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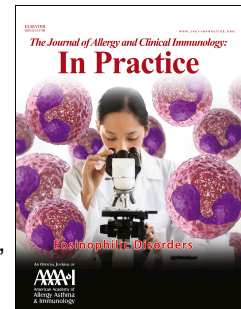
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Conflict of interest

The authors declare no conflict of interest related to this study. Dr. Vähätalo reports personal fees from Astra Zeneca, outside the submitted work. Dr. Lehtimäki reports grants and personal fees from Orion Pharma, personal fees from Astra Zeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from Circassia, personal fees from GSK, personal fees from Mundipharma, personal fees from Novartis, personal fees from Sanofi, shares of Ausculthing Oy, outside the submitted work. Dr. Tuomisto reports personal fees from Boehringer Ingelheim, personal fees from Astra Zeneca, personal fees from GlaxoSmithKline, non-financial support from Chiesi, outside the submitted work. Dr. Karjalainen reports personal fees from Astra Zeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from Sanofi, personal fees from GlaxoSmithKline, personal fees from Novartis, personal fees from Orion Pharma, outside the submitted work. Dr. Niemelä has nothing to disclose. Dr. Ilmarinen is employee of GlaxoSmithKline, reports personal fees from GlaxoSmithKline, personal fees from Novartis, personal fees from Mundipharma, personal fees from Astra Zeneca, outside the submitted work. Dr. Kankaanranta reports personal fees from Astra Zeneca, personal fees from Orion Pharma, personal fees from Mundipharma, personal fees from Boehringer Ingelheim, personal fees from Chiesi Pharma AB, personal fees from GlaxoSmithKline, personal fees from MSD, personal fees from Novartis, personal fees from Sanofi Genzyme, outside the submitted work.

Abstract

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 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 (SAAS), 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/year.

Results Patients were dispensed median 6 (IQR 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 ($\text{BMI} \geq 30$) and high AQ20 (Airways Questionnaire 20) symptom scores at baseline predicted high long-term SABA use (IRR 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 used more oral corticosteroid and antibiotic courses vs. 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 recognised in clinical practice.

This study is registered at www.ClinicalTrials.gov with identifier number NCT02733016

Running head: Long-term use of short-acting β_2 -agonists in adult-onset asthma

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Highlights box

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 overreliance on short-acting β_2 -agonists (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 overreliance 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.

Key words asthma, adult-onset, reliever therapy, short-acting β_2 -agonists, asthma treatment, asthma control, obesity, prognosis, long-term, follow-up

Abbreviations

- ICS: inhaled corticosteroid
- FEV₁: forced expiratory volume in one second
- GINA: Global Initiative for Asthma
- FVC: forced vital capacity
- BD: bronchodilator
- FeNO: exhaled nitric oxide
- IgE: immunoglobulin E
- IL-6: interleukin 6
- hsCRP: high-sensitivity C-reactive protein
- AQ20: Airways Questionnaire 20
- ACT: asthma control test
- BMI: body mass index
- SABA: short-acting β_2 -agonist
- SAAS: Seinäjoki Adult Asthma Study
- LABA: long-acting β_2 -agonist

Introduction

Frequent use of short-acting β_2 -agonists (SABA) is one of the key indicators for non-controlled asthma [1]. In patients using SABA or LABA (long-acting β_2 -agonist) regularly, response to bronchodilators may be reduced due to downregulation 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 ≥ 3 canisters per year [5,7,10]. These estimates may be biased because inclusion (i.e., the definition of asthma) was based on dispensed medication for obstructive airway diseases (ATC 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 (COPD). Most of the studies investigating SABA use have been cross-sectional and assessed medication use in short-term, usually over a one-year period. Remission rates range from 20-65% in early-onset asthma [11-13] to 3-11% in adult-onset asthma [11,14,15], highlight the need for long-term study for more precise estimates of patients' medication-related behaviour.

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], i.e. they are over-reliant on SABA. Therefore, our objective was to determine if patients with high SABA use and overreliance 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 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) as part of the Seinäjoki Adult Asthma Study (SAAS). 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). 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) in which data on e.g. 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 Online Repository). 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 healthcare [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 E4), 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. 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) to cumulative prescribed doses of ICS (μg) by using a method combining medication possession ratio (MPR) and proportion of days covered (PDC) formulas (Figure E5, Figure E6) (see Online Repository) [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 three 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); 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 analysed the number of patients who had high use of SABA and were on maintenance ICS but were not dispensed any second controllers (LABA [long-acting β_2 -agonist] or LAMA [long-acting muscarinic antagonist]) 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 two groups by asthma control at follow-up visit, which were defined according to the Global Initiative for Asthma (GINA) 2010 report [28] as previously reported [14]. Patients with non-controlled 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 (SD), or median (interquartile range; IQR). Comparison of baseline and follow-up values were evaluated by related samples Wilcoxon signed rank test or McNemar test. Comparison of groups with SABA use of ≥ 3 or < 3 canisters annually were analysed by using independent samples t-test, Mann-Whitney U test and Fisher's exact test. A negative binomial regression analysis was performed to analyse 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 follow-up period. We calculated the incidence rate ratios (IRRs) with 95% CI 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 FEV₁ (%) and BMI. The natural logarithm of the length of follow-up was set as off-set variable. A P value <0.05 was regarded as statistically significant. Statistical analyses were performed using IBM SPSS statistics software, version 27 (IBM SPSS, Armonk, NY, USA).

Results

Patient characteristics

The study population consisted of 203 patients with adult-onset asthma and the majority were females (58%), with mean age of asthma onset of 46 (SD 14) years (Table E2). Half of the patients were current or ex-smokers (Table E2). At the 12-year follow-up visit, patients had generally higher BMI, better lung function and lower blood eosinophil counts compared to the baseline visit (Table E2).

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 1AB, Figure E3). Most patients used ≥ 3 canisters of ICS (60%) and < 2 canisters of SABA (88%) per year, on average (Figure 2AB). 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 E2).

High use and over-reliance on SABA

The patients were divided into two 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 since all high SABA users were also dispensed ICS during the follow-up. Of these, only two patients were dispensed <3 canisters of ICS annually (Table E3). 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 pre-defined criteria for SABA-overreliance, only these 5 patients (2%) were found to have any signs of SABA over-reliance. Possible undertreatment was recognised in 2 (1%) patients as they were high SABA users but were not dispensed ICS+LABA or ICS+LAMA (Table E3).

Factors predicting high use of SABA

Since 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 to patients with less SABA use (Table 1). Therefore, we carried out a negative binomial test to find out which factors or features at the time of asthma diagnosis predicted higher use of SABA during forthcoming 12 years (Table 2). Age at diagnosis of asthma, sex, BMI, AQ20 scores, smoking and diagnostic FEV₁ (% 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 2).

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

Patients with high SABA use (≥ 3 SABA canisters/year) 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/year) were dispensed median 6 (3-12) canisters of SABA during the 12-year period, corresponding to 1 (1-3) puff per week (Figure 3AB, Figure E4). 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 to patients with low SABA use (Figure 3CD, Figure E4, Table 3). 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 4). In addition, 86% of high SABA users had non-controlled asthma (according to GINA 2010 criteria) and over one quarter of the patients had severe asthma according to ERS/ATS criteria (Table 5). Moreover, patients with high SABA use had more symptoms, were dispensed higher amounts of oral corticosteroids and antibiotics and had a higher number of emergency department visits and asthma-related healthcare contacts compared to 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 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 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 oral corticosteroid and antibiotic courses compared to patients using <3 SABA canisters/year.

High use of SABA in asthma has been associated with increased risk of exacerbations, mortality and healthcare utilisation [5,6,8,29]. It has been suggested that prolonged or repetitive use of SABA leads to desensitisation and attenuated bronchodilator response. However, corticosteroids increase the β_2 -receptor gene transcription compensating for the down-regulation of β_2 -receptors induced by chronic exposure to β -agonists such as SABA [2,3]. Over-reliance on SABA, i.e. high use of SABA with insufficient use of ICS, neglects both the treatment of airway inflammation and reversing the down-regulation of β_2 -receptors 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]. Though the safety concerns about SABA have been acknowledged for decades, recent studies have revealed that nearly one third of asthma patients 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 US [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 oral corticosteroid and antibiotic courses compared to those using < 3 SABA canisters/year.

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/year). 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 two patients were dispensed < 3 canisters of ICS annually. In addition, high SABA users had better adherence to ICS treatment compared to low SABA users. These findings conflict with a study conducted in the UK [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 oral corticosteroid dispensations and respiratory-related hospitalisations compared to normal-weight patients [34]. These findings emphasise the need to include weight-management strategies into treatment, as patients who are obese at diagnosis appears to have poorer long-term prognosis of asthma. Moreover, at 12-year follow-up visit 86% of patients with high SABA use (≥ 3 SABA canisters/year) had non-controlled asthma. These patients had also higher BMI and higher total number of comorbidities (e.g. diabetes, coronary artery disease and mental health medications) than patients using < 3 SABA canisters/year. Similar findings were seen in 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 to 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/year had higher blood neutrophil counts than patients with < 3 SABA canisters/year [34,36,37]. Poorer asthma control and higher neutrophilia combined with high dispensed doses of ICS in patients with high SABA use indicates 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 beside of lifestyle interventions. In addition, the use of rescue medication has major part in 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 to patients with low SABA use. These results indicate that socioeconomic status may play a role in medication behaviour. In contrast to our current findings, lower education and income has 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 (i.e. symptomatic needing SABA) [25,41]. However, we did not find any difference in lung function measurements or lung-function decline between the patients with high or low SABA use over the 12 years. Moreover, an Australian study reported that SABA over-users were more likely to have depression (11.1% vs 5.7%) and a higher proportion of SABA over-users had uncontrolled asthma [33]. In our SAAS cohort, 86% of the patients with high SABA use had non-controlled asthma and depression was more common in high SABA users compared to 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.

Though 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 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, i.e., 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 to patients using less SABA. These findings suggest that patients characterised as high SABA users with confirmed asthma diagnosis should not all be categorised as SABA overusers or SABA overreliant, since 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 recognised 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 oral corticosteroids and antibiotics compared to patients using less SABA. Since high SABA use indicated more severe asthma, these patients should be recognised in clinical practice.

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Authors' contributions

Conception and design, H.K., L.E.T., O.N., and P.I.; Data analysis, I.V. and P.I.; Data collection, H.K., L.E.T., O.N., P.I., and I.V.; Manuscript writing, I.V., P.I., and H.K.; Manuscript review and editing, I.V., P.I., H.K., L.E.T., J.K., O.N., and L.L.

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Figure legends

Figure 1. (A) Average SABA and ICS canisters dispensed 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 is not normally distributed, but for clarity mean and SD values are given here and median and IQR values in the results section.

Figure 2. (A) The average annual dispensed number of SABA canisters during 12 years divided in four categories and, (B) the average annual dispensed number of ICS canisters divided in four categories. In A-B the cut-off of 3 canisters is selected to show how many patients were dispensed on average <1 SABA canister and ≥ 3 ICS canisters annually.

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/year) 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/year) 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.

Table 1. Characteristics of asthma patients at baseline (at the time of diagnosis) according to their level of later SABA use (n=203).

	SABA use during 12 years		p value
	<3 SABA canisters/year n=182	≥3 SABA canisters/year n=21	
Age (y)	46 (14)	49 (12)	0.232 ^a
Female gender n (%)	104 (57.1)	14 (66.7)	0.487 ^b
BMI, kg/m ²	27.2 (4.8)	29.6 (6.3)	0.041 ^a
Smokers (incl. ex) n (%)	92 (50.5)	11 (52.4)	>0.999 ^b
Smoking history, pack-y	11 (5-20)	15 (8-25)	0.636 ^c
Pack-y ≥10 and post-BD	14 (7.9)	1 (4.8)	>0.999 ^b
FEV ₁ /FVC<0.7 n (%)			
Pre-bd FEV ₁ % pred	82 (70-92)	87 (76-98)	0.085 ^c
Pre-bd FVC % pred	90 (79-100)	97 (83-105)	0.193 ^c
Pre-bd FEV ₁ /FVC	0.75 (0.69-0.80)	0.78 (0.73-0.81)	0.383 ^c
Blood eosinophils (10 ⁹ /l)	0.27 (0.15-0.43)	0.32 (0.13-0.40)	0.765 ^c
Total IgE (kU/l)	82 (34-166)	91 (39-213)	0.766 ^c
hsCRP	5 (5-5)	5 (2-9)	0.988 ^c
Daily ICS use n (%)	14 (7.7)	2 (10)	0.664 ^b
AQ20 score	6 (3-9)	8 (7-12)	0.017 ^c
Hypertension n (%)	28 (15.4)	7 (33.3)	0.061 ^b
Coronary artery disease n (%)	9 (4.9)	2 (9.5)	0.318 ^b
Diabetes n (%)	4 (2.2)	0 (0)	>0.999 ^b

Data was presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, Smoking history, pack-y= pack years of smokers, FEV₁= forced expiratory volume in 1 second, FVC= forced vital capacity, IgE= immunoglobulin E, FeNO= fraction of NO in exhaled air, BD= bronchodilator, ICS= inhaled corticosteroid, AQ20= airways questionnaire 20. Statistical significances were evaluated by independent samples t-test (^a), Fisher's exact test (^b) or by independent samples Mann-Whitney U test (^c).

Table 2. 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).

	Adjusted Incidence rate ratio (Adjusted 95% CI)	p value
Age of asthma onset	1.01 (0.99-1.02)	0.182
Female gender	1.10 (0.78-1.53)	0.574
Ex or current smoker	1.12 (0.83-1.52)	0.444
preFEV ₁ % (baseline)	1.01 (0.99-1.01)	0.235
BMI <25	1	
BMI at diagnosis 25-29.9	1.19 (0.83-1.69)	0.334
BMI at diagnosis ≥30	1.53 (1.01-2.30)	0.043
AQ20 score	1.04 (1.00-1.08)	0.035

BMI= body mass index, FEV₁= forced expiratory volume in 1 second, AQ20= Airways Questionnaire 20.

Table 3. Characteristics of asthma patients 12 years after diagnosis and medication used during 12-years according to their level of SABA use (n=203).

	SABA use during 12 years		p value
	<3 SABA canisters/year n=182	≥3 SABA canisters/year n=21	
At 12-year follow-up visit			
Demographics			
Age (y)	58 (14)	61 (12)	0.252 ^a
Female gender n (%)	104 (57.1)	14 (66.7)	0.487 ^b
BMI, kg/m ²	27.7 (24.3-30.9)	30.8 (28.1-33.3)	0.014 ^c
Smokers (incl. ex) n (%)	95 (52.2)	12 (57.1)	0.818 ^b
Smoking history, pack-y	15 (6-30)	18 (5-31)	0.781 ^c
Pack-y ≥10 and post-BD	31 (17.2)	3 (14.3)	>0.999 ^b
FEV ₁ /FVC<0.7 n (%)			
Education years over 12 n (%)	58 (32.2)	2 (9.5)	0.041 ^b
Monthly gross income (€)	2085 (1438-2700)	1600 (1080-2300)	0.091 ^c
Asthma medication			
Daily SABA n (%)	13 (7.1)	10 (47.6)	<0.001 ^b
Daily LABA n (%)	83 (45.6)	13 (61.9)	0.173 ^b
Daily Theophylline n (%)	2 (1.1)	2 (9.5)	0.054 ^b
Daily add-on drug n (%)	89 (48.9)	14 (66.7)	0.167 ^b
Comorbidities			
Number of comorbidities	1 (0-2)	2 (1-4)	0.007 ^c
Allergy and/or rhinitis n (%)	126 (69.2)	16 (76.2)	0.620 ^b
Chronic obstructive pulmonary disease n (%)	31 (17.2)	3 (14.2)	>0.999 ^b
Diabetes n (%)	22 (12.1)	7 (33.3)	0.016 ^b
Coronary artery disease n (%)	16 (8.8)	5 (23.8)	0.049 ^b
Depression/Mental health medication n (%)	21 (11.5)	6 (28.6)	0.041 ^b
Co-medications (non-respiratory)	1 (0-3)	3 (2-7)	0.001 ^c
Medication used during 12 years			
Prescribed daily dose of ICS (µg budesonide equivalents)	800 (598-1000)	936 (800-1265)	0.008 ^c
Dispensed daily dose of ICS (µg budesonide equivalents)	470 (271-771)	912 (673-1512)	<0.001 ^c
12-year average ICS adherence	65 (37)	98 (32)	<0.001 ^a
Controller-to-total ratio (ICS/(SABA+ICS))	0.86 (0.71-0.93)	0.55 (0.50-0.60)	<0.001 ^c

Data was presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, Smoking history, pack-y= pack years of smokers, FEV₁= forced expiratory volume in 1 second, FVC= forced vital capacity, BD= bronchodilator, ICS= inhaled corticosteroid, Daily SABA= self-reported daily use of short-acting β_2 -agonist, Daily LABA= self-reported daily use of long-acting β_2 -agonist, Daily add-on drug= self-reported daily use of long-acting β_2 -agonist, leukotriene receptor antagonist, tiotropium or theophylline, control-to-total ratio= dispensed inhaled corticosteroid canisters divided by the sum of dispensed short-acting β_2 -agonist canisters and inhaled corticosteroid canisters. Adherence was calculated as total cumulative ICS dispensed (µg) / total cumulative ICS prescribed (µg) over 12-years. Number of comorbidities were evaluated separately and as the sum of all comorbidities reported at the 12-year follow-up visit. Statistical significances were evaluated by independent samples t-test (^a), Fisher's exact test (^b) or by independent samples Mann-Whitney U test (^c).

Table 4. Lung function and markers of inflammation in patients according to their level of SABA use (n=203).

	SABA use during 12 years		
	<3 SABA canisters/year n=182	≥3 SABA canisters/year n=21	p value
Lung function at follow-up			
Pre-bd FEV ₁ % pred	86 (76-94)	89 (76-104)	0.351
Pre-bd FVC % pred	96 (87-106)	101 (88-116)	0.213
Pre-bd FEV ₁ /FVC	0.74 (0.66-0.79)	0.72 (0.68-0.75)	0.692
FEV ₁ Reversibility mL	90 (30-163)	90 (0-140)	0.786
FEV ₁ Reversibility % of initial FEV ₁	3.2 (1-6.7)	4.2 (0.15-5.5)	0.995
Lung function change			
ΔFEV ₁ mL·year ⁻¹	-40 (-66 to -23)	-53 (-63 to -32)	0.167
ΔFEV ₁ % pred·year ⁻¹	-0.47 (-1.1 to 0.19)	-0.55 (-1.1 to -0.9)	0.693
ΔFEV ₁ /FVC year ⁻¹	-0.005 (-0.008 to -0.001)	-0.005 (-0.009 to -0.002)	0.643
Markers of inflammation			
Blood eosinophils (10 ⁹ /l)	0.17 (0.10-0.27)	0.14 (0.08-0.27)	0.369
Total IgE (kU/l)	60 (24-164)	76 (26-160)	0.808
FeNO (ppb)	11 (5-19)	8 (5-21)	0.484
Blood neutrophils (10 ⁹ /l)	3.7 (2.9-4.7)	4.5 (3.5-6.2)	0.042
IL-6 (pg/ml)	1.8 (1.2-3.0)	2.3 (1.2-5.2)	0.317
hsCRP	1.2 (0.59-2.5)	1.2 (0.5-5.2)	0.689

Data was presented as median (interquartile range). FEV₁= forced expiratory volume in 1 second, FVC= forced vital capacity, ΔFEV₁= change in pre-bronchodilator-FEV₁ from the maximum value during the first 2.5 years after diagnosis and start of treatment to 12-year follow-up visit, BD= bronchodilator, IgE= immunoglobulin E, FeNO= fraction of NO in exhaled air, IL-6= Interleukin 6, hsCRP= High-sensitivity C-reactive protein. Statistical significances were evaluated by independent samples Mann-Whitney U test.

Table 5. Symptoms, medication and health care use in patients according to their level of SABA use (n=203).

	SABA use during 12 years		
	<3 SABA canisters/year n=182	≥3 SABA canisters/year n=21	p value
Symptoms of asthma			
AQ20 score	4 (1-7)	6 (4-7)	0.018 ^c
ACT score	22 (20-24)	19 (15-21)	<0.001 ^c
Asthma control n (%)			0.044 ^b
Controlled	66 (36.3)	3 (14.3)	
Non-controlled	116 (63.7)	18 (85.7)	
Burden of asthma			
Dispensed oral corticosteroids for asthma per year (mg prednisolone)	51 (0-162)	142 (12-451)	0.005 ^c
Dispensed oral corticosteroids during 12-year follow-up (mg prednisolone)	600 (0-1920)	1800 (150-5430)	0.006 ^c
Dispensed antibiotic courses during 12-year follow-up	2 (0-5)	4 (1-9)	0.032 ^c
Fulfil severe asthma criteria according to ERS/ATS n (%)	6 (3.3)	6 (28.6)	<0.001 ^b
Emergency department visits	0 (0-0)	0 (0-1)	0.003 ^c
Range	0-10	0-18	
Asthma-related health care visits	14 (9-22)	20 (13-43)	0.009 ^c
Asthma control visits	6 (3-10)	7 (4-12)	0.427 ^c
Three or more sick leaves during the past 2 years n (%)	6 (4.1)	1 (7.1)	0.482 ^b

Data was presented as n (%) or median (interquartile range). AQ20= Airways Questionnaire 20, ACT= asthma control test, ERS= European Respiratory Society, ATS= American Thoracic Society, Asthma-related health care visits= all respiratory related scheduled and unscheduled contacts to healthcare due to asthma. Asthma control was defined according to GINA 2010²⁸ and non-controlled included both partially and uncontrolled asthma. Dispensed oral corticosteroids, asthma-related healthcare visits, asthma control visits and hospital in-patient periods have been examined during whole 12 years follow-up period. Statistical significances were evaluated by Fisher's exact test (^b) or by independent samples Mann-Whitney U test (^c).

