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Original Article

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Real-world Treatment Patterns, Outcomes, and Healthcare Resource Utilization in Newly Treated Korean Patients With Asthma: A Retrospective Cohort Study

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ABSTRACT

Purpose: Although asthma treatment guidelines recommend regular inhaled medication, real-world treatment patterns and outcomes in South Korea have not been examined. We examined real-world treatment patterns and outcomes among patients treated for asthma in South Korea.
Methods: This retrospective cohort study utilized data from the South Korean National Health Insurance database (2013–2016). Newly treated patients with asthma aged ≥18 years without history of chronic obstructive pulmonary disease were included. Initial and maintenance medication prescriptions were examined. Treatment discontinuation and switch were described. Asthma exacerbation rates, poor asthma control, and healthcare resource utilization (HRU) were compared between maintenance treatment groups (inhaled versus oral) using adjusted incidence rate ratios (aIRR) and hazard ratios (aHR).
Results: Overall, 1,054,707 patients initiated any asthma medication; 37,868 patients initiated inhaled (n = 9,983, 26.4%) or oral (n = 27,885, 73.6%) maintenance medication. More patients initiating inhaled versus oral asthma medication discontinued treatment within 12 months (94.4% vs. 86.3%; $P < 0.0001$). Patients treated with inhaled and oral medication switched treatment (2.5% and 2.3%; $P = 0.4160$, respectively). Patients initiating inhaled medication had significantly lower rates of asthma exacerbation (aIRR, 0.52; 95% CI, 0.39–0.69), lack of asthma control (aHR, 0.55; 95% CI, 0.48–0.62; $P < 0.0001$), all-cause and asthma-related HRU versus oral medication.
Conclusions: Despite current asthma guidelines, more patients in South Korea were prescribed oral than inhaled medications, resulting in suboptimal asthma management and

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Disclosure

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Data Sharing Statement

This study was conducted using Korean health insurance claims data. We were granted access to data from the HIRA during the study period. Since all data are kept and managed by HIRA, the authors are not authorized to provide related research data to third parties.

increased HRU. This study highlights the need to reduce oral corticosteroid prescriptions for optimized treatment in asthma management.

Keywords: Asthma; clinical guidelines; primary care; pharmacology; inhalation devices; health resource; Korea

INTRODUCTION

Asthma is a common chronic respiratory disorder[1] affecting more than 350 million people globally.[2] The prevalence of asthma among adults in South Korea is 2%–8%[3-5] and increasing over time.[1,5] South Korea's National Health Insurance (NHI) database estimated that the prevalence of asthma increased from 4,944 to 5,707 patients per 100,000 adults from 2006 to 2010.[7]

An important treatment goal in asthma is to achieve and maintain asthma control, which is made possible by optimal medication and adherence.[1-8] The Korean Asthma Guidelines recommend initial treatment with inhaled corticosteroid (ICS)-containing controller medication, with oral medications such as leukotriene receptor antagonist (LTRA) or theophylline (monotherapy or with ICS) as other controller options, but they only recommend short-acting beta$_2$-agonist (SABA) as an as-needed reliever. Add-on treatment to inhaled medications includes oral corticosteroids (OCS), which was recommended by both the Global Initiative for Asthma (GINA) and the Korean Asthma Guidelines.[1-8]

There are barriers to implementing these guidelines in clinical practice. For example, oral medications (LTRA and OCS) are frequently prescribed in South Korea,[9,10] and are more commonly prescribed by primary care physicians than ones at secondary or tertiary care. This is important because most patients with asthma in South Korea are managed in a primary care setting.[10,11] Common internal barriers to prescribing inhaled medications include patients' preferences for oral medications, difficulty in using inhalers even with proper training, and concern over ICS side effects. Common external barriers are patient refusal, cost, and a shortage of time for physicians to train patients in proper inhaler technique.[9]

Prescription of inadequate asthma medication may lead to increased hospital admissions and poorer patient outcomes,[12-14] affecting clinical outcomes and quality of life,[15,16] with consequent societal economic and healthcare burdens.[16,17] Using the Health Insurance Review and Assessment Service (HIRA) database, which covers 98% of the total population of South Korea,[18] we examined the real-world treatment patterns of newly diagnosed patients with asthma and compared clinical and economic outcomes between patients initiating inhaled versus oral asthma maintenance medication.

MATERIALS AND METHODS

Data source

Data entered in the Korean NHI database from 1 January 2013 to 31 December 2016 were extracted for this study. The Korean HIRA, an independent group created to review medical claims data and to assess the quality of healthcare in the country, provided HIRA database access to study collaborators in South Korea (See **Supplementary Data S1**).

Study design

This was a retrospective, longitudinal, open-cohort study (**Fig. 1** and **Supplementary Fig. S1**). All definitions of the terms described in the methods can be found in **Table 1**. Patients were included according to the following criteria: ≥ 18 years of age, ≥ 1 asthma diagnosis

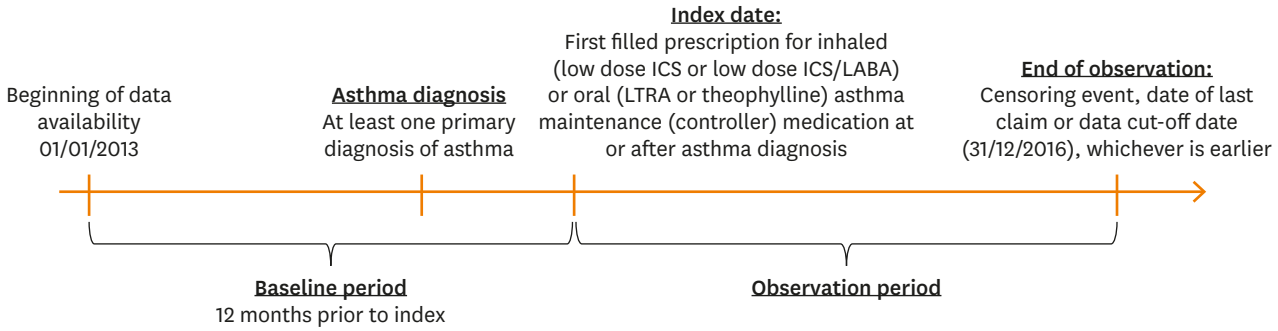

Fig. 1. Study design scheme for asthma prescribing patterns for asthma maintenance medications (not to scale).
ICS, inhaled corticosteroids; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene-receptor antagonist.

Table 1. Definitions of outcomes

Term	Description
All-cause and asthma-related HRU events	HRU outcomes were outpatient visits, ER visits and hospitalizations and length of hospitalization. Asthma-related HRU events had a claim with a primary or secondary diagnosis of asthma (ICD-10 code: J45.x–J46.x)
Baseline period	Among patients initiating asthma medication, the baseline period was defined as the 12-month period prior to the first prescription for any asthma medication. Among patients who initiated on either inhaled or oral asthma maintenance medication, the baseline period was defined as the 12-month period prior to the first prescription for an asthma maintenance medication
Confounders	Data on the following potential confounders were collected in the 12-month baseline period prior to, or on, the index date: demographic characteristics, asthma-related comorbidities, use of selected medications (injectable steroids, antibiotics), recorded as Yes/No; baseline all-cause, asthma-comorbidity-related, and asthma-related HRU; CCI* comorbidities, physician specialty, institutional setting
Discontinuation (of index asthma maintenance medication)	A gap of ≥ 90 days between the end of the days of supply of one prescription claim and the beginning of a subsequent prescription claim. Combination regimens: if one medication was discontinued prior to another in the same regimen, discontinuation was defined as a gap of ≥ 90 days between the end of days of supply of one prescription claim and the beginning of a subsequent prescription claim for the last medication in the combination
Exacerbation event	Defined as: a) treatment with OCS with an average daily dose† of ≥ 20 mg prednisone (or equivalent) that lasted for ≥ 3 days with an asthma code recorded in any resource utilization setting within ± 14 days. In order for two adjacent OCS prescription claims to be counted as two independent events (i.e. exacerbations), the two OCS prescription claims must have occurred ≥ 7 days apart; or b) an asthma-related ER visit (diagnosis codes: ICD-10-CM: J45.x–J46.x) with a linked prescription claim for OCS or injectable steroids, or a prescription within ± 7 days of the visit; or; c) an asthma-related hospitalization (discharge codes: ICD-10-CM: J45.x–J46.x) with a linked prescription claim for OCS or injectable steroids, or a prescription claim within ± 7 days of the hospitalization
Index date	For patients initiating asthma medication, index date was defined as the date of the first prescription for any asthma medication. For patients initiating either inhaled or oral asthma maintenance medication, index date was defined as the date of first prescription for asthma maintenance medication when there was a 30-day cumulative prescription of the maintenance medication within 3 months of the index date
Medication augmentation	Addition of a new medication (prescription ≥ 60 days) to the index medication, prior to first discontinuation of the index medication, or a prescription for a new medication (lasting ≥ 60 days) of which the index medication was a component within 30 days of discontinuation of index medication
Poor asthma control/lack of asthma control	Escalation of care from primary to secondary or tertiary care settings (i.e. having an asthma-related visit in the next level of care) or medication augmentation was a proxy for lack of asthma symptom control
Switch (to another type of asthma maintenance medication)	A claim of a maintenance medication different from the index medication (i.e. oral to inhaled or vice versa) 90 days after the end of the days of supply of the index medication, and no continued use of the index medication. For a combination regimen, switching was defined as a claim of a maintenance medication different from medications in the index combination 90 days after the end of days of supply of the last medication in the combination, and no continued use of any medications from the index combination

HRU, healthcare resource utilization; ER, emergency room; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; CCI, Charlson Comorbidity Index; OCS, oral corticosteroids.
*A modified CCI without chronic pulmonary disease and malignancies was used (patients with these diagnosis codes were excluded at baseline); †The average daily dose of OCS = (number of tablets × tablet strength) / number of days supplied.

claim (International Classification of Diseases, 10th Revision [ICD-10] codes J45, J46)[19] between 2013–2015, ≥ 1 filled prescription of asthma medication (**Supplementary Table S1**) on or after asthma diagnosis, and with ≥ 12-month continuous eligibility prior to the index date (baseline period) without a filled asthma medication prescription. For all analyses, patients with ≥ 1 chronic obstructive pulmonary disease diagnosis claim (ICD-10-CM codes J40, J41.x, J42, J43.x, and J44),[1] ≥ 1 inpatient diagnosis of malignancy and ≥ 2 outpatient diagnoses of malignancy in the 12 months prior to index date were excluded. Among patients initiating either inhaled or oral asthma maintenance medication, those with prescriptions for both inhaled and oral asthma medication up to 30 days after the index date (excluding prescriptions during hospitalization) were excluded. For the analysis of inhaled versus oral maintenance asthma medications (defined in **Supplementary Table S1**), maintenance medication was defined as a 30-day cumulative drug supply of inhaled or oral asthma maintenance medication (*i.e.,* low dose ICS, low dose ICS/LABA, LTRAs, or theophylline) within 3 months of treatment initiation on or following an asthma diagnosis. To identify initiation of maintenance therapy, maintenance asthma medications were consistent with GINA Steps 2 and 3 (**Supplementary Data S1**).

Age, sex, insurance type, medical physician specialty, healthcare institutional setting at index date, asthma-related comorbidities (defined by ICD-10 codes; and their related healthcare resource utilization [HRU]), all-cause HRU, asthma-related HRU, and diagnoses of comorbidities that form the Charlson Comorbidity Index during the 12 months period (baseline) prior to the index date were identified.

Outcomes

For patients initiating asthma medication, dispensing of asthma medication during the 1-year post-index period was reported by the institutional setting at index date. Number of prescriptions and days of supply for each asthma medication (**Supplementary Table S1**) were reported. Among patients initiating inhaled or oral asthma maintenance medication, index treatment discontinuation and switch (See **Table 1** for full outcomes definitions) and frequency of clinical events 30 days prior to discontinuation or switching were reported; clinical events of interest included asthma exacerbations, all-cause and asthma-related (associated with an asthma ICD-10 diagnosis code, *i.e.* J45.x–J46.x) hospitalizations, OCS prescription, and claim for pulmonary function test. Episodes of poor asthma control, exacerbations and all-cause and asthma-related HRU events *(i.e.* outpatient visits, emergency department [ED] visits, hospitalizations, and ER visit or hospitalization in *post hoc* analysis) were also described. Poor asthma control, exacerbations, and HRU events were assessed from index date until 60 days after deviating from index asthma maintenance medication, to account for any carry-over effects after index treatment discontinuation, augmentation, or switch.

Statistical analysis

Summary statistics are presented, including mean ± standard deviation for continuous data, and relative frequencies and proportions for categorical data. For comparing patients who initiated inhaled versus oral asthma medications, continuous variables were compared using *t* tests and Wilcoxon rank- and chi-squared tests for categorical variables. Kaplan-Meier analysis was used to estimate time to event (*e.g.*, discontinuation and switch) while censoring those without the event of interest. Unadjusted and propensity score-adjusted Cox proportional hazard models were used to evaluate the risk of lack of asthma control and exacerbation for inhaled versus oral maintenance medication; hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Unadjusted and propensity score-adjusted Poisson

regression was used to compare asthma exacerbation rates; incidence rate ratios (IRRs) are presented with 95% CIs. The impact of initiating inhaled versus oral medications on each HRU outcome was evaluated using unadjusted and propensity scored-adjusted negative binomial models (and zero-inflated negative binomial model for ED visits and hospitalization to adjust for a large number of patients with zero events); results are presented as IRRs with 95% CIs. Propensity scores were used to adjust for measured baseline confounding variables. Analyses were stratified by ≥ 3 and < 3 secondary/tertiary care visits for asthma-related events per year.

All statistical analyses were conducted using SAS Enterprise Guide, version 7.1 (SAS Institute, Cary, NC, USA), and the programs were independently reviewed to ensure that the protocol was reflected consistently. All statistical tests were 2-sided; $\alpha = 0.05$.

Ethics statement

This study underwent full protocol review and approval by the Institutional Review Board of Ewha Womans University (EWIRB-20-3.0-20170901). Patient-level HIRA data that did not contain patient-identifiable information were provided. After performing data analysis, we received an aggregated results table from the HIRA. No intervention was provided to patients. Patients were not contacted during the course of the study.

RESULTS

Study population

Overall, 2,427,446 patients with ≥1 claim with an associated asthma diagnosis code between 2013–2015 in HIRA data were identified. Of these, 1,054,707 and 37,868 were eligible for inclusion in the analyses for those initiating any asthma medication and maintenance medications, respectively (**Fig. 2** and **Supplementary Fig. S2**).

Inhaled versus oral asthma maintenance medications

Among 37,868 patients initiating asthma maintenance medication, 9,983 (26.4%) received inhaled and 27,885 (73.6%) received oral medication. The demographics and clinical characteristics of these patients are summarized in **Table 2**.

Treatment discontinuation and switch over

Significantly more patients initiating inhaled versus oral maintenance medication discontinued treatment within 12 months (9,421 [94.37%] vs. 24,074 [86.33%]; $P < 0.0001$; **Table 3**). Some patients treated with inhaled and oral asthma medication switched treatment and there were no significant differences in those experiencing treatment switch (246 [2.5%] vs. 647 [2.3%]; $P = 0.4160$). Prior to discontinuing treatment, patients treated with inhaled versus oral maintenance medication experienced significantly fewer clinical events, such as all-cause hospitalization (2.4% vs. 6.1%; $P < 0.0001$) and OCS prescription (6.8% vs. 17.4%; $P < 0.0001$).

Uncontrolled asthma and asthma exacerbation events

Patients receiving inhaled maintenance medication had fewer exacerbations than those receiving oral medication (**Table 4**). Asthma exacerbation rate per 1,000 person-years was 19.00 (95% CI, 14.69–24.58) for those initiating inhaled medication and 37.61 (95% CI, 34.03–41.56) for those initiating oral medication. After propensity score adjustments, the IRR for asthma exacerbations remained lower for inhaled versus oral medication (0.52 [95% CI, 0.39–0.69]). Similar associations were found in the analysis stratified by ≥ 3 and < 3

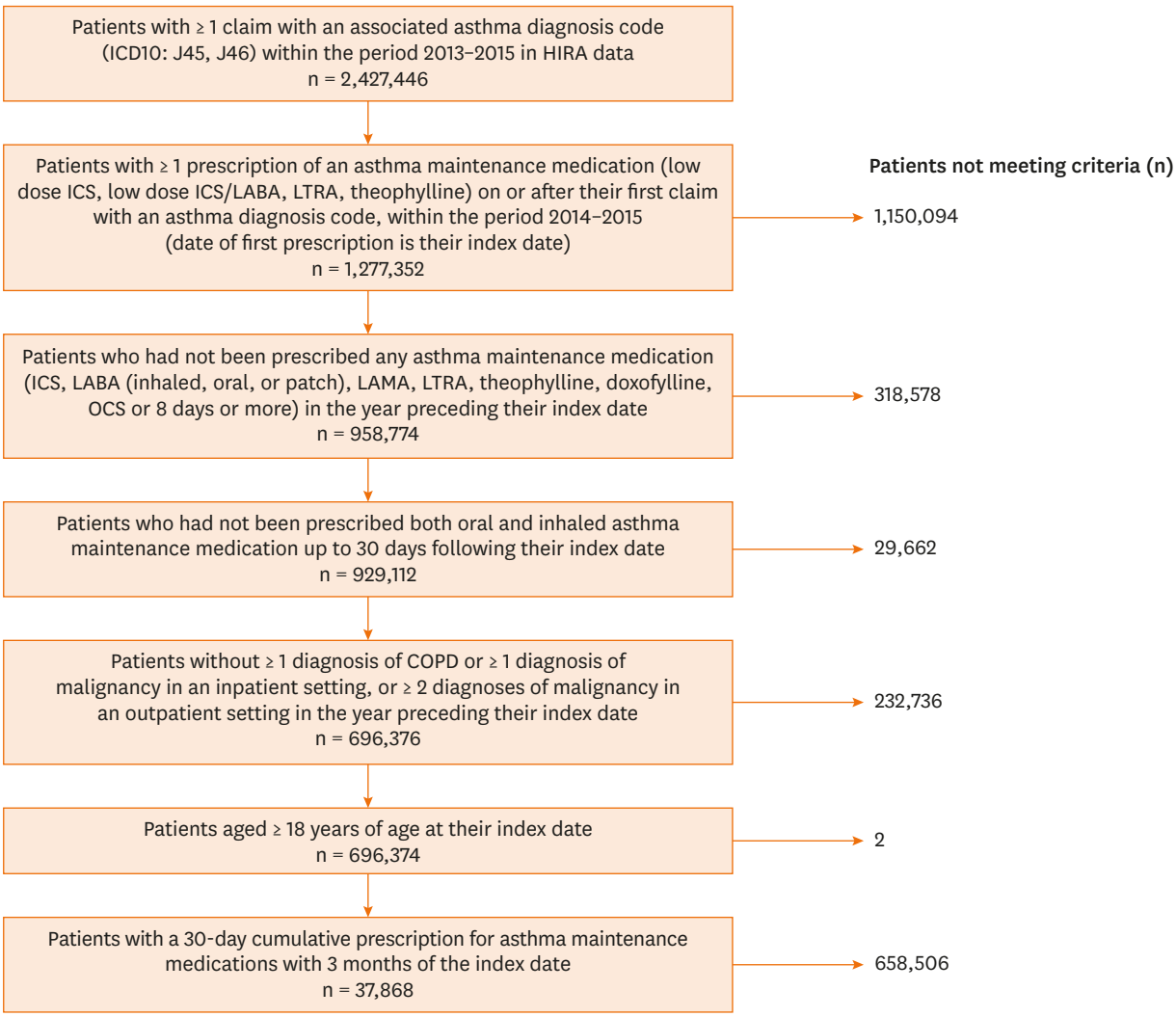

Fig. 2. Patient selection for prescribing patterns, clinical outcomes and healthcare resource utilization for inhaled versus oral treatment asthma maintenance medication.
ICD-10, International Classification of Disease, 10th Revision; HIRA, Health Insurance Review and Assessment Service; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonist; LRTA, leukotriene-receptor antagonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids; COPD, chronic obstructive pulmonary disease.

secondary/tertiary care visits for asthma per year. Patients treated with inhaled medication were less likely to experience poor asthma control and exacerbations than those treated with oral medication. After propensity score adjustments, the HR for poor asthma control was significantly lower for inhaled versus oral medication (0.55 [95% CI, 0.48–0.62]; $P < 0.0001$). A significantly lower HR was observed for first exacerbation for inhaled versus oral medication (0.51 [95% CI, 0.35–0.75]; $P = 0.0005$). Similar associations were found in the analysis stratified by ≥ 3 and < 3 secondary/tertiary care visits for asthma per year.

All-cause and asthma-related HRU

HRU rates were lower for inhaled versus oral asthma maintenance medication use (**Table 5**), as shown by the propensity score-adjusted IRRs for all-cause outpatient visits (0.75 [95% CI, 0.74–0.76]), all-cause hospitalizations (0.80 [95% CI, 0.69–0.91]), all-cause combined outcome of ER visits or hospitalization (0.80 [95% CI, 0.71–0.91]), asthma-related outpatient

Table 2. Baseline demographic and clinical characteristics of patients receiving asthma maintenance medications*

Characteristics	Total population (n = 37,868)		*P* value
	Inhaled medication (n = 9,983)	Oral medication (n = 27,885)	
Age in years, mean ± SD (median [IQR])	47.28 ± 17.51 (46 [33–60])	56.08 ± 18.17 [57 (43–71)]	< 0.0001
Age categories (yr), No. (%)			< 0.0001
18–29	1,864 (18.67)	2,643 (9.48)	
30–39	1,884 (18.87)	3,081 (11.05)	
40–49	1,775 (17.78)	4,153 (14.89)	
50–59	1,862 (18.65)	5,374 (19.27)	
60–69	1,326 (13.28)	5,049 (18.11)	
≥ 70	1,272 (12.74)	7,585 (27.20)	
Female sex, No. (%)	5,184 (51.93)	15,887 (56.97)	< 0.0001
Insurance type, No. (%)			< 0.0001
Health insurance	9,663 (96.79)	26,002 (93.25)	
Medical aid	320 (3.21)	1,883 (6.75)	
Specialty of physician seen at index date, No. (%)			< 0.0001
Internal medicine	7,009 (70.21)	15,730 (56.41)	
Otolaryngologist	1,167 (11.69)	3,849 (13.80)	
General practitioner	892 (8.94)	4,486 (16.09)	
Pediatrician	317 (3.18)	973 (3.49)	
Family medicine	273 (2.73)	1,348 (4.83)	
Others	325 (3.26)	1,499 (5.38)	
Institutional setting at index date, No. (%)			< 0.0001
Primary hospital	6,328 (63.39)	19,413 (69.62)	
Secondary hospital	469 (4.70)	1,874 (6.72)	
Tertiary hospital	3,186 (31.91)	6,598 (23.66)	
Charlson Comorbidity Index, mean ± SD	0.92 ± 1.32	1.34 ± 1.59	< 0.0001

SD, standard deviation; IQR, interquartile range.
*Please see online **Supplementary Table S1** for a list of the classes of asthma medications included.

Table 3. Treatment discontinuation and treatment switch, inhaled versus oral asthma maintenance medication users*

Characteristics	12 mon (n = 37,868)			24 mon (n = 19,374)		
	Inhaled medication (n = 9,983)	Oral medication (n = 27,885)	*P* value	Inhaled medication (n = 4,814)	Oral medication (n = 14,560)	*P* value
Discontinuation of therapy						
Discontinuation event, No. (%)	9,421 (94.37)	24,074 (86.33)	< 0.0001	4,707 (97.78)	13,646 (93.72)	< 0.0001
Time to discontinuation, days						
Mean ± SD	71.95 ± 41.44	77.97 ± 57.93	< 0.0001	83.97 ± 73.55	104.31 ± 108.82	0.7467
Median (IQR)	61 (61–76)	61 (32–101)		61 (61–76)	66 (36–123)	
Time to discontinuation (KM estimate), days						
Mean ± SE	84.38 ± 0.62	105.89 ± 0.52	< 0.0001	97.33 ± 1.58	138.94 ± 1.39	< 0.0001
Median (95% CI)	62 (not estimable)	72 (71–73)		62 (not estimable)	72 (71–74)	
Switch of therapy ≥ 1 switch event, No. (%)	246 (2.46)	647 (2.32)	0.4160	241 (5.01)	650 (4.46)	0.1197
No. of switch events						
Mean ± SD	0.03 ± 0.23	0.04 ± 0.28	0.4369	0.07 ± 0.35	0.08 ± 0.45	0.1446
Median (IQR)	0 (0–0)	0 (0–0)		0 (0–0)	0 (0–0)	
Time to first switch, days						
Mean ± SD	173.65 ± 79.50	168.40 ± 73.01	0.5670	327.69 ± 187.11	318.42 ± 183.78	0.5344
Median (IQR)	168 (108–238)	161 (112–226)		308 (168–476)	285.5 (154–476)	
Time to first switch (KM estimate), days						
Mean ± SE	345.68 ± 0.30	337.02 ± 0.17	0.4183	683.31 ± 1.32	707.85 ± 0.77	0.1216
Median (95% CI)	Not estimable	Not estimable		Not estimable	Not estimable	

SD, standard deviation; IQR, interquartile range; KM, Kaplan-Meier; SE, standard error; CI, confidence interval; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonist; LRTA, leukotriene-receptor antagonists.
*12 (or 24) months stratum includes patients with index date at least 12 (or 24) months prior to date of data cutoff. Inhaled asthma maintenance medications include (A) low dose ICS, (B) low dose ICS + LABA in a single device, (C) low dose ICS + LABA in multiple devices; oral asthma maintenance medications include (A) low dose sustained-release theophylline, (B) LTRAs.

Table 4. Asthma exacerbation rates, inhaled versus oral asthma maintenance medication users

Variables	No. of patients	Sum of person-years	No. of events	Rate per 1,000 person-years (95% CI)	Unadjusted IRR (95% CI)	*P* value	PS-adjusted IRR (95% CI)	*P* value
Total population (n = 37,868)								
Oral medication	27,885	14,491.75	545	37.61 (34.03–41.56)	1 (ref)	< 0.0001	1 (ref)	< 0.0001
Inhaled medication	9,983	4,104.82	78	19.00 (14.69–24.58)	0.51 (0.38, 0.67)		0.52 (0.39–0.69)	
Patients with ≥ 3 secondary/tertiary care visits for asthma-related events per year (n = 4,584)								
Oral medication	3,386	2,158.41	362	167.72 (147.57–190.61)	1 (ref)	< 0.0001	1 (ref)	< 0.0001
Inhaled medication	1,198	748.35	52	69.49 (49.76–97.03)	0.41 (0.29, 0.59)		0.47 (0.32–0.68)	
Patients with < 3 secondary/tertiary care visits for asthma-related events per year (n = 33,284)								
Oral medication	24,499	12,333.34	183	14.84 (12.72–17.30)	1 (ref)	0.0020	1 (ref)	0.0111
Inhaled medication	8,785	3,356.47	26	7.75 (5.28–11.36)	0.52 (0.35, 0.79)		0.58 (0.38–0.88)	

CI, confidence interval; IRR, incidence rate ratio; PS, propensity score; ref, reference.

Table 5. Healthcare resource utilization, inhaled versus oral asthma maintenance medication users

Variables	Unadjusted IRR (95% CI)	*P* value	PS-adjusted IRR (95% CI)	*P* value
Total population (n = 37,868)				
All-cause HRU				
Outpatient visits	0.61 (0.60–0.63)	< 0.0001	0.75 (0.74–0.76)	< 0.0001
Emergency room visits	0.83 (0.67–1.03)	0.0862	0.89 (0.72–1.11)	0.2970
Hospitalizations	0.70 (0.61–0.80)	< 0.0001	0.80 (0.69–0.91)	0.0012
ER visits or hospitalization	0.71 (0.63–0.80)	< 0.0001	0.80 (0.71–0.91)	0.0004
Asthma-related HRU				
Outpatient visits	0.62 (0.60–0.63)	< 0.0001	0.64 (0.62–0.66)	< 0.0001
ER visits	0.62 (0.31–1.23)	0.1698	0.56 (0.29–1.09)	0.0865
Hospitalizations	0.29 (0.18–0.46)	< 0.0001	0.29 (0.17–0.50)	< 0.0001
ER visits or hospitalization	0.43 (0.29–0.63)	< 0.0001	0.43 (0.29–0.63)	< 0.0001
Patients with ≥ 3 secondary/tertiary care visits for asthma-related events per year (n = 4,584)				
All-cause HRU				
Outpatient visits	0.71 (0.68–0.74)	< 0.0001	0.86 (0.83–0.90)	< 0.0001
Emergency room visits	0.92 (0.64–1.32)	0.6543	0.98 (0.68–1.43)	0.9349
Hospitalizations	0.73 (0.58–0.94)	0.0128	0.90 (0.71–1.15)	0.4062
ER visits or hospitalization	0.75 (0.61–0.93)	0.0090	0.92 (0.75–1.14)	0.4386
Asthma-related HRU				
Outpatient visits	0.68 (0.65–0.71)	< 0.0001	0.69 (0.66–0.72)	< 0.0001
ER visits	0.89 (0.40–1.96)	0.7756	0.80 (0.44–1.45)	0.4673
Hospitalizations	0.39 (0.24–0.64)	0.0002	0.46 (0.28–0.74)	0.0013
ER visits or hospitalization	0.61 (0.38–0.96)	0.0341	0.71 (0.45–1.12)	0.1443
Patients with < 3 secondary/tertiary care visits for asthma-related events per year (n = 33,284)				
All-cause HRU				
Outpatient visits	0.60 (0.59–0.61)	< 0.0001	0.73 (0.72–0.74)	< 0.0001
Emergency room visits	0.78 (0.59–1.03)	0.0754	0.87 (0.68–1.13)	0.3040
Hospitalizations	0.70 (0.59–0.82)	< 0.0001	0.78 (0.66–0.93)	0.0066
ER visits or hospitalization	0.70 (0.61–0.81)	< 0.0001	0.79 (0.68–0.91)	0.0014
Asthma-related HRU				
Outpatient visits	0.60 (0.58–0.62)	< 0.0001	0.64 (0.62–0.65)	< 0.0001
ER visits	0.44 (0.07–2.60)	0.3658	Not estimable	-
Hospitalizations	0.11 (0.04–0.30)	< 0.0001	0.11 (0.04–0.31)	< 0.0001
ER visits or hospitalization	0.15 (0.06–0.36)	< 0.0001	0.15 (0.06–0.36)	< 0.0001

IRR, incidence rate ratio; CI, confidence interval; PS, propensity score; HRU, healthcare resource utilization; ER, emergency room.

visits (0.64 [95% CI, 0.62–0.66]), asthma-related hospitalizations (0.29 [95% CI, 0.17–0.50]) and asthma-related combined outcome of ED visits or hospitalization (0.43 [95% CI, 0.29–0.63]). Similar results were found for all-cause ED visits and asthma-related ED visits, although these results were not statistically significant (**Supplementary Table S2**).

DISCUSSION

Our study focused on the real-world treatment patterns of newly diagnosed patients with asthma, looking specifically in a primary care setting where a large number of patients with asthma are cared for.[20] We found that patients in South Korea were frequently treated with oral rather than inhaled asthma medication at the time of asthma diagnosis and commonly treated with oral rather than inhaled asthma maintenance medication, demonstrating a discrepancy between current guidelines[1,8] and clinical practice. Our findings were similar to three previously published South Korean database studies (2013–2016), in which only approximately 20%–30% of patients with asthma were prescribed inhaled medications.[10,11,21] Another study in South Korea found increasing LTRA prescriptions over a 5-year period.[7] In South Korea, there may be a traditional preference for physicians, particularly in a primary care setting, to prescribe oral asthma medications.[7,9]

As HIRA does not cover inhaler technique education and there is limited time allocated to each patient, it is difficult to educate patients and monitor their treatment adherence.[7] The increased number of discontinuations seen with inhaled medications compared with oral medications may be a direct result of this lack of education. However, as inhaled medications provide improved efficacy,[1] decreased side effects[22,23] and fewer exacerbations (even in cases of severe asthma) than oral medications,[24] improving awareness of the benefits of inhaled medications versus oral medications through physician, and patient education may increase both the prescription of inhaled medications and its adherence.

Patients treated with inhaled versus oral asthma maintenance medication were more likely to discontinue treatment, but less likely to experience clinical events, such as hospitalization and OCS prescription, prior to discontinuing treatment. Across both treatment groups, the most common clinical events in the 30-day period prior to medication discontinuation were OCS prescription and all-cause hospitalization, which could indicate that these patients' asthma symptoms were not sufficiently controlled by their maintenance treatment. However, medication compliance cannot be confirmed, and there is a possibility that OCS may have been prescribed for reasons other than exacerbations or insufficient asthma symptom control, such as later use in emergency situations.

Our results also demonstrated that patients treated with inhaled maintenance medication were less likely to experience poor asthma control or exacerbations, and had lower all-cause and asthma-related HRU versus those treated with oral maintenance medication. A study using primary care electronic medical records from the United Kingdom and France analyzed prescription trends among patients with asthma. Primary care physicians were likely to insufficiently prescribe ICS medication, thereby increasing the risk of exacerbation in patients with inadequate symptom control and increased HRU.[25] Similarly, our study showed that patients with newly treated asthma in a primary care setting were more likely to be prescribed oral versus inhaled medications, and those using oral medications had higher HRU rates versus inhaled medications, suggesting poorly controlled asthma. Since asthma treatment is often initiated in the primary care setting[20] with medications listed in GINA Steps 2 and 3,[2] in order to create a homogenous study population with respect to asthma severity, our study only included patients prescribed low-dose ICS, excluding patients prescribed medium- or high-dose ICS. However, as certain new asthma cases may initially be treated with medium- or high-dose ICS or ICS/LABA, this may have excluded patients receiving ICS likely to have poorly controlled asthma.

Pulmonary function data were not available in the claims-based HIRA database, preventing the categorization of patients by disease severity. It was also not possible to predict asthma severity using proxies, such as exposure to OCS,[26] due to the prescribing patterns in this population. Additionally, lack of adherence may have affected clinical outcomes, but was not assessed; this is a general limitation of claims data. Although only "newly treated" asthma patients were included, it was not possible to ensure that these patients had never been previously treated for asthma. Although propensity score analysis was used to adjust for baseline differences between our treatment groups, this can only adjust for confounding by measured covariates, not those left unmeasured. Finally, we used a 60-day period to account for any carry-over treatment effects after index treatment discontinuation, augmentation, or switch. This may have resulted in attribution of events that were due to the new treatment (after augmentation or switch) to the index treatment.

A significant strength of the study was the use of the HIRA database, comprising almost the entire South Korean population, due to the almost complete coverage of NHI; the results were informative regarding prescribing patterns in the entire country. The study population comprised a broad age range, represented men and woman equally, and the main treatment categories (oral and inhaled medications) were well represented. There is no previous literature on the effects of suboptimal asthma prescribing practices in South Korea on asthma clinical outcomes and asthma-related HRU, so our study fills this knowledge gap. The definition used to identify asthma in this study (at least 1 asthma diagnosis code and 1 asthma medication) may have led to an overestimation of patients with asthma. However, an alternative definition of 1 asthma diagnosis and 2 asthma medications or at least 2 asthma diagnoses used in a previous study had the potential to underdiagnose patients.[27] With this in mind, we decided to capture most patients with a likely asthma diagnosis to inform our study.

In conclusion, real-world treatment patterns for asthma in South Korea showed that a considerable proportion of patients with asthma were initially treated with oral rather than inhaled medications, especially in primary care. Most patients treated with oral and inhaled maintenance medication discontinued treatment and few patients switched treatment during the follow-up period. Patients treated with inhaled maintenance medication were less likely to have uncontrolled asthma or exacerbations, and had lower all-cause and asthma-related HRU than those treated with oral asthma maintenance medication. The data from this real-world study suggest a gap between current asthma guidelines and clinical practice, highlighting the current unmet needs of patients with asthma in South Korea. Additional studies are needed to understand the drivers of oral medication overuse and further efforts to close this gap, particularly in primary care, are required.

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SUPPLEMENTARY MATERIALS

Supplementary Data S1
Supplementary methods

Click here to view

Supplementary Table S1
List of asthma medications assessed for patients newly initiating asthma medication

Click here to view

Supplementary Table S2
Descriptive statistics of HRU, inhaled versus oral asthma maintenance medication users*

Click here to view

Supplementary Table S3
Baseline demographic and clinical characteristics of eligible patients with at least one prescription for an asthma medication*

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Supplementary Table S4
Distribution of index asthma medication prescriptions, by institutional setting at index date

Click here to view

Supplementary Table S5
Prescribing patterns of asthma medications in the year following the index date

Click here to view

Supplementary Fig. S1
Study design scheme for asthma prescribing patterns for all asthma medications (not to scale).

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Supplementary Fig. S2
Patient selection for asthma medication prescribing patterns.

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Supplementary Data S1. Supplementary methods

HIRA database

The HIRA database contains all claims information of inpatient and outpatient care in clinics and hospitals, including demographic information, diagnoses (International Classification of Diseases, 10th revision [ICD-10][1]), procedures, prescription records (name of prescribed drugs, formula, dose, prescription duration) and costs.

Study design

Global Initiative for Asthma (GINA) steps include inhaled therapies as the preferred controller, and oral therapies or a combination of oral and inhaled therapies as a secondary option.[2] Low-, medium- and high-dose inhaled corticosteroids (ICS) and ICS/long-acting beta2 agonist (LABA) were categorized as in GINA guidelines.[2]

Supplementary Results

Asthma prescribing patterns

The 1,054,707 patients newly initiating any asthma medication had showed, the median age was 47 years and that 617,851 (58.58%) were female. The demographics and clinical characteristics of these patients are summarized in Supplementary Table S3. Common asthma-related comorbidities were gastro-oesophageal reflux disease (n = 263,668 [24.99%]) and hypertension (n = 240,507 [22.80%]). Most patients were treated at a primary (n = 929,777 [88.16%]) versus secondary (n = 55,612 [5.27%]) or tertiary (n = 69,318 [6.57%]) hospital at index visit.

Patients were frequently treated for asthma with oral rather than inhaled maintenance medication at the time of asthma diagnosis and in the year following (Supplementary Tables S4 and S5). For oral medications, 491,252 (46.58%) patients were prescribed OCS, 252,419 (23.93%) LTRA, 208,834 (19.80%) theophylline, and 93,156 (8.83%) doxofylline. For inhaled medications, 87,212 (8.27%) patients were prescribed ICS, 103,342 (9.80%) short-acting bronchodilator, 37,171 (3.52%) SABA/ICS, 32,669 (3.10%) long-acting beta$_2$-agonist (LABA), 32,308 (3.06%) ICS+LABA, 1,827

(0.17%) long-acting muscarinic antagonist (LAMA) and 849 (0.08%) LAMA/LABA. Patients may have received multiple oral and inhaled medications (alone or in combination) at baseline. Patients treated in primary institutions were less likely to receive inhaled medications than those treated in secondary or tertiary institutions. Patients were more likely to receive oral versus inhaled asthma maintenance medication 1 year after initial asthma diagnosis (data not shown). Average prescription duration for oral medications was generally shorter compared with inhaled medications (Supplementary Table S3).

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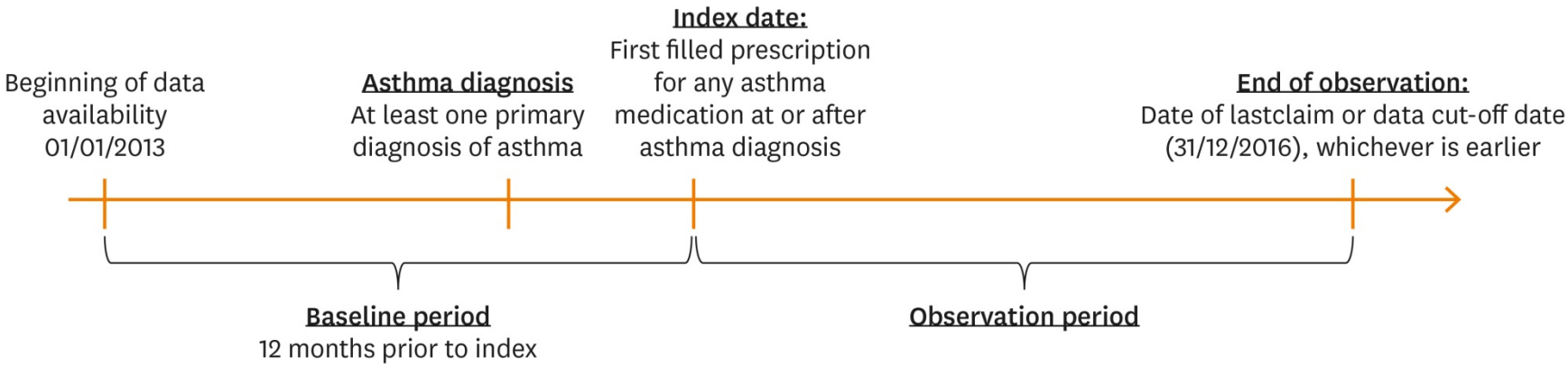
Supplementary Fig. S1. Study design scheme for asthma prescribing patterns for all asthma medications (not to scale).



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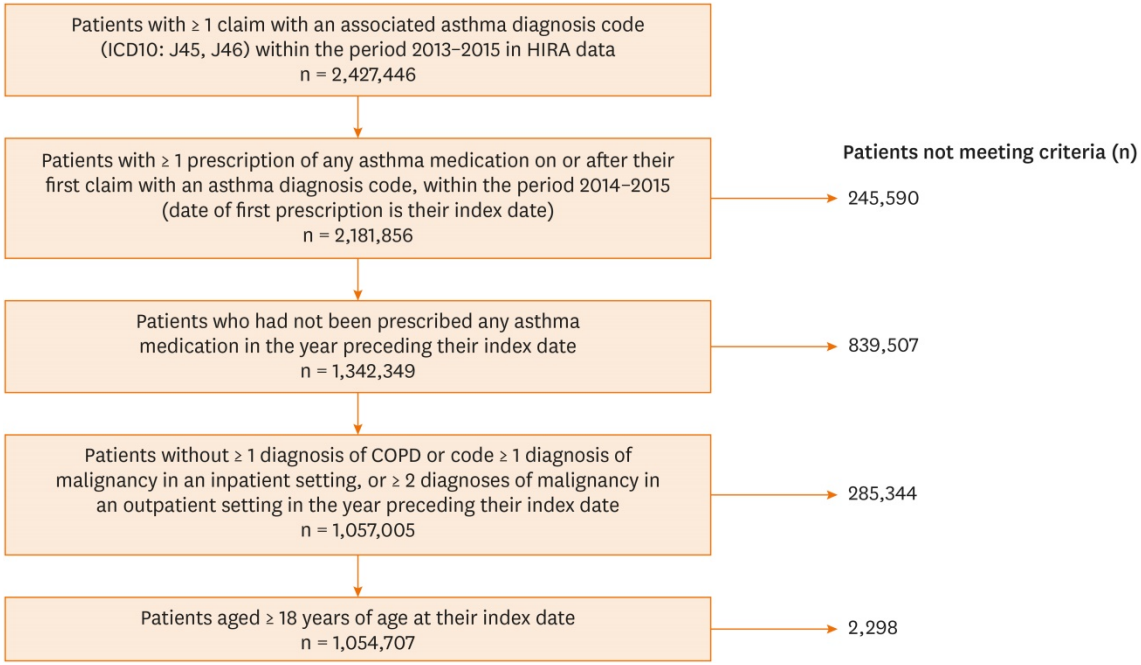
Supplementary Fig. S2. Patient selection for asthma medication prescribing patterns.



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