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Controller therapy in Asians and whites with persistent Asthma

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Abstract

Background: Little is known concerning the relative effectiveness of LTRAs compared to ICSs as monotherapy or LABA as add-on therapy in the Asian population.

Objectives: In this retrospective cohort study, we examined the comparative effectiveness of montelukast to ICS as a first-line monotherapy and as an add-on in comparison with LABA on asthma exacerbations among Asian and non -Hispanic white persistent asthma patients in a large managed care organization.

Methods: The three add-on comparisons were montelukast plus low-dose ICS versus LABA plus low-dose ICS, montelukast plus low-dose ICS versus medium-dose ICS, and montelukast plus medium-dose ICS versus LABA plus medium-dose ICS. Patients were identified based on ICD-9 diagnosis codes and administrative pharmacy dispensing. Exacerbations were defined as asthma emergency department visit or hospitalization, or asthma outpatient visits requiring systemic corticosteroid dispensing. Patient demographic and clinical characteristics were balanced by using inverse probability treatment weighting. Multivariable robust Poisson and Cox-proportional hazards regression models were applied to estimate rate ratios and hazard ratios.

Results: Compared with low-dose ICS monotherapy, montelukast monotherapy evidenced a lower incidence rate (RR 0.89, CI 0.79-0.99, p=0.03) but similar hazard rate (HR 0.96, CI 0.86-1.06, p=0.43) of asthma exacerbation in white patients 12 years of age or older. No difference was observed in Asian patients or in white children 4-11 years of age. All other comparisons did not reveal a statistically significant difference in incidence or hazard rate.

Conclusion: In a real-world comparative effectiveness study, asthma exacerbation rates were similar among guideline alternative controller regimens in Asians and whites.

Keywords: Anti-asthma agents, asthma control, asthma impairment, asthma risk, montelukast, persistent asthma

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Abbreviations:
CI: Confidence interval
ED: Emergency department visit
GERD: Gastroesophageal reflux disease
ICD-9: The International Classification of Diseases, 9th Revision
HEDIS: Healthcare Effectiveness Data and Information Set
HR: hazard ratio
IPTW: inverse probability treatment weight
KPSC: Kaiser Permanente Southern California
LABA: long-acting beta-agonist
OCS: Oral corticosteroids
RR: rate ratio
SABA: short-acting beta-agonists

Introduction

The Global Initiative for Asthma (GINA)[1] and National Asthma Education and Prevention Program (NAEPP)[2] guidelines, established based on evidence and expert opinion, recommend age-varying step-care levels of treatment based on a patient's asthma severity prior to treatment or level of control after therapy is instituted. For each step-care level, preferred treatments and alternative therapies are recommended.

Inhaled corticosteroids (ICS) are recommended step-2 care for asthma patients of all ages by GINA and NAEPP as the first-line controller medication in mild persistent asthma patients, while leukotriene receptor antagonists (LTRA) are one of the alternatives. For higher step-level care, various combinations of ICS and long-acting beta2-agonists (LABA) or LTRA, or higher dose ICS are recommended by the guidelines, based on age of the patient.

Studies examining the effectiveness of LTRA in comparison with ICS as a first-line monotherapy, or the effectiveness of LTRA as an add-on in comparison with another active control noted inconsistent findings. Meta-analyses of randomized clinical trials favored ICS as the first-line monotherapy compared to LTRA[3,4] and LABA as an add-on compared to LTRA[5] in patients with mild or moderate asthma. Similar findings were reported from a population-based administrative database study in which ICS+LABA therapy appeared more effective than ICS+LTRA therapy in the management of asthma when the treatments were uninterrupted.[6] However, in children 5-15 years of age, LTRA was associated with a lower risk of asthma exacerbation compared to ICS among patients who had no prior exacerbations.[7] Asthma-related hospitalizations and emergency department (ED) visits were found to be less frequent in patients who were treated with LTRA+ICS compared with those with LABA+ICS.[8] Two randomized real-world pragmatic trials comparing LTRA with an ICS as first-line controller medication and LTRA with a LABA as an add-on to an ICS did not reveal any statistically significant differences.[9] In addition, a recent randomized clinical trial provided evidence that supports the use of montelukast as add-on therapy to low-dose ICS in elderly patients with mild asthma.[10]

In Asian countries, the use of montelukast as a first treatment choice in school-aged children ranged from 0% in India and Sri Lanka to 72% in China.[11] Few studies have evaluated asthma controller therapy specifically in Asian populations.[12-14] Given the paucity of information on the use of LTRA and its effectiveness in Asian patients with asthma, we studied the comparative effectiveness of montelukast as the most frequently prescribed LTRA, to ICS as a first-line monotherapy and as an add-on in comparison with LABA on asthma exacerbations among Asian and non-Hispanic white persistent asthma patients in a large managed care organization.

Methods

Study design

This is a retrospective cohort study based on administrative outpatient pharmacy dispensing records and healthcare utilization data extracted from Kaiser Permanente Southern California (KPSC) research data warehouse. KPSC is an integrated health maintenance organization that serves more than 4 million health plan enrollees, about 16% of the region's population. Race/ethnicity distribution, demographics and socioeconomic status are representative of the Southern California region.[15] The study protocol was approved by the KPSC institutional review board.

Study cohort and follow-up

We identified a group of Asian and non-Hispanic white health plan enrollees who had at least one ICD-9 diagnosis code of asthma (493.x) in an inpatient, ED visit, or outpatient setting, and 4 or more Healthcare Effectiveness Data Information Set (HEDIS) asthma rescue medications or asthma controllers within a period of 365 days any time between 2002 and 2013 (**Figure 1**). Race and ethnicity information was extracted from the KPSC research data warehouse.[16] The study cohort met the following eligibility criteria on the date a non-theophylline asthma controller was first dispensed between 2003 and 2013: (1) at least 4 years of age, (2) was not pregnant and (3) continuously enrolled in the health plan with pharmacy benefit in the past 12 months (gaps of 31 days or shorter were allowed), (4) had no encounter diagnoses of chronic obstructive pulmonary disease (COPD) or other pertinent illnesses (footnote d. of **Figure 1**). The requirement of continuous enrollment allowed adequate data to define study variables. During the course of the study, it was discovered that the internal codes (see "Study end points") were incomplete in 2003-2004. Thus, both the treatment periods (see "Asthma controller medications and treatment periods") as well as the end points in 2003-2004 were removed from the analyses (**Figure 1**).

For each person in the cohort, follow up began on the date the initial non-theophylline asthma controller was first dispensed and ended with the earliest of the following events: pregnancy, dis-enrollment from the health plan or loss of pharmacy benefit, death, or study end date of 6/30/2014 (**Figure 2A**). For the time-to-event outcome, the follow-up also ended on the date that the outcome occurred the first time if it happened before pregnancy, dis-enrollment, death, or end of the study.

Asthma controller medications and treatment periods

A treatment period was first defined as the time interval between the prescription start date and the end of the days of supply. Consecutive treatment periods of the same medication were bridged if the gaps were 7 days or less (i.e. medication was considered to be continuous) to allow for a realistic lag in prescription pick-up. For all asthma controllers included in the study, instructions from physicians and pharmacists were reviewed to determine days supply to assure accuracy of reporting. For ICS, the average daily dosage was calculated by (number of canisters * number of puffs per canister * strength per puff)/(days supply) for each treatment period. Then the treatment period was categorized into low-, medium-, and high-dose, based on the recommendation specified by the GINA guideline for the diagnosis and management of childhood and adult asthma.[1]

Because asthma controller medications may be intermittently dispensed and may change over time, a patient could have one or more dispensed medications which may or may not overlap. Patients were assumed to use the medications concomitantly if two treatment periods overlapped (**Figure 2B**). The first 7 days of a treatment period were excluded from the analyses to allow the medications to be fully effective during the observed risk windows and to eliminate the remaining

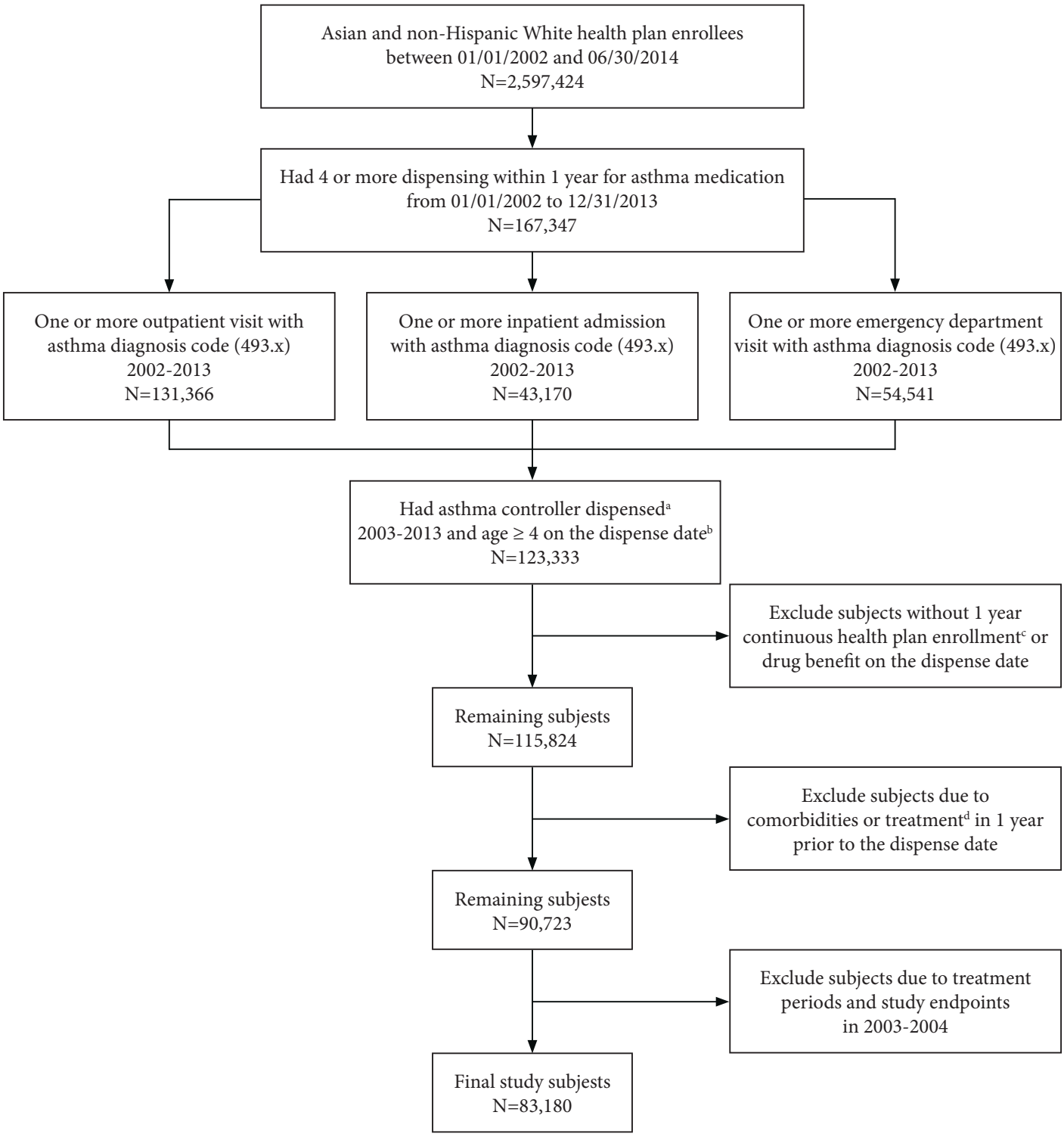

Figure 1. Cohort identification consort diagram

a. Not including theophylline
b. Dispense date: The first qualifying dispense date for a controller medication. The same definition applies to all following steps.
c. Gaps 31 days or less were allowed
d. Exclusions due to comorbidities or treatment: chronic obstructive pulmonary disease, chronic obstructive asthma, emphysema, cystic fibrosis, chronic bronchitis, bronchiolitis obliterans, hypereosinophilic syndromes (eosinophilic granulomatosis with polyangiitis or eosinophilic esophagitis), cardiovascular conditions (angina pectoris, heart failure, acute myocardial infarction), endocrine disorders (systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease), ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, cirrhosis, known biliary abnormalities with the exception of Gilbert's syndrome or asymptomatic gallstones, granulomatosis with polyangiitis, sarcoidosis, other autoimmune disorders, immune deficiency, HIV, drug addiction, active respiratory cancer requiring any therapy except for antihormonal therapy, immunosuppressant therapy), pregnancy, and immunosuppressant or theophylline treatment.

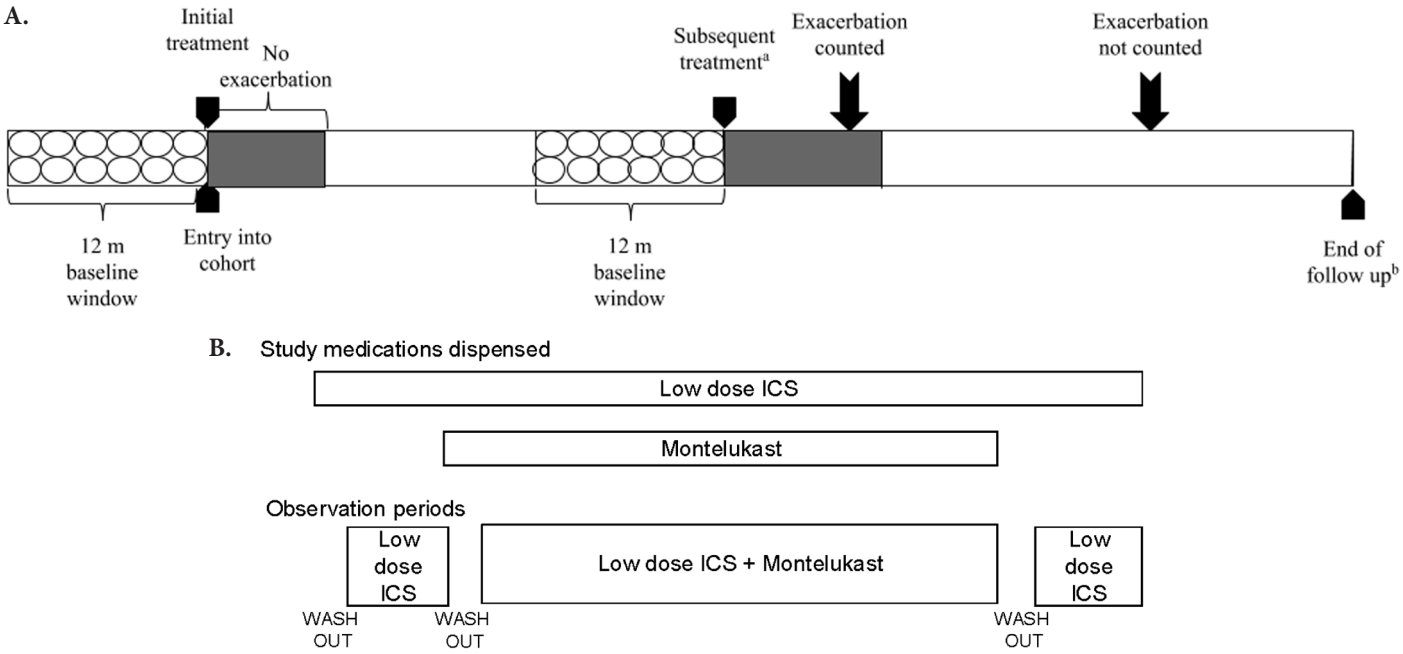

Figure 2. Study design

A. Characterizing treatment and follow-up periods
   a. Same or different from the initial treatment
   b. Earliest of the following events: became pregnant, dis-enrolled from the health plan or lost pharmacy benefit, death or 6/30/2014 (study end date). For the time-to-event outcome, the follow-up also ended on the day that the first exacerbation occurred.

B. Characterizing observation periods in details

effects of previous medications (if any). The analyses also included the day after the ending of a treatment period because the effects of the medications were expected to last for at least 24 hours. Treatment periods that were 7 days or less in length were removed from the analyses since these treatment periods could be too short for the drugs to become fully effective.

Next, each observation period was classified into one of the following eight mutually exclusive categories: montelukast monotherapy, low-dose ICS monotherapy, low-dose ICS + montelukast, low-dose ICS + LABA, medium-dose ICS monotherapy, medium-dose ICS + montelukast, medium-dose ICS + LABA and other. The asthma controllers filled in the 6 months prior to the initial asthma controller dispensing were included in the classification of treatment periods, if the supply of such medications allowed the consumption during the follow-up period. All except the treatment periods labeled as "other" were included in the analyses.

Montelukast monotherapy, a first line monotherapy treatment, was compared with low-dose ICS monotherapy. Three additional comparisons involving add-on treatments were conducted: (1) montelukast + low-dose ICS versus LABA + low-dose ICS, (2) montelukast + low-dose ICS versus medium-dose ICS, and (3) montelukast + medium-dose ICS versus LABA + medium-dose ICS. Since the add-on therapies are generally recommended by the guideline to treat patients whose asthma care step-level is 2 or higher, the three comparisons listed above involving add-on therapies excluded treatment periods if the patient's step-care level was determined to be 1 in the 12 months prior to the beginning of those treatment periods.

Study end points

The primary study end-point was an asthma exacerbation, defined as a hospitalization or ED visit with a principal diagnosis of asthma (ICD-9 code 493.x), or an oral corticosteroid dispensing accompanied by an outpatient visit with an internal healthcare code within 7 days indicating acute exacerbation, status asthmaticus, acute asthma attack, uncontrolled asthma, or asthmatic bronchitis as the reason for the visit.[17] Events that occurred during an observation window of a certain treatment were attributed to the treatment. End-points that occurred outside of observation periods were not counted. A new asthma exacerbation episode had to occur on at least the 8th day after the previous exacerbation.

Patient characteristics and clinical measures

Patient characteristics and clinical measures (referred to as "covariates") at the time of the initial dispensing of a controller medication were defined using the information in the 12 months prior to the beginning of the first qualifying treatment period. Level of education was derived based on patients' addresses and block-group level estimates provided by Nielson, Inc. (www.nielson.com). Clinical characteristics included Charlson comorbidity index,[18] comorbidities such as allergic rhinitis, sinusitis, acute upper infections, anxiety, conjunctivitis, musculoskeletal disease, specialist visits (allergist, pulmonologist), prior year asthma exacerbations, Asthma Medication Ratio (AMR) and asthma care step-level (**Table 1**). The AMR was defined as the same approach previously.[17] A ratio of >0.5 is the minimum quality measure cutoff point for

Table 1. Demographic and clinical characteristics of patients at the time of the initial dispensing of a controller medication

	Montelukast monotherapy (N=5491)	Low-dose ICS monotherapy (N=26744)	Low-dose ICS + Montelukast (N=555)	Low-dose ICS + LABA (N=3373)	Medium-dose ICS + Montelukast (N=566)	Medium-does ICS (N=38905)	Medium-dose ICS + LABA (N=7546)	Total (N=83180)
Age, mean (SD)	38.4 (22.45)	33.5 (24.84)	23.5 (22.67)	44.5 (20.08)	36.0 (22.58)	44.3 (21.67)	49.9 (17.22)	40.8 (23.12)
Age group								
4-7	669 (12.2%)	6048 (22.6%)	227 (40.9%)	27 (0.8%)	62 (11%)	1888 (4.9%)	6 (0.1%)	8927 (10.7%)
8-11	429 (7.8%)	2466 (9.2%)	68 (12.3%)	140 (4.2%)	57 (10.1%)	2073 (5.3%)	29 (0.4%)	5262 (6.3%)
12-44	1804 (32.9%)	7800 (29.2%)	123 (22.2%)	1368 (40.6%)	207 (36.6%)	13005 (33.4%)	2565 (34%)	26872 (32.3%)
45-54	1005 (18.3%)	3460 (12.9%)	47 (8.5%)	668 (19.8%)	87 (15.4%)	7429 (19.1%)	1711 (22.7%)	14407 (17.3%)
55-64	939 (17.1%)	3468 (13%)	62 (11.2%)	629 (18.6%)	102 (18%)	7522 (19.3%)	1717 (22.8%)	14439 (17.4%)
65+	645 (11.7%)	3502 (13.1%)	28 (5%)	541 (16%)	51 (9%)	6988 (18%)	1518 (20.1%)	13273 (16%)
Race								
Asian/Pacific Islander	870 (15.8%)	5804 (21.7%)	118 (21.3%)	443 (13.1%)	99 (17.5%)	7145 (18.4%)	1087 (14.4%)	15566 (18.7%)
White	4621 (84.2%)	20940 (78.3%)	437 (78.7%)	2930 (86.9%)	467 (82.5%)	31760 (81.6%)	6459 (85.6%)	67614 (81.3%)
Education of high school or higher (geocoded), mean (SD)	84.3 (12.78)	83.5 (13.40)	83.5 (13.42)	84.8 (12.91)	82.3 (14.03)	82.8 (13.46)	83.8 (13.14)	83.3 (13.36)
Female	3297 (60%)	14477 (54.1%)	294 (53%)	1993 (59.1%)	344 (60.8%)	23245 (59.7%)	4535 (60.1%)	48185 (57.9%)
Charlson index score								
0	1293 (23.5%)	6087 (22.8%)	68 (12.3%)	715 (21.2%)	93 (16.4%)	10101 (26%)	1521 (20.2%)	19878 (23.9%)
1	3700 (67.4%)	18519 (69.2%)	458 (82.5%)	2320 (68.8%)	424 (74.9%)	24531 (63.1%)	5058 (67%)	55010 (66.1%)
2+	498 (9.1%)	2138 (8%)	29 (5.2%)	338 (10%)	49 (8.7%)	4273 (11%)	967 (12.8%)	8292 (10%)
Asthma step-care level								
1	1689 (30.8%)	18520 (69.2%)	142 (25.6%)	1134 (33.6%)	157 (27.7%)	27990 (71.9%)	2705 (35.8%)	52337 (62.9%)
2	1150 (20.9%)	5147 (19.2%)	129 (23.2%)	348 (10.3%)	94 (16.6%)	818 (2.1%)	138 (1.8%)	7824 (9.4%)
3	542 (9.9%)	1823 (6.8%)	210 (37.8%)	1319 (39.1%)	78 (13.8%)	7096 (18.2%)	1268 (16.8%)	12336 (14.8%)
4	1350 (24.6%)	1159 (4.3%)	66 (11.9%)	423 (12.5%)	222 (39.2%)	2793 (7.2%)	2740 (36.3%)	8753 (10.5%)
5	687 (12.5%)	87 (0.3%)	8 (1.4%)	144 (4.3%)	14 (2.5%)	190 (0.5%)	652 (8.6%)	1782 (2.1%)
6	73 (1.3%)	8 (0%)	0 (0%)	5 (0.1%)	1 (0.2%)	18 (0%)	43 (0.6%)	148 (0.2%)
Asthma medication ratio								
<0.5	2999 (54.6%)	6311 (23.6%)	287 (51.7%)	1334 (39.5%)	281 (49.6%)	8542 (22%)	2670 (35.4%)	22424 (27%)
0.5-0.74	1398 (25.5%)	9513 (35.6%)	182 (32.8%)	1042 (30.9%)	185 (32.7%)	16211 (41.7%)	2309 (30.6%)	30840 (37.1%)
>=0.75	1094 (19.9%)	10920 (40.8%)	86 (15.5%)	997 (29.6%)	100 (17.7%)	14152 (36.4%)	2567 (34%)	29916 (36%)
Allergic rhinitis	2365 (43.1%)	5982 (22.4%)	243 (43.8%)	760 (22.5%)	244 (43.1%)	8334 (21.4%)	1936 (25.7%)	19864 (23.9%)
Any sinusitis	1287 (23.4%)	4415 (16.5%)	111 (20%)	534 (15.8%)	130 (23%)	6893 (17.7%)	1303 (17.3%)	14673 (17.6%)
Acute upper respiratory infections	1051 (19.1%)	6737 (25.2%)	181 (32.6%)	478 (14.2%)	123 (21.7%)	8156 (21%)	1136 (15.1%)	17862 (21.5%)
Conjunctivitis	426 (7.8%)	1868 (7%)	55 (9.9%)	174 (5.2%)	51 (9%)	2107 (5.4%)	363 (4.8%)	5044 (6.1%)
Endocrine	1759 (32%)	7214 (27%)	98 (17.7%)	1088 (32.3%)	168 (29.7%)	13719 (35.3%)	2956 (39.2%)	27002 (32.5%)
GERD	717 (13.1%)	2174 (8.1%)	51 (9.2%)	396 (11.7%)	67 (11.8%)	4432 (11.4%)	1110 (14.7%)	8947 (10.8%)
Infectious disease	1091 (19.9%)	5459 (20.4%)	145 (26.1%)	486 (14.4%)	132 (23.3%)	6560 (16.9%)	1191 (15.8%)	15064 (18.1%)
Musculoskeletal disease	1929 (35.1%)	7878 (29.5%)	122 (22%)	1228 (36.4%)	190 (33.6%)	14937 (38.4%)	3155 (41.8%)	29439 (35.4%)
Pneumonia	357 (6.5%)	2734 (10.2%)	86 (15.5%)	137 (4.1%)	48 (8.5%)	2867 (7.4%)	430 (5.7%)	6659 (8%)
Pharyngitis	546 (9.9%)	3091 (11.6%)	74 (13.3%)	233 (6.9%)	69 (12.2%)	3436 (8.8%)	470 (6.2%)	7919 (9.5%)
≥1 asthma exacerbation	899 (16.4%)	5104 (19.1%)	153 (27.6%)	439 (13%)	129 (22.8%)	6285 (16.2%)	1307 (17.3%)	14316 (17.2%)

GERD: Gastroesophageal reflux disease; OCS: Oral corticosteroid

Table 1. (Continued)

	Montelukast monotherapy (N=5491)	Low-dose ICS monotherapy (N=26744)	Low-dose ICS + Montelukast (N=555)	Low-dose ICS + LABA (N=3373)	Medium-dose ICS + Montelukast (N=566)	Medium-does ICS (N=38905)	Medium-dose ICS + LABA (N=7546)	Total (N=83180)
Anxiety	514 (9.4%)	1833 (6.9%)	36 (6.5%)	282 (8.4%)	58 (10.2%)	3528 (9.1%)	778 (10.3%)	7029 (8.5%)
Depression	667 (12.1%)	2443 (9.1%)	30 (5.4%)	404 (12%)	68 (12%)	5021 (12.9%)	1027 (13.6%)	9660 (11.6%)
Commercial	4399 (80.1%)	20412 (76.3%)	449 (80.9%)	2664 (79%)	455 (80.4%)	28979 (74.5%)	5762 (76.4%)	63120 (75.9%)
Medicaid/State sponsors	249 (4.5%)	1622 (6.1%)	56 (10.1%)	91 (2.7%)	49 (8.7%)	1608 (4.1%)	160 (2.1%)	3835 (4.6%)
Medicare	595 (10.8%)	3169 (11.8%)	26 (4.7%)	464 (13.8%)	52 (9.2%)	6379 (16.4%)	1296 (17.2%)	11981 (14.4%)
Private pay	561 (10.2%)	3562 (13.3%)	41 (7.4%)	424 (12.6%)	40 (7.1%)	5689 (14.6%)	1035 (13.7%)	11352 (13.6%)
Allergy department visits	1883 (34.3%)	2952 (11%)	181 (32.6%)	633 (18.8%)	183 (32.3%)	4189 (10.8%)	1503 (19.9%)	11524 (13.9%)
Pulmonary department visits	483 (8.8%)	689 (2.6%)	11 (2%)	229 (6.8%)	48 (8.5%)	1472 (3.8%)	913 (12.1%)	3845 (4.6%)
Atopic dermatitis	240 (4.4%)	1054 (3.9%)	51 (9.2%)	89 (2.6%)	33 (5.8%)	822 (2.1%)	155 (2.1%)	2444 (2.9%)
Nasal polyposis	140 (2.5%)	128 (0.5%)	9 (1.6%)	34 (1%)	8 (1.4%)	198 (0.5%)	106 (1.4%)	623 (0.7%)
OCS daily dosage ≥5mg/day	211(3.8%)	542(2%)	41(7.4%)	58(1.7%)	24(4.2%)	389(1%)	153(2%)	1418(1.7%)
Observation period starting year								
2005-2006	2124 (38.7%)	10984 (41.1%)	170 (30.6%)	1610 (47.7%)	250 (44.2%)	19337 (49.7%)	3205 (42.5%)	37680 (45.3%)
2007-2008	827 (15.1%)	4954 (18.5%)	92 (16.6%)	533 (15.8%)	88 (15.5%)	7935 (20.4%)	1112 (14.7%)	15541 (18.7%)
2009-2010	657 (12%)	4659 (17.4%)	81 (14.6%)	559 (16.6%)	60 (10.6%)	5739 (14.8%)	1240 (16.4%)	12995 (15.6%)
2011-2012	877 (16%)	4445 (16.6%)	91 (16.4%)	528 (15.7%)	83 (14.7%)	4324 (11.1%)	1336 (17.7%)	11684 (14%)
2013-2014	1006 (18.3%)	1702 (6.4%)	121 (21.8%)	143 (4.2%)	85 (15%)	1570 (4%)	653 (8.7%)	5280 (6.3%)
Observation period starting month								
Jan	756 (13.8%)	3091 (11.6%)	84 (15.1%)	435 (12.9%)	86 (15.2%)	4715 (12.1%)	993 (13.2%)	10160 (12.2%)
Feb	679 (12.4%)	3208 (12%)	77 (13.9%)	439 (13%)	76 (13.4%)	4635 (11.9%)	973 (12.9%)	10087 (12.1%)
Mar	671 (12.2%)	3044 (11.4%)	58 (10.5%)	395 (11.7%)	57 (10.1%)	4741 (12.2%)	881 (11.7%)	9847 (11.8%)
Apr	511 (9.3%)	2415 (9%)	58 (10.5%)	310 (9.2%)	65 (11.5%)	3583 (9.2%)	701 (9.3%)	7643 (9.2%)
May	457 (8.3%)	2250 (8.4%)	38 (6.8%)	278 (8.2%)	30 (5.3%)	3313 (8.5%)	614 (8.1%)	6980 (8.4%)
Jun	342 (6.2%)	1746 (6.5%)	41 (7.4%)	225 (6.7%)	35 (6.2%)	2653 (6.8%)	569 (7.5%)	5611 (6.7%)
Jul	324 (5.9%)	1478 (5.5%)	29 (5.2%)	218 (6.5%)	29 (5.1%)	2202 (5.7%)	461 (6.1%)	4741 (5.7%)
Aug	345 (6.3%)	1474 (5.5%)	29 (5.2%)	207 (6.1%)	35 (6.2%)	2133 (5.5%)	456 (6%)	4679 (5.6%)
Sept	349 (6.4%)	1582 (5.9%)	28 (5%)	197 (5.8%)	29 (5.1%)	2271 (5.8%)	462 (6.1%)	4918 (5.9%)
Oct	383 (7%)	2106 (7.9%)	47 (8.5%)	256 (7.6%)	41 (7.2%)	2924 (7.5%)	463 (6.1%)	6220 (7.5%)
Nov	315 (5.7%)	2164 (8.1%)	33 (5.9%)	206 (6.1%)	43 (7.6%)	2811 (7.2%)	492 (6.5%)	6064 (7.3%)
Dec	359 (6.5%)	2186 (8.2%)	33 (5.9%)	207 (6.1%)	40 (7.1%)	2924 (7.5%)	481 (6.4%)	6230 (7.5%)

determining controller medication dispensing.[17] Prior asthma care step-care level was based on the medications dispensed in the year prior to any given treatment period.

Except for gender, race/ethnicity, geocoded education and insurance indicators (commercial, Medicaid/State sponsored, Medicare and private pay), which were assumed to remain constant over the study period, all other covariates were also defined for each treatment period using the information in the 12 months prior to the beginning of each treatment period. These time-varying covariates were incorporated in the calculation of weights described below.

Statistical analyses

The unit of analysis was the observation period. The adjusted rate ratios between any two comparison groups were estimated by robust Poisson regression models, and the hazard ratios were estimated by Cox proportional hazards regression models. Because patients potentially had multiple observation periods and these periods were not independent observations, the generalized estimating equations (GEE) approach was applied to estimate a marginal treatment effect in the multivariable Poisson regression and the multivariable Cox proportional hazards regression models, accounting for

the correlation among the multiple treatment periods within a patient.[19]

The adjustment of patient demographic and clinical characteristics in the multivariable models described above was achieved by using inverse probability treatment weighting (IPTW).[20,21] For each planned comparison, a propensity score (PS) was first estimated for each treatment period as the conditional probability of having a treatment given a set of covariates.[22] Then the weight was derived by inversing the predicted probability of receiving the treatment. For example, when montelukast monotherapy was compared with low-dose ICS monotherapy, a PS was first estimated as the probability of receiving low-dose ICS monotherapy, given covariates. Then the weight was calculated as 1/PS for low-dose ICS monotherapy periods and 1/(1-PS) for montelukast monotherapy periods. Trimming was applied to standardized weights if they were larger than 20.[23,24] Weighting by the inverse probability of treatment results in a pseudo-population in which treatment assignment is independent of the measured covariates. The IPTW-based method offered an advantage over the traditional regression adjustment in our study because IPTW combined many covariates into a weight, and thus allowed us to handle many covariates at once. The covariates being included in the adjustment are shown in the footnote of **Table 3**.

The analyses were stratified by race (non-Hispanic white and Asian) and age group (≥12 and 4-11 years of age). SAS (version 9.3 for Windows, SAS Institute, Cary, NC) was used for analyses with significance set at P<.05 and 2-tailed.

Results

Characteristics of the study cohort

83,180 patients were identified as qualified study subjects (**Figure 1**). Demographic and clinical characteristics of patients at the time of the initial dispensing of a controller medication (baseline) are presented in **Table 1**. 81.3% of study subjects were white and 57.9% were female. Patients who were treated with montelukast monotherapy, low-dose ICS monotherapy, low-dose ICS + montelukast, or medium-dose ICS + montelukast seemed to be younger on average, compared to patients with other treatment patterns. Rhinitis was more common among patients who were treated with montelukast, consistent with its indication for rhinitis in addition to asthma. Patients prescribed montelukast, either as a monotherapy or as an add-on, had a higher rate of allergist visits in the past 12 months compared to patients without montelukast therapy. About 70% of low-dose ICS monotherapy and medium-lose ICS monotherapy recipients had level 1 asthma step-care in the prior 12 months.

Treatment effects

A total of 583,617 treatment periods were included in the analysis (439,875 (white ≥12 years), 82,534 (Asian ≥12 years), 42,065 (white 4-11 years), and 19,143 (Asian 4-11 years)). The average length of treatment periods was 66.6 days, and the average length of total observation periods was 1.28 years (1.37, 1.28, 0.70, and 0.71 for white ≥12, Asian ≥12, white 4-11 and Asian 4-11 years of age, respectively). Only 1.7% of patients had more than one event during one observation period. The number of patients, number of treatment periods, total length of observation periods, the number of asthma exacerbations and the unadjusted rate per 1,000 person-year follow-up time for each treatment type are presented in **Table 2** by race (non-Hispanic white and Asian) and age group (≥12 and 4-11 years of age). The rate of asthma exacerbation ranged from 144/1,000 to 582/1,000 person-years for the treatment groups being compared.

Table 2. Number of patients, number of treatment periods, total length of treatment periods, number of events and unadjusted rate/1,000 treated person-years

	Number of patients	Number of treatment periods	Total length of observation periods (in years)	Number of events	Unadjusted rate/1,000 person-years
Treatment periods of Montelukast monotherapy and low-dose ICD monotherapy: step-care level 1-5					
Montelukast monotherapy					
White 12+	10910	49257	9878.34	1854	187.68
Asian 12+	2106	8846	1706.36	354	207.46
White 4-11	2038	7232	1283.33	328	255.59
Asian 4-11	697	2284	388.68	123	316.46
Low-dose ICS monotherapy					
White 12+	29025	81984	18336.54	2823	153.95
Asian 12+	6244	16732	3591.05	628	174.88
White 4-11	7051	19158	3527.60	840	238.12
Asian 4-11	3308	9378	1798.99	416	231.24
Treatment periods involving add-on therapy comparisons: step-care level 2+					
Low-dose ICS + Montelukast					
White 12+	1798	4006	622.74	120	192.70
Asian 12+	343	772	133.69	24	179.52
White 4-11	889	2271	323.49	100	309.13
Asian 4-11	339	822	115.81	30	259.04

Table 2. (Continued)

	Number of patients	Number of treatment periods	Total length of observation periods (in years)	Number of events	Unadjusted rate/1,000 person-years
Low-dose ICS + LABA					
White 12+	6829	27348	5532.46	797	144.06
Asian 12+	1112	4101	746.78	119	159.35
White 4-11	384	1142	192.67	57	295.84
Asian 4-11	117	340	62.59	17	271.61
Medium-dose ICS					
White 12+	32142	134556	22389.66	3784	169.01
Asian 12+	6598	25041	4159.08	886	213.03
White 4-11	3212	6985	1069.58	287	268.33
Asian 4-11	1654	3952	605.86	160	264.09
Medium-dose ICS + Montelukast					
White 12+	3306	8741	1258.83	289	229.58
Asian 12+	655	1592	226.26	61	269.60
White 4-11	612	1375	177.20	63	355.53
Asian 4-11	234	471	66.34	23	346.70
Medium-does ICS + LABA					
White 12+	15774	78879	14157.19	2625	185.42
Asian 12+	2786	13487	2349.78	529	225.13
White 4-11	118	220	28.45	7	246.05
Asian 4-11	31	60	8.59	5	582.07

Table 3. Unadjusted and IPTW adjusted characteristics in the 12 months prior to montelukast monotherapy and low-dose ICS monotherapy treatment periods of white patients 12+ years of age

	Unadjusted		IPTW adjusted	
	Montelukast monotherapy (N=49,257)	Low-dose ICS monotherapy (N=81,984)	Montelukast monotherapy (N=49,187)	Low-dose ICS monotherapy (N=81,485)
Age at the beginning of treatment, mean (SD)	50.9 (18.22)	51.3 (20.24)	51.0(19.79)	50.7(19.67)
Age group				
12-44	29.70%	32.00%	31.10%	32.70%
45-54	21.20%	17.90%	18.50%	18.80%
55-64	26.70%	22.10%	24.90%	22.60%
65+	22.40%	28.00%	25.50%	25.90%
Education of high school or higher (geocoded), mean (SD)	83.8 (12.67)	84.0 (12.88)	83.6(13.03)	84.2(12.73)
Female	69.50%	62.80%	65.70%	65.30%
Charlson index				
0	25.30%	30.50%	28.80%	28.80%
1	63.70%	59.80%	61.20%	61.20%
2+	11.10%	9.70%	10.00%	10.00%
Asthma step-care level				
1	5.20%	29.20%	19.60%	19.90%
2	22.10%	40.80%	33.90%	33.30%
3	10.70%	22.30%	17.70%	17.60%
4	40.70%	6.50%	19.90%	19.70%
5-6	21.20%	1.20%	9.00%	9.50%
Asthma controller ratio				
<0.5	46.60%	28.10%	37.00%	36.20%
0.5-0.74	30.70%	36.90%	33.70%	33.90%
>=0.75	22.70%	35.00%	29.30%	29.90%
Allergic rhinitis	35.30%	19.40%	26.00%	26.0%
Sinusitis	27.70%	17.70%	22.40%	23.10%
Acute upper respiratory infections	13.60%	14.50%	13.90%	14.10%
Anxiety	15.70%	12.00%	13.30%	13.70%

Table 3. (Continued)

	Unadjusted		IPTW adjusted	
	Montelukast monotherapy (N=49,257)	Low-dose ICS monotherapy (N=81,984)	Montelukast monotherapy (N=49,187)	Low-dose ICS monotherapy (N=81,485)
Conjunctivitis	6.80%	4.90%	5.50%	5.40%
Depression	21.50%	16.70%	18.10%	18.10%
Endocrine	50.50%	45.10%	46.80%	46.60%
GERD	21.90%	14.70%	17.60%	17.40%
Infectious disease	21.00%	17.60%	19.10%	19.30%
Musculoskeletal disease	54.00%	47.60%	49.60%	49.80%
Pneumonia	6.00%	5.40%	5.60%	5.70%
Pharyngitis	7.70%	7.20%	7.40%	7.60%
History of exacerbation	22.50%	14.60%	18.20%	17.90%
Skin disease	41.40%	37.30%	38.90%	38.90%
Commercial	80.70%	72.80%	75.40%	75.80%
Medicaid/State sponsors	2.30%	2.50%	2.70%	2.40%
Medicare	12.80%	18.80%	16.50%	16.40%
Private pay	10.30%	16.90%	14.60%	14.50%
Allergy department Visits	32.30%	12.50%	21.00%	21.00%
Pulmonary department visits	14.80%	5.80%	9.80%	9.80%
Atopic dermatitis	2.00%	1.30%	1.70%	1.60%
Nasal polyposis	3.20%	1.20%	2.20%	2.70%
OCS daily dosage ≥5mg	6.40%	1.70%	3.80%	3.90%
Observation period starting year				
2005-2006	14.40%	20.90%	17.90%	18.00%
2007-2008	18.20%	20.50%	19.80%	19.50%
2009-2010	18.20%	21.30%	19.10%	19.90%
2011-2012	20.50%	22.50%	21.10%	22.00%
2013-2014	28.70%	14.80%	22.00%	20.60%
Observation period starting month				
Jan	9.10%	9.60%	9.10%	9.80%
Feb	8.40%	9.00%	8.20%	8.90%
Mar	9.30%	9.50%	9.20%	9.50%
Apr	9.00%	8.40%	8.70%	8.70%
May	9.60%	8.60%	9.00%	8.70%
Jun	8.90%	7.80%	8.40%	8.00%
Jul	7.40%	7.30%	7.30%	7.20%
Aug	7.60%	7.10%	7.70%	7.00%
Sept	7.40%	7.20%	7.40%	7.20%
Oct	7.90%	8.50%	8.20%	8.30%
Nov	7.70%	8.40%	8.10%	8.10%
Dec	7.90%	8.70%	8.70%	8.50%

Adjustment was made by Inverse Probability Treatment Weight (IPTW). The same weights were applied to both robust Poisson regression models and Cox-proportional hazards regression models. Because weights >20 were set to 20, the IPTW adjusted "N"s (number of treatment periods) may be less than the unadjusted "N"s. For patients 12+ years of age, covariates included in IPTW calculation were age, gender, geocoded education level, Charlson comorbidity index, asthma step-care level, asthma controller ratio, allergic rhinitis, sinusitis, acute upper respiratory infections, anxiety, depression, conjunctivitis, endocrine, Gastroesophageal reflux disease (GERD), infectious disease, musculoskeletal disease, pneumonia, pharyngitis, history of asthma exacerbation, skin disease, insurance indicators (commercial, Medicare, Medicaid/State sponsored programs, private pay), allergy specialist visit, pulmonology specialist visit, atopic dermatitis, nasal polyposis, average oral corticosteroid (OCS) daily dosage ≥ 5mg per day and observation period starting year. For children 4-11 years of age, all the covariates listed above were applied except for anxiety, depression, pulmonology specialist visit, nasal polyposis and Medicare coverage.

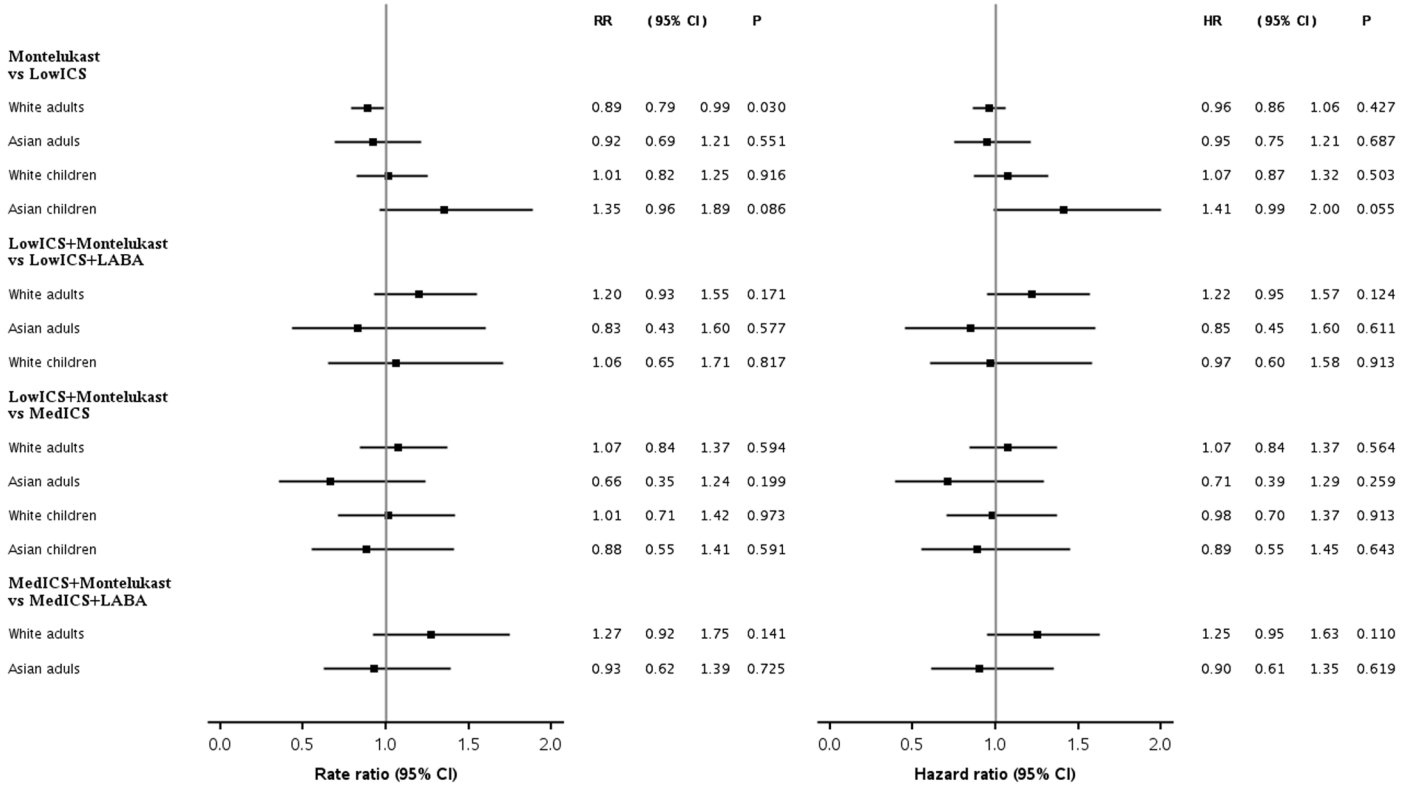

Figure 3. Inverse probability treatment weight (IPTW) adjusted rate ratio (RR) and hazard ratio (HR) of asthma exacerbation during follow up.

LowICS: Low-dose ICS; MedICS: Medium-dose ICS; RR: rate ratio; HR: hazards ratio; CI: confidence interval.

The crude and adjusted covariates being used to compare montelukast monotherapy and low-dose ICS monotherapy for white patients ≥12 years of age are shown in **Tables 3**. The adjusted covariates were well balanced between the two treatment groups. Balance was achieved for other comparison groups (data available upon request). Compared with low-dose ICS monotherapy, montelukast monotherapy evidenced a lower incidence rate (RR 0.89, CI 0.79-0.99, p=0.03) but similar hazard rate (HR 0.96, CI 0.86-1.06, p=0.43) of asthma exacerbation in white patients 12 years of age or older (**Figure 3**). Comparisons between montelukast monotherapy and low-dose ICS monotherapy among whites 4-11 years of age, Asians ≥12 years of age, and Asians 4-11 years of age did not reveal a statistically significant difference in asthma exacerbation rate. In addition, no statistical differences were seen in the rate of asthma exacerbations in any of the other three step-care treatment comparisons stratified by age or ethnicity (**Figure 3**). In the analyses of time to 1st asthma exacerbation, none of the comparisons yielded a statistically significant difference in hazard rates (**Figure 3**).

Due to the small number of events, montelukast add-on versus LABA add-on therapies were not compared in Asian children 4-11 years of age. For the same reason, the comparison between montelukast + median-dose ICS and LABA + median-dose ICS was not made for white children 4-11 years of age.

Discussion

We analyzed the relative effectiveness of alternative controller step-care level therapies in a population of non-Hispanic White and Asian patients with persistent asthma. A lower incidence rate of asthma exacerbations (p=0.03), but similar hazard rate (p=0.43) was seen in White patients ≥12 years of age treated with montelukast monotherapy compared to low-dose ICS monotherapy. However, the inconsistency of the results highlights the uncertainty of the positive finding, which might be due to a Type I error, given the large number of treatment comparisons made, or due to the differences in the analysis methods (i.e. incidence rate analysis included all the events within the observation windows, while the time-to-event analysis utilized only the first event for patients who had multiple events). Supportive of the aforementioned suggestion, all other comparisons by ethnicity or by age of the alternative step-care treatment comparisons (montelukast versus LABA added to low-dose ICS or medium-dose ICS, or montelukast added to low-dose ICS versus medium-dose ICS monotherapy) showed non-significant differences for either the incidence rate or the hazard rates of asthma exacerbation.

Prior real-world comparative effectiveness findings of the present studied treatments were inconsistent. Blais et al. reported that among children 5-11 years of age, LTRA was associated with a lower risk of asthma exacerbations compared to ICS among patients who had no prior exacerbation (RR = 2.3; 95% CI: 1.3–4.0), but the risk of exacerbations were similar among patients with one or more prior exacerbations (RR = 1.6; 0.8–3.1). However, in two pragmatic trials

including patients 12-80 years of age, LTRA was shown to be equivalent to an ICS as first-line controller therapy (rate ratio = 1.27; 0.83-1.92) and to LABA as add-on therapy (rate ratio = 1.02; 0.74-1.41).[9] Sadatfsfavi et al. provided evidence of the superiority of ICS+LABA over ICS+LTRA with less asthma related outpatient visits and medication dispensing when the data were analyzed using partial treatment periods in which treatments were uninterrupted (i.e. follow-up stopped when treatment switched); however, no difference was observed between the two treatments when analyzed by intention to treat.[6]

Unlike prior real-world studies,[6,7,9] the current study monitored therapy changes over time for each patient. Compared to studies defining treatment patterns based on intention to treat (ITT),[9] the design of the current study was less likely to misclassify treatments and thus more likely to detect an effect if one existed because ignoring treatment pattern changes (e.g. ITT) was more likely to bias towards the null. On the other hand, studies relying solely on the initial treatment period for each patient without including treatment periods after class switch or class addition or reduction, as reported in some prior studies (e.g. Blais et al., uninterrupted analysis in the study of Sadatsafavi et al.) made conclusions only based on partial information. This may also lead to bias, especially in studies with long follow-up time. Another strength of the current study is the adjustment of patient characteristics that were specific to each treatment period. Due to the lengthy study period (up to 9.5 years), patient characteristics may change considerably.

Differences in adherence among treatment groups may lead to erroneaous results (i.e. true effects are either masked or inflated). This is especially a concern in real-world studies in which adherence is not optimzied. In reality, variations in adherence to different therapies could be large within a study and the variations may go in different directions in different studies. For example, in a real-world clinical study, ICS+LABA was reported to have better adherene compared to that of ICS+LTRA therapy.[6] However, in two pragmatic trails, adherence seemed to be higher with LTRA compared to ICS (median percentage of adherence 65% vs. 41%, p=0.11) in the firstline controller therapy trial, and much higher with ICS+LRTA compared to ICS+LABA (median percentage of adherence 74% vs. 46%, P<0.001) in the add-on therapy trial. When both adherence and an outcome of interest are superior for one therapy compared to another, it is difficult to determine whether the improved treatment effect was a result or a cause of higher adherence. In the current study, adherence was not reported because exposure was tracked on a daily basis based on the information (e.g. types of medication dispensed, physician instructions, and days supply) collected administratively. Any time windows in which no treatment was given were not included in the study.

Although 2- or 4-week wash out periods are common in clinical trials to examine maximal effects of asthma drugs compared to placebo or comparative medication, it is important to include early treatment benefits of exacerbation reduction in observational studies. Previous studies demonstrated clinical effectiveness within one week of initiating ICS or montelukast, and diminution of effect within one week of discontinuation of ICS or montelukast. For example, immediate anti-inflammatory effects of ICS on airway blood flow response were observed in a dose dependent manner as early as 15 minutes and peaked at 60 minutes.[25] Szefler et al. reported that the time to 50% of maximum response to ICS administration in adolescents and adults with asthma was 1 week or less for peak expiratory flow (5 days), FEV_1 (< 1-week), symptoms (1-day), and albuterol use (2-days).[26] Kharitonov et al. reported a rapid reduction in exhaled breath condensates and symptoms within 5 days of ICS administration in patients with mild asthma and significant worsening of fractionated exhaled nitric oxide, peak expiratory flow, and symptoms within 1 week of discontinuing ICS.[27] Similarly, diminution of ICS effectiveness was seen within 1 week for FEV_1 and bronchial reactivity by both Phillips et al.[28] and Vathenen et al.[29] For montelukast, its onset of action is rapid with significant protection against exercise-induced bronchoconstriction after a single dose, beginning as early as 2 hours after administration and persisting about 24 hours in adults[30] and lasting for 12 hours in children.[31] The beneficial effect of montelukast on daytime symptoms, albuterol use, and lung function were gone by 1-week after discontinuation of montelukast compared to placebo in adults with chronic asthma.[32] The findings above supported the use of a 7-day period in the present study.

To our knowledge, our study is the first population-based study in which the comparative effectiveness of montelukast was examined among Asian adults and children. All three real-world studies mentioned above were based on predominently white populations, reaching ≥97% of study subjects in one study.[9] The studies of Sadatsafavi et al. and Blais et al., were conducted using adminitrative databases in Canada and the distributions of race and ethnicity in these studies were not mentioned.[6,7] Unfortunately, two of the four planned comparisons (montelukast monotherapy versus low-dose ICS monotherapy, montelukast + medium-dose ICS versus LABA + medium-dose ICS) among Asian children 4-11 years of age were not possible due to the small number of events in these groups. Among those comparisons made among Asian patients, most of them had low statistical power. Leukotrienes, potent lipid mediators including cysteinyl leutotrienes and LTB4, play an improtant role in asthma.[33,34] No data is available on the relative roles of leukotrienes in Asians compared to non-Asian, but ethnic differences are possible.

The findings need to be interpreted with caution given its limitations. First, although the balance between the treatment groups being compared was well achieved for known patient demographic and other characteristics, there were potential confounders not captured in the administrative data (e.g. allergen sensitivity, behaviral risk factors such as smoking status, obesity, and lung function). Information on smoking and body mass index was not available for the entire study period and thus was not included in the analysis. The propensity score analysis can never mimic real randomized control trials in which both measured and unmeasured covariates are balanced. Second, medications, though prescribed for a specific period, may not be used regularly, raising some uncertainty about adherence. This remains a challenge for medication effectiveness studies based on administrative data. Third, during the study period, information on race/ethnicity was unknown for about 10-15% of health plan enrollees with persistent asthma

(unpublished data). Finally, statistical power was low for some of the comparisons being made, especially for Asian patients.

In summary, the present real-world observational study demonstrated no statistical difference in asthma exacerbation among alternative step-care level controller therapies. The data do not provide sufficient evidence to alter current asthma guideline recommendations. The lessons learned from this complex administrative study may help future comparative effectiveness studies based on administrative data.

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Conflict of Interets

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Authorship

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors and were entirely responsible for the conduct of the study and writing of the manuscript.

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