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TITLE PAGE

Prescription patterns, adherence and characteristics of non-adherence in children with asthma in primary care.

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ABSTRACT PAGE:

Abstract:

Adherence to treatment remains important for successful asthma management.

Knowledge about asthma medication use and adherence in real-life offer opportunities to improve asthma treatment in children.

Objective: To describe prescription patterns, adherence and factors of adherence to drugs in children with asthma.

Methods: Population-based cohort study in a Dutch primary care database (IPCI), containing medical records of 176,516 children, aged 5-18 years, between 2000-2012. From asthma medication prescriptions, age, gender, seasonal and calendar year rates were calculated. Adherence was calculated using medication possession ratio (MPR) and ratio of controller-to-total-asthma-drug. (CTT). Characteristics of children with high vs. low adherence were compared.

Results: The total asthma cohort (n=14,303; 35,181 person-years (PY) of follow-up) was mainly treated with short-acting β_2 -agonists (SABA; 40users/100 PY) and inhaled corticosteroids (ICS;32/100 PY). Median MPR for ICS was 56%. Children with good adherence (Q4=MPR>87%) were younger at start of ICS, more often visited specialists and had more exacerbations during follow-up compared to children with low adherence (Q1=MPR<37%).

Conclusion: In Dutch primary care children with asthma were mainly prescribed SABA, and ICS. Adherence to ICS was relatively low. Characteristics of children with good adherence were compatible with more severe asthma suggesting that adherence is driven by treatment-need or intensity of medical follow-up.

Key words: Asthma treatment, cohort study, paediatric asthma, prescription patterns, treatment adherence

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INTRODUCTION

Respiratory drugs are frequently prescribed in children.(1) According to the Global Initiative for Asthma (GINA), paediatric asthma can be treated with quick relievers, inhaled short-acting β_2 -agonists (SABA) and/or controllers: inhaled corticosteroids (ICS) with or without concomitant use of long-acting β_2 -agonists (LABA), or leukotriene receptor antagonists (LTRA).(2) Despite treatment, many children with asthma are not achieving good symptom control. A major cause of uncontrolled asthma is suboptimal adherence to maintenance treatment.(3) In practice, adherence to asthma treatment is commonly low, ranging between 30 to 70% (4-7), and lower in real life than in clinical trials. Improving adherence to ICS may reduce the burden of uncontrolled asthma resulting in fewer asthma-related emergency department visits and hospitalizations.(3, 8) Observational studies consistently show that asthma therapy is not always used in concordance with guidelines: massive consumption of SABAs and underuse of ICS has

been reported.(9) Furthermore, some patients use LABA without concomitant ICS, whereas in asthma, LABAs are advised only in combination with ICS because LABAs might mask ongoing symptoms, do not treat the underlying inflammation and, when given alone, carry a possibly higher risk of death from asthma.(10-12) The extent to which LABA monotherapy actually occurs in children is unknown. Knowledge on the use of and adherence to asthma treatment in real life may offer opportunities to optimize asthma treatment in children by new adherence interventions. Therefore we investigated prescription patterns of asthma drugs and treatment adherence to asthma controller therapy, by conducting a cohort study using primary care data from a large database containing complete electronic medical records of more than 1 million patients.

METHODS

Setting We conducted a population-based cohort study within the Integrated Primary Care Information database (IPCI), a longitudinal observational dynamic database containing the complete electronic records of >450 general practitioners (GPs) throughout the Netherlands.(13) In the Dutch healthcare system, patients are registered with a single GP who acts as a gatekeeper for secondary care.(14) Details of the database have been published elsewhere.(13, 15) Briefly, IPCI contains the complete electronic medical records of $\pm 1,500,000$ patients, containing anonymous longitudinal data on demographics, symptoms and diagnosis (coded and free text), referrals, laboratory findings, discharge letters, and prescriptions. The system complies with European Union guidelines on the use of data for medical research and has been

proven valid for pharmaco-epidemiological studies.(15) The scientific and ethical advisory board of IPCI approved this study (nr 07/55 2011).

Study cohort The dynamic study cohort source population comprised all children aged 5-18 years with a database history of ≥ 12 months (n=176,516). The study period was from the first of January 2000 until the first of January 2012. Follow-up started on the first of January 2000, the date on which the required 1 year of follow-up was obtained, or on their 5th birthday, whichever came last. All patients were followed from study entry until the end of the study period, until they left the GP practice or until their 18th birthday, whichever occurred first.

Asthma Case identification and validation All children who were 5-18 years old during the study period with physician diagnosed asthma were identified. First, all potential asthma cases were retrieved by an automated search on ICPC (International Classification of Primary Care) asthma codes ('R96') and free text relevant to asthma. . Asthma was defined as "definite" if diagnosed by a paediatrician. "Probable" asthma was defined as asthma diagnosed by the GP with at least 2 additional records of asthma diagnoses or prescriptions of asthma medications in the 1 year following the initial diagnosis of asthma. If at any time during the follow-up asthma was diagnosed, the child was considered asthmatic from date of first diagnosis until the end of follow-up. As this broad automated search resulted in a high number of potential asthma cases (n=63,618), machine learning was used to facilitate the validation, as described in detail elsewhere.(16) The validity of this machine learning approach was reasonable good

with a sensitivity of 95% and a specificity of 67% within the testset of 5,032 manually annotated medical records.(16) For verification of the total asthma cohort, the medical records of all predicted definite and 25% of probable asthma cases were manually reviewed by one of the authors (ME).

Prescriptions To describe patterns of use, all prescriptions for asthma drugs were selected by ATC code R03.(17) These prescriptions were further categorized into SABA, LABA, SAMA, ICS, fixed combination of ICS+LABA (FDC-ICS/LABA), cromones, xanthines, or LTRA. (Detailed overview in e-Table 1) Further analysis did not include SAMA, cromones or xanthines, due to low numbers. Detailed information on further categorization of type and dose of ICS, adapted from the GINA guidelines, is showed in e-Table 2.

Annual user prevalence rates of asthma drugs were determined by the number of children that received ≥ 1 prescription of that drug in a given calendar year divided by the number of person-years in that calendar year. Annual user prevalence reflects the proportion of children that used a specific drug class in a specific year. If a child received prescriptions of 2 drug classes, this child contributed to both drug classes. If >1 prescription of the same drug was used in 1 year, this was only counted once in the numerator. Prevalence of use was stratified by calendar year, age (assessed on the 1st January of each follow-up year), and gender. 95% confidence intervals (CI) around the prevalence were estimated based on the Poisson distribution.(18)

The overall month - and seasonal user rates over 2000-2012 were determined by the total number of children receiving ≥ 1 prescription of ICS or FDC-ICS/LABA in a given month (or season) summed for 2000-2011 divided by the number of person-months in that month (or season) summed for 2000-2011.

Among ICS users, the proportion of FDC-ICS/LABA prescriptions among the total ICS prescriptions was calculated per calendar year. Single ingredient LABA (SI-LABA) prescriptions were further classified as 'SI-LABA without ICS' or 'SI-LABA with ICS', either in 1 inhaler or in 2 separate inhalers.

Adherence Adherence to asthma medication was assessed using both the medication possession ratio (MPR) and the controller to total ratio (CTT). The MPR for each class of controller medication was calculated by dividing the total number of days' supply of that medication prescribed by the total days of follow-up, multiplied by 100, and

expressed as a percentage: $MPR = \frac{\text{Days of drug supply}}{\text{follow-up (days)}} \times 100$. Where days of drug supply

equals the number of days that prescriptions should last based on the dosing instructions of the prescriber (Days of drug supply = number of doses in a prescription divided by the dosing frequency). The follow-up period was the interval between first and last prescription for that patient. MPR was truncated to 200 if $MPR > 200$. MPR could be higher than 100% when there was overlap in prescriptions or in case patients use a higher dose (number of puffs/day) than originally prescribed.

Adherence assessed by CTT was defined as [prescriptions of controllers] divided by [prescriptions of controllers + relievers] as described by Schatz et al.(19) Patients with a ratio of ≥ 0.5 or higher were classified as high-ratio patients, and those with a ratio of < 0.5 were classified as low-ratio patients.

To compare characteristics of high vs. low adherent children, we selected all children with ≥ 2 ICS prescriptions and at least 2 years of follow-up, follow-up was censored at 2 years. In these children, the ICS MPR was calculated and patient characteristics of the highest quartile (Q4) were compared to the lowest quartile (Q1).

Co variables To analyse differences in adherent and non-adherent children, the following characteristics were collected: gender, age at start ICS/LABA, severe asthma exacerbation rate, specialist visit rate, number of infections during follow-up, and underlying comorbidity of eczema, conjunctivitis or allergic rhinitis. Asthma exacerbations were defined as emergency department visits or hospitalizations or oral corticosteroid prescriptions, all for asthma. Asthma exacerbations within 7 days after a previous exacerbation were counted as only 1 exacerbation.

Statistical analysis Descriptive analyses were used to describe patient characteristics. Chi square test or Mann-Whitney-U-tests or Poisson regression models were used to test the differences/rates in characteristics/rates between subgroups e.g. adherent and non-adherent groups, and SI-LABA vs. SI-LABA+SI-ICS groups. Kruskal-Wallis test was used to test differences between MPRs. Poisson regression models were used to fit annual ICS user rates over calendar time. A p-value of <0.05 was considered

statistically significant. Analyses were conducted using SPSS for Windows version 20.0 (SPSS INC, Chicago, IL, USA) and Episheet.(18)

RESULTS

The source population comprised 176,516 children between 5-18 years during the study period. Upon automated text validation, these were classified in 16,139 asthma cases.

After manual validation, the final asthma cohort consisted of 14,303 children (3,340 definite and 10,963 probable asthma cases according to the predefined algorithm as described above) with 35,118 PY of follow-up. Baseline characteristics of the asthma cohort are described in Table 1.

During 2000-2012 children with asthma mainly received prescriptions for SABA (38 users/100 PY) and ICS (31 users/100 PY). Detailed numbers are reported in e-Table 3.

Asthma drug prescriptions were most frequent in the younger age categories with no differences between boys and girls up to the age of 13 years. From the age of 13 onwards, SABA, ICS and FDC-ICS/LABA were more prescribed to girls. Most children were prescribed Fluticasone propionate in low or middle dose, only 10% received a high dose. (e-Table 4) With regard to type of device, most children between 5-8 years of age used an MDI to inhale ICS, more details are shown in e-Table 5. Concomitant prescriptions of LTRA during ICS were observed in 216 children, during FDC ICS/LABA in 197 children and during LABA in 31 children (e-Table 6.). None of the GPs prescribed or continued Omalizumab for a child in the asthma cohort.

We observed a seasonal pattern with more prescriptions for ICS during the winter and a peak in September, this pattern was observed in all calendar years and for the total study period. (e-Figure 1 and 2) Poisson regression analyses showed that the proportion of ICS users decreased with increasing calendar time. ($p < 0.001$) The use of SI-ICS decreased, while the proportion of FDC-ICS/LABA users increased over time from 2 users/100PY in 2000 to 10 users/100 PY in 2011. (Figure 2)

The overall annual prevalence of LABA use was 27.8/100PY of which the majority was FDC-ICS/LABA (24.3/100PY). LABA was more prescribed to older children and to girls, especially after the age of 13 years. The prevalence of SI-LABA + SI-ICS (as 2 separate inhalers) was 2.9/100PY and of SI-LABA use without concomitant ICS was 1.8/100PY. (Figure 3) Use of SI-LABA decreased over time with prevalence rates of 1.44/100PY (SI-LABA without ICS) and 1.52/100PY (SI-LABA with ICS) in 2011. Of all children receiving SI-LABA ($n=305$), 122 children (40%) had no concomitant ICS use. They had less severe asthma, were older at the first LABA prescription (13.5 vs. 11.5 years, $p < 0.001$), had fewer specialist visits and fewer severe asthma exacerbations compared to children with SI-LABA with ICS. (e-Table 7)

Adherence Median MPRs for LTRA, FDC-ICS/LABA, and ICS were significantly different, with MPRs 77.1, 61.3, and 56.0%, respectively. ($p < 0.001$) (Figure 4) Good adherence ($MPR > 0.8$) was observed in almost 46% of the LTRA users and in 34% of the FDC-ICS/LABA users. For ICS, only 33% of the users had good adherence ($MPR \geq 0.8$).

Univariate Poisson regression analyses of users with ≥ 2 prescriptions of ICS and 24 months of follow-up (n=2,397) showed that patients with a high MPR (Q4 MPR>87) were younger at start of ICS, had more specialist visits and more severe asthma exacerbations compared to patients with a low MPR (Q1 MPR<37). Differences were similar when comparing patients with MPR ≥ 0.8 to MPR <0.8. (Table 2.)

The CTT ratio was calculated for all patients using controllers and/or relievers. Sixty percent of the patients (n=5,519) had a high CTT ratio (CTT ≥ 0.5) and used a mean of 5.0 controllers, whereas patients with a low-CTT ratio used 1.5 controllers. Patients with a good adherence (CTT ratio>0.5) were younger at asthma diagnosis (χ^2 , p=0.004) and at start of medication (p=0.009) compared to patients with a low CTT ratio.

DISCUSSION

This longitudinal, population based cohort study, covering a study period of 12 years, provides annual- and seasonal prescription patterns for asthma medication in children in the Netherlands. SABA and ICS were most frequently used, whereas SI-LABA was rarely prescribed and decreased over time. Adherence to asthma medications was suboptimal as only 31% of the ICS users had an MPR >0.8. Adherence to LTRA was significantly higher than to ICS, which may be due to the fact that this is oral medication, also 'steroid phobia' may play a role.

ICS was the most frequently prescribed controller medication. SI-ICS decreased over time, whereas the use of FDC-ICS increased. Only 1.8 users/100PY received SI-LABA without concomitant ICS use, which is comparable to other studies.(20-22) SI-LABA as monotherapy does not comply with current national(23, 24) and international asthma guidelines(25).

We observed seasonal patterns in ICS use, with the lowest rate in august and an increase in the winter. After checking our data, this coincides with severe asthma exacerbation patterns in this asthma cohort.

Overall, the prevalence of ICS prescriptions decreased over time. This might partly be caused by the fact that recent asthma guidelines advise to taper ICS to the minimum effective dose or to stop if possible.(25)

Adherence to controller medications was low, in line with recent literature.(26) Actual MPRs are probably even lower, as we only considered prescription data and not dispensing data, and even if all prescribed medication would be dispensed, not all dispensed medication would be actually (correctly) taken. It was emphasized by the European Respiratory Society Task Force that Correct inhaler technique is one of the prerequisites of successful asthma treatment and this inhalation technique should be taught, taught back and checked . (27) Internet based training offers possibilities to enhance correct inhalation techniques, e.g. the webpage ADMIT, this is a European place for information about obstructive pulmonary diseases and different treatment options with focus on inhalation therapy. Here patients as well as health care professionals can find various supports in order to achieve asthma control. Recently, a

Dutch website on inhalation techniques in the Netherlands has been launched. (28)

The fact that the adherence in our study is relatively low might be due to the chosen methodology (=MPR) to assess adherence. Children might be adherent to ICS, stop due to few symptoms (but use rescue medication as needed) and be adherent to ICS again when symptoms return.

We performed a cluster analysis where we checked the timing of prescriptions. Four clusters were identified, but none of these clusters identified patients with periodic asthma (periodic prescribing at regular time intervals). Use of MPR to assess adherence might probably be too conservative in patients with periodic asthma. Future studies should investigate optimal adherence measures based on asthma phenotypes.

The low adherence to ICS can also be explained by the fact that in contrast to guidelines, many children use ICS as rescue medication, and that as a result of improper ICS prescribing, where patients are not asked to return for a follow-up visit, children who need long-term ICS therapy experience unmonitored discontinuation of therapy without corresponding order from their physician.(29)

Variations in adherence rates have been reported due to different study designs, adherence measures, and populations studied.(8) Characteristics of children with good adherence were compatible with more severe asthma, suggesting that adherence is driven by treatment need or intensity of medical follow-up. The design of our study was

not suitable to investigate the association between adherence and exacerbations as we did not censor on severe asthma exacerbation.

Knowledge about asthma drug use and real life adherence may offer opportunities to optimize asthma treatment in children.

Promising results have been shown by targeting new adherence interventions, like speech recognition telephone calls, or by other e-health tools, or disease management programmes.(30-32) Another opportunity to improve adherence is to enhance the promising pharmacist-led targeted interventions in patients with asthma. In the Netherlands, the pharmacist's role is shifting from a compounder, dispenser, and specialist of medication toward a patient-oriented healthcare professional.(33)

A recent published review presents seven national asthma programmes across Europe, including the asthma programme of the Netherlands. (34) A programme was defined as a well described activity, developing strategies to reduce asthma mortality and morbidity across Europe. Published data of the three evaluated programmes showed that, thanks to rigorous efforts, it is possible to improve patients' quality of life and reduce hospitalisation, asthma mortality, sick leave and disability pensions. The direct and indirect costs, both for the individual patient and for society, can be significantly reduced.

The main strengths of our study are the large population based cohort with detailed information on prescriptions and comorbidities over a long study period. The design precluded selection bias due to non-responder or recall bias, and because patients

were registered with one GP, where data were collected as part of routine patient care, irrespective of any research question. In addition, we were able to study age- and gender-specific asthma treatment patterns as the database captured all GP prescriptions with detailed information on dosage and duration. Limitations are the lack of dispensing data and actual drug intake. Our adherence rates might be underestimated as specialist prescribing is not routinely captured in the database. However, this bias is probably non-substantial as GPs play a central role in the care of patients and prescriptions initiated by the specialist are often continued by the GP.(35)

CONCLUSION

In Dutch primary care children with asthma were mainly prescribed SABA and ICS. ICS adherence was low, with only 31% of the patients having an MPR ≥ 0.8 . Characteristics of children with good adherence were suggestive of more severe asthma, and driven by treatment need or intensity of medical follow-up. These findings indicate that there is room for improvement of adherence to treatment, especially in children with milder forms of asthma.

Table 1. Baseline characteristics for the total asthma cohort.

	Total asthma cohort n (%)
Subjects (n)	14,303
Gender (male)	8,400 (59%)
Age at cohort entry (years)(mean, sd)	10.2 (4%)
Follow-up time after asthma diagnosis (years)(mean, sd)	2.5 (2%)
Eczema (till cohort entry)	3,852 (27%)
Allergic rhinitis (till cohort entry)	2,541 (18%)
Conjunctivitis (till cohort entry)	821 (6%)
Lower economic status (ever)	501 (4%)

n=number of subjects, sd=standard deviation

Table 2. Characteristics of children with >1 ICS prescription and 24 months of follow-up comparing Q1 vs. Q4 MPR and MPR<0.8 vs. ≥0.8.

	MPR Q1 MPR <37	MPR Q4 MPR >87	p- value	MPR <0.8	MPR ≥0.8	p- value	
Number of patients	599	598		1,659	738		
Gender (boys)	59%	56%	ns	60%	56%	ns	
Age at start ICS (years, sd)	10.0 (3.4)	9.1 (3.4)	<0.00 1	9.5 (3.3)	9.1 (3.4)	0.001	
Age at start asthma drug (years, sd)	7.9 (3.9)	7.0 (3.9)	<0.00 1	7.4 (3.8)	7.0 (3.9)	0.001	
Eczema*(n, %)	184 (31%)	212 (36%)	ns	552 (33%)	261 (35%)	ns	
Allergic rhinitis*(n, %)	159 (27%)	165 (28%)	ns	423 (26%)	208 (28%)	ns	
Conjunctivitis*(n, %)	56 (9%)	42 (7%)	ns	148 (9%)	54 (7%)	ns	
Children with ≥1 specialist visits during follow-up (n, %)	33 (6%)	91 (15%)	<0.00 1	152 (9%)	114 (15%)	<0.00 1	
Children with exacerbation during follow-up (n, %)	26 (4%)	42 (7%)	<0.05	80(5%)	49(7%)	ns	
			Poisson RR (95% CI)			Poisson RR (95% CI)	
Specialist visits during follow- up (rate/PY, 95% CI)^	0.04 (0.03- 0.05)	0.12 (0.10- 0.14)	1.50 (1.34- 1.68)	<0.00 1	0.06 (0.06- 0.07)	0.12 (0.10- 0.14)	1.23 (1.15- 1.31)
Severe asthma exacerbations during follow- up^^ (rate/PY, 95% CI)	0.03 (0.04- 0.06)	0.05 (0.02- 0.04)	1.21 (1.05- 1.40)	0.009	0.03 (0.03- 0.04)	0.05 (0.04- 0.06)	1.14 (1.03- 1.26)

Ns=not significant, Sd= standard deviation, 95% CI= 95% confidence interval

* diagnosed prior to 1st ICS prescription.

Ns=not significant, 95% CI= 95% confidence interval

^Specialist visit rate= number of visits to the specialist (for asthma) per person-year

^^Exacerbation rate= number of severe asthma exacerbations (hospitalizations, ED visit or corticosteroid course for asthma) per person-year

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LEGENDS:

Figure 1. Asthma drug use per 100 PY in the total asthma cohort by age (years) and gender.

Figure 2. Annual prevalence of total ICS use categorized into SI-ICS and FDC-ICS/LABA users per 100 PY in children with physician diagnosed asthma and treated during follow-up in 2000-2012.

Figure 3. All LABA users (SI-LABA without SI-ICS, SI-LABA with SI-ICS, and FDC-ICS/LABA) per 2 years of age stratified by gender, in children with physician diagnosed asthma and treated during follow-up.

Figure 4. Medication Possession Ratio (MPR) boxplot by drug.

□= 25th-75th percentile, |-----|-----|= minimum-median-maximum, ◇= mean.

Online supplements

Online e-Table 1. Online supplement: ATC codes grouped by drug class and drugname.

Online e-Table 2. Categorization of ICS doses into 'low', 'medium' and 'high'(adapted from GINA guidelines).

Online e-Table 3. Online supplement: Prevalence of asthma drug use per 100 PY in the asthma cohort by age and gender.

Online e-Table 4. Categorization of number of children with prescriptions, and number of prescriptions for 'low', 'medium' and 'high'dose ICS.

Online e-Table 5. Categorization of children with prescriptions per device stratified by age category.

Online e-Table 6. Number of patients with prescriptions per medication class and with prescriptions with concomitant use of LTRA.

Online e-Table 7. Children with SI-LABA; categorized in patients with and without concomitant SI- ICS.

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Ns=not significant, 95% CI= 95% confidence interval

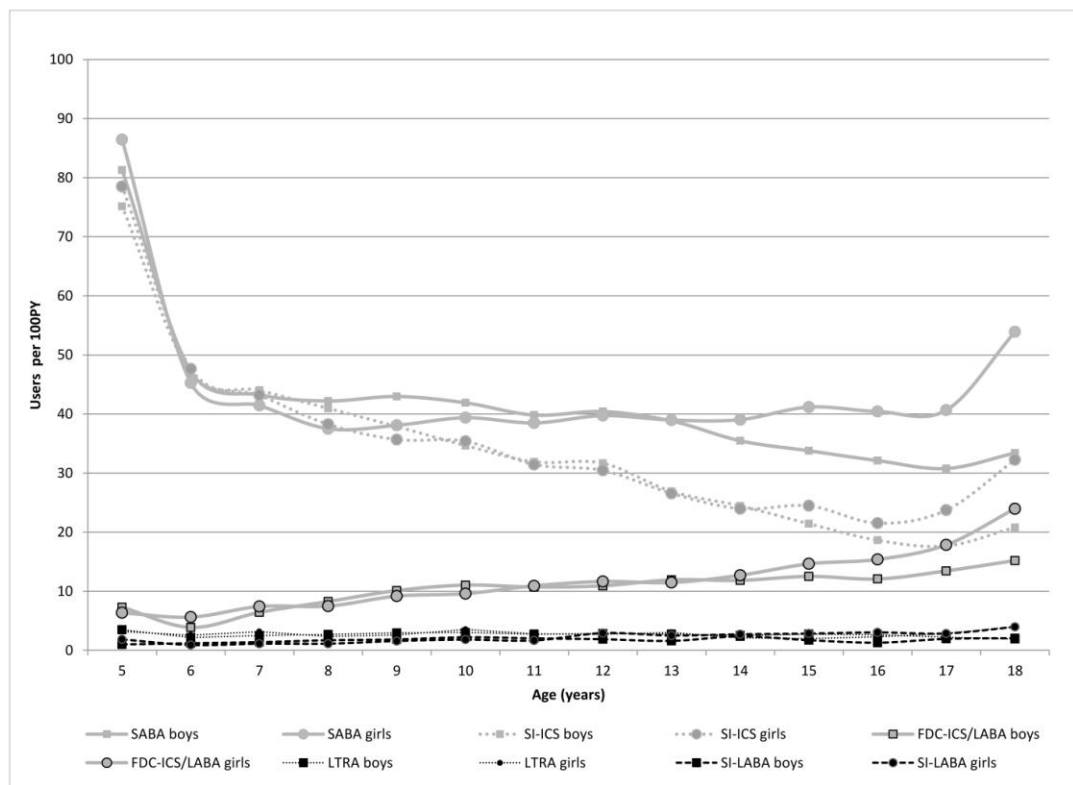
Specialist visit rate*= number of visits to the specialist (for asthma) per person-year

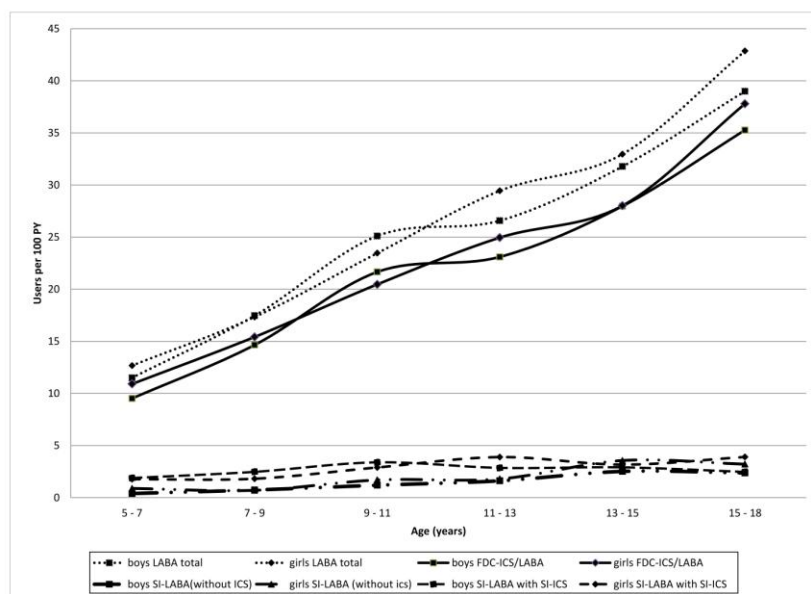
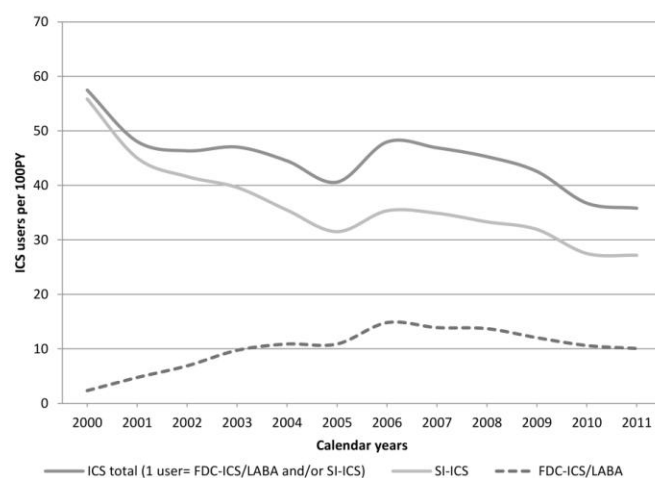
Exacerbation rate **= number of severe asthma exacerbations (hospitalizations, ED visit or corticosteroid course for asthma) per person-year

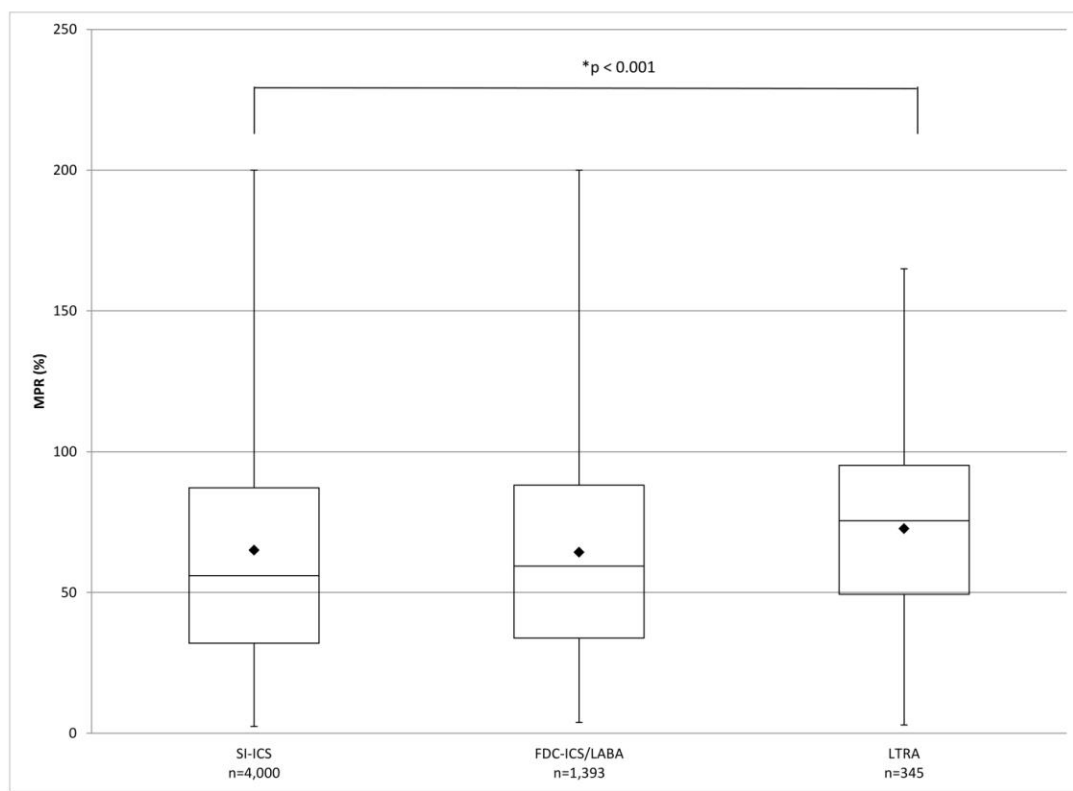
*The total number of patients within the different asthma therapies is not equal to the number of patients receiving asthma therapy, as patients can use several therapies during follow up.

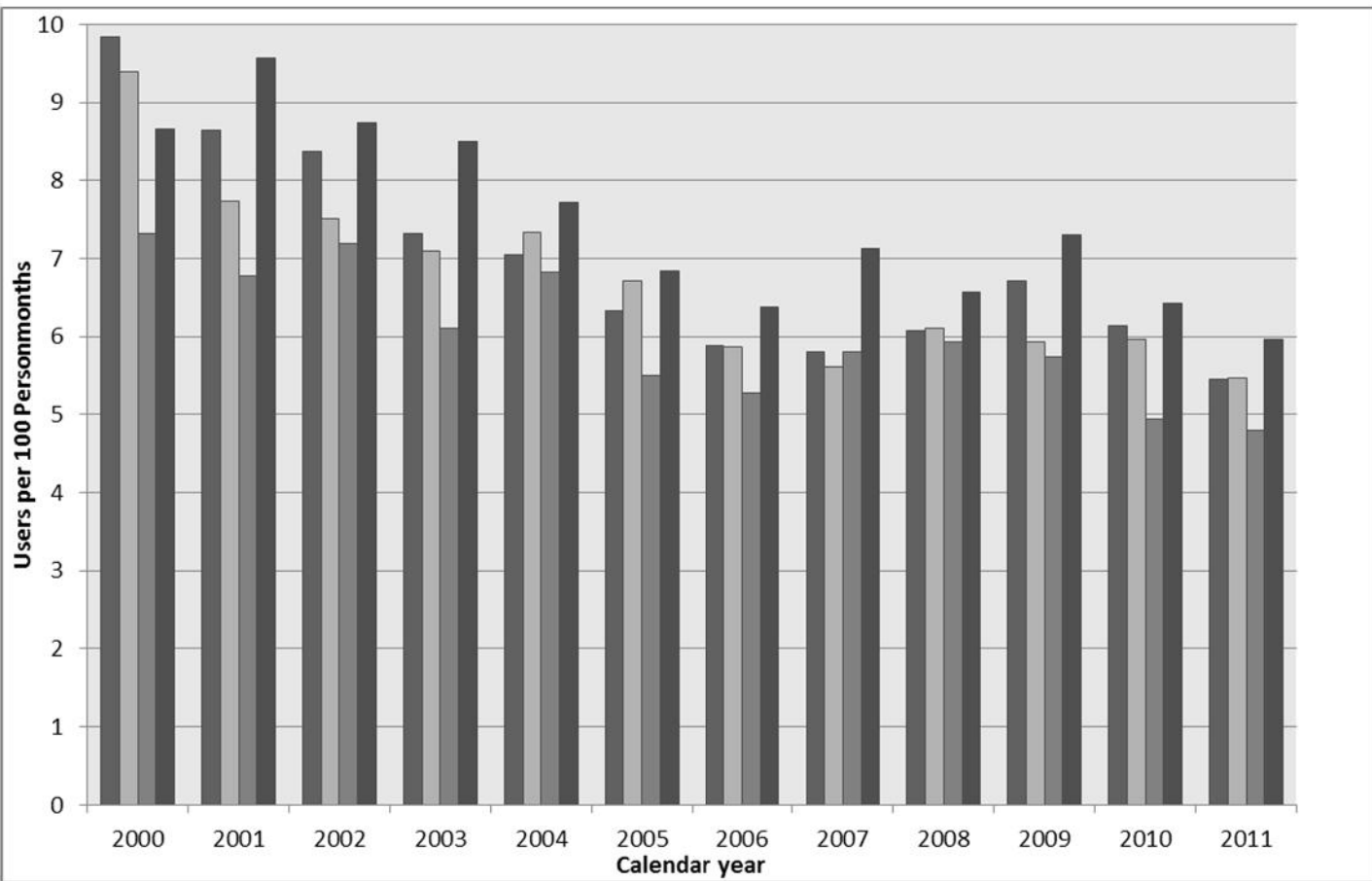
Online e-figure 1. ICS (SI-ICS plus FDC-ICS/LABA) user rate per month (per 100 person months) per calendar year during the study period 2000-2012.

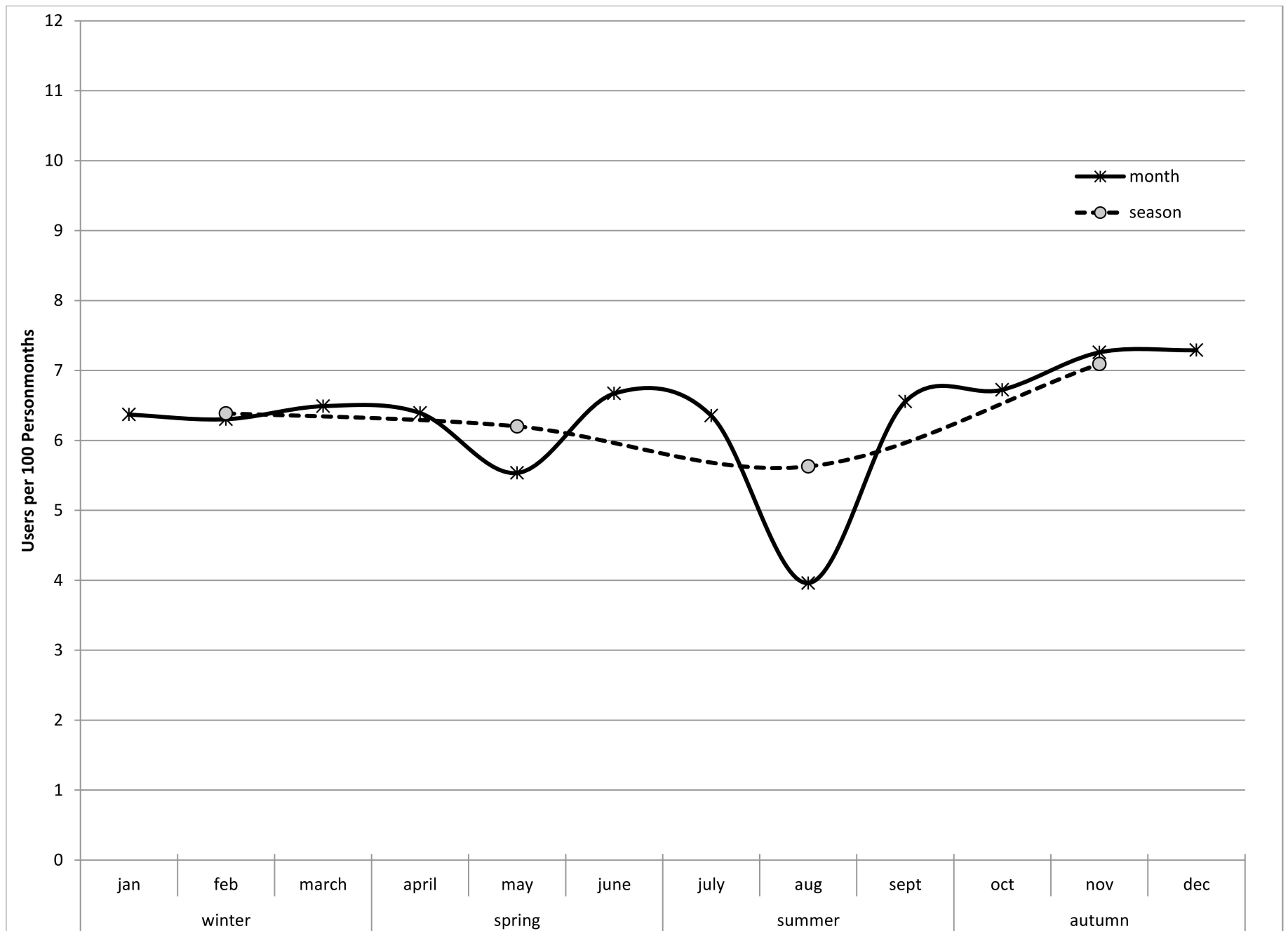
Online e-Figure 2. Total ICS (SI-ICS plus FDC-ICS/LABA) user rate per month (per 100 person months) and per season during the study period 2000-2012.











Online Table 1. Online supplement: ATC codes grouped by drug class and drugname.

ATC code	Drug class	Drug
R03AC02	SABA	aerolin
R03AC02	SABA	airomir
R03AC02	SABA	salbutamol
R03AC02	SABA	ventolin
R03AC03	SABA	bricanyl
R03AC03	SABA	terbutaline
R03AC04	SABA	berotec
R03AC04	SABA	fenoterol
R03AC12	LABA	salmeterol
R03AC12	LABA	serevent
R03AC13	LABA	atimos
R03AC13	LABA	foradil
R03AC13	LABA	formoterol
R03AC13	LABA	oxis
R03AK03	fixb2atro	berodual
R03AK03	fixb2atro	fenoterol/ipratropium
R03AK04	fixb2atro	combivent
R03AK04	fixb2atro	salbutamol/ipratropium
R03AK06	FDC-ICS/LABA	salmeterol/fluticason
R03AK06	FDC-ICS/LABA	seretide
R03AK07	FDC-ICS/LABA	budesonide/formoterol
R03AK07	FDC-ICS/LABA	beclometason/formoterol
R03AK07	FDC-ICS/LABA	foster
R03AK07	FDC-ICS/LABA	ymbicort
R03AK07	FDC-ICS/LABA	sinestic
R03BA01	ICS	aerobec
R03BA01	ICS	becloforte
R03BA01	ICS	beclometason
R03BA01	ICS	becotide
R03BA01	ICS	beclodin
R03BA01	ICS	qvar
R03BA02	ICS	budesonide
R03BA02	ICS	pulmicort
R03BA05	ICS	flixotide
R03BA05	ICS	fluticason
R03BA08	ICS	alvesco
R03BA08	ICS	ciclesonide
R03BB01	SAMA	atrovent
R03BB01	SAMA	ipratropium

R03BB01	SAMA	ipraxa
R03BB04	LAMA	spiriva
R03BB04	LAMA	tiotropium
R03BC01	cromones	cromoglicinezuur
R03BC01	cromones	lomudal
R03BC03	cromones	nedocromil
R03BC03	cromones	tilade
R03CC02	SABA	salbutamol
R03CC02	SABA	ventolin
R03CC03	SABA	terbutaline
R03DA04	xanthines	theofylline
R03DA04	xanthines	theolair
R03DC03	LTRA	montelukast
R03DC03	LTRA	singulair

E-Table 2. Categorization of ICS doses into ‘low’, ‘medium’ and ‘high’ (adapted from GINA guidelines).

ICS	ATC (single use)	ATC (fixed combination)	Children 5-11 years (dose in microgram)			Adults and adolescents (dose in microgram)		
			low	medium	high	low	medium	high
Beclomethasone dipropionate (HFA MDI)	R03BA01	R03AK08	50-100	>100-200	>200	100-200	>200-400	>400
Beclomethasone (DPI)	R03BA01	R03AK08	100-200	>200-400	>400	200-500	>500-1000	>1000
Budesonide (MDI)	R03BA02	Not available	100-200	>200-400	>400	200-400	>400-800	>800
Budesonide (DPI)	R03BA02	R03AK07	100-200	>200-400	>400	200-400	>400-800	>800
Budesonide (NEB)	R03BA02	Not available	250-500	>500-1000	>1000	500-1000	>1000-2000	>2000
Ciclesonide (HFA MDI)	R03BA08	Not available	80	>80-160	>160	80-160	>160-320	>320
Fluticasone propionate (DPI)	R03BA05	R03AK06, R03AK10, R03AK11	100-200	>200-400	>400	100-250	>250-500	>500
Fluticasone propionate (HFA MDI)	R03BA05	R03AK06, R03AK10, R03AK11	100-200	>200-500	>500	100-250	>250-500	>500
Fluticasone (NEB)	R03BA05	Not available	100-250	>250-500	>500	100-250	>250-500	>500

Online e-Table 3. Online supplement: Prevalence of asthma drug use per 100 PY in the asthma cohort by age and gender.

Age	ICS		LTRA		SABA		LABA		FDC ICS/LABA	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
5	75.0	78.5	3.5	3.2	81.3	86.4	1.0	1.9	7.3	6.3
6	46.9	47.6	2.2	2.6	47.2	45.3	1.2	0.9	3.9	5.6
7	44.0	43.1	2.5	3.2	43.2	41.4	1.4	1.1	6.4	7.4
8	40.9	38.3	2.7	2.3	42.2	37.5	1.7	1.1	8.3	7.5
9	37.9	35.7	2.9	2.6	43.0	38.1	1.8	1.6	10.1	9.2
10	34.7	35.4	3.0	3.5	41.9	39.4	2.2	1.8	11.0	9.6
11	31.9	31.5	2.7	2.8	39.8	38.5	2.0	1.7	10.7	10.9
12	31.7	30.5	2.8	2.7	40.4	39.7	1.9	2.9	10.9	11.7
13	26.9	26.6	2.8	3.0	38.8	39.0	1.6	2.5	11.9	11.5
14	24.5	24.0	2.5	2.1	35.5	39.0	2.4	2.7	11.8	12.7
15	21.4	24.5	2.7	2.0	33.8	41.2	1.7	2.8	12.5	14.6
16	18.6	21.5	2.6	2.3	32.1	40.4	1.3	3.0	12.1	15.4
17	17.7	23.7	2.2	2.9	30.8	40.7	1.9	2.9	13.4	17.9
18	20.8	31.9	1.9	3.8	33.4	53.9	2.1	4.0	15.2	24.0

e-Table 4. Categorization of number of children with prescriptions, and number of prescriptions for 'low', 'medium' and 'high' dose ICS.

ICS	ATC		Children 5-11 years (n)				Children > 12 years (n)				
			Dose				Dose				
			low	medium	high	Total children 5-11	low	medium	high	Total children >12	Total children 5-18
Beclomethasone dipropionate (MDI/DPI)	R03BA01 R03AK08	Pt	231	596	174		295	92	29	n.a.	
		Pres	533	1890	563	2986	777	233	69	1079	4065
		% pres	18	63	19		72	22	6		
Budesonide (MDI/DPI/NEB)	R03BA02 R03AK07	Pt	218	335	79		644	188	15		
		Pres	621	1043	193	1857	1833	453	26	2312	4169
		% pres	33	56	10		79	20	1		
Ciclesonide (MDI)	R03BA08	Pt	16	20	3		47	16	3		
		Pres	70	65	9	144	182	46	3	231	375
		% pres	49	45	6		79	20	1		
Fluticasone propionate (MDI/DPI/NEB)	R03BA05 R03AK06 R03AK10 R03AK11	Pt	1575	1919	399		1248	1342	242		
		Pres	5832	6536	1281	13649	3993	4373	719	9085	22734
		% pres	43	48	9		44	48	8		
TOTAL		Pres % pres	7056 38	9534 51	2046 11	18636	6785 53	5105 40	817 6	12707	31343

* patients could belong to more than 1 age category during the study period.

e-Table 5. Categorization of children with prescriptions per device stratified by age category.

Type Device ICS	Patients (n)	Prescription (n)	Proportion prescriptions per age category (%)
5-8 years			
DPI	463	1,337	12
MDI	2,674	9,407	87
NEB	16	57	1
total		10,801	
9-12 years			
DPI	1,131	3,778	48
MDI	1,449	4,015	51
NEB	9	14	0
total		7,807	
12-15 years			
DPI	1,513	4,591	67
MDI	859	2,215	32
NEB	13	22	0
Total		6,828	
15-18 years			
DPI	1,537	4,736	80
MDI	480	1,160	20
NEB	5	11	0
total		5,907	
total		31,343	

* patients could belong to more than 1 age category during the study period.

E-Table 6. Children with 1 prescription during follow up, stratified by medication class, and concomitant use of LTRA during other drug use.

Drug (≥1 prescription during follow up)	Children (number)
ICS	5,749
FDC-ICS/LABA	1,987
LTRA	507
LABA	386
SABA	7,544
Other R03 drugs	448
Concomitant drugs	
ICS+LTRA	216
FDC-ICS/LABA+LTRA	197
LABA+LTRA	31

Online e-Table 7. Children with SI-LABA; categorized in patients with and without concomitant SI- ICS.

	SI-LABA no SI-ICS	SI-LABA+SI-ICS	p-value χ^2	RR*	p-value Poisson
Number of patients (n)	122	183			
Age first LABA prescription (years, sd)	13.5 (3.1)	11.5 (3.8)	p<0.001		
Gender (boys) (%)	47%	55%	ns		
Specialist visit rate * till first LABA (rate/PY, 95% CI)	0.12 (0.07-0.19)	0.34 (0.25-0.54)		2.92 (1.60-5.31)	p<0.001
Specialist visit rate* after first LABA (rate/PY, 95% CI)	0.13 (0.09-0.18)	0.27 (0.23-0.33)		2.13 (1.42-3.20)	p<0.001
Exacerbation rate** till first LABA (rate/PY, 95% CI)	0.08 (0.04-0.15)	0.55 (0.43-0.69)		6.57 (3.40-12.72)	p<0.001
Exacerbation rate ** after first LABA (rate/PY, 95% CI)	0.04 (0.02-0.07)	0.09 (0.07-0.12)		2.57 (1.21-5.50)	p=0.015

Ns=not significant, 95% CI= 95% confidence interval

Specialist visit rate*= number of visits to the specialist (for asthma) per person-year

Exacerbation rate **= number of severe asthma exacerbations (hospitalizations, ED visit or corticosteroid course for asthma) per person-year