

# Risk of Hospitalized Cardiovascular Events Associated with LAMA/LABA/ICS FDC versus LABA/ICS FDC in Patients with Chronic Obstructive Pulmonary Disease: A Nationwide Cohort Study

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**Background:** Clinical trial data showed a potential, albeit conflicting, higher cardiovascular risk associated with an inhaled triple therapy of long-acting muscarinic antagonists, long-acting  $\beta_2$  agonists, and inhaled corticosteroids (LAMA/LABA/ICS) versus LABA/ICS in patients with chronic obstructive pulmonary disease (COPD). Evidence from routine care environments remains scant. We sought to assess cardiovascular safety profiles of LAMA/LABA/ICS versus LABA/ICS, targeting fixed-dose combination (FDC) single inhalers.

**Methods:** This cohort study conducted in a nationwide Taiwanese database recruited patients with COPD who received LAMA/LABA/ICS FDC or LABA/ICS FDC between 2019/1/1 and 2022/12/31. We applied Cox regression models with variable-ratio propensity score (PS) matching to compare hospitalized cardiovascular events, including acute myocardial infarction, unstable angina, ischemic stroke, heart failure, and cardiac dysrhythmia, between the treatment groups.

**Results:** A total of 28,851 patients ( $n=5,836$  for LAMA/LABA/ICS FDC and  $n=23,015$  for LABA/ICS FDC) were included in the PS-matched cohort. The hazard ratio (HR) of composite cardiovascular events comparing LAMA/LABA/ICS FDC to LABA/ICS FDC was 1.00 (95% confidence interval [CI], 0.78–1.28) and the results did not materially change for individual outcomes. There was also no increased risk associated with LAMA/LABA/ICS FDC in patients having prior hospitalized cardiovascular episodes (HR, 0.86; 95% CI, 0.62–1.20), having prior hospitalized COPD exacerbations (HR, 0.93; 95% CI, 0.62–1.39), or receiving treatment longer than one year (HR, 0.76; 95% CI, 0.38–1.54).

**Conclusion:** This Taiwanese cohort study did not find a higher risk of various cardiovascular outcomes comparing LAMA/LABA/ICS FDC versus LABA/ICS FDC in patients with COPD, even in high-risk subpopulations.

**Keywords:** chronic obstructive pulmonary disease, long-acting muscarinic antagonists, LAMA, long-acting  $\beta_2$  agonists, LABA, inhaled corticosteroids, ICS, inhaled triple therapies, fixed-dose combinations, FDC, cardiovascular events, cohort study

## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease primarily caused by tobacco smoking and exposure to toxic particles and gases. The complex pathophysiological features include inflammation of lung tissues and damage of the airways and alveoli, leading to decline in lung function, airflow limitation, and chronic respiratory symptoms. COPD also often coexists with systemic comorbidities.<sup>1,2</sup> In terms of disease burden, it ranked as the fourth leading cause of death worldwide in 2021, accounting for 5% of the total 68 million deaths.<sup>3</sup> A Danish cohort study showed, among patients with COPD, the 1-year and 3-year mortality risk was 2–12% and 10–37%, respectively, depending on disease severity.<sup>4</sup> Another Spanish cohort study reported that the 1-year hospitalization risk due to any

causes or respiratory causes was 26% and 17%, respectively, in this population.<sup>5</sup> These findings underscore the importance of appropriate management strategies to mitigate the tremendous health impact of COPD.

Long-acting muscarinic antagonists (LAMA), long-acting  $\beta_2$  agonists (LABA), and inhaled corticosteroids (ICS) are the mainstay treatments for COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommended use of a dual therapy of LABA/ICS as an initial therapy for patients with a high exacerbation risk, a high symptom burden, and high blood eosinophil counts ( $\geq 300$  cells/ $\mu\text{L}$ ) before 2023.<sup>6</sup> However, since 2023, the role of LABA/ICS has been replaced by a triple therapy of LAMA/LABA/ICS.<sup>7</sup> Clinical trials have also showed that LAMA/LABA/ICS is more efficacious in decreasing exacerbation attacks, reducing respiratory symptoms, and improving lung function than LABA/ICS.<sup>8–10</sup>

Despite a superior efficacy profile of LAMA/LABA/ICS, a potentially increased risk of cardiovascular events was observed in two 52-week pivotal trials. In the Informing the Pathway of COPD Treatment (IMPACT) trial, LAMA/LABA/ICS had a higher incidence rate of ischemic heart disease and cerebrovascular events compared to LABA/ICS (for ischemic heart disease: 26.1 versus 18.5 per 1,000 person-years; rate ratio, 1.41; 95% confidence interval [CI], 1.03–1.93; for cerebrovascular events: 12.1 versus 9.3 per 1,000 person-years; rate ratio, 1.30; 95% CI, 0.83–2.05).<sup>8</sup> In the Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial, the hazard ratio (HR) of myocardial infarction, stroke, and cardiovascular death was 1.25 (95% CI, 0.73–2.15) comparing LAMA/LABA/ICS to LABA/ICS, mainly driven by higher events of myocardial infarction and stroke in the LAMA/LABA/ICS group.<sup>9</sup> Another 52-week efficacy trial, TRILOGY, did not suggest any cardiovascular safety concerns, reporting similar risks of myocardial infarction, stroke, heart failure, arrhythmia, and cardiovascular death—2.2% for LAMA/LABA/ICS versus 2.5% for LABA/ICS.<sup>10</sup> Limited observational studies examined cardiovascular safety comparing LAMA/LABA/ICS versus LABA/ICS and the results were also discrepant. An early nested case-control study found that an add-on treatment of LAMA to LABA/ICS was associated a  $>1.5$ -fold increased risk of ischemic heart disease, stroke, heart failure, and arrhythmia. However, LAMA and LABA/ICS were administered via different inhalers.<sup>11</sup> In contrast, another recent cohort study comparing LAMA/LABA/ICS and LABA/ICS, both of which were administered via fixed-dose combination (FDC) single inhalers, did not show an elevated risk of myocardial infarction (HR, 1.00; 95% CI, 0.56–1.79) and stroke (HR, 1.06; 95% CI, 0.48–2.36) associated with LAMA/LABA/ICS FDC within one-year of follow-up. Of note, this study did not assess the outcomes of unstable angina, heart failure and arrhythmia. This study also did not evaluate whether the risk associated LAMA/LABA/ICS FDC was more pronounced in high-risk patient populations, such as those with prior hospitalized cardiovascular episodes or those receiving treatment longer than one year.<sup>12</sup>

Because there is scant and inconsistent cardiovascular safety evidence for LAMA/LABA/ICS FDC and patients with COPD commonly coexist with cardiovascular disease, the present cohort study sought to investigate a broad spectrum of cardiovascular outcomes comparing LAMA/LABA/ICS FDC and LABA/ICS FDC in this population. We also examined cardiovascular safety across several substantial patient subgroups by underlying disease and baseline characteristics, prior maintenance medication use, individual study treatment, and study treatment duration.

## Methods

### Data Source

We utilized data from the Taiwan National Health Insurance Research Database (NHIRD), a nationwide, representative database containing de-identified healthcare information of nearly 23 million individuals covered under the mandatory national health insurance system. Specifically, the Taiwan NHIRD contains demographic and enrollment data as well as diagnosis and procedure records and pharmacy dispensing claims from outpatient visits, emergent department visits, and hospital admissions.<sup>13,14</sup> The present study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of the National Yang-Ming Chiao Tung University approved this study (YM110117E) and exempted the Informed consent because of the retrospective nature of the study and the analysis of anonymous data.

### Eligible Cohort

This cohort study conducted in the Taiwan NHIRD recruited patients with COPD who received LAMA/LABA/ICS FDC or LABA/ICS FDC between 2019/1/1 and 2022/12/31. Patients with COPD were defined as those with at least one diagnosis

code (International Classification of Diseases, Tenth Revision diagnoses codes of J41-44) in any diagnosis positions in the claims of outpatient visits, emergency department visits, or hospital admissions.<sup>15</sup> LAMA/LABA/ICS FDC or LABA/ICS FDC treatment was defined according to outpatient pharmacy dispensing claims (see [eTable 1](#)). The date of the earliest dispensing of a LAMA/LABA/ICS FDC or LABA/ICS FDC following a COPD diagnosis was defined as the cohort entry date. Of note, patients were required to have no dispensing of any LAMA/LABA/ICS FDC within 365 prior to cohort entry. However, because patients who received LAMA/LABA/ICS FDC may switch from LABA/ICS FDC treatment in the real-world settings, we allowed patients with prior use of LABA/ICS FDC to be included in the cohort and handled their prior use records as one of the covariates. A subgroup analysis stratified by prior use of LABA/ICS FDC was also conducted to assess the risk of LAMA/LABA/ICS FDC as a switch therapy or an initial therapy (see [the subsequent analysis plans](#)). [eMethods](#) describe detailed exclusion criteria and [eFigure 1](#) shows the research framework in a visualized format.

## Outcome Measures

Our outcome of interest was non-fatal cardiovascular episodes, including composite and individual cardiovascular events. The composite cardiovascular events were determined according to the earliest hospitalization for acute myocardial infarction, unstable angina, ischemic stroke, congestive heart failure, or cardiac dysrhythmia after cohort entry using inpatient diagnosis codes recorded in the primary position. Several validation studies using administrative claims data have demonstrated that, for each individual cardiovascular event, the algorithms had positive predictive values ranging from 80% to 100%.<sup>16-21</sup> See [eTable 2](#) for codes.

We mainly followed patients with an on-treatment approach. Specifically, the follow-up started on the date after cohort entry and ended at any cardiovascular outcome occurrence, study FDC treatment change or discontinuation, death, or end of data (2022/12/31), whichever came first. For LAMA/LABA/ICS FDC initiators, treatment change was defined as a dispensing of LABA/ICS FDC or another LAMA/LABA/ICS FDC. For LABA/ICS FDC users, treatment change was defined as a dispensing of LAMA-containing regimens or another LABA/ICS FDC. For both treatment groups, treatment discontinuation occurred when more than 60 days elapsed between the end of one dispensing and the start of the subsequent dispensing, if any. The discontinuation date was 60 days after the end of the last dispensing.

## Confounder Measures

There were >100 potential baseline confounders, including (1) age at cohort entry, (2) sex, (3) COPD duration, (4) cardiovascular and other comorbidities, (5) cardiovascular and other medications, and (6) healthcare services for cardiovascular disease or other reasons. We ascertained these characteristics according to corresponding healthcare records captured within 365 days prior to (or at) cohort entry (except COPD duration, which was based on the duration from the earliest recorded date of COPD diagnosis, looking back until 2014/01/01, to cohort entry). [eTable 3–eTable 5](#) detailed covariate definitions.

## Statistical Analysis

To mitigate the curse of dimensionality due to fewer events and numerous confounders in a multivariable regression model,<sup>22</sup> we collapsed above >100 confounders into a single propensity score (PS) and conducted PS matching, followed by outcome estimation in the PS-matched cohort. Specifically, we calculated the probabilities of initiating LAMA/LABA/ICS FDC versus using LABA/ICS FDC (ie, PS) with logistic regression conditional on all aforementioned claims-based covariates. A 1:10 variable-ratio PS matching algorithm was applied by matching one LABA/LAMA/ICS FDC initiator with up to 10 LABA/ICS FDC users with a nearest-neighbor algorithm (no replacement and a matching caliper of 0.025 on the PS scale).<sup>23</sup> The standardized mean difference was then used to assess covariate distribution between treatment groups before and after PS matching. A magnitude <0.1 in absolute value represented negligible imbalance.<sup>24</sup> For composite cardiovascular events, the incidence rates and 95% CIs for LAMA/LABA/ICS FDC initiators and LABA/ICS FDC users were estimated based on a Poisson distribution. The outcome occurrence over time was visualized with cumulative incidence plots. With traditional Cox proportional hazards models, we computed HRs and 95% CIs comparing LAMA/LABA/ICS FDC with LABA/ICS FDC. We also computed incidence rates and HRs for individual cardiovascular events. Aforementioned analyses were conducted without and with PS matching accounting for different matching ratios.<sup>23</sup>

## Additional Analyses

Four pre-specified subgroup analyses were performed for composite cardiovascular events. First, we examined if the cardiovascular risk associated with LAMA/LABA/ICS FDC varied by underlying disease and baseline characteristics, such as prior hospitalized cardiovascular episodes, prior hospitalized COPD exacerbations, or prior COVID-19 episodes. Second, we explored if the risk differed by prior maintenance medication use, including LABA/ICS FDC and LAMA containing regimens. Third, we conducted 10 pairwise treatment comparisons separately (two LAMA/LABA/ICS FDC and five LABA/ICS FDC). Fourth, we assessed if the risk became pronounced with longer treatment duration (1–90, 91–180, 181–365, and >365 days). In each subgroup analysis, the PS was re-estimated and patients were re-matched.<sup>25</sup> The Wald test was used to evaluate if there were significantly heterogeneous effects across patient subgroups ( $p$ -value <0.05).

Six pre-specified sensitivity analyses were also performed. First, we extended the grace period from 60 days to 90 days to define study treatment discontinuation. Second, besides the on-treatment approach, an intention-to-treat follow-up approach was applied irrespective of treatment change or discontinuation after cohort entry. Third, we computed subdistribution HRs with the Fine-Gray subdistribution hazard model to consider an impact of competing risk from mortality.<sup>26</sup> Fourth, we restricted study patients to those with cohort entry dates between 2019 and 2021 to reduce an impact from including patients who entered the cohort in 2022 and had <365 days of follow-up duration. Fifth, we estimated high-dimensional propensity scores (hd-PS) which simultaneously included aforementioned >100 predefined covariates and 100 empirically identified covariates from the Taiwan NHIRD to improve confounding control.<sup>27,28</sup> Sixth, we further incorporated 11 substantial clinical measurements obtained from the Taiwan National Health Insurance (NHI) Laboratory Database<sup>29</sup> and the Taiwan COPD pay-for-performance (P4P) Database<sup>30</sup> for PS estimation and matching. These measurements included laboratory examination results, lung function test results, systolic blood pressure, and health behavior. Of note, a multiple imputation technique was used to overcome an issue of missing values.<sup>31</sup>

Analyses of the present study were carried out using SAS 9.4 (SAS Institute, Cary, NC). The two-sided tests were conducted, with a 95% CI excluding the null (corresponding to a  $p$ -value <0.05) indicating statistical significance in the main analysis. To identify any potential cardiovascular safety signals associated with LAMA/LABA/ICS FDC in different clinical contexts, we did not account for multiplicity and remained the same significant level for the predefined, additional analyses. The present work was part of our series of research which aimed for exploring the effectiveness and safety of newly marketed maintenance therapies. The study designs and statistical methods were in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement and the principles of pharmacoepidemiologic studies, which were therefore also used and described in our previous publication.<sup>32</sup> Nevertheless, both studies were conducted independently and share different values. Specifically, the present study examined cardiovascular risk of LAMA/LABA/ICS FDC using more updated Taiwanese healthcare data from 2019 to 2022, while our previous publication assessed cardiovascular risk of LAMA/LABA FDC using Taiwanese healthcare data from 2017 to 2020. Because LAMA/LABA/ICS FDC is indicated for patients with frequent exacerbation attacks and high eosinophil counts and LAMA/LABA FDC tends to be prescribed for patients with more dyspnea symptoms, the target populations and clinical implications of the two studies are different. See more elaboration in the discussion section.

## Results

### Study Cohort

There were 58,371 study patients. Among 8,189 LAMA/LABA/ICS FDC initiators, umeclidinium/vilanterol/fluticasone (71%) was prescribed more frequently than glycopyrronium/formoterol/beclomethasone (29%). Among 50,182 LABA/ICS FDC users, there was a variety of medication use, including formoterol/budesonide (30%), formoterol/beclomethasone (27%), salmeterol/fluticasone (21%), vilanterol/fluticasone (21%), and formoterol/fluticasone (<1%) (eFigure 2). There was an increased use of LAMA/LABA/ICS FDC and a decreased use of LABA/ICS FDC with time (eTable 6).

LAMA/LABA/ICS FDC initiators tended to be male (88% versus 68%) and had a longer mean COPD duration (1,481 days versus 1,071 days) compared to LABA/ICS FDC users. LAMA/LABA/ICS FDC initiators were also more

likely to have a history of cancer; take selective  $\beta$  blockers, inhaled short-acting bronchodilators, LAMA/LABA FDC, ICS, and systemic corticosteroids; and have more frequent emergency department visits or hospital admissions for any cause or for COPD compared to LABA/ICS FDC users. LAMA/LABA/ICS FDC initiators were more likely to hospitalize for cardiovascular disease and access cardiovascular related examinations (eg, echocardiography) as well. Instead, LABA/ICS FDC users tended to have influenza, rheumatoid arthritis, and osteoarthritis and use LABA/ICS FDC and cyclooxygenase-2 nonselective non-steroidal anti-inflammatory drugs. After 1:10 variable-ratio PS matching, 28,851 patients remained in the analysis (5,836 LAMA/LABA/ICS FDC initiators and 23,015 LABA/ICS FDC users). All baseline claims-based characteristics became comparable between treatment groups, with standard mean differences  $<0.1$  (most of them  $<0.01$ ) (Table 1, eTable 7, and eFigure 3).

**Table 1** Select Baseline Patient Characteristics by Study Treatment

| Variables                               | Before PS Matching (n=58,371) |                  |                                    | After 1:10 Variable-Ratio PS Matching (n=28,851) |                      |                                    |
|-----------------------------------------|-------------------------------|------------------|------------------------------------|--------------------------------------------------|----------------------|------------------------------------|
|                                         | LAMA/LABA/<br>ICS FDC         | LABA/ICS FDC     | Standardized<br>Mean<br>Difference | LAMA/LABA/<br>ICS FDC                            | LABA/ICS FDC         | Standardized<br>Mean<br>Difference |
|                                         | n=8,189                       | n=50,182         |                                    | n=5,836                                          | n=23,015             |                                    |
|                                         |                               |                  |                                    | n=5,836 <sup>a</sup>                             | n=5,836 <sup>a</sup> |                                    |
| <b>Demographics, mean (SD) or n (%)</b> |                               |                  |                                    |                                                  |                      |                                    |
| Age, years                              | 70.52 (10.55)                 | 69.52 (12.62)    | 0.086                              | 70.11 (10.87)                                    | 70.52 (11.57)        | -0.037                             |
| Male                                    | 7,226 (88.24)                 | 33,948 (67.65)   | 0.513                              | 4,956 (84.92)                                    | 4,947 (84.77)        | 0.004                              |
| COPD duration, days <sup>b</sup>        | 1481.25 (1026.42)             | 1071.44 (908.02) | 0.423                              | 1336.26 (1037.02)                                | 1325.42 (963.98)     | 0.011                              |
| <b>Comorbidities, n (%)</b>             |                               |                  |                                    |                                                  |                      |                                    |
| Hypertension                            | 4,887 (59.68)                 | 29,983 (59.75)   | -0.001                             | 3,494 (59.87)                                    | 3,512 (60.18)        | -0.006                             |
| Ischemic heart disease or angina        | 2,394 (29.23)                 | 13,265 (26.43)   | 0.063                              | 1,718 (29.44)                                    | 1,756 (30.09)        | -0.014                             |
| Myocardial infarction                   | 308 (3.76)                    | 1,432 (2.85)     | 0.051                              | 220 (3.77)                                       | 218 (3.74)           | 0.002                              |
| Cardiac dysrhythmia                     | 1,415 (17.28)                 | 8,108 (16.16)    | 0.030                              | 1,008 (17.27)                                    | 1,073 (18.39)        | -0.029                             |
| Congestive heart failure                | 1,532 (18.71)                 | 8,206 (16.35)    | 0.062                              | 1,060 (18.16)                                    | 1,100 (18.85)        | -0.018                             |
| Cerebrovascular disease                 | 1,247 (15.23)                 | 8,188 (16.32)    | -0.030                             | 933 (15.99)                                      | 985 (16.88)          | -0.024                             |
| Peripheral vascular disease             | 258 (3.15)                    | 1,505 (3.00)     | 0.009                              | 174 (2.98)                                       | 179 (3.07)           | -0.005                             |
| Diabetes mellitus                       | 2,328 (28.43)                 | 14,844 (29.58)   | -0.025                             | 1,692 (28.99)                                    | 1,716 (29.40)        | -0.009                             |
| Hyperlipidemia                          | 3,068 (37.46)                 | 19,961 (39.78)   | -0.048                             | 2,246 (38.49)                                    | 2,258 (38.69)        | -0.004                             |
| Pneumonia                               | 1,214 (14.82)                 | 7,016 (13.98)    | 0.024                              | 881 (15.10)                                      | 877 (15.03)          | 0.002                              |
| Influenza                               | 203 (2.48)                    | 2,230 (4.44)     | -0.108                             | 161 (2.76)                                       | 161 (2.76)           | NA                                 |
| Acute bronchitis                        | 3,229 (39.43)                 | 22,196 (44.23)   | -0.097                             | 2,366 (40.54)                                    | 2,385 (40.87)        | -0.007                             |
| COVID-19                                | 420 (5.13)                    | 1,632 (3.25)     | 0.094                              | 296 (5.07)                                       | 288 (4.93)           | 0.006                              |
| Post-COVID-19                           | 40 (0.49)                     | 274 (0.55)       | -0.008                             | 27 (0.46)                                        | 30 (0.51)            | -0.007                             |
| Any cancer other than lung cancer       | 1,139 (13.91)                 | 5,159 (10.28)    | 0.111                              | 751 (12.87)                                      | 767 (13.14)          | -0.008                             |
| Lung cancer                             | 547 (6.68)                    | 1,830 (3.65)     | 0.137                              | 351 (6.01)                                       | 353 (6.05)           | -0.001                             |
| <b>Concurrent medication use, n (%)</b> |                               |                  |                                    |                                                  |                      |                                    |
| ACEIs or ARBs                           | 3,769 (46.03)                 | 22,672 (45.18)   | 0.017                              | 2,738 (46.92)                                    | 2,762 (47.33)        | -0.008                             |
| Selective $\beta$ blockers              | 2,264 (27.65)                 | 11,503 (22.92)   | 0.109                              | 1,607 (27.54)                                    | 1,627 (27.88)        | -0.008                             |
| Non-selective $\beta$ blockers          | 1,081 (13.20)                 | 7,248 (14.44)    | -0.036                             | 828 (14.19)                                      | 835 (14.31)          | -0.003                             |
| Dihydropyridine CCBs                    | 2,476 (30.24)                 | 15,176 (30.24)   | NA                                 | 1,764 (30.23)                                    | 1,802 (30.88)        | -0.014                             |
| Non-dihydropyridine CCBs                | 1,175 (14.35)                 | 6,088 (12.13)    | 0.065                              | 780 (13.37)                                      | 788 (13.50)          | -0.004                             |
| Diuretics                               | 2,612 (31.90)                 | 13,814 (27.53)   | 0.096                              | 1,840 (31.53)                                    | 1,887 (32.33)        | -0.017                             |
| Other anti-hypertensive agents          | 976 (11.92)                   | 4,858 (9.68)     | 0.072                              | 663 (11.36)                                      | 679 (11.63)          | -0.009                             |
| Nitrates                                | 1,563 (19.09)                 | 8,503 (16.94)    | 0.056                              | 1,127 (19.31)                                    | 1,191 (20.41)        | -0.027                             |
| Anti-arrhythmic agents                  | 921 (11.25)                   | 4,337 (8.64)     | 0.087                              | 605 (10.37)                                      | 642 (11.00)          | -0.021                             |
| Digoxin                                 | 247 (3.02)                    | 1,283 (2.56)     | 0.028                              | 178 (3.05)                                       | 190 (3.26)           | -0.012                             |
| Aspirin                                 | 2,389 (29.17)                 | 13,605 (27.11)   | 0.046                              | 1,711 (29.32)                                    | 1,768 (30.29)        | -0.021                             |
| Clopidogrel                             | 984 (12.02)                   | 5,078 (10.12)    | 0.060                              | 695 (11.91)                                      | 686 (11.75)          | 0.005                              |
| Warfarin                                | 111 (1.36)                    | 721 (1.44)       | -0.007                             | 84 (1.44)                                        | 81 (1.39)            | 0.004                              |
| Direct thrombin or factor Xa inhibitors | 609 (7.44)                    | 2,947 (5.87)     | 0.063                              | 402 (6.89)                                       | 428 (7.33)           | -0.017                             |
| Statins                                 | 2,643 (32.28)                 | 15,710 (31.31)   | 0.021                              | 1,894 (32.45)                                    | 1,876 (32.15)        | 0.007                              |

(Continued)

**Table 1** (Continued).

| Variables                                                                     | Before PS Matching (n=58,371) |                |                                    | After 1:10 Variable-Ratio PS Matching (n=28,851) |                      |                                    |
|-------------------------------------------------------------------------------|-------------------------------|----------------|------------------------------------|--------------------------------------------------|----------------------|------------------------------------|
|                                                                               | LAMA/LABA/<br>ICS FDC         | LABA/ICS FDC   | Standardized<br>Mean<br>Difference | LAMA/LABA/<br>ICS FDC                            | LABA/ICS FDC         | Standardized<br>Mean<br>Difference |
|                                                                               | n=8,189                       | n=50,182       |                                    | n=5,836                                          | n=23,015             |                                    |
|                                                                               |                               |                |                                    | n=5,836 <sup>a</sup>                             | n=5,836 <sup>a</sup> |                                    |
| Fibrates                                                                      | 287 (3.50)                    | 2,118 (4.22)   | −0.037                             | 225 (3.86)                                       | 243 (4.16)           | −0.016                             |
| Insulin                                                                       | 978 (11.94)                   | 4,675 (9.32)   | 0.085                              | 650 (11.14)                                      | 676 (11.58)          | −0.014                             |
| Metformin                                                                     | 1,458 (17.80)                 | 9,000 (17.93)  | −0.003                             | 1,052 (18.03)                                    | 1,040 (17.82)        | 0.005                              |
| Sulfonylurea                                                                  | 730 (8.91)                    | 4,876 (9.72)   | −0.028                             | 540 (9.25)                                       | 558 (9.56)           | −0.011                             |
| Glinides                                                                      | 220 (2.69)                    | 1,287 (2.56)   | 0.008                              | 157 (2.69)                                       | 159 (2.72)           | −0.002                             |
| Thiazolidinedione                                                             | 254 (3.10)                    | 1,478 (2.95)   | 0.009                              | 191 (3.27)                                       | 198 (3.39)           | −0.007                             |
| Alpha-glucosidase inhibitors                                                  | 202 (2.47)                    | 1,265 (2.52)   | −0.003                             | 153 (2.62)                                       | 150 (2.57)           | 0.003                              |
| Dipeptidyl peptidase-4 inhibitors                                             | 1,087 (13.27)                 | 6,306 (12.57)  | 0.021                              | 776 (13.30)                                      | 782 (13.40)          | −0.003                             |
| Sodium-glucose cotransporter 2 Inhibitors                                     | 381 (4.65)                    | 1,775 (3.54)   | 0.056                              | 271 (4.64)                                       | 265 (4.54)           | 0.005                              |
| Glucagon-like peptide-1 receptor agonists                                     | 29 (0.35)                     | 194 (0.39)     | −0.005                             | 21 (0.36)                                        | 17 (0.29)            | 0.012                              |
| Inhaled short-acting bronchodilators                                          | 4,876 (59.54)                 | 19,762 (39.38) | 0.412                              | 3,141 (53.82)                                    | 3,158 (54.11)        | −0.006                             |
| LABA                                                                          | 105 (1.28)                    | 362 (0.72)     | 0.056                              | 73 (1.25)                                        | 92 (1.58)            | −0.028                             |
| LAMA                                                                          | 715 (8.73)                    | 3,418 (6.81)   | 0.072                              | 550 (9.42)                                       | 606 (10.38)          | −0.032                             |
| LABA/ICS FDC                                                                  | 265 (3.24)                    | 18,896 (37.65) | −0.944                             | 265 (4.54)                                       | 286 (4.90)           | −0.017                             |
| LABA/LAMA FDC                                                                 | 5,736 (70.05)                 | 5,066 (10.10)  | 1.546                              | 3,386 (58.02)                                    | 3,403 (58.31)        | −0.006                             |
| ICS                                                                           | 1,167 (14.25)                 | 1,176 (2.34)   | 0.442                              | 430 (7.37)                                       | 383 (6.56)           | 0.032                              |
| Systemic bronchodilators                                                      | 6,121 (74.75)                 | 35,507 (70.76) | 0.090                              | 4,304 (73.75)                                    | 4,328 (74.16)        | −0.009                             |
| Systemic corticosteroids                                                      | 5,413 (66.10)                 | 29,433 (58.65) | 0.154                              | 3,808 (65.25)                                    | 3,824 (65.52)        | −0.006                             |
| Oral antibiotics commonly used for COPD exacerbations                         | 5,101 (62.29)                 | 30,942 (61.66) | 0.013                              | 3,654 (62.61)                                    | 3,716 (63.67)        | −0.022                             |
| <b>Healthcare services, mean (SD) or n (%)</b>                                |                               |                |                                    |                                                  |                      |                                    |
| No. of outpatient visits                                                      | 40.45 (26.22)                 | 39.61 (25.81)  | 0.032                              | 40.35 (26.99)                                    | 40.44 (25.90)        | −0.003                             |
| No. of outpatient visits due to cardiovascular disease <sup>c</sup>           | 12.01 (12.69)                 | 11.74 (12.65)  | 0.021                              | 11.93 (12.76)                                    | 11.83 (12.22)        | 0.008                              |
| No. of outpatient visits due to COPD                                          | 9.67 (8.66)                   | 6.29 (7.38)    | 0.420                              | 8.30 (8.04)                                      | 8.12 (8.58)          | 0.021                              |
| No. of emergency department visits                                            | 1.26 (2.36)                   | 1.00 (2.11)    | 0.118                              | 1.24 (2.39)                                      | 1.29 (2.45)          | −0.019                             |
| No. of emergency department visits due to cardiovascular disease <sup>c</sup> | 0.26 (0.86)                   | 0.22 (0.83)    | 0.045                              | 0.26 (0.90)                                      | 0.27 (0.82)          | −0.012                             |
| No. of emergency department visits due to COPD                                | 0.30 (1.03)                   | 0.14 (0.71)    | 0.177                              | 0.26 (1.02)                                      | 0.26 (0.88)          | −0.006                             |
| No. of hospitalizations                                                       | 0.86 (1.56)                   | 0.63 (1.33)    | 0.159                              | 0.81 (1.51)                                      | 0.83 (1.56)          | −0.015                             |
| No. of hospitalizations due to cardiovascular disease <sup>c</sup>            | 0.60 (1.31)                   | 0.46 (1.11)    | 0.118                              | 0.57 (1.26)                                      | 0.58 (1.26)          | −0.012                             |
| No. of hospitalizations due to COPD                                           | 0.49 (1.14)                   | 0.25 (0.77)    | 0.250                              | 0.40 (0.99)                                      | 0.41 (1.05)          | −0.010                             |
| Pneumococcal or influenza vaccinations                                        | 5,055 (61.73)                 | 24,619 (49.06) | 0.257                              | 3,361 (57.59)                                    | 3,389 (58.07)        | −0.010                             |
| Echocardiography                                                              | 2,888 (35.27)                 | 14,181 (28.26) | 0.151                              | 2,016 (34.54)                                    | 2,066 (35.40)        | −0.018                             |
| BNP, proBNP, or NT-proBNP test                                                | 2,462 (30.06)                 | 9,902 (19.73)  | 0.241                              | 1,641 (28.12)                                    | 1,721 (29.49)        | −0.030                             |
| Spirometry test                                                               | 5,557 (67.86)                 | 22,442 (44.72) | 0.480                              | 3,690 (63.23)                                    | 3,755 (64.34)        | −0.023                             |

**Notes:** <sup>a</sup>One LABA/LAMA/ICS FDC initiator versus one randomly sampled LABA/ICS FDC user in each matched subset. <sup>b</sup>COPD duration was defined as the duration from the first recorded date of COPD diagnosis (looking back until 2014/01/01) to the cohort entry date. <sup>c</sup>Cardiovascular disease included hypertension, ischemic heart disease or angina, myocardial infarction, coronary revascularization, cardiac dysrhythmia, congestive heart failure, cerebrovascular disease, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral vascular disease, diabetes mellitus, and hyperlipidemia.

**Abbreviations:** ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; COVID, coronavirus disease; FDC, fixed-dose combination; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$  agonists; LAMA, long-acting muscarinic antagonists; NA, not applicable; NT, n-terminal; PS, propensity score; SD, standard deviation.

## Study Outcomes Comparing LAMA/LABA/ICS FDC to LABA/ ICS FDC

In terms of composite cardiovascular events, the incidence rate was 24.85 per 1,000 person-years for LAMA/LABA/ICS FDC initiators and 28.35 per 1,000 person-years for LABA/ICS FDC users in the PS-matched cohort during a mean follow-up duration of approximately 205 days. LAMA/LABA/ICS FDC did not present an increased risk compared to LABA/ICS FDC, with a HR after PS matching of 1.00 (95% CI, 0.78–1.28) (Table 2). The results were in line with the cumulative incidence plots (eFigure 4).

**Table 2** Follow-Up, Incidence Rate, and HR of Cardiovascular Events Comparing LAMA/LABA/ICS FDC to LABA/ICS FDC

|                                        | Before PS Matching<br>(n=58,371) |                            | After 1:10 Variable-Ratio PS Matching (n=28,851) |                            |
|----------------------------------------|----------------------------------|----------------------------|--------------------------------------------------|----------------------------|
|                                        | LAMA/LABA/ICS FDC<br>(n=8,189)   | LABA/ICS FDC<br>(n=50,182) | LAMA/LABA/ICS FDC<br>(n=5,836)                   | LABA/ICS FDC<br>(n=23,015) |
| <b>Composite cardiovascular events</b> |                                  |                            |                                                  |                            |
| Number of events                       | 158                              | 741                        | 117                                              | 316                        |
| Mean follow-up days (SD)               | 316.81 (276.45)                  | 239.46 (306.59)            | 294.65 (263.56)                                  | 181.75 (224.60)            |
| Incidence rate <sup>a</sup> (95% CI)   | 22.24 (19.03–26.00)              | 22.52 (20.96–24.20)        | 24.85 (20.73–29.79)                              | 28.35 (22.79–35.27)        |
| HR (95% CI) <sup>b</sup>               | 1.03 (0.86–1.22)                 | Ref                        | 1.00 (0.78–1.28)                                 | Ref                        |
| <b>Acute myocardial infarction</b>     |                                  |                            |                                                  |                            |
| Number of events                       | 39                               | 181                        | 30                                               | 79                         |
| Mean follow-up days (SD)               | 319.43 (276.95)                  | 241.05 (307.94)            | 296.87 (263.98)                                  | 183.11 (226.09)            |
| Incidence rate <sup>a</sup> (95% CI)   | 5.45 (3.98–7.45)                 | 5.47 (4.72–6.32)           | 6.32 (4.42–9.05)                                 | 7.05 (4.56–10.90)          |
| HR (95% CI) <sup>b</sup>               | 1.04 (0.73–1.47)                 | Ref                        | 1.02 (0.62–1.68)                                 | Ref                        |
| <b>Unstable angina</b>                 |                                  |                            |                                                  |                            |
| Number of events                       | <5                               | 21                         | <5                                               | 13                         |
| Mean follow-up days (SD)               | 320.22 (277.52)                  | 241.54 (308.40)            | 298.78 (264.66)                                  | 183.46 (226.33)            |
| Incidence rate <sup>a</sup> (95% CI)   | 0.42 (0.13–1.30)                 | 0.63 (0.41–0.97)           | 0.42 (0.11–1.68)                                 | 0.62 (0.14–2.69)           |
| HR (95% CI) <sup>b</sup>               | 0.72 (0.21–2.42)                 | Ref                        | 0.54 (0.10–2.87)                                 | Ref                        |
| <b>Ischemic stroke</b>                 |                                  |                            |                                                  |                            |
| Number of events                       | 55                               | 263                        | 37                                               | 107                        |
| Mean follow-up days (SD)               | 319.19 (277.11)                  | 240.80 (307.65)            | 296.89 (264.34)                                  | 182.95 (225.71)            |
| Incidence rate <sup>a</sup> (95% CI)   | 7.69 (5.90–10.01)                | 7.95 (7.04–8.97)           | 7.80 (5.65–10.77)                                | 9.65 (6.65–14.00)          |
| HR (95% CI) <sup>b</sup>               | 0.96 (0.72–1.29)                 | Ref                        | 0.82 (0.53–1.28)                                 | Ref                        |
| <b>Congestive heart failure</b>        |                                  |                            |                                                  |                            |
| Number of events                       | 55                               | 256                        | 42                                               | 107                        |
| Mean follow-up days (SD)               | 319.06 (277.40)                  | 240.94 (308.08)            | 296.79 (264.55)                                  | 182.86 (225.82)            |
| Incidence rate <sup>a</sup> (95% CI)   | 7.69 (5.90–10.01)                | 7.73 (6.84–8.74)           | 8.86 (6.55–11.98)                                | 9.81 (6.78–14.20)          |
| HR (95% CI) <sup>b</sup>               | 1.08 (0.81–1.45)                 | Ref                        | 1.21 (0.81–1.81)                                 | Ref                        |
| <b>Cardiac dysrhythmia</b>             |                                  |                            |                                                  |                            |
| Number of events                       | 7                                | 42                         | 7                                                | 17                         |
| Mean follow-up days (SD)               | 320.24 (277.49)                  | 241.55 (308.45)            | 297.7 (264.61)                                   | 183.49 (226.44)            |
| Incidence rate <sup>a</sup> (95% CI)   | 0.97 (0.46–2.05)                 | 1.27 (0.94–1.71)           | 1.47 (0.70–3.09)                                 | 2.08 (0.93–4.63)           |
| HR (95% CI) <sup>b</sup>               | 0.75 (0.33–1.67)                 | Ref                        | 0.70 (0.25–1.95)                                 | Ref                        |

**Notes:** <sup>a</sup>The unit of incidence rate was per 1,000 person-years. The incidence rate after 1:10 PS matching was weighted by the inverse of the matching ratio. <sup>b</sup>The HR after 1:10 PS matching was stratified on the matching ratio.

**Abbreviations:** CI, confidence interval; FDC, fixed-dose combination; HR, hazard ratio; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$  agonists; LAMA, long-acting muscarinic antagonists; PS, propensity score; SD, standard deviation.

Congestive heart failure and ischemic stroke were the most common cardiovascular events, followed by acute myocardial infarction, cardiac dysrhythmia, and unstable angina. LABA/LAMA/ICS FDC was in general not associated with an elevated risk of individual events. The HR after PS matching was 1.02 (95% CI, 0.62–1.68) for acute myocardial infarction, 0.54 (95% CI, 0.10–2.87) for unstable angina, 0.82 (95% CI, 0.53–1.28) for ischemic stroke, 1.21 (95% CI, 0.81–1.81) for congestive heart failure, and 0.70 (95% CI, 0.25–1.95) for cardiac dysrhythmia (Table 2).

## Findings of Additional Analyses

We did not find an increased risk of composite cardiovascular events associated with LAMA/LABA/ICS FDC even in patients having prior cardiovascular episodes (HR, 0.86; 95% CI, 0.62–1.20), having prior hospitalized COPD exacerbations (0.93 [95% CI, 0.62–1.39]), or receiving treatment longer than one year (0.64 [95% CI, 0.18–2.23]). Age, sex, COPD duration, as well as prior use of LABA/ICS FDC or LAMA containing regimens also did not modify the cardiovascular safety profile ([eTable 8](#)). The comparison of individual LAMA/LABA/ICS FDC versus individual LABA/ICS FDC generated similar findings except the comparison with formoterol/fluticasone showing unstable estimates and wide CIs ([eTable 9](#)). In terms of treatment duration-response relation for LAMA/LABA/ICS FDC, the HR was 1.18 (95% CI, 0.85–1.65) within 90 days, 0.60 (95% CI, 0.29–1.22) during 91–180 days, 0.71 (95% CI, 0.34–1.46) during 181–365 days, and 0.76 (95% CI, 0.38–1.54) after 365 days since cohort entry ([eTable 10](#)). [Figure 1](#) summarizes the results of subgroup analyses and the p-values for test of homogeneity across all patient subgroups ranged from 0.237 to 0.946.

When we applied a grace period of 90 days to define study treatment discontinuation in the on-treatment approach, the HR after PS matching was 1.02 (95% CI, 0.80–1.28) for composite cardiovascular events ([eTable 11](#)). The intention-to-treat approach generated a longer follow-up duration (mean follow-up day of 651 days) and an HR after PS matching of 1.00 (95% CI, 0.84–1.20) ([eTable 11](#) and [eTable 12](#)). The results did not change meaningfully after addressing competing risk from mortality or restricting study patients to those with cohort entry years between 2019 and 2021 ([eTable 11](#)). The HR after hd-PS matching (0.91 [95% CI, 0.70–1.17]) also did not differ materially from that was derived from the main analysis ([eTable 11](#)). There were 48,757 patients (84% of the study patients) with at least one clinical measurement extracted from either the NHI Laboratory Database or the COPD P4P Database ([eTable 13](#)). The PS-matched analysis after multiple imputation yielded comparable distribution of these measurements between the treatment groups ([eTable 14](#)) and the HR did not indicate a higher risk associated with LABA/LAMA/ICS FDC (1.02 [95% CI, 0.75–1.38]) ([eTable 11](#)). See [Figure 2](#) for the findings of each sensitivity analysis.

## Discussion

Among more than 25,000 cohort patients identified from the Taiwan NHIRD, use of LAMA/LABA/ICS FDC versus use of LABA/ICS FDC did not seem to have a higher risk of various cardiovascular outcomes, including acute myocardial infarction, unstable angina, stroke, heart failure, and cardiac dysrhythmia. There was also no apparent, increased cardiovascular risk in high-risk subpopulations, such as those having prior hospitalized cardiovascular episodes, having prior hospitalized COPD exacerbations, or receiving treatment longer than one year. The findings did not change meaningfully in several predefined sensitivity analyses, including different approaches to controlling for confounding.

## Cardiovascular Safety of LAMA/LABA/ICS FDC in IMPACT, ETHOS, and TRILOGY Trials and the Present Taiwanese Cohort Study

Our results should be interpreted in the context of conflicting cardiovascular safety alerts derived from clinical trial data for LAMA. Pharmacologically, LAMA may block muscarinic 2 and muscarinic 3 receptors in the heart tissues, leading to cardiovascular complications.<sup>33</sup> Earlier clinical trials found that LAMA (mainly tiotropium) may have an elevated risk of ischemic heart disease, stroke, and arrhythmia.<sup>34,35</sup> Nonetheless, a large-scale placebo-controlled randomized trial and a meta-analysis did not confirm the increased cardiovascular risk.<sup>36,37</sup> Similarly, for LAMA/LABA/ICS FDC (including umeclidinium/vilanterol/fluticasone, glycopyrronium/formoterol/budesonide, and glycopyrronium/formoterol/beclomethasone), the potential cardiovascular safety concerns were only observed in the IMPACT and ETHOS trials<sup>8,9</sup> but not in other trials (TRIOLOGY, FULFIL, and KRONOS).<sup>10,38,39</sup> Of note, none of these efficacy trials were specifically designed to evaluate the cardiovascular risk of LAMA/LABA/ICS FDC.

Moreover, it should be recognized that these LAMA/LABA/ICS FDC trials excluded patients with significant underlying cardiovascular disease but included patients with more severe COPD. For example, patients included in IMPACT, ETHOS, and TRILOGY trials had a mean COPD Assessment Test (CAT) score of nearly 20 and a mean predicted forced expiratory

volume in one second (FEV<sub>1</sub>) value ranging from 36–46%; >20% patients experienced a severe COPD exacerbation in the prior year. However, our study patients had a mean CAT score of nearly 10 and a mean predicted FEV<sub>1</sub> value of approximately 60%; <20% patients experienced a severe COPD exacerbation at baseline. Our study patients also tended to be older and had more male ([eTable 15](#)). Our null findings should not be interpreted as an advocate of using LAMA/LABA/ICS FDC in the daily practice rather supporting their use with an awareness of proper indications.

## Cardiovascular Safety of LAMA/LABA/ICS FDC in an UK Cohort Study and the Present Taiwanese Cohort Study

To our knowledge, there was only one UK cohort study exploring cardiovascular safety comparing LAMA/LABA/ICS FDC with LABA/ICS FDC, which showed no increased risk of myocardial infarction and stroke associated with LAMA/LABA/ICS FDC.<sup>7</sup> Our Taiwanese cohort study further observed no elevated risk of unstable angina, heart failure, and cardiac dysrhythmia associated with LAMA/LABA/ICS FDC. There was also no more pronounced risk in high-risk subpopulations. In terms of prior maintenance medication use, our analysis stratified by prior use of LABA/ICS FDC examined the risk of LAMA/LABA/ICS FDC as an initial treatment or a switch treatment from LABA/ICS FDC. Our analysis stratified by prior use of LAMA containing regimens minimized the concern that the cardiovascular risk might mitigate and not be easy to identify in patients who have received LAMA containing treatment for a while.

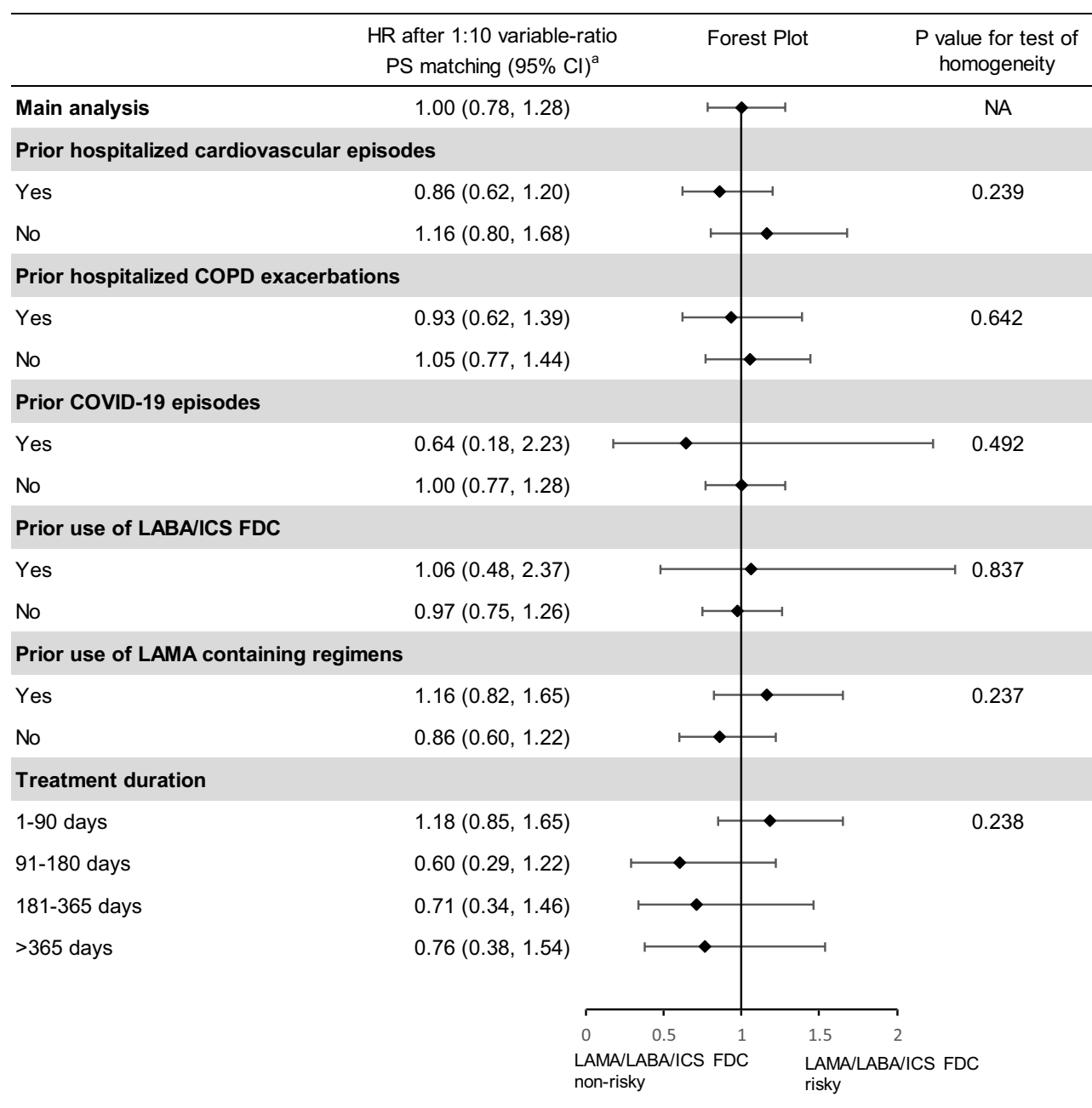
## Strengths and Limitations of the Study

The present cohort study conducted in the nationwide Taiwanese database identified a representative Asian population and comprehensively ascertained information on inhaled medication use, cardiovascular events, and substantial covariates. Through validated claim-based outcome algorithms, the absolute and relative risk estimates for various cardiovascular events and for various patient subgroups provided complementary safety evidence to the findings of available efficacy trials and the previous UK cohort study. As [eTable 6](#) showed, there has been a temporal trend of increased use of LAMA/LABA/ICS FDC and decreased use of LABA/ICS FDC in the real-world settings. The updated treatment guideline also recommends LAMA/LABA/ICS FDC rather than LABA/ICS FDC for patients with frequent exacerbation attacks and high eosinophil counts, who are susceptible to adverse cardiovascular events.<sup>6</sup> Our results therefore provide scientific information for LAMA/LABA/ICS FDC initiation or switching use in eligible patients with minimal cardiovascular safety concerns. Our results also expanded cardiovascular safety spectrums for newly marketed combination maintenance treatments in light of our previous publication focusing on LAMA/LABA FDC.<sup>32</sup>

However, we still had some limitations. First, our current cohort excluded patients with a history of asthma and therefore cannot generalize the results to this population.

Second, we did not include LAMA/LABA/ICS free-combination therapies delivered via different inhalers as exposure of interest. However, the GOLD guideline prefers FDC over free-combination triple therapies.<sup>6</sup> Recent cohort studies also found that the FDC triple therapies may have better adherence and clinical outcomes than free-combination triple therapies.<sup>40,41</sup> Moreover, our preliminary data showed that <2% of triple therapy prescriptions were from FDC inhalers in 2019, the year they were first reimbursed in Taiwan. This proportion increased to >55% by 2022 and is expected to continue rising thereafter. Therefore, our approach based on FDC inhalers fits contemporary practice patterns. Third, although we aimed to depict comprehensive cardiovascular safety profiles, certain subpopulations, such as patients with prior LABA/ICS FDC use or a history of COVID-19, had a limited sample size. Similarly, we had few events for certain outcomes, such as unstable angina. These resulted in less precise estimates.

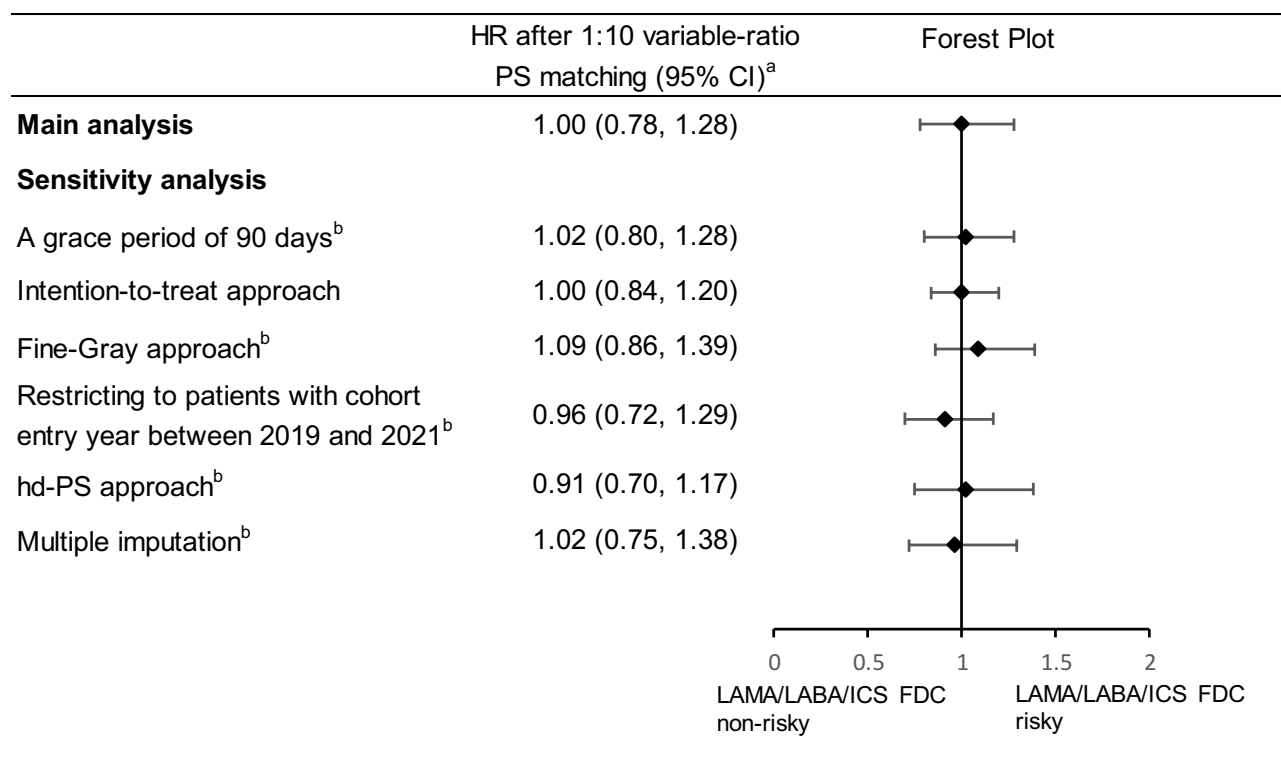
Fourth, our on-treatment approach obtained a short mean follow-up duration of 205 days. Nevertheless, our subgroup analysis with treatment duration longer than one year ([Figure 1](#)) and our sensitivity analysis using an intention-to-treat approach with a mean follow-up duration of 651 days ([Figure 2](#)) remained suggesting no increased cardiovascular risk associated with LAMA/LABA/ICS FDC. Finally, the possibility of residual confounding may not be entirely ruled out although we applied different PS matching algorithms and included different types of covariates



**Figure 1** HR of composite cardiovascular events comparing LAMA/LABA/ICS FDC to LABA/ICS FDC by underlying disease, prior maintenance medication use, and treatment duration of LAMA/LABA/ICS FDC<sup>a</sup>, after PS matching. <sup>a</sup>The HR after PS matching was stratified on the inverse of the matching ratio. <sup>b</sup>Based on an on-treatment approach.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; CI, confidence interval; FDC, fixed-dose combination; HR, hazards ratio; ICS, Inhaled corticosteroids; LABA, long-acting  $\beta_2$  agonists; LAMA, long-acting muscarinic antagonists; NA, not applicable; PS, propensity score.

(claims data and clinical measurements) to enhance confounding control. Since patients who initiated LAMA/LABA/ICS FDC were generally sicker than those on LABA/ICS FDC, we expect that the findings would remain supporting no increased cardiovascular risk associated with LAMA/LABA/ICS FDC, even with more comprehensive covariate adjustment.



**Figure 2** HR of composite cardiovascular events comparing LAMA/LABA/ICS FDC to LABA/ICS FDC in different sensitivity analyses, after PS matching.

**Abbreviations:** CI, confidence interval; FDC, fixed-dose combination; hd-PS, high-dimensional propensity score; HR, hazards ratio; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$  agonists; LAMA, long-acting muscarinic antagonists; PS, propensity score.

## Conclusion

This Taiwanese cohort study did not find a higher risk for a variety of cardiovascular outcomes comparing LAMA/LABA/ICS FDC versus LABA/ICS FDC in patients with COPD, even in high-risk subpopulations. The findings offer substantial reassurance regarding cardiovascular safety of LAMA/LABA/ICS FDC and support their appropriate use, if clinically indicated.

## Data Sharing Statement

The data used in the current study were obtained from the Applied Health Research Data Integration Service from the National Health Insurance Administration, Taiwan, which are not publicly available given the data protection policy. However, the authors are willing to have further discussion if there are any questions.

## Acknowledgments

The results were presented, in part and in an oral presentation abstract, at the ISPE's 16th Asian Conference on Pharmacoepidemiology on October 12-14, 2024 at the University of Tokyo, Tokyo, Japan.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

## References

- Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381:1257–1266. doi:10.1056/NEJMr1900500
- Agusti A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381:1248–1256. doi:10.1056/NEJMr1900475
- World Health Organization. The top 10 causes of death. Available from: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>. Accessed on January 10, 2025.
- Gedebjerg A, Szépligeti SK, Wackerhausen LH, et al. Prediction of mortality in patients with chronic obstructive pulmonary disease with the new global initiative for chronic obstructive lung disease 2017 classification: a cohort study. *Lancet Respir Med*. 2018;6(3):204–212. doi:10.1016/S2213-2600(18)30002-X
- López-Pardo ME, Candal-Pedreira C, Valdés-Cuadrado L, Represas-Represas C, Ruano-Ravina A, Pérez-Ríos M. Factors related with hospital attendance and mortality in patients with COPD: a case-control study in a real-life setting. *Int J Chron Obstruct Pulmon Dis*. 2022;17(7):809–819.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary diseases. 2022 report. Available from: <https://goldcopd.org/2022-gold-reports/>. Accessed on January 10, 2025.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary diseases. 2023 report. Available from: <https://goldcopd.org/2023-gold-report-2/>. Accessed on January 10, 2025.
- Lipson DA, Barnhart F, Brealey N, et al. IMPACT investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671–1680. doi:10.1056/NEJMoa1713901
- Rabe KF, Martinez FJ, Ferguson GT, et al. ETHOS investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35–48. doi:10.1056/NEJMoa1916046
- Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting  $\beta_2$ -agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet*. 2016;388(10048):963–973. doi:10.1016/S0140-6736(16)31354-X
- Liou JT, Lin CW, Tsai CL, et al. Risk of severe cardiovascular events from add-on tiotropium in chronic obstructive pulmonary disease. *Mayo Clin Proc*. 2018;93(10):1462–1473. doi:10.1016/j.mayocp.2018.05.030
- Suissa S, Dell'Aniello S, Ernst P. Single-inhaler triple vs long-acting beta2-agonist-inhaled corticosteroid therapy for COPD: comparative safety in real-world clinical practice. *Chest*. 2024;167(3):712–723. doi:10.1016/j.chest.2024.10.025
- National Health Insurance Administration. 2022–2023 National health insurance annual report. Available from: <https://www.nhi.gov.tw/ch/cp-3153-f49da-2456-1.html>. Accessed on January 10, 2025.
- Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). *Epidemiol Health*. 2018;40:e2018062.
- Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD*. 2009;6:388–394. doi:10.1080/15412550903140865
- Coloma PM, Valkhoff VE, Mazzaglia G, et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. *BMJ Open*. 2013;3:e002862.
- Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832.
- Hsieh MT, Hsieh CY, Tsai TT, Wang YC, Sung SF. Performance of ICD-10-CM diagnosis codes for identifying acute ischemic stroke in a national health insurance claims database. *Clin Epidemiol*. 2020;12:1007–1013. doi:10.2147/CLEP.S273853
- Bosco-Lévy P, Duret S, Picard F, et al. Diagnostic accuracy of the international classification of diseases, tenth revision, codes of heart failure in an administrative database. *Pharmacoepidemiol Drug Saf*. 2019;28:194–200. doi:10.1002/pds.4690
- Hennessy S, Leonard CE, Freeman CP, et al. Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in medicaid and medicare claims data. *Pharmacoepidemiol Drug Saf*. 2010;19:555–562. doi:10.1002/pds.1869
- Hennessy S, Leonard CE, Newcomb C, Kimmel SE, Bilker WB. Cisapride and ventricular arrhythmia. *Br J Clin Pharmacol*. 2008;66:375–385. doi:10.1111/j.1365-2125.2008.03249.x
- D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265–2281. doi:10.1002/(SICI)1097-0258(19981015)17:19<2265::AID-SIM918>3.0.CO;2-B
- Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA. The nearest-neighbor matching algorithm in the Pharmacoepidemiology Toolbox. Available from: <http://www.drugapi.org/dope-downloads/>. Accessed on January 10, 2025.
- Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399–424. doi:10.1080/00273171.2011.568786

25. Wang SV, Jin Y, Fireman B, et al. Relative performance of propensity score matching strategies for subgroup analyses. *Am J Epidemiol.* 2018;187(8):1799–1807. doi:10.1093/aje/kwy049
26. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med.* 2017;36(27):4391–4400. doi:10.1002/sim.7501
27. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology.* 2009;20(4):512–522. doi:10.1097/EDE.0b013e3181a663cc
28. Rassen JA, Blin P, Kloss S, et al. High-dimensional propensity scores for empirical covariate selection in secondary database studies: planning, implementation, and reporting. *Pharmacoepidemiol Drug Saf.* 2023;32(2):93–106. doi:10.1002/pds.5566
29. Lee PC, Kao FY, Liang FW, Lee YC, Li ST, Lu TH. Existing data sources in clinical epidemiology: the Taiwan National Health Insurance Laboratory Databases. *Clin Epidemiol.* 2021;13:175–181. doi:10.2147/CLEP.S286572
30. National Health Insurance Administration. COPD pay-for-performance program [Chinese]. Available from: <https://www.nhi.gov.tw/ch/lp-2833-1.html>. Accessed on January 10, 2025.
31. Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. *Stat Med.* 2019;38(26):5120–5132. doi:10.1002/sim.8355
32. Chen CY, Pan SW, Hsu CC, Liu JJ, Kumamaru H, Dong YH. Comparative cardiovascular safety of LABA/LAMA FDC versus LABA/ICS FDC in patients with chronic obstructive pulmonary disease: a population-based cohort study with a target trial emulation framework. *Respir Res.* 2023;24(1):239. doi:10.1186/s12931-023-02545-9
33. Cazzola M, Calzetta L, Matera MG. The cardiovascular risk of tiotropium: is it real? *Expert Opin Drug Saf.* 2010;9(5):783–792. doi:10.1517/14740338.2010.500611
34. Singh S, Loke YK, Enright P, Furberg CD. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. *Thorax.* 2013;68(1):114–116. doi:10.1136/thoraxjnl-2011-201275
35. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. A systematic review and meta-analysis. *JAMA.* 2008;300(12):1439–1450. doi:10.1001/jama.300.12.1439
36. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropim in chronic obstructive pulmonary disease. *N Eng J Med.* 2008;359(15):1543–1554. doi:10.1056/NEJMoa0805800
37. Celli B, Decramer M, Leimer I, Vogel U, Kesten S, Tashkin DP. Cardiovascular safety of tiotropium in patients with COPD. *Chest.* 2010;137(1):20–30. doi:10.1378/chest.09-0011
38. Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2017;196(4):438–446. doi:10.1164/rccm.201703-0449OC
39. Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med.* 2018;6(10):747–758. doi:10.1016/S2213-2600(18)30327-8
40. Pollack M, Rapsomaniki E, Anzueto A, et al. Effectiveness of single versus multiple inhaler triple therapy on mortality and cardiopulmonary risk reduction in COPD: the SKOPOS-MAZI study. *Am J Med.* 2025;138(4):650–659.e10. doi:10.1016/j.amjmed.2024.11.007
41. Alcázar-Navarrete B, Jamart L, Sánchez-Covisa J, Juárez M, Graefenhain R, Sicras-Mainar A. Clinical characteristics, treatment persistence, and outcomes among patients with COPD treated with single- or multiple-inhaler triple therapy: a retrospective analysis in Spain. *Chest.* 2022;162(5):1017–1029. doi:10.1016/j.chest.2022.06.033

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