Original Article

CMJ

www.cmj.ac.kr

When is LABA/LAMA Better than LAMA in GOLD Group B or D Patients for Reducing Acute Exacerbations of COPD?

Hong-Joon Shin[1], Yu-Il Kim[1], Youlim Kim[2], Chang Youl Lee[3], Seung Won Ra[4], Ji-Yong Moon[5], Ki-Suck Jung[6], Kwang Ha Yoo[2], Kyeong-Cheol Shin[7], and Sung-Chul Lim[1,*]; KOCOSS Cohort Study Group

[1]Division of Pulmonary Medicine, Department of Internal Medicine, Chonnam National University Hospital, Gwangju, [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, [3]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, [4]Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, [5]Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, [6]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, [7]Division of Pulmonology and Allergy, Regional Center for Respiratory Disease, Yeungnam University Medical Center, Daegu, Korea

Long-acting β_2-agonist (LABA)/long-acting muscarinic-antagonist (LAMA) dual therapy has been found to be more effective than LAMA monotherapy in the treatment of chronic obstructive pulmonary disease (COPD). However, among patients with group B or D COPD, the characteristics of patients for whom LABA/LAMA dual therapy is superior to LAMA monotherapy in minimizing acute exacerbations remain unknown. With data from a prospective COPD cohort, subgroup analyses were conducted to determine whether LABA/LAMA dual therapy was superior to LAMA monotherapy in reducing the rate of acute exacerbations in group B and D COPD patients. Group B and D COPD patients taking LAMA or LABA/LAMA were enrolled according to the 2022 Global initiative for Chronic Obstructive Pulmonary Disease guidelines. A total of 737 patients were included in this study: 600 with group B COPD and 137 with group D COPD. Compared with patients taking LAMA monotherapy, those taking LABA/LAMA had a significantly lower incidence of acute exacerbations over 1 year. In the subgroup of patients ≥70 years old, there was a significantly lower risk of severe COPD exacerbations among group B patients taking LABA/LAMA than among those taking LAMA monotherapy (odds ratio [OR], 0.258; 95% confidence interval [CI], 0.095–0.703). In contrast, in the subgroup of group D patients with COPD Assessment Test scores ≥25, compared with LAMA monotherapy, LABA/LAMA treatment was associated with lower risk of severe COPD exacerbations (OR, 0.115; 95% CI, 0.018-0.749). The combination of LABA and LAMA was found to be superior to LAMA monotherapy, especially for treating older adults with group B COPD, as well as for group D patients with severe symptoms.

Key Words: *Chronic Obstructive Pulmonary Disease; Bronchodilator Agents; Combined Modality Therapy*

Article History:
Received August 18, 2023
Revised August 28, 2023
Accepted September 4, 2023

Corresponding Author:
Sung-Chul Lim
Division of Pulmonary Medicine,
Department of Internal Medicine,
Chonnam National University Hospital,
42 Jaebong-ro, Dong-gu,
Gwangju 61469, Korea
Tel: +82-62-220-6570
Fax: +82-62-225-8578
E-mail: lscmd@jnu.ac.kr

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory airway disease that is primarily caused by smoking. COPD has a high prevalence worldwide, and it is associated with high mortality and morbidity rates.[1-4] To improve symptoms and prevent deterioration, proper management of COPD after diagnosis is essential. Recently published Global Initiative for Chronic Obstruc-

https://doi.org/10.4068/cmj.2023.59.3.180

tive Lung Disease (GOLD) guidelines recommend long-acting β_2-agonist (LABA)/long-acting muscarinic-antagonist (LAMA) dual therapy as an initial treatment option for patients in group B. Further, groups C and D are grouped into group E, and LABA/LAMA dual therapy is recommended as an initial treatment option for this latter group.[5]

Until the GOLD 2023 recommendation, long-acting bronchodilator (LABD) monotherapy had been recommended for group B, and LAMA monotherapy or LABA/LAMA dual therapy had been recommended for group D.[6] Additionally, when the blood eosinophil count exceeded 300/mm^3, inhaled corticosteroid (ICS)/LABA was recommended as an initial trial.[6] Compared with LABD monotherapy, LABA/LAMA dual therapy has been associated with better lung function, symptoms, and quality of life, with no differences in side effects.[7-10] However, LABD monotherapy was recommended over LABA/LAMA dual therapy because the superiority of dual therapy in reducing acute exacerbations had not been clearly demonstrated.[9,10] The 2023 GOLD guidelines recognize the superiority of LABA/LAMA dual therapy and recommend dual therapy as an initial treatment option rather than LABD monotherapy.[5] However, among GOLD group B and D COPD patients, it remains unknown which subgroups of patients would be the most likely to benefit more from LABA/LAMA dual therapy over LABD monotherapy for reducing acute exacerbations.

Using data from the Korea COPD Subgroup Study (KOCOSS) cohort, we conducted subgroup analyses to determine whether LABA/LAMA dual therapy is superior to LAMA monotherapy in reducing the frequency of acute group B and D COPD exacerbations.

MATERIALS AND METHODS

1. Study design and patients

The KOCOSS cohort study is a longitudinal, prospective, non-interventional, and observational study of South Korean patients with COPD (NCT02800499). The cohort data were collected and analyzed between January 2012 and December 2018. The inclusion criteria were age >40 years; cough, sputum, dyspnea; and post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity <0.7. The exclusion criteria included history of asthma, inability to complete pulmonary function tests, history of myocardial infarction or cerebrovascular events within 3 months before enrollment, current pregnancy at the time of enrollment, history of rheumatoid arthritis, history of or current malignancy (metastatic cancer, leukemia, lymphoma), ongoing irritable bowel syndrome, and recent history of systemic steroid use for a condition other than COPD for more than 8 weeks. Group B and D COPD patients taking LAMA or LABA/LAMA were enrolled according to the 2022 GOLD guidelines.[5] We excluded patients who were taking LABA, ICS, ICS/LABA, or roflumilast.

According to the Declaration of Helsinki, the protocol was approved by the institutional review boards at each participating center (CNUH-2012-070). Informed consent was obtained from all patients before their participation in the study.

Baseline characteristics captured for study purposes were as follows: age, sex, body mass index (BMI), smoking duration, underlying disease (hypertension, diabetes mellitus, heart failure, ischemic heart disease, bronchiectasis, or previous tuberculosis), previous medical history (LAMA, LABA, LAMA/LABA, ICS/LABA, and roflumilast), pulmonary function test results, laboratory findings (white blood cell count, hemoglobin concentration, platelet count, neutrophil differential count, lymphocyte differential count, eosinophil differential count, total albumin level, and creatinine level), COPD Assessment Test (CAT) scores, modified Medical Research Council (mMRC) dyspnea scale ratings, scores on the SGRQ-C (COPD-specific version of the St. George's Respiratory Questionnaire), 6-minute walk distance, and COPD exacerbations in the previous 12 months.

2. Definitions

An acute exacerbation of COPD was defined as a worsening of any respiratory symptom, including increased sputum volume, purulence, or increased dyspnea.[6] Group B and group D COPD patients were defined according to the GOLD 2022 guidelines[6]: group B, symptomatic (mMRC >2 or CAT >10) and low risk of exacerbation (0 or 1 moderate or severe exacerbation without hospital admission in the previous year); group D, symptomatic (mMRC >2 or CAT >10) and high risk of exacerbation (>2 exacerbations or >1 exacerbation in the previous year leading to hospital admission).

A moderate exacerbation was defined as the need for treatment with antibiotics or oral corticosteroids.[6] COPD exacerbations that required hospitalization or attendance at the emergency room were classified as severe exacerbations.[6]

3. Statistical analyses

In all cases, the data are expressed as mean (standard deviation) or a number (percentage). Using the chi-square test (for categorical variables) or Student's t test (for continuous variables), demographic and clinical variables were compared between the LAMA and LABA/LAMA groups. Univariate logistic regression analysis was conducted to identify factors associated with severe exacerbations within 1 year. Multivariate logistic regression analysis was conducted using a backward method and variables with p-values <0.1 from the univariate analysis. Subgroup analyses were conducted using the data from both group B and D patients to determine the differences between LABA/LAMA dual therapy and LAMA monotherapy in terms of the risk of acute COPD exacerbations. The univariate analysis considered subgroups according to the following criteria and cut-offs: age, 70 years; FEV1 (%) predicted, 50%; CAT score, 25; mMRC, 3; BMI, <18.5, 18.5-25, and ≥ 25. All statistical analyses were conducted using SPSS Statistics for Windows, version 23.0 (IBM Corp. Armonk, NY, USA). p-values <0.05 were considered statistically significant.

RESULTS

We screened 2,694 COPD patients during the cohort period (Fig. 1). Of these, a total of 1,258 patients were excluded because they were taking the following drugs: ICS/LABA (n=1,043), roflumilast (n=102), and LABA (n=87), or ICS (n=26). An additional 353 patients were excluded because it was impossible to determine the drug they were taking at the time of enrollment. The remaining 1,083 COPD patients were taking LAMA or LABA/LAMA. Among these, 348 belonged to groups A or C. Finally, a total of 737 COPD patients were included in this study: group B (n=600) and group D (n=137).

Table 1 shows the baseline characteristics of the LAMA and LABA/LAMA groups. The mean ages were 69.0 years in the LAMA group and 69.9 years in the LABA/LAMA group. Men predominated in both groups, representing 92.0% of the LAMA group and 93.1% of the LABA/LAMA group. There were no significant intergroup differences in underlying diseases. Patients in the LAMA group frequently used LAMA or LABA/ICS before cohort registration, and patients in the LABA/LAMA group more frequently used LABA/LAMA before cohort registration. There was no significant intergroup difference in mean post-bronchodilator FEV_1 (%). Baseline laboratory findings were also not significantly different between the groups. In terms of respiratory symptoms, there were no significant intergroup differences in mean CAT score, mean mMRC score, or mean SGRQ-C score.

Overall, the incidence of acute COPD exacerbations was significantly lower among patients taking LABA/LAMA than among patients taking LAMA only (Table 2 and Fig. 2). However, there was no significant difference between the group B patients taking LABA/LAMA and those taking LAMA monotherapy in terms of the incidence of acute exacerbations of COPD. Among group D patients, the incidence of moderate exacerbations was significantly lower among those taking LABA/LAMA compared with those taking LAMA monotherapy (8.3% vs. 23.4%). However, in terms of severe exacerbations, there was a non-significant trend toward the patients taking LABA/LAMA dual therapy having a lower incidence than those taking LAMA monotherapy (11.7% vs. 26.0%; p=0.051).

Multivariate logistic regression analysis revealed that, among group B patients, a lower baseline post-bronchodilator FEV_1 (%) and a lower baseline serum albumin level were associated with a higher risk of a severe acute COPD exacerbation over 1 year (Table 3). However, LABA/LAMA dual therapy was not associated with severe exacerbations over 1 year in the group B patients. In contrast, the multivariate logistic regression analysis showed that, among patients in group D, a higher baseline CAT score was associated with a greater risk of a severe acute COPD exacerbation over 1 year (Table 4). Additionally, LABA/LAMA dual therapy decreased the risk of severe exacerbations over 1 year in the group D patients (odds ratio [OR], 0.248; 95% confidence interval [CI], 0.087-0.707; p=0.009).

Compared with LAMA treatment, LABA/LAMA treatment in the group B subgroup of patients ≥70 years old was significantly associated with a reduced risk of severe COPD exacerbations over 1 year (OR, 0.258; 95% CI, 0.095-0.703) (Fig. 3). In contrast, among group D patients, LABA/LAMA treatment was significantly associated with a lower risk of severe COPD exacerbations in the subgroup of patients with CAT scores ≥25 (OR, 0.115; 95% CI, 0.018-0.749) (Fig. 3).

DISCUSSION

We investigated the efficacy of LABA/LAMA dual therapy for preventing severe exacerbations of GOLD group B and D patients in this large prospective cohort study. Among group B patients, LABA/LAMA dual therapy had no significant effect on the risk of severe exacerbations over 1 year of follow-up. However, among patients ≥70 years of age, compared with LAMA monotherapy, LABA/LAMA dual therapy was associated with a significantly lower risk of severe exacerbations. Moreover, among patients in group

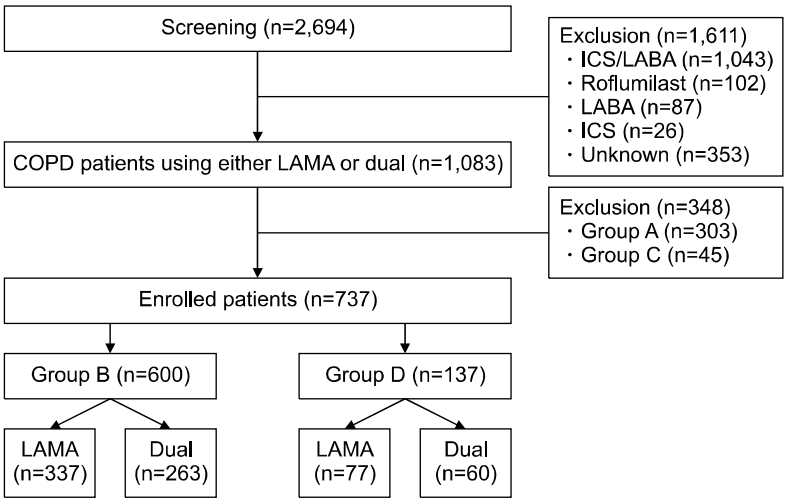

FIG. 1. Study enrollment flowchart. COPD: chronic obstructive pulmonary disease, ICS: inhaled corticosteroid, LABA: long-acting β_2 agonist, LAMA: long-acting muscarinic antagonist.

Table 1. Comparison of clinical characteristics between patients who received LAMA monotherapy and those who received LABA/LAMA dual therapy

Variables	LAMA (n=414)	LABA/LAMA (n=323)	p-value
Age, years, mean (SD)	69.0 (8.1)	69.9 (8.1)	0.133
Male, n (%)	379 (92.0)	297 (93.1)	0.672
Body mass index, kg/m^2, mean (SD)	23.3 (3.3)	22.9 (3.2)	0.201
Smoking pack-years, mean (SD)	41.0 (23.3)	42.4 (26.6)	0.484
Hypertension, n (%)	167 (40.3)	132 (40.9)	0.940
Diabetes, n (%)	77 (18.6)	60 (18.6)	>0.999
Heart failure, n (%)	17 (4.1)	10 (3.1)	0.556
Ischemic heart disease, n (%)	22 (5.3)	15 (4.6)	0.736
Bronchiectasis, n (%)	27 (6.5)	33 (10.2)	0.078
Previous tuberculosis, n (%)	105 (25.4)	85 (26.3)	0.799
Previous treatment			
LAMA, n (%)	266 (64.3)	23 (7.1)	<0.000
LABA, n (%)	3 (0.7)	2 (0.6)	>0.999
LABA/LAMA, n (%)	15 (3.6)	167 (21.7)	<0.000
LABA/ICS, n (%)	53 (12.8)	14 (4.3)	<0.000
Roflumilast, n (%)	4 (1.0)	10 (3.1)	0.054
Group B, n (%)	337 (81.4)	263 (81.4)	>0.999
Group D, n (%)	77 (18.6)	60 (18.6)	>0.999
Post-bronchodilator FEV_1, L, mean (SD)	1.74 (0.53)	1.84 (3.14)	0.529
Post-bronchodilator % predicted FEV_1, mean (SD)	64.0 (15.7)	61.7 (18.2)	0.087
Post-bronchodilator FVC, L, mean (SD)	3.25 (0.78)	3.58 (4.78)	0.177
Post-bronchodilator % predicted FVC, mean (SD)	84.5 (16.1)	84.9 (19.2)	0.746
Post-bronchodilator FEV_1/FVC	53.4 (11.0)	50.7 (12.1)	0.002
White blood cells, /mm^3, mean (SD)	7,505 (2,617)	7,471 (2,313)	0.869
Hemoglobin, g/dL, mean (SD)	14.1 (1.4)	14.1 (2.2)	0.914
Platelet, ×1000/mm^3, mean (SD)	241.3 (75.7)	252.6 (80.7)	0.079
Neutrophil, %, mean (SD)	57.9 (11.4)	58.5 (11.5)	0.549
Lymphocyte, %, mean (SD)	29.4 (9.3)	28.9 (9.7)	0.506
Eosinophil, %, mean (SD)	3.5 (3.8)	3.3 (3.2)	0.656
Albumin, g/dL, mean (SD)	4.3 (0.3)	4.3 (0.5)	0.297
Creatinine, mg/dL, mean (SD)	0.99 (0.26)	1.02 (0.66)	0.319
CAT score, mean (SD)	16.3 (5.8)	16.7 (6.5)	0.490
mMRC score, mean (SD)	1.4 (0.8)	1.5 (0.8)	0.218
SGRQ-C score, mean (SD)	2.27 (0.74)	2.31 (0.71)	0.490
6-minute walk distance, m, mean (SD)	377.0 (115.0)	386.1 (106.3)	0.372
Previous exacerbation, n (%)	80 (19.3)	60 (18.6)	0.850
Previous moderate exacerbation, n (%)	45 (10.9)	39 (12.1)	0.641
Previous severe exacerbation, n (%)	77 (18.6)	59 (18.3)	0.924

Data are presented as number (%) or mean (SD). LAMA: long-acting muscarinic antagonist, LABA: long-acting β_2 agonist, ICS: inhaled corticosteroid, FEV_1: forced expiratory volume in 1 second, L: liters, FVC: forced vital capacity, CAT: COPD Assessment Test, mMRC: modified Medical Research Council, SGRQ-C: COPD-specific version of St. George's Respiratory Questionnaire.

D, compared with LAMA alone, LABA/LAMA dual therapy was associated with a lower risk of severe exacerbations over 1 year. Also, compared with LAMA monotherapy, LABA/LAMA dual therapy was associated with a significantly lower risk of severe COPD exacerbations over 1 year among group D patients with severe symptoms (CAT ≥25).

Compared with LABA monotherapy, LABA/LAMA dual therapy has been associated with superior improvements in lung function, symptoms, and quality of life in patients with COPD.[7-10] Oba et al.[9] demonstrated that LABA/LAMA dual therapy minimizes COPD exacerbations in high-risk individuals more than ICS/LABA dual therapy or LABA monotherapy; in their meta-analsysis, LAMA monotherapy and LABA/LAMA dual therapy were not significantly different in terms of associated exacerbation rates. In the present study, compared with LAMA monotherapy, LABA/LAMA dual therapy more effectively minimized the incidence of COPD exacerbations. There was, however, no difference between the exacerbation rates associated with LABA/LAMA dual therapy vs. LAMA monotherapy among group B patients. Compared with the LAMA monotherapy, LABA/LAMA dual therapy was associated with a significantly lower rate of moderate exacerbations among group

D patients. Combining LABA and LAMA is expected to have synergistic effects.[11-13] Therefore, it is essential to select patients for whom LABA/LAMA dual therapy is expected to be effective in acute exacerbations. To date, it has not been clearly elucidated which specific group B and D patients should receive LABA/LAMA dual therapy.

The 2022 GOLD guidelines recommend LABD monotherapy for group B patients with a relatively low risk of exacerbations.[6] Even in group B patients, poor outcomes, such as acute deterioration and death, occur frequently.[14-16] Factors associated with COPD exacerbations among group B patients include previous moderate exacerbations, age, and BMI.[15,16] It may be necessary for group B patients with a high risk of experiencing acute exacerbations to receive more intensive treatment in view of the morbidity and mortality associated with acute exacerbations. The meta-analysis conducted by Oba et al.,[9] demonstrated LABA/LAMA dual therapy to be more effective than LABA alone in reducing exacerbations in the low-risk group. Despite this, there was no difference between LABA/LAMA treatment and LAMA monotherapy in terms of their associated acute exacerbation rates, even among low-risk patients.[9] Similarly, in the EMAX ("early maximisation of bronchodilation for improving COPD stability") trial, there was no difference in the associated exacerbation rate between LABA/LAMA dual therapy and LAMA monotherapy over 6 months.[17] In the present study, over 1 year, compared with LAMA monotherapy, LABA/LAMA dual therapy was associated with a lower rate of COPD exacerbations among group B patients ≥70 years old. The 2023 GOLD guidelines recommend LABA/LAMA dual therapy initially for group B patients; however, it is necessary to clarify the subsets of patients for whom LABA/LAMA dual therapy is more likely superior to LABD monotherapy in minimizing acute exacerbations. A prospective study is, therefore, required to investigate the active treatment of older group B patients prescribed the LABA/LAMA combination regimen.

According to the 2022 GOLD guidelines, either LAMA monotherapy or LABA/LAMA dual therapy can be used as initial therapy. The LABA/LAMA combination is recommended with CAT scores ≥20. The large-scale randomized SPARK and DYNAGITO trials found no significant differ-

TABLE 2. Comparisons of 1-year acute exacerbation rates between LAMA monotherapy and LABA/LAMA dual therapy groups

	LAMA	LABA/LAMA	p-value
All patients (n=737)			
All exacerbations	60 (14.5)	30 (9.3)	0.041
Moderate exacerbations	49 (11.8)	23 (7.1)	0.034
Severe exacerbations	57 (13.8)	28 (8.7)	0.036
Group B (n=600)			
All exacerbations	40 (11.9)	23 (8.7)	0.230
Moderate exacerbations	31 (9.2)	18 (6.8)	0.368
Severe exacerbations	37 (11.0)	21 (8.0)	0.265
Group D (n=137)			
All exacerbations	20 (26.0)	7 (11.7)	0.051
Moderate exacerbations	18 (23.4)	5 (8.3)	0.022
Severe exacerbations	20 (26.0)	7 (11.7)	0.051

LABA: long-acting β_2 agonist, LAMA: long-acting muscarinic antagonist.

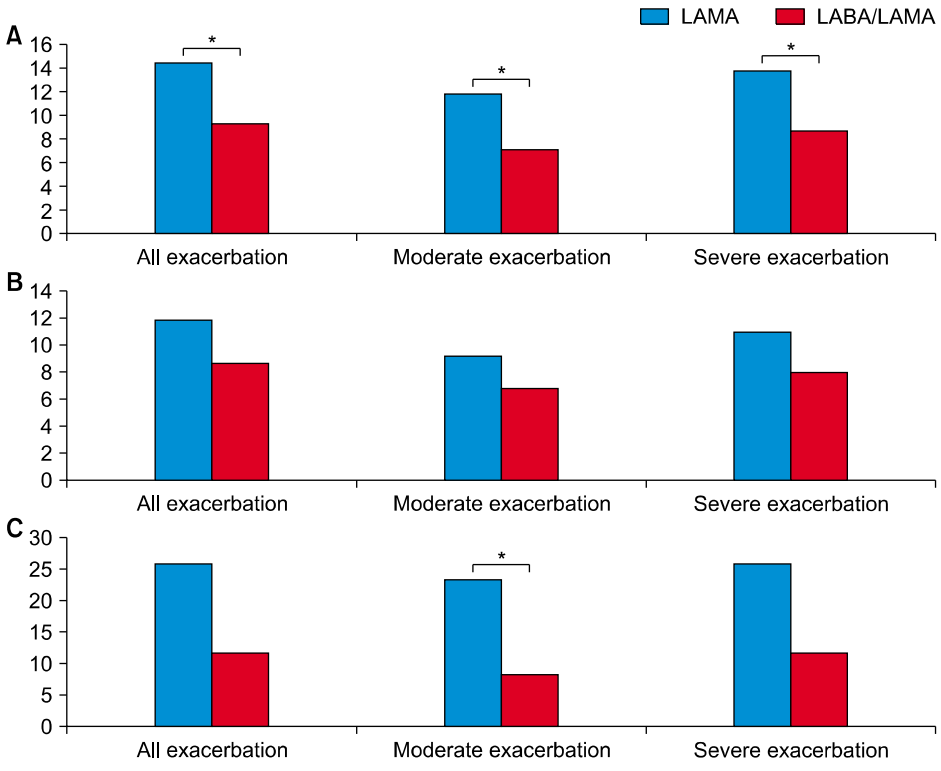

FIG. 2. Comparisons of associated 1-year acute exacerbation rates between LAMA monotherapy and LABA/LAMA dual therapy. LAMA: long-acting muscarinic antagonist, LABA: long-acting β_2 agonist. *p-value < 0.05.

Table 3. Factors associated with severe acute exacerbations over 1 year of follow-up (group B)

Variable	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
	Univariate analysis			Multivariate analysis		
Age	0.978	0.967-1.033	>0.999			
Male sex	1.519	0.455-5.066	0.497			
Body mass index	0.963	0.886-1.047	0.380			
Smoking, pack–years	1.005	0.994-1.016	0.372			
Hypertension	1.275	0.740-2.196	0.381			
Diabetes	0.571	0.252-1.295	0.180			
Ischemic heart disease	1.872	0.690-5.079	0.218			
Heart failure	0.415	0.055-3.134	0.394			
Bronchiectasis	0.537	0.162-1.778	0.309			
Old tuberculosis	1.041	0.561-1.934	0.898			
FEV_1, % predicted	0.980	0.965-0.996	0.015	0.975	0.957-0.994	0.008
FVC, % predicted	0.992	0.978-1.007	0.307			
CAT score	1.005	0.958-1.053	0.851			
mMRC score	1.321	0.965-1.807	0.082			
6–minute walk distance	0.999	0.996-1.002	0.443			
SGRQ-C score	0.985	0.673-1.442	0.939			
Baseline WBC	1.001	0.878-1.140	0.989			
Baseline eosinophil	1.014	0.928-1.108	0.757			
Baseline platelet count	0.999	0.996-1.003	0.775			
Baseline albumin	0.455	0.215-0.965	0.040	0.454	0.207-0.994	0.048
LABA/LAMA treatment	0.704	0.401-1.234	0.220			

FEV_1: forced expiratory volume in 1 second, L: liters, FVC: forced vital capacity, CAT: COPD assessment test, mMRC: modified Medical Research Council, SGRQ-C: COPD-specific version of St. George's Respiratory Questionnaire, WBC: white blood cell, LABA: long-acting β_2 agonist, LAMA: long-acting muscarinic antagonist.

Table 4. Factors associated with severe acute exacerbations over 1 year of follow-up (group D)

Variable	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
	Univariate analysis			Multivariate analysis		
Age	0.980	0.928-1.035	0.477			
Male	2.600	0.318-21.241	0.373			
Body mass index	0.314	0.940-1.214	0.314			
Smoking, pack–years	0.993	0.975-1.012	0.475			
Hypertension	1.157	0.490-2.733	0.739			
Diabetes	1.023	0.346-3.027	0.968			
Ischemic heart disease	0.000	0.000-0.000	0.999			
Heart failure	1.372	0.137-13.729	0.788			
Bronchiectasis	1.680	0.308-9.167	0.549			
Old tuberculosis	1.073	0.426-2.705	0.881			
FEV_1, % predicted	0.999	0.973-1.026	0.960			
FVC, % predicted	0.997	0.971-1.023	0.815			
CAT score	1.085	1.021-1.154	0.008	1.103	1.033-1.178	0.004
mMRC score	1.283	0.763-2.157	0.347			
6–minute walk distance	1.000	0.996-1.004	0.974			
SGRQ-C score	1.286	0.737-2.244	0.376			
Baseline WBC	1.028	0.910-1.161	0.659			
Baseline eosinophil	0.978	0.884-1.081	0.660			
Baseline platelet count	0.998	0.992-1.003	0.430			
Baseline albumin	0.842	0.310-2.289	0.736			
LABA/LAMA treatment	0.376	0.147-0.962	0.041	0.248	0.087-0.707	0.009

FEV_1: forced expiratory volume in 1 second, L: liters, FVC: forced vital capacity, CAT: COPD assessment test, mMRC: modified Medical Research Council, SGRQ-C: COPD-specific version of St. George's Respiratory Questionnaire, WBC: white blood cell, LABA: long-acting β_2 agonist, LAMA: long-acting muscarinic antagonist.

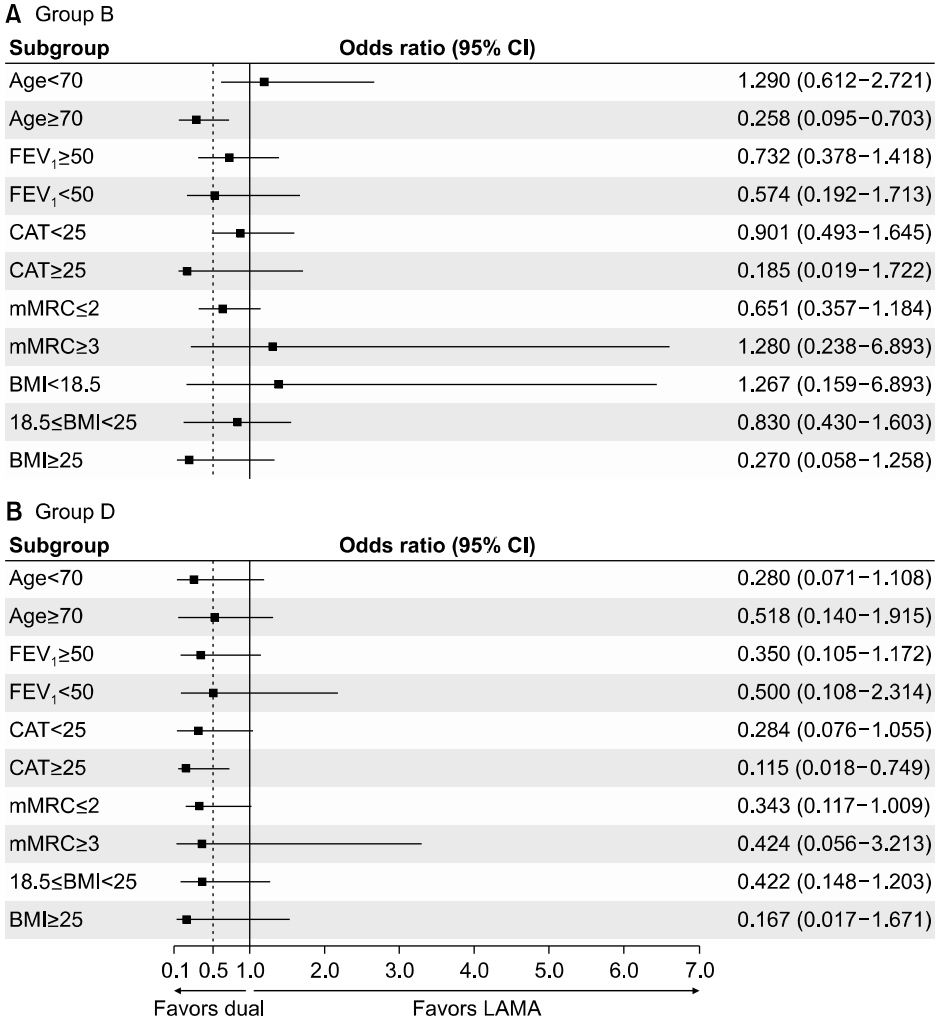

FIG. 3. Subgroup analysis of groups B and D. FEV_1: forced expiratory volume in 1 second, CAT: COPD Assessment Test, mMRC: modified Medical Research Council, BMI: body mass index, LAMA: long-acting muscarinic antagonist.

ences between LAMA and LABA/LAMA in terms of COPD exacerbation rates.[18,19] Moreover, in the DYNAGITO trial, the group receiving ICS/LABA at baseline was more likely to benefit from LABA/LAMA dual therapy than from LAMA monotherapy.[19] The CAT score, however, was not included in the analysis. The LABA/LAMA combination is recommended if COPD symptoms are severe (CAT ≥20), but there is no clear basis for the CAT ≥20 standard. COPD patients with a CAT score ≥10 are at a higher risk of exacerbations than patients with a CAT score <10. In a multicenter prospective study, CAT scores >13.5 (area under the curve, 0.864; p=0.001) significantly predicted future acute exacerbations of COPD.[20] In the present study, group D patients with CAT scores ≥25 had lower risk of acute exacerbations in association with the LABA/LAMA dual therapy than with LAMA monotherapy. Therefore, group D patients with CAT scores ≥25 should receive active treatment with LAMA/LABA rather than LAMA monotherapy, and a prospective study is needed to determine the effectiveness of this approach. LABA/LAMA dual therapy has been shown to reduce moderate/severe exacerbations pooled data from the TONADO and DYNAGITO trials,[21] and to reduce exacerbations leading to hospitalization[22]; therefore, it is expected that LABA/LAMA dual therapy will mitigate deterioration in group D patients. LABA/LAMA dual therapy is, thus, considered a valid initial treatment option for group E patients according to the 2023 GOLD guidelines.[5]

The study had several limitations. First, because the patients enrolled in this study were not treatment-naive, we advise caution when making treatment recommendations based on the results of this study. Second, even though this was a prospective cohort study, it was not a randomized controlled study; therefore, variables not directly addressed by this study may have affected the outcomes. However, since this study used real-world data, it has the advantage of comparing LABA/LAMA dual therapy and LAMA monotherapy in COPD patients treated in clinical practice. Third, since this study only examined exacerbations of COPD over 1 year, further research and randomized clinical trials are needed to compare LABA/LAMA dual therapy with LAMA monotherapy over longer follow-up periods.

In conclusion, LABA/LAMA dual therapy reduces COPD exacerbations more effectively than LAMA monotherapy. To reduce the frequency of acute exacerbations in older GOLD group B patients and group D patients with severe

symptoms, it is reasonable to select LABA/LAMA dual therapy over LAMA monotherapy.

ACKNOWLEDGEMENT

This work was supported by the Research Program funded Korea National Institute of Health (Fund CODE 2016 ER670100, 2016ER670101, 2016ER670102, 2018ER67100, 2018ER67101, 2018ER67102, 2021ER120500, 2021ER12 0501 and 2021ER120502).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008;5:549-55.
2. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27:397-412.
3. Park SC, Kim DW, Park EC, Shin CS, Rhee CK, Kang YA, et al. Mortality of patients with chronic obstructive pulmonary disease: a nationwide populationbased cohort study. Korean J Intern Med 2019;34:1272-8.
4. van Manen JG, Bindels PJ, IJzermans CJ, van der Zee JS, Bottema BJ, Schadé E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. J Clin Epidemiol 2001;54:287-93.
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2023 report [Internet]. Fontana: GOLD; 2023 [cited 2023 Mar 15]. Available from: https://goldcopd.org/2023-gold-report-2/
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2022 report [Internet]. Fontana: GOLD; 2022 [cited 2022 Nov 7]. Available from: https://goldcopd.org/2022-gold-reports/
7. Chen CY, Chen WC, Huang CH, Hsiang YP, Sheu CC, Chen YC, 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;14:1753466 620937194.
8. 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: 1133-43.
9. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. Cochrane Database Syst Rev 2018;12: CD012620.
10. Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Bader G, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2017;12:907-22.
11. Calzetta L, Matera MG, Cazzola M. Pharmacological interaction between LABAs and LAMAs in the airways: optimizing synergy. Eur J Pharmacol 2015;761:168-73.
12. Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LAMA/ LABA for the treatment of stable COPD. Chest 2016;149:1181-96.
13. Calzetta L, Matera MG, Cazzola M, Rogliani P. Optimizing the development strategy of combination therapy in respiratory medicine: from isolated airways to patients. Adv Ther 2019;36:3291-8.
14. Kobayashi S, Hanagama M, Ishida M, Sato H, Ono M, Yamanda S, et al. Clinical characteristics and outcomes in Japanese patients with COPD according to the 2017 GOLD classification: the Ishinomaki COPD Network Registry. Int J Chron Obstruct Pulmon Dis 2018;13:3947-55.
15. Løkke A, Hilberg O, Lange P, Ibsen R, Stratelis G, de Fine Licht S, et al. Disease trajectories and impact of one moderate exacerbation in GOLD B COPD patients. Int J Chron Obstruct Pulmon Dis 2022;17:569-78.
16. Vanfleteren LEGW, Lindberg A, Zhou C, Nyberg F, Stridsman C. Exacerbation risk and mortality in global initiative for chronic obstructive lung disease group A and B patients with and without exacerbation history. Am J Respir Crit Care Med 2023;208: 163-75.
17. Vogelmeier CF, Jones PW, Kerwin EM, Boucot IH, Maltais F, Tombs L, et al. Efficacy of umeclidinium/vilanterol according to the degree of reversibility of airflow limitation at screening: a post hoc analysis of the EMAX trial. Respir Res 2021;22:279.
18. Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandström T, Taylor AF, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med 2013;1:199-209.
19. Calverley PMA, Anzueto AR, Carter K, Grönke L, Hallmann C, Jenkins C, 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;6:337-44.
20. Miravitlles M, García-Sidro P, Fernández-Nistal A, Buendía MJ, Espinosa de Los Monteros MJ, Esquinas C, et al. The chronic obstructive pulmonary disease assessment test improves the predictive value of previous exacerbations for poor outcomes in COPD. Int J Chron Obstruct Pulmon Dis 2015;10:2571-9.
21. Wedzicha JA, Buhl R, Singh D, Vogelmeier CF, de la Hoz A, Xue W, 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; 37:4266-79.
22. Ichinose M, Nishimura M, Akimoto M, Kurotori Y, Zhao Y, de la Hoz A, et al. Tiotropium/olodaterol versus tiotropium in Japanese patients with COPD: results from the DYNAGITO study. Int J Chron Obstruct Pulmon Dis 2018;13:2147-56. Erratum in: Int J Chron Obstruct Pulmon Dis 2018;13:3587.