Original Article

Short-Acting Beta-2-Agonist Exposure and Severe Asthma Exacerbations: SABINA Findings From Europe and North America

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What is already known about this topic? Although the Global Initiative for Asthma no longer recommends short-acting beta-2 agonists (SABA) without concomitant inhaled corticosteroids for patients with asthma aged 12 years or older, U.S. guidelines only partially address this concept and continue to recommend SABA-only treatment for intermittent asthma.

What does this article add to our knowledge? Independent of maintenance therapy, increasing SABA exposure leaves patients across North America and Europe at risk of severe exacerbations. In the United States, SABA monotherapy–treated patients represented most patients, with over half experiencing 1 or more annual severe exacerbations.

How does this study impact current management guidelines? These findings indicate possible undertreatment of patients with asthma and highlight potential gaps in U.S. guidelines. As addressed by the Global Initiative for Asthma, our findings underscore the need for symptom-based use of an inhaled corticosteroid with a fast-acting bronchodilator as a rescue/reliever to potentially mitigate the occurrence of severe exacerbations across all asthma severities.

BACKGROUND: Expert national/global asthma management recommendations raise the issue whether a safe threshold of short-acting beta-2 agonist (SABA) use without concomitant inhaled corticosteroids (ICS) exists.

OBJECTIVE: To examine SABA and maintenance therapy associations with severe asthma exacerbations across North America and Europe.

METHODS: Observational analyses of 10 SABa use IN Asthma (SABINA) datasets involving 1,033,564 patients (≥12 y) from Canada, France, the Netherlands, Poland, Spain, the United Kingdom, and the United States. Negative binomial models (incidence rate ratio [IRR] [95% CI adjusted for prespecified-covariates]) evaluated associations between SABA and exacerbations.

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Abbreviations used
GINA- Global Initiative for Asthma
HCP- Health care provider
ICS- Inhaled corticosteroids
IRR- Incidence rate ratio
NAEPP- National Asthma Education and Prevention Program
OCS- Oral corticosteroids
SABA- Short-acting beta-2 agonist
SABINA- SABa use IN Asthma

RESULTS: Across severities, 40.2% of patients were prescribed/possessed 3 or more SABA canisters/y. Per the Global Initiative for Asthma (GINA) 2018 definitions, steps 3 to 5—treated patients prescribed/possessing 3 or more versus 1 or 2 SABAs experienced more severe exacerbations (IRR 1.08 [95% CI 1.04–1.13], U.S. Medicare; IRR 2.11 [95% CI 1.96–2.27], Poland). This association was not observed in all step 1 or 2—treated patients (the Netherlands, IRR 1.25 [95% CI 0.91–1.71]; U.S. commercial, IRR 0.92 [95% CI 0.91–0.93]; U.S. Medicare, IRR 0.74 [95% CI 0.71–0.76]). We hypothesize that this inverse association between SABA and severe exacerbations in the U.S. datasets was attributable to the large patient population possessing fewer than 3 SABA and no maintenance therapy and receiving oral corticosteroid bursts without face-to-face health care provider encounters. In U.S. SABA monotherapy—treated patients, 3 or more SABAs were associated with more emergency/outpatient visits and hospitalizations (IRR 1.31 [95% CI 1.29–1.34]). Most GINA 2 to 5—treated study patients (60.6%) did not have maintenance therapy for up to 50% of the time; however, the association of 3 or more SABAs and severe exacerbations persisted (IRR 1.32 [95% CI 1.18–1.49]) after excluding these patients and the independent effect was further confirmed when U.K. SABA data were analyzed as a continuous variable in patients with up to 100% annual coverage for ICS-containing medications.

CONCLUSIONS: Increasing SABA exposure is associated with severe exacerbation risk, independent of maintenance therapy. As addressed by GINA, based on studies across asthma severities where as-needed fast-acting bronchodilators with concomitant ICS decrease severe exacerbations compared with SABA, our findings highlight the importance of avoiding a rescue/reliever paradigm utilizing SABA monotherapy. **(J Allergy Clin Immunol Pract 2022;10:2297-309)**

Key words: *Asthma; Asthma management; Short-acting beta-2 agonists; Inhaled corticosteroids; Severe exacerbations*

INTRODUCTION

Asthma affects approximately 339,000,000 people worldwide.[1] Across severities, patients remain at risk of exacerbations despite effective treatments targeting underlying inflammation.[2,3] When used acutely, short-acting beta-2 agonists (SABAs) provide rapid symptom relief and can be life-saving.[4] However, beta-2 agonists have no inherent anti-inflammatory activity,[4] and their use without concomitant inhaled corticosteroids (ICS) may be proinflammatory.[5]

Budesonide-formoterol (ICS and a fast-acting bronchodilator fixed-dose combination) used as a rescue/reliever or as maintenance and rescue/reliever reduces exacerbation risk in patients with asthma aged 12 years or older of all severities compared with as-needed SABA, budesonide maintenance plus as-needed SABA, or budesonide-formoterol maintenance plus as-needed SABA.[6-12] Although not universally adopted, the Global Initiative for Asthma (GINA) has not recommended as-needed SABA without concomitant ICS for patients aged 12 years or older since 2019.[13] In adults and adolescents, GINA 2021 recommends as-needed low-dose ICS-formoterol as the preferred reliever across all therapy steps (track 1; controller and preferred reliever).[2] Moreover, GINA advises against distinguishing between intermittent and mild persistent asthma because patients in both groups are at risk of severe exacerbations and this risk is reduced by ICS-containing treatment.[2]

The 2020 focused updates to the U.S. National Asthma Education and Prevention Program (NAEPP) guidelines also preferentially recommend use of fast-acting bronchodilators with concomitant ICS for patients aged 12 years or older treated as mild, moderate, and severe persistent asthma at steps 2 to 4. The NAEPP guidelines continue to distinguish intermittent from mild persistent asthma and recommend as-needed SABA monotherapy for the intermittent population. The use of SABA as rescue/reliever therapy is also a component of preferred therapy for those requiring severe asthma treatment at steps 5 and 6.[14,15]

Through a series of real-world observational studies, the SABa use IN Asthma (SABINA) program examines patterns of prescription/possession of SABA and ICS-containing medication as a surrogate measure of medication use.[16] In the United Kingdom[17] and Sweden,[18] prescription/possession of 3 or more

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SABA canisters/y was associated with increased exacerbation risk and asthma-related health care utilization. Moreover, in Sweden, prescription of 3 or more SABA canisters/y increased the risk of all-cause, respiratory, and asthma-related mortality.[18]

Utilizing an epidemiological investigation of 10 North American and European datasets in more than 1,000,000 patients, the present SABINA analyses were undertaken to determine whether the association of SABA exposures and severe asthma exacerbations is universal and to understand how diverse asthma management practices, health care systems, and insurance types affect SABA-associated severe exacerbations. Some of the analyses were previously reported in an abstract.[19]

METHODS

Study design

Data on medication prescription (sent to pharmacy) or possession (filled prescriptions) were obtained from national or administrative claims, medical records, and pharmacy databases (Figure 1A) in the participating SABINA countries who had approval from their scientific committee, including local experts, and performed the analyses by September 1, 2020. Data from Canada, France, the Netherlands, Poland, Spain, the United Kingdom, and the United States were included (Figure E1 and Table E1 for further details on the methodologies used in each country-specific analyses; available in this article's Online Repository at www.jaci-inpractice.org). Datasets from Canada (Alberta and Nova Scotia) and the United States (commercial, Medicaid, and Medicare) were analyzed separately because they represented populations of differing demographics, health care insurance, and/or socioeconomic status.

The primary objective was to evaluate how similarities and differences across North American and European health care delivery systems affect associations between SABA prescription/possession (exposure) and the number of severe asthma exacerbations (dependent variable as the outcome). Secondary objectives were to determine whether a safe threshold for prescription of SABA canisters/y exists and to understand how maintenance medication mitigates severe exacerbation risk.

Patient populations, exposures, and outcome variables

Patients aged 12 years or older with current asthma according to diagnostic code and prescription/possession of 1 or more SABA canisters/y formed the minimum criteria for inclusion in the analyses (Figure 1). Because the objective of the analyses was to examine the association between SABA prescription/possession and the number of severe asthma exacerbations per year, patients without prescription/possession of SABA and potentially on maintenance and reliever therapy were excluded. The SABINA countries with methodological variations deemed to have a serious impact on the prespecified main analysis were excluded (shown in red in Figure 1), whereas countries with complete alignment (green) or methodological variations having minimal (yellow) or medium (orange) impact were included. A SABA prescription/possession was evaluated as a dichotomized variable (≥3 or 1–2 canisters/y) across all countries and, in addition, as a continuous variable in the United Kingdom. To capture the association of SABA monotherapy as a rescue/reliever with severe exacerbations, asthma treatment was classified using GINA 2018 definitions. To further harmonize and compare, we aimed to define severe asthma exacerbations according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[20]: prescription/possession of asthma-related oral corticosteroid (OCS) bursts (≥3 d) or emergency department/accident/emergency visit or hospitalization for asthma. Variations from any prespecified definitions are noted in Figure 1.

Statistical analysis

Patient characteristics, exposures, and outcome data were described as mean (SD) for continuous variables and absolute and relative frequencies for categorical variables. Negative adjusted binomial models were used to assess the association between SABA prescription/possession (≥3 vs 1–2 canisters/y) and severe exacerbations. To adjust for potential confounders, the models included the following prespecified covariates, which were selected *a priori*[17]: age, sex, comorbidities, prior exacerbations, GINA treatment step (1–2 vs 3–5), and maintenance medicine (proportion of days covered) (Figure 1B). Using SABA prescription/possession, incidence rate ratios (IRRs) of severe exacerbations were estimated and results presented overall and stratified as GINA 1 to 2 and GINA 3 to 5 treatment groups. Multiple comparisons were adjusted by using a conservative Bonferroni correction, with P of .0125 or less as the cut-off. *Post hoc* sensitivity analyses were performed to further explore the robustness of the association between SABA and severe exacerbations and the potential role of SABA monotherapy in the U.S. GINA 1 dataset by comparing IRRs with GINA 2 to 5—treated patients. In the U.S. datasets, severe exacerbations requiring OCS bursts without a face-to-face health care provider (HCP) evaluation (prescribed over telephone consultation) and those that were serious enough to necessitate emergency, face-to-face HCP evaluations or hospitalizations were also evaluated in GINA 1—treated patients.

Stratification analyses. A stratification analysis probed the associations between SABA prescription/possession (dichotomized) and severe exacerbations in GINA 2 to 5—treated patients with 50% or greater maintenance therapy in datasets of the main analyses. To further assess the strength of association between SABA and severe exacerbations in these patients, a *post hoc* meta-analysis of findings from the stratification analysis was performed to obtain a summary estimate across all datasets using a random-effects model based on log IRRs and their standard errors, with the inverse variance method being used for pooling the different data sources. The interplay between SABA and ICS was further probed by evaluating the association between SABA prescription as a continuous variable and severe exacerbations in the U.K. dataset using a negative binomial model in all GINA 2 to 5—treated patients and at each GINA step separately, with results stratified by 50% or greater, 75% or greater, and 100% or greater maintenance therapy. For patients with 12 or more SABA prescriptions during the baseline year, these were capped at 13 prescriptions and linear representations of cubic splines were used[21]; the model included all prespecified selected covariates.

To evaluate the potential recommendation for monitoring SABA prescriptions[22,23] and identifying at-risk patients, an additional *post hoc* analysis determined a data-driven cut-off for the level for SABA canisters associated with a clinically relevant 20%[24] increased incidence of severe exacerbations. This was performed by modelling the association between SABA prescriptions and the number of severe exacerbations and incrementally plugging in values for SABA prescriptions starting at 1 canister and recording the corresponding exacerbation rate until a 20% increase in incidence was observed.

RESULTS

Patient characteristics and SABA patterns

Data from 1,033,564 patients with asthma were analyzed. Mean (SD) age ranged from 23.2 (13.1) years U.S. Medicaid to 72.2 (6.9) years (U.S. Medicare). Patients were predominantly female (ranging from 55.8% in Canada [Alberta] to 68.2% in

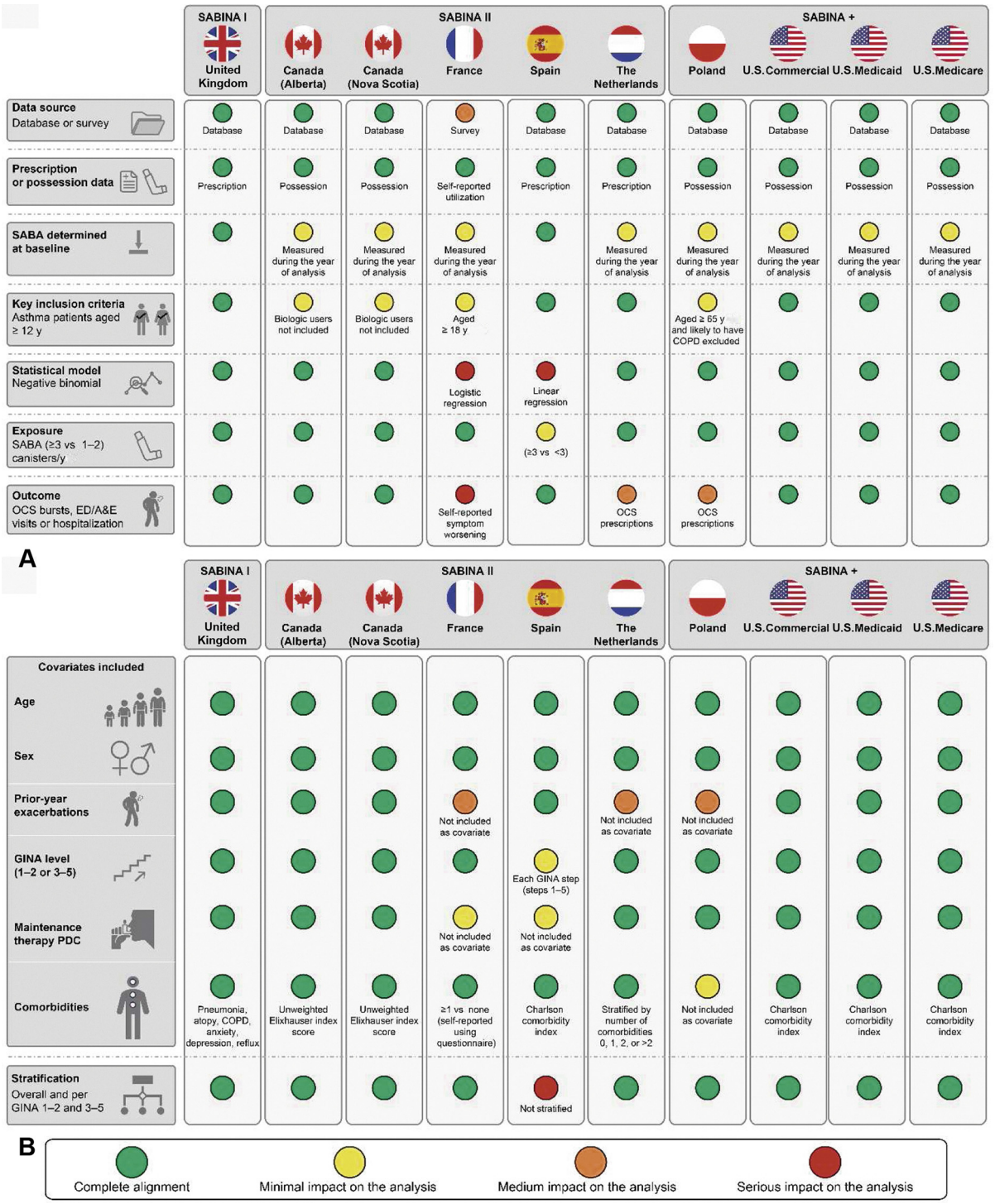

FIGURE 1. Methodological variations across countries related to (**A**) study design and (**B**) covariates included in the analyses. Patients aged ≥ 12 y with current asthma according to diagnostic code and prescription/possession of ≥ 1 SABA canisters/y were included. Data on medication prescription/possession were obtained from SABINA I (United Kingdom), 4 SABINA II countries (Canada, France, Spain, and the Netherlands), and 2 SABINA+ countries (Poland and the United States) (see Figure E1 for more details related to the key pillars of the SABINA program). France and Spain were excluded from the main analyses owing to methodological variations being incompatible with the prespecified analysis. Data from countries with methodological variations incompatible with the analyses (shown in red) are presented in the Online Repository. The Spanish dataset included patients with no SABA prescriptions, representing 0.1% of the population. In the United States, maintenance therapy for patients at GINA step 2 also included leukotriene modifiers (prescribed in two-thirds of patients). *A&E,* Accident and emergency; *COPD,* chronic obstructive pulmonary disease; *ED,* emergency department; *PDC,* proportion of days covered.

U.S. Medicare; Table I). Based on prescription/possession, 56.5% of patients were treated as mild asthma (GINA 1–2). However, more patients from Canada (Alberta; 58.6%), the United Kingdom (63.4%), Poland (66.7%), the Netherlands (68.8%), and Spain (73.4%) were treated as moderate-to-severe asthma (GINA 3–5). Overall, 40.2% of patients in the main analysis were prescribed/possessed 3 or more SABA canisters/y, ranging between 26.0% (the Netherlands) and 63.2% (Canada [Nova Scotia]).

Associations between SABA and severe asthma exacerbations

All 8 main analysis datasets revealed a numerically lower mean number of severe exacerbations for prescription/possession of 1 or 2 versus 3 or more SABA canisters/y for GINA 1 to 5− and GINA 2 to 5−treated patients (Table E2; available in this article's Online Repository at www.jaci-inpractice.org). In GINA 1 to 5 patients, the lowest mean (SD) number of severe exacerbations in both SABA groups was observed in the Netherlands (0.16 [0.50] vs 0.23 [0.60]) and the highest in U.S. Medicare (0.95 [1.54] vs 1.06 [1.59]).

Across GINA 1 to 5, except for U.S. Medicare, prescription/possession of 3 or more versus 1 or 2 SABA canisters/y was associated with an increased incidence of severe exacerbations after adjusting for covariates (Figure 2A). The highest IRR was observed in Poland (adjusted IRR 2.15 [95% CI 2.01–2.30]) and the weakest in the U.S. commercial dataset (adjusted IRR 1.02 [95% CI 1.01–1.03]). For U.S. Medicare patients, prescription/possession of 3 or more versus 1 or 2 SABA canisters/y was associated with a reduced incidence of severe exacerbations (adjusted IRR 0.89 [95% CI 0.86–0.91]). Although France and Spain were unable to provide data to determine an IRR, use of 3 or more SABA canisters/y was associated with an increased risk of having 1 or more severe exacerbation versus 1 or 2 SABAs (based on reported odds ratios and regression coefficients, respectively; Tables E3−E5; available in this article's Online Repository at www.jaci-inpractice.org).

Across all countries and datasets, more severe exacerbations were observed with prescription/possession of 3 or more versus 1 or 2 SABA canisters/y among GINA 3 to 5−treated patients. The highest IRR was observed in Poland, followed by U.S. Medicaid, the Netherlands, the United Kingdom, and Canada (Nova Scotia) (Figure 2B). In GINA 1 to 2−treated patients, results were not uniform. In the United Kingdom, Canada (Alberta and Nova Scotia), Poland, and U.S. Medicaid, prescription/possession of 3 or more versus 1 or 2 SABA canisters/y was associated with an increased incidence of severe exacerbations. This association was not significant for the Netherlands (IRR 1.25 [95% CI 0.91–1.71]), and a lower IRR of severe exacerbations with possession of 3 or more versus 1 or 2 SABA canisters/y was observed in the U.S. Medicare (IRR 0.74 [95% CI 0.71–0.76]) and commercial datasets (IRR 0.92 [95% CI 0.91−0.93]; Figure 2C). In addition, multiple comparisons revealed that all datasets passed the Bonferroni-corrected threshold of P of .0125 or less, except GINA 1 to 2−treated patients in the Netherlands ($P = .163$), with U.S. commercial and Medicare datasets (both $P < .001$; Table E6; available in this article's Online Repository at www.jaci-inpractice.org) showing an inverse association between SABA and severe asthma exacerbations (Figure 2C).

U.S. GINA 1 sensitivity analysis. Patients possessing SABA monotherapy (GINA 1 equivalent) represented the largest treatment group within each U.S. dataset (Table I), comprising 51.8% of all U.S. patients. The SABA monotherapy treatment also predominated in the GINA 1 to 2−treated population: Medicaid, 80.9%; commercial insurance, 75.8%; and Medicare, 72.0%. A greater percentage of GINA 1 patients in the lower (required to have ≥2 SABA fills/y) versus higher SABA group (≥3 SABA fills/y) experienced 1 or more severe exacerbations (66.8% vs 52.5% of commercial; 58.8% vs 51.1% of Medicaid; and 73.2% vs. 49.8% of Medicare, respectively; Figure 3A). Overall, only 16.7% of GINA 1−treated patients experienced exacerbations that were serious enough to necessitate a face-to-face assessment by an HCP, whereas 61.9% experienced any severe exacerbation type (requiring OCS bursts and/or unscheduled clinician or emergency department/urgent care visits or hospitalization). The disproportionate impact of GINA 1 on all U.S. observations is shown by comparing the incidence of severe exacerbations relative to SABA exposure groups for the GINA 1 to 5− versus 2 to 5−treated populations. For all U.S. datasets combined, GINA 2 to 5−treated patients exhibited a higher incidence of severe exacerbations for possession of 3 or more versus 1 or 2 SABA canisters/y (IRR 1.23 [95% CI 1.22–1.24]) compared with GINA 1 to 5 (IRR 1.03 [95% CI 1.02–1.04]; Figure 3B). However, after excluding OCS bursts from the definition of severe exacerbations, exposure to 3 or more SABA canisters/y was associated with an increased incidence of exacerbations serious enough to necessitate emergency, face-to-face HCP evaluations or hospitalizations (IRR 1.31 [95% CI 1.29–1.34] in U.S. SABA monotherapy−treated patients; Figure 3C). Similarly, for the total U.S. GINA 1 to 5−treated population, the proportion of patients experiencing 1 or more severe exacerbation requiring face-to-face HCP evaluation or hospitalization was also higher among patients possessing 3 or more versus 1 or 2 SABA canisters/y (35.5% vs 25.1%).

Association of SABA with severe exacerbations among patients with 50% or greater annual ICS coverage. Overall, 60.6% of all GINA 2 to 5−treated patients did not have prescription/possession of maintenance therapy for up to 50% of the time (Figure 4). Meta-analysis of the incidence rate data (based on Figure 4) showed that prescription/possession of 3 or more versus 1 or 2 SABA canisters/y was associated with a 32% (adjusted IRR 1.32 [95% CI 1.18–1.49]) higher risk of severe exacerbations across all datasets combined, independent of ICS use and other exacerbation risk factors. Although the effect estimates showed increased severe exacerbation risk with higher SABA prescription/possession, marked heterogeneity was observed between datasets (heterogeneity statistic, $I^2 = 95\%$). In 6 of the 8 individual datasets, the increased risk-associated lower CI did not overlap the null value (IRR = 1). In the U.S. Medicare (IRR 1.02 [95% CI 0.97–1.07]) and Canada Nova Scotia (IRR 1.29 [95% CI 0.98–1.70]) populations, 3 or more versus 1 or 2 SABA canisters/y was associated with a numerically higher severe exacerbation incidence. All datasets included in the stratification analyses, with the exception of Canada (Nova Scotia; $P = .073$) and U.S. Medicare ($P = .435$), passed the Bonferroni-corrected threshold of P of .0125 or less (Table E6).

TABLE I. Patient characteristics

	SABINA I	SABINA II					SABINA +			
Parameter	United Kingdom	Canada (Alberta)	Canada (Nova Scotia)	France	Spain	The Netherlands	Poland	U.S. commercially insured	U.S. Medicaid	U.S. Medicare
Total patients, n	187,675	71,629	5,009	673	39,555	9,474	46,628	483,874	151,439	37,608
Age (y), mean (SD)	42.82 (20.43)	38.8 (16.6)	42.8 (18.0)	44.4 (17.0)	49.8 (20.7)	44.1 (18.9)	44.1 (15.7)	37.8 (16.3)	23.2 (13.1)	72.2 (6.9)
Female, n (%)	108,266 (57.7)	40,025 (55.8)	2,964 (59.2)	401 (59.6)	25,394 (64.2)	5,546 (58.5)	26,081 (55.9)	294,837 (60.9)	90,904 (60.0)	25,662 (68.2)
Asthma treatment steps, n (%)										
GINA 1−2	68,652 (36.6)	29,689 (41.4)	2,642 (52.7)	401 (59.6)	10,536 (26.6)	2,960 (31.2)	15,511 (33.3)	322,271 (66.6)	111,716 (73.8)	19,604 (52.1)
GINA 1	37,118 (19.8)	17,942 (25.0)	1,629 (32.5)	NA	6,030 (15.3)	1,669 (17.6)	9,806 (21.0)	244,303 (50.5)	90,392 (59.7)	14,122 (37.6)
GINA 2	31,534 (16.8)	11,747 (16.4)	1,013 (20.2)	NA	4,506 (11.4)	1,291 (13.6)	5,705 (12.2)	77,968 (16.1)	21,324 (14.1)	5,482 (14.6)
GINA 3−5	119,023 (63.4)	41,940 (58.6)	2,367 (47.3)	272 (40.4)	29,019 (73.4)	6,514 (68.8)	31,117 (66.7)	161,603 (33.4)	39,723 (26.2)	18,004 (47.9)
GINA 3	65,218 (34.8)	24,278 (33.9)	1,434 (28.6)	NA	15,884 (40.2)	2,877 (30.4)	NA	42,193 (8.7)	12,422 (8.2)	4,359 (11.6)
GINA 4	52,191 (27.8)	10,145 (14.2)	704 (14.1)	NA	10,104 (25.5)	3,449 (36.4)	NA	GINA 4, 5: 119,410 (24.7)	GINA 4/5: 27,301 (18.0)	GINA 4, 5: 13,645 (36.3)
GINA 5	1,614 (0.9)	7,517 (10.5)	229 (4.6)	NA	3,031 (7.7)	188 (2.0)	NA			
SABA prescription/possession (canisters/y), n (%)										
1−2	91,920 (49.0)	38,259 (53.4)	1,842 (36.8)	423 (62.8)	28,203 (71.3)*	7,015 (74.0)	29,167 (62.6)	322,052 (66.6)†	80,405 (53.1)†	23,005 (61.2)†
≥3	95,755 (51.0)	33,370 (46.6)	3,167 (63.2)	250 (37.2)	11,352 (28.7)	2,459 (26.0)	17,461 (37.4)	161,822 (33.4)	71,034 (46.9)	14,603 (38.8)
Mean (SD)	4.1 (4.0)	3.9 (4.4)	7.2 (7.4)	NA	3.3 (3.6)	2.3 (1.9)	3.5 (5.2)	2.77 (2.92)	3.72 (3.72)	3.05 (3.18)
Prior-year exacerbation history (year prior to the study), n (%)										
0	143,063 (76.2)	60,458 (84.4)	3,747 (74.8)	NA	18,433 (46.6)	NA	NA	277,182 (57.3)	86,988 (57.4)	19,875 (52.8)
≥1	44,612 (23.8)	11,171 (15.6)	1,262 (25.2)	341 (50.6)	21,122 (53.4)	NA	NA	206,692 (42.7)	64,451 (42.6)	17,733 (47.2)
Mean (SD)	0.41 (1.03)	0.32 (1.14)	0.44 (1.02)	NA	0.8 (1.0)	NA	NA	0.8 (1.3)	0.8 (1.3)	1.0 (1.6)

NA, Not available.

*Data presented for ≤ 2 SABA canisters/y.

†In the United States, patients at GINA 1 were required to have ≥ 2 SABA fills to be included in the analyses.

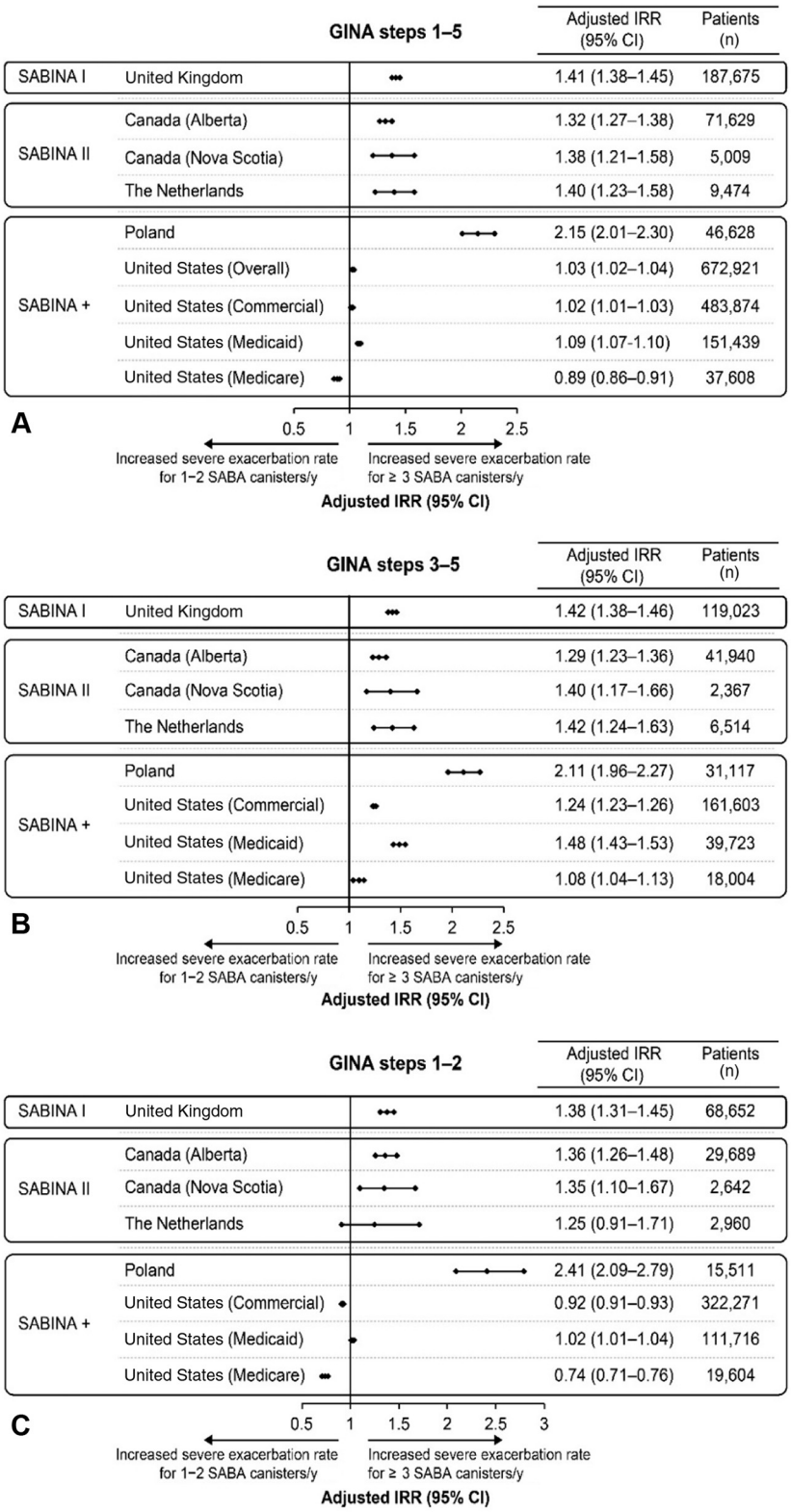

FIGURE 2. Association between SABA prescription/possession (≥3 vs 1−2 canisters/y) and severe asthma exacerbations/y in patients treated with (**A**) GINA 1−5, (**B**) GINA 3−5, and (**C**) GINA 1−2. The association between SABA prescription/possession and severe asthma exacerbations was evaluated using a negative binomial model. The analyses were adjusted for age, sex, comorbidities, prior exacerbations, GINA treatment step (1–2 vs 3–5), and maintenance medicine PDC. Prior exacerbations were not included as a covariate in Poland and the Netherlands, whereas comorbidities were not included as a covariate in Poland. Patients aged ≥ 65 y and those likely to have COPD were excluded from the Polish dataset. *COPD,* Chronic obstructive pulmonary disease; *PDC*, proportion of days covered.

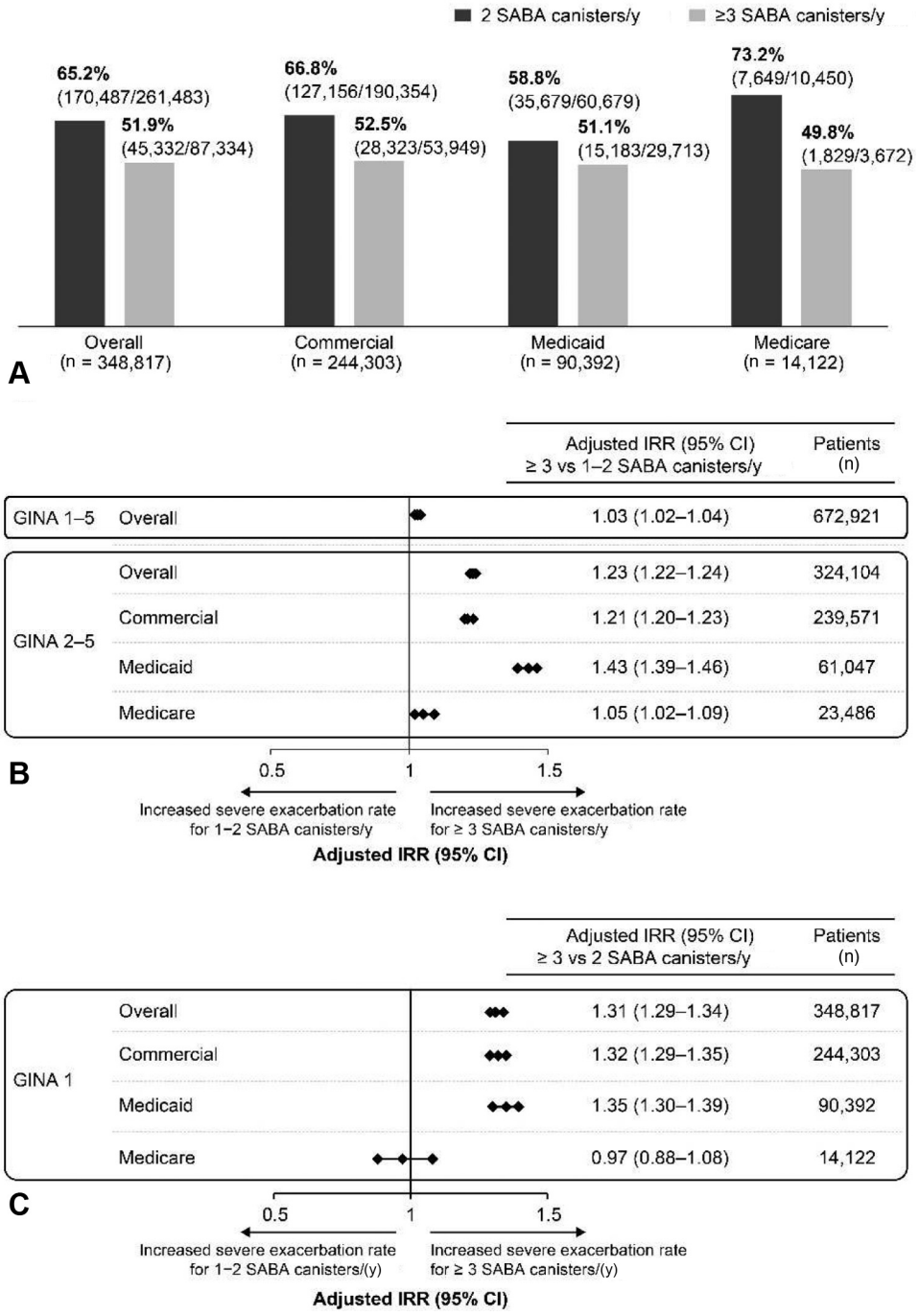

FIGURE 3. Associations of SABA possession with severe exacerbations during the year of analysis in U.S. patients showing (**A**) percentage of GINA 1—treated patients* with ≥ 1 severe exacerbation; (**B**) contrasting IRRs of severe exacerbations for GINA 1—5— vs GINA 2—5—treated patients; (**C**) impact of SABA on incidence of severe exacerbations accompanied by a face-to-face HCP visit† for GINA 1—treated patients. *PDC,* Proportion of days covered. The association between SABA possession and severe asthma exacerbations was evaluated using a negative binomial model. The analyses were adjusted for age, sex, comorbidities, prior exacerbations, GINA treatment step (1–2 vs 3–5), and maintenance medicine PDC. *U.S. GINA 1—treated patients were required to have ≥ 2 SABA fills/y according to local expert recommendation. †Severe exacerbations requiring a face-to-face contact with an HCP associated with unscheduled ambulatory clinic, urgent care, and emergency department visits or hospitalizations.

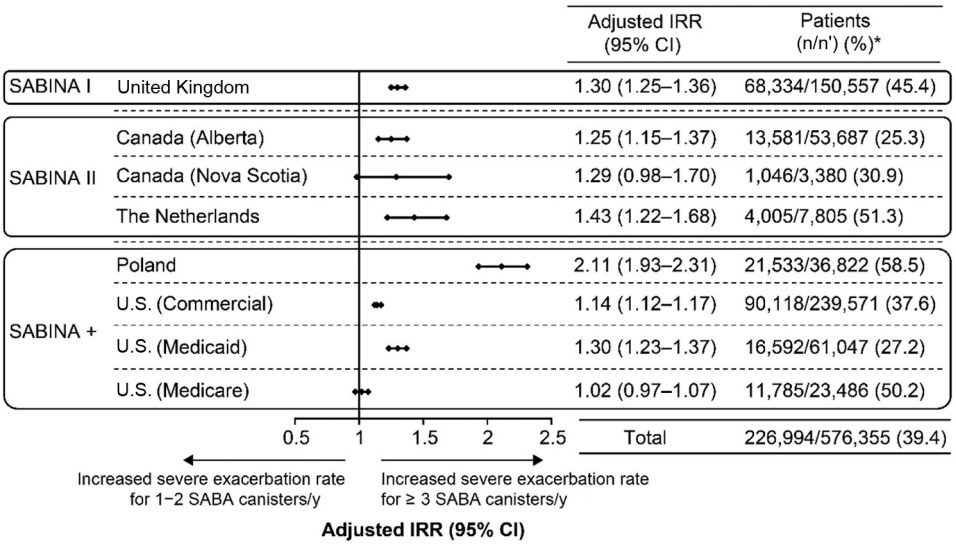

FIGURE 4. Association between SABA (≥3 vs 1−2 canisters/y) and severe asthma exacerbations/year in GINA 2−5−treated patients prescribed/possessing maintenance therapy ≥ 50% of the time. *COPD,* Chronic obstructive pulmonary disease; *n,* number of patients included in the analysis; *N',* total number of GINA 2−5 patients; *PDC,* proportion of days covered. Prior exacerbations were not included as a covariate in Poland and the Netherlands, whereas comorbidities were not included as a covariate in Poland. Patients aged ≥ 65 y and those likely to have COPD were excluded from the Polish dataset. *Proportion of patients (GINA 2−5) prescribed (≥50%) anti-inflammatory maintenance therapy. The association between SABA prescription/possession and severe asthma exacerbations was evaluated using a negative binomial model. The analyses were adjusted for age, sex, comorbidities, prior exacerbations, GINA treatment step (1–2 vs 3–5), and maintenance medicine PDC.

Analysis of SABA as a continuous variable in the U.K. dataset. After adjusting for the main analysis covariates, including ICS proportion of days covered, prescription of SABA canisters remained associated with severe exacerbations on a continuous scale in U.K. GINA 2 to 5−treated patients. This association persisted even in patients with 50% or greater, 75% or greater, and 100% or greater ICS-containing therapy, showing that the association of SABA prescriptions with severe exacerbations was independent of ICS (Figure 5). Results were similar when data were stratified by individual GINA steps (2−5) and after excluding patients with 50% or less of ICS-containing therapy at each treatment level (Figure E2; available in this article's Online Repository at www.jaci-inpractice.org). A *post hoc* analysis of SABA canisters revealed that increasing SABA prescriptions from 1 to 2.7 canisters/y was accompanied by a clinically relevant 20% increased incidence of severe exacerbations (Table E7; available in this article's Online Repository at www.jaci-inpractice.org). Moreover, severe exacerbations increased with increasing prescriptions of ICS-containing therapy, as previously described,[25-27] indicative of confounding by disease severity.

DISCUSSION

This analysis in more than 1,000,000 patients with asthma provides the largest multicountry, real-world evidence exploring how treatment patterns of SABA and maintenance therapy affect the frequency of severe exacerbations. Overarching similarities across countries on the association of SABA prescription/possession with severe exacerbations, combined with several notable inter- and intracountry differences, provide unique insights into the impact that variations in health care delivery, insurers, and HCP/patient approaches to asthma management may have on severe exacerbations.

Overall, 40.2% of GINA 1 to 5−treated patients were prescribed/possessed 3 or more SABA canisters/y, and only 39.4% of GINA 2 to 5−treated patients received maintenance therapy 50% or more of the time. Across countries, stratifying for 50% or more GINA 2 to 5 maintenance exposure revealed that prescription/possession of 3 or more versus 1 or 2 SABA canisters/y was associated with a 32% increased incidence of severe exacerbations, independent of ICS-containing medications. In the United Kingdom, SABA as a continuous variable further confirmed the association with severe exacerbations, regardless of prescribed ICS. This suggests that patients remain uncontrolled despite potentially reasonable exposure to their prescribed maintenance therapy,[28] highlighting underestimation of asthma severity, as per GINA treatment steps, and/or the need for timely ICS administration to control worsening airway inflammation.

Similarities and clinically relevant differences across Europe and Canada

The association between prescription/possession of 3 or more SABA canisters/y and severe exacerbations (IRRs across GINA steps [1–5, 1–2, and 3–5] and stratified analysis [steps 2–5]) was comparable in the United Kingdom (IRR 1.30–1.42), Canada (Alberta [IRR 1.25–1.36], Nova Scotia [IRR 1.29–1.40]), and the Netherlands (IRR 1.25–1.43). The strongest association was consistently reported for Poland (IRR 2.11–2.41) and may be attributable to underfunding of the health care system,[29] potentially resulting in high use of inexpensive systemic corticosteroids. Poland and the Netherlands used an overall similar methodology, and patients had comparable baseline

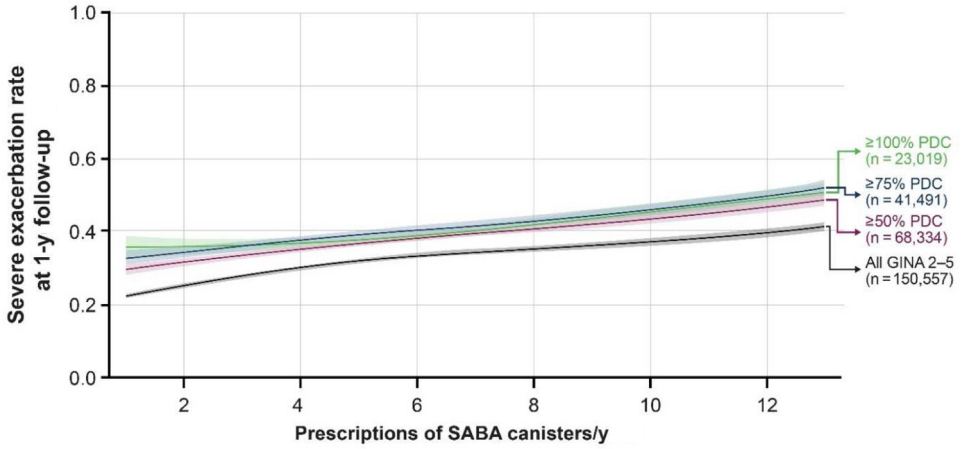

FIGURE 5. Association between SABA prescriptions at baseline and severe exacerbations during follow-up in patients from the United Kingdom with GINA 2–5 treatment stratified by PDC of ICS-containing therapy. Shaded areas represent 95% CIs. The association between SABA prescription and severe asthma exacerbations was evaluated using a negative binomial model. The analysis was adjusted for age, sex, atopy, depression, anxiety, reflux, pneumonia, COPD, prior exacerbations, GINA level (2 vs 3–5), and maintenance therapy use PDC. ICS PDC $\geq$ 100% implies that the patients had more than full coverage for ICS-containing medications. *COPD,* Chronic obstructive pulmonary disease; *PDC*, proportion of days covered.

characteristics; thus, the stronger association between SABA and severe exacerbation rates in Poland may be related to a considerable proportion of patients with uncontrolled symptoms (measured by possession of $\geq$ 3 canisters/y) being treated with systemic corticosteroids (proportion of uncontrolled patients with $\geq$ 2 OCS prescriptions was 7.2% in Poland vs 4.3% in the Netherlands; *post hoc* calculation).

Health care access and severe asthma exacerbations

Results from Canada highlight the influence of access to health care on asthma morbidity. Findings from Alberta, a large representative sample of the Canadian population, demonstrated that possession of 3 or more versus 1 or 2 SABA canisters/y was consistently associated with an increased severe exacerbation incidence across GINA steps, which was replicated in the smaller Nova Scotia population. Although Nova Scotia as a province has a lower socioeconomic status than Alberta,[30] associations between possession of 3 or more versus 1 or 2 SABA canisters/y and number of severe exacerbations for both Canadian datasets were concordant with those for the United Kingdom, another country with similar health care accessibility and using comparable methodologies.

Clinically relevant similarities and differences for the United States

Differences in the U.S. patient characteristics and insurance types provide valuable insights. Elderly patients with asthma, as in the Medicare population, have been reported to have poorer perception of declining lung function, less allergy symptoms, and greater comorbidities than younger patients.[31-33] Therefore, SABA use before the onset of a severe exacerbation may be attenuated, owing to decreased warning signs and/or symptoms of asthma being mistakenly attributed to other comorbid conditions.

Although the U.S. Medicaid and commercial datasets comprised younger patients, the Medicaid population consistently showed the strongest association of severe exacerbations with possession of 3 or more SABA canisters/y. Factors such as lower socioeconomic status,[34] limited access to quality care,[34,35] and wide coverage for quick-relief medications[36] may influence which therapies are used. A SABA rescue/reliever medication is the most widely covered asthma treatment in most states' Medicaid programs[36]; thus, ICS-containing maintenance therapy may be deprioritized or rationed.

A striking difference was observed between the United States and other countries for GINA 1 to 2—treated patients, in which possession of 3 or more SABA canisters/y was associated with a lower incidence of severe exacerbations in U.S. commercial and Medicare GINA 1 to 2—treated patients. Even in U.S. Medicaid GINA 1 to 2, the significant association of increased severe exacerbations with possession of 3 or more SABA canisters/y showed the lowest IRR across all main analysis datasets. Of note, an overwhelming majority of U.S. GINA 1 or 2 patients were treated as GINA 1. These SABA monotherapy—treated patients demonstrated substantial severe exacerbation risk, independent of SABA exposure. Notably, most severe exacerbations in U.S. GINA 1—treated patients were characterized by an OCS burst without a health care visit. Consequently, the escalation of SABA for symptom relief without any possession of ICS, even for a week, may have been accompanied by increased airway reactivity,[37,38] resulting in a severe exacerbation. Whereas OCS burst treatment, likely prescribed over a telephone consultation, would have quickly reduced the need for additional SABA, the lack of a face-to-face HCP encounter resulted in a missed opportunity for addition of ICS therapy in a presumably mild population. Such scenarios could explain the stronger association between possession of 1 or 2 versus 3 or more SABA canisters/y and increased incidence of severe exacerbations in patients treated as having intermittent disease.

However, a higher number of severe exacerbations serious enough to necessitate an emergency, face-to-face HCP outpatient visit, or hospitalization was observed for SABA monotherapy—treated patients possessing 3 or more SABA canisters/y. These data are concordant with observations that

U.S. patients and HCPs tend to underestimate the consequences of asthma symptoms,[39] relying predominantly on SABA for rapid relief.[28,40] These findings suggest the need for ICS administration, either as regular maintenance treatment or intermittently, to address variability in airway inflammation in SABA monotherapy—treated patients and lend support to the GINA recommendation of not distinguishing intermittent from mild persistent asthma. Both populations experience severe exacerbations, and the use of ICS-containing treatments, either taken as regular maintenance therapy and/or concomitantly with as-needed fast-acting bronchodilators, can reduce this exacerbation risk[2]; with the latter approach leveraging the inherent relief-seeking behavior of patients when symptomatic.

Defining the threshold for SABA use in asthma management

A threshold for SABA prescription/possession (≥3 canisters/y) can serve as a practical and quantitative measure of reliance on SABA and aid in tracking rescue/reliever use. In view of findings from the U.K. continuous modeling data and the lack of consensus on appropriate versus excessive use of rescue/reliever therapy,[14,22] an evidence-backed binary classification of SABA (≥3 vs 1–2 canisters/y) may not fully describe the continuous association between prescription/possession of SABA and severe asthma exacerbations. Because increasing SABA prescriptions from 1 to 2.7 canisters/y was associated with a clinically relevant 20% increased incidence of severe exacerbations, careful monitoring of SABA use at any level can help identify at-risk patients.[41] Other exacerbation risk factors, such as seasonal triggers, poor ICS adherence, and incorrect inhaler technique, should also be routinely monitored.[2]

Clinical implications

Our results show that widespread SABA use in North America and Europe leaves patients across GINA 1 to 5 at risk of severe exacerbations and OCS exposures that could lead to acute/chronic complications.[42,43] Moreover, prescription/possession of SABA is associated with severe asthma exacerbations independent of whether maintenance therapy is prescribed by an HCP or possessed by a patient. Our results show that, for many patients with asthma, adherence to maintenance treatment remains suboptimal and some may be undertreated and in need of a review of their current therapeutic regimen. However, given that exacerbations still occurred in those with prescription/possession of maintenance treatment compatible with reasonable and even full adherence, our findings also emphasize the potential need for revisiting the rescue/reliever paradigm to provide ICS concomitantly with a fast-acting bronchodilator. Patients often increase SABA use when symptoms first appear and increase ICS use only at the peak of asthma worsening.[44] However, the period before an exacerbation accompanied by worsening of inflammation-driven symptoms may offer a window of opportunity[28] for intervention. Based on patients' inherent symptom relief—seeking behavior, use of a fast-acting rescue/reliever that provides concomitant ICS may allow treatment to be timed with the onset of increasing inflammation, a management strategy demonstrated to improve outcomes[6-12,45,46] and currently supported by GINA.[2]

The concept of avoiding SABA rescue/reliever without concomitant ICS, as outlined by GINA 2019 recommendations,[13] was only partially incorporated in the NAEPP 2020 focused updates for asthma management.[14] These guidelines recommend use of a fast-acting bronchodilator with concomitant ICS for patients aged 12 years or older with mild, moderate, and severe persistent asthma at treatment steps 2 to 4.[14] Unlike the GINA 2019 report,[13] the NAEPP Expert Panel Working Group was not charged to address rescue/reliever therapy for patients with intermittent asthma (step 1) or those with severe persistent disease at steps 5 and 6; therefore, data gaps remain within the U.S. asthma management guidelines with respect to whether SABA alone as a rescue/reliever should be considered for these populations. Our SABINA findings may help to inform on these data gaps for patients with intermittent and severe persistent asthma and underscore the need for HCPs to closely monitor both impairment and risk domains of control. Many SABA monotherapy—treated patients may have met the criteria for persistent asthma, and GINA 3 to 5—treated patients exhibited more severe exacerbations with greater SABA use, indicating possible undertreatment of patients. However, a potential benefit across all asthma severities might also be gained by employing a fast-acting bronchodilator with concomitant ICS therapy for as-needed symptom relief to address the underlying variability of airway inflammation leading to symptoms and exacerbations.

Limitations

Prescription/possession data do not inform on actual or appropriate medication use. Although analyses were adjusted for key exacerbation risk factors, other patient characteristics may impact severe exacerbations; however, extensive covariate analyses performed by Bloom et al[17] suggested that the model was robust. Data analyses stratified by each individual GINA step could not be performed by all countries; therefore, only the strata of steps 1 to 2 and 3 to 5 were prespecified. Given the real-world nature of this study, it was not possible to measure all components of asthma control; therefore, patients were grouped by treatment and not actual disease severity, as suggested in GINA 2021.[2] Severe exacerbations were defined per ATS/ERS definitions[20]; however, components of the definitions (OCS burst, hospitalization, and emergency outpatient visit) may have different implications owing to differential health care practices (eg, OCS over the phone vs OCS following a face-to-face HCP encounter). Exclusion of patients with no SABA prescription/possession may have precluded assessment of well-controlled asthma patients across disease severities, but it would also have led to inclusion of patients on ICS-formoterol rescue/reliever. Because adherence to ICS-containing treatments is known to be approximately 50% in asthma patients,[47] an arbitrary threshold of 50% or greater prescription/possession of maintenance therapy was selected to ensure inclusion of sufficient patients for exploring the independent association between SABA prescription/possession and severe exacerbations. Whereas, in some countries, SABA exposure was assessed during baseline and severe exacerbations during follow-up (preferred by epidemiologists), exposure and outcome assessments were performed in the same year for most datasets (clinically preferred). Our analysis precluded determination of reverse causality (ie, whether SABA prescription/possession is simply a result of severe exacerbations). Finally, our findings are limited to specific countries in North America and Europe; however, further SABINA analyses evaluating the association of SABA exposure with multiple asthma outcomes in an additional 24 countries across 5 continents are now available.[48]

CONCLUSION

This multicountry analysis consistently showed that prescription/possession of SABA rescue/reliever was associated with severe asthma exacerbations, independent of ICS across all asthma severities. Moreover, severe exacerbation incidence increased with increasing SABA canisters, independent of maintenance therapy. Even patients with anti-inflammatory maintenance therapy at levels consistent with adequate adherence are prescribed/possess multiple SABA canisters, suggesting that they remain uncontrolled and at risk of severe exacerbations. An ICS-containing rescue/reliever, as suggested by GINA and now recommended for some patients with persistent asthma by NAEPP, rather than as-needed SABA alone, may be needed to control symptoms and prevent severe exacerbations for all patients.

Author contributions. J. K. Quint, S. Arnetorp, J. Nuevo, C. Cabrera, I. Gilbert, and R. J. P. van der Valk were responsible for concept and design. All authors were responsible for acquisition, analysis, or interpretation of data; drafting the manuscript; critical revision of the manuscript for important intellectual content; and writing the manuscript and the decision to submit it for publication. J. K. Quint, S. Arnetorp, E. Penz, N. L. Lugogo, I. Gilbert, and R. J. P. van der Valk were responsible for statistical analysis. I. Gilbert and R. J. P. van der Valk provided administrative, technical, or material support. J. K. Quint, I. Gilbert, and R. J. P. van der Valk provided supervision. All authors were involved in the writing of the manuscript and the decision to submit the manuscript for publication.

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REFERENCES

1. Global Asthma Network (GAN). The Global Asthma Report; 2018. Accessed March 22, 2021. http://www.globalasthmareport.org
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention; 2021. Accessed May 6, 2021. http://ginasthma.org/
3. Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. J Allergy Clin Immunol Pract 2017;5:918-27.
4. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? Eur Respir J 2017;50:1701103.
5. Aldridge RE, Hancox RJ, Robin Taylor D, Cowan JO, Winn MC, Frampton CM, et al. Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma. Am J Respir Crit Care Med 2000;161:1459-64.
6. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019;380:2020-30.
7. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019;394:919-28.
8. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007;61:725-36.
9. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zheng J, Gustafson P, et al. Effect of a single day of increased as-needed budesonide-formoterol use on short-term risk of severe exacerbations in patients with mild asthma: a post-hoc analysis of the SYGMA 1 study. Lancet Respir Med 2021;9:149-58.
10. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76.
11. Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest 2006;129:246-56.
12. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 2004;20:1403-18.

13. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention; 2019. Accessed March 22, 2021. http://ginasthma.org/
14. National Heart, Lung, and Blood Institute. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Accessed March 22, 2021. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines
15. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) Guidelines 2007 Working Draft. Accessed March 22, 2021. https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf
16. Cabrera CS, Nan C, Lindarck N, Beekman M, Arnetorp S, van der Valk RJP. SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting beta2-agonist use in asthma. Eur Respir J 2020;55:1901858.
17. Bloom CI, Cabrera C, Arnetorp S, Coulton K, Nan C, van der Valk RJP, et al. Asthma-related health outcomes associated with short-acting β_2-agonist use: an observational UK study as part of the SABINA global program. Adv Ther 2020; 37:4190-208.
18. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J 2020;55:1901872.
19. Quint J, Arnetorp S, Janson C, Boarino S, Kocks JW, Gilbert I, et al. Late breaking abstract—short-acting ß2-agonist use in asthma in Western societies. Eur Resp J 2020;56:2629.
20. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
21. Harrell FE Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd ed. New York: Springer; 2015.
22. McKibben S, Bush A, Thomas M, Griffiths C. "Tossing a coin:" defining the excessive use of short-acting beta 2-agonists in asthma—the views of general practitioners and asthma experts in primary and secondary care. NPJ Prim Care Respir Med 2018;28:26.
23. Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol 2012;109:403-7.
24. Bonini M, Di Paolo M, Bagnasco D, Baiardini I, Braido F, Caminati M, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur Respir Rev 2020;29:190137.
25. Blakey JD, Price DB, Pizzichini E, Popov TA, Dimitrov BD, Postma DS, et al. Identifying risk of future asthma attacks using UK medical record data: a Respiratory Effectiveness Group initiative. J Allergy Clin Immunol Pract 2017;5. 1015-24.e8.
26. Papi A, Ryan D, Soriano JB, Chrystyn H, Bjermer L, Rodriguez-Roisin R, et al. Relationship of inhaled corticosteroid adherence to asthma exacerbations in patients with moderate-to-severe asthma. J Allergy Clin Immunol Pract 2018;6. 1989-98.e3.
27. Lugogo N, Gilbert I, Tkacz J, Gandhi HN, Goshi N, Lanz ML. Real-world patterns and implications of short-acting beta2-agonist use in patients with asthma in the USA. Ann Allergy Asthma Immunol 2021;126:681-689.e1.
28. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC Pulm Med 2006;6:13.
29. European Commission. State of Health in the EU—Poland, Country Health Profile; 2017. Accessed March 22, 2021. https://www.euro.who.int/__data/assets/pdf_file/0006/355992/Health-Profile-Poland-Eng.pdf?ua=1
30. Statistics Canada. Socioeconomic Status in Canadian Provinces. Government of Canada. Accessed March 22, 2021. https://www150.statcan.gc.ca/n1/pub/81-590-x/2007001/tables/5002494-eng.htm
31. Battaglia S, Benfante A, Spatafora M, Scichilone N. Asthma in the elderly: a different disease? Breathe (Sheff) 2016;12:18-28.
32. Connolly M, Crowley J, Charan N, Nielson C, Vestal R. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. Thorax 1992;47:410-3.
33. Mathur SK, Nyenhuis SM. Changes in immune function in asthma in the elderly. Aging Health 2009;5:551-9.
34. Kaiser Commission on Medicaid and the Uninsured. Medicaid: A Lower-Cost Approach to Serving a High-Cost Population. Policy Brief; 2004. Accessed March 22, 2021. https://www.kff.org/wp-content/uploads/2013/01/medicaid-a-lower-cost-approach-to-serving-a-high-cost-population.pdf
35. Cook NL, Hicks LS, O'Malley AJ, Keegan T, Guadagnoli E, Landon BE. Access to specialty care and medical services in community health centers. Health Aff (Millwood) 2007;26:1459-68.
36. Pruitt K, Yu A, Kaplan BM, Hsu J, Collins P. Medicaid coverage of guidelines-based asthma care across 50 states, the District of Columbia, and Puerto Rico, 2016−2017. Prev Chronic Dis 2018;15:E110.
37. Hancox RJ. Concluding remarks: can we explain the association of beta-agonists with asthma mortality? A hypothesis. Clin Rev Allergy Immunol 2006;31:279-88.
38. Reddel HK. Reply: about the recommendation of the GINA strategy report on asthma step 1. Eur Respir J 2021;57:2004226.
39. Murphy KR, Chipps B, Beuther DA, Wise RA, McCann W, Gilbert I, et al. Development of the asthma impairment and risk questionnaire (AIRQ): a composite control measure. J Allergy Clin Immunol Pract 2020;8:2263-2274.e5.
40. Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 Asthma Insight and Management survey. Allergy Asthma Proc 2012;33:54-64.
41. Silver HS, Blanchette CM, Kamble S, Petersen H, Letter M, Meddis D, et al. Quarterly assessment of short-acting β2-adrenergic agonist use as a predictor of subsequent health care use for asthmatic patients in the United States. J Asthma 2010;47:660-6.
42. Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic literature review of systemic corticosteroid use for asthma management. Am J Respir Crit Care Med 2020;201:276-93.
43. McBrien CN, Menzies-Gow A. Time to FOCUS on oral corticosteroid stewardship in asthma management. Respirology 2019;24:304-5.
44. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. Am J Respir Crit Care Med 1999;160: 594-9.
45. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.
46. Rogliani P, Ritondo BL, Ora J, Cazzola M, Calzetta L. SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis. Eur Respir J 2020; 56:2000625.
47. Williams LK, Pladevall M, Xi H, Lafata JE, Ownby DR, Johnson CC. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 2004;114:1288-93.
48. Bateman ED, Price DB, Wang C-H, Khattab A, Schonffeldt P, Catanzariti A, et al. Short-acting β_2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. Eur Resp J 2022;59:2101402.

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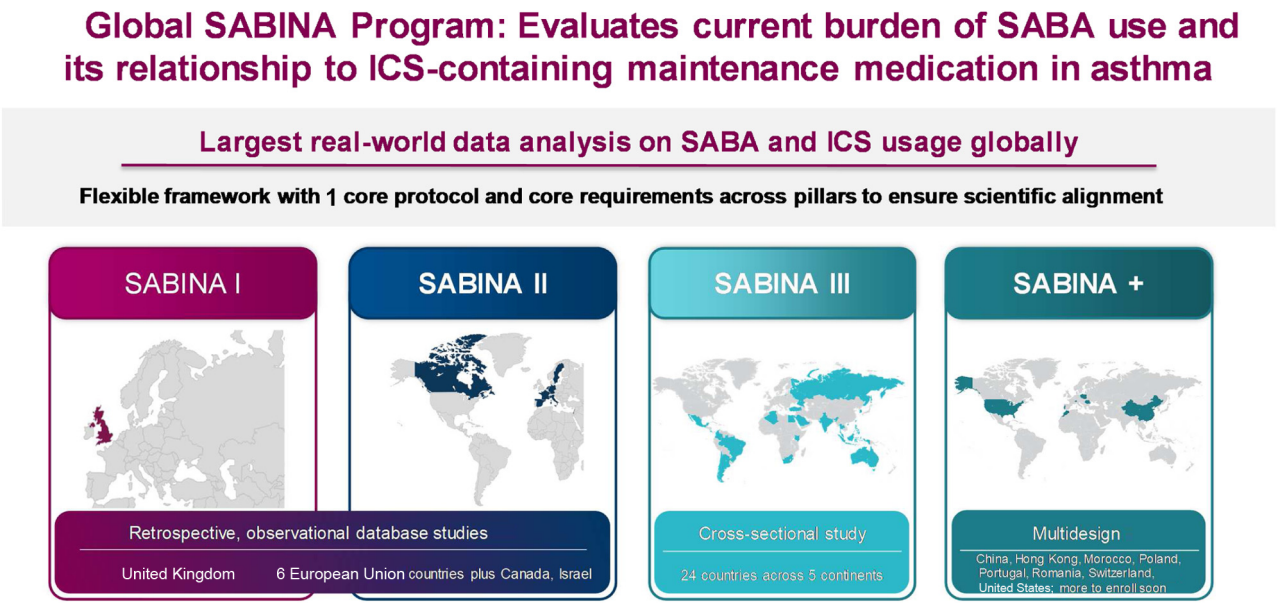

FIGURE E1. The key pillars included in the SABINA program. The SABINA program originally included the SABINA I, SABINA II, and SABINA III pillars. All 3 pillars share a common objective and design principles from a granular core protocol (SABINA I) to ensure scientific alignment and harmonization of results. To accommodate the growing interest among countries, SABINA + was recently included as an additional pillar in the program, with more countries due to enroll shortly.

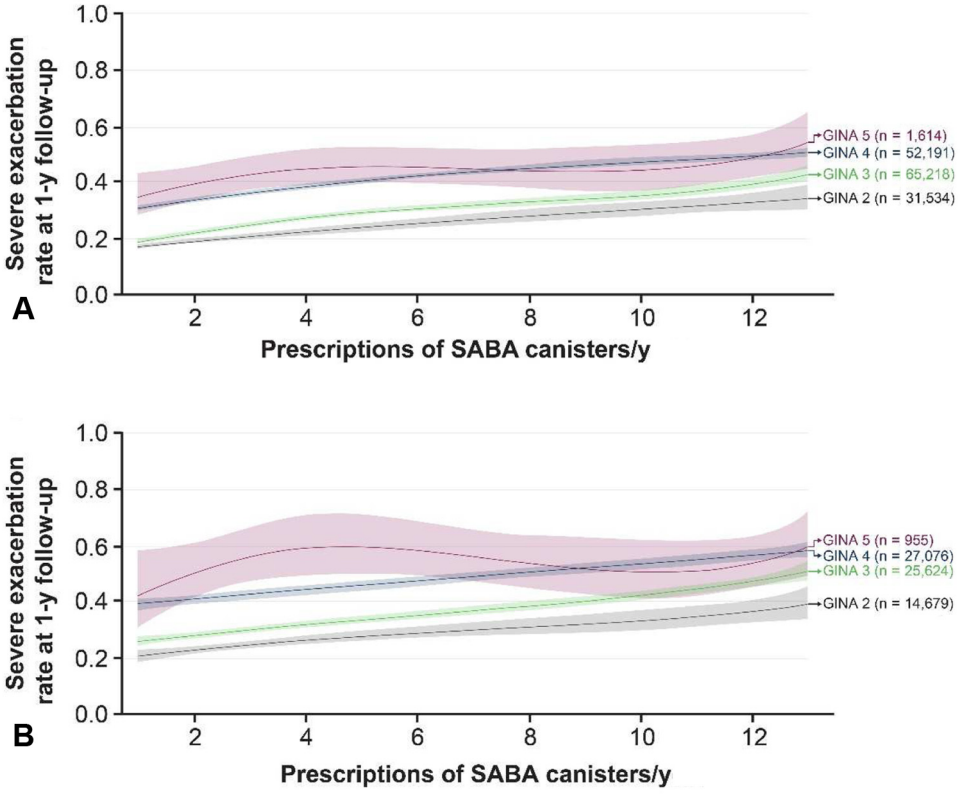

FIGURE E2. Association between use of SABA at baseline (prior year) and severe exacerbations during follow-up in patients from the United Kingdom (**A**) at GINA 2–5 (n = 150,557) and (**B**) at GINA 2–5 (n = 68,334) among patients (≥50%) prescribed ICS-containing therapy. The association between SABA prescriptions and severe asthma exacerbations was evaluated using a negative binomial model. The analysis was adjusted for age, sex, atopy, depression, anxiety, reflux, pneumonia, COPD, prior exacerbations, and maintenance therapy use PDC. *COPD,* Chronic obstructive pulmonary disease; *PDC,* proportion of days covered.

TABLE E1. Additional details about the countries included in the analyses*

SABINA I	United Kingdom	Study design: The SABINA U.K. study was a retrospective, longitudinal, open-cohort study that used primary care electronic health care records from patients with asthma aged ≥ 12 years. Linked hospital admission data were obtained from the Hospital Episode Statistics database. Baseline year was 12 mo before the index date. The index date was set as the latest date of any of the following: asthma diagnosis, 12th birthday, start of the study period (April 1, 2008), 1 y after the GP practice began recording research quality data (CPRD quality control), or 1 y after their continuous CPRD practice registration date. The incidence rate of severe exacerbations was calculated during the total study follow-up of 1 y. The patient follow-up ended at the earliest date of death, the end of the study period (December 31, 2019), the last CPRD data collection date, or the date transferred out of a CPRD practice. Linked pseudonymized data were provided for this study by CPRD. Data were linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select practices consented to this process at a practice level, with individual patients having the right to opt out. Comorbidities considered were pneumonia, atopy, COPD, anxiety, depression, and reflux. Maintenance therapy (PDC) was based on the annual coverage of ICS-containing therapy for eligible patients.
SABINA II	Canada (Alberta and Nova Scotia)	Study design: This was a retrospective, longitudinal, open-cohort study utilizing provincial administrative data from Alberta (including pharmacy, hospital, and physician billing and emergency/urgent care) and Nova Scotia (linked with pharmacy and discharge records). Comorbidities were assessed using the unweighted Elixhauser index score. Maintenance therapy was defined as PDC with an ICS prescription within the first year post-index. Statistical analysis was conducted with the R software (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria) using the survival package version 2.43-3.
	France	Study design: This was a cross-sectional survey (ASTHMAPOP) conducted in 2018 to collect up-to-date epidemiological data on asthma prevalence in adults in France, including the burden of disease according to GINA treatment steps, and assess the level of asthma control. A 4-page, self-administered questionnaire was mailed to people aged ≥ 18 y belonging to the Kantar-TNS panel, which comprised people representative of the French population in terms of age, sex, region, and socioeconomic status; no exclusion criteria were applied. The main population analyzed included all people with asthma, identified based on self-report in the self-administered questionnaire; asthma diagnosis was not based on physicians' assessment. The characteristics of people with asthma were described in comparison with those without asthma. Asthma was classified by treatment steps per the GINA 2017 report, according to prescribed treatments as declared by respondents based on a preestablished list of medications. Data were analyzed using logistic regression and adjusted for the following covariates: age, sex, GINA level, and comorbidities. Comorbidities (categorized as ≥ 1 vs none) were self-reported based on a predefined list in the questionnaire and included food allergies, anxiety/depression, obstructive sleep apnea, chronic bronchitis, COPD, emphysema, cataract, diabetes, atopic dermatitis/other skin allergy, glaucoma, hypercholesterolemia, hypertension, osteoporosis, cardiac disease, nasal polyposis, gastroesophageal reflux disease, allergic rhinitis, nasal allergy, and sinusitis. Statistical analysis was performed using the R software (version 1.2.1355, R Foundation for Statistical Computing, Vienna, Austria).

(continued)

TABLE E1. *(Continued)*

	Spain	Study design: This was a longitudinal, retrospective study conducted in primary and specialized care settings in Spain using the BIGPAC Medical Records Database to assess the clinical consequences (severe exacerbations and mortality) in patients with SABA overuse according to GINA treatment steps in usual clinical practice. Patients with asthma (ICD-10-CM: J45-J46) aged $\geq$ 12 y who attended $\geq$ 2 health care consultations during 2017 and had a 1-y follow-up available in the database were included. Data from Spain were analyzed using a stepwise multivariate linear regression model. Comorbidities included COPD, history of hypertension, diabetes mellitus, obesity, ischemic heart disease (angina, acute myocardial infarction), cerebrovascular accident (stroke, peripheral arterial disease), arrhythmia, heart failure, renal failure, chronic kidney disease, pulmonary vascular disease, depressive syndrome, malignant neoplasms, pneumonia, anemia, bone fractures, and osteoporosis. As summary variables of general comorbidity, the following were used: (a) the CCI as an approximation to severity (categories: 0, 1, 2, and 3+) and (b) the number of chronic comorbidities. These variables were obtained at study initiation. Statistical analyses were performed using SPSS software version 23.0 (IBM Corp., Armonk, NY).
	The Netherlands	Study design: The aim of the Dutch cohort study was to provide insight into the use of ICS, LABA, and SABA by patients with asthma in daily practice and how this medication use is related to asthma outcomes over the year 2016. Data were derived from the Nivel Primary Care Database (Nivel-PCD), which includes routine care data originating from electronic medical records from GPs across the Netherlands. The participating GPs constitute a representative sample of the total population of Dutch GPs. Within the Dutch health care system, all residents are mandatorily registered with 1 GP, who keeps track of the patient's complete medical record and fulfills a gatekeeper role for access to medical specialists. The database consists of longitudinal information of patient characteristics (age and sex), GP consultations, diagnoses (ICPC-1), and drug prescriptions (ATC). Comorbidities were categorized as 0, 1, 2, or $>$ 2 without R96 asthma and R91, R95 COPD. Maintenance therapy PDC was operationalized as CMA7, which was calculated by dividing the number of days of theoretical use by the number of days between the start (January 1, 2016) and the end of the observation window (December 31, 2016). Days of theoretical use were calculated by extracting the total number of gap days (days for which no medication was available) from the total time period between the start and the end of the observation window, accounting for a carryover for all prescriptions within and before the observation window. For the latter, prescriptions issued in Q4 of 2015 for which the duration crosses January 1, 2016, were included. Data analyses were performed using Stata/SE 15.1 for Windows (StataCorp, College Station, Texas).
SABINA +	Poland	Study design: Because national quality standards for asthma have not yet been introduced in Poland, this was the first nationwide study analyzing pharmacy records (drug purchase data). Asthma patients were defined as those who purchased (at least once within 6 mo) drugs from R03 class, excluding patients on LABA, LAMA, LABA/LAMA, and LABA/LAMA/ICS (assuming COPD therapy). The accuracy of selection has been confirmed via a subanalysis of patients in the age group of 18 to 35 years, which revealed the same results as for the entire analyzed population. Because deidentified retrospective claims data were used, the analysis was considered as "not human subjects research" and, therefore, exempted from IRB approval. Maintenance medication PDC was based on the number of canisters of ICS and ICS/LABA per year. Statistical analysis was conducted using the R software (version 3.5.5, R Foundation for Statistical Computing, Vienna, Austria).

(continued)

TABLE E1. *(Continued)*

United States	Study design: This was a retrospective, observational cohort study. Data source included deidentified claims data from the United States contained in the IBM MarketScan commercial, Medicare Supplemental, and Multistate Medicaid Research databases. Because deidentified retrospective claims data were used, the analysis was considered as "not human subjects research" and, therefore, exempted from IRB approval. Comorbidities were assessed based on CCI. The PDC was based on the maintenance therapy possession ratio for all therapies (100% for patients at GINA step 1). Patients with the following combinations of systemic corticosteroid claims were assessed: OCS only, injection corticosteroid only, both OCS and injection corticosteroids. All patients were categorized by the presence or absence of maintenance medication during the 12-mo post-index period. At GINA 2, approximately 70% of patients in the United States were on leukotriene modifiers. In addition, patients were indexed on a random SABA prescription fill to ensure that the population comprised a combination of those with newly diagnosed asthma as well as those with long-term asthma. Data were scrutinized 1 y pre- and post-index SABA to ensure that patients with a diagnostic code for COPD were excluded. Programming was conducted using WPS version 4.1 (World Programming, UK), and statistical analyses were conducted with the R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

ATC, Anatomical therapeutic chemical; *CCI,* Charlson Comorbidity Index; *CMA-7,* continuous multiple-interval measures of medication availability; *COPD,* chronic obstructive pulmonary disease; *CPRD,* Clinical Practice Research Datalink; *GP,* general practitioner; *ICD-10-CM,* International Classification of Diseases-10th Revision, Clinical Modification; *ICPC,* International Classification of Primary Care; *IRB,* institutional review board; *LABA,* long-acting beta-2 agonist; *LAMA,* long-acting muscarinic antagonist; *NHS,* National Health Service; *PDC,* proportion of days covered; *Q4,* fourth quarter; *TNS,* Taylor Nelson Sofres.
*Where applicable, studies were approved by each country's IRB or ethics committee.

TABLE E2. Outcome: severe exacerbations and IRR values during the year of analysis*†

	SABINA I	SABINA II			SABINA +			
	United Kingdom	Canada (Alberta)	Canada (Nova Scotia)	The Netherlands	Poland	U.S. commercially insured	U.S. Medicaid	U.S. Medicare
GINA steps 1−5								
1−2 SABA canisters/y	0.19 (0.67) (n = 91,920)	0.23 (0.94) (n = 38,259)	0.32 (0.92) (n = 1,842)	0.16 (0.50) (n = 7,015)	0.17 (0.7) (n = 29,167)	0.72 (1.23) (n = 322,052)	0.63 (1.11) (n = 80,405)	0.95 (1.54) (n = 23,005)
≥3 SABA canisters/y	0.50 (1.28) (n = 95,755)	0.36 (1.21) (n = 33,370)	0.46 (1.11) (n = 3,167)	0.23 (0.60) (n = 2,459)	0.36 (1.2) (n = 17,461)	0.98 (1.51) (n = 161,822)	0.94 (1.49) (n = 71,034)	1.06 (1.59) (n = 14,603)
IRR (95% CI)	2.63 (2.59−2.68)	1.57 (1.52−1.61)	1.44 (1.31−1.58)	1.44 (1.30−1.59)	2.12 (2.04−2.20)	1.36 (1.35−1.37)	1.49 (1.47−1.51)	1.12 (1.09−1.14)
GINA steps 2−5								
1−2 SABA canisters/y	0.22 (0.73) (n = 65,184)	0.27 (1.07) (n = 27,650)	0.38 (1.05) (n = 1,247)	0.18 (0.53) (n = 5,930)	0.17 (0.7) (n = 24,284)	0.73 (1.28) (n = 131,698)	0.63 (1.15) (n = 19,726)	0.89 (1.48) (n = 12,555)
≥3 SABA canisters/y	0.54 (1.33) (n = 85,373)	0.41 (1.32) (n = 26,037)	0.53 (1.22) (n = 2,133)	0.28 (0.66) (n = 1,875)	0.38 (1.2) (n = 12,538)	0.99 (1.57) (n = 107,873)	0.99 (1.60) (n = 41,321)	1.05 (1.59) (n = 10,931)
IRR (95% CI)	2.45 (2.41−2.50)	1.52 (1.47−1.56)	1.39 (1.25−1.55)	1.56 (1.40−1.73)	2.24 (2.14−2.33)	1.36 (1.34−1.37)	1.57 (1.54−1.60)	1.18 (1.15−1.21)

*Values are mean (SD).

†A meta-analysis revealed that prescription/possession of ≥ 3 vs 1–2 SABA canisters/y was associated with increased unadjusted IRR (95% CI) of severe exacerbations in patients at GINA steps 1–5 (IRR 1.59 [95% CI1.33–1.91]) and 2–5 (IRR 1.61 [95% CI 1.33–1.96]).

TABLE E3. Association between SABA prescriptions and asthma severe exacerbations in the year of analysis in patients from France*

Parameter	≥3 vs 1−2 SABA canisters/y
Across all GINA treatment steps	
Number of patients	673
Number of events	341
Person follow-up years	NA
OR (95% CI)	2.09 (1.47−2.99)
P value	<.000001
Split by GINA treatment steps	
GINA steps 1−2	
Number of patients	401
Number of events	178
Person follow-up years	NA
OR (95% CI)	2.26 (1.39−3.72)
P value	.00114
GINA steps 3−5	
Number of patients	272
Number of events	163
Person follow-up years	NA
OR (95% CI)	1.82 (1.08−3.06)
P value	.0244

NA, Not available; *OR,* odds ratio.
*France was unable to provide data to determine IRR and, hence, data are reported as OR. The association between SABA prescriptions and severe asthma exacerbations was evaluated using a logistic regression model.

TABLE E4. Severe exacerbations at baseline and follow-up (at mo 12) by SABA use (canisters/year) for patients from Spain

Exacerbations	<3 SABA canisters/y	≥3 SABA canisters/y	Total
≥1 previous exacerbation, n (%)	10,002 (47.4)	11,116 (52.6)	21,118 (100.0)
≥1 follow-up exacerbation, n (%)	6,565 (36.9)	11,230 (63.1)	17,795 (100.0)
Number of previous severe exacerbations, mean (SD)	0.4 (0.5)	2.0 (0.6)	0.9 (0.9)
Number of follow-up severe exacerbations, mean (SD)	0.2 (0.4)	1.9 (0.7)	0.7 (0.9)

TABLE E5. Association between SABA prescriptions (≥3 vs <3 canisters/y) and severe asthma exacerbations at 1-y follow-up in patients from Spain*

	Coefficients			95% CI	
Variables in the final model	Regression coefficient	Standard error	*P* value	Lower limit	Upper limit
Constant	0.118	0.008	<.001	0.102	0.135
SABA overuse (≥3 canisters/y)	1.523	0.010	<.001	1.504	1.543
Charlson Comorbidity Index	0.072	0.003	<.001	0.067	0.078
Previous severe exacerbations, n	0.068	0.005	<.001	0.059	0.077
Sex (female)	0.060	0.006	<.001	0.048	0.071
GINA steps	0.007	0.002	.004	0.002	0.012

*The association between SABA prescriptions and severe asthma exacerbations was evaluated using a linear regression model. Spain was unable to provide data to determine IRR and, hence, data are reported as regression coefficients (mean delta in linear regression).

TABLE E6. Association between SABA prescription/possession (≥3 vs 1−2 canisters/y) and severe asthma exacerbations/year in GINA 1−5−treated patients, GINA 3−5−treated patients, GINA 1−2−treated patients, and GINA 2−5−treated patients prescribed/possessing maintenance therapy ≥ 50% of the time*

Dataset	IRR (95% CI)	*P* value
GINA 1−5−treated patients		
United Kingdom	1.41 (1.38—1.45)	<.001
Canada (Alberta)	1.32 (1.27—1.38)	<.001
Canada (Nova Scotia)	1.38 (1.21—1.58)	<.001
The Netherlands	1.40 (1.23—1.58)	<.001
Poland	2.15 (2.01—2.30)	<.001
U.S. overall	1.03 (1.02—1.04)	<.001
U.S. commercial	1.02 (1.01—1.03)	<.001
U.S. Medicaid	1.09 (1.07—1.10)	<.001
U.S. Medicare	0.89 (0.86—0.91)	<.001
GINA 3−5−treated patients		
United Kingdom	1.42 (1.38—1.46)	<.001
Canada (Alberta)	1.29 (1.23—1.36)	<.001
Canada (Nova Scotia)	1.40 (1.17—1.66)	<.001
The Netherlands	1.42 (1.24—1.63)	<.001
Poland	2.11 (1.96—2.27)	<.001
U.S. commercial	1.24 (1.23—1.26)	<.001
U.S. Medicaid	1.48 (1.43—1.53)	<.001
U.S. Medicare	1.08 (1.04—1.13)	<.001
GINA 1−2−treated patients		
United Kingdom	1.38 (1.31—1.45)	<.001
Canada (Alberta)	1.36 (1.26—1.48)	<.001
Canada (Nova Scotia)	1.35 (1.10—1.67)	.005
The Netherlands	1.25 (0.91—1.71)	.163
Poland	2.41 (2.09—2.79)	<.001
U.S. commercial	0.92 (0.91—0.93)	<.001
U.S. Medicaid	1.02 (1.01—1.04)	.007
U.S. Medicare	0.74 (0.71—0.76)	<.001
GINA 2−5−treated patients prescribed/possessing maintenance therapy ≥ 50% of the time		
United Kingdom	1.30 (1.25—1.36)	<.001
Canada (Alberta)	1.25 (1.15—1.37)	<.001
Canada (Nova Scotia)	1.29 (0.98—1.70)	.073
The Netherlands	1.43 (1.22—1.68)	<.001
Poland	2.11 (1.93—2.31)	<.001
U.S. commercial	1.14 (1.12—1.17)	<.001
U.S. Medicaid	1.30 (1.23—1.37)	<.001
U.S. Medicare	1.02 (0.97—1.07)	.435

COPD, Chronic obstructive pulmonary disease; *PDC*, proportion of days covered.

*The association between SABA prescription/possession and severe asthma exacerbations was evaluated using a negative binomial model. The analyses were adjusted for age, sex, comorbidities, prior exacerbations, GINA treatment step (1–2 vs 3–5), and maintenance medicine PDC. Prior exacerbations were not included as a covariate in Poland and the Netherlands, whereas comorbidities were not included as a covariate in Poland. Patients aged ≥ 65 y and those likely to have COPD were excluded from the Polish dataset. Multiple comparisons were adjusted by using conservative Bonferroni correction, with $P \leq .0125$ as the cut-off for patients treated per GINA steps 1–5, 3–5, 1–2, and 2–5 with prescription/possession of maintenance therapy ≥ 50% of the time.

TABLE E7. Determination of data-driven cut-off for the level for SABA canisters associated with a clinically relevant 20% increased incidence of severe exacerbations

SABA canisters	Severe exacerbations (y 1)	SE	Lower CI	Upper CI	Type (ICS coverage)	% change
1	0.224	0.003	0.218	0.229	Overall/any ICS PDC	0
1.2	0.231	0.003	0.226	0.236	Overall/any ICS PDC	3
1.5	0.238	0.002	0.233	0.243	Overall/any ICS PDC	6
1.7	0.245	0.002	0.241	0.249	Overall/any ICS PDC	9
2.0	0.252	0.002	0.248	0.256	Overall/any ICS PDC	12
2.2	0.258	0.002	0.254	0.262	Overall/any ICS PDC	15
2.5	0.265	0.002	0.260	0.269	Overall/any ICS PDC	18
2.7	0.271	0.002	0.266	0.275	Overall/any ICS PDC	21

PDC, Proportion of days covered; *SE,* standard error.