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Effects of Asthma Medication Type on Asthma Exacerbation in a Real-World Setting

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Purpose: Currently, there are multiple options for the pharmacological treatment of asthma. This study aimed to compare the effects of different asthma medications on exacerbation in a real-world setting.
Materials and Methods: We retrospectively reviewed electronic medical records of asthma patients who visited the hospital from November 1, 2016 to October 31, 2019. The number of asthma exacerbations requiring administration of systemic steroids was the primary outcome. A time-varying Cox regression analysis was used to reflect the real-world setting: variable usage times, discontinuation, and switching of medication.
Results: Among 937 patients with asthma, 228 (24.3%) experienced asthma exacerbation during the study period. Asthma exacerbation was observed in patients using short-acting β_2-agonists (SABA) alone (50.4% vs. 28.6%, $p<0.001$) as well as in patients not using inhaled corticosteroids (ICS) (58.8% vs. 40.3%, $p<0.001$), long-acting β_2-agonists (LABA) (54.8% vs. 36.1%, $p<0.001$), and leukotriene receptor antagonists (71.5% vs. 50.8%, $p<0.001$). A time-varying Cox regression analysis of asthma exacerbations according to the duration of asthma medication showed that SABA alone increased the risk of asthma exacerbation [hazard ratio (HR), 1.834; 95% confidence interval (CI), 1.299–2.588; $p=0.001$], whereas ICS-LABA decreased the risk (HR, 0.733; 95% CI, 0.538–0.997; $p=0.048$). However, in the subgroup analysis according to medication type, specific ingredients showed no significant differences.
Conclusion: In the real world, asthma medications affect asthma exacerbation variably according to the medication type.

Key Words: Asthma, medication, exacerbation, prognosis

INTRODUCTION

Asthma is a chronic airway disease requiring sustained pharmacological management. Various asthma medications have been developed, and recent studies have revealed that their benefits and risks vary according to the medication type.[1,2] Short-acting β_2-agonists (SABA) can relax the airway smooth muscle and relieve acute asthma symptoms; however, isolated SABA use without proper control might have harmful effects in patients with asthma.[3-5] In addition, recent studies have shown that the use of inhaled corticosteroids (ICS) containing formoterol leads to better outcomes than SABA[6,7] due to it being a rapid-onset long-acting β_2-agonist (LABA). Moreover, ICS can also control airway inflammation, thus providing a survival benefit.[8] Comparing the various types of medications is helpful to determine the best option for asthma control; however, head-to-head comparison studies are currently lacking.

Many patients use their asthma medications for varying periods, frequently stop medication, or freely switch to other asthma medications. Therefore, in this study, we performed time-varying Cox analysis, which allowed us to consider these highly variable and fluctuating real-world situations.[9] This analysis considered the usage time of asthma medications, discontinuation of drugs, and switching to other medications.[10,11] In this study, we aimed to compare the effects of different asthma medications on exacerbations, which is the most important asthma clinical outcome,[12] to reveal the superiority or inferiority of each asthma medication type using time-varying Cox regression.

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MATERIALS AND METHODS

Patients and study design

This was a retrospective study without any intervention. Patients with asthma who visited Gangnam Severance Hospital, Seoul, South Korea from November 1, 2016 to October 31, 2019 were enrolled. Asthma was diagnosed based on clinical history and objective findings, including bronchodilator response, provocation test (inhaled methacholine, histamine, and exercise), and exhaled nitric oxide, based on the Global INitiative for Asthma (GINA) report. In addition, only asthma patients who did not correspond to asthma–chronic-obstructive-pulmonary-disease overlap syndrome were enrolled; patients were diagnosed with asthma–chronic-obstructive-pulmonary-disease overlap syndrome by the two major criteria and at least one minor criterion [major criteria: post-bronchodilator forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) <70%, smoking history ≥10 pack-years; minor criteria: lack of response in acute bronchodilator tests, reduced lung diffusion capacity, low variability in airway obstruction, age >40 years, and presence of emphysema on chest computed tomography].[13] Patients who used asthma medications at least twice per year were enrolled. Electronic medical records, including baseline characteristics, underlying diseases, results of spirometry, prescribed medication, and history of exacerbations, were reviewed. The choice of asthma medication type was made according to the physician's discretion. Results of pulmonary function tests were assessed after bronchodilator use. Asthma exacerbation was defined as worsening of clinical symptoms requiring systemic steroid treatment. The study flow is shown in Fig. 1.

Asthma medication

Asthma medication included the following types: ICS, inhaled LABA, oral LABA, patch LABA, systemic corticosteroids, leukotriene receptor antagonists (LTRA), xanthine, inhaled SABA, oral SABA, and inhaled long-acting muscarine antagonists (LAMA; tiotropium). Additionally, we analyzed the effects of specific ingredients in various asthma medication types on asthma exacerbation. For comparison between the effect of ingredients categorized according to medication type, the groups were divided according to the medication type, as follows: a group that did not use any ingredient within the medication type, a group that used only one specific ingredient within the medication type over the study duration, and a group that changed ingredients within the medication type over the study duration (switch group).

Charlson comorbidity index and clinical outcomes

We included 17 underlying diseases, which are well-known underlying conditions that affect the mortality rate and are frequently used to calculate Charlson comorbidity index (CCI).[7] The primary outcome was the occurrence of asthma exacerbation, defined as the need for systemic steroid administration at least for 1 week to relieve worsened symptoms of asthma.

Ethics

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (number: 3-2020-0352). The requirement for informed consent was waived due to the minimal risk and retrospective nature of this study.

Statistical analysis

We used Student's t-test and chi-square test to compare the continuous and categorical variables between the groups, respectively. We also used a time-varying Cox regression analysis to define the risk factors for clinical outcomes, especially considering the duration of use of each asthma medication type. In addition, we performed subgroup analysis to compare the effects of specific ingredients belonging to each medication

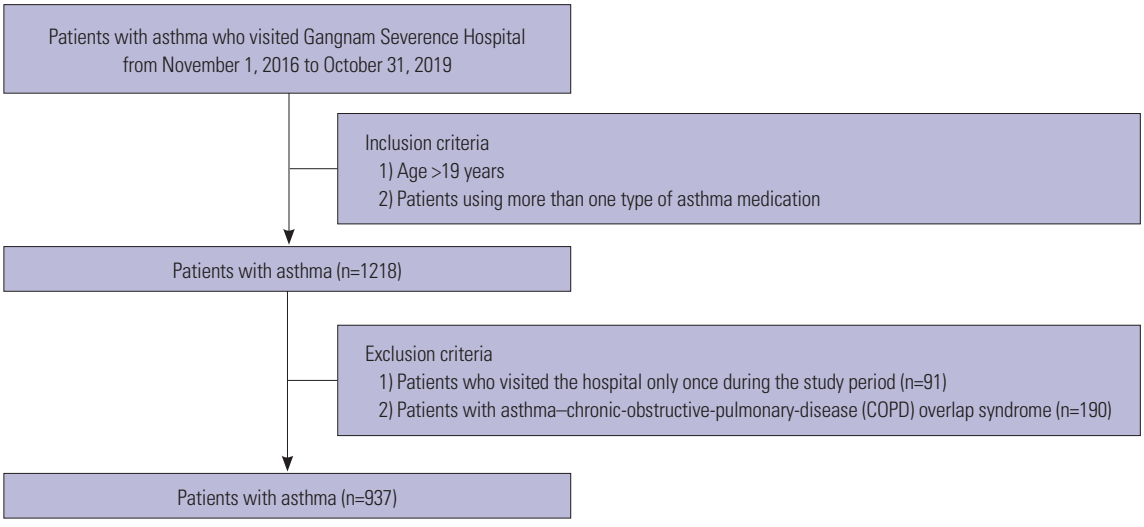

Fig. 1. Schematic diagram of study design.

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type. To evaluate the multicollinearity between variables, the variance inflation factor (VIF) of each variable was calculated; variables >5 in VIFs were omitted in multivariate Cox regression analyses.

Kaplan–Meier curves were drawn to evaluate cumulative asthma exacerbations among the groups. *P*-values <0.05 were considered statistically significant. All statistical analyses were conducted with R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Survival analysis was conducted using the "survminer" R package.

RESULTS

Baseline characteristics and clinical outcomes

Among 937 patients with asthma, 228 experienced exacerbation during the study period. The average age at baseline was 45.0 years, and most patients were female (58.5%). Baseline age, sex, body mass index (BMI), and CCI were not significantly different between the non-exacerbation and exacerbation groups (Table 1). However, baseline pulmonary function tests [FVC, FEV_1, and forced expiratory flow at 25%–75% of FVC ($FEF_{25–75\%}$)] showed significantly worse results in the exacerbation group than in the non-exacerbation group. All-cause mortality rate was significantly higher in the exacerbation group (n=4; 1.8%) than in the non-exacerbation group (n=1; 0.1%; p=0.017).

Differences in asthma medication use between groups

To determine which medication type more effectively prevents asthma exacerbations, we compared the usage of asthma medication between patients with and without exacerbation. In the exacerbation group, the percentage of SABA-only users (50.4%) was higher than that in the non-exacerbation group (28.6%, p<0.001). Conversely, the percentage of ICS (59.7% vs. 41.2%, p<0.001), LABA (63.9% vs. 45.2%, p <0.001), LTRA (49.2% vs. 28.5%, p<0.001), and xanthine (19.3% vs. 12.7%, p=0.023) users was higher in the non-exacerbation group than in the exacerbation group (Table 2). There was no significant difference in the percentage of LAMA users between the groups (3.1% vs. 2.2%, p=0.626).

Results of time-varying Cox regression for asthma exacerbation

Time-varying Cox regression with consideration of the usage duration of asthma medication showed that some type of asthma medication can be significantly associated with asthma exacerbation. In the univariate subgroup analysis according to

Table 1. Baseline Characteristics and Clinical Outcomes of Study Subjects

Group	Total (n=937)	Non-exacerbation group (n=709)	Exacerbation group (n=228)	*p* value
Baseline characteristics				
Age (yr)	45.0 [33.0; 57.0]	44.0 [33.0;57.0]	46.5 [33.0; 57.0]	0.792
Sex				0.426
Male	389 (41.5)	300 (42.3)	89 (39.0)	
Female	548 (58.5)	409 (57.7)	139 (61.0)	
BMI (kg/m^2)	23.4 [21.0; 25.9]	23.2 [21.1;25.8]	23.6 [20.5; 26.2]	0.757
CCI score				0.114
0	541 (57.7)	425 (59.9)	116 (50.9)	
1	232 (24.8)	167 (23.6)	65 (28.5)	
2	73 (7.8)	53 (7.5)	20 (8.8)	
Above 3	91 (9.7)	64 (9.0)	27 (11.8)	
Pulmonary function test at first visit				
FVC (L)	3.5 [2.9; 4.3]	3.6 [3.0; 4.4]	3.4 [2.8; 4.1]	0.017
FVC (z-score)	-0.5 [-1.4; 0.5]	-0.4 [-1.4; 0.5]	-0.7 [-1.6; 0.4]	0.021
FEV_1 (L)	2.6 [2.1; 3.2]	2.7 [2.1; 3.3]	2.4 [1.9; 2.9]	<0.001
FEV_1 (z-score)	-1.2 [-2.2; -0.3]	-1.1 [-2.0; -0.2]	-1.6 [-2.7; -0.6]	<0.001
FEV_1/FVC (%)	0.8 [0.6; 0.8]	0.8 [0.7; 0.8]	0.7 [0.6; 0.8]	0.010
FEV_1/FVC (z-score)	-1.3 [-2.5; -0.3]	-1.1 [-2.4; -0.3]	-1.4 [-3.1; -0.5]	0.003
$FEF_{25–75\%}$ (L/sec)	2.1 [1.2; 3.0]	2.2 [1.3; 3.1]	1.8 [0.9; 2.8]	0.001
$FEF_{25–75\%}$ (z-score)	-1.1 [-2.3; -0.1]	-1.0 [-2.0; -0.1]	-1.6 [-2.8; -0.4]	0.001
Clinical outcomes				
Mortality	5 (0.5)	1 (0.1)	4 (1.8)	0.017

BMI, body mass index; CCI, Charlson comorbidity index; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; $FEF_{25–75\%}$, forced expiratory flow at 25%–75%.
Data are presented as median [quartile 1; quartile 3] or number (%).

Table 2. Usage of Asthma Medication according to Exacerbation Occurrence

Group	Total (n=937)	Non-exacerbation group (n=709)	Exacerbation group (n=228)	*p* value
SABA				
Non-SABA group	151 (16.1)	116 (16.4)	35 (15.4)	0.718
SABA only	318 (33.9)	203 (28.6)	115 (50.4)	<0.001
SABA with other treatment	468 (49.9)	390 (55.0)	78 (34.2)	<0.001
ICS				
Non-ICS group	420 (44.8)	286 (40.3)	134 (58.8)	<0.001
Beclometasone group	19 (2.0)	16 (2.3)	3 (1.3)	0.381
Budesonide group	74 (7.9)	63 (8.9)	11 (4.8)	0.048
Ciclesonide group	9 (1.0)	8 (1.1)	1 (0.4)	0.353
Fluticasone group	362 (38.6)	296 (41.7)	66 (28.9)	<0.001
Switch group*	53 (5.7)	40 (5.6)	13 (5.7)	0.973
LABA				
Non-LABA group	381 (40.7)	256 (36.1)	125 (54.8)	<0.001
LABA inhaler group	438 (46.7)	360 (50.8)	78 (34.2)	<0.001
LABA p.o. group	48 (5.1)	39 (5.5)	9 (3.9)	0.857
Switch group*	70 (7.5)	54 (7.6)	16 (7.0)	0.765
LAMA (tiotropium)	27 (2.9)	22 (3.1)	5 (2.2)	0.626
LTRA				
Non-LTRA	523 (55.8)	360 (50.8)	163 (71.5)	<0.001
Montelukast	395 (42.2)	339 (47.8)	56 (24.6)	<0.001
Pranlukast	18 (1.9)	9 (1.3)	9 (3.9)	<0.001
Switch group*	1 (0.1)	1 (0.1)	0 (0.0)	>0.999
Xanthine				
Non-xanthine	771 (82.3)	572 (80.7)	199 (87.3)	0.023
Aminophylline	5 (0.5)	4 (0.6)	1 (0.4)	0.821
Doxofylline	9 (1.0)	6 (0.8)	3 (1.3)	0.527
Theophylline	148 (15.8)	123 (17.3)	25 (11.0)	0.021
Switch group*	4 (0.4)	4 (0.6)	0 (0.0)	>0.999

SABA, short-acting β_2-agonist inhaler; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist inhaler; LTRA, leukotriene receptor antagonist.
*Switch group includes patients who changed to a different ingredient within the same medication type.

drug class, the long-term use of SABA alone without ICS significantly increased the risk of asthma exacerbation [hazard ratio (HR), 2.448; 95% confidence interval (CI), 1.908–3.141; $p<0.001$]. In contrast, ICS-LABA significantly decreased the risk of asthma exacerbation (HR, 0.541; 95% CI, 0.417–0.701; $p<0.001$). Since SABA-only and ICS-LABA treatments were negatively correlated with each other (VIF=5.210), we separated these two variables in the multivariate analysis, which showed similar results after adjusting for age, sex, BMI, CCI, and other drug use (SABA-only in the multivariable analysis A: HR, 1.834; 95% CI, 1.299–2.588; $p=0.001$ and ICS-LABA in the multivariable analysis B: HR, 0.733; 95% CI, 0.538–0.997; $p=0.048$) (Table 3). In the multivariate analysis B (with ICS-LABA), LTRA (HR, 0.577; 95% CI, 0.396–0.839; $p=0.004$) and xanthine (HR, 0.413; 95% CI, 0.182–0.940; $p=0.035$) were significantly associated with a lower risk of asthma exacerbation. However, in the subgroup analysis according to each medication type, the ingredients did not show significant effects or differences in the multivariate analysis (Table 3).

Kaplan–Meier analysis of asthma exacerbation

A Kaplan–Meier analysis with log-rank test was used to define the effect of each specific drug use on asthma exacerbation. SABA-only users were more likely to have asthma exacerbation compared to other patients (total $p<0.001$) (Fig. 2A). Non-ICS users tended to have a higher likelihood of asthma exacerbation than ICS users (total $p<0.001$), with no significant difference according to the ICS therapeutic agent (Fig. 2B). Inhaled LABA use significantly reduced the risk of asthma exacerbation (total $p<0.001$) (Fig. 2C), and LAMA also showed a protective effect (total $p=0.014$) (Fig. 2D). Montelukast users had a better prognosis for asthma exacerbation compared to non-LTRA users; however, the same was not observed among pranlukast users ($p<0.001$ and $p=0.991$, respectively) (Fig. 2E). In addition, theophylline use seemed to be a preventive factor for asthma exacerbation (total $p=0.013$) (Fig. 2F).

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Table 3. Time-Varying Cox Regression Analysis of Asthma Exacerbations

Variables	Univariate analysis		Multivariate analysis A		Multivariate analysis B	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (yr)	0.988 (0.979–0.996)	0.005	0.990 (0.981–1.000)	0.047	0.989 (0.979–0.998)	0.023
Sex, male	0.987 (0.779–1.250)	0.913	0.940 (0.718–1.231)	0.654	0.930 (0.710–1.217)	0.595
Initial BMI	0.970 (0.939–1.003)	0.071	0.983 (0.949–1.018)	0.332	0.984 (0.950–1.018)	0.346
CCI score	0.913 (0.831–1.002)	0.055	0.964 (0.879–1.058)	0.440	0.964 (0.879–1.058)	0.439
Treatment						
Medication type*						
SABA only	2.448 (1.908–3.141)	<0.001	1.834 (1.299–2.588)	0.001	Omitted	
ICS-LABA	0.541 (0.417–0.701)	<0.001	Omitted		0.733 (0.538–0.997)	0.048
ICS single inhaler	1.033 (0.426–2.507)	0.942	1.558 (0.628–3.866)	0.339	1.015 (0.413–2.498)	0.974
LTRA	0.459 (0.335–0.629)	<0.001	0.724 (0.478–1.097)	0.128	0.577 (0.396–0.839)	0.004
Xanthine	0.347 (0.171–0.702)	0.003	0.518 (0.225–1.194)	0.123	0.413 (0.182–0.940)	0.035
LABA p.o.	0.573 (0.282–1.164)	0.124	0.815 (0.351–1.892)	0.634	0.557 (0.245–1.264)	0.162

Drug ingredient analysis in subgroups	Univariate analysis		Multivariate analysis†	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
ICS-LABA use group				
Beclometasone-formoterol	0.724 (0.266–1.972)	0.528	0.687 (0.235–2.013)	0.494
Budesonide-formoterol	0.801 (0.403–1.592)	0.526	0.676 (0.295–1.551)	0.356
Fluticasone-formoterol	1.754 (1.166–2.639)	0.007	1.290 (0.695–2.395)	0.420
Fluticasone-salmeterol	0.287 (0.071–1.166)	0.081	0.272 (0.062–1.191)	0.084
Fluticasone-vilanterol	1.892 (1.172–3.055)	0.009	1.614 (0.818–3.186)	0.167
LTRA use group				
Pranlukast	1.400 (0.343–5.717)	0.639	0.733 (0.095–5.646)	0.766
Montelukast	1.747 (1.134–2.691)	0.011	1.210 (0.713–2.053)	0.480
Xanthine use group				
Aminophylline	0.000 (0.000–999.999)	0.997		
Doxofylline	2.108 (0.494–8.993)	0.314	1.610 (0.345–7.501)	0.544
Theophylline	2.464 (0.954–6.361)	0.062	1.414 (0.491–4.075)	0.521

HR, hazard ratio; CI, confidence interval; BMI, body mass index; CCI, Charlson comorbidity index; SABA, short-acting β_2-agonist inhaler; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist inhaler; LTRA, leukotriene receptor antagonist.
*In the medication type, "SABA-only" was highly correlated with "ICS/LABA." Therefore, we separated "SABA-only" and "ICS/LABA" in the multivariate analysis; †Each variable was adjusted for age, sex, CCI score, initial BMI, and other medication use.

DISCUSSION

This real-world study showed that different types of asthma medications can have variable effects on the risk of exacerbation. We used a time-varying Cox regression analysis to reflect the real-world setting while considering the duration of asthma medication use, drug discontinuation, and switch to other medication types. To the best of our knowledge, this is the first study to compare the effects of asthma medications using a time-varying Cox regression analysis to reflect the real-world setting. In addition, we also used a simple Kaplan–Meier analysis with log-rank test to simplify subgroup comparisons. These two analyses showed similar results: 1) long-term use of SABA alone was a significant risk factor for asthma exacerbation; 2) ICS/LABA combination reduced the risk of asthma exacerbation; and 3) there was no significant difference according to the ingredients of asthma medication in asthma exacerbation.

Recent GINA guidelines recommend against the prescription of SABA-only treatment without ICS in all patients with asthma. SABA can relieve acute symptoms; however, it cannot control inflammation or prevent exacerbation, and can even aggravate hyper-responsiveness.[4] A recent big data study demonstrated that high SABA inhaler use was significantly associated with an increase in exacerbation risk and asthma-related healthcare utilization.[14] Moreover, recent well-designed studies have revealed that ICS treatment can reduce the risk of asthma exacerbation compared to SABA-only treatment,[6,15] which is supported by the findings of the present real-world study. Therefore, ICS-containing therapy is more preferable than SABA-only treatment in patients with asthma.

In this study, the percentage of SABA-only treatment in the previous year was 35%, which could be considered high. However, previous studies have shown a similar SABA prescription rate or prevalence of overuse (8%–58%) globally.[14,16,17] Since many patients with asthma have been dependent on SABA for numerous years, they easily recognize the small difference in

onset time between SABA and rapid-onset LABA. Various patients with asthma want to use SABA, and many physicians are also accustomed to this classical prescription. As previously described, the GINA report no longer recommends SABA-only therapy[18]; therefore, this prescription pattern is expected to change. Nevertheless, it may take a long time before this change

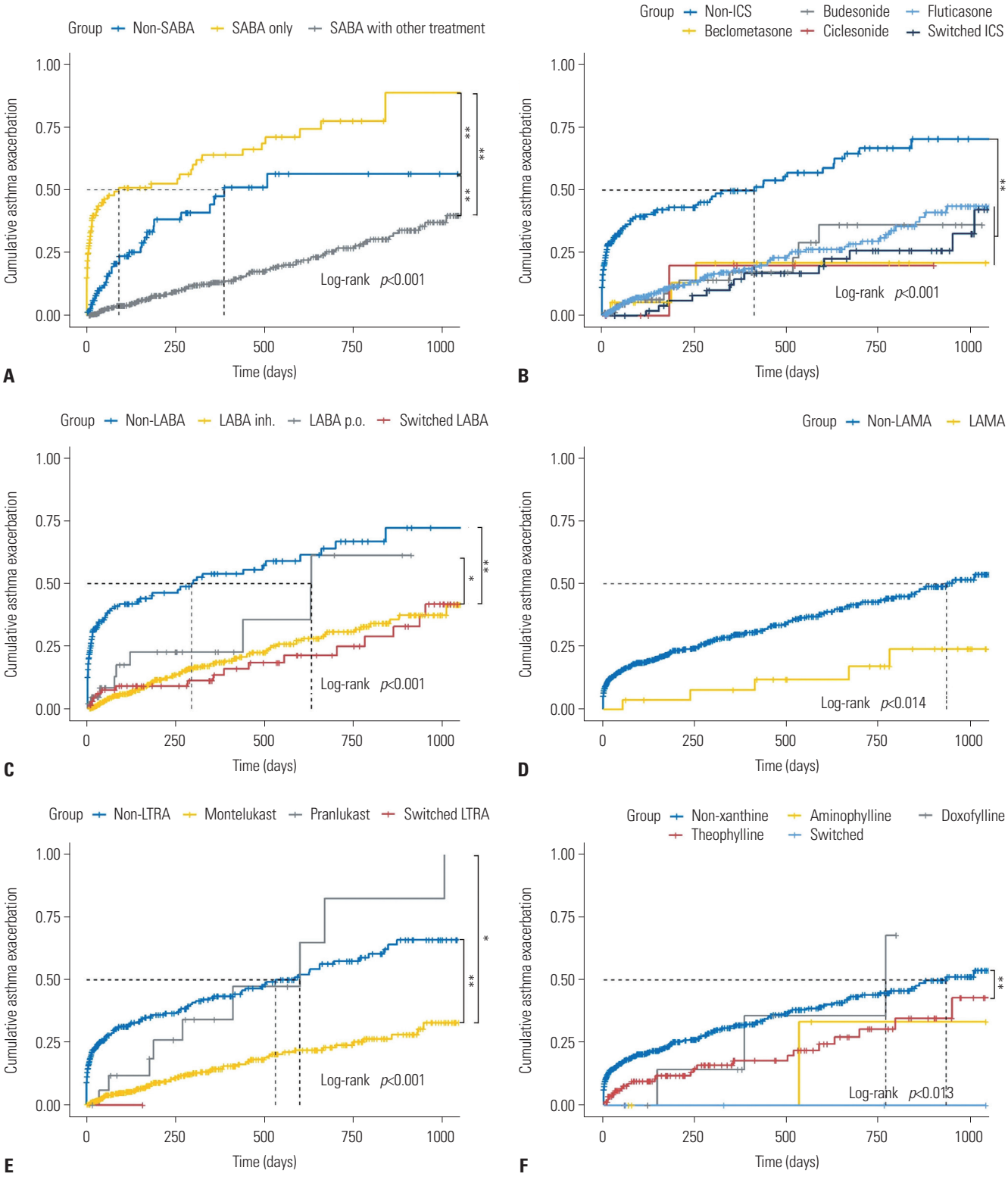

Fig. 2. Kaplan–Meier curve for asthma exacerbation. (A) SABA group. (B) ICS group. (C) LABA group. (D) LAMA group. (E) LTRA group. (F) Xanthine group. *p<0.05, **p<0.01. SABA, short-acting β_2-agonist inhaler; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist inhaler; LAMA, long-acting muscarinic antagonist inhaler; LTRA, leukotriene receptor antagonist.

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is translated into clinical practice.

ICS-LABA is a fundamental treatment option in asthma. This real-world study also confirmed that the long-term use of ICS-LABA can prevent asthma exacerbations. Previous studies have revealed that use of ICS-LABA can improve asthma prognosis.[19] However, compliance with ICS-LABA therapy is not sufficient in the real-world setting.[20] Many patients with asthma do not use ICS-LABA daily, saving the inhaler use for specific occasions; they frequently stop the treatment regimen and also frequently switch to other inhalers. The time-varying Cox regression analysis used in this study revealed that the longer ICS-LABA was used, the less likely it was for asthma exacerbations to occur. In addition, the preventive effects of ICS and LABA in asthma exacerbation were also demonstrated both in the Kaplan–Meier curve and in the history of previous asthma medication in this study. Conversely, ICS alone did not show significant preventive effect on asthma exacerbation in the current study. Among the patients included in this study, 11 patients used ICS alone, accounting for 1.2% of total patients, and only one of them experienced acute asthma exacerbation during the study period. In the analysis of time-varying Cox regression, the ICS-alone prescription date was 4480 days compared to the total prescription date of 217708 days, and the ratio was 2.1%. Since ICS alone may not have shown statistical effectiveness due to the very small number of days, further research is needed.

LTRA and xanthine also showed significant effects in multivariate analysis A. However, this effect was not present in multivariate analysis B, and the statistical significance was relatively weak compared to SABA alone and ICS-LABA. LTRA and xanthine are recommended as secondary options for asthma control in the GINA guidelines, since previous studies have demonstrated that they have an effect, which is significant but not superior to ICS with and without LABA.[21] More specifically, the effects of LTRA have been shown to be more pronounced in older and female patients.[22,23] Xanthine has also shown significant effects in patients with asthma.[24] All of these are good alternatives for patients with asthma; however, ICS-LABA should be the preferred option.

This study aimed to differentiate the effects of various types of asthma medications according to specific ingredients; however, we could not find any ingredient-related differences. Some previous studies, including well-designed randomized controlled trials and network meta-analyses, have attempted to compare the effects of asthma medications, and have revealed no significant differences in efficacy according to the active ingredients.[25] Although we could not include sufficient data, the current study also showed no active ingredient-related differences in a time-varying Cox regression analysis. Some active ingredients (pranlukast, oral LABA, and theophylline) showed a significant difference compared with others in the Kaplan–Meier curve and in the history of previous asthma medication; however, further large-scale studies are needed to confirm this.

To the best of our knowledge, this is the first study to confirm the effects of different asthma medication types in exacerbation risk using a time-varying Cox regression to reflect aspects of the real-world setting, such as variable usage duration, frequent discontinuation, and switch between medication types. We also used a simple Kaplan–Meier curve and chi-square test to analyze the history of previous asthma medication use. Since these methods showed similar results, we consider our findings to be reliable. However, this study also had some limitations, as it was designed as a single-center design that only included a small number of participants. Additionally, the multivariate analysis of drug active ingredients showed non-significant findings in all types of asthma medications. Moreover, in some subgroups (for example, pranlukast and aminophylline), the number of patients was too small to interpret the results. Lastly, we could not adjust for other clinical factors, such as the attending physician, inhaler technique, and adherence rate.

In conclusion, this study confirmed that SABA-only treatment without ICS-containing inhaler is frequently prescribed, and it significantly increases the risk of asthma exacerbation in a real-world setting. The longer the patients with asthma use ICS-LABA, the less likely they experience exacerbation. However, we could not obtain significant results regarding the ingredients of asthma medications. Further subgroup analyses are needed to define the differences between specific ingredients.

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AUTHOR CONTRIBUTIONS

Conceptualization: Hye Jung Park. Data curation: Chang-Hwa Kim and Jaeuk Lee. Formal analysis: Yong Jun Choi and Hye Jung Park. Funding acquisition: Hye Jung Park. Investigation: Yong Jun Choi and Hye Jung Park. Methodology: Min Kwang Byun, Jae Hwa Cho, and Hye Jung Park. Project administration: Chang-Hwa Kim. Resources: Yong Jun Choi and Hye Jung Park. Software: Yong Jun Choi. Supervision: Min Kwang Byun, Jae Hwa Cho, and Hye Jung Park. Validation: Min Kwang Byun and Hye Jung Park. Visualization:Yong Jun Choi and Hye Jung Park. Writing—original draft: Yong Jun Choi and Hye Jung Park. Writing—review & editing: Yong Jun Choi and Hye Jung Park. Approval of final manuscript: all authors.

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