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Association of asthma–chronic obstructive pulmonary disease overlap syndrome with coronary artery disease, cardiac dysrhythmia and heart failure: a population-based retrospective cohort study

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ABSTRACT

Objectives Patients with asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) and cardiovascular diseases (CVDs) share common risk factors. However, the association between ACOS and the incidence of CVDs has not been reported. This study investigated the relationship between CVDs and ACOS in the general population.

Setting Data were obtained from Taiwan's National Health Insurance Research Database for the period 2000 to 2010.

Participants The ACOS cohort comprised patients (n=5814) who had received a diagnosis of asthma and COPD. The non-ACOS cohort comprised patients who had not received a diagnosis of asthma or COPD and were matched to the ACOS cohort (2:1) by age, sex and index date (n=11 625).

Primary and secondary outcome measures The cumulative incidence of CVDs—coronary artery disease (CAD), cardiac dysrhythmia (CD) and heart failure (HF)—was calculated. Cox proportional regression analysis was employed to examine the relationship between ACOS and CVDs.

Results After adjustment for multiple confounding factors—age, sex, comorbidities and medications—patients with ACOS were associated with a significantly higher risk of CVDs; the adjusted HRs (aHRs; 95% CI) for CAD, CD and HF were 1.62 (1.50 to 1.76), 1.44 (1.30 to 1.61) and 1.94 (1.73 to 2.19), respectively, whereas those of beta-blockers treatment for CAD, CD and HF were 1.19 (0.92 to 1.53), 0.90 (0.56 to 1.45) and 0.82 (0.49 to 1.38). The aHR of atenolol treatment for CD was 1.72 (1.01 to 2.93). The aHRs (95% CIs) of ACOS without acute exacerbation of COPD (AE-COPD) for CAD, CD and HF were 1.85 (1.70 to 2.01), 1.57 (1.40 to 1.77) and 2.07 (1.82 to 2.35), respectively.

Conclusion ACOS was associated with higher CVD risk, even without the presence of previous comorbidities or AE-COPD. No significant differences in CVD events were observed in the ACOS cohort using beta-blockers, except for those using atenolol for treating CD.

Strengths and limitations of this study

- The strength of this study is its use of population-based data to perform a longitudinal assessment of the risk of cardiovascular diseases in patients with asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS).
- The data are highly representative of the general population and minimised the likelihood of selection bias.
- To avoid bias, only patients with a medication possession ratio of ≥80 were included in this analysis.
- The causal relationships could not be established owing to the retrospective cohort study design.
- Currently, there is no universally accepted definition of ACOS, which makes it difficult to clarify its epidemiology and pathophysiology.

INTRODUCTION

Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS)[1 2] is a newly recognised, systemic inflammatory disease[3 4] that shares the characteristics of asthma and COPD.[5 6] ACOS is a form of airway and pulmonary vessel disease[7 8] that is associated with a disproportionate number of exacerbations and a higher overall healthcare burden[9] than either asthma or COPD alone.

Cardiovascular diseases (CVDs), includes coronary artery disease (CAD), cardiac dysrhythmia (CD) and heart failure (HF). Respiratory failure in an acute exacerbation of COPD (AE-COPD) may contribute to hypoxaemia and hypercapnia.[10] These complications are associated with atherosclerosis[11] and CVDs.[12] Therefore, the incidence of HF increases with an increase in the incidence of CD. In addition, the use of a

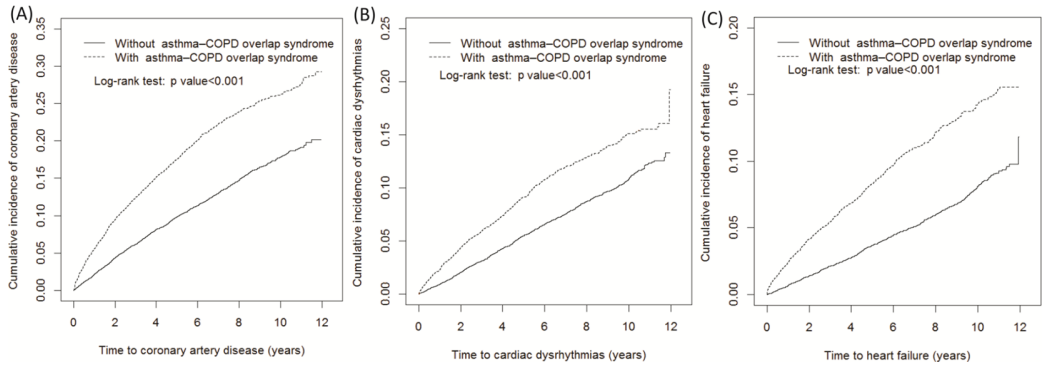

Figure 1 Cumulative incidence of coronary artery disease (A), cardiac dysrhythmia (B) and heart failure (C) of patients with and without critical illness, as determined using propensity score matching. COPD, chronic obstructive pulmonary disease.

bronchodilator is associated with CAD and HF.[13] CD and CAD are predisposing factors of sudden death. Previous studies suggest a beneficial effect of beta-blockers on AE in mild to moderate COPD.[14 15] However, benefits are less obvious in severe COPD and coexistent CVDs.[15] The role of beta-blockers[14] (eg, β1-adrenoceptor blockers) in AE-COPD with CAD, CD and HF, such as in elderly with severe cases,[15] is still being debated.[16 17]

Patients with ACOS have higher frequency of hospital admission and bronchodilator use[18]; therefore, ACOS may also be associated with[5] CVDs.[19] However, the relationship between ACOS and the risk of CVDs in the general population has not been reported in detail.

Beta-blockers (eg, β1-adrenoceptor blockers) may have an anti-inflammatory effect in patients with COPD and protect[16] their cardiovascular system.[20] Additionally, beta-blockers may play a role in patients with ACOS and coexistent CVDs.[5 14] Therefore, we conducted this nationwide population-based cohort study to investigate the relationship between ACOS and CVDs including CAD, CD and HF. In addition, we evaluated the role of beta-blockers in the relationship of patients with ACOS which has not been examined in any previous study.

MATERIALS AND METHODS

Data source

This retrospective study used data from the Longitudinal Health Insurance Database 2000 (LHID2000), a subset of the National Health Insurance Research Database (NHIRD). The LHID2000 includes the data of 1 000 000 patients randomly sampled from all the enrollees of the National Health Insurance (NHI) programme in Taiwan from 1996 to 2000, with follow-up data collected until 2011.[21] Studies have detailed the specifications of the NHI programme and the LHID2000.[22] Diseases were defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Ethics statement

The NHIRD encrypts patients' personal information to protect their privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received and prescriptions. Therefore, patient consent is not required to access the NHIRD.

Sampled participants

The ACOS cohort included patients aged ≥40 years who had received a diagnosis of COPD (ICD-9-CM codes 491, 492 and 496) between 1 January 2000 and 31 December 2010. The index date was defined as the date when asthma[23] was first diagnosed.[7 24] We excluded patients who had a history of CAD (ICD-9-CM codes 410–414), CD (ICD-9-CM code 427) and HF (ICD-9-CM code 428) before the index date or were younger than 40 years. For each patient in the ACOS cohort, two patients without ACOS were randomly selected for the same period (2000–2010) by using the same exclusion criteria as those applied to the ACOS cohort. This non-ACOS cohort was matched (2:1) to the ACOS cohort by sex, age (every 5-year span) and index year. Diagnosis of COPD is based on clinical symptoms or signs and pulmonary function test (PFT) results according to the strict policy of bronchodilator use[2] in Taiwan. If a physician (eg, a local medical doctor) does not record clinical symptoms or signs and performed a PFT, the physician does not receive the application fee. In the study by Cheng *et al*, patients with COPD underwent chest X-ray (84.7%), PFT (58.4%) and CT (39.4%) in a hospital; the results of those examinations support the diagnosis of COPD in the NHIRD.[25] The non-ACOS[26] cohort included patients without either asthma or COPD.[27]

Outcomes and relevant variables

The major outcomes were a new diagnosis of CAD (ICD-9-CM codes 410–414), CD (ICD-9-CM code 427) or HF (ICD-9-CM code 428). All study patients were followed until they received a diagnosis of a major outcome, they withdrew from the NHI programme or 31 December 2011, whichever occurred first. Comorbidities potentially related to the major outcomes include diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidaemia (ICD-9-CM code 272), hyperuricaemia (ICD-9-CM code 790.6), end-stage renal disease (ICD-9-CM code 585), bone fracture (ICD-9-CM

codes 800–829), pneumonia (ICD-9-CM codes 480–486), mental disorders (ICD-9-CM codes 290–319), stroke (ICD-9-CM codes 430–438) and tobacco dependency (ICD-9-CM code 305.1). Medications possibly associated with the major outcomes were also evaluated, including bisoprolol, atenolol, metoprolol and beta-blockers (only patients with a medication possession ratio (MPR) of ≥80 were included in this analysis). Severe COPD with acute exacerbation was defined as AE-COPD (ICD-9-CM codes 491.21, 491.22, 492.8, 518.81, 518.82 and 518.84).

Statistical analysis

The demographic factors, comorbidities and medications of the ACOS and non-ACOS cohorts were compared using the χ^2 test for categorical variables and Student's t-test for continuous variables. To estimate the risk of the major outcomes, incidence density rates were calculated for both cohorts as the number of major outcome events divided by the sum of the whole follow-up period in years (per 1000 person-years). The cumulative incidence curves of the major outcomes were assessed using the Kaplan-Meier method, and the differences in tested curves were analysed using the log-rank test. Univariate and multivariate Cox proportional hazard regression models were used to examine the effect of the ACOS cohort in the risks of the major outcomes, which were reported as HRs with 95% CIs. Variables with significant differences in the univariate Cox model were included in the multivariate model. The significance level was set at p<0.05. Data analysis was performed using SAS software, V.9.4 (SAS Institute).

RESULTS

We enrolled 5814 and 11 625 patients in the ACOS and non-ACOS cohorts, respectively. In the ACOS cohort, 58.5% and 46.8% of patients were men and were aged ≥65 years, respectively (table 1). The mean age was 63.8±12.2 and 63.3±12.2 years in the ACOS and non-ACOS

Table 1 Demographics and comorbidities of the ACOS and non-ACOS cohorts

	ACOS				
	No (n=11 625)		Yes (n=5814)		
Variable	n	%	n	%	p Value
Sex					0.99
Female	4828	41.5	2414	41.5	
Male	6797	58.5	3400	58.5	
Age, years					0.99
40–49	1950	16.8	975	16.8	
50–64	4242	36.5	2121	36.5	
≥65	5433	46.7	2718	46.8	
Mean (SD)*	63.3	12.2	63.8	12.2	0.55
Comorbidity					
Diabetes	1449	12.5	774	13.3	0.11
Hypertension	4221	36.3	2799	48.1	<0.001
Hyperlipidaemia	2169	18.7	1418	24.4	<0.001
Hyperuricaemia	176	1.51	140	2.41	<0.001
End-stage renal disease	25	0.22	6.	0.10	0.10
Bone fractures	1243	10.7	794	13.7	<0.001
Pneumonia	494	4.25	1045	18.0	<0.001
Mental disorders	2960	25.5	2435	41.9	<0.001
Stroke	476	4.09	362	6.23	<0.001
Tobacco dependency	54	0.46	76	1.31	<0.001
Medicine					
Bisoprolol	44	0.38	26	0.45	0.50
Atenolol	137	1.18	49	0.84	0.04
Metoprolol	7	0.06	3	0.05	0.82
Beta-blockers	217	1.87	89	1.53	0.11

χ^2 test.
*Student's t-test.
ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome.

Table 2 Incidence rates and adjusted HRs of coronary artery disease, cardiac dysrhythmia and heart failure in the ACOS and non-ACOS cohorts after stratification by sex, age, comorbidities (no/yes) and medications (no/yes)

	ACOS							
	No			Yes			Compared with non-ACOS cohort	
Variables	Event	PY	Rate	Event	PY	Rate	Crude HR (95% CI)	Adjusted HR†(95% CI)
Coronary artery disease								
Overall	1450	72458	20.0	1147	32580	35.2	1.74 (1.61 to 1.88)***	1.62 (1.50 to 1.76)***
Sex								
Female	519	31337	16.6	416	14337	29.0	1.73 (1.52 to 1.97)***	1.51 (1.32 to 1.73)***
Male	931	41122	22.6	731	18243	40.1	1.76 (1.59 to 1.94)***	1.68 (1.52 to 1.86)***
Age, years								
40–49	98	13957	7.02	97	6720	14.4	2.05 (1.55 to 2.71)***	1.58 (1.17 to 2.13)**
50–64	461	27863	16.6	405	12667	32.0	1.92 (1.68 to 2.19)***	1.67 (1.45 to 1.92)***
≥65	891	30639	29.1	645	13192	48.9	1.66 (1.50 to 1.84)***	1.57 (1.42 to 1.75)***
Comorbidity‡								
No	382	32438	11.8	166	7923	21.0	1.78 (1.48 to 2.14)***	1.82 (1.52 to 2.18)***
Yes	1068	40021	26.7	981	24656	39.8	1.48 (1.36 to 1.62)***	1.56 (1.43 to 1.70)***
Cardiac dysrhythmia								
Overall	862	75887	11.4	622	35785	17.4	1.53 (1.38 to 1.69)***	1.44 (1.30 to 1.61)***
Sex								
Female	313	32716	9.57	221	15643	14.1	1.48 (1.24 to 1.75)***	1.42 (1.19 to 1.71)***
Male	549	43171	12.7	401	20141	19.9	1.56 (1.37 to 1.78)***	1.46 (1.28 to 1.67)***
Age, years								
40–49	62	14149	4.38	47	7001	6.71	1.54 (1.05 to 2.24)*	1.32 (0.88 to 1.98)
50–64	218	29249	7.45	164	14117	11.6	1.56 (1.27 to 1.91)***	1.33 (1.07 to 1.65)**
≥65	582	32489	17.9	411	14667	28.0	1.56 (1.38 to 1.77)***	1.46 (1.28 to 1.67)***
Comorbidity‡								
No	274	33057	8.29	117	8255	14.2	1.71 (1.38 to 2.13)***	1.80 (1.45 to 2.23)***
Yes	588	42830	13.7	505	27530	18.3	1.33 (1.19 to 1.50)***	1.44 (1.28 to 1.63)***
Heart failure								
Overall	616	77072	7.99	588	36054	16.3	2.04 (1.82 to 2.28)***	1.94 (1.73 to 2.19)***
Sex								
Female	251	33058	7.59	217	15708	13.8	1.81 (1.51 to 2.17)***	1.60 (1.32 to 1.94)***
Male	365	44014	8.29	371	20345	18.2	2.20 (1.90 to 2.54)***	2.17 (1.87 to 2.52)***
Age, years								
40–49	19	14379	1.32	24	7110	3.38	2.56 (1.41 to 4.68)**	2.17 (1.15 to 4.11)*
50–64	136	29493	4.61	148	14255	10.4	2.24 (1.78 to 2.83)***	1.92 (1.50 to 2.45)***
≥65	461	33200	13.9	416	14688	28.3	2.04 (1.79 to 2.33)***	1.86 (1.62 to 2.13)***
Comorbidity‡								
No	154	33673	4.57	83	8430	9.85	2.16 (1.66 to 2.82)***	2.31 (1.77 to 3.02)***
Yes	462	43399	10.7	505	27623	18.3	1.71 (1.51 to 1.94)***	1.91 (1.69 to 2.17)***

Rate denotes incidence rate (per 1000 person-years) and Crude HR denotes relative HR.
*p<0.05, **p<0.01, ***p<0.001.
†Covariables found to be significantly associated with coronary artery disease, cardiac dysrhythmia and heart failure in the univariate Cox proportional regression model were further analysed using a multivariate Cox proportional regression model.
‡Individuals with diabetes, hypertension, hyperlipidaemia, hyperuricaemia, end-stage renal disease, bone fracture, pneumonia, mental disorders, stroke and tobacco dependency were classified in the comorbidity group.
ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; PY, person-years.

cohorts, respectively. Compared with the non-ACOS cohort, the ACOS cohort tended to have hypertension, hyperlipidaemia, hyperuricaemia, bone fracture, pneumonia, mental disorders, stroke and tobacco dependency. In addition, fewer patients in the ACOS cohort used atenolol than in the non-ACOS cohort (0.84% vs 1.18%). The cumulative incidence rates of CAD, CD and HF were higher in the ACOS cohort than in the non-ACOS cohort (figure 1). The overall incidence density rate of CAD was 35.2 and 20.0 per 1000 person-years in the ACOS and non-ACOS cohorts, respectively (table 2). The corresponding adjusted HR (aHR) of CAD was 1.62 (95% CI 1.50 to 1.76) after adjustment for age; sex; comorbidities, namely diabetes, hypertension, hyperlipidaemia, pneumonia, mental disorders and stroke and the use of bisoprolol, atenolol, metoprolol or beta-blockers. The sex-specific ACOS-to-non-ACOS cohort relative risk of CAD was significant in both women (aHR=1.51; 95% CI 1.32 to 1.73) and men (aHR=1.68; 95% CI 1.52 to 1.86). The age-specific ACOS-to-non-ACOS cohort relative risk of CAD was higher for those aged 40–49 years (aHR=1.58; 95% CI 1.17 to 2.13), those aged 50–64 years (aHR=1.67; 95% CI 1.45 to 1.92) and those aged ≥65 years (aHR=1.57; 95% CI 1.42 to 1.75). Patients without comorbidities in the ACOS cohort were associated with a significantly higher risk of CAD (aHR=1.82; 95% CI 1.52 to 2.18), CD (aHR=1.80; 95% CI 1.45 to 2.23) and HF (aHR=2.31; 95% CI 1.77 to 3.02) than those in the non-ACOS cohort. We compared the risk of CAD, CD and HF in the two cohorts with regard to the variables of sex, age and the presence of comorbidities. The risk of CAD, CD and HF was higher in the ACOS cohort than in the non-ACOS cohort, except for those aged 40–49 years, who were not associated with a significantly higher risk of CD.

The results of the univariate and multivariate Cox proportional hazards regression models used to analyse the contribution of age, sex, comorbidities and medications to the three outcome events are listed in table 3. The risk of CAD, CD and HF increased with age, and men had a higher risk of CAD and CD than did women. Diabetes was associated with a higher risk of CAD and HF, and hypertension was associated with a higher risk of CAD, CD and HF. Patients with hyperlipidaemia had a higher risk of CAD. Pneumonia was associated with a higher risk of CD and HF, whereas patients with mental disorders had a higher risk of CAD. Patients with stroke had a higher risk of HF. In the ACOS cohort, patients who received atenolol treatment were associated with a higher risk of CD (aHR=1.72; 95% CI 1.01 to 2.93). The aHRs (95% CIs) of beta-blocker treatment for CAD, CD and HF were 1.19 (0.92 to 1.53), 0.90 (0.56 to 1.45) and 0.82 (0.49 to 1.38), respectively.

In the ACOS cohort, the aHRs (95% CIs) of patients without AE-COPD for CAD, CD and HF were 1.85 (1.70 to 2.01), 1.57 (1.40 to 1.77) and 2.07 (1.82 to 2.35), respectively (table 4). In the ACOS cohort, patients without AE-COPD were associated with a higher risk of CVDs. Meanwhile, the aHR (95% CI) of patients with AE-COPD for HF was 1.64 (1.36 to 1.97) in the ACOS cohort. The patients with AE-COPD were associated with a higher risk of HF in the ACOS cohort.

DISCUSSION

In this study, the ACOS cohort had more comorbidities and a higher risk of CVDs than did the non-ACOS cohort (aHRs for CAD, CD and HF=1.62, 1.44 and 1.94, respectively; all p<0.001). These findings are consistent with those of a retrospective cohort study conducted by van Boven *et al*, who reported a strong association of CVDs with hospitalisation for ACOS,[28] and those of a study conducted by Hekking *et al*, who discovered that prescriptions for CVDs were the most prevalent in patients with ACOS.[29] We also found that even patients without comorbidities in the ACOS cohort were associated with a significantly higher risk of CVDs during the follow-up period (aHRs for CAD, CD and HF=1.82, 1.80 and 2.31, respectively; all p<0.001).

Inflammation is systemic in COPD, and this contributes to the development of various crucial comorbidities.[30] Strong associative evidence[3–5 11 31–33] confirmed that inflammatory cells or mediators in COPD are relevant to the development of CVDs. The exact mechanism underlying the association between ACOS and CVDs is unclear; however, it may be partially explained by systemic inflammation in both patients with ACOS and those with CVDs. Gao *et al*[26] reported that the levels of inflammatory markers in the sputum and serum were higher in patients with ACOS than in healthy controls, those with only asthma and those with only COPD.[3] From a biological viewpoint, several studies have reported an association between increased levels of inflammatory markers (eg, cytokine) and an increased risk of CVDs, including CAD,[31] CD[32] and HF.[33] Taken together, these findings may support the association with CVDs[34] of systemic pulmonary vessel[35] (eg, the pulmonary artery[7]) and airway inflammation[3] accompanied by hypoxaemia[36] and atherosclerosis[12] of the vessel[11] in ACOS,[7] as observed in younger adults in the present study (age ≥40 to <65 years; p<0.05 for CAD, CD and HF, except for CD (age 40–49 years, p>0.05)). Meanwhile, patients without AE-COPD who were in the ACOS cohort (aHRs for CAD, CD and HF=1.85, 1.57 and 2.07, respectively; all p<0.05) were still associated with the risk of CVDs; this result is consistent with that of a previous study.[37]

Comorbidities, such as atherosclerosis-related diseases[12] (eg, diabetes, hypertension and hyperlipidaemia; all p<0.05) and hypoxaemia-related diseases[27] (eg, pneumonia; p<0.05), were associated with the risk of CVDs (eg, CAD[7]) in the current study; this finding is also consistent with those of previous studies.[7 11 12]

Beta-blockers (eg, selective β1-adrenoceptor blockers) have nearly the same anti-inflammatory effect on inflammatory processes.[17] Beta-blockers have antioxidant properties,[38] and they are used to treat CAD,[39] HF[40] and CD. Atenolol,[41] metoprolol[42] and bisoprolol[43] treatments have

Table 3 Crude and adjusted HRs of coronary artery disease, cardiac dysrhythmia and heart failure in association with ACOS cohort, sex, age, comorbidities and medications in Cox regression models

	Coronary artery disease		Cardiac dysrhythmia		Heart failure	
Variable	**Crude HR (95% CI)**	**Adjusted HR† (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR† (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR† (95% CI)**
ACOS	1.74 (1.61 to 1.88)***	1.62 (1.50 to 1.76)***	1.53 (1.38 to 1.69)***	1.44 (1.30 to 1.61)***	2.04 (1.82 to 2.28)***	1.94 (1.73 to 2.19)***
Age, years (per year increase)	1.03 (1.03 to 1.04)***	1.03 (1.02 to 1.03)***	1.05 (1.05 to 1.06)***	1.05 (1.04 to 1.05)***	1.07 (1.07 to 1.08)***	1.07 (1.06 to 1.07)***
Sex (women vs men)	1.36 (1.25 to 1.47)***	1.31 (1.21 to 1.42)***	1.36 (1.22 to 1.51)***	1.20 (1.08 to 1.34)**	1.19 (1.06 to 1.34)**	1.00 (0.89 to 1.12)
Comorbidity						
Diabetes	1.69 (1.53 to 1.86)***	1.23 (1.10 to 1.37)***	1.08 (0.92 to 1.25)	–	1.73 (1.50 to 2.01)***	1.24 (1.07 to 1.44)**
Hypertension	2.40 (2.22 to 2.59)***	1.77 (1.63 to 1.93)***	1.82 (1.65 to 2.02)***	1.26 (1.13 to 1.41)***	2.68 (2.39 to 3.01)***	1.59 (1.40 to 1. 80)***
Hyperlipidaemia	1.49 (1.37 to 1.63)***	1.15 (1.05 to 1.26)**	1.06 (0.93 to 1.20)	–	1.08 (0.94 to 1.24)	–
Hyperuricaemia	1.40 (1.07 to 1.83)*	0.93 (0.71 to 1.22)	1.00 (0.66 to 1.51)	–	1.62 (1.12 to 2.34)*	0.99 (0.68 to 1.44)
End-stage renal disease	1.56 (1.65 to 3.73)	–	2.33 (0.88 to 6.20)	–	0.70 (0.10 to 4.97)	–
Bone fractures	1.13 (1.00 to 1.27)	–	1.32 (1.14 to 1.54)***	1.09 (0.94 to 1.28)	1.43 (1.21 to 1.68)***	1.07 (0.90 to 1. 26)
Pneumonia	1.44 (1.26 to 1.64)***	0.99 (0.87 to 1.14)	1.90 (1.63 to 2.23)***	1.34 (1.13 to 1.57)***	2.19 (1.85 to 2.58)***	1.28 (1.07 to 1.52)**
Mental disorders	1.39 (1.28 to 1.50)***	1.14 (1.05 to 1.24)**	1.25 (1.13 to 1.40)***	1.09 (0.97 to 1.21)	1.27 (1.12 to 1.42)***	0.95 (0.84 to 1.08)
Stroke	1.59 (1.35 to 1.89)***	0.93 (0.79 to 1.11)	1.65 (1.32 to 2.05)***	1.00 (0.80 to 1.26)	2.52 (2.05 to 3.09)***	1.26 (1.02 to 1.56)*
Tobacco dependency	0.87 (0.48 to 1.57)	–	0.74 (0.31 to 1.79)	–	0.96 (0.40 to 2.31)	–
Medicine						
Bisoprolol	1.77 (1.00 to 3.12)*	0.99 (0.54 to 1.79)	1.25 (0.52 to 3.00)	–	1.62 (0.67 to 3.91)	–
Atenolol	1.21 (0.17 to 8.61)	–	1.86 (1.27 to 2.73)**	1.72 (1.01 to 2.93)*	2.02 (1.35 to 3.03)***	1.73 (0.97 to 3.08)
Metoprolol	1.21 (0.17 to 8.61)	–	4.13 (1.03 to 16.5)*	3.01 (0.70 to 13.0)	2.31 (0.33 to 16.4)	–
Beta-blockers	1.94 (1.45 to 2.59)***	1.19 (0.92 to 1.53)	1.53 (1.10 to 2.13)*	0.90 (0.56 to 1.45)	1.58 (1.10 to 2.28)*	0.82 (0.49 to 1.38)

Crude HR denotes relative HR.
*p<0.05, **p<0.01, ***p<0.001.
†Covariables found to be significantly associated with coronary artery disease, cardiac dysrhythmia and heart failure in the univariate Cox proportional regression model were further analysed using the multivariate Cox proportional regression model.
ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome.

Table 4 Incidences and HRs of coronary artery disease, cardiac dysrhythmia and heart failure in the ACOS cohort stratified by AE-COPD

Variable	N	Event	PY	Rate	Crude HR (95% CI)	Adjusted HR† (95% CI)
Coronary artery disease						
Non-ACOS	11 625	1450	72 458	20.0	1 (reference)	1 (reference)
All ACOS						
Without AE-COPD	4373	934	24 507	38.1	1.89 (1.74 to 2.05)***	1.85 (1.70 to 2.01)***
With AE-COPD	1441	213	8073	26.4	1.31 (1.13 to 1.51)***	1.05 (0.90 to 1.21)
Cardiac dysrhythmia						
Non-ACOS	11 625	862	75 887	11.4	1 (reference)	1 (reference)
All ACOS						
Without AE-COPD	4373	482	27 336	17.6	1.55 (1.39 to 1.73)***	1.57 (1.40 to 1.77)***
With AE-COPD	1441	140	8448	16.6	1.45 (1.22 to 1.74)***	1.11 (0.93 to 1.34)
Heart failure						
Non-ACOS	11 625	616	77 072	7.99	1 (reference)	1 (reference)
All ACOS						
Without AE-COPD	4373	438	27 636	15.9	1.98 (1.75 to 2.24)***	2.07 (1.82 to 2.35)***
With AE-COPD	1441	150	8418	17.8	2.22 (1.86 to 2.65)***	1.64 (1.36 to 1.97)***

Rate denotes incidence rate (per 1000 person-years) and Crude HR denotes relative HR.
*p<0.05, **p<0.01, ***p<0.001.
†Covariables found to be significantly associated with coronary artery disease, cardiac dysrhythmia and heart failure in the univariate Cox proportional regression model were further analysed using a multivariate Cox proportional regression model.
ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; PY, person-years.

been reported to exert a cardioprotective effect in patients with CVDs. No significant differences were observed in CVD events in patients who received β1-adrenoceptor blockers between the ACOS and non-ACOS cohorts (bisoprolol for CAD, aHR=0.99; metoprolol for CD, aHR=3.01; atenolol for HF, aHR=1.73; all p>0.05), which is different from the cardioprotective effect of COPD observed in a previous study.[39] This result may be attributable to higher systemic,[3 26] airway[8 34] and pulmonary vessel inflammation[3 34] in the ACOS cohort than in the COPD cohort and a higher frequency of AE-COPD,[7 27 44] which aggravates these inflammatory conditions. The higher incidence of HF (aHR=1.64; p<0.05) identified in the ACOS cohort with AE-COPD supports this speculation. This may explain the reason for no significant differences in CVD events in patients who received beta-blockers between the ACOS and non-ACOS cohorts (aHRs for CAD, CD and HF=1.19, 0.90 and 0.82, respectively; all p>0.05). In the ACOS cohort, patients who used selective β1-adrenoceptor blockers (eg, atenolol) still had a higher risk of CD (aHR=1.72; p<0.05) than the non-ACOS cohort. These results warrant more studies to elucidate the exact mechanisms underlying the associations among beta-blocker use, ACOS and CVDs.

The frequency of AE-COPD in the ACOS cohort compared with that in the non-ACOS cohort (eg, patients with only COPD, patients with only asthma and patients without asthma or COPD) that was determined in our study is different from those reported in previous studies.[1 2 24] In our previous study,[7] the frequency of AE-COPD was higher in the ACOS cohort than in the non-ACOS cohort (patients without asthma or COPD). The results of this study revealed that the frequency of CAD and CD events did not differ between the ACOS cohort with a higher frequency of AE-COPD and the non-ACOS cohort (aHRs for CAD and CD=1.05 and 1.11, respectively; all p>0.05). One possible explanation is that the ACOS cohort with AE-COPD had a higher frequency of hospitalisation and intensive care (oxygen provision, chest care and increased dosage of bronchodilators/inhaler corticosteroids or oral corticosteroids and use of antibiotics),[24 45 46] which may have reduced the number of hypoxaemia or hypercapnia events. This strategy may have counterbalanced[2] the risk of CAD and CD in the ACOS cohort with AE-COPD.[1] Studies conducted in Korea[1] and Japan[47] have reported that the lung function of patients with ACOS may be recovered by medication. Meanwhile, the ACOS cohort appeared to be more responsive to bronchodilators[34] and inhaled corticosteroids[48] compared with the COPD-only cohort; this finding supports the results of our study. However, the risk of HF in the ACOS cohort with AE-COPD was still higher (aHR=1.64; p<0.05)[49] than that in the non-ACOS cohort. In Chung *et al*'s study,[44] the frequency of AE-COPD in the ACOS cohort (aHR=2.58; p<0.05) was higher than that in the COPD-only cohort. The risk of HF (aHR=1.26; p<0.05) was higher in the ACOS cohort than in the COPD cohort. These findings are consistent with those of the current study. Additional randomised controlled trials should be conducted to confirm different findings in different cohorts (eg, ACOS- and COPD-only cohorts) and our speculations.

The results of this study imply that ACOS itself is associated with the risk of CVDs, even without the presence of previous comorbidities or AE-COPD. In addition,

beta-blockers may play a role in CVD development. The results of this study indicate that physicians should be alert to detect ACOS early in adults aged ≥40 years. Thus, quitting smoking, chest care and regular follow-ups under a multidisciplinary team may be beneficial for preventing the complications of ACOS.

The strength of this study was its use of population-based data to perform a longitudinal assessment of the risk of CVDs in patients with ACOS. The data used is highly representative of the general population and minimised the likelihood of selection bias. The Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease Committees jointly created the term ACOS to acknowledge the daily reality of patients who have features of both asthma and COPD. In the present study, we defined patients with ACOS as those with concurrent, physician-diagnosed COPD and asthma. This definition is similar to the diagnostic criteria used in other recent studies.[11 13 23 24 27] In addition, we also considered lifestyle (eg, tobacco dependency) and the effects of medications (eg, beta-blockers). To avoid bias, only patients with an MPR of ≥80 were included in this analysis. Furthermore, the ACOS cohort was derived from patients with COPD who had received a PFT. Owing to the diagnosis of the COPD, we monitored the benefits of the inhaler and prescribed the long-term inhaler largely based on the PFT in Taiwan.[27 50] For example, grading of severity of airflow limitation in COPD based on postbronchodilator forced expiratory volume in 1 s.[28–30] Tobacco dependency and COPD-related diseases[24 27] (diabetes, hypertension, hyperlipidaemia, hyperuricaemia, end-stage renal disease, bone fracture, pneumonia, mental disorders and stroke) were included in the analysis. The programme of continuity of care for patients with COPD in Taiwan is well-established, and the related medical policy may have avoided confounding factors in this study.

LIMITATIONS

No universally accepted definition of ACOS currently exists, which makes it difficult to clarify its epidemiology and pathophysiology. The definition and factors for classifying a patient as having ACOS differ between studies. In this study, we defined ACOS according to the presence of both asthma and COPD based on ICD-9-CM codes. This was probably the most substantial limitation of this study. However, the ACOS cohort was derived from COPD groups[23] aged ≥40 years, as it was in studies conducted in Japan[2] and Korea,[1 9] and was based on ICD-9-CM codes used in a study recently conducted in the USA.[24] The Non-Interventional Study of COPD Patients with Asthma Overlap Syndrome in Vietnam and Taiwan (ClinicalTrials.gov identifier: NCT02878252) may address this point in the near future. Finally, data on cytokines were not available in this study. Bias resulting from unknown confounders may have affected our results.

CONCLUSION

ACOS was associated with the risk of CVDs, even without the previous presence of comorbidities or AE-COPD. No significant differences in CVD events were observed in patients who used beta-blockers in the ACOS cohort, except for those who used atenolol to treat CD.

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