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RESEARCH ARTICLE

Relationship between heart failure, concurrent chronic obstructive pulmonary disease and beta-blocker use: a Danish nationwide cohort study

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Aims To compare the hazard of all-cause, chronic obstructive pulmonary disease (COPD) and heart failure (HF) hospitalization in carvedilol vs. metoprolol/bisoprolol/nebivolol users with COPD and concurrent HF from 2009 to 2012, and to evaluate the use and persistence in treatment of these β-blockers, their impact on the risk of COPD-related hospitalization, and the factors important for their selection.

Methods and results Cox and logistic regression were used for both unadjusted and adjusted analyses. Carvedilol users had a higher hazard of being hospitalized for HF compared with metoprolol/bisoprolol/nebivolol users in both the unadjusted [hazard ratio (HR) 1.74; 95% confidence interval (CI) 1.65–1.83] and adjusted (HR 1.61; 95% CI 1.52–1.70) analyses. No significant differences were found for all-cause and COPD hospitalization between the two groups. Carvedilol users had a significant lower restricted mean persistence time than metoprolol/bisoprolol/nebivolol users. Patients exposed to carvedilol had an odds ratio (OR) of 1.38 (95% CI 1.23–1.56) for being hospitalized due to COPD within 60 days after redeeming the first carvedilol prescription, which was similar to that observed in metoprolol/bisoprolol/nebivolol users (OR 1.37; 95% CI 1.27–1.48). Patients with concurrent chronic kidney disease had a higher probability of receiving carvedilol (OR 1.16; 95% CI 1.04–1.29).

Conclusion Carvedilol prescription carried an increased hazard of HF hospitalization and lower restricted mean persistence time among patients with COPD and concurrent HF. Additionally, we found a widespread phenomenon of carvedilol prescription at variance with the European Society of Cardiology guidelines and potential for improving the proportion of patients treated with β-blockers.

Keywords Non-cardio-selective β-blockers • Carvedilol • Heart failure • Chronic obstructive pulmonary disease • Clinical guidelines • Hospitalization • Denmark

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Introduction

Since 2008, the European Society of Cardiology (ESC) clinical management guidelines for acute and chronic heart failure (HF) have stated that a more selective β1-adrenoreceptor antagonist (i.e., bisoprolol, metoprolol succinate, or nebivolol) is preferred for patients with chronic obstructive pulmonary disease (COPD).[1–4] Subsequently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) clinical guidelines endorsed these recommendations in 2011, suggesting that whenever β-blockers are needed in accordance with respective guidelines,[1–4] cardio-selective β-blockers should be preferred over non-selective β-blockers for patients with COPD.[5] There is evidence to suggest that β-1-selective and non-selective β-blockers have different clinical effects in COPD.[1,6–11] The lack of pharmacological selectivity for the β-1 receptor could result in adverse respiratory reactions, such as bronchoconstriction and worsening of lung function.[8–11] Although the pulmonary consequences of β-2 blockade are well known, little information is known regarding the magnitude of these consequences in a real-world setting, and clinical studies are needed.[12] Documented differences in the potentially harmful effects of β-2 blockade between cardio-selective and non-cardio-selective β-blockade are mainly derived from indirect evidence.[8–11] These studies have inherent limitations, such as small sample sizes, a single-blinded design, the use of β-blockers with intrinsic sympathomimetic activity and a randomization approach that is not always clear.[12] On a national scale, the extent to which the international guidelines have been followed in this regard it is unknown. It is important to know whether adherence to guidelines needs to be reinforced. Therefore, we conducted a nationwide study to investigate the differences between carvedilol and metoprolol/bisoprolol/nebivolol users in terms of the risk of all-cause, COPD-, and HF-related hospitalization among patients with COPD and concurrent HF during the period 2009–2012. Moreover, this study aimed to evaluate the use of and persistence in treatment with carvedilol or metoprolol/bisoprolol/nebivolol, the factors that are important in their selection and their impact on the risk of being hospitalized for COPD.

Methods

Data sources

The permanent Civil Personal Register number is a unique 10-digit number that is assigned to all Danish residents. This number makes it possible to link information from different registers on an individual level. Through this identifier, we were able to collect information on the prescription redemption, hospitalization diagnoses, causes of death, and vital status of Danish citizens using the Danish National Patient Registry, Danish Registry of Medicinal Product Statistics, and the National Causes of Death Registry, respectively.

Study population

All patients with a diagnosis of COPD from 1 January 2009 to 31 December 2012 were identified in the Danish registries. The year 2009 was chosen to allow a grace period after the release of ESC guidelines to allow the recommendations to be integrated into routine clinical practice. Patients who had primary or secondary hospitalization diagnoses coded as J42, J43, J44 in accordance with the International Statistical Classification of Diseases and Related Health Problems 10th Revisions (ICD 10) or as ICD-8 codes 491 or 492 were defined as having COPD. The diagnosis of COPD has been validated in the Danish Patient Registry and has a verification rate of 92% among hospitalized patients.[13] From this preliminary population, we selected our study population, which was comprised of patients with concurrent HF who were treated with β-blockers used for HF (see supplementary material online, *Table S1*). Those patients with a primary or secondary hospitalization diagnosis codified as ICD10 codes I110, I42, I50, and J819 were defined as having HF. A patient was defined as being treated with non-cardio-selective β-blockers with an authorised indication for HF if he or she had redeemed prescriptions for carvedilol. Similarly, we defined a patient as treated with cardio-selective β-blockers with an authorised indication for HF if he or she had redeemed prescriptions for metoprolol, bisoprolol, or nebivolol (see supplementary material online, *Table S1*). Those β-blockers represent the only β-blockers used for HF in Denmark from 2009 to 2012. We classified β-blockers as cardio- or non-cardio-selective according to an expert consensus document on β-blockers[14] and according to the Anatomical Therapeutic Chemical classification system proposed by the World Health Organization.

Follow-up period

We followed the study population from the index date to death or the end of follow-up on 31 December 2012. The index date was the date when patients who had already been diagnosed with HF and COPD redeemed the first prescription for carvedilol, metoprolol, bisoprolol or nebivolol. 1 January 2009 was used as the index date for patients who fulfilled these requirements prior to 1 January 2009.

Outcomes

The first, second and third primary outcomes were the hazard ratio (HR) of being hospitalized for COPD, HF and all causes within 60 days after redeeming the first β-blocker prescription for carvedilol users vs. metoprolol/bisoprolol/nebivolol users. The secondary outcome was the proportion of patients with COPD and HF that received carvedilol as opposed to metoprolol, bisoprolol and nebivolol and their geographical distribution. The tertiary outcome was the odds ratio (OR) of being hospitalized for COPD 60 days after and 60 days before the redemption of the first carvedilol or metoprolol/bisoprolol/nebivolol prescription. We also examined persistence in treatment with carvedilol or metoprolol/bisoprolol/nebivolol; the cumulative incidence of all-cause, HF and COPD hospitalization following carvedilol or metoprolol/bisoprolol/nebivolol discontinuation; and the predictors of carvedilol selection.

Statistical analysis

The study covariates included age, year of inclusion in the cohort, vital status, concurrent pharmacological treatments (listed in the supplementary material online, *Table S2*), and co-morbidities (listed in the supplementary material online, *Table S3*). Operative definitions of the co-morbidities presented in the supplementary material online,

Table 1 Socio-demographic characteristics of patients with chronic obstructive pulmonary disease and concurrent heart failure at the first claimed prescription of β-blockers used for heart failure in the period 2009–2012 on the entire Danish national territory

Variable	Level	Carvedilol (*n* = 3902)	Metoprolol (*n* = 8548)	Bisoprolol (*n* = 1804)	Nebivolol (*n* = 85)	Total (*n* = 14 339)	*P*-value
Diagnosis type	COPD diagnosis unspecified	23 (0.6)	45 (0.5)	13 (0.7)	1 (1.2)	82 (0.6)	
	COPD as primary diagnosis	1558 (39.9)	3458 (40.5)	708 (39.2)	40 (47.1)	5764 (40.2)	
	COPD as secondary diagnosis	2076 (53.2)	4594 (53.7)	1002 (55.5)	36 (42.4)	7708 (53.8)	
	COPD as secondary diagnosis during psychiatric examination	3 (0.1)	19 (0.2)	9 (0.5)	0 (0.0)	31 (0.2)	
	COPD as reference diagnosis	242 (6.2)	432 (5.1)	72 (4.0)	8 (9.4)	753 (5.3)	0.0005
Path type	COPD diagnosis made during an hospitalization of at least 24 h	2398 (61.5)	5548 (64.9)	1216 (67.4)	52 (61.2)	9214 (64.3)	
	COPD diagnosis made during an hospital access of at least 12 h	41 (1.1)	84 (1.0)	22 (1.2)	0 (0.0)	147 (1.0)	
	COPD diagnosis made during an outpatient examination	1341 (34.4)	2651 (31.0)	530 (29.4)	32 (37.6)	4554 (31.8)	
	COPD diagnosis made at an emergency department	122 (3.1)	265 (3.1)	36 (2.0)	1 (1.2)	424 (3.0)	0.0002
Time since first heart failure diagnosis	Mean (SD)	4.0 (4.6)	3.9 (4.9)	4.0 (4.9)	4.1 (4.6)	3.9 (4.8)	0.4683
Time since first COPD diagnosis	Mean (SD)	3.7 (5.5)	4.3 (5.8)	5.5 (6.5)	4.8 (5.6)	4.3 (5.8)	<0.0001
Year of first prescription of β-blockers for heart failure	2009	1525 (39.1)	3572 (41.8)	884 (49.0)	34 (40.0)	6015 (41.9)	
	2010	893 (22.9)	1918 (22.4)	365 (20.2)	18 (21.2)	3194 (22.3)	
	2011	840 (21.5)	1743 (20.4)	326 (18.1)	18 (21.2)	2927 (20.4)	
	2012	644 (16.5)	1315 (15.4)	229 (12.7)	15 (17.6)	2203 (15.4)	<0.0001
Age	Mean (SD)	72.6 (9.9)	75.7 (9.8)	74.7 (9.2)	74.8 (9.8)	74.7 (9.9)	<0.0001
Gender	Male	2611 (66.9)	4686 (54.8)	1047 (58.0)	43 (50.6)	8387 (58.5)	< 0.0001
History of stroke or systemic thromboembolism	Yes	808 (20.7)	2025 (23.7)	385 (21.3)	19 (22.4)	3237 (22.6)	0.0015
Peripheral arterial disease	Yes	718 (18.4)	1 543 (18.1)	332 (18.4)	12 (14.1)	2605 (18.2)	0.7467
History of alcohol abuse	Yes	603 (15.5)	1213 (14.2)	229 (12.7)	10 (11.8)	2055 (14.3)	0.0361
Lever disorder	Yes	222 (5.7)	476 (5.6)	93 (5.2)	2 (2.4)	793 (5.5)	0.5047
Acute kidney disease	Yes	489 (12.5)	949 (11.1)	176 (9.8)	6 (7.1)	1620 (11.3)	0.0072
Chronic kidney disease	Yes	882 (22.6)	1 740 (20.4)	355 (19.7)	16 (18.8)	2993 (20.9)	0.0166
Arterial embolism	Yes	1076 (27.6)	2602 (30.4)	480 (26.6)	25 (29.4)	4183 (29.2)	0.0006
Diabetes mellitus	Yes	1171 (30.0)	2498 (29.2)	494 (27.4)	25 (29.4)	4188 (29.2)	0.2487
Hypertension	Yes	2322 (59.5)	5668 (66.3)	1132 (62.7)	67 (78.8)	9189 (64.1)	<0.0001
History of acute myocardial infarction	Yes	1676 (43.0)	3394 (39.7)	711 (39.4)	31 (36.5)	5812 (40.5)	0.0038
History of syncope	Yes	634 (16.2)	1322 (1 5.5)	289 (16.0)	12 (14.1)	2257 (1 5.7)	0.6776
Atrial fibrillation	Yes	1698 (43.5)	4825 (56.4)	966 (53.5)	37 (43.5)	7526 (52.5)	<0.0001
Ventricular arrhythmia	Yes	662 (17.0)	1231 (14.4)	261 (14.5)	12 (14.1)	2166 (15.1)	0.0023
Selective β-2-adrenoreceptor agonists inhalants – short acting	Yes	1436 (36.8)	3188 (37.3)	852 (47.2)	33 (38.8)	5509 (38.4)	<0.0001
Selective β-2-adrenoreceptor agonists oral – short acting	Yes	87 (2.2)	228 (2.7)	49 (2.7)	2 (2.4)	366 (2.6)	0.6155
Selective β-2-adrenoreceptor agonists inhalants – long acting	Yes	337 (8.6)	793 (9.3)	225 (12.5)	8 (9.4)	1363 (9.5)	<0.0001

Table 1 Continued

Variable	Level	Carvedilol (*n* = 3902)	Metoprolol (*n* = 8548)	Bisoprolol (*n* = 1804)	Nebivolol (*n* = 85)	Total (*n* = 14 339)	*P*-value
Selective β-2-adrenoreceptor agonists oral – long acting	Yes	6 (0.2)	13 (0.2)	3 (0.2)	0 (0.0)	22 (0.2)	0.9850
Anticholinergics – short acting	Yes	57 (1.5)	138 (1.6)	48 (2.7)	0 (0.0)	243 (1.7)	0.0036
Anticholinergics – long acting	Yes	969 (24.8)	1994 (23.3)	592 (32.8)	29 (34.1)	3584 (25.0)	<0.0001
Glucocorticoids inhalants	Yes	566 (14.5)	1383 (16.2)	441 (24.4)	16 (18.8)	2406 (16.8)	<0.0001
Phosphodiesterase inhibitors	Yes	66 (1.7)	192 (2.2)	88 (4.9)	2 (2.4)	348 (2.4)	<0.0001
Antileucotrienes	Yes	42 (1.1)	117 (1.4)	49 (2.7)	2 (2.4)	210 (1.5)	<0.0001
Glucocorticoids + selective β-2-adrenoreceptor agonists inhalants	Yes	1446 (37.1)	3033 (35.5)	872 (48.3)	39 (45.9)	5390 (37.6)	<0.0001
Anticholinergics + selective β-2-adrenoreceptor agonists inhalants	Yes	445 (11.4)	1093 (12.8)	392 (21.7)	13 (15.3)	1943 (13.6)	<0.0001
Mast cell stabilizer + selective β-2-adrenoreceptor agonists inhalants	Yes	27 (0.7)	121 (1.4)	24 (1.3)	1 (1.2)	173 (1.2)	0.0047

COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table S3, are described elsewhere.[15] For descriptive purposes, we compared the baseline characteristics (taken at the index date) of the patients who received prescriptions for carvedilol, metoprolol, bisoprolol and nebivolol using the analysis of variance (ANOVA) for continuous variables and Fisher's exact test for categorical variables. Cumulative incidence curves were generated to compare cumulative incidence for all-cause, COPD and HF hospitalization for both cohorts. Gray's test was used to evaluate the hypotheses that cause-specific cumulative functions were equal for the carvedilol and the metoprolol, bisoprolol, nebivolol users. In both the adjusted and unadjusted analyses, Cox regression was used to compare the hazard of being hospitalized for COPD, HF, and all causes between carvedilol users and metoprolol, bisoprolol, and nebivolol users. The unadjusted analysis was performed using Cox regression with only outcome and exposure. For the adjusted analysis, the aforementioned study covariates were used. Multivariable adjusted logistic regression was used to assess the predictors of carvedilol use vs. metoprolol/bisoprolol/nebivolol use in the study population. The persistence analysis was defined as the time in treatment without discontinuation and was based on the assumptions of the calculations of daily dosages, which are described elsewhere.[16] The probability of being alive and discontinuing the pharmacological treatment with carvedilol or metoprolol/bisoprolol/nebivolol was assessed using the Aalen-Johansson estimator. For each patient who discontinued the pharmacological treatment with carvedilol or metoprolol/bisoprolol/nebivolol, cumulative incidence curves for all-cause, COPD and HF hospitalization within 450 days after discontinuation were generated. For each patient who filled a prescription for carvedilol or metoprolol/bisoprolol/nebivolol, we compared the odds of being hospitalized for COPD 60 days before and 60 days after the redemption of the first carvedilol or metoprolol/bisoprolol/nebivolol prescription. For this purpose, a conditional logistic regression adjusted for the aforementioned study covariates was used. Finally, a sensitivity analysis was performed to compare the odds of being hospitalized for COPD during the 60 days before and the 60 days after filling the first carvedilol or metoprolol/bisoprolol/nebivolol prescription by removing those patients who died within 60 days of filling the prescription. Data analysis was performed using R (version 3.2.2, R Development Core Team, Austria), and data management was performed using SAS statistical software (version 9.4, SAS Institute, Inc., Cary, NC, USA).

Compliance with ethical standards

The study was approved by the Danish Data Protection Agency. In Denmark, register-based retrospective studies do not require ethical approval.

Results

Overall, 90 179 patients with a diagnosis of COPD were identified. Of these, 24 999 patients had a concurrent diagnosis of HF, and 14 898 out of the 24 999 (59.6%) had at least one filled prescription for β-blockers. For 14 339 out of the 14 898 (96.2%) patients who received a prescription for β-blockers, the prescribed β-blockers had a registered indication for HF (*Table 1*). In total, 3902 out of 14 339 patients (27.2%) filled a prescription for a non-cardio-selective β-blocker indicated for HF, or carvedilol, contributing to a follow-up period of 7567 person-years (*Figure 1*). Metoprolol, bisoprolol and nebivolol users contributed to follow-up periods of 15 225, 3541 and 161 person-years, respectively. Among the patients who received carvedilol prescriptions, 1156 out of the 3902 (29.6%) started pharmacological treatment with carvedilol for the first time during the period 2009–2012.

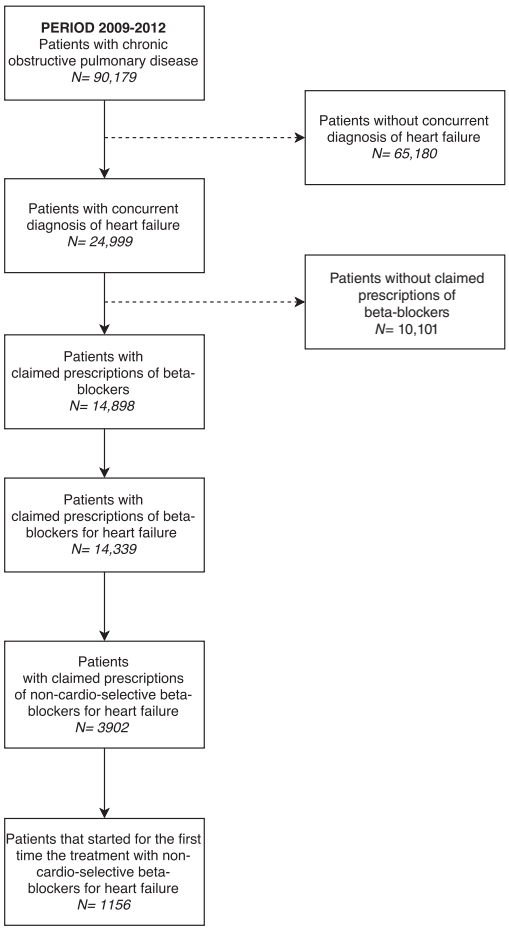

Figure 1 Flowchart of the study population of patients with chronic obstructive pulmonary disease and concurrent heart failure and filled prescriptions for β-blockers used for heart failure in 2009–2012 for the entire Danish national territory.

Comparison of all-cause, chronic obstructive pulmonary disease, and heart failure hospitalization between carvedilol and metoprolol/nebivolol/bisoprolol users with chronic obstructive pulmonary disease and concurrent heart failure in 2009–2012

Cause-specific cumulative incidence curves for carvedilol and metoprolol/bisoprolol/nebivolol users are provided in *Figure 2*. Within 60 days of the redemption of the first β-blocker prescription, carvedilol users had a higher hazard of hospitalization for HF compared with the metoprolol, bisoprolol, and nebivolol users in both the unadjusted [HR 1.74; 95% confidence interval (CI) 1.65–1.83] and adjusted (HR 1.61; 95% CI 1.52–1.70) analyses. No statistically significant differences were found for the hazard of being hospitalized for all causes (unadjusted HR 1.05; 95% CI 0.99–1.10; adjusted HR 1.02; 95% CI 0.96–1.07) or COPD (unadjusted HR 0.98; 95% CI 0.90–1.07; adjusted HR 1.01; 95% CI 0.93–1.10) when comparing carvedilol users and metoprolol/bisoprolol/nebivolol users in both unadjusted and adjusted analyses.

Geographical distribution of claimed prescriptions for carvedilol, metoprolol, nebivolol, and bisoprolol for heart failure

The 14 339 patients with concurrent COPD and HF who received β-blockers for HF during the observational period included 4294 (29.9%) patients from the Capital Region, 2447 (17.1%) from the Zealand Region, 2971 (20.7%) from the South Region, 3179 (22.2%) from the Central Denmark Region, 1429 (10.0%) from the North Region, and 19 (0.1%) with no reported region. Overall, 1234 (28.7%) patients residing in the Capital Region claimed a prescription for carvedilol, compared with 3060 (71.3%) who received prescriptions for metoprolol, bisoprolol, or nebivolol. The proportion of patients who filled a prescription for carvedilol was 25.5% ($n = 625$) for the Zealand Region and 30.2% ($n = 898$) for South Region, compared with 74.5% ($n = 1822$) and 69.8% ($n = 2073$) who received metoprolol/bisoprolol/nebivolol, respectively. Similarly, 954 (30.0%) and 187 (13.1%) patients who resided in the Central Denmark and North Regions filled prescriptions for carvedilol, compared with 2225 (70.0%) and 1242 (86.9%), respectively, who received metoprolol, bisoprolol, or nebivolol.

Characteristics of patients who filled prescriptions for carvedilol, metoprolol, nebivolol, and bisoprolol in 2009–2012

Elderly people composed the majority of the study population (mean age: 72.6 ± 9.9 years), and the majority were men (66.9%). Most patients had COPD as the secondary ($n = 2076$; 53.2%) or primary diagnosis ($n = 1558$; 39.9%), mainly during a hospitalization of at least 24 h ($n = 2398$; 61.5%) or during an outpatient examination ($n = 1341$; 34.4%). Important cardiovascular co-morbidities included hypertension ($n = 2322$; 59.5%), a history of acute myocardial infarction ($n = 1676$; 43.0%) and atrial fibrillation ($n = 1698$; 43.5%). The concurrent pharmacological treatments with a registered indication for COPD are shown in *Table 1*.

Carvedilol and metoprolol/nebivolol/bisoprolol users' hospitalization due to chronic obstructive pulmonary disease

Of 3902 patients treated with carvedilol, 1729 (44.4%) were hospitalized 5272 times for COPD. Given that this cohort had an observational period of 7567 person-years, the hospitalization rate was 69 hospitalizations per 100 person-years. Of 10 437 patients treated with metoprolol/nebivolol/bisoprolol instead, 4270 (40.9%) were hospitalized 12 342 times for COPD. Given that this cohort had an observational period of 18 927 person-years, the hospitalization rate was 65 hospitalizations per 100 person-years. During the 60 days following redemption of the first prescription, the

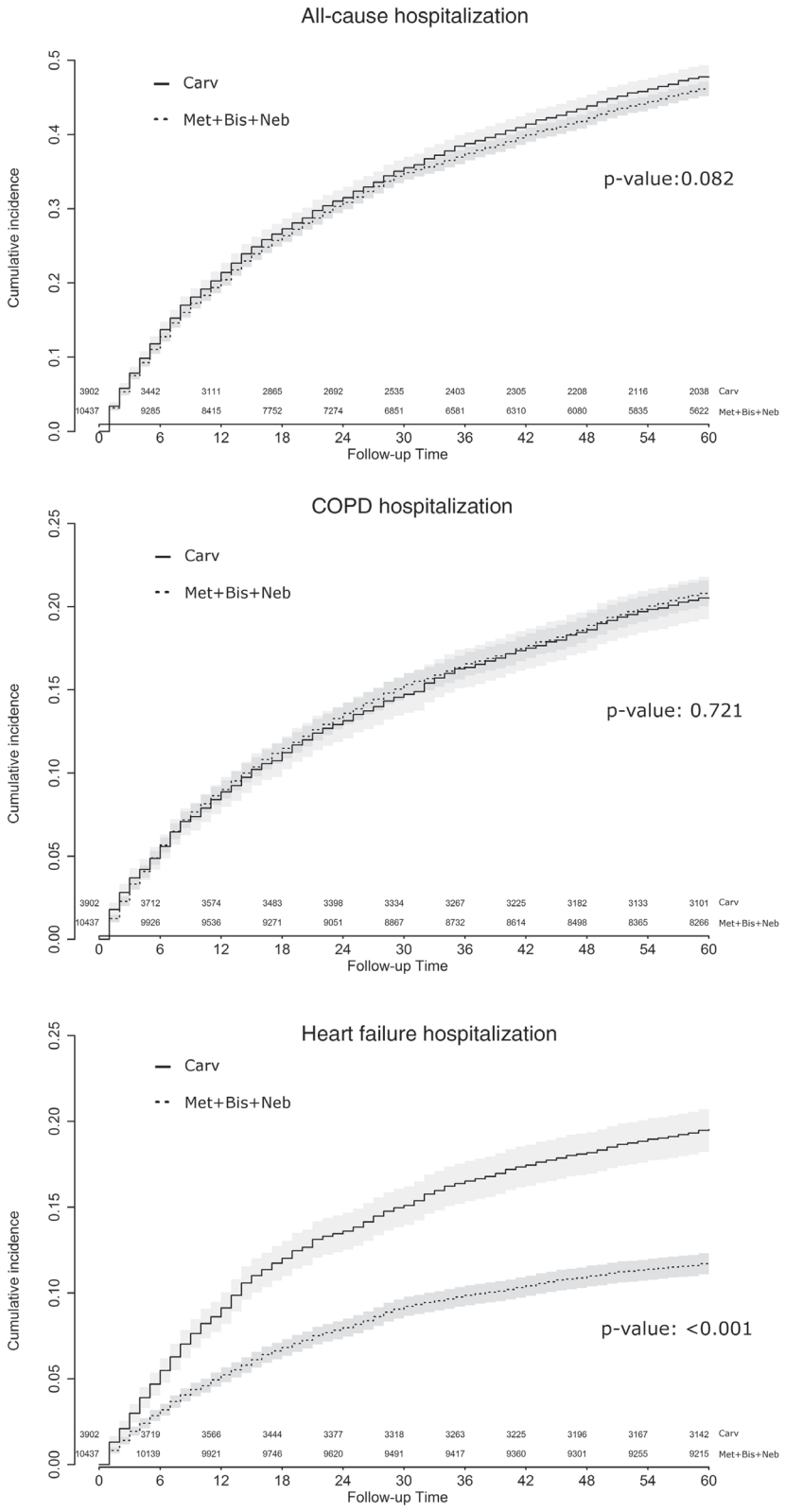

Figure 2 Cumulative incidence curves for all-cause, chronic obstructive pulmonary disease (COPD) and heart failure hospitalization for carvedilol users vs. metoprolol, bisoprolol, nebivolol users.

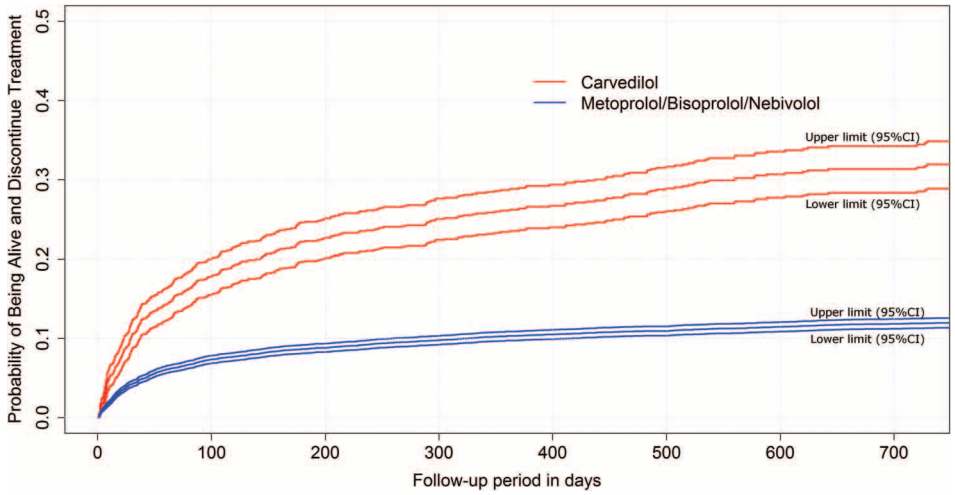

Figure 3 Aalen-Johansen estimate of the probability of being alive and discontinuing carvedilol or metoprolol/nebivolol/bisoprolol in the study population of naïve patients with concurrent heart failure and chronic obstructive pulmonary disease in 2009–2012 in Denmark. CI, confidence interval.

3902 patients who filled prescriptions for carvedilol had an OR of 1.38 (95% CI 1.23–1.56) for being hospitalized for COPD compared with themselves during an equivalent period prior to filling the prescription. Similarly, the 10 437 patients who filled prescriptions for metoprolol/nebivolol/bisoprolol had an OR of 1.37 (95% CI 1.27–1.48) for being hospitalized for COPD compared with themselves during an equivalent period prior to filling the prescription.

Sensitivity analysis: carvedilol and metoprolol/nebivolol/bisoprolol users' hospitalization for chronic obstructive pulmonary disease after removing patients who died within 60 days of redeeming the first prescription for carvedilol or metoprolol/nebivolol/bisoprolol

In total, 328 (8.4%) out of 3902 patients died within 60 days of redeeming their first prescription for carvedilol. The remaining 3574 (91.6%) patients had 1.32 (95% CI 1.16–1.50) times higher odds of being hospitalized for COPD during the first 60 days after redeeming the first prescription for carvedilol compared with themselves during an equivalent period prior to redeeming the prescription. Similarly, 864 (8.3%) out of 10 437 patients died within 60 days of redeeming their first prescription for metoprolol/nebivolol/bisoprolol. The remaining 9573 (91.7%) patients had 1.31 (95% CI 1.21–1.42) times higher odds of being hospitalized for COPD during the first 60 days after redeeming the first prescription for metoprolol/nebivolol/bisoprolol compared with themselves during an equivalent period prior to redeeming the prescription.

Persistence in carvedilol or metoprolol/nebivolol/bisoprolol treatment in patients with chronic obstructive pulmonary disease and concurrent heart failure

The 1156 patients who started carvedilol for the first time during the study period had a restricted mean persistence duration of 507 days, which showed a protracted period of treatment with carvedilol (*Figure 3*). In total, 20% of patients discontinued carvedilol treatment within 139 days of the index date. Similarly, patients who started metoprolol/nebivolol/bisoprolol for the first time during the study period had a restricted mean persistence duration of 815 days which was statistically significant higher than those observed with carvedilol ($P < 0.0001$) (*Figure 3*). In total, 8% of patients discontinued metoprolol/nebivolol/bisoprolol treatment within 139 days of the index date. Supplementary material online, *Figures S1* and *S2* show the cumulative incidence curves for all-cause, COPD and HF hospitalization within 450 days of discontinuation for those patients who discontinued the pharmacological treatment with carvedilol or metoprolol/nebivolol/bisoprolol.

Predictive factors for filling carvedilol prescriptions vs. metoprolol/nebivolol/bisoprolol among patients with chronic obstructive pulmonary disease and concurrent heart failure

Chronic kidney disease (OR 1.16; 95% CI 1.04–1.29) was positively associated with filling prescriptions for carvedilol. In contrast, hypertension (OR 0.75; 95% CI 0.69–0.81) and atrial fibrillation (OR 0.62; 95% CI 0.57–0.67) were negatively associated with filling prescriptions for carvedilol. We found that the following drugs with

a registered indication for COPD were negatively associated with redeeming a prescription for carvedilol: inhaled glucocorticoids (OR 0.75; 95% CI 0.67–0.85), anticholinergics/inhaled selective β-2-adrenoreceptor agonists (OR 0.80; 95% CI 0.71–0.90) and short-acting inhaled selective β-2-adrenoreceptor agonists (OR 0.88; 95% CI 0.81–0.96).

Discussion

This study provided data regarding the prescription of carvedilol for HF patients with concurrent COPD in a manner that is at variance with the recommendations given in the ESC guidelines. Carvedilol use was associated with an increased hazard of hospitalization for HF compared with metoprolol, bisoprolol, and nebivolol use. No statistically significant differences were found when comparing the hazard of all-cause and COPD hospitalization. We cannot exclude the possibility of a significant misdiagnosis of exacerbation of COPD and decompensation of HF. Exacerbation of COPD can be difficult to distinguish from the worsening of HF, particularly in patients with both diseases.[5,17] Despite being unable to provide a causal explanation, we can speculate that the antagonistic effect of carvedilol on prejunctional and post-junctional β-2 receptors played an important role in the observed increase in risk.[18] The aforementioned pharmacodynamic effects may have revealed a cholinergic tone in the respiratory tract and consequently a contraction of the airway. This phenomenon could have led to the exacerbation of signs and symptoms of COPD. It is well established that the impact of cardio-selective β-blockers on the forced expiratory volume in 1 second (FEV_1) is mitigated by their higher selectivity for β-1 adrenal receptors.[8,19] Consistent with this hypothesis, the use of cardio-selective β-blockers has been associated with a minimal dose-related reduction in FEV_1 hyperresponsiveness to methacholine and a reduced risk of adverse respiratory reaction, even in more severe patients.[20] Clinical trials have shown that treatment with non-cardio-selective β-blockers in patients with the aforementioned clinical conditions is associated with a reduction in FEV_1, increased airway hyperresponsiveness and reduced efficacy of bronchodilator treatment.[21] These effects have been associated with less favourable effects on pulmonary function that resulted in an increased risk of pulmonary adverse drug reactions among users of non-cardio-selective β-blockers compared with users of cardio-selective β-blockers.[21,22] However, we cannot rule out the possibility that, in our study population, COPD exacerbation may have accompanied worsening of HF, or vice versa.[5] Interestingly, in this study, chronic kidney disease was among the predictors of receiving carvedilol. We supposed that the beneficial clinical effect of carvedilol in patients with chronic kidney disease[23] could have led physicians to choose this drug for this sub-population. In contrast, patients with co-morbidities such as atrial fibrillation had a lower likelihood of receiving a carvedilol prescription. The increased odds of carvedilol prescriptions for chronic kidney disease patients could be because the beneficial effect of cardio-selectivity, which was observed in patients receiving treatment with β-blockers for atrial fibrillation,[25] led physicians to prefer treatment with β-blockers with enhanced β-1 adrenal-receptor selectivity. Similarly, in the case of hypertension, which was negatively associated with filled carvedilol prescriptions, we believe that the clinical benefit of cardio-selectivity could have led physicians to prescribe medicines with enhanced β-1 adrenal-receptor selectivity. In fact, cardio-selectivity was an important predictor of the extent of the anti-hypertensive effect of β-blockers, mainly due to the reduced anti-hypertensive effectiveness of β-2 adrenal-receptor antagonism in the vessels, which mediates vasodilatation, and through the increase in systolic blood pressure variability caused by the reduced selectivity for β-1 adrenal receptors.[26,27] As expected, a claimed prescription for inhaled glucocorticoids or anticholinergic/selective β-2-adrenoreceptor agonist inhalants was negatively associated with receiving carvedilol. In fact, according to the GOLD guidelines, glucocorticoids and the associated anticholinergics/selective β-2-adrenoreceptor agonists are typically recommended for more advanced stages of COPD,[5] which may have discouraged physicians from prescribing carvedilol. The use of short-acting selective β-2-adrenoreceptor agonist inhalants, which are typically used to treat acute bronchoconstriction, was negatively associated with receiving a prescription for carvedilol. We believe that carvedilol's lack of pharmacological selectivity for β-1 receptors, which is well known to induce bronchoconstriction and worsening lung function,[8–11] could have discouraged physicians from prescribing these drugs for patients with ongoing recurrent acute bronchoconstriction events.

Finally, despite the known clinical benefit of β-blockers for the study population, only 60% of patients received a β-blocker for HF. Solid evidence suggests that β-blockers are typically well tolerated in COPD patients and may reduce both cardiovascular and COPD mortality and its exacerbations. In this regard, calls for action are necessary to increase Danish physicians' awareness of the risk associated with not prescribing β-blockers for eligible patients.[28,29]

Limitations

The main limitation of this study is its observational, non-randomized design, which does not allow the exclusion of the possible effect of unmeasured confounders. Furthermore, in many patients, it can be difficult to distinguish between worsening of HF and exacerbation of COPD.

Conclusion

This study found that carvedilol users had an increased risk of being hospitalized for HF compared with patients who used metoprolol, bisoprolol, or nebivolol and that there were no statistically significant differences in the risk of hospitalization for all causes and COPD. Additionally, we found a widespread phenomenon of carvedilol prescriptions that are at odds with ESC guidelines and a considerable proportion of patients who could benefit from β-blockers but were not prescribed them. A call to action is needed to emphasize the importance of adhering to clinical guidelines given the severe clinical implications of neglecting them.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Cumulative incidence curves for all causes, chronic obstructive pulmonary disease and heart failure hospitalization within 450 days from those patients that discontinued the pharmacological treatment with carvedilol.

Figure S2. Cumulative incidence curves for all causes, chronic obstructive pulmonary disease and heart failure hospitalization within 450 days from those patients that discontinued the pharmacological treatment with metoprolol/nebivolol/bisoprolol.

Table S1. Operative definition of non-cardio-selective and cardio-selective β-blockers.

Table S2. Concurrent pharmacological treatment considered as study covariates in statistical analyses.

Table S3. Diagnoses, surgical procedures, and medicines used for co-morbidities.

Conflict of interest: none declared.

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