



Relationships Between Bronchodilators, Steroids, Antiarrhythmic Drugs, Antidepressants, and Benzodiazepines and Heart Disease and Ischemic Stroke in Patients With Predominant Bronchiectasis and Asthma

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Objective: We investigated the effects of medication on heart disease and ischemic stroke (HDS) risk in patients with predominant bronchiectasis-asthma combination (BCAS).

Methods: BCAS and non-BCAS cohorts ($N = 588$ and $1,118$, respectively) were retrospectively enrolled. The cumulative incidence of HDS was analyzed using Cox proportional regression; propensity scores were estimated using non-parsimonious multivariable logistic regression. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for HDS were calculated, adjusting for sex, age, comorbidities, and medication {long- and short-acting β_2 agonists and muscarinic antagonists (LABAs/SABAs and LAMAs/SAMAs), steroids [inhaled corticosteroid steroids (ICSs), oral steroids (OSs)], antiarrhythmics, antidepressants (fluoxetine), benzodiazepines (alprazolam, fludiazepam), statins and antihypertensive drugs (diuretics, cardioselective beta blockers, calcium channel blockers (CCBs) and angiotensin converting enzyme inhibitors (ACEi), angiotensin II blockers)}.

Results: Compared with the non-BCAS cohort, the BCAS cohort taking LABAs, SABAs, SAMAs, ICSs, OSs, antiarrhythmics, and alprazolam had an elevated HDS risk [aHRs (95% CIs): 2.36 (1.25–4.33), 2.65 (1.87–3.75), 2.66 (1.74–4.05), 2.53 (1.61–3.99), 1.76 (1.43–2.18), 9.88 (3.27–30.5), and 1.73 (1.15–2.58), respectively except fludiazepam 1.33 (0.73–2.40)]. The aHRs (95% CIs) for LABAs ≤ 30 days, DDDs < 415 , ICSs ≤ 30

days were 1.10 (0.38–3.15), 2.95 (0.22–38.8), 1.45 (0.76–2.77). The aHRs (95% CIs) for current and recent alprazolam were 1.78 (1.09–2.93) and 777.8 (1.34–451590.0); for current and past fludiazepam were 1.39 (0.75–2.59) and 1.29 (0.42–4.01) and for past alprazolam was 1.57 (0.55–4.46); respectively. The aHRs (95% CIs) for alprazolam >30 DDDs, fludiazepam >20 DDDs, ICSs \leq 415 DDDs, and OSs DDDs \leq 15 were 1.60 (0.78–3.29), 2.43 (0.90–6.55), 5.02 (1.76–14.3), and 2.28 (1.43–3.62), respectively.

Conclusion: The bronchodilators, steroids, and antiarrhythmics were associated with higher risk of HDS, even low dose use of steroids. However, the current use of LABAs/ICSs were not associated with HDS. Benzodiazepines were relatively safe, except for current or recent alprazolam use. Notably, taking confounders into account is crucial in observational studies.

Keywords: heart disease, ischemic stroke, bronchiectasis-asthma combination, NHIRD, National Health Insurance Research Database, medicine

INTRODUCTION

Asthma and bronchiectasis are chronic inflammatory diseases (1–4). Bronchiectasis may be linked to asthma (BCAS) and is a frequent comorbidity (3, 5–7). BCAS is associated with frequent hospitalization, and a high blood eosinophil count is an additional phenotypic feature of severe eosinophilic asthma. To ensure precise and personalized treatment, BCAS should be considered as a separate entity (3, 5–7).

In the era of COVID-19, heart disease and ischemic stroke (HDS) has been reported as the most severe complication in patients with BCAS (8). Moreover, BCAS is associated with diseases related to arterial thrombosis, such as myocardial infarction and ischemic stroke (9). Psychiatric problems have also been observed in patients with COVID-19 and BCAS (10). Therefore, the effect of medications such as anti-anxiety drugs [benzodiazepines (BZDs)] in patients with BCAS is an urgent Research Topic.

We speculated that the high level of inflammation associated with atherosclerosis increases the risk of HDS (11, 12). Thus, we investigated the relationship between HDS and various drugs, including bronchodilators, steroids, antiarrhythmic drugs, anti-depressants, BZDs, and antihypertensive drugs in patients with BCAS cohort from the general population.

METHODS

Data Source

To clarify the risk of HDS in the BCAS cohort, we used the Longitudinal Health Insurance Database 2000 (LHID 2000) compiled by the Taiwan National Health Research Institutes. International Classification of Diseases, Ninth Revision, Clinical

Abbreviations: BCAS, bronchiectasis-asthma combination; LABA, long-acting beta2 agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta2 agonist; SAMA, short-acting muscarinic antagonists; aHR, adjusted hazard ratio; CI, confidence interval; ICSs, inhaled corticosteroids; OSs, oral steroids; BZDs, benzodiazepines; NHIRD, National Health Insurance Research Database; LHID, Longitudinal Health Insurance Database; ICD-9-CM, International Classification of Diseases, Ninth revision, Clinical Modification.

Modification (ICD-9-CM) diagnoses (maximum of five) were recorded in this study. In the National Health Insurance Research Database (NHIRD), ICD-9-CM codes and the ICD-9 Procedure Coding System (ICD-9-PCS) were adopted to define diagnostic and procedure codes, respectively. Pursuant to the Personal Information Protection Act, individual identifiers are encrypted before being released for research. The NHIRD has been used in various studies and provides high-quality information on diagnoses, hospitalizations, and prescriptions.

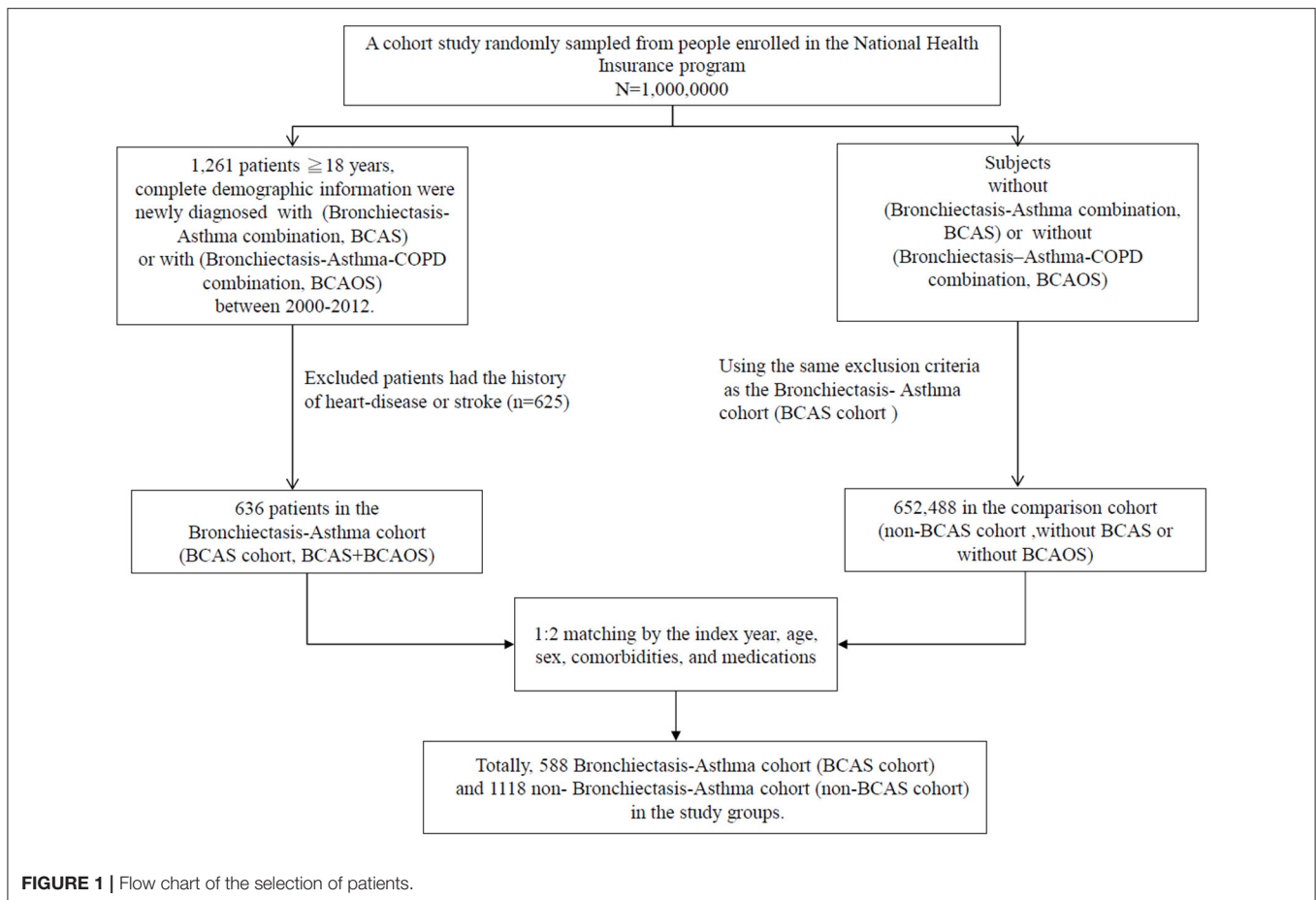
Ethics Statement

The NHIRD encrypts personal information to protect patients' privacy. It 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. The study protocol was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115-AR4), which also specifically waived the informed consent requirement.

Study Population

This BCAS cohort was selected from the cumulative outpatient and inpatient population from the LHID 2000. **Figures 1, 2** shows the process of selecting participants for study cohorts. We identified patients diagnosed with new bronchiectasis (ICD-9-CM code 494) or with new chronic obstructive pulmonary disease (COPD, ICD-9-CM Codes 491, 492, and 496) from claims data for 2000–2012.

The primary exclusion criteria were: (1) aged <18 years; (2) incomplete demographic information. The inclusion criteria ($n = 1,261$) were new diagnoses of asthma, bronchiectasis, and COPD having two outpatient visits or one inpatient visit. Patients aged ≥ 18 years having (the new bronchiectasis and new asthma combination [(ICD-9-CM Code 493), BCAS] or new BCAS and new COPD combination (BCAOS) were selected for the BCAS cohort entered into study. The control groups (non-BCAS cohort) were selected from the population without BCAS cohort. The non-BCAS cohort including the



rest of the bronchiectasis or COPD or asthma or patients with immunosuppressants such as steroids use who are without a diagnosis of BCAS cohort. The secondary exclusion criteria including: diagnoses of heart disease or stroke ($n = 625$) before entry into the study. Before matching, ACOS cohort included 636 patients, non-BCAS cohort included 652,488 subjects. The study period was from January 1, 2000 to December 31, 2013 (Figures 1, 2).

Patients in the BCAS cohort were matched to individuals in the non-BCAS cohort according to gender, age (5-year span), comorbidities, medications, and year of entry into the study by frequency matching. After 1: 2 matching, the BCAS ($n = 588$) including the (6, pure BCAS and 7, BCAS+COPD, BCAOS). The non-BCAS cohort ($n = 1,118$) including the (1: pure bronchiectasis) = ((1 + 4 + 6 + 7, new bronchiectasis) - (4, BCOS) - (6, BCAS) - (7, BCAOS)), (2: pure COPD) = ((2 + 4 + 5 + 7, new COPD) - (4, BCOS) - (5, ACOS) - (7, BCAOS)), (3: pure asthma) = ((3 + 5 + 6 + 7, new asthma) - (5, ACOS) - (6, BCAS) - (7, BCAOS)), (4: bronchiectasis + COPD, BCOS), (5: asthma + COPD, ACOS) and (8: others - such as patients with steroids use) (Figure 2). We defined the index date of case-cohort by the first date of drugs prescription after a diagnosis of BCAS and we restricted the case-cohort to patients with used drugs for more than 28 days. [For the ICD-9-CM codes for

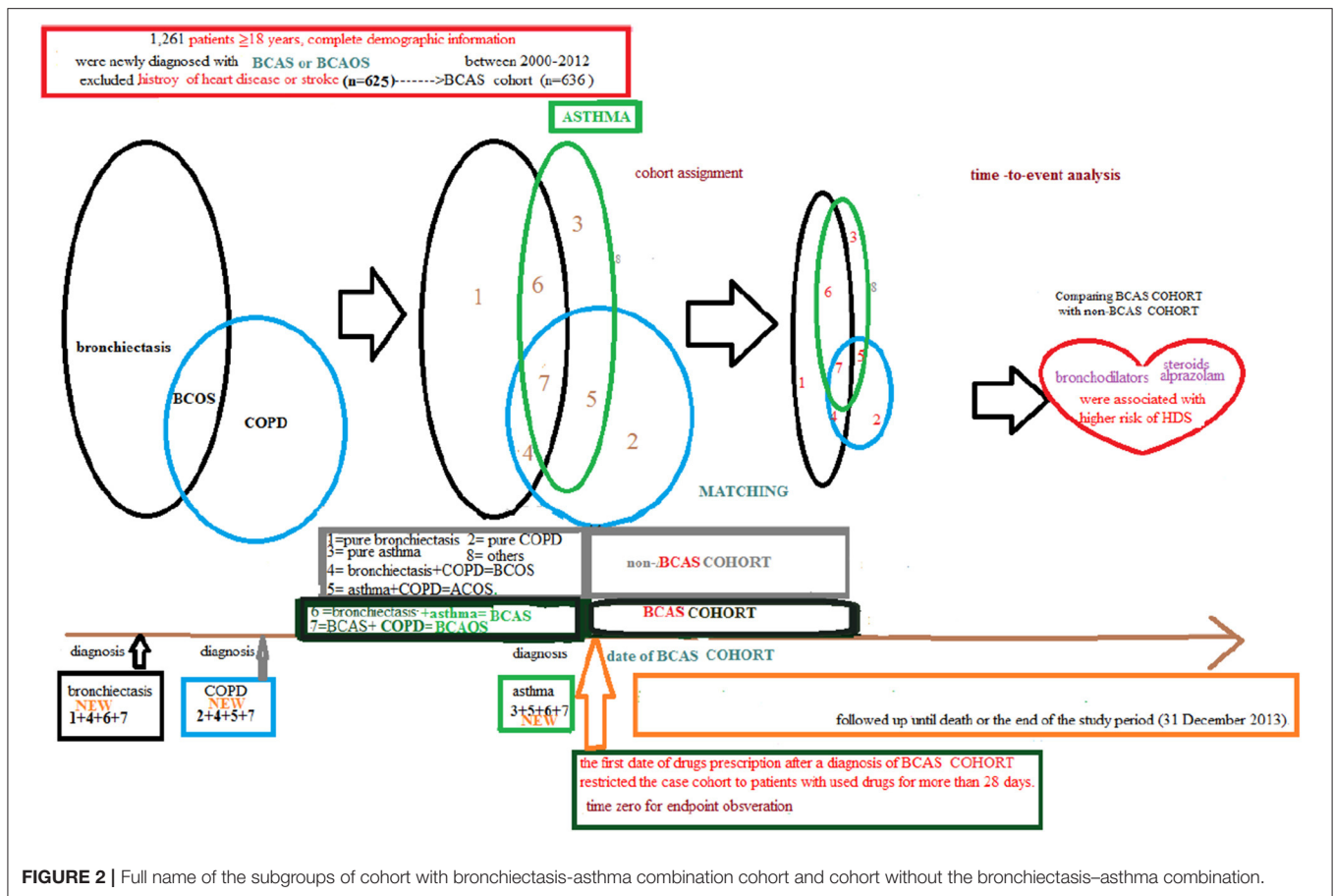
comorbidities and the Anatomical Therapeutic Chemical (ATC) codes for medications, see **Supplementary Table 1**].

These patients were followed up until the occurrence of heart disease (ICD-9-CM codes 410–414, 425–429) or ischemic stroke (ICD-9-CM codes 433, 434, 435, and 436), death, withdrawal from the insurance program, or the end of the study period (December 31, 2013). For full names of comorbidities and medications (**Supplementary Table 1**).

Statistical Analysis

The propensity scores (PS) for each patient were estimated using non-parsimonious multivariable logistic regression, with receipt of patients with or without BCAS cohort as the independent variable. We incorporated clinically relevant covariates (comorbidities, drugs, etc.) into our analysis—the primary analysis. The (heart disease or ischemic stroke, HDS) as dependent variables (13).

The BCAS cohort was compared with the non-BCAS cohort concerning variables, and the Wilcoxon rank-sum test was used to compare continuous variables between the BCAS cohort and the non-BCAS cohort, as necessary. The incidence density rates (per 1,000 person-years) were analyzed to estimate the HDS incidence in the BCAS cohort and the non-BCAS cohort stratified by gender, age, comorbidities, and medications. The



annual incidence density rate was calculated by dividing the number of newly diagnosed HDS cases by the number of person-years at risk for BCAS cohort in each subgroup from 2000 to 2013. The comparison of the risk of HDS between the BCAS cohort and the non-BCAS cohort was calculated using Cox proportional hazard regression models. The analysis was adjusted for gender, age, comorbidities, and medications. The significance threshold was set at $\alpha = 0.05$ for the a priori hypotheses. All analyses were performed using SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics of the Study Population of the Propensity Score-Matched Population

Table 1 displays the distributions of age, comorbidities, and medications between the two cohorts. After PS-matching, the BCAS cohort comprised 588 patients, and the non-BCAS cohort included 1,118 patients. The two cohorts had a similar gender distribution. The mean age (SD) of patients was 54.66 (± 32.2) years in the BCAS cohort and 56.53 (± 34.0) years in the non-BCAS cohort (Wilcoxon rank-sum test, $p = 0.02$). Patients were predominately aged between 40 and 64 years. The demographic

data of the BCAS cohort were similar to those of the non-BCAS cohort in terms of gender, age, comorbidities grouped and medications (bronchodilators, steroids, antiarrhythmic drugs, antidepressants, BZDs, statins, and antihypertensive drugs), with no significant differences between the BCAS cohort and non-BCAS cohort, except the use of long-acting $\beta 2$ agonists (LABAs), inhaled corticosteroid steroids (ICSs), diuretics, cardioselective beta blockers, angiotensin converting enzyme inhibitors (ACEi), and calcium channel blockers (CCBs) were significantly more frequent in the BCAS cohort than in the non-BCAS cohort.

Comparison of HDS Risk Between the BCAS Cohort and Non-BCAS Cohorts, With Patients Without Comorbidities or Medications as the Reference Group

As shown in Table 2, the incidence density rates of HDS were higher in the BCAS cohort than in the non-BCAS cohort (51.5 vs. 33.1 per 1,000 person-years). The results revealed that BCAS cohort had a higher risk of HDS than the non-BCAS cohort [adjusted hazard ratio (aHR) = 1.79; 95% confidence interval (CI) = 1.48–2.18]. The risks of HDS were 13.5-fold and 23.5-fold higher in patients aged 40–64 years (95% CI = 3.33–54.7) and ≥ 65 years (95% CI = 5.74–96.0), the patients aged < 20 years as reference. Patients with rheumatoid arthritis (adjusted HR =

TABLE 1 | Baseline characteristics of study population before and after matching based on propensity scores between two cohorts.

Variable	Original population				p-value*	PS-matching population				p-value*
	BCAS cohort (n = 636)		Non-BCAS cohort (n = 652,488)			BCAS cohort (n = 588)		Non-BCAS cohort (n = 1,118)		
	N	%	N	%		N	%	N	%	
Gender					0.0014					0.11
Female	350	55.0	317,605	48.7		323	54.9	569	60.9	
Male	286	45.0	334,883	51.3		265	45.1	549	49.1	
Age at baseline, year					<0.0001					0.001
<20	27	4.25	146,757	22.4		25	4.25	54	4.83	
20–39	87	13.6	267,629	41.0		81	13.7	153	13.6	
40–64	333	52.3	207,251	31.7		315	53.5	494	44.1	
≥65	189	29.7	30,855	4.73		167	28.4	417	37.3	
Mean (SD) [†]	54.92 (32.3)		34.35 (49.6)		<0.0001	54.66 (32.2)		56.53 (34.0)		0.02
Comorbidity										
Pulmonary tuberculosis	78	12.2	2,428	0.37	<0.0001	70	11.9	116	10.3	0.33
Non-tuberculosis mycobacterium	5	0.79	148	0.02	<0.0001	4	0.68	6	0.54	0.71
Rheumatoid arthritis	13	2.04	5,043	0.77	0.0003	9	1.53	22	1.97	0.52
Diffuse connective disease	12	1.89	4,599	0.70	0.0004	10	1.70	24	2.15	0.53
Pneumonia	202	31.7	22,265	3.41	<0.0001	177	30.1	329	29.4	0.77
COPD	349	54.8	18,575	2.85	<0.0001	315	53.5	632	56.5	0.24
Diabetes	69	10.8	21,527	3.30	<0.0001	64	10.8	128	11.4	0.72
Aspergillosis	2	0.31	20	0.003	<0.0001	2	0.34	0	0	0.05
Candidiasis	1	0.16	14	0.002	<0.0001	1	0.17	1	0.09	0.64
Endemic mycoses	0	0	41	0.01	0.84	0	0	0	0	–
Mounier-Kuhn	0	0	59	0.01	0.81	0	0	0	0	–
Cystic fibrosis	0	0	3	0.0004	0.95	0	0	0	0	–
Hypertension	216	33.9	56,003	8.57	<0.0001	194	32.9	405	36.2	0.18
Hyperlipidemia	100	15.7	38,046	5.83	<0.0001	93	15.8	218	19.5	0.06
Pulmonary embolism	0	0	84	0.01	0.77	0	0	2	0.18	0.30
Depression	5	0.79	3,056	0.47	0.24	5	0.85	10	0.89	0.92
Smoking										
Tobacco dependence	1	0.16	597	0.09	0.58	1	0.17	2	0.18	0.96
Tobacco use disorder complicating pregnancy	0	0	0	0	–	0	0	0	0	–
Medication										
LABA	132	20.7	582	0.09	<0.0001	116	19.73	149	13.3	0.0005
LAMA	13	2.04	95	0.01	<0.0001	12	2.04	16	1.43	0.34
SABA	260	40.8	13,426	2.06	<0.0001	234	39.8	432	38.6	0.64
SAMA	179	28.1	8,524	1.31	<0.0001	159	27.0	299	26.7	0.89
ICSs	209	32.8	937	0.14	<0.0001	184	31.2	239	21.3	<0.0001
Oss	585	91.9	469,554	71.96	<0.0001	538	91.5	1028	91.9	0.74
Anti-arrhythmic	46	7.23	15,413	2.36	<0.0001	43	7.31	81	7.25	0.95
Alprazolam	169	26.5	71,361	10.9	<0.0001	155	26.3	296	26.4	0.95
Fluoxetine	0	0	224	0.03	0.64	0	0	0	0	–
Fludiazepam	80	12.5	28,789	4.41	<0.0001	72	12.2	144	12.8	0.70
Statins	52	8.18	29,369	4.50	<0.0001	52	8.84	125	11.2	0.13
Anti-hypertensive drugs										
Diuretics	73	11.5	31,369	4.81	<0.0001	70	11.9	261	23.4	<0.0001
Beta blockers	84	13.2	64,661	9.91	0.005	82	14.0	199	17.8	0.04
Calcium channel blockers	128	20.1	59,686	9.15	<0.0001	125	21.3	313	28.0	0.003
Angiotensin converting enzyme inhibitors	43	6.76	24,049	3.69	<0.0001	42	7.14	123	11.0	0.01
Angiotensin II blockers	53	8.33	13,320	2.04	<0.0001	49	8.33	96	8.59	0.86

*P-value using chi-square for the comparisons between with and without BCAS cohort.

[†] Average age using Wilcoxon rank-sum test for verification.

BCAS cohort, Bronchiectasis-Asthma combination cohort; COPD, Chronic obstructive pulmonary disease; LABAs/LAMAs, long-acting β_2 -agonist or muscarinic antagonist; SABAs/SAMAs, short-acting β_2 -agonist or muscarinic antagonist, steroids; ICSs, inhaled corticosteroid steroids; Oss, oral steroids; Beta blockers, cardioselective beta blockers (atenolol, bisoprolol, metoprolol).

TABLE 2 | Cox model measured hazard ratios and 95% confidence interval of heart-disease or ischemic stroke associated with gender, age, and comorbidity after propensity matching between two cohorts.

	Heart-disease or ischemic stroke			Crude HR (95%CI)	Adjusted HR (95%CI)
	Event	PY	IR		
BCAS cohort					
No	250	7,549	33.1	1 (reference)	1 (reference)
Yes	182	3,532	51.5	1.54 (1.28–1.87)***	1.79 (1.48–2.18)***
Gender					
Female	213	6,060	35.1	1 (reference)	1 (reference)
Male	219	5,021	43.6	1.22 (1.01–1.47)*	1.19 (0.98–1.45)
Age					
<20	2	861	2.32	1 (reference)	1 (reference)
20–39	16	2,090	7.65	3.25 (0.74–14.15)	2.54 (0.58–11.1)
40–64	203	5,270	38.5	15.94 (3.95–64.19)***	13.5 (3.33–54.7)***
≥65	211	2,860	73.7	29.9 (7.42–120.48)***	23.5 (5.74–96.0)***
Comorbidity					
Pulmonary tuberculosis					
No	388	10,132	38.2	1 (reference)	1 (reference)
Yes	44	949	46.3	1.16 (0.85–1.58)	–
Non-tuberculosis mycobacterium					
No	430	11,036	38.9	1 (reference)	1 (reference)
Yes	2	45	44.4	1.07 (0.26–4.32)	–
Rheumatoid arthritis					
No	419	10,939	38.3	1 (reference)	1 (reference)
Yes	13	142	91.5	2.31 (1.33–4.01)**	2.47 (1.41–4.32)**
Diffuse connective disease					
No	424	10,884	38.9	1 (reference)	1 (reference)
Yes	8	197	40.6	1.00 (0.50–2.02)	–
Pneumonia					
No	304	8,410	36.1	1 (reference)	1 (reference)
Yes	128	2,671	47.9	1.25 (1.02–1.54)*	0.95 (0.76–1.18)
COPD					
No	165	5,673	29.0	1 (reference)	1 (reference)
Yes	267	5,408	49.3	1.62 (1.33–1.97)***	1.18 (0.96–1.45)
Diabetes					
No	360	10,149	35.4	1 (reference)	1 (reference)
Yes	72	932	77.2	2.05 (1.59–2.65)***	1.35 (1.04–1.76)*
Aspergillosis					
No	431	11,073	38.9	1 (reference)	1 (reference)
Yes	1	8	125	2.93 (0.41–20.86)	–
Candidiasis					
No	431	11,077	38.9	1 (reference)	1 (reference)
Yes	1	4	250	6.51 (0.91–46.59)	–
Endemic mycoses					
No	432	11,081	38.9	1 (reference)	1 (reference)
Yes	0	0	0	–	–
Mounier-Kuhn					
No	432	11,081	38.9	1 (reference)	1 (reference)
Yes	0	0	0	–	–
Cystic fibrosis					
No	432	11,081	38.9	1 (reference)	1 (reference)

(Continued)

TABLE 2 | Continued

	Heart-disease or ischemic stroke			Crude HR (95%CI)	Adjusted HR (95%CI)
	Event	PY	IR		
Yes	0	0	0	–	–
Hypertension					
No	216	8,031	26.8	1 (reference)	1 (reference)
Yes	216	3,050	70.8	2.52 (2.08–3.04)***	1.67 (1.35–2.07)***
Hyperlipidemia					
No	339	9,433	35.9	1 (reference)	1 (reference)
Yes	93	1,648	56.4	1.50 (1.19–1.89)***	1.13 (0.89–1.44)
Pulmonary embolism					
No	432	11,063	39.0	1 (reference)	1 (reference)
Yes	0	18	0	–	–
Depression					
No	428	11,014	38.8	1 (reference)	1 (reference)
Yes	4	67	59.7	1.44 (0.53–3.85)	–
Smoking					
Tobacco dependence					
No	432	11,058	39.0	1 (reference)	1 (reference)
Yes	0	23	0	–	–
Tobacco use disorder complicating pregnancy					
No	432	11,081	38.9	1 (reference)	1 (reference)
Yes	0	0	0	–	–
LABA					
Non-use	382	9,500	40.2	1 (reference)	1 (reference)
Use	50	1,581	31.6	0.76 (0.56–1.02)	–
LAMA					
Non-use	427	10,907	39.1	1 (reference)	1 (reference)
Use	5	174	28.7	0.72 (0.29–1.74)	–
SABA					
Non-use	297	6,846	43.3	1 (reference)	1 (reference)
Use	135	4,235	31.8	0.72 (0.59–0.89)**	0.67 (0.54–0.83)***
SAMA					
Non-use	336	8,257	40.6	1 (reference)	1 (reference)
Use	96	2,824	33.9	0.82 (0.65–1.03)	–
ICSs					
Non-use	341	8,365	40.7	1 (reference)	1 (reference)
Use	91	2,716	33.5	0.81 (0.64–1.02)	–
OSs					
Non-use	67	471	142.2	1 (reference)	1 (reference)
Use	365	10,610	34.4	0.24 (0.19–0.32)***	0.31 (0.23–0.41)***
Anti-arrhythmic					
Non-use	408	10,307	39.5	1 (reference)	1 (reference)
Use	24	774	31.0	0.77 (0.51–1.17)	–
Alprazolam					
Non-use	328	7,816	41.9	1 (reference)	1 (reference)
Use	104	3,265	31.8	0.76 (0.61–0.95)*	0.87 (0.69–1.09)
Fluoxetine					
Non-use	432	11,081	38.9	1 (reference)	1 (reference)
Use	0	0	0	–	–
Fludiazepam					

(Continued)

TABLE 2 | Continued

	Heart-disease or ischemic stroke			Crude HR (95%CI)	Adjusted HR (95%CI)
	Event	PY	IR		
Non-use	376	9,404	39.9	1 (reference)	1 (reference)
Use	56	1,677	33.3	0.85 (0.64–1.13)	–
Statins					
Non-use	397	9,593	41.4	1 (reference)	1 (reference)
Use	35	1,488	23.5	0.58 (0.41, 0.82)**	0.50 (0.35, 0.71)**
Anti-hypertensive drugs					
Diuretics					
Non-use	364	8,974	40.6	1 (reference)	1 (reference)
Use	68	2,106	32.3	0.78 (0.60, 1.01)	–
Beta blockers					
Non-use	370	8,847	41.8	1 (reference)	1 (reference)
Use	62	2,234	27.8	0.69 (0.53, 0.90)**	0.80 (0.60, 1.05)
Calcium channel blocker					
Non-use	328	7,837	41.9	1 (reference)	1 (reference)
Use	104	3,244	32.1	0.78 (0.63, 0.97)*	0.67 (0.53, 0.85)**
Angiotensin converting enzyme inhibitors					
Non-use	388	9,818	39.5	1 (reference)	1 (reference)
Use	44	1,263	34.9	0.89 (0.65–1.22)	–
Angiotensin II blockers					
Non-use	393	10,020	39.2	1 (reference)	1 (reference)
Use	39	1,061	36.8	0.94 (0.68, 1.31)	–

BCAS cohort, Bronchiectasis-Asthma combination cohort; COPD, Chronic obstructive pulmonary disease.

PY, person-years; IR, incidence rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval; HR adjusted for BCAS cohort, gender, age, Rheumatoid arthritis, Pneumonia, COPD, Diabetes, Hypertension, Hyperlipidemia, SABAs, OSs, Alprazolam, Statins, Beta blocking blockers, and Calcium channel blockers.

LABAs/LAMAs, long-acting β_2 -agonist or muscarinic antagonist; SABAs/SAMAs, short-acting β_2 -agonist or muscarinic antagonist, steroids; ICSs, inhaled corticosteroid steroids; OSs, oral steroids; Beta blockers, cardioselective beta blockers (atenolol, bisoprolol, metoprolol).

–, Unable to calculate because of there are few or no events in with and without BCAS cohort.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

2.47; 95% CI = 1.41–4.32), diabetes (aHR = 1.35; 95% CI = 1.04–1.76), and hypertension (aHR = 1.67; 95% CI = 1.35–2.07) had a significantly elevated risk of HDS, patients without comorbidities as reference. Patients taking SABAs (aHR = 0.67; 95% CI = 0.54–0.83), OSs (aHR = 0.31; 95% CI = 0.23–0.41), statins (aHR = 0.50; 95% CI = 0.35–0.71), and CCBs (aHR = 0.67; 95% CI = 0.53–0.85) had a significantly lower risk of HDS, with patients not using the (SABAs, OSs, statins, CCBs) as references.

Risk of HDS Among the BCAS Cohort and the Non-BCAS Cohort on Comorbidities and Medication

As shown in **Table 3**, 182 patients with HDS in the BCAS cohort and 250 patients with HDS in the non-BCAS cohort were included in this analysis. After adjustment for age, comorbidities,

and medications, the BCAS cohort had a higher risk of HDS than the non-BCAS cohort among female (aHR = 1.42; 95% CI = 1.07–1.88), male (aHR = 2.39; 95% CI = 1.82–3.14), patients aged 20–39 years (aHR = 4.26; 95% CI = 1.38–13.2), patients aged 40–64 years (aHR = 1.57; 95% CI = 1.18–2.08), and patients over 65 years (aHR = 2.07; 95% CI = 1.55–2.76), patients with pneumonia (aHR = 2.39; 95% CI = 1.63–3.50), COPD (aHR = 2.15; 95% CI = 1.67–2.77), patients with diabetes (aHR = 1.84; 95% CI = 1.12–3.02), patients with hypertension (aHR = 1.87; 95% CI = 1.42–2.46), patients with hyperlipidaemia (aHR = 1.73; 95% CI = 1.12–2.67), patients using LABAs (aHR = 2.36; 95% CI = 1.25–4.43), patients using SABAs (aHR = 2.65; 95% CI = 1.87–3.75), patients using SAMAs (aHR = 2.66; 95% CI = 1.74–4.05), patients using ICSs (aHR = 2.53; 95% CI = 1.61–3.99), patients using OSs (aHR = 1.76; 95% CI = 1.43–2.18), patients using antiarrhythmic drugs (aHR = 9.88; 95% CI = 3.27–30.5), and patients using BZDs (alprazolam: aHR = 1.73; 95% CI = 1.15–2.58). All medications were associated with an increased risk of HDS, except fludiazepam (aHR = 1.33; 95% CI = 0.73–2.40).

Comparison Between Different Durations From the Last Day of Medication Use to HDS Occurrence Among the BCAS Cohort and the Non-BCAS Cohort

Table 4 shows that relative to the non-BCAS cohort, the BCAS cohort had a significantly higher risk of HDS between the final day of use and the HDS event. The aHRs and 95% CI of the patients in the **Table 4** display below: patients with LABAs > 90 days (aHRs = 4.58; 95% CI = 1.71–12.3), SABAs \leq 30 days (aHRs = 2.80; 95% CI = 1.81–4.33), SAMA \leq 30 days (aHRs = 3.00; 95% CI = 1.78–5.04), ICSs > 90 days (aHRs = 4.61; 95% CI = 2.18–9.76), OSs \leq 30 days (aHRs = 1.80; 95% CI = 1.43–2.25), antiarrhythmic drugs \leq 30 days (aHRs = 6.69; 95% CI = 1.55–28.8), and alprazolam \leq 30 days (aHRs = 1.78; 95% CI = 1.09–2.93); 30–90 days (aHRs = 777.8; 95% CI = 1.34–451590.0).

However, for LABAs (\leq 30 days), SABA (30–90days, >90days), SAMAs (>90 days), ICSs (\leq 30 days), OSs (>90 days), alprazolam (>90 days), fludiazepam (\leq 30 days, >90 days) were not associated with the HDS.

Comparison of HDS for Different Cumulative Daily Defined Doses of Medication in the BCAS Cohort and Non-BCAS Cohort

As shown in **Table 5**, relative to the non-BCAS cohort, a significant higher risk of HDS was observed for the cumulative daily defined dose (cDDD) of 416–2,300 DDDs for LABAs (aHR = 18.7; 95% CI = 1.29–272.7); >165 DDDs for SABAs [aHR = 3.31, 95% (1.65–6.65)]; \leq 415, 415–1500, >1500 DDDs for ICSs (aHR = 5.02; 95% CI = 1.76–14.3; aHR = 2.58; 95% CI = 1.22–5.46; and aHR = 3.34; 95% CI = 1.40–7.97, respectively); \leq 15, 16–155, and >155 DDDs for OSs (aHR = 2.28; 95% CI = 1.43–3.62; aHR = 1.90; 95% CI = 1.28–2.81; and aHR = 1.95; 95% CI

TABLE 3 | Incidence rate and hazard ratio of ischemic stroke or heart-disease between two cohorts stratified by gender, age, comorbidities and drug use after propensity matching.

	BCAS cohort						Crude HR (95% CI)	Adjusted HR (95% CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
Gender								
Female	130	4,018	32.35	83	2,041	40.66	1.23 (0.94–1.63)	1.42 (1.07–1.88)*
Male	120	3,531	33.9	99	1,491	66.39	1.97 (1.51–2.57)***	2.39 (1.82–3.14)***
Age								
<20	2	577	3.46	0	284	0	–	–
20–39	7	1,429	4.89	9	661	13.61	2.65 (0.98–7.13)	4.26 (1.38–13.2)*
40–64	109	3,380	32.24	94	1,890	49.73	1.53 (1.16–2.02)**	1.57 (1.18–2.08)***
≥65	132	2,163	61.02	79	697	113.34	1.85 (1.40–2.45)***	2.07 (1.55–2.76)***
Comorbidity								
Pulmonary tuberculosis								
No	224	6,947	32.24	164	3,185	51.49	1.58 (1.29–1.94)***	1.91 (1.56–2.34)***
Yes	26	602	43.18	18	247	72.87	1.24 (0.67–2.26)	1.57 (0.82–2.99)
Non-tuberculosis mycobacterium								
No	249	7,515	33.13	181	3,522	51.39	1.54 (1.27–1.87)***	1.84 (1.52–2.24)***
Yes	1	34	29.41	1	10	100	1.73 (0.10–27.89)	–
Rheumatoid arthritis								
No	241	7,460	32.30	178	3,479	51.16	1.57 (1.29–1.91)***	1.87 (1.54–2.28)***
Yes	9	89	101.12	4	53	75.47	0.78 (0.22–2.70)	–
Diffuse connective disease								
No	245	7,396	33.12	179	3,488	51.31	1.54 (1.27–1.87)***	1.86 (1.52–2.26)***
Yes	5	153	32.67	3	44	68.18	2.17 (0.51–9.20)	0.83 (0.06–10.37)
Pneumonia								
No	180	5,766	31.21	124	2,644	46.89	1.49 (1.18–1.87)***	1.63 (1.29–2.05)***
Yes	70	1,783	39.25	58	888	65.31	1.68 (1.19–2.38)**	2.39 (1.63–3.50)***
COPD								
No	98	3,744	26.17	67	1,929	34.73	1.31 (0.96–1.79)	1.37 (0.99–1.89)
Yes	152	3,805	39.94	115	1,603	71.74	1.78 (1.40–2.28)***	2.15 (1.67–2.77)***
Diabetes								
No	210	6,932	30.29	150	3,217	46.62	1.53 (1.24–1.88)***	1.81 (1.46–2.25)***
Yes	40	617	64.82	32	315	101.58	1.56 (0.98–2.50)	1.84 (1.12–3.02)**
Aspergillosis								
No	250	7,549	33.11	181	3,524	51.36	1.54 (1.27–1.87)***	1.87 (1.54–2.27)***
Yes	0	0	–	1	8	125	–	–
Candidiasis								
No	249	7,547	32.99	182	3,531	51.54	1.55 (1.28–1.88)***	1.88 (1.55–2.28)***
Yes	1	2	500	0	1	0	–	–
Endemic mycoses								
No	250	7,549	33.11	182	3,532	51.52	1.54 (1.28–1.87)***	1.87 (1.54–2.27)***
Yes	0	0	0	0	0	0	–	–
Mounier-Kuhn								
No	250	7,549	33.11	182	3,532	51.52	1.54 (1.28–1.87)***	1.87 (1.54–2.27)***
Yes	0	0	0	0	0	0	–	–
Cystic fibrosis								
No	250	7,549	33.11	182	3,532	51.52	1.54 (1.28–1.87)***	1.87 (1.54–2.27)***
Yes	0	0	0	0	0	0	–	–
Hypertension								
No	124	5,385	23.02	92	2,645	34.78	1.49 (1.14–1.96)**	1.81 (1.37–2.40)***

(Continued)

TABLE 3 | Continued

	BCAS cohort						Crude HR (95% CI)	Adjusted HR (95% CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
Yes	126	2,164	58.22	90	887	101.46	1.73 (1.32–2.27)***	1.87 (1.42–2.46)***
Hyperlipidemia								
No	192	6,355	30.21	147	3,078	47.75	1.57 (1.26–1.94)***	1.82 (1.46–2.27)***
Yes	58	1,194	48.57	35	454	77.09	1.56 (1.02–2.37)*	1.73 (1.12–2.67)*
Pulmonary embolism								
No	250	7,530	33.20	182	3,532	51.52	1.54 (1.27–1.87)***	1.85 (1.52–2.24)***
Yes	0	19	0	0	0	0	–	–
Depression								
No	248	7,498	33.07	180	3,516	51.19	1.54 (1.27–1.86)***	1.85 (1.52–2.24)***
Yes	2	51	39.21	2	16	125	2.02 (0.28–14.41)	–
Smoking								
Tobacco dependence								
No	250	7,534	33.18	182	3,524	51.64	1.55 (1.28–1.87)***	1.85 (1.52–2.25)***
Yes	0	15	0	0	8	0	–	–
Tobacco use disorder complicating pregnancy								
No	250	7,549	33.11	182	3,532	51.52	1.54 (1.28–1.87)***	1.85 (1.52–2.25)***
Yes	0	0	0	0	0	0	–	–
Drug use								
LABA								
Non-use	228	6,658	34.24	154	2,842	54.18	1.57 (1.28–1.93)***	1.83 (1.49–2.25)***
Use	22	891	24.69	28	690	40.57	1.65 (0.94–2.88)	2.36 (1.25–4.43)*
LAMA								
Non-use	249	7,452	33.41	178	3,455	51.51	1.53 (1.26–1.86)***	1.83 (1.50–2.22)***
Use	1	97	10.30	4	77	51.94	4.92 (0.54–44.34)	–
SABA								
Non-use	186	4,737	39.26	111	2,109	52.63	1.32 (1.05–1.68)*	1.62 (1.27–2.05)***
Use	64	2,812	22.75	71	1,423	49.89	2.18 (1.55–3.06)***	2.65 (1.87–3.75)***
SAMA								
Non-use	207	5,677	36.46	129	2,579	50.01	1.36 (1.09–1.69)**	1.69 (1.35–2.12)***
Use	43	1,872	22.97	53	953	55.61	2.40 (1.61–3.60)***	2.66 (1.74–4.05)***
ICSs								
Non-use	211	5,976	35.30	130	2,389	54.41	1.53 (1.23–1.90)***	1.72 (1.38–2.14)***
Use	39	1,573	24.79	52	1,143	45.49	1.83 (1.21–2.78)**	2.53 (1.61–3.99)***
OSs								
Non-use	38	352	107.95	29	119	243.69	2.05 (1.26–3.34)**	2.40 (1.44–3.99)**
Use	212	7,197	29.45	153	3,413	44.82	1.52 (1.23–1.87)***	1.76 (1.43–2.18)***
Anti-arrhythmic								
Non-use	240	7,026	34.15	168	3,281	51.20	1.49 (1.22–1.82)***	1.72 (1.41–2.11)***
Use	10	523	19.12	14	251	55.77	3.01 (1.32–6.81)**	9.88 (3.27–30.5)***
Alprazolam								
Non-use	189	5,349	35.33	139	2,467	56.34	1.58 (1.27–1.97)***	1.88 (1.50–2.34)***
Use	61	2,200	27.72	43	1,065	40.37	1.44 (0.98–2.14)	1.73 (1.15–2.58)**
Fluoxetine								
Non-use	250	7,549	33.11	182	3,532	51.52	1.54 (1.28–1.87)***	1.86 (1.53–2.26)***
Use	0	0	0	0	0	0	–	–
Fludiazepam								

(Continued)

TABLE 3 | Continued

	BCAS cohort						Crude HR (95% CI)	Adjusted HR (95% CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
Non-use	215	6,398	33.60	161	3,006	53.55	1.59 (1.29–1.95)***	1.94 (1.57–2.39)***
Use	35	1,151	30.40	21	526	39.92	1.30 (0.75–2.23)	1.33 (0.73–2.40)

BCAS cohort, Bronchiectasis-Asthma combination cohort; COPD, Chronic obstructive pulmonary disease; PY, person-years; IR, incidence rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval.

HR adjusted for BCAS cohort, gender, age, Rheumatoid arthritis, Pneumonia, COPD, Diabetes, Hypertension, Hyperlipidemia, SABAs, OSs, Alprazolam, Statins, Beta blockers, and Calcium channel blockers.

LABAs/LAMAs, long-acting β 2-agonist or muscarinic antagonist; SABAs/SAMAs, short-acting β 2-agonist or muscarinic antagonist, steroids; ICSS, inhaled corticosteroid steroids; OSs, oral steroids; Beta blockers, cardioselective beta blockers (atenolol, bisoprolol, metoprolol).

–, Unable to calculate because of there are few or no events in with and without BCAS cohort.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

= 1.26–3.02, respectively); and 6–30 DDDs for alprazolam (aHR = 2.31; 95% CI = 1.09–4.89).

However, there were not associated with the risk of the HDS for LABAs at ≤ 415 DDDs and $> 2,300$ DDDs, LAMA at any dose, SABAs at ≤ 1 DDDs and 2–165 DDDs, alprazolam at ≤ 5 and > 30 DDDs, and fludiazepam at ≤ 5 , > 6 –20, and > 20 DDDs.

The Kaplan–Meier analysis for the cumulative incidence of HDS revealed significant differences between the BCAS cohort and the non-BCAS cohort (log-rank test, $p < 0.0001$) as being statistically significant in HDS (Figure 3).

Validation of Bronchiectasis With Asthma

Patients with BCAS cohort were derived from the bronchiectasis, asthma and COPD group presenting as the (6: bronchiectasis and asthma combination, BCAS) or (7: BCAS and COPD combination, BCAOS) in the general population (predominant BCAS (Figure 4).

SUMMARY FINDINGS OF RESULTS

Immortal Time Bias

To resolve the immortal time bias in this observational study, we established a 1-year confirmation period (14). Users were defined as patients who needed to start using medications and had at least one prescription and received treatment for at least 28 days within 1 year after BCAS cohort diagnosis. Non-users were defined as patients who did not receive a prescription for these drugs and were not treated for at least 28 days within 1 year after BCAS cohort diagnosis (Table 6).

Under a multiple disciplinary team, the pay-for-performance (P4P) of asthma including an initial visit for new patients, outpatient care and hospitalization, first prescription, emergency visits, drug refill prescriptions, and providers for producing an improvement in performance based on quality measures was determined (14, 15). This strict policy helped us to avoid immortal time bias in this study (16).

Statins, Beta Blockers, Angiotensin-Converting Enzyme Inhibitors Angiotensin II-Receptor Blockers Use and Target Level for Hypertension, Diabetes, Low Density Lipoprotein-Cholesterol

Oxidative stress has been implicated in many pathophysiological conditions in the HDS, including hyperlipidemia, hypertension, and diabetes (17). These diseases associated with the higher risk of HDS in the BCAS cohort (Table 3) (18). The statins, beta blockers, renin-angiotensin system (RAS) inhibitors (e.g., ACEi, angiotensin II-receptor blockers, ARBs) with anti-inflammatory and oxidative stress effects (19). Experimental studies have shown reciprocal relationships between insulin resistance and endothelial dysfunction. Hyperlipidemia and hypertension have a synergistic deleterious effect on insulin resistance and endothelial dysfunction. Unregulated RAS is a key factor in the pathogenesis of atherosclerosis and hypertension. Various strategies with different classes of antihypertensive medications to reach target goals have failed to attenuate the residual HDS further. Of interest, treating hyperlipidemia with statins in hypertensive patients are associated with the lower HDS risk further (20). In previous study, statins therapy are associated with the higher risk for insulin resistance and type 2 diabetes mellitus. Fortunately, RAS inhibitors attenuate the endothelial dysfunction and risk of insulin resistance (21). In this regard, combined therapy with statins and RAS inhibitors not only demonstrates additive/synergistic effects on endothelial dysfunction and insulin resistance but also lowering cholesterol levels and blood pressure (BP) when compared with either monotherapy in patients having hypertension, hyperlipidemia (22).

Meanwhile, increased carotid intima-media thickness (CIMT) is associated with an increased risk for ischemic stroke (23). Calcium channel blockers (CCBs) and RAS inhibitors such as ARBs have a role for improving the nitric oxide production, modulating the oxidative stress, and attenuating the risk of CIMT in patients with hypertension (24). Thus, ARBs and CCBs use were associated with the lower risk of HDS such as ischemic stroke. Altogether, combined therapy with the statins and RAS

TABLE 4 | Incidence rate and hazard ratio of ischemic stroke or heart-disease between two cohorts stratified by current, recent and past use.

	BCAS cohort						Crude HR (95%CI)	Adjusted HR (95%CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
Drug-use days		7,549			3,532			
LABA								
Non-use	228	6,658	34.24	154	2,842	54.18	1.57 (1.28–1.93)***	1.86 (1.51, 2.29)***
Current use (≤30 d)	14	319	43.88	12	173	69.36	1.64 (0.76–3.56)	1.10 (0.38, 3.15)
Recent use (30–90 d)	1	41	24.39	1	27	37.03	1.50 (0.09–23.98)	–
Past use (>90 d)	7	531	13.18	15	490	30.61	2.29 (0.93–5.63)	4.58 (1.71, 12.3)**
LAMA								
Non-use	249	7,452	33.41	178	3,455	51.51	1.53 (1.26–1.86)***	1.85 (1.52, 2.25)***
Current use (≤30 d)	0	51	0	3	44	68.18	–	–
Recent use (30–90 d)	0	3	0	0	0		–	–
Past use (>90 d)	1	43	23.25	1	33	30.30	1.52 (0.09–24.57)	–
SABA								
Non-use	186	4,737	39.26	111	2,109	52.63	1.32 (1.05–1.68)*	1.62 (1.27, 2.05)***
Current use (≤30 d)	40	778	51.41	47	350	134.28	2.58 (1.69–3.93)***	2.80 (1.81, 4.33)***
Recent use (30–90 d)	1	99	10.10	2	42	47.61	3.65 (0.32–40.75)	1.58 (0.33, 7.59)
Past use (>90 d)	23	1,935	11.88	22	1,031	21.33	1.80 (1.00–3.23)*	1.73 (0.79, 3.81)
SAMA								
Non-use	207	5,677	36.46	129	2,579	50.01	1.36 (1.09–1.69)**	1.70 (1.36, 2.13)***
Current use (≤30 d)	27	674	40.05	37	262	141.22	3.49 (2.12–5.74)***	3.00 (1.78, 5.04)***
Recent use (30–90 d)	1	78	12.82	0	25	0	–	–
Past use (>90 d)	15	1,120	13.39	16	666	24.02	1.79 (0.88–3.62)	0.48 (0.14, 1.65)
ICSs								
Non-use	211	5,976	35.30	130	2,389	54.41	1.53 (1.23–1.90)***	1.75 (1.40, 2.18)***
Current use (≤30 d)	20	415	48.19	23	208	110.57	2.35 (1.29–4.30)**	1.45 (0.76, 2.77)
Recent use (30–90 d)	1	58	17.24	2	43	46.51	2.87 (0.26–31.75)	–
Past use (>90 d)	18	1,100	16.36	27	892	30.26	1.84 (1.01–3.35)*	4.61 (2.18, 9.76)***
OSs								
Non-use	38	352	107.95	29	118	245.76	2.05 (1.26–3.34)**	2.40 (1.44–3.99)***
Current use (≤30 d)	175	2,272	77.02	141	999	141.14	1.83 (1.46–2.28)***	1.80 (1.43–2.25)***
Recent use (30–90 d)	6	680	8.82	0	352	0	–	–
Past use (>90 d)	31	4,245	7.30	12	2,063	5.81	0.78 (0.40–1.53)	1.51 (0.76–2.99)
Anti-arrhythmic								
Non-use	240	7,026	34.15	168	3,281	51.20	1.49 (1.22–1.82)***	1.80 (1.47–2.20)***
Current use (≤30 d)	6	172	34.88	5	46	108.69	4.24 (1.12–16.0)*	6.69 (1.55, 28.8)*
Recent use (30–90 d)	2	54	37.03	2	14	142.85	3.08 (0.43–22.01)	–
Past use (>90 d)	2	297	6.73	7	191	36.64	5.50 (1.13–26.69)*	–
Alprazolam								
Non-use	189	5,349	35.33	139	2,467	56.34	1.58 (1.27–1.97)***	1.88 (1.50–2.34)***
Current use (≤30 d)	35	385	90.90	23	180	127.77	1.41 (0.83–2.40)	1.78 (1.09–2.93)*
Recent use (30–90 d)	2	128	15.62	4	56	71.42	4.00 (0.72–22.09)	777.8 (1.34–451590.0)*
Past use (>90 d)	24	1,687	14.22	16	829	19.30	1.33 (0.70–2.51)	1.57 (0.55–4.46)
Fluoxetine								
Non-use	250	7,549	33.11	182	3,532	51.52	1.54 (1.28–1.87)***	1.86 (1.53–2.26)***
Current use (≤30 d)	0	0	0	0	0	0	–	–
Recent use (30–90 d)	0	0	0	0	0	0	–	–
Past use (>90 d)	0	0	0	0	0	0	–	–
Fludiazepam								
Non-use	215	6,398	33.60	161	3,006	53.55	1.59 (1.29–1.95)***	1.94 (1.57–2.39)***

(Continued)

TABLE 4 | Continued

	BCAS cohort						Crude HR (95%CI)	Adjusted HR (95%CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
Current use (≤ 30 d)	11	129	85.27	10	53	188.67	2.14 (0.90–5.08)	1.39 (0.75–2.59)
Recent use (30–90 d)	1	28	35.71	0	46	0	–	–
Past use (> 90 d)	23	994	23.13	11	427	25.76	1.10 (0.54–2.27)	1.29 (0.42–4.01)

BCAS cohort, Bronchiectasis-Asthma combination cohort; COPD, Chronic obstructive pulmonary disease.

PY, person-years; IR, incidence rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval.

HR adjusted for BCAS cohort, gender, age, Rheumatoid arthritis, Pneumonia, COPD, Diabetes, Hypertension, Hyperlipidemia, SABAs, OSs, Alprazolam, Statins, Beta blockers and Calcium channel blockers.

LABAs/LAMAs, long-acting $\beta 2$ -agonist or muscarinic antagonist; SABAs/SAMAs, short-acting $\beta 2$ -agonist or muscarinic antagonist, steroids; ICSs, inhaled corticosteroid steroids; OSs, oral steroids; Beta blockers, cardioselective beta blockers (atenolol, bisoprolol, metoprolol).

–, Unable to calculate because of there are few or no events in with and without BCAS cohort.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

inhibitors/CCBs may be the optimal management strategies in patients with hypertension, hyperlipidemia, diabetes to prevent HDS (25). In recent Taiwan NHIRD study reveal that the combined these cardioprotective drugs-statins, cardioselective beta-blockers, RAS inhibitors and CCBs have benefits for the HDS among the asthma or COPD support these speculations (26, 27). In our study, the (statins, CCBs) users have the lower risk of the HDS, with patients not using (statins, CCBs) as reference. These results were in line with previous meta-analysis study (24).

The hypertension Taiwan guideline 2010 recommended the lowering of target BP to $< 130/80$ mmHg for HDS (2015, $< 140/90$ mmHg for stroke; $< 130/80$ mmHg for coronary artery disease or diabetes) (28). In general, Taiwanese physicians follow the current hypertension treatment guidelines relatively well, a high success rate of 63% in achieving the BP goal of $< 140/90$ mmHg in outpatient clinics of hospital among general population (29). Guidelines of diabetes care for glycemic control have consistently targeted hemoglobin A1c (HbA1c) values $< 7\%$, pointing to the HDS benefits of maintaining HbA1c in this range while remaining mindful of the risks of hypoglycemia (30). The lipid guidelines for high risk patients recommended pragmatic goals for low density lipoprotein-cholesterol (LDL-C) of < 70 mg/dL (< 100 mg/dl, 2000–2009) for those at highest HDS (31, 32). A P4P programme is a management strategy that encourages healthcare providers to deliver high quality of care, and helps the BCAS cohort with these comorbidities to receive the management under these guidelines such as HbA1c $< 7.0\%$, BP $< 140/90$ mmHg, and LDL-C < 100 mg/dL (33–35).

Health Behavior Nutraceuticals Food Habits in Relation to the HDS

Nutraceuticals, functional foods and supplements with a serum LDL-C lowering effect, the possible mechanism including: (1) absorption inhibitors: plant sterols and stanols, soluble fiber, oat fibers, psyllium, probiotics; (2) LDL synthesis inhibition: red yeast rice, bergamot, artichoke; (3) LDL excretion improving: soy proteins, berberine, and green tea extracts (36–38). Thus, they could represent useful compounds that are associated with lower risk of HDS by acting parallel to statins or as adjuvants

in case of drugs failure or in situations where statins cannot be used (39). When statins are not available such as intolerance, side effects, or patient preference. The nutraceuticals (e.g., Bergamot-Derived Polyphenolic Fraction) and functional food-related diet (e.g., Mediterranean diet supplemented with extra-virgin olive oil or nuts) may help us for solve these problems (36, 40, 41). Among foods, beetroot juice has the most convincing evidence of lowering the BP. Among nutrients, magnesium, potassium and vitamin C supplements were associated with the lower BP. Notably, the use of nutraceuticals should never substitute the one of conventional drugs, when their prescription is indicated by the international guidelines. However, physical activity, healthy diet, and nutraceuticals may play an auxiliary role for prevention of HDS (36, 38, 40).

The diabetes P4P program for caring patients with diabetes alone and diabetes with comorbid hypertension and hyperlipidemia from a single payer in Taiwan could help the BCAS cohort to improve the health behavior and food habits including poor dietary practices, physical inactivity, and cigarette smoking (13, 33, 34). The lifestyle measures that are recommended to lower HDS including salt restriction, alcohol limitation, body reduction, cessation of smoking, diet adaptation, and exercise adoption. The strict policy of the health behavior, food habits, and higher adherence of medications such as statins and CCBs among the BCAS cohort (about 10.8% of diabetes) receiving the chronic care program may help patients to achieve the target BP, HbA1c, and LDL-C (42, 43). These complementary and integrative therapies have a critical role for attenuating the risk of HDS in BCAS cohort with comorbidities such as hyperlipidemia.

DISCUSSION

To the best of our knowledge, this study is the first to investigate the relationship between BZDs and the risk of HDS between the BCAS cohort and the non-BCAS cohort in the English literature to date. This general population study revealed four major findings. First, BZDs such as fludiazepam even current use were not associated with a higher risk of HDS in the BCAS cohort

TABLE 5 | Incidence rate and hazard ratio of ischemic stroke or heart-disease between two cohorts stratified by cumulative dose of drug.

	BCAS cohort						Crude HR (95%CI)	Adjusted HR (95%CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
Cumulative dose of drug								
LABA (DDD)								
Non-use	228	6,829	33.38	132	2,791	47.29	1.41 (1.14–1.75)**	1.76 (1.43–2.16)***
≤415	5	124	40.32	9	116	77.58	1.83 (0.61–5.49)	2.95 (0.22–38.8)
416–2,300	11	407	27.02	23	315	73.01	2.71 (1.32–5.57)**	18.7 (1.29, 272.7)*
>2,300	6	189	31.74	18	310	58.06	1.84 (0.73–4.64)	11.4 (0.45–10.5)
LAMA(DDD)								
Non-use	238	7,297	32.61	156	3,292	47.38	1.44 (1.18–1.77)***	1.70 (1.37–2.12)***
≤30	4	69	57.97	10	97	103.09	1.71 (0.53–5.46)	3.78 (0.37, 38.5)
31–210	4	96	41.66	8	61	131.14	2.66 (0.80–8.88)	2.97 (1.36, 6.51)
>210	4	87	45.97	8	82	97.56	2.00 (0.60–6.69)	3.11 (0.90, 10.8)
SABA (DDD)								
Non-use	199	6,111	32.56	98	2,388	41.03	1.26 (0.99–1.60)	1.57 (1.23–2.01)***
≤1	23	631	36.45	19	274	69.34	1.88 (1.02–3.46)*	1.29 (0.62–2.69)
2–165	14	350	40	31	371	83.55	2.03 (1.08–3.82)*	1.79 (0.91–3.55)
>165	14	457	30.63	34	499	68.13	2.22 (1.19–4.14)*	3.31 (1.65–6.65)***
SAMA (DDD)								
Non-use	224	6,934	32.30	128	2,959	43.25	1.33 (1.07–1.66)**	1.64 (1.32–2.05)***
≤1.5	0	0		0	0		–	2.18 (1.17–4.09)***
1.6–5	22	453	48.56	30	342	87.71	1.79 (1.03–3.11)*	–
>5	4	162	24.69	24	231	103.89	3.83 (1.32–11.06)*	7.91 (1.76–35.6)***
ICSs (DDD)								
Non-use	215	6,235	34.48	108	2,354	45.87	1.33 (1.05–1.68)*	1.54 (1.22–1.95)***
≤415	10	461	21.69	11	199	55.27	2.55 (1.08–6.02)*	5.02 (1.76–14.3)**
416–1,500	13	508	25.59	32	511	62.62	2.36 (1.23–4.50)**	2.58 (1.22–5.46)*
>1,500	12	345	34.78	31	468	66.23	1.81 (0.93–3.54)	3.34 (1.40–7.97)**
OSs (DDD)								
Non-use	102	1,738	58.68	46	452	101.76	1.72 (1.21–2.44)**	2.77 (1.44–2.97)***
≤15	55	2,136	25.74	32	683	46.85	1.81 (1.17–2.80)**	2.28 (1.43–3.62)**
16–155	55	2,012	27.33	51	962	53.01	1.90 (1.30–2.79)***	1.90 (1.28–2.81)**
>155	38	1,663	22.85	53	1,435	36.93	1.62 (1.07–2.47)*	1.95 (1.26–3.02)**
Anti-arrhythmia								
Non-use	244	7,398	32.98	171	3,416	50.05	1.51 (1.24–1.84)***	1.81 (1.49, 2.21)***
≤35	1	64	15.62	8	88	90.90	5.80 (0.72–46.73)	–
36–65	0	0		0	0		–	–
>65	5	87	57.47	3	28	107.14	1.41 (0.33–6.07)	–
Alprazolam (DDD)								
Non-use	189	5,349	35.33	139	2,469	56.29	1.58 (1.27–1.97)***	1.88 (1.50–2.34)***
≤5	22	687	32.02	7	229	30.56	0.96 (0.41–2.25)	1.70 (0.64–4.48)
6–30	19	742	25.60	19	393	48.34	1.92 (1.01–3.62)*	2.31 (1.09–4.89)*
>30	20	771	25.94	17	441		1.56 (0.81–2.99)	1.60 (0.78–3.29)
Fluoxetine								
Non-use	250	7,549	33.11	182	3,532	51.52	1.54 (1.28–1.87)***	1.86 (1.53–2.26)***
≤	0	0	0	0	0	0	–	–
-	0	0	0	0	0	0	–	–
>	0	0	0	0	0	0	–	–
Fludiazepam								
Non-use	215	6,398	33.60	161	3,006	53.55	1.59 (1.29–1.95)***	1.94 (1.57–2.39)***

(Continued)

TABLE 5 | Continued

	BCAS cohort						Crude HR (95%CI)	Adjusted HR (95%CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
≤5	14	401	34.91	4	142	28.16	0.78 (0.25–2.40)	1.27 (0.33–4.82)
6–20	9	351	25.64	8	191	41.88	1.61 (0.62–4.18)	1.22 (0.35–4.17)
>20	12	399	30.07	9	193	46.63	1.56 (0.66–3.72)	2.43 (0.90–6.55)

BCAS cohort, Bronchiectasis-Asthma combination cohort; COPD, Chronic obstructive pulmonary disease; PY, person-years; IR, incidence rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval.

HR adjusted for BCAS cohort, gender, age, Rheumatoid arthritis, Pneumonia, COPD, Diabetes, Hypertension, Hyperlipidemia, SABAs, OSs, Alprazolam, Statins, Beta blockers, and Calcium channel blockers.

LABAs/LAMAs, long-acting β2-agonist or muscarinic antagonist; SABAs/SAMAs, short-acting β2-agonist or muscarinic antagonist, steroids; ICSs, inhaled corticosteroid steroids; OSs, oral steroids; Beta blockers, cardioselective beta blockers (atenol, bisoprolol, metoprolol).

–, Unable to calculate because of there are few or no events in with and without BCAS cohort.

*p < 0.05, **p < 0.01, ***p < 0.001.

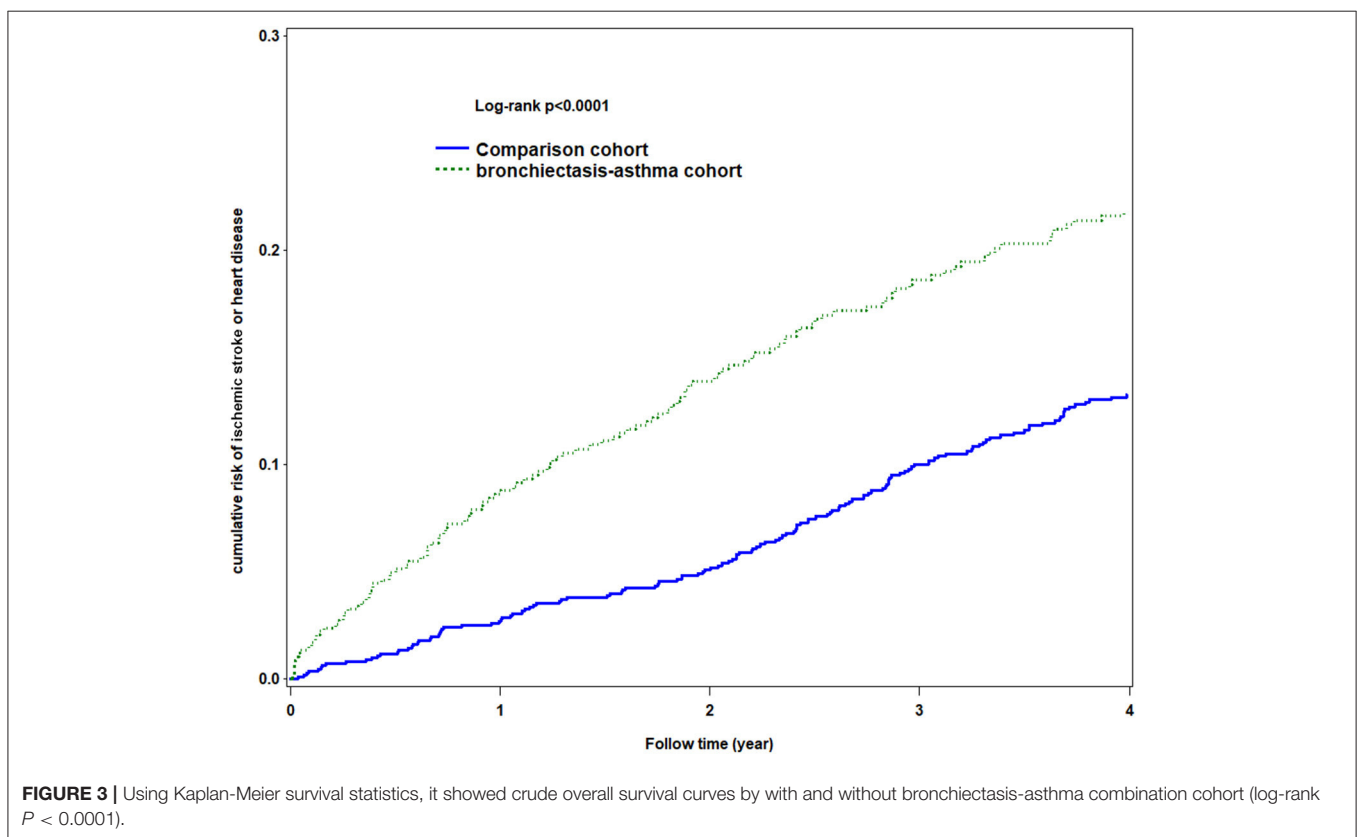


FIGURE 3 | Using Kaplan-Meier survival statistics, it showed crude overall survival curves by with and without bronchiectasis-asthma combination cohort (log-rank $P < 0.0001$).

comparing with the non-BCAS cohort. However, the (current, recent) use and medium dosage of alprazolam were associated with a higher risk of HDS. Second, steroids (past ICSs, current OSs, any dose ICSs/OSs) were associated with a higher risk of HDS, even at a low dose, in the BCAS cohort than in the non-BCAS cohort. In addition, with patients not using OSs as the reference group, the results revealed that OSs use was associated with a lower risk of HDS. Third, the high dosage and current use of SABAs were associated with a higher risk of HDS. However, with patients without using SABAs as the reference group, SABAs

were associated with a lower risk of HDS. Forth, the current use of LABAs/ICSs were not associated with HDS.

Anxiety may contribute to a cross-reaction with central processing at the cortical and brain stem level and the autonomic nerves, changing the electrophysiology of the myocardium and leading to cardiac arrhythmia. Relieving anxiety may attenuate the risk of HDS, including cardiac arrhythmia and heart failure, in the BCAS cohort. Similar to that, Balon et al. reported that BZDs may be associated with the lower risk of HDS, such as coronary artery disease and heart failure (44, 45). Meanwhile,

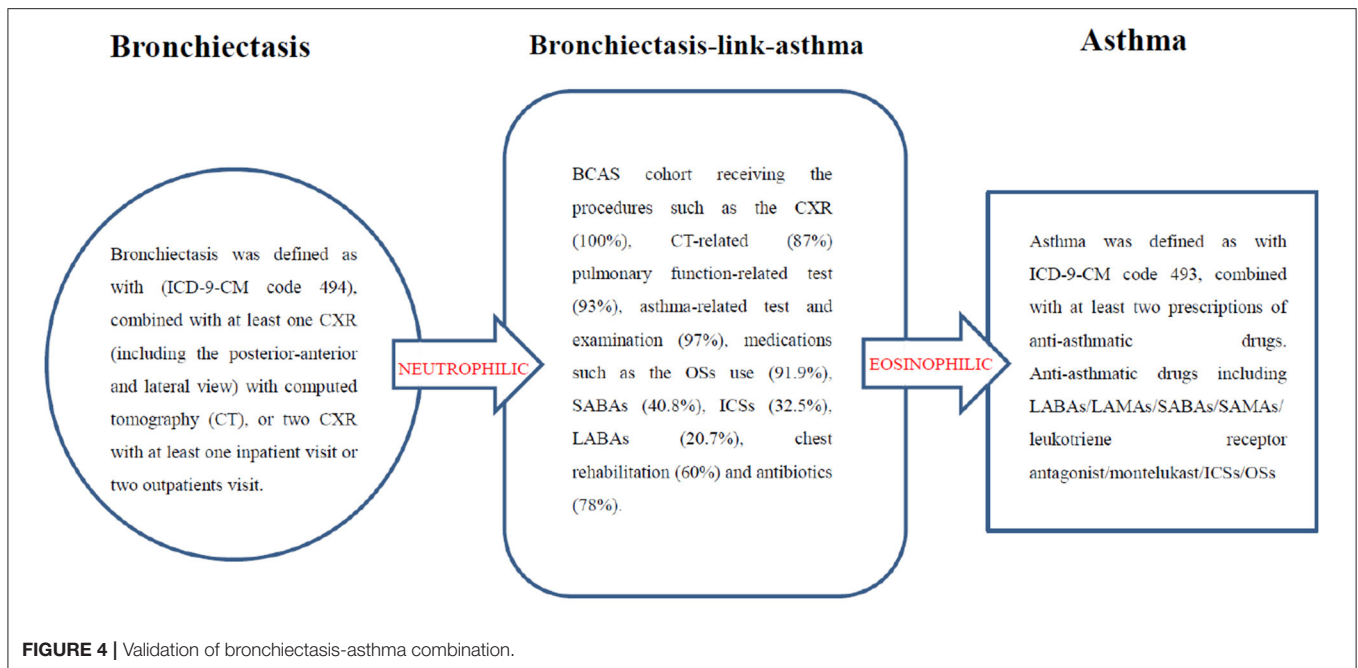


TABLE 6 | Summary findings of results.

	A	B	Past	Recent	Current	High	Medium	Low
LABAs	+		+		0	0	+	0
SABAs	+	-	0		+	+	0	0
LAMAs						0	0	0
SAMAs	+		0		+	+		+
ICSs	+		+		0	+	+	+
OSs	+	-	0		+	+	+	+
Anti-Arrhythmic	+				+			
Alprazolam	+	0	0	+	+	0	+	0
Fludiazepam	0		0		0	0	0	0
Statins		-						
Beta blockers: cardioselective		0						
Calcium channel blockers		-						

A, In general, LABAs, SABAs, SAMAs, ICSs, OSs, antiarrhythmic drugs, and alprazolam were associated with a higher risk of HDS. LAMAs Fludiazepam were not associated with increased HDS risk.

B, Using patients who were not taking medication as the reference group, SABAs, OSs, Statins, and CCBs were associated with an attenuated risk of HDS.

+, increased risk; -, decreased risk; 0, no association with risk.

LABAs, long-acting β_2 agonists; LAMAs, long-acting muscarinic antagonists; SABAs, short-acting β_2 agonists; SAMAs, short-acting muscarinic antagonists; ICSs, inhaled corticosteroid steroids; OSs, oral steroids; CCBs, calcium channel blockers.

Huang et al. reported that the lower dose of BZDs provided neuroprotection (45–47). Furthermore, Patorno et al. revealed little to no increase in all-cause mortality associated with BZDs initiation in the general population (48). These findings indicate that BZDs are not associated with significant risk of HDS support our results. However, the current study suggests that the (current, recent) use of alprazolam is associated with a higher risk of HDS; a possible explanation for this is the rebound response of insomnia with the (current, recent) use of intermediate-acting alprazolam (49). Rebound insomnia is associated with a higher risk of HDS. Fludiazepam is long acting and has a lower

withdrawal response, which may prevent rebound insomnia and was not associated with the risk of HDS (50).

The BCAS cohort involves the impairment of the immune system, and steroids aggravate immune deficiency accompanied by infection, which may lead to a higher risk of HDS (51). In addition, the systemic effects of steroids can promote hyperglycaemia, hypertension, and hyperlipidaemia, contributing to HDS development. According to Yao et al., the highest rates of GI bleeding, sepsis, and heart failure occurred within the first month after the initiation of steroid therapy, which is in line with our results (52). However, the adverse

reaction to OSs is attenuated after 30 days of use (52–54). This finding may explain why the past use of OSs was not associated with the higher risk of HDS. Notably, general steroid use (past ICSs, current OSs, any dose ICSs/OSs) were associated with a higher risk of HDS, even at a low dose (52, 54).

In the BCAS cohort, poor lung function and quality scores are linked to higher levels of cytokines, eosinophils, and neutrophils compared to the non-BCAS cohort (2, 3). The anti-inflammatory effects (55, 56) of bronchodilators (LABAs/LAMAs, SABAs/SAMAs), steroids, and antiarrhythmic drugs are limited; thus, the effect of these drugs for ameliorating the progression of persistent artery stiffness was suboptimal. Therefore, compared with the non-BCAS cohort, the BCAS cohort who used bronchodilators (current or high SABAs/SAMAs, steroids), and antiarrhythmic drugs (current use) had higher risks of HDS (5, 11, 57). However, with patients not using (SABAs, OSs) as the reference group, (SABAs, OSs) use were associated with a lower risk of HDS. As mentioned before, the complementary and integrative therapies under multidisciplinary team may play an auxiliary role for helping these patients to change their lifestyles, increase their adherence to medications (58). For example, the overuse of SABAs is relatively low in Taiwan compared with that in other countries (15.9%, similar to Germany but lower than that in other European countries), indicating that well-trained teams may encourage the BCAS cohort who use (SABAs, OSs) to attend regular follow-up appointments, promoting continued care for hypertension, and a higher quality of life and thus attenuating the risk of HDS (59). Notably, we found that the (current LABAs/ICSs, any dose LAMAs) use were not associated with the HDS. The current use of LABAs/ICSs (e.g., formoterol/budesonide) seem to be superior to current use of SABAs/OSs in select scenarios such as avoiding the HDS in BCAS cohort with diabetes/hypertension. The recent Chen et al. study concluded that the risk of HDS was associated with COPD patients with preexisting cardiovascular disease and history of frequent exacerbations rather than associated with the use of LABAs/ICSs support these speculations (60–63). However, these findings warrant further research.

In summary, because of the increased risk of HDS, the bronchodilators, antiarrhythmic drugs, and steroids could be used after evaluation of the benefit in the BCAS cohort and low doses were suggested (64). Steroids could be used only in select cases, even at low doses. BZDs such as fludiazepam are relatively safe; however, the current or recent use of alprazolam are associated with a high risk of HDS (65).

Strengths

The medical records in the NHIRD are highly accurate, making this database a strong resource for population-based cardiovascular and stroke research (66, 67). Bronchodilators, steroids (ICSs and OSs), statins and antihypertensive drug use in Taiwan follows international guidelines. Furthermore, the NHIRD-based identification of asthma, COPD, and bronchiectasis-related diseases, such as PTB and pneumonia, has been validated in several recent reports (60, 68, 69). Therefore,

this well-established method prevented potential biases in this study.

Limitations

The limitations of this study include bias and confounding variables. First, the results of observational studies are not as accurate as those of randomized control trials (RCT). Therefore, we performed a propensity score matching analysis to address this point (70). However, this retrospective study is usually lower evidence than the RCT trials because a retrospective study is subject to have many unknown confounding factors such as the other health problems. Meanwhile, old records were not designed to be used for future studies (67). Second, the NHIRD provides no detailed information on patients regarding factors such as their lifestyle, body mass index (or obesity), habits (such as smoking and alcoholic drinking), physical activity, socioeconomic status, or family history; all of which are possible confounding factors in this study. Third, the registries in the NHI claims are primarily used for administrative billing and are not verified for scientific purposes. Fourth, lack of individual laboratory data such as BP, HBA1c, LDL-C, cytokine level, imaging findings in the NHIRD may be the other study limitation.

Fifth, in the sensitivity analysis, we found that the (current LABAs, any dose LAMAs) use were not associated with the HDS. In contrast, Wang et al. reported new initiation of (LABAs, LAMAs) in patients with COPD is associated with an ~1.5-fold increased cardiovascular disease, irrespective of prior cardiovascular disease status and history of exacerbations (53). In this study, we also found that (SABAs at DDD > 165, SAMAs at DDD > 5, past LABAs) use were associated with higher risk of HDS. Therefore, primary effect of the (bronchodilators) on the HDS among BCAS cohort could not explain these different findings. Perhaps, the primary effect of the BCAS cohort, or the joint effect of the BCAS cohort and individual comorbidity, or the combination effect of the medications with the BCAS cohort and their comorbidities contributing to HDS in this study. Thus, when we interpret these results, we should take the other confounding factors such as comorbid-related HDS into account. Altogether, the effect of the bronchodilators on the risk HDS warrants further research.

CONCLUSION

The bronchodilators, steroids, and antiarrhythmic drugs were associated with higher risk of HDS, even low dose use of steroids. However, the current use of LABAs/ICSs use were not associated with HDS. The use of the BZDs is relatively safe, except for the current or recent use of alprazolam. Notably, taking confounders into account is crucial in observational studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can

submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (email: stcarolwu@mohw.gov.tw) for further assistance. All relevant data are within the paper. Requests to access the datasets should be directed to email: stcarolwu@mohw.gov.tw.

ETHICS STATEMENT

This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (Institutional Review Board permit number: CMUH104-REC2-115-AR2). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

J-JY and C-HK: conception and design. C-HK: administrative support. All authors: collection and assembly of data, data analysis and interpretation, manuscript writing, final approval

of manuscript, contributed to the article, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2022.797623/full#supplementary-material>

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