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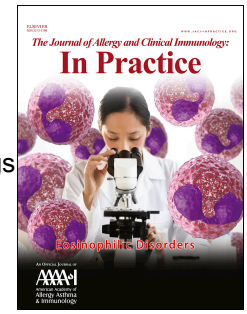

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Short-acting β_2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and North America

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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ABSTRACT

Background: Expert national/global asthma management recommendations raise the issue whether a safe threshold of short-acting β_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 years) from Canada, France, the Netherlands, Poland, Spain, United Kingdom (UK), and United States (US). Negative binomial models (incidence rate-ratio [95% confidence interval]) adjusted for prespecified-covariates]) evaluated associations between SABA and exacerbations.

Results: Across severities, 40.2% of patients were prescribed/possessed ≥3 SABA canisters/year. Per GINA-2018 definitions, step 3–5-treated patients prescribed/possessing ≥3 vs. 1–2 SABA experienced more severe exacerbations (between 1.08 [1.04–1.13], US-Medicare; 2.11 [1.96–2.27], Poland). This association was not observed in all step 1–2-treated patients (the Netherlands 1.25 [0.91–1.71]; US-commercial 0.92 [0.91–0.93]; US-Medicare 0.74 [0.71–0.76]). We hypothesize that this inverse association between SABA and severe exacerbations in the US datasets was attributable to the large patient population possessing <3 SABA and no maintenance therapy and receiving oral corticosteroid bursts without face-to-face healthcare provider encounters. In US SABA monotherapy-treated patients, ≥3 SABA was associated with more emergency/outpatient visits and hospitalizations (1.31 [1.29–1.34]). Most GINA 2–5-treated study patients (60.6%) did not have maintenance therapy for up to 50% of the time; however, the association of ≥3 SABA and severe exacerbations persisted (1.32 [1.18–1.49]) after excluding these patients

and the independent effect was further confirmed when UK SABA data was 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.

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HIGHLIGHTS

What is already known about this topic?

Although the Global Initiative for Asthma (GINA) no longer recommends SABA without concomitant ICS for patients with asthma aged ≥12 years, US 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 US, SABA monotherapy-treated patients represented most patients, with over half experiencing ≥1 annual severe exacerbation.

How does this study impact current management guidelines?

These findings indicate possible undertreatment of patients with asthma and highlight potential gaps in US guidelines. As addressed by GINA, our findings underscore the need for symptom-based use of an ICS with a fast-acting bronchodilator as a rescue/reliever to potentially mitigate the occurrence of severe exacerbations across all asthma severities.

Key words: *Asthma, Asthma management, Short-acting β_2-agonists, Inhaled corticosteroids, Severe exacerbations*

Abbreviations used:

ATS: American Thoracic Society

CI: Confidence interval

ERS: European Respiratory Society

GINA: Global Initiative for Asthma

HCP: Healthcare provider

ICS: Inhaled corticosteroid

IRR: Incidence rate ratio

NAEPP: National Asthma Education and Prevention Program

OCS: Oral corticosteroid

PDC: Proportion of days covered

SABA: Short-acting β_2-agonist

SABINA: SABa use IN Asthma

SD: Standard deviation

UK: United Kingdom

US: United States

INTRODUCTION

Asthma affects ~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 β_2-agonists (SABAs) provide rapid symptom relief and can be life-saving.[4] However, β_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 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 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, as 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 United States (US) National Asthma Education and Prevention Program (NAEPP) guidelines also preferentially recommend use of fast-acting bronchodilators with concomitant ICS for patients aged ≥12 years treated as mild, moderate, and severe persistent asthma at steps 2–4. 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 (UK)[17] and Sweden,[18] prescription/possession of ≥3 SABA canisters/year was associated with increased exacerbation risk and asthma-related healthcare utilization. Moreover, in Sweden, prescription of ≥3 SABA canisters/year increased the risk of all-cause, respiratory, and asthma-related mortality.[18]

Utilizing an epidemiologic investigation of 10 North American and European datasets in >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, healthcare 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, UK, and US were included (see **Figure E1 and Table E1** in the Online Repository for further details on the methodologies used in each country-specific analyses). Datasets from Canada (Alberta and Nova Scotia) and the US (commercial, Medicaid, and Medicare) were analyzed separately as they represented populations of differing demographics, healthcare insurance, and/or socioeconomic status.

The primary objective was to evaluate how similarities and differences across North American and European healthcare 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/year exists and to understand how maintenance medication mitigates severe exacerbation risk.

Patient populations, exposures, and outcome variables

Patients aged ≥12 years with current asthma according to diagnostic code and prescription/possession of ≥1 SABA canister/year formed the minimum criteria for inclusion in the analyses (**Figure 1**). As the objective of the analyses was to examine

the association between SABA prescription/possession and the number of severe asthma exacerbations/year, patients without prescription/possession of SABA and potentially on maintenance and reliever therapy (MART) were excluded. SABINA countries with methodological variations deemed to have a serious impact on the prespecified main analysis were excluded (red in **Figure 1**), while countries with complete alignment (green) or methodological variations having minimal (yellow) or medium (orange) impact were included. SABA prescription/possession was evaluated as a dichotomized variable (≥3 or 1–2 canisters/year) across all countries and additionally as a continuous variable in the UK. 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 OCS bursts (≥3 days) or emergency department/accident/emergency visit or hospitalization for asthma. Variations from any pre-specified definitions are noted in **Figure 1.**

Statistical analysis

Patient characteristics, exposures, and outcome data were described as mean (standard deviation [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/year) 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 [PDC]) (**Figure 1B**). Using SABA prescription/possession, incidence rate ratios (IRRs) of severe exacerbations were estimated and results presented overall and stratified as GINA 1–2 and GINA 3–5 treatment groups. Multiple comparisons were adjusted by using a conservative Bonferroni correction, with $P \leq 0.0125$ 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 US GINA 1 dataset by comparing IRRs with GINA 2–5-treated patients. In the US datasets, severe exacerbations requiring OCS bursts without a face-to-face healthcare provider (HCP) evaluation (prescribed over telephonic 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 2–5-treated patients with ≥50% 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 UK dataset using a negative binomial model in all GINA 2–5-

treated patients and at each GINA step separately, with results stratified by ≥50%, ≥75%, and ≥100% maintenance therapy. For patients with ≥12 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 pre-specified 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 cutoff 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 (US Medicaid) to 72.2 (6.9) years (US Medicare). Patients were predominantly female (ranging from 55.8% in Canada [Alberta] to 68.2% in US 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 UK (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 SABA canisters/year, 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 1–2 vs. ≥3 SABA canisters/year for GINA 1–5- and GINA 2–5-treated patients (see **Table E2** in the Online Repository). In GINA 1–5 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 US Medicare (0.95 [1.54] vs. 1.06 [1.59]).

Across GINA 1–5, except for US Medicare, prescription/possession of ≥3 vs. 1–2 SABA canisters/year was associated with an increased incidence of severe exacerbations after adjusting for covariates (**Figure 2A**). The highest IRR was observed in Poland (adjusted IRR [95% confidence interval (CI)], 2.15 [2.01–2.30]) and the weakest in the US commercial dataset (1.02 [1.01–1.03]). For US Medicare

patients, prescription/possession of ≥3 vs. 1–2 SABA canisters/year was associated with a reduced incidence of severe exacerbations (0.89 [0.86–0.91]). Although France and Spain were unable to provide data to determine an IRR, use of ≥3 SABA canisters/year was associated with an increased risk of having ≥1 severe exacerbation vs. 1–2 SABA (based on reported odds ratios and regression coefficients, respectively; see **Tables E3–E5** in the Online Repository).

Across all countries and datasets, more severe exacerbations were observed with prescription/possession of ≥3 vs. 1–2 SABA canisters/year among GINA 3–5-treated patients. The highest IRR was observed in Poland, followed by US Medicaid, the Netherlands, the UK, and Canada (Nova Scotia) (**Figure 2B**). In GINA 1–2-treated patients, results were not uniform. In the UK, Canada (Alberta and Nova Scotia), Poland, and US Medicaid, prescription/possession of ≥3 vs. 1–2 SABA canisters/year was associated with an increased incidence of severe exacerbations. This association was not significant for the Netherlands (1.25 [0.91–1.71]), and a lower IRR of severe exacerbations with possession of ≥3 vs. 1–2 SABA canisters/year was observed in the US Medicare (0.74 [0.71–0.76]) and commercial datasets (0.92 [0.91–0.93]; **Figure 2C**). Additionally, multiple comparisons revealed that all datasets passed the Bonferroni-corrected threshold of $P \leq 0.0125$, except GINA 1–2-treated patients in the Netherlands ($P=0.163$), with US Commercial and Medicare datasets (both $P<0.001$; **Table E6**) showing an inverse association between SABA and severe asthma exacerbations (**Figure 2C**).

US GINA 1 sensitivity analysis

Patients possessing SABA monotherapy (GINA 1 equivalent) represented the largest treatment group within each US dataset (**Table I**), comprising 51.8% of all US patients. SABA monotherapy treatment also predominated in the GINA 1−2-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/year) vs. higher SABA group (≥3 SABA fills/year) experienced ≥1 severe exacerbation (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 US observations is shown by comparing the incidence of severe exacerbations relative to SABA exposure groups for the GINA 1–5- vs. 2–5-treated populations. For all US datasets combined, GINA 2–5-treated patients exhibited a higher incidence of severe exacerbations for possession of ≥3 vs. 1–2 SABA canisters/year (1.23 [1.22–1.24]) compared with GINA 1–5 (1.03 [1.02–1.04]; **Figure 3B**). However, after excluding OCS bursts from the definition of severe exacerbations, exposure to ≥3 SABA canisters/year was associated with an increased incidence of exacerbations serious enough to necessitate emergency, face-to-face HCP evaluations or hospitalizations (1.31 [1.29–1.34] in US SABA monotherapy-treated patients; **Figure 3C**). Similarly, for the total US GINA 1–5-treated population, the proportion of patients experiencing ≥1 severe exacerbation requiring face-to-face HCP evaluation or hospitalization was also higher among patients possessing ≥3 vs. 1–2 SABA canisters/year (35.5% vs. 25.1%).

Association of SABA with severe exacerbations among patients with ≥50% annual ICS coverage

Overall, 60.6% of all GINA 2–5-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 vs. 1–2 SABA canisters/year was associated with a 32% (adjusted IRR [95% CI], 1.32 [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 US Medicare (1.02 [0.97–1.07]) and Canada Nova Scotia (1.29 [0.98–1.70]) populations, ≥3 vs. 1–2 SABA canisters/year was associated with a numerically higher severe exacerbation incidence. All datasets included in the stratification analyses, with the exception of Canada (Nova Scotia; *P*=0.073) and US Medicare (*P*=0.435), passed the Bonferroni-corrected threshold of *P*≤0.0125 (**Table E6)**.

Analysis of SABA as a continuous variable in the UK dataset

After adjusting for the main analysis covariates, including ICS PDC, prescription of SABA canisters remained associated with severe exacerbations on a continuous scale in UK GINA 2–5-treated patients. This association persisted even in patients with ≥50%, ≥75%, and ≥100% 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% of ICS-containing therapy at each treatment level (see **Figures E2A and E2B** in the Online Repository). A post hoc analysis of SABA canisters revealed that increasing SABA prescriptions from 1 to 2.7 canisters/year was accompanied by a clinically relevant 20% increased incidence of severe exacerbations (**Table E7**). 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 >1,000,000 patients with asthma provides the largest multi-country, 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 intra-country differences, provide unique insights into the impact that variations in healthcare delivery, insurers, and HCP/patient approaches to asthma management may have on severe exacerbations.

Overall, 40.2% of GINA 1–5-treated patients were prescribed/possessed ≥3 SABA canisters/year, and only 39.4% of GINA 2–5-treated patients received maintenance therapy ≥50% of the time. Across countries, stratifying for ≥50% GINA 2–5 maintenance exposure revealed that prescription/possession of ≥3 vs. 1–2 SABA was associated with a 32% increased incidence of severe exacerbations, independent of ICS-containing medications. In the UK, 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 SABA canisters/year and severe exacerbations (IRRs across GINA steps [1–5, 1–2, and 3–5] and stratified

analysis [steps 2–5]) was comparable in the UK (1.30–1.42), Canada (Alberta [1.25–1.36], Nova Scotia [1.29–1.40]), and the Netherlands (1.25–1.43). The strongest association was consistently reported for Poland (2.11–2.41) and may be attributable to underfunding of the healthcare 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 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 ≥3 canisters/year) being treated with systemic corticosteroids (proportion of uncontrolled patients with ≥2 oral corticosteroid [OCS] prescriptions was 7.2% in Poland vs. 4.3% in the Netherlands; post hoc calculation).

Healthcare access and severe asthma exacerbations

Results from Canada highlight the influence of access to healthcare on asthma morbidity. Findings from Alberta, a large representative sample of the Canadian population, demonstrated that possession of ≥3 vs. 1–2 SABA canisters/year 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 vs. 1–2 SABA canisters/year and number of severe exacerbations for both Canadian datasets were concordant with those for the UK, another country with similar healthcare accessibility and using comparable methodologies.

Clinically relevant similarities and differences for the US

Differences in the US 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 US Medicaid and commercial datasets comprised younger patients, the Medicaid population consistently showed the strongest association of severe exacerbations with possession of ≥3 SABA canisters/year. 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. 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 US and other countries for GINA 1–2-treated patients, where possession of ≥3 SABA canisters/year was associated with a lower incidence of severe exacerbations in US commercial and Medicare GINA 1–2-treated patients. Even in US Medicaid GINA 1–2, the significant association of increased severe exacerbations with possession of ≥3 SABA canisters/year showed the lowest IRR across all main analysis datasets. Of note, an overwhelming majority of US GINA 1–2 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 US GINA 1-treated patients were characterized by an OCS burst without a healthcare 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. While OCS burst treatment, likely prescribed over a telephonic 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 1–2 vs. ≥3 SABA canisters/year 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 SABAs canisters/year. These data are concordant with observations that US 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/year) 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 UK continuous modeling data and the lack of consensus on appropriate vs. excessive use of rescue/reliever therapy,[14,22] an evidence-backed binary classification of SABA (≥3 vs. 1–2 canisters/year) may not fully describe the continuous association between prescription/possession of SABA and severe asthma exacerbations. As increasing SABA prescriptions from 1 to 2.7 canisters/year 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 1–5 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 sub-optimal 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 with mild, moderate, and severe persistent asthma at treatment steps 2–4.[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 US 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

549 may have met the criteria for persistent asthma, and GINA 3–5-treated patients
550 exhibited more severe exacerbations with greater SABA use, indicating possible
551 undertreatment of patients. However, a potential benefit across all asthma severities
552 might also be gained by employing a fast-acting bronchodilator with concomitant ICS
553 therapy for as-needed symptom relief to address the underlying variability of airway
554 inflammation leading to symptoms and exacerbations.
555
556 **Limitations**
557 Prescription/possession data do not inform on actual or appropriate medication use.
558 Although analyses were adjusted for key exacerbation risk factors, other patient
559 characteristics may impact severe exacerbations; however, extensive covariate
560 analyses performed by Bloom et al[17] suggested that the model was robust. Data
561 analyses stratified by each individual GINA step could not be performed by all
562 countries; therefore, only the strata of steps 1–2 and 3–5 were prespecified. Given
563 the real-world nature of this study, it was not possible to measure all components of
564 asthma control; therefore, patients were grouped by treatment and not actual
565 disease severity, as suggested in GINA 2021.[2] Severe exacerbations were defined
566 per ATS/ERS definitions;[20] however, components of the definitions (OCS burst,
567 hospitalization, and emergency outpatient visit) may have different implications due
568 to differential healthcare practices (eg, OCS over the phone vs. OCS following a
569 face-to-face HCP encounter). Exclusion of patients with no SABA
570 prescription/possession may have precluded assessment of well-controlled asthma
571 patients across disease severities, but it would also have led to inclusion of patients
572 on ICS-formoterol rescue/reliever. Since adherence to ICS-containing treatments is
573 known to be approximately 50% in asthma patients,[47] an arbitrary threshold of ≥50%

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. While 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]

CONCLUSIONS

This multi-country 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.

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FIGURE LEGENDS

Figure 1. Methodological variations across countries related to (A) study design and (B) covariates included in the analyses

Patients aged ≥12 years with current asthma according to diagnostic code and prescription/possession of ≥1 SABA canister/year were included. Data on medication prescription/possession were obtained from SABINA I (UK), 4 SABINA II countries (Canada, France, Spain, and the Netherlands), and 2 SABINA+ countries (Poland and the US) (Please see Figure E1 in the Online Repository for more details related to the key pillars of the SABINA program). France and Spain were excluded from the main analyses due 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 US, 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; *GINA*, Global Initiative for Asthma; *OCS*, oral corticosteroid; *PDC*, proportion of days covered; *SABA*, short-acting β_2-agonist; SABINA, *SABa* use IN Asthma; *UK*, United Kingdom; *US*, United States.

Figure 2. Association between SABA prescription/possession (≥3 vs. 1–2 canisters/year) and severe asthma exacerbations/year 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, while comorbidities were not included as a covariate in Poland. Patients aged ≥65 years and those likely to have COPD were excluded from the Polish dataset.

CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; *PDC,* proportion of days covered; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *UK*, United Kingdom; *US*, United States.

Figure 3. Associations of SABA possession with severe exacerbations during the year of analysis in US 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

*US GINA 1-treated patients were required to have ≥2 SABA fills/year 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. 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.

CI, confidence interval; *GINA*, Global Initiative for Asthma; *HCP*, healthcare provider; *IRR*, incidence rate ratio; *PDC,* proportion of days covered; *SABA*, short-acting β_2-agonist; *US*, United States.

Figure 4. Association between SABA (≥3 vs. 1–2 canisters/year) and severe asthma exacerbations/year in GINA 2–5-treated patients prescribed/possessing maintenance therapy ≥50% of the time

*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. Prior exacerbations were not included as a covariate in Poland and The Netherlands, while comorbidities

were not included as a covariate in Poland. Patients aged ≥65 years and those likely to have COPD were excluded from the Polish dataset.

CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; *N*, number of patients included in the analysis; *N'*, total number of GINA 2–5 patients; *PDC,* proportion of days covered; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *UK*, United Kingdom; *US*, United States.

Figure 5. Association between SABA prescriptions at baseline and severe exacerbations during follow-up in patients from the UK 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 ≥100% implies that the patients had more than full coverage for ICS-containing medications.

CI, confidence interval; *COPD*, chronic obstructive pulmonary disease; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *PDC*, proportion of days covered; *SABA*, short-acting β_2-agonist; *UK*, United Kingdom.

Table I. Patient characteristics

	SABINA I	SABINA II					SABINA +			
	UK	**Canada (Alberta)**	**Canada (Nova Scotia)**	**France**	**Spain**	**The Netherlands**	**Poland**	**US Commercially Insured**	**US Medicaid**	**US Medicare**
Total patients, n	187,675	71,629	5,009	673	39,555	9,474	46,628	483,874	151,439	37,608
Age (years), 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)	n/a	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)	n/a	4,506 (11.4)	1,291 (13.6)	5,705 (12.2)	77,968 (16.1)	21,324 (14.1)	5,482 (14.6)

	SABINA I	SABINA II					SABINA +			
	UK	**Canada (Alberta)**	**Canada (Nova Scotia)**	**France**	**Spain**	**The Netherlands**	**Poland**	**US Commercially Insured**	**US Medicaid**	**US Medicare**
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)	n/a	15,884 (40.2)	2,877 (30.4)	n/a	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)	n/a	10,104 (25.5)	3,449 (36.4)	n/a	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)	n/a	3,031 (7.7)	188 (2.0)	n/a			
SABA prescription/possession (canisters/year), 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)	n/a	3.3 (3.6)	2.3 (1.9)	3.5 (5.2)	2.77 (2.92)	3.72 (3.72)	3.05 (3.18)

	SABINA I	SABINA II					SABINA +			
	UK	**Canada (Alberta)**	**Canada (Nova Scotia)**	**France**	**Spain**	**The Netherlands**	**Poland**	**US Commercially Insured**	**US Medicaid**	**US Medicare**
Prior-year exacerbation history (year prior to the study), n (%)										
0	143,063 (76.2)	60,458 (84.4)	3,747 (74.8)	n/a	18,433 (46.6)	n/a	n/a	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)	n/a	n/a	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)	n/a	0.8 (1.0)	n/a	n/a	0.8 (1.3)	0.8 (1.3)	1.0 (1.6)

*Data presented for ≤2 SABA canisters/year.

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

GINA, Global Initiative for Asthma; *n/a*, not available; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *SD*, standard deviation; *UK*, United Kingdom; *US*, United States.

ONLINE REPOSITORY

Table E1. Additional details about the countries included in the analyses

SABINA I	UK	**Study design:** The SABINA UK study was a retrospective, longitudinal, open-cohort study that used primary care electronic healthcare records from patients with asthma aged ≥12 years. Linked hospital admission data were obtained from the Hospital Episode Statistics database. Baseline year was 12 months 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 year after the GP practice began recording research quality data (CPRD quality control), or 1 year after their continuous CPRD practice registration date. The incidence rate of severe exacerbations was calculated during the total study follow-up of 1 year. 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 years 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 pre-established 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).
	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 ≥12 years who attended ≥2 healthcare consultations during 2017 and had a 1-year 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, USA).
	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 healthcare 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 start (January 1, 2016) and 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 start and 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, TX, USA).
SABINA +	Poland	**Study design:** As 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 months) 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 18–35 years, which revealed the same results as for the entire analyzed population. Since 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).
	US	**Study design:** This was a retrospective, observational cohort study. Data source included deidentified claims data from the US contained in the IBM MarketScan Commercial, Medicare Supplemental, and Multistate Medicaid Research databases. Since 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. 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-month post-index period. At GINA 2, approximately 70% of patients in the US were on leukotriene modifiers. Additionally, 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 year 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), while statistical analyses were conducted with the R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

Where applicable, studies were approved by each country's IRB or ethics committee.

ATC, anatomical therapeutic chemical; *CCI*, Charlson Comorbidity Index; *COPD*, chronic obstructive pulmonary disease; *CPRD*, Clinical Practice Research Datalink; *GINA*, Global Initiative for Asthma; *GP*, general practitioner; *ICD*, International Classification of Diseases; *ICPC*, International Classification of

Primary Care; *ICS*, inhaled corticosteroid; *IRB*, institutional review board; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *NHS*, National Health Service; *OCS*, oral corticosteroid; *PDC*, proportion of days covered; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *UK*, United Kingdom; *US*, United States.

Table E2. Outcome: mean (SD) severe exacerbations and IRR values during the year of analysis

		SABINA I	SABINA II			SABINA +			
		UK	**Canada (Alberta)**	**Canada (Nova Scotia)**	**The Netherlands**	**Poland**	**US Commercially Insured**	**US Medicaid**	**US Medicare**
GINA steps 1–5	1–2 SABA canisters/year	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/year	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/year	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/year	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)

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

CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *SD*, standard deviation; *UK*, United Kingdom; *US*, United States.

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

	≥3 vs. 1–2 SABA canisters/year
Across all GINA treatment steps	
Number of patients	673
Number of events	341
Person follow-up years	n/a
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	n/a
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	n/a
OR (95% CI)	1.82 (1.08–3.06)
P value	.0244

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.

CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; *n/a*, not available; *OR*, odds ratio; *SABA*, short-acting β_2-agonist.

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

Exacerbations	**<3 SABA canisters/year**	**≥3 SABA canisters/year**	**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)

SABA, short-acting β_2-agonist; *SD*, standard deviation.

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

Variables in the final model	Coefficients		*P* value	95% CI	
	Regression coefficient	Standard error		Lower limit	Upper limit
Constant	0.118	0.008	<.001	0.102	0.135
SABA overuse (≥3 canisters/year)	**1.523**	0.010	<.001	**1.504**	**1.543**
Charlson Comorbidity Index	0.072	0.003	<.001	0.067	0.078
Previous severe exacerbations (number)	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).

CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; *SABA*, short-acting β_2-agonist.

Table E6. Association between SABA prescription/possession (≥3 vs. 1–2 canisters/year) and severe asthma exacerbations/year in (A) GINA 1–5-treated patients, (B) GINA 3–5-treated patients, (C) GINA 1–2-treated patients, and (D) GINA 2–5-treated patients prescribed/possessing maintenance therapy ≥50% of the time

Dataset	IRR (CI)	*P*-value
(A) GINA 1–5-treated patients		
UK	1.41 (1.38–1.45)	<0.001
Canada (Alberta)	1.32 (1.27–1.38)	<0.001
Canada (Nova Scotia)	1.38 (1.21–1.58)	<0.001
Netherlands	1.40 (1.23–1.58)	<0.001
Poland	2.15 (2.01–2.30)	<0.001
US Overall	1.03 (1.02–1.04)	<0.001
US Commercial	1.02 (1.01–1.03)	<0.001
US Medicaid	1.09 (1.07–1.10)	<0.001
US Medicare	0.89 (0.86–0.91)	<0.001
(B) GINA 3–5-treated patients		
UK	1.42 (1.38–1.46)	<0.001
Canada (Alberta)	1.29 (1.23–1.36)	<0.001
Canada (Nova Scotia)	1.40 (1.17–1.66)	<0.001
Netherlands	1.42 (1.24–1.63)	<0.001
Poland	2.11 (1.96–2.27)	<0.001
US Commercial	1.24 (1.23–1.26)	<0.001
US Medicaid	1.48 (1.43–1.53)	<0.001
US Medicare	1.08 (1.04–1.13)	<0.001
(C) GINA 1–2-treated patients		
UK	1.38 (1.31–1.45)	<0.001
Canada (Alberta)	1.36 (1.26–1.48)	<0.001
Canada (Nova Scotia)	1.35 (1.10–1.67)	0.005
Netherlands	1.25 (0.91–1.71)	0.163
Poland	2.41 (2.09–2.79)	<0.001
US Commercial	0.92 (0.91–0.93)	<0.001

US Medicaid	1.02 (1.01–1.04)	0.007
US Medicare	0.74 (0.71–0.76)	<0.001
(D) GINA 2–5-treated patients prescribed/possessing maintenance therapy ≥50% of the time		
UK	1.30 (1.25–1.36)	<0.001
Canada (Alberta)	1.25 (1.15–1.37)	<0.001
Canada (Nova Scotia)	1.29 (0.98–1.70)	0.073
Netherlands	1.43 (1.22–1.68)	<0.001
Poland	2.11 (1.93–2.31)	<0.001
US Commercial	1.14 (1.12–1.17)	<0.001
US Medicaid	1.30 (1.23–1.37)	<0.001
US Medicare	1.02 (0.97–1.07)	0.435

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, while comorbidities were not included as a covariate in Poland. Patients aged ≥65 years and those likely to have COPD were excluded from the Polish dataset. Multiple comparisons were adjusted by using conservative Bonferroni correction, with P ≤0.0125 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.

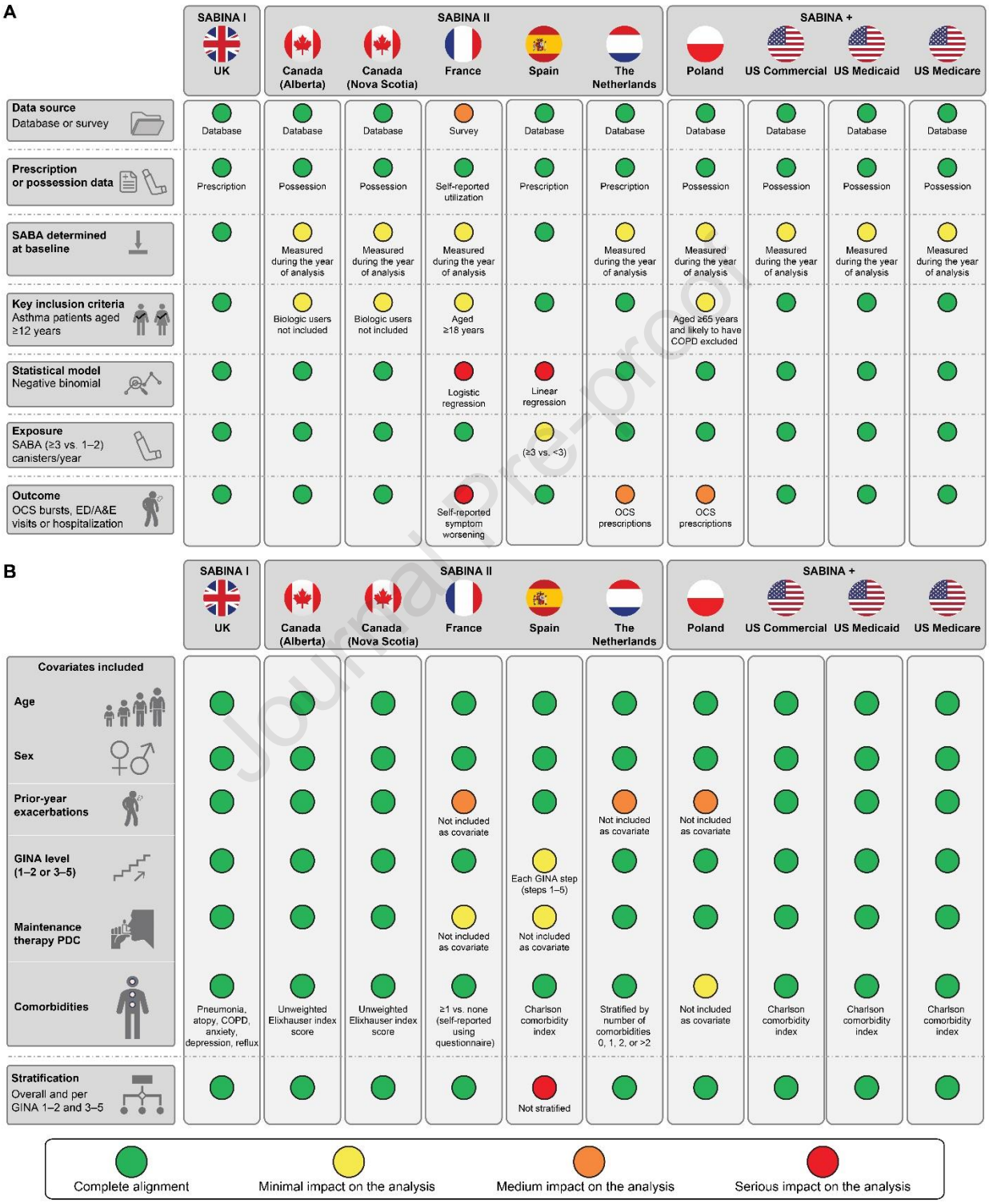
CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; *PDC,* proportion of days covered; *SABA*, short-acting β_2-agonist; *UK*, United Kingdom; *US*, United States.

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

SABA canisters	Severe exacerbations (year 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%

CI, confidence interval; *ICS,* inhaled corticosteroid; *PDC*, proportion of days covered; *SABA*, short-acting β_2-agonist; *SE*, standard error.

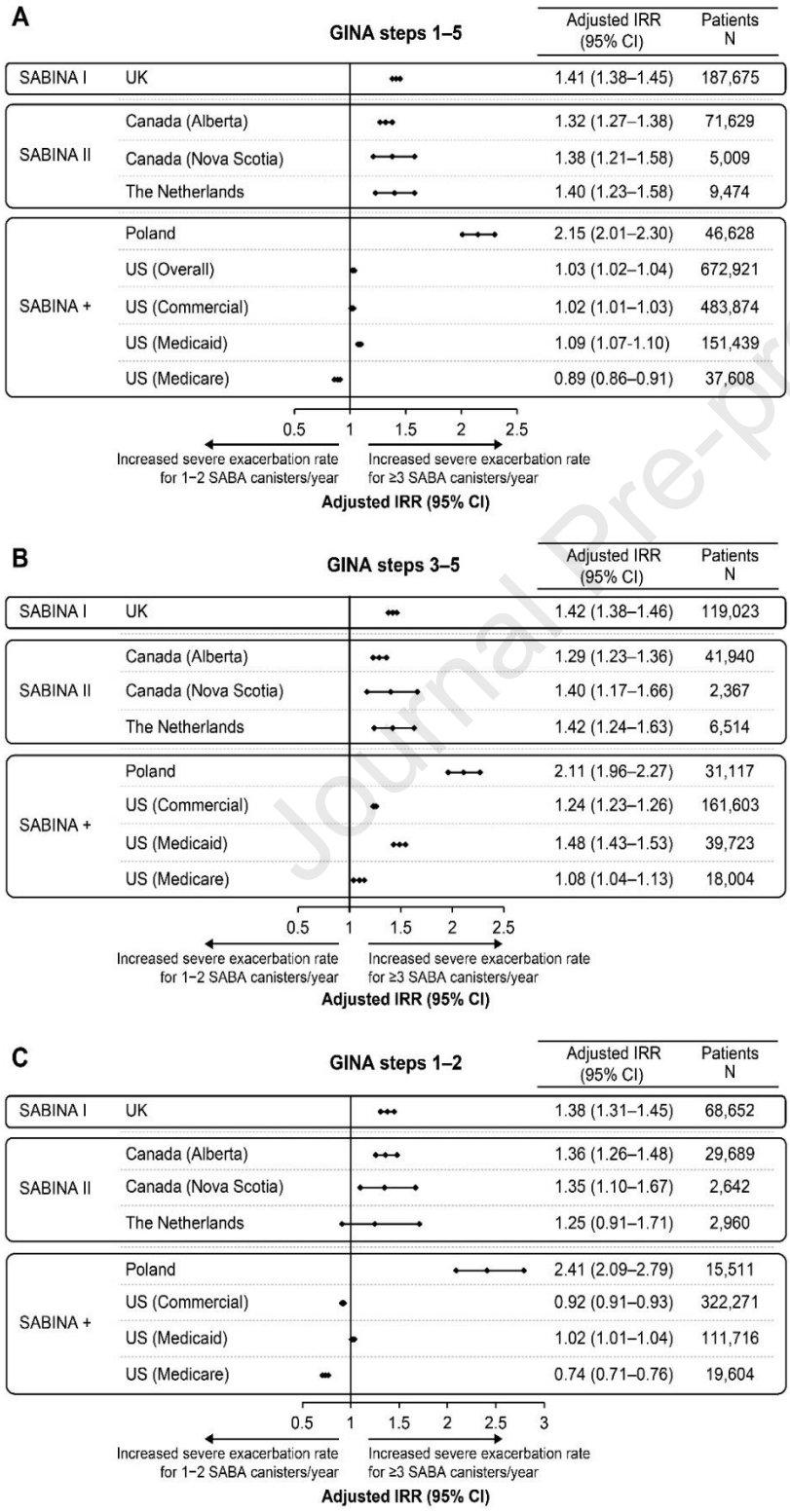
Figure 1. Methodological variations across countries related to (A) study design and (B) covariates included in the analyses



Patients aged ≥12 years with current asthma according to diagnostic code and prescription/possession of ≥1 SABA canister/year were included. Data on medication prescription/possession were obtained from SABINA I (UK), 4 SABINA II countries (Canada, France, Spain, and the Netherlands), and 2 SABINA+ countries (Poland and the US) (Please see Figure E1 in the Online Repository for further details related to the key pillars of the SABINA program). France and Spain were excluded from the main analyses due 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 US, 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; *GINA*, Global Initiative for Asthma; *OCS*, oral corticosteroid; *PDC*, proportion of days covered; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *UK*, United Kingdom; *US*, United States.

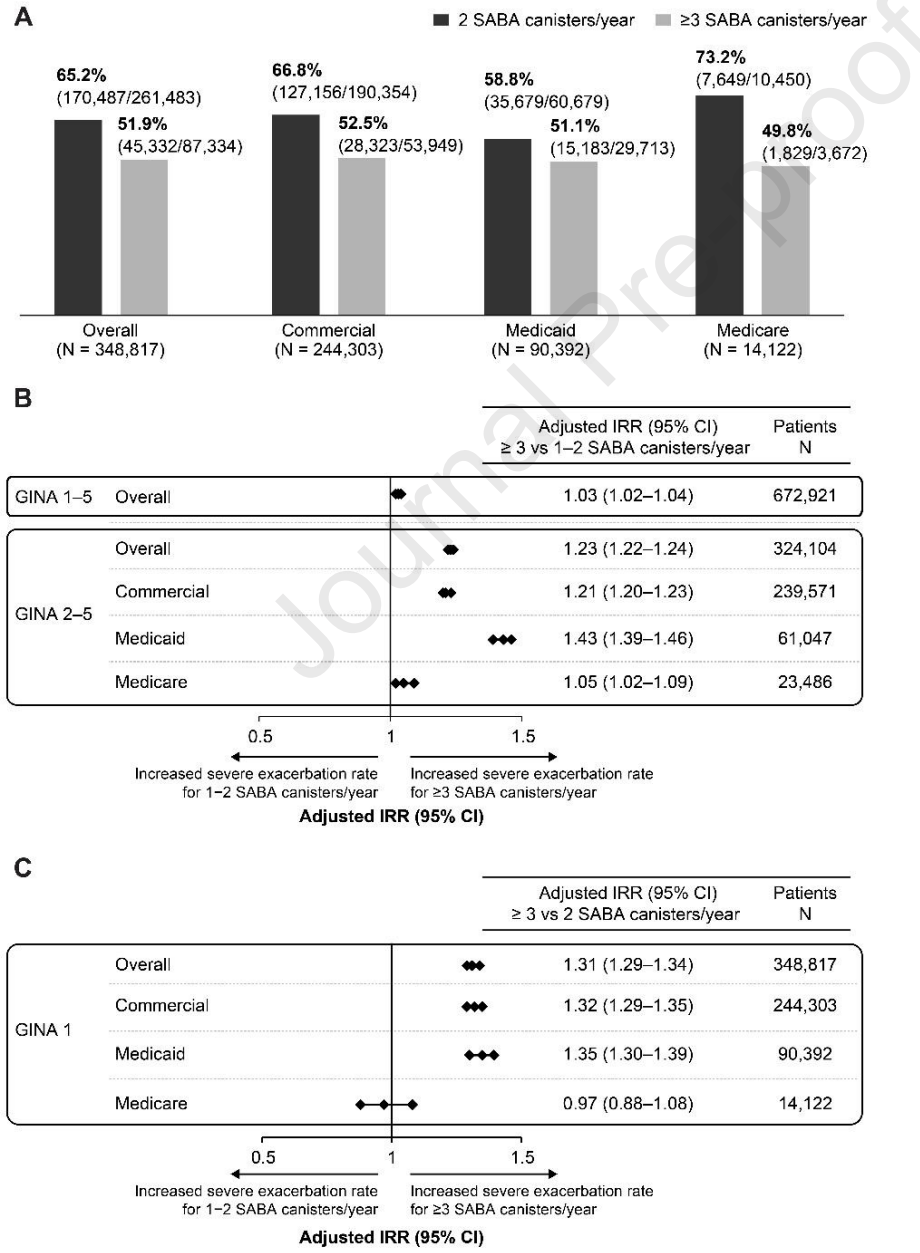
Figure 2. Association between SABA prescription/possession (≥3 vs. 1–2 canisters/year) and severe asthma exacerbations/year in patients treated with (A) GINA 1–5, (B) GINA 3–5, and (C) GINA 1–2



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, while comorbidities were not included as a covariate in Poland. Patients aged ≥65 years and those likely to have COPD were excluded from the Polish dataset.

CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; *PDC,* proportion of days covered; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *UK*, United Kingdom; *US*, United States.

Figure 3. Associations of SABA possession with severe exacerbations during the year of analysis in US 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

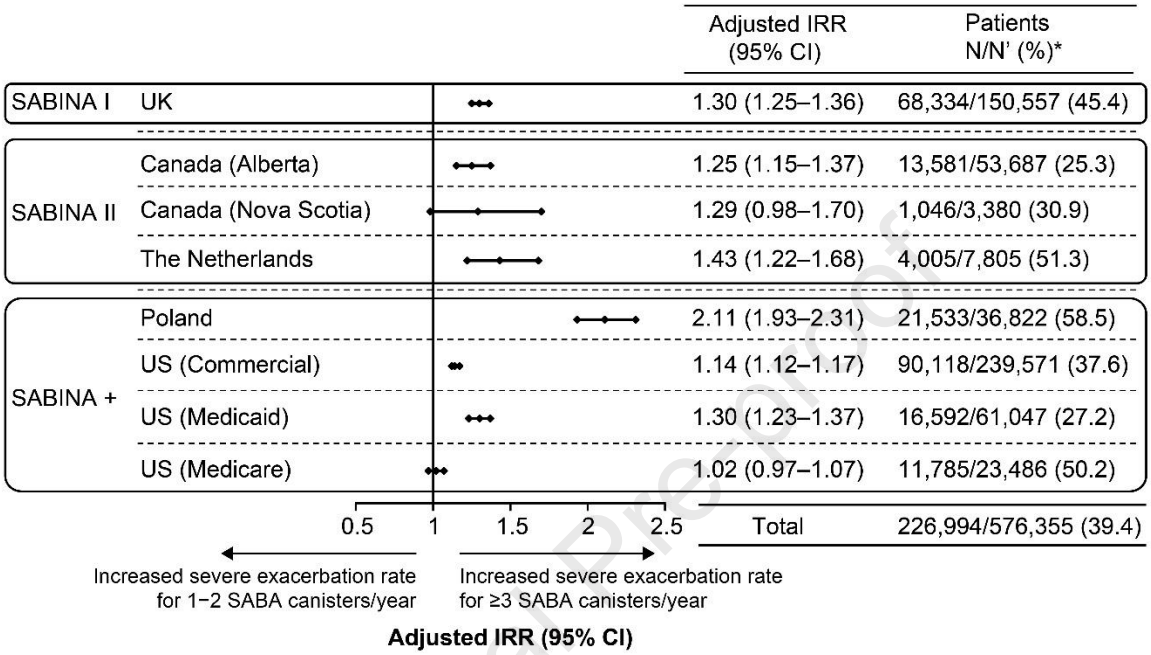


*US GINA 1-treated patients were required to have ≥2 SABA fills/year according to local expert recommendation.

†Severe exacerbations requiring a face-to-face contact with HCP associated with unscheduled ambulatory clinic, urgent care, and emergency department visits or hospitalizations. 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.

CI, confidence interval; *GINA*, Global Initiative for Asthma; *HCP*, healthcare provider; *IRR*, incidence rate ratio; *PDC,* proportion of days covered; *SABA*, short-acting β_2-agonist; *US*, United States.

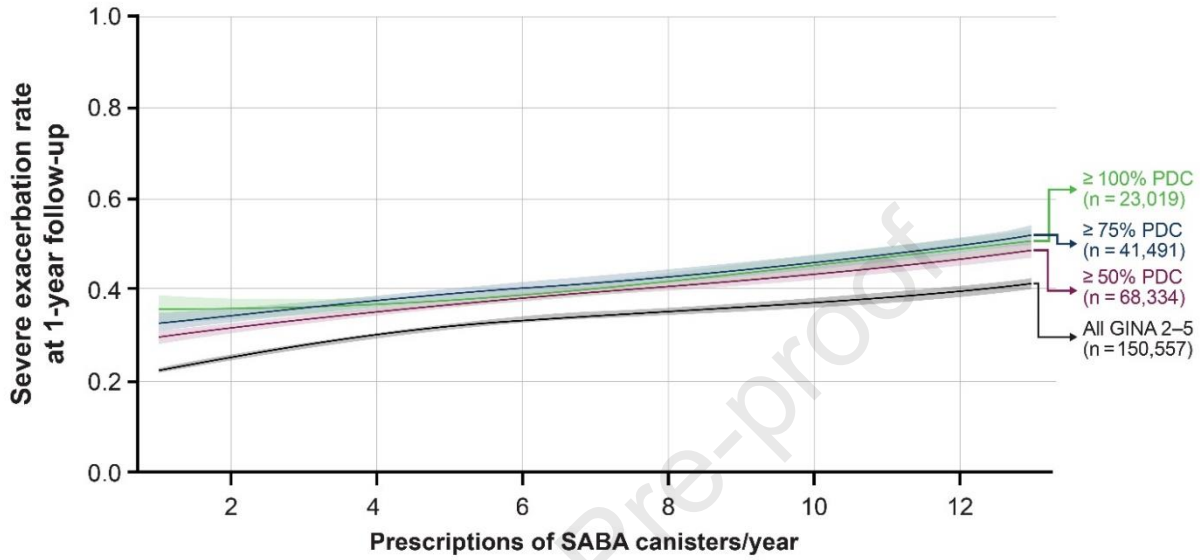
Figure 4. Association between SABA (≥3 vs. 1–2 canisters/year) and severe asthma exacerbations/year in GINA 2–5-treated patients prescribed/possessing maintenance therapy ≥50% of the time



*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. Prior exacerbations were not included as a covariate in Poland and The Netherlands, while comorbidities were not included as a covariate in Poland. Patients aged ≥65 years and those likely to have COPD were excluded from the Polish dataset.

CI, confidence interval; *GINA*, Global Initiative for Asthma; *IRR*, incidence rate ratio; N, number of patients included in the analysis; *N'*, total number of GINA 2–5 patients; *SABA*, short-acting β_2-agonist; *PDC,* proportion of days covered; *SABINA*, SABa use IN Asthma; *UK*, United Kingdom; *US*, United States.

Figure 5. Association between SABA prescriptions at baseline and severe exacerbations during follow-up in patients from the UK 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 ≥ 100% implies that the patients had more than full coverage for ICS-containing medications.

CI, confidence interval; *COPD*, chronic obstructive pulmonary disease; *GINA*, Global Initiative for Asthma; *ICS*, *inhaled corticosteroid; PDC, proportion of days covered; SABA*, short-acting β_2-agonist; *UK*, United Kingdom.

Figure E1.

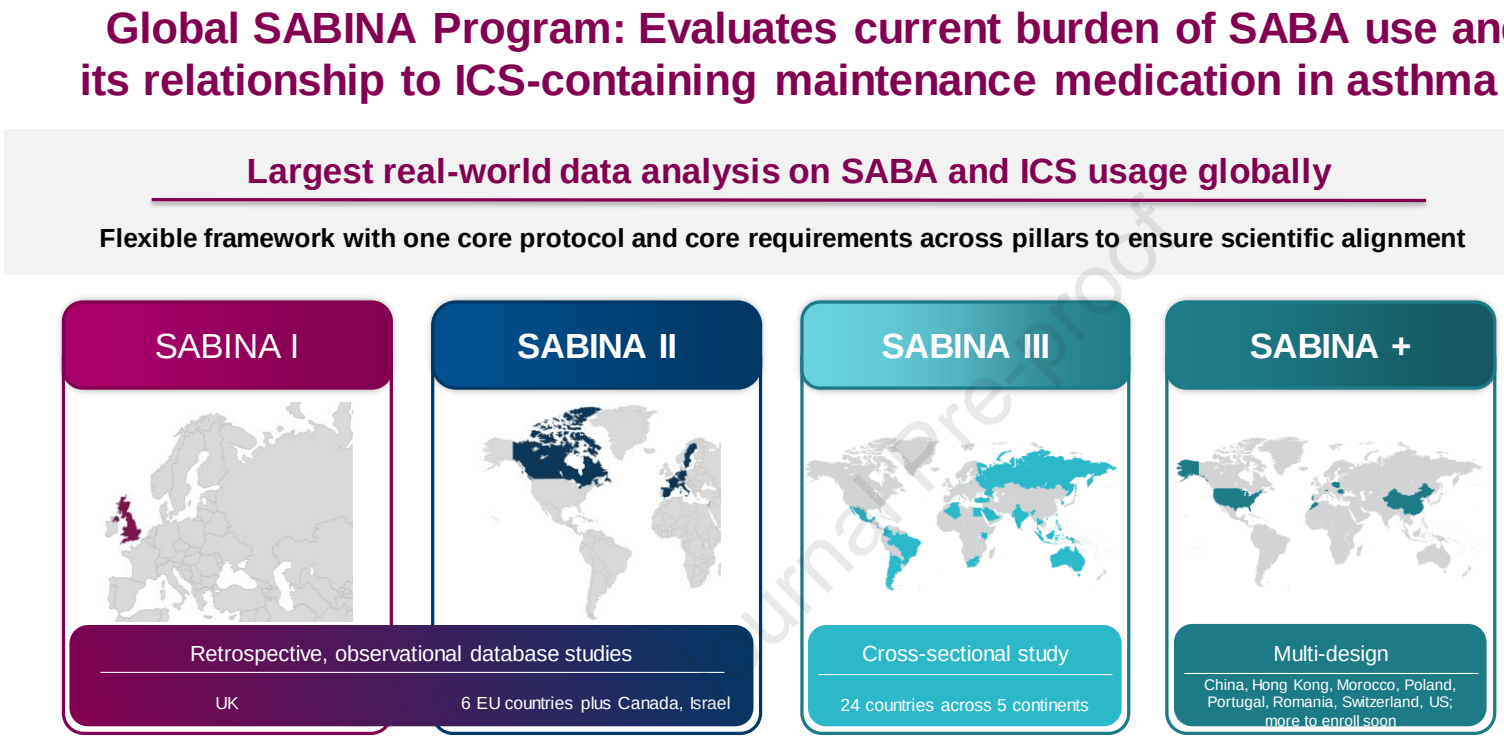
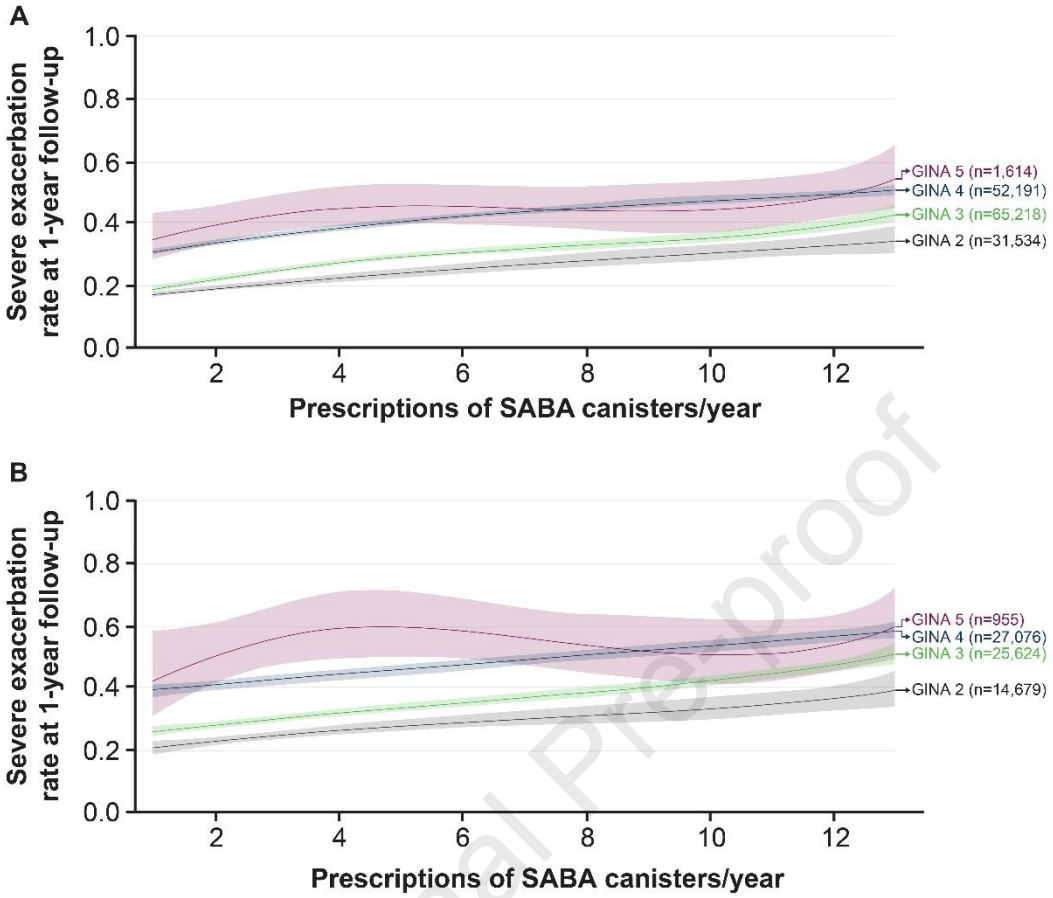

Global SABINA Program: Evaluates current burden of SABA use and its relationship to ICS-containing maintenance medication in asthma
Largest real-world data analysis on SABA and ICS usage globally
Flexible framework with one core protocol and core requirements across pillars to ensure scientific alignment
SABINA I
SABINA II
SABINA III
SABINA +
Retrospective, observational database studies
UK
6 EU countries plus Canada, Israel
Cross-sectional study
24 countries across 5 continents
Multi-design
China, Hong Kong, Morocco, Poland, Portugal, Romania, Switzerland, US; more to enroll soon

Figure E2.



ONLINE REPOSITORY FIGURE LEGENDS

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.

EU, European Union; *ICS*, inhaled corticosteroid; *SABA*, short-acting β_2-agonist; *SABINA*, SABa use IN Asthma; *UK*, United Kingdom; *US*, United States.

Figure E2. Association between use of SABA at baseline (prior year) and severe exacerbations during follow-up in patients from the UK (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; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *PDC*, proportion of days covered; *SABA*, short-acting β_2-agonist; UK, United Kingdom.