Respiratory Medicine (2014) 108, 737–744

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Multicentric study on the beta-blocker use and relation with exacerbations in COPD

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Received 21 October 2013; accepted 12 February 2014
Available online 20 February 2014

KEYWORDS
Adrenergic beta-antagonists;

Summary
Chronic obstructive pulmonary disease (COPD) is frequently associated with chronic heart failure (CHF) or coronary artery disease (CAD). In spite of the recommendation to use beta-blockers (BB) they are likely under-prescribed to patients with concurrent COPD and heart

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http://dx.doi.org/10.1016/j.rmed.2014.02.009

Adverse effects;
Chronic obstructive pulmonary disease;
Emergency treatment;
Myocardial infarction;
Heart failure

diseases. To find out the prevalence of use of BB, 256 COPD patients were consecutively recruited by pulmonary physicians from 14 hospitals in 7 regions of Spain in their outpatient offices if they had a diagnosis of COPD, were not on long-term oxygen therapy, had CHF or CAD, and met the criteria for BB treatment.

In patients with indication 58% (95%CI, 52—64%) of the COPD patients and 97% of the non-COPD patients were on BB ($p < 0.001$). In patients with COPD, several factors were independently related to at least one visit to the emergency room in the previous year such as use of BB, adjusted OR = 0.27 (95% CI 0.15—0.50), GOLD stage D, OR = 2.52 (1.40—4.53), baseline heart rate >70, OR 2.19 (1.24—3.86) use of long-acting beta$_2$-agonists OR = 2.18 (1.29—3.68), previous episodes of left ventricular failure OR 2.27 (1.19—4.33) and diabetes, OR = 1.82 (1.08—3.38).

We conclude that, according to what is recommended by current guidelines, BB are still under-prescribed in COPD patients. COPD patients with CHF or CAD using BB suffer fewer exacerbations and visits to the ER. GOLD stage, use of long-acting beta$_2$-agonists, baseline heart rate and comorbidities are also risk factors for exacerbations in this population.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbi-mortality worldwide [1] and it is frequently associated with a number of comorbidities [1]. Population studies have shown that the prevalence of chronic heart failure (CHF) in COPD patients ranges between 8% and 27% [2,3] and for coronary artery disease (CAD) it is between 15% and 25% [2,3].When present, cardiac comorbidities have a substantial negative impact on the survival of COPD [4].

There is a bulk of evidence showing that the use of beta-blockers (BB) increases survival in both patients with CHF [5] and CAD [6]. "Post-hoc" analysis of the COPD populations included in large trials on the use BB after acute myocardial infarction [6] or CHF [3] suggest a protective effect of these drugs in such patients. Moreover, there is evidence showing the safety of using BB — especially cardioselective ones— in COPD [7].

In spite of the evidence and recommendation for their use [1,8—10], BB are likely under-prescribed [3,11—15] to patients with coexistent COPD and heart diseases. This is largely due to concerns about precipitating respiratory deterioration.

The two aims of this study were 1) to determine the frequency of guidelines concordant BB use in COPD patients assisted at outpatient clinics in 14 hospitals from 7 regions of Spain and 2) to identify whether the use of BB was related to frequent exacerbations (i.e ≥2 exacerbations) the previous year or to severe exacerbations requiring an emergency room (ER) visit.

Methods

This is an analytical cross-sectional study. COPD patients were consecutively recruited, by pulmonary physicians of the participating hospitals in their outpatient offices between May 2012 and May 2013. Inclusion criteria were: a previous diagnosis of COPD [1] and CHF or CAD made at least one year earlier, criteria for BB treatment (i.e. left ventricular ejection fraction (LVEF) ≤40%, active coronary heart disease or a previous acute myocardial infarction) and no contraindications for BB treatment (heart rate < 60 beats/min prior to treatment, symptomatic hypotension, evidence of significant fluid retention in patients also treated with angiotensin converting enzyme inhibitors, diuretics and salt restriction, signs of peripheral hypoperfusion, PR interval >0.24 s, second or third degree atrioventricular block (except with pacemakers), history of severe bronchospasm or peripheral arterial disease with ischemia at rest). Patients were also excluded if they had other chronic pulmonary conditions (interstitial disease, asthma, cancer) or were on long-term oxygen therapy.

A concomitant cohort of patients diagnosed with CAD or CHF, meeting the criteria for the use of BB mentioned before and not known to have COPD, was also recruited in the outpatient offices by cardiologists of the same centres to compare the use of BB between COPD and non-COPD patients.

Sample size was projected to achieve 5% accuracy in estimating the frequency of BB use by a normal, bilateral 95%, asymptotic confidence interval for an anticipated frequency of use of 70%, resulting in 268 patients needed to be included. With this sample size, and the mentioned proportion (i.e. 70%), differences of at least 12% could be detected in the rate of exacerbation by means of bilateral χ^2 with an alpha error of 5% and a statistical power of 0.8. An additional sample of at least 59 non-COPD patients was needed to detect differences of 20% in the proportion of use of BB with an alpha error of 5% and a statically power of 0.9.

The study was approved by the clinical research ethical committees of the participating hospitals and regions and all patients signed an informed consent form.

Outcome measurements

The most recent spirometry, echocardiographic LVEF, EKG and hemoglobin concentrations were obtained from the medical records. Heart Rate (HR) was measured in the last EKG available within the previous year with the patient on

BB. The impact of the disease was measured by the COPD Assessment Test (CAT©, 2009 GlaxoSmithKline companies. Last Updated: February 26, 2012). Use of cardiac and respiratory drugs, other comorbidities, exacerbations or admissions were systematically obtained through direct interviews and from the available medical records. Exacerbation was defined as any change in a previously stable clinical state requiring health care resources (i.e unscheduled visits, changes in medication, or a visit to the ER).

Statistical analysis

Interval variables are expressed as mean and standard deviation within parenthesis, proportion are expressed with their standard error within parenthesis. Interval variables are compared by means of bilateral unpaired student t, and proportions by means of bilateral χ^2. Multiple logistic regressions were used to determine the variables related with $\geq$2 exacerbations in the previous year, and with exacerbations attended at the ER. Missing data for the variables included in the initial model were excluded from the analysis.

Results

Two hundred and fifty six COPD patients and 101 non-COPD patients were included. Missing data for the variables included in the initial model were random and not higher than 1%. Patients in the COPD group were slightly older and more overweight, had a history of more intense exposure to cigarette smoke and in a higher proportion of them, heart failure was the indication for BB. However, no differences in LVEF were observed between both groups (Table 1). The non-COPD group had a higher proportion of patients with a history of coronary artery disease and of females (Table 1). With regard to other risk factors; while the proportion of patients with dyslipidemia was higher in the non-COPD group, no differences were observed in the frequency of systemic hypertension or diabetes (Table 1).

Only 148, 58% (95%CI, 52%—64%) of the COPD patients with indication were on BB, while this proportion was 97% (94%—100%) in the non-COPD group. With regard to other cardiac drugs a significantly larger proportion of patients with COPD were on calcium antagonists (Table 1). However, no differences were observed in the use of other type of drugs including angiotensin converting enzyme inhibitors, angiotensin receptor II antagonists, nitrites, diuretics, antiarrhythmic drugs, aspirin, other antiplatelet drugs, oral anticoagulants, oral antidiabetic drugs, insulin or lipid-lowering drugs.

When looking at the specific BB molecules, a larger proportion of non-COPD patients were on atenolol while bisoprolol was more prescribed to the COPD group (Fig. 1). Nonetheless, the overall use of cardioselective BB was not different (68% in the non-COPD group and 67% in the COPD group).

We see small differences in several variables between those on BB and those without them (Table 2) within the COPD subgroup. The group of COPD patients on BB had a larger proportion of subjects with several comorbidities such as anemia, diabetes, systemic hypertension, overweight and history of acute episodes of left ventricular failure. From a functional point of view, they had worse cardiac function; however, they were less obstructive. In spite of these facts, they were less symptomatic and had suffered fewer exacerbations in the last year (Table 2).

Very few of our patients were in GOLD combined assessment stage C (Table 3). Regarding the other stages, a higher proportion of patients on BB belonged to stages A and B and a lower proportion to stage D (Table 3).However, only the differences in the latter were significant ($p < 0.026$).

Table 1 Comparison between COPD and non-COPD patients of some relevant variables. Mean (SD).

Variable	COPD ($n = 256$)	Non-COPD ($n = 101$)	p
Female (%)	6.7 (1.5)	29 (4.5)	0.000
Age (years)	72.2 (8.9)	69.9 (11.8)	0.010
BMI (kg/m^2)	29.5 (4.9)	28.0 (4.8)	0.018
LVEF (%)	43.7 (13.3)	38.8 (14.4)	0.011
packs-year	51.0 (24.3)	38.1 (20.0)	0.000
Active smoker (%)	14.1 (2.2)	15.1(3.5)	0.865
Hb (mg/dl)	13.1 (2.3)	11 (2.0)	0.102
Anemia (%)	28.7(2.8)	27.7 (4.5)	0.664
CHD (%)	74.6 (2.7)	86.1 (3.4)	0.023
LVF (%)	25.4 (2.7)	13.9 (3.4)	0.022
Systemic hypertension	75.5 (2.7)	70.4 (4.5)	0.334
Diabetes (%)	37.4 (3.0)	36.6 (4.7)	0.892
Dyslipidemia (%)	58.1 (3.0)	73.3 (4.3)	0.007
HR (bpm)	78.1 (16.7)	71.2 (15.4)	0.001
BB (%)	58.2 (3.1)	97.0 (3.1)	0.000
Calcium antagonists (%)	37.9 (3.0)	21.8 (4.1)	0.004

Female: female proportion, BMI: body mass index, LVEF: left ventricular ejection fraction, Hb: blood hemoglobin concentration, CHD: Coronary heart disease, LVF: history of left ventricular failure episodes, HR: resting heart rate (beats per minute), BB: on beta-blockers.

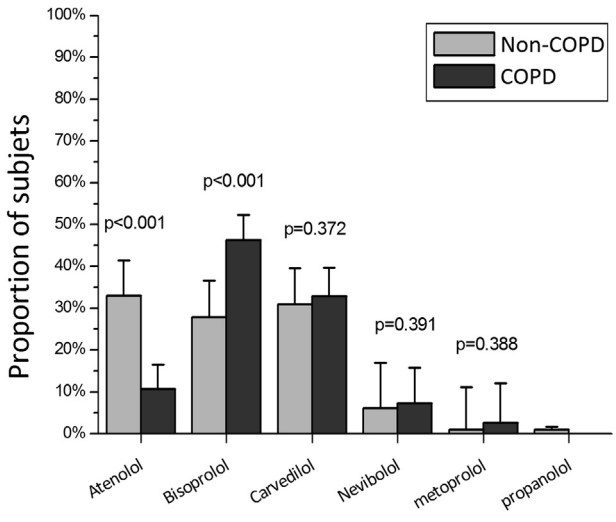

Figure 1 Differences in beta-blockers use between COPD and non-COPD patients. BB: with beta-blocker treatment, No BB: without beta-blocker treatment.

Table 2 Comparisons of some relevant variables between COPD with and without beta-blockers. Mean (SD).

Variable	BB (n = 149)	No BB (n = 107)	p
Female (%)	10.9 (2.6)	0.9 (29.9)	0.001
Age (years)	71.1 (9.6)	73.7 (7.9)	0.022
BMI (kg/m^2)	30.2 (5.0)	28.5 (4.7)	0.020
LVEF (%)	41.7 (13.1)	50.7 (11.5)	0.011
packs-year	49.2 (23.8)	43.7 (13.3)	0.159
Active smoker (%)	17.6 (3.1)	10.2(2.9)	0.108
Anemia (%)	23.8 (3.5)	35.5(4.6)	0.000
Hb (mg/dl)	13.7 (2.0)	12.0 (2.6)	0.042
CAD (%)	72.3 (3.7)	77.8 (4.0)	0.383
LVF (%)	45.2 (4.1)	29.9 (4.4)	0.018
Systemic arterial hypertension	82.2 (3.1)	66.4 (4.5)	0.005
Diabetes (%)	43.5 (4.1)	29.9 (4.4)	0.019
Dyslipidemia (%)	57.4 (4.1)	58.9 (4.7)	0.897
Overweight (BMI > 29.9 kg/m^2)	56.4 (4.1)	29.0 (4.4)	0.000
Systemic hypertension	82.3 (3.1)	66.0 (4.6)	0.000
Atrial fibrillation (%)	18.1 (3.1)	18.7 (3.7)	0.388
Dyspnea (mMRC)	2.2 (1.0)	2.51 (1.2)	0.011
CAT	16.2 (6.8)	18.1 (8.4)	0.046
N° Exacerbations	1.25 (1.6)	1.65 (1.6)	0.135
N° Exacerbations ER	0.65 (1.2)	1.12 (1.4)	0.092
Exacerbations ≥2 (%)	16.1 (3.0)	31.8 (4.5)	0.000
Exacerbations (ER) %	36.9 (3.9)	58.8 (4.7)	0.000
Exacerbaitions ≥2 or ER (%)	38.8 (4.0)	58.8 (4.7)	0.000
HR (bpm)	76.7 (14.9)	80.1 (18.8)	0.125
FEV_1 %predicted	58.7 (16.9)	52.1 (18.4)	0.003
FVC %predicted	76.4 (19.6)	79.3 (22.7)	0.282
FEV_1/FVC %	56.7 (10.4)	49.6 (11.5)	0.000

BB: On beta-blocker treatment, No BB: without beta-blocker treatment, Female: female proportion, BMI: body mass index, LVEF: left ventricular ejection fraction, Hb hemoglobin blood concentration, CAD: Coronary artery disease, LVF: history of left ventricular failure episodes, mMRC: Medical Research Council modified scale, CAT: COPD assessment test, ER: exacerbations attended in the Emergency Room, HR: heart rate (beats per minute),FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity.

Table 3 Use of beta-blockers by Global Initiative for Chronic Obstructive Lung disease risk assessment group (GOLD) combined COPD assessment.

GOLD	BB		No BB		All	
	N	%	*N*	%	*N*	%
A	37	25%	21	20%	58	23%
B	65	44%	39	36%	104	41%
C	8	5%	5	5%	13	5%
D	39	26%	42	39%	81	32%
Total	149		107		256	

BB: On beta-blocker treatment, No BB: without beta-blocker treatment . "*n*" number. "%" column percentage, GOLD.

With respect to respiratory medication (Fig. 2), it is noteworthy that there was less overall use of long-acting beta$_2$-adrenergic drugs (LABA) and ultra-LABA (once a day LABA) in those on BB. Moreover the use of LABA was also different with a higher proportion of patients on ultra-LABA and fewer patients on the more veteran LABAs. As LABA were mostly used in fixed-dose combinations, less use of inhaled corticosteroids was also found in COPD patients on BB (Table 4). The overall use of inhaled anticholinergic drugs (i.e. tiotropium and ipratropium as standalone long-term anticholinergic drug) was also lower in the BB group as compared with the non-BB group (Table 4).

Regarding other medications, patients on BB used more vasodilators and diuretics.

Several of the studied factors (Table 5) were associated with either ≥2 exacerbations or at least one exacerbations attended at the ER in the previous year. In general terms, these factors were lung function (i.e. FEV_1 <50% predicted) and symptoms either measured by the mMRC or the CAT® — and consequently the GOLD combined assessment stages A (lower risk) and D (higher risk) since they are directly derived from them— use of BB, hypolipemiants and the presence of comorbidities such as anemia, diabetes, atrial fibrillation and previous episodes of LVF. Interestingly the use of LABA —usually in combinations with inhaled corticosteroids— were associated with a higher risk of exacerbation. Multiple linear regressions showed that BB treatment, as well as being in GOLD combined risk assessment stages D, were independent risk factors for both multiple exacerbations and exacerbations attended at the ER, while comorbidities and use of LABA were independent factors increasing the risk of exacerbations attended at the ER (Table 6).

Discussion

In spite of the evidence in favor [10,16,17], and guideline recommendations [1,9,10], the proportion of COPD patients with indication for BB drugs because of a heart disease, who

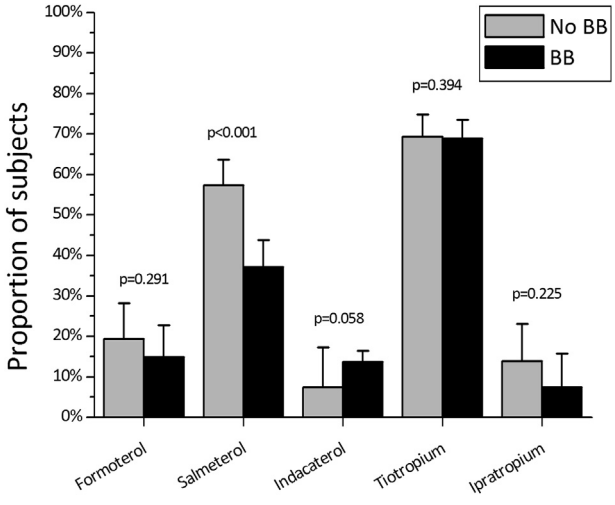

Figure 2 Differences in bronchodilators use between COPD patients with and without beta-blockers. BB: with beta-blocker treatment, No BB: without beta-blocker treatment.

Table 4 Use of drugs by COPD and non-COPD patients. Mean (SD).

Variable	BB (n = 148)	No-BB (n = 108)	p
Ca-antagonists (%)	38.5 (4.0)	37 (4.6)	0.896
ACE Inhibitors (%)	47.5 (4.1)	36.1 (4.6)	0.074
ARB (%)	32.4 (3.8)	32.4 (4.5)	0.383
Aspirin (%)	64.6 (3.9)	69.8 (4.4)	0.388
Anti-platelet agents (%)	37 (4.0)	32.7 (4.5)	0.482
Oral anticoagulants (%)	14.3 (2.9)	13.9 (3.3)	0.928
Lipid-lowering (%)	41.8 (4.1)	48.1 (4.8)	0.482
Diuretics (%)	30.6 3.8)	18.5 (3.7)	0.068
Antiarrhythmics (%)	11.6 (2.6)	9.3 (2.8)	0.023
Oral antidiabetics (%)	7.5 (4.0)	6.5 (2.4)	0.758
Insulin (%)	2.8 (2.2)	1.4 (1.1)	0.428
Rescue BD (%)	75.7 (3.5)	68.5 (4.5)	0.205
LABA (%)	52 (1.4)	76.9 (4.1)	0.000
ultra-LABA (%)	20.9 (4.1)	7.4 (2.5)	0.003
LABA + U (%)	72.9 (3.3)	84.3 (3.5)	0.032
ICE (%)	55.4 (4.1)	77.8 (4.0)	0.000
LAMA (%)	71.6 (3.7)	80.4 (3.8)	0.101
LAMA + SAMA (%)	76.4 (3.5)	83.6 (3.9)	0.009
Roflumilast (%)	4.1 (1.6)	9.3 (2.8)	0.092

Ca-antagonists: calcium channel blockers, ACE Inhibitors: angiotensin converting enzyme inhibitors, ARB angiotensin-2 receptor blockers BD:bronchodilators, LABA: long-acting beta2-agonists,LABA + U: proportion of patients on LABA or ultra-LABA. LAMA: long-acting antimuscarinic agent. SAMA: short acting antimuscarining agent used as standalone chronic antimuscarininc treatmet, ICE: inhaled corticosteroids.

are actually on BB in Spain is around 58%, while in patients not believed to have COPD managed by cardiologist is 97% (Table 1). The latter is about 15% higher than what has been previously described in another Spanish outpatient population of patients with heart conditions requiring these drugs [18]. However, if patients with respiratory disease, bradycardia, cognitive deterioration or difficulties for the follow-up of the treatment are subtracted, as they were in the present work, the figures of both studies are similarly high [18].

There is very little previous information about the use of BB in COPD in Spain or, as a matter of fact, in other European countries. In the candesartan in heart failure (CHARM) study, patients were recruited between 1999 and 2001 from 26 countries of Asia, Europe —including Spain— North-America, Oceania and South-Africa. Thirty two percent of the patients receiving bronchodilators and 57.6% those without bronchodilator therapy were on BB [3]. Separated information for Spain was not provided though. In another study in the Netherlands, patients with indication of BB after coronary artery surgery BB were prescribed in 50.3% of patients without COPD or asthma, 25.2% of patients with COPD or asthma on beta-agonists and 12.5% of patients with severe COPD or asthma [12]. In an analysis of cross-sectional data from 61 primary care practices (377 439 patients) participating in the Scottish Continuous Morbidity Recording scheme only 18% of individuals with hearth failure and COPD were prescribed beta-blockers vs. 41% in those without COPD [15].

Compared with published data form UK and USA our data suggest that the prescription of BB in patients with heart disease has doubled in the last decade in both patients with and without COPD [3,11–15,19]. Caution is needed when comparisons with other series in different settings and from different countries are made, nonetheless same trend of increased use of BB in COPD has been noticed in the Worcester (Massachusetts) Heart Attack Study cohort [20].

We observed a tendency to prescribe BB to those COPD patients with worse cardiac function and a history of previous episodes of LVF (Table 2). Not surprisingly there is a higher proportion of COPD patients on the $beta_1$-selective bisoprolol (Fig. 1). However, carvedilol is as frequently used in COPD patients as in non-COPD patients (Fig. 1) in spite of the fact that it reduces lung function more than $beta_1$-selective BB [21],. The higher use of angiotensin converting enzyme inhibitors and diuretics in the BB group are probably a reflection of worse cardiac function in those with COPD in which BB are prescribed.

We were surprised to find an overall decrease in the use of long-term BD both LAMA and LABA (Table 4). The reasons for this are not clear, but the perception that they can interfere with BB, and non-adherence by patients with several medications [22], may play a role. Interestingly enough, there is a decrease in the proportion of patients treated with "traditional" LABAs in the BB group, in part compensated by an increase in the use of ultra-LABA. This may show the fear to prescribe "traditional" LABA by those physicians more aware of cardiac disease management —those also more prone to use BB— since there is some evidence associating "traditional" LABA to increased mortality in both patients with CHF and with CAD [23–26]. The reduction in the use of "LABA" results in less inhaled corticosteroids use as well since "traditional" LABA were almost always prescribed in fixed-dose combinations in this cohort.

Another interesting finding of this study is that COPD patients using BB are less symptomatic and have both fewer exacerbations and fewer exacerbations attended at the ER in spite of receiving less respiratory medication. Several factors are related to exacerbations (Table 5), but only GOLD stage, use of BB, use of LABA (including ultra-LABA) and comorbidities have independent effects (Table 6). Anecdotally an HR $>$ 70 bpm was associated to a higher risk of exacerbations, what may indicate that not only beta-blockade, but effective beta-blockade is the likely protective factor.

The relationship between GOLD stage and exacerbations have been recently described in the ECLIPSE cohort [27] and our study corroborates that GOLD groups differ in other aspects apart from those used for their somehow questionable definition [28]. The association between LABA and exacerbations attended at the ER is also in keeping with other observational evidence [3,8,23–25,29] what together makes necessary and urgent to perform randomized trials enrolling patients with significant COPD and CHF or CAD to determine the risks and benefits of LABA, particularly in combination with LAMA [8,12]. Meanwhile, careful use of LABA and short-acting $beta_2$-agonists in COPD patients with significant cardiac comorbidites is warranted [8,25,30].

BB had a clear protective effect regarding exacerbations in COPD patients (Table 6). In a retrospective cohort study

Table 5 Unadjusted OR for factors associated with exacerbations in the COPD group.

Exacerbations (≥2)				Exacerbations(ER)			
Variables	OR	(95% CI)	*p*	Variables	OR	(95% CI)	*p*
GOLD D	3.74	(2.03–6.89)	0.000	GOLD A	0.26	(0.13–0.50)	0.000
mMRC ≥ 2	5.30	(2.02–13.89)	0.001	mMRC ≥ 2	3.46	(1.89–6.36)	0.000
FEV_1% *P*<50%	2.70	(1.48–4.91)	0.001	FEV_1%*P*<50%	2.74	(1.62–4.62)	0.000
hypolipemiants	0.56	(0.40–0.80)	0.001	GOLD D	3.20	(1.85–5.56)	0.000
BB	0.41	(0.23–0.75)	0.004	BB	0.41	(0.25–0.68)	0.001
CAT ≥ 10	5.87	(1.76–19.61)	0.004	CAT ≥ 10	3.48	(1.72–7.03)	0.001
GOLD A	0.26	(0.10–0.68)	0.006	LABA + U	2.69	(1.42–5.12)	0.002
Combinations	2.20	(1.12–4.35)	0.023	Anemia	2.70	(1.54–4.74)	0.001
Diabetes	1.87	(1.03–3.40)	0.039	Combinations	2.10	(1.23–3.56)	0.006
HR ≥ 70 bpm	2.09	(1.02–4.29)	0.045	HR ≥ 70 bpm	2.18	(1.24–3.82)	0.006
LVEF	1.02	(0.99–1.04)	0.143	A. fibrillation	0.41	(0.21–0.79)	0.008
LABA + U	1.74	(0.80–3.81)	0.164	LVF	1.92	(1.15–3.20)	0.013
SHT	1.70	(0.80–3.60)	0.168	Diabetes	1.87	(1.12–3.13)	0.017
Ca-antagonist	1.45	(0.80–2.63)	0.217	Antiarrhytmics	1.49	(1.02–2.18)	0.042
LAMA	1.52	(0.73–3.15)	0.259	BMI ≥ 30 kg/m^2	0.78	(0.47–1.27)	0.313
LVF	1.39	(0.77–2.51)	0.279	LVEF	1.01	(0.99–1.03)	0.446
Active smoker	0.62	(0.25–1.57)	0.315	Female sex	1.33	(0.50–3.57)	0.526
A. fibrillation	0.72	(0.35–1.47)	0.366	AIA	0.85	(0.51–1.42)	0.536
Anemia	1.32	(0.70–2.49)	0.385	GOLD C	0.72	(0.23–2.26)	0.572
AIA	0.78	(0.42–1.45)	0.436	hypolipemiants	1.06	(0.79–1.42)	0.709
GOLD B	0.79	(0.43–1.44)	0.437	Active smoker	1.13	(0.56–2.26)	0.736
BMI ≥ 30 kg/m^2	0.83	(0.46–1.50)	0.538	LAMA	0.92	(0.52–1.63)	0.780
Antiarrhytmics	1.09	(0.73–1.64)	0.661	GOLD B	0.94	(0.57–1.55)	0.811
Female	1.05	(0.33–3.35)	0.936	Ca-antagonist	0.95	(0.57–1.58)	0.854
GOLD C	0.00	(0.00–0.00)	0.999	SHT	0.95	(0.54–1.69)	0.866

OR: odds ratio,95%IC: ninety-five percent confidence interval, GOLD: GOLD combined assessment stage, mMRC: Medical Research Council modified scale, FEV1%*P*<50%: Forced expiratory volume in the first second lower than 50% of predicted, BB: on beta-blocker treatment, CAT: COPD assessment test, combinations: combinations of LABA + inhaled corticosteroids, HR: heart rate,, LVEF: left ventricular ejection fraction, LABA: long-acting beta2 agonist, LABA + U: use of LABA or ultra-LABA, SHT: systemic arterial hypertension, Ca-antagonist: calcium channel blockers, LAMA: long acting antimuscarinic agents, LVF: history of left ventricular failure episodes, A. fibrillation: atrial fibrillation in the ECG, AIA: history of acute ischemic attack, BMI: body mass index; , Female: female sex,.

using a disease specific database of COPD patients (TARDIS) in Scotland, BB reduced mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD, independently of overt cardiovascular disease and cardiac drugs [17]. Another retrospective study also showed a reduction in ER visits or hospitalizations with BB in COPD patients [31]. Finally BB appears to reduce mortality in those admitted by acute exacerbations of COPD [13].

Limitations

This is a retrospective study; however, both the use of BB and exacerbations attended at the ER, as well as the other explanatory variables, could be obtained with great accuracy by interviewing the patients and reviewing medical records. These records are currently accessible in Spain from the electronic medical database (at least for the

Table 6 Adjusted OR for factors associated with exacerbations in the COPD group.

Exacerbations (≥2)				Exacerbations (ER)			
Variables	OR	(95% CI)	*p*	Variables	OR	(95% CI)	*p*
BB	0.26	(0.14–0.50)	0.000	BB	0.27	(0.15–0.50)	0.000
GOLD D	2.64	(1.43–4.93)	0.002	GOLD D	2.52	(1.40–4.53)	0.003
Diabetes	2.04	(1.07–3.91)	0.031	HR > 70	2.19	(1.24–3.86)	0.007
				LABA + U	2.18	(1.29–3.68)	0.015
				LVF	2.27	(1.19–4.33)	0.012
				Diabetes	1.82	(1.08–3.38)	0.048

OR: odds ratio,95%IC: ninety-five percent confidence interval, BB: on beta-blocker treatment GOLD: GOLD combined risk assessment group. HR > 70 heart rate >70 bpm LABA: long-acting $beta_2$ agonist, LABA + U: use of LABA or ultra-LABA, LVF: history of acute left ventricular failure episodes.

region where patients live). To establish the prevalence of BB use in non-COPD, participant patients were recruited from cardiologist outpatient offices. They may represent a more severe and better controlled population than if they had been recruited from other settings. It also assured the most thorough observation of current indications for BB in cardiac patients as the gold standard to compare with. Regarding the comparability of COPD using and not using BB or having or not having exacerbations, we used a nested design. This design paradigmatically satisfies the study base principle; however we did not match patients for lung function, age or any other variable because we wanted to know, as close as possible, the actual clinical practice, even at the expense of losing causal strength in the associations found. Therefore groups resulted slightly statistically different in some variables. The clinical relevance of most of such differences do not seem to be great, but they uncover the difficulty of controlling all the known and unknown factors and stresses need for clinical trials in patients with COPD and CHF or CAD. These clinical trials, particularly on the safety of bronchodilators already approved and of widespread use in such patients, will be difficult to set up though; meanwhile observational evidence, such as that provided by this study, will be the only available one.

Conclusions

The use of BB in COPD patients in Spain is lower than what is recommended by current guidelines. COPD patients with CHF or CAD have fewer exacerbations and visits to the ER and are less symptomatic if they use BB, in spite of worse cardiac function and less use of long-term BD. GOLD stage and comorbidities are also risk factors for exacerbations.

Acknowledgments

Pedro Luis Sánchez. Servicio de Cardiología, Hospital Universitario Gregorio Marañón, Madrid. Pablo Piñón and Eduardo Barge, Servicio de Cardiología, Complejo Hospitalario Universitario de A Coruña), María Soledad Iravedra and Pablo González (Unidad de Gestión Clínica de Cardiología, Hospital Universitario "Puerto Real").

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