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Beta-blockers reduce severe exacerbation in patients with mild chronic obstructive pulmonary disease with atrial fibrillation: a population-based cohort study

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ABSTRACT

Background and objective Beta-blockers (BBs) decrease mortality and acute exacerbation (AE) rates in patients with chronic obstructive pulmonary disease (COPD) and cardiovascular disease; however, information on their effects in patients with COPD and atrial fibrillation (AF) is limited. We aimed to assess the AE risk in patients with different severities of COPD and AF receiving BBs compared with that in patients receiving calcium channel blockers (CCBs).

Methods This retrospective cohort study used data from the Taiwan National Health Insurance Database from 2009 to 2018. Outcomes included AE-related emergency room visits and hospitalisation. HRs and 95% CIs were estimated using the Cox proportional hazards model. COPD severity was classified as mild or severe based on exacerbation history. Sensitivity analyses included treatment and subgroup analyses, and competing risk adjustment.

Results After propensity score matching, 4486 pairs of BB and CCB users from 13 462 eligible patients were included. The exacerbation risk for BB users was lower (HR 0.80; 95% CI 0.72 to 0.89) than that of CCB users. After stratification, BB benefits persisted in the mild COPD group (HR 0.75; 95% CI 0.66 to 0.85), unlike the severe COPD group (HR 0.95; 95% CI 0.75 to 1.20). The results of the subgroup analysis showed consistent protective effects even in patients without heart failure or myocardial infarction (adjusted HR 0.82; 95% CI 0.71 to 0.94).

Conclusion We found that BB use in patients with mild COPD and AF was associated with a lower exacerbation risk than CCB use, and that close monitoring of BB use in patients with severe COPD and AF is warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Beta-blockers (BBs) present benefits for patients with chronic obstructive pulmonary disease (COPD) with cardiovascular disease or congestive heart failure, in terms of exacerbation reduction.

WHAT THIS STUDY ADDS

⇒ BBs are more effective in reducing exacerbation compared with the other standard treatment, calcium channel blocker, in patients with mild COPD with atrial fibrillation (AF). Close monitoring of acute exacerbation is needed when using BBs in patients with severe COPD, especially among those with COPD and AF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The stigma of BBs causing bronchoconstriction is no longer observed in patients with mild COPD with AF when they are treated with BBs. The importance of treating comorbidities in patients with COPD for better outcomes cannot be overemphasised.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, accounting for approximately 6% of all deaths in 2019.[1] Acute exacerbation (AE) of COPD occurs more frequently with the increasing severity of COPD and associated comorbidity of cardiovascular disease (CVD).[2–4] Patients with COPD and comorbid atrial fibrillation (AF) have a worse clinical prognosis and greater disease burden.[5 6] Therefore, treatment that focuses on COPD and AF remains the core strategy for these cases. Beta-blockers (BBs) and non-dihydropyridine calcium channel blockers (non-DHP CCBs) are the drugs of choice for rate control in patients with AF. However, findings regarding BB use in COPD and AF are inconclusive in the current literature. According to the European Society for Cardiology 2020 guidelines for AF, BBs are not recommended for patients with severe COPD or asthma.[7] Conversely, according to the American Heart Association 2014 guidelines and Taiwan 2016 guidelines for the management of AF, BBs are listed as drugs for patients with COPD because of their improved survival

benefits.[8 9] An observational cohort study also indicated that BB use is associated with a lower risk of all-cause mortality compared with non-DHP CCB use in patients with comorbid COPD and AF.[10]

A randomised controlled trial revealed that BBs increased the incidence of AE in patients with COPD without CVD.[11] Meanwhile, BB use has the opposite effect on the incidence of AE in patients with COPD and comorbid CVD. Recently, a meta-analysis concluded that BBs are beneficial in reducing AE among patients with COPD and CVD, most of whom had heart failure (HF) and myocardial infarction (MI).[12] Notably, no studies have focused on AE results between BB users and non-users among patients with COPD and AF. Another limitation of this meta-analysis is that the severity of COPD varied among the studies, which may have affected the consistency of the results.

Moreover, a population-based cohort study demonstrated the benefits of BB use in patients with COPD and AF. Especially, the Rotterdam study aimed to examine the association between the use of BBs and the risk of AE in COPD among patients with and without a cardiovascular indication (including AF) for BB use.[13] In patients with a cardiovascular indication for BBs, current use of cardioselective BBs reduced the risk of COPD exacerbation by 31%.[14] AF is a common comorbidity in patients with COPD and is associated with more respiratory events.[14] However, the effect of BB use in this population remains unknown. Hence, this study aimed to examine the association between BB use and the risk of AE in patients with comorbid COPD and AF. We also investigated the effects of COPD severity and comorbidities.

METHODS

Study design and data sources

We conducted a retrospective cohort study using an active comparator and new user design. Data were obtained from the Taiwan National Health Insurance Database (NHID). The NHID, established in 1995, is a single-payer system in Taiwan that has contracted 92.4% of the medical institutions nationwide and is regulated by the Bureau of National Health Insurance.[15] The database contains basic patient characteristics, International Classification of Diseases (ICD) codes of diagnoses, Anatomical Therapeutic Chemical (ATC) codes of drug prescription, and a registry of hospitalisation and emergency room (ER) visits. All claims data from the different datasheets were anonymously linked with personal identification numbers.[15]

Study population

Between 2009 and 2018, patients with COPD and new-onset AF were recruited from the NHID. The cases of COPD and AF were identified using ICD codes confirmed in previous validation studies.[16 17] Patients with COPD were marked with ICD9-CM (491, 492, 496) or ICD10-CM (J41, J42, J43, J44),[18] while those with AF were marked with ICD9-CM (427.31) or ICD10-CM (I48.0, I48.1, I48.2 and I48.91). The need for at least one hospital admission or two or more outpatient visits within 90 days was also considered when selecting the patients. All participants were aged between 40 and 100 years on the first day of COPD diagnosis. Patients diagnosed with asthma or AF before being diagnosed with COPD were excluded.

The index drugs, including BBs and non-DHP CCBs, were identified using ATC codes (online supplemental table 1). The index date was the first date of prescription of the index drug after AF diagnosis. To establish a new incident user design, patients exposed to index drugs within 1 year before the index date were excluded. Additionally, those who did not use the index drugs or used both BBs and non-DHP CCBs on the index date were excluded. Propensity score matching was applied to the enrolled patients, and the matching variables were baseline variables excluding COPD severity.

Covariates

The baseline characteristics included age, sex and cohort entry date. Data on the frequency of COPD AE, COPD severity, comorbidities and co-medications were collected during the baseline period (1 year before the index date). The frequency of past AE was defined as the number of ER visits or hospital admissions within 1 year before the index date. COPD severity was classified as follows: (1) mild, patients did not experience AE or went to the ER once during the baseline period; and (2) severe, patients experienced AE at least once during hospitalisation or at least twice during ER visits during the baseline period.[19]

Comorbidities were identified using ICD codes during the baseline period (online supplemental table 2). The only exception was coronary revascularisation, which was identified using procedural codes. We collected medication data for COPD within 6 months before the index date and medication data for CVD within 1 year before the index date (online supplemental table 3).

Outcomes

The primary outcome was AE diagnosis in patients who had experienced ER visits or hospitalisation due to COPD. An episode was identified using ICD codes (ICD9-CM:491, 492 and 496; ICD10-CM: J41, J42, J43 and J44), which were validated in the NHID.[20] The follow-up period was 1 year after the index date. Eligible patients were followed up until the outcome occurred, the patient died or the study ended (31 December 2018).

Statistical analyses

Continuous variables are presented as means and SDs, whereas categorical variables are presented as absolute values with relative frequencies (%). The standardised mean difference (SMD) was used to measure differences in the baseline characteristics between the matched groups. We used propensity score matching with the Cox

proportional hazards model to estimate the HRs and 95% CIs. Time-to-event analysis was performed using the Kaplan-Meier curve and log-rank test. The observation period was 1 year after the index date. Subgroup analyses were performed using multivariate regression analysis. Adjusted HRs (aHRs) and 95% CIs were estimated using a Cox proportional hazards model. The adjusted variables included age, sex, index year, past AE frequency, comorbidities, inhaled therapy, xanthine use, systemic steroid use and co-medication. The results of the subgroup analyses are presented as forest plots, and the level of significance was set at $p<0.05$.

Sensitivity analyses

Four sensitivity analyses were performed to examine the robustness of the results. First, to determine the effects of drug compliance, we performed an as-treated sensitivity analysis. We set a 90-day grace period for the treatment analysis. Patients were censored in the sensitivity analysis when they discontinued, switched or received augmented index drugs for >90 days. Second, because of the high mortality rate associated with COPD exacerbation, adjustments for competing risks of death are needed. Thus, sensitivity analyses included analyses using a subdistribution hazard (SDH) model. Third, as the existing literature mostly focuses on patients with COPD and coexisting HF and MI, we stratified the patients into five subgroups: HF, no HF, MI, no MI, and neither HF nor MI. Subgroup analysis was conducted to examine the effects of BBs in patients with different subgroups of comorbidities. Finally, for unmeasured confounders, we used E-values to assess the potential effects of smoking. The E-value was used to quantify the effects of unmeasured confounding factors on the results. Using the statistics, we also identified the minimum number of confounding factors required to be present to invalidate the observed association.

Patient and public involvement

There is no patient and public involvement in this study.

RESULTS

Baseline characteristics

The baseline cohort consisted of 13 462 eligible patients with COPD and incident AF. After 1:1 propensity score matching, 4486 matched pairs were identified between the BB and non-DHP CCB groups. The baseline characteristics of the study cohort were described according to the two groups (tables 1–4). The study population consisted of 70% male patients with an average age of approximately 80 years. The frequency of past AE was 0.3 times per year, whereas 81.2% of patients did not experience AE of COPD during the baseline period. An SMD <0.1 indicated that all baseline covariates, including comorbidities and co-medication, were balanced. The patients were classified into the mild and severe COPD groups according to their history of exacerbation. Approximately 88.1% of the BB users and 86.7% of the non-DHP CCB users had mild COPD. In the propensity score-matched cohort, there were 2347 selective BB users and 2139 non-selective BB users. The proportion of selective BB users was 52.3% among the BB group.

Risk of acute exacerbation

The time-to-event curve of AE was plotted using the Kaplan-Meier method (figure 1). There was a visible difference between the two lines, indicating that BB

Table 1 Baseline characteristics of patients with COPD with AF in the BB and non-DHP CCB groups, before and after PS matching

	Before PS matching (N=13 462)			After PS matching (N=8972)		
	BB (7590)	Non-DHP CCB (5872)	SMD	BB (4486)	non-DHP CCB (4486)	SMD
Male, n (%)	5160 (68)	4224 (71.9)	−0.1	3123 (69.6)	3138 (70)	−0.01
Age, mean±SD	78.3±10.6	80.7±9.9	−0.2	79.7±10.2	79.8±10.2	−0.01
40–75 years, n (%)	2426 (32.0)	1350 (23.0)		1155 (25.7)	1200 (26.7)	
≧75 years, n (%)	5164 (68.0)	4522 (77.0)		3331 (74.3)	3286 (73.3)	
Frequency of past AE, n (%)	0.2±0.7	0.4±1.1	−0.3	0.3±0.9	0.3±0.8	0.01
0	6596 (86.9)	4432 (75.5)		3647 (81.2)	3647 (81.2)	
1	673 (8.9)	864 (14.7)		548 (12.2)	544 (12.1)	
2	191 (2.5)	311 (5.3)		176 (3.9)	170 (3.8)	
≧3	130 (1.7)	265 (4.5)		122 (2.7)	132 (2.9)	
COPD severity by AE history, n (%)						
Mild	6970 (91.8)	4833 (82.3)		3952 (88.1)	3890 (86.7)	
Severe	620 (8.2)	1039 (17.7)		534 (11.9)	596 (13.3)	

AE, acute exacerbation; AF, atrial fibrillation; BB, beta-blocker; non-DHP CCB, non-dihydropyridine calcium channel blocker; COPD, chronic obstructive pulmonary disease; PS, propensity score; SMD, standardised mean difference.

Table 2 Baseline characteristics of study cohort—comorbidities

	Before PS matching (N=13 462)			After PS matching (N=8972)		
	BB (7590)	non-DHP CCB (5872)	SMD	BB (4486)	non-DHP CCB (4486)	SMD
Comorbidity, n (%)						
Hypertension	5366	3739	0.15	2997	2986	0.01
Heart failure	2913	2130	0.04	1709	1708	0
Myocardial infarction	480	254	0.09	238	225	0.01
Coronary revascularisation	333	139	0.11	142	135	0.01
Ischaemic heart disease	2617	1654	0.14	1421	1376	0.02
Cardiac dysrhythmia	1960	1253	0.11	1065	1040	0.01
Cerebrovascular disease	2036	1781	–0.1	1327	1306	0.01
Hyperthyroidism	140	67	0.06	63	60	0.01
Hypothyroidism	132	92	0.01	76	76	0
Diabetes mellitus	2162	1494	0.07	1190	1183	0
Dyslipidaemia	1697	938	0.16	835	832	0
Chronic kidney disease	1123	630	0.12	537	539	0
Pulmonary hypertension	92	132	–0.1	80	70	0.02
Cancer	882	832	–0.1	584	587	0

BB, beta-blocker; non-DHB CCB, non-dihydropyridine calcium channel blocker; PS, propensity score; SMD, standardised mean difference.

users experienced less AE during the 1-year observation period. The log-rank test revealed a significant difference (p=0.0005) between the BB and non-DHP CCB groups. The BB users had a lower risk of AE than non-DHP CCB users, with an HR of 0.80 (95% CI 0.72 to 0.89). In the mild COPD group, the HR of BBs was 0.75 (95% CI 0.66 to 0.85), whereas in the severe COPD group, the HR of BBs was 0.95 (95% CI 0.75 to 1.20) (table 5). The risk of AE was not associated with BBs in patients who experienced frequent exacerbation during the baseline period.

Sensitivity analysis

The results of the as-treated and SDH model analyses were consistent with the findings of the main analysis. The HRs of AE after propensity score matching were 0.66 (95% CI 0.56 to 0.78), 0.64 (95% CI 0.52 to 0.78) and 0.83 (0.62 to 1.10) in the whole cohort, mild group and severe group, respectively (table 5). After adjusting the competing risk, the HR of AE in BB users was 0.84 (95% CI 0.76 to 0.94) compared with that of the non-DHP CCB group (online supplemental table 4). BB users had a significantly lower

Table 3 Baseline characteristics of study cohort—COPD medication within 6 months

	Before PS matching (n=13 462)			After PS matching (n=8972)		
	BB (7590)	non-DHP CCB (5872)	SMD	BB (4486)	non-DHP CCB (4493)	SMD
COPD medication within 6 months, n (%)						
Long-acting inhalation	972 (12.8)	1310 (22.3)	–0.3	789 (17.6)	796 (17.7)	0
LABA+LAMA+ICS	824 (10.9)	1186 (20.9)	–0.3	691 (15.4)	694 (15.5)	0
LABA+LAMA	126 (1.7)	118 (2)	–0	88 (2)	91 (2)	0
LABA+ICS	394 (4.2)	570 (9.7)	–0.2	492 (11)	493 (11)	0
LABA	86 (1.1)	103 (1.8)	–0.1	74 (1.6)	69 (1.5)	0
LAMA	252 (3.3)	308 (5.2)	–0.2	360 (8)	359 (8)	0
Short-acting inhalation	2161 (28.5)	3063 (52.2)	–0.5	1861 (41.4)	1848 (41.1)	0.01
Xanthine	3038 (40)	3384 (57.6)	–0.36	2279 (50.7)	2269 (50.5)	0
Systemic steroid	3203 (42.2)	3618 (61.6)	–0.4	2410 (53.6)	2391 (53.2)	0.01

BB, beta-blocker; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; non-DHP CCB, non-dihydropyridine calcium channel blocker; PS, propensity score; SMD, standardised mean difference.

Table 4 Baseline characteristics of study cohort—cardiovascular medication

	Before PS matching (n=13 462)			After PS matching (n=8972)		
	BB (7590)	non-DHP CCB (5872)	SMD	BB (4486)	non-DHP CCB (4486)	SMD
Cardiovascular medication, n (%)						
Antiplatelet	2584	1276 (21.7)	0.28	1190 (26.5)	1168 (26)	0.01
Anticoagulant	4951	3477 (59.2)	0.12	2871 (63.9)	2851 (63.5)	0.01
Class 1 antiarrhythmic drugs	980	649 (11.1)	0.06	547 (12.2)	515 (11.5)	0.02
Amiodarone	2508	2411 (41.1)	−0.17	1662 (37)	1656 (36.9)	0
Class III, except amiodarone	167	79 (1.3)	0.06	84 (1.9)	75 (1.7)	0.02
Digoxin	2011	1913 (32.6)	−0.13	1351 (30.1)	1358 (30.2)	0
ACEI/ARB	4683	2849 (48.5)	0.27	2430 (54.1)	2442 (54.4)	−0.01
Statin	1779	913 (15.5)	0.2	823 (18.3)	830 (18.5)	0
DM medication, n (%)	2152	1719 (29.3)	−0.02	1294 (28.8)	1293 (28.8)	0

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; DM, diabetes mellitus; non-DHP CCB, non-dihydropyridine calcium channel blocker; PS, propensity score; SMD, standardised mean difference.

risk of AE in the mild COPD group, whereas there was no significant difference between BB and non-DHP users in the severe COPD group. This indicated that BBs lower the risk of AE, particularly in patients with mild COPD. The forest plot provides summary statistics of the aHR for the different subgroups (figure 2). The aHRs of those who had HF and who did not were 0.77 (95% CI 0.66 to 0.89) and 0.81 (95% CI 0.71 to 0.92), respectively. Similarly, the aHRs of those who had MI and those who did not have MI were 0.47 (95% CI 0.29 to 0.75) and 0.80

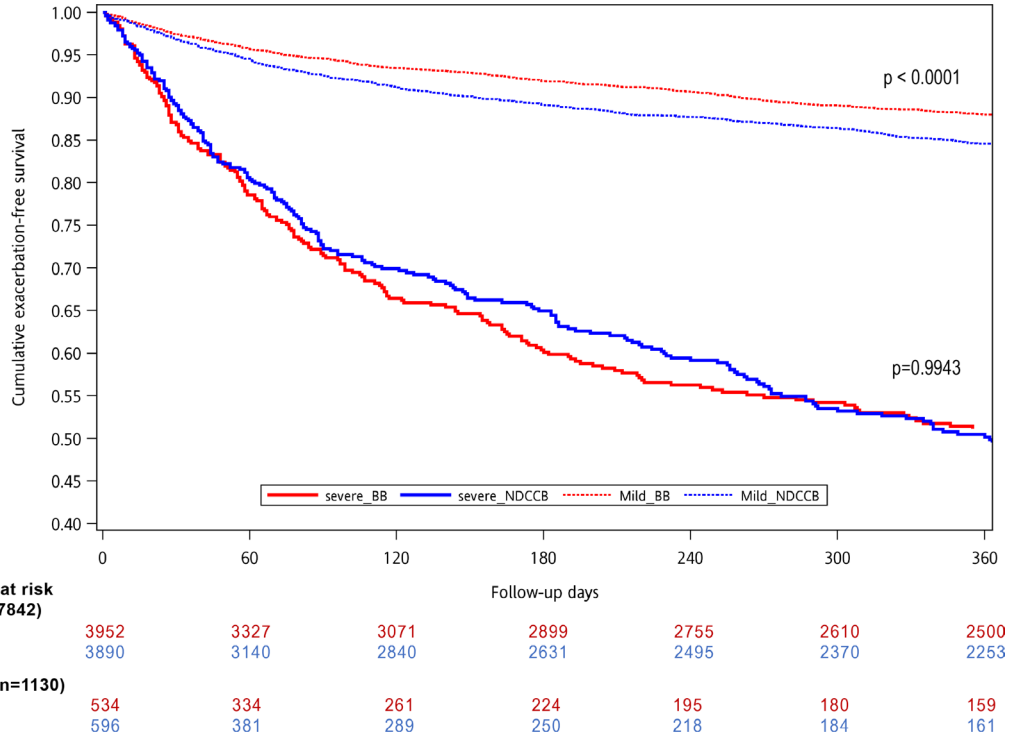

Figure 1 Kaplan-Meier curves of acute exacerbation. The Kaplan-Meier curves display the exacerbation-free survival of the four different groups of patients. Beta-blocker (BB) and non-dihydropyridine calcium channel blocker (NDCCB) users were classified into the mild and severe chronic obstructive pulmonary disease (COPD) groups based on their exacerbation histories. Visual inspection suggested that exacerbation-free survival was more favourable for patients who received BBs than for those who received NDCCBs in the mild COPD group. The log-rank test indicated a significant difference in the survival curves of the mild COPD group, whereas no significant difference was observed in the survival curves of the severe COPD group.

Table 5 HRs of acute exacerbation among patients with COPD with AF under BB use compared with non-DHP CCB use, using intention-to-treat and as-treated analyses

	Number		Intention-to-treat		As-treated	
	Crude	After PS matching	Crude HR (95% CI)	HR after matching (95% CI)	Crude HR (95% CI)	HR after matching (95% CI)
All included patients						
Non-DHP CCB, n	7590	4486	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BB, n	5872	4486	0.44 (0.40 to 0.48)	0.80 (0.72 to 0.89)	0.31 (0.27 to 0.36)	0.66 (0.56 to 0.78)
Mild COPD						
Non-DHP CCB, n	4833	3897	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BB, n	6970	3954	0.44 (0.40 to 0.50)	0.75 (0.66 to 0.85)	0.33 (0.28 to 0.39)	0.64 (0.52 to 0.78)
Severe COPD						
Non-DHP CCB, n	1039	596	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BB, n	620	539	0.82 (0.70 to 0.96)	0.95 (0.75 to 1.20)	0.63 (0.49 to 0.80)	0.83 (0.62 to 1.10)

AF, atrial fibrillation; BB, beta-blocker; non-DHP CCB, non-dihydropyridine calcium channel blocker; COPD, chronic obstructive pulmonary disease; PS, propensity score.

(95% CI 0.73 to 0.89), respectively. Finally, we examined the aHR in patients without HF or MI. Among the 8089 participants, BB users had a lower risk of AE than non-DHP CCB users (aHR 0.82; 95% CI 0.71 to 0.94). The results revealed the robust benefit of BBs in reducing AE in patients with COPD, AF and other comorbidities. In this study, the E-value was 1.61 (online supplemental file 5). As the risk ratio between BBs and smoking was 1.01 in the literature, the unmeasured smoking factor did not affect our results.[21]

DISCUSSION

In the present study, patients with COPD and AF had a lower risk of AE when receiving BBs than when receiving non-DHP CCBs (HR 0.80; 95% CI 0.72 to 0.89). In the mild COPD group, BB users showed a significantly decreased risk of exacerbation compared with CCB users (HR 0.75; 95% CI 0.66 to 0.85). In the severe COPD group, BBs were not associated with decreased AE (HR 0.95; 95% CI 0.75 to 1.20). BB use in patients with COPD

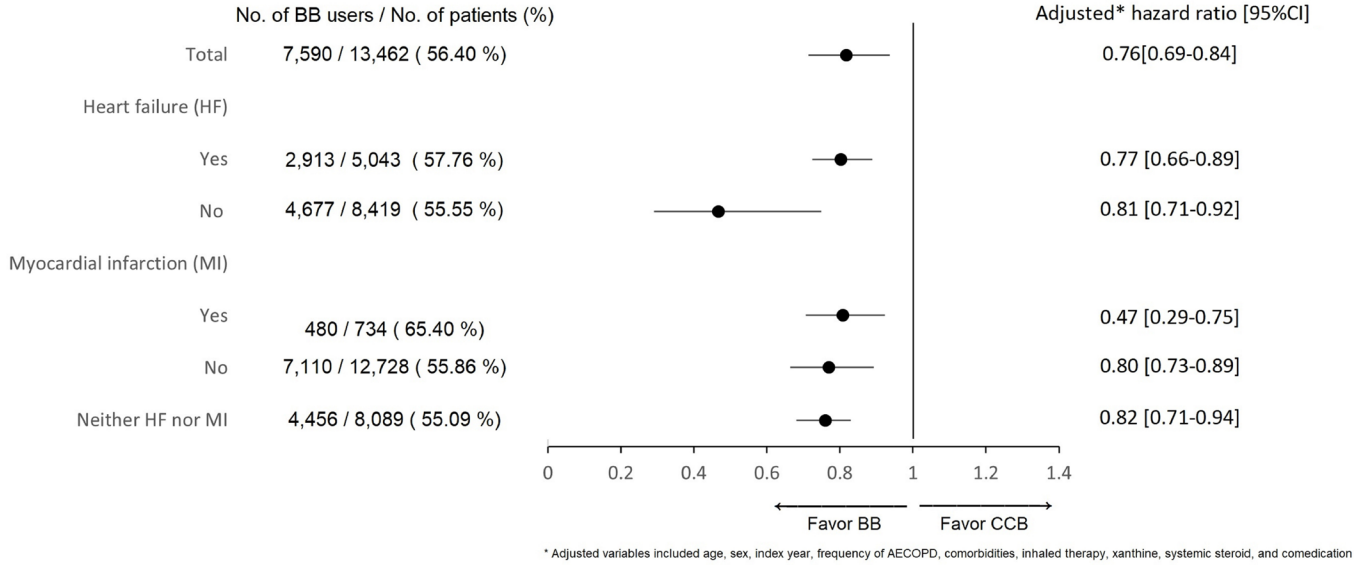

Figure 2 HRs of acute exacerbation in subgroups with different comorbidities. This forest plot illustrates the effects of heart failure and myocardial infarction on exacerbation in patients with chronic obstructive pulmonary disease and atrial fibrillation. The values are point estimates and 95% CIs of HRs of beta-blocker (BB) users compared with non-dihydropyridine calcium channel blocker (CCB) users. This figure indicates that BBs have a protective effect regardless of whether the selected patients have comorbidities of interest. *Adjusted variable included age, sex, index year, frequency of acute exacerbation of chronic obstructive pulmonary disease, comorbidities, inhaled therapy, xanthine, systemic steroid and co-medication.

and AF was associated with a lower risk of AE, particularly in those with less prior exacerbation. These results were consistent with the findings of the sensitivity analysis, indicating no increased risk of AE with BB use in patients with severe COPD. Furthermore, this association was consistent regardless of the presence of HF or MI in patients with COPD and AF. These results corresponded to the meta-analysis of patients with COPD and CVD that compared BB and non-BB users (HR 0.75; 95% CI 0.66 to 0.85).[12] Additionally, these results confirm previous literature findings, implying that exacerbation history is a reliable factor in predicting the next episode of AE.

We inferred that BBs reduced the incidence of AE by stabilising the comorbid CVD. According to the literature, BBs can reduce the exacerbation of COPD in two ways: by reducing inflammation and lung mucus secretion, and by reducing airway hyper-responsiveness.[12] Garlichs *et al* suggested that the BBs propranolol, metoprolol and celiprolol reduce the basal and stimulated release of endothelin-1, a bronchoconstrictive peptide that plays a role in the exacerbation of COPD.[22 23] According to the literature, the long-term use of BBs, resulting in a cardioprotective effect and reduction of inflammatory substances, may lessen the events of COPD AE, which are triggered by CVDs. BBs may also alleviate AE by reducing airway hyper-responsiveness. Airway hyper-responsiveness is defined as an exaggerated response of the airway after exposure to irritants, which manifests as airway narrowing. The Lung Health Study indicated that more than two-thirds of patients with mild or early COPD have airway hyper-responsiveness.[24] This is considered a characteristic of asthma; however, many patients with COPD also show positive findings of airway hyper-responsiveness in lung function tests.[25] An open-label pilot study recruited 10 patients with mild asthma who were treated with nadolol, a non-selective BB, over 9 weeks. These findings suggest that the chronic administration of BBs is well tolerated and ameliorates airway hyper-responsiveness.[26] Finally, long-term use of inhaled beta-agonists, a cornerstone therapy for COPD, leads to the downregulation of beta-adrenoreceptors.[27 28] With the administration of BBs, the downregulation of beta-adrenoreceptors can be reversed, which in turn enhances the therapeutic effects of inhaled beta-agonists.[29] In summary, the mechanism by which BBs attenuate AE is based on a decrease in inflammation, a reduction in airway hyper-responsiveness and the reversal of beta-adrenoreceptor downregulation.

According to previous studies, when BBs are required in patients with COPD and definite CVD, the pulmonary outcomes are favourable in most patients with COPD. In this nationwide study, we focused on patients with COPD and comorbid AF because BBs and CCBs are indicated for AF treatment according to major guidelines. Whether BB use is a better strategy than CCB use for reducing exacerbation in patients with COPD and AF has not been addressed previously. According to a previous randomised controlled trial, the use of BB in patients with COPD increases the risk of exacerbation when not comorbid with CVD.[11] This trial evidence is somewhat controversial with respect to our study findings, which can be explained by the difference in treatable COPD traits between the trial cohort and our study cohort. Not all trial participants were eligible for BB treatment, whereas all patients with COPD in our study had comorbid AF. Whether BBs are beneficial for AE reduction in patients with unindicated COPD remains to be clarified in future studies. The therapeutic effectiveness of exacerbation prevention and safety issues in real-world practice were further examined in our study. According to the study findings, patients with COPD and AF treated with BBs experienced significantly less exacerbation than those treated with CCB. The benefit of BBs in reducing exacerbation was consistent in patients with mild COPD and AF, defined as less than two exacerbation events in the previous year, but not in those with severe COPD and AF. For those who had a higher risk of AE, a previous study showed that they had more comorbidities than those with a low risk of AE.[30] The complexity of comorbidities may partially explain why BBs are not as effective in preventing AE compared with CCB for individuals with severe COPD. This is because other comorbidities that cannot be treated with BB, even if they are the intended target, can influence the triggering of the AE in COPD. Furthermore, a lower forced expiratory volume in 1 s (FEV_1) is more prevalent in the high-risk exacerbation group, as indicated by a previous study. This issue should be addressed through standard COPD care rather than the use of BB.[18] A multidisciplinary care model should be introduced to patients with COPD with complex comorbidities in the long run.[31] Our findings also provided an insight that early control of comorbidities in mild COPD is significant and effective in exacerbation prevention, which corresponded to the importance of treating comorbidities in patients with COPD recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[32]

The use of BBs in patients with COPD and AF is associated with a significant reduction in severe exacerbation compared with the use of CCBs, especially for those with mild disease severity, which accounts for more than 70% of the population with COPD. For patients with severe COPD, defined in our study as frequent exacerbation within the previous year, the higher disease burden on the airway was not relieved by BB use. It is important to introduce the population with severe COPD into the multidisciplinary care model in a timely manner because of the complex comorbidities and enhanced inhaled therapy, such as the introduction of inhaled corticosteroids for patients with eosinophilic inflammation or the prompt use of dual bronchodilator therapy. The aforementioned approach remains the core policy recommended by the GOLD guidelines for reducing AE related to increased disease activity caused by intrapulmonary insults.

The major strength of this retrospective study was that we retrieved data from the NHID, a national database

comprising more than 99% of the Taiwanese population. Because the effects of BBs are not the same in asthma and COPD, the results may differ. Only patients with COPD were included; those with associated asthma were excluded. The active comparator and new-user design prevented health initiator bias and confounding by indication. We also applied propensity score matching to increase compatibility between the two groups. To our knowledge, our study is the first to focus on AE results in patients with COPD and AF. In this study, we used the exacerbation history during the baseline period (1 year before the index date) to classify the severity of COPD. The results showed that the effect of BBs on decreasing AE was confined to the mild COPD group; this finding has not been reported in the literature.

This study had several limitations. First, the NHID did not record all risk factors for AE, including smoking status, body mass index, FEV_1 or compliance with COPD treatment and co-medications. To reduce the impact of unmeasured confounding factors, we used a comparative design comparing CCBs with BBs, as their therapeutic roles in rate control in patients with AF are similar. Because of the lack of spirometry data in the NHID, we examined the proportion of spirometry tests between the two comparisons. The proportions of spirometry tests in our matched cohort were 40.9% and 40.3% in the BB and CCB groups, respectively (online supplemental table 5). The data indicated that COPD diagnosis was not limited to the results of spirometry, but was a composite clinical judgement based on patient characteristics, including age and smoking history. Additionally, we calculated the E-values, which showed that the smoking status did not affect the main results. Second, compliance and adherence of the selected cohort were unknown; therefore, we applied both as-treated and intention-to-treat analyses. We also focused on new incident cases to reduce confounding factors according to indication. Third, these findings cannot be generalised to all patients with AF, as the study focused only on rate-controlling agents and included patients treated with BBs or CCBs as first-line therapy. Patients who received rhythm control agents or required second-line treatment were excluded from the study. However, we included co-medication with amiodarone or digoxin as covariates in propensity score matching. Finally, the study results may have been affected by polymorphisms in beta-2 receptors. The literature has stated that patients who have an increased risk of COPD have a higher proportion of specific beta-2 receptors in their airway smooth muscle cells.[33] The polymorphisms may contribute to differential responses in different COPD subgroups; however, the homogeneity of our study population could not address this issue. However, we did not measure the differential effect of BB in patients with bronchodilator reversibility because of the lack of data. Although we attempted to minimise bias by using an active comparison study design and propensity score matching of baseline characteristics, the current study design could not retrieve relevant data. Further research should examine the effect of BB on beta-2 receptor downregulation and on bronchodilator reversibility in humans.

This study aimed to examine the effectiveness of BBs compared with non-DHP CCBs in preventing exacerbation in patients with COPD and AF. This study indicated that the use of BBs in populations with COPD and AF did not increase the risk of AE. The significant benefit of BB-reduced AE was confined to patients with mild COPD among those with COPD and AF. Close monitoring of AE is needed when using BBs in patients with severe COPD, including those with COPD and AF.

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Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Data may be obtained from a third party and are not publicly available. First, the Taiwan National Health Insurance Database was used as the data source for this study. These are second-hand data that can be used only by Taiwanese and can be assessed only on-site. The raw or processed data required to reproduce these findings cannot be shared, for legal reasons (website: https://dep.mohw.gov.tw/dos/lp-2506-113.html). Second, to obtain data for this study, please contact the Department of Statistics, Ministry of Health and Welfare, Taiwan (tel no: +886-2-8590-6811); contact person: Ms Chang (tel no: +886-2-8590-6818; email: styun@mohw.gov.tw).

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