

A Comparison of Leukotriene Receptor Antagonists to Low-Dose Inhaled Corticosteroids in the Elderly with Mild Asthma



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What is already known about this topic? Inhaled corticosteroids (ICSs) are generally known to reduce the risk of asthma exacerbation to a greater extent than leukotriene receptor antagonists (LTRAs) in adult patients with asthma. However, few studies have evaluated the effectiveness of both treatments in elderly patients with asthma.

What does this article add to our knowledge? The risk of asthma exacerbation during treatment with LTRAs was not different from that during treatment with low-dose ICSs in elderly patients with asthma, so both treatments can be considered equally effective.

How does this study impact current management guidelines? Treatment with LTRAs can be considered a reasonable alternative first-line therapy for elderly patients with mild asthma.

BACKGROUND: Although elderly patients with asthma have clinical characteristics different from those of young adults, few studies or guidelines have focused on specific treatments for this population.

OBJECTIVE: This study compared the effectiveness of leukotriene receptor antagonists (LTRAs) versus inhaled corticosteroids (ICSs) in elderly patients with asthma in real-world settings.

METHODS: We extracted records for elderly patients with asthma who were newly prescribed LTRAs or low-dose ICSs from January 2003 to December 2010 from National Sample Cohort data of Korea. We defined the first prescription date for each medication as the index date. We compared the risks of asthma exacerbation between the 2 groups using Cox

proportional-hazard regression after propensity score-based inverse probability of treatment weighting to balance covariates between treatment groups. We also compared asthma-related health care resource utilization and medication compliance in both groups using chi-square test and *t* test.

RESULTS: The number of identified patients newly treated with LTRAs and low-dose ICSs was 1571 and 121, respectively. The risks of asthma exacerbation in the LTRA and low-dose ICS groups after weighting were not significantly different (hazard ratio, 0.98; 95% CI, 0.65-1.54). The proportion with high compliance (medication possession ratio $\geq 80\%$) in the LTRA group was higher than that in the low-dose ICS group.

CONCLUSIONS: The effectiveness of LTRAs was not different from that of low-dose ICSs regarding the risk of asthma exacerbation in elderly patients with asthma in real-world settings. Given the practical benefits gained from convenient administration, LTRAs can be considered a reasonable alternative first-line therapy for elderly patients with mild asthma. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2642-52)

Key words: Asthma; Elderly; Asthma exacerbation; Inhaled corticosteroids (ICSs); Leukotriene receptor antagonists (LTRAs)

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INTRODUCTION

Prevalence of asthma in the elderly is rising and has become a health issue.^{1,2} The global elderly population is growing very rapidly and is projected to more than double by 2050 compared with 2015, and the rate of increase in the number of the “oldest-old” people aged 80 years or older is faster than that of the elderly overall.³ Given these demographics, the proportion of elderly people among patients with asthma is likely to increase further in the future.

Abbreviations used

ED- Emergency department

GINA- Global Initiative for Asthma

HR- Hazard ratio

ICD-10- International Classification of Diseases, Tenth Revision

ICS- Inhaled corticosteroid

IPTW- Inverse probability of treatment weighting

LABA- Long-acting β -agonist

LTRA- Leukotriene receptor antagonist

MPR- Medication possession ratio

OCS- Oral corticosteroid

PS- Propensity score

RCT- Randomized controlled trial

SABA- Short-acting β -agonist

SCS- Systemic corticosteroid

The clinical characteristics of asthma differ between the elderly and the younger people.^{4,5} Multiple comorbidities in elderly patients may alter the symptoms and severity of asthma, which makes the prognosis of asthma in the elderly more difficult to predict.^{4,6} In addition, elderly patients are vulnerable to mental illnesses and psychosocial alienation, which have significant associations with asthma exacerbation.^{7,8} For these reasons, the elderly tend to have more frequent and longer hospitalizations due to asthma exacerbation, which often leads to a high mortality rate.^{9,10} However, there is little information on the treatment of elderly patients with asthma because most of them have been excluded from randomized controlled trials (RCTs).¹¹

Inhaled corticosteroids (ICSs) are recommended as the first-line treatment for asthma, because they are the most effective anti-inflammatory drugs for treating persistent asthma in adults.¹² Leukotriene receptor antagonists (LTRAs), which are used in oral formulations, are also effective, but several RCTs have shown that they have lower efficacy than ICSs.¹³⁻¹⁵ However, optimal therapeutic effects of ICSs cannot be expected if they are used improperly. A previous study showed that the effects of ICSs vary greatly depending on the health literacy of elderly patients with asthma because the use of inhalers is complex and requires technical learning.¹⁶ Therefore, when choosing a first-line therapy for elderly patients with asthma, physicians will face a choice between the apparent greater efficacy of ICSs, which are difficult to administer, and the practical benefits of LTRAs, which are more convenient to administer.

To date, few studies have evaluated the effectiveness of LTRAs versus ICSs in a real-world population. A previous study on children reported a similar risk of asthma exacerbation between LTRAs and ICSs.¹⁷ However, no studies have focused specifically on elderly patients with asthma. Therefore, we performed a retrospective cohort study to compare the real-world effectiveness of LTRAs and ICSs in relation to the risk of asthma exacerbation in elderly patients with asthma using a Korean national health insurance database. Moreover, we analyzed asthma-related health care resource utilization to infer the level of asthma control in each group.

METHODS

Data source

We used data from the National Health Insurance Service-National Sample Cohort established by the National Health

Insurance Service of South Korea, which is a population-based cohort obtained by random sampling according to age group, sex, participant eligibility status, and income level (NHIS-2017-2-462). National Health Insurance Service-National Sample Cohort consists of approximately 1 million individuals, accounting for 2.2% of the total eligible Korean population in 2002. These individuals were followed up through 2013.¹⁸ National Health Insurance Service-National Sample Cohort contains data on insurance eligibility, claims for medical services, medical care institutions, and general health examinations for patients followed for 12 successive years. The insurance eligibility database includes socioeconomic variables such as sex, age recorded at 5-year intervals, type of health insurance, level of income, and variables related to death. The database for medical services consists of records of medical procedures, drug prescriptions, clinical diagnoses according to the *International Classification of Diseases, Tenth Revision* (ICD-10), and associated expenditures.

Patients and study design

In our retrospective cohort study, we constructed a cohort of elderly patients who had asthma (ICD-10 codes J45 and J46) as their primary or secondary diagnosis and were newly prescribed LTRAs or low-dose ICSs during the cohort enrollment period from January 1, 2003, to December 31, 2010. We set the date of first prescription of LTRAs alone or low-dose ICSs alone without other asthma controller medications (ie, medication of the opposite group, theophyllines, medium-to-high-dose ICSs, long-acting beta-agonists [LABAs], ICS/LABA combinations, or oral LABAs) as the index date. We limited ICS users to those who were prescribed low-dose ICSs to ensure comparability among the patients in terms of disease severity, as recommended for the step 2 treatment by the Global Initiative for Asthma (GINA) guideline (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).¹⁹ Inclusion criteria were as follows: (1) patients who had at least 2 primary or secondary diagnoses of asthma and prescriptions for asthma-related medications during the cohort enrollment period; (2) patients who had at least 1 prescription for LTRAs alone or low-dose ICSs alone; and (3) patients older than 65 years at the date when LTRAs or low-dose ICSs were newly prescribed. Patients were excluded if they met the following criteria: (1) patients with a history of chronic bronchitis, emphysema, other chronic obstructive pulmonary disease, bronchiectasis, respiratory tuberculosis, and malignant neoplasm of the bronchus and the lung (see Table E2 in this article's Online Repository at www.jaci-inpractice.org); and (3) patients with at least 1 prescription for ICSs or ICS/LABA combinations or LTRAs within 1 year before the index date. This study was approved by the Institutional Review Board of Sungkyunkwan University (approval no. SKKU-2017-05-002). All the personal identifying information of the included patients was excluded so that all the patients remained anonymous. Therefore, the need for informed consent for this study was waived by the institutional review board.

Exposure measurements

Patients were classified as either the LTRA group or the low-dose ICS group according to the medication they were prescribed at the index date. The preindex period was defined as a 1-year period before the index date and was used to obtain data on the characteristics of patients. Patients were followed up for 3 years after the index date.

Outcome measurements

To estimate the real-world effectiveness of each treatment, the primary outcome was the hazard ratio (HR) for asthma exacerbation in the LTRA group compared with that in the low-dose ICS group. Based on a previous study,²⁰ an asthma exacerbation was defined as experiencing at least 1 of the following 3 events: systemic corticosteroid (SCS) burst, emergency department (ED) visit, or hospitalization with asthma as the primary or secondary diagnosis. An SCS burst was defined as an outpatient visit requiring the use of high-dose oral corticosteroids (OCSs) for at least 3 days or 1 SCS injection. An ED visit due to asthma exacerbation was defined as that requiring the use of high-dose OCSs or SCS injection. Hospitalization due to asthma exacerbation was defined as that requiring the use of high-dose OCSs for at least 3 days or 1 SCS injection. High-dose OCS was defined as a medication equivalent to 30 mg prednisolone per day.^{19,21} Follow-up was discontinued when patients met 1 of the following criteria for censoring events: death due to any cause, treatment change (ie, switching from the medication that was prescribed at the index date to another asthma controller medication or adding another asthma controller medication), or the end of the 3-year follow-up period.

A secondary outcome was asthma-related health care resource utilization within the first year after the index date, because previous studies have demonstrated that the level of asthma control is associated with the amount of health care resource utilization.^{22,23} Two types of secondary outcomes were evaluated: the frequency of asthma-related medical visits and the use of asthma-related medications. The 3 types of medical visits included asthma-related outpatient visits, ED visits, and hospitalizations. We analyzed the proportion of patients who experienced each type of medical visits at least once and the mean rate of visits per patient. In terms of the use of asthma-related medications, we examined the proportion of patients who were prescribed asthma controller medications other than the index medication, as well as the proportion of patients who were prescribed each type of symptom reliever medications (ie, short-acting β -agonists [SABAs] or short-acting muscarinic-antagonists). To verify the effectiveness of initial treatments, we further analyzed asthma-related health care resource utilization within 90 days after the index date because GINA guideline recommends that patients' response should be reviewed after 2 to 3 months of starting initial controller treatment.¹⁹ In addition, we compared the proportion of patients who changed treatment within 90 days or 1 year after the index date, and the time to treatment change between the 2 groups.

Finally, we analyzed treatment compliance, which was expected to affect the real-world effectiveness of treatments in both groups. Treatment compliance until the first exacerbation or censoring of patients was calculated by the medication possession ratio (MPR) method, in which the total prescription days for the asthma controller medication from the index date to the first exacerbation or censoring were divided by the total observation days from the index date to the first exacerbation or censoring. The mean and SD of MPR were calculated and patients were classified into 3 categories on the basis of their MPRs: low compliance (MPR < 50%); medium compliance (50% $\leq$ MPR < 80%); and high compliance (MPR $\geq$ 80 %).²⁴

Potential confounders

We collected the following data from the preindex period: sex, the season during which the index date occurred,²⁵ Charlson comorbidity index score, and level of medical institution visited at the index date. The following circulatory diseases, which may affect pulmonary function in the preindex period, were considered: hypertension, hyperlipidemia, arrhythmia, diabetes, congestive heart failure, ischemic heart

disease, cerebrovascular disease, and other heart diseases (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). We also included the following comorbidities associated with poor asthma control based on previous studies and guidelines: gastroesophageal reflux disease, depression, anxiety, atopy, rhinitis, sinusitis, dementia, and renal failure (Table E3).^{5,19} Moreover, arthritis, especially in the hands, which can affect the choice of inhaler or oral medications, was added as a potential confounder (Table E3). Because of the lack of a specified ICD-10 code for rheumatoid arthritis in the hands, we included all ICD-10 codes for rheumatoid arthritis, regardless of the specific body region. Similarly, we included all ICD-10 codes for osteoarthritis, except for codes that clearly indicate different body regions, such as hip joints or knee joints. In addition, we considered asthma-related health care resources utilization in the preindex period, such as outpatient visits, ED visits, hospitalizations, and use of SABAs, as a potential confounder.

Statistical analyses

To control the effect of confounders and enhance the determination of causality between independent and dependent variables, we used the propensity score (PS)-based inverse probability of treatment weighting (IPTW) method. The IPTW method uses the whole data set but reweights individuals to achieve a balanced average treatment effect²⁶; therefore, the IPTW method allows us to maintain the greatest number of patients in the analysis. We calculated the IPTW using PS for receiving LTRA treatment. PS was estimated using multivariable logistic regression with the selected covariates summarized in Table I. To evaluate the goodness of fit for regression model, we calculated the c-statistic of the logistic regression for the propensity model and conducted a Hosmer-Lemeshow goodness-of-fit test. The weights for the LTRA group were the inverse of PS, and those for the ICS group were the inverse of (1 – PS). Subsequently, to reduce the instability of IPTW estimators, stabilized weights were calculated by replacing the numerator with the marginal probability of receiving the actual treatment.²⁶ After applying stabilized IPTW, we assessed covariate balance by comparing the baseline characteristics between the 2 groups. Additional description of the IPTW method and our rationale are included in this article's Online Repository at www.jaci-inpractice.org.

A multivariable Cox proportional-hazard model was used to assess the risk of combined asthma exacerbation in the LTRA group compared with that in the low-dose ICS group. The survival time to the first asthma exacerbation for the LTRA and the low-dose ICS groups was depicted as a Kaplan-Meier plot, and statistical significance was tested using the log-rank test. We also analyzed the risk according to the type of asthma exacerbation, namely, SCS burst, ED visit, and hospitalization. We calculated the unadjusted HR, as well as the adjusted HR corrected for the following covariates from the follow-up period to account for their time-varying effects on the outcomes: diagnoses of gastroesophageal reflux disease, depression, anxiety, atopy, rhinitis, and sinusitis.

We conducted sensitivity analyses to confirm the robustness of our results. We changed the definition of asthma exacerbation from requiring the use of high-dose OCSs for at least 3 days to 5 or 7 days, based on GINA guideline, which recommends the use of OCSs for 3 to 7 days in the case of asthma exacerbation.¹⁹ To account for the effect of compliance in the 2 groups, we additionally performed a multivariable Cox proportional-hazard analysis adjusting for the MPR of each patient.

Differences in categorical variables between the 2 groups were tested using chi-square test or Fisher exact test, and continuous variables were analyzed using *t* test. In addition, we used the generalized

TABLE I. Baseline characteristics of patients treated with LTRAs or low-dose ICSs

Characteristic	Unweighted data			Weighted [†] data		
	LTRAs* (n = 1571)	ICSs* (n = 121)	P value	LTRAs* (n = 1570)	ICSs* (n = 114)	P value
Male (%)	34.4	34.7	.9399	34.4	31.2	.4830
Season of index date (%)						
Spring	28.6	27.3	.3299	28.5	30.6	.9164
Winter	26.7	22.3		26.4	24.2	
Fall	24.9	32.2		25.4	24.3	
Summer	19.8	18.2		19.7	20.9	
CCI score, mean ± SD	1.6 ± 1.6	1.7 ± 1.8	.6340	1.6 ± 1.6	1.6 ± 1.7	.8038
Preindex comorbidity (%)						
Hypertension (uncomplicated)	52.8	45.5	.1206	52.2	46.4	.2327
Hypertension (complicated)	6.4	6.6	.9372	6.4	5.4	.6721
Hyperlipidemia	25.3	22.3	.4604	25.1	26.3	.7770
Gastroesophageal reflux disease	17.1	11.6	.1185	16.7	17.5	.8126
Arrhythmia	2.5	5.8	.0415 [‡]	2.6	1.8	.5767
Depression	7.7	9.9	.3829	7.8	6.7	.6738
Anxiety	12.6	10.7	.5508	12.5	12.6	.9748
Atopy	2.7	1.7	.7671	2.7	3.0	.8119
Rhinitis	43.9	33.9	.0328	43.1	39.0	.3881
Sinusitis	12.9	10.7	.5010	12.7	13.9	.7267
Diabetes (uncomplicated)	15.0	13.2	.5922	14.9	18.2	.3489
Diabetes (complicated)	10.1	12.4	.4131	10.3	12.2	.5189
Congestive heart failure	4.2	3.3	.6337	4.2	6.0	.3430
Dementia	2.0	0.0	.1640 [‡]	1.9	0.0	.1382
Ischemic heart diseases	12.2	9.9	.4649	11.9	8.6	.2856
Other heart diseases	5.8	9.9	.0675	6.0	4.9	.6231
Cerebrovascular diseases	10.7	9.9	.7895	10.7	14.2	.2413
Renal failure	0.5	0.0	1.0000 [‡]	0.5	0.0	.4616
Arthritis	12.0	9.9	.5010	11.8	13.5	.5873
Patients with asthma-related health care resources utilization in the preindex period (%)						
SABAs use ≥1	3.9	5.8	.3303	4.0	3.4	.7288
Outpatient visits ≥1	21.5	35.5	.0004	22.5	20.7	.6563
ED visits ≥1	0.2	0.0	1.0000 [‡]	0.2	0.0	.6525
Hospitalizations ≥1	0.9	0.8	1.0000 [‡]	0.9	0.3	.5280
Level of medical institution at the index date (%)						
General hospital	9.9	38.0	<.0001	11.9	12.4	.7313
Hospital	4.7	6.6		4.8	3.5	
Clinics	83.6	53.7		81.5	81.0	
Public health center	1.9	1.7		1.9	3.1	

CCI, Charlson comorbidity index.

Bold indicates $P < .05$.

*Identified by medications at the index date.

[†]A pseudopopulation was created by weighting the original population with stabilized weights calculated using PSs for receiving LTRA.

[‡]Tested by Fisher exact test.

linear model with the log link function and the Poisson distribution to test the differences in the frequency of asthma exacerbation between the 2 groups. All tests were 2-tailed with an alpha level of 0.05, and the P value was adjusted using the Bonferroni method for multiple comparisons. All data handling and statistical analyses were performed using SAS Software 9.4 (Cary, NC).

RESULTS

Baseline characteristics and PS matching

We identified 1692 patients with asthma aged 65 years or older who were newly prescribed LTRAs alone or low-dose ICSs alone between January 1, 2003, and December 31, 2010. Among these patients, 1571 were newly treated with LTRAs and 121 were newly

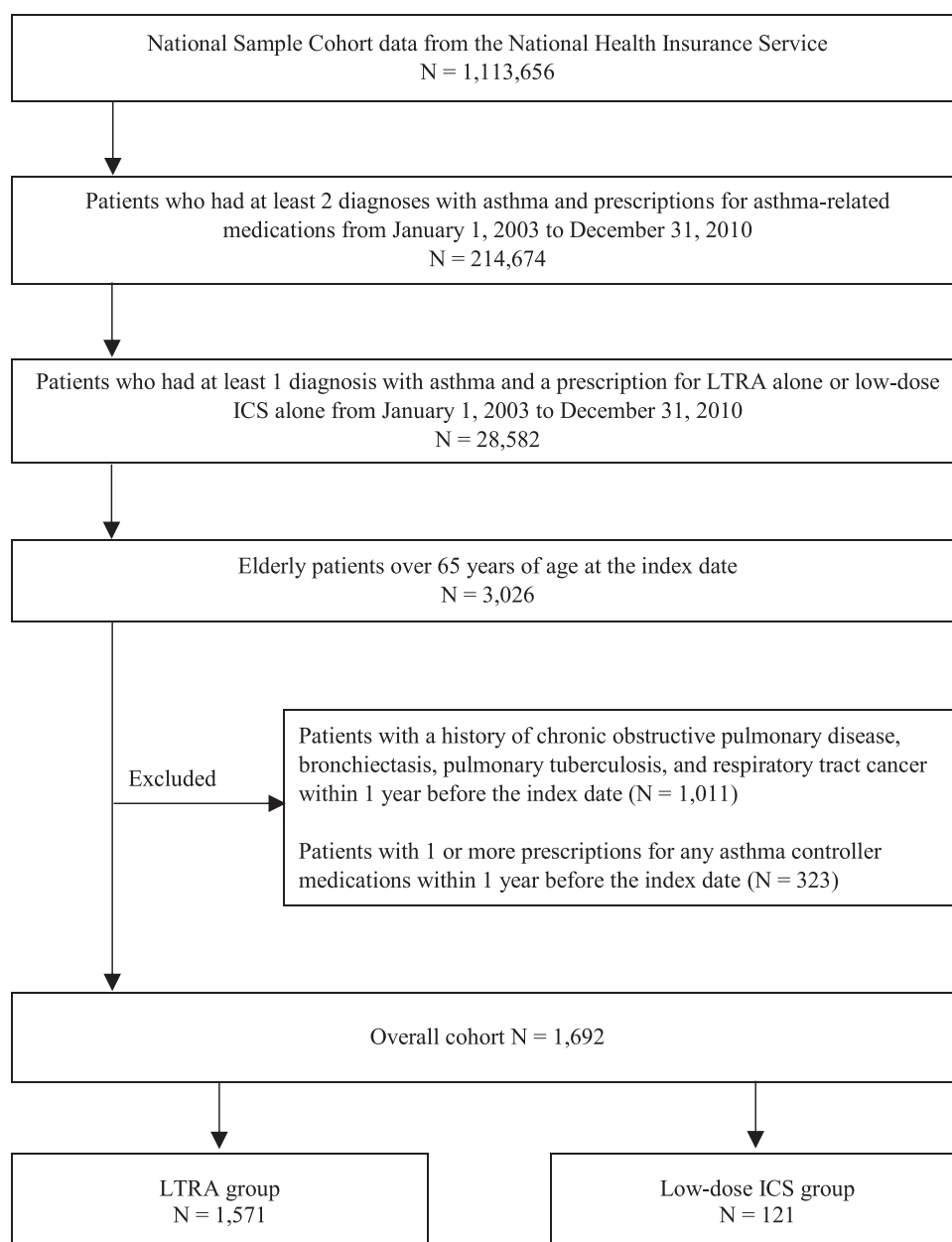


FIGURE 1. Selection of the study cohort population from the National Health Insurance Service-National Sample Cohort data using a retrospective cohort design.

treated with low-dose ICSs (Figure 1). After applying stabilized IPTW, pseudopopulations with 1570 and 114 patients were produced in the LTRA group and the low-dose ICS group, respectively. The c-statistic of the propensity model was 0.75, and Hosmer-Lemeshow goodness-of-fit test showed that the model was well fitted ($P = .3629$). The distribution characteristics of weights obtained by IPTW are presented in Table E4 in this article's Online Repository at www.jaci-inpractice.org. In the weighted population with stabilized IPTW, the patient characteristic variables, presence of comorbidities, and asthma-related health care resource utilization in the preindex period were not significantly different between the 2 groups (Table I).

Risk of asthma exacerbation

The results presented in Table II show that the risks of combined asthma exacerbation between the 2 groups after weighting and adjustment for the covariates were not significantly different (HR, 0.98; 95% CI, 0.65-1.54). A Kaplan-Meier curve showed no difference between the 2 groups ($P = .9918$) (Figure 2). The risk of SCS burst (HR, 1.07; 95% CI, 0.68-1.75) and hospitalization (HR, 0.69; 95% CI, 0.24-2.50) was similar to that of combined exacerbation, showing no significant difference between the 2 groups. Of the 3 different types of asthma exacerbation, no ED visit was observed before censoring in either group. Sensitivity analyses that applied high-dose OCS

TABLE II. Risk of asthma exacerbation in the LTRA group vs the low-dose ICS group obtained from Cox proportional-hazard model

Asthma exacerbation	LTRAs* (n = 1571)		Low-dose ICSs* (n = 121)		Unweighted data		Weighted† data	
	Person-years	Events	Person-years	Events	Unadjusted HR (95% CI)	Adjusted‡ HR (95% CI)	Unadjusted HR (95% CI)	Adjusted‡ HR (95% CI)
Main analysis								
Combined exacerbation	3017.58	246	192.45	25	0.70 (0.47-1.06)	0.73 (0.48-1.10)	0.97 (0.65-1.52)	0.98 (0.65-1.54)
SCS burst	3026.70	231	194.66	21	0.79 (0.51-1.24)	0.81 (0.52-1.27)	1.06 (0.68-1.74)	1.07 (0.68-1.75)
Hospitalization	3306.81	22	210.55	4	0.40 (0.14-1.16)	0.49 (0.17-1.42)	0.62 (0.22-2.22)	0.69 (0.24-2.50)
Sensitivity analysis modifying the definition of exacerbation: use of high-dose OCSs for at least 5 d								
Combined exacerbation	3025.03	237	192.48	24	0.70 (0.46-1.07)	0.73 (0.48-1.11)	1.03 (0.66-1.69)	1.04 (0.66-1.70)
SCS burst	3034.15	222	194.69	20	0.79 (0.50-1.26)	0.81 (0.51-1.28)	1.15 (0.69-1.98)	1.15 (0.69-1.98)
Hospitalization	3306.81	21	210.55	4	0.38 (0.13-1.12)	0.47 (0.16-1.37)	0.59 (0.20-2.11)	0.67 (0.23-2.44)
Sensitivity analysis modifying the definition of exacerbation: use of high-dose OCSs for at least 7 d								
Combined exacerbation	3025.03	236	192.48	24	0.70 (0.46-1.07)	0.72 (0.47-1.10)	1.03 (0.66-1.68)	1.03 (0.66-1.69)
SCS burst	3034.15	221	194.69	20	0.79 (0.50-1.25)	0.81 (0.51-1.28)	1.14 (0.69-1.97)	1.14 (0.69-1.97)
Hospitalization	3306.81	21	210.55	4	0.38 (0.13-1.12)	0.47 (0.16-1.37)	0.59 (0.20-2.11)	0.67 (0.23-2.44)

*Defined by the medication prescribed at the index date.

†A pseudopopulation was created by weighting the original population with stabilized weights calculated using PSs for receiving LTRAs.

‡Adjusted for comorbidities during follow-up period (gastroesophageal reflux diseases, depression, anxiety, atopy, rhinitis, and sinusitis).

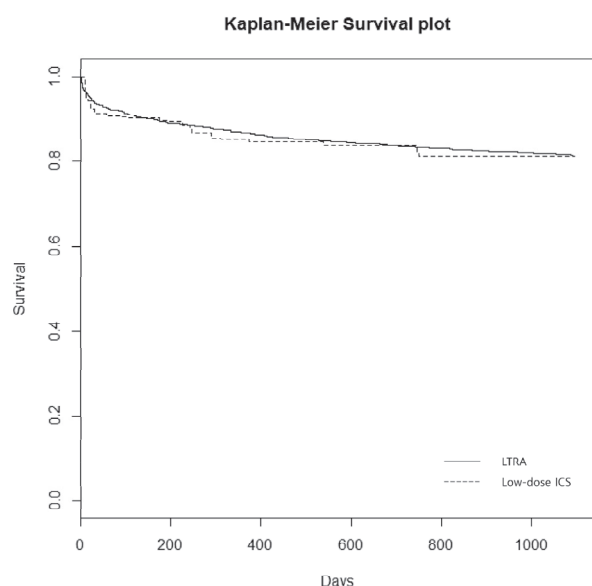


FIGURE 2. Kaplan-Meier curve for acute exacerbation-free survival in the LTRA and the low-dose ICS groups.

prescription period cutoff of 5 or 7 days also showed no significant differences between the 2 groups.

Asthma-related medical visit

The rate of asthma-related outpatient visits within 90 days after the index date in the LTRA group (1.27 ± 2.00) was significantly higher than that in the low-dose ICS group (0.92 ± 1.42) ($P = .0014$), whereas the rate within 1 year after the index date in the LTRA group (2.80 ± 4.47) was similar to that in the low-dose group (2.90 ± 4.96) ($P = .5632$) (Table III). There was no significant difference in the proportion of patients with ED visits between the 2 groups within 90 days ($P = .6442$) or within 1 year ($P = .5922$). The rate of hospitalization after the index date showed no difference between the groups within either 90 days ($P = .6929$) or 1 year ($P = .4170$).

Asthma-related medication use

Within 90 days after the index date, the proportion of patients who were prescribed the medication of the opposite group was significantly lower in the LTRA group (0.2%) than in the low-dose ICS group (1.2%) ($P = .0378$) (Table IV). Within 1 year, the difference between the groups was more noticeable, with 0.2% and 4.9% of patients in the LTRA and low-dose ICS groups, respectively ($P < .0001$). The proportion of patients who were prescribed SABAs at least once was significantly lower in the LTRA group (9.9%) than in the low-dose ICS group (23.3%) within 90 days after the index date ($P < .0001$), and this difference remained significant during the 1-year follow-up (LTRA, 14.3%; low-dose ICS, 25.8%; $P = .0020$). The proportion of patients who changed their treatments significantly differed between the LTRA group (18.8%) and the ICS group (26.6%) within 90 days ($P = .0408$). Compliance showed significantly different distributions between the 2 groups ($P = .0410$), and the proportion of patients with high compliance ($\text{MPR} \geq 80\%$) in the LTRA group was higher than that in the low-dose ICS group (Table IV).

MPR-adjusted risk of asthma exacerbation

As a result of adjusting for the MPR of each patient, the HR for the risk of combined asthma exacerbation in the LTRA group versus the low-dose ICS group was 1.12 (0.73-1.78) (Table V). For SCS burst and hospitalization, the HRs were 1.23 (0.77-2.03) and 0.68 (0.23-2.44), respectively.

DISCUSSION

Our retrospective cohort study using a multivariable Cox proportional-hazard regression model showed that the risk of asthma exacerbation in the LTRA group was not significantly different from that in the low-dose ICS group in elderly patients with mild asthma. These results remained consistent across the different types of asthma exacerbation. Sensitivity analyses applying different prescription days of OCSs to define the asthma exacerbation also showed results consistent with the main results of our study. In the results of the analysis for medical visits, the amount of asthma-related ED visits and hospitalizations within 1 year after the first use of LTRA was not significantly different from that of low-dose ICS, suggesting that the level of asthma control of both groups was comparable.

In our analysis, 1571 and 121 patients were selected for the LTRA group and the low-dose ICS group, respectively. The large discrepancy in the number of patients between the 2 groups is likely to be a reflection of the low prescription rate of ICSs in Korea.^{27,28} Furthermore, limiting ICSs to a low dose in our study may have enlarged the difference between the number of patients in the 2 groups. Considering the relatively small number of patients in the low-dose ICS group, we used the IPTW method, which allowed us to retain the original sample size to minimize the loss of information and the reduction of statistical power in the process of controlling the confounding factors.

Our results are in agreement with those of a previous pragmatic trial that targeted 12 to 80 aged patients who had impaired asthma-related quality of life and evaluated the real-world effectiveness of LTRA compared with that of ICS.²⁹ The study reported that there was no significant difference in the frequency of asthma exacerbation between the 2 groups during a 2-year period, and adherence in the LTRA group was higher than in the ICS group (65% vs 41%). The discrepancy between the effectiveness in real-world studies and the efficacy in RCTs could be explained by the lack of compliance with ICS treatment in elderly patients with asthma. Several previous studies have reported that compliance in adult patients with asthma treated with inhalants is lower than compliance with oral medications.^{30,31} Moreover, another study showed that low compliance with inhalants, especially ICSs, was associated with frequent occurrence of several asthma-related outcomes, including hospitalization and filling prescriptions for oral steroids.³² In the elderly, various factors including mental status, physical health, and socioeconomic factors lead to further decreased compliance with prescribed medications.^{33,34} In particular, the frequency of drug administration is an important factor affecting compliance in the elderly because this population is typically taking multiple medications for treatment of multiple comorbidities. A previous systematic review showed that compliance was significantly reduced by 10% when medications were taken twice per day compared with once per day.³⁵ LTRAs are orally administered once a day, whereas ICSs usually require inhalation more than once a day; hence, LTRAs can allow for simpler and more

TABLE III. Asthma-related visits to medical institutions in weighted* data

Asthma-related medical visit	LTRAs† (n = 1570)	Low-dose ICSs† (n = 114)	P value
Follow-up within 90 d after the index date			
Outpatient visit			
% of patients with ≥1 outpatient visit	52.6	41.8	.0259
Outpatient visits per patient, mean ± SD	1.27 ± 2.00	0.92 ± 1.42	.0014‡
ED visit			
% of patients with ≥1 ED visit	0.1	0.0	.6442
ED visits per patient, mean ± SD	0.001 ± 0.03	0.00 ± 0.00	—
Hospitalization			
% of patients with ≥1 hospitalization	1.6	1.5	.9234
Hospitalizations per patient, mean ± SD	0.02 ± 0.18	0.02 ± 0.12	.6929‡
Days of hospitalization, mean ± SD	6.7 ± 5.5	7.8 ± 1.6	.7890
Follow-up within 1 y after the index date			
Outpatient visit			
% of patients with ≥1 outpatient visit	66.2	60.7	.2304
Outpatient visits per patient, mean ± SD	2.80 ± 4.47	2.90 ± 4.96	.5632‡
ED visit			
% of patients with ≥1 ED visit	0.3	0.0	.5922
ED visits per patient, mean ± SD	0.003 ± 0.07	0.00 ± 0.00	—
Hospitalization			
% of patients with ≥1 hospitalization	3.0	1.5	.3614
Hospitalizations per patient, mean ± SD	0.04 ± 0.27	0.03 ± 0.21	.4170‡
Days of hospitalization, mean ± SD	11.9 ± 20.6	9.1 ± 2.0	.3193

Bold indicates $P < .05$ after adjustment.

*A pseudopopulation was created by weighting the original population with stabilized weights calculated using PSs for receiving LTRAs.

†Defined by the medication prescribed at the index date.

‡Tested by Poisson regression.

convenient dosing regimens than do ICSs, with the expectation of them having similar treatment effectiveness.

The result of our study regarding compliance showed that the LTRA group had a greater proportion of patients with high compliance than the low-dose ICS group. However, the mean MPR was not significantly different between the 2 groups, which disagreed with the results of previous studies.^{30,31} In addition, the results of MPR-adjusted Cox proportional-hazard analysis showed no significant difference in the risk of asthma exacerbation between the 2 groups. This can be explained by the overall low level of compliance in our study than that in previous studies due to some factors. The first possible explanation is that we targeted patients with mild asthma. A previous study showed that milder asthma was associated with a larger proportion of patients with low compliance.³⁶ The second is that because we only included new users of LTRA or low-dose ICSs, new user design may have resulted in low compliance and biased the overall results to the null due to small person-time of use of drugs.

Although our study could not measure whether inhalation skill of elderly patients was adequate, this could be another factor that affected our results. Previous studies have shown that the misuse of inhalers was strongly correlated with advanced age, which contributed to difficulty in controlling symptoms in elderly patients and increased their frequencies of ED visits and hospitalizations.³⁷ In the elderly, drug delivery of ICSs is more likely to decline because of poor skill of inhaler use due to their low cognitive and physical capabilities compared with younger adults.³⁸ In this study, the proportion

of patients who changed treatment from the index medication to other medications was higher in the ICS group than in the LTRA group within 90 days after the index date. This suggests the possibility that there were more patients with poor control of symptoms with ICSs than with LTRAs. A higher proportion of patients were prescribed SABAs in the low-dose ICS group than in the LTRA group, suggesting that the symptoms were not effectively controlled in the low-dose ICS group. According to a previous study comparing asthma-related outcomes of the 2 treatments in nonelderly adult patients, the odds of being prescribed SABAs more than 6 times per year was 29% lower in the LTRA group than in the ICS group,³⁹ which was consistent with our results.

The present study has several strengths. First, we used real-world data that could reflect actual patient outcomes occurring under the influence of a mix of diverse variables, such as compliance parameters or changing treatments.⁴⁰ Although RCT best evaluates the original efficacy of an intervention because it targets the most ideal environment and participants, it has low generalizability to the actual practice of treating patients. Our results can provide additional practical evidence for the elderly in real-world settings that RCTs do not usually cover. We also used representative sample data from the entire Korean population, so our results have excellent generalizability. Second, to our knowledge, this is the first study to compare the effectiveness of LTRAs and ICSs in elderly patients with asthma. Considering that the elderly have particular clinical characteristics and occupy a significant proportion of patients and society, there is a considerable need to develop treatment guidelines for this

TABLE IV. Use of asthma-related medications in weighted* data

Asthma-related medication use	LTRAs† (n = 1570)	Low-dose ICSs† (n = 114)	P value
Follow-up within 90 d after the index date			
Use of asthma controller medications (%)			
Medication of the opposite group	0.2	1.2	.0378
Moderate- to high-dose ICSs	0.1	2.7	<.0001
ICS/LABA combinations	5.9	7.1	.6035
Oral LABAs	5.6	8.8	.1555
Theophyllines	12.3	10.1	.4892
Use of symptom reliever medications (%)			
SABA			
≥1 prescription	9.9	23.3	<.0001
≥2 prescriptions	4.4	6.2	.7410
SAMA			
≥1 prescription	2.5	2.0	>.9999
≥2 prescriptions	1.2	0.9	>.9999
Changing treatment			
% of patients with changing treatment	18.8	26.6	.0408
Time to changing treatment (d), mean ± SD	31.6 ± 26.0	36.3 ± 26.1	.3519
Time to changing treatment (d), median	28	31	—
Follow-up within 1 y after the index date			
Use of asthma controller medications (%)			
Medication of the opposite group	0.2	4.9	<.0001
Moderate- to high-dose ICSs	0.4	2.7	.0030
ICS/LABA combinations	10.3	12.6	.4215
Oral LABAs	11.5	15.1	.2529
Theophyllines	22.6	17.5	.2045
Use of symptom reliever medications (%)			
SABA			
≥1 prescription	14.3	25.8	.0020
≥2 prescriptions	8.2	12.1	.2656
SAMA			
≥1 prescription	3.6	3.2	>.9999
≥2 prescriptions	1.9	1.4	.8994
Changing treatment			
% of patients with changing treatment	31.3	36.9	.2021
Time to changing treatment (d), mean ± SD	102.9 ± 102.5	96.4 ± 98.7	.5123
Time to changing treatment (d), median	64	53	—
Compliance‡ until the first exacerbation or censoring			
% MPR < 50%	78.2	75.5	.0410
50% ≤ % MPR < 80%	3.9	8.5	
80% ≤ % MPR	17.9	16.0	
Mean ± SD	0.24 ± 0.36	0.27 ± 0.33	.3878

SAMA, Short-acting muscarinic-antagonist.

Bold indicates $P < .05$ after adjustment using Bonferroni correction for multiple comparisons.

*A pseudopopulation was created by weighting the original population with stabilized weights calculated using PSs for receiving LTRA.

†Defined by the medication prescribed at the index date.

‡The total number of days of controller prescribed divided by the total observation days.

population. The results of our study will provide an important basis for determining optimal treatment strategies for elderly patients with asthma.

Some potential limitations should be considered when interpreting our findings. First, because this study used claims data, we were only provided the information on the prescribed medications, not the actual amount administered to the patients. However, because we aimed to evaluate outcomes reflecting whether the

patients actually took the medications, our results are acceptable. Second, it is possible that diagnostic coding was incomplete because the claims data were collected to request reimbursement for health care services provided, not for clinical purpose. Previous studies that compared diagnostic coding of claims data of Korea with actual medical records found that the validity of diagnostic coding was 72.3% to 87.2% for diabetes, and more than 70% for acute myocardial infarction.^{41,42} Third, because of a lack of clinical

TABLE V. MPR-adjusted analysis for risk of asthma exacerbation in the LTRA group vs the low-dose ICS group obtained from Cox proportional-hazard model

Asthma exacerbation	Adjusted HR	
	Unweighted data	Weighted* data
Combined exacerbation	1.07 (0.70-1.63)	1.12 (0.73-1.78)
SCS burst	1.19 (0.75-1.87)	1.23 (0.77-2.03)
Hospitalization	0.57 (0.19-1.67)	0.68 (0.23-2.44)

*A pseudopopulation was created by weighting the original population with stabilized weights calculated using PSs for receiving LTRA.

records to identify disease severity, we only included patients in step 2 based on a stepwise approach in GINA guideline. Therefore, our results are not necessarily generalizable to patients with more severe asthma. In addition, because the definition of “low-dose” ICS was based on the prescription data, we could not rule out the possibility that we included patients who used moderate- to high-dose ICS in practice. If the patients who used moderate- to high-dose ICS were included in the low-dose ICS group, our results may have underestimated the risk of asthma exacerbation in the LTRA group compared with that in the low-dose ICS group. Finally, because of the observational nature of our study, there may exist residual confounding factors that we could not capture, such as the smoking status, family history of asthma, food allergies, and living conditions of patients.

In conclusion, our study showed that the risk of asthma exacerbation in the LTRA group was not different from that in the low-dose ICS group. This may have been due to the low compliance with ICS treatment among elderly patients with asthma. Therefore, given the practical benefits gained from convenient administration, LTRA treatment could be considered a reasonable alternative to low-dose ICS treatment as a first-line therapy in elderly patients with mild asthma. Our results can provide evidence for establishing optimal treatment guidelines for elderly patients with asthma.

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Additional description for conducting IPTW

PS matching and IPTW are 2 different ways to control for confounding factors and obtain unbiased estimates of average treatment effects in observational studies. According to a previous study that evaluated the performance of PS matching and IPTW where asthma-related outcomes were the primary end point, the 2 methods produced similar results and each method had its particular strengths.^{E1} Therefore, it was recommended that the most suitable method to fulfill a particular study should be selected considering study objectives, end points, and the available data sets.

In our analysis, there was a large discrepancy in the number of patients between the 2 groups, 1571 and 121 for the LTRA group and the low-dose ICS group, respectively. In this situation, using PS matching caused some concerns not only about a loss of information resulting from the reduced sample size of the LTRA group but also about a reduction in statistical power due to the small sample size of the low-dose ICS group. However, the use of IPTW allowed us to retain the original sample size, thereby

keeping the highest statistical power and minimizing the loss of information.

Weights for the LTRA group were the inverse of PS, and those for the ICS group were the inverse of $(1 - PS)$. Subsequently, to reduce instability of IPTW estimators due to the impact of extreme weights in patients with very low PS, stabilized weights were calculated by replacing the numerator with the marginal probability of receiving the actual treatment.^{E2} Then, we compared the baseline characteristics in both pseudopopulation groups obtained by using the stabilized IPTW. There were some variables that were significantly different between the 2 groups at a .05 level of significance (diabetes without complications, and arthritis). Therefore, we trimmed high weights downward, with a cutoff at the 95th percentile.^{E3}

Table E4 describes the distribution characteristics of weights obtained by IPTW and stabilized IPTW. For reference, the risk of asthma exacerbation in the LTRA group versus the low-dose ICS group in a population weighted with stabilized IPTW before trimming is also presented in Table E5.

TABLE E1. List of low-dose ICSs

Name	Dose
Beclomethasone dipropionate	100 µg/dose or less
Budesonide	200 µg/dose or less
Ciclesonide	80 µg/dose or less
Fluticasone propionate	125 µg/dose or less

TABLE E2. ICD-10 code for comorbidities of exclusion criteria for study population

Comorbidities	ICD-10 code
Chronic bronchitis	J40, J41, J42
Emphysema	J43
Other chronic obstructive pulmonary disease	J44
Bronchiectasis	J47
Respiratory tuberculosis	A15, A16
Malignant neoplasm of bronchus and lung	C34, D022

TABLE E3. ICD-10 code for comorbidities as potential confounders to calculate the PS

Comorbidities	ICD-10 code
Hypertension (uncomplicated)	I10
Hypertension (complicated)	I11-I15
Hyperlipidemia	E78
Arrhythmia	I47, I49
Diabetes (uncomplicated)	E109, E119, E129, E139, E149
Diabetes (complicated)	E100, E101, E102, E103, E104, E105, E106, E107, E108, E110, E111, E112, E113, E114, E115, E116, E117, E118, E120, E121, E122, E123, E124, E125, E126, E127, E128, E130, E131, E132, E133, E134, E135, E136, E137, E138, E140, E141, E142, E143, E144, E145, E146, E147, E148
Congestive heart failure	I50
Ischemic heart diseases	I20-I25
Valvular heart disease	I05-I08, I34-I39
Cerebrovascular diseases	I60-I69, G45
Other heart diseases	I00-I02, I09, I26-I28, I30-I33, I40-I49, I51-I52
Gastroesophageal reflux disease	K21
Depression	F32-F33
Anxiety	F40-F42
Atopy	L20
Rhinitis	J30-J31
Sinusitis	J01, J32
Dementia	F00-F03
Renal failure	N17-N19
Arthritis	M05-M06, M15, M18-M19

TABLE E4. The distribution characteristics of weights obtained by IPTW and stabilized IPTW

Distribution characteristics	IPTW	Stabilized IPTW	Stabilized IPTW (after trimming at 95%)
Mean	2.02	1.00	1.00
Median	1.05	0.97	0.97
SD	5.52	0.32	0.23
Minimum	1.00	0.11	0.11
Maximum	138.24	9.90	3.02

TABLE E5. Risk of asthma exacerbation in the LTRA group vs the low-dose ICS group in weighted population with stabilized IPTW before trimming

Asthma exacerbation	Weighted* data	
	Unadjusted HR (95% CI)	Adjusted† HR (95% CI)
Combined exacerbation	1.07 (0.71-1.69)	1.07 (0.71-1.69)
SCS burst	1.18 (0.75-1.93)	1.17 (0.75-1.93)
Hospitalization	0.68 (0.24-2.45)	0.72 (0.25-2.59)

*A pseudopopulation was created by weighting the original population with stabilized weights calculated using PSs for receiving LTRA.

†Adjusted for comorbidities during the follow-up period (gastroesophageal reflux diseases, depression, anxiety, atopy, rhinitis, and sinusitis).

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