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ORIGINAL RESEARCH

Prescription Patterns of New Use of Fixed-Dose Combination Inhalers in Patients with Chronic Obstructive Pulmonary Disease: Long-Acting β2 Agonists Plus Long-Acting Muscarinic Antagonists versus Long-Acting β2 Agonists Plus Inhaled Corticosteroids

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Background: The clinical guideline recommends use of long-acting β2 agonists/long-acting muscarinic antagonists (LABA/LAMA) or long-acting β2 agonists/inhaled corticosteroids (LABA/ICS) combination therapies for patients with severe chronic obstructive pulmonary disease (COPD). The fixed-dose combination (FDC) inhalers of LABA/LAMA and LABA/ICS were reimbursed in Taiwan in 2015 and in 2002, respectively. This study aimed to examine prescription patterns of new use of either FDC therapy in real-world practice.

Methods: We identified COPD patients who initiated LABA/LAMA FDC or LABA/ICS FDC between 2015 and 2018 from a population-based Taiwanese database with 2 million, randomly sampled beneficiaries enrolled in a single-payer health insurance system. We compared number of LABA/LAMA FDC and LABA/ICS FDC initiators in each calendar year, from different hospital accreditation levels, and cared for by different physician specialties. We also compared baseline patient characteristics between LABA/LAMA FDC and LABA/ICS FDC initiators.

Results: A total of 12,455 COPD patients who initiated LABA/LAMA FDC (n=4019) or LABA/ICS FDC (n=8436) were included. Number of LABA/LAMA FDC initiators increased apparently (n=336 in 2015 versus n=1436 in 2018), but number of LABA/ICS FDC initiators decreased obviously (n=2416 in 2015 versus n=1793 in 2018) over time. The preference of use of LABA/LAMA FDC varied across clinical environments. The proportions of LABA/LAMA FDC initiators were more than 30% in the setting of non-primary care clinics (eg, medical centers) and in the services of chest physicians; but were only less than 10% in primary care clinics and non-chest physicians' services (eg, family medicine physicians). LABA/LAMA FDC initiators appeared to be older, male, to have more comorbidities, and to utilize resources more frequently compared to LABA/ICS FDC initiators.

Conclusion: This real-world study found evident temporal trends, variations in healthcare provider, and differences in patient characteristics among COPD patients who initiated LABA/LAMA FDC or LABA/ICS FDC.

Keywords: chronic obstructive pulmonary disease, new users, long-acting β2 agonists/long-acting muscarinic antagonists fixed-dose combination, LABA/LAMA FDC, long-acting β2 agonists/inhaled corticosteroids fixed-dose combination, LABA/ICS FDC, temporal trends, healthcare provider characteristics, patient characteristics

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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with substantial impacts on health globally, which is ranked as the third and the eighth leading cause of death worldwide and in Taiwan, respectively.[1,2] According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, long-acting bronchodilators are the mainstay pharmacological treatment of COPD. Combination therapies of long-acting β2 agonists plus long-acting muscarinic antagonists (LABA/LAMA) or long-acting β2 agonists plus inhaled corticosteroids (LABA/ICS) are recommended for patients with apparent dyspnea symptoms or frequent exacerbation history at initial diagnosis or with suboptimal response to monotherapy of long-acting bronchodilators during follow-up.[3]

Theoretically, when combination therapies are indicated, there is an advantage of using medications with different mechanisms in a single inhaler, a so-called fixed-dose combination (FDC) inhaler. The products of LABA/ICS FDC have been marketed in the world for several decades. A number of studies have also noticed that use of LABA/ICS combination therapy, mainly driven by LABA/ICS FDC, is very common in COPD patients,[4–6] although a potential increased risk of lower respiratory tract infections remains concerning.[7,8] In contrast, although LABA/LAMA combination treatment is also suggested by the GOLD guideline, the products of LABA/LAMA FDC have only been available in the market within the last 10 years (eg, 2013 in the European Union and the US; 2015 in Canada and Taiwan). It is expected that this may spur use of LABA/LAMA combination treatment in daily practice. Several studies have described temporal trends of LABA/LAMA combination treatment (including FDC and free combination forms);[9–12] however, few studies have specifically focused on the uptake of these new FDC products.[12] Furthermore, prescription patterns may vary across geographic areas. It is therefore necessary to analyze domestic data, examine the status of drug utilization in each country, and identify potential clinical issues, if any.

The products of LABA/LAMA FDC and LABA/ICS FDC were reimbursed in Taiwan on May 1, 2015 and March 1, 2002, respectively, which provides an opportunity to explore prescription patterns of new use of LABA/LAMA and LABA/ICS FDC in COPD patients in real-world settings. Specifically, the present study aimed to examine potential temporal trends, variations in healthcare provider characteristics, and differences in patient characteristics for both recommended alternative treatments.

Methods

Database

A compulsory, single-payer National Health Insurance program started in Taiwan in 1995; 99% of the 23 million residents were enrolled in the program by June 2021.[13] The Taiwan National Health Insurance Research Database (NHIRD) contains complete information on enrollment and demographic records; diagnosis, procedure, and health services data from hospital admissions and outpatient visits; and pharmacy dispensing claims from hospital admissions and outpatient visits of each beneficiary.[14] The dataset used in the present study consists of a random sample of 2 million individuals from the Taiwan NHIRD, with longitudinally linked data for beneficiaries from 2010 to 2018. All data are de-identified by scrambling the identification codes of patients and healthcare providers.[14] The study protocol was approved by the National Yang-Ming Chiao Tung University Research Ethics Committee. Informed consent was waived given the retrospective nature of the study and the analysis of anonymous data.

Study Population and Study Drugs

We identified patients who initiated LABA/LAMA FDC or LABA/ICS FDC at outpatient visits between January 1, 2015 and December 31, 2018 using the World Health Organization's Anatomical Therapeutic Chemical Classification System codes (see Appendix Table 1 for list of codes). Initiation of LABA/LAMA FDC or LABA/ICS FDC was defined as first LABA/LAMA FDC or LABA/ICS FDC dispensing during the study period with no prior dispensing for either study drug in the preceding 365 days; during this period, patients were required to have interactions with the healthcare systems, defined as having at least one hospital admission or outpatient visit in this window. The index date was the date of the first dispensing of either study drug. We further restricted the cohort patients to those aged between 40 and 100 years on

the index date, with at least one inpatient or outpatient COPD diagnosis (see Appendix Table 2 for codes) within 365 days before the index date. This algorithm provided a sensitivity of 85.0% and a specificity of 78.4%.[15]

To specify if patients were LABA/LAMA FDC or LABA/ICS FDC initiators, we excluded patients who simultaneously initiated both LABA/LAMA FDC and LABA/ICS FDC or who simultaneously initiated LABA, LAMA, and ICS on the index date. We also excluded patients who initiated more than one type of LABA/LAMA FDC or LABA/ICS FDC on the index date.

Temporal Trends, Healthcare Provider Characteristics, and Patient Characteristics for Use of LABA/LAMA FDC or LABA/ICS FDC

To examine potential changes in the use of LABA/LAMA FDC or LABA/ICS FDC over time, we stratified LABA/LAMA FDC or LABA/ICS FDC initiators according to the years of index dates (2015, 2016, 2017, and 2018). To explore healthcare provider characteristics, we captured the accreditation level of the hospitals where the initiation prescriptions were from (medical centers, metropolitan hospitals, district hospitals, or primary care clinics) and the specialty of the physicians who prescribed the study drugs (chest, internal medicine, family medicine, and others). We also assessed patient characteristics of LABA/LAMA FDC or LABA/ICS FDC initiators, including demographics (age on the index date and sex), comorbidities (cardiovascular diseases, asthma, pneumonia, cancer, and psychiatric disorders), and the Charlson comorbidity score, which are widely used to assess general comorbidities),[16–18] as well as resource utilization at baseline.

We determined if patients had comorbidities based on any inpatient and outpatient diagnosis except asthma, which required at least 3 diagnosis records at baseline to prevent misclassification between asthma and other conditions. We measured resource utilization based on records of hospital admission or outpatient visits due to any reasons, cardiovascular diseases, or COPD. All the information was assessed within 365 days before the index date. See Appendix Table 3 for detailed definitions of comorbidities.

Statistical Analysis

We applied the Cochran–Armitage trend test to assess whether there was a significant, temporal trend for use of LABA/LAMA FDC and LABA/ICS FDC. We used the chi-square test to examine if there was a significant variation in healthcare provider characteristics, including the accreditation level of the hospitals and the specialty of the physicians, between treatment groups. A p-value of <0.05 was considered statistically significant. For patient characteristics, we computed standardized differences for each characteristic, with a value of >0.1 in absolute terms indicating a clinically meaningful difference between treatment groups.[19,20] We also conducted multivariate logistic regression, with a 95% CI not including the null suggesting an independent predictor of initiating LABA/LAMA FDC or LABA/ICS FDC. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Eligible Patients

There were 12,455 eligible patients identified; the mean (SD) age of patients was 69 (12) years and 68% were male. Among LABA/LAMA FDC initiators (n=4019), vilanterol/umeclidinium (44%) was the most frequently used medication, followed by indacaterol/glycopyrronium (39%) and olodaterol/tiotropium (17%). Among LABA/ICS FDC initiators (n=8436), salmeterol/fluticasone was prescribed predominantly (36%), followed by formoterol/budesonide (28%), formoterol/beclomethasone (24%), vilanterol/fluticasone (11%), and formoterol/fluticasone (1%) (Figure 1).

Temporal Trends Between LABA/LAMA FDC and LABA/ICS FDC Treatment Groups

As shown in Figure 2, the number of initiators rose only slightly between 2015 (n=2752) and 2018 (n=3229). During the entire study period, the number of initiators with LABA/LAMA FDC was lower than that with LABA/ICS FDC. However, there was an apparent increased use of LABA/LAMA FDC but an evident decreased use of LABA/ICS FDC over time. Specifically, among 2752 patients who initiated either FDC class in 2015, 12% (n=336) and 88% (n=2416)

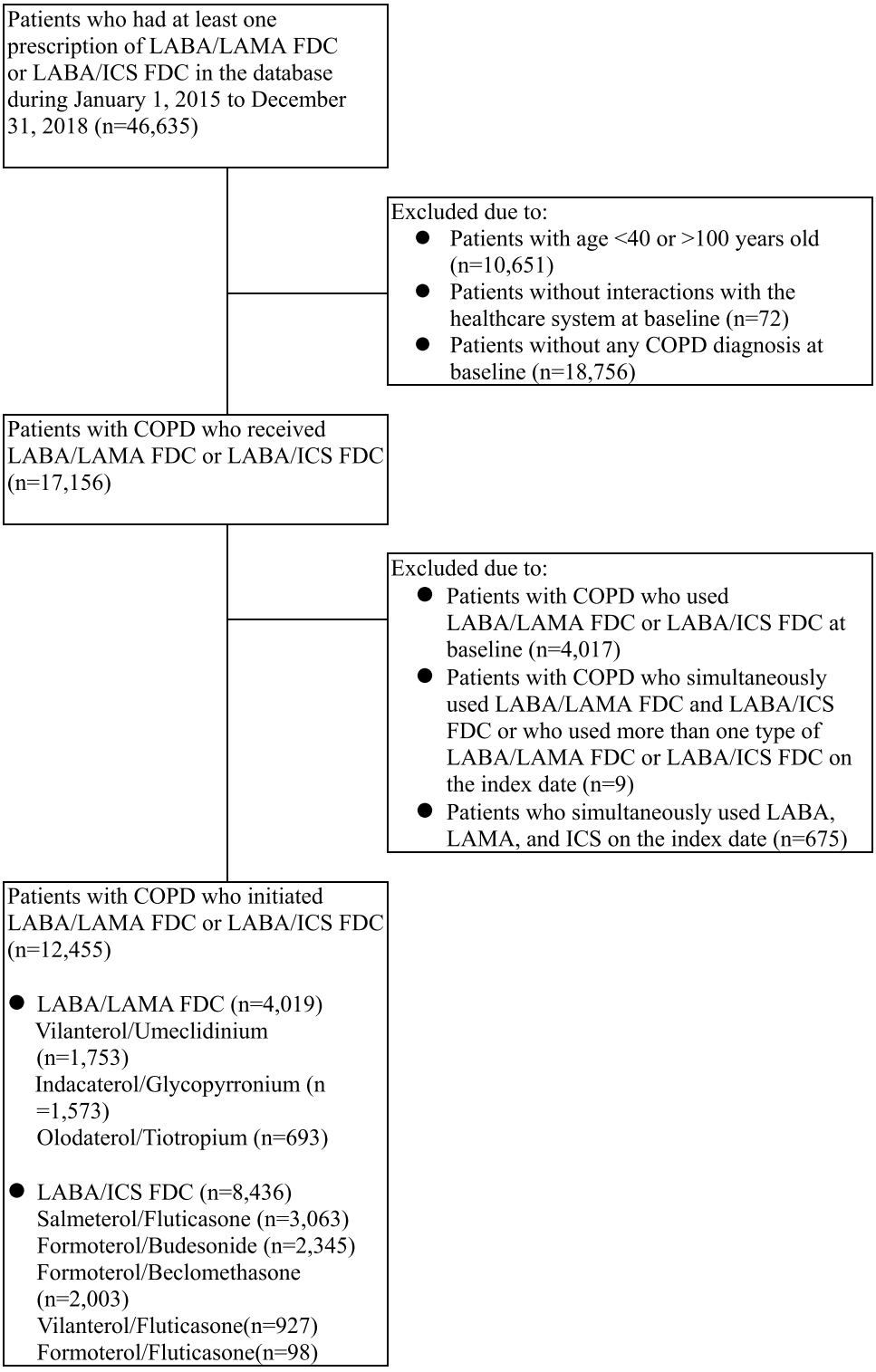

Figure 1 Flow chart of the study population assembly.
Abbreviations: COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists.

initiated LABA/LAMA FDC and LABA/ICS FDC, respectively. Nevertheless, in 2018, the proportion of each FDC class become closer, with 44% initiating LABA/LAMA FDC and 56% initiating LABA/ICS FDC. The Cochran–Armitage trend test suggested a significant temporal change in use of both FDC products (p-value <0.001).

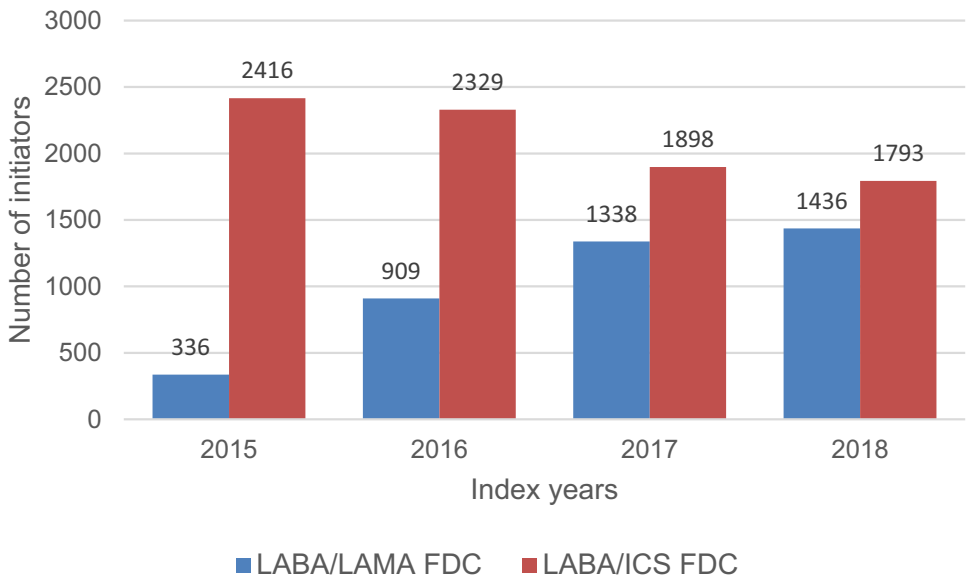

Figure 2 Temporal trends for use of LABA/LAMA FDC and LABA/ICS FDC.
Abbreviations: FDC, fixed-dose combination; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists.

Healthcare Provider Characteristics Between LABA/LAMA FDC and LABA/ICS FDC Treatment Groups

Figure 3A shows number of initiators with each FDC class across the accreditation levels of the hospitals. Most patients received FDC products from regional hospitals (n=5161), followed by medical centers (n=3390), district hospitals (n=2434), and primary care clinics (n=517). There were 133 LABA/LAMA FDC initiators and 820 LABA/ICS FDC initiators with missing information on hospital accreditation levels. Use of LABA/LAMA FDC was less common than use of LABA/ICS FDC at each hospital accreditation level. However, the differences in proportions of both FDC initiators in the settings of non-primary care clinics tended to be smaller than those in primary care clinics. For example, among 3390 FDC initiators in medical centers, 37% (n=1265) used LABA/LAMA FDC and 63% (n=1265) used LABA/ICS FDC. Nevertheless, among 517 FDC initiators in primary care clinics, only 9% (n=44) received LABA/LAMA FDC and up to 91% (n=473) received LABA/ICS FDC. The chi-square test indicated a significant difference in the type of FDC products across hospital accreditation levels (p-value <0.001).

Most patients received FDC prescriptions from physicians with the chest specialty (n=9737), followed by internal medicine (n=1096), other specialties (n=1052; otorhinolaryngology and cardiology mainly), and family medicine (n=570). Overall, use of LABA/LAMA FDC was less frequent than use of LABA/ICS FDC in different physician specialties. However, it was noticed that, among patients who received FDC products from chest physicians (n=9737), 37% (n=3648) had LABA/LAMA FDC and 63% (n=6089) had LABA/ICS FDC. While among patients who received FDC products from family medicine physicians (n=570), there were only 8% (n=43) with LABA/LAMA FDC and up to 92% (n=527) with LABA/ICS FDC. There was a significant difference in the type of FDC products across physician specialties (Figure 3B, chi-square p-value <0.001).

Patient Characteristics Between LABA/LAMA FDC and LABA/ICS FDC Treatment Groups

Table 1 shows patient characteristics of both FDC initiators. LABA/LAMA FDC initiators tended to be older (71 vs 68 years) and to be male (86% vs 59%); were more likely to have any cancer or lung cancer and to have higher Charlson comorbidity scores; and were more likely to have outpatient visits due to COPD, hospital admissions due to COPD, and hospital admissions due to any reason. In contrast, LABA/ICS FDC initiators were more likely to have asthma (ie, asthma–COPD

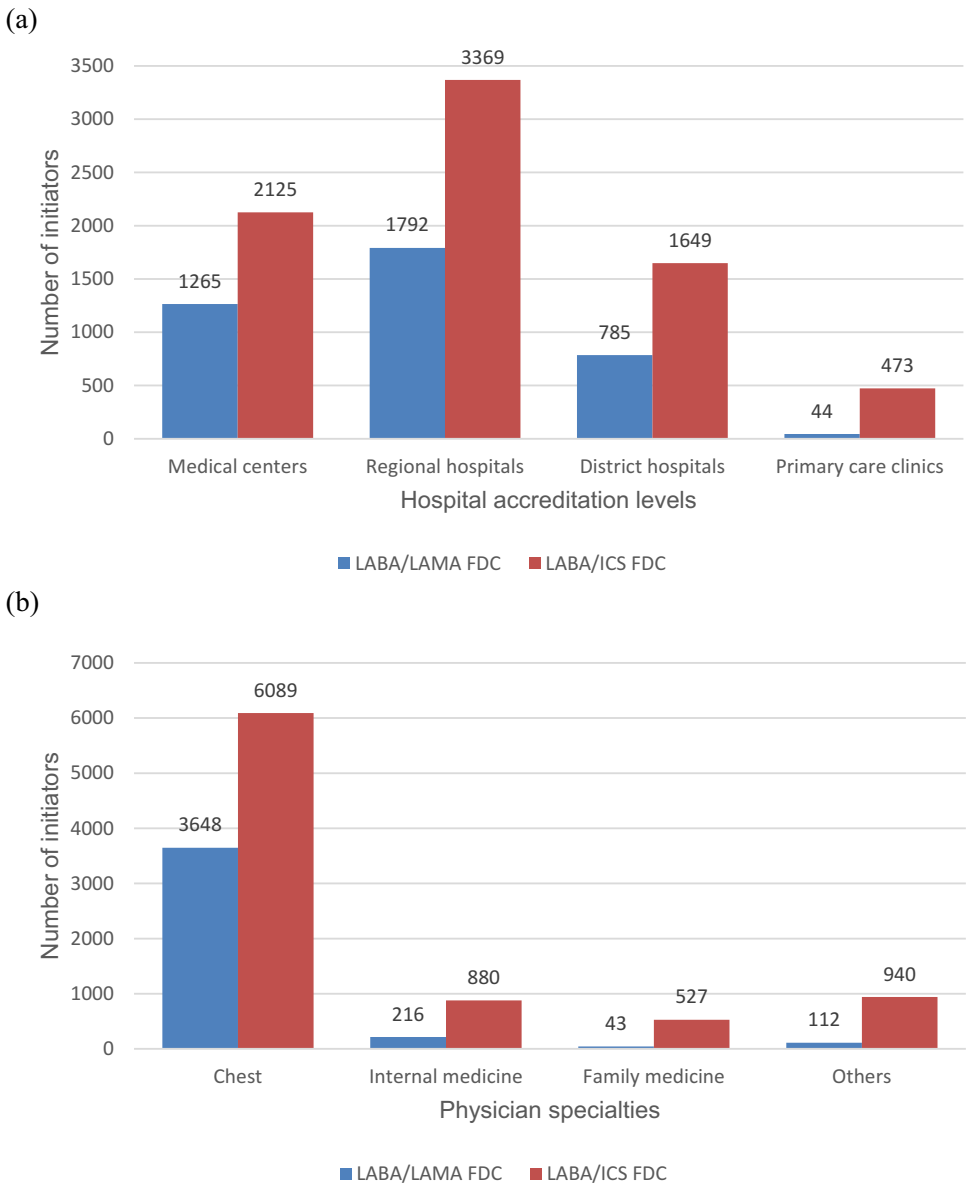

Figure 3 Healthcare provider characteristics for use of LABA/LAMA FDC and LABA/ICS FDC. (**A**) Hospital accreditation levels[a]. (**B**) Physician specialties.
Notes: [a]There were 133 LABA/LAMA FDC initiators and 820 LABA/ICS FDC initiators with missing information on hospital accreditation levels.
Abbreviations: FDC, fixed-dose combination; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists.

overlap syndrome). In the multivariate logistic regression analysis, we noticed that old age, male sex, any cancer, lung cancer, anxiety, as well as outpatient visits or hospital admissions due to COPD were independent predictors of initiating LABA/LAMA FDC, with ORs >1 and 95% CIs not including the null. In contrast, asthma was a strong, independent predictor of initiating LABA/ICS FDC (0.36; 95% CI, 0.32–0.40).

Table 1 Demographics, Comorbidities, and Medication Use of LABA/LAMA FDC and LABA/ICS FDC Initiators

Variables[a]	LABA/LAMA FDC (n=4019)	LABA/ICS FDC (n=8436)	Standardized Difference	Multivariate OR (95% CI)
Demographics				
Age on index date, mean (SD)	71.16 (11.44)	67.83 (12.90)	0.273	1.019 (1.015–1.022)
Male	3445 (85.72)	4968(58.89)	0.628	3.61 (3.26–4.01)

(*Continued*)

Table 1 (Continued).

Variables[a]	LABA/LAMA FDC (n=4019)	LABA/ICS FDC (n=8436)	Standardized Difference	Multivariate OR (95% CI)
Comorbidities				
Hypertension	2207 (54.91)	4639 (54.99)	−0.002	0.87 (0.76–0.98)
Ischemic heart disease	1042 (25.93)	1908 (22.62)	0.077	1.10 (0.99–1.23)
Myocardial infarction	114 (2.84)	174 (2.06)	0.050	1.08 (0.82–1.43)
Coronary revascularization	83 (2.07)	142 (1.68)	0.029	0.98 (0.71–1.35)
Cardiac dysrhythmia	572 (14.23)	1094 (12.97)	0.037	0.98 (0.86–1.11)
Congestive heart failure	587 (14.61)	1194 (14.15)	0.013	1.01 (0.88–1.15)
Peripheral vascular disease	101 (2.51)	149 (1.77)	0.051	1.30 (0.98–1.72)
Hyperlipidemia	1100 (27.37)	2516 (29.82)	−0.054	1.01 (0.92–1.11)
Diabetes mellitus	973 (24.21)	2117 (25.09)	−0.020	0.95 (0.85–1.06)
Asthma	386 (9.60)	2143 (25.40)	−0.425	0.36 (0.32–0.40)
Pneumonia	1304 (32.45)	2577 (30.55)	0.041	1.05 (0.95–1.16)
Any cancer except lung cancer	449 (11.17)	663 (7.86)	0.113	1.18 (1.00–1.40)
Lung cancer	232 (5.77)	217 (2.57)	0.161	2.02 (1.62–2.53)
Depressive disorder	250 (6.22)	668 (7.92)	−0.066	0.98 (0.82–1.17)
Anxiety disorder	401 (9.98)	878 (10.41)	−0.014	1.21 (1.05–1.39)
Psychotic disorder	194 (4.83)	360 (4.27)	0.027	1.07 (0.88–1.32)
Bipolar disorder	49 (1.22)	138 (1.64)	−0.035	0.95 (0.66–1.38)
Charlson comorbidity score	2.87 (2.18)	2.64 (1.91)	0.112	1.00 (0.97–1.03)
Resource utilization				
Number of outpatient visits in the past 365 days				
≥4	3981 (99.05)[b]	8379 (99.32)[b]	−0.030	0.62 (0.31–1.23)
3	22 (0.55)[b]	37 (0.44)[b]	0.016	0.67 (0.28–1.59)
1 or 2	16 (0.40)[b]	20 (0.24)[b]	0.028	Ref
Number of hospital admissions in the past 365 days				
≥2	648 (16.12)[b]	1198 (14.20)[b]	0.054	1.02 (0.86–1.21)
1	985 (24.51)[b]	1802 (21.36)[b]	0.075	1.10 (0.97–1.24)
0	2386 (59.37)[b]	5436 (64.44)[b]	−0.105	Ref
Number of outpatient visits due to COPD in the past 365 days				
≥2	3024 (75.24)[b]	5436 (64.44)[b]	0.237	2.89 (2.00–4.18)
1	953 (23.71)[b]	2805 (33.25)[b]	−0.213	1.98 (1.36–2.89)
0	42 (1.05)[b]	195 (2.31)[b]	−0.098	Ref
Number of hospital admissions due to COPD in the past 365 days				
≥2	191 (4.75)[b]	275 (3.26)[b]	0.076	1.14 (0.89–1.45)
1	640 (15.92)[b]	961 (11.39)[b]	0.132	1.24 (1.07–1.44)
0	3188 (79.32)[b]	7200 (85.35)[b]	−0.159	Ref
Number of outpatient visits due to CV disease[c] in the past 365 days				
≥2	2530 (62.95)[b]	5122 (60.72)[b]	0.046	1.05 (0.90–1.22)
1	198 (4.93)[b]	388 (4.60)[b]	0.015	1.08 (0.87–1.33)
0	1291 (32.12)[b]	2926 (34.68)[b]	−0.054	Ref

(*Continued*)

Table 1 (Continued).

Variables[a]	LABA/LAMA FDC (n=4019)	LABA/ICS FDC (n=8436)	Standardized Difference	Multivariate OR (95% CI)
Number of hospital admissions due to CV disease[c] in the past 365 days				
≥2	846 (21.05)[b]	1738 (20.60)[b]	0.011	0.85 (0.75–0.97)
1	771 (19.18)[b]	1416 (16.79)[b]	0.062	1.00 (0.89–1.12)
0	2402 (59.77)[b]	5282 (62.61)[b]	−0.058	Ref

Notes: [a]Data are demonstrated as number (n) and percentage (%) of patients unless otherwise specified. [b]Percentage of patients may be more or less than 100% due to rounding. [c]CV disease includes hypertension, ischemic heart disease, myocardial infarction, coronary revascularization, cardiac dysrhythmia, congestive heart failure, cerebrovascular disease, and peripheral vascular disease.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; FDC, fixed-dose combination; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists; OR, odds ratio.

Discussion

This population-based, real-world study showed evident temporal trends, variations in healthcare provider, and differences in patient characteristics among COPD patients who initiated LABA/LAMA FDC or LABA/ICS FDC, both of which are recommended alternative choices for those with severe disease. There was an apparent increased use of LABA/LAMA FDC but an obvious decreased use of LABA/ICS FDC since the availability of the first LABA/LAMA FDC product in Taiwan in 2015. LABA/LAMA FDC tended to be prescribed in the setting of non-primary care clinics and by physicians with the chest specialty compared to LABA/ICS FDC. LABA/LAMA FDC initiators appeared to be more vulnerable than LABA/ICS FDC initiators.

Comparison with Existing Studies

Temporal Trends for LABA/LAMA FDC or LABA/ICS FDC Use

Several researchers have depicted temporal trends of COPD maintenance medications. Although the timeframes ranged from 1 to 6 years across studies conducted in South Korea, France, and Canada, these studies generally indicated that use of LABA/LAMA combination therapy increased over time.[9–12] Other maintenance medications, including LABA/ICS combination therapy, LABA/ICS/LAMA combination therapy, LABA monotherapy, and LAMA monotherapy, may follow a decreased or stable temporal trend during the same observational windows (see Appendix Table 4 for detailed information).[9–12] Most of these studies, however, did not specifically classify LABA/LAMA combination therapy into either FDC or free combination forms.[9–11] One Canadian population-based study noticed that there was a rapid uptake of LABA/LAMA FDC (up to 283 users per 100,000 populations from 2015 to 2016) among elderly COPD patients treated with maintenance medications.[12] The uptake of LABA/LAMA FDC, nevertheless, had no profound impacts on the reduction of LABA/ICS FDC use within the same window.[12]

The present study targeted patients who initiated either LABA/LAMA FDC or LABA/ICS FDC. This facilitates figuring out treatment selection when physicians would like to prescribe FDC maintenance medications indicated for similar disease severity. We observed that LABA/LAMA FDC became more dominant during a 4-year observation window. Cumulative literature pointed out that LABA/LAMA FDC may be more efficacious while having less adverse reactions such as lower respiratory tract infections than LABA/ICS FDC.[21–24] Our results, to some extent, reflect that FDC prescription patterns in daily practice may adhere to the recommendations of available evidence.

Healthcare Provider Characteristics for LABA/LAMA FDC or LABA/ICS FDC Use

Although some studies have indicated that COPD treatment selection may differ across healthcare providers, limited studies examined the scenario of determining LABA/LAMA FDC or LABA/ICS FDC therapy among healthcare providers with different backgrounds and in different environments.[25–27] In a US health survey study, Mannino et al found that chest physicians may have a higher preference for LABA/LAMA FDC compared to primary care physicians.[27]

Extending Mannino et al's findings, the present study suggested that physicians who were chest physicians or who worked in the setting of non-primary care clinics (eg, medical centers) were more likely to prescribe LABA/LAMA FDC than those who were non-chest physicians (eg, family medicine physicians) or who stayed in primary care clinics. It is possible that physicians with a chest specialty or working in the setting of non-primary care clinics are more familiar with the suggestions of available evidence and the role of LABA/LAMA FDC. In addition, LABA/LAMA FDC are generally more expensive than LABA/ICS FDC and therefore more likely to be available in medical centers, regional hospitals, or district hospitals than in primary care clinics. These may partially explain the variations in use of both FDC therapies across various settings. These findings also facilitate the development of strategies to reduce inappropriate use of LABA/ICS FDC, if concerned and needed, for the target audience.

Patient Characteristics for LABA/LAMA FDC or LABA/ICS FDC Use

Some comparative effectiveness or safety studies of LABA/LAMA and LABA/ICS combination therapies (either FDC or free combination forms) noticed that baseline patient characteristics differed between treatment groups.[23,24,28,29] For example, in one study using a US commercial claims database, Samp et al showed that patients who started LABA/LAMA combination therapy were older, more likely to be male, had more comorbidities, including cardiovascular diseases, any cancer, lung cancer, mental health disorder, and pneumonia, and had more frequent resource utilization due to COPD compared to patients who started LABA/ICS combination therapy.[29]

Similar to Samp et al's results, our study also found that LABA/LAMA FDC initiators were generally more vulnerable than LABA/ICS FDC initiators. In the multivariate logistic regression analysis, we further showed that old age, male sex, several comorbidities (including any cancer, lung cancer, and anxiety), and outpatient visits or hospital admissions due to COPD were independent predictors of using LABA/LAMA FDC rather than LABA/ICS FDC. Although both FDC products are listed as alternative treatments in the clinical guideline, it is possible that physicians still prefer to prescribe LABA/LAMA FDC, a new product, for sicker patients. Our results also deserveattention in controlling for patient characteristics (ie, confounders) when undergoing comparative effectiveness and safety research for both FDC therapies in real-world settings.

Of interest, in terms of cardiovascular comorbidities, it seemed that the differences between treatment groups were more obvious in Samp et al's study than in ours. Specifically, in Samp et al's study, proportions of hypertension, congestive heart failure, heart disease, and arrhythmia between LABA/LAMA combination therapy and LABA/ICS combination therapy were 39% versus 34%, 12% versus 6%, 20% versus 10%, and 20% versus 11%, respectively.[29] Nevertheless, in our study, corresponding proportions for individual diseases between LABA/LAMA FDC and LABA/ICS FDC groups were 55% versus 55%, 15% versus 14%, 26% versus 23%, and 14% versus 13%, respectively. Given the pharmacological effects of LABA on β_2 receptors and LAMA on M3 receptors, there may be potential concerns regarding cardiovascular safety when prescribing LABA and LAMA, either monotherapy or combination therapy, for patients with cardiovascular comorbidities. Our study, however, demonstrated that underlying cardiovascular diseases may not be a substantial issue when deciding between LABA/LAMA FDC and LABA/ICS FDC treatment in Taiwan.

Unlike Samp et al's study in which patients with asthma were excluded,[29] the present study retained this subpopulation in the cohort and observed that asthma was a strong, independent predictor of initiating LABA/ICS FDC. This result was in line with the GOLD guideline suggestions that LABA/ICS FDC is preferred rather than LABA/LAMA FDC when patients have concomitant diagnoses of asthma and COPD.[3]

Strengths and Limitations of the Present Study

The present study was conducted using a population-based Taiwanese database derived from a single-payer health insurance system. The comprehensive information on demographics, diagnosis and procedure records, medication use, and resource utilization enhances the representativeness and validity of our results for COPD patients in an Asian country. We demonstrated treatment selection of either LABA/LAMA or LABA/ICS FDC products, both of which are indicated for similar COPD disease severity. The 4-year temporal trends, variations in healthcare provider characteristics,

and differences in patient characteristics are useful to examine prescription patterns in real-world settings and, to some extent, to assess if the patterns cohere with the suggestions of the GOLD guideline.

However, we need to recognize that prescription patterns may be different in a longer timeframe. In addition, information on COPD classification (eg, COPD GOLD A–D groups), lung function test measures (eg, forced expiratory volume within one second, FEV1), and laboratory data (eg, eosinophil counts) is not available in the current claims database. Therefore, continual follow-up with more complete information on clinical parameters would require evaluation of the appropriateness of use of both FDC products in COPD patients in future studies.

Conclusion

This population-based study demonstrated 4-year temporal trends, variations in healthcare provider characteristics, and differences in patient characteristics for new use of LABA/LAMA FDC and LABA/ICS FDC in Asian COPD patients.

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The current work is based on Pei-An Liao's master's thesis finished in 2021. The results are accessible, in part and in an abstract, on the website of the National Digital Library of Theses and Dissertations in Taiwan (https://etds.ncl.edu.tw/cgi-bin/gs32/gsweb.cgi/ccd=XZOqEu/webmge?switchlang=en). However, the complete manuscript has not been published and is not under simultaneous consideration for publication elsewhere.

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

1. World Health Organization. Global health estimates: life expectancy and leading causes of death and disability 2019. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates. Accessed August 25, 2022.
2. Taiwan Ministry of Health and Welfare. 2020 Cause of death statistics. Available from: https://www.mohw.gov.tw/lp-5256-2.html. Accessed August 25, 2022.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Diseases; 2022. Available from: https://goldcopd.org/2022-gold-reports-2/. Accessed August 25, 2022.
4. Parkin L, Barson D, Zeng J, Horsburgh S, Sharples K, Dummer J. Patterns of use of long-acting bronchodilators in patients with COPD: a nationwide follow-up study of new users in New Zealand. *Respirology*. 2018;23:583–592.
5. Price D, Miravitlles M, Pavord I, et al. First maintenance therapy for COPD in the UK between 2009 and 2012: a retrospective database analysis. *NPJ Prim Care Respir Med*. 2016;26:16061.
6. Gruffydd-Jones K, Brusselle G, Jones R, et al. Changes in initial COPD treatment choice over time and factors influencing prescribing decisions in UK primary care: in UK primary care: a real-world study. *NPJ Prim Care Respir Med*. 2016;26:16002.
7. Dong YH, Chang CH, Wu FL, et al. Use of inhaled corticosteroids in patients with COPD and the risk of TB and influenza: a systematic review and meta-analysis of randomized controlled trials. *Chest*. 2014;145:1286–1297.
8. Chen H, Sun J, Huang Q, et al. Inhaled corticosteroids and the pneumonia risk in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. *Front Pharmacol*. 2021;12:691621.
9. Lee SH, Lee JH, Yoon HI, et al. Change in inhaled corticosteroid treatment and COPD exacerbations: an analysis of real-world data from the KOLD/KOCOSS cohorts. *Respir Res*. 2019;20:62.
10. Roche N, Aguilaniu B, Li PZ, Hess D; COLIBRI collaborators. Trends over time in COPD treatment choices by respiratory physicians: an analysis from the COLIBRI-COPD French cohort. *Respir Med*. 2019;156:8–14. doi:10.1016/j.rmed.2019.07.023

11. Bloom CI, Elkin SL, Quint JK. Changes in COPD inhaler prescriptions in the United Kingdom, 2000 to 2016. *Int J Chron Obstruct Pulmon Dis*. 2019;14:279–287. doi:10.2147/COPD.S190086
12. Parkin L, Khuu W, Stanbrook MB, Tadrous M, Martins D, Gomes T. Trends in the utilisation of COPD therapeutic regimens before and after the introduction of LAMA/LABA combination products: a population-based study. *Respir Med*. 2018;143:1–7. doi:10.1016/j.rmed.2018.08.001
13. National Health Insurance Administration. 2021-2022 National Health Insurance Annual Report. Available from: https://www.nhi.gov.tw/Content_List.aspx?n=9223A12B5B31CB37&topn=4864A82710DE35ED. Accessed August 25, 2022.
14. Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). *Epidemiol Health*. 2018;40:e2018062. doi:10.4178/epih.e2018062
15. 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.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*. 1987;40:373–383.
17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
18. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
19. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ*. 2005;330:960–962.
20. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107.
21. Calzetta L, Marco FD, Blasi F, et al. Impact of ICS/LABA and LABA/LAMA FDCs on functional and clinical outcomes in COPD: a network meta-analysis. *Pulm Pharmacol Ther*. 2019;59:101855.
22. Horita N, Goto A, Shibata Y, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2017;2:CD012066.
23. Quint JK, Montonen J, Esposito DB, et al. Effectiveness and safety of COPD maintenance therapy with tiotropium/olodaterol versus LABA/ICS in a US claims database. *Adv Ther*. 2021;38:2249–2270.
24. Wang MT, Lai JH, Huang YL, et al. Comparative effectiveness and safety of different types of inhaled long-acting β2-agonist plus inhaled long-acting muscarinic antagonist vs inhaled long-acting β2-agonist plus inhaled corticosteroid fixed-dose combinations in COPD: a propensity score-inverse probability of treatment weighting cohort study. *Chest*. 2021;160:1255–1270.
25. Sharif R, Cuevas CR, Wang Y, Arora M, Sharma G. Guideline adherence in management of stable chronic obstructive pulmonary disease. *Respir Med*. 2013;107:1046–1052.
26. Desalu OO, Onyedum CC, Adeoti AO, et al. Guideline-based COPD management in a resource-limited setting - physicians' understanding, adherence and barriers: a cross-sectional survey of internal and family medicine hospital-based physicians in Nigeria. *Prim Care Respir J*. 2013;22:79–85.
27. Mannino D, Siddall J, Small M, Haq A, Stiegler M, Bogart M. Treatment Patterns for Chronic Obstructive Pulmonary Disease (COPD) in the United States: results from an Observational Cross-Sectional Physician and Patient Survey. *Int J Chron Obstruct Pulmon Dis*. 2022;17:749–761.
28. Moretz C, Sharpsten L, Bengtson LG, et al. Real-world effectiveness of umeclidinium/vilanterol versus fluticasone propionate/salmeterol as initial maintenance therapy for chronic obstructive pulmonary disease (COPD): a retrospective cohort study. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1721–1737.
29. Samp JC, Joo MJ, Schumock GT, Calip GS, Pickard AS, Lee TA. Comparative effectiveness of long-acting beta2 -agonist combined with a long-acting muscarinic antagonist or inhaled corticosteroid in chronic obstructive pulmonary disease. *Pharmacotherapy*. 2017;37:447–455.