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Overuse of short-acting β_2-agonists in asthma is associated with increased risk of exacerbation and mortality: A nationwide cohort study of the global SABINA programme

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INTRODUCTION

Worldwide, up to 30 million children and adults under the age of 45 years have asthma [1], with exacerbations ranging from mild attacks interrupting daily life and work productivity, to severe and life-threatening episodes [2]. Asthma deaths have, until now, become rare in developed countries [3]. During the last two decades there has, however, been a lack of improvement in asthma control [4] and a plateauing of mortality rates [5], which may be related to poor adherence to inhaled corticosteroids (ICS) and/or overuse of short-acting β_2 agonists (SABA) for symptom relief [6] [7]. The increasing trend in overuse of SABA is worrisome, as these agents do not address the underlying inflammatory pathology that gives rise to worsening symptoms. Indeed, the latest iteration of the Global Initiative for Asthma (GINA) report no longer recommends treatment with SABA alone, noting that such therapy does not protect against severe exacerbations and that regular or frequent use actually increases the risk of such events [8]. Used both as a monotherapy and in combination with ICS, SABA overuse is associated with an increased risk of exacerbations, and excessive use ($\geq$11 canisters/year) has been associated with an increased asthma-related mortality risk [8-14]. Nevertheless, contemporary population-based data on use, risk factors and impact of long-term SABA use on exacerbations and mortality are scarce, prompting the initiation of the global SABINA (SABA use IN Asthma) programme. The aim of the SABINA programme is to describe asthma medication prescription patterns, the extent of SABA over-prescription and its subsequent impact on clinical and healthcare resource utilization outcomes via a series of observational studies in more than 25 countries.

The aims of the present study were to describe the use of SABA over an 8-year period in a nationwide cohort of asthma patients in Sweden; evaluate the demographic and clinical

determinants of SABA overuse; and to investigate the associations between SABA (over)use and the risk of exacerbation, all-cause mortality and respiratory-related death.

METHODS

Study design and data sources

This was a retrospective, population-based cohort study utilizing national Swedish health registries: (1) the National Patient Register covering all hospital admissions since 1987 and out-patient specialist visits since 2001; (2) the Prescribed Drug Registry, covering all collected outpatient drug prescriptions since July 2005 using anatomical Therapeutic Chemical (ATC) codes; and (3) the Cause of Death Register [15-17]. Sweden has a publicly funded healthcare system, with equal access for all patients, regardless of socioeconomic status or geographic localization. Individual patient data were linked by the Swedish National Board of Health and Welfare using each individual's unique personal identification number, which was then replaced by a study identification number in order to secure anonymization of the patients prior to data analysis. The study protocol was approved by the Stockholm Regional Ethics Committee (registration number 2017/4:2) [18, 19].

Study population

The study population included all asthma patients, defined as individuals aged 12–45 years who collected two or more drugs for obstructive lung disease (ATC R03) from pharmacies in any one-year period during 2006-2014 in Sweden, a validated proxy for asthma (Figure 1) [15]. The lower age cut off was selected due to differences in asthma management pattern for younger patients, whereas the upper of 45 years was to mitigate the risk of including patients with COPD. Patients with a diagnosis of COPD (J44), and/or collection of adrenergics in combination with anticholinergics, were excluded. To examine oral corticosteroid (OCS) collections indicated for asthma only, patients with diagnosis of other conditions for which OCS may be prescribed were excluded (i.e., Crohn's disease [K50], ulcerative colitis [K51], rheumatoid arthritis [M05], emphysema [J43], bronchiectasis [J47], cystic fibrosis [E84] and

current malignancy [C00-97]). Medical history data were retrieved from the National Patient Register using ICD-10 codes from 10 years prior to index date.

Study measures

SABA use was quantified as the number of canisters collected per calendar year. To enable comparison of different types and number of doses in the SABA canisters, a standardized SABA canister unit was defined as 150 doses. The definition of SABA overuse in the present study was calculated assuming that 2 puffs were used on each occasion and that a patient with well-controlled asthma would not use their SABA reliever more than twice/week: which equals a maximum of two SABA canisters per year [20]. In practice, this means that the collection of 3 or more SABA canisters annually was considered as overuse [20]. During the baseline period, patients were grouped by the number of collected SABA canisters: ≤2 (considered appropriate use), 3-5, 6-10, and 11+ (excessive use) [10, 11]. The index date was the date of the second asthma drug collection, and the baseline period was from the index date up to one-year post index.

ICS use included both monotherapy and fixed combinations (in budesonide equivalents). The mean daily ICS dose was defined as: low-dose, ≤400 µg; medium-dose, 401–800µg; and high-dose, >800 µg [8]. Patients were classified into different treatment severity steps based on their asthma-related drug use during the baseline period (details provided in Supplementary data, Table S1).

Co-morbidity

Comorbidities were identified based on diagnoses (ICD-10 codes) recorded as part of inpatient and outpatient hospital care. Charlson Comorbidity Index (as marker for the co-

morbidity burden/fragility of patients) was estimated for the different SABA canisters groups [21].

Outcomes

Asthma exacerbation was defined as either a pharmacy collection of a course of OCS, or emergency room visits and/or hospitalisations due to asthma. All-cause, respiratory-related (J00-J99) and asthma-related (J45-J46) mortality was investigated during the observation period. Identification of asthma exacerbation and death were performed from the first day after the baseline period (last patient included 2014-12-31) until date of death, emigration, or end of observation (31 December 2016), whichever occurred first. The use of SABA and ICS was described for the first 3 years after the baseline period.

Statistical analyses

Baseline characteristics were described as mean (standard deviation [SD]) for continuous variables and absolute and relative frequencies for categorical variables. Logistic regression models were applied to estimate odds ratios (OR) with 95% confidence intervals (CI) of possible risk factors for SABA overuse (>2 [3 or more] canisters) during the baseline period. Age at asthma diagnosis, sex, treatment steps, hypnotics and sedative drugs and comorbidity were explored individually as well as in multivariable adjusted analysis. Risk of exacerbation and mortality, post index date, by baseline SABA use was assessed by hazard ratios (HR) with 95% CI in Cox proportional hazard models. Exacerbation was assessed by time to first exacerbation after baseline period. As a sensitivity analysis, a stratification for patients with and without exacerbations during the baseline period was performed. In all regression analyses, both crude estimates as well as estimates adjusted for age at asthma diagnosis, sex, treatment steps and comorbidity were calculated. Exacerbation-free survival by baseline

period SABA use, stratified by baseline period ICS use (no/yes), was evaluated through Kaplan-Meier graphs. Of note, in all assessment of exacerbation during follow-up patients with treatment step 5 during the baseline period were excluded since these patients are regular users of OCS. Statistical analyses were performed using R version 3.3.2 (R foundation for Statistical Computing, Vienna, Austria, 2013).

RESULTS

Overall, 365,324 asthma patients (mean age 27.6 years, 55% women) were included (Figure 1), of whom 30% overused SABA: 76,619 (21.0%) collected 3-5 canisters, 27,065 (7.4%) 6-10 canisters, and 7140 (2%) collected 11 canisters or more during the one-year baseline period (Table 1). The observation period covered on average 85.4 (range 0.03 to 120) months after the one-year baseline period. Half of the included patients were at treatment steps 1 and 2; and 34% and 16% were in steps 3 and 4, respectively.

After the one-year baseline period, patients collecting >2 SABA canisters were similar regarding age and sex compared to those not overusing SABA, but had more asthma exacerbations, asthma-related hospitalizations, and outpatient hospital visits (Table 1). Also, SABA overuse was associated with a greater comorbidity burden.

During the one-year baseline period, the collection of ICS and LABA, both as monotherapy and in combinations, was similar irrespective of baseline SABA use. Treatment with OCS, however, differed between the SABA groups, with a higher prevalence of OCS use in patients who collected a higher number of SABA canisters (Table 1). In addition, the use of antidepressants, hypnotics, and sedatives was greater in patients with SABA overuse (Table 1).

Patterns of ICS and SABA use over time

Among patients collecting >2 SABA canisters/year over a three-year period after baseline, the proportion of patients in all three SABA overuse groups was stable, and in parallel, the use of ICS was stable and did not change during the three-year period (despite continuous SABA overuse) (Figure S1). From a full population perspective, approximately 85% of asthma

patients overusing SABA at baseline had continuous overuse during the observation period, whereas the proportion of patients not collecting any ICS was more than doubled at the end of observation (Table S2).

Factors associated with SABA overuse

Males, adolescents, and older patients were more likely to overuse SABA compared to females and those in the 18 to 24-year age group, respectively (Table 2). Compared to patients in treatment step 3, patients in the other treatment steps had greater risk of overusing SABA, with a 50% and 90% increased risk for patients in treatment steps 1 and 5, respectively. In addition, use of hypnotics and sedative drugs and increasing comorbidity burden were associated with increased risk of SABA overuse.

Exacerbations

Increasing number of collected SABA canisters was associated with an increased risk of exacerbations in a dose-dependent manner after adjusting for treatment step, Charlson Comorbidity Index, sex, and age (Figure 2). Irrespective of treatment step, patients overusing SABA (>2 [3 or more] canisters/year) were at an increased risk of exacerbations in a dose-dependent manner compared to those not overusing SABA. In the sensitivity analysis where patients were stratified into 2 groups: with or without exacerbations during the baseline period, the exacerbation risk and SABA use was similar in both groups (Table S3). Similarly, SABA overuse was associated with more exacerbations irrespective of whether concomitant ICS was used at baseline or not (Figure 3). A small proportion of patients (2.3%) were collecting LABA without concomitant ICS. In this group, SABA overuse was associated with a two-fold greater exacerbation risk (data not shown).

Mortality

During the observation period, 1,365 (0.54%) of the asthma patients in the group collecting ≤2 SABA canisters/year died compared with 1,199 (1.07%) among the patients collecting >2 (3 or more) SABA canisters at baseline (Table 3 and Figure 4). The mortality rate increased with increasing number of collected SABA canisters (Figure 4). After adjusting for treatment step, Charlson Comorbidity Index, sex, and age, increasing number of SABA canisters collected was associated with greater risk of all-cause, respiratory-, and asthma-related mortality in a dose-dependent manner (Figure 5).

DISCUSSION

In this nationwide asthma cohort study, which was conducted as part of the global SABINA programme, about one third of all asthma patients in Sweden were overusing SABA. Male sex, age, use of hypnotics and sedative drugs, and increasing comorbidity burden were main determinants of SABA overuse. Notably, SABA overuse was also associated with an increased risk of exacerbation and all-cause-, respiratory-, and asthma-specific mortality compared to appropriate SABA use.

A key finding of the present study was the observed association of SABA overuse with dose-dependent increased risk of all-cause mortality. Indeed, while 6 times as many patients died in the excessive SABA use group (11+ canisters collected) compared to the group with appropriate SABA use, an association between SABA overuse and risk of all-cause mortality was also found at lower levels of SABA overuse. Other studies have reported an association between excessive SABA use and increased risk of asthma-related deaths, and our findings for respiratory and asthma-specific deaths are therefore in keeping with these previous studies [16-18, 22]. Although most of the studies regarding SABA overuse and asthma mortality were done in the 1990s, our findings from contemporary data emphasizes the fact that SABA overuse continues to be a risk factor for mortality and that there is a dose-dependent trend above 3 or more canisters collected per year.

As the majority of deaths in our study cohort are not related to asthma, our findings indicate that SABA overuse may be a general marker for increased risk among asthma patients. In addition, a parallel association between all SABA overuse and increased risk of respiratory and asthma-related deaths was also observed. Our data showed an increased use of antidepressants, hypnotics, and sedatives in patients with SABA overuse, indicating a frailer

patient group. Regardless of whether there is a causal effect of SABA use and these adverse effects, or if they are mainly a marker for more severe asthma and/or a reflection the frailty of the patients, increased use of SABA should alert clinicians to monitor these patients more closely [10, 23, 24].

No significant changes in the proportion of patients in the different SABA overuse groups were seen among the those consistently collecting >2 SABA canisters/year over a three-year period after baseline. Interestingly, this persistent long-term SABA overuse did not trigger any significant changes in asthma management, as no concomitant increase in maintenance ICS therapy was identified. This may be explained by the Swedish health care setting, where annual reviews in primary care, and referrals to specialist care for asthma patients are scarce, as previously reported by Larsson et al [25]. In addition, Janson et al recently showed that asthma patients in Sweden, regardless of exacerbation frequency, did not have more frequent healthcare visits or alterations in asthma medications than patients with less exacerbations had [26]. That study suggested that repeated prescriptions of asthma drugs may be issued without proper consultation with the treating physicians.

An additional observation from our study is that mild and severe asthma, i.e. treatment steps 1 (without concomitant use of maintenance ICS therapy) and 5, compared to step 3 were both associated with an increased risk of SABA overuse. This highlights the need of appropriate drug therapy for mild asthma patients [24]. This has also been noted in the recently updated GINA report, where SABA without ICS should no longer be a treatment option in mild asthma [8]. Other important predictors for SABA overuse were male sex, younger age, and having a greater use of hypnotics and sedative drugs, as well as increasing comorbidity burden indicating a generally more frail patient population. These findings are in line with

those of other studies [9, 12], as well as our findings of an association between the use of increased number of SABA canisters and risk of exacerbations, both for patients with and without concomitant use of maintenance ICS therapy [11, 23].

The present findings have several potential clinical implications. According to GINA, patients with well-controlled asthma should not have need for reliever therapy (SABA) more than twice weekly. The definition of SABA use in the present study is calculated assuming that 2 puffs are used on each occasion, which equals a maximum of two SABA canisters per year. In practice, this means collection of 3 or more SABA canisters annually is considered as overuse. A large proportion (30%) of asthma patients in our study had SABA overuse. Of these, almost one in ten patients used >6 canisters/year, and for the majority of these patients, SABA overuse was maintained throughout a three-year observation period. With SABA overuse being a clear marker of patients with an increased risk of exacerbations and mortality [12], this is quite remarkable.

One of the strengths of the present study is the nationwide perspective, thus including all asthma patients in Sweden during the study period. The nationwide data ensured that selection bias was minimized, and consequently the generalizability of the study findings is enhanced. One limitation of the study is the use of pharmacy collection of drugs for obstructive lung disease as a proxy for asthma diagnosis and treatment, and the lack of access to primary care data where asthma diagnosis may commonly be captured. The collection of drugs for obstructive lung disease has, however, been shown to be a suitable proxy for asthma diagnosis in this age group in validation studies from Sweden [15]. To mitigate the risk of including patients with COPD, a number of exclusion criteria were applied, including patient aged >45 years, COPD diagnosis, and use of COPD-specific drugs. Similarly, as some OCS use could

relate to other conditions than asthma, patients with conditions for which OCS may be prescribed were excluded. Another potential limitation was that SABA use was based on collected prescriptions, which may not fully reflect patients' actual medication use. It should be noted that co-morbidities managed only in primary care were not captured in our database and may thereby be underestimated in our study. In addition, the possibility of coding errors cannot be completely ruled out; however, validation studies have reported high correlation between data in the Swedish National Patient Register and diagnoses in medical records [15, 16].

In conclusion, the present findings demonstrate that a large proportion of asthma patients in Sweden are overusing SABA, and that such overuse may be maintained for several years without any addition or dose adjustment of the maintenance ICS. SABA overuse was associated with a dose-dependent increased risk of exacerbations and increased all-cause, respiratory and asthma-related mortality risk. Such findings emphasize that monitoring of SABA usage should be a key strategy in improving asthma management.

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the Stockholm regional ethics committee (registration number 2017/4:2). The linkage of registers data was approved and performed by the Swedish National Board of Health and Welfare. Patients do not need to give consent for use of public register data in Sweden.

Consent for publication

All authors read and approved the final manuscript. All authors gave consent to publish these data.

Availability of data and material

The dataset supporting the conclusions of this article can be available upon request.

Competing interests

PH and GT are employed by AstraZeneca.

FW is employed at Statisticon for which AstraZeneca is a client.

CJ has received payments for educational activities from AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, and Teva, and has served on advisory boards arranged by AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva.

BIN and ME report no conflict of interest relevant to this article.

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Authors' contributions

Data collection was performed by CJ. Statistical analysis was conducted by FW and BIN.

Analysis, interpretation and drafting of the manuscript was conducted by BIN and PH and in cooperation with the other authors. All authors approved the manuscript before submission.

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Table 1. Baseline characteristics by use of SABA during baseline year

	No. of SABA canisters collected during the baseline year			
	0-2 (n=254,500)	**3-5 (n=76,619)**	**6-10 (n=27,065)**	**11+ (n=7140)**
Female, n (%)	14,2316 (55.9)	41,412 (54.0)	13,747 (50.8)	3570 (50.0)
Age				
Mean (SD)	27.6 (11.0)	26.8 (11.2)	28.6 (11.1)	31.9 (10.1)
Age categories, n (%)				
12-17	69,140 (27.2)	24,515 (32.0)	6732 (24.9)	994 (13.9)
18-24	41,458 (16.3)	11,086 (14.5)	3599 (13.3)	777 (10.9)
25-34	57,759 (22.7)	16,441 (21.5)	6490 (24.0)	1867 (26.1)
35-45	86,143 (33.8)	24,577 (32.1)	10,244 (37.8)	3502 (49.0)
Any exacerbation, n (%)*	32,653 (12.8)	13,071 (17.1)	5754 (21.3)	2049 (28.7)
Hospitalization rate, asthma main cause, per/1000PY (95% CI)*	1.0 (0.9-1.1)	2.8 (2.4-3.1)	6.1 (5.2-7.1)	17.9 (14.8-21.0)
Outpatient visits rate, asthma main cause, per/1000PY (95% CI)*	132.1 (130.7-133.6)	197.3 (194.1-200.4)	232.5 (226.8-238.3)	252.2 (240.6-263.9)
Comorbidities, n (%)				
Chronic rhinitis	727 (0.3)	219 (0.3)	65 (0.2)	15 (0.2)
Nasal polyps	983 (0.4)	276 (0.4)	131 (0.5)	42 (0.6)
Other acute lower respiratory infections	711 (0.3)	239 (0.3)	116 (0.4)	63 (0.9)
Chronic bronchitis	300 (0.1)	84 (0.1)	32 (0.1)	14 (0.2)
Pneumonia and influenza	1142 (0.4)	411 (0.5)	217 (0.8)	89 (1.2)
Charlson Comorbidity Index, n (%)				
0	194,343 (76.4)	53,646 (70.0)	18,091 (66.8)	4432 (62.1)
1	57,751 (22.7)	22,064 (28.8)	8588 (31.7)	2535 (35.5)
2	1841 (0.7)	672 (0.9)	274 (1.0)	124 (1.7)
3+	565 (0.2)	237 (0.3)	112 (0.4)	49 (0.7)
Pharmacy collected medications				
Any inhaled corticosteroids (ICS) (including fixed combinations)	185,650 (72.9)	53,251 (69.5)	20,440 (75.5)	5396 (75.6)
Inhaled corticosteroids	122,517 (48.1)	39,685 (51.8)	14,997 (55.4)	3685 (51.6)
Long-acting β2-agonists (LABA)	25,791 (10.1)	5253 (6.9)	2593 (9.6)	902 (12.6)
ICS/LABA combination**	73,711 (29.0)	18,375 (24.0)	7550 (27.9)	2333 (32.7)
Leukotriene modifiers	20,405 (8.0)	6666 (8.7)	2947 (10.9)	827 (11.6)
Short-acting β_2-agonists	134,954 (53.0)	76,619 (100.0)	27,065 (100.0)	7140 (100.0)
Oral corticosteroids	32,546 (12.8)	12,971 (16.9)	5706 (21.1)	2026 (28.4)
Anticolinergics	943 (0.4)	213 (0.3)	114 (0.4)	54 (0.8)
N-acetylcysteine	10,299 (4.0)	3837 (5.0)	1892 (7.0)	785 (11.0)
Antibiotics	34,726 (13.6)	10,656 (13.9)	4172 (15.4)	1412 (19.8)
Antiviral agents	4948 (1.9)	1489 (1.9)	534 (2.0)	139 (1.9)
Cough and cold treatments	44,087 (17.3)	14,468 (18.9)	5848 (21.6)	1905 (26.7)
Antihistamines	83,025 (32.6)	30,490 (39.8)	10,885 (40.2)	2781 (38.9)
Nasal corticosteroids	63,483 (24.9)	21,090 (27.5)	7374 (27.2)	1821 (25.5)
Antidepressants	26,268 (10.3)	8610 (11.2)	3694 (13.6)	1214 (17.0)
Hypnotics and sedatives	16,043 (6.3)	5990 (7.8)	2611 (9.6)	951 (13.3)
Cardiovascular drugs	20,943 (8.2)	7876 (10.3)	3144 (11.6)	1010 (14.1)

* During the baseline year. ** Only fixed combinations

Number in brackets denotes % if not stated otherwise.

Abbreviation: SD, standard deviation.

Table 2. Factors associated with SABA overuse (>2 [3 or more] collected canisters/year)

	Crude OR (95% CI)	Adjusted OR (95% CI)
Age range		
12-17	1.24 (1.22-1.27)	1.16 (1.14-1.19)
18-24	1.00	1.00
25-34	1.14 (1.12-1.17)	1.17 (1.14-1.20)
35-45	1.19 (1.16-1.22)	1.22 (1.19-1.25)
Sex		
Female	1.00	1.00
Male	1.12 (1.11-1.14)	1.12 (1.10-1.14)
Treatment step		
1	1.40 (1.38-1.43)	1.51 (1.48-1.53)
2	1.09 (1.07-1.11)	1.13 (1.11-1.15)
3	1.00	1.00
4	1.21 (1.18-1.23)	1.14 (1.12-1.17)
5	2.12 (1.98-2.27)	1.90 (1.77-2.04)
Hypnotics and sedatives drug use		
No	1.00	1.00
Yes	1.41 (1.37-1.44)	1.40 (1.37-1.44)
Charlson Comorbidity Index		
0	1.00	1.00
1	1.45 (1.43-1.47)	1.54 (1.51-1.56)
2	1.48 (1.37-1.60)	1.40 (1.29-1.51)
3+	1.80 (1.58-2.04)	1.60 (1.40-1.82)

Regression of time to >2 SABA canisters/year, unadjusted or mutually adjusted for the factors in the model.

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3. Cause of death among asthma patients by use of SABA during baseline year

	No. of SABA canisters collected during the baseline year			
	0-2 (n=254,500)	**3-5 (n=76,619)**	**6-10 (n=27,065)**	**11+ (n=7140)**
Vital status				
Alive	253,135 (99.5)	76,011 (99.2)	26,690 (98.6)	6924 (97.0)
Dead	1365 (0.5)	608 (0.8)	375 (1.4)	216 (3.0)
Cause of death				
Suicide	199 (14.6)	82 (13.5)	48 (12.8)	19 (8.8)
Cardiovascular related	178 (13.1)	91 (15.0)	50 (13.3)	28 (13.0)
Poisoning by accident	131 (9.6)	52 (8.6)	42 (11.2)	18 (8.3)
Respiratory related	43 (3.2)	19 (3.1)	20 (5.3)	18 (8.3)
Asthma related	7 (0.5)	4 (0.7)	5 (1.3)	12 (5.6)
Malignancy related	196 (14.4)	68 (11.2)	28 (7.5)	18 (8.3)
Other	618 (45.3)	296 (48.7)	187 (49.9)	115 (53.2)

Number in brackets denotes %.

Figure titles and Caption / Legend

Figure 1. Flow chart of study population

Figure 2. Associations between baseline SABA use and treatment step and subsequent risk of asthma exacerbation

Adjusted for age at asthma diagnosis, sex, treatment step and comorbidity. Canister: ≤2 canisters, patients collecting 2 or less SABA canisters during the baseline year; 3+ canisters, patients collecting 3 or more SABA canisters during the baseline year.

Abbreviations: CI, confidence interval; HR, hazard ratio.

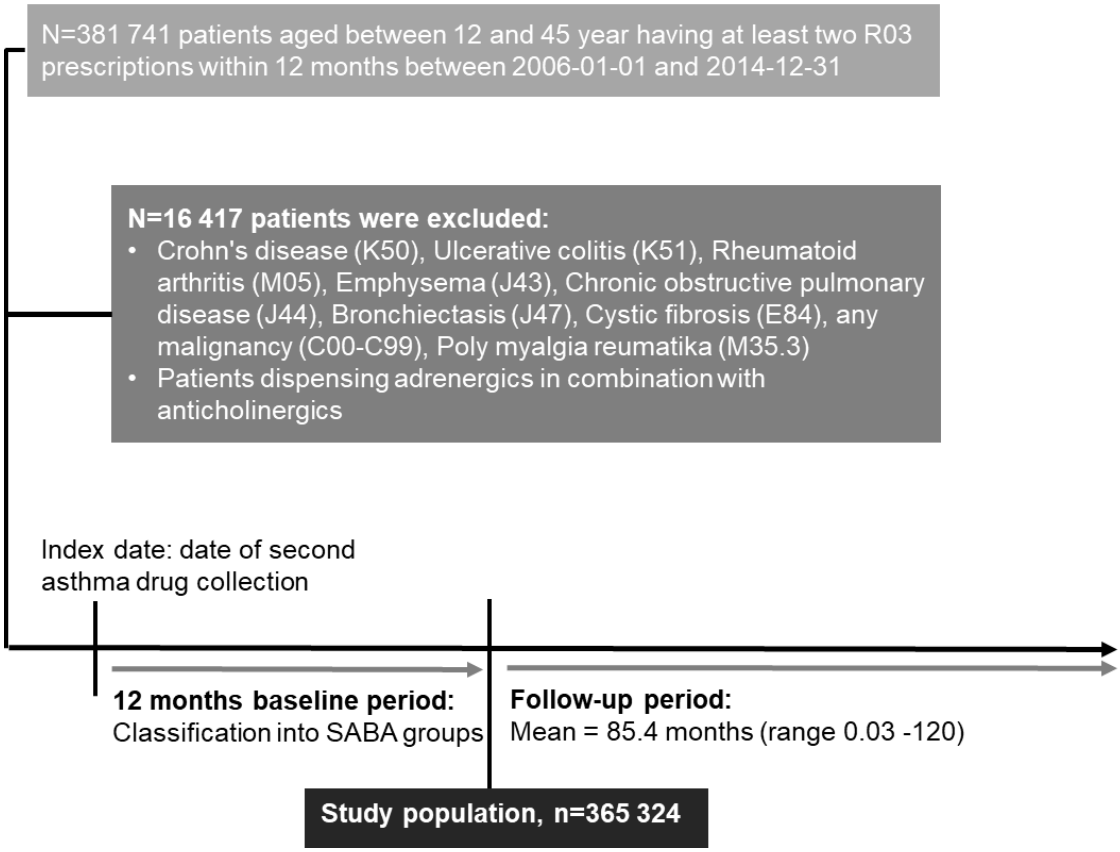
Figure 3. Exacerbation-free survival in different baseline period SABA use groups. Top panel: patients not treated with ICS during the baseline year, n=100,588. Lower panel: patients treated with ICS during the baseline year, n=264,736

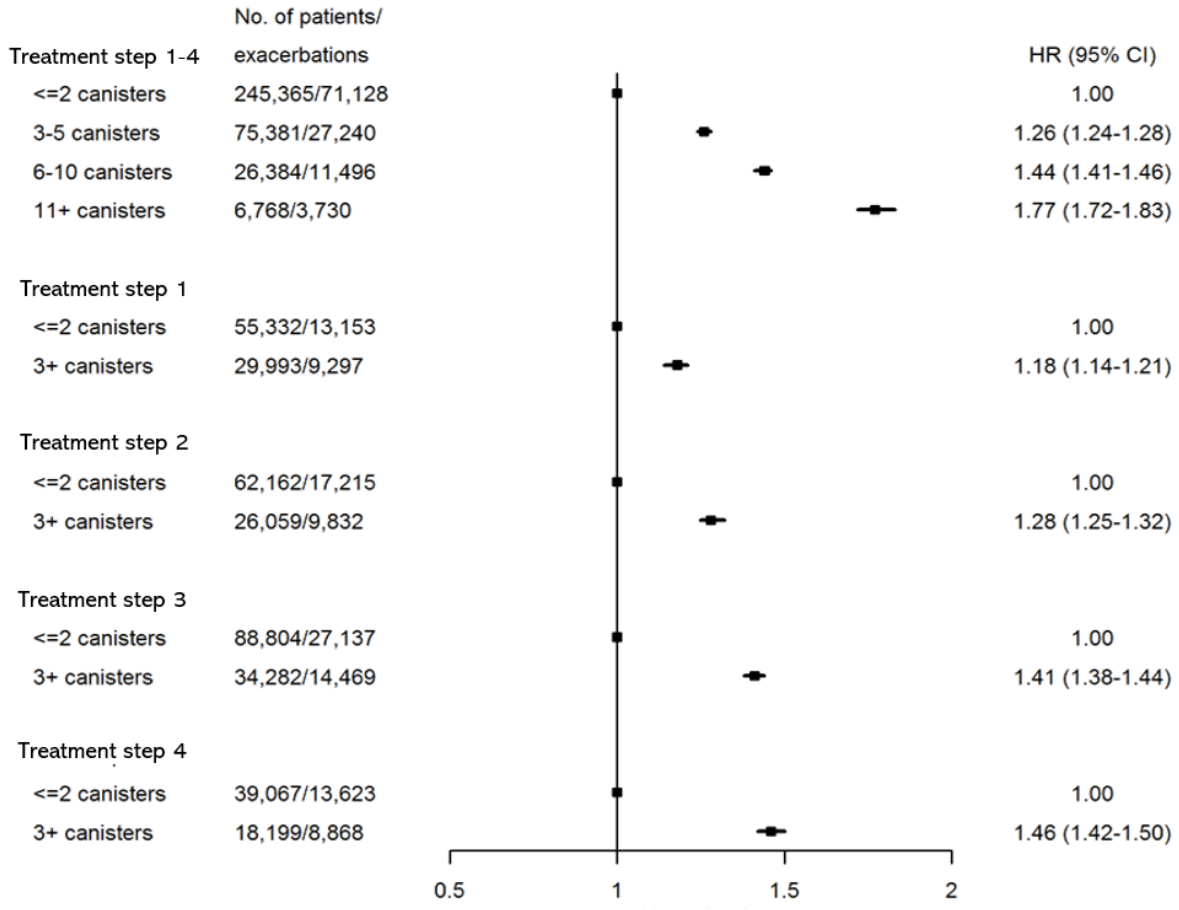
Figure 4. Kaplan-Meier plot of overall survival by baseline SABA use

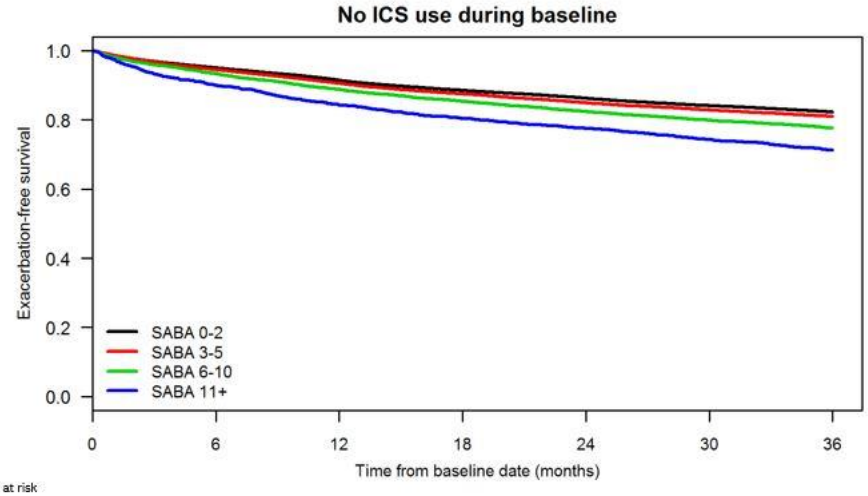
Figure 5. Association between baseline SABA use and risk of mortality

Adjusted for treatment step, Charlson Comorbidity Index, sex and age. Canisters: ≤2 canisters, patients collecting 2 or less SABA canisters during the baseline year; 3+ canisters: patients collecting 3 or more SABA canisters during the baseline year.

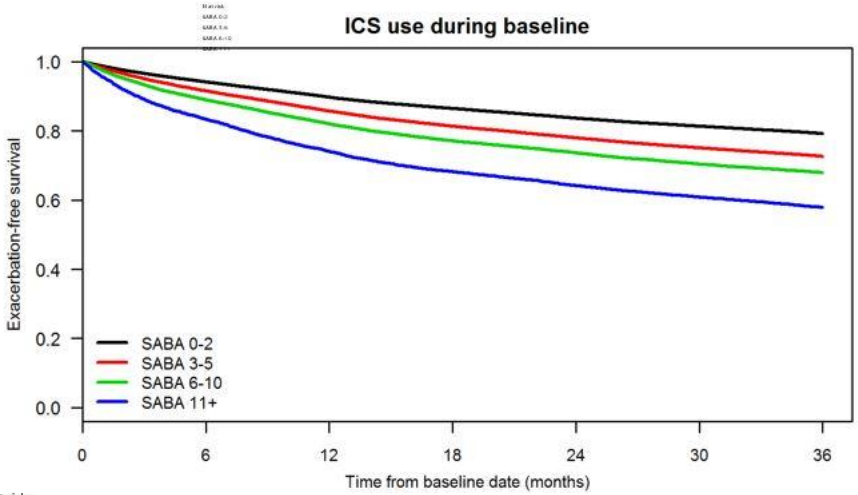
Abbreviations: CI, confidence interval; HR, hazard ratio.


N=381 741 patients aged between 12 and 45 year having at least two R03 prescriptions within 12 months between 2006-01-01 and 2014-12-31
N=16 417 patients were excluded:
• Crohn's disease (K50), Ulcerative colitis (K51), Rheumatoid arthritis (M05), Emphysema (J43), Chronic obstructive pulmonary disease (J44), Bronchiectasis (J47), Cystic fibrosis (E84), any malignancy (C00-C99), Poly myalgia reumatika (M35.3)
• Patients dispensing adrenergics in combination with anticholinergics
Index date: date of second asthma drug collection
12 months baseline period:
Classification into SABA groups
Follow-up period:
Mean = 85.4 months (range 0.03 -120)
Study population, n=365 324

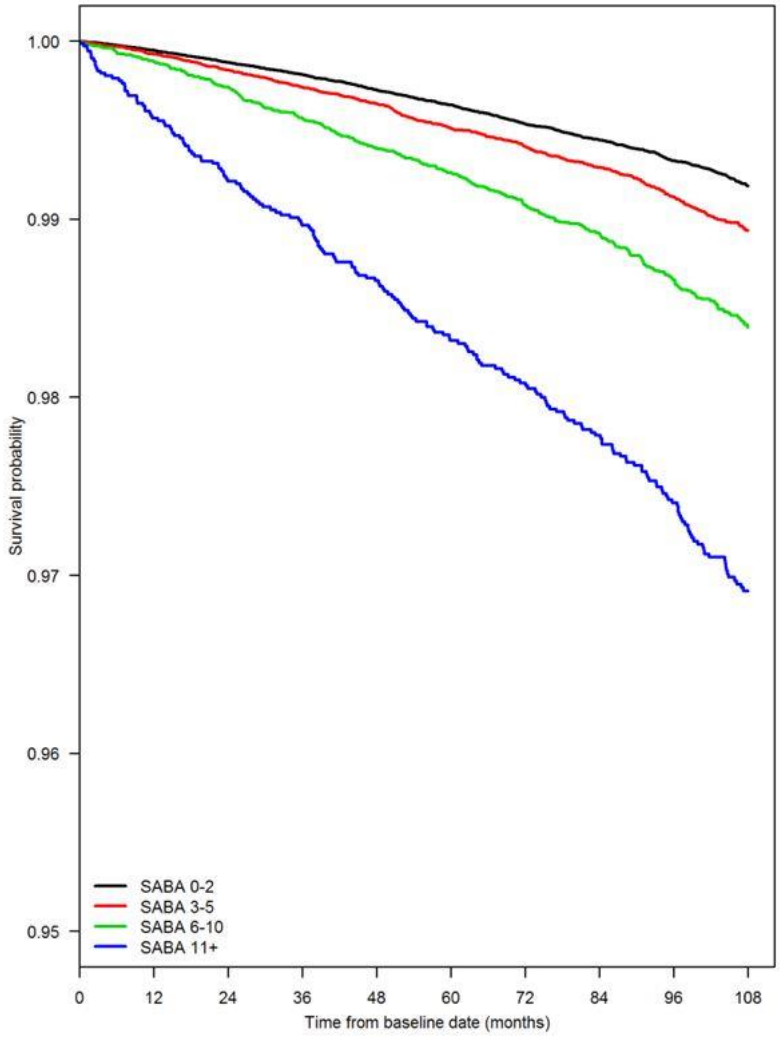

No. of patients/
Treatment step 1-4
exacerbations
HR (95% CI)
<=2 canisters
245,365/71,128
1.00
3-5 canisters
75,381/27,240
1.26 (1.24-1.28)
6-10 canisters
26,384/11,496
1.44 (1.41-1.46)
11+ canisters
6,768/3,730
1.77 (1.72-1.83)
Treatment step 1
<=2 canisters
55,332/13,153
1.00
3+ canisters
29,993/9,297
1.18 (1.14-1.21)
Treatment step 2
<=2 canisters
62,162/17,215
1.00
3+ canisters
26,059/9,832
1.28 (1.25-1.32)
Treatment step 3
<=2 canisters
88,804/27,137
1.00
3+ canisters
34,282/14,469
1.41 (1.38-1.44)
Treatment step 4
<=2 canisters
39,067/13,623
1.00
3+ canisters
18,199/8,868
1.46 (1.42-1.50)
0.5
1
1.5
2



N at risk							
SABA 0-2	68851	65385	62892	57946	52750	49082	44843
SABA 3-5	23368	22077	21141	19837	18498	17461	16441
SABA 6-10	6625	6171	5872	5530	5213	4944	4694
SABA 11+	1744	1566	1463	1380	1313	1249	1180



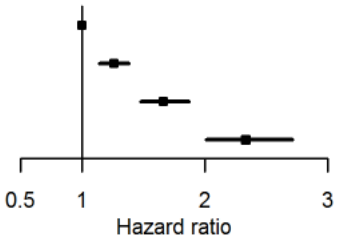
N at risk							
SABA 0-2	185649	174670	166484	154358	141569	132664	122672
SABA 3-5	53251	48719	45612	41932	38516	36007	33533
SABA 6-10	20440	18163	16752	15412	14306	13369	12530
SABA 11+	5396	4490	3986	3618	3343	3135	2932



N at risk										
SABA 0-2	254500	254367	230860	210403	187331	165549	142973	118674	91999	54765
SABA 3-5	76619	76563	71316	66801	61790	56015	49939	43024	34937	22584
SABA 6-10	27065	27034	25769	24552	23280	21836	20212	18503	16436	13034
SABA 11+	7140	7109	6912	6729	6539	6321	6078	5820	5500	4994

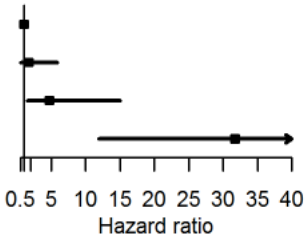
Overall mortality

Baseperiod SABA use	No. of patients/no. of deaths	HR (95% CI)
<=2 canisters	254,500/1,365	1.00
3-5 canisters	76,619/608	1.26 (1.14-1.38)
6-10 canisters	27,065/375	1.66 (1.48-1.87)
11+ canisters	7,140/216	2.33 (2.01-2.71)



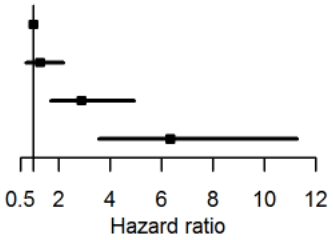
Asthma-related mortality

Baseperiod SABA use	No. of patients/no. of deaths	HR (95% CI)
<=2 canisters	254,500/7	1.00
3-5 canisters	76,619/4	1.70 (0.49-5.88)
6-10 canisters	27,065/5	4.70 (1.47-15.04)
11+ canisters	7,140/12	31.72 (11.88-84.70)



Respiratory-related mortality

Baseperiod SABA use	No. of patients/no. of deaths	HR (95% CI)
<=2 canisters	254,500/43	1.00
3-5 canisters	76,619/19	1.26 (0.73-2.17)
6-10 canisters	27,065/20	2.87 (1.67-4.92)
11+ canisters	7,140/18	6.33 (3.56-11.26)



Supplementary data

Figure S1. Proportion of patients on ICS therapy in different SABA overuse groups, according to continuous overuse of SABA during the baseline year (top panel) and after 3 years follow-up (lower panel)

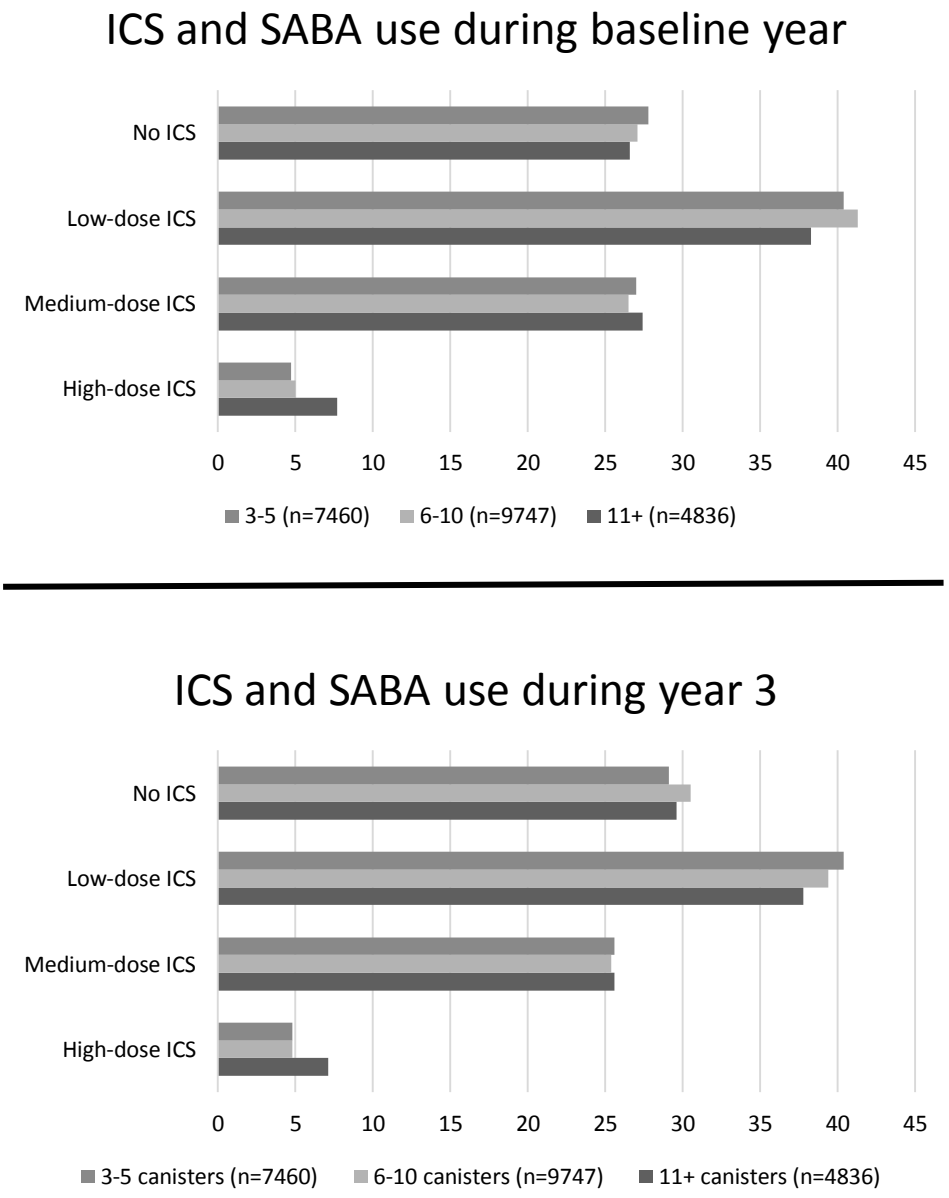


Table S1. Definition of treatment steps

Treatment step	Definition
Step 0	- No dispensing of SABA, LABA, LTRA or ICS
Step 1	- SABA monotherapy
Step 2	- Low-dose ICS - LTRA monotherapy
Step 3	- Medium-/high-dose ICS - Low-dose ICS + LABA or LTRA
Step 4	- Medium-/high-dose ICS + LABA - Medium-/high-dose ICS + LABA or tiotropium - Medium-/high-dose ICS + LTRA
Step 5	- Continuous use of oral steroids (OCS)* - Continuous use of anti-IgE or anti-IL5

*Equivalent to a cumulative dosage of ≥1000 mg prednisolone per year

Table S2. SABA and ICS use during study period

	Baseline year (n=365,324)	**Follow-up year 1 (n=365,324)**	**Follow-up year 2 (n=365,073)**	**Follow-up year 3 (n=334,847)**
SABA canisters, n (%)				
0-2	254,500 (69.7%)	301,413 (82.5%)	306,849 (84.1%)	283,385 (84.6%)
3-5	76,619 (21.0%)	41,846 (11.5%)	37,540 (10.3%)	32,589 (9.7%)
6-10	27,065 (7.4%)	16575 (4.5%)	15,304 (4.2%)	13,861 (4.1%)
11+	7140 (2.0%)	5490 (1.5%)	5380 (1.5%)	5012 (1.5%)
ICS dose, n (%)				
No ICS	100,587 (27.5%)	203,484 (55.7%)	214,575 (58.8%)	205,755 (61.4%)
Low dose	149,925 (41.0%)	94,964 (26.0%)	90,310 (24.7%)	79,185 (23.6%)
Medium dose	98,449 (26.9%)	57,820 (15.8%)	51,987 (14.2%)	43,126 (12.9%)
High dose	16,363 (4.5%)	9056 (2.5%)	8201 (2.2%)	6781 (2.0%)

Table S3. Risk of exacerbation after baseline period stratified by history of exacerbation during baseline period

	Crude		Adjusted	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
No exacerbation at baseline				
Baseline SABA use				
≤2 canisters	1.00		1.00	
3-5 canisters	1.16 (1.14-1.18)	<0.001	1.20 (1.18-1.22)	<0.001
6-10 canisters	1.34 (1.31-1.37)	<0.001	1.33 (1.30-1.36)	<0.001
11+ canisters	1.72 (1.65-1.79)	<0.001	1.62 (1.55-1.69)	<0.001
Exacerbation at baseline				
Baseline SABA use				
≤2 canisters	1.00		1.00	
3-5 canisters	1.21 (1.18-1.24)	<0.001	1.19 (1.16-1.22)	<0.001
6-10 canisters	1.37 (1.32-1.42)	<0.001	1.33 (1.29-1.38)	<0.001
11+ canisters	1.60 (1.51-1.69)	<0.001	1.53 (1.45-1.61)	<0.001

Adjusted for treatment step (GINA 2018), gender, age, and Charlson Comorbidity Index.