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Treatment patterns and related clinical consequences in adults with asthma

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Declaration of interest

All authors declare no conflict of interest related to this study.

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Abstract

Objective: A stepwise therapeutic management is recommended for asthma patients by the Global Initiative for Asthma (GINA). Little is known about the recommendations applied in real world settings. This study aims to associate Treatment Step with clinical events in patients with mild or severe asthma.

Methods: A retrospective claims database analysis included adult patients with mild (GINA step 1) or severe asthma (GINA step 4). Maximum Treatment Step was measured within the first and second 90-day period after index date (the first date of asthma diagnosis during the inclusion period). Step-down was defined as a Treatment Step change from a higher to lower step, while Step-up was defined as a Treatment Step change from a lower to higher step. The primary outcome was a composite endpoint of asthma-related clinical events, measured at the third 90-day period.

Results & Conclusions: A total of 6,354 mild-asthma patients and 5,695 severe-asthma patients were included. In mild-asthma, when compared to No Change in Treatment Step, Step-down was associated with a lower risk of future clinical events [adjusted odds ratio (OR) 0.80, 95%confidence interval (95%CI); 0.69-0.94], while Step-up was not associated with a change in clinical events [OR 0.98, 95%CI; 0.77-1.27]. In severe-asthma patients, Step-down was not associated with a change in clinical events [OR 0.94, 95%CI; 0.81-1.10], while Step-up was associated with a higher risk of future

clinical events [OR 2.07, 95%CI; 1.29-3.33]. Our findings reassure the appropriateness of stepping-down treatment in mild-asthma patients. Clinicians should closely monitor and/or provide detailed asthma action plans for severe-asthma patients who are stepping-up treatment.

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Introduction

Worldwide, approximately 334 million people are asthmatic, accounting for 0.6% of total hospital admissions.[1] In the United States (US), asthma prevalence is 8.7% for children and 7.4% for adults. US asthma hospitalization rates are 14.1 per 10,000 individuals, while mortality rates are 10.6 per 1 million individuals.[2] In order to reduce future hospitalizations and deaths due to asthma, it is critical to incorporate management plans that focus on asthma control.

The Global Initiative for Asthma (GINA) guidelines [3] suggest a stepwise therapeutic management strategy for asthma patients. In situations where a patient is not under control, a Step-up in Treatment Step should be considered. In contrast, if a patient is consistently controlled, the GINA guidelines recommend a sequential Step-down, or decrease, in Treatment Step. Decreases to Treatment Step should continue until the patient reaches the lowest Treatment Step, Treatment Step 0, or until it becomes impossible to continue Step-down without losing control.

Although Treatment Steps are dynamic processes, most asthma outcomes research focuses on asthma guideline Treatment Steps as static or cross-sectional exposures.[4-6] In 2016, a study was conducted by Adachi et al.[7] to determine the effect of Step-down on asthma control. Researchers found that the majority of patients with well-controlled, moderate to severe asthma in Treatment Step 3 [lowdose inhaled corticosteroid (ICS) with long-acting beta agonist (LABA)] randomized to Step-down to Treatment Step 2 [low dose ICS alone] remained in control. Despite the results of the Adachi et al. study, it is difficult to extrapolate the benefits of Step-down in a fixed setting to a shifting environment. Another study[8] was conducted to determine the number of non-eosinophilic severe asthma patients who could stop or step down ICS treatment. The study revealed that 39% of patients could stop ICS and 28% could step down ICS treatment by reducing ICS dose without any exacerbation. However, the study did not evaluate the effect of treatment step down on clinical outcomes. Little is known about Treatment Step management recommendations applied in real world settings. How might real world application of Treatment Step management alter future asthma-related outcomes in patients with mild or severe asthma?

On a per person basis, the highest burden rests within the subpopulation of patients classified with severe asthma (Treatment Step 4). Alternatively, asthma patients are frequently placed within a milder category, Treatment Step 1, and receive prescribed reliever medication. There are warranted reasons to explore research in these subsets: to reduce the harm associated with the overuse of

short-acting beta agonists in mild instances, to counteract the heightened burden of asthma in severe instances. Findings in these categories might present important signals to patients and clinicians, signals which can be monitored more closely to provide detailed action plans to counteract risk of exacerbations.

This retrospective observational study aimed to associate asthma Treatment Step (Step-down or Step-up) with clinical events in patients with mild or severe asthma. We hypothesized that asthma Treatment Step changes were associated with clinical events in both patients with mild and severe asthma.

Material and methods

Data sources

Data were collected retrospectively from a 10% random sample within the PharMetrics® claims database from 2006 to 2014. The database contained paid claims data (medical and pharmacy) from over 98 US health plans. While claims are primarily paid by private commercial insurance, Medicare, Medicaid, and self-insured patients are also represented. Available data included demographics, medical claims, prescription fill information, and diagnosis [international classification of diseases version 9 clinical modification (icd-9-cm)].

Study population, index date, and follow-up

Patients aged >12 at index date with asthma (defined by icd-9-cm as 493.xx), at least two records of asthma diagnosis within one year, and at least two years of follow-up from 2006 to 2013 were included. The rationale for requiring at least two years of follow-up for this cohort was to conduct longitudinal research beyond the scope of the study with the same cohort. Longer follow-up duration beyond what was initially needed for this analysis was required for comparison purposes and due to the ample sample sizes for the present study.

The GINA 2014 Treatment Steps 0 through 5 characterized an individual's highest asthma Treatment Step within a 90-day time period (**Figure 1**).^[9] Patients with mild asthma were defined as patients starting at Treatment Step 1. Patients with severe asthma were defined as patients starting at Treatment Step 4. The index date was defined as the first date of asthma diagnosis during the inclusion period. Patients diagnosed with the following diseases were excluded: cystic fibrosis (icd-9; 277.0x), chronic obstructive pulmonary diseases (491.xx, 492.xx, 494.xx and 496.xx), respiratory tract

cancer (160.xx–164.xx or 231.xx), bronchopulmonary dysplasia (770.7x), respiratory distress syndrome (769.xx), Addison's disease (255.4x), glomerulonephritis (580.xx-582.xx), multiple sclerosis (340.xx), polymyositis/dermatomyositis (710.3x, 710.4x), rheumatoid arthritis (714.xx), scleroderma (710.1x), Sjogren's syndrome (710.2x), systemic lupus erythematosus (710.0x), uveitis (360.11, 363.20 364.3x), vitiligo (709.01), Wegener's granulomatosis (446.4), primary systemic vasculitis (447.6).

Exposure of interest

Three 90-day periods after treatment initiation were used to determine Treatment Step and outcomes. The first and second 90-day periods were used to determine Treatment Step changes. The third 90-day period was used to determine outcomes. The highest asthma Treatment Step within the first and second 90-day period was determined.

Step-down was defined as a change in Treatment Step from a higher Treatment Step in the first 90-day period to a lower Treatment Step in the second 90-day period. Step-up was defined as a change in Treatment Step from a lower Treatment Step in the first 90-day period to a higher Treatment Step in the second 90-day period. No change was defined as remaining at the same maximum Treatment Step over both 90-day time intervals.

Outcomes of interest

The primary outcome of this study was to generate a composite endpoint of asthma clinical events. Classification of a composite endpoint includes one of the following: 1) asthma-related hospitalization, 2) asthma-related emergency department visit, 3) asthma-related outpatient exacerbation (including oral steroid burst claim with an oral steroid dispensation $\pm$ 5 days), or 4) outpatient visits for lower respiratory tract infection treated with antibiotics. All asthma clinical events were separately analyzed as secondary endpoints.[4, 10, 11] Outcomes of interest were determined at the third 90-day period, allowing observed change patterns in Treatment Step to occur prior to the measurement of clinical events.

Data analysis

Two 90-day periods after treatment initiation were used to define change patterns (Step-up, Step-down, or No Change in Treatment Step). Descriptive statistics were used to detail patient characteristics and outcomes. Multivariate polytomous logistic regression was used to associate

change patterns (X) and clinical events that occurred after a change in treatment (clinical outcomes) (Y). Clinical events were observed throughout the third 90-day period.

Example: A patient was observed as Treatment Step 1 in the first 90-day period, Treatment Step 2 in the second 90-day period, and hospitalized in the third 90-day period. Because the patient experienced a degrade in condition, he would be categorized into the Step-up group. Due to the patient's hospitalization in the third 90-day period, he experienced a composite clinical outcome.

There were several potential confounders included in the model: US census region per patient, age, season of index date, number of continuous eligibility after inclusion, number of continuous eligibility before inclusion, healthcare coverage, number of diseased patients diagnosed, allergic rhinitis, obesity, eczema, obstructive sleep apnea, gastroesophageal reflux disease, respiratory infection, number of hospitalizations, number of asthma-related hospitalizations, number of emergency department visit, number of asthma-related emergency department visit, number of medical visits, number of medical procedures, number of medications, cost of treatment, number of asthma-related medical visits, number of lower respiratory tract infection-related visits, and Charlson' comorbidity index. Potential covariates were chosen based on a literature review of factors influencing asthma control.[12, 13] The potential confounders were assessed within 6 months prior to the index date. Hosmer-Lameshow goodness-of-fit test was used to determine the appropriateness of model fitting.

Results

Baseline cohort characteristics are show in Table 1.

A total of 12,049 patients with either mild or severe asthma were included. Of those, 6,354 patients had mild asthma and 5,695 patients had severe asthma.

In the mild asthma cohort, the mean age was 34.44 ($\pm$ 15.53) years. 37.91% of the group were male. 82.40% of patients had commercial health coverage. The average number of asthma-related hospitalizations 6 months prior to the index date was 3.62 ($\pm$ 60.06) per 1,000 individuals.

In the severe asthma cohort, the mean age was 40.08 ($\pm$ 14.74) years. 38.26% of the group were male. 85.95% of patients had commercial health coverage. The average number of asthma-related hospitalizations 6 months prior to the index date was 6.32 ($\pm$ 89.66) per 1,000 individuals.

Asthma treatment step pattern

Table 2 shows the change in asthma Treatment Step for the mild and severe asthma cohorts. Seven hundred mild asthma patients (11.02%) stepped up (Treatment Step 1 to Treatment Step 2 or greater) in the second 90-day treatment period. 3,981 mild asthma patients (62.65%) moved to no asthma-related treatment (Treatment Step 0). Eighty-nine severe asthma patients (1.56%) stepped up (Treatment Step 4 to Treatment Step 5). 2,181 severe asthma patients (38.30%) stepped down (Treatment Step 4 to Treatment Step 3 or lower).

Clinical outcomes

Mild asthma cohort

In mild asthma patients, 994 patients (15.64%) experienced the composite endpoint in the third 90-day period. One hundred twenty-five patients (1.97%) were hospitalized. Three hundred and ten patients (4.88%) visited the emergency department for asthma control. Three hundred and five patients (4.80%) visited an outpatient department for asthma-related exacerbation while 502 patients (7.90%) visited an outpatient department for a lower respiratory tract infection treatment (Table 2).

Adjusted odds ratio (OR) for Step-down patients compared to No Change patients was 0.80 (0.69 to 0.94). Step-up patients compared to No Change patients had an adjusted OR of 0.98 (0.77 to 1.24). The Hosmer-Lameshow test indicated a good fit of the model ($p = 0.80$). Adjusted ORs for secondary endpoints are detailed in Table 3.

Severe asthma cohort

In the severe asthma cohort, 893 patients (15.68%) experienced the composite endpoint in the third 90-day period. Ninety-nine patients (1.74%) were hospitalized. Two hundred and fourteen patients (3.76%) visited the emergency department for asthma control. Three hundred and forty-six patients (6.08%) visited an outpatient department for asthma-related exacerbation while 495 patients (8.69%) visited an outpatient department for a lower respiratory tract infection treatment (Table 2).

Adjusted OR was 0.94 (0.81 to 1.10) for Step-down patients compared to No Change patients. In contrast, the adjusted OR was 2.07 (1.29 to 3.33) for Step-up patients compared to No Change patients. The Hosmer-Lameshow test indicated a good fit of the model ($p = 0.47$). Adjusted ORs for secondary endpoints are detailed in Table 3.

Discussion

First, this study highlights a large percentage of persistent mild and severe asthma patients change Treatment Steps. In those patients observed on SABA alone (Treatment Step 1) for three months, approximately 74% switched Treatment Steps with the majority of these moving to no rescue inhaler claims over the following three-month window. In those patients observed on medium/high-dose combination controller medications (Treatment Step 4) for three months, nearly 40% switched Treatment Steps with the majority of these moving down to lower intensive controlled medication management over the following three-month window. These high observed rates of Treatment Step switching support the real-world aspects of asthma whereby continued clinical monitoring and management are important in achieving control. This study further indicates that changes in Treatment Step were associated with future clinical events. Interestingly, the proportion of patients that experienced the exacerbation composite outcome were similar in the mild and severe asthma cohorts. Although this observation suggests that mild and severe asthma cohorts seek out exacerbation-related health services, the study did not exhaustively investigate the reasons why patients had asthma exacerbations. We did, however, find interesting associations with Treatment Step changes and the risk of asthma exacerbation. For patients with mild asthma, a decrease in Treatment Step was associated with decreased odds of composite outcomes when compared to No Change in Treatment Step. No association between Step-up and No Change was observed in mild-asthma patients. For patients with severe asthma, an increase in Treatment Step was associated with an increased odds of the composite outcome when compared to No Change in Treatment Step. Notably, no association between Step-down and No Change was observed in severe asthma patients. Therefore, Step-down in severe asthma can be viewed as a successful management strategy in those whom exhibit control over a sufficient period of time.

This study highlights that a proportion of mild asthma patients are able to maintain, or improve, asthma control while stepping down their asthma treatment. This observed maintenance, or improvement, may be related to the higher likelihood of symptom control seen in patients with Treatment Step decreases. It is likely that patients with Treatment Step decreases have higher awareness of worsening symptoms and are able to avoid exacerbation through proper preemptive management. A previous randomized pragmatic trial conducted by Usmani et al. demonstrated similar

findings.[14] Usmani et al. noted Treatment Step decreases in patients on fluticasone propionate/formoterol fumarate to not be associated with an increased risk of asthma exacerbation or asthma control. In our study, such an association was not observed in the severe asthma cohort.

An association between Step-up and an increase of clinical events was observed in severe asthma patients but not in mild asthma patients. Patients with uncontrolled severe asthma are at risk of asthma exacerbation[15, 16] and are highly likely to Step-up from Treatment Step 4 to Treatment Step 5 to control their symptoms. It is possible that asthma exacerbations represent strong predictors for increased Treatment Step in patients with severe asthma.[3] Given our study design, Treatment Step increase was observed prior to the measurement of clinical events. This factor places greater weight on exacerbation as a precipitator. It should be noted that Step-up, in the severe asthma population, did not achieve outcomes on par with Step-up in the mild asthma population. This is potentially due to the severe asthma cohort's higher count of treatment non-responders. The observed signal within the primary composite endpoint for the severe cohort's Step-up in Treatment Step was driven by changes in outpatient visits with corresponding oral steroid burst prescriptions. The costs of such encounters would not be as extreme as if we observed most of the signal to be within asthma hospitalizations, but such outpatient costs remain important to the patient, health system, and society.[17]

Clinically, the findings of this study reinforce previous clinical guidelines and findings from previous studies. The results are encouraging in that they demonstrate, in a real-world clinical setting, prescribers are likely following guidelines and are making changes in asthma therapy using a stepwise approach. The results of this study should provide confidence to prescribers in stepping down therapy in patients that have been well controlled for a 3-month period regardless of if they have mild or severe asthma as patients typically will do very well and often do not experience worsening asthma symptoms. Although monitoring after any step change in therapy is important, this study emphasizes the importance of closely monitoring patients with severe asthma that require a step up in therapy. The results of this study confirm asthma in this situation is difficult to control with patients often experiencing minimal or no response to traditional controller medications.

This study showed only the association of changes in Treatment Step with clinical events. It did not compare the effectiveness of different treatment options. In March of 2017, a study by Murray et al. compared the effectiveness of different treatment options for Treatment Step increases in

children.[18] Murray et al. discovered that pediatric patients with uncontrolled asthma at Treatment Step 2 could benefit from the three main treatment options for Step-up [1) increasing ICS dose, 2) changing to fixed dose ICS/LABA combination (FDC), and 3) adding leukotriene receptor antagonist (LTRA)]. In terms of achieving asthma control, FDC was determined most effective.

When examining each clinical outcome, changes in Treatment Step were only associated with asthma-related outpatient exacerbation. They were not associated with asthma-related hospitalization, asthma-related ED visit, and outpatient visits for lower respiratory tract infection. The observed association was likely due to patient access to prescribing physicians with the ability to easily increase Treatment Step in the outpatient clinical setting. Prescribing physicians might monitor or provide detailed asthma action plans which require an increase in Treatment Step.

There were several limitations to this study. First, this study used the clinical events as proxy measures for asthma control. The proxy measurement may not be consistent with patient-reported control but the study definition of control remains an important clinical and patient-centered outcome. Moreover, in medical databases the proxy measures in this study are often the only accessible information for analysis and decision making, which justifies their relevance for real-life research. Second, because we could not physically assess patients' asthma severity, we assumed asthma Treatment Step at the beginning to determine their asthma severity. This assumption might have led to patient misclassification. However, in order to clearly determine if patients had mild or severe asthma, the patients needed to be on Treatment Step 1 or Treatment Step 4 for several months. We believe that the approach is acceptable to be used as a proxy to determine patients' asthma severity at the beginning of observation. Third, the association between changes in Treatment Step and outcomes may be masked by unmeasured or unknown variables, such as appropriate inhaler technique, environmental factors, and adherence to medication. Fourth, Given that we did not measure adherence or persistent to asthma Treatment Steps during each 90-day window, we cannot be certain that a Treatment Step increase or decrease is characteristic of the entire 90-day time period. The interpretation of the findings should include that of patients who only temporarily increase Treatment Steps as these would trigger this study's definition of Treatment Step increase. Further, temporary Treatment Step decreases would not be measured within this study design since we found the maximum Treatment Step within each 90-day period. Last, the Treatment Step algorithm and observed associations should not be interpreted to populations with no commercial health plans, such

as Medicare or Medicaid, or populations outside of the United States due to possible differences in practice patterns and aspects of generalizability.

Conclusions

Step-down was associated with a decrease of clinical events in the mild asthma cohort. This observed finding reassures the appropriateness of stepping-down treatment in adult mild asthma patients who remain well-controlled, as recommended by GINA guidelines.[3] Clinicians may consider Step-down for such patients who remain well controlled. On the other hand, Step-up was associated with an increase of asthma exacerbations in the severe asthma cohort. Clinicians may need to closely monitor and/or provide detailed asthma action plans for severe-asthma patients at the time of a Treatment Step increase.

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Table 1 Demographics and other baseline characteristics

Characteristics	Total (N, %) (N = 12,049)	Mild asthma cohort (N, %) (N = 6,354)	Severe asthma cohort (N, %) (N = 5,695)
Age (Mean $\pm$ SD)	37.11 $\pm$ 15.42	34.44 $\pm$ 15.53	40.08 $\pm$ 14.74
Gender			
Male	4,587 (38.07)	2,409 (37.91)	2,178 (38.26)
Female	7,461 (61.92)	3,945 (62.09)	3,516 (61.74)
Missing data	1 (0.01)	0 (0)	1 (0.02)
US census region			
East	3,237 (26.87)	1,666 (26.22)	1,571 (27.59)
Mid-west	4,015 (33.32)	2,118 (33.33)	1,897 (33.31)
South	3,185 (26.43)	1,668 (26.25)	1,517 (26.64)
West	1,612 (13.38)	902 (14.20)	710 (12.47)
Season of index date			
Summer	3,082 (25.58)	1,470 (23.14)	1,612 (28.31)
Fall	3,727 (30.93)	1,977 (31.11)	1,750 (30.73)
Winter	2,720 (22.57)	1,492 (23.48)	1,228 (21.56)
Spring	2,520 (20.91)	1,415 (22.27)	1,105 (19.40)
Number of continuous eligibility before inclusion (Mean $\pm$ SD), (days)	617.57 (436.60)	678.54 (456.70)	549.55 (403.04)
Number of continuous eligibility after inclusion (Mean $\pm$ SD), (days)	1,375.23 (504.17)	1,345.71 (487.19)	1,408.16 (520.56)
Healthcare coverage			
Commercial	10,131 (84.08)	5,236 (82.40)	4,895 (85.95)
SCHIP	51 (0.42)	35 (0.55)	16 (0.28)
Medicaid	412 (3.42)	277 (4.36)	135 (2.37)
Medicare	60 (0.50)	27 (0.42)	33 (0.58)
Self-insured	1,331 (11.05)	738 (11.61)	593 (10.41)
Unknown/missing	64 (0.53)	41 (0.65)	23 (0.40)
Number of diseases	6.37 (6.53)	5.98 (6.31)	6.79 (6.74)
Allergic rhinitis	1,736 (14.41)	674 (10.61)	1,062 (18.65)
Obesity	405 (3.36)	209 (3.29)	196 (3.44)
Eczema	360 (2.99)	187 (2.94)	173 (3.04)
Obstructive sleep apnea	602 (5.00)	246 (3.87)	356 (6.25)
Gastrointestinal reflux disease	41 (0.34)	13 (0.20)	28 (0.49)
Respiratory tract infection	2,852 (23.67)	1,458 (22.95)	1,394 (24.48)
Total healthcare utilization (Mean $\pm$ SD) (per 1,000 individuals over six months)			
Number of hospitalizations	29.46 $\pm$ 220.64	28.64 $\pm$ 226.80	30.04 $\pm$ 213.58
Number of emergency visits	123.16 $\pm$ 328.64	136.45 $\pm$ 343.29	108.34 $\pm$ 310.84
Number of medical visits	5,416.96 $\pm$ 7,070.26	4,939.72 $\pm$ 6,796.86	5,949.43 $\pm$ 7,327.33
Number of medical procedures	9,329.40 $\pm$ 10,831.69	8,833.18 $\pm$ 10,431.06	9,883.06 $\pm$ 11,236.95
Number of drug claims	5,075.94 $\pm$ 4,889.65	4,097.26 $\pm$ 4,390.54	6,167.87 $\pm$ 5,178.74
Asthma-related utilization (Mean $\pm$ SD)			

(per 1,000 individuals over six months)			
Number of asthma-related hospitalizations	4.89 ± 75.52	3.62 ± 60.06	6.32 ± 89.66
Number of asthma-related emergency visits	10.46 ± 101.73	7.55 ± 86.59	10.37 ± 116.24
Number of asthma-related medical visits	38.43 ± 263.29	16.83 ± 166.06	62.51 ± 338.85
Number of respiratory tract infection-related visits	48.63 ± 299.89	26.60 ± 227.40	73.22 ± 362.56
Baseline cost of treatment within 6 months before index date (Mean ± SD)	\$2,441.57 (7,047.05)	\$2021.12 (6928.07)	\$2,910.66 (7,148.95)
Charlson's comorbidity index			
0-1	11,667 (96.83)	6,184 (97.32)	5,483 (96.28)
2-3	335 (2.78)	143 (2.25)	192 (3.37)
>4	47 (0.39)	27 (0.42)	20 (0.35)

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Table 2 The number of asthma Treatment Step within 90-day periods and outcomes in patients with mild or severe asthma

Variables	Mild asthma cohort (N = 6,354)	Severe asthma cohort (N = 5,695)
Asthma treatment pattern (1st to 2nd 90-day period)		
- No change in Treatment Step	1,673 (26.33)	3,425 (60.14)
- Step-down	3,981 (62.65)	2,181 (38.30)
- Step-up	700 (11.02)	89 (1.56)
Clinical events in the 3rd 90-day period		
Primary composite endpoint *	994 (15.64)	893 (15.68)
Secondary endpoint [#]		
- asthma-related hospitalization	125 (1.97)	99 (1.74)
- asthma-related emergency visit	310 (4.88)	214 (3.76)
- asthma-related outpatient exacerbation	305 (4.80)	346 (6.08)
- outpatient visits for lower respiratory tract infection	502 (7.90)	495 (8.69)

*The composite endpoint included asthma-related hospitalization, asthma-related emergency visit, asthma-related outpatient exacerbation, outpatient visits for lower respiratory tract infection. The composite endpoint was coded as "yes" once the patients experienced one of the composite endpoints within the 3rd 90-day period.

[#]Secondary endpoints were separately presented from the composite outcome. Those secondary endpoints were not mutually exclusive. Each patient might have >1 category of events but the patient would be counted only once for the composite endpoints.

Table 3 Association of asthma Treatment Step and clinical events

Analysis*	Adjusted odds ratio (95% confident interval)	
	Mild asthma cohort	Severe asthma cohort
Primary endpoints		
- Step-down VS. No Change in Treatment Step	0.80 (0.69 to 0.94)	0.94 (0.81 to 1.10)
- Step-up VS. No Change in Treatment Step	0.98 (0.77 to 1.24)	2.07 (1.29 to 3.33)
Asthma-related hospitalization		
- Step-down VS. No Change in Treatment Step	0.86 (0.57 to 1.29)	1.05 (0.69 to 1.61)
- Step-up VS. No Change in Treatment Step	1.08 (0.58 to 2.01)	1.74 (0.53 to 5.77)
Asthma-related emergency visit		
- Step-down VS. No Change in Treatment Step	0.89 (0.69 to 1.16)	1.10 (0.83 to 1.46)
- Step-up VS. No Change in Treatment Step	0.90 (0.60 to 1.36)	0.65 (0.16 to 2.67)
Asthma-related outpatient exacerbation		
- Step-down VS. No Change in Treatment Step	0.66 (0.51 to 0.85)	0.80 (0.63 to 1.02)
- Step-up VS. No Change in Treatment Step	0.93 (0.63 to 1.35)	3.58 (2.08 to 6.15)
Outpatient visits for lower respiratory tract infection		
- Step-down VS. No Change in Treatment Step	0.91 (0.73 to 1.12)	0.92 (0.75 to 1.12)
- Step-up VS. No Change in Treatment Step	0.96 (0.69 to 1.32)	1.48 (0.80 to 2.74)

*The analyses was conducted using polytomous logistic regression. All potential confounders were included in the analyses but some were excluded from the final models. Potential confounders included US census region, age, season of the index date, number of continuous eligibility after inclusion, number of continuous eligibility before inclusion, healthcare coverage, number of diseases patient diagnosed, allergic rhinitis, obesity, eczema, obstructive sleep apnea, gastroesophageal reflux disease, respiratory infection, number of hospitalization, number of asthma-related hospitalization, number of emergency department visit, number of asthma-related emergency department visit, number of medical visit, number of medical procedure, number of medication, cost of treatment, number of asthma-related medical visit, number of lower respiratory tract infection-related visit, and Charlson' comorbidity index

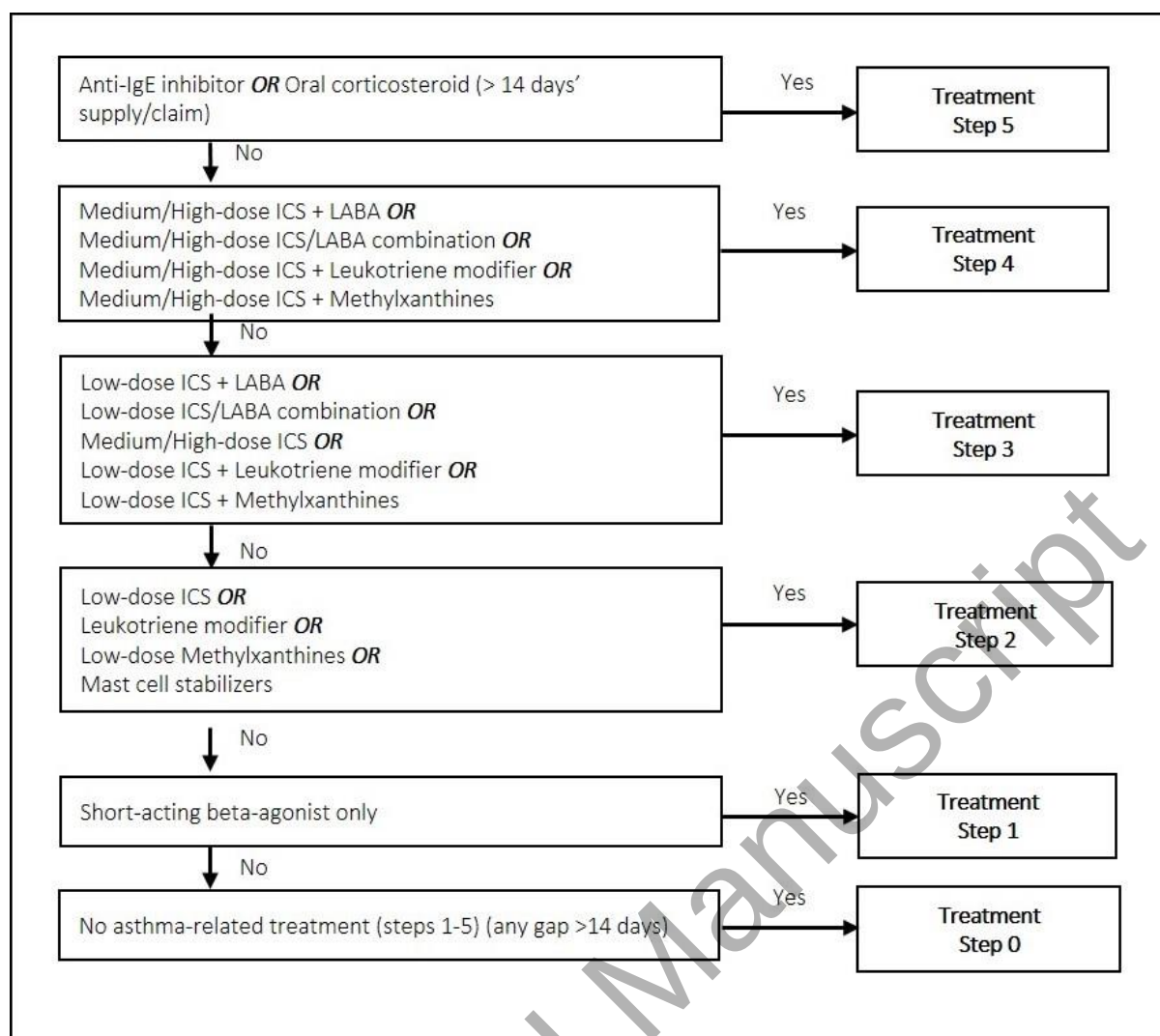


Figure 1 Asthma Treatment Step algorithm (adapted from GINA guideline 2014)

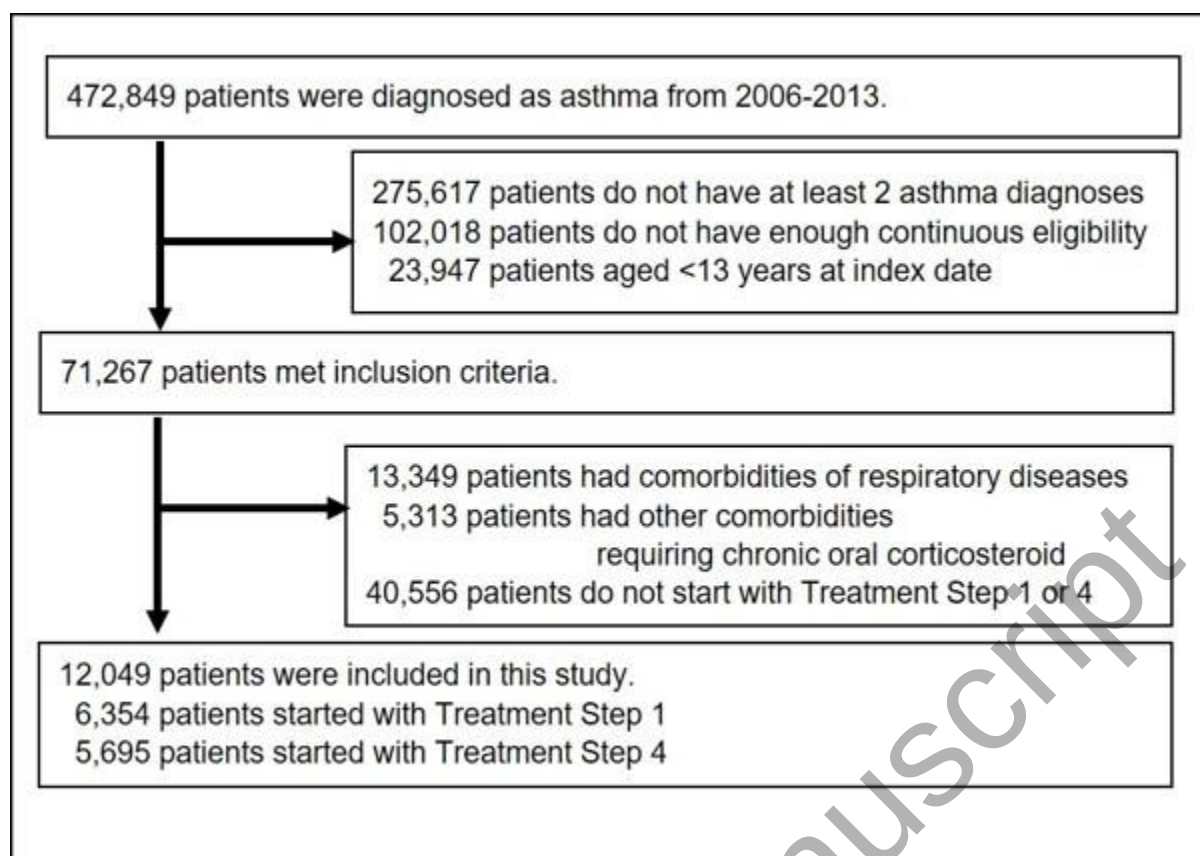


Figure 2 A flow of patient selection