High use of short-acting β_2-agonists in COPD is associated with an increased risk of exacerbations and mortality

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High SABA use is relatively common among Swedish patients with COPD and is associated with a higher risk of exacerbations and all-cause mortality. This association, however, is not found in patients using inhaled corticosteroids as maintenance treatment. https://bit.ly/45W2p50

Cite this article as: Janson C, Wiklund F, Telg G, *et al*. High use of short-acting β_2-agonists in COPD is associated with an increased risk of exacerbations and mortality. *ERJ Open Res* 2023; 9: 00722-2022 [DOI: 10.1183/23120541.00722-2022].

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Received: 20 Dec 2022
Accepted: 23 April 2023

Abstract

Background Short-acting β_2-agonist (SABA) overuse has been associated with an increased risk of exacerbations in asthma; however, less is known about SABA use in COPD. Our aim was to describe SABA use and investigate potential associations between high SABA use and the risk of future exacerbations and mortality in COPD.

Methods This observational study identified COPD patients in primary care medical records in Sweden. Data were linked to the National Patient Registry, the Prescribed Drug Registry and the Cause of Death Registry. The index date was 12 months after the date of COPD diagnosis. During a 12-month prior to index baseline period, information on SABA use was collected. Patients were followed with respect to exacerbations and mortality for 12 months post index.

Results Of the 19 794 COPD patients included (mean age 69.1 years, 53.3% females), 15.5% and 7.0% had collected ⩾3 or ⩾6 SABA canisters during the baseline period, respectively. A higher level of SABA use (⩾6 canisters) was independently associated with a higher risk of both moderate and severe exacerbations (hazard ratio (HR) 1.28 (95% CI 1.17–1.40) and 1.76 (95% CI 1.50–2.06), respectively) during follow-up. In total, 673 (3.4%) patients died during the 12-month follow-up period. An independent association was found between high SABA use and overall mortality (HR 1.60, 95% CI 1.07–2.39). This association, however, was not found in patients using inhaled corticosteroids as maintenance treatment.

Conclusion In COPD patients in Sweden, high SABA use is relatively common and associated with a higher risk of exacerbations and all-cause mortality.

Introduction

COPD is estimated to affect between 300 and 400 million people globally [1]. The disease has a large negative impact on health status [2], is associated with high societal cost nationally [3] and is the third most common cause of death globally [4]. The recommended pharmacological maintenance treatment for COPD comprises long-acting muscarinic antagonists (LAMAs), long-acting β_2-agonists (LABAs) and inhaled corticosteroids (ICS) in combination with LABAs or LAMAs+LABAs [5] with short-acting β_2-agonists (SABAs) and short-acting muscarinic antagonists used as reliever medication [5].

In recent years, much attention has been focused on the overuse of SABAs in asthma. Studies have shown that in many countries, over one third of patients with asthma are using ⩾3 canisters of SABAs per year [6–9]. Overuse of SABAs, indicating that asthma is not well controlled, has been associated with an increased risk both of exacerbations [6, 8, 9] and of mortality [6]. Moreover, SABA overuse has been associated with an increased carbon footprint due to the emission of greenhouse gases [10].

In contrast, less is known about the use and possible effects of high use of SABAs in COPD. In a retrospective analysis of clinical trial data, Jenkins *et al*. [11] reported that the level of SABA use during the first month of the study was predictive of the risk of exacerbations in the following 10-month period of the study. A correlation between a high level of SABA use and a low health status measured with the COPD Assessment Test has also been described [12], while a reduction in the use of SABAs has been reported as a clinical outcome in treatment trials [13–15]. Notably, an observational registry study from the UK reported that SABA use was associated with an increased risk of cardiovascular events in COPD [16].

The aims of this study, therefore, were to describe the use of SABAs and investigate potential associations between high SABA use and the risk of future exacerbations and mortality in patients with COPD in Sweden. Our hypothesis was that high SABA use is associated with an increased risk of exacerbations and mortality in COPD.

Materials and methods

Study population

In this observational cohort study, patients with COPD were identified in primary care medical records [17]. Data from the medical records were linked to the National Patient Registry, the Swedish Prescribed Drug Registry and the Cause of Death Registry by the Swedish National Board of Health and Welfare. The primary healthcare centres included in the study were either publicly funded (Region Stockholm) or both publicly and privately funded (Region Uppsala), and covered ∼2.7 million inhabitants. The linked database was managed by the Department of Medical Sciences, Respiratory Medicine at Uppsala University, Sweden. Registry data linkage was approved and performed by the Swedish National Board of Health and Welfare, and individual patient consents to participate were not collected as they are not required in Sweden when de-identified public register data are used for research. The study protocol was reviewed and approved by the Regional Ethics Committee in Uppsala, Sweden (reference number 2016/486), and the study was performed in accordance with applicable legislation on non-interventional studies and/or observational studies.

Patients aged ⩾40 years and diagnosed with COPD (ICD-code J44) in the medical records between January 2006 and December 2017 were included in the study. The index date was set at 12 months after the date of the COPD diagnosis. A baseline period of 12 months before the index was used to collect information on SABA use. Patients were followed with respect to exacerbations and mortality for 12 months post index (figure 1).

Patients were categorised in Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups based on the exacerbation history during the baseline year [5]. Because of lack of information on symptoms, the patients were categorised as either GOLD A and B or GOLD E.

Patients with asthma (ICD-10 J45, J46), Crohn's disease (K50), ulcerative colitis (K51), rheumatoid arthritis (M05) or polymyalgia rheumatica (M35.3) registered at any time prior to the index date were excluded, as were patients with a record of malignant disease (C00–C43, C45–C96) except for basal cell carcinoma up to 12 months prior to the index date (figure 1).

Measurements

To align with the definition of SABA overuse in asthma studies [6–9], a standardised SABA canister unit was defined as 150 doses and high SABA use was defined as a collection of ⩾3 canisters at the pharmacy

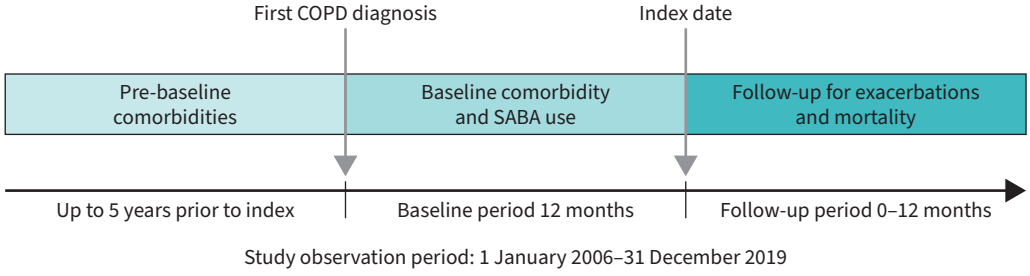

FIGURE 1 Study design. SABA: short-acting β_2-agonist.

at any time during the baseline year. Patients were stratified by baseline SABA use into the following three groups: 0–2, 3–5 and ⩾6 canisters to allow for comparison with the Swedish study of SABA use in asthma [6]. In addition, overall SABA use was quantified as the number of canisters collected per calendar year during the study period.

Other inhaled COPD treatments were identified in the Prescribed Drug Registry as collections of prescribed medications during a 4-month window prior to the study index date to minimise the risk of misclassification of patients' inhaler use due to changes in medication during the 12-month baseline period.

Comorbidities (ICD-10 codes) were identified up to 5 years prior to the index date. The Charlson Comorbidity Index (CCI) was calculated at the index date and the date of the first exacerbation using the ICD-10 coding algorithm developed by Quan *et al*. [18, 19] by summing the weighted scores for all individual comorbidities. Comorbidity medications were described for the 12-month baseline period (figure 1).

Outcomes

Moderate exacerbations were defined as COPD-related emergency room visits (visits with an ICD-10 code J44.0 or J44.1) and/or administration of oral corticosteroids (ATC code H02AB) and/or respiratory antibiotics (ATC code J01AA02, J01AA07, J01CA01, J01CA04). Severe exacerbations were defined as COPD-related hospitalisations. Recurrent exacerbations within 14 days were considered as one exacerbation.

Mortality data (all-cause and respiratory-related) were collected from the Cause of Death Registry.

Statistical methods

Baseline characteristics were described as mean±SD for continuous variables and absolute and relative frequencies for categorical variables. For each individual, the follow-up period for exacerbations and mortality started on the index date (12 months after the COPD diagnosis) and ended 12 months after the index date.

Differences between the SABA groups were evaluated using a Kruskal–Wallis test (continuous variables) and a Chi-square test (categorical variables).

Sub-hazard ratios (SHRs) for both moderate and severe exacerbations during the observation time were determined based on baseline SABA use with a 95% confidence interval (CI) and accounting for competing risk of death. The SHRs were analysed both as crude and as adjusted for age, sex, maintenance treatments and comorbidities (Model 1); and for age, sex, maintenance treatment, comorbidities and exacerbations (Model 2).

Hazard ratios (HRs) were determined using a Cox model for overall mortality and adjusted for age, sex, maintenance treatment and comorbidities (Model 1); and for age, sex, maintenance treatment, comorbidities and exacerbations (Model 2). Assessment of SABA use and overall mortality was also performed stratified by maintenance treatment, and the differential effect of SABAs by maintenance treatment was explored through a likelihood ratio test of the interaction term between SABAs and maintenance treatment. Causes of death were based on diagnosis codes (ICD-10) in the Cause of Death Registry.

A sensitivity analysis on the association of SABA use and exacerbations were made in patients without exacerbations during the baseline period.

Results

Overall, this study included 19 794 patients with a COPD diagnosis (mean age 69.1 years, 53.3% females) of whom 5958 (30.1%) had collected SABAs during the baseline year (table 1). Of these, 3071 (15.5%) and 1389 (7.0%) had collected ⩾3 canisters and ⩾6 canisters, respectively. Patients with a higher SABA use more often used ICS treatment and experienced exacerbations during the baseline period than patients using less SABA (table 1).

Among patients who collected six or more SABA canisters during baseline, almost half were defined as GOLD E patients, whereas the corresponding number for those collecting 0 to 2 SABA canisters was 25% (table 1). The proportion of patients using three or more SABA canisters during baseline was 16.2% in

TABLE 1 Baseline characteristics of the study population

	All	SABA: 0–2[#]	SABA: 3–5[#]	SABA: ⩾6[#]
Patients n	19 794	16 723	1682	1389
Males	9243 (46.7)	7931 (47.4)	715 (42.5)	597 (43.0)
Age years	69.1±10.4	69.2±10.4	68.6±10.4	68.1±10.0
Treatment[¶]				
No treatment	5163 (26.1)	4930 (29.5)	171 (10.2)	62 (4.5)
LAMA or LABA	5218 (26.4)	4646 (27.8)	356 (21.2)	216 (15.6)
LAMA and LABA	802 (4.1)	669 (4.0)	81 (4.8)	52 (3.7)
ICS	904 (4.6)	612 (3.7)	175 (10.4)	117 (8.4)
ICS+LAMA or ICS+LABA	3381 (17.1)	2685 (16.1)	379 (22.5)	317 (22.8)
ICS+LAMA+LABA	4326 (21.9)	3181 (19.0)	520 (30.9)	625 (45.0)
Exacerbations (any type)				
0	11 514 (58.2)	10 258 (61.3)	764 (45.4)	492 (35.4)
1	4892 (24.7)	4101 (24.5)	441 (26.2)	350 (25.2)
2	1775 (9.0)	1317 (7.9)	239 (14.2)	219 (15.8)
3	730 (3.7)	498 (3.0)	110 (6.5)	122 (8.8)
4+	883 (4.5)	549 (3.3)	128 (7.6)	206 (14.8)
GOLD groups				
A and B	14 797 (74.8)	13 035 (77.9)	1048 (62.3)	714 (51.4)
E	4997 (25.2)	3688 (22.1)	634 (37.7)	675 (48.6)
Charlson Comorbidity Index[+]				
CCI: 0–1	11 096 (56.1)	9226 (55.2)	1013 (60.2)	857 (61.7)
CCI: 2	4544 (23.0)	3869 (23.1)	347 (20.6)	328 (23.6)
CCI: 3	2117 (10.7)	1846 (11.0)	155 (9.2)	116 (8.4)
CCI: 4	1067 (5.4)	929 (5.6)	84 (5.0)	54 (3.9)
CCI: 5+	970 (4.9)	853 (5.1)	83 (4.9)	34 (2.4)

Data are presented as n, n (%) or mean±SD. SABA: short-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroids; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CCI: Charlson Comorbidity Index. [#]: number of SABA canisters collected during the baseline year; [¶]: collections during the 4 months prior to the index date; [+]: determined up to 5 years before the index date.

GOLD E and 11.9% in GOLD A and B (supplementary table S1). In GOLD A and B, 30% of the patients were not using any maintenance treatment and 17% were on triple treatment at baseline. The corresponding numbers for the GOLD E group were 15% and 35%, respectively (supplementary table S1).

There were no differences in sex, age or the CCI between patients who used a high number of SABA canisters and those who did not (table 1). Additionally, >30% of patients in the SABA 3–5 canister group and 20% in the SABA ⩾6 canister group had either no maintenance treatment or treatment with only one long-acting bronchodilator at baseline. The use of SABAs over time showed a U-form pattern with the highest proportion of patients using ⩾3 canisters of SABAs in the first and last years of the study (figure 2). During the same period the proportion of patients using LAMA and LABA but not ICS had increased from 21% in 2006 to 41% in 2017, whereas the proportion using ICS with or without long-acting bronchodilators had decreased from 62% to 28%.

Patients with a high SABA use also had a higher use of N-acetylcysteine, antibiotics and cough medication compared to those with a lower SABA use, whereas no differences were seen in cardiovascular or psychiatric medication use (table 2).

A higher level of SABA use was associated with a higher risk of both moderate and severe exacerbations during the follow-up period (figure 3). This association remained statistically significant after adjusting for potential confounders (table 3). Moreover, in a sensitivity analysis that included only patients without exacerbations during the baseline period, this association remained (supplementary Table S2).

In total, 673 (3.4%) patients died during the 12-month follow-up period. Overall mortality was found to be associated with high SABA use (table 4), an association that remained statistically significant both after adjusting for baseline maintenance treatment and exacerbations (table 4) and after excluding patients without any exacerbations during the baseline period (supplementary Table S3).

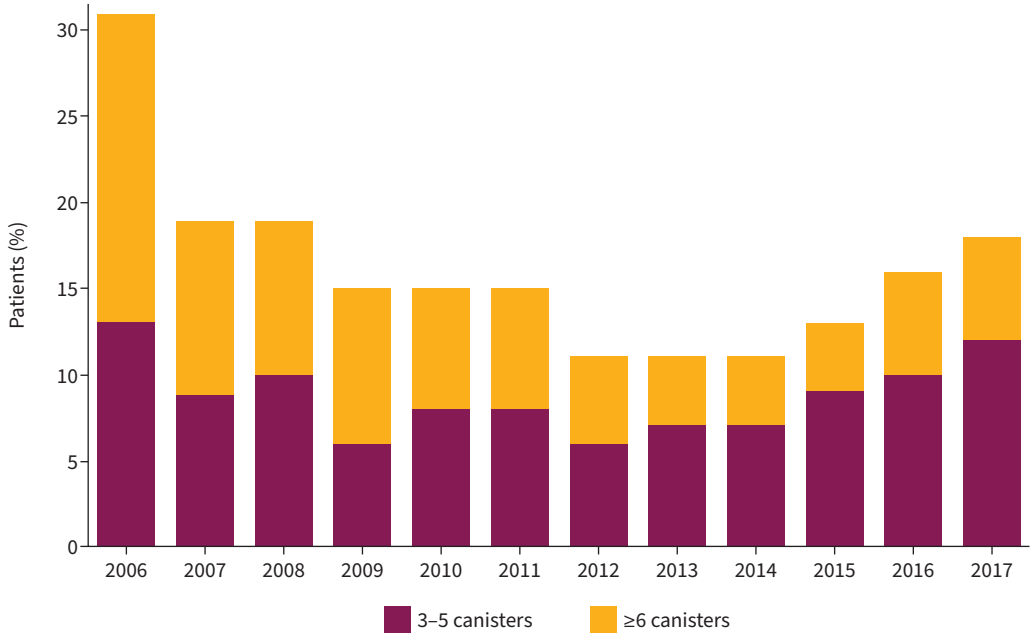

FIGURE 2 Annual use of short-acting β_2-agonists (3–5 and ⩾6 canisters) during the study period.

After patients were stratified by their maintenance treatment, those using LAMAs and or LABAs and ⩾6 SABA canisters per year had an increased risk of mortality. There was no association between SABAs and mortality in patients using ICS combined with LABAs and/or LAMAs (figure 4). A significant interaction was found when comparing patients with ⩾6 canisters of SABAs with those using less SABAs in relation to maintenance treatment and mortality ($p_{interaction}$=0.02).

TABLE 2 Concomitant baseline medications

	All	SABA: 0–2#	SABA: 3–5#	SABA: ⩾6#
Patients n	19 794	16 723	1682	1389
PD4 antagonists	51 (0.3)	31 (0.2)	6 (0.4)	14 (1.0)
N-acetylcysteine	6446 (32.6)	4865 (29.1%)	770 (45.8)	811 (58.4)
Cardiovascular	14 009 (70.8)	11 789 (70.5)	1220 (72.5)	1000 (72.0)
Anti-dyslipidaemics	6562 (33.2)	5643 (33.7)	544 (32.3)	375 (27.0)
Statins	6447 (32.6)	5543 (33.1)	536 (31.9)	368 (26.5)
Fibrates	100 (0.5)	83 (0.5)	12 (0.7)	5 (0.4)
Anti-hypertensives	11 167 (56.4)	9490 (56.7)	952 (56.6)	725 (52.2)
β-blockers	7523 (38.0)	6461 (38.6)	615 (36.6)	447 (32.2)
ACEi	5181 (26.2)	4429 (26.5)	414 (24.6)	338 (24.3)
ARBs	3814 (19.3)	3207 (19.2)	338 (20.1)	269 (19.4)
Antibiotics	6725 (34.0)	5267 (31.5)	739 (43.9)	719 (51.8)
Cough medications	8459 (42.7)	6578 (39.3)	963 (57.3)	918 (66.1)
Antihistamines	2387 (12.1)	1872 (11.2)	286 (17.0)	229 (16.5)
Nasal corticosteroids	1913 (9.7)	1504 (9.0)	234 (13.9)	175 (12.6)
Antidepressant	4282 (21.6)	3524 (21.1)	417 (24.8)	341 (24.6)
Anxiolytics	3706 (18.7)	2988 (17.9)	394 (23.4)	324 (23.3)
Hypnotics and sedatives	5957 (30.1)	4932 (29.5)	559 (33.2)	466 (33.5)
Bifosfonates	955 (4.8)	781 (4.7)	84 (5.0)	90 (6.5)
Calcium/vitamin D	140 (0.7)	119 (0.7)	9 (0.5)	12 (0.9)

Data are presented as n (%). SABA: short-acting β_2-agonist; PD4: phosphodiesterase-4; ACEi: angiotensin-converting enzyme inhibitor; ARBs: angiotensin II receptor blockers. #: number of SABA canisters collected during the baseline year.

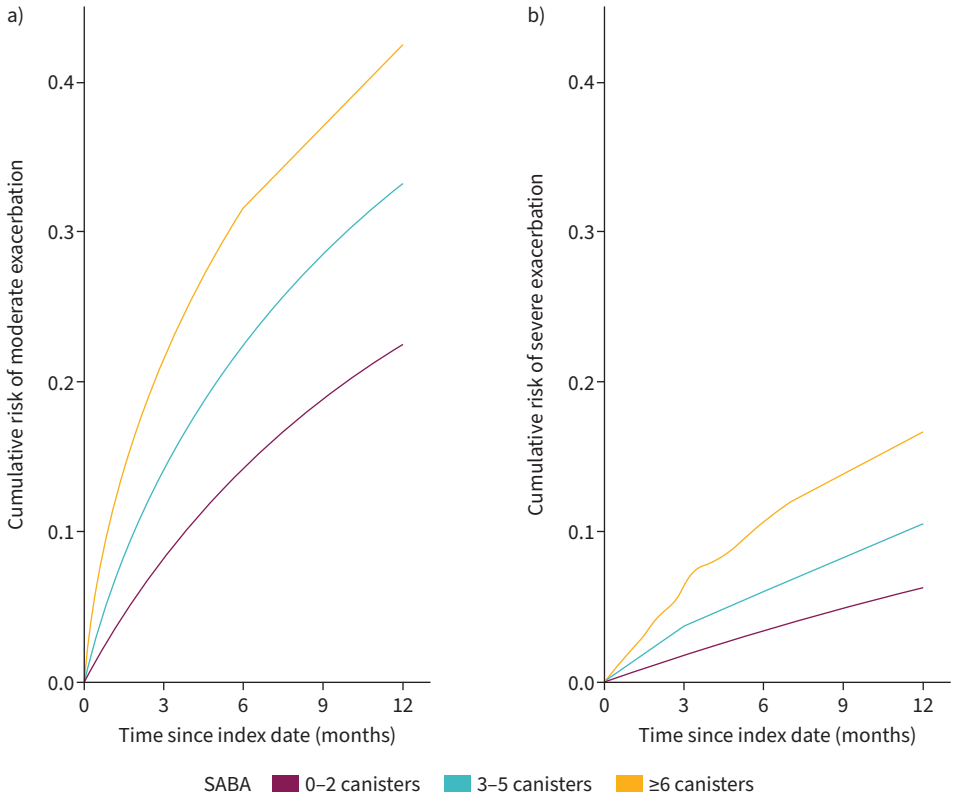

FIGURE 3 Cumulative risk of a) moderate and b) severe exacerbation by baseline short-acting β_2-agonist use accounting for the competing risk of death. SABA: short-acting β_2-agonist.

The most common cause of death was cardiovascular disease. There were no clear associations between SABA use and any specific cause of death (supplementary Table S4).

Discussion

The main findings of this observational cohort study of almost 20 000 patients with COPD in primary care in Sweden were that high use of SABAs is relatively common in patients with COPD and that high SABA use was associated with a higher risk of exacerbations and all-cause mortality in this patient group. The association between SABAs and mortality was, however, not seen in patients with COPD who used ICS in combination with LABAs and/or LAMAs.

TABLE 3 Sub-hazard ratios and 95% confidence interval of moderate and severe COPD exacerbations after the index date by baseline SABA use accounting for competing risks of death

	Crude	Model 1[#]	Model 2[¶]
Moderate exacerbations: SABA baseline[+]			
0–2	1	1	1
3–5	1.59 (1.46–1.72)	1.35 (1.24–1.47)	1.14 (1.04–1.25)
⩾6	2.27 (2.08–2.46)	1.78 (1.63–1.94)	1.28 (1.17–1.40)
Severe exacerbations: SABA baseline[+]			
0–2	1	1	1
3–5	1.75 (1.49–2.06)	1.48 (1.26–1.75)	1.29 (1.09–1.52)
⩾6	2.91 (2.52–3.37)	2.33 (2.01–2.71)	1.76 (1.50–2.06)

SABA: short-acting β_2-agonist. [#]: adjusted for age, sex, maintenance treatment and comorbidities; [¶]: adjusted for age, sex, maintenance treatment and comorbidities, and number of baseline exacerbations; [+]: number of SABA canisters collected during the baseline year.

TABLE 4 Hazard ratio with corresponding 95% confidence intervals of overall mortality by baseline SABA use

	Model 1[#]	Model 2[¶]
SABA baseline[+]		
0–2	1	1
3–5	1.14 (0.84–1.55)	1.18 (0.87–1.61)
⩾6	1.69 (1.13–2.51)	1.60 (1.07–2.39)

SABA: short-acting β_2-agonist. [#]: adjusted for age, sex and comorbidities; [¶]: adjusted for age, sex, comorbidities, maintenance treatment and baseline exacerbations; [+]: number of SABA canisters collected during the baseline year.

Studies investigating the use of SABAs in real-world COPD populations are scarce. In contrast, increasing evidence shows that the overuse of SABAs in asthma is common and associated with asthma exacerbations and both respiratory and all-cause mortality [6–8]. Hence, the Global Initiative for Asthma guidelines no longer recommend SABAs as monotherapy for asthma [20]. In our study, we showed that 31.1% of patients collected SABAs during the 12-month baseline period. In a recent Canadian study, 41.5% of COPD patients had collected SABAs during a 2-year baseline period [21]; in that study, the use of SABAs decreased during the study period (1997–2015), whereas we found that SABA use was highest in the first and the last years of the study period (2006–2017). We had expected that the trend for SABA use would have been similar to the report from the Canadian study. We have no explanation as to why we saw an increased use of SABA at the end of the study period in our study. During the study period, we observed an increased use of long-acting bronchodilators and a decreased use of ICS reflecting the national COPD guidelines applicable at the time [22]. In the present study, a high use of SABA was more common in patients in the GOLD E group compared to GOLD A and B, whereas there was no association between SABA use and comorbidities. The prevalence of high SABA use in Sweden was lower in patients with COPD than in those with asthma as in our study, 15.5% of patients with COPD were high SABA users, whereas in a previous study of Swedish patients with asthma, 30% overused SABAs [6].

In a smaller study by Fan *et al.* [23], SABA overuse in COPD was common and associated with increased disease severity and symptoms. We found that a high use of SABAs was associated with an increased risk of exacerbations in line with previous reports for asthma [6, 8, 9]. Other studies have also shown an association between SABA overuse and the disease severity and burden of COPD [12, 23]. A systematic review from 2017 reported that a reduction in the number of rescue puffs per day was associated with a decrease in the rate of moderate or severe exacerbations [13]. It could be argued that a high SABA use signals disease deterioration. Indeed, the onset of a COPD exacerbation is often preceded by lung function decline [24] and deterioration in the symptoms of dyspnoea, sore throat, cough and those of a common cold [25], with an

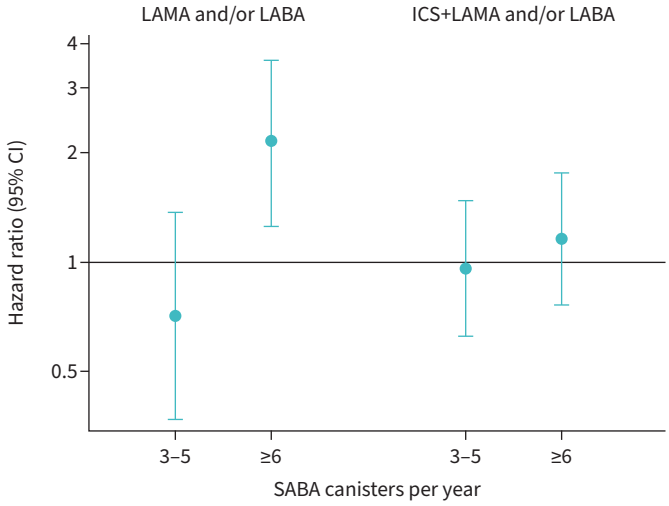

FIGURE 4 Association between short-acting β_2-agonist use and mortality with patients stratified by type of maintenance treatment used. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting β_2-agonist.

increased use of rescue medication [26]. In addition, a *post hoc* analysis of the RISE study, a randomised clinical trial that included COPD patients with a history of exacerbations, showed that COPD symptom-related deteriorations treated with increased SABA doses are common and contribute to negative outcomes [27]. In this study, COPD symptom-related attacks were typically unreported by patients. In fact, previous research has indicated that as many as half of all COPD exacerbations may go underreported and thus lead to suboptimal treatment [28–30]. In our study, a high use of SABAs was associated with an increased risk of exacerbations. Notably, 20–30% of the high SABA users had either no maintenance treatment or only a long-acting bronchodilator at baseline. This is consistent with another Swedish study, which reported that after a severe COPD exacerbation leading to hospitalisation, more than one third of patients with COPD were either untreated or undertreated, *i.e.*, treated with only a LABA or a LAMA [31].

Our finding that high SABA use in the baseline period was associated with an increased risk of exacerbations and mortality during follow-up may suggest that high SABA use is a marker of more severe disease and should, therefore, trigger the treating physician to assess a patient's COPD status and adjust treatment accordingly. It is, however, possible that the high use of SABAs could have negative effects *per se*. In asthma, high SABA use has been associated with increased bronchial responsiveness and development of tolerance to the bronchodilating effect of β_2-agonists [32]. A reduced effect of LABAs in patients with COPD who are high SABA users has also been reported [14]. Some studies indicate that ICS inhibit β_2-receptor downregulation by increasing the expression of the receptor [33]. This could explain why the association between SABAs and mortality was observed in patients who were only using long-acting bronchodilators and not in those using ICS in combination with LAMAs and LABAs. Almost one in five patients were treated with ICS+LAMA or LABA. ICS+LABA is no longer a recommended COPD treatment according to GOLD guidelines [5]. In patients treated with ICS+LABA, where a change of treatment is considered, our results highlight the importance of a thorough evaluation to determine if these patients will benefit the most from treatment with dual bronchodilators or if they should be stepped up to triple therapy and thus retain the ICS component. High SABA use may also have negative cardiovascular effects [16]; however, we found no association between the use either of SABAs and/or cardiovascular drugs, or cardiovascular mortality. In this study, we excluded patients that had concurrent asthma. Had we included this group of patients, the proportion using ICS would have been higher and the association between SABA use and mortality possibly lower.

An important strength of our study was the large, unselected and population-based cohort of patients with COPD, which allowed us to explore real-world data covering both primary and secondary care. Moreover, primary care electronic medical record data were linked with national healthcare registries with high quality and coverage providing a solid and unique dataset. This study also has some limitations that should be considered when interpreting the results. The major limitation is that clinical data, such as lung function measurements, smoking, cough status and symptoms, were not available in our data set. The lack of lung function measurements in our data may suggest a risk that patients were misclassified at diagnosis, although it should be noted that spirometry is available in almost all primary healthcare centres in Sweden [34]. In addition, the lack of lung function data made it impossible to categorise the patients based on the severity of COPD by use of the GOLD 1–4 classification [5]. We have tried to mitigate this limitation by categorising patients in GOLD A+B or E groups as a measure of disease severity. Emergency room visits were defined by ICD-10 codes for acute disease, but it is not known how frequently these codes are used, and exacerbations may be underreported in this study. In addition, reported treatments were based on pharmacy claims, which may not fully reflect patients' actual medication use.

In conclusion, we found that a high use of SABAs is relatively common among patients with COPD in Sweden and that this is associated with a higher risk of exacerbations and all-cause mortality. Interestingly, this association was not seen in patients on ICS. Patients with high SABA use should be followed closely to ensure optimal COPD treatment and management.

Provenance: Submitted article, peer reviewed

Acknowledgements: Grażyna Söderbom, Klipspringer AB, is acknowledged for editorial support sponsored by AstraZeneca.

Data sharing: The dataset supporting the conclusions of this article are available upon request.

Support statement: The study and editorial support was sponsored by AstraZeneca. Funding information for this article has been deposited with the Crossref Funder Registry.

Author contributions: All authors significantly contributed to the work reported either in the study conception, design, execution; data acquisition, analysis, and interpretation; or in all of these areas. All authors also participated in drafting, revising or critically reviewing the article; read and approved the final version to be published; agreed on the journal to which the article has been submitted; and, agreed to be accountable for all aspects of the work. All authors consent to publish these data.

Conflict of interest: C. Janson has received payments for educational activities from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva, and has served on advisory boards arranged by AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva. F. Wiklund is employed at Statisticon of which AstraZeneca is a client. G. Telg and G. Stratelis are employed by AstraZeneca. H. Sandelowsky has received honoraria for educational activities from Boehringer Ingelheim, Novartis, AstraZeneca, Chiesi, and TEVA, an unrestricted research grant from AstraZeneca, and has served on advisory boards arranged by AstraZeneca, Novartis, Chiesi, and GlaxoSmithKline.

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