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 β2 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...
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 antianxiety 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, antiarrhythmics, antidepressants, 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 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 493) 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 outpatients 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 (BACOS) 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 subcohort 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 | PS-matching population |
|-----------------------------------------------|---------------------|------------------------|
|                                               | 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                                        |   |   |   |   |   |   |   |   |
| 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 | 70 | 11.9 | 116 | 10.3 |
| Non-tuberculosis mycobacterium                | 5 | 0.79 | 148 | 0.02 | 4 | 0.68 | 6 | 0.54 |
| Rheumatoid arthritis                          | 13 | 2.04 | 5,043 | 0.77 | 9 | 1.53 | 22 | 1.97 |
| Diffuse connective disease                    | 12 | 1.89 | 4,599 | 0.70 | 10 | 1.70 | 24 | 2.15 |
| Pneumonia                                     | 202 | 31.7 | 22,265 | 3.41 | 177 | 30.1 | 329 | 29.4 |
| COPD                                          | 349 | 54.8 | 18,575 | 2.85 | 315 | 53.5 | 632 | 56.5 |
| Diabetes                                      | 69 | 10.8 | 21,527 | 3.30 | 64 | 10.8 | 128 | 11.4 |
| Aspergillosis                                 | 2 | 0.31 | 20 | 0.003 | 2 | 0.34 | 0 | 0.005 |
| Candidias                                     | 1 | 0.16 | 14 | 0.002 | 1 | 0.17 | 1 | 0.09 |
| Endemic mycoses                               | 0 | 0 | 41 | 0.01 | 0 | 0 | 0 | – |
| Mounier-Kuhn                                  | 0 | 0 | 59 | 0.01 | 0 | 0 | 0 | – |
| Cystic fibrosis                               | 0 | 0 | 3 | 0.0004 | 0.95 | 0 | 0 | 0 | – |
| Hypertension                                  | 216 | 33.9 | 56,003 | 8.57 | 194 | 32.9 | 405 | 36.2 |
| Hyperlipidemia                                | 100 | 15.7 | 38,046 | 5.83 | 93 | 15.8 | 218 | 19.5 |
| Pulmonary embolism                            | 0 | 0 | 84 | 0.01 | 0 | 0 | 0 | 2 |
| Depression                                    | 5 | 0.79 | 3,056 | 0.47 | 5 | 0.85 | 10 | 0.89 |
| Smoking                                       | 1 | 0.16 | 597 | 0.09 | 1 | 0.17 | 2 | 0.18 |
| Tobacco dependence                            | 0 | 0 | 0 | 0 | – | 0 | 0 | 0 | – |
| Tobacco use disorder complicating pregnancy   | 0 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| Medication                                    |   |   |   |   |   |   |   |   |
| LABA                                          | 132 | 20.7 | 582 | 0.09 | <0.0001 | 116 | 19.73 | 149 | 13.3 |
| LAMA                                          | 13 | 2.04 | 96 | 0.01 | <0.0001 | 12 | 2.04 | 16 | 1.43 |
| SABA                                          | 260 | 40.8 | 13,426 | 2.06 | <0.0001 | 234 | 39.8 | 432 | 38.6 |
| SAMA                                          | 179 | 28.1 | 8,524 | 1.31 | <0.0001 | 159 | 27.0 | 299 | 26.7 |
| ICSS                                          | 209 | 32.8 | 937 | 0.14 | <0.0001 | 184 | 31.2 | 239 | 21.3 |
| Oss                                           | 585 | 91.9 | 469,554 | 71.96 | <0.0001 | 538 | 91.5 | 1028 | 91.9 |
| Anti-arrhythmnic                              | 46 | 7.23 | 15,413 | 2.36 | <0.0001 | 43 | 7.31 | 81 | 7.25 |
| Alprazolam                                    | 169 | 26.5 | 7,136 | 10.9 | <0.0001 | 155 | 26.3 | 296 | 26.4 |
| 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 |
| Statins                                       | 52 | 8.18 | 29,369 | 4.50 | <0.0001 | 52 | 8.84 | 125 | 11.2 |
| Anti-hypertensive drugs                       |   |   |   |   |   |   |   |   |
| Diuretics                                     | 73 | 11.5 | 31,369 | 4.81 | <0.0001 | 70 | 11.9 | 261 | 23.4 |
| Beta blockers                                 | 84 | 13.2 | 64,661 | 9.91 | 0.005 | 82 | 14.0 | 199 | 17.8 |
| Calcium channel blockers                      | 128 | 20.1 | 59,886 | 9.15 | <0.0001 | 125 | 21.3 | 313 | 28.0 |
| Angiotensin converting enzyme inhibitors      | 43 | 6.76 | 24,049 | 3.69 | <0.0001 | 42 | 7.14 | 123 | 11.0 |
| Angiotensin II blockers                       | 53 | 8.33 | 13,320 | 2.04 | <0.0001 | 49 | 8.33 | 96 | 8.59 |

*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 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).
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) |
|----------------------------------|------------------|--------------------|
| Heart-disease or ischemic stroke | 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                               | 398 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) – |
| Candidias                        |                  |                    |
| No                               | 431 11,077 38.9  | 1 (reference) 1 (reference) |
| Yes                              | 1 4 250          | 6.51 (0.91–46.59) – |
| Endemic mycoses                  |                  |                    |
| No                               | 432 11,061 38.9  | 1 (reference) 1 (reference) |
| Yes                              | 0 0 0            | – – – |
| Mounier-Kuhn                     |                  |                    |
| No                               | 432 11,061 38.9  | 1 (reference) 1 (reference) |
| Yes                              | 0 0 0            | – – – |
| Cystic fibrosis                  |                  |                    |
| No                               | 432 11,061 38.9  | 1 (reference) 1 (reference) |

(Continued)
included in this analysis. After adjustment for age, comorbidities, cohort and 250 patients with HDS in the non-BCAS cohort were included. 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 hyperlipidemia (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 ICs (aHR = 2.53; 95% CI = 1.61–3.99), patients using OAs (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 ≤30 days (aHRs = 2.80; 95% CI = 1.81–4.33), SAMAs ≤30 days (aHRs = 3.00; 95% CI = 1.78–5.04), ICs > 90 days (aHRs = 4.61; 95% CI = 2.18–9.76), OAs ≤30 days (aHRs = 1.80; 95% CI = 1.43–2.25), antiarrhythmic drugs ≤30 days (aHRs = 6.69; 95% CI = 1.55–28.8), and alprazolam ≤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 (≤30 days), SABA (30–90days), ≥90days), SAMAs (>90 days), ICs (≤30 days), OAs (>90 days), alprazolam (>90 days), fludiazepam (≤30 days, >90 days) were not associated with the HDS.

**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 hyperlipidemia (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 ICs (aHR = 2.53; 95% CI = 1.61–3.99), patients using OAs (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 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 significantly 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% CI = 1.65–6.65); ≤415, 415–1500, >1500 DDDs for ICs (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); ≤15, 16–155, and >155 DDDs for OAs (aHR = 2.28; 95% CI = 1.43–3.62; aHR = 1.90; 95% CI = 1.28–2.81; and aHR = 1.95; 95% CI = 1.05–3.62).
| BCAS cohort | No | Yes | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------|----|-----|-------------------|---------------------|
| **Gender**  |    |     |                   |                     |
| Female      | 130| 83  | 1.23 (0.94–1.63)  | 1.42 (1.07–1.88)*   |
| Male        | 120| 99  | 1.97 (1.51–2.57)** | 2.39 (1.82–3.14)** |
| **Age**     |    |     |                   |                     |
| <20         | 2  | 0   | –                 | –                   |
| 20–39       | 7  | 9   | 2.65 (0.98–7.13)  | 4.26 (1.38–13.2)*   |
| 40–64       | 109| 94  | 1.53 (1.16–2.02)** | 1.57 (1.18–2.08)** |
| ≥65         | 132| 79  | 1.85 (1.40–2.45)** | 2.07 (1.55–2.76)** |
| **Comorbidity** |    |     |                   |                     |
| Pulmonary tuberculosis |    |     |                   |                     |
| No          | 224| 164 | 1.58 (1.29–1.94)*** | 1.91 (1.56–2.34)*** |
| Yes         | 26 | 18  | 1.24 (0.67–2.26)  | 1.57 (0.82–2.99)    |
| Non-tuberculosis mycobacterium |    |     |                   |                     |
| No          | 249| 181 | 1.54 (1.27–1.87)*** | 1.84 (1.52–2.24)*** |
| Yes         | 1  | 1   | 1.73 (0.10–27.89) | –                   |
| Rheumatoid arthritis |    |     |                   |                     |
| No          | 241| 178 | 1.57 (1.29–1.91)*** | 1.87 (1.54–2.28)*** |
| Yes         | 9  | 4   | 0.78 (0.22–2.70)  | –                   |
| Diffuse connective disease |    |     |                   |                     |
| No          | 245| 179 | 1.54 (1.27–1.87)*** | 1.86 (1.52–2.26)*** |
| Yes         | 5  | 3   | 2.17 (0.51–9.20)  | 0.83 (0.06–10.37)   |
| Pneumonia   |    |     |                   |                     |
| No          | 180| 124 | 1.49 (1.18–1.87)*** | 1.63 (1.29–2.05)*** |
| Yes         | 70 | 58  | 1.68 (1.19–2.38)** | 2.39 (1.63–3.50)*** |
| COPD        |    |     |                   |                     |
| No          | 98 | 67  | 1.31 (0.96–1.79)  | 1.37 (0.99–1.89)    |
| Yes         | 152| 115 | 1.78 (1.40–2.28)*** | 2.15 (1.67–2.77)*** |
| Diabetes    |    |     |                   |                     |
| No          | 210| 150 | 1.53 (1.24–1.88)*** | 1.81 (1.46–2.25)*** |
| Yes         | 40 | 32  | 1.56 (0.98–2.50)  | 1.84 (1.12–3.02)** |
| Aspergillosis |    |     |                   |                     |
| No          | 250| 181 | 1.54 (1.27–1.87)*** | 1.87 (1.54–2.27)*** |
| Yes         | 0  | 1   | –                 | –                   |
| Candidiasis |    |     |                   |                     |
| No          | 249| 182 | 1.55 (1.28–1.88)*** | 1.88 (1.55–2.28)*** |
| Yes         | 1  | 0   | –                 | –                   |
| Endemic mycoses |    |     |                   |                     |
| No          | 250| 182 | 1.54 (1.28–1.87)*** | 1.87 (1.54–2.27)*** |
| Yes         | 0  | 0   | –                 | –                   |
| Mounier-Kuhn |    |     |                   |                     |
| No          | 250| 182 | 1.54 (1.28–1.87)*** | 1.87 (1.54–2.27)*** |
| Yes         | 0  | 0   | –                 | –                   |
| Cystic fibrosis |    |     |                   |                     |
| No          | 250| 182 | 1.54 (1.28–1.87)*** | 1.87 (1.54–2.27)*** |
| Yes         | 0  | 0   | –                 | –                   |
| Hypertension |    |     |                   |                     |
| No          | 124| 92  | 1.49 (1.14–1.96)*** | 1.81 (1.37–2.40)*** |
| BCAS cohort | No | Yes | Event | PY | IR | Event | PY | IR | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------|----|-----|--------|----|----|--------|----|----|-------------------|----------------------|
| Yes         | 126| 2,164| 58.22  | 90 | 887| 101.46 | 1.73 (1.32–2.27)** | 1.87 (1.42–2.46)*** |
| Hyperlipidemia | 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 | 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  | 248| 7,498| 33.07  | 180| 3,516| 51.19 | 1.54 (1.27–1.86)** | 1.85 (1.52–2.24)*** |
| Yes         | 2  | 54   | 39.21  | 2  | 16  | 125    | 2.02 (0.28–14.41) | –                    |
| Smoking     | Tobacco dependence | 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 | 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 | 55.81 | 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      | –                | –                    |

(Continued)
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).

**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 risk for HDS (18). 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 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).
TABLE 4 | Incidence rate and hazard ratio of ischemic stroke or heart-disease between two cohorts stratified by current, recent and past use.

| Drug-use days | Non-use | Current use (<30 d) | Recent use (30–90 d) | Past use (>90 d) | Crude HR (95%CI) | Adjusted HR (95%CI) |
|---------------|---------|---------------------|----------------------|------------------|------------------|-------------------|
| BCAS cohort   | Event   | PY                  | IR                   | Event            | PY               | IR                |
| LABA          | 7,549   | 6,658               | 34.24                | 2,842            | 54.18            | 1.57 (1.28–1.93)***| 1.86 (1.51, 2.29)***|
| Non-use       | 228     | 3,532               | –                    | –                | –                | –                 |
| Current use   | 14      | 319                 | 43.88                | 12               | 173              | 1.64 (0.76–3.56)  | 1.10 (0.38, 3.15)  |
| Recent use    | 1       | 41                  | 24.39                | 1                | 27               | 1.50 (0.09–23.98) | –                 |
| Past use      | 7       | 531                 | 13.18                | 15               | 490              | 2.29 (0.93–5.63)  | 4.58 (1.71, 12.3)***|
| LAMA          | 249     | 7,452               | 33.41                | 3,455            | 51.51            | 1.53 (1.26–1.86)***| 1.85 (1.52, 2.25)***|
| Non-use       | 0       | 3                   | 0                    | –                | –                | –                 |
| Current use   | 0       | 3                   | 0                    | 0                | 0                | –                 |
| Recent use    | 1       | 43                  | 23.25                | 1                | 33               | 1.52 (0.09–24.57) | –                 |
| SABA          | 186     | 4,737               | 39.26                | 2,109            | 52.63            | 1.32 (1.05–1.68)* | 1.62 (1.27, 2.05)***|
| Non-use       | 40      | 778                 | 51.41                | 47               | 350              | 2.58 (1.69–3.93)***| 2.80 (1.81, 4.33)***|
| Current use   | 1       | 99                  | 10.10                | 2                | 42               | 3.65 (0.32–40.75) | 1.58 (0.33, 7.59)  |
| Past use      | 23      | 1,935               | 11.88                | 2                | 1,031            | 1.80 (1.00–3.23)* | 1.73 (0.79, 3.81)  |
| SAMA          | 207     | 5,677               | 36.46                | 2,579            | 50.01            | 1.36 (1.09–1.69)**| 1.70 (1.36, 2.13)**|
| Non-use       | 27      | 674                 | 40.05                | 37               | 262              | 3.49 (2.12–5.74)***| 3.00 (1.78, 5.04)**|
| Current use   | 1       | 78                  | 12.82                | 0                | 25               | –                 |
| Recent use    | 15      | 1,120               | 13.39                | 16               | 666              | 1.79 (0.88–3.62)  | 0.48 (0.14, 1.65)  |
| ICSs          | 211     | 5,976               | 35.30                | 130              | 2,389            | 54.41            | 1.53 (1.23–1.90)***| 1.75 (1.40, 2.18)**|
| Non-use       | 20      | 415                 | 48.19                | 23               | 208              | 110.57           | 2.35 (1.29–4.30)**| 1.45 (0.76, 2.77)  |
| Current use   | 1       | 58                  | 17.24                | 2                | 43               | 46.51            | 2.87 (0.26–31.75) | –                 |
| Past use      | 18      | 1,100               | 16.36                | 27               | 892              | 30.26            | 1.84 (1.01–3.35)* | 4.61 (2.18, 9.76)***|
| OSs           | 38      | 352                 | 107.95               | 29               | 118              | 245.76           | 2.05 (1.26–3.34)**| 2.40 (1.44–3.99)**|
| Non-use       | 175     | 2,272               | 77.02                | 141              | 999              | 141.14           | 1.83 (1.46–2.28)**| 1.80 (1.43–2.25)**|
| Current use   | 6       | 680                 | 8.82                 | 0                | 352              | 0                | –                 |
| Recent use    | 31      | 4,245               | 7.30                 | 12               | 2,063            | 5.81             | 0.78 (0.40–1.53)  | 1.51 (0.76–2.99)  |
| Past use      | 240     | 7,026               | 34.15                | 168              | 3,281            | 51.20            | 1.49 (1.22–1.82)**| 1.80 (1.47–2.20)**|
| Anti-arrhythmic| 6       | 172                 | 34.88                | 5                | 46               | 108.69           | 4.24 (1.12–16.0)* | 6.69 (1.55, 28.8)*|
| Non-use       | 275     | 7,549               | 33.11                | 182              | 3,532            | 51.52            | 1.54 (1.28–1.87)***| 1.86 (1.53–2.26)***|
| Current use   | 0       | 0                   | 0                    | 0                | 0                | –                | –                 |
| Past use      | 2       | 297                 | 6.73                 | 7                | 191              | 36.64            | 5.50 (1.13–26.69)* | –                 |
| Alprazolam    | 189     | 5,349               | 35.33                | 139              | 2,467            | 56.34            | 1.58 (1.27–1.97)***| 1.88 (1.50–2.34)**|
| Non-use       | 35      | 385                 | 90.90                | 23               | 180              | 127.77           | 1.41 (0.83–2.40)  | 1.78 (1.09–2.93)*|
| Current use   | 2       | 128                 | 15.62                | 4                | 56               | 71.42            | 4.00 (0.72–22.09) | 777.8 (1.34–451590.0)*|
| Past use      | 24      | 1,687               | 14.22                | 16               | 829              | 19.30            | 1.33 (0.70–2.51)  | 1.57 (0.55–4.46)  |
| Fluoxetine    | 250     | 7,549               | 33.11                | 182              | 3,532            | 51.52            | 1.54 (1.28–1.87)***| 1.86 (1.53–2.26)***|
| Non-use       | 0       | 0                   | 0                    | 0                | 0                | –                | –                 |
| Past use      | 0       | 0                   | 0                    | 0                | 0                | –                | –                 |
| Fludiazepam   | 215     | 6,398               | 33.60                | 161              | 3,006            | 53.55            | 1.59 (1.29–1.95)***| 1.94 (1.57–2.39)***|

(Continued)
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 | | |
|-------------|-------------|-------------|
| Event PY IR | Event PY IR | Crude HR (95%CI) | Adjusted HR (95%CI) |
| 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 | 1.07 (0.64–1.80) | 3.78 (0.37–38.5) |
| 31–210 | 4 | 96 | 41.66 | 8 | 61 | 131.14 | 2.66 (0.80–8.88) | 2.97 (1.36–6.5) |
| >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)* | 3.78 (0.37, 38.5) |
| 2–165 | 14 | 350 | 41.66 | 8 | 61 | 131.14 | 2.03 (1.08–3.82)* | 1.79 (0.91-3.55) |
| >165 | 14 | 457 | 30.63 | 34 | 499 | 88.13 | 2.22 (1.19–4.14)* | 3.31 (1.65–6.65)** |
| SAM(A) (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 | 0 | 0 | – | 2.18 (1.17–4.09)** |
| 1.6–5 | 22 | 453 | 48.56 | 30 | 342 | 87.17 | 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 | 1.88 (1.06–3.46)* | 5.02 (1.76–14.3)** |
| 416–1,500 | 13 | 508 | 25.59 | 32 | 311 | 83.55 | 2.03 (1.08–4.00)* | 2.58 (1.22–5.46)* |
| >1,500 | 12 | 345 | 34.78 | 31 | 488 | 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 | 883 | 46.85 | 1.81 (1.17–2.80)* | 2.28 (1.43–3.62)** |
| 16–155 | 55 | 2,012 | 27.33 | 51 | 962 | 62.62 | 2.36 (1.23–5.40)* | 2.58 (1.22–5.46)* |
| >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 | 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 (1.31–3.21)* | 2.31 (1.09–4.89)* |
| >30 | 20 | 771 | 25.94 | 17 | 441 | 51.52 | 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)** | 1.96 (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

| Event | PY  | IR    | Crude HR (95%CI) | Adjusted HR (95%CI) |
|-------|-----|-------|------------------|---------------------|
| Event | PY  | IR    | No               | Yes                |
| ≤5    | 14  | 401   | 34.91 0.78 (0.25–2.40) | 1.27 (0.33–4.82)  |
| 6–20  | 9   | 351   | 25.64 1.61 (0.62–4.18) | 1.22 (0.35–4.17)  |
| >20   | 12  | 399   | 30.07 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,
FIGURE 4 | Validation of bronchiectasis-asthma combination.

TABLE 6 | Summary findings of results.

|               | A | B | Past | Recent | Current | High | Medium | Low |
|---------------|---|---|------|--------|---------|------|--------|-----|
| LABAs         | + | – | 0    | 0      | 0       | +    | 0      | 0   |
| SABAs         | + | – | 0    | 0      | +       | +    | 0      | 0   |
| LAMAs         | + | – | 0    | 0      | +       | +    | +      | +   |
| SAMAs         | + | – | 0    | 0      | 0       | +    | +      | +   |
| ICSs          | + | – | 0    | 0      | 0       | +    | +      | +   |
| OSs           | + | – | 0    | 0      | +       | +    | +      | +   |
| Anti-Arrhythmic | + |   |      |        |         |      |        |     |
| Fludiazepam   | 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 β2 agonists; LAMAs, long-acting muscarinic antagonists; SABAs, short-acting β2 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 ICs, current OSs, any dose ICs/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 compassion of 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 mention 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 the (current LABAs/ICsSs, any dose LAMAs) use were not associated with the HDS. The current use of LABAs/ICsSs (e.g., formoterol/budesonide) seem to be superior to current use of SABAs/OSs in select scenario such as avoiding the HDS in BCAS cohort with diabetes/hypertension. The recent Chen et al. study concluded 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/ICsSs 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 was 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 (ICsSs 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. Forth, lack of individual laboratory data such as BP, HBA1c, LDL-C, cytokine level, imaging finding 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 warrant 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/ICsSs 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.

**FUNDING**

This study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW110-TDU-B-212-124004), China Medical University Hospital (DMR-109-231, DMR-110-089, DMR-111-090, DMR-111-091), and Ministry of Science and Technology (MOST 110-2321-B-039-003). The funders had no role in the study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

**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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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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