, or the influence of pulmonary disease severity on β-blocker prescription practices[44,45].

Dransfield et al.[19] corroborate these findings by observing a trend toward a reduction in COPD-related hospitalizations among those using β-blockers. However, compared to individuals treated with a selective β1 agent, subjects treated with a non-selective β-blocker had a 25% chance of readmission within 30 days[21]. But Mentz et al.[23] found no evidence that β-blocker selectivity interfered with readmission.

Huang et al.[29] found that individuals with COPD who received selective β-blockers had a lower risk of severe exacerbations, especially current users. On the other hand, subjects who used non-selective β-blockers had a higher risk of severe exacerbations in a dose- and duration-dependent manner.

Huang et al.[29] also found betaxolol to be the most effective selective β-blocker in reducing the risk of severe exacerbations. Betaxolol is considered to be highly cardioselective, and is less likely than other selective β-blockers to cause pulmonary adverse effects. For non-selective blockers, labetalol and propranolol were found to be significantly associated with an increased risk of severe exacerbations[29]. This may be because labetalol can significantly reduce FEV_1 and FVC, while propranolol can reduce FEV_1 and the bronchodilator effect of formoterol, thus increasing airway hyperresponsiveness[43].

Another study found the use of carvedilol to be associated with an increased risk of hospitalization for CHF, compared to the use of metoprolol, bisoprolol, and nebivolol[46]. Zvizdic et al.[36] showed that the use of β-blockers reduced the number of exacerbations over a 12-month period in Global Initiative for Obstructive Lung Disease (GOLD) II individuals. In GOLD III, a severe stage of COPD, the number of exacerbations was not therapy-dependent.

One study has shown that individuals with COPD taking β-blockers are less symptomatic and have fewer exacerbations, despite receiving fewer respiratory medications. Several factors are related to exacerbations, but only the GOLD stage, use of β-blockers, use of long-acting beta-agonists (LABA) (including ultra-LABA), and comorbidities had independent effects[25]. In this study, a heart rate greater than 70 bpm was associated with a higher risk of exacerbations, which may indicate that not just β-blockade, but effective β-blockade is the likely protective factor. For Puente-Maestu et al.[25], β-blockers showed a clear protective effect against exacerbations in individuals with COPD.

An overall decrease in long-term bronchodilator use, both long-acting muscarinic antagonists and LABA, was observed. The reasons for this are not clear, but the perception that they can interfere with the β-blocker, and the non-adherence of patients to various medications[47], may play a role. Interestingly, there is a decrease in the proportion of individuals treated with "traditional" LABAs in the bronchodilator group, which is partly offset by an increase in the use of ultra-LABA. This may show the fear of prescribing "traditional" LABA by physicians who are more aware of the management of heart disease—and also more likely to use β-blockers—as there is evidence associating "traditional" LABA with increased mortality in subjects with CHF and CAD[25].

3. Disease severity/severity of illness

Regarding disease severity, Dransfield et al.[19] maintained that cardioselective β-blockers have no demonstrable effect on lung function, regardless of disease severity or bronchodilator reversibility, and that COPD individuals with heart disease seem to derive the same benefits from these drugs as the general population[48].

Oda et al.[30], which compared the annual changes in lung function in individuals with COPD who took or did not take β-blockers, it was found that the decline in FEV_1 did not differ significantly between the two groups. The use of β-blockers did not compromise the FEV_1 of subjects with COPD. The non-selective β-blocker used was carvedilol, which, according to the authors, is relatively tolerable in individuals with COPD, promoting mild bronchodilation induced by alpha-adrenergic blockade[49].

Meanwhile, Key et al.[31] showed that β-blockade had a minimal effect on lung function and dynamic hyperinflation. Bronchodilators, including β-agonists, are known to produce relatively rapid relaxation of airway smooth muscle and improve expiratory flow rate, but it is questionable whether this is the mechanism by which they act in subjects with COPD, where prominent abnormalities are increased peripheral resistance and the loss of lung elastic recoil[50].

In individuals with COPD, β-agonists have been shown to reduce inspiratory resistance, but their main effect is to reduce end-expiratory lung volume, which allows the individual to exercise longer, before reaching a critical and limited volume of inspiratory reserve. Therefore, drugs that antagonize airway β receptors,

and consequently reduce caliber through their effects on smooth muscle, may have little effect on measurements of airway function in individuals with COPD, as this is not predominantly determined by the smooth muscle of the airways[31,51].

Key et al.[31] found that the airway resistance and specific conductance remained unchanged, and β-blockade did not lead to a significant change in end-expiratory lung volume and magnitude of dynamic hyperinflation during exercise. However, clinical trials have shown that treatment with non-selective β-blockers in individuals with COPD is associated with a reduction in FEV_1, increased airway hyperresponsiveness, and reduced efficacy of bronchodilator treatment[43], which resulted in an increased risk of adverse reactions to pulmonary medications among non-selective β-blocker users, compared to selective β-blocker users[46].

Mentz et al.[23] argued that the potential risk of adverse pulmonary effects of non-cardioselective β-blockers can be balanced by an alternative set of systemic, cardiac, and pulmonary benefits. For example, β2 adrenergic receptors represent a greater proportion of total cardiac β receptors in individuals with CHF, compared to healthy subjects. Individuals with CHF may benefit from antagonism of these receptors by non-selective agents.

Furthermore, non-selective β-blockers can attenuate the negative effects of β2 agonists, including dysrhythmogenesis, ischemia, and inflammation[23]. Carvedilol has antioxidant, free radical scavenging, and insulin-sensitizing effects, while β2 adrenergic receptor antagonism can reduce the release of noradrenaline from myocardial adrenergic nerve terminals, and reduce the complications of hypokalemia[52].

From the perspective of COPD, non-cardioselective β-blockers can attenuate pulmonary desensitization due to prolonged β2 adrenergic receptor activation with β-agonists. β-Blockers reduce airway hyperresponsiveness, increase pulmonary β2 receptor regulation, and reduce the need for β-agonists. β-Blockers can attenuate the presence of inflammation and reduce mortality and pulmonary exacerbations in subjects with COPD[3,53].

This systematic review and meta-analysis have potential relevance; the protocol for this review was submitted to and registered in the PROSPERO, with the aim of minimizing the risk of publication bias and duplication of reviews that answer the same clinical question. This record also allows us to evaluate the conduct of the study and the quality of reporting its results, increasing transparency and reproducibility.

This study also chose to specifically include a type of study (cohort studies) that allowed better comparison between results; in addition, the authors believe that for the chosen outcomes (disease severity, exacerbations, or mortality) it would be better to include longitudinal studies to evaluate the results over a longer period.

Regarding the limitations of this systematic review and meta-analysis, there was a high rate of heterogeneity between the articles, mainly in relation to the cardiovascular comorbidities studied, and the β-blockers used. In addition, many studies do not describe the dose prescribed for each β-blocker, which makes it impossible to compare them adequately.

Another limitation, which is associated with the severity of the disease outcome, was the variability in the ways in which the assessment of lung function was presented in the studies, a factor that also made it impossible to include some articles in the meta-analysis. Due to the form of presentation in each included study, it was also not possible to carry out a meta-analysis evaluating the difference between the diseases.

In conclusion, the use of β-blockers in individuals with COPD and associated cardiovascular diseases caused positive effects on the mortality and exacerbations outcomes, compared to the results of individuals who did not use them. The severity of the disease caused a slight change in FEV_1. These data contribute to greater safety in the use of β-blockers in this population profile. However, there was high heterogeneity between the studies, especially in relation to cardiovascular comorbidities and the β-blocker used. As a result, further studies are needed: both observational cohort and clinical trials that aim to study the effect of using a specific β-blocker in COPD associated with a specific cardiovascular comorbidity.

Authors' Contributions

Conceptualization: all authors. Methodology: dos Santos NC, Camelier AA, Maciel RRBT, Camelier FWR. Formal analysis: dos Santos NC, Camelier AA, Maciel RRBT, Camelier FWR. Data curation: all authors. Software: dos Santos NC, Camelier AA, Maciel RRBT, Camelier FWR. Validation: dos Santos NC, Camelier AA, Maciel RRBT, Camelier FWR. Investigation: all authors. Writing - original draft preparation: all authors. Writing - review and editing: dos Santos NC, Camelier AA, Maciel RRBT, Camelier FWR. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

We thank the Stricto Sensu Graduate Program in Pharmaceutical Sciences (PPGFARMA) for their support and encouragement.

Funding

No funding to declare.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2020 report [Internet]. Fontana: GOLD; 2020 [cited 2024 Apr 10]. Available from: https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf.
2. Oca MM, Varela MVI, Acuna A, Schiavi E, Rey MA, Jardim J, et al. Brazilian guidelines for the management of COPD (adaptation for Brazil of the Latin American Consensus of COPD) [Internet]. Asa Sul: Brazilian Society of Pulmonology and Tisiology; 2016 [cited 2024 Apr 10]. Available from: https://sbpt.org.br/consensos-diretrizes-nacionais.
3. Bottega TS. Comorbidities and mortality in chronic obstructive pulmonary disease (master's thesis). Porto Alegre: Federal University of Rio Grande do Sul; 2014.
4. Azambuja R, Bettencourt M, da Costa CH, Rufino R. Panorama da doença pulmonar obstrutiva crônica [An overview of chronic obstructive pulmonary disease]. Rev HUPE 2013;12:13-8.
5. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347-65.
6. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013;162:237-51.
7. 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;107:1514-9.
8. Sevenoaks MJ, Stockley RA. Chronic obstructive pulmonary disease, inflammation and co-morbidity: a common inflammatory phenotype? Respir Res 2006;7:70.
9. Boudestein LC, Rutten FH, Cramer MJ, Lammers JW, Hoes AW. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. Eur J Heart Fail 2009;11:1182-8.
10. Short PM, Anderson WJ, Elder DH, Struthers AD, Lipworth BJ. Impact of left ventricular hypertrophy on survival in chronic obstructive pulmonary disease. Lung 2015;193:487-95.
11. Funk GC, Lang I, Schenk P, Valipour A, Hartl S, Burghuber OC. Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. Chest 2008;133:1354-9.
12. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M, et al. Left atrial and ventricular filling in chronic obstructive pulmonary disease. an echocardiographic and Doppler study. Am J Respir Crit Care Med 2000;162(2 Pt 1):670-5.
13. Smith BM, Prince MR, Hoffman EA, Bluemke DA, Liu CY, Rabinowitz D, et al. Impaired left ventricular filling in COPD and emphysema: is it the heart or the lungs? The Multi-Ethnic Study of Atherosclerosis COPD Study. Chest 2013;144:1143-51.
14. Lipworth B, Wedzicha J, Devereux G, Vestbo J, Dransfield MT. Beta-blockers in COPD: time for reappraisal. Eur Respir J 2016;48:880-8.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
16. Fuchs SC, Paim BS. Revisão sistemática de estudos observacionais com metanálise [Meta-analysis and systematic review of observational studies]. Rev HCPA 2010;30:294-31.
17. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
18. Au DH, Bryson CL, Fan VS, Udris EM, Curtis JR, McDonell MB, et al. Beta-blockers as single-agent therapy for hypertension and the risk of mortality among patients with chronic obstructive pulmonary disease. Am J Med 2004;117:925-31.
19. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. Thorax 2008;63:301-5.
20. van Gestel YR, Hoeks SE, Sin DD, Welten GM, Schouten O, Witteveen HJ, et al. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. Am J Respir Crit Care Med 2008;178:695-700.
21. Stefan MS, Rothberg MB, Priya A, Pekow PS, Au DH, Lin-

denauer PK. Association between β-blocker therapy and outcomes in patients hospitalised with acute exacerbations of chronic obstructive lung disease with underlying ischaemic heart disease, heart failure or hypertension. Thorax 2012;67:977-84.
22. Quint JK, Herrett E, Bhaskaran K, Timmis A, Hemingway H, Wedzicha JA, et al. Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. BMJ 2013;347:f6650.
23. Mentz RJ, Wojdyla D, Fiuzat M, Chiswell K, Fonarow GC, O'Connor CM. Association of beta-blocker use and selectivity with outcomes in patients with heart failure and chronic obstructive pulmonary disease (from OPTIMIZE-HF). Am J Cardiol 2013;111:582-7.
24. Angeloni E, Melina G, Roscitano A, Refice S, Capuano F, Lechiancole A, et al. β-Blockers improve survival of patients with chronic obstructive pulmonary disease after coronary artery bypass grafting. Ann Thorac Surg 2013;95:525-31.
25. Puente-Maestu L, Calle M, Ortega-Gonzalez A, Fuster A, Gonzalez C, Marquez-Martin E, et al. Multicentric study on the beta-blocker use and relation with exacerbations in COPD. Respir Med 2014;108:737-44.
26. Lee DS, Markwardt S, McAvay GJ, Gross CP, Goeres LM, Han L, et al. Effect of β-blockers on cardiac and pulmonary events and death in older adults with cardiovascular disease and chronic obstructive pulmonary disease. Med Care 2014;52 Suppl 3:S45-51.
27. Kubota Y, Asai K, Furuse E, Nakamura S, Murai K, Tsukada YT, et al. Impact of β-blocker selectivity on long-term outcomes in congestive heart failure patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:515-23.
28. Dong YH, Chang CH, Wu LC, Lai MS. Use of cardioselective β-blockers and overall death and cardiovascular outcomes in patients with COPD: a population-based cohort study. Eur J Clin Pharmacol 2016;72:1265-73.
29. Huang YL, Lai CC, Wang YH, Wang CY, Wang JY, Wang HC, et al. Impact of selective and nonselective beta-blockers on the risk of severe exacerbations in patients with COPD. Int J Chron Obstruct Pulmon Dis 2017;12:2987-96.
30. Oda N, Miyahara N, Ichikawa H, Tanimoto Y, Kajimoto K, Sakugawa M, et al. Long-term effects of beta-blocker use on lung function in Japanese patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2017;12:1119-24.
31. Key A, Parry M, West MA, Asher R, Jack S, Duffy N, et al. Effect of β-blockade on lung function, exercise performance and dynamic hyperinflation in people with arterial vascular disease with and without COPD. BMJ Open Respir Res 2017;4:e000164.
32. Liao KM, Lin TY, Huang YB, Kuo CC, Chen CY. The evaluation of β-adrenoceptor blocking agents in patients with COPD and congestive heart failure: a nationwide study. Int J Chron Obstruct Pulmon Dis 2017;12:2573-81.
33. Lim KP, Loughrey S, Musk M, Lavender M, Wrobel JP. Beta-blocker under-use in COPD patients. Int J Chron Obstruct Pulmon Dis 2017;12:3041-6.
34. Maltais F, Buhl R, Koch A, Amatto VC, Reid J, Gronke L, et al. β-Blockers in COPD: a cohort study from the TONADO research program. Chest 2018;153:1315-25.
35. Rezaei SS, Rinner C, Ratajczak P, Grossmann W, Gall W, Wolzt M. Use of beta-blocker is associated with lower mortality in patients with coronary artery disease with or without COPD. Clin Respir J 2018;12:2627-34.
36. Zvizdic F, Begic E, Mujakovic A, Hodzic E, Prnjavorac B, Bedak O, et al. Beta-blocker use in moderate and severe chronic obstructive pulmonary disease. Med Arch 2019;73:72-5.
37. Thomas CD, Dupree LH, DeLosSantos M, Ferreira JA. Evaluation of the protective effects of β-blockers in the management of acute exacerbations of chronic obstructive pulmonary disease. J Clin Pharm Ther 2019;44:109-14.
38. Lin R, Peng H, Nguyen LP, Dudekula NB, Shardonofsky F, Knoll BJ, et al. 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;21:115-24.
39. Ling Y, Saleem W, Shee CD. Concomitant use of beta-blockers and beta2-agonists. Eur Respir J 2008;31:905-6.
40. Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med 2010;170:880-7.
41. Chang CL, Mills GD, McLachlan JD, Karalus NC, Hancox RJ. Cardio-selective and non-selective beta-blockers in chronic obstructive pulmonary disease: effects on bronchodilator response and exercise. Intern Med J 2010;40:193-200.
42. Su VY, Chang YS, Hu YW, Hung MH, Ou SM, Lee FY, et al. Carvedilol, bisoprolol, and metoprolol use in patients with coexistent heart failure and chronic obstructive pulmonary disease. Medicine (Baltimore) 2016;95:e2427.
43. van der Woude HJ, Zaagsma J, Postma DS, Winter TH, van Hulst M, Aalbers R. Detrimental effects of beta-blockers in COPD: a concern for nonselective beta-blockers. Chest 2005;127:818-24.
44. Dart RA, Gollub S, Lazar J, Nair C, Schroeder D, Woolf SH. Treatment of systemic hypertension in patients with pulmonary disease: COPD and asthma. Chest 2003;123:

222-43.
45. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;2005:CD003566.
46. Sessa M, Mascolo A, Mortensen RN, Andersen MP, Rosano GM, Capuano A, et al. Relationship between heart failure, concurrent chronic obstructive pulmonary disease and beta-blocker use: a Danish nationwide cohort study. Eur J Heart Fail 2018;20:548-56.
47. Fallis BA, Dhalla IA, Klemensberg J, Bell CM. Primary medication non-adherence after discharge from a general internal medicine service. PLoS One 2013;8:e61735.
48. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. Ann Intern Med 2002;137:715-25.
49. Malerba M, Montuschi P, Radaeli A, Pirisi M. Role of beta-blockers in patients with COPD: current perspective. Drug Discov Today 2015;20:129-35.
50. Calverley PM, Albert P, Walker PP. Bronchodilator reversibility in chronic obstructive pulmonary disease: use and limitations. Lancet Respir Med 2013;1:564-73.
51. Dellaca RL, Pompilio PP, Walker PP, Duffy N, Pedotti A, Calverley PM. Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. Eur Respir J 2009;33:1329-37.
52. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7-13.
53. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. BMJ 2011;342:d2549.