

Original Article



Cardiovascular Medication Use and Risk of Acute Exacerbation in Patients With Asthma-COPD Overlap (CVACO Study)

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ABSTRACT

Purpose: Current clinical guidelines are unclear regarding the association of cardiovascular medication with the risk of acute exacerbation (AE) in patients with asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO).

Methods: We conducted a retrospective cohort study by interrogating the claims database of Taipei Veterans General Hospital. Patients with coexistent fixed airflow limitation and asthma were enrolled as an ACO cohort between 2009 and 2017. Exposure to cardiovascular medications, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), non-selective beta-blockers, cardioselective beta-blockers, dihydropyridine (DHP) calcium channel blockers (CCBs), and non-DHP CCBs, in 3-month period each served as time-dependent covariates. Patients receiving a cardiovascular medication ≥ 28 cumulative daily doses were defined as respective cardiovascular medication users. Patients were followed up until December 31, 2018. The primary endpoint was severe AE, defined as hospitalization or emergency department visit for either asthma, COPD, or respiratory failure. The secondary outcome was moderate AE.

Results: The final study cohort consisted of 582 ACO subjects, with a mean follow-up period of 2.98 years. After adjustment, ARB (hazard ratio [HR], 0.64, 95% confidence interval [CI], 0.44–0.93, $P = 0.019$), cardioselective beta-blocker (HR, 0.29, 95% CI, 0.11–0.72, $P = 0.008$) and DHP CCB (HR, 0.66, 95% CI, 0.45–0.97, $P = 0.035$) therapies were associated with lower risks of severe AE. ARB (HR, 0.42, 95% CI, 0.30–0.62, $P < 0.001$) and DHP CCB (HR, 0.55, 95% CI, 0.38–0.80, $P = 0.002$) therapies were associated with lower risks of moderate AE.

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Disclosure

There are no financial or other issues that might lead to conflict of interest.

Cardioselective beta-blockers, ARBs, and DHP CCBs were associated with lower risks of severe AE in frequent exacerbators. ACEI, non-selective beta-blocker, or non-DHP CCB use did not change the risk of severe AE.

Conclusions: ARB, cardioselective beta-blocker, and DHP CCB therapies may lower the risk of AE in patients with ACO.

Keywords: Asthma; chronic obstructive pulmonary disease; beta-adrenergic blockers; angiotensin converting enzyme inhibitors; angiotensin II receptor blockers; calcium channel blockers

INTRODUCTION

Cardiovascular diseases are among the most prevalent comorbidities of chronic obstructive pulmonary disease (COPD)^{1,2} and asthma.³ Cardiovascular medications are used not only to treat hypertension, arrhythmia, ischemic heart disease, and other cardiovascular diseases, but also to reduce the morbidity and mortality of heart failure and acute myocardial infarction. However, the prescription of cardiovascular medications to patients with coexisting cardiovascular and obstructive lung diseases raises a significant dilemma posed by the risks of pulmonary side effects.

Beta-blockade reduces the incidence of cardiovascular events in patients with COPD and is associated with lower in-hospital and all-cause mortality rates among patients with COPD and cardiovascular disease.⁴ Beta-blockade appears to decrease pulmonary function both in the general population and in patients with obstructive lung disease. However, a meta-analysis⁵ has demonstrated that cardioselective beta-blockers do not impair lung function in patients with COPD. Nonetheless, prescription rates of beta-blockers among COPD patients remain low due to concerns regarding the potential reduction of lung function.⁶ Treatment guidelines⁷ recommend the use of cardioselective beta-blockers in COPD patients with heart failure or myocardial infarction. According to the international asthma guideline,⁸ asthma is considered a relative contraindication to beta-blockade due to the risks of provoking asthma attacks and exacerbating airway reactivity. However, randomized controlled trials⁹ have suggested that cardioselective beta-blockers are safe in asthmatic patients.

Angiotensin converting enzyme inhibitors (ACEIs) are widely used to treat cardiovascular diseases such as hypertension, congestive heart failure, and myocardial infarction. However, ACEIs induce cough and bronchospasm as common respiratory side effects, especially in Asian populations.¹⁰ Because of these respiratory side effects, the utility of ACEI and angiotensin II receptor blocker (ARB) therapies is unclear during exacerbations of obstructive airway disease.

The role of ion channels in airway smooth muscle contraction suggests that they may represent an important therapeutic target. The calcium channel is one of the predominant ion channels in airway smooth muscles; consequently, the potential clinical benefit of calcium channel blockers (CCBs) on acute exacerbation (AE) of airway disease deserves further investigation.¹¹

Asthma-COPD overlap syndrome, also known as asthma-COPD overlap (ACO), is a clinical disorder with the features of both asthma and COPD. ACO is very common, with a prevalence of 2.0% in the general population.¹² In our previous work,¹³ 32.8% of the Asian COPD

patients were considered to have ACO because of previous diagnoses of asthma. Notably, patients with ACO are at increased risk of cardiovascular diseases¹⁴ including heart failure, underscoring the importance of the effects of cardiovascular medications in ACO. Our previous work¹⁵ has demonstrated the beneficial effect of cardiovascular medications in patients with coexisting COPD and heart failure in a real-world setting. The aim of this study was to investigate the effects of ACEI/ARB, beta-blocker, and CCB therapies on AE of ACO in a real-world setting.

MATERIALS AND METHODS

Data source

This retrospective observational cohort study was conducted at Taipei Veterans General Hospital, a 3,000-bed tertiary referral hospital in Taiwan. The claims database of Taipei Veterans General Hospital was interrogated. The accuracy of diagnoses recorded in the claims database of Taipei Veterans General Hospital, such as sleep apnea,¹⁶ pneumonia,¹⁶ asthma,¹³ COPD,^{13,15} heart failure,¹⁵ tuberculosis contact,¹⁷ and tuberculosis,¹⁸ has been validated in our previous work. The accuracy of the diagnosis of asthma in this claims database is excellent (92.0% sensitivity).¹³

Study population

Patient data were retrieved from 2009 through 2018 to evaluate the impact of ACEIs/ARBs, beta-blockers, and CCBs on AE in patients with ACO. According to COPD⁷ and asthma⁸ clinical guidelines, ACO defined as persistent airflow limitation with clinical features associated with asthma. In accordance with a global expert consensus¹⁹ and guidelines,²⁰ the identification of ACO requires the diagnosis of COPD plus a previous diagnosis of asthma. COPD patients were defined as subjects who met all the following criteria: 1) at least 6 diagnoses of COPD at outpatient chest clinics; 2) age \geq 40 years; 3) use of at least one respiratory medicine; and 4) fixed airflow limitation determined by pulmonary function testing. Patients with asthma were defined as those with at least 6 outpatient diagnoses of asthma and who had been prescribed at least one respiratory medicine in outpatient chest clinics during January 2009 to December 2017. Index dates were defined as the dates when the diagnoses of asthma and COPD first coexisted. Patients under 40 years of age on the index date, those without any prescriptions of respiratory medicines during study period, and those with incomplete data were excluded from the study. Respiratory medicines included short-acting bronchodilators (SABDs), inhaled corticosteroids (ICSs), long-acting β 2-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), ICS/LABA combinations, LABA/LAMA combinations and methylxanthines. Patients who took \geq 28 days of any respiratory medication within one year before the index date were assigned to respective respiratory medication groups. Respiratory medication groups were: SABDs including short-acting β ₂ agonists (albuterol, fenoterol, terbutaline, procaterol), and short-acting muscarinic antagonists (ipratropium); LABAs (olodaterol, indacaterol); LAMAs (tiotropium, umeclidinium, glycopyrronium); ICSs (budesonide, fluticasone, ciclesonide), ICS/LABA combinations (fluticasone/salmeterol, budesonide/formoterol, beclomethasone/formoterol, fluticasone/vilanterol), LABA/LAMA combinations (indacaterol/glycopyrronium, vilanterol/umeclidinium, oladaterol/tiotropium), and methylxanthines (aminophylline, theophylline). The study protocol was approved by the Institutional Review Board of Taipei City Hospital (TCHIRB-10809010-W). The Institutional Review Board approval was obtained and informed consent was waived for this retrospective study.

Potential confounders and severity classification

Age, sex, comorbidities, smoking status, nutrition status (body mass index [BMI]), lung function (forced expiratory volume in 1 second [FEV1]), Charlson comorbidity index, exacerbation frequency of COPD or asthma, and respiratory medication use before the index date were considered potential confounders. We identified the following comorbidities diagnosed before enrollment that might confound the results: hypertension, ischemic heart disease, heart failure, dysrhythmia, cerebrovascular disease, hyperlipidemia, diabetes mellitus, lung cancer, other malignancy, chronic kidney disease, chronic liver disease, gastroesophageal reflux disease, anxiety, osteoporosis, bronchiectasis, allergic rhinitis, and idiopathic pulmonary fibrosis. We calculated the Charlson comorbidity index based on coded data available in the claims database using the codes and methods described by Deyo *et al.*²¹

Based on clinical practice guidelines for COPD⁷ and asthma,⁸ a previous history of AE is an important prognostic factor associated with future exacerbations. Moderate AE of COPD and asthma was defined by the frequency of prescription of rescue oral corticosteroids at outpatient clinics within 1 year before enrollment. Severe AE of COPD and asthma was defined by the frequency of hospitalizations for COPD and asthma within 1 year before enrollment. Based on the number of AEs per year, patients were assigned to either the 0 AE/year, 1 AE/year, or ≥ 2 AE/year groups.

Baseline eosinophil counts were obtained. Baseline eosinophil counts were defined as the most recent blood eosinophil count before enrollment. Based on baseline eosinophil percentages, patients were assigned to either $< 2\%$ or $\geq 2\%$ groups.

Cardiovascular medication exposure

We analyzed the effects of cardiovascular medications, including ACEIs, ARBs, non-selective beta-blockers, cardioselective beta-blockers, dihydropyridine (DHP) CCBs and non-DHP CCBs, on AE. Exposure to cardiovascular medications was considered time-dependent covariates and analyzed every 90 days after enrollment. Patients who took ≥ 28 days of each cardiovascular medication during each 90-day follow-up period were assigned to respective cardiovascular medication groups. ACEIs were captopril, enalapril, lisinopril, perindopril, ramipril, cilazapril, fosinopril, and imidapril. ARBs were losartan, valsartan, irbesartan, telmisartan, olmesartan, and azilsartan. Cardioselective beta-blockers were bisoprolol, metoprolol, atenolol, and acebutolol. Non-selective beta-blockers were carvedilol, labetalol, propranolol, and sotalol. DHP CCBs were amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, lacidipine, lercanidipine, and benidipine. Non-DHP CCBs were verapamil and diltiazem.

Outcome assessment

The primary outcome was severe AE. Severe AE was defined as a hospitalization or emergency department visit for asthma attack, COPD exacerbation, or respiratory failure with recorded symptoms of wheezing or dyspnea. The secondary outcome was moderate AE. Moderate AE was defined as the prescription of rescue oral corticosteroids at outpatient clinics with recorded symptoms of wheezing or dyspnea. All patients were followed up from the index date to the earliest outcome occurrence, death, loss to follow-up, or the end of the study (2018/12/31).

Statistical analysis

Comparisons of the baseline characteristics of users and non-users of each cardiovascular medication were made by the χ^2 test for categorical variables, and Student's *t* test for continuous variables. Users were defined as receiving each cardiovascular medication for ≥ 28

days during each 90-days follow-up period and the others were defined as non-users. Effects of cardiovascular medication on AE were analyzed by a time-dependent Cox-proportional hazard model to calculate crude and adjusted hazard ratios (HRs). Other potential confounders, including sex, age, BMI, smoking status, FEV1 (% predicted), comorbidities, Charlson comorbidity index, number of moderate exacerbations, number of severe exacerbations, and number of specific bronchodilators used, were determined at baseline and were calculated as non-time-dependent covariates. Ninety-five percent confidence intervals (95% CIs) were calculated after adjustment for possible confounding factors. Two-tailed *P* values < 0.05 were considered significant. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Study population

A total of 7,603 COPD patients were diagnosed at chest clinics between January 1, 2009 and December 31, 2017. We excluded patients with incomplete data (*n* = 258), those aged < 40 years (*n* = 313), those without COPD medication (*n* = 368), those without post-bronchodilator pulmonary function testing (*n* = 4,553), those with post-bronchodilator FEV1/forced vital capacity ≥ 0.7 (*n* = 405), and those without a diagnosis of asthma (*n* = 1,124). The final study population consisted of 582 ACO patients. The follow-up periods for severe and moderate AEs were 1,732.20 and 1,351.43 person-years, respectively (**Fig. 1**). Two hundred twenty-eight and 286 ACO patients experienced severe and moderate AEs, respectively.

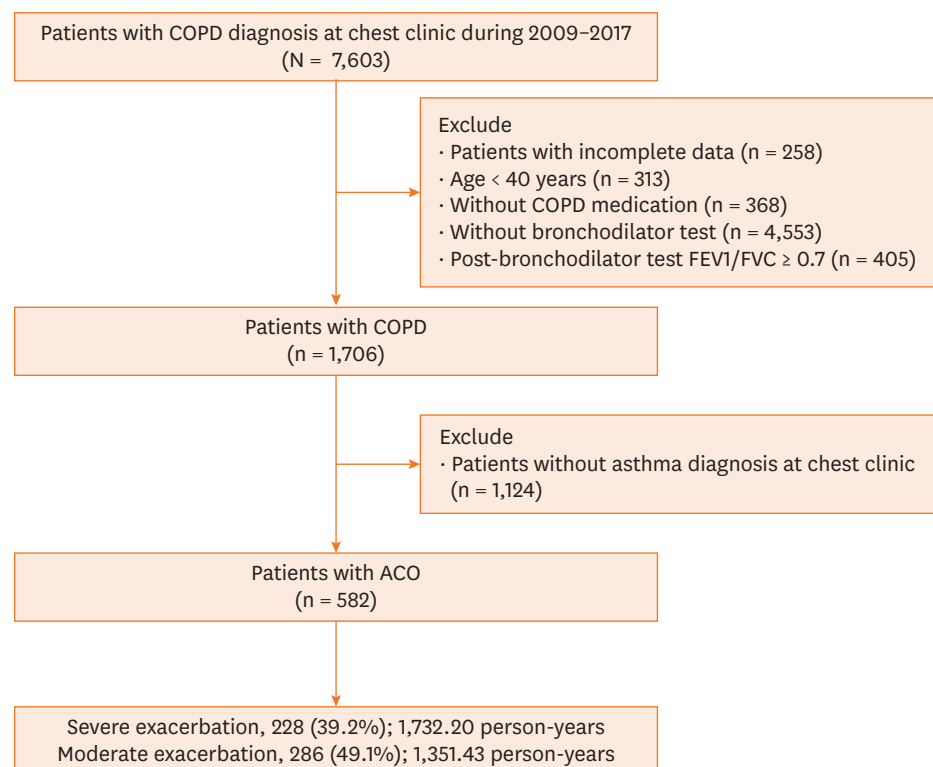


Fig. 1. Flow diagram summarizing the process of enrollment.

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACO, asthma-chronic obstructive pulmonary disease overlap.

Demographic characteristics

Table 1 shows the baseline characteristics of the study cohort. There were more males in beta-blocker users than in non-users (92.7% vs. 81.9%; $P = 0.026$). There were no differences in sex distribution between ACEI/ARB users and non-users or between CCB users and non-users. Mean age was older in beta-blocker users vs. non-users (mean age, 79.8 vs. 74.9 years; $P < 0.001$); ACEI/ARB users vs. non-users (mean age, 78.7 vs. 73.8 years; $P < 0.001$); and CCB users vs. non-users (mean age, 78.6 vs. 73.4 years; $P < 0.001$). Compared with non-users, CCB users had a higher prevalence of smoking ($P = 0.040$) and a higher mean BMI ($P = 0.004$). ACEI/ARB users had a higher mean BMI than non-users ($P = 0.014$). Beta-blocker, ACEI/ARB, and CCB users had higher prevalence rates of comorbidities and Charlson comorbidity indices than non-users.

Table 1. Baseline characteristics of the asthma-chronic obstructive pulmonary disease overlap cohort (N = 582)

Characteristics	Total (N = 582)	Beta-blocker (n = 68)	No beta-blocker (n = 514)	P value	ACEI/ARB (n = 197)	No ACEI/ARB (n = 385)	P value	CCB (n = 229)	No CCB (n = 353)	P value
Age (yr)	75.4 ± 11.1	79.8 ± 9.1	74.9 ± 11.2	< 0.001	78.7 ± 9.4	73.8 ± 11.6	< 0.001	78.6 ± 9.9	73.4 ± 11.4	< 0.001
Sex				0.026			0.611			0.899
Male	484 (83.2)	63 (92.7)	421 (81.9)		166 (84.3)	318 (82.6)		191 (83.4)	293 (83.0)	
Smoking				0.104			0.077			0.040
Never	219 (37.6)	25 (36.8)	194 (37.7)		77 (39.1)	142 (36.9)		89 (38.9)	130 (36.8)	
Ex-smokers	244 (41.9)	35 (51.5)	209 (40.7)		90 (45.7)	154 (40.0)		105 (45.9)	139 (39.4)	
Current	119 (20.5)	8 (11.8)	111 (21.6)		30 (15.2)	89 (23.1)		35 (15.3)	84 (23.8)	
BMI				0.082			0.014			0.004
< 25	395 (67.9)	40 (58.8)	355 (69.1)		119 (60.4)	276 (71.7)		138 (60.3)	257 (72.8)	
≥ 25 & < 30	150 (25.8)	25 (36.8)	125 (24.3)		65 (33.0)	85 (22.1)		76 (33.2)	74 (21.0)	
≥ 30	37 (6.4)	3 (4.4)	34 (6.6)		13 (6.6)	24 (6.2)		15 (6.6)	22 (6.2)	
Comorbidity										
Hypertension	238 (40.9)	51 (75.0)	187 (36.4)	< 0.001	153 (77.7)	85 (22.1)	< 0.001	168 (73.4)	70 (19.8)	< 0.001
Ischemic heart disease	140 (24.1)	32 (47.1)	108 (21.0)	< 0.001	79 (40.1)	61 (15.8)	< 0.001	90 (39.3)	60 (14.2)	< 0.001
Heart failure	49 (8.4)	10 (14.7)	39 (7.6)	0.047	28 (14.2)	21 (5.5)	< 0.001	26 (11.4)	23 (6.5)	0.040
Dysrhythmia	63 (10.8)	12 (17.7)	51 (9.9)	0.054	33 (16.8)	30 (7.8)	0.001	35 (15.3)	28 (7.9)	0.005
Cerebrovascular disease	62 (10.7)	11 (16.2)	51 (9.9)	0.116	31 (15.7)	31 (8.1)	0.005	36 (15.7)	26 (7.4)	0.001
Hyperlipidemia	100 (17.2)	25 (36.8)	75 (14.6)	< 0.001	59 (30.0)	41 (10.7)	< 0.001	57 (24.9)	43 (12.2)	< 0.001
Diabetes mellitus	77 (13.2)	19 (27.9)	58 (11.3)	< 0.001	48 (24.4)	29 (7.5)	< 0.001	46 (20.1)	31 (8.8)	< 0.001
Lung cancer	24 (4.1)	4 (5.9)	20 (3.9)	0.438	8 (4.1)	16 (4.2)	0.957	9 (3.9)	15 (4.3)	0.850
Other malignancy	54 (9.3)	8 (11.8)	46 (9.0)	0.452	20 (10.2)	34 (8.8)	0.603	22 (9.6)	32 (9.1)	0.826
Chronic kidney disease	14 (2.4)	7 (10.3)	7 (1.4)	< 0.001	11 (5.6)	3 (0.8)	< 0.001	8 (3.5)	6 (1.7)	0.168
Chronic liver disease	29 (5.0)	5 (7.4)	24 (4.7)	0.339	9 (4.6)	20 (5.2)	0.743	12 (5.2)	17 (4.8)	0.818
GERD	139 (23.9)	23 (33.8)	116 (22.6)	0.041	44 (22.3)	95 (24.7)	0.531	60 (26.2)	79 (22.4)	0.291
Anxiety	44 (7.6)	8 (11.8)	36 (7.0)	0.163	17 (8.6)	27 (7.0)	0.485	22 (9.6)	22 (6.2)	0.133
Osteoporosis	33 (5.7)	4 (5.9)	29 (5.6)	0.936	14 (7.1)	19 (4.9)	0.284	13 (5.7)	20 (5.7)	0.996
Bronchiectasis	194 (33.3)	28 (41.2)	166 (32.3)	0.144	68 (34.5)	126 (32.7)	0.665	77 (33.6)	117 (33.1)	0.905
Allergic rhinitis	250 (43.0)	33 (48.5)	217 (42.2)	0.323	88 (44.7)	162 (42.1)	0.550	104 (45.4)	146 (41.4)	0.334
Idiopathic pulmonary fibrosis	7 (1.2)	0 (0.0)	8 (1.4)	0.417	1 (0.5)	6 (1.6)	0.198	2 (0.9)	5 (1.4)	0.268
Charlson comorbidity index										
1	315 (54.1)	20 (29.4)	295 (57.4)	< 0.001	75 (38.1)	240 (62.3)	< 0.001	101 (44.1)	214 (60.6)	< 0.001
2	117 (20.1)	16 (23.5)	101 (19.7)		46 (23.4)	71 (18.4)		54 (23.6)	63 (17.9)	
≥ 3	150 (25.8)	32 (47.1)	118 (23.0)		76 (38.6)	74 (19.2)		74 (32.3)	76 (21.5)	
Cardiovascular medications*										
0	304 (52.2)	-	304 (59.1)		-	304 (79.0)		-	304 (86.1)	
1	119 (20.4)	5 (7.4)	114 (22.2)	0.004	40 (20.3)	79 (20.5)	0.951	74 (32.3)	45 (12.7)	< 0.001
2†	115 (19.8)	19 (27.9)	96 (18.7)	0.071	109 (55.3)	6 (1.6)	< 0.001	102 (44.5)	13 (3.7)	< 0.001
3	44 (7.6)	44 (64.7)	0		44 (22.3)	0		44 (19.2)	0	

Values are presented as number (%) or mean ± standard deviation.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BMI, body mass index; GERD, gastroesophageal reflux disease.

*Cardiovascular medications presented the number of cardiovascular medications including beta-blocker, ACEI/ARB and CCB.

†Beta-blocker + ACEI/ARB (n = 13), beta-blocker + CCB (n = 6), ACEI/ARB + CCB (n = 96).

Disease severity

Table 2 presents the disease severity of the study population. There were no significant differences in lung function between respective cardiovascular medication user and non-user groups. Three hundred thirty-four of the 582 study patients (57.4%) experienced no moderate AEs, 97 (16.7%) had one moderate exacerbation, and 151 (26.0%) had ≥ 2 moderate AEs within 1 year before enrollment. Four hundred sixty-three (79.6%), 82 (14.1%), and 37 (6.4%) patients experienced 0, 1, and ≥ 2 severe AEs within 1 year before enrollment, respectively. There were no differences in either moderate or severe AEs between users and non-users of respective cardiovascular medications. The use of almost all of the respiratory medications was similar between respective cardiovascular medication user and nonuser groups. Additionally, there were no differences in the number of specific bronchodilators used between respective cardiovascular medication users and non-users. Baseline blood eosinophil counts before enrollment were available in 385 ACO patients, among whom the mean baseline blood eosinophil count was 2.78%. Baseline blood eosinophil counts were similar between respective cardiovascular medication users and non-users.

Table 2. Basic disease severity of ACO cohort (N = 582)

Characteristics	Total (N = 582)	Beta-blocker (n = 68)	No Beta-blocker (n = 514)	P value	ACEI/ARB (n = 197)	No ACEI/ARB (n = 385)	P value	CCB (n = 229)	No CCB (n = 353)	P value
Lung function (% pred)										
FEV1/FVC	0.55 ± 0.11	0.56 ± 0.09	0.55 ± 0.11	0.316	0.55 ± 0.11	0.55 ± 0.11	0.458	0.56 ± 0.11	0.45 ± 0.11	0.118
FEV1	68.0 ± 21.6	69.5 ± 21.6	67.8 ± 21.7	0.549	67.4 ± 20.9	68.3 ± 22.0	0.654	69.5 ± 22.1	67.0 ± 21.3	0.190
FEV1 \geq 80	160 (27.5)	21 (30.9)	139 (27.0)	0.394	50 (25.4)	110 (28.6)	0.350	66 (28.8)	94 (26.3)	0.951
FEV1 < 80 & \geq 50	303 (52.1)	33 (48.5)	270 (52.5)		104 (52.8)	199 (51.7)		117 (51.1)	186 (52.7)	
FEV1 < 50 & \geq 30	103 (17.7)	14 (20.6)	89 (17.3)		40 (20.3)	63 (16.4)		40 (17.5)	63 (17.9)	
FEV1 < 30	16 (2.8)	0 (0)	16 (3.1)		3 (1.5)	13 (3.4)		6 (2.6)	10 (2.8)	
No. of moderate exacerbations*										
0	334 (57.4)	45 (66.2)	289 (56.2)	0.297	120 (60.9)	214 (55.6)	0.469	134 (58.5)	200 (56.7)	0.865
1	97 (16.7)	9 (13.2)	88 (17.1)		30 (15.2)	67 (17.4)		36 (15.7)	61 (17.3)	
≥ 2	151 (26.0)	14 (20.6)	137 (26.7)		47 (23.9)	104 (27.0)		59 (25.8)	92 (26.1)	
No. of severe exacerbations*										
0	463 (79.6)	56 (82.4)	407 (79.2)	0.750	159 (80.7)	304 (79.0)	0.782	188 (82.1)	275 (77.9)	0.451
1	82 (14.1)	9 (13.2)	73 (14.2)		25 (12.7)	57 (14.8)		29 (12.7)	53 (15.0)	
≥ 2	37 (6.4)	3 (4.4)	34 (6.6)		13 (6.6)	24 (6.2)		12 (5.2)	25 (7.1)	
Respiratory medications*										
SABD	167 (28.7)	16 (23.5)	151 (29.4)	0.316	57 (28.9)	110 (28.6)	0.927	69 (30.1)	98 (27.8)	0.537
ICSs	107 (18.4)	13 (19.1)	94 (18.3)	0.868	34 (17.3)	73 (19.0)	0.616	42 (18.3)	65 (18.4)	0.982
LABA	116 (19.9)	11 (16.2)	105 (20.4)	0.410	37 (18.8)	79 (20.5)	0.620	53 (23.1)	63 (17.9)	0.118
ICS/LABA combination	494 (84.9)	57 (83.8)	437 (85.0)	0.796	162 (82.2)	332 (86.2)	0.202	191 (83.4)	303 (85.8)	0.424
LAMA	295 (50.7)	29 (42.7)	266 (51.8)	0.158	99 (50.3)	196 (50.9)	0.881	110 (48.0)	185 (52.4)	0.303
LABA/LAMA combination	18 (3.1)	2 (2.9)	16 (3.1)	0.290	10 (5.1)	8 (2.1)	0.030	8 (3.5)	10 (2.8)	0.172
Theophylline	453 (77.8)	53 (77.9)	400 (77.8)	0.982	154 (78.2)	299 (77.7)	0.889	181 (79.0)	272 (77.1)	0.573
No. of specific bronchodilators used†										
0	3 (0.5)	2 (2.9)	1 (0.2)	0.058	2 (1.0)	1 (0.3)	0.504	2 (0.9)	1 (0.3)	0.468
1	39 (6.7)	4 (5.9)	35 (6.8)		13 (6.6)	26 (6.8)		13 (5.7)	26 (7.4)	
≥ 2	540 (93.0)	62 (91.2)	478 (93.0)		182 (92.4)	358 (93.0)		214 (93.5)	326 (92.3)	
Baseline blood eosinophil count‡										
Mean ± SD (%)	(n = 385) 2.78 ± 2.9	(n = 47) 2.47 ± 2.3	(n = 338) 2.83 ± 3.0	0.343	(n = 133) 2.86 ± 2.3	(n = 252) 2.74 ± 2.4	0.693	(n = 152) 3.03 ± 3.3	(n = 233) 2.62 ± 2.7	0.207
$\geq 2\%$	189 (49.1)	21 (44.7)	168 (49.7)	0.519	67 (50.4)	122 (48.4)	0.714	82 (54.0)	107 (45.9)	0.124
< 2%	196 (50.9)	26 (55.3)	170 (50.3)		66 (49.6)	130 (51.6)		70 (46.0)	126 (54.1)	

Values are presented as number (%) or mean ± SD.

ACO, asthma-chronic obstructive pulmonary disease overlap; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; SABD, short-acting bronchodilator; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

*Data within 1 year before enrollment was calculated.

†Baseline blood eosinophil counts before enrollment were not available in 197 ACO patients.

Effect of different cardiovascular medications on acute exacerbation in ACO cohorts

Kaplan-Meier analysis disclosed that beta-blocker use was associated with a lower cumulative incidence of moderate (log-rank test, $P = 0.013$) and severe AEs (log-rank test, $P = 0.021$; **Fig. 2A**) compared with non-use. The cumulative incidence rates of AE were similar between cardioselective beta-blocker users and nonselective beta-blocker users (**Fig. 3A**). ACEI/ARB use was associated with a lower cumulative incidence of moderate AE compared with non-use (log-rank test, $P < 0.001$; **Fig. 2B**). ARB use was associated with a lower cumulative incidence of moderate AE (log-rank test, $P < 0.001$) and severe AE (log-rank test, $P = 0.018$; **Fig. 3B**) compared with non-use. CCB use was associated with a lower cumulative incidence of moderate AE (log-rank test, $P < 0.001$; **Fig. 2C**) compared with non-use. However, the cumulative incidence rates of severe AE were similar between ACEI/ARB users and non-users and between CCB users and non-users and between DHP CCB users and non-DHP CCB users. After adjustment, cardioselective beta-blockers, ARBs, and DHP CCBs were associated with significantly lower risks of severe AE (cardioselective beta-blockers: HR, 0.29, 95% CI, 0.11–0.72, $P = 0.008$; ARBs: HR, 0.64, 95% CI, 0.44–0.93, $P = 0.019$; DHP CCB: HR, 0.66, 95% CI, 0.45–0.97, $P = 0.035$; **Table 3**). ARB (HR, 0.42, 95% CI, 0.30–0.62, $P < 0.001$) and DHP CCB (HR, 0.55, 95% CI, 0.38–0.80, $P = 0.002$) were associated with significantly lower risks of moderate AE. However, the use of either non-selective beta-blockers, ACEIs, or non-DHP CCBs was not associated with significantly lower moderate and severe AEs. Subgroup analyses demonstrated that beta-blockers, ARBs, and DHP CCBs were associated with lower risks of severe AE in frequent exacerbators. In contrast, cardiovascular medications were not associated with lower risk of severe AE in non-exacerbators (**Table 3**).

DISCUSSION

This study was conducted by interrogating the claims database of ACO patients in a real-world setting. Our results indicate that the administration of cardiovascular medications was associated with significantly lower risks of AEs in patients with ACO. After adjusting for all confounders, cardioselective beta-blocker, ARB, and DHP CCB therapies were associated with significantly lower risks of severe AEs.

Our previous work¹⁵ associated cardioselective beta-blocker therapy with a lower mortality risk in patients with COPD-heart failure overlap. Importantly, cardioselective beta-blocker use was associated with a lower mortality risk than non-selective beta-blocker therapy. This study yielded similar results. The use of cardioselective beta-blockers was associated

Table 3. Medication effects on severe acute exacerbations in asthma-chronic obstructive pulmonary disease overlap patients

Subgroup analysis	Severe exacerbation		Moderate exacerbation		Severe exacerbation in frequent exacerbators [†]		Severe exacerbation in non-exacerbators [†]	
	HR (95% CI) [*]	P value	HR (95% CI) [*]	P value	HR (95% CI) [*]	P value	HR (95% CI) [*]	P value
Cardioselective beta-blocker	0.29 (0.11–0.72)	0.008	0.63 (0.31–1.25)	0.184	0.26 (0.06–1.11)	0.069	0.56 (0.17–1.87)	0.345
Non-selective beta-blocker	0.53 (0.19–1.44)	0.211	0.50 (0.20–1.26)	0.140	0.20 (0.03–1.53)	0.122	0.60 (0.17–2.09)	0.420
ACEI	1.40 (0.58–3.34)	0.452	0.50 (0.12–2.05)	0.333	0.67 (0.19–2.39)	0.539	3.01 (0.83–10.91)	0.093
ARB	0.64 (0.44–0.93)	0.019	0.42 (0.30–0.62)	< 0.001	0.43 (0.26–0.73)	0.002	1.01 (0.59–1.75)	0.963
Dihydropyridine CCB	0.66 (0.45–0.97)	0.035	0.55 (0.38–0.80)	0.002	0.47 (0.27–0.82)	0.007	0.77 (0.43–1.38)	0.386
Non-dihydropyridine CCB	0.79 (0.49–1.26)	0.320	0.68 (0.42–1.09)	0.105	0.93 (0.50–1.72)	0.814	0.78 (0.33–1.83)	0.567

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HR, hazard ratio; CI, confidence interval.

^{*}Age, sex, smoking status, body mass index, comorbidity, Charlson comorbidity index, forced expiratory volume in 1 second, number of moderate exacerbations, number of severe exacerbations, and number of specific bronchodilators used were included in the Cox multivariate analysis.

[†]Frequent exacerbators include individuals who have experienced more than one acute exacerbation within a year before enrollment.

CV Medication Use and Risk of AE in ACO

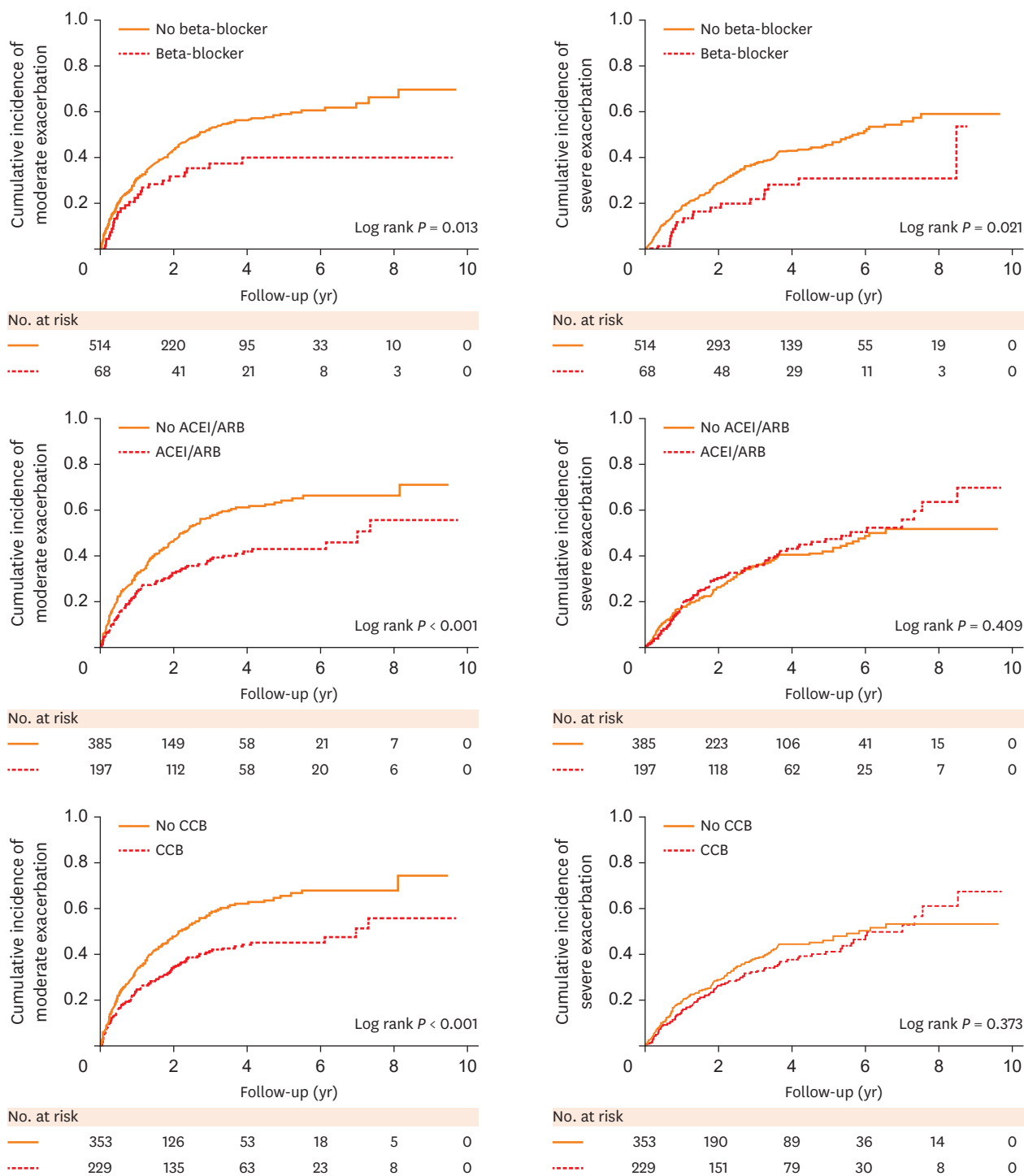


Fig. 2. Kaplan-Meier curves: cumulative incidence of moderate and severe exacerbations in asthma-chronic obstructive pulmonary disease overlap patients. (A) Beta-blocker. (B) ACEI/ARB. (C) CCB.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

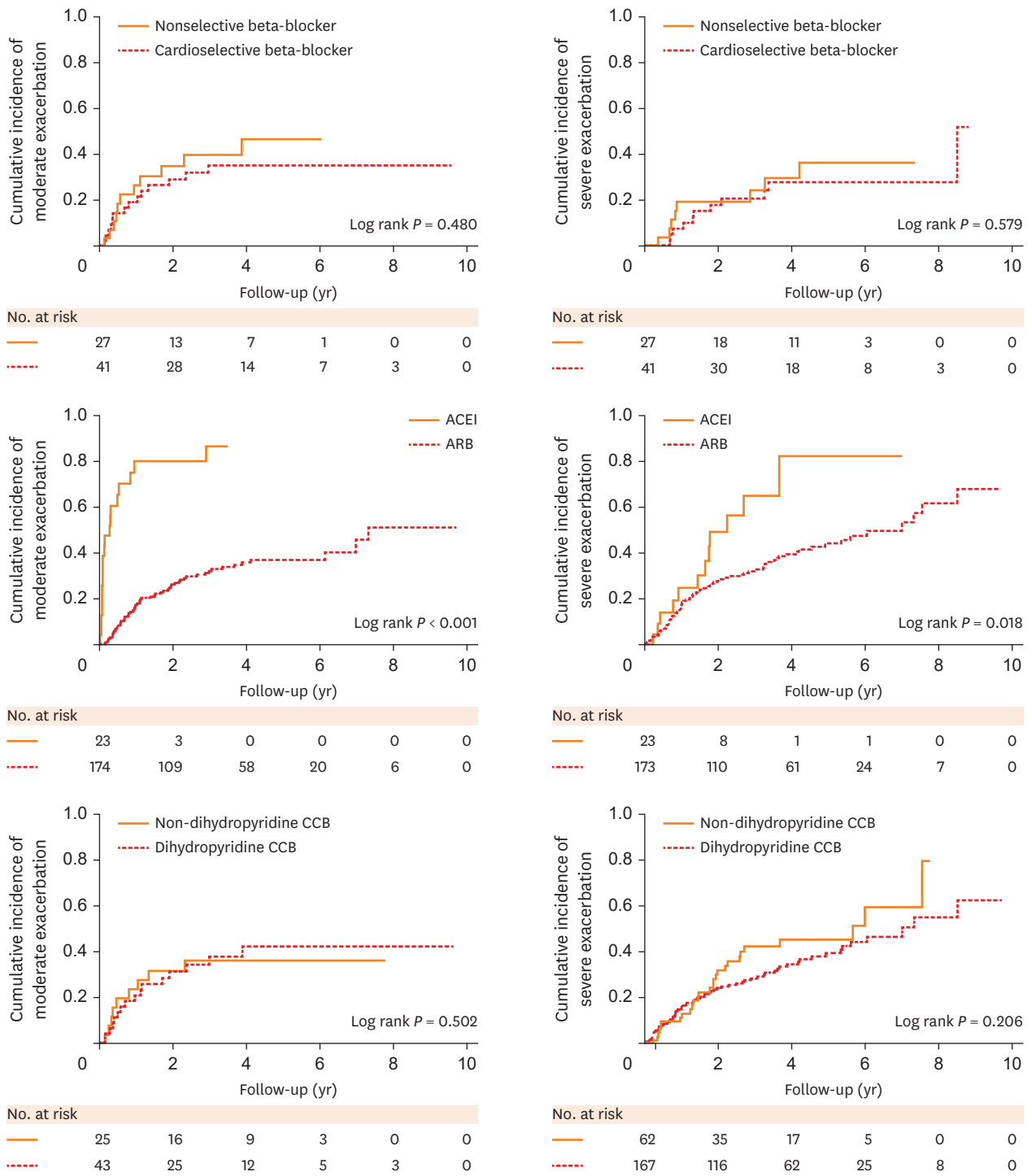


Fig. 3. Kaplan-Meier curves: cumulative incidence of moderate and severe exacerbations in asthma-chronic obstructive pulmonary disease overlap patients. (A) Cardioselective beta-blocker vs. nonselective beta-blocker. (B) ACEI vs. ARB. (C) Dihydropyridine CCB vs. non-dihydropyridine CCB. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

with a reduced risk of COPD exacerbation. Beta-blockers, especially non-selective beta-blockers, can reduce pulmonary function both in the general population and in patients with obstructive lung diseases. A meta-analysis²² reported that the administration of nonselective beta-blockers significantly decreased lung function as evidenced by a 13.42% reduction in FEV1; however, cardioselective beta-blocker therapy did not change lung function or the incidence of respiratory symptoms in patients with COPD. The international COPD guideline⁷ recommends the use of cardioselective beta-blockers in COPD patients with coexisting cardiovascular diseases (*e.g.*, heart failure and acute myocardial infarction). Nonetheless, beta-blockers are not uncommonly withheld from patients with asthma due to concerns regarding the risk of provoking AE. The safety of beta-blocker use in patients with ACO remains unclear; consequently, physicians may avoid beta-blockade in the treatment of cardiovascular diseases in this patient population. Our study indicates that beta-blockers could be well tolerated and that cardioselective beta-blocker therapy may be associated with a lower risk of AE in patients with ACO. Given their demonstrated benefits in the reduction of cardiac events and AE, beta-blockers should be considered for patients with ACO.

Bronchial hyperresponsiveness is a key characteristic of asthma and also present in ACO. Bronchial hyperresponsiveness is associated with a rapid decline in lung function and significantly associated with AEs of asthma and COPD.²³ ACEIs are often associated with an increased incidence of cough with bronchial hyperreactivity that may impair pulmonary function. The incidence of ACEI-related cough is higher in Chinese than in non-Chinese populations. A study of 191 Hong Kong patients found persistent cough in 44% of patients taking an ACEI compared with 11.1% of age- and sex-matched controls receiving alternative medications ($P < 0.001$).²⁴ In contrast, a controlled retrospective cohort study in New Zealand associated ACEI therapy with higher incidence rates of cough and bronchospasm compared with controls (12.3% vs. 2.7%, $P < 0.001$ and 5.5% vs. 2.3%, $P < 0.001$, respectively)²⁵; however, the incidence rates were substantially lower than those reported in the aforementioned Hong Kong study. Our study population entirely comprised Chinese patients, who carry the highest risk of adverse respiratory effects of ACEIs. In our previous work, ARB therapy was associated with a lower mortality risk than ACEI use in Chinese patients with COPD-heart failure overlap.¹⁵ In this study of Chinese patients with ACO, the risk of AE was lower in ARB than in ACEI recipients.

DHP CCBs are exclusively selective antagonists of voltage-sensitive L-type calcium channels, which are predominant in airway smooth muscles.²⁶ Airway smooth muscles play a central role in bronchial hyperreactivity and airway remodeling in asthma. Calcium channel activation facilitates calcium influx to trigger bronchospasm via airway smooth muscle contraction. *In vivo* models have demonstrated that blockade of L-type calcium channels inhibits airway smooth muscle contraction.^{27,28} The central role of voltage-sensitive L-type calcium channels in bronchospasm has led to investigations suggesting that L-type CCBs may benefit the control of asthma.¹¹ In this study, the use of DHP CCBs, which are selective blockers for voltage-sensitive L-type calcium channels, was associated with a lower risk of AE than non-DHP CCBs in patients with ACO.

This was a retrospective, observational cohort study and consequently has several limitations. First, we were unable to ascertain side effects of cardiovascular medications, which were not consistently recorded in administrative claims data. Secondly, results were based on a retrospective design at a tertiary referral hospital in Taiwan; thus, our sample is more representative of the spectrum of the disease in the Asian population. All patients included in

this study were Taiwanese. Because Asian patients are at high risk of bronchospasm and other respiratory side effects of ACEIs, future studies are warranted to verify the generalizability of our findings. Thirdly, most subjects in this study were males (83.2%). This finding was unsurprising because COPD is a male-predominant airway disease. In addition, Taipei Veterans General Hospital is a tertiary referral hospital established to care for veterans, most of whom are male. Fourthly, the sample size in this study was not large enough to analyze the effects of respective cardiovascular medications. The HRs of several cardiovascular drugs were insignificantly low or high. Finally, baseline blood eosinophil counts were not included in the adjustment due to the absence of baseline blood eosinophil counts of 197 patients. However, there were no differences in baseline blood eosinophil counts between respective cardiovascular medication users and non-users. We believe that the effect of omitting baseline blood eosinophil counts in the adjustment was limited.

In conclusion, this study associated ARB, cardioselective beta-blocker, and DHP CCB therapies with lower risks of severe AE in patients with ACO. ARB therapy carried a lower risk of AE compared with ACEI use. Cardioselective beta-blocker use was associated with a lower risk of AE compared with nonselective beta-blocker treatment. DHP CCBs users experienced fewer AEs compared with non-DHP CCBs users. Further well-designed prospective studies in patients with ACO are warranted.

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