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ORIGINAL RESEARCH

Comparing Costs and Healthcare Resource Utilization (HCRU) Using LAMA versus LABA/ICS at Treatment Initiation for COPD: Findings from CITRUS (Comparing the Incidence of Tiotropium and ICS/LABA in Real-World Use in South Korea) Study

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Background: COPD causes substantial economic burden on healthcare. Alternative treatment strategies for COPD can be associated with different costs dependent upon their relative safety and effectiveness. We compared costs and healthcare resource utilization (HCRU) associated with LAMA or LABA/ICS initiation.

Methods: Using the Korean National Health Insurance Service database, we enrolled COPD patients initiating treatment with LAMA or LABA/ICS between January 2005 and April 2015. Propensity score matched individuals were compared on all-cause and COPD-related medical costs and HCRU over a three-year follow-up period.

Results: A total of 2444 patients were enrolled in each treatment group. LAMA group was associated with significantly lower costs than LABA/ICS group, both in all-cause (403.08 vs 474.50 USD per patient per month [PPPM], cost ratio 1.18, 95% confidence interval [CI]=1.10–1.26, $p<0.0001$) and COPD-related (216.37 vs 267.32 USD PPPM, cost ratio 1.24, 95% CI=1.13–1.35, $p<0.0001$) medical costs. All-cause HCRU was not significantly different between groups, while COPD-related HRCU was higher in LAMA group (0.66 vs 0.60 medical visits PPPM, $p<0.0001$).

Conclusion: COPD patients initiating treatment with LAMA were associated with lower all-cause and COPD-related medical costs than those starting with LABA/ICS despite the similar all-cause HCRU and higher COPD-related HCRU. Initiation with LAMA is a cost-efficient option for the treatment of COPD.

Keywords: chronic obstructive pulmonary disease, inhaled corticosteroids, long-acting beta-2 agonists, long-acting muscarinic receptor antagonists, medical cost

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease. The global prevalence of COPD is estimated to be 10.3%.[1] COPD was the third leading cause of death worldwide in 2019,[2] and the most

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common cause of death from non-communicable diseases (NCDs) in 2016.[3] COPD also causes significant healthcare resource utilization and economic burden across countries, including South Korea.[4–6]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, initial therapy should be chosen based on the severity of dyspnea and the risk of exacerbation. Inhaled bronchodilators such as long-acting muscarinic antagonists (LAMA), long-acting beta-2 agonists (LABA), or a combination of both are the critical components of COPD treatment. Although the American Thoracic Society (ATS) and GOLD 2023 update recently announced that LAMA/LABA combination therapy is more effective than LAMA or LABA monotherapy[1,7] in patients with dyspnea or exercise tolerance, LAMA monotherapy still remains a widely used and valuable component in COPD treatment,[8,9] especially in GOLD group A.

Unlike asthma, where inhaled corticosteroids (ICS) are an essential part of treatment, the GOLD 2023 guidelines do not encourage the use of LABA/ICS in COPD.[1,10] The use of ICS as a component of triple therapy is reserved for patients with recurrent exacerbations and high blood eosinophil count.[1,11] However, ICS is widely prescribed in real-world practice outside of the above recommendation.[12,13] A recent US study showed that LABA/ICS is used in 28.5% of patients with moderate or severe exacerbations, while only 5.7% of patients utilized triple therapy.[14]

The INSPIRE study demonstrated that LAMA monotherapy is similar to LABA/ICS in exacerbation prevention.[15] Additionally, in a real-world study, treatment with LABA/ICS showed no exacerbation risk reduction over LAMA except in a group of patients with eosinophils above 4%.[16] However, no real-world study compares LAMA with LABA/ICS treatment regarding medical costs and healthcare resource utilization (HCRU). This study compared all-cause medical costs and HCRU between LAMA and LABA/ICS during a three-year follow–up period using a health insurance claims database in primary and secondary care. We also explored COPD-related medical costs and HCRU rates between the treatment groups.

Materials and Methods

Study Design

This study was a retrospective, non-interventional cohort study using a national health insurance claims database from the National Health Insurance Service (NHIS) from South Korea.[17] The NHIS data provides demographic characteristics and healthcare information of COPD patients, including comorbidities and medical treatment. The study period was from January 1, 2002 through April 30, 2016, consisting of the baseline period of 36 months and the patient enrollment period of 124 months (January 1, 2005 to April 30, 2015). The definition of index date was the date of the first prescription date of LAMA or fixed-dose combination (FDC) of LABA/ICS for COPD treatment during the enrollment period. The baseline period is defined as 36 months before the index date to assess patients' baseline demographic information and comorbidities. Enrolled patients were followed for a minimum of 12 months and a maximum of 124 months from the index date (Figure 1A). The follow-up ended when the LAMA or LABA/ICS was discontinued, or the study period ended.

Study Population

We used the International Classification of Diseases, Tenth Revision (ICD-10) code to confirm COPD. Patients with ICD-10 code (J43.x-44.x, except J430), as the primary diagnosis or within the first four additional diagnoses, were considered to have COPD.[18,19] Then, we enrolled the patients for the analysis who met the following criteria: Patients aged ≥55 years as of the index date; Patients who were prescribed with LAMA monotherapy or LABA/ICS FDC for the first time during the enrollment period; Patients who were prescribed with LAMA monotherapy or LABA/ICS FDC at least twice within 12 months from the index date. The LAMAs included tiotropium bromide, aclidinium bromide, glycopyrronium bromide, and umeclidinium bromide. The FDCs of ICS and LABA were salmeterol and fluticasone, formoterol and budesonide, vilanterol and fluticasone furoate, and formoterol and fluticasone. We excluded the current asthma patients with active treatment at the index date but included patients with past asthma history who were recorded with ≥1 claim with ICD-10 codes for asthma in the previous 36 months before the index date. We also minimized the selection of asthma patients by excluding patients aged <55 years.

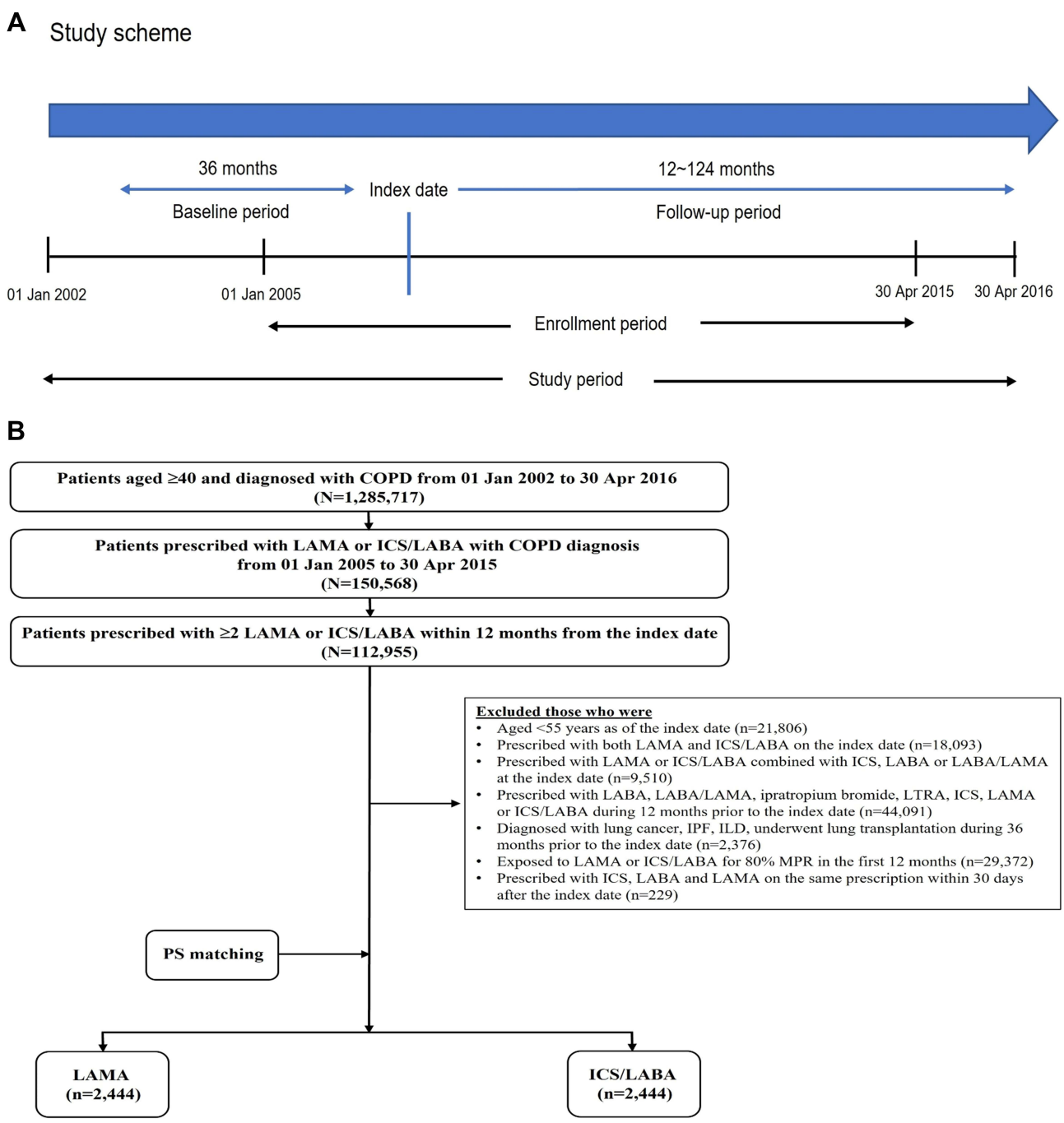

Figure 1 (**A**) Study scheme. (**B**) Study flow chart.
Abbreviations: LAMA, long-acting muscarinic antagonist; LABA/ICS, long-acting beta-2 agonist plus inhaled corticosteroids; COPD, chronic obstructive pulmonary disease; MPR, medical possession rate; LTRA, leukotriene receptor antagonist; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

We also excluded the patients on any combinations other than LAMA or LABA/ICS at the index date or who received any inhaler treatments in the previous 12 months before the index date. Patients with their medical possession rate (MPR) ≤80% in the first 12 months were also excluded.

Study Outcome

The co-primary outcomes of this study were all-cause medical costs and all-cause HCRU over a three-year follow-up period. COPD-related medical costs and COPD-related HCRU were secondary outcomes.

Medical costs per-person-per-month (PPPM) were obtained overall and separately based on the type of service (inpatient visit, outpatient visit, or pharmacy visit). All-cause and COPD-related medical costs, consisting of services covered by the NHIS and co-payment, included the total medical, hospitalization, outpatient, and pharmacy costs during 12, 24, and 36 months of follow-up, were calculated. The medical costs were shown as the mean cost PPPM. All costs were converted to US dollars using the average 2019 exchange rate: 1 USD = 1166.51 KRW (South Korean Won).

All-cause and COPD-related HCRU included any services directly provided by the healthcare system during 12, 24, and 36 months of follow-up period from the index date, including inpatient visit, outpatient visit, and pharmacy visit. HCRU rate was presented as the number of any medical visits PPPM. For outpatient visits, HCRU was confined to outpatient visits with the ICD-10 code of COPD (J43.x–J44.x, except J430) with the prescription of COPD-related medication. For inpatient visits, analyses were confined to hospitalization with the ICD-10 codes of COPD or COPD-related diseases (pneumonia: J12.x–J17.x, pulmonary thromboembolism: I26, I26.0, and I26.9; dyspnea: R06.0; or acute respiratory distress syndrome: J80) with the prescription of COPD-related medication.[20–22]

Propensity Score Matching and Statistical Analysis

We used the propensity score (PS) matching to reduce the potential confounding and to balance comparability between LAMA and LABA/ICS treatment groups, because the initial treatment is likely to be selected according to the demographics and baseline characteristics of the patients. PS was estimated using multiple logistic regression analysis based on age, sex, income quartiles, modified Charlson Comorbidity Index (CCI), asthma history, and COPD exacerbation history.

Patients' baseline demographic and clinical characteristics were analyzed using descriptive statistics. Continuous and categorical variables were summarized using descriptive statistics. The comparison of descriptive statistics between study groups was evaluated by *t*-test for continuous variables and chi-squared test for categorical variables. HCRU rates and medical costs were also analyzed using descriptive statistics and presented as the number of inpatient hospitalizations, outpatient visits, outpatient pharmacy dispensations, and the mean cost PPPM. In addition, we conducted subgroup analyses according to sex, age group, and history of asthma or COPD exacerbation.

We compared the difference in medical costs and HCRU rates between the study groups by *t*-test for parametric and Wilcoxon rank-sum test for non-parametric variables. In addition, the medical costs and HCRU rates were calculated and compared across the study groups using a generalized linear model (GLM) with gamma distribution for costs and Poisson, negative binomial, or zero-inflated negative binomial distribution for HCRU rates based on the overdispersion parameter and the number of zeros. All statistical tests were two-sided with a significance level of 0.05. We used the SAS® 9.4 software (SAS Institute, North Carolina, US) via SAS Enterprise Guide version 6.1 for the statistical analysis.

Ethics Approval

This study protocol followed the Declaration of Helsinki and was approved by the ethical committee of Konkuk University Medical Center (Institutional Review Board No.: KUMC2020-06-013). Informed consent was waived because only de-identified data were used for analytical purposes.

Results

Baseline Characteristics

Figure 1B shows the flow chart of the study. The total of 1,285,717 patients aged at least 40 years and diagnosed with COPD from January 1, 2002 to April 30, 2016 was screened. Among them, 112,955 patients were prescribed with either LAMA or LABA/ICS at least twice within 12 months from the index date. After the application of the aforementioned exclusion criteria and PS matching, 4888 COPD patients were included in this study: 2444 in the LAMA group and the rest 2444 in LABA/ICS group. Table 1 shows the demographic characteristics of each treatment group. The mean age of the enrolled patients was 69.7 years, and males comprised 75% of the cohort. About 10% of the patients were treated at clinics without inpatient units while 90% of the patients were treated in secondary care facilities. Twenty-five percent of the patients had a history of COPD exacerbation, and 48% of them had a history of asthma.

Table 1 Demographic and Clinical Characteristics in PS Matched Population

	All (n=4888)	LAMA (n=2444)	LABA/ICS (n=2444)	*p*-value
Observational period, days (mean± SD)	746.85±641.0	812.47±692.6	681.1±577.68	<0.001
Age, year (mean± SD)	69.7±7.9	69.6 ±7.9	69.7±7.9	0.53
Age group, years, n (%)				0.61
55 to < 65	1396 (29)	697 (29)	699 (29)	
65 to < 75	2106 (43)	1068 (44)	1038 (42)	
≥ 75	1386 (28)	679 (28)	707 (29)	
Sex, n (%)				0.29
Male	3676 (75)	1854 (76)	1822 (75)	
Female	1212 (25)	590 (24)	622 (25)	
Income level, quartile, n (%)				0.77
1st quartile	768 (16)	376 (15)	392 (16)	
2nd quartile	634 (13)	311 (13)	323 (13)	
3rd quartile	935 (19)	473 (19)	462 (19)	
4th quartile	1641 (34)	838 (34)	803 (33)	
Medical aid	910 (19)	446 (18)	464 (19)	
Hospital type				0.85
General hospital	4046 (83)	2024 (83)	2022 (83)	
Hospital	356 (7)	184 (8)	172 (7)	
Clinic	463 (9)	225 (9)	238 (10)	
Others	23 (<1.0)	11 (<1.0)	12 (<1.0)	
History of COPD exacerbation, n (%)				0.88
None	3648 (75)	1831 (75)	1817 (74)	
One moderate	485 (10)	238 (10)	247 (10)	
≥ 2 moderate or ≥ 1 severe	755 (15)	375 (15)	380 (16)	
History of Asthma, n (%)				0.91
No	2530 (52)	1263 (52)	1267 (52)	
Yes	2358 (48)	1181 (48)	1177 (48)	
History of Pneumonia, n (%)				0.37
No	4377 (90)	2179 (89)	2198 (90)	
Yes	511 (10)	265 (11)	246 (10)	
mCCI, Mean±SD	1.97±1.83)	1.95±1.84)	1.99±1.82)	0.19
Distribution of mCCI score, n (%)				0.59
0, 1	2814 (58)	1428 (58)	1386 (57)	
2	447 (9)	213 (9)	234 (10)	
3	919 (19)	452 (18)	467 (19)	
≥ 4	708 (14)	351 (14)	357 (15)	
mCCI category, n (%)				
Congestive heart failure	529 (11)	259 (11)	270 (11)	0.61
Dementia	165 (3)	83 (3)	82 (3)	0.94
Chronic pulmonary disease	3780 (77)	1891 (77)	1889 (77)	0.95
Rheumatologic disease	223 (5)	115 (5)	108 (4)	0.63
Mild liver disease	1050 (21)	531 (22)	519 (21)	0.68
Diabetes with chronic complications	466 (10)	228 (9)	238 (10)	0.63
Hemiplegia or paraplegia	50 (1)	24 (1)	26 (1)	0.78
Renal disease	123 (3)	54 (2)	69 (3)	0.17
Any malignancy, including lymphoma and leukemia	490 (10)	232 (9)	258 (11)	0.22
Moderate or severe liver disease	51 (1)	27 (1)	24 (1)	0.67
Metastatic solid tumor	44 (1)	20 (1)	24 (1)	0.54
HIV	0 (0.0)	0 (0.0)	0 (0.0)	NA

Abbreviation: MCCI, modified Charlson Comorbidity Index.

The follow-up period was significantly longer in the LAMA treatment group than in the LABA/ICS treatment group (812.3 days vs 681.1 days). However, other baseline characteristics did not differ significantly between treatment groups.

Medical Costs

For three years of follow-up, the adjusted all-cause medical cost in the LAMA and LABA/ICS treatment group was 403.08 USD and 474.50 USD PPPM, respectively (Figure 2, Tables 2 and 3). The cost ratio was 1.18 (95% confidence interval [CI] =1.10–1.26, $p<0.0001$). The COPD-related medical cost was also lower in LAMA compared to LABA/ICS treatment group (216.37 vs 267.32 USD PPPM, cost ratio 1.24, 95% CI=1.13–1.35, $p<0.0001$). These differences were maintained irrespective of the site of care (Figure 2). Regardless of age and history of asthma, the all-cause and COPD-related medical costs in the LAMA treatment group were lower than those in the LABA/ICS treatment group (Tables 2 and 3). For the patients without a history of COPD exacerbations, both costs were significantly lower in the LAMA treatment group. LAMA reduced the all-cause medical cost for patients with a high risk of exacerbation. However, the COPD-related medical cost was similar between the treatment groups for patients with a high risk of exacerbation (Tables 2 and 3).

Healthcare Resource Utilization (HCRU)

Table 4 shows all-cause HCRU for three years of follow-up. The all-cause HCRU rate was not significantly different between the LAMA and LABA/ICS treatment groups (2.81 vs 2.73 visits PPPM, respectively, $p=0.2875$). In subgroup analyses, inpatient hospitalization and ER visit rates were significantly lower in the LAMA treatment group than in the LABA/ICS treatment group. LABA/ICS treatment was associated with higher all-cause HCRU than LAMA treatment for patients without asthma history (Table S1). COPD-related HCRU was lower in the LABA/ICS group compared to the LAMA group (0.60 vs 0.66 visits PPPM, respectively, $p<0.0001$), resulting from a significant difference in outpatient visits (Table 4).

Discussion

In this study, we compared the all-cause and COPD-related medical costs and healthcare resource utilization (HCRU) in COPD patients of initial treatment with either LAMA or LABA/ICS. We found that initiation with LAMA treatment for COPD costs an average of 403.08 USD PPPM for all-cause medical cost and 216.37 USD PPPM for COPD-related medical cost which were lower than those of patients initiating treatment with LABA/ICS. Most of the differences resulted from the

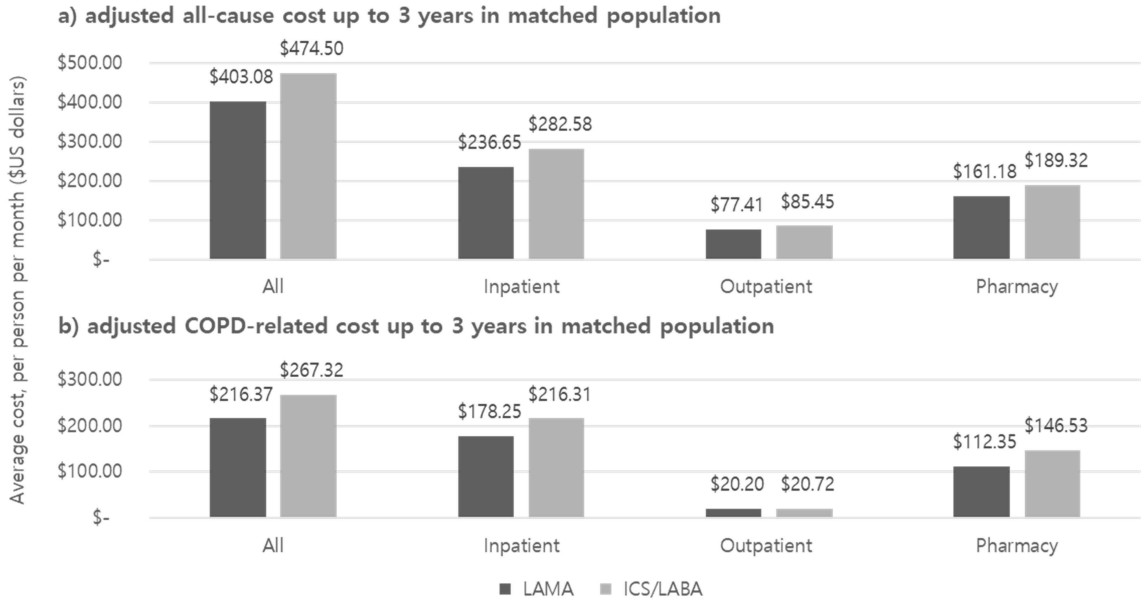

Figure 2 All-cause and COPD-related cost up to 3 years in the matched population. (**a**) Adjusted all-cause cost up to 3 years in the matched population. (**b**) Adjusted COPD-related cost up to 3 years in the matched population.

Table 2 Adjusted All-Cause Medical Cost* Up to 3 Years in the Matched Population

	All-Cause Cost			
	LAMA (n=2444)	**LABA/ICS (n=2444)**	**Cost Ratio (95% CI)**	***p*-value**
All cost per person per month (USD)				
Total	403.08	474.50	1.18 (1.10–1.26)	<0.0001
Inpatient	236.65	282.58	1.19 (1.04–1.37)	0.0103
Outpatient	77.41	85.45	1.10 (1.03–1.18)	0.0030
Pharmacy	161.18	189.32	1.18 (1.13–1.12)	<0.0001
Age groups				
55 to < 65	401.35	477.95	1.19 (1.06–1.34)	0.0040
65 to < 75	432.92	508.43	1.17 (0.07–1.29)	0.0006
75+	411.03	472.62	1.15 (1.02–1.29)	0.0019
Sex				
Male	418.02	488.68	1.17 (1.10–1.25)	<0.0001
Female	347.59	417.82	1.20 (1.03–1.41)	0.0208
History of asthma				
No	361.96	445.25	1.23 (1.12–1.35)	<0.0001
Yes	431.12	485.05	1.13 (1.03–1.22)	0.0062
History of COPD exacerbation				
None	360.86	431.35	1.20 (1.11–1.29)	<0.0001
One moderate	424.95	501.49	1.18 (1.04–1.35)	0.0132
≥2 moderate or ≥ 1 severe	372.66	388.25	1.04 (0.89–1.22)	0.6164

Note: *USD (US dollars); 1 USD = 1166.51 KRW (South Korean won).

Table 3 Adjusted COPD-Related Medical Cost* Up to 3 Years in the Matched Population

	COPD-Related Cost			
	LAMA (n=2444)	**LABA/ICS (n=2444)**	**Cost Ratio (95% CI)**	***p*-value**
All cost per person per month (USD)				
Total	216.37	267.32	1.24 (1.13–1.35)	<0.0001
Inpatient	178.25	216.31	1.21 1.03–1.43)	0.0212
Outpatient	20.20	20.72	1.04 (0.95–1.11)	0.5024
Pharmacy	112.35	146.53	1.30 (1.24–1.37)	<0.0001
Age groups				
55 to < 65	257.89	310.93	1.21 (1.03–1.41)	0.0182
65 to < 75	194.63	250.93	1.29 (1.14–1.45)	<0.0001
75+	244.63	293.68	1.20 (1.03–1.40)	0.0197
Sex				
Male	216.27	271.34	1.26 (1.15–1.37)	<0.0001
Female	190.70	221.48	1.16 (0.94–1.44)	0.1746
History of asthma				
No	177.48	234.25	1.32 (1.18–1.48)	<0.0001
Yes	248.24	284.99	1.15 (1.02–1.29)	0.0216
History of COPD exacerbation				
None	183.74	236.68	1.29 (1.17–1.42)	<0.0001
One moderate	193.50	226.32	1.17 (0.98–1.40)	0.0853
≥2 moderate or ≥ 1 severe	225.37	227.93	1.01 (0.82–1.26)	0.9183

Note: *USD (US dollars); 1 USD = 1166.51 KRW (South Korean won).

Table 4 All-Cause and COPD-Related Healthcare Utilization* Up to 3 Years

	All-Cause Healthcare Utilization			*p*-value	COPD-Related Healthcare Utilization			*p*-value
	All (n=4888)	LAMA (n=2444)	LABA/ICS (n=2444)		All (n=4888)	LAMA (n=2444)	LABA/ICS (n=2444)	
Inpatient or outpatient								
Total	2.77 ± 2.12	2.81 ± 2.30	2.73 ± 1.93	0.2875	0.63 ± 0.43	0.66 ± 0.39	0.60 ± 0.47	<0.001
Inpatient visits	0.07 ± 0.12	0.06 ± 0.10	0.07 ± 0.13	0.0062	0.03 ± 0.08	0.03 ± 0.07	0.03 ± 0.10	0.543
Outpatient visits	2.70 ± 2.11	2.75 ± 2.29	2.66 ± 1.92	0.4602	0.60 ± 0.42	0.63 ± 0.38	0.56 ± 0.46	<0.001
ER visits	0.04 ± 0.08	0.03 ± 0.08	0.04 ± 0.09	0.0002	0.01 ± 0.04	0.01 ± 0.03	0.01 ± 0.05	0.080
ICU visits	0.01 ± 0.02	0.00 ± 0.02	0.01 ± 0.02	0.4907	0.00 ± 0.02	0.00 ± 0.01	0.00 ± 0.02	0.363
Age groups								
55 to < 65	2.39 ± 1.82	2.43 ± 1.88	2.36 ± 1.76	0.7870	0.59 ± 0.42	0.63 ± 0.36	0.56 ± 0.46	<0.001
65 to < 75	2.96 ± 2.30	2.97± 2.48	2.95 ± 2.09	0.1585	0.63 ± 0.42	0.66 ± 0.43	0.60 ± 0.42	<0.001
75+	2.86 ± 2.09	2.94 ± 2.36	2.79 ± 1.78	0.5752	0.66 ± 0.47	0.69 ± 0.35	0.64 ± 0.55	<0.001
Sex								
Male	2.73 ± 2.09	2.75± 2.20	2.70 ± 1.97	0.4260	0.65 ± 0.44	0.67 ± 0.40	0.64 ±0.48	<0.001
Female	2.90 ± 2.23	2.98 ±2.60	2.82 ± 1.81	0.5438	0.56 ± 0.40	0.63 ± 0.35	0.64 ± 0.43	<0.001
History of asthma								
No	2.60 ± 2.00	2.58 ± 2.16	2.63 ± 1.83	0.0119	0.61 ± 0.40	0.64 ± 0.37	0.59 ± 0.43	<0.001
Yes	2.95 ± 2.23	3.05 ± 2.42	2.85 ± 2.02	0.2808	0.65 ± 0.47	0.69 ± 0.41	0.61 ± 0.52	<0.001
History of COPD exacerbation								
None	2.72 ± 2.12	2.76 ± 2.27	2.69 ± 1.97	0.7008	0.59 ± 0.38	0.62 ± 0.36	0.55 ±0.39	<0.001
1 moderate	2.82 ± 1.77	2.72 ± 1.74	2.92 ± 1.80	0.1502	0.74 ± 0.64	0.73 ± 0.36	0.75 ± 0.82	0.005
≥ 2 moderate or ≥ 1 severe	2.96 ± 2.31	3.08 ± 2.73	2.83 ± 1.79	0.5441	0.78± 0.49	0.80 ± 0.48	0.75 ± 0.50	0.022

Note: *Numbers of any medical visit per person per month (inpatient or outpatient).

inpatient hospitalization cost, which was lower in the LAMA treatment group. The cost ratio for all-cause and COPD-related medical costs with LABA/ICS treatment was 1.18 and 1.24, respectively ($p<0.0001$, Tables 2 and 3), compared to the LAMA treatment. This economic benefit was obtained by decreasing the risk of severe exacerbation, defined as worsening of symptoms requiring hospitalization.[1] As exacerbation is a significant contributor to the economic burden of COPD and most medical expenses of exacerbation arise from hospitalization,[23,24] this finding can be interpreted as LAMA can reduce severe exacerbations compared to LABA/ICS for treatment naïve COPD patients. However, the economic benefit of starting COPD treatment with LAMA disappeared in patients with a high risk of exacerbation (frequent exacerbator or severe exacerbator in the previous year).

Compared with the results regarding medical costs, the analyses of HCRU showed a different pattern. The all-cause HCRU rate was not significantly different between the LAMA and LABA/ICS treatment groups (2.81 vs 2.73 visits PPPM, respectively, $p=0.2875$). The COPD-related HCRU was higher in the LAMA group than the LABA/ICS group (0.60 vs 0.66 visits PPPM, respectively, $p<0.0001$). This finding was not consistent with that of a previous large, randomized study, which reported a similar rate of HCRU between the treatment groups.[14] However, the main difference in HCRU was due to the difference in outpatient visits in our study. This pattern was preserved in patients without a history of asthma (Tables S1 and S2). As frequent outpatient visits can reduce the risk of COPD exacerbation by earlier and more prompt adjustment of inhaler therapy,[25] this finding of more outpatient visits in the LAMA treatment group can be another explanation for decreased severe exacerbations and reduced medical costs described above.

Our real-world findings of reduced medical costs in the LAMA compared to the LABA/ICS treatment group provided more rationale for using LAMA bronchodilators over LABA/ICS combination as an initial treatment for the patients with low risk of exacerbation, showing the reduced medical cost directly and the increased adherence indirectly, in addition to the delayed escalation to triple therapy.[17] The findings of our study also provide another aspect, medical costs, to the recent changes in the GOLD 2023 update, in which the role of LABA/ICS in COPD is much diminished and the addition of ICS at treatment initiation is only suggested as a component of triple therapy for GOLD risk group E.[1] Furthermore, although other recent real-world comparative studies showed that LABA/ICS was as effective as LAMA or LAMA/

LABA combination in preventing exacerbation, in the same studies LABA/ICS was associated with pneumonia more than LAMA or LAMA/LABA.[16,26] Therefore, our study adds financial insight to the recent recommendation in which the use of ICS should be limited to patients with a high risk of exacerbation, preferably as a component of triple therapy.[1]

The recently released ATS guidelines for COPD recommend the LAMA/LABA combination for symptomatic patients over LAMA monotherapy. However, there was no consideration of medical cost in this recommendation.[27] Although several studies suggest superiority of LAMA/LABA compared to LAMA monotherapy in exacerbation prevention,[28–30] there are also reports showing adequacy of LAMA monotherapy regarding exacerbation.[31–34] As lower financial status and poverty are consistently associated with COPD,[1] initiation with LAMA can be an acceptable option in treating COPD patients with a low risk of exacerbation, especially in low-income countries.

The strength of our study was that we used propensity score matching to reduce the confounding effect. Also, the operational definition of COPD used in this study is well replicated[18–22] and validated in several previous studies,[12,35,36] suggesting that the results of our study reflected the actual real-world situation of COPD management well enough. Moreover, we enrolled treatment naïve patients, which contributes to the existing literature with a different type of study population in COPD assessing economic burden. However, this study has several limitations. This study was based on a health insurance claims database, so we could not assess lung function data, inhaler adherence or technique. Even though we used propensity score matching, some residual confounding from missing covariates, including baseline lung function measures and symptom scores, might influence the results. Also, although we showed that LAMA and LABA/ICS group did not differ in the history of exacerbations, other severity measures such as mMRC (Modified Medical Research Council) grade were not given. Furthermore, we did not investigate the influence of smoking on the inhaler medications such as ICS, which could have contributed to the utilization of medical resources in our patients. For inhaler adherence, we only enrolled patients with medical possession rate (MPR) over 80% in the first 12 months, and with such inclusion criterion we think that the issue of adherence was well controlled. Another limitation of our study is relatively long study period (January 1, 2002 through April 30, 2016), which could contain influences of advancements in COPD treatment and inhaler devices.

In summary, COPD patients initiating treatment with LAMA were associated with lower all-cause and COPD-related medical costs than those starting with LABA/ICS. There was no difference in all-cause HCRU but higher COPD-related HCRU in patients initiating treatment with LAMA, resulting from a significant difference in outpatient visits. LAMA monotherapy is a cost-efficient option for treatment initiation of symptomatic COPD.

Institutional Review Board Statement

This study protocol followed the Declaration of Helsinki and was approved by the ethical committee of Konkuk University Medical Center (Institutional Review Board No.: KUMC2020-06-013).

Abbreviations

COPD, chronic obstructive pulmonary disease; HCRU, healthcare resource utilization; ICS, inhaled corticosteroids; KRW, South Korean Won; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic receptor antagonists; PPPM, per-patient-per-month; PS, propensity score.

Data Sharing Statement

The National Health Insurance Service data is an open and public data to which any researcher can request access at https://nhiss.nhis.or.kr.

Informed Consent Statement

Informed consent was waived because only de-identified data were used for analytical purposes.

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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References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2023. Available from: www.goldcopd.org. Accessed June 27, 2024.
2. World Health Organization. Top 10 cause of death 2019 [Internet]. Geneva (CH): World Health Organization; 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed June 27, 2024.
3. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. 2017;390(10100):1151–1210.
4. Kim C, Kim Y, Yang DW, et al. Direct and indirect costs of chronic obstructive pulmonary disease in Korea. *Tuberc Respir Dis*. 2019;82(1):27–34. doi:10.4046/trd.2018.0035
5. Foo J, Landis SH, Maskell J, et al. Continuing to confront COPD international patient survey: economic impact of COPD in 12 countries. *PLoS One*. 2016;11(4):e0152618. doi:10.1371/journal.pone.0152618
6. Iheanacho I, Zhang S, King D, Rizzo M, Ismaila AS. Economic burden of chronic obstructive pulmonary disease (COPD): a systematic literature review. *Int J Chronic Obstr*. 2020;15:439–460. doi:10.2147/COPD.S234942
7. Calverley PMA. Guidance for the better care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2020;201(9):1022–1023. doi:10.1164/rccm.202002-0459ED
8. 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
9. Choi JY, Milne S, Yunus F, Rhee CK, Matsunaga K. Current chronic obstructive pulmonary disease treatment status in Asia: a position statement of the Asian pacific society of respirology. *Tuberc Respir Dis*. 2022;85(3):279–282. doi:10.4046/trd.2022.0020
10. Agusti A, Fabbri LM, Singh D, et al. Inhaled corticosteroids in COPD: friend or foe? *Eur Respir J*. 2018;52(6):1801219. doi:10.1183/13993003.01219-2018
11. Singh D. Blood eosinophil counts in chronic obstructive pulmonary disease: a biomarker of inhaled corticosteroid effects. *Tuberc Respir Dis*. 2020;83(3):185–194. doi:10.4046/trd.2020.0026
12. Jo YS, Yoo KH, Park YB, et al. Relationship between changes in inhalation treatment level and exacerbation of chronic obstructive pulmonary disease: nationwide the health insurance and assessment service database. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1367–1375. doi:10.2147/COPD.S248616
13. Zeng Y, Cai S, Chen Y, et al. Current status of the treatment of COPD in China: a multicenter prospective observational study. *Int J Chron Obstruct Pulmon Dis*. 2020;15:3227–3237. doi:10.2147/COPD.S274024

14. Bogart M, Germain G, Laliberté F, Lejeune D, Duh MS. Real-world treatment patterns and switching following moderate/severe chronic obstructive pulmonary disease exacerbation in patients with commercial or medicare insurance in the United States. *Int J Chron Obstruct Pulmon Dis*. 2023;18:1575–1586. doi:10.2147/COPD.S398816
15. Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*. 2008;177(1):19–26. doi:10.1164/rccm.200707-973OC
16. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Respir Med*. 2018;6(11):855–862. doi:10.1016/S2213-2600(18)30368-0
17. Lee YJ, Rhee CK, Hwang YI, et al. Escalation time to open triple combination therapy from the initiation of LAMA versus ICS/LABA in COPD management: findings from comparing the incidence of tiotropium and ICS/LABA in real-world use in South Korea (CITRUS) study. *J Pers Med*. 2021;11(12):1325. doi:10.3390/jpm11121325
18. Lee J, Lee JH, Kim JA, Rhee CK. Trend of cost and utilization of COPD medication in Korea. *Int J Chron Obstruct Pulmon Dis*. 2017;12:27–33. doi:10.2147/COPD.S121687
19. Kim J, Rhee CK, Yoo KH, et al. The health care burden of high grade chronic obstructive pulmonary disease in Korea: analysis of the Korean health insurance review and assessment service data. *Int J Chron Obstruct Pulmon Dis*. 2013;8:561–568. doi:10.2147/COPD.S48577
20. Kim C, Yoo KH, Rhee CK, et al. Health care use and economic burden of patients with diagnosed chronic obstructive pulmonary disease in Korea. *Int J Tuberc Lung Dis*. 2014;18(6):737–743. doi:10.5588/ijtld.13.0634
21. Kim J, Kim K, Kim Y, et al. The association between inhaled long-acting bronchodilators and less in-hospital care in newly-diagnosed COPD patients. *Respir Med*. 2014;108(1):153–161. doi:10.1016/j.rmed.2013.08.003
22. Lim JU, Kim K, Kim SH, et al. Comparative study on medical utilization and costs of chronic obstructive pulmonary disease with good lung function. *Int J Chronic Obstr*. 2017;12:2711–2721. doi:10.2147/COPD.S143244
23. Yu AP, Yang H, Wu EQ, Setyawan J, Mocarski M, Blum S. Incremental third-party costs associated with COPD exacerbations: a retrospective claims analysis. *J Med Econ*. 2011;14(3):315–323. doi:10.3111/13696998.2011.576295
24. Pasquale MK, Sun SX, Song F, Hartnett HJ, Stemkowski SA. Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis*. 2012;7:757–764. doi:10.2147/COPD.S36997
25. Park HJ, Byun MK, Kim T, et al. Frequent outpatient visits prevent exacerbation of chronic obstructive pulmonary disease. *Sci Rep*. 2020;10(1):6049. doi:10.1038/s41598-020-63064-x
26. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness and safety of LABA-LAMA vs LABA-ICS treatment of COPD in real-world clinical practice. *Chest*. 2019;155(6):1158–1165. doi:10.1016/j.chest.2019.03.005
27. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. an official American thoracic society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;201(9):e56–e69. doi:10.1164/rccm.202003-0625ST
28. Mammen MJ, Pai V, Aaron SD, Nici L, Alhazzani W, Alexander PE. Dual LABA/LAMA Therapy versus LABA or LAMA monotherapy for chronic obstructive pulmonary disease. A systematic review and meta-analysis in support of the American thoracic society clinical practice guideline. *Ann Am Thorac Soc*. 2020;17(9):1133–1143. doi:10.1513/AnnalsATS.201912-915OC
29. Chen CY, Chen WC, Huang CH, et al. LABA/LAMA fixed-dose combinations *versus* LAMA monotherapy in the prevention of COPD exacerbations: a systematic review and meta-analysis. *Ther Adv Respir Dis*. 2020;14:1753466620937194. doi:10.1177/1753466620937194
30. Wedzicha JA, Buhl R, Singh D, et al. Tiotropium/olodaterol decreases exacerbation rates compared with tiotropium in a range of patients with COPD: pooled Analysis of the TONADO®/DYNAGITO® Trials. *Adv Ther*. 2020;37(10):4266–4279. doi:10.1007/s12325-020-01438-3
31. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6(5):337–344. doi:10.1016/S2213-2600(18)30102-4
32. Rogliani P, Calzetta L, Braido F, et al. LABA/LAMA fixed-dose combinations in patients with COPD: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3115–3130. doi:10.2147/COPD.S170606
33. Barrecheguren M, Monteagudo M, Miravitlles M. Population-based study of LAMA monotherapy effectiveness compared with LABA/LAMA as initial treatment for COPD in primary care. *NPJ Prim Care Respir Med*. 2018;28(1):36. doi:10.1038/s41533-018-0102-x
34. Lee SH, Rhee CK, Yoo K, et al. Direct switch from tiotropium to indacaterol/glycopyrronium in chronic obstructive pulmonary disease patients in Korea. *Tuberc Respir Dis*. 2021;84(2):96–104. doi:10.4046/trd.2020.0109
35. Seon Cheol Park DWK, Eun CP, Cheung SS, Chin KR, Young AK, Young SK. Mortality of patients with chronic obstructive pulmonary disease: a nationwide populationbased cohort study. *Korean J Intern Med*. 2019;34(6):1272–1278. doi:10.3904/kjim.2017.428
36. Chung SM, Lee SY. Evaluation of appropriate management of chronic obstructive pulmonary disease in Korea: based on health insurance review and assessment service (HIRA) claims. *Tuberc Respir Dis*. 2017;80(3):241–246. doi:10.4046/trd.2017.80.3.241