

# Cardiovascular Events According to Inhaler Therapy and Comorbidities in Chronic Obstructive Pulmonary Disease

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**Background:** COPD coexists with many concurrent comorbidities. Cardiovascular complications are deemed to be major causes of death in COPD. Although inhaler therapy is the main therapeutic intervention in COPD, cardiovascular events accompanying inhaler therapy require further investigation. Therefore, this study aimed to investigate new development of cardiovascular events according to each inhaler therapy and comorbidities.

**Methods:** This study analyzed COPD patients (age  $\geq 40$  years, N = 199,772) from the Health Insurance Review and Assessment Service (HIRA) database in Korea. The development of cardiovascular events, from the index date to December 31, 2020, was investigated. The cohort was eventually divided into three arms: the LAMA/LABA group (N = 28,322), the ICS/LABA group (N = 11,812), and the triple group (LAMA/ICS/LABA therapy, N = 6174).

**Results:** Multivariable Cox analyses demonstrated that, compared to ICS/LABA therapy, triple therapy was independently associated with the development of ischemic heart disease (HR: 1.22, 95% CI: 1.04–1.43), heart failure (HR: 1.45, 95% CI: 1.14–1.84), arrhythmia (HR: 1.72, 95% CI: 1.41–2.09), and atrial fibrillation/flutter (HR: 2.31, 95% CI: 1.64–3.25), whereas the LAMA/LABA therapy did not show a significant association. Furthermore, emergency room visit during covariate assessment window was independently associated with the development of ischemic heart disease, heart failure, arrhythmia, and atrial fibrillation/flutter ( $p < 0.05$ ).

**Conclusion:** Our data suggest that cardiovascular risk should be considered in COPD patients receiving triple therapy, despite the confounding bias resulting from disparities in each group.

**Keywords:** COPD, inhaler therapy, cardiovascular event, comorbidities

## Introduction

Chronic obstructive pulmonary disease (COPD) is a global health issue with increasing prevalence, morbidity, and mortality.<sup>1,2</sup> COPD coexists with many concurrent co-morbidities, including hypertension, ischemic heart disease, chronic heart failure, osteoporosis, muscle weakness, depression, and lung cancer.<sup>3–5</sup> Cardiovascular complications are deemed to be major causes of death in COPD.<sup>3–5</sup> The development of cardiovascular comorbidities in COPD is explained by several mechanisms, including lung hyperinflation, hypoxemia, pulmonary hypertension, systemic inflammation, oxidative stress, and exacerbations.<sup>6,7</sup>

Current guidelines recommend the use of inhaled long-acting bronchodilators in symptomatic COPD patients because beneficial effects of inhaled long-acting bronchodilators including long-acting  $\beta_2$ -agonists (LABA) and long-acting muscarinic antagonists (LAMA) in COPD have been documented in several clinical trials.<sup>8–10</sup> Inhaled long-acting bronchodilators can reduce the frequency and severity of acute exacerbations, improve exercise tolerance, and ameliorate health status.<sup>9,10</sup> Recent studies have suggested that triple therapy with LAMA/LABA/inhaled corticosteroids (ICS) is superior to LABA/ICS due to a lower rate of acute exacerbations and a better quality of life in moderate-to-severe COPD with a history of acute exacerbations.<sup>11,12</sup>

Despite the pivotal role of inhaler therapy in COPD, concerns have been raised over adverse events, especially cardiovascular complications associated with exposure to LAMA or LABA.<sup>13–16</sup> Whether LABA/LAMA therapy is related to cardiovascular events is still under debate. Some multiple observational studies have reported an increased risk of adverse cardiovascular events from LABA/LAMA therapy,<sup>13–16</sup> while others have reported contradictory results.<sup>8,10,17</sup> Accordingly, cardiovascular outcomes associated with inhaler therapy require further investigation since previous large randomized clinical trials (RCTs) have reported no evidence of increased cardiovascular events when excluding patients with a history of recent cardiovascular disease and life-threatening cardiovascular events.<sup>8,10</sup> Incomplete medication records and a dropout rate of more than 50% among eligible patients might have weakened causality or generalizability.<sup>14,16,18</sup> So far, few studies have examined the development of cardiovascular comorbidities concerning new therapeutic interventions of inhaler therapy, including LABA/LAMA/ICS combination, in a real-world setting.

Hence, the objective of this study was to investigate the development of new cardiovascular events according to each inhaler treatment and comorbidities in COPD using a Korean Health Insurance Review and Assessment Service (HIRA) database.

## Methods

### Data Sources

HIRA is an agency that evaluates all medical claims data in South Korea. It has accumulated all medical reimbursement records, which can be used to assess nationwide impact of an illness and subsequent health care.<sup>19,20</sup> In this study, we retrospectively analyzed data registered in the HIRA between January 1, 2015, and December 31, 2020.

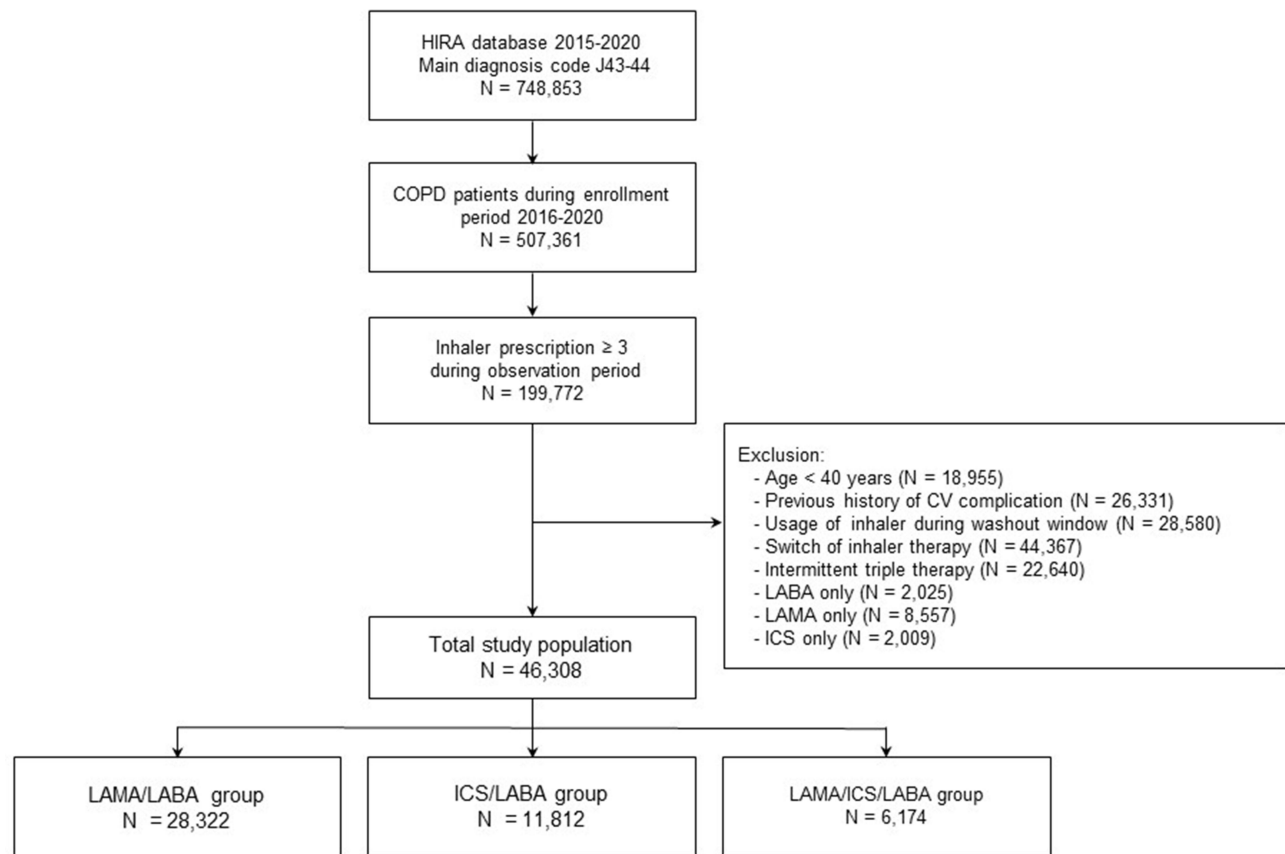
### Study Population

Similar to the criteria used in a previous report including HIRA data, COPD was defined with the following criteria: 1) age  $\geq 40$  years old, 2) International Classification of Disease, Tenth Revision (ICD-10) codes for COPD or emphysema (J43–J44), and 3) use of one or more COPD medications at least twice per year. COPD medications included 1) LAMA; 2) LABA; 3) LAMA + LABA; 4) ICS; 5) ICS plus LABA; 6) triple therapy (LAMA + LABA + ICS); 7) phosphodiesterase-4 (PDE-4) inhibitors; 8) theophylline; and 9) mucolytics.<sup>20,21</sup>

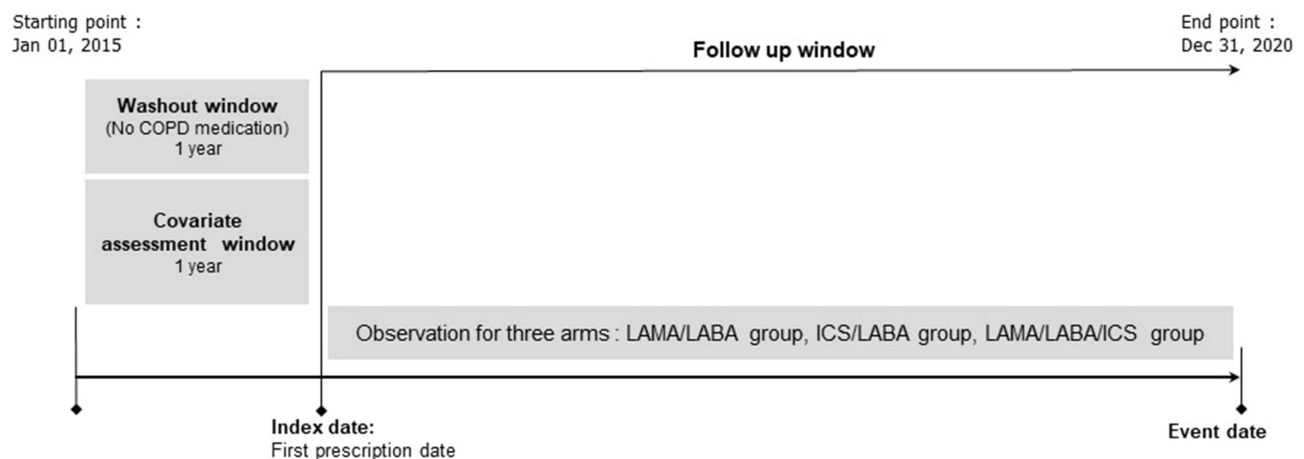
### Study Design

Among COPD patients identified from a retrospective cohort study based on HIRA database, we analyzed those who were followed up from January 1, 2016, to December 31, 2020. Among them, COPD patients who had received inhaler prescriptions three or more times during the observation period were included ( $\geq 40$  years of age,  $N = 199,772$ ). The date of the first prescription of inhaled respiratory medication was defined as an index date. The enrolled patients had no prior history of inhaler therapy before the index date.

The washout window as well as the covariate assessment window was 1 year before the index date. Patients were excluded by the following criteria: previous histories of cardiovascular complications during covariate assessment window (the period focused on comorbidity examination); usage of inhaler during washout window (the period investigated for the medication exposure); switch of inhaler therapy, intermittent triple treatment, LABA only therapy, LAMA only therapy, or ICS only therapy during observation period; age less than 40 years (Figure 1). The final enrolled cohort consisted of 46,308 patients in three arms: LAMA/LABA group ( $N = 28,322$ ), ICS/LABA group ( $N = 11,812$ ), and triple-based group (LAMA/ICS/LABA therapy,  $N = 6,174$ ). The development of new cardiovascular events as primary outcomes from the index date until December 31, 2020, was investigated (Figure 2).



**Figure 1** Flow diagram of the study population.



**Figure 2** Study design.

## Definition of Co-Morbidities

Cardiovascular outcomes were identified when COPD patients made an inpatient or emergency department visit with a primary diagnosis of ischemic heart disease (ICD-10 codes I20-I25), myocardial infarction (I21-I22), heart failure (I50), arrhythmia (I44-I49), atrial fibrillation or atrial flutter (I48), hemorrhagic stroke (I60-I62), or ischemic stroke (I63-I66).

Other co-morbidities were defined based on ICD-10 codes: asthma (J45-46), hypertension (I10-15), diabetes mellitus (E10–E14), tuberculosis (A15, A19, and B90), diffuse interstitial lung disease (J84), and lung cancer (C33-C34). The Charlson Comorbidity index was analyzed as described previously.<sup>22</sup>

## Statistical Analyses

Baseline characteristics are presented as mean  $\pm$  standard deviation. A one-way analysis of variance for continuous variables and a chi-squared test for categorical variables were used. Differences in medication use and prevalence of cardiovascular complications among three groups were tested by chi-squared test and adjusted by Bonferroni correction for multiple comparisons. Proportional hazard assumption was assessed using Schoenfeld residuals for the Cox proportional hazards regression model. Multivariable Cox proportional hazards regression analyses were performed to identify significant risk factors predicting the development of cardiovascular events after adjusting for age, sex, and comorbidities such as asthma, hypertension, diabetes mellitus, tuberculosis, diffuse interstitial lung disease, lung cancer, the Charlson Comorbidity index score, history of hospitalization, and emergency room visit. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for the risk of cardiovascular events. A threshold of  $p < 0.05$  was deemed significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## Ethics Statement

The present study was approved by the Institutional Review Board of Ajou University Hospital (AJOUIRB-EXP-2021-582). The data accessed complied with relevant data protection and privacy regulations. The requirement for informed consent from patients analyzed was waived by the ethical review board.

## Results

### Baseline Characteristics of This Cohort

A total of 46,308 COPD patients were enrolled for the final analysis. In this final cohort, 45.9% had hypertension, 23.3% had diabetes mellitus, and 46.7% had a Charlson Comorbidity index score  $\geq 3$  (Table 1). This cohort was classified into three groups: LAMA/LABA therapy, ICS/LABA therapy, and triple (ICS/LABA/LAMA) therapy (Figure 1). The triple therapy group had a higher proportion of men, older age, higher Charlson Comorbidity Index score, and more frequent hospitalizations and emergency room visits during the covariate assessment window (all  $p < 0.001$ ) (Table 1 and Table 2). Medication status is presented in [Supplementary Table 1](#).

### Cumulative and Annual Incidences of Cardiovascular Events

During the observation period, ischemic heart disease developed significantly ( $p < 0.001$ ) higher in the triple therapy group (4.3%) than in the LAMA/LABA group (3.7%) and the ICS/LABA group (3.1%) (Table 3). The development of arrhythmias and atrial fibrillation/flutter was also higher in the triple therapy group ( $p < 0.001$ ) (Table 3). Ischemic stroke also occurred more frequently in the triple therapy group (2.8%) than in the LAMA/LABA group (2.2%) ( $p < 0.05$ ) (Table 3). The annual incidence of ischemic heart disease, heart failure, arrhythmia, and atrial fibrillation/flutter occurred most frequently in the first year of inhaler therapy, and the frequency decreased as therapeutic duration became longer (Figure 3, [Supplementary Table 2](#)).

### Independent Variables for the Development of Cardiovascular Events

Univariable Cox regression analysis showed that, compared to ICS/LABA therapy, LAMA/LABA therapy was significantly associated with the occurrence of ischemic heart disease (HR: 1.32, 95% CI: 1.17–1.48) and atrial fibrillation/flutter (HR: 1.39, 95% CI: 1.03–1.87) ([Supplementary Tables 3 and 4](#)).

Another univariable Cox regression analysis showed that triple therapy was significantly associated with the occurrence of ischemic heart disease (HR: 1.50, 95% CI: 1.28–1.75), heart failure (HR: 1.84, 95% CI: 1.45–2.33), arrhythmia (HR: 2.07, 95% CI: 1.70–2.51), and atrial fibrillation/flutter (HR: 2.87, 95% CI: 2.05–4.03), compared to ICS/LABA therapy ( $p < 0.05$ ) ([Supplementary Tables 3 and 4](#)).

**Table 1** Baseline Characteristics of Cohort

	Total	LAMA/ LABA	ICS/LABA	LAMA/ LABA/ICS	p-value
<b>Number</b>	46,308	28,322	11,812	6174	
<b>Age (years)</b>	68.5 ± 10.1	68.8 ± 9.5	67.6 ± 11.3	68.9 ± 10.3	<0.001**
<b>Age distribution (years), N (%)</b>					<0.001**
40–49	1766 (3.8)	728 (2.6)	808 (6.8)	230 (3.7)	
50–59	7171 (15.5)	4092 (14.4)	2119 (17.9)	960 (15.5)	
60–69	14,880 (32.1)	9593 (33.9)	3422 (29.0)	1865 (30.2)	
70–79	15,978 (34.5)	10,220 (36.1)	3624 (30.7)	2134 (34.6)	
80–	6513 (14.1)	3689 (13.0)	1839 (15.6)	985 (16.0)	
<b>Gender (male), N (%)</b>	37,256 (80.5)	24,139 (85.2)	8204 (69.5)	4913 (79.6)	<0.001**
<b>Co-morbidities during covariate assessment window, N (%)</b>					
Asthma (J45–J46)	22,113 (47.8)	10,280 (36.3)	7790 (66.0)	4043 (65.5)	<0.001**
Hypertension (I10–I15)	21,256 (45.9)	12,755 (45.0)	5181 (43.9)	3320 (53.8)	<0.001**
Diabetes mellitus (E10–E14)	10,773 (23.3)	6602 (23.3)	2524 (21.4)	1647 (26.7)	<0.001**
Tuberculosis (A15, A19, B90)	2292 (5.0)	1619 (5.7)	343 (2.9)	330 (5.3)	<0.001**
Diffuse interstitial lung disease (J84)	402 (0.9)	281 (1.0)	72 (0.6)	49 (0.8)	0.001**
Lung cancer (C33–C34)	829 (1.8)	641 (2.3)	101 (0.9)	87 (1.4)	<0.001**
<b>Charlson Comorbidity Index score</b>	3.0 ± 2.4	3.0 ± 2.5	2.8 ± 2.3	3.1 ± 2.3	<0.001**
<b>Charlson Comorbidity Index score, N (%)</b>					<0.001**
0 (CCI score = 0)	2721 (5.9)	1943 (6.9)	510 (4.3)	268 (4.3)	
1 (CCI score = 1)	12,198 (26.3)	7185 (25.4)	3577 (30.3)	1436 (23.3)	
2 (CCI score = 2)	9776 (21.1)	5788 (20.4)	2775 (23.5)	1213 (19.6)	
3 (CCI score ≥ 3)	21,613 (46.7)	13,406 (47.3)	4950 (41.9)	3257 (52.8)	

**Note:** A p-value less than 0.01 is marked by \*\*. The percentage is provided in parentheses.

**Abbreviations:** LABA, long-acting β<sub>2</sub>-agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

**Table 2** Hospital Visit During Covariate Assessment Window

	Total	LAMA/ LABA	ICS/LABA	LAMA/LABA/ ICS	p-value
<b>Inpatient hospitalization</b>					
▪ Respiratory related (J00–J99)					
0	39,464 (85.2)	24,508 (86.5)	10,070 (85.2)	4886 (79.1)	<0.001**
1	4803 (10.4)	2763 (9.8)	1204 (10.2)	836 (13.5)	
≥ 2	2041 (4.4)	1051 (3.7)	538 (4.6)	452 (7.3)	
▪ Any reason					
0	27,936 (60.3)	16,915 (59.7)	7667 (64.9)	3354 (54.3)	<0.001**
1	9471 (20.5)	5962 (21.1)	2124 (18.0)	1385 (22.4)	
≥ 2	8901 (19.2)	5445 (19.2)	2021 (17.1)	1435 (23.2)	
<b>Emergency room visit</b>					
▪ Respiratory related (J00–J99)					<0.001**
0	42,317 (91.4)	26,020 (91.9)	10,913 (92.4)	5384 (87.2)	
1	3206 (6.9)	1876 (6.6)	715 (6.0)	615 (10.0)	
≥ 2	785 (1.7)	426 (1.5)	184 (1.6)	175 (2.8)	
▪ Any reason					
0	35,740 (77.2)	21,848 (77.1)	9472 (80.2)	4420 (71.6)	<0.001**
1	7148 (15.4)	4428 (15.6)	1580 (13.4)	1140 (18.5)	
≥ 2	3420 (7.4)	2046 (7.2)	760 (6.4)	614 (9.9)	

**Note:** A p-value less than 0.01 is marked by \*\*. The percentage is provided in parentheses.

**Abbreviations:** LABA, long-acting β<sub>2</sub>-agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

**Table 3** Cumulative Incidence of Cardiovascular Events During Observation Period

						Multiple Comparison with Bonferroni Correction		
	Total	LAMA/ LABA	ICS/LABA	Triple	p-value	LAMA/ LABA vs ICS/LABA	LAMA/ LABA vs Triple	ICS/ LABA vs Triple
<b>Cumulative incidence of cardiovascular events for 5 years, N (%)</b>								
Cardiovascular								
Ischemic heart disease (I20 - I25)	1689 (3.7)	1057 (3.7)	364 (3.1)	268 (4.3)	<0.001**	0.004**	0.073	<0.001**
Myocardial infarction (I21 - I22)	362 (0.8)	212 (0.8)	97 (0.8)	53 (0.9)	0.575	I	I	I
Heart failure (I50)	584 (1.3)	313 (1.1)	142 (1.2)	129 (2.1)	<0.001**	I	<0.001**	<0.001**
Arrhythmia (I44 – I49)	943 (2.0)	541 (1.9)	200 (1.7)	202 (3.3)	<0.001**	0.423	<0.001**	<0.001**
Atrial fibrillation /flutter (I48)	314 (0.7)	176 (0.6)	57 (0.5)	81 (1.3)	<0.001**	0.286	<0.001**	<0.001**
Cerebrovascular								
Hemorrhagic stroke (I60-I62)	206 (0.4)	114 (0.4)	62 (0.5)	30 (0.5)	0.213	0.273	I	I
Ischemic stroke (I63-I66)	1083 (2.3)	631 (2.2)	278 (2.4)	174 (2.8)	0.021*	I	0.016*	0.176

**Notes:** A p-value less than 0.05 is marked by\* and a p-value less 0.01 by \*\*. The percentage is provided in parentheses.

**Abbreviations:** LABA, long-acting  $\beta_2$ -agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

Multivariable Cox analyses demonstrated that compared to ICS/LABA therapy, triple therapy was independently associated with the development of ischemic heart disease (HR: 1.22, 95% CI: 1.04–1.43), heart failure (HR: 1.45, 95% CI: 1.14–1.84), arrhythmia (HR: 1.72, 95% CI: 1.41–2.09), and atrial fibrillation/flutter (HR: 2.31, 95% CI: 1.64–3.25), whereas the LAMA/LABA therapy did not show a significant association (Table 4 and Table 5). In addition, emergency room visit was independently associated with the development of ischemic heart disease, heart failure, arrhythmia, and atrial fibrillation/flutter (all  $p < 0.05$ ) (Table 4L and Table 5). Multivariable analyses also found that tuberculosis (HR: 1.43, 95% CI: 1.10 – 1.85), diffuse interstitial lung disease (HR: 2.00, 95% CI: 1.24 – 3.24), older age, and hypertension were independently associated with the development of arrhythmia (all  $p < 0.05$ ) (Table 5).

## Discussion

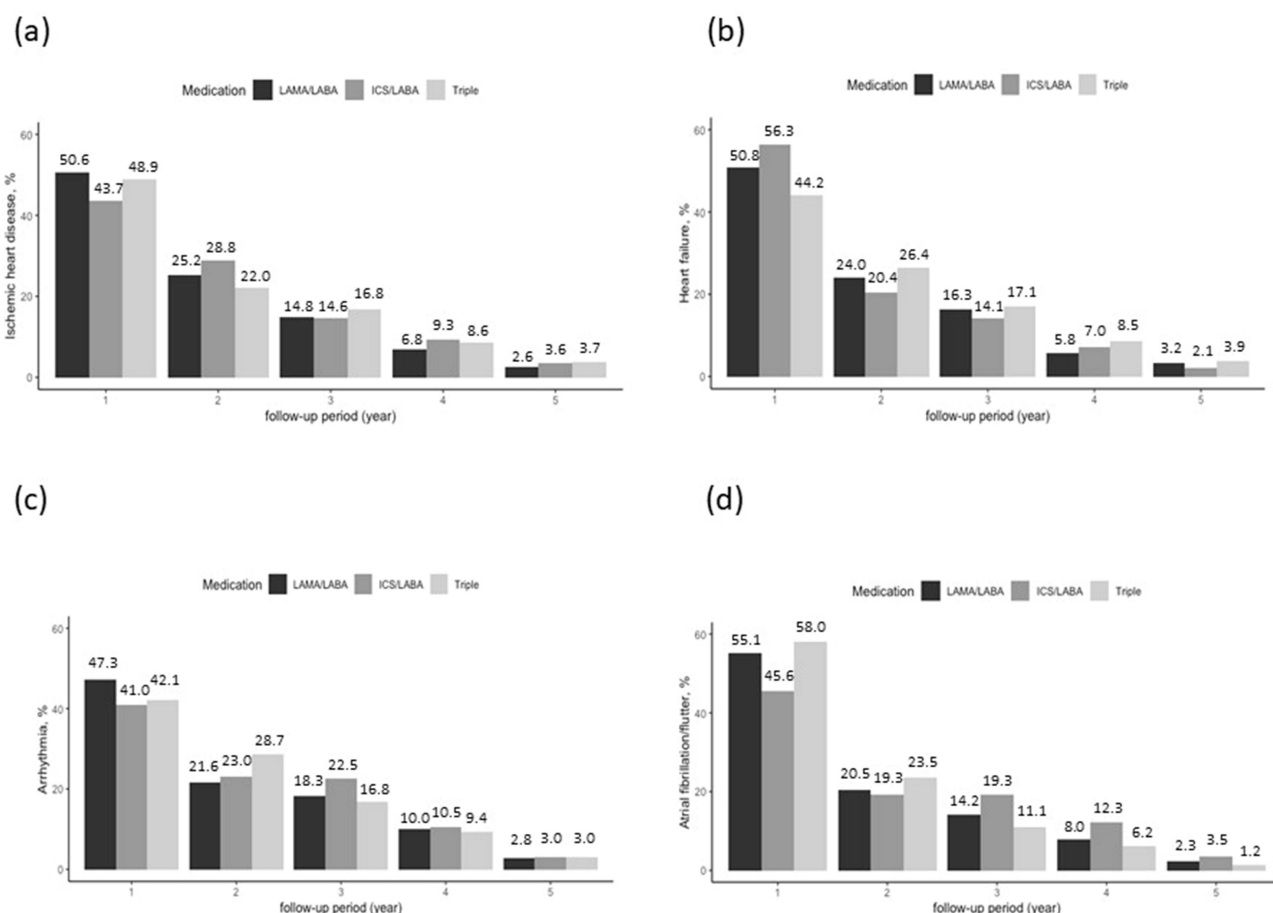
This observational study based on real-world data performed a comprehensive analysis of cardiovascular events in COPD according to each inhaler therapy and comorbidities in Korean population. Our data showed that triple therapy, compared to ICS/LABA therapy, was independently associated with cardiovascular events in a Korean COPD population. The current study also found an independent association between emergency room visit during covariate assessment window and cardiovascular events, in addition to other well-known risk factors such as diabetes mellitus, hypertension, and old age.

Our study has several interesting findings. First, our multivariable analysis demonstrated that triple therapy, compared to ICS/LABA therapy, independently contributed to the development of cardiovascular events, including ischemic heart disease, heart failure, arrhythmia, and atrial fibrillation/flutter. In contrast, multivariable analysis revealed no differences in cardiovascular outcomes between LAMA/LABA and ICS/LABA. This study aimed to investigate the independent effect of triple therapy on cardiovascular outcomes through multivariate analysis, adjusting for major risk factors of cardiovascular disease, hospitalization, and Charlson Comorbidity index. However, this study could still harbor the risk of confounding bias due to disparities among the three groups and the potential impact of missing confounders, as the triple therapy group had higher rates of co-morbidities, more frequent hospitalizations, and emergency room visits.

Despite these limitations, the current study thoroughly examined major cardiovascular events, including ischemic heart disease, heart failure, and cardiac arrhythmias, as primary outcomes in COPD patients newly initiated on inhalers.

Our findings are supported by previous studies reporting that LAMA-based therapy is associated with cardiovascular complications.<sup>15,23,24</sup> A recent meta-analysis of 51 RCTs on combination therapies in COPD has reported that LAMA/LABA or triple therapy can increase cardiovascular risk compared to ICS/LABA.<sup>23</sup> A meta-analysis of five RCTs has





**Figure 3** The annual incidence of cardiovascular events. (a) Annual incidence of ischemic heart disease. (b) Annual incidence of heart failure. (c) Annual incidence of arrhythmia. (d) Annual incidence of atrial fibrillation/flutter. The percentage is presented on top of each bar.

shown that tiotropium mist inhaler is significantly associated with cardiovascular and all-cause mortality.<sup>24</sup> Several studies have also reported that new initiation of long-acting  $\beta$ -agonists and anticholinergics is associated with an increased risk of serious cardiovascular events.<sup>15,18,25</sup> However, large RCTs including TORCH, UPLIFT, and FLAME

**Table 4** Multivariable Analysis of Risk Factors for the Development of Ischemic Heart Disease and Heart Failure in COPD

Variables	Multivariable Cox Regression ANALYSIS			
	Ischemic Heart Disease		Heart Failure	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Therapeutic intervention				
LAMA/LABA therapy	1.08 (0.95 – 1.22)	0.242	0.93 (0.75 – 1.14)	0.471
LAMA/LABA/ICS therapy	1.22 (1.04 – 1.43)	0.014*	1.45 (1.14 – 1.84)	0.003**
ICS/LABA therapy	Ref.		Ref.	
Age group (years)				
40–49	Ref.		Ref.	
50–59	1.19 (0.80 – 1.79)	0.389	6.49 (0.89 – 47.59)	0.066
60–69	1.78 (1.21 – 2.61)	0.003**	8.30 (1.16 – 59.62)	0.036*
70–79	1.84 (1.26 – 2.70)	0.002**	18.14 (2.54 – 129.68)	0.004**
80–	1.76 (1.19 – 2.62)	0.005**	35.78 (5.00 – 256.00)	<0.001**

(Continued)

**Table 4** (Continued).

Variables	Multivariable Cox Regression ANALYSIS			
	Ischemic Heart Disease		Heart Failure	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Sex (male)	1.96 (1.68 – 2.29)	<0.001**	0.85 (0.70 – 1.04)	0.109
Asthma	0.87 (0.78 – 0.96)	0.006**	0.89 (0.75 – 1.06)	0.176
Hypertension	1.77 (1.59 – 1.97)	<0.001**	1.97 (1.62 – 2.40)	<0.001**
Diabetes mellitus	1.20 (1.07 – 1.35)	0.002**	1.09 (0.91 – 1.31)	0.363
Tuberculosis	0.84 (0.66 – 1.07)	0.164	0.77 (0.50 – 1.21)	0.261
Diffuse interstitial lung disease	1.24 (0.78 – 1.98)	0.364	0.88 (0.37 – 2.14)	0.785
Lung cancer	0.81 (0.57 – 1.15)	0.233	0.58 (0.3 – 1.13)	0.111
Charlson Comorbidity Index score				
0 (CCI score = 0)	Ref.		Ref.	
1 (CCI score = 1)	0.76 (0.59 – 0.96)	0.024*	0.85 (0.49 – 1.46)	0.553
2 (CCI score = 2)	0.85 (0.66 – 1.08)	0.184	0.77 (0.44 – 1.35)	0.362
3 (CCI score ≥ 3)	1.03 (0.81 – 1.31)	0.806	1.39 (0.82 – 2.36)	0.216
Inpatient hospitalization (any reason)				
0	Ref.		Ref.	
1	1.12 (0.99 – 1.28)	0.084	1.42 (1.14 – 1.77)	0.002**
≥2	1.11 (0.96 – 1.28)	0.174	1.27 (1.00 – 1.62)	0.053
Emergency room visit (any reason)				
0	Ref.		Ref.	
1	1.06 (0.92 – 1.22)	0.459	1.51 (1.21 – 1.89)	<0.001**
≥2	1.64 (1.38 – 1.95)	<0.001**	2.33 (1.79 – 3.02)	<0.001**

**Notes:** A p-value less than 0.05 is marked by\* and a p-value less than 0.01 by\*\*.

**Abbreviations:** CI, confidence interval; LABA, long-acting  $\beta_2$ -agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids; Ref, reference.

**Table 5** Multivariable Analysis of Risk Factors for the Development of Arrhythmia in COPD

Variables	Multivariable Cox Regression Analysis			
	Arrhythmia		Atrial Fibrillation/Flutter	
	Hazard Ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Therapeutic intervention				
LAMA/LABA therapy	1.09 (0.92 – 1.30)	0.301	1.23 (0.90 – 1.68)	0.192
LAMA/LABA/ICS therapy	1.72 (1.41 – 2.09)	<0.001**	2.31 (1.64 – 3.25)	<0.001**
ICS/LABA therapy	Ref.		Ref.	
Age group (years)				
40–49	Ref.		Ref.	
50–59	1.00 (0.59 – 1.69)	0.989	1.28 (0.44 – 3.68)	0.649
60–69	1.21 (0.73 – 1.99)	0.456	1.38 (0.50 – 3.81)	0.536
70–79	2.03 (1.24 – 3.32)	0.005**	2.47 (0.91 – 6.75)	0.078
80–	3.05 (1.85 – 5.03)	<0.001**	3.35 (1.21 – 9.27)	0.020*
Sex (male)	1.15 (0.97 – 1.37)	0.098	1.24 (0.92 – 1.68)	0.156
Asthma	0.90 (0.79 – 1.04)	0.143	0.97 (0.76 – 1.23)	0.798
Hypertension	1.33 (1.16 – 1.54)	<0.001**	1.68 (1.30 – 2.17)	<0.001**
Diabetes mellitus	1.08 (0.93 – 1.26)	0.313	0.99 (0.77 – 1.28)	0.945
Tuberculosis	1.43 (1.10 – 1.85)	0.007**	1.04 (0.62 – 1.75)	0.892
Diffuse interstitial lung disease	2.00 (1.24 – 3.24)	0.005**	0.98 (0.32 – 3.07)	0.976
Lung cancer	1.01 (0.66 – 1.55)	0.971	1.13 (0.58 – 2.22)	0.720

(Continued)



**Table 5** (Continued).

Variables	Multivariable Cox Regression Analysis			
	Arrhythmia		Atrial Fibrillation/Flutter	
	Hazard Ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Charlson Comorbidity Index score				
0 (CCI score = 0)	Ref.		Ref.	
1 (CCI score = 1)	0.87 (0.59 – 1.29)	0.497	0.56 (0.29 – 1.06)	0.077
2 (CCI score = 2)	1.19 (0.81 – 1.75)	0.390	0.77 (0.41 – 1.45)	0.419
3 (CCI score ≥ 3)	1.52 (1.04 – 2.22)	0.030*	1.23 (0.67 – 2.25)	0.501
Inpatient hospitalization (any reason)				
0	Ref.		Ref.	
1	1.10 (0.92 – 1.31)	0.299	0.98 (0.72 – 1.34)	0.898
≥2	1.06 (0.88 – 1.29)	0.534	1.19 (0.86 – 1.64)	0.291
Emergency room visit (any reason)				
0	Ref.		Ref.	
1	1.52 (1.28 – 1.81)	<0.001**	1.51 (1.12 – 2.03)	0.008**
≥2	1.75 (1.39 – 2.20)	<0.001**	1.49 (1.01 – 2.21)	0.047*

**Notes:** A p-value less than 0.05 is marked by\* and a p-value less 0.01 by \*\*.

**Abbreviations:** CI, confidence interval; LABA, long-acting  $\beta_2$ -agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids; Ref, reference.

studies suggested otherwise.<sup>8,10,26</sup> Recent RCTs comparing ICS/LABA/LAMA with LAMA/LABA or ICS/LABA combinations have provided no evidence of an excess cardiovascular risk by triple therapy.<sup>12,27,28</sup> A recent IMPACT study demonstrated that triple therapy could result in a significantly lower annual rate of COPD exacerbations, greater improvements in both lung functions, and a significant reduction in all-cause mortality without any cardiovascular risk, although that study excluded severe cardiac disease or abnormal electrocardiography at baseline.<sup>12</sup> Even observational studies have shown contradicting results.<sup>15,29</sup> In a large observational study conducted by Suissa et al, long-acting bronchodilator treatment of COPD in the real-world-setting did not increase the risk of most cardiovascular events.<sup>29</sup> However, a study by Wang et al showed that new initiation of LABA or LAMA in COPD was associated with an approximate 1.5-fold increase of severe cardiovascular risk, irrespective of prior cardiovascular disease status or history of exacerbations.<sup>15</sup> The study of Wang et al might explain why previous relevant RCTs did not find an increased cardiovascular risk with LABA or LAMA therapy.<sup>15</sup> The greatest risk of cardiovascular disease emerged around the 30th day following initiation of LABA and LAMA therapy.<sup>15</sup> However, a substantial proportion of participants with prior LABA or LAMA usage was included in previous RCTs.<sup>8,10,30</sup> Moreover, highly strict inclusion criteria set by RCTs can result in a limited external validity to real-world application, since less than 20% of patients in real-life settings would meet the selection criteria commonly adopted by RCTs on COPD.<sup>31</sup> Accordingly, the issue remains unclear due to limitations of both study types, such as limited generalizability, inclusion of patients already using the study medications in RCTs, and a lack of randomization in observational studies.<sup>32</sup>

Hence, our study excluded COPD patients with a history of cardiovascular comorbidities during covariate assessment window and observed the development of new cardiovascular events after the initiation of inhaler therapy. This study found that triple therapy, comprising LAMA, LABA, and ICS in a real-world setting, was associated with more cardiovascular events, which could be explained by several mechanisms. The suppression of parasympathetic control by long-acting anticholinergics and the stimulation of sympathetic tone by LABA might lead to tachyarrhythmia, myocardial ischemia, stroke, and death.<sup>16,33</sup> The potential cardiovascular risk of LAMA is attributable to antagonizing M3 receptor-mediated cardiac functions, whereas ICS therapy may reduce the risk of cardiovascular events because atherosclerosis is a pro-inflammatory condition.<sup>34–36</sup> The systemic anti-inflammatory effect of ICS can modulate the risk of cardiovascular events and ameliorate cardiovascular disease by reducing exacerbations.<sup>37</sup> However, considering the

limitation that the triple therapy group had higher rates of co-morbidities, which may make them more susceptible to cardiovascular events, further verification appears to be necessary.

Second, our data found that COPD patients with tuberculosis or diffuse interstitial lung disease during covariate assessment window had a higher incidence of arrhythmia during the observation period. Although firm evidence linking arrhythmia and COPD with tuberculosis or diffuse interstitial lung disease has not yet been reported, this finding is supported by a study conducted by Yakar et al.<sup>38</sup> According to their study, patients with a history of tuberculosis had an earlier onset of COPD, lower FEV<sub>1</sub> values, more severe hypercapnia, more frequent hospitalizations, and a lower survival rate, compared to those without a history of tuberculosis.<sup>38</sup>

Additionally, a recent study has demonstrated that COPD patients with diffuse interstitial lung disease have a high mortality rate and a rapid decline in lung function.<sup>39</sup> Further investigation with a larger cohort is necessary to confirm these results.

Third, this study discovered that emergency room visit during covariate assessment window was independently associated with the development of ischemic heart disease, heart failure, arrhythmia, and atrial fibrillation/flutter. The increased cardiovascular risk associated with an emergency room visit can be explained by the correlation between cardiovascular risk and COPD exacerbation, because severe COPD exacerbations often necessitate hospitalization or emergency room visits.<sup>40,41</sup>

Several limitations of this study should be acknowledged. First, due to an observational design of this study, the causal link could not be firmly suggested as in a randomized control study. Second, because this study was conducted with a claim database, some potential confounders including pulmonary function test, hypercholesterolemia, laboratory tests, and air pollution that might contribute to the occurrence of cardiovascular disease were not analyzed. Third, the definition of COPD and cardiovascular disease by ICD code can harbor a potential risk of overdiagnosis or misdiagnosis because these diseases should be confirmed by tests such as spirometry, electrocardiogram, echocardiography, or coronary artery angiography. Fourth, information about smoking status, respiratory symptoms, and family history were not available in this cohort. Fifth, this study could have a confounding bias, as co-morbidities and hospitalizations were not evenly matched among the three arms. Sixth, the precise therapeutic duration of each inhaler could not be obtained due to the limitations of the HIRA data source. Seventh, social factors such as occupation and income level were not investigated as causal factors for the development of cardiovascular outcomes. Seventh, medication adherence was not measured.

In conclusion, our data demonstrated that the development of cardiovascular events in COPD was associated with triple therapy compared to ICS/LBA therapy, suggesting cardiovascular risk should be considered in COPD patients receiving triple therapy. However, further verification is necessary, considering the confounding bias resulting from disparities in each group.

## Abbreviations

COPD, Chronic obstructive pulmonary disease; CI, confidence intervals; PDE-4 inhibitor, phosphodiesterase-4 inhibitor; HIRA, Health Insurance Review and Assessment Service; HR, Hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; RCT, randomized clinical trial.

## Data Sharing Statement

HIRA is open and public data to which any researcher can get access through the website (<https://www.hira.or.kr>).

## Ethics Approval and Consent to Participate

The present study was approved by the Institutional Review Board of Ajou University Hospital (AJOU-IRB-EXP-2021-582). The requirement for informed consent from patients analyzed was waived by the ethical review board.

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## 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

All authors have nothing to declare regarding relevant financial activities and relationships/conditions/circumstances that present a potential conflict of interest.

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