Original Article

Long-Term Use of Short-Acting β_2-Agonists in Patients With Adult-Onset Asthma

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What is already known about this topic? Short-term studies have associated high use of short-acting β_2-agonists (SABA) with increased risk of exacerbations, emergency visits, and asthma-related costs. However, no studies exist on long-term SABA use with clinical examinations of patients with asthma.

What does this article add to our knowledge? High use and over-reliance on SABA is infrequent in patients with clinically confirmed adult-onset asthma. Obesity and higher symptom score at diagnosis predicted higher long-term SABA use.

How does this study impact current management guidelines? Although high use and over-reliance on SABA are infrequent in patients with confirmed adult-onset asthma, high SABA use indicates more severe asthma and is associated with obesity at diagnosis emphasizing early recognition of these patients.

BACKGROUND: Short-term studies have associated high use of short-acting β_2-agonists (SABA) with increased risk of exacerbations, emergency visits, and asthma-related costs. However, no studies exist on long-term SABA use, and previous studies on the topic have not included information about adherence to inhaled corticosteroids (ICS) nor disease control, both affecting the need of SABA.

OBJECTIVE: To evaluate the clinical characteristics of SABA and ICS usage in newly diagnosed adult-onset asthma patients during a 12-year follow-up period.

METHODS: In the Seinäjoki Adult Asthma Study, 203 patients with adult-onset asthma were followed for 12 years. Information on dispensed SABA and ICS during the follow-up was obtained from the Finnish Social Insurance Institution. High SABA use was defined as ≥36 canisters in 12 years, corresponding to an average of ≥3 dispensed canisters/y.

RESULTS: Patients were dispensed median 6 (interquartile range: 3-16) SABA canisters and 48 (18-67) ICS canisters over 12 years, corresponding to 2 (1-4) and 11 (5-16) puffs/week, respectively. Only 10% of the patients were classified as high SABA users during this period. Obesity (body mass index ≥30) and high Airways Questionnaire 20 symptom scores at baseline predicted high long-term SABA use (incidence rate ratio: 1.53 [1.01-2.30] and 1.04 [1.00-1.08], respectively). High SABA users had higher ICS adherence, higher blood neutrophil counts, more comorbidities, and

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Abbreviations used
ACT- Asthma Control Test
AQ20- Airways Questionnaire 20
BD- Bronchodilator
BDP- Beclomethasone dipropionate
BMI- Body mass index
FEV_1- Forced expiratory volume in 1 second
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
IQR- Interquartile range
LABA- Long-acting β_2-agonist
LAMA- Long-acting muscarinic antagonist
OCS- Oral corticosteroids
SAAS- Seinäjoki Adult Asthma Study
SABA- Short-acting β_2-agonist
SD- Standard deviation

used more oral corticosteroid and antibiotic courses versus low SABA users.
CONCLUSION: High SABA use was infrequent in patients with confirmed adult-onset asthma. However, as high SABA use is associated with more severe asthma, these patients should be recognized in clinical practice. **(J Allergy Clin Immunol Pract 2022;10:2074-83)**

Key words: *Asthma; Adult-onset; Reliever therapy; Short-acting β_2-agonists; Asthma treatment; Asthma control; Obesity; Prognosis; Long-term; Follow-up*

Frequent use of short-acting β_2-agonists (SABA) is one of the key indicators for noncontrolled asthma.[1] In patients using SABA or long-acting β_2-agonist (LABA) regularly, response to bronchodilators (BDs) may be reduced because of down-regulation of β_2-receptors, a phenomenon known as desensitization.[2,3] Excessive use of SABA has been reported to be strongly associated with increased risk of asthma-related deaths, asthma exacerbations, emergency visits, and asthma-related costs.[4-9]

In previous cross-sectional and retrospective studies, high SABA use has been reported to be common with approximately 20% of patients using $\geq$3 canisters per year.[5,7,10] These estimates may be biased because inclusion (ie, the definition of asthma) was based on dispensed medication for obstructive airway diseases (Anatomical Therapeutic Chemical code R03) or diagnosis code in the database, resulting in the possible inclusion of patients without clinically confirmed asthma or patients with other diseases such as chronic obstructive pulmonary disease. Most of the studies investigating SABA use have been cross-sectional and assessed medication use in short term, usually over a 1-year period. Remission rates range from 20%-65% in early-onset asthma[11-13] to 3%-11% in adult-onset asthma[11,14,15] and highlight the need for a long-term study of more precise estimates of patients' medication-related behavior.

Over-reliance on SABA and high use of SABA are often used as synonyms, which they are not. The former is a subset of the latter and includes only those who use a lot of SABA without sufficient/adequate maintenance treatment. The latter includes all subjects who use a lot of SABA also including those with adequate maintenance medication. Therefore, the aim of the present study was to assess how patients with clinically confirmed new-onset adult asthma use SABA during the 12-year follow-up period after asthma diagnosis. Previous studies have indicated that high SABA users often have insufficient dispensing of controller medication,[16] that is, they are over-reliant on SABA. Therefore, our objective was to determine if patients with high SABA use and over-reliance on SABA exist in a cohort of patients with adult-onset asthma and how these patients differ from those using less SABA. To achieve this goal, we assessed dispensed amounts of SABA and inhaled corticosteroids (ICS) during the whole 12-year follow-up and evaluated patients' asthma control and adherence to ICS treatment.

METHODS

Study design and patients

This prospective, 12-year follow-up study included 203 patients with diagnosis of new-onset adult asthma (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org) as part of the Seinäjoki Adult Asthma Study (SAAS) (ClinicalTrials.gov ID NCT02733016). All new asthma patients 15 years of age or older were included during the period of 1999-2002, representing over 94% of patients diagnosed with novel asthma in Seinäjoki Central Hospital, Finland. Asthma diagnosis was made by a respiratory specialist based on lung function measurements and typical symptoms of asthma. The study protocol, diagnostic criteria, and inclusion/exclusion criteria have been published earlier[17] (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Importantly, patients with comorbidities or smoking history were included. A written informed consent was obtained to a study protocol approved by the ethics committee of Tampere University Hospital, Tampere, Finland.

The study involved the baseline and 12-year follow-up visits (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org) in which data on, for example, symptoms, comorbidities, and medication were collected.[14,17-20] In addition, demographics of the patients such as age, gender, level of education, and monthly gross income (€) were collected, and lung function was evaluated based on spirometry measurements (see this article's Online Repository at www.jaci-inpractice.org). After diagnosis, patients were treated according to the principles of the Finnish Asthma Programme.[21] From the original cohort of 257 patients, 203 (79%) returned for the 12-year follow-up visit. Data were gathered from all asthma-related visits: primary and secondary care as well as private health care.[22]

Assessment of dispensed SABA and ICS

Data from dispensed SABA and ICS were obtained from the Finnish Social Insurance Institution, which records purchased medication from all Finnish pharmacies. SABA use was quantified as canisters collected annually (per calendar year) and cumulatively (during 12 years) over the 12-year period. To account for different number of doses in different types of canisters (Table E2, available in this article's Online Repository at www.jaci-inpractice.org), we counted all doses of dispensed SABA during 12-year follow-up and divided the sum by 150 to express SABA use as standard canisters of 150 doses. Dispensed ICS was expressed similarly as canisters of 150 doses. The controller-to-total medication ratio[23,24] was computed by dividing dispensed ICS canisters by the sum of dispensed SABA and ICS canisters during the follow-up period. The 12-year adherence was calculated by comparing cumulative dispensed doses of ICS (μg)

with cumulative prescribed doses of ICS (μg) by using a method combining medication possession ratio and proportion of days covered formulas (Figures E2 and E3, available in this article's Online Repository at www.jaci-inpractice.org) (see this article's Online Repository at www.jaci-inpractice.org).[19,25]

High SABA use was defined as ≥36 SABA canisters in 12 years, corresponding to an average of ≥3 dispensed canisters per year.[1,5,7,10] SABA over-reliance was classified into 3 categories: (1) high SABA use (≥36 canisters in 12 years) and no dispensed ICS canisters during the follow-up; (2) high SABA use and <36 dispensed canisters of ICS (corresponding to <3 dispensed canisters per year on average); and (3) high SABA use and fewer ICS than SABA canisters dispensed. If a patient on maintenance ICS uses a lot of SABA, a need for step-up in maintenance medication is indicated. We therefore also analyzed the number of patients who had high use of SABA and were on maintenance ICS but were not dispensed any second controllers (LABA or long-acting muscarinic antagonist [LAMA]) to reveal signs of undertreatment.

Evaluation of symptoms, asthma control, and dispensed oral corticosteroids

Patients filled out the Airways Questionnaire 20 (AQ20) at baseline visit, and symptoms were measured during the follow-up visit both with AQ20[26] and Asthma Control Test (ACT).[27] The AQ20 is a short well-validated questionnaire to measure and quantify disturbances in the airway-specific quality of life where higher scores indicate poor quality of life.[26] ACT is a widely used self-administered tool for identifying those with poorly controlled asthma (low ACT scores).[27]

To define asthma control, patients were separated into 2 groups by asthma control at the follow-up visit, which were defined according to the Global Initiative for Asthma (GINA) 2010 report[28] as previously reported.[14] Patients with noncontrolled asthma (partially controlled or uncontrolled asthma) had at least one of the following features: symptoms of asthma or need for rescue treatment more than twice weekly, decreased lung function (<80% predicted), or limitation of activities due to asthma.

Dispensed doses of oral corticosteroids (OCS) (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up as previously described.[19] Regarding dispensed OCS, only those prescribed as part of asthma treatment were considered.

Statistical analyses

The results are shown as mean (standard deviation [SD]), or median (interquartile range [IQR]). Comparison of baseline and follow-up values was evaluated by the related samples Wilcoxon signed-rank test or the McNemar test. Comparison of groups with SABA use of ≥3 or <3 canisters annually was analyzed by using the independent samples *t*-test, Mann-Whitney *U* test, and Fisher exact test. A negative binomial regression analysis was performed to analyze factors predicting high SABA use (number of dispensed SABA canisters over 12 years). We used only baseline characteristics recorded at asthma diagnosis as covariates to predict SABA use at the follow-up period. We calculated the incidence rate ratios with 95% confidence interval for SABA canister use. Owing to overdispersion, we used negative binomial regression and adjusted it for age of asthma onset, sex, smoking status, AQ20, diagnostic forced expiratory volume in 1 second (FEV_1) (%), and body mass index (BMI). The natural logarithm of the length of follow-up was set as an off-set variable. A *P* value of <.05 was regarded as statistically significant. Statistical analyses were performed using IBM SPSS statistics software, version 27 (IBM SPSS, Armonk, NY).

RESULTS

Patient characteristics

The study population consisted of 203 patients with adult-onset asthma and the majority were females (58%), with the mean age of asthma onset of 46 (SD, 14) years (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Half of the patients were current or ex-smokers (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). At the 12-year follow-up visit, patients had generally higher BMI, better lung function, and lower blood eosinophil counts compared with the baseline visit (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Patterns of SABA and ICS use during 12-year follow-up

Patients with adult-onset asthma were dispensed a median of 6 (IQR: 3-16) canisters of SABA and 48 (18-67) canisters of ICS during 12 years, corresponding to use of median 2 (1-4) SABA and 11 (5-16) ICS puffs per week (Figure 1, *A* and *B*; Figure E4, available in this article's Online Repository at www.jaci-inpractice.org). Most patients used ≥3 canisters of ICS (60%) and <2 canisters of SABA (88%) per year, on average (Figure 2, *A* and *B*). When considering long-term, cumulative use, 58% (n = 118) of patients used <10 canisters of SABA and 59% were dispensed ≥40 canisters of ICS during 12 years (Figure E5, available in this article's Online Repository at www.jaci-inpractice.org).

High use and over-reliance on SABA

The patients were divided into 2 groups according to their use of SABA during the 12-year follow-up period (≥3 or <3 canisters annually). Of the study patients, 10% (n = 21) were classified as high SABA users (≥36 canisters in 12 years, corresponding to ≥3 dispensed canisters per year, on average). Over-reliance on SABA was infrequent because all high SABA users were also dispensed ICS during the follow-up. Of these, only 2 patients were dispensed <3 canisters of ICS annually (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Moreover, in 12 years of follow-up, 5 patients classified as high SABA users were dispensed fewer ICS canisters than SABA. By using any of the predefined criteria for SABA over-reliance, only these 5 patients (2%) were found to have any signs of SABA over-reliance. Possible undertreatment was recognized in 2 (1%) patients as they were high SABA users but were not dispensed ICS+LABA or ICS+LAMA (Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

Factors predicting high use of SABA

Because over-reliance on SABA was infrequent in this cohort of patients with new adult-onset asthma, we continued analysis in patients with high SABA use (on average ≥3 dispensed canisters of SABA in each year of the follow-up). Patients with high SABA use had higher BMI and poorer quality of life measured by AQ20 at the time of diagnosis compared with patients with less SABA use (Table I). Therefore, we carried out a negative binomial test to find out which factors or features at the time of

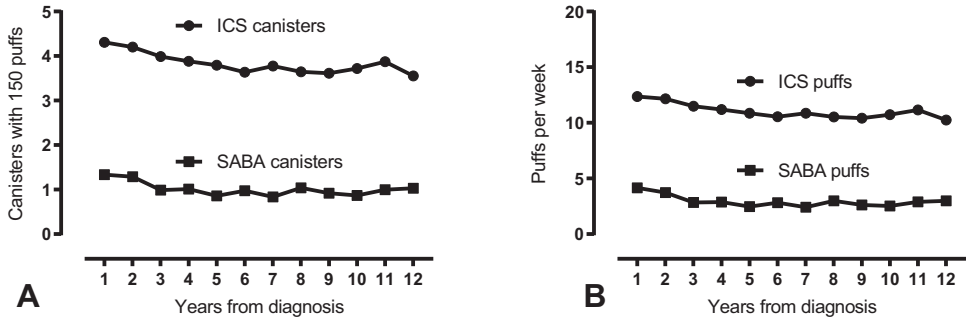

FIGURE 1. (**A**) Average SABA and ICS canisters dispensed per year during 12-year follow-up. (**B**) Average SABA and ICS puffs used per week during 12-year follow-up. Patients were dispensed mean 13 (SD 17) canisters of SABA and 48 (SD 33) canisters of ICS during 12 years corresponding to use of mean 3 (SD 4) SABA and 11 (SD 8) ICS puffs per week. Data are not normally distributed, but for clarity mean and SD values are given here and median and interquartile range values in the results section. *ICS*, Inhaled corticosteroids; *SABA*, short-acting β_2-agonists; *SD*, standard deviation.

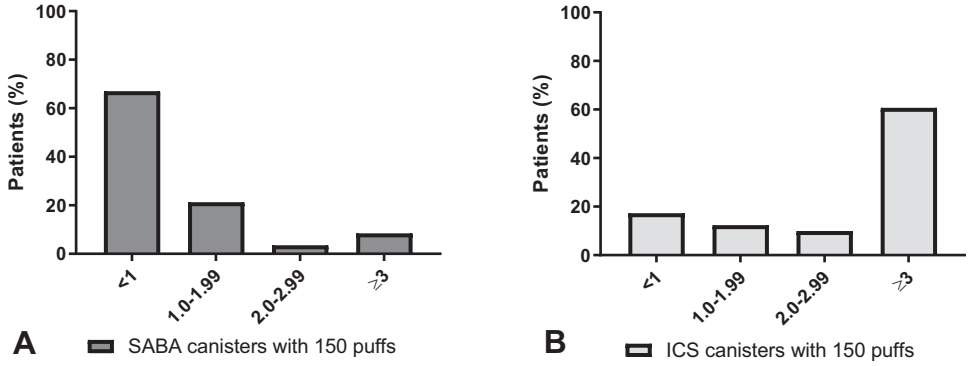

FIGURE 2. (**A**) The average annual dispensed number of SABA canisters during 12 years divided into 4 categories and (**B**) the average annual dispensed number of ICS canisters divided into 4 categories. In (**A**) and (**B**), the cutoff of 3 canisters is selected to show how many patients were dispensed on average <1 SABA canister and ≥3 ICS canisters annually. *ICS*, Inhaled corticosteroids; *SABA*, short-acting β_2-agonists.

asthma diagnosis predicted higher use of SABA during forthcoming 12 years (Table II). Age at diagnosis of asthma, sex, BMI, AQ20 scores, smoking, and diagnostic FEV_1 (% predicted) were included in the final model. BMI ≥ 30 and higher AQ20 scores at diagnosis remained significant predictors for higher long-term SABA use (Table II).

Factors associated with high SABA use at 12-year follow-up

Patients with high SABA use (≥3 SABA canisters/y) were dispensed median 49 (39-69) canisters of SABA during the 12-year period, corresponding to 12 (9-16) puffs per week. Patients with low SABA use (<3 canisters/y) were dispensed median 6 (3-12) canisters of SABA during the 12-year period, corresponding to 1 (1-3) puff per week (Figure 3, *A* and *B*; Figure E6, available in this article's Online Repository at www.jaci-inpractice.org). However, high SABA users were also dispensed higher doses of ICS, had better 12-year adherence to ICS treatment (98% vs 65% calculated as total cumulative ICS dispensed [μg]/total cumulative ICS prescribed [μg] over 12 years), higher BMI, less education years, and more comorbidities compared with patients with low SABA use (Figure 3, *C* and *D*; Figure E6, available in this article's Online Repository at www.jaci-inpractice.org; Table III). There was no difference in lung function measurements or inflammatory markers except for blood neutrophil counts, which were higher for those dispensed ≥3 SABA canisters annually (Table IV). In addition, 86% of high SABA users had noncontrolled asthma (according to GINA 2010 criteria), and over one quarter of the patients had severe asthma according to European Respiratory Society/American Thoracic Society criteria (Table V). Moreover, patients with high SABA use had more symptoms, were dispensed higher amounts of OCS and antibiotics, and had a higher number of emergency department visits and asthma-related health care contacts compared with patients dispensed <3 SABA canisters annually.

DISCUSSION

In this real-life cohort of patients with newly diagnosed adult-onset asthma, we evaluated the relation of SABA and ICS usage and whether high SABA use or over-reliance on SABA exists from the time of diagnosis to the 12-year follow-up visit. Only 10% of patients were classified as high SABA users corresponding to ≥3 dispensed SABA canisters annually during the 12-year follow-up period. Over-reliance on SABA was infrequent; all high SABA

TABLE I. Characteristics of asthma patients at baseline (at the time of diagnosis) according to their level of later SABA use (n = 203)

Variable	SABA use during 12 y		*P* value
	<3 SABA canisters/y (n = 182)	≥3 SABA canisters/y (n = 21)	
Age (y)	46 (14)	49 (12)	.232*
Female gender, n (%)	104 (57.1)	14 (66.7)	.487†
BMI (kg/m^2)	27.2 (4.8)	29.6 (6.3)	.041*
Smokers (incl. ex), n (%)	92 (50.5)	11 (52.4)	>.999†
Smoking history (pack-y)	11 (5-20)	15 (8-25)	.636‡
Pack-y ≥ 10 and post-BD FEV_1/FVC < 0.7, n (%)	14 (7.9)	1 (4.8)	>.999†
Pre-BD FEV_1% pred	82 (70-92)	87 (76-98)	.085‡
Pre-BD FVC% pred	90 (79-100)	97 (83-105)	.193‡
Pre-BD FEV_1/FVC	0.75 (0.69-0.80)	0.78 (0.73-0.81)	.383‡
Blood eosinophils (10^9/L)	0.27 (0.15-0.43)	0.32 (0.13-0.40)	.765‡
Total IgE (kU/L)	82 (34-166)	91 (39-213)	.766‡
hsCRP	5 (5-5)	5 (2-9)	.988‡
Daily ICS use, n (%)	14 (7.7)	2 (10)	.664†
AQ20 score	6 (3-9)	8 (7-12)	.017‡
Hypertension, n (%)	28 (15.4)	7 (33.3)	.061†
Coronary artery disease, n (%)	9 (4.9)	2 (9.5)	.318†
Diabetes, n (%)	4 (2.2)	0 (0)	>.999†

Data are presented as n (%), mean (SD), or median (interquartile range).
AQ20, Airways questionnaire 20; *BD*, bronchodilator; *BMI*, body mass index; *FeNO*, fraction of NO in exhaled air; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *hsCRP*, high-sensitivity C-reactive protein; *ICS*, inhaled corticosteroid; *pack-y*, pack years of smokers; *SABA*, short-acting β2-agonists; *SD*, standard deviation.
*Statistical significances were evaluated by the independent samples *t*-test.
†Statistical significances were evaluated by the Fisher exact test.
‡Statistical significances were evaluated by the independent samples Mann-Whitney *U* test.

TABLE II. Features of patients at the time of asthma diagnosis and their association with high SABA use (≥3 canisters annually during 12-year follow-up) as evaluated by negative binomial regression analysis (n = 203)

Variable	Adjusted incidence rate ratio (adjusted 95% CI)	*P* value
Age of asthma onset	1.01 (0.99-1.02)	.182
Female gender	1.10 (0.78-1.53)	.574
Ex or current smoker	1.12 (0.83-1.52)	.444
pre-FEV_1% (baseline)	1.01 (0.99-1.01)	.235
BMI < 25	1	
BMI at diagnosis 25-29.9	1.19 (0.83-1.69)	.334
BMI at diagnosis ≥30	1.53 (1.01-2.30)	.043
AQ20 score	1.04 (1.00-1.08)	.035

AQ20, Airways Questionnaire 20; *BMI*, body mass index; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 second; *SABA*, short-acting β_2-agonists.

users were also dispensed ICS during the follow-up, and none of them was using only SABA. Only 2.5% of patients showed a medication use feature suggesting some degree of SABA over-reliance. Obesity (BMI ≥30) and higher symptom score at the time of diagnosis predicted higher SABA use during the follow-up. High SABA users had better 12-year adherence to ICS, more respiratory-related emergency visits, and used more OCS and antibiotic courses compared with patients using <3 SABA canisters/y.

High use of SABA in asthma has been associated with increased risk of exacerbations, mortality, and health care utilization.[5,6,8,29] It has been suggested that prolonged or repetitive use of SABA leads to desensitization and attenuated BD response. However, corticosteroids increase the β_2-receptor gene transcription compensating for the downregulation of β_2-receptors induced by chronic exposure to β-agonists such as SABA.[2,3] Over-reliance on SABA, that is, high use of SABA with insufficient use of ICS, neglects both the treatment of airway inflammation and reversing the downregulation of β_2-reseptors, which increases the risk for negative outcomes of asthma.[2,3] These interactions are often poorly understood by the patients.[30]

Various thresholds and definitions have been used to quantify use and reliance on SABA, but previous findings indicate an increased risk associated with ≥3 canisters of SABA annually defined as "high use" or "overuse."[1,5,29,31] Although the safety concerns about SABA have been acknowledged for decades, recent studies have revealed that nearly one-third of patients with asthma are classified as high SABA users.[5,7,10,31] A key finding of the present study was that only 10% of the adult patients with clinically confirmed asthma were dispensed ≥3 canisters of SABA annually during the 12-year follow-up. Recent studies from Sweden[5] and the United States[31] showed that a higher number of dispensed SABA canisters was associated with increased risk of exacerbation, which corresponds to our findings that high SABA users had more respiratory-related emergency visits, and they used more OCS and antibiotic courses compared with those using <3 SABA canisters/y.

There is no settled definition of SABA "over-reliance," and it has been used as a synonym for high SABA use.[32] In this study, over-reliance was assessed by combining information on dispensed SABA and ICS canisters, and defined as high SABA use and simultaneous underuse of ICS (0-2 canister/y). Over-reliance on SABA was infrequent in our study, given that all high SABA users were also dispensed ICS during the follow-up, and of these, only 2 patients were dispensed <3 canisters of ICS annually. In addition, high SABA users had better adherence to ICS treatment compared

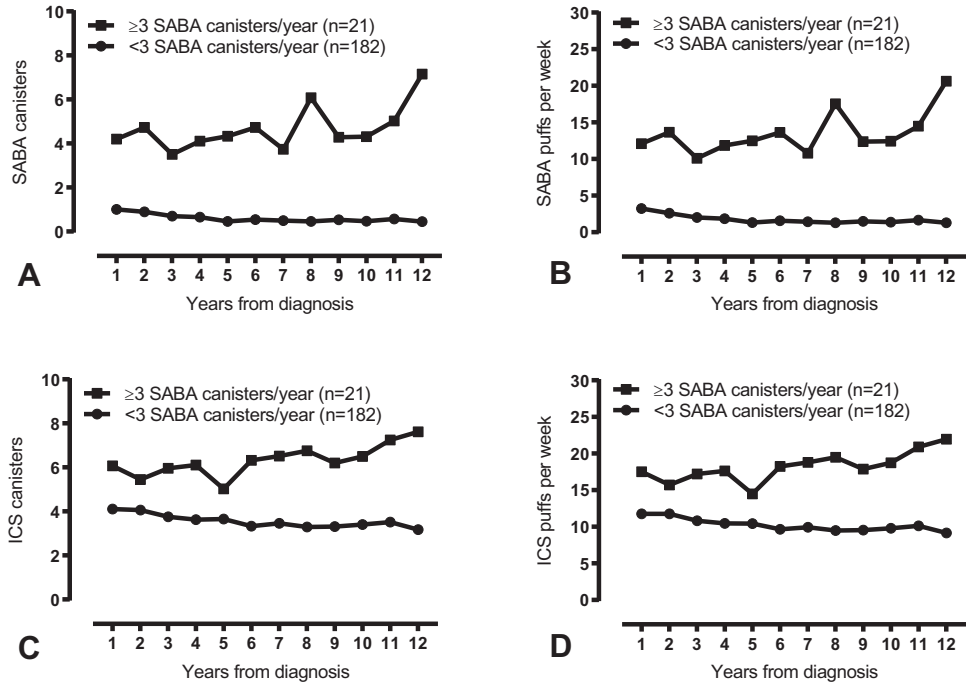

FIGURE 3. (**A**) The average annual dispensed number of SABA canisters; (**B**) SABA puffs per week; (**C**) average annual dispensed number of ICS canisters; (**D**) ICS puffs per week in patients with use of ≥3 or <3 SABA canisters annually during the 12-year follow-up. Patients with high SABA use (≥3 SABA canisters/y) were dispensed mean 55 (SD 22) SABA and 76 (SD 31) ICS canisters during the 12-year period, corresponding to 13 (SD 5) SABA and 18 (SD 8) ICS puffs per week. Patients with low SABA use (<3 canisters/y) were dispensed mean 8 (SD 7) SABA and 45 (SD 31) ICS canisters during the 12-year period, corresponding to 2 (SD 2) SABA and 11 (SD 7) ICS puffs per week. *ICS*, Inhaled corticosteroids; *SABA*, short-acting β_2-agonists; *SD*, standard deviation.

with low SABA users. These findings conflict with a study conducted in the United Kingdom[16] where overuse of SABA predicted lower ICS use. However, SABA use was assessed from prescription data, likely overestimating the use of SABA as the medication may not be dispensed from the pharmacy.[9,16] Moreover, high SABA use has been previously evaluated in register-based cross-sectional studies,[5,6,8-10,29,31,33] where the diagnosis of asthma may not be clinically confirmed, and therefore patients without confirmed diagnosis of asthma may be included, potentially increasing the number of dispensed SABA canisters.

We were not able to identify any other study evaluating factors predicting future high SABA use in long term. Therefore, a negative binomial regression analysis was performed, and after adjustments, BMI ≥30 and higher AQ20 symptom scores at the time of diagnosis predicted higher SABA use during the 12-year follow-up. In our recent study, patients who were obese (BMI ≥30) at diagnosis had more frequent OCS dispensations and respiratory-related hospitalizations compared with normal-weight patients.[34] These findings emphasize the need to include weight-management strategies into treatment, as patients who are obese at diagnosis appear to have poorer long-term prognosis of asthma. Moreover, at the 12-year follow-up visit, 86% of patients with high SABA use (≥3 SABA canisters/y) had noncontrolled asthma. These patients had also higher BMI and higher total number of comorbidities (eg, diabetes, coronary artery disease, and mental health medications) than patients using <3 SABA canisters/y. Similar findings were seen in a recent study where nearly all patients with difficult-to-control asthma had ≥1 comorbidity and these patients had higher prevalence of cardiovascular disease, obesity, and anxiety/depression compared with patients with not-difficult-to-treat asthma.[35] Higher neutrophil counts have also been related to more severe asthma phenotypes, which was also seen in this study where the patients with ≥3 SABA canisters/y had higher blood neutrophil counts than patients with <3 SABA canisters/y.[34,36,37] Poorer asthma control and higher neutrophilia combined with high dispensed doses of ICS in patients with high SABA use indicate that these patients may have had non−type 2 inflammation. Therefore, more research should focus on non−type 2 asthma and its mechanism to find out more stratified therapeutic approaches besides lifestyle interventions. In addition, the use of rescue medication has major part in the assessment of asthma control; therefore, future studies should also assess asthma control independently of SABA use.

Previous register-based studies have identified increased risks for adverse asthma-related outcomes with high SABA use.[5,6,10,31] However, many studies lack clinical information on these patients.[5,6,8,10,31] In this study, high SABA users were dispensed more ICS, but they had higher BMI, more comorbidities, and were less educated compared with patients with low SABA use. These results indicate that socioeconomic status may play a role in medication behavior. In contrast to our current findings, lower education and income have been associated with poorer adherence to controllers by others.[38-40] Poor adherence to ICS may lead to enhanced lung function decline, especially when asthma is not controlled (ie, symptomatic needing SABA).[25,41] However, we did not find any difference in lung function measurements or lung

TABLE III. Characteristics of asthma patients 12 years after diagnosis and medication used during 12 years according to their level of SABA use (n = 203)

Variable	SABA use during 12 y		*P* value
	<3 SABA canisters/y (n = 182)	≥3 SABA canisters/y (n = 21)	
At 12-y follow-up visit			
Demographics			
Age (y)	58 (14)	61 (12)	.252*
Female gender, n (%)	104 (57.1)	14 (66.7)	.487†
BMI (kg/m^2)	27.7 (24.3-30.9)	30.8 (28.1-33.3)	.014‡
Smokers (incl. ex), n (%)	95 (52.2)	12 (57.1)	.818†
Smoking history (pack-y)	15 (6-30)	18 (5-31)	.781‡
Pack-y ≥ 10 and post-BD FEV_1/FVC < 0.7, n (%)	31 (17.2)	3 (14.3)	>.999†
Education years over 12, n (%)	58 (32.2)	2 (9.5)	.041†
Monthly gross income (€)	2085 (1438-2700)	1600 (1080-2300)	.091‡
Asthma medication			
Daily SABA, n (%)	13 (7.1)	10 (47.6)	<.001†
Daily LABA, n (%)	83 (45.6)	13 (61.9)	.173†
Daily theophylline, n (%)	2 (1.1)	2 (9.5)	.054†
Daily add-on drug, n (%)	89 (48.9)	14 (66.7)	.167†
Comorbidities			
No. of comorbidities	1 (0-2)	2 (1-4)	.007‡
Allergy and/or rhinitis, n (%)	126 (69.2)	16 (76.2)	.620†
Chronic obstructive pulmonary disease, n (%)	31 (17.2)	3 (14.2)	>.999†
Diabetes, n (%)	22 (12.1)	7 (33.3)	.016†
Coronary artery disease, n (%)	16 (8.8)	5 (23.8)	.049†
Depression/mental health medication, n (%)	21 (11.5)	6 (28.6)	.041†
Comedications (nonrespiratory)	1 (0-3)	3 (2-7)	.001‡
Medication used during 12 y			
Prescribed daily dose of ICS (μg budesonide equivalents)	800 (598-1000)	936 (800-1265)	.008‡
Dispensed daily dose of ICS (μg budesonide equivalents)	470 (271-771)	912 (673-1512)	<.001‡
12-y average ICS adherence	65 (37)	98 (32)	<.001*
Controller-to-total ratio (ICS/(SABA+ICS))	0.86 (0.71-0.93)	0.55 (0.50-0.60)	<.001‡

Data are presented as n (%), mean (SD), or median (interquartile range). Adherence was calculated as total cumulative ICS dispensed (μg)/total cumulative ICS prescribed (μg) over 12 years. Number of comorbidities was evaluated separately and as the sum of all comorbidities reported at the 12-year follow-up visit.

BD, Bronchodilator; *BMI*, body mass index; *Control-to-total ratio*, dispensed inhaled corticosteroid canisters divided by the sum of dispensed short-acting β_2-agonist canisters and inhaled corticosteroid canisters; *Daily add-on drug*, self-reported daily use of long-acting β_2-agonist, leukotriene receptor antagonist, tiotropium, or theophylline; *Daily LABA*, self-reported daily use of long-acting β_2-agonist; *Daily SABA*, self-reported daily use of short-acting β_2-agonist; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *pack-y*, pack years of smokers; *SD*, standard deviation.

*Statistical significances were evaluated by the independent samples *t*-test.

†Statistical significances were evaluated by the Fisher exact test.

‡Statistical significances were evaluated by the independent samples Mann-Whitney *U* test.

function decline between the patients with high or low SABA use over the 12 years. Moreover, an Australian study reported that SABA overusers were more likely to have depression (11.1% vs 5.7%), and a higher proportion of SABA overusers had uncontrolled asthma.[33] In our SAAS cohort, 86% of the patients with high SABA use had noncontrolled asthma and depression was more common in high SABA users compared with patients using less SABA (28.6% vs 11.5%). In addition, we report here that diabetes and coronary artery disease were more common among high SABA users. Therefore, more studies are needed to evaluate the role of other diseases, lifestyle, and socioeconomic status in pursuing asthma control and assessing the use of rescue treatment.

Although the study is based on pharmacy dispensation data, there are also some limitations to be addressed. Dispensed medication may not correspond to actual use of inhaler, and therefore, patients' use of relievers and controllers may be overestimated. Moreover, patients may have had an incorrect inhalation technique, although the technique was carefully instructed to all patients at initiation of new medication according to the principles of the Finnish practical care guidelines.[21] Previous studies have described long-term trends in prescribing SABA,[9,42] but we did not find any study combining information on long-term SABA and ICS usage with clinical examinations of patients with asthma. In this exceptionally long follow-up study, asthma diagnosis was confirmed by a respiratory physician and with lung function measurements, ensuring that only patients with confirmed new adult-onset asthma were included. In addition, the study included information on asthma control, lung function, and adherence to controllers from diagnosis to 12-year follow-up. All refills of SABA and ICS inhalers were obtained from the Finnish Social Insurance Institution, which records all purchased medication from Finnish pharmacies.

The prevalent perception is that high use of SABA and its negative consequences result from over-reliance on SABA, that is,

TABLE IV. Lung function and markers of inflammation in patients according to their level of SABA use (n = 203)

Variable	SABA use during 12 y		*P* value
	<3 SABA canisters/y (n = 182)	≥3 SABA canisters/y (n = 21)	
Lung function at follow-up			
Pre-BD FEV_1% pred	86 (76-94)	89 (76-104)	.351
Pre-BD FVC % pred	96 (87-106)	101 (88-116)	.213
Pre-BD FEV_1/FVC	0.74 (0.66-0.79)	0.72 (0.68-0.75)	.692
FEV_1 reversibility mL	90 (30-163)	90 (0-140)	.786
FEV_1 reversibility % of initial FEV_1	3.2 (1-6.7)	4.2 (0.15-5.5)	.995
Lung function change			
ΔFEV_1 mL/y	−40 (−66 to −23)	−53 (−63 to −32)	.167
ΔFEV_1 % pred/y	−0.47 (−1.1 to 0.19)	−0.55 (−1.1 to −0.9)	.693
ΔFEV_1/FVC/y	−0.005 (−0.008 to −0.001)	−0.005 (−0.009 to −0.002)	.643
Markers of inflammation			
Blood eosinophils (10^9/L)	0.17 (0.10-0.27)	0.14 (0.08-0.27)	.369
Total IgE (kU/L)	60 (24-164)	76 (26-160)	.808
FeNO (ppb)	11 (5-19)	8 (5-21)	.484
Blood neutrophils (10^9/L)	3.7 (2.9-4.7)	4.5 (3.5-6.2)	.042
IL-6 (pg/mL)	1.8 (1.2-3.0)	2.3 (1.2-5.2)	.317
hsCRP	1.2 (0.59-2.5)	1.2 (0.5-5.2)	.689

Data are presented as median (interquartile range). Statistical significances were evaluated by the independent samples Mann-Whitney *U* test.
BD, Bronchodilator; *ΔFEV_1*, change in prebronchodilator-FEV_1 from the maximum value during the first 2.5 years after diagnosis and start of treatment to 12-year follow-up visit; *FeNO*, fraction of NO in exhaled air; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *hsCRP*, high-sensitivity C-reactive protein; *SABA*, short-acting β_2-agonists.

TABLE V. Symptoms, medication, and health care use in patients according to their level of SABA use (n = 203)

Variable	SABA use during 12 y		*P* value
	<3 SABA canisters/y (n = 182)	≥3 SABA canisters/y (n = 21)	
Symptoms of asthma			
AQ20 score	4 (1-7)	6 (4-7)	.018*
ACT score	22 (20-24)	19 (15-21)	<.001*
Asthma control, n (%)			.044†
Controlled	66 (36.3)	3 (14.3)	
Noncontrolled	116 (63.7)	18 (85.7)	
Burden of asthma			
Dispensed oral corticosteroids for asthma per year (mg prednisolone)	51 (0-162)	142 (12-451)	.005*
Dispensed oral corticosteroids during 12-y follow-up (mg prednisolone)	600 (0-1920)	1800 (150-5430)	.006*
Dispensed antibiotic courses during 12-y follow-up	2 (0-5)	4 (1-9)	.032*
Fulfills severe asthma criteria according to ERS/ATS, n (%)	6 (3.3)	6 (28.6)	<.001†
Emergency department visits	0 (0-0)	0 (0-1)	.003*
Range	0-10	0-18	
Asthma-related health care visits	14 (9-22)	20 (13-43)	.009*
Asthma control visits	6 (3-10)	7 (4-12)	.427*
Three or more sick leaves during the past 2 y, n (%)	6 (4.1)	1 (7.1)	.482†

Data are presented as n (%) or median (interquartile range). Asthma control was defined according to GINA 2010[28] and noncontrolled included both partially and uncontrolled asthma. Dispensed oral corticosteroids, asthma-related health care visits, asthma control visits, and hospital in-patient periods have been examined during whole 12-year follow-up period.
ACT, Asthma Control Test; *AQ20*, Airways Questionnaire 20; *Asthma-related health care visits*, all respiratory related scheduled and unscheduled contacts to health care due to asthma; *ATS*, American Thoracic Society; *ERS*, European Respiratory Society; *SABA*, short-acting β_2-agonists.
*Statistical significances were evaluated by the independent samples Mann-Whitney *U* test.
†Statistical significances were evaluated by the Fisher exact test.

underuse of controller medication such as ICS.[32] This assumption was not confirmed in this study of patients with clinically confirmed asthma, as those with higher SABA use had better 12-year adherence to ICS treatment compared with patients using less SABA. These findings suggest that patients characterized as high SABA users with confirmed asthma diagnosis should not all be categorized as SABA overusers or SABA over-reliant, because high SABA users had, despite use of ICS, more frequent symptoms, poorer asthma control, and more often severe asthma—all possible reasons leading to higher demand of SABA. However, as high

SABA use indicates more severe asthma, high SABA users should be recognized in clinical practice and frequent SABA use should be regarded as a sign to intervene.

In conclusion, high SABA use occurred only in 10% of the patients with confirmed adult-onset asthma, and significant over-reliance on SABA was not identified. Obesity and high symptoms at diagnosis predicted higher long-term SABA use. Importantly, high SABA users had more frequent exacerbations, emergency visits, and courses of OCS and antibiotics compared with patients using less SABA. Because high SABA use indicated more severe asthma, these patients should be recognized in clinical practice.

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Lung function measurements

Lung function measurements were performed using a spirometer (Vmax Encore 22; Viasys Healthcare, Palm Springs, Calif) according to international and national recommendations and Finnish reference values.[E1-E3] Lung function measurement points: (1) baseline (ie, time of asthma diagnosis), (2) the maximum lung function (Max: 0-2.5) during the first 2.5 years after diagnosis (ie, after start of anti-inflammatory therapy) based on the highest prebronchodilator forced expiratory volume in 1 s (% predicted), and (3) after 12 years of follow-up. Lung function measurements after the diagnosis of asthma were taken while patients were on medication, without pauses or withholding therapy.

Laboratory measurements

Fraction of exhaled nitric oxide was measured with a portable rapid-response chemiluminescent analyzer according to American Thoracic Society standards (flow rate 50 mL/s; NIOX System, Aerocrine, Solna, Sweden).[E4] Venous blood was collected and white blood cell differential counts were determined. Total IgE levels were measured using ImmunoCAP (Thermo Scientific, Uppsala, Sweden).[E4] Serum levels of IL-6 were determined by ELISA (R&D Systems, Minneapolis, Minn), and high-sensitivity C-reactive protein was measured using the particle-enhanced immunoturbidimetric method on the Roche Cobas 8000 automated clinical chemistry analyzer (Roche Diagnostics, Basel, Switzerland).

Evaluation of SABA use

The different short-acting β_2-agonist (SABA) inhalers dispensed by the patients in the Seinäjoki Adult Asthma Study are shown in Table E2. Ventoline Diskus (Accuhaler) (GlaxoSmithKline, London, United Kingdom; 60 puffs per inhaler, 200 μg salbutamol per dose) is the most used SABA inhaler in Finland, which is also the case in our study population. Because of the difference in puffs contained per inhaler (range: 60-400), we adopted the definition of a standard canister from the previous study from Sweden.[E5] Moreover, in the current Global Initiative for Asthma report, regular or overuse of SABAs has been set to ≥3 canisters of SABA (eg, dispensing of 3 or more 200-dose canisters in a year, corresponding to average use more than daily). If the patient used at least 3 SABA inhalers (with 150 puffs) in a year, the total daily average SABA use was more than 1 puff daily (1.2 puffs/d). Therefore, high SABA use was defined as ≥36 SABA canisters in 12 years, corresponding to an average of ≥3 dispensed canisters per year.

Computation of adherence

Prescribed doses for each patient for each year of the follow-up were calculated based on medical records.[E6-E8] All drug and dose changes were taken into account individually for each patient, and finally all doses were converted to beclomethasone dipropionate (BDP) equivalents (Figure E2).[E7] Patients' dispensed doses of inhaled corticosteroids (ICS) were obtained from the Finnish Social Insurance Institution, which records all purchased medication from any Finnish pharmacy (Figure E2).[E6,E8] By comparing dispensed doses with prescribed ICS doses, it was possible to evaluate adherence of a single patient during the 12-year follow-up period as previously reported.[E6] In the case of ranged doses prescribed, for example, 1 to 2 puffs 2 times daily, we interpreted that patients were adherent when the minimum ICS doses were dispensed.

The 12-year adherence was calculated by comparing total cumulative dispensed doses of ICS with total cumulative 12-year prescribed doses.[E6,E8] The most commonly used cutoff point (≥80%) in respiratory literature was also used in this study to distinguish patients with better (≥80%) and poorer (<80%) 12-year adherence.[E9-E11] To obtain a view on the variability of adherence at long-term follow-up, annual adherence was calculated for each patient individually for each year by dividing yearly dispensed ICS doses by yearly prescribed ICS doses (μg BDP equivalents).[E6-E8] Overall, the extensive 12-year follow-up period and the fact that long-term medication is prescribed continuously enhanced the evaluation of 12-year ICS adherence including initiation of medication and periods of persistence and temporary nonpersistence (Figure E3). Moreover, 1 recent publication has used time-varying adherence to describe patients' adherence behavior, and this method was adapted in the present study (Figure E3).[E12] However, time-varying proportion of days covered cannot account for the dose ranges of asthma medication, and therefore we modified the form by using μg/μg and described the time-varying behavior in each year of the follow-up. In conclusion, all patients have their individual 12-year time-varying scope of adherence enabling the comparison of both average 12-year adherence and annual adherence of the patients.

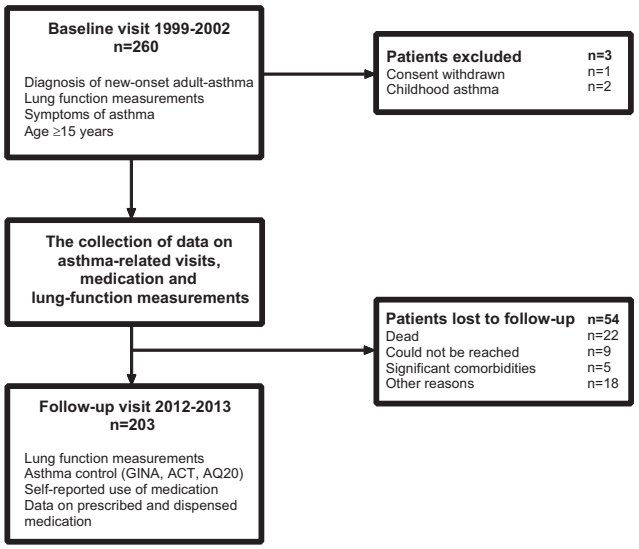

FIGURE E1. Flowchart of the study. *ACT*, Asthma Control Test; *AQ20*, Airways Questionnaire 20; *GINA*, Global Initiative for Asthma.

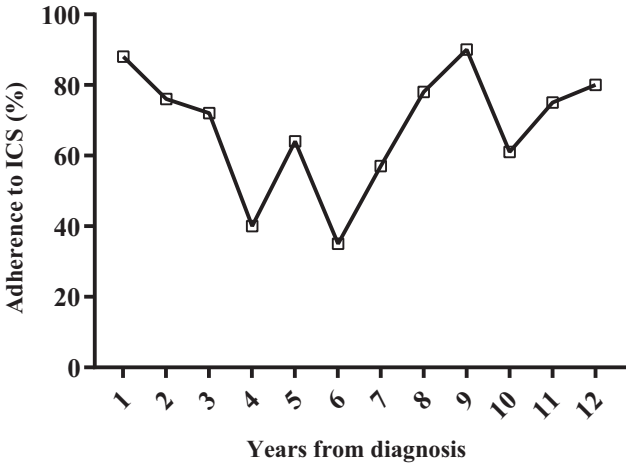

FIGURE E2. Twelve-year ICS adherence of 1 example patient. *ICS*, Inhaled corticosteroid.

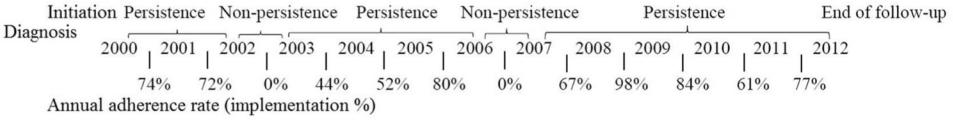

FIGURE E3. Time-varying adherence of 1 example patient (the average 12-year adherence of the example patient is 68%).

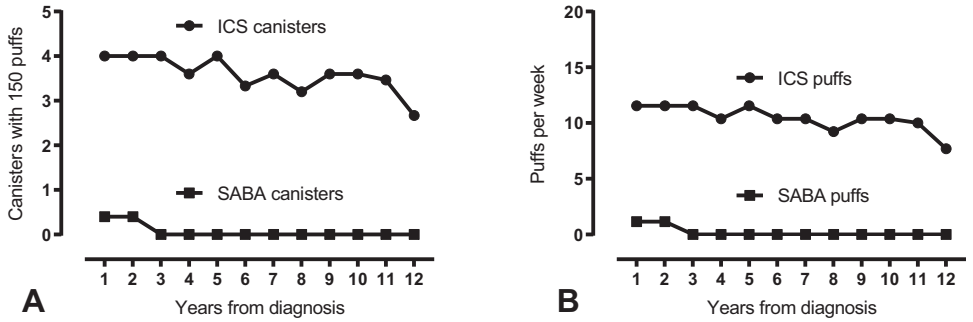

FIGURE E4. (**A**) Median SABA and ICS canisters per year dispensed during 12-year follow-up. (**B**) Median SABA and ICS puffs used per week during 12-year follow-up. *ICS*, Inhaled corticosteroid; *SABA*, short-acting β_2-agonists.

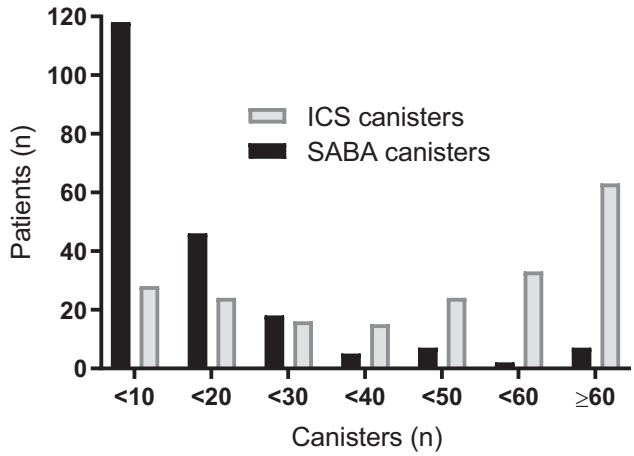

FIGURE E5. Cumulative dispensed ICS and SABA canisters during 12-year follow-up. *ICS*, Inhaled corticosteroid; *SABA*, short-acting β_2-agonists.

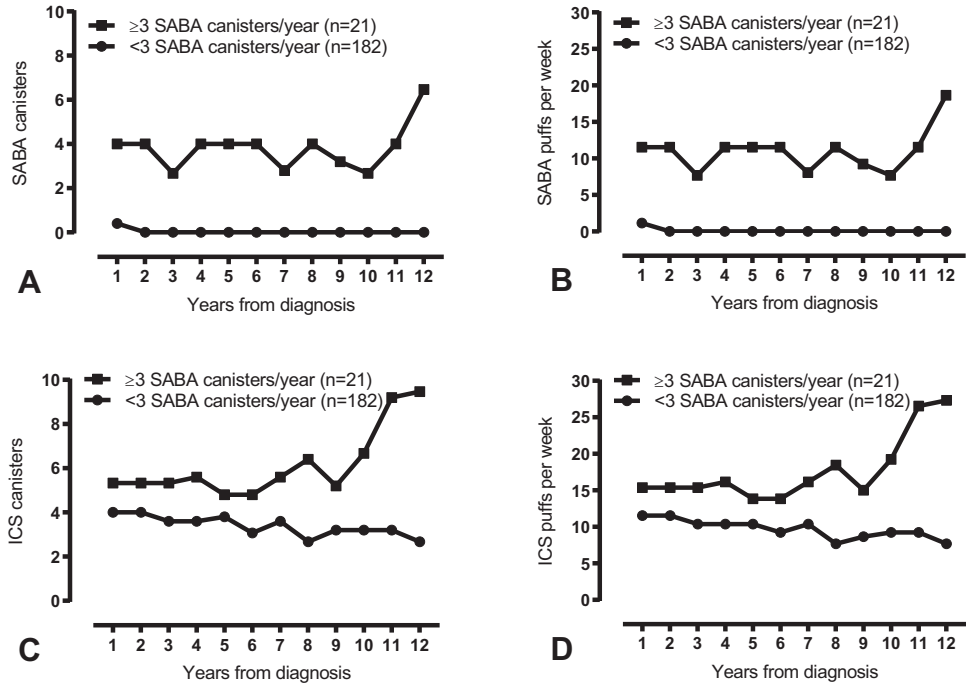

FIGURE E6. (**A**) The median annual dispensed number of SABA canisters; (**B**) SABA puffs per week; (**C**) median annual dispensed number of ICS canisters; (**D**) ICS puffs per week in patients with use of $\geq$3 or $<$3 SABA canisters annually during the 12-year follow-up. *ICS*, Inhaled corticosteroid; *SABA*, short-acting β_2-agonists.

TABLE E1. The inclusion and exclusion criteria used in the SAAS

Inclusion criteria
A diagnosis of new-onset asthma made by a respiratory specialist
Diagnosis confirmed by at least one of the following objective lung function measurements:*
FEV_1 reversibility in spirometry of at least 15% and 200 mL after 400 μg of salbutamol
Diurnal variability (≥20% on at least 3 d) or repeated reversibility (≥15%/60 L/min on at least 3 occasions) during a 2-wk PEF monitoring
A significant decrease in FEV_1 (15%) or PEF (20%) in response to exercise or allergen challenge test
A significant reversibility in FEV_1 (at least 15% and 200 mL) or mean PEF (at least 20%) in response to a trial with oral or inhaled glucocorticoids
Symptoms of asthma
Age ≥15 y
Exclusion criteria
Physical or mental inability to provide signed informed consent
Diagnosis of asthma below the age of 15 y
Of note:
Patients with comorbidities, either any other lung disease or any other significant disease, were not excluded
Patients were not excluded because of smoking, alcohol use, or any other lifestyle factor
Respiratory symptoms or any other disease during childhood was not a reason to exclude patients, but a diagnosis of asthma at age <15 years was an exclusion criterion

Published earlier: Kankaanranta et al 2015.[E13]
FEV_1, Forced expiratory volume in 1 second; *PEF*, peak expiratory flow, *SAAS*, Seinäjoki Adult Asthma Study.

TABLE E2. Inhalers containing SABA dispensed in the SAAS

Brand	Strength	Puffs per inhaler	Active substance
Airomir autohaler	0.1 mg/dose	200	Salbutamol
Airomir	0.1 mg/dose	200	Salbutamol
Atrovent comp eco	50 μg/dose	200	Fenoterol
Bricanyl turbuhaler	0.25 mg/dose	200	Terbutaline
Bricanyl	0.25 mg/dose	400	Terbutaline
Bricanyl turbuhaler	0.5 mg/dose	100	Terbutaline
Bricanyl turbuhaler	0.5 mg/dose	200	Terbutaline
Buventol easyhaler	100 μg/dose	200	Salbutamol
Buventol easyhaler	200 μg/dose	60	Salbutamol
Buventol easyhaler	200 μg/dose	200	Salbutamol
Salbutamol turbuhaler	50 μg/dose	200	Salbutamol
Ventoline	0.2 mg/dose	100	Salbutamol
Ventoline	1 mg/mL	20 × 2.5 mL (no puffs)	Salbutamol
Ventoline diskus	200 μg/dose	60	Salbutamol
Ventoline evohaler	0.1 mg/dose	200	Salbutamol
Ventoline rotadisk	0.2 mg/dose	15 × 8 (no puffs)	Salbutamol

SAAS, Seinäjoki Adult Asthma Study; *SABA*, short-acting β_2-agonists.

TABLE E3. Characteristics of study population at baseline (asthma diagnosis) and 12-year follow-up visit (n = 203)

Variable	Baseline (n = 203)	Follow-up (n = 203)	*P* value
Age (y)	46 (14)	58 (14)	
Female gender, n (%)	118 (58.1)	118 (58.1)	
BMI (kg/m^2)	27.1 (24.2-29.8)	28.1 (24.4-31.3)	<.001*
Smokers (incl. ex), n (%)	103 (50.7)	107 (52.7)	.125†
Smoking history (pack-y)	12 (5-21)	16 (6-30)	<.001*
Pack-y ≥ 10 and post-BD FEV_1/FVC < 0.7, n (%)	15 (7.4)	34 (16.7)	<.001†
Daily ICS use, n (%)	16 (7.9)	155 (76.4)	<.001†
Pre-BD FEV_1% pred	83 (71-92)	86 (76-96)	<.001*
Pre-BD FVC % pred	90 (79-100)	96 (87-106)	<.001*
Pre-BD FEV_1/FVC	0.75 (0.69-0.80)	0.73 (0.66-0.79)	<.001*
Post-BD FEV_1% pred	88 (77-99)	90 (80-98)	.010*
Post-BD FVC % pred	94 (82-102)	98 (88-107)	<.001*
Post-BD FEV_1/FVC	0.79 (0.74-0.83)	0.75 (0.69-0.81)	<.001*
Blood eosinophils (10^9/L)	0.28 (0.15-0.42)	0.16 (0.10-0.27)	<.001*
Total IgE (kU/L)	84 (35-174)	61 (24-163)	.046*
CRP	5 (5-5)	1.2 (0.57-2.5)	<.001*
AQ20 score	7 (4-10)	4 (2-7)	<.001*
Hypertension, n (%)	30 (14.8)	69 (34)	<.001†
Coronary artery disease, n (%)	10 (4.9)	21 (10.3)	<.001†
Diabetes, n (%)	3 (1.5)	29 (14.3)	<.001†

AQ20, Airways Questionnaire 20; *BMI*, body mass index; *CRP,* C-reactive protein; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid.

*Statistical significances were evaluated by the related samples Wilcoxon signed-rank test (if non-normally distributed).

†Statistical significances were evaluated by the McNemar test (categorical variables).

TABLE E4. High use of SABA and over-reliance on SABA during 12 years in patients with new adult-onset asthma

Variable	n (%)
Total population	203 (100)
High use of SABA	
High use of SABA (≥36 SABA canisters in 12 y)	21 (10)
Over-reliance on SABA using different definitions	
High use of SABA (≥36 canisters in 12 y) and no dispensed ICS canisters during the follow-up	0 (0)
High use of SABA and <36 dispensed canisters of ICS (corresponding to on average <3 dispensed ICS canisters per year)	2 (1.0)
High use of SABA and fewer ICS canisters dispensed than SABA	5 (2.5)
Possible undertreatment	
High use of SABA and no dispensed ICS+LABA or ICS+LAMA	2 (1.0)

Number of over-reliant patients was 5 (2.5%) by any definition.

ICS, Inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *SABA*, short-acting β_2-agonists.

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