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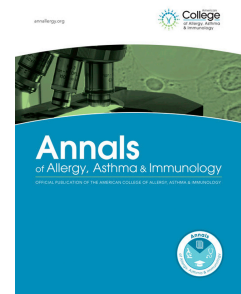
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Real-World Patterns and Implications of Short-Acting Beta₂-Agonist Use in Patients with Asthma in the USA

Running Title: Real-World Patterns of Short-Acting Beta₂-Agonist Use

Njira Lugogo MD¹, Ileen Gilbert MD², Joseph Tkacz MS³, Hitesh Gandhi MBBS², Nadia Goshi MPH², Miguel J. Lanz MD⁴

¹*Michigan Medicine, University of Michigan, Ann Arbor, MI;* ²*AstraZeneca, Wilmington, DE;* ³*IBM Watson Health, Cambridge, MA;* ⁴*AAADRS Clinical Research Center, Coral Gables, FL*

Corresponding Author: Ileen Gilbert, AstraZeneca, 1800 Concord Pike, Wilmington, DE 19803, USA

Phone: +1 262-227-0686; E-mail: ileen.gilbert@astrazeneca.com

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NL made substantial contributions to analysis and interpretation of data; contributed to drafting the article and reviewed the article critically for important intellectual content; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work related to its accuracy or integrity.

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Abbreviations: FDA – Food and Drug Administration; GINA – Global Initiative for Asthma; ICS – inhaled corticosteroids; LABA – long-acting beta₂-agonist; LAMA – Long-acting muscarinic antagonist; LM – leukotriene modifiers; MPR – maintenance medication possession; OCS – oral corticosteroids; SABA – short-acting beta₂-agonist; SCS – systemic corticosteroids

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1 Introduction

2 Asthma is a heterogeneous chronic inflammatory disease that fluctuates over time in symptom
3 control and risk of exacerbations. Phenotypically, asthma is marked by episodic coughing,
4 wheezing, and breathlessness that vary in intensity and occur against a backdrop of fluctuating
5 airway inflammation.^{1,2} Treatment involves bronchodilators, such as short-acting beta₂-agonists
6 (SABA) or long-acting beta₂-agonists (LABA) combined with inhaled corticosteroids (ICS), and
7 anti-inflammatory agents, used as monotherapy or in combination with other maintenance
8 medications. The goal of asthma management is to improve symptoms and quality of life and
9 reduce exacerbations, loss of lung function, and side effects from both acute and long-term use
10 of medications.³

11 The Global Initiative for Asthma (GINA) recommends a stepwise approach to determining the
12 appropriate maintenance treatments for patients with asthma.⁴ Based upon the body of global
13 clinical data,⁵⁻⁸ GINA has recently emphasized that for all patients with asthma aged ≥ 12 years,
14 treatment with a SABA alone is no longer recommended.⁴ For patients in GINA Steps 1 and 2
15 and those in GINA Steps 3-5 receiving ICS/LABA maintenance therapy containing a fast-acting
16 LABA, the preferred rescue/reliever is now as-needed low-dose budesonide-formoterol or low-
17 dose beclomet(h)asone-formoterol.^{4,9}

18 There are no fixed-dose combination ICS/fast-acting beta₂-agonist therapies approved by the
19 Food and Drug Administration (FDA) for use as a rescue medication in the United States (USA).
20 SABA are used for acute relief of asthma symptoms, as they quickly mitigate coughing,
21 wheezing, and breathlessness.^{2,4} Despite their short-term effectiveness, frequent use of SABA
22 without concomitant ICS is not recommended due to concerns about increased risk of fatal or

near-fatal exacerbations and the availability of maintenance therapies that address underlying inflammation while providing more consistent symptom control.^{10,11} Although guidelines recommend that asthma treatment should focus on stepping up maintenance medication until SABA usage for daytime symptoms is under 3 times per week,^{2,4} several studies have shown continued reliance on SABA and underuse of maintenance medication.¹²⁻¹⁹

Approximately 25 million individuals in the USA are currently diagnosed with asthma.²⁰ The annual costs of asthma are reported to be in excess of \$81 billion, with \$50 billion in medical costs and \$29 billion in asthma-related mortality.²¹ Notably, use of SABA has been linked to an increase in severe asthma exacerbations and higher health care costs.^{13,16} Further US-based investigations are needed to understand real-world SABA utilization patterns and their consequences across the full spectrum of asthma severity. The aim of this study was to quantify the real-world prescription fill patterns of SABA and maintenance medications along with the associated morbidity of exacerbations among commercially insured US patients with asthma aged ≥ 12 years.

Methods

Study Design

This analysis utilized a retrospective observational design that assessed administrative claims for individuals who filled 1 SABA and ≥ 1 maintenance medication prescription or ≥ 2 SABA prescriptions with or without maintenance fills between September 30, 2014, and September 30, 2016. Disease severity, maintenance medication possession ratio (MPR) as a measure of adherence, and exacerbations over the 12 months following the earliest SABA fill were compared between patient cohorts stratified by SABA and maintenance fills per year.

Data Sources

Two IBM MarketScan Research Databases were used: Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits (Medicare) Databases. The Commercial database contains the inpatient, outpatient medical, and outpatient prescription drug experiences of tens of millions of patients annually, whereas the Medicare database contains both medical and pharmacy data of individuals with Medicare supplemental insurance paid for by employers. Both databases provide detailed use and outcomes data for health care services incurred in both the inpatient and outpatient settings across a variety of health plans, including preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations.

All study data were obtained using International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Healthcare Common Procedure Coding System codes, and National Drug Codes. Unique identifiers are used to link person-level enrollment data to medical and outpatient prescription drug claims. All database records are statistically de-identified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board approval to conduct this study was not necessary.

Inclusion Criteria

The Commercial and Medicare databases were used to identify patients aged ≥ 12 years with ≥ 1 prescription for a SABA—specifically albuterol sulfate, levalbuterol hydrochloride, or pirbuterol

acetate—between September 30, 2014, and September 30, 2016 (study period). The service date of the first SABA prescription during the study period was defined as the index date. Patients were required to have ≥ 12 months of continuous medical and pharmacy benefits enrollment prior to and following the index date. Additionally, patients were required to have ≥ 1 inpatient or ≥ 2 outpatient non-diagnostic claims with evidence of asthma (ICD-9-CM: 493.%2 [except 493.81]; ICD-10-CM: J45.%1 [except J45990]) during the 12-month pre-index period or within 60 days following the index date. Patients were excluded if they had evidence of a chronic lower respiratory illness other than asthma, primary eosinophilic disorders, cancer, or a select set of autoimmune disorders at any time during the 12-month pre- and post-index periods (**eTable 1**).

To further ensure that the patients being studied actually had asthma, patients were required to have either at least one other SABA or an asthma maintenance medication fill in the 12 months post-index. The following asthma maintenance medications were included in the analysis: ICS, LABA, long-acting muscarinic antagonists (LAMA), ICS/LABA, LABA/LAMA, leukotriene modifiers (LM), methylxanthines, biologic therapies, and systemic corticosteroids (SCS).

Treatment Group Stratifications

Patients were placed into one of three SABA use cohorts based on the total number of SABA claims, including the index fill, during the 12-month post-index period. The placement of patients into SABA use cohorts was determined based on clinical relevance following an examination of the distribution of SABA fills across the study population:

- Low SABA use cohort: 1 SABA canister fill and ≥ 1 maintenance fill in the post-index period;

- Medium SABA use cohort: 2–3 SABA canister fills, with or without evidence of maintenance fills during the 12 months post-index; and
- High SABA use cohort: ≥ 4 SABA canister fills, with or without maintenance medications during the 12 months post-index.

Based on the National Asthma Education and Prevention Program Guidelines, and assuming that one SABA canister contains 200 puffs, or 100 doses of rescue therapy, patients in the low SABA use cohort met the criteria for “well-controlled” asthma symptoms, with an average of ≤ 2 doses of rescue medication per week over a year; those in the medium SABA use cohort met criteria for “not well-controlled” asthma, with an average of ≥ 3 doses but not daily use of SABA each week; and those in the high SABA use cohort met criteria for “very poorly controlled” asthma, with an average of ≥ 1 dose of SABA per day.

Patients were also stratified according to their predominant treatment based on the GINA 2018 guidelines using the class and strength of their prescribed maintenance medication(s).²² Patients with no maintenance medication use were assigned to GINA Step 1. Patients with evidence of either low-dose ICS or LM use were assigned to GINA Step 2. Patients with evidence of low-dose ICS/LABA, LM with a low-dose ICS, or medium-/high-dose ICS use were assigned to GINA Step 3. Patients using medium-/high-dose ICS/LABA, with or without a third agent, were assigned to GINA Step 4/5. Patients with evidence of chronic SCS use with any other asthma therapy(s) were assigned to GINA Step 5. Chronic SCS use was defined as outpatient prescription or outpatient medical claims for SCS covering $\geq 50\%$ (180 days) of the post-index period, as assessed by total days’ supply divided by days of clinical benefit.

Outcomes

Patient age and sex were recorded on the index date. Adherence to maintenance medication was measured using MPR as calculated by dividing the sum of days' supply by the number of days between the date of the first maintenance medication fill and the last day of the post-index period.

The presence and frequency of exacerbations were measured during the post-index period. Asthma exacerbations were defined as: (1) A claim for a SCS of >3 days' supply of an oral corticosteroid (OCS) or a steroid injection (2) An inpatient hospitalization with a primary diagnosis of asthma; (3) An emergency department visit or other outpatient visit with a diagnosis of asthma exacerbation and a SCS fill: for chronic SCS users (SCS claims covering > 180 days of the 12- month post-index period) an emergency department or other outpatient visit with diagnosis of asthma exacerbation that required either 3 days' supply of OCS or a single corticosteroid injection within a 5-day window of the visit date.

Statistical Analyses

Mean and standard deviation (SD) were reported for continuous variables. Between-group statistical significance was determined using one-way analysis of variance. Frequencies and percentages were reported for categorical variables, and between-group statistical significance was determined using Chi-square tests. The alpha level for all statistical tests was 0.05.

Results

Among the 135,540 asthma patients who met the study criteria (**Figure 1**), 62.8% were female, and mean(SD) age was 40.9(18.3) years on the index date. The proportions of patients included

in the 3 SABA cohort groups were 28% (N=38,158)) in the low SABA, 47% (N=63,045) in the medium SABA, and 25% (N=34,337) in the high SABA use group. (Table 1). Overall, the mean annual number of SABA fills was 3.0(2.7), and the median was 2. The low SABA use cohort, by definition, had only one fill during the 12-month post-index period, with a mean days' supply (as per prescription directives) of 29.4(21.2). Patients in the medium SABA use cohort had a mean of 2.3(0.5) fills and 68.0(48.2) days' supply, and those in the high SABA use cohort had 6.4(3.3) fills and 188.4(117.6) days' supply.

A histogram of the number of SABA fills in the post-index period is shown in **Figure 2A**.

Overall, 71.8% of asthma patients filled ≥ 2 SABA prescriptions, indicating that approximately 3 in 4 patients had uncontrolled asthma (not well- or very poorly controlled) during the post-index period. Moreover, nearly half (46.7%) of SABA refills occurred within 2 months of a previous SABA fill (**Figure 2B**).

Disease Severity

25,554 (18.9%) patients had no claims for an asthma maintenance medication in the 12-month post-index period (**Table 1**). By definition, none of these patients were in the low SABA use cohort, as patients with only 1 SABA and no maintenance fills were not included in the study. 18,124 patients treated with SABA only were in the medium SABA use cohort, and 7,430 were in the high SABA use cohort. Among the 81.2% of patients who had ≥ 1 claim for an asthma maintenance medication, the mean MPR was 0.59(0.35). MPR differed significantly between exposure groups, respectively ($P < 0.001$).

GINA treatment steps also differed significantly between the SABA use cohorts (**Figure 3 and Table 1**). In all SABA use groups, GINA Step 4/5 was the most common treatment level for maintenance medication usage, followed by GINA Step 3 and GINA Step 2. Less than 2% of any SABA use cohort had evidence of chronic SCS use; however, chronic SCS use was most common in the high SABA use cohort and least common among patients with low SABA use. Among patients who used a maintenance medication in the post-index period (N=109,986), increasing severity, as defined by GINA step therapy, was associated with a higher percentage of patients with ≥ 2 SABA fills (uncontrolled asthma) during the 12-month post-index period (**Figure 4**): GINA 2, 57.9%; GINA 3, 64.0%; GINA 4/5 without chronic SCS use, 69.5%; and chronic SCS use, 78.7%, $P < 0.001$.

Exacerbations

Among all patients, 53.8% had evidence of ≥ 1 annual exacerbation post-index. The mean rate of exacerbations/person/year was 1.22(1.30) (**Table 2**). With increasing SABA fills, the proportion of patients with ≥ 1 annual severe exacerbation and the mean exacerbation rate increased (low SABA: 48.5%, 1.00[1.45]; medium SABA: 54.3%, 1.20[1.62]; high SABA: 58.7%, 1.50[1.94], $P < 0.001$, for both analyses; (**Figure 5**). Similarly, higher SABA use among patients without evidence of chronic SCS use was observed for severe exacerbations associated with hospitalizations, emergency room visits, other ambulatory encounters, and SCS bursts ($P < 0.001$ for all exacerbation types). Less than half of patients (46.2%) had no exacerbations, 23.5% had 1, and 30.3% had ≥ 2 exacerbations during the post-index period. Those with 0, 1, or ≥ 2 annual exacerbations differed in mean number of SABA fills (2.8 [2.6], 2.9 [2.5], and 3.3 [2.9] respectively, $P < 0.001$ [**Figure 6**]).

Discussion

In this retrospective, observational study of patients with asthma who filled ≥ 1 annual prescription for a SABA inhaler, severe exacerbations occurred across all SABA fill cohorts, with the proportion of patients having exacerbations increasing with increasing SABA exposure. Inpatient admissions for asthma were relatively rare events, whereas exacerbations requiring a short burst of SCS were common, occurring in almost half of the patients in the low SABA use cohort and more than half of all patients in the medium and high SABA groups. Adherence to asthma maintenance medications, as measured by MPR, was suboptimal for all SABA cohorts, but was highest among patients within the high SABA use group. Of note, all of these patients had large employer Commercial insurance or Medicare Advantage, thus minimizing the cost barrier to access pharmacotherapy.

These real-world US data highlight the relationship between progressive reliance on SABA and asthma morbidity across the spectrum of asthma control and disease severity. Asthma severity and asthma control are two components critical to patient management. Severity is a measure of intrinsic disease intensity; whereas control is the degree to which the manifestations of asthma are minimized by treatment.²³ Severity can be measured by the minimum level of treatment required to achieve optimal control, whereas control can be measured in part by the frequency of SABA use for acute symptom management.^{2,23} Patients require regular monitoring as severity and control shift with age, season, trigger exposure, and development of comorbid conditions.¹⁵

Looking at annual SABA claims to assign a level of asthma control assumes that SABA use occurs at a relatively regular rate throughout the year. Asthma, however, is dynamic in its symptom manifestations due to variability in degree and/or activation of underlying airway

inflammation. Our own data show that even with apparent low SABA prescription claims indicating rescue medication use within the well-controlled asthma category, 50% of patients with only 1 SABA canister fill had SCS claims indicative of ≥ 1 annual exacerbation. Notably, reflecting the fluctuating nature of asthma, patients appear to refill their SABA in bursts, similar to how SCS are used intermittently to treat severe exacerbations. Approximately half of all the SABA refills occurred within a 1- to 2-month time period, equating to the use of 100 doses of SABA over 30 to 60 days—that is, rescue use multiple times a day for the period between fills.

Similarly, a US administrative claims study found that of 36,662 patients with a 12-month period of controlled asthma, 54% experienced a period of uncontrolled asthma in the two following years.¹⁷ Evidence suggests that patients compensate for temporal increases in symptoms by becoming further reliant on SABA rather than by increasing the dosage or changing the type of maintenance medication.²⁴⁻²⁶ For example, a study of SABA usage over 12 years concluded that although the overall inappropriate use of SABA decreased from 8.7% in 2002 to 4.6% in 2013, after an initial period of stabilization, inappropriate use subsequently increased over time.²⁵

Of note, our study showed that of patients with SABA utilization indicative of not well-controlled or very poorly controlled asthma, 66% and 56%, respectively, were at GINA Steps 1-3, indicating an opportunity to add or intensify the use of anti-inflammatory therapy in response to symptom-driven SABA use. Even for those patients on GINA Steps 4/5, adherence measures indicated suboptimal usage of anti-inflammatory medications. Studies on patient behavior during times of uncontrolled disease leading to exacerbations reveal that instead of optimizing anti-inflammatory maintenance therapy, patients seek immediate relief from symptoms by using their SABA.²⁶ The INSPIRE study used structured interviews to evaluate over 3,000 patients from 11

countries, including the US, who were receiving maintenance therapy.²⁶ The study revealed that nearly 3 out of 4 patients were not in the well-controlled asthma category based on SABA use and/or Asthma Control Questionnaire scores. Moreover, patients were well aware of the warning signs of worsening asthma, but they most commonly turned to SABA during the peak period of symptoms and used inhaled corticosteroid-containing therapies to a lesser extent and later in the course of their deteriorations. Patients felt they could manage periods of symptom worsening without physician input and reported that when symptoms abated, both SABA and anti-inflammatory therapy use were decreased. Of note, 51% also reported that they had experienced an unplanned visit for an asthma exacerbation in the previous year.²⁶

Given the large proportion of patients in our study showing exacerbations across all GINA severities and SABA use groups (53.8%), and that 16.7% collected more than 4 canisters of SABA annually (over 400 doses/365 days), it is important to note recommendations regarding rescue/reliever therapy put forth in the latest GINA report.⁴ GINA takes into consideration the body of evidence on the use of an ICS with a fast-acting bronchodilator as rescue/reliever therapy versus a SABA alone and concludes that for adolescents and adults at risk of exacerbations, regardless of other therapies, exacerbations could be reduced with a combination of low-dose ICS and formoterol as maintenance and rescue/reliever compared to maintenance therapy and as-needed SABA.⁴ For maintenance therapy initiation in patients with symptoms twice a month or more but without exacerbation risk, low dose ICS-formoterol as needed or regular low-dose ICS are the GINA-preferred therapeutic options.⁴ Moreover, GINA no longer recommends SABA monotherapy for patients experiencing symptoms less than twice a month, as even in this population SABA use without an ICS places patients at risk for exacerbations and death.²⁷ GINA notes that for patients with mild asthma, data now exist that show an acceptable

safety profile and efficacy in exacerbation reduction with low dose ICS-formoterol as needed.^{4,7,8,28} Additional studies examining the incidence of exacerbations in patients with mild to moderate asthma have shown that combining a SABA with an ICS, in either a single device or two separate devices taken simultaneously for symptoms, provides a benefit relative to SABA alone as rescue/reliever.^{29,30} This benefit was observed in patients with and without regular maintenance therapy, and ICS and SABA was non-inferior with respect to exacerbations compared to physician- or FeNO-guided maintenance adjustments with SABA monotherapy as rescue. However, it must be noted that there are no ICS/SABA fixed-dose combination therapies currently FDA-approved for use as a rescue/reliever therapy in the US.

The equivalence of as-needed budesonide-formoterol to maintenance budesonide in preventing exacerbations in the SYGMA studies,^{7,8} despite a substantially lower total exposure of ICS, indicates that the timing of the ICS dosing may be more important than the total dose administered. Concomitant use of an ICS with every dose of SABA taken is a treatment paradigm that addresses both the variable airway inflammation characteristic of asthma as well as suboptimal use of anti-inflammatory maintenance therapy,^{31,32} as demonstrated in this study cohort (overall mean[SD] MPR 59[35]). ICS have rapid non-genomic anti-inflammatory effects, reducing airway blood flow within 30 minutes after administration and reducing sputum eosinophils within hours of administration.^{31,33} They also prevent the down-regulation of pulmonary β_2 -receptors that can result from frequent use of β_2 -agonist bronchodilators such as SABA. In turn, β_2 -agonists enhance the genomic actions of corticosteroids by increasing gene transcription and inhibiting airway smooth-muscle contraction, plasma extravasation, and influx of inflammatory cells.^{32,33} These actions may explain why concomitant administration of ICS

with β_2 -agonists clearly reduces the risk of exacerbations when used as rescue/reliever therapy versus SABA alone.^{7,8,28,31,32}

This study has several limitations. The MarketScan Research Databases rely on administrative claims data that are not collected explicitly for research purposes. Claims data relies on the assumption that fills equal use, which may not be correct. Diagnostic coding on administrative claims is recorded by physicians to support reimbursement, and as such, diagnoses may be coded incorrectly, or not at all, potentially introducing measurement error. Adherence was calculated using the service date and days' supply information found on outpatient prescription drug claims, and although it is assumed that the medication was taken as directed, this cannot be confirmed using claims data. Claims data may also be skewed by patients, particularly adolescents, requesting additional SABA inhalers for use at school, college or work, although most schools now allow students to keep their inhaler with them rather than being stored with a school nurse.

Measures of asthma severity, asthma control, and related medications were based in part on filled prescriptions. Administrative claims databases are not able to capture impairment indices other than SABA fill data as a marker of rescue/reliever medication use and cannot determine if any portion of the SABA use could be attributed to the prevention of exercise-induced bronchospasm, either of which could change the measure of asthma control. There were also limitations in capturing exacerbations in patients with chronic SCS use or visits without concurrent claims for SCS. Age, sex, race/ethnicity, and insurance plan are also factors that may contribute to differential outcomes in asthma. Results of this analysis may not be generalizable to asthma patients with other insurance types or without health insurance coverage, as the current cohort's benefits plan would have served to minimize financial barriers to access of medications;

283 however, poor asthma control was observed even in this cohort. More extensive evaluations on
284 larger and more diverse populations are currently being undertaken.³⁴

285 Regardless of SABA exposure, disease severity, or maintenance medication adherence, patients
286 with asthma are at risk for severe exacerbations. As annual SABA fills increased, so did the rate
287 of SCS prescription claims. This analysis suggests that the underlying fluctuating airway
288 inflammation of asthma may not be adequately addressed with the current rescue and
289 maintenance treatment paradigms. Health care providers should be vigilant for lack of asthma
290 control and the potential of exacerbations even in patients whose disease appears mild or whose
291 annual SABA use is low.

Real-World Patterns and Implications of Short-Acting Beta₂-Agonist Use Among Adolescent and Adult Patients with Asthma in the United States

Supplementary data

eTable 1. List of exclusionary diagnoses

Diagnosis
Allergic bronchopulmonary aspergillosis
Alpha 1 anti-trypsin deficiency
Bronchiectasis
Churg-Strauss syndrome
COPD
Crohn's Disease
Cystic fibrosis
Eosinophilic pneumonia
Hyper eosinophilic syndrome
Hyperventilation syndrome
Lupus
Obesity hypoventilation syndrome
Primary ciliary dyskinesia
Psoriatic arthritis
Pulmonary fibrosis
Respiratory cancer
Rheumatoid Arthritis
Scleroderma
Sjogrens syndrome
Ulcerative Colitis
Vasculitis
Wegener's granulomatosis

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Table 1. Asthma medication utilization in the 12-month post-index period

	Total		Low SABA Use: 1 fill/12 Months		Medium SABA Use: 2–3 fills/12 Months		High SABA Use: ≥4 fills/12 Months		<i>p</i> ¹
	N = 135,540		N = 38,158 28.2%		N = 63,045 46.5%		N = 34,337 25.3%		
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	
Total SABA Fills (Mean, SD)	3.00	2.67	1.00	0.00	2.34	0.47	6.42	3.29	
Total SABA Days' Supply (Mean, SD)	85.8	89.8	29.4	21.2	68.0	48.2	181.4	117.6	<0.001
Maintenance Medication Possession Ratio (Mean, SD)	0.59	0.35	0.53	0.37	0.59	0.35	0.66	0.32	
GINA Treatment Step (N, %)									
Step 1 (No controller medication use)	25,554	18.9%	N/A	~	18,124	28.7%	7,430	21.6%	<0.001
Step 2 (LM only or low-dose ICS only)	25,469	18.8%	10,735	28.1%	10,075	16.0%	4,659	13.6%	<0.001
Step 3 (Low-dose ICS/LABA or LM+ICS or medium/high-dose ICS)	32,298	23.8%	11,638	30.5%	13,514	21.4%	7,146	20.8%	<0.001
Step 4/5 (With or without medium/high-dose ICS/LABA ± third agent and no chronic SCS use)	50,630	37.4%	15,447	40.5%	20,671	32.8%	14,512	42.3%	<0.001
Step 5 (Chronic SCS use ^b with or without medium/high dose ICS/LABA)	1,589	1.2%	338	0.9%	661	1.0%	590	1.7%	<0.001

¹Between group comparison across the three SABA Use cohorts

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LM, leukotriene modifier; SABA, short-acting beta agonist; SCS, systemic corticosteroid; SD, standard deviation

Table 2. Frequency of exacerbations and associated health care utilization in the follow-up period

	Total		Low SABA Use: 1 fill/12 Months		Medium SABA Use: 2-3 fills/12 Months		High SABA Use: ≥4 fills/12 Months		<i>p</i> ¹
	N = 135,540		N = 38,158 28.2%		N = 63,045 46.5%		N = 34,337 25.3%		
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	
Presence of an Exacerbation (N, %)	72,910	53.8%	18,525	48.5%	34,242	54.3%	20,143	58.7%	<0.001
Exacerbations/person/year, mean(SD)	1.22	1.30	1.00	1.45	1.20	1.62	1.50	1.94	<0.001
Asthma-related inpatient hospitalization among all patients ^{2,3} , N (%)	533	0.4%	58	0.2%	213	0.3%	262	0.8%	<0.001
Specific service utilization associated with SCS prescriptions among patients without chronic SCS use, N (%)									
Short burst of SCS ⁴	72,412	53.4%	18,456	48.4%	34,057	54.0%	19,899	58.0%	<0.001
Emergency Room	6,296	8.7%	970	5.3%	2,848	8.4%	2,478	12.5%	<0.001
Other Outpatient Setting	44,212	61.1%	9,568	51.8%	20,427	60.0%	14,217	71.4%	<0.001
Inpatient Setting	426	0.6%	65	0.4%	172	0.5%	189	0.9%	<0.001

¹Between group comparison across the SABA use cohorts

²Includes patients with chronic SCS use

³Includes inpatient asthma hospitalization claims

⁴Counts and proportions of patients with place of service use. Denominator is SCS bursts

SABA, short-acting beta agonist; SCS, systemic corticosteroid; SD, standard deviation

Figure Legends

Figure 1. Patient Selection.

Figure 2. Histograms of (A) the number of SABA fills per patient in the post-index period and (B) the number of months elapsed between SABA fills

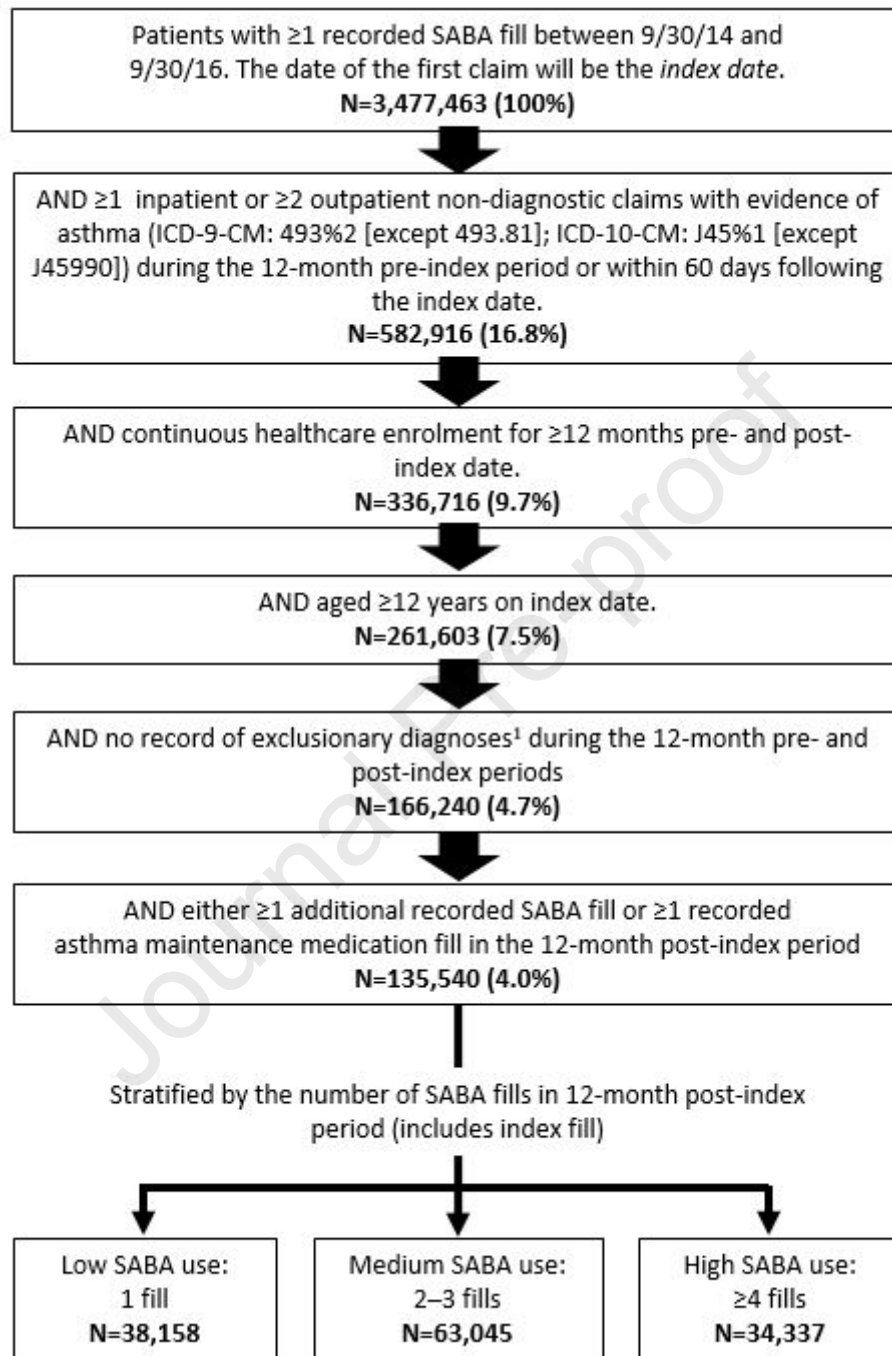
Figure 3. SABA use cohorts stratified by GINA therapy step for all patients with ≥ 1 claim for an asthma controller medication

Figure 4. Percentage of patients with ≥ 2 SABA fills/year by GINA treatment step

Figure 5. Percentage of patients in each SABA fill group with ≥ 1 exacerbation over the 12-month post-index period, showing exacerbation criteria

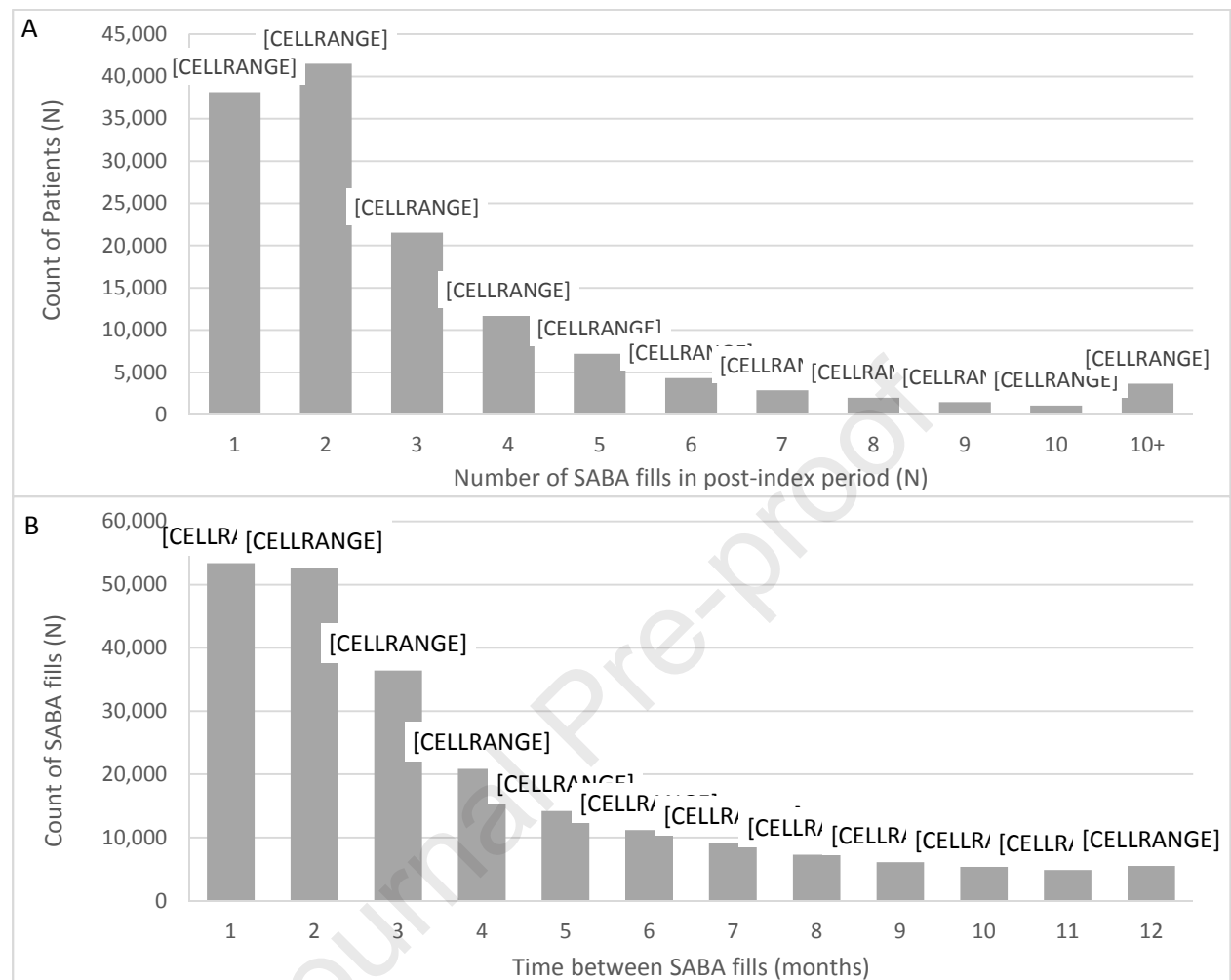
Figure 6: SABA fills vs 0, 1 or ≥ 2 severe exacerbations

Figure 1.



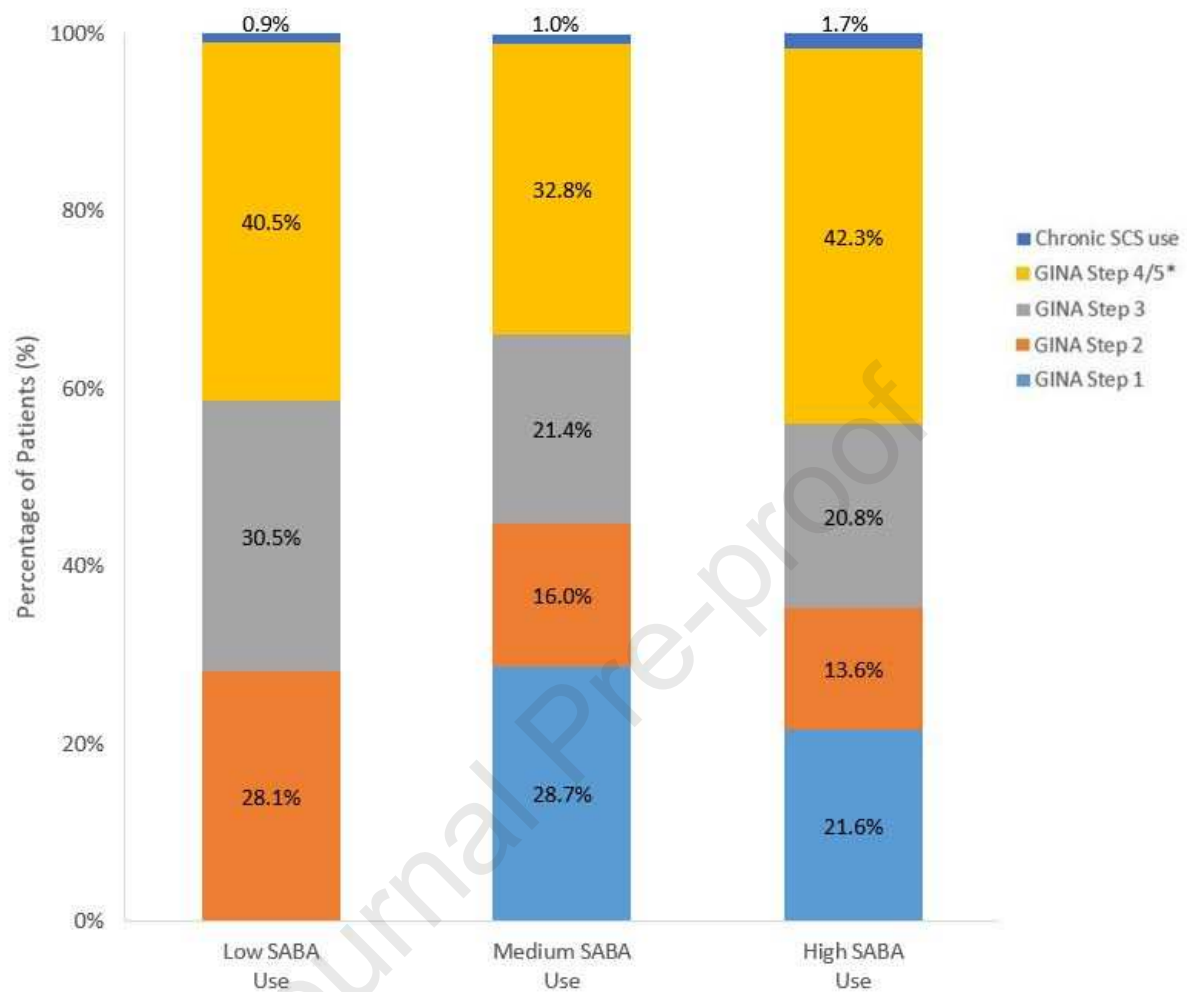
¹Presence of chronic lower respiratory illness other than asthma, primary eosinophilic disorders, cancer, or an autoimmune disorder resulted in exclusion. SABA, short-acting beta₂-agonist

Figure 2.



SABA, short-acting beta₂-agonist

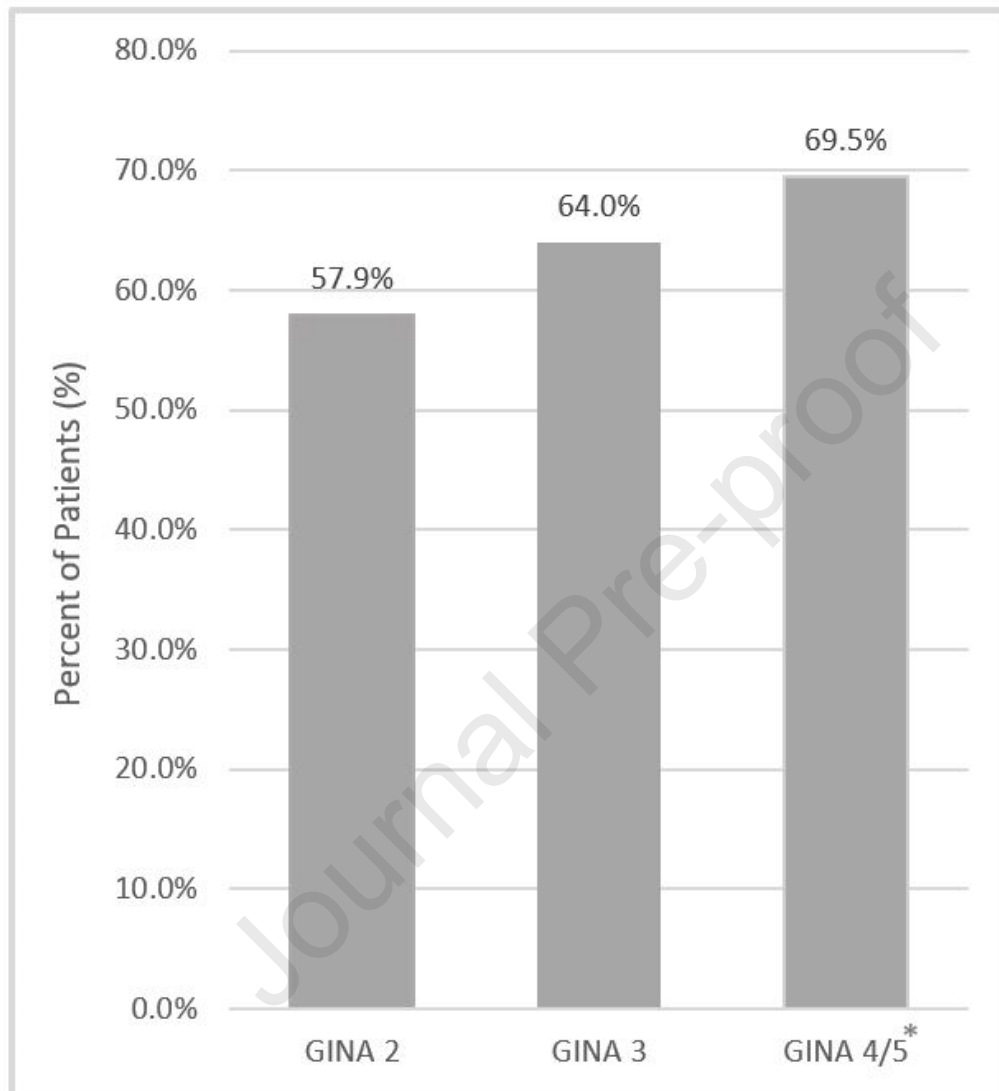
Figure 3.



*GINA 4/5 does not include patients with chronic systemic corticosteroid use.

GINA, Global Initiative for Asthma; SABA, short-acting beta₂-agonist; SCS, systemic corticosteroid

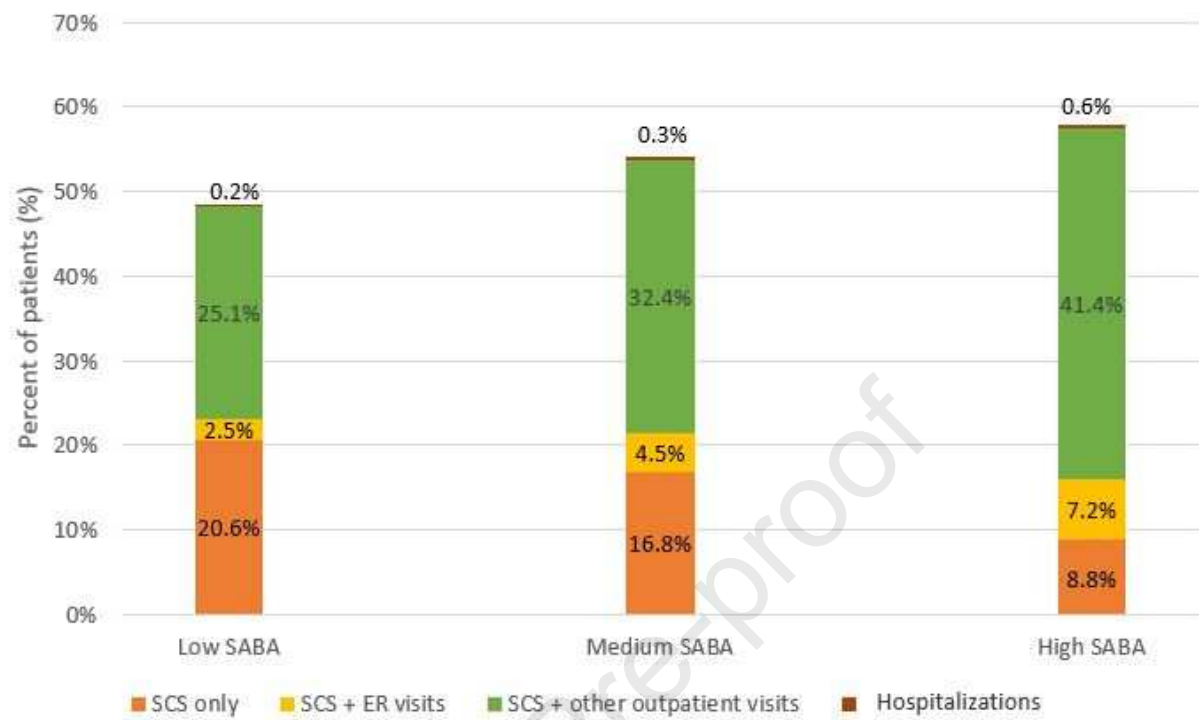
Figure 4.



*GINA 4/5 does not include patients with chronic systemic corticosteroid use.

GINA, Global Initiative for Asthma; SABA, short-acting beta₂-agonist

Figure 5.



ER, emergency room; SABA, short-acting beta₂-agonist; SCS, systemic corticosteroids

Figure 6.

