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Early View

Original research article

SABA use as an indicator for asthma exacerbation risk: an observational cohort study (SABINA Canada)

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SABA use as an indicator for asthma exacerbation risk: an observational cohort study (SABINA Canada).

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Abstract

Background: Patients with asthma use SABA to relieve symptoms but SABA alone does not treat underlying inflammation. Thus, overreliance on SABA may result in poor asthma control and negative health outcomes.

Objective: To describe use of SABA and characterize the relationship to severe exacerbations in the Canadian provinces of Nova Scotia (NS) and Alberta (AB).

Methods: In this longitudinal Canadian SABINA (SABA In Asthma) study, patients with an asthma diagnosis were identified between 2016-2020 within two provincial administrative datasets (Health Data Nova Scotia and Alberta Health Services). All patients were followed for ≥24 months, with the first 12 months used to measure baseline asthma severity. Medication use and the relationship of SABA overuse (≥3 canisters/year) with severe asthma exacerbations were characterized descriptively and via regression analysis.

Results: A total of 115,478 patients were identified (NS n=8,034; AB n=107,444). SABA overuse was substantial across both provinces (NS: 39.4%; AB: 28.0%) and across all baseline disease severity categories. Patients in NS with SABA overuse had a mean (SD) annual rate of 0.46(1.11) exacerbations, compared to 0.30(1.36) for those with <3 canisters of SABA. AB had a mean (SD) rate of 0.31(0.86), and 0.17(0.62), respectively. Adjusted risk of severe exacerbation was associated with SABA overuse (NS IRR=1.36 [95% CI 1.18-1.56]; AB IRR=1.32 [95% CI 1.27-1.38]).

Conclusion: This study supports recent updates to CTS and GINA guidelines for asthma care. SABA overuse is associated with increased risk of severe exacerbations and can be used to identify patients at a higher risk for severe exacerbations.

Introduction

Asthma is a chronic disease affecting nearly ten percent of Canadians and nearly 65,000 asthma exacerbations occur each year.[1-4] It is estimated that over 50% of patients with asthma continue to experience exacerbations and regular symptoms throughout their daily life.[5,6] During periods of poor control, rescue inhalers containing short-acting beta agonists (SABA) are commonly used to relieve acute symptoms despite leaving the underlying airway inflammation untreated. However, the overuse of SABA (3+ canisters a year) is associated with asthma-related hospital admissions, emergency department (ED) visits, and overall increase in healthcare costs.[7-20] Previous studies have found that excessive use (12+ annual canisters) is even associated with an increased risk of death.[19,21-23]

In 2017, O'Byrne, *et al* highlighted paradoxes of asthma management.[23] At the time, SABA alone was recommended for patients categorized as Global Initiative for Asthma (GINA) Step One even though asthma is a chronic airway inflammatory disease. O'Byrne noted that when patients progress to GINA Step Two, they initiate regular ICS therapy and are asked to minimize the as-needed SABA upon which they previously relied. This change requires a mindset shift, where pharmacotherapy is no longer autonomous, symptom-based, and associated with fast-acting relief. Instead, patients are expected to adhere to daily or twice daily doses of ICS-based maintenance therapy regardless of their symptoms. However, this means patients do not experience the rapid symptom relief associated with their previous treatment regimen. As a result, they may undervalue adherence to maintenance therapy and simply increase SABA use when symptoms arise. While there have been some targeted studies of the use of SABA in Canada[24], little has been done to quantify the scale of overuse and the impact on patient outcomes.

The SABA in Asthma (SABINA) study is a global programme to evaluate utilization and clinical outcomes related to SABA use in asthma; this study is the Canadian contribution to that programme.[15,25] The objectives of this paper were to describe the use of SABA and characterize the relationship to severe exacerbations in the two Canadian provinces of Nova Scotia (NS) and Alberta (AB).

Materials and Methods

Study design and data sources

This study is a retrolective cohort study[26] using administrative claims datasets from Health Data Nova Scotia (HDNS)[27] and Alberta Health Services (AHS)[28]. These are provincial health data repositories for nearly one million individuals in Nova Scotia (NS) and over four million individuals in Alberta (AB). Both datasets include demographics (e.g. sex, date of birth), and administrative claims information on publicly reimbursed health resource use (e.g. medication dispensation, physician visits) and outcomes (e.g., hospital admissions and mortality). Data from both provinces were analyzed and reported separately to account for variability in content and coding as well as recognition of data security and privacy requirements from both health systems.{Doyle, 2020 #125}

Study period definitions

This study used the most recent available data at the time of extraction: from October 2016 to March 2019 for NS, and April 2016 to March 2020 for AB. Three time periods were defined within the study: the *baseline period* was used to assess case definition, and to characterize baseline comorbidity, asthma disease severity, the frequency of asthma-related prescription claims (see Appendix Table 2), physician visits, and exacerbations in the 12 months following the diagnosis meeting the case definition. The *index date* occurred at the end of the baseline period, or 365 days after the first date on which the patient had an eligible diagnosis and was used to summarize the age and sex of the patient (Appendix Figure 1). The remainder of the follow-up was the *study period* and was used to measure study exposures and outcomes. The study period began at index and ended at the time of censoring, the first occurrence of patients moving out of province, death, or by the end of the study March 2019 in NS (March 2020 in AB).

Eligibility criteria

Data were linked at the individual level to identify a patient cohort for analysis. Patients who were diagnosed with asthma and had at least two consecutive years of follow-up data

were eligible for inclusion.[29,30] We used a validated case definition for asthma within Canadian administrative datasets (≥2 physician visits in a two-year period or ≥1 hospital admission with a diagnosis of asthma [ICD-9-CM 493 or ICD-10-CA J45]).[31] Patients were included in the study population if they were ≥12 years-old, with active records (or known reason for inactivity, e.g. death) throughout the study period. Patients were excluded if they were ≥35 years with a diagnosis of chronic obstructive pulmonary disease (COPD), if they had less than 12 months of data available prior to the index date, if they did not have active asthma (no records of asthma diagnosis or treatment following the index date), or if they had severe asthma and were using biologic therapies for disease management (see Supplementary Appendix Table 1).

Baseline asthma severity definitions

Asthma severity in the baseline period was determined using average daily dose for ICS (low, medium, high dose) as per the Canadian Thoracic Society (CTS) guidelines.[32] Baseline asthma severity was also categorized into GINA Steps 1-5 per the 2018 GINA recommendations[33] (see Supplementary Appendix). Under the CTS definition, patients meeting the case definition but not using any ICS or SABA in the baseline period were included but presented as a distinct subgroup ("mild, no prescription") throughout the analysis.

Study variables

The exposures of interest included use (i.e. prescriptions dispensed) of ICS[i] and SABA (see Supplementary Appendix Table 2 for included drug identification numbers). SABA dispensations were standardized to a 150-dose canister (for consistency with the global SABINA program[19,25]) and annualized over the study period. SABA overuse was defined as three or more canisters per year,[17] and twelve or more canisters used per year was considered as excessive use.[34]. An exploratory analysis using the average number of

[i] ICS in this study refers to all ICS-containing products, i.e. including both ICS monotherapy as well as ICS/LABA combination therapy.

SABA doses per week was also calculated, defining three or more doses of SABA as 'beyond the suggested use', and 10 or more doses as overuse, as per the CTS guidelines.[34] This alternative quantification permits broader interpretation of the study result in Canadian practice. All dosage calculation assumed all dispensed medication was completely utilized over the study period.[25] Details of how dispensed prescription medication was used to estimate annual use and weekly use are described in the Supplementary Appendix.

Outcomes of interest included severe asthma exacerbations and all-cause mortality. Severe exacerbations were defined by dispensation of short-course (≤10 days) oral corticosteroids (OCS),{Reddel, 2006 #123} or by hospital admission or emergency department (ED) visit with a primary complaint of asthma (see Supplementary Appendix Table 3).

Ethics approval

This study received ethical approval from the health sciences research ethics boards (REB) at Dalhousie University (REB2019-4959 / November 29, 2019) and the Health Research Ethics board of Alberta (HREBA; REB20-0010 / March 5, 2020) for secondary use of information for research. All individual identifiable information was anonymized prior to data analysis and small number subgroups were not reported to prevent identification.

Statistical analysis

Patient demographics and baseline characteristics including age, sex, comorbidity burden summarized using the Elixhauser comorbidity score,[35] and health seeking events were presented descriptively. Post-index medication use and exacerbations were also descriptively summarized for the overall cohort and stratified by baseline disease severity and SABA use over the study period. The association between SABA overuse and the number of severe exacerbations was further evaluated by means of a negative binomial regression adjusting for demographic and clinical characteristics. This analysis was limited to the first year of the study period to standardize follow-up available across the two

patient populations. The unadjusted and adjusted association between SABA overuse and rate of severe exacerbations was reported using incidence rate ratio (IRR) and 95% confidence intervals (CI), overall and stratified by GINA step. Subgroup analysis among patients using ≥6 canisters of ICS (that is, adherent to 50% or more days of maintenance annually) was also performed to stratify patients by maintenance therapy compliance.[ii] All analyses were limited to available data and no missing data were imputed. All results were reported separately by provincial data source.

Results

A total of 115,478 patients were included in the study (NS=8,034; AB=107,444) (Appendix Figure 2). At index, the mean (SD) age (NS: 43.4 (18.3), AB: 39.7 (17.1)) and Elixhauser comorbidity score (NS: 2.01 (1.27), AB: 1.21 (1.07)) among patients from NS were slightly higher than patients from AB (Table 1). Commonly observed comorbid diagnoses included anxiety (NS: 16.2%, AB: 27.6%), diabetes (NS: 7.5%, AB: 1.8%), gastroesophageal reflux (NS: 4.2%, AB: 0.9%), pneumonia (NS: 4.4%, AB: 4.5%), and bone fractures (NS: 2.4%, AB: 6.6%;Appendix Table 4).

Medication Use

In the baseline period, >80% of both cohorts received no or low-dose ICS, meeting the case definition of mild asthma. Approximately 11% (NS) and 27% (AB) of patients had no asthma-related prescription use in the baseline period. In both cohorts, patients filled a mean (SD) of 5 (5) asthma medication prescriptions and had two outpatient visits in the baseline period (SD of1.3 and 2.8 for NS and AB, respectively) (Table 1).

During the study period, most patients in both provinces received ICS-based maintenance therapy combined with a SABA rescue inhaler (Figure 1). In patients who did not fill any prescription during the baseline year, the majority of patients in NS (n=542, 61.6%) also

ii Note here that number of canisters were used as a measure of compliance rather than proportion of days covered, as a more reliable measure for compliance in Canadian claims data.{Blais, 2014 #120}

did not receive ICS-containing or SABA medications during the entire study period. Conversely, most patients in AB within this group were dispensed either ICS-containing or SABA medication during the study period (55.8% with SABA monotherapy, 2.5% with ICS-containing therapy, and 28.3% with ICS-containing and SABA). Further trends in use of ICS and SABA during the study period are available in Table 2 and Appendix Table 5, stratified by baseline disease severity defined using CTS and GINA, respectively.

Throughout the study period, between 28% and 39% of patients met the definition of SABA overuse (NS=3,167, 39.4% and AB=30,032, 28.0%) across all baseline disease severity categories. In both provinces, the percentage of patients overusing SABA was associated with baseline severity of disease. Excessive use of SABA was also higher in NS (961, 12.0%) than AB (3,624, 3.4%) and this excessive use of SABA also increased with baseline severity of disease (Table 2). In exploratory analyses using doses as the unit of measure, approximately 50-60% of patients in both provinces used an average of at least three doses of SABA per week for the study period, indicating use beyond the suggested amount, and the proportion of patients using at least 10 doses per week was comparable to that observed for the overuse definition of ≥3 canisters per year (Figure 2).

Exacerbations:

Between 10% and 25% of patients experienced a severe exacerbation during the baseline period (NS=24.5%, AB=11.6%) (Table 1). During the study period, few patients had any severe exacerbation (NS=9.5%, AB=7.9%; Table 3). Annual rates of severe exacerbations increased with SABA use (Figure 3) and baseline asthma severity (Figure 4), with estimates being consistently higher in the NS cohort (Table 3). Mean (SD) estimates of annual exacerbations in NS increased from to 0.30 (1.36) among patients with appropriate use, to 0.46 (1.11) among those with SABA overuse and 0.60 (1.31) among those with excessive use of SABA. In AB, annual estimates increased from 0.17 (0.62) to 0.31 (0.86) and 0.49 (1.19) respectively. When stratifying by baseline disease severity, in NS, estimates increased from 0.27 (1.09) among those with mild asthma (no prescriptions) to 0.81 (2.23) among those with severe asthma, and respectively in AB, estimates increased from 0.17 (0.66) to 0.34 (0.91). A similar trend was noted when baseline disease severity was classified using GINA steps. Patients defined as GINA Step 5 demonstrated annual

rate of exacerbation 6 to 9 times greater than found in patients of GINA Step 1 (Appendix Table 6).

Risk of severe exacerbation in the first year of the study period was higher in patients who overused SABA when adjusted for age, sex, and baseline comorbidities (NS IRR= 1.36, 95% CI 1.18 to 1.56; AB IRR=1.32 95% CI 1.27 to 1.38; Figure 5). The effect estimates were consistent between provinces (albeit not significant in NS) among patients with high utilization of ICS-containing medication (6+ canisters) and when stratified by disease severities (GINA steps). These effect estimates also remained within bounds of the main analysis, albeit with larger confidence intervals associated with smaller sample size.

Discussion

More than 25% of patients with mild asthma were observed to have SABA overuse in the Canadian provinces of Nova Scotia and Alberta. SABA overuse was associated with an increased rate of severe exacerbations and this association remained when stratified by ICS use (≥6 canisters ICS/year). The results of the present study are consistent with prior Canadian studies characterizing SABA use nearly two decades ago[7] and those describing an association with higher risk of mortality and other poor health outcomes.[21, 30{To, 2022 #118}] Of these studies, Fitzgerald et al. identified individuals who used ≥2 doses of SABA per week in the absence of any ICS or used >9 canisters of SABA during the year and no more than 100 µg/day of ICS. They found that inappropriate SABA use was associated with a 45% increased risk of hospital admissions and a 25% increased risk of ED visits in the 3 month period following that inappropriate use.[7] In addition, a recent Canadian study including prevalent asthma patients ≥65 years of age found 14% of patients to have overused SABA (≥3 canisters/year), and an associated increased risk of severe asthma exacerbations, ranging from 59%-126% among those using 3-5 canisters and ≥6 canisters per year.{To, 2022 #118} Thus, while definitions of SABA overuse vary in specificity,[36] the association between overuse of SABA and poor health outcomes was consistent with the results found in our study.

Internationally, SABA overuse varied from 10% to approximately 40% depending on study design.{Vähätalo, 2022 #124}[16,17] Results from the SABINA participating countries of similar health systems using claims data were comparable to those found in this study.[16,17] In these countries, the rate of SABA overuse in a real-world setting ranged from 32% (Italy) to 38% (UK), and associated with a corresponding increased risk of exacerbations of 27% (Italy) and 41% (UK).{Di Marco, 2021 #94}{Quint, 2022 #128} While differences in access, policies, healthcare, and/or environment may contribute to differences in outcomes, this study observed a rate of SABA overuse ranging from 28% (AB) to 39% (NS) and an estimated adjusted increased risk of severe exacerbations ranging from 32% (AB) to 36% (NS). As such this study contributes to the body of evidence and supports a common finding of increased risk of exacerbation associated with SABA overuse.[36]

The availability of comprehensive population-based data is a key strength of this study, adding to the generalizability of our results across Canada. In addition, asthma-related prescriptions are comprehensively captured in these data, as SABA can only be dispensed via prescription in Canada. Nonetheless, the use of administrative claims data in this context is also associated with several limitations. Prescription dispensation does not confirm actual use (and the timing of use) of study medications; for example, patients may acquire new inhalers prior to fully utilizing prior inhalers. As a result, while associations between SABA overuse and exacerbation outcomes were estimated in this study, causal inference of this relationship is not possible. In addition, claims data do not present additional clinical detail such as a measure of asthma control. As a result, medication and health resource use were used to characterize outcomes and baseline disease severity. Similarly, the dispensation of OCS used to define exacerbations would be subject to the same limitations. Therefore, in the absence of symptom or disease scores the disease characteristics of these included patients is largely based on dispensed medication rather than actual use and clinical evaluation.

Implications for practice

Several randomized trials have already detailed a reduced risk of severe exacerbations in patients receiving budesonide/formoterol as needed compared to SABA alone, highlighting

ICS/LABA as an advantageous combination relative to SABA in patients with mild asthma.[37-41] Among the population of very mild and mild asthma patients, it is now recommended by both GINA and CTS guidelines that patients with poorly controlled asthma or well-controlled asthma at a high risk of exacerbation should be started on daily ICS with as needed SABA, or budesonide/formoterol as needed.[34,42] In our study, we found that this guidance would imply an immediate change in treatment strategy for 28% of the AB and 39% of the NS cohort – those patients who were overusing SABA to manage their asthma symptoms and who were at increased risk of severe exacerbation. As a result, these findings support the recent CTS guidelines for mild to moderate asthma:

1. Patients with very mild and mild asthma may still be at risk of severe exacerbations and their disease control should be regularly assessed;
2. SABA use can be used as an indicator of partially controlled or uncontrolled asthma and ≥3 canisters of SABA in a year is considered as overuse;
3. Overuse of SABA is associated with a higher risk of exacerbation.

These findings may also have implications for patients with moderate to severe asthma. For these patients, the CTS stratifies by risk of exacerbation and recommends escalation of ICS dose and/or consideration of biologics therapy where appropriate. SABA use in these patients may provide a simple indicator with which to estimate asthma control. Indeed, the CTS now includes 3 or more doses of SABA per week as indicator of partial/uncontrolled asthma.

Primary care providers and specialists may consider implementing these findings by reviewing with their patients the number of doses of SABA used in a week as a simple and objective way to identify patients who have partially controlled or uncontrolled asthma. This approach has also been highlighted by the Health Quality Ontario (HQO) updated asthma quality standard, recommending assessing SABA use at least annually with a recommended cut-off of 3 or more canisters.[43]

SABA use is a call to action:

- For physicians: SABA use should be regularly reviewed with patients, regardless of disease severity
- For pharmacists: the pharmacy represents a valuable opportunity to identify potential SABA overuse, provide education to patients, and offer feedback to prescribing clinicians.
- For patients: patients should be made aware of the implications of SABA overuse and use this simple metric to help manage their disease and advocate for better care.

Conclusion

More than 25% of patients in this study overused SABA medication during the study period. SABA overuse was associated with increased risk of severe exacerbation outcomes. These findings support the recent updates to the CTS guidelines for asthma care[42], the NHLBI and GINA recommendations,[44] and the HQO asthma quality standard.[43] Weekly or annual estimates of SABA utilization represent a simple metric for loss of disease control to physicians, pharmacists, and patients and should be implemented as a simple call to action for all stakeholders.

Acknowledgments and disclosure

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Conflict of Interest: S.G. Noorduyn, M. Soliman, and M. Talukdar are employees of AstraZeneca Canada Inc. C. Qian and K. Johnston are employees of Broadstreet HEOR, which received funds from AstraZeneca Canada Inc. for this work. B.L. Walker has received advisory board and speaker's honoraria from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, and Sanofi, unrelated to this work. P. Hernandez received funding from AstraZeneca to his institution and company for data acquisition and covered costs to conduct study at local site. He has received grants paid to his institution from Canadian Institute of Health Research, Boehringer Ingelheim; Cyclomedica; Grifols; Vertex, and received speaker honoraria from AstraZeneca; Boehringer Ingelheim; Janssen. He received honoraria and participated in advisory boards from Acceleron; AstraZeneca; Boehringer Ingelheim; GSK; Janssen; Novartis; Sanofi; Takeda; Teva; Valeo. He volunteered at Canadian Thoracic Society as an executive committee and Board member unrelated to this work. E. Penz has received research funds paid to her institution from AstraZeneca and Saskatchewan Cancer Agency, CIHR, SHRF and Respiratory Research Centre paid to her institution unrelated to this work. She has received consulting fees from GlaxoSmithKline, AstraZeneca, and Sanofi Genzyme unrelated to this work. She received honoraria for participation on advisory boards, lecture series, educational events from AstraZeneca, GlaxoSmithKline, Sanofi, Boehringer Ingelheim, and International Centre for Evidence-Based Medicine (ICEBM), unrelated to this work. She is a Co-Chair COPD Assembly of Canadian Thoracic Society, Medical Lead at the Lung Cancer Screening Prevention Program, Saskatchewan Cancer Agency, and a Board Member, Institute for Cancer Research Advisory Board, Canadian Institute for Health Research.

Consent for publication: The publication of study results was not contingent on the sponsor's approval or censorship of the manuscript.

Tables & Figures

Table 1: Patient demographics at baseline among patients with asthma in Nova Scotia and Alberta*

	Primary study cohort	
	Nova Scotia (N=8,034)	**Alberta (N=107,444)**
Follow-up, median (IQR), days	442 (386, 490)	730 (730,730)
Sex, n(%)		
Male	3,171 (39.5)	46,910 (43.7)
Female	4,863 (60.5)	60,534 (56.3)
Age		
Mean (SD)	43.4 (18.3)	39.7 (17.1)
Median (IQR)	43.0 (29.0, 57.0)	38.0 (26.0, 52.0)
Elixhauser comorbidity score, mean (SD)	2.01 (1.27)	1.21 (1.07)
Asthma severity, n(%)		
Mild asthma	6,694 (83.3)	91,189 (84.9)
Mild, no prescription	880 (11.0)	29,353 (27.3)
Mild, excluding those with no prescription	5,814 (72.4)	61,836 (57.6)
Moderate asthma	998 (12.4)	10,412 (9.7)
Severe asthma, no biologic treatment	342 (4.3)	5,843 (5.4)
All outpatient visits		
Mean (SD)	1.9 (1.3)	1.6 (2.8)
Median (IQR)	2.0 (1.0, 2.0)	1.0 (0.0, 2.0)
Asthma-specific prescriptions		
Mean (SD)	5.4 (5.1)	5.0 (4.5)
Median (IQR)	4.0 (2.0, 8.0)	4.0 (2.0, 7.0)
Exacerbations[†], n(%)		
Emergency Department (ED) visits		
0	7,922 (98.6)	102,098 (95.0)
1	100 (1.2)	4,341 (4.0)
2	11 (0.1)	709 (0.7)
3	<5 (0)	176 (0.2)
4+	<5 (0)	62 (0.1)
Hospitalizations (excluding ED visits)		
0	8,033 (100)	106,303 (98.9)
1	<5 (0)	1,071 (1.0)
2	<5 (0)	58 (0.1)
3	<5 (0)	11 (0.0)
4+	<5 (0)	<5 (0)
Prescriptions for OCS		
0	6,171 (76.8)	93,070 (86.6)
1	1,210 (15.1)	10,054 (9.4)
2	375 (4.7)	2,501 (2.3)
3	129 (1.6)	882 (0.8)
4+	149 (1.9)	937 (0.9)
Severe exacerbations[‡]		
0	6,149 (76.5)	95,030 (88.4)
1	1,218 (15.2)	8,855 (8.2)
2	381 (4.7)	2,150 (2.0)
3	137 (1.7)	699 (0.7)
4+	149 (1.9)	710 (0.7)

Cohorts include patients with an asthma diagnosis identified between 2016 and 2020 within two provincial administrative datasets (Health Data Nova Scotia and Alberta Health Services).

*one year following diagnosis

[†]unique visit dates and/or admission dates

[‡]note that if more than one of the above events (hospitalization or ED with primary dx of asthma, or oral corticosteroid) occur within a 2-week window, this will be counted as one exacerbation

Table 2 ICS and SABA use during the study period by baseline disease severity

	Nova Scotia					Alberta				
		Baseline asthma severity					*Baseline asthma severity*			
	Overall (N=8,034)	Mild, no prescription (N=880)	Mild, with prescription (N=5,814)	Moderate (N=998)	Severe (N=342)	Overall (N=107,444)	Mild, no prescription (N=29,353)	Mild, with prescription (N=61,836)	Moderate (N=10,412)	Severe (N=5,843)
ICS dose										
No ICS	3,301 (41.1)	738 (83.9)	2,539 (43.7)	17 (1.7)	7 (2.0)	29,356 (27.3)	20,296 (69.1)	8,820 (14.3)	150 (1.4)	90 (1.5)
Reduced	484 (6.0)	-	-	347 (34.8)	137 (40.1)	7,320 (6.8)	-	-	4,651 (44.7)	2,669 (45.7)
Stable	3,878 (48.3)	-	2,960 (50.9)	582 (58.3)	198 (57.9)	66,150 (61.6)	-	49,197 (79.6)	4,976 (47.8)	3,084 (52.8)
Increased	371 (4.6)	142 (16.1)	315 (5.4)	52 (5.2)	-	4,618 (4.3)	9,057 (30.9)	3,819 (6.2)	635 (6.1)	-
SABA use (canisters/ year)										
0	2,641 (32.9)	592 (67.3)	1,696 (29.2)	274 (27.5)	79 (23.1)	22,356 (20.8)	4,662 (15.9)	13,817 (22.3)	2,726 (26.2)	1,151 (19.7)
1-2	2,226 (27.7)	214 (24.3)	1,686 (29)	245 (24.5)	81 (23.6)	55,056 (51.2)	17,148 (58.4)	31,613 (51.1)	4,075 (39.1)	2,220 (38.0)
3+	3,167 (39.4)	74 (8.4)	2,432 (41.8)	479 (48.0)	182 (53.2)	30,032 (28.0)	7,543 (25.7)	16,406 (26.5)	3,611 (34.7)	2,472 (42.3)
12+	961 (12.0)	7 (0.8)	724 (12.5)	161 (16.1)	69 (20.2)	3,624 (3.4)	1,000 (3.4)	1,715 (2.8)	495 (4.8)	414 (7.1)

ICS: inhaled corticosteroids; SABA: short-acting beta agonists

Overall includes all patients in respective provinces; Mild, no prescription includes patients with no prescription dispensed in the baseline period; Mild, with prescription includes patients with an average daily dose of ICS that is considered to be a low dose in the baseline period; Moderate includes patients with an average daily dose of ICS that is considered to be a moderate dose in the baseline period; Severe includes patients with an average daily dose of ICS that is considered to be a high-dose in the baseline period.

Table 3 Severe exacerbations by SABA use during study period and baseline disease severity

	Nova Scotia				Alberta			
	SABA use during the study period, canisters				**SABA use during study period, canisters**			
Annual exacerbations* *n(%)*	Overall (N=8,034)	<3 (N=4,867)	3+ (N=3,167)	12+ (N=961)	Overall (N=107,444)	<3 (N=77,412)	3+ (N=30,032)	12+ (N=3,624)
<1	7,270 (90.5)	4,508 (92.6)	2,762 (87.2)	811 (84.4)	98,997 (92.1)	72,613 (93.8)	26,384 (87.9)	2,952 (81.5)
1 to 2	391 (4.9)	192 (3.9)	199 (6.3)	59 (6.1)	6,115 (5.7)	3,578 (4.6)	2,537 (8.4)	406 (11.2)
2+	373 (4.6)	167 (3.4)	206 (6.5)	91 (9.5)	2,332 (2.2)	1,221 (1.6)	1,111 (3.7)	266 (7.3)
Annual exacerbations *mean rate per patient (SD)*	0.36 (1.27)	0.30 (1.36)	0.46 (1.11)	0.60 (1.31)	0.21 (0.70)	0.17 (0.62)	0.31 (0.86)	0.49 (1.19)
	Baseline severity				**Baseline severity**			
Annual exacerbations* *n (%)*	Mild, no prescription (N=880)	Mild, with prescription (N=5,814)	Moderate (N=998)	Severe** (N=342)	Mild, no prescription (N=29,353)	Mild, with prescription (N=61,836)	Moderate (N=10,412)	Severe** (N=5,843)
<1	819 (93.1)	5,305 (91.2)	871 (87.3)	274 (80.4)	27,607 (94.1)	56,931 (92.1)	9,390 (90.2)	5,069 (86.8)
1 to 2	30 (3.4)	277 (4.8)	61 (6.1)	23 (6.7)	1,288 (4.4)	3,609 (5.8)	710 (6.8)	508 (8.7)
2+	31 (3.5)	232 (4.0)	66 (6.6)	44 (12.9)	458 (1.6)	1,296 (2.1)	312 (3.0)	266 (4.6)
Annual exacerbations *mean rate per patient (SD)*	0.27 (1.09)	0.32 (0.94)	0.51 (2.25)	0.81 (2.23)	0.17 (0.66)	0.21 (0.66)	0.25 (0.82)	0.34 (0.91)

* Multiple events (hospitalization or ED with primary dx of asthma, oral corticosteroid dispensation, death) within a 2-week window are considered one exacerbation.
** Patients with severe asthma not utilizing a biologic therapy

References

1. Public Health Agency of Canada. Asthma and Chronic Obstructive Respiratory Disease (COPD) in Canada. . (2019).
2. Public Health Agency of Canada. Asthma in Canada. (2018).
3. Public Health Agency of Canada. FAST FACTS ABOUT ASTHMA DATA COMPILED FROM THE 2011 SURVEY ON LIVING WITH CHRONIC DISEASES IN CANADA. (2015).
4. CIHI. Emergency Department (ED) Visits: Volumes and Median Length of Stay by Triage Level, Visit Disposition, and Main Problem. (2017).
5. Quirt, J., Hildebrand, K.J., Mazza, J., Noya, F. & Kim, H. Asthma. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology* **14**, 50 (2018).
6. FitzGerald, J.M., Boulet, L.-P., McIvor, R.A., Zimmerman, S. & Chapman, K.R. Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. *Can Respir J* **13**(2006).
7. FitzGerald, J.M., Tavakoli, H., Lynd, L.D., Al Efraij, K. & Sadatsafavi, M. The impact of inappropriate use of short acting beta agonists in asthma. *Respiratory medicine* **131**, 135-140 (2017).
8. Silver, H.S.*, et al.* Relationship between short-acting β2-adrenergic agonist use and healthcare costs. *Am J Manag Care* **17**, 19-27 (2011).
9. Patel, M.*, et al.* Metrics of salbutamol use as predictors of future adverse outcomes in asthma. *Clin Exp Allergy* **43**, 1144-1151 (2013).
10. Senthilselvan, A., Lawson, J.A., Rennie, D.C. & Dosman, J.A. Regular use of corticosteroids and low use of short-acting β2-agonists can reduce asthma hospitalization. *Chest* **127**, 1242-1251 (2005).

11. Bårnes, C.B. & Ulrik, C.S. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* **60**, 455-468 (2015).
12. Rabe, K.F.*, et al.* Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* **114**, 40-47 (2004).
13. Makhinova, T., Barner, J.C., Richards, K.M. & Rascati, K.L. Asthma controller medication adherence, risk of exacerbation, and use of rescue agents among Texas Medicaid patients with persistent asthma. *J Manag Care Spec Pharm* **21**, 1124-1132 (2015).
14. Attar, D.*, et al.* Healthcare costs associated with short-acting ß2-agonist use in asthma: an observational UK study from the SABINA global programme. (Eur Respiratory Soc, 2021).
15. Bateman, E.D.*, et al.* Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. *European Respiratory Journal* (2021).
16. Di Marco, F.*, et al.* The Burden of Short-Acting β2-Agonist Use in Asthma: Is There an Italian Case? An Update from SABINA Program. *Advances in therapy*, 1-15 (2021).
17. Janson, C.*, et al.* SABINA: An Overview of Short-Acting β(2)-Agonist Use in Asthma in European Countries. *Advances in therapy* **37**, 1124-1135 (2020).
18. Montero-Arias, F.*, et al.* Overprescription of Short-Acting Beta2-Agonists in Asthma Patients from 6 Latin American Countries: Results from the SABINA International Study. in *TP15. TP015 UPDATES IN ADHERENCE AND TREATMENT OF LUNG DISEASE* A1610-A1610 (American Thoracic Society, 2021).
19. Nwaru, B.I.*, et al.* Overuse of short-acting β2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J* **55**(2020).

20. Price, D.*, et al.* Prescriptions of short-acting β2-agonists in patients with asthma in primary care: a SABINA III multicountry analysis. in *10th IPCRG World Conference: Breathing & Living well* (2021).
21. Suissa, S.*, et al.* A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *American journal of respiratory and critical care medicine* **149**, 604-610 (1994).
22. Pavord, I.D.*, et al.* After asthma: redefining airways diseases. *The Lancet* **391**, 350-400 (2018).
23. O'Byrne, P.M., Jenkins, C. & Bateman, E.D. The paradoxes of asthma management: time for a new approach? *Eur Respir J* **50**, 1701103 (2017).
24. To, T.*, et al.* Is Overreliance on SABA Associated with Health Risks in the Older Asthma Population? *ERJ Open Research* (2022).
25. Cabrera, C.S.*, et al.* SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting β2-agonist use in asthma. *European Respiratory Journal* **55**(2020).
26. Schneider, B. Analysis of therapeutic efficacy in observational cohort studies. Vol. 47 S35-S37 (2001).
27. Dalhousie University. Health Data Nova Scotia.
28. Alberta Health, A.a.P.R.B. Overview of Administrative Health Datasets. (2017).
29. Lougheed, M.D.*, et al.* Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults. *Canadian Respiratory Journal : Journal of the Canadian Thoracic Society* **19**, 127-164 (2012).
30. Lougheed, M.D.*, et al.* Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J* **19**(2012).

31. Gershon, A.S.*, et al.* Identifying patients with physician-diagnosed asthma in health administrative databases. *Canadian Respir J* **16**, 183-188 (2009).

32. Lougheed, M.D.*, et al.* Canadian Thoracic Society Asthma Management Continuum–2010 Consensus Summary for children six years of age and over, and adults. *Canadian respiratory journal* **17**, 15-24 (2010).

33. Global initiative for asthma. Global strategy for asthma management and prevention (2018 update). (GINA, 2018).

34. GINA. Global Initiative for Asthma: Global strategy for asthma management and prevention (Updated 2020). *Rev Fr d'Allergologie d'Immunologie Clin [Internet]* **36**, 685-704 (2020).

35. Elixhauser, A., Steiner, C., Harris, D.R. & Coffey, R.M. Comorbidity measures for use with administrative data. *Medical care*, 8-27 (1998).

36. Amin, S., Soliman, M., McIvor, A., Cave, A. & Cabrera, C. Usage Patterns of Short-Acting β(2)-Agonists and Inhaled Corticosteroids in Asthma: A Targeted Literature Review. *The journal of allergy and clinical immunology. In practice* **8**, 2556-2564.e2558 (2020).

37. Bateman, E.D.*, et al.* As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. *New England Journal of Medicine* **378**, 1877-1887 (2018).

38. O'Byrne, P.M.*, et al.* Inhaled combined budesonide–formoterol as needed in mild asthma. *New England Journal of Medicine* **378**, 1865-1876 (2018).

39. O'Byrne, P.M.*, 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. *The Lancet Respiratory Medicine* **9**, 149-158 (2021).

40. Beasley, R.*, et al.* Controlled trial of budesonide–formoterol as needed for mild asthma. *New England Journal of Medicine* **380**, 2020-2030 (2019).

41. Hardy, J., *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. *The Lancet* **394**, 919-928 (2019).

42. Yang, C.L., *et al.* 2021 Canadian Thoracic Society Guideline–A focused update on the management of very mild and mild asthma. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*, 1-41 (2021).

43. Ontario Health. Asthma Care in the Community for People 16 Years of Age and Older. Quality Standard. https://www.hqontario.ca/Evidence-to-Improve-Care/Quality-Standards/View-all-Quality-Standards/Asthma-in-Adults/The-Quality-Standard-In-Brief. (2020).

44. Cloutier, M.M., *et al.* 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *Journal of Allergy and Clinical Immunology* **146**, 1217-1270 (2020).

Figure 1: Overall treatment patterns over the study period, stratified by baseline severity

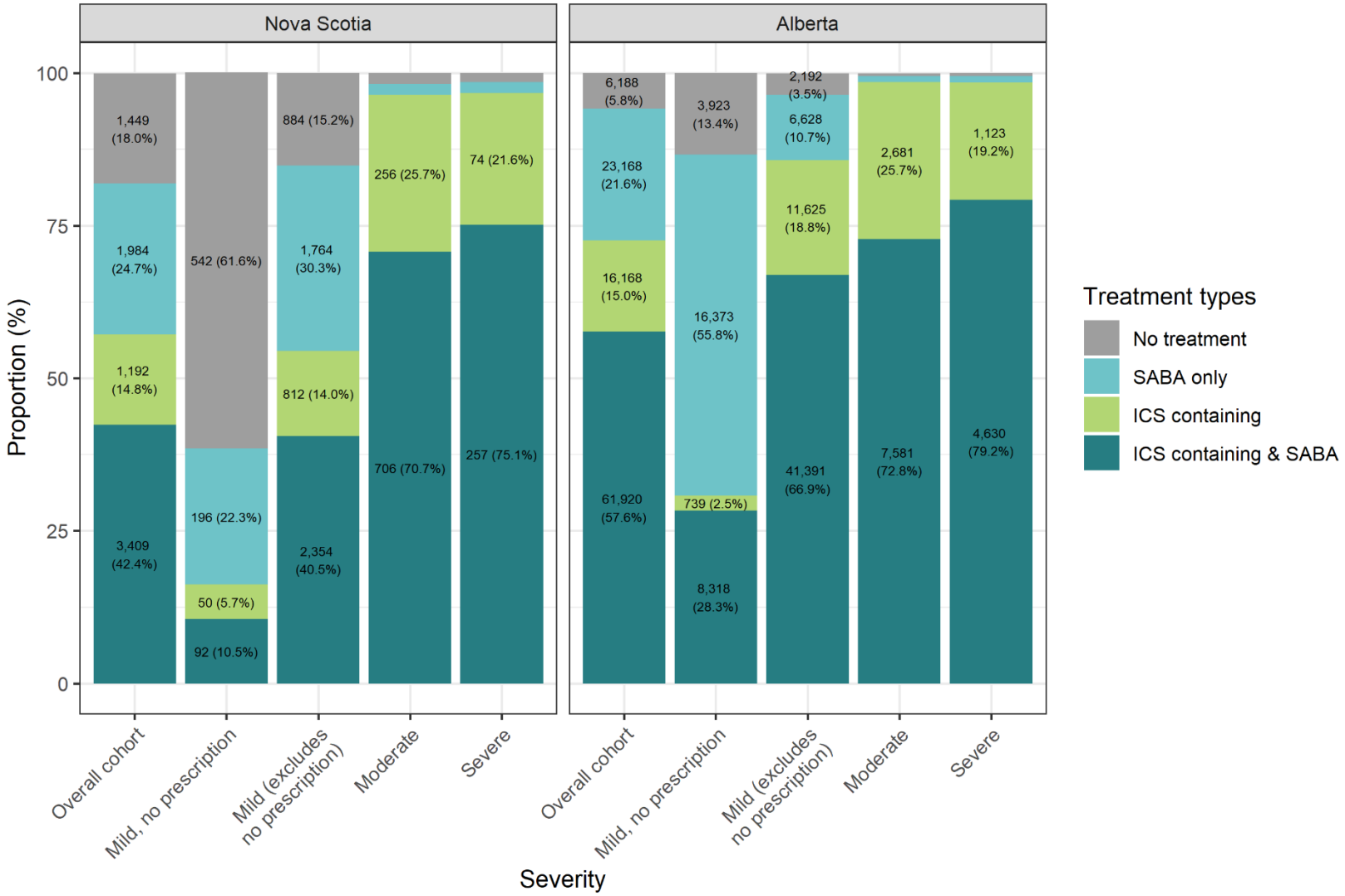


Figure 2: Overuse and excessive use of SABA, during the study period, stratified by baseline severity

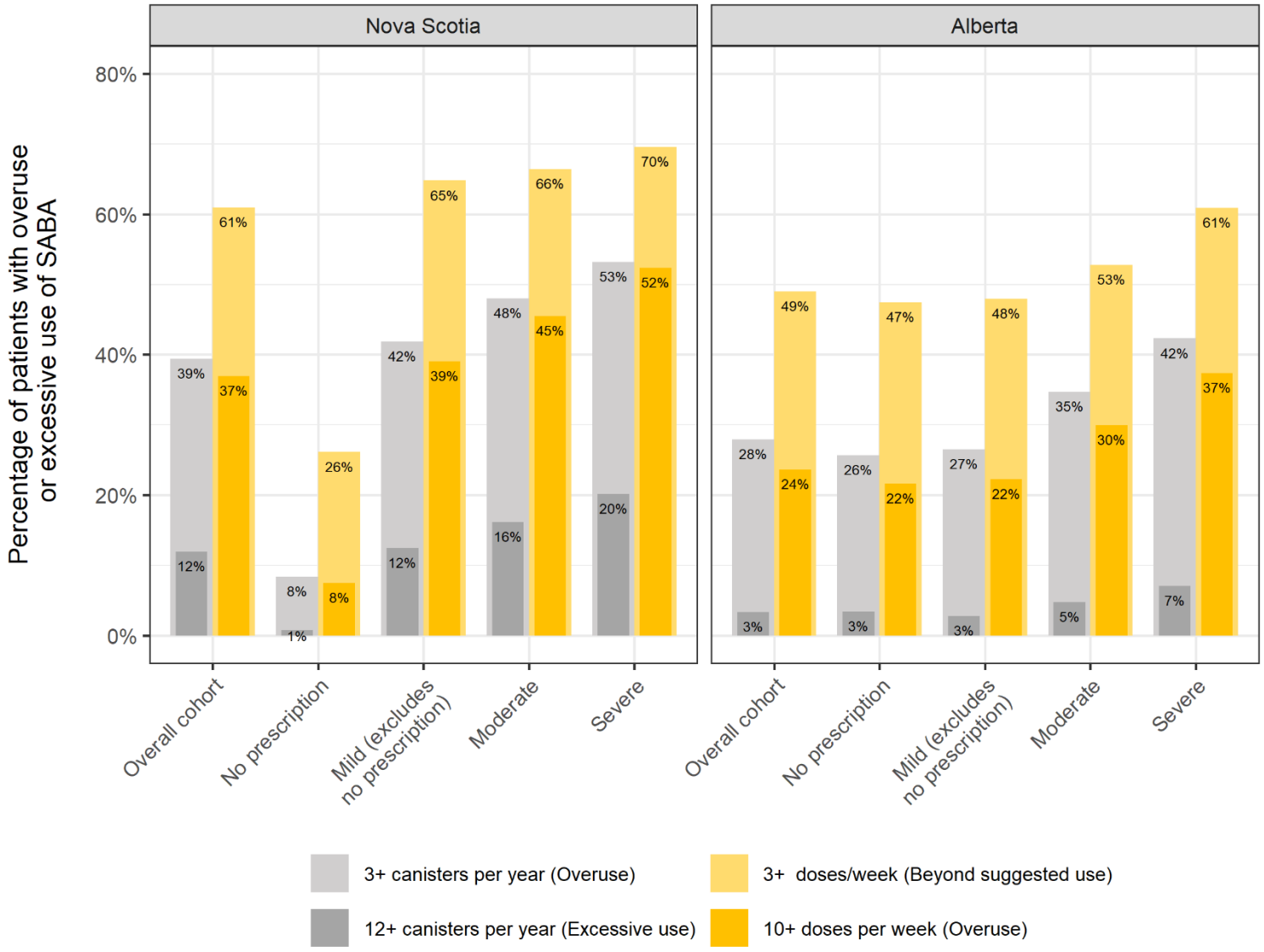


Figure 3: Number of severe exacerbations by SABA use during the study period

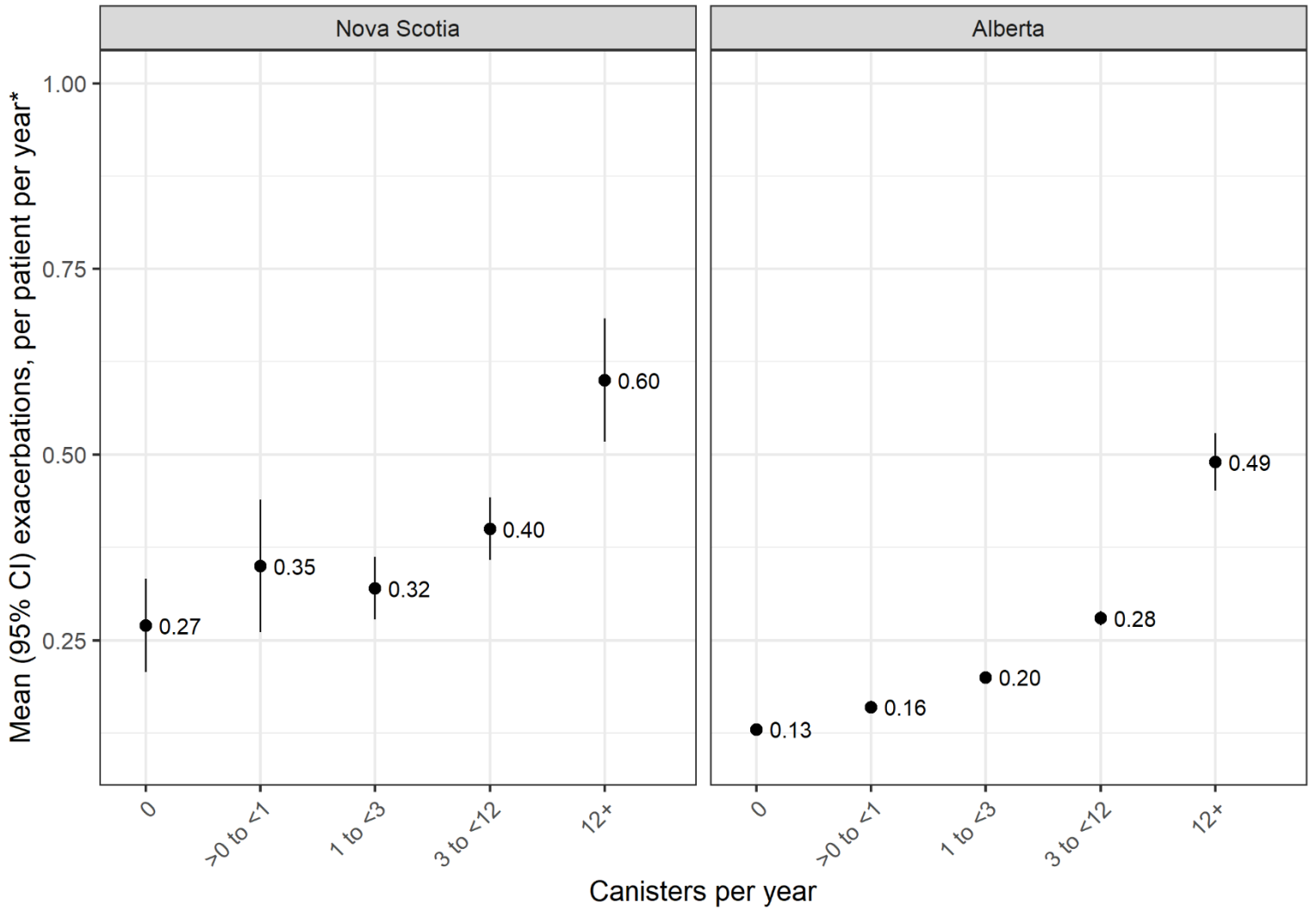
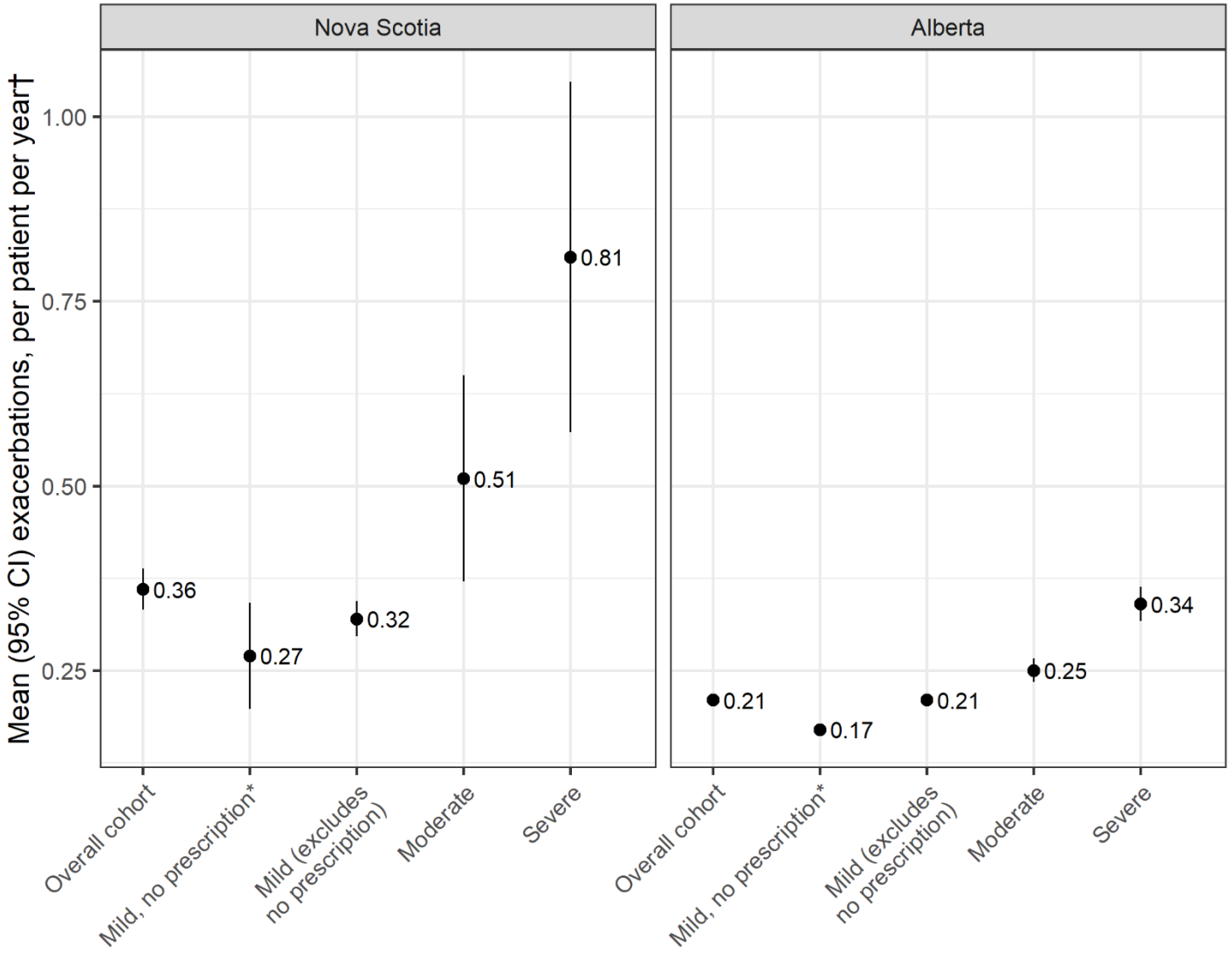
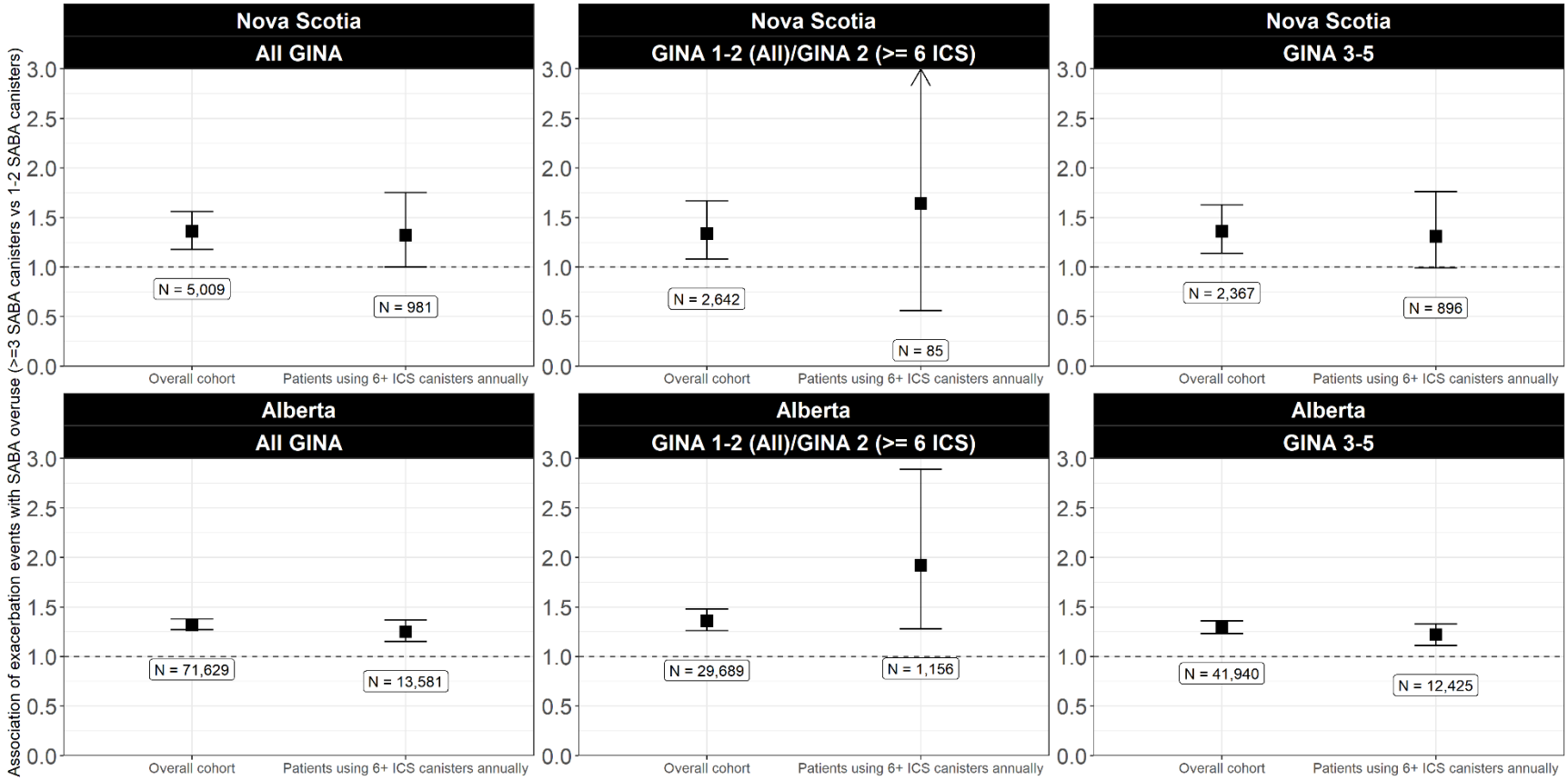


Figure 4: Number of severe exacerbations by baseline asthma severity



*Patients who did not have an ICS or SABA prescription at anytime throughout the baseline period
†Note that if more than one event (hospitalization or ED with primary dx of asthma, or oral corticosteroid) occur within a 2-week window, this will be counted as one exacerbation; also includes death

Figure 5: Adjusted incidence rate ratio for exacerbations associated with SABA overuse (≥3 canisters vs. <3 canisters per year), stratified by baseline disease severity and ICS coverage*



*Adjusted for age, sex, comorbidities, proportion of days covered by ICS, and exacerbation history (number of exacerbations) during the baseline period.

Supplementary Appendix

Methods

Defining asthma severity

Using the CTS definitions for ICS prescription, patients were considered to have mild asthma with a low daily dose of up to 250mcg of beclomethasone equivalent. Moderate disease was defined as having a medium daily dose of between 251 and 500 mcg of beclomethasone, or equivalent. Severe asthma was defined as having a high daily dose of >500 mcg of beclomethasone or equivalent. Similar methodology was used to define the GINA steps, with medication types also taken into consideration: Step 1 included patients with no controller treatment, Step 2 included patients with low dose ICS product, leukotriene receptor antagonist (LTRA), or low-dose theophylline alone, Step 3 included patients using low dose combination product of ICS with LABA or LTRA and/or theophylline, or medium/high dose of ICS alone; Step 4 included patients with medium/high dose for combination product of ICS with LABA and/or LTRA, theophylline, and/or tiotropium; and Step 5 included the patients treated with maintenance OCS (excluding OCS use of ≤10 days) with or without any other inhalers were included in Step 5.

Cleaning dispensed prescription claims data for SABA use

For each prescription claim:

- The drug identification number (DIN) was used to obtain package size from the product monograph
- The dispensed quantity was used to divide the package size
- If the quotient is a whole number, it was then assumed that the unit was inhalations
- If the quotient is not a whole number, and dispensed prescription claim has an attached unit indicating it was a canister, it was then assumed that the units were indeed canisters and multiplied by package size to get total number of inhalations
- If the quotient is not a whole number and dispensed prescription claim has an attached unit indicating it was inhalations, it was then assumed that the units were indeed inhalations
- If the quotient is not a whole number and dispensed prescription claim did not have a clear unit attached, then the prescriptions claims with a quantity <30 were assumed to be in units of canisters, and for those above that threshold they were considered as number of inhalations

All of the number of inhalations were tallied up and divided by 150 to get the total number of canisters per year.

Results
Mortality:

In NS, 0.8% of the overall cohort died during the study period. This ranged from 0.6% among mild patients (excluding those without prescription) to 2.6% among severe patients. Mortality among patients in AB was lower, with a mortality rate of 0.07% among the overall cohort. Mortality in AB was predominately observed among patients with severe disease (0.14%), followed by patients with no prescription of any severity at baseline (0.09%); mild and moderate asthma patients in AB had similar mortality rates of 0.06% and 0.05%, respectively.

Appendix Table 1: Oral corticosteroid and biologics drug codes

	Generic Name	ATC/DDD	DIN(s)
Oral corticosteroids	Prednisone	H02AB07	00550957, 00312770, 00021695, 00232378, 00271373
	Prednisolone	H02AB06	02230619,02245532
	Methylprednisolone	H02AB04	00036129, 00030988
	Dexamethasone	H02AB02	02239534, 02250055, 02261081, 01946897, 01964976, 01964968, 01964070, 02279363
	Hydrocortisone	H02AB09	00030910, 00030929
	Cortisone	H02AB10	00280437
Biologics	Omalizumab	R03DX05	2260565, 02459787, 02459795
	Mepolizumab	R03DX09	02449781
	Reslizumab	R03DX08	02456419
	Benralizumab	R03DX10	02473232
	Dupilumab	D11AH05	02470365

Appendix Table 2: Anatomical therapeutic chemical (ATC) classification codes and drug identification numbers (DINs) of commonly used ICS and SABAs in Canada.

	Generic Name	ATC/DDD	DIN(s)
ICS	**Beclomethasone**	R03BA01 R03AK08	02242029, 02242030
	Fluticasone propionate*	R03BA05 R03AK06 R03AK11	02467895, 02467909, 02467917, 02237245, 02237246, 02237247, 02244291, 02244292, 02244293 02240835, 02240836, 02240837, 02245126, 02245127, 02474611, 02474638, 02474646
	Budesonide*	R03BA02 R03AK07 R03AK12	02229099, 01978918, 01978926, 00851752, 00851760, 00852074, 02465949, 02465957 02245385, 02245386, 02248218
	Ciclesonide	R03BA08	02285606, 02285614
	Mometasone	R03BA07 R03AK09	02243595, 02243596, 02438690 02361744, 02361752, 02361760
	Fluticasone furoate*	R03BA09 R03AK10	02446561, 02446588 02408872, 02444186
SABA	**Salbutamol**	R03AC02	02469359, 02232570, 02245669, 02208229, 02208237, 02208245, 02419858, 02326450, 01926934, 02173360, 02243115, 02241497, 02213419, 02213427, 02213486
	Terbutaline	R03AC03	00786616
***include ICS/LABAs**			

Appendix Table 3 Outcome identifying codes

		Code type	Codes
Exacerbation	Short course oral corticosteroids	ATC/DDD	H02AB07, H02AB06, H02AB04, H02AB01, H02AB02, H02AB09, H02AB10
		DINs	00550957, 00312770, 00021695, 00232378, 00271373 02230619,02245532 01934325, 01934333, 01934341, 00030759, 00030767, 00036129, 00030988, 02231893, 02231895, 02241229, 00030678, 00036137, 02367947, 02367955, 02367963, 02367971 00028096 02250055, 02261081, 02387743, 00874582, 00664227, 01977547, 02412888, 02412896, 02204266, 02204274, 01946897, 01964976, 01964968, 01964070, 02279363, 00783900 00030910, 00030929 00280437
	Hospital admission/ Emergency room visits for asthma (primary diagnosis)	ICD-9	493
		ICD-10	J45
Comorbidities	Gastro-oesophageal reflux	ICD-9	530.8
		ICD-10	K21.9
	Anxiety	ICD-9	300
		ICD-10	F41
	Heart failure	ICD-9	428
		ICD-10	I50
	Pulmonary vascular diseases	ICD-9	415-417
		ICD-10	I26-I28
	Pneumonia	ICD-9	480-487.0
		ICD-10	J10.0, J11.0, J12-J18
	Ischemic heart disease	ICD-9	410-414
		ICD-10	I20-I25
	Arrhythmia	ICD-9	427
		ICD-10	I47-I49
	Myocardial infarction	ICD-9	410
		ICD-10	I21
	Angina	ICD-9	413
		ICD-10	I20
	Diabetes	ICD-9	250.x0, 250.x2
		ICD-10	E11
	Bone fractures	ICD-9	800-829
		ICD-10	S02, S12, S22, S32, S42, S52, S62, S72, S82, S92
	Chronic kidney disease	ICD-9	585
		ICD-10	N18
	Osteoporosis	ICD-9	733.0
		ICD-10	M81
	Depression	ICD-9	296.2, 296.3
		ICD-10	F32, F33
	Anemia	ICD-9	280, 281, 285.9
		ICD-10	D50-53, D64.9

Appendix Table 4 Individual comorbidities at baseline

	Nova Scotia	Alberta
	(N=8,034)	(N=107,444)
Asthma-related conditions, n(%)		
Gastroesophageal reflux	388 (4.2)	958 (0.9)
Anxiety	1,298 (16.2)	29,699 (27.6)
Other co-morbid conditions, n(%)		
Heart failure	55 (0.7)	915 (0.9)
Pulmonary vascular diseases	25 (0.3)	732 (0.7)
Pneumonia	351 (4.4)	4,839 (4.5)
Ischemic heart disease	242 (3.0)	4,105 (3.8)
Arrhythmia	139 (1.7)	4,130 (3.8)
Myocardial infarction	30 (0.4)	421 (0.4)
Angina	41 (0.5)	2,113 (2.0)
Diabetes	602 (7.5)	1,981 (1.8)
Bone fractures	192 (2.4)	7,111 (6.6)
Chronic kidney disease	45 (0.6)	958 (0.9)
Osteoporosis	70 (0.9)	958 (0.9)
Depression	59 (0.7)	958 (0.9)
Anemia	303 (3.8)	4,038 (3.8)

Appendix Table 5 ICS and SABA use by baseline disease severity (GINA steps) during study period

	Nova Scotia					Alberta				
	Baseline asthma severity (GINA)					Baseline asthma severity (GINA)				
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**
	(N=2,642)	(N=1,541)	(N=2,453)	(N=1,049)	(N=349)	(N=25,396)	(N=16,472)	(N=39,367)	(N=11,835)	(N=14,374)
ICS use, n(%)										
No ICS	2,148 (81.3)	583 (37.8)	426 (17.4)	15 (1.4)	129 (37.0)	17,747 (69.9)	3,685 (22.4)	4,760 (12.1)	157 (1.3)	3,007 (20.9)
Reduced	-	-	84 (3.4)	366 (34.9)	34 (9.7)	-	-	887 (2.3)	5,436 (45.9)	1,237 (8.6)
Stable	477 (18.1)	894 (58.0)	1,714 (69.9)	628 (59.9)	165 (47.3)	7,505 (29.6)	12,156 (73.8)	31,154 (79.1)	6,018 (50.8)	9,317 (64.8)
Increased	17 (0.6)	64 (4.2)	229 (9.3)	40 (3.8)	21 (6.0)	144 (0.6)	631 (3.8)	2,611 (6.6)	381 (3.2)	851 (5.9)
Annual SABA use, n(%)										
0	904 (34.2)	432 (28.0)	902 (36.8)	293 (27.9)	110 (31.5)	4,009 (15.8)	2,569 (15.6)	10,276 (26.1)	3,057 (25.8)	2,445 (17.0)
1-2	704 (26.6)	506 (26.8)	673 (27.5)	254 (24.3)	89 (25.5)	14,915 (58.7)	9,695 (58.9)	18,878 (48.0)	4,507 (38.1)	7,061 (49.1)
3+	1,034 (39.1)	603 (39.1)	878 (35.8)	502 (47.9)	150 (43.0)	6,472 (25.5)	4,208 (25.5)	10,213 (25.9)	4,271 (36.1)	4,868 (33.9)
12+	336 (12.7)	175 (11.4)	223 (9.1)	173 (16.5)	54 (15.5)	848 (3.3)	397 (2.4)	1,026 (2.6)	597 (5.0)	756 (5.3)

ICS: inhaled corticosteroids; SABA: short-acting beta agonists

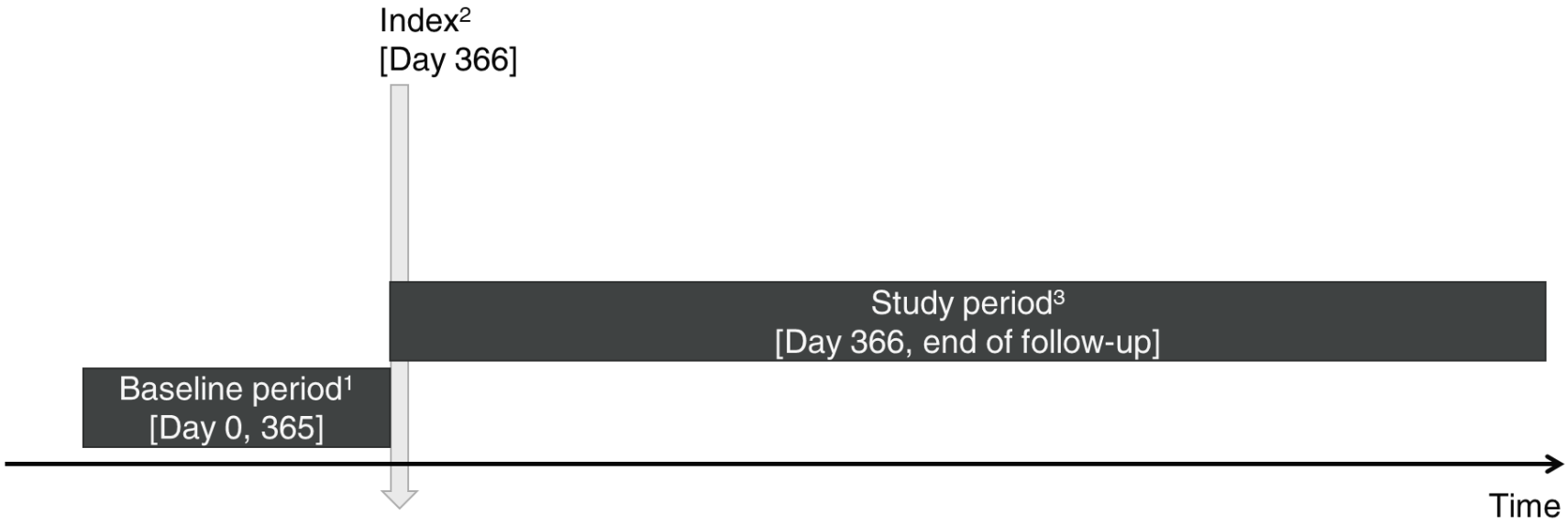
*excluding patients with no prescription for ICS at baseline

Note that those with 'reduced' ICS are those that had moved down an ICS dose category (low, medium, high), whereas those with 'increased' ICS are those that moved up a category, and stable are those who remained in the same category.

Appendix Table 6 Severe exacerbations by baseline disease severity (GINA steps) during study period

	Nova Scotia					Alberta				
Annual exacerbations*	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**
n(%)	(N=2,642)	(N=1,541)	(N=2,453)	(N=1,049)	(N=349)	(N=25,396)	(N=16,472)	(N=39,367)	(N=11,835)	(N=14,374)
<1	2,483 (94)	1430 (92.8)	2,257 (92)	919 (87.6)	181 (51.9)	24,336 (95.8)	15,757 (95.7)	37,182 (94.4)	11,061 (93.5)	10,661 (74.2)
1 to 2	99 (3.7)	70 (4.5)	120 (4.9)	66 (6.3)	36 (10.3)	881 (3.5)	595 (3.6)	1,791 (4.5)	627 (5.3)	2,221 (15.5)
2+	60 (2.3)	41 (2.7)	76 (3.1)	64 (6.1)	132 (37.8)	179 (0.7)	120 (0.7)	394 (1.0)	147 (1.2)	1,492 (10.4)
Annual exacerbations, *mean rate per patient (SD)*	0.22 (0.7)	0.23 (0.7)	0.27 (0.71)	0.50 (2.33)	2.16 (2.82)	0.12 (0.36)	0.12 (0.37)	0.14 (0.41)	0.16 (0.45)	0.70 (1.53)

Appendix Figure 1 Study design diagram



1. Used to assess case definition and to characterize baseline comorbidity, asthma disease severity, the frequency of asthma-related prescription claims, physician visits, and exacerbations; note that baseline period started at the first eligible diagnosis meeting the case definition of ≥2 physician visits in a two-year period or ≥1 hospital separation admission with a diagnosis of asthma [ICD-9-CM 493 or ICD-10-CA J45], with the earliest date possible being October 1st, 2016 for Nova Scotia and April 1st, 2016 for Alberta
2. Used to characterize the age and sex of patients included
3. Used to measure all study outcomes; note that end of follow-up was defined as the first occurrence of death, emigration from the province, or the end of the study period (Nova Scotia: March 31st 2019; Alberta: March 31st, 2020)

Appendix Figure 2 Study consort diagram