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REVIEW ARTICLE

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Therapeutic use of cardioselective beta-blockers for patients with chronic obstructive pulmonary disease: a review of current clinical evidence

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ABSTRACT

Cardiovascular diseases, such as hypertension, coronary artery diseases (CAD), arrhythmias, and chronic heart failure (CHF), often require treatment with beta-blockers. These conditions frequently coexist with chronic obstructive pulmonary disease (COPD), which can complicate therapeutic decisions. Indeed, patients with moderate-to-severe COPD are frequently not given these agents out of concern for possible bronchoconstriction arising from blockade of β_2-adrenoceptors in the airways. Observational studies, and meta-analyses support the cardiovascular benefits of β-blockade in people with COPD and cardiovascular diseases. Recent trials evaluating cardioselective β-blockade suggest that cardioselective beta-blockers such as bisoprolol, metoprolol and nebivolol are safe and likely beneficial in those patients that would benefit from their intake due to presence of cardiac comorbid diseases. The aim of this systematic review is to summarise the recent trials and indications for use of cardioselective β-blockers in patients with COPD.

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Beta-blockers; hypertension; cardiovascular disease; heart failure; chronic obstructive pulmonary disease, bisoprolol, metoprolol

Introduction

β-blockers are one of the five main classes of drugs used for the management of hypertension, arrhythmias, coronary artery disease (CAD), and chronic heart failure (CHF). Hypertension (for example) and chronic obstructive pulmonary disease (COPD) are both common conditions, with an estimated global presence of about 30%[1] and about 11%[2], respectively, so it is unsurprising that these conditions often arise in the same individuals. Almost one-third (30%) of CHF patients enrolled in a randomised trial had comorbid COPD[3].

Most people with hypertension, CAD or CHF will require pharmacologic therapy to minimise the risk of major adverse cardiovascular events or premature mortality. COPD exacerbations are also life-threatening and are a frequent cause of emergency admissions[4]. In this setting it is clearly crucial that a cardiovascular drug regimen should not exacerbate airway dysfunction in a patient with cardiovascular problems and COPD. Stimulation of β_2-adrenoceptors relaxes bronchial smooth muscle, and long-acting β_2-agonists are a mainstay of the pharmacological management of COPD[5]. For many years, physicians have often been reluctant to prescribe a β-blocker to a patient with an indication for this treatment if COPD is also present, due to concern over the possibility of bronchoconstriction and exacerbation of COPD resulting from β_2-adrenoceptor blockade. However, this approach potentially denies patients access to evidence-based and guideline-driven care for patients likely to benefit from a β-blocker. Recent research has clarified the risk/benefit profile of β-blockers in this population and this review summarises the current evidence relating to the therapeutic use of β-blockade in people with COPD.

Review methodology

This is a narrative review based on a PubMed search conducted in November 2025 using the search string: (*"beta-block*" [ti] OR "beta block*" [ti] OR "β1-block*" [ti] OR " β1-adrenoceptor" [ti] OR "beta-1 adrenoceptor" [ti] OR β1-receptor [ti] OR "beta-1 receptor" [ti] OR bisoprolol [ti] OR atenolol [ti] OR nebivolol [ti] OR metoprolol [ti] OR carvedilol [ti] OR labetolol [ti]) AND ("chronic obstructive pulmonary disease" OR COPD*). Preference was given to systematic reviews/meta-analyses, analyses from randomised, controlled trials (RCTs) and

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larger observational studies (>200 patients at baseline). Reference lists of reviewed publications and authors' and reference collections provided further material for review.

Overview of β-blockers with reference to COPD

Relative β_1-adrenoceptor selectivity (cardioselectivity)

β-blockers are a highly heterogeneous class, with important pharmacological differences between individual agents in terms of selectivity for different β-receptor subtypes, pharmacokinetics, physicochemical properties and the manner in which they interact with the β-receptor protein, among others[6]. This section will focus primarily on selectivity between β_1- and β_2-adrenoceptors as the main determinant of the pulmonary safety of β-blockers.

The prototype β-blocker, propranolol, blocks both β_1- and β_2-adrenoceptors. Atenolol was the first member of this class to demonstrate selectivity for β_1-adrenoceptors. However, in-vitro experiments and studies in humans have suggested that bisoprolol and nebivolol demonstrated greater selectivity for blockade of the β_1- vs. β_2-adrenoceptor compared with atenolol[7,8]. One of these studies showed that the selectivity for β_1- vs. β_2-adrenoceptors in intact cells was 13.5-fold for bisoprolol, 4.7-fold for atenolol, and 2.3-fold for metoprolol[7]. A randomised clinical study found that metoprolol was β_1-selective at lower, but not higher doses, consistent with these findings[9]. In another study, clinically significant blockade of β_2-adrenoceptors occurred with atenolol when the highest of its recommended doses (100 mg) was given, in contrast to bisoprolol that maintained β_1-adrenoceptor selectivity[10]. Indeed, bisoprolol and nebivolol are both highly β_1-adrenoceptor selective, although different studies have provided conflicting accounts of their relative selectivity[11–13]. For example, experimental studies with varying designs have shown nebivolol to be about 2–4-fold more β_1-adrenoceptor selective vs. bisoprolol[11,12], or found that bisoprolol was about 4–5-fold more β_1-adrenoceptor selective vs. nebivolol[13]. No direct comparison of the β_1-adrenoceptor selectivity of nebivolol and atenolol appears to be available, although functional studies that measured effects on blood glucose and lipids[13,14] or on β_2-adrenoceptor-mediated hypokalaemia[8] in human subjects confirmed the greater β_1-adrenoceptor selectivity of nebivolol.

Other smooth muscle relaxing effects described for some β-blockers appear to be of limited relevance to the use of these agents in people with airways disease. Labetalol and carvedilol also exert additional vasodilator actions by blocking α_1-adrenoceptors in vascular smooth muscle. Blockade of α_1-adrenoceptors appears to have little effect on the tone of bronchial smooth muscle, including in people with asthma[15].

Current European drug labelling and airways disease

The labelling (Summaries of Product Characteristics; SmPC) for all β-blockers contains contraindications and/or warnings and precautions relating to the use of β-blockers in people with airway dysfunction (details from SmPCs from the United Kingdom for some of the more commonly used β-blockers are summarised in Table 1). These relate mostly to patients with asthma or bronchospasm, rather than chronic, non-reactive forms of COPD and for most agents preclude their use where the patient has ever had "wheezing", "bronchospasm" or "asthma". Most agents have precautions/warnings against their use in patients with obstructive pulmonary disorders, unless their use is clinically justified. Among the drugs listed in Table 1, only the SmPC for bisoprolol stresses the importance of starting treatment at the lowest possible dose in this population.

Patient Information leaflets (PIL; not shown in Table 1) also carry inconsistent instructions relating to individual β-blockers for people with airways diseases. Those for propranolol, carvedilol, labetalol, nebivolol and metoprolol tell patients not to take their medicine if they have ever had breathing difficulties, asthma, wheezing, etc. The PIL for atenolol stresses the need for the patient with a history of asthma to talk to the doctor before taking the medicine, while the PIL for bisoprolol advises the patient to contact their physician if respiratory symptoms worsen, or if new ones arise.

All of the drugs summarized above and in the Table 1 are available as generic preparations, and many different preparations exist, with the likelihood of variations between them. Reviewing all of these is beyond the scope of this review. Nevertheless, it is clear that the current labelling for β-blockers with regard to airways diseases is inconsistent, as shown by the heterogeneity of contraindications and precautions relating to their use in people with airways dysfunction shown in Table 1. The labelling also does not clarify their use in important presentations of airways diseases (e.g. asthma vs. COPD), and does not differ in

Table 1. Overview of orally administered β-blockers.

Drug	α_1 blockade	Beta-1 selectivity	ISA	Half life (h)	Elimination	Contraindications relating to airway dysfunction	Precautions relating to airway dysfunction
Acebutolol	No	Yes	Yes	3–4	Hepatic (primary) Renal (secondary)	Severe asthma or severe COPD	Use with utmost care in patients with obstructive airways diseases and where compelling indications for their use are present
Atenolol	No	Yes	No	6–9	Renal	No specific contraindication relating to airways disease	Avoid in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use (use with caution).
Betaxolol	No	Yes	No	14–22	Hepatic (primary) Renal (secondary)	Reactive airway disease including severe bronchial asthma or a history of severe bronchial asthma, severe COPD[c]	Use with caution in those with or with history of mild/moderate bronchial asthma, or mild/moderate COPD[c]
Bisoprolol	No	Yes	No	9–12	Renal and hepatic	Severe bronchial asthma	Should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use (then use with caution, starting at the lowest possible dose)
Carvedilol	Yes	No	No	7–10	Biliary (primary) Hepatic (secondary)	History of bronchospasm or asthma	Use with caution in patients with COPD with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk
Celiprolol	No	Yes	Yes	4–5	Minimally metabolised, mainly excreted unchanged	Acute asthma, severe asthma, severe COPD	Avoided in chronic obstructive airways disease, and in patients with history of bronchospasm or asthma, unless there are compelling clinical reasons for their use (then use with " utmost caution" under specialist supervision
Labetalol	Yes	No	Yes (β_2)	3–4	Hepatic	History of wheezing or asthma	Should not be used in patients with asthma or a history of obstructive airways disease unless no alternative treatment is available; take appropriate precautions against the risk of inducing bronchospasm
Metoprolol	No	Yes	No	3–4[a]	Hepatic *via* CYP2D6 (polymorphic)	Severe asthma or history of severe bronchospasm.	Should be avoided in patients with reversible obstructive airway disease without compelling clinical reasons for use
Nadolol	No	No	No	20–24	Renal	Bronchial asthma or a history of asthma	Should be avoided in bronchospastic diseases
Nebivolol	No	Yes[b]	No	10–12[c]	Hepatic	History of bronchospasm and bronchial asthma	Use with caution in patients with chronic obstructive pulmonary disorders
Penbutolol	No	No	Yes	5	Hepatic	Bronchial asthma[e]	In general, patients with bronchospastic diseases should not receive ß-blockers[e]
Pindolol	No	No	Yes	3–4	Hepatic (primary) Renal (secondary)	Bronchial asthma[e]	No additional warnings or precautions relating to airways disease[e]
Propranolol	No	No	No	3–4	Hepatic	History of bronchial asthma or bronchospasm	No additional warnings or precautions relating to airways disease
Sotalol[§]	No	No	No	12	Renal	History of chronic obstructive airway disease or bronchial asthma	No additional warnings or precautions relating to airways disease
Timolol	No	No	No	4–5	Hepatic (primary) Renal (secondary)	Reactive airway disease incl. bronchial asthma or a history of bronchial asthma, or severe COPD[d]	Use with caution in mild/moderate COPD and only where benefits outweigh risks.

[a]7–9 h in poor metabolizers. Also increases nitric oxide production which results in relaxation of airway smooth muscle. [b]19–32 h in poor metabolizers. [d]Refers to an eye drops preparation used in the management of glaucoma. Contraindications (bold text) and precautions (non-bold, bulleted text) were abstracted from Summaries of Product Characteristics available at www.medicines.org.uk (one sample product was used to provide this information and other products with the same active ingredient may have slightly different contraindications and warnings); where no SmPC was available, information was from a manufacturer's website[d] US prescribing information[e]); these have been paraphrased for conciseness here and prescribers should always read the full label relevant to their area. Abbreviation. COPD, chronic obstructive pulmonary disease.

a consistent manner according to the β_1-adrenoceptor selectivity of the β-blocker in question.

Clinical studies of cardioselective β-blockade in people with COPD

Randomised, controlled trials

The effect of cardioselective beta-blockers was assessed in a meta-analysis of RCTs, in which cardioselective beta-blockers were administered to almost 400 patients with either asthma or COPD and responsive bronchoconstriction[16]. Overall, when considering cardioselective beta-blockers, although single dose use was related to an 8% decrease of FEV1, it was also associated with a 5–9% increase in the response to a bronchodilator. Sustained use was not associated with changes in baseline FEV1 and long-term therapy did not increase respiratory symptoms or the use of inhaled beta-agonist. In a study of methacholine inhalation challenge in people with COPD, the administration of propranolol 80 mg reduced both FEV1 and the bronchodilating effect of formoterol, together with an increase in airway hyperresponsiveness to methacholine[17]. Conversely, metoprolol 100 mg\day increased airway responsiveness only, without affecting FEV1 or the formoterol response.

The effect of selective beta-blockers metoprolol and bisoprolol were compared with carvedilol (which is a non-cardioselective beta-blocker and an alpha-blocker) in 35 patients with COPD and CHF[18]. FEV1 was lowest with carvedilol and highest with bisoprolol (carvedilol 1.85 L/s [95% CI 1.67 to 2.03] metoprolol 1.94 L/s [1.73 to 2.14], bisoprolol 2.00 L/s [1.79 to 2.22], but the six-minute walk distance was not different among groups.

Table 2 summarises the main findings of randomised controlled trials (RCTs) of β-blockers in populations with COPD[19–34]. Table 3 summarises selected details of the patient populations at baselines of the three major placebo-controlled RCTs of β-blockers in this population: the Bisoprolol to Prevent Adverse Cardiac Events (PACE) study[19] and the Bisoprolol in COPD Study (BICS) study[20] evaluated bisoprolol and the BLOCK COPD study evaluated metoprolol[21,22]. The populations of these trials were broadly similar: mean FEV1 in treatment groups was between 41% and 51%, most used inhaled corticosteroids together with one or two long-acting bronchodilators,. Few in BICS and none in PACE used long-term O_2 therapy, although two-fifths in BLOCK COPD used supplemental O_2 in the previous year, as this was included alongside recent exacerbations among recruitment criteria that defined the required severity of COPD for inclusion in the trial. All had reported COPD exacerbations.

PACE randomised 280 patients with COPD (FEV1 30–70% on a bronchodilator and at least one COPD exacerbation in the previous 2 years) and randomised them to bisoprolol (up to 5 mg) or placebo for 2 years[19]. There was no difference between groups for outcomes related to all-cause mortality, cardiorespiratory hospitalisations, major adverse cardiac events, moderate or severe COPD exacerbations, FEV_1, COPD symptoms, quality of life, or adverse events. The 1-year, randomised, placebo-controlled Bisoprolol in COPD Study (BICS) evaluated bisoprolol (up to 5 mg/day) in a population with moderate-to-severe COPD who were known to be at risk of exacerbations due to a history of at least two COPD exacerbations in the previous year that required intervention with corticosteroids and/or antibiotics[20,35]. The presence of cardiovascular indications for a β-blocker (CHF or recent acute coronary syndromes) was an exclusion criterion. There was no difference between the bisoprolol and placebo groups in the rate of COPD exacerbations (incidence rate ratio [IRR] 0.97 [95%CI 0.84 to 1.13], $p = 0.72$) or in the rate of COPD hospitalisations (IRR 1.00 [95%CI 0.67 to 1.50]). The time to first exacerbation was 96 days with bisoprolol and 70 with placebo (hazard ratio [HR] 0.94). There was also no difference between bisoprolol and placebo in the risk of the secondary outcomes of non-COPD hospitalisations (IRR 1.47 [95%CI 0.88 to 2.55]) or all-cause mortality (IRR 0.77 (95%CI 0.34 to 1.73]). There was a possible statistically borderline increase in dyspnea but not in COPD symptoms overall or serious adverse events (SAE; relative risk 1.01 [95%CI 0.62 to 1.66]).

The BLOCK COPD study was conducted in a population of 532 individuals with moderate or severe COPD and at least one emergency visit or admission for COPD exacerbation(s), or prescription of supplementary O_2, in the previous year[21,22]. As with BICS, patients were excluded if they had a cardiovascular indication for β-blockade (myocardial infarction or revascularization within the previous 36 months or HFrEF). Randomisation was to extended-release metoprolol (25–100 mg, depending on tolerability) or placebo for 336 days. The metoprolol group experienced an increased risk of COPD exacerbation leading to hospitalization during nearly one year follow-up (92 versus 58 hospitalizations, rate ratio 1.6 [95%CI 1.1 to 2.4]), leading to early termination of the trial. This severe exacerbation risk was not mediated by changes in lung function or bronchodilator responsiveness in the metoprolol group. Those in the metoprolol arm

Table 2. Randomised, controlled evaluations of cardioselective β-blockers in patients with COPD.

Ref	N	Treatments	Duration	Overview of main findings
[19]	280	Bisoprolol[a] Placebo	2 y	PACE trial – no significant difference between bisoprolol and placebo for the incidence of all-cause mortality (estimate 0·86 [0.39 to 1.94]), cardiorespiratory hospitalisations (estimate 0.89 [0.54 to 1.47]), major cardiac hospitalisations (0% vs. 0.3%), moderate COPD exacerbations (estimate 0.97 [0.66 to 1.43]), severe COPD exacerbations (36% in each group required corticosteroids and antibiotics for exacerbations), or FEV1 (45·1 [SD 14·9] vs. 46·5 [SD 15·5] at study end). Also no difference for COPD symptoms, quality of life, or adverse events.
[20]	514	Bisoprolol[a] Placebo	1 y	BICS Study – bisoprolol administered in COPD patients without CHF or recent cardiovascular disease (i.e. without a cardiovascular indication for β-blockade)[q]: no difference between groups in rates of exacerbations in people with COPD at high risk of exacerbations (IRR 0.97 [0.84 to 1.13], $p = 0.72$). No significant effect on FEV1 (mean treatment difference −4.53 [10.2 to 1.16]).
[21,22]	536	Metoprolol[h] Placebo	336 d	BLOCK COPD study – metoprolol administered to patients with COPD without a cardiovascular indication for β-blockade[r]: no difference for overall exacerbations (HR 1.12 [0.88 to 1.42]), but higher risk of exacerbations of at least moderate severity (HR 1.46 [1.03 to 2.06]), severe or very severe exacerbations (HR 2.08 [1.37 to 3.14]), and hospitalisation for exacerbations for metoprolol vs. placebo (HR 1.91 [1.29 to 2.83]); no significant reduction in FEV1 (mean treatment difference −0.78 [−2.25 to 0.69]) for metoprolol vs. placebo.
[17]	15	Metoprolol[k] Propranolol[j] Celiprolol[l] Placebo[n]	4 d	FEV1 was impaired only on propranolol (2.08 L vs. 2.24 L for placebo at day 4, $p < 0.05$). The increase in GEV1 in response to formoterol was smaller with propranolol (6.7%) vs. placebo (16.9%). The dose of methacholine required to induce a 20% fall in FEV1 was smaller for propranolol (2.06 mg/mL) and metoprolol (2.02 mg/mL) vs. placebo (3.16 mg/mL). No other statistically significant effects were observed.
[18]	51	Bisoprolol[f] Metoprolol[f] Carvedilol[f]	6 w	FEV1 was lower with carvedilol (1.85 L/s) vs. metoprolol (1.94 L/s) or bisoprolol (2.0 L/s; $p < 0.001$) in a population with mild-to-moderate CHF and COPD.
[23]	40	Bisoprolol Atenolol	6 mo	No difference between treatments: both were associated with a slight increase in airway resistance, which increased with therapy duration, and a small but significant decrease in FEV_1 and peak expiratory flow rate; no effect on bronchitis symptoms. Peak exploratory flow rate did not differ significantly between the bisoprolol and atenolol groups at baseline (6.3 vs. 6.1 L/min) or after treatment (5.9 vs. 6.0 L/min).
[24]	12	Bisoprolol Atenolol	Single dose	Atenolol, but not bisoprolol, increased airway resistance up to 4 h after dosing. FEV1 at baseline was 1.3–2.0 L.
[25]	11	Bisoprolol[a] Celiprolol[b]	4 w	No difference between groups for the rate of dynamic hyperinflation (DH) between resting inspiratory capacity and exercise isotime inspiratory capacity at 4 min in patients with moderate-to-severe COPD: mean DH was −490 mL (−820 to −130) for celiprolol and −420 mL (−610 to −230) for bisoprolol, compared with baseline of −470 mL (−730 to −200), $p = 0.87$ overall; mean FEV1 was 52%, 52% and 54%m respectively ($p = 0.90$).
[26]	27	Bisoprolol[c] Placebo	2 w	Modest reduction in inspiratory capacity on exercise with bisoprolol vs. placebo (–0.50 L vs −0.41 L, $p = 0.01$); no significant difference for exercise duration in a population with COPD (305 vs 353 s, $p = 0.11$).
[27]	63	Bisoprolol[d] Carvedilol[e]	6 w[p]	FEV1 increased significantly on bisoprolol (1,561 mL to 1,698 mL, $p = 0.046$) but not carvedilol (1,,704 mL to 1,734 mL, $p = 0.44$) in a population with mild-to-moderate CHF and COPD; 1 patient in the carvedilol group withdrew due to respiratory side-effects (no such withdrawals occurred for bisoprolol).
[28]	27	Bisoprolol[g] Placebo	4 mo	Reduction in FEV1 with bisoprolol vs. placebo (–70 mL vs. +120 mL, $p = 0.01$), with no difference for the mean number of COPD exacerbations (0.50 vs. 0.31, respectively, $p = 0.44$), symptoms or quality of life .
[29]	11	Metoprolol[i] Propranolol[j] Placebo	1 w	Reduced bronchodilator response to salbutamol with propranolol vs. placebo in subjects with COPD; trend to lower bronchodilator response after a high-dose challenge with metoprolol (190 mg), but no effect of lower dose. Mean area under the salbutamol dose–response curve (AUC, FEV1 recovery in L.min) was 3.12 for placebo, 2.55 for metoprolol 0.95 mg (p = NS vs. placebo), 2.31 for metoprolol 1.90 mg ($p = 0.076$ vs. placebo), 1.20 for propranolol ($p = 0.0006$ vs. placebo). Mean FEV1 after treatment was 1.6 L for placebo, 1.54 L for metoprolol 0.95 mg. 1.59 for metoprolol 1.90 mg and 0.48 for propranolol (only propranolol was significantly different from placebo, $p = 0.0289$).
[30]	10	Propranolol[j] Oxprenolol[j] Atenolol[k] Celiprolol[l]	1 w	Oxprenolol and propranolol reduced FEV1 (by −14% and by −16%, respectively) and prevented a bronchodilator response to a β_2-adrenoceptor agonist; atenolol and celiprolol had no effect on these parameters,
[31]	20	Nebivolol[m] Nifedipine	2 w	Nebivolol reduced FEV1 by −109 mL ($p < 0.05$) in a population with hypertension and COPD, but this was considered not to be clinically significant.
[32]	50	Metoprolol CR[n] Metoprolol IR[o]	3 mo	No effect of either metoprolol formulation on FEV1: mean baseline and final values were 54.5% (SD 13.4) vs 54.3% (SD 13) for metoprolol CR group and 49.6% (SD 14.5) vs 53.2 (SD 12.8) for standard metoprolol.

(*continued*)

Table 2. Continued.

Ref	N	Treatments	Duration	Overview of main findings
[33]	12	Atenolol Pindolol Bopindolol	Single dose	Atenolol 100 mg induced an increase in airway resistance that persisted for 24 h, while increses in airway resistance with pindolol or bopindolol were small and transient.
[34]	15	Atenolol Propranolol	3 w	Both atenolol 100 mg and propranolol 40 mg significantly increased airway resistance (maximal mid-expiratory flow rate or peak flow rate at times up to 90 min post-dose (no significant effects occurred after 7 days treatment).

[a]Up to 5 mg/day. [b]Up to 400 mg/day. [c]10 mg/day. Mean daily doses were [d]6.4 mg and [e]47 mg. [f]In this crossover study, patients were switched to the next β-blocker at a dose calculated to provide equivalent β_1-adrenoceptor blockade. [g]Titrated to maximum tolerated dose (mean achieved dose was 7.3 mg). [h]Up to 100 mg/day. [i]95 mg. [j]80 mg. [k]100 mg. [l]200 g. [m]5 mg/day. [n]Average dose 92.5 mg/day. [o]Average dose 189 mg/day. [p]Maintenance treatment phase after drug titration. [q]Patients were excluded if they had a myocardial infarction or acute coronary syndrome within the previous year. [r]Myocardial infarction or revascularization within the previous 36 months or heart failure with reduced left ventricular ejection fraction. Abbreviations. BICS, Bisoprolol in COPD Study; BLOCK COPD, β-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease study; CHF, congestive heart failure; ER, extended release; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IR, immediate release; HR, hazard ratio; IRR, incidence rate ratio. Figures in parentheses accompanying risk estimates are 95% confidence intervals.

Table 3. Selected baseline characteristics of patients enrolled in major randomised, controlled trials of β-blockers in populations with COPD included in table 2.

Trial	Key mean baseline characteristics (β-blocker vs. Placebo)
PACE[19]	• Mean post-bronchodilator FEV1 44% vs. 46%. • Recent history of exacerbations was not reported; however, according to recruitment criteria, all had ≥1 COPD exacerbation in previous 2 y. • 66% vs. 76% used ICS, 72: vs. 79% used LABA; 45% vs. 55% used LAMA; 64% vs. 64% used SABA; ≤15% used other respiratory medicines (information on use of inhaled combination therapies was not reported). • Long-term O_2 therapy was an exclusion criterion.
BICS[20]	• Mean baseline FEV1: 49% vs. 51%. • No. of exacerbations in the last 12 months: 3.5 vs. 3.6 (0.4 vs. 0.5 required hospitalisation). • 74% vs. 73% used ICS/LABA/LAMA combinations (≤12% of any group used other single use/combinations of inhaled respiratory drugs). • 6.2% vs. 3.5% were on long-term O_2.
BLOCK COPD[21]	• Post-bronchodilator FEV1 41% vs. 41%. • Mean hospitalisations in last 12 months: 0.7 vs. 0.5. • 58% vs. 61% used ICS/LABA/LAMA combinations (<20% of any group used other single use/combinations of inhaled respiratory drugs). • Used supplemental O_2 in last 12 months: 40% vs. 40%.

Abbreviations. LABA, long-acting β_1-agonist; SABA, short-acting β_1-agonist; ICS, inhaled corticosteroid; LAMA, long-ac ting muscarinic antagonist.

had a similar time until first exacerbation of 202 days, versus 222 days among those in the placebo group (HR 1.05 [95%CI 0.8 to 1.3]). This trial was terminated early after an interim analysis reported futility for achievement of the primary endpoint and safety concerns. There was no difference between groups for the primary endpoint, the overall risk of COPD exacerbations (rate ratio, 1.05 [95%CI 0.85 to 1.28]). Further exploratory analyses suggested an increased risk with metoprolol vs. placebo of severe exacerbations (rate ratio 1.51 [95%CI 1.00 to 2.29]) or of very severe exacerbations (rate ratio 3.71 [95%CI 1.10 to 16.98]). A post hoc analysis of the BLOCK COPD database found that while metoprolol did not affect FEV1 significantly relative to placebo, there was a significant decrease in log-transformed FEV1 only at day 28; this change was considered unlikely to have accounted for the increased rate of severe exacerbations on metoprolol[22]. An independent commentary on this study noted that the premature termination of the study likely hindered quantitative comparison of the risk of exacerbations between subgroups[36]. Thus, the underlying reason for this apparent association with metoprolol with more severe exacerbations in BLOCK COPD remains unclear.

These studies also reported no significant difference in non-COPD hospitalisations or cardiovascular events between groups. Of note, BICS and BLOCK COPD administered beta-blockers with the specific aim of assessing their effect on COPD exacerbations, and excluded patients with a CV indication for beta-blocker therapy. PACE allowed clinically stable patients with a history of prior cardiovascular disease or coronary heart disease, but the prevalence of these conditions at baseline was low (6% and 11%, respectively). Accordingly,. A lack of effect of β-blocker therapy on cardiovascular outcomes was unsurprising as these trials were not designed to detect this.

Bisoprolol was the most studied β-blocker in other, smaller and shorter, trials in populations with COPD (Table 2). These evaluations reported modest or no deleterious effects on respiratory parameters with bisoprolol, compared with placebo or other cardioselective β-blockers, and no increase in the risk of COPD exacerbations[23–28]. Two studies reported respiratory benefits (greater forced expiratory volume in 1 s [FEV1]) with bisoprolol compared with carvedilol, a non-cardioselective β-blocker[18,27].

Other randomised trials reported a lack of effect of the cardioselective agents nebivolol[31] or metoprolol[32] on pulmonary function, or more pronounced effects on lung function of non-selective β-blockers (propranolol, oxprenolol), compared with agents with at least some β_1-adrenoceptor selectivity (atenolol, celiprolol)[17,29,30]. Several, mainly small ($N = 12–40$), randomised trials demonstrated potentially adverse effects of atenolol (increased airway resistance) in populations with COPD with[23,24] or without[33,34] comorbid angina pectoris. Two of these trials, from the same group, reported that the effects of atenolol and bisoprolol in patients with COPD were either similar (slight decrease in FEV1/increase in airway resistance[23]) or opposite (increased airway resistance only with atenolol[24])

A note of caution is required when discussing this evidence due to the relatively short duration of follow-up of most of the studies described in Table 2. Of the studies described there, follow-up durations >6 months were described only for PACE (2 years[19]) BICS (1 year[20]) and BLOCK COPD (~11 months[21,22]).

Observational data

Maintained cardiovascular benefits of β-blockade in people with COPD

It is important to demonstrate that the cardiovascular benefits of β-blockers occur in populations with COPD. Table 4 summarises studies that reported the effects of β-blockade on mortality or cardiovascular outcomes in people with COPD and acute coronary syndrome (ACS) or myocardial infarction (MI)[37–45], CHF with reduced left ventricular ejection fraction (HFrEF)[46–55], coronary artery disease[56,57], or other presentations of cardiovascular disease[58–63].

Within these studies, a large database study ($N = 14,789$) showed that the improvement in cardiovascular outcomes with β-blockade post-MI in people with COPD was limited to cardioselective β-blockers only: hazard ratios (95%CI) for cardioselective vs. non-cardioselective β-blockers were 0.93 (0.89 to 0.96) for mortality, 0.96 (0.93 to 0.998) for MACE and 0.84 (0.78 to 0.91) for hospitalisation for heart failure (Figure 1)[39]. A similar benefit was seen when bisoprolol was compared with carvedilol directly[39]. A nationwide study in Taiwan of 23,116 survivors of MI who had comorbid COPD found that cardioselective β-blockers were associated with reduced mortality (HR 0.93 [95%CI 0.89 to 0.98], $p < 0.01$) while non-selective β-blocker groups were not (HR 0.98 [95%CI 0.94 to 1.02; $p = 0.38$)[40]. The majority of other studies found that cardioselective β-blockade was more effective in improving outcomes in the setting of comorbid COPD plus HFrEF or cardiovascular disease[39,40,49,52–55,58,61], although others reported similar[51], or lower[46] efficacy associated with cardioselectivity.

These were mostly cardiovascular studies, and only limited (or no) information was provided on respiratory disease status at baseline for most studies. Where data on this were provided, indices of the severity of COPD and respiratory treatments were generally well balanced between subpopulations receiving or not receiving a β-blocker (Table 4). However, confounding remains a possibility, as one study, for example, reported that the no β-blocker group had twice the rate of previous exacerbations, compared with the β-blocker group[44]. Observational studies in general are susceptible to multiple sources of confounding. While observational studies are of interest in summarising the totality of evidence, they are by definition hypothesis generating and their findings must always be confirmed by appropriately designed RCTs. It is also possible that the presence of COPD may have influenced the prescription of a β-blocker. Table 4 also contains data on parameters relating to the severity of respiratory dysfunction at baseline, where this was reported (it often was not). These data do not indicate a major difference in COPD severity between the subpopulations receiving or not receiving a β-blocker, although the extent of information available on this was very limited. It would be expected that the underlying severity of COPD may influence the risk of an adverse respiratory reaction to a β-blocker (although the main RCTs in this area were conducted in a population already at risk of exacerbations, as described above), rather than the effect of a β-blocker on clinical cardiovascular outcomes.

Rates of COPD exacerbations

Multiple observational studies[64–72] reported a reduced risk of COPD exacerbations in patients with COPD treated with a β-blocker. Meta-analyses that included observational studies have reported reduced exacerbation rates in patients with COPD and comorbid cardiovascular disease who were receiving vs. not receiving a β-blocker[73–75]. Starting a β-blocker during hospitalisation for a COPD

Table 4. Overview of major observational studies of clinical outcomes associated with β-blocker therapy in populations with cardiovascular diseases complicated by comorbid COPD.

Ref	N	Overview of main findings
Populations with acute coronary syndromes or acute myocardial infarction		
[37]	113,650	Intervention at admission with a β-blocker was associated with reduced incidence of death (risk ratio 0.332 [0.119 to 0.923]), HF (risk ratio 0.625 [0.414 to 0.943]), and a cardiovascular composite endpoint (risk ratio: 0.616[0.418 to 0.908]).
[38]	3,531	β-blocker at discharge did not influence a composite of all-cause mortality, revascularization, or hospitalisation (HR 1.01 [0.66 to 1.54]) or risk of MACE (HR 1.11 [0.65 to 1.92]).
[39]	14,789	Cardioselectivity of β-blocker treatment was associated with lower risk of mortality (HR 0.93 [0.89 to 0.96]), MACE (HR 0.96 [0.93 to 0.998]), or HF hospitalisation (HR 0.84 [0.78 to 0.91]).
[40]	23,116	Reduced mortality risk with cardioselective β-blockers (HR 0.93 [0.89 to 0.98]) but not with non-selective β-blockers (HR 0.98 [0.94 to 1.02]), each compared with no β-blocker. Similar proportions for with vs. without β-blocker received ICS (31% vs. 32%), SABA (50% vs. 55%) or SAMA (38% vs. 39%).
[41]	23,754	Lower mortality risk for β-blocker vs. no β-blocker (HR 0.88 [0.84 to 0.93]) and for β-blocker vs. non-dihydropyridine calcium channel blocker (HR 0.91 [0.83 to 0.99]) during the 14 days post discharge following AMI (no mortality difference at 1 year post discharge). 11% of the β-blocker group and 12% of the control group had severe COPD.
[42]	1,573	Reduced risk of all-cause mortality (HR 0.73 [0.60 to 0.90]) and cardiovascular mortality (HR 0.77 [0.61 to 0.97]) for use vs. non-use of a β-blocker.
[43]	4,858	Discharge with vs. without β-blocker was associated with lower 7-year all-cause mortality (HR 0.87 [0.78 to 0.98]). Of patients with COPD, 60% of the β-blocker group and 50% of the non-β-blocker group used inhaled therapy for COPD.
[44]	1,063	Reduced 3-year mortality when a β-blocker was started after admission (HR 0.50 [0.36 to 0.69]) or if pre-existing β blocker therapy was continued (HR 0.59 [0.44 to 0.79]). 15% of the no β-blocker group, 7.4% of those who took a β-blocker before admission and 3% who started β-blocker after admission had frequent exacerbations.
[45]	54,962	Reduced mortality associated with β-blockade in patients with COPD or asthma (RR 0.85 [0.73 to 1.00]), benefit was similar to patients similar to patients without COPD or asthma (RR 0.86 [0.81 to 0.92]).
Heart failure with reduced left ventricular ejection fraction		
[46]	5,232	Lower 2-year all-cause mortality with non-selective β-blockade (HR 0.37 [0.19 to 0.70]) or cardioselective β-blockade (HR 0.58 ([0.34 to 0.99]) in patients admitted with acute decompensated CHF and COPD; cardiovascular mortality reduced only with non-selective β-blocker but not with a cardioselective β-blocker (HRs 0.37 [0.19 to 0.73] and 0.66 [0.37 to 1.17], respectively). Mean baseline FEV1 did not differ according to β-blocker use or non-use (1.6 vs. 1.5 L, $p = 0.34$).
[47]	1,843	Lower all-cause mortality with β-blocker in patients with (HR 0.39 [0.16 to 0.98)]) or without (0.62 [0.46 to 0.83]) COPD.
[48]	14,111	Lower all-cause mortality with β-blocker in patients with (HR 0.74 [0.64 to 0.84)]) or without (0.79 [0.74 to 0.84]) COPD.
[49]	11,558	Survival benefit with bisoprolol vs. no β-blocker at lower or higher dose (HRs 0.76 [0.59 to 0.97] and 0.40 [0.26 to 0.63], respectively, but no significant survival benefit for carvedilol or metoprolol.
[50]	132	β-blocker therapy vs. no β-blocker reduced mortality (HR 0.41 [0.17 to 0.99]); no other covariate influenced mortality risk. Mean baseline FEV1 was 1.6 L for β-blocker use and 1.5 L for no β-blocker use.
[51]	2,670	Nonselective and cardioselective β-blockers reduced 60–90 day mortality similarly, irrespective of the presence or absence of comorbid COPD.
[52,53]	51,214	Higher risk of HF hospitalisation with carvedilol vs. cardioselective β-blockers (metoprolol, bisoprolol, nebivolol; HR 1.29 [1.18 to 1.40]); there were 106 (76 to 134) additional HF cases/10,000 pat-y for carvedilol vs. cardioselective agents. Respiratory medication use at baseline did not differ between groups.
[54]	24,999	More HF hospitalisations with carvedilol vs. bisoprolol, metoprolol or nebivolol (HR 1.74 [1.65 to 1.83] and adjusted (HR 1.61 [1.52 to 1.70]).
[55]	5,084	β-blocker associated with lower risk of composite of CV death or total HF hospitalisation (RR 0.74 [0.58 to 0.96]) with no increased risk of severe COPD exacerbations (RR 0.99 [0.73 to 1.35]) in a HF registry in Sweden. 7% on β-blocker and 5% not on β-blocker had dyspnoea at rest; respiratory treatments did not differ according to β-blocker use.
Other presentations of cardiovascular disease		
[56]	65,717	Lower mortality rates in a population with CAD who received vs. did not receive a β-blocker whether they also had COPD (8.1% vs. 22.0%, respectively) or did not have COPD (5.6% vs. 22.2%).
[57]	388	Lower mortality with vs. without β-blocker after CABG (7.7% vs. 18.3%, $p = 0.03$). Similar proportions receiving vs. not receiving cardioselective β-blocker had severe COPD (21% vs. 22%; FEV1 30–<50%) or very severe COPD (4% vs. 6%; FEV1 < 30%).
[58]	4,493	Reduced mortality associated with cardioselective β-blocker use (HR 0.62 [0.50 to 0.77]) but not with nonselective β-blocker use (HR 1.01 [0.75 to 1.36]) in a population with acute bronchitis. Respiratory medicine use (β-blocker non-users vs, users: β_1-agonists 35% vs. 27%, $p < 0.001$, anticholinergics 35% vs. 31%, $p = 0.006$, ICS 31% vs. 33%, $p = 0.215$).
[59]	3,371	Cardioselective β-blocker use was associated with reduced 30-day mortality (OR 0.37 [0.19 to 0.72]) and long-term mortality (OR 0.73 [0.60 to 0.88]) following vascular surgery for atherosclerotic conditions. Proportions for β-blocker vs. no β-blocker receiving respiratory medications were 13% vs. 18% for bronchodilator and 23% vs. 11% for ICS.

(*continued*)

Table 4. Continued.

Ref	N	Overview of main findings
[60]	1,966	Lower mortality with β-blocker vs. calcium channel blocker in older patients with COPD and hypertension (HR 0.57 [0.33 to 0.89]); similar effects for comparison between β-blockers and other medications. Proportions with COPD exacerbations at baseline were 21% for β-blocker or angiotensin converting enzyme inhibitor, 16% for α-blocker, 13% for thiazide, 21% for calcium channel blocker and 15% for other antihypertensive class.
[61]	35,082	β-blocker therapy did not influence in-hospital mortality (OR 0.88 [0.71 to 1.09]) or 30-day readmission (OR 0.96 [0.89 to 1.03]) in patients hospitalised for COPD exacerbation; non-selective β-blocker increased the rate of 30-day readmission vs. cardioselective β-blocker (OR 1.25 [1.08 to 1.44]). 13% of users and non-users of β-blockers had an admission for COPD exacerbation in the previous year; corresponding figures for ≥2 COPD admissions were 6% and 8%, respectively.
[62]	1,062	β-blockade did not influence the risk of cardiac events (HR 1.18 [0.85 to 1.62]) or death (HR 0.87 [0.67 to 1.13]) in older patients with cardiovascular disease. 15% of β-blocker users and 19% of non-users required home O_2 provision ($p = 0.987$).
[63]	950	Trend to increased risk of mortality with vs. without a β-blocker (HR 1.37 [0.99 to 1.89]).

Indices of respiratory function at baseline are shown when provided in the source puiblication. Abbreviations. AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; HR, hazard ratio; OR, odds ratio; RR, relative risk; SABA, short ac ting β_1-agonist; SAMA, short acting antimuscarinic agent. Figures in parentheses alongside risk estimates are 95% confidence intervals. This table does not contain information on COPD exacerbations or other pulmonary outcomes, which are discussed separately in this review.

exacerbation was shown to be safe[76], or even reduced the risk of adverse outcomes associated with the exacerbation, particularly the development of arrhythmias[77]. Some studies found a significantly higher risk of exacerbations with nonselective vs. cardioselective β-blockers[50,78]. Other observational studies showed no difference in rates of exacerbations or other adverse pulmonary outcomes with vs. without β-blockade[40,62,63,79–84], including in a population at high risk of exacerbations[61]. Receipt of β-blockade was associated with reduced risk of mortality among patients hospitalised for COPD exacerbation in another study[85]. Finally, a report from the Rotterdam cohort suggested that β-blockers reduced the risk of exacerbations only in patients with a cardiovascular indication for β-blocker therapy[64]. These studies are reported here for completeness, although the apparently beneficial effects of β-blockade on the frequency of exacerbations were not confirmed by the PACE[19], BICS[20] and BLOCK COPD[20] RCTs, which demonstrated no protection from exacerbations by β-blockade, as described above. It is likely that these positive findings arose from confounding in these observational studies.

It is important to consider how COPD exacerbations are defined in patients with coexisting cardiovascular comorbidities. Worsening of symptoms related to arrhythmias, hypertensive crises, myocardial ischaemia, or decompensated CHF may be favourably influenced by β-blockers, particularly cardioselective agents. Although it may not always be clinically straightforward to distinguish the underlying cause of symptom deterioration in patients with COPD and concomitant cardiovascular disease, such events should not necessarily be classified as true COPD exacerbations, since their pathophysiology, management, and prevention differ. Nonetheless, β-blockers prescribed for valid cardiovascular indications should not be discontinued during genuine COPD exacerbations.

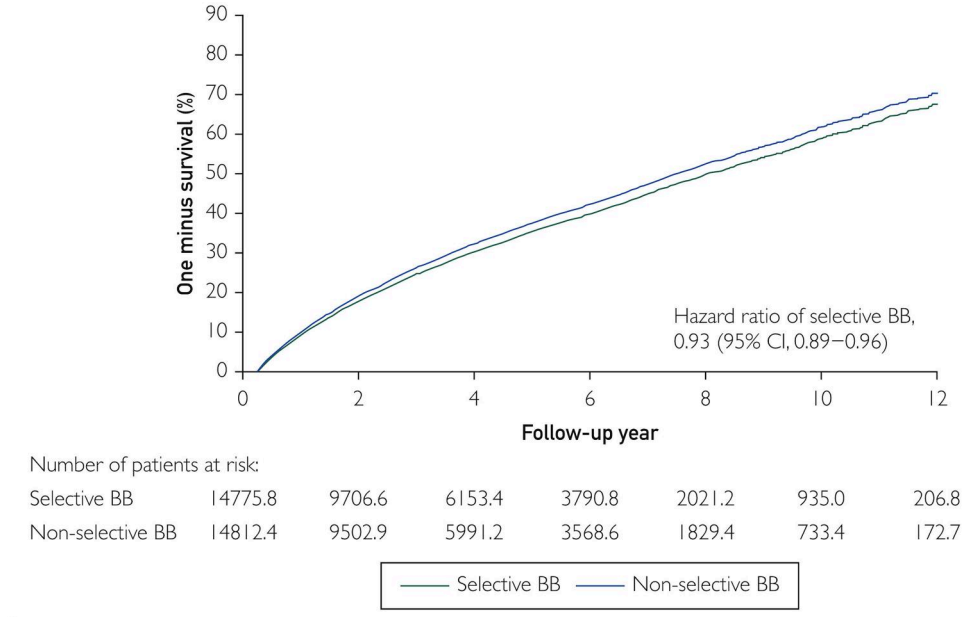
Effects on other indices of pulmonary function

Receipt or non-receipt of β-blockade did not influence pulmonary function in observational cohorts of individuals with COPD[86–88]. Other data also demonstrated the safety of combining β-blockade with inhaled therapies for COPD[86,89]. A study using spirometry carried out in patients homes found similar, small reductions in FEV1 of 100–120 mL following administration of inhaled corticosteroid/bronchodilator therapy with or without additional bisoprolol 5 mg[90]. Carvedilol reduced FEV1, while bisoprolol did not, in patients with COPD also receiving inhaled therapies in another study[91]. Propranolol, but not metoprolol, markedly reduced FEV1 and forced vital capacity (FVC) in a small study in 12 patients with COPD[92]. Another study demonstrated improved pulmonary function with β-blockade in patients with CHF and COPD[93].

Another observational study noted no effect of β-blocker on pulmonary function during exercise[94]. β-blockade did not reduce health-related quality of life in a population with COPD, consistent with a lack of adverse effects on respiration[95]. Finally, patients with COPD tolerated carvedilol well in one study, while patients with asthma did not, with more withdrawals for pulmonary adverse events[96].

Systematic reviews and meta-analyses

Systematic reviews and meta-analyses published during or after 2020 supported reduced mortality in populations with cardiovascular disease and COPD who were treated vs. not treated with a β-blocker[73–75]. Key



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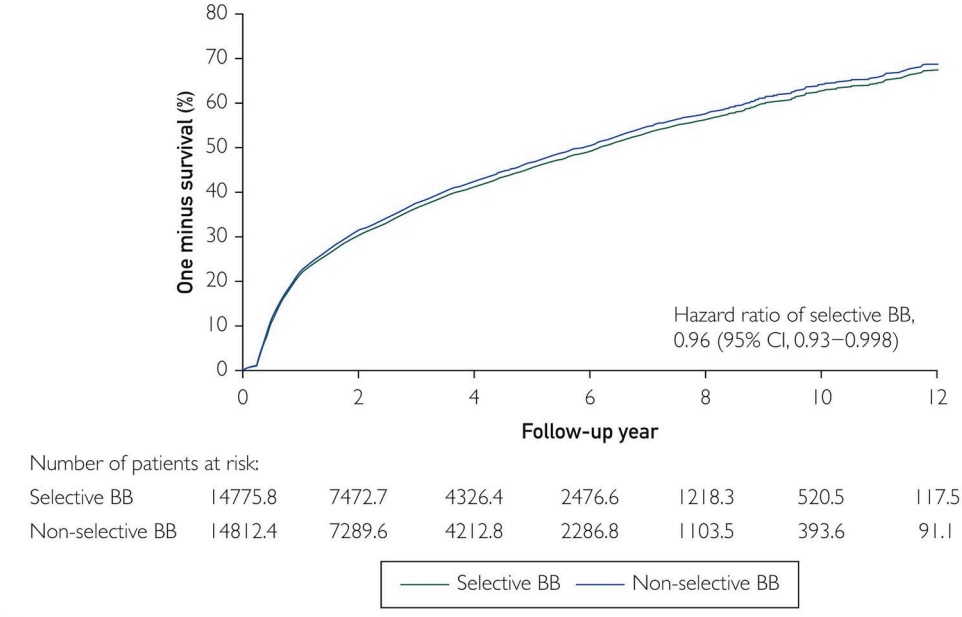

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Figure 1. Survival curves over a 12-year follow-up for time to all-cause mortality (panel A) or MACE (panel B) in a population with COPD prescribed cardioselective or non-cardioselective β-blockers in a retrospective analysis of the Taiwan National Health Insurance Research Database.[39]

Abbreviations. BB, β-blockers; COPD, chronic obstructive pulmonary disease; MACE, major adverse cardiovascular events. Reproduced unaltered from reference[39] according to the CC BY-NC-ND license (creativecommons.org/licenses/by-nc-nd/4.0/).

outcomes from these studies are summarised briefly below, focussing on mortality (effects of β-blockers on COPD exacerbations are discussed above):

Dos Santos et al. (2024)[73] reviewed 20 observational studies in patients with COPD and comorbid cardiovascular disease. Receipt of a β-blocker halved the risk of mortality in this population (odds ratio [OR] 0.50 [95% CI 0.39 to 0.63]; $p < 0.00001$).

Yang et al. (2020)[74] included 12 RCTs and 37 observational studies in their meta-analysis of studies that recruited patients with COPD and comorbid cardiovascular disease. The risk of mortality was reduced in patients receiving vs. not receiving a β-blocker (HR 0.70 [95% CI 0.59 to 0.83), with a trend towards a larger benefit for those receiving cardioselective β-blockade (HR 0.60 [95% CI 0.48 to 0.76] vs. no β-blocker) rather than a non-cardioselective

β-blocker (HR 0.74 [95% CI 0.60 to 0.90] vs. no β-blocker).

Gulea et al (2021)[75] included 14 RCTs and 21 observational studies that involved administration of atenolol, bisoprolol, carvedilol, celiprolol, metoprolol, propranolol, labetalol to patients with COPD with or without cardiovascular conditions. Hazard ratios for mortality were variable between studies and ranged from 0.46–1.19 (IC HRs <1 indicated reduced mortality on β-blockade), which precluded a pooled analysis. Only one study reported a IC HR for mortality >1, however, and this was conducted in patients with severe COPD requiring long-term oxygen therapy. Only propranolol reduced FEV1, consistent with the results of RCTs discussed in Table 2 and above.

Another systematic review and meta-analysis focussed only on evaluations of bisoprolol, but did not include mortality outcomes[97]. Compared with control (placebo or other non-bisoprolol treatment), receipt of bisoprolol was associated with better FEV1 and FVC, and greater functional status (6-minute walk test), and lower circulating levels of inflammatory cytokines (IL-6, IL-8, and C-reactive protein). These findings were similar in subgroups with and without CHF.

Clinical perspectives on the use of β-blockade in people with COPD

β-blockers remain underused in people with COPD

Substantial and recent clinical evidence shows that people with indications for β-blocker treatment are less likely to receive this treatment if they also have COPD. Patients with CHF and COPD in Italy were only half as likely to receive a β-blocker compared with patients with CHF and no COPD[98]. Only 57% of COPD patients who survived an ACS in New Zealand received a β-blocker in the 6 months after discharge from hospital, with lower rates of β-blocker use associated with higher severity of COPD[99]. In the USA, 30% of patients with a compelling indication for β-blockade who had been hospitalised for a COPD exacerbation did not receive a β-blocker after discharge[100]. Numerous other, older, observational studies conducted in populations with COPD around the world reported reduced rates of prescription of a β-blocker in patients with a clear indication for β-blockade or indicating COPD as a factor that reduced the likelihood of prescription of a β-blocker[101–110]. One study suggested that other comorbidities and other treatments drove selection of carvedilol over cardioselective β-blockers among patients with CHF and COPD[111]. In another study, patients with comorbid HFrEF and COPD received lower doses of β-blocker on average and fewer patients with COPD received the maximum recommended dose of β-blockade (7% vs. 17%, respectively)[112]. Higher doses of β-blockers were associated with a reduction in the risk of sudden death, especially in patients with ≥2 comorbidities, though the interactions between β-blocker dose, COPD specifically and outcomes was not described.

Use in patients with COPD-asthma overlap

A systematic review of 27 studies reported that 27% of people with asthma also have COPD and that 30% of people with COPD also have asthma[113]. The inconsistency of labelling for different β-blockers complicates their use in people with asthma-COPD overlap who also have cardiovascular indications for β-blockade. For example, with regard to the three most cardioselective β-blockers, bisoprolol and metoprolol are contraindicated in patients with severe asthma (and severe bronchospasm in the case of metoprolol) and nebivolol is contraindicated in any patient with a history of asthma or bronchospasm (Table 1). A history of asthma was an exclusion criterion in PACE[19], BLOCK COPD[21] and BICS (if diagnosed before age 40 years)[20], which limits the evidence base for the safety of β-blockade in people with comorbid COPD and asthma. The therapeutic use of a β-blocker in a patient with asthma-COPD overlap should be undertaken with caution and with consideration of the severity of asthma and with careful reference to the drug label.

Use in populations with COPD and comorbid atrial fibrillation (AF)

Atrial fibrillation (AF) is a common comorbidity in patients with COPD, with an estimated prevalence of approximately 10%, while COPD is present in nearly 12% of individuals with AF[114–116]. The coexistence of these conditions becomes increasingly frequent with advancing age, and COPD-related factors, including impaired lung function, chronic hypoxemia, systemic inflammation, and acute exacerbations, may contribute to the development and maintenance of AF[114,116]. In addition, traditional cardiovascular risk factors such as obesity, hypertension, diabetes mellitus, and coronary artery disease are highly prevalent in this population and further increase the likelihood of AF[117].

People with comorbid AF and COPD are at 3–4-fold higher risk of adverse cardiovascular outcomes or mortality, compared with people with AF but no COPD[118]. A study from the Asia-Pacific Heart Rhythm Society AF Registry reported reduced mortality in a COPD

population with AF in those who received a β-blocker (odds ratio 0.55 [95%CI 0.36 to 0.84]) versus those who did not, suggesting that β-blockade modifies the association between COPD and mortality risk in the setting of AF[118]. In other studies, receipt of a β-blocker during admission for AF or for heart rate control in the Intensive Care Unit did not influence subsequent clinical outcomes in populations with COPD[119,120].

Importantly, patients with concomitant COPD and AF should not be regarded as a homogeneous clinical entity. Rather, they frequently present with a complex constellation of coexisting cardiovascular and respiratory comorbidities, including heart failure, ischemic heart disease, pulmonary hypertension, and obstructive sleep apnea (OSA)[121,122], each of which may independently contribute to adverse cardiovascular outcomes. Consequently, a comprehensive and individualized cardiovascular risk assessment is warranted in patients with COPD and AF, taking into account the cumulative burden of comorbid disease and the potential interactions between respiratory and cardiovascular pathophysiological mechanisms. This holistic approach should also guide therapeutic decisions, including the use of β-blockers, which should be considered according to the patient's overall cardiovascular risk profile and comorbidity burden rather than on the basis of COPD or AF alone.

Use in patients with overlap syndrome (OVS): COPD and obstructive sleep apnoea (OSA)

The coexistence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), commonly referred to as overlap syndrome, is associated with a substantially increased cardiovascular burden compared with either condition alone. A cohort study from Spain reported a prevalence of OVS of 32% among a population of 428 subjects with COPD[123], although other studies have reported lower and higher prevalences of OVS among populations with COPD[124,125]. Several mechanisms have been implicated in this excess cardiovascular risk, among which enhanced sympathetic nervous system activation appears to play a central role[126]. Intermittent hypoxia, sleep fragmentation, and recurrent arousals characteristic of OSA, together with chronic hypoxemia, systemic inflammation, and pulmonary dysfunction associated with COPD, contribute to sustained sympathoexcitation[126–129]. This results in increased heart rate, peripheral vasoconstriction, endothelial dysfunction, and adverse cardiovascular remodeling, thereby promoting the development of arrhythmias, ischemic heart disease, and heart failure, specifically often right heart failure[127]. Given the recognized contribution of sympathetic overactivity to cardiovascular risk in patients with overlap syndrome, cardiovascular risk stratification should be particularly careful in this population., when β-blocker therapy is indicated according to current cardiovascular guidelines, treatment decisions should take into account the patient's overall cardiovascular risk profile, including the potential impact of the heightened sympathetic activation associated with the coexistence of COPD and OSA.

Looking ahead

The observations of reduced rates of COPD exacerbations in people with COPD receiving a β-blocker in observational studies contrast with the neutral effects of cardioselective beta-blockers on outcomes in the recent trials, as discussed above. Overall, although β-blockers do not reduce exacerbation risk in COPD *per se*, β_1-selective antagonists appear to be safe to use for the treatment of cardiovascular disease in the majority of patients with COPD. Accordingly, it appears reasonable to conclude that evidence-based treatment with β-blockade can be used safely for COPD patients with indications for this treatment. The judicious use of cardioselective β-blockers, in particular, does not compromise pulmonary safety in people with COPD. A recent expert commentary highlighted the potential importance of higher β_1-adrenoceptor selectivity with bisoprolol vs. metoprolol for optimising pulmonary safety, especially for patients at higher risk of COPD exacerbations[130].

Nevertheless, recent data, reviewed above, suggests that β-blockers continue to be underused in people with cardiovascular diseases and indications for β-blockers. A recent (2024) expert commentary from the USA recommended that bisoprolol should be considered for the management of CHF in patients with comorbid COPD, due to its higher β_1- vs. β_2-adrenoceptor selectivity[131]. These authors also called for a head-to-head trial to compare bisoprolol with metoprolol in patients with COPD. A study from the Netherlands from 2018 concluded that prescribers were largely unaware of potential issues arising from the use of non-selective β-blockers in people with COPD[132]. Better education of physicians, especially these who deliver primary care, will be important in establishing better evidence-based care for people with COPD and cardiovascular diseases. Harmonising of the labelling for β-blockers, as discussed above, would help here.

Updating of guidelines may also be needed given the current evidence base. For example, the 2024 guideline for the management of hypertension from the European Society of Cardiology notes that cardioselective β-blockers can be used at low doses in people with asthma, but does not mention COPD[133]. The 2023 hypertension guideline from the European Society of Hypertension includes COPD in a category of "*Selected other conditions in which therapy with BBs [β-blockers] can be favourable*", in support of their cautious use in people with compelling indications[134].

The heterogeneity of drug labelling (Table 1) should also be addressed, with a more consistent approach to prescribing information built on the results of the PACE, BICS and BLOCK COPD RCTs, that demonstrated no effect overall on the risk of COPD exacerbations in populations with COPD with a history of recent exacerbations. The unexplained association of metoprolol with more severe exacerbations in the latter trial requires more research, although no such association was seen in the other trials. Accordingly, bisoprolol was safe for use in COPD at the doses used (up to 5 mg) and the statement in the European bisoprolol label, "*Should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use*" appears to be no longer evidence-based, at least with regard to the dosages of up to 5 mg used in PACE and BICS. Bisoprolol is indicated for the management of cardiovascular conditions at a usual dose of 10 mg, with a maximum available dose of 20 mg. While the cautious approach in PACE and BICS was justified, and consistent with the label, it would be of interest to carefully evaluate higher doses in future to maximise efficacy against comorbid cardiovascular conditions. Changes to drug labels would need to be conducted according to randomised clinical evaluations of individual β-blockers, given the high level of heterogeneity of this class in terms of β_1-adrenoceptor selectivity and other properties, as described above.

Finally, it should be noted that appropriate management of COPD according to relevant respiratory management guidelines is paramount to the preservation of health and quality of life of people with COPD, including *via* minimisation of the risk of COPD exacerbations. The potential importance of cardioselectivity in a β-blocker is to facilitate its safe use within the management of other conditions amenable to β-blockade that are common in (especially older) people with COPD, such as CHF or coronary artery disease. Other criteria beyond cardioselectivity may influence the choice of β-blocker for a patient with COPD and an indication for β-blockade. These include pharmacokinetics (once-daily administration may help to limit the potential for polypharmacy for a patient already receiving multiple respiratory and other medicines) and available dosages (although the labelling for β-blockers tends to restrict their use to lower doses compared with the dose range used for cardiovascular conditions).

The severity of COPD should also be considered. The three major RCTS in this area (PACE[19], BICS[20] and BLOCK COPD[21,22]) recruited populations at a generally high risk of exacerbations and an increased overall risk of exacerbations was not observed with β-blockade in any of them. Further RCTs with β-blockers in populations with less severe COPD are needed to better understand their effects in this population.

Limitations of our review

The main limitation of our review is its narrative structure, although we did use a structured search methodology as described above. The evidence base itself is limited given that the major RCTs in this area have focussed on only two agents, bisoprolol and metoprolol, with less information available on other cardioselective agents, such as nebivolol. In addition, most of the available RCTs for review were small, heterogeneous and of short duration: while their results are interesting in terms of defining whether the studied β-blockers affected respiratory function or not in individual studies, their ability to predict whether β-blockers can be used safely for long-term cardiovascular management in people with COPD is limited.

Conclusions

A substantial database of clinical evidence from randomised, trials, observational studies and meta-analyses confirms that cardioselective β-blockers appear to be safe for the management of cardiovascular disease in the majority of patients with COPD. Concerns over the possibility of bronchoconstriction have led to under prescription of a β-blocker for people with COPD and cardiovascular diseases. Although β-blockers do not reduce exacerbation risk in COPD *per se*, their potential for cardiovascular benefit in patients with comorbid cardiovascular disease supports the use of cardioselective β-blockade in this population. The high likelihood of comorbidity among people with COPD, especially where AF and/or OVS is present requires a holistic approach to the management of these

patients that takes into account their often complex medical needs.

Transparency

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