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Beta-blockers in patients with chronic obstructive disease and coexistent cardiac illnesses

Luis Puente-Maestu[1,2,3*], Luis Antonio Álvarez-Sala[2,3,4] and Javier de Miguel-Díez[1,2,3]

Abstract

Chronic obstructive pulmonary disease is prevalent condition commonly associated with cardiovascular diseases. When both are combined the prognosis of the patient worsens. One cornerstone therapy for most cardiac diseases is beta-blockade, however concerns about its potential harmful effects on airways function often restrains their use in patients with COPD and coexistent cardiac diseases. While selective beta$_1$ adrenergic blockers seem to have a better safety profile, other non-selective beta-blockers can be securely utilized in stable COPD patients with no or little reactivity when they are indispensable and used with caution.

Evidence provided by *post hoc* analysis of clinical trials and large observational studies suggests a beneficial effect of beta-blockers on mortality and exacerbations in mild to moderate COPD patients. Benefits are less obvious in severe COPD.

Studies on the actual use of beta-blockers suggest that many cardiac patients with COPD (or *vice versa*) who can benefit from beta-blocker utilization do not receive such medication as it is recommended in the guidelines because of die-hard, not justified in most cases, concerns on safety.

Keywords: Cardioselective, COPD exacerbations, COPD mortality, Heart failure, Coronary artery disease, Beta-blockers

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent condition affecting 6–10 % of the general population and 11–18 % of the individuals older than 65 years [1]. Many patients with COPD have concomitant heart illnesses susceptible of treatment with beta-blocker agents (BB). In population studies, the prevalence of heart failure (HF) [2–9], coronary artery disease [2–5, 10–13] and arterial hypertension [2, 4, 11, 12], double those of the healthy control population and are usually higher than 20 %. In fact, at least one of these heart conditions is present in 25–35 % of the patients with COPD [2, 5, 6, 11, 14]. Moreover, supraventricular arrhythmias —in some cases also susceptible to treatment with BB— are frequent in COPD as well [2–4, 15, 16]. Cardiovascular comorbidities occur even at the early stages of COPD, as it was shown in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study, in which the risk of cardiovascular disease, hypertension and diabetes was already increased in patients with chronic bronchitis without pulmonary function abnormalities yet (Global Initiative for Chronic Obstructive Lung Disease stage 0) [11].

There is very strong, high quality, evidence demonstrating increased survival in patient with HF [16–19] and CAD [20] with BB therapy; nonetheless it is not unusual for physicians to consider COPD as contraindication to the use of BB [21] mainly because of concerns that they might induce bronchospasm and worsen lung function [22–25].

In this article, we will review the evidence for the benefits and safety of use of BB's in individuals with COPD and coexistent cardiovascular diseases.

Review

Impact of cardiovascular disease in copd outcomes

Cardiac comorbidity has a substantial impact on the survival of COPD. In an observational study of 5648

* Correspondence: lpuente.hgugm@salud.madrid.org
[1]Servicio de Neumología, Hospital General Universitario Gregorio Marañón, c/Doctor Ezquerdo 46, Madrid 28007, Spain
[2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
Full list of author information is available at the end of the article

patients with COPD, cardiovascular morbidity and mortality was approximately two times higher than in historical controls without COPD [26]. The most common cause of cardiovascular morbidity and mortality was HF secondary to CAD [26]. In the towards a revolution in COPD health (TORCH®)[26] study, heart diseases accounted for 27 % of the deaths —second after respiratory processes [26] — which is a remarkable number considering that patients with known serious heart disease were excluded from the trial. In the Lung Health Study, a study of smoking intervention with medical advice and nicotine replacement therapy, in which more than 5900 patients with relatively mild COPD were followed for about 15 years, 30 % of the deaths were due to either HF or CAD [27]. A retrospective study of the 11,493 COPD patients included in the health care databases maintained by the government of Saskatchewan, Canada during 1997–2000, reported one and half to four-fold increase in 3-year risk of cardiovascular death for different causes [overall relative risk (RR) for all cardiovascular causes = 2.1, 95 % confidence interval 1.8–2.4] compared with age- and sex-matched controls without COPD [3].

Cardiovascular events are common during exacerbations and are associated with increased risk of death. Troponin elevation takes place in a large number of patients (18–27 %) [28] undergoing COPD exacerbations requiring hospitalization [29–31]. This elevation is an independent predictor of mortality both during the exacerbation episode [29] and o,-term [30]. Ventricular arrhythmias and atrial fibrillation were independent predictors of mortality in a cohort of 580 patients having COPD as primary disease who were hospitalized in the respiratory unit of a university hospital from 1981 to 1990 [Odds ratio (OR) = 1.91, 1.10–3.31 and 2.27, 1.14–4.51, respectively] [32]. Several studies aimed to measure the incidence of left ventricular dysfunction in COPD exacerbations found a significant association between elevated brain natriuretic peptide or N-terminal fragment proNT-pro brain natriuretic peptide and increased cardiovascular mortality [33–36]

Cardiovascular disease also leads to hospitalization of COPD patients, left ventricular dysfunction may be present in more than 30 % of acute dyspnea episodes in COPD patients attended at the emergency room or admitted to the hospital [33, 35–37]. In the Lung Health Study [27] cardiovascular causes accounted for 42 % of first hospitalizations and 44 % of second hospitalizations, while respiratory causes accounted for only 14 % of admissions [27]. Raised troponin levels during an acute COPD exacerbation appears to increase the risk of further admissions [34, 36]

Impact of copd on cardiovascular diseases outcome

From the cardiac perspective there is strong epidemiological evidence showing that the forced expiratory volume in the first second [38] (FEV_1) is a marker for cardiovascular mortality [39–45]. It has been estimated that for every 10 % decrease in FEV_1, cardiovascular mortality increases by 28 % and non-fatal coronary events by almost 20 % [39]. In the cohort of the Northern California Kaiser Permanente Medical Care Program ($n = 45{,}966$), COPD was an independent predictor of cardiovascular hospitalization and mortality over an average follow-up time of nearly 3 years [46]. In database of the Worcester Heart Failure Study (a population-based investigation that includes residents of the Worcester, Massachusetts, metropolitan area) 9748 patients were hospitalized with acute decompensation of HF during the years 1995, 2000, 2002 and 2004. Among those who survived to hospital discharge, patients with COPD had a significantly higher risk of death along the next year than patients who had no previous diagnosis of COPD (RR = 1.10, 1.06–1.14) [47]. Among 4284 consecutive patients who underwent percutaneous coronary intervention in three tertiary medical centers in New York City between 1998 and 1999, 3-year mortality was 21 % for patients diagnosed with COPD ($n = 183$, 4.3 %) versus 9 % in those without COPD ($p < 0.001$) [48]. Furthermore, with a hazard ratio (HR) >2 (HR = 2.1, 1.5–3.0, $p < 0.001$), COPD was the strongest predictor of late mortality in the Cox proportional-hazard model after adjustment for demographic, clinical, and angiographic differences [48]. In one study of 860 patients with COPD and 10,048 without COPD of the National Heart Lung and Blood Institute, COPD was associated with higher mortality rates and repeat revascularization within 1 year after a percutaneous coronary intervention (HR 1.30, 1.01–1.67) [49]. Interestingly, in this study the higher proportion of adverse outcomes was associated with lower rates of use of BB [49].

Beta-blockers

Beta-adrenoceptors (B-ARs) are situated throughout the cardiac sarcolemma and bronchial and vascular smooth muscles [50, 51]. While a majority of the B-ARs of myocardium are of the $beta_1$ type (B_1-ARs), a considerable proportion (20 %–25 %) are $beta_2$-adrenoreceptos (B_2-ARs) [50, 51], however this quantity increases up to 40 % in the failing heart [28], likely as result of the selective downregulation of B_1-ARs observed in HF with little or no change in B_2-ARs [28]. Both types of B-ARs of the myocardium, if activated, have a positive inotropic effect [50, 51]. B-ARs in the bronchial and vascular smooth muscle are mostly B_2-ARs and when stimulated

cause broncho- and vaso-dilatation [22, 24, 50, 51]. There is a third type of B-ARs ($beta_3$), which role is not yet fully understood [52].

Beta-blockers are drugs capable of blocking B-ARs with little or no agonist effect and when administered reduce myocardial contractility at least in the short term [53]. Because of this, the use of BB was once thought to be contraindicated in patients with systolic dysfunction. Paradoxically, though, some BB's have proven striking morbidity and mortality benefits in the management of patients with cardiac diseases [19, 20, 54–65] and currently they are considered standard therapy for hypertension, angina, post myocardial infarction, some tachyarrhythmias and congestive HF [17, 66].

BB's have several ancillary properties (i.e., partial agonism, cardioselectivity, membrane stabilizing effect, lipophilicity/hydrophility, vasodilating actions and inverse antagonism) than need to be taken into account when selecting them for the treatment of heart diseases [67, 68]. Some of them can be relevant when treating patients with COPD.

Selectivity

Beta-blockers are classified into three generations (Table 1) [50, 51, 60]. The first generation agents (such as propranolol, sotalol, timolol, and nadolol) are non-selective and block B_1-ARs and B_2-ARs. The second-generation agents are the cardio-selective agents (such as acebutolol, atenolol, bisoprolol, celiprolol, and metoprolol). The third generation agents have vasodilatory properties [50, 51] mediated either by nitric oxide release, i.e. nebivolol or carvedilol [52], by added alpha-adrenergic blockade as in labetolol and carvedilol [52].

Table 1 Type of beta-blockers

NON SELECTIVE
Intrinsic sympathomimetic activity
• Pindololol
• Oxeprenol
No intrinsic sympathomimetic activity
• Nadolol
• Propanololol
• Sotalol
• Timolol
CARIDOSELECTIVE
Intrinsic sympathomimetic activity
• Celiprolol
• Acebutolol
No intrinsic sympathomimetic activity
• Atenolol
• Bisoprolol
• Metoprolol
WITH ALPHA-BLOCKING ACTIVITY
• Carvedilol
• Labetolol
• Nevibololhowever no differences were observed among the non-selective

The blockage of B_2-ARs can cause smooth muscle contraction and hence bronchospasm in predisposed individuals [50, 51]. Cardio-selective BB's have less impact on lung function and symptoms and preserve, in different magnitude, the bronchodilator effect of B_2-ARs agonists (see below) [50, 51]; however, it should be borne in mind that while cardio-selective BB mainly block B_1-ARs, at high doses they are able to block B_2-ARs as well and can adversely affect the airways [50, 51]. Therefore, the classification into 'cardio-selective' BB's and non-selective BB's is important, but oversimplified.

Intrinsic sympathomimetic activity

The therapeutic importance of intrinsic sympathomimetic activity (ISA) in COPD patients is questionable. Apparently, ISA is able to partially offset the increase in airway resistance that results from beta-blockade both at rest and during exertion [69], however no differences were observed among the non-selective BB's pindolol —an agent with ISA— and propranolol, oxprenolol and timolol —without ISA— in the reduction of FEV_1 and the complete inhibition the bronchodilator response to inhaled isoprenaline [70]. On the contrary with the cardio-selective BB's atenolol and metoprolol the effect on FEV_1 was less pronounced and some bronchodilator effect remained [70]. There is also evidence suggesting that BB's with ISA lead to a downregulation of B_2-ARs [71]. This finding is consistent with the observation that BB's with ISA do not produce the long-term increase in B_2-agonist response seen with other BB's [51]. Since agents with ISA offer less cardio-protection than BB's without this property, these drugs are not recommendable in COPD patients with cardiac diseases.

Inverse agonist activity

BB's do not simply block the receptor, but may further inactivate receptor activity beyond its baseline value (i.e., they decrease the constitutive spontaneous activity of the receptor in the absence of agonist) [72]. This effect, called inverse agonist activity, is independent of the B-AR selectivity and thus the of B_1-ARsselective metoprolol and bisoprolol have (modest) inverse activity [53, 67] as well as some non-selective BB such as timolol, propranolol or nadolol [53, 67], whereas carvedilol shows no inverse activity [53, 72].

Inverse agonist activity is important when B-ARs are downregulated because of chronic sympathetic activation, as occur in chronic HF [51, 53, 73]. In animal

models of asthma, BB's with inverse agonist activity significantly increased B-ARs density in lung membranes [73] and with time were able to reverse the attenuation of the effect of salbutamol in airway relaxation induced by chronic HF [53]. These effects have been also documented in humans with mild asthma in whom chronic treatment with nadolol, a BB with Inverse agonist activity, enhanced the bronchodilator response to salbutamol over time [22].

Safety of BB in COPD

Selective beta$_1$ adrenergic blockade

There are reports that in some predisposed patients BB, especially the non-selective ones, are able to trigger bronchospasm [74–78]; however several small studies of single-dose treatment or treatment for periods ranging from 2 days to 12 weeks provide prospective evidence demonstrating the short term safety of cardio-selective BB in COPD [79–81]. Long-term prospective evidence is scarcer. In one small study ($n = 27$) that examined the use of bisoprolol in patients with both HF and COPD a significant reduction in FEV_1 was observed at 4 months (−70 vs +120 ml in the non-beta-blocker group $p < 0.01$), however symptoms and quality of life were not altered [82]. Metoprolol was well tolerated for 3 months by 50 patients with coexistent CAD and mild to severe COPD. Patients remained free of adverse respiratory effects and FEV_1 was unchanged [83]. In a randomized, double-blind, crossover trial, 40 CAD patients with mild COPD and significant reversibility received either bisoprolol 5 mg or atenolol 50 mg [84]. FEV_1 declined significantly (~0.2 l) over 6 months in both treatment arms. Although lacking a concurrent placebo group, lung function parameters normalized during the placebo washout periods, suggesting beta-blockade could have caused bronchoconstriction [84].

Selective beta$_1$-blockade does not attenuate the bronchodilation induced by beta$_2$ agonists [24, 79, 81, 85].

Non-selective BB combined with alpha-blockade

The acute administration of labetalol at maximal dose did not affected FEV_1 in 11 hypertensive patients with mild to moderate COPD [86, 60]. In a retrospective analysis of the tolerance to carvedilol, 13 out of 89 patients with coexistent COPD and HF who received the drug for at least 3 months could not tolerate it [87]. The reasons for intolerance were not specified. Forty-three patients with HF and COPD with negative acute bronchodilator test receiving carvedilol were followed for a mean of 2.4 years and only 1 patient did not tolerate carvedilol because of COPD exacerbation [88]. In contrast, only 50 % of 12 patients with asthma tolerated carvedilol [88] (Table 2). In one study of 63 (Table 2) elderly patients with mild to moderate HF and moderate to severe COPD, patients were randomized to bisprolol or carvedilol. While only in one patient of the carvedilol group the study medication had to be withdrawn because of wheezing, there were no differences between groups in the number of patients in which the BB had to be suspended (3 each) [89]. FEV_1 significantly increased in bisoprolol (~130 ml) but not carvedilol (~30 ml) [89]. A randomized, open label, crossover trial involving 51 subjects receiving optimal therapy for HF (Table 2) examined the effects of switching baseline BB treatment to carvedilol, metoprolol or bisoprolol for 6 weeks before resuming their original BB. Of the 51 subjects, thirty -five had coexistent mild to moderate COPD. In them FEV_1 was lowest with carvedilol and highest with bisoprolol (~150 ml or 8 % of difference). Response to salbutamol was tested in 53 HF patients on background BB therapy and it was significantly higher in patients on bisoprolol as compared to carvedilol ($p = 0.04$) [90].

In summary the available evidence suggest that the third generation non-selective BB produce demonstrable changes in airway function in patients with COPD and tend to worsen airflow obstruction more than beta$_1$ selective agents.

Post-hoc analysis of prospective studies

The analysis of COPD populations included in large studies on the use BB with HF [91, 92] show a protective effect comparing those on BB with those not using them [60].

Cohort and administrative database studies

Two meta-analysis of cohort studies have shown a protective effects of BB in patients with COPD and concomitant use of BB for CAD, HF or other reasons RR 0.69 (0.62–0.78) [93] and 0.72 (0.63 to 0.83) [94] respectively. A protective effect on the development of exacerbations was also observed in one of them [94]. Among 3834 residents of Alberta, Canada, aged 65 years or older, diagnosed with COPD who had at least one hospitalization for heart failure between April 1, 1994, and March 31, 1998 included in the Canadian Institute for Health Information database and followed a median of 21 month (Table 3), those on BB ($n = 242$) showed lower risk of all causes mortality (HR = 0.78, 0.63–0.95) [95]. In a cohort of 1966 patients (66 ± 11 years) enrolled in general internal medicine clinics at seven Veterans Affairs medical centers between December 1996 and October 1999, Those who had a diagnosis of both COPD and hypertension and were receiving single-agent antihypertensive therapy were studied (Table 3). Compared with calcium channel blockers, BB were associated with a decrease in mortality from any cause after adjusting for other risk factors (HR = 0.57, 0.33–0.89). The association was similar when beta-blockers were compared

Table 2 Clinical trials that have addressed the effect of beta-blockers on clinical of functional pulmonary outcomes in patients with concomitant cardiac and obstructive respiratory conditions

	Population/design	n	Drug (mean daily dose)	Follow-up	Outcomes
Hawkins et al. [82]	HF with moderate COPD/ randomized, controlled, double-blinded	27 (14/13)	Bisoprolol (7.3 mg) vs placebo	4 month	FEV_1 significantly decreased (−70 vs. +120 ml) SF-36↑ n.s. 2.6 vs 0.5 No increase in exacerbations
Kotlyar et al. [88]	HF with moderate COPD o Asma/quasi-experimental	31COPD/12 Asthma	Carvedilol (29 mg COPD/19 mg asthma)	2.4 year	In 1 COPD (3 %) and 3 asthmatics (25 %) the drug had to be withdraw because of worsening of the respiratory condition
Lainscak et al. [89]	Elderly HF with moderate COPD/randomized, controlled, open-label	63 (32/31)	Bisoprolol (47 mg) vs Carvedilol (6.4 mg)	4–6 weeks	1 patient of the carvedilol group had to be withdrawn because of "wheezing", no differences between groups in the number of patients in which the BB had to be suspended (3 each). FEV1 significantly increased in bisoprolol (~130 ml) but not carvedilol (~30 ml)
Jabbour et al. [90].	HF with moderate COPD/ randomized, open label, triple-crossover	35	Bisoprolol vs metoprolol vs carvedilol equivalent dose but mean not specified	6 month	FEV1 ~ 150 ml or 8 % higher with bisoprolol and metoprolol than with carvedilol
Camrari et al. [92]	CAD with moderate to severe COPD/quasi-experimental	50	Metoprolol (93 mg CR or 189 mg conventional)	3 month	No change in FEV_1 No adverse events
Dorow et al. [91]	CAD with moderate COPD/ randomized, double-blind crossover	40 (20/20)	Atenolol (50 mg) vs bisoprolol (5 mg)	6 month	FEV_1 declined significantly (~0.2 l) in both treatment arms.

FEV_1 forced expiratory volume in the first second; *HF* heart failure; *CAD* Coronary artery disease; *COPD* chonic obstructive lung disease; *n.s.* non-significant; *SF-36;* Shor form health survey questionnaire

with several other antihypertensive medications and was independent of whether the patient had a pre-existing cardiac disease [96]. The medical records of 41,814 COPD patients (22 % on BB) and 3819 asthmatics (17 % on BB) with myocardial infarction were abstracted by the Cooperative Cardiovascular Project, which was sponsored by the Health Care Financing Administration for Medicare payment [20] (Table 3). BB treatment reduced the 2-yr mortality (OR = 0.60, 0.57–0.63) similarly than in the non-COPD population [20]. A different analysis the same database included 54,962 with acute myocardial infarction as main discharge diagnosis and with COPD or asthma (defined by an established diagnosis previous to the admission or prescription respiratory medication in the medical records) (Table 3). Both respiratory conditions were pooled together for the analysis and patients were stratified according to severity based on the use of medication (yes or not ≥1

Table 3 Association between beta-blockers and all–cause mortality in patients with chronic obstructive lung disease in observational studies

	Population	n with COPD	Follow-up	Adjusted risk (95 % CI)
Sin et al. [95]	Heart failure	3834	median 21 month	0.78 (0.63–0.95)
Hawkins et al. [91]	Heart failure	1258	median 25 month	0.74 (0.68–0.80)
Gottlieb et al. [20]	Myocardial infarction	41,814	2 years	0.60 (0.57–0.63)
Chen et al. [97]	Myocardial infarction	10,988	1 year	0.86 (0.73–1.00)
Van Gestel et al. [112]	Vascular disease	1205	median 5 years	0.73 (0.60–0.88)
Au et al. [96]	Hypertension	1966	2 years	0.57 (0.33–0.89)
Rutten et al. [99]	COPD primary care	2230	7.2 years	0.68 (0.56–0.83)
Lee at al. [102]	Multiple conditions	1062	median 44 months	0.87 (0.67-1.13)
Dransfield et al. [103]	COPD exacerbation	825	—	0.39 (0.14–0.99)
Stefan et al. [104]	COPD exacerbation	10,174	—	088 (0.71–1.09)
Short et al. [101]	COPD primary care	5977	4.3 years	0.78 (0.67–0.92)

prescription of oral corticosteroids or ≥1 admission the previous year). While BB showed a protective effect in those with mild/moderate COPD or asthma, no survival benefit (No harm either) was found with BB in the elderly and those with severe pulmonary disease [97]. As adherence to treatment was not available it is possible that those older or sicker could not take the BB as prescribed. In a retrospective observational cohort study 11,592 adult patients registered in the General Electric Centricity electronic medical record database with a diagnosis of asthma and/or COPD identified from August 1, 1997 to December 31, 2005 who were taking BB for at least 30 days were compared with patients who had never received BB (controls) (Table 3). Of these patients, 3062 were on cardio-selective and 690 on non-selective BB; 7840 were controls. While in patients with asthma, BB, particularly the non-selective ones, increased the risk of admission or visits to the emergency department, in patients with COPD alone, $beta_1$-selective BB had a protective effect for hospitalizations, RR = 0.64 (0.43–0.96) while non-selective BB had not (RR 1.02, 0.52–2.02) [98]. In the Utrecht General Practitioners Network Database (Table 3), 2230 patients were identified who were older than 45 years with a diagnosis of COPD between 1996 and 2006. During a mean follow-up of 7.2 (2.8) years, 686 patients (30.8 %) died and 1055 (47.3 %) had at least 1 exacerbation of COPD. BB had a protective effect for both outcomes with adjusted hazard ratios of 0.68 (0.56–0.83) and 0.71 (0.60–0.83) respectively for mortality and exacerbations [99]. In a retrospective study of the Premier Perspective database involving 56,394 patients admitted with the diagnosis of COPD (Table 3), the all-cause in-hospital mortality was 2.4 %. BB use had an independent protective effect on in-hospital mortality (RR = 0.76, 0.67–0.86) [100]. In a recent retrospective cohort study in Scotland of 5996 COPD patients with concomitant CAD, HF or other vascular diseases, an overall 22 % reduction in all-cause mortality was seen in those on BB therapy (88 % of the BB used were cardio-selective) [101]. Furthermore, additive benefits to BB were observed with any of the possible combinations of inhaled therapy compared with controls (receiving only inhaled therapy with short acting bronchodilators) [101].

In partial contrast with the previous findings a recent study of the 2004–2007 Medicare Current Beneficiary Survey cohorts (a nationally representative sample of Medicare beneficiaries) including 1062 elderly patients (age = 77 ± 7 years) with COPD and CAD (half with and half without BB), BB did not appear to have any protective effect on cardiac events, pulmonary events, or all-cause mortality (Table 3) [102]. In this study specific factors of older people such as functional and cognitive status were determinants of receiving BB and of experiencing the outcomes and may have influenced the results. In addition the sample size, while large, included much less patients than the other studies mentioned above and there is the possibility of a lack of statistical power to detect the protective effects of BB. In any case it has to be stressed that no harmful effect on respiratory events was observed on the BB group.

Exacerbations

A relatively small retrospective study (n = 825) of the administrative data from the University of Alabama Hospital [60] suggested that BB use during exacerbations reduced mortality (OR = 0.39, 0.14 to 0.99) [103] (Table 3). In a much larger retrospective cohort study (n = 35,082) of patients older than 40 years with CAD, CHF or hypertension, who were hospitalized for an acute exacerbation of COPD from the 1st of January, 2006 to the 1st of December, 2007 at 404 acute care hospitals throughout the USA, 29 % were treated with BB in the first two hospital days, including 22 % with $beta_1$-selective and 7 % with non-selective BB (Table 3) [104]. There was no association between BB therapy and in-hospital mortality (OR = 0.88, 0.71–1.09), 30-day readmission (OR = 0.96, 0.89–1.03) or late mechanical ventilation (OR = 0.98, 0.77–1.24). However, when compared with $beta_1$ selective BB, receiving non-selective BB's was associated with an increased risk of 30-day readmission, OR = 1.25 (1.08 to 1.44) [104].

In another study 8390 individuals with a diagnosis of asthma or COPD and receiving treatment with a BB or another cardiovascular agent were identified in 2000–2001 from three Veterans Administration databases in Iowa and Nebraska (USA) (Table 3) [105]. The HR for hospital admission for asthma or COPD during the observation year was not different for patients taking and not taking BB and no difference was noted with selective versus nonselective beta-blockers. Curiously enough, the hospital admission rate was lower with atenolol than metoprolol [105].

Considered together, the cumulative evidence from trials observational studies and meta-analysis indicates that selective $beta_1$-blokers should not be withheld when COPD coexists with cardiovascular diseases, because the benefits for their cardiac conditions far outweigh the risks [80, 106]. While cardio-selective agents cause less functional impairment, beta-blockade with both selective and non-selective agents, when required, beneficially impacts mortality [20, 93, 94, 97, 99, 101]. Therefore, current guidelines from the Heart Failure Society of America recommend BB in all patients with coexistent COPD and HF or CAD [106, 107].

Current use of BB

In spite of the evidence in favor and guidelines recommendations [106–109], the proportion of COPD patients with indication for BB drugs because of a heart disease who are actually on BB remains low [103, 108, 110–113]. In one recent study in Spain BB were prescribe in around 58 % of those COPD patients attended at specialized COPD clinics in whom BB were indicated, while in patients not believed to have COPD and managed by cardiologist the rate was 97 %. This proportion may be lower in the primary care settings [5]. While caution is needed when comparing information between different situations and different countries, it appears that there is a trend to increase the prescription of BB in COPD patients who need them for cardiovascular disease [5, 97, 110, 111, 114]; This is consistent with the trend to an increasing use of BB in COPD noticed in the Worcester (Massachusetts) Heart Attack Study cohort [115].

Some evidence suggests that to be effective in reducing admissions, BB therapy must adequately control heart rate (i.e. heart rate < 70 min^{-1}) [113, 116].

The use of BB in patients with COPD and CHF can be substantially and safely increased by a structured outpatient program [117].

Conclusions

In summary, there is a bulk of evidence suggesting that BB therapy is safe in COPD patients who need it for coexistent cardiovascular diseases. Epidemiological evidence suggested that its use reduces mortality and the risk of exacerbations in general terms; Benefits are less evident in those older or with more severe disease.

Therapy should be attempted with selective $beta_{-1}$ adrenergic blockade, but if necessary patients with concomitant stable mild to moderate COPD who do not have reversible airway obstruction can tolerate non-selective BB. Selective BB is recommended in patients with severe COPD or who have reversible airway obstruction. In these patients a close initial monitoring and management by physicians with experience is recommend.

Observational evidence suggests that BB therapy does not increase the risk of in-hospital mortality or late mechanical ventilation during exacerbations; therefore it is not necessary to routinely withdraw them during these episodes.

Abbreviations

B-AR: Beta adrenorecpetor; BB: Beta-blocker; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in the first second; HF: Hearth failure; HR: Hazard ratio; ISA: Intrinsic sympathomimetic activity; OR: Odds ratio; RR: Relative risk; 95 % CI: 95 % confidence interval.

Competing interests

The authors declare that they do not have competing interests.

Authors' contributions

Luis Puente-Maestu: Redacted the draft manuscript and tables. Luis Antonio Álvarez-Salas Walther: Helped in the writing of the draft. Javier de Miguel Díez : Helped in the writing of the draft.All authors read and approved the final manuscript.

Author details

[1]Servicio de Neumología, Hospital General Universitario Gregorio Marañón, c/Doctor Ezquerdo 46, Madrid 28007, Spain. [2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain. [3]Facultad de Medicina Universidad Complutense de Madrid (UCM), Madrid, Spain. [4]Servicio de Medicina Interna Hospital General Universitario Gregorio Marañón, Madrid, Spain.

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