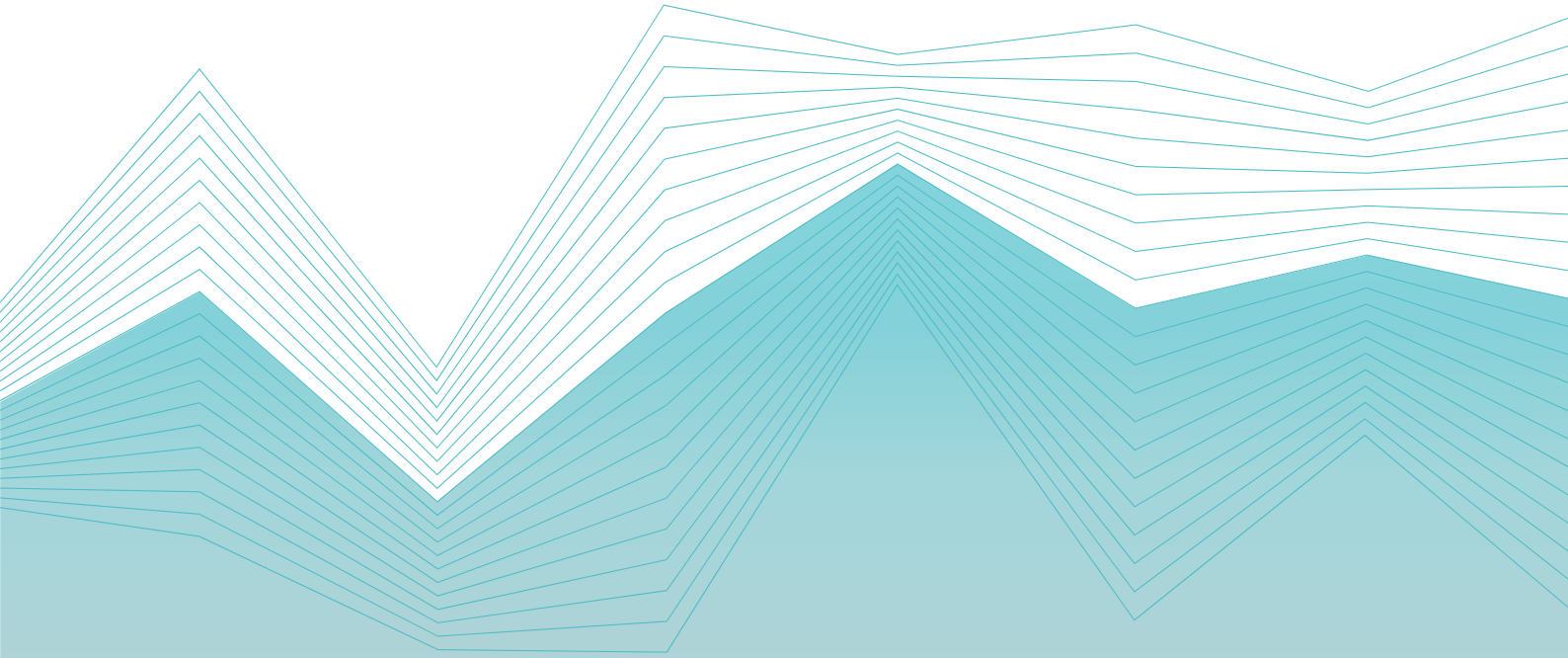
Asthma medication in Dutch primary care

Asthma medication use and its relation with asthma outcomes



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Preface

This study provides insight into the medication use of patients with asthma in Dutch primary care. It also provides insight into the relationship between asthma patients' adherence to inhaled medication and asthma outcomes (i.e. exacerbations, indicated by a prescription for a short oral corticosteroids course, and self-reported asthma control), in relation to the severity of the illness (based on the classification proposed by the Global Initiative for Asthma). We used data derived from the Nivel Primary Care Database, which includes routine care data originating from electronic medical records from general practitioners across the Netherlands.

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The authors,
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Content

Summary

Asthma is a chronic disease of the lungs, and it is estimated that about 10% of the Dutch population have asthma. Most patients with asthma are treated by their GP and it is mainly treated with medication. A stepwise approach to treatment of asthma is recommended by the Global Initiative for Asthma (GINA) and is followed by the asthma treatment guideline of the Dutch College of General Practitioners (NHG). The first step is medication of SABA as-needed, followed by adding controller medication (ICS) to the as-needed SABA. In the next steps LABA is added, and thereafter the ICS dosage is increased. In the last step (step 5) add-on treatment is added to step 4, e.g. biological medication or low dose OCS.

Although asthma can be effectively treated, many patients have suboptimal asthma control, on avarage around 45% of the asthma patients. About one out of three patients report deviations from their prescribed controller medication. Poor asthma control increases the risk of exacerbations, which often require hospitalization and have a negative impact on patients' quality of life.

The relationship between adherence to ICS medication and asthma outcomes is complex and current research showed contradictory findings. Some find that a higher level of ICS adherence is associated with a lower risk of asthma exacerbations, other observational studies concluded that higher ICS adherence levels are associated with even an increased risk of asthma exacerbations. Insight into the situation in the Netherlands is currently lacking. The aim of the this study is therefore: What is the current medication use of patients with asthma in primary care in relation to the severity of asthma and the risk of exacerbations and asthma control?

In total, we include 21,369 patients from12 years and older who received at least two prescriptions for inhalation medication for their asthma in 2016. Our population consisted of more females (60%) than makes, one-third had no comorbidity, and 25% had two or more other chronic diseases, 43% of the patients were treated according GINA step 4. ICS adherence of over 80% was reached by 38% of the patients, 41% had no SABA prescriptions, and 3.5% had six or more SABA prescriptions, and 13% of the patients had at least one exacerbation in 2016. ICS adherence had no linear association with as-needed SABA, as both patents with low ICS or high ICS adherence had a high number of SABA prescriptions. Results of the multivariable model to predict at least one exacerbation showed no significant relation with ICS adherence, yet it did showed an U-shape relation with the number of SABA as-needed prescription. Compared to no-SABA prescriptions, patients with one to five prescriptions had a lower risk of experiencing an exacerbation, whereas patients with six or more SABA prescriptions had a significantly higher risk (1.4 times higher (1.1 – 1.8)). This risk was independent of age, sex, ICS adherence, asthma severity, comedication or comorbidity.

For a limited number of patients information on self-reported asthma control as measured with the ACQ-score was available (N= 2,388). Half of the patients (51%) perceived their asthma as being controlled. Controlled asthma was positively associated with ICS adherence and was negatively associated with the number of SABA prescriptions. The more SABA prescriptions, the higher the risk of having an uncontrolled asthma.

For GPs it is important to recognize that according to the SABA use of their patients with asthma, different approaches to achieving optimal asthma control (both symptom control as well as decreasing the occurrence of exacerbations) are needed.

Our study revealed that a higher number of SABA prescriptions (six or more) was associated with a higher risk of exacerbations and a higher risk of having an uncontrolled asthma. Yet, a higher number of SABA prescriptions was also associated with being more adherent to ICS. So, improving ICS adherence in these patients is not the way to achieve better asthma control or reduce the risk of exacerbations. In these patients improvement in asthma control need to be sought in the technique a patient uses to take their controller medication, do they have the proper technique, and also whether the patient actually achieves asthma control with their controller medication dosage, or should it be increased. This information might guide the GP were to find room for improvement to reduce the occurrence of exacerbations and improve experienced asthma control.

1 Introduction

1.1 Asthma in the Netherlands

Asthma is a chronic respiratory condition due to inflammation of the air passages in the lungs. It occurs in all age groups and is characterized by recurrent attacks of breathlessness and wheezing.[1] In 2018, an estimated 636,200 people in the Netherlands visited their general practitioner (GP) for asthma complaints; 272,000 men and 364,200 women.[2] In that year, 81,900 new patients (38,400 men and 43,500 women) received the diagnosis asthma from their GP. This corresponds with 4.5 per 1,000 men and 5.0 per 1,000 women.[3] Considerable healthcare costs are involved with the treatment of asthma. In 2017, the total cost for asthma was 427.3 million euros, of which 37% was spent on medicines and medical aids, 37% on hospital care and 19% on primary care.[4]

1.1.1 Treatment of asthma

Most patients with asthma are treated by their GP, and it is mainly treated with medication. Of all patients with asthma who had at least one contact with their GP for asthma in 2014, 87% used a medicine for obstructive airway diseases (Lambooij et al. 2016).
A stepwise approach to treatment of asthma is recommended by the Global Initiative for Asthma (GINA, 2016) and is followed in the asthma treatment guideline of the Dutch College of General Practitioners (NHG) (Smeele et al. 2015). Table 1 describes this stepwise approach, as it was defined in 2016.

Table 1.1 GINA stepwise approach to asthma treatment in 2016 (simplified)

Step 1	Step 2	Step 3	Step 4	Step 5
As-needed SABA	Low dose ICS and as-needed SABA	Combination of low dose ICS with LABA and as-needed SABA	Combination of medium/high dose ICS with LABA and as-needed SABA	Medication added to step 4 (e.g. biological medication, low dose OCS)

The first step consists of an as-needed short-acting beta agonist (SABA) for a quick relief of asthma symptoms, without any controller medication. This treatment is recommended for patients who rarely experience asthma symptoms, who do not wake at night due to asthma, who have had no exacerbations in the last year, and who have a normal FEV_1 (forced expiratory volume, i.e. the maximal amount of air one can forcefully exhale in one second). If this treatment is not adequate (SABA is needed for more than twice a week), or if patients more often experience asthma symptoms (also during the night) or have risk factors for exacerbations (e.g. a low FEV_1 or being hospitalized for asthma), treatment can be started at or stepped up to step 2. In this step low dose inhaled corticosteroids (ICS) is added to the as-needed SABA. In step 3, a long-acting beta agonists (LABA) is added to low dose ICS plus as-needed SABA. LABA given as monotherapy (i.e. without ICS controller medication) is not recommended, since it has been associated with more serious adverse events and asthma-related deaths (Morales et al. 2013).

[1] https://www.who.int/respiratory/asthma/definition/en/

[2] https://www.volksgezondheidenzorg.info/onderwerp/astma/cijfers-context/huidige-situatie#node-prevalentie-astma-huisartsenpraktijk.

[3] https://www.volksgezondheidenzorg.info/onderwerp/astma/cijfers-context/huidige-situatie#node-aantal-nieuwe-gevallen-van-astma-huisartsenregistratie

[4] https://www.volksgezondheidenzorg.info/onderwerp/astma/kosten/zorguitgaven#node-zorguitgaven-astma-naar-sector

However, even though studies find a decrease in LABA monotherapy (Belhassen et al. 2019), there are still patients relying on this type of treatment (Van Ganse et al. 2020). In step 4, the dosage of the controller medication is increased to medium/high dose ICS/LABA plus as-needed SABA and is recommended for patients who have troublesome asthma symptoms on most days (including waking during the night) and especially if there are risk factors for exacerbations. In step 5, add-on treatment to the medication in step 4 is recommended, e.g. biological medication or low dose OCS. This add-on treatment is recommended for patients with a history of exacerbations, for patients with severe allergic asthma, and for patients with severe eosinophilic asthma. Severity of asthma can be assessed from the level of treatment, which is based on the dose and type of asthma medication patients use. In 2016, GINA defined mild asthma as asthma that can be controlled with treatment step 1 or step 2, moderate asthma can be controlled with step 3, and severe asthma requires step 4 or step 5 treatment (GINA, 2016).
A study from 2014 showed that in the Netherlands, the most commonly used controller medications for asthma are ICS (35%) and the ICS/LABA combination (36%). SABA, alone or in combination with ICS and/or LABA, was used by 57% of patients with asthma (Lambooij et al. 2016).

In 2018, the GINA recommendations were updated, changing step 1 from starting with only as-needed SABA to starting with low dose ICS with an as-needed SABA. However, since the current study uses data from 2016, we follow the GINA recommendations from 2016 (further elaborated upon in paragraph 2.2).

1.1.2 Asthma control

Although asthma can be effectively treated, many patients have suboptimal asthma control.
The REALISE study among 8,000 patients from 11 European countries, including the Netherlands, uncontrolled asthma was found in 45% of patients (Price et al. 2014). Asthma control comprises two domains: symptom control and reduction of risk factors. Risk factors for poor outcomes are, amongst others, low ICS adherence, poor inhaler technique, high SABA use, and exposure to smoke or allergens. Controller medication needs to be taken regularly to reduce the frequency and severity of asthma symptoms, however, adherence to ICS medication is often low (Vasbinder et al. 2016, Heins et al. 2018, TherapietrouwMonitor.nl, 2013). When asked, about one in three patients with asthma reported deviations from their prescribed regimen, with the most frequently mentioned reason that they only use their controller medication when they experience symptoms (Heins et al. 2018). A good inhaler technique is crucial for the medication to reach its target and be effective. However, critical inhalation errors are highly prevalent across all types of inhaler devices (Price et al. 2017) and are associated with poor health outcomes (Kocks et al. 2018). In addition, a survey study among patients with asthma showed that they regularly experience problems with the use of their inhalers (Zwikker et al. 2015). Poor asthma control increases the risk of exacerbations, which is an acute worsening of symptoms and lung function. Exacerbations often require hospitalization, and have a negative impact on patients' quality of life (Sundh et al. 2017). Moreover, a history of exacerbations increases the risk of having a next one. A short course of oral corticosteroids (OCS) is often used to treat moderate to severe exacerbations.

1.1.3 Medication use and asthma outcomes

The relationship between adherence to ICS medication and asthma outcomes is complex. Although a systematic review showed that a higher level of ICS adherence is associated with a lower risk of asthma exacerbations (Engelkes et al. 2015), other observational studies concluded that higher ICS adherence levels are associated with increased use of reliever medication (Elkout et al. 2012) or even an increased risk of asthma exacerbations (Vasbinder et al. 2016).

A recent study using UK prescription data showed that SABA over-use was the only strong predictor for lower ICS adherence levels, but this lower adherence did not impact asthma control (Vervloet et al. 2019).

1.2 Aim & research questions

Insight into the current medication use of Dutch asthma patients in relation to the severity of asthma and the risk of exacerbations and asthma control is currently lacking. What medication do patients use to treat their asthma? Which patients have exacerbations, which patients are treated with OCS chronically, how is this related to the use of ICS and SABA, how is it related to adherence, and how does this relate to asthma control?
To fill these knowledge gaps, the aim of this study is to provide insight into the use of ICS, LABA and SABA of patients with asthma in daily practice, and how this medication use is related to (i) the occurrence of exacerbations (a short OCS course), and (ii) self-reported asthma control for all patients with asthma and, where relevant, divided into groups based on age, sex, comedication, comorbidity and GINA class.

The central research question is:
What is the current medication use of patients with asthma in primary care in relation to the severity of asthma and the risk of exacerbations and asthma control ?

Eight subquestions will be answered (for the total groups of patients with asthma and where relevant for subgroups of patients). The first five questions will give answers about the current medication use, the last three questions concern associations between medication use and asthma outcomes.

Medication use

a) What is the average adherence to ICS of patients with asthma, and what percentage of patients is nonadherent to ICS?
b) What percentage of patients with asthma (over)uses SABA?
c) What percentage of patients with asthma requires one or more OCS courses per year?
d) What percentage of patients with asthma uses OCS chronically?
e) What percentage of patients with asthma uses LABA as monotherapy and what is their adherence level?

Associations between medication use and asthma outcomes

f) What is the relationship between SABA use and ICS adherence?
g) What is the relationship between SABA use, ICS adherence and exacerbations?
h) What is the relationship between SABA use, ICS adherence and self-reported asthma control?

1.3 Structure of this report

In the next chapter, the methods used in this study will be described. Chapter 3 provides insight into the patient sample for this study. In Chapter 4, the medication use of our patient sample will be described (research questions a-e). Chapter 5 addresses the associations between medication use and asthma outcomes (research questions f-h). In the Appendices, additional information can be found about (A) the list of comedication and comorbidities, (B) GINA stepwise treatment, (C) extra tables per chapter, and (D) results of sensitivity analyses.

2 Methods

2.1 Study design and data source

This is a cohort study including patients with asthma (see for further information on the patient sample paragraph 2.2) in which we investigate the extent of medication use and its relation with asthma outcomes over the year 2016.

Data used in this study were derived from the Nivel Primary Care Database (Nivel-PCD), which includes routine care data originating from electronic medical records from GPs across the Netherlands. The participating GPs constitute a representative sample of the total population of Dutch GPs. Within the Dutch health care system all residents are mandatorily registered with one GP, who keeps track of the patient's complete medical record and fulfils a gatekeeper role for access to medical specialists. The database consists of longitudinal information of patient characteristics (age, sex), GP consultations, diagnoses and drug prescriptions. Diagnoses are recorded by the GP using the International Classification of Primary Care version 1 (ICPC-1). Prescriptions are coded using the Anatomical Therapeutic Chemical Classification system (ATC).

This study has been approved according to the governance code of Nivel Primary Care Database, under number NZR-00318.050. Dutch law allows the use of electronic health records for research purposes under certain conditions. According to this legislation, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (Dutch Civil Law, Article 7:458).

2.2 Patient sample

2.2.1 Patient selection

Patients aged 12 years and older diagnosed with asthma (ICPC-code R96) who received at least two prescriptions of inhalation medication in ATC groups R03A and/or R03B in 2016 were selected for this study. Patients had to be registered in the general practice in the period of 2015 to 2017. Patients who were also diagnosed with chronic obstructive pulmonary disease (COPD, ICPC-code R95) were excluded, since these patients follow different treatment steps to manage their illness and a distinction between inhaler medication to treat their asthma or to treat their COPD cannot be made easily.

2.2.2 Demographic and clinical information

The following demographic and clinical patient characteristics were used to investigate subgroups of patients: age, sex, comedication and comorbidity. Patients were categorized in five age categories, 12-17, 18-39, 40-54, 55-64 and 65 years and older, based on their age in 2016. Comedication is based on a specified list including other lung medication and relevant medication for asthma patients (see Appendix A, Table A1). Patients are categorized in four subgroups according to the number of other chronic medication besides asthma medication: nochronic medication, one, two, or more than two other chronic medications. This categorization is also used for comorbidity, which is based on the chronic illness list of the National Institute for Public Health and the Environment (RIVM), excluding COPD and asthma (see Appendix A, Table A2).

2.2.3 GINA classification

The GINA classification is based on the dose and the type of medication that patients use for their asthma (Global Initiative for Asthma 2016) (see Table 2.1 and Appendix B, table B1 for details on dosages). GINA class in this study is determined for the year 2016, and is based on the maximum dose that a patient is prescribed in that year. For example, when a patient received three different prescriptions in 2016 and one of those prescriptions is within GINA step 5, the patient is classified in the 5th class of GINA, regardless of the other medications used. Not every patient with asthma could be allocated in one of the GINA classes due to missing information on dosages or instruction of use , or medication combinations not fitting for the GINA classification. More information on these unclassified patients can be found in Appendix B.

Table 2.1 GINA classification per 2016

Step 1	Step 2	Step 3	Step 4	Step 5
SABA	Low dose ICS	Low dose ICS + LABA	Medium/high dose ICS + LABA	Add tiotropium mist inhaler
	LTRA	Low dose ICS + LABA + LTRA	Medium/high dose ICS + LABA + tiotropium	Add anti-IgE treatment
	Low dose theophylline	Low dose ICS + LABA + theophylline	Medium/high dose ICS + LTRA	Add anti-IL5 treatment
		Low dose ICS + LTRA	Medium/high dose ICS + theophylline	Add low dose OCS
		Low dose ICS + theophylline		
		Medium/high dose ICS		

2.3 Data preparation

Several data preparation steps were required before the start of the analyses. These concerns preparation of data for creating variables for daily dose, strength of the medication (for identifying exacerbations and classifying patients according to GINA), and adherence.

2.3.1 Daily dose

To calculate the daily dose, we needed information on instructions of use given by the GP and the strength of the prescribed medication. Instructions of use are registered in free text fields and can vary among GPs and GP information systems. Usually, use instructions are systematically coded following the 'Gebruiksvoorschrift' table composed by the Dutch college of General Practitioners (NHG)[5]. The format is frequency, time unit, number of dosages per intake, and dosage unit, for example 1D1I, which means once daily one inhalation. A GP can register up to three different use instructions per prescription. However, since not all GPs follow the standard format of the NHG table, the following assumptions were made to calculate the daily dose based on the text variables mentioned above:

1. When instructions included a range of numbers, for example 1-2D1I we used the mean of the instructed dosage. In this example we would calculate 1.5D1I.

[5] https://www.nhg.org/themas/artikelen/nhg-tabel-code-gebruiksvoorschrift

2. If the instruction included an “if needed” instruction we only included prescriptions if the “if needed” instruction was added as an extra option. For example 1D1I;if needed 1 extra inhalation.
3. If a prescription has a missing use instruction, but the patient has received an earlier prescription for the same medication that did include an instruction, then we assume that the instruction is continued. For example, a patient received one prescription of beclometason/formoterol with the use instruction 1D1I, the next prescription of beclometason/formoterol for this patient is without an instruction. We then impute the missing instruction with 1D1I.

2.3.2 Strength of the prescribed medication

The strength of the medication is based on the Dutch drug database ‘G-standaard’, which covers information about licensed medicines; unlicensed medicines (e.g. raw materials and compounding preparations); vitamins and other nutritional supplements; homoeopathic medicines and medical devices[6]. We can link the information registered in the GP information system (the prescription code) to the prescription information in the ‘G-standaard’. When a prescription code for a prescription is missing, we complete the information with that of other prescriptions if the following requirements are met:

1. The patient has more prescriptions of the same medicine, for which the prescription code is available - either in the past or in the future.
2. The use instruction of the prescription has not changed. For example, if a prescription code is missing and the use instructions changed from 1D1I to 1D2I, this could indicate a different dosage and thus a different prescription code.

2.3.3 Adherence

Further data preparation steps were needed to calculate adherence. Adherence can only be calculated for medication that is prescribed as a fixed daily dose regimen. For as-needed medication, such as SABA, adherence is not relevant.

The following information is required to calculate adherence: the ATC code, the prescription date, the daily dose, and the prescription duration. All variables except for the duration were readily available in the data (daily dose after performing the in 2.3.1. described preparation steps). The duration in days was computed by dividing the number of prescribed doses by the daily dose.
For the number of prescribed doses, two variables in the data were combined: number and unit (e.g. number = 180, unit= doses, but also number =1, unit=canister). However, several obstacles were identified with these variables, and assumptions were made to overcome these obstacles, explained below.

- When number had a missing value, regardless of whether unit was available, the prescription duration could not be calculated (17% of prescriptions);
- When unit had a missing value (52% of prescriptions), the number of prescribed doses was estimated based on information in the ‘G-standaard’ about the content of the prescribed canister (i.e. the number of doses within one canister). This latter information is written in the variable content. For example, if *number represented the number of doses*: number =120, unit=missing , content=120, then unit was imputed with 120/120=1. Reliable imputations were values ≥1 for number representing doses. If *number represented the number of canisters*, e.g. number=1, unit =missing, content =120, then unit was replaced by

[6] https://www.z-index.nl/english

content. Reliable replacements were made for number representing canisters up to a maximum of 12.

If the prescription duration could not be calculated for one of the prescriptions a patient received for ICS in 2016, this patient was excluded from the adherence analyses.

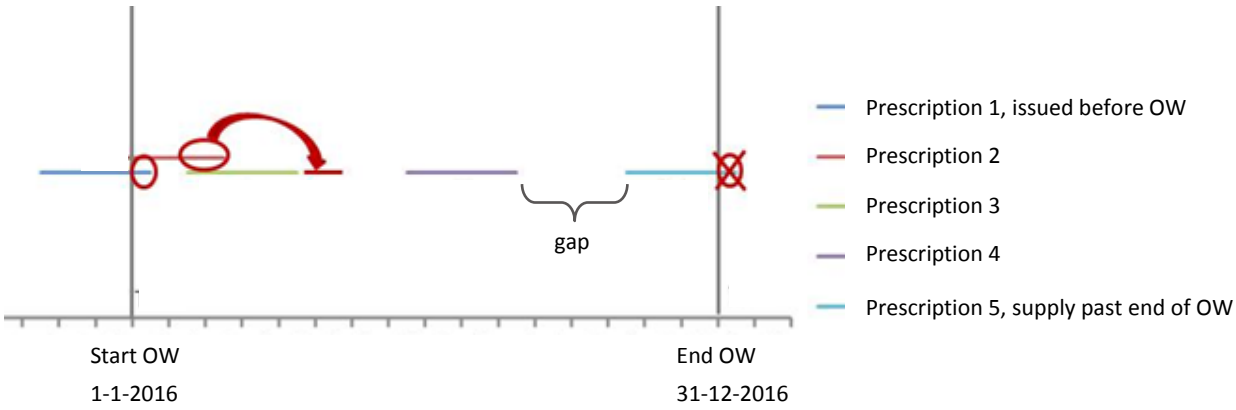
2.4 Outcome variables

2.4.1 Adherence to ICS

In adherence studies, it is important to distinguish between three temporal stages of adherence, being (1) initiation, whether the patient actually starts with the treatment; (2) implementation, whether the patient's actual dosing corresponds with the prescribed dosing regimen; and (3) discontinuation, when the patient stops taking treatment before the end of the prescribed regimen (Vrijens et al. 2012). These stages represent different types of behaviour and subsequently require different approaches. In this study we focus on stage 2, the quality of the implementation of patients' prescribed regimen for asthma medication.

We used the Continuous multiple-interval Measures of medication Availability (CMA) to operationalize adherence, more specifically the CMA7. This operationalization, in contrast to CMA1 to CMA6, takes into account carry-over from prescriptions before the observation window (see prescription 1 in Figure 2.1) as well as within the observation window (see prescription 2 Figure 2.1). The CMA7 assumes that, before and within the observation window, the medication is used as prescribed and oversupply from previous prescriptions is used first, followed by the new medication supply (indicated by the red arrow in Figure 2.1). Supply after the end of the observation window is disregarded (see prescription 5 in Figure 2.1). With CMA7, the observation window (OW) is equal for every patient.

Figure 2.1 Illustration of the CMA7 in the current study, adapted from Souverein et al. 2016



CMA7 is calculated by dividing the number of days of theoretical use by the number of days between start to end of the observation window. Days of theoretical use are calculated by extracting the total number of gap days (days for which no medication is available) from the total time period between the start and the end of the observation window, accounting for carry-over for all prescriptions within and before the observation window.

We calculated CMA7 over 2016 (thus our observation window was from 01-01-2016 to 31-12-2016), taking into account carry-over from 2015. We expressed the CMA7 as a percentage (by multiplying with 100). We created two categorical measures for CMA7. One for which we divide CMA7 in the following six categories:

- 50% or less;
- 51-60%;
- 61-70%;
- 71-80%;
- 81-90%;
- 91-100%.

And one for which we classify patients as adherent (CMA7 >80%) or non-adherent (CMA7 ≤80%)
For readability purposes, we will refer to CMA7 as 'ICS adherence' throughout the report.

2.4.2 Use of SABA

A patient was identified as SABA user when the patient received at least one prescription of salbutamol (R03AC02) or terbutaline (R03AC03). Patients were grouped in the following categories:

- 0 SABA prescriptions
- 1 SABA prescription
- 2-5 SABA prescriptions
- 6-11 SABA prescriptions
- 12 or more SABA prescriptions

To determine use of SABA medication according to the NHG guideline Asthma, patients were grouped in the following categories:

- ≥2 SABA prescriptions
- ≥6 SABA prescriptions
- ≥12 SABA prescriptions

Percentages of SABA use are calculated within each subgroup and are tested with a chi^2-test for significant differences. The SABA categories are not exclusive, so patients in the last category (12 or more SABA prescriptions) are also in the first categories.

2.4.3 OCS courses (exacerbations)

We operationalised an exacerbation as a prescription for a short OCS course. An OCS course is defined as a prednisolone (H02AB06) or prednisone (H02AB07) prescription of at least 20mg daily dosage for a respiratory disease (other than COPD) or if a tapering scheme was given. Patients without a diagnosis linked to their OCS prescription were included in the analyses if there was no other known diagnosis for the OCS prescriptions. For example if a patient has two OCS prescriptions, for one the diagnosis is missing and for the other the diagnosis is dermatitis/atopic eczema, the patient will not be included as a patient with an OCS course for asthma. If both prescriptions had a missing diagnosis the patient is included. If two prescriptions fall within a time range of 14 days, this is seen as one OCS-course. Patients are grouped in the following categories:

- 0 OCS-courses
- ≥ 1 OCS-course
- ≥ 2 OCS-courses
- ≥ 3 OCS-courses
- ≥ 4 OCS-courses

Percentages of OCS-courses are calculated within each subgroup and are tested with a chi²-test for significant differences. The categories are not exclusive, so patients in the last category are also included in the preceding categories.

2.4.4 Chronic OCS use

Patients are defined as chronic OCS users when they have a minimum of three prescriptions of prednisolone (H02AB06) or prednisone (H02AB07) with a daily dose of 5mg or lower and which are prescribed for a respiratory disease (other than COPD) or the diagnosis is missing (without any other known diagnoses for the prescription, see also paragraph 2.4.3.).

2.4.5 Asthma control

Asthma control was determined based on self-report, with the Asthma Control Questionnaire (ACQ) (Juniper et al., 1999). This questionnaire contains seven questions, five to assess asthma symptoms over the past seven days, one to assess daily use of reliever medication and one question for the clinician to add the FEV_1 resulting from spirometry test. The ACQ score is usually calculated as the mean of the 7 questions and therefore ranges between 0 (totally controlled) and 6 (completely uncontrolled). However, the FEV_1 score is not always available.

GPs can register a score per question of the ACQ within their registration system. But they can also only register the sum score of the 6 questions or the sum score of the 7 questions (including the FEV_1 score). In determining an ACQ-score for a patient we took the following steps.

1. If all 7 separate questions were available, we calculated the sum score of the 7 questions;
2. If all 6 separate questions were available, we calculated the sum score of the 6 questions;
3. If there was only a sum score available we first took the 7-item sum score;
4. If there was only a sum score available of the 6-item version, we took that score;
5. If there were separate questions available of at least 5 questions, we calculated the sum score of those 5 questions.

We only include one ACQ-score per patient, if there were more ACQ-scores per patient, the last known in 2016 is included. If there is no a score available in 2016 at all, we include ACQ-scores of the first quarter of 2017.

Asthma control can be classified into controlled asthma (ACQ score <0.75), partially controlled (ACQ score between 0.75 and 1.5) and uncontrolled asthma (ACQ score >1.5) (Juniper et al, 2006).

2.5 Data analyses

Descriptive analyses were performed to describe the medication use of patients (ICS adherence, SABA use, OCS courses, chronic OCS treatment, LABA monotherapy). Differences between groups according to sex, age, comedication, comorbidity and GINA class were tested with Chi^2 test. Results were significant for p-value <0.05.

Multilevel logistic regression analyses were performed to investigate the associations between SABA use, ICS adherence, exacerbations and asthma control, to take into account clustering of patients within general practices. Therefore, each model had two levels: general practice and patient. The analyses were controlled for sex, age, comedication, comorbidity and GINA class.
For each association, we used multilevel logistic regression analyses. For the association between SABA use, ICS adherence and exacerbations, having one or more exacerbations compared to none was the outcome variable.

For the association between SABA use, exacerbations and ICS adherence, being adherent (ICS adherence >80%) compared to being nonadherent (ICS adherence ≤80%) was the outcome variable. For the association between SABA use, ICS adherence and asthma control, having controlled asthma (ACQ<0.75) compared to having partially or uncontrolled asthma (ACQ score ≥0.75) was the outcome variable. Odds ratios with 95% confidence intervals were provided. An odds ratio >1 indicates a higher risk of having 1 or more exacerbations, a higher chance of being adherent to ICS, and a higher chance of having controlled asthma, respectively.

3 Patient characteristics

Our patient population consists of 21,369 patients with asthma. Their background characteristics are described in Table 3.1. Six out of ten patients are female. About 7% of the patients are adolescents, whereas the largest age-category is the 40 to 54 year olds (28%) and nearly a quarter of the patients are 65 years and older. About 12% of the patients have no comedication, though the largest category of patients uses more than two other chronic medication (46%). Around 37% of patients have no comorbidity. More than four out of ten patients are treated according to GINA step 4.

Table 3.1 Characteristics of patients with asthma in our study (N=21,369)

	N (%)
Sex	
Male	8,614 (40.3)
Female	12,755 (59.7)
Age	
12-17 year	1,544 (7.2)
18-39 year	4,703 (22.0)
40-54 year	5,930 (27.8)
55-64 year	4,030 (18.9)
65+ year	5,162 (24.2)
Comedication	
0	2,568 (12.0)
1	4,345 (20.3)
2	4,655 (12.8)
>2	9,801 (45.9)
Comorbidity	
0	7,836 (36.7)
1	4,943 (23.1)
2	3,324 (15.6)
>2	5,266 (24.6)
GINA class (n=20,469)[#]	
1	1,740 (8.5)
2	2,560 (12.5)
3	6,843 (33.4)
4	8,772 (42.9)
5	554 (2.7)

[#] *Not all patients could be classified according to GINA*

Looking at patient characteristics per GINA class (Table 3.2), we see that women are overrepresented in higher GINA classes: 70% of patients in GINA class 5 is female compared to 53% in GINA class 1. Younger patients more often classify in the lower GINA classes compared to older patients.

And though the majority of patients in each GINA class has more than two other chronic medications, this number of patients also increases with GINA class, from 33% of patients in GINA class 1 up to 76% in GINA class 5 having more than two other chronic medications.

Table 3.2 Patient characteristics per GINA class (N=20,469)

	GINA1 (N=1,740)	GINA2 (N=2,560)	GINA3 (N=6,843)	GINA4 (N=8,772)	GINA5 (N=554)
Sex	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male	819 (47.1)	1,132 (44.2)	2,677 (39.1)	3,468 (39.5)	166 (30.0)
Female	921 (52.9)	1,428 (55.8)	4,166 (60.9)	5,304 (60.5)	388 (70.0)
Age					
12-17 year	232 (13.3)	605 (23.6)	436 (6.4)	243 (2.8)	1 (0.2)
18-39 year	567 (32.6)	640 (25.0)	1,633 (23.9)	1,670 (19.0)	36 (6.5)
40-54 year	493 (28.3)	545 (21.3)	1,946 (28.4)	2,594 (29.6)	98 (17.7)
55-64 year	223 (12.8)	352 (13.7)	1,211 (17.7)	1,928 (22.0)	149 (26.9)
65+ year	225 (12.9)	418 (16.3)	1,617 (23.6)	2,337 (26.6)	270 (48.7)
Comedication					
0	321 (18.5)	518 (20.2)	875 (12.8)	733 (8.4)	9 (1.6)
1	461 (26.5)	682 (26.6)	1,519 (22.2)	1,495 (17.0)	32 (5.8)
2	386 (22.2)	553 (21.6)	1,537 (22.5)	1,887 (21.5)	95 (17.2)
>2	572 (32.9)	807 (31.5)	2,912 (42.6)	4,657 (53.1)	418 (75.5)
Comorbidity					
0	837 (48.1)	1,362 (53.2)	2,613 (38.2)	2.702 (30.8)	53 (9.6)
1	416 (23.9)	498 (19.5)	1,680 (24.5)	2.053 (23.4)	89 (16.1)
2	224 (12.9)	300 (11.7)	1,053 (15.4)	1.500 (17.1)	106 (19.1)
>2	263 (15.1)	400 (15.6)	1,497 (21.9)	2.517 (28.7)	306 (55.2)

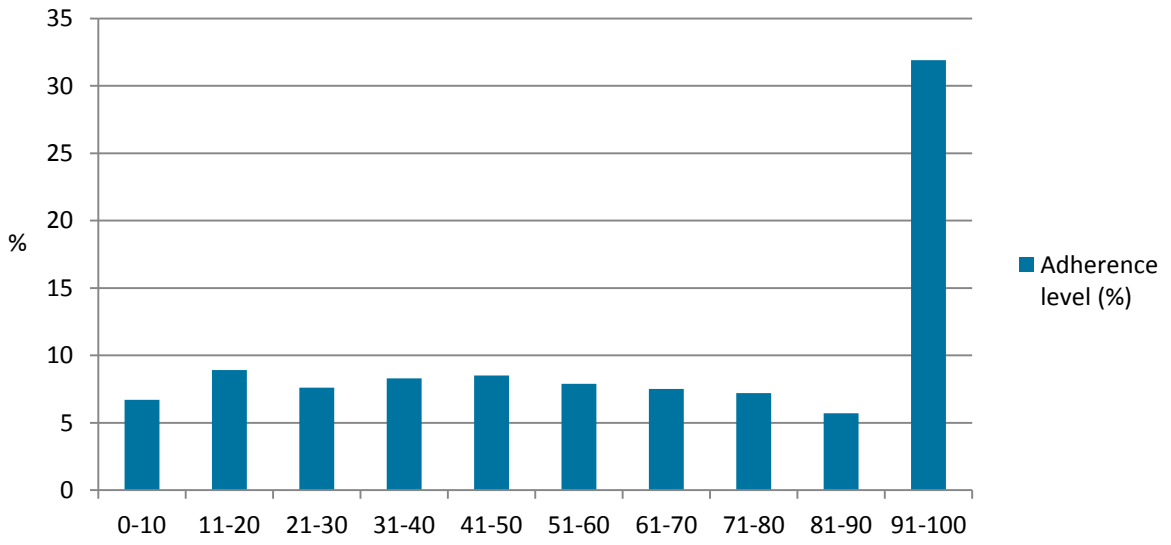
4 Medication use

This chapter describes the results of the first five descriptive subquestions. These concern patients' ICS adherence level (paragraph 4.1), the percentage of patients (over)using SABA (paragraph 4.2), the percentage of patients requiring one or more OCS courses (paragraph 4.3), the percentage of patients on chronic OCS treatment (paragraph 4.4) and the percentage of patients using LABA monotherapy and their adherence level (paragraph 4.5).

4.1 ICS adherence of patients with asthma

Out of the 21,369 asthma patients in our study, 17,790 (83.3%) patients used ICS or an ICS/LABA combination. ICS adherence could be calculated for 13,756 (77.3%) patients (see paragraph 2.3.3. for exclusion reasons). The average ICS adherence in our population is 61.6% (SD: 32.7). Almost a third of patients had an adherence rate between 91-100%. About 26% of patients have an adherence level of 100%, which means that these patients had medication available for all days in 2016 (see Figure 4.1).

Figure 4.1. Distribution of ICS adherence of patients in our study population (N=13,756)



When ICS adherence is categorized into the six predefined categories (Table 4.1), we see that for 40% of patients their adherence rate is 50% or less, and exceeds 90% for almost a third of patients.

Table 4.1 ICS adherence in six categories

ICS adherence	n	%
≤ 50%	5,488	39.9
51-60%	1,084	7.9
61-70%	1,025	7.5
71-80%	990	7.2
81-90%	783	5.7
91-100%	4,386	31.9
Total	13,756	100.0

Using the commonly used cut-off point of ≤80% to classify patients as nonadherent, 62% of patients in our study population are nonadherent to their ICS medication (Figure 4.2).

Figure 4.2 Percentage of patients identified as (non)adherent to ICS medication

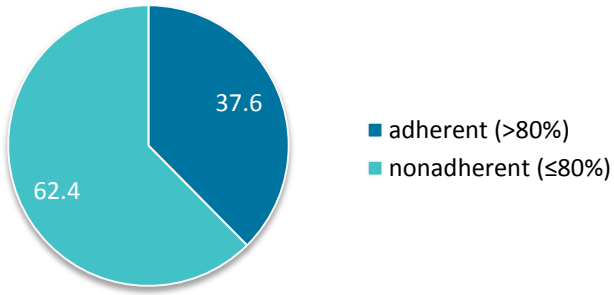


Table 4.2 shows the average ICS adherence of patients grouped by age, sex, number of comedication, number of comorbidities and GINA class. Testing the trend in average adherence showed significant differences within each subgroup. Women, older patients, patients with more comedication, more comorbidities or in a higher GINA class, have a higher average ICS adherence than men, younger patients, patients with less comedication or comorbidity or in a lower GINA class.

Table 4.2 Average ICS adherence of asthma patients (N=13,756) by sex, age, comedication, comorbidity and GINA class. The trend in average adherence was significant within all subgroups (p<0.05).

	ICS adherence
Sex	**Mean (SD)**
Male (n=5,531)	60.8% (32.7)
Female (n=8,225)	62.1% (32.8)
Age	
12-17 year (n=981)	51.5% (33.6)
18-39 year (n=2,919)	52.4% (33.4)
40-54 year (n=3,800)	60.6% (32.8)
55-64 year (n=2,692)	65.6% (31.4)
65+ year (n=3,364)	70.4% (29.8)
Comedication	
0 (n=1.618)	55.9% (31.9)
1 (n=2,768)	58.8% (33.0)
2 (n=2,978)	59.7% (32.9)
>2 (n=6,392)	65.1% (32.3)

- Table 4.2 will be continued -

Comorbidity	
0 (n=4,945)	56.0% (33.1)
1 (n=3,146)	61.4% (32.5)
2 (n=2,158)	64.2% (32.6)
>2 (n=3,507)	68.0% (31.0)
GINA class (n=13,694)[#]	
2 (n=1,743)	52.9% (32.7)
3 (n=4,886)	58.7% (33.9)
4 (n=6,672)	65.7% (31.3)
5 (n=393)	67.2% (29.6)

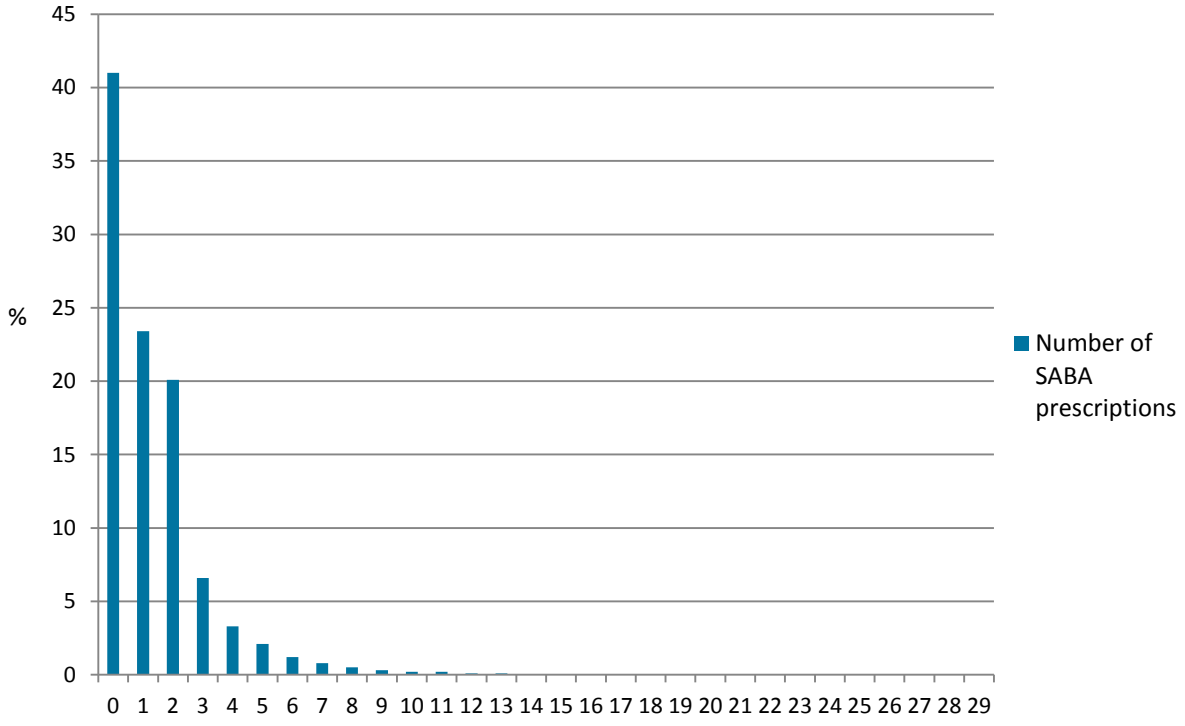
[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA and no ICS*

We also looked at differences in sex, age, comedication, comorbidity and GINA class per ICS adherence category, which can be found in Table C1 in Appendix C. The trend in categorized ICS adherence was significant within all subgroups except for sex.

4.2 SABA use of patients with asthma

Of the 21,369 patients with asthma, 8,760 (41.0%) received no SABA prescriptions in 2016. Almost a quarter of patients received one SABA prescription and about one in five patients received two prescriptions (Figure 4.3). Five patients had 20 or more SABA prescriptions in 2016, with one patient having 29 prescriptions.

Figure 4.3 Percentage of patients per number of SABA prescriptions for our total group (N=21,369).



Classifying SABA use in the predefined categories (Table 4.3), we additionally see that 32.1% of patients received between 2-5 SABA prescriptions and 3.5% of patients received six or more prescriptions in 2016.

Table 4.3 Number of SABA prescriptions issued per patient for the total group of asthma patients (N=21,369)

SABA prescriptions	n	%
0	8,760	41.0
1	4,996	23.4
2-5	6,864	32.1
6-11	671	3.1
≥12	78	0.4
Total	21,369	100.0

A total of 12,609 patients received at least one SABA prescription. Table 4.4 shows the average number of SABA prescriptions per subgroup of patients. The mean ranges from 2.0 to 2.7. The median is 2 for all subgroups.

Table 4.4 Mean number of SABA prescriptions of asthma patients with at least 1 SABA prescription (N=12,609), by sex, age, comedication, comorbidity and GINA class

	N	Mean	SD	Min	Max
Sex					
Male	5,090	2.4	2.0	1	29
Female	7,519	2.2	1.8	1	22
Age					
12-17 year	1,323	2.0	1.4	1	12
18-39 year	3,544	2.4	2.1	1	29
40-54 year	3,694	2.4	2.1	1	22
55-64 year	2,066	2.2	1.7	1	16
65+ year	1,982	2.2	1.6	1	13
Comedication					
0	1,641	2.2	1.7	1	15
1	2,767	2.3	1.9	1	22
2	2,796	2.3	1.9	1	29
>2	5,405	2.3	2.0	1	21
Comorbidity					
0	5,475	2.2	1.8	1	20
1	2,982	2.4	2.1	1	29
2	1,768	2.3	1.8	1	15
>2	2,384	2.3	1.9	1	22

- Table 4.4 will be continued -

GINA class (n=12,202)					
1	1,669[#]	2.9[#]	1.7	1	14
2	1,841	2.0	1.6	1	15
3	3,950	2.2	1.9	1	22
4	4,482	2.3	2.0	1	29
5	260	2.7	2,4	1	17

[#] *Due to our study's selection criterion of having minimally two prescriptions R03A or R03B in 2016, we induce a higher number of SABA prescriptions for patients in GINA class 1 and a higher mean number of prescriptions as well.*

Of the 12,609 patients who received *at least one SABA prescription* in 2016, 3,310 (26.3%) patients received two or more, 496 (3.9%) six or more and 59 (0.5%) 12 or more SABA prescriptions. Table 4.5 shows the percentage of patients within these subgroups using SABA. Men and patients in a higher GINA class more often received at least two SABA prescriptions compared to women and patients in a lower GINA class. Regarding age, especially patients between 18 and 54 years received at least two SABA prescriptions a year.

Table 4.5 The percentage of patients using SABA, categorised in no, one or more, 2 or more, 6 or more, 12 or more SABA prescriptions in 2016, by sex, age, comedication, comorbidity and GINA class. Note that the first two columns comprise the whole sample (N=21,369).The last three columns are refinements of the second column (≥1 SABA prescriptions). Thus these percentages per row are calculated from the subgroup of patients having at least one SABA prescription (e.g. 3,127 of 5,090 (61.4%) males using SABA have at least two or more SABA prescriptions in 2016). Differences within each SABA category were tested within each subgroup (e.g. males versus females).

	0 SABA prescriptions (N=8,760)	≥1 SABA prescriptions (N=12,609)	≥2 SABA prescriptions (N=7,613)	≥6 SABA prescriptions (N=749)	≥12 SABA prescriptions (N=78)
	n (%)	n (%)	n (%)	n (%)	n (%)
Sex					
Male	3,525 (40.9)	5,090 (59.1)	3,127 (61.4)*	354 (7.0)*	38 (0.8)
Female	5,236 (41.1)	7,519 (59.0)	4,486 (59.7)*	395 (5.3)*	40 (0.5)
Age					
12-17 year	221 (14.3)*	1,323 (85.7)*	786 (59.4)*	44 (3.3)*	1 (0.1)*
18-39 year	1,159 (24.6)*	3,544 (75.4)*	2,186 (61.7)*	262 (7.4)*	31 (0.9)*
40-54 year	2,236 (37.7)*	3,694 (62.3)*	2,277 (61.6)*	269 (7.3)*	30 (0.8)*
55-64 year	1,964 (48.7)*	2,066 (51.3)*	1,212 (58.7)*	90 (4.4)*	10 (0.5)*
65+ year	3,180 (61.6)*	1,982 (38.4)*	1,152 (58.1)*	86 (4.2)*	6 (0.3)*
Comedication					
0	927 (36.1)*	1,641 (63.9)*	980 (59.7)	88 (5.4)	4 (0.2)
1	1,578 (36.3)*	2,767 (63.7)*	1,687 (61.0)	163 (5.9)	21 (0.8)
2	1,859 (39.9)*	2,796 (60.1)*	1,685 (60.3)	158 (5.7)	16 (0.6)
>2	4,396 (44.9)*	5,405 (55.2)*	3,261 (60.3)	340 (6.3)	37 (0.7)
Comorbidity					
0	2,361 (30.1)*	5,475 (69.9)*	3,259 (59.5)	311 (5.7)	32 (0.6)
1	1,961 (39.7)*	2,982 (60.3)*	1,829 (61.3)	197 (6.6)	26 (0.9)
2	1,556 (46.8)*	1,768 (53.2)*	1,064 (60.2)	101 (5.7)	8 (0.5)
>2	2,882 (54.7)*	2,384 (45.3)*	1,461 (61.3)	140 (5.9)	12 (0.5)

- Table 4.5 will be continued -

GINA class (n=20,469)					
1	71 (4.1)#*	1,669 (95.9)#*	1,629 (97.6)#*	127 (7.6)#*	7 (0.4)#*
2	719 (28.1)*	1,841 (71.9)*	949 (55.6)*	82 (4.5)*	5 (0.3)*
3	2,893 (42.3)*	3,950 (57.7)*	2,092 (53.0)*	286 (5.6)*	25 (0.6)*
4	4,290 (48.9)*	4,482 (51.1)*	2,562 (57.2)*	286 (6.4)*	36 (0.8)*
5	294 (53.1)*	260 (46.9)*	172 (66.2)*	18 (6.9)*	4 (1.5)*

** significant at level p<0.05*

 # Due to our study's selection criterion of having minimally two prescriptions R03A or R03B in 2016, we induce a higher number of SABA prescriptions for patients in GINA class 1 and a high mean number of prescriptions as well.

4.3 Patients with asthma requiring one or more short OCS courses

The majority of patients (n=18,546; 86.8%) required no short OCS course in 2016, i.e. had no exacerbation in 2016. In total, 2,823 (13.2%) patients were prescribed one or more courses, 684 (3.2%) two or more courses, 165 (0.8%) patients required three or more and for 52 (0.2%) patients, four or more OCS courses were prescribed in 2016. In Table 4.6 it can be seen that women, older patients, patients with more other chronic medication and more other chronic illnesses as well as patients in a higher GINA class more often required one or more short OCS courses than men, younger patients, patients with less comedication and comorbidity and patients in a lower GINA class.

Table 4.6 Percentage of patients with asthma requiring no, one or more, two or more, three or more, or four or more short OCS courses in 2016, by sex, age, comedication, comorbidity and GINA-class. Note that the first two columns comprise the whole sample (N=21,369).The last three columns are refinements of the second column (≥1 OCS course). Thus these percentages per row are calculated from the subgroup of patients having at least one OCS course (e.g. 209 of 915 (22.8%) males have at least two or more OCS courses in 2016). Differences within each OCS category were tested within each subgroup (e.g. males versus females).

	0 OCS courses (N=18,546)	≥1 OCS courses (N=2,823)	≥2 OCS courses (N=684)	≥3 OCS courses (N=165)	≥4 OCS courses (N=52)
	n (%)	n (%)	n (%)	n (%)	n (%)
Sex					
Male	7,699 (89.4)*	915 (10.6)*	209 (22.8)*	47 (5.1)*	14 (1.5)*
Female	10,847 (85.0)*	1,908 (15.0)*	475 (24.9)*	118 (6.2)*	38 (2.0)*
Age					
12-17 year	1,475 (95.5)*	69 (4.4)*	10 (14.5)*	1 (1.4)*	1 (1.4)
18-39 year	4,236 (90.1)*	467 (9.9)*	97 (20.8)*	23 (4.9)*	8 (1.7)
40-54 year	5,154 (86.9)*	776 (13.1)*	180 (23.2)*	43 (5.5)*	14 (1.8)
55-64 year	3,425 (85.0)*	605 (15.0)*	161 (26.6)*	45 (7.4)*	12 (2.0)
65+ year	4,256 (82.5)*	906 (17.6)*	233 (25.7)*	53 (5.8)*	17 (1.9)

- Table 4.6 to be continued -

Comedication					
0	2,500 (97.4)*	65 (2.7)*	9 (13.8)*	1 (1.5)*	0 (0.0)*
1	4,040 (93.0)*	305 (7.0)*	44 (14.4)*	8 (2.6)*	2 (0.7)*
2	4,128 (88.7)*	527 (11.3)*	101 (19.2)*	20 (3.8)*	5 (0.9)*
>2	7,878 (80.4)*	1,923 (19.6)*	530 (27.6)*	136 (7.1)*	45 (2.3)*
Comorbidity					
0	7,180 (91.6)*	656 (8.4)*	122 (18.6)*	23 (3.5)*	7 (1.1)*
1	4,320 (87.4)*	623 (12.6)*	128 (20.5)*	30 (4.8)*	11 (1.8)*
2	2,802 (84.3)*	522 (15.7)*	133 (25.5)*	35 (6.7)*	13 (2.5)*
>2	4,244 (80.6)*	1,022 (19.4)*	301 (29.5)*	77 (7.5)*	21 (2.1)*
GINA class (n=20,469)					
1	1,621 (93.2)*	119 (6.8)*	12 (10.1)*	2 (1.7)*	0 (0.0)
2	2,402 (93.8)*	158 (6.2)*	21 (13.3)*	1 (0.6)*	0 (0.0)
3	6,147 (89.8)*	696 (10.2)*	119 (17.1)*	18 (2.6)*	6 (0.9)
4	7,202 (82.1)*	1,570 (17.9)*	427 (27.2)*	105 (6.7)*	34 (2.1)
5	383 (69.1)*	171 (30.9)*	74 (43.3)*	34 (19.9)*	12 (7.0)

** significant at level p<0.05*

4.4 Patients with asthma receiving chronic low dose OCS treatment

Of the 21,369 patients with asthma, 182 (1%) patients received chronic OCS treatment, which was defined as a minimum of three prescriptions for OCS with a daily dose of 5mg and prescribed for a diagnosis in the R-chapter (respiratory diseases, excluding COPD). Women, older patients, patients using more than two other chronic medications and patients with more than two other chronic illnesses significantly more often received OCS chronic treatment than men, younger patients, and patients using less than two other chronic medications or having less than two other chronic illnesses (Table 4.7). Patients using chronic low dose OCS treatment are, by definition, all allocated to GINA class 5.

Table 4.7 OCS chronic treatment of patients with asthma (N=182)

	chronic OCS treatment
Sex	**n (%)**
Male	55 (30.2)
Female	127 (69.8)
Age	
12-17 year	0 (0.0)
18-39 year	8 (4.4)
40-54 year	28 (15.4)
55-64 year	48 (26.4)
65+ year	98 (53.8)

- Table 4.7 to be continued -

Comedication	
0	0 (0.0)
1	13 (7.1)
2	22 (12.1)
>2	147 (80.8)
Comorbidity	
0	16 (8.8)
1	24 (13.2)
2	28 (15.4)
>2	114 (62.6)

4.5 Patients with asthma using LABA monotherapy and their adherence

Of the 21,369 asthma patients in our sample, 160 (0.7%) patients received LABA as monotherapy. The majority is female (61%) and 39% is 65 years or older. Four out of ten patients use more than two other chronic medications and more than a third have more than two other chronic illnesses (Table 4.8). These patients could not be allocated to a GINA class since LABA monotherapy is not recommended as treatment.

Table 4.8 Patients receiving LABA monotherapy (N=160)

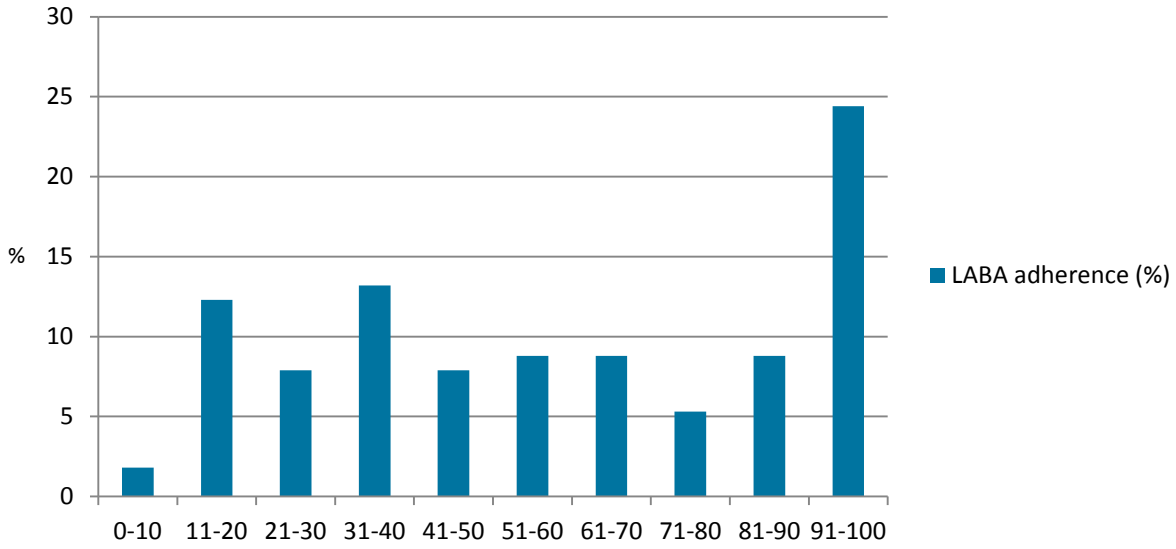
	LABA monotherapy
Sex	**n (%)**
Male	62 (38.8)
Female	98 (61.3)
Age	
12-17 year	2 (1.3)
18-39 year	20 (12.5)
40-54 year	43 (26.9)
55-64 year	32 (20.0)
65+ year	63 (39.4)
Comedication	
0	26 (16.3)
1	32 (20.0)
2	38 (23.8)
>2	64 (40.0)
Comorbidity	
0	36 (22.5)
1	41 (25.6)
2	28 (17.5)
>2	55 (34.4)

Adherence to LABA medication

For 114 of these 160 (71%) patients an adherence ratio could be calculated. Missing information on the prescribed daily dose and/or prescribed amount hindered the computation of the duration of issued LABA prescriptions for 46 patients, which is required to calculate adherence (see for more details paragraph 2.3.3.). The distribution of LABA adherence is illustrated in Figure 4.4.

The average adherence of the 114 patients using LABA monotherapy is 59.3% (SD: 30.9) and ranges between 8.5 - 100.0%. About a quarter of patients had a LABA adherence of more than 90%, indicating that they had the medication available for nearly every day of the year 2016.

Figure 4.4 Distribution of adherence to LABA monotherapy among 114 patients with asthma.



5 Associations between medication use and asthma outcomes

Three research sub questions concerned associations between SABA use, ICS adherence, exacerbations and asthma control. This chapter described these associations. Paragraph 5.1 shows the association between SABA use and ICS adherence. Paragraph 5.2 describes how SABA use and ICS adherence are associated with exacerbations on the one hand and how SABA use and exacerbations are associated with ICS adherence on the other hand. Finally, in paragraph 5.3, the association between SABA use, ICS adherence and self-reported asthma control is described.

5.1 The association between SABA use and ICS adherence

ICS adherence has no linear association with SABA use. What can be seen in Table 5.1 is that both patients with no SABA prescriptions as well as patients with six or more SABA prescriptions have a higher ICS adherence than patients with one to five SABA prescriptions. Significant differences were found in mean ICS adherence between the SABA categories ($p<0.05$).

Table 5.1 Mean ICS adherence per category of SABA prescriptions

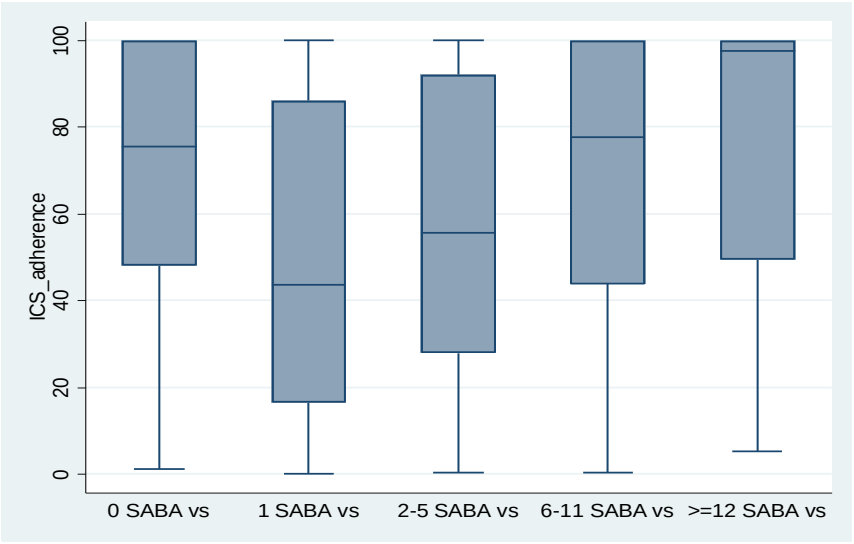
		ICS adherence
SABA prescriptions	**n (%)**	**Mean (SD)**
0 SABA prescriptions	5,916 (43.0)	70.6% (29.0)
1 SABA prescription	3,615 (26.3)	50.0% (34.7)
2-5 SABA prescriptions	3,794 (27.6)	57.5% (32.2)
6-11 SABA prescriptions	381 (2.8)	69.7% (31.1)
12 or more SABA prescriptions	50 (0.4)	73.1% (33.0)
Total	13,756 (100.0)	

Table 5.2 shows that for each ICS adherence category, the mean number of SABA prescriptions is quite similar within each group, with a mean of 1.2 or 1.3.

Table 5.2 Mean number of SABA prescriptions per ICS adherence category

		SABA prescriptions
ICS adherence	**n (%)**	**Mean (SD)**
≤ 50%	5,488 (39.9)	1.3 (1.6)
51-60%	1,084 (7.9)	1.2 (1.7)
61-70%	1,025 (7.5)	1.2 (1.7)
71-80%	990 (7.2)	1.2 (1.8)
81-90%	783 (5.7)	1.3 (1.9)
91-100%	4,386 (31.9)	1.2 (2.1)
Total	13,756 (100.0)	

Figure 5.1 Forest plot (nog in Excel maken!)



5.2 The association between SABA use, ICS adherence and exacerbations

First, we analyzed whether SABA use and ICS adherence are associated with having one or more exacerbations in 2016, controlling for demographic and clinical characteristics of patients (paragraph 5.2.1.). Second, we analyzed whether SABA use and (the number of) exacerbations are associated with being adherent to ICS, also controlled for demographic and clinical characteristics of patients (paragraph 5.2.2.).

5.2.1 Characteristics that are associated with having one or more exacerbations

ICS adherence could be calculated for 13,756 patients with asthma. The average ICS adherence of this total group is 61.6% with an SD of 32.7 (range 0-100) (see also paragraph 4.1). The majority of these patients (87%) did not require a short OCS course in 2016 (see Table 5.3), indicating that they had no moderate to severe exacerbations.

Table 5.3 Number of OCS courses for patients for whom ICS adherence could be calculated (N=13,756)

Nr OCS courses	n	%
0	11,947	86.9
1	1,387	10.1
2	318	2.3
3	67	0.5
≥4	37	0.3
Total	13,756	100.0

The multilevel analysis revealed that a higher number of SABA prescriptions, older age, having comedication and comorbidities and a higher GINA class are associated with the use of one or more OCS courses, thus having one or more exacerbations (Table 5.4). Sex and ICS adherence were not clearly associated with the occurrence of exacerbations. Compared to no SABA prescription, we see that the odds of requiring an OCS course increases with the number of SABA prescriptions, up to 6-11 prescriptions. Having 12 prescriptions or more does not further increase these odds, though it should be noted that this category comprises a small number of patients.

About 6% of variance (indicated by the intraclass correlation) can be attributed to the general practice level, which means that there are minor differences between general practices in whether their patients have exacerbations or not.

Table 5.4. Results of multilevel logistic regression analysis in which we investigate which variables (ICS adherence in categories, SABA use, sex, age, number of comedication, number of comorbidities and GINA class) are associated with having 1 or more OCS courses (indicating one or more exacerbations) compared to no OCS courses, while taking into account that patients (N=13,694) are nested within general practices (N=195).

	Odds Ratio	95% Confidence interval	p-value
ICS adherence (ref=≤50%)			
51-60%	0.78	0.62-0.98	**0.032**
61-70%	0.91	0.74-1.14	0.422
71-80%	0.89	0.72-1.11	0.316
81-90%	0.93	0.73-1.19	0.570
91-100%	1.13	0.99-1.30	0.074
SABA use (ref=0 prescriptions)			
1 SABA prescription	1.67	1.45-1.92	**0.000**
2-5 SABA prescriptions	2.26	1.98-2.57	**0.000**
6-11 SABA prescriptions	3.36	2.55-4.43	**0.000**
≥12 SABA prescriptions	3.09	1.53-6.23	**0.002**
Sex (ref=male)			
Female	1.12	1.00-1.25	0.052
Age (ref=12-17 year)			
18-39 year	1.74	1.22-2.49	**0.002**
40-54 year	1.99	1.40-2.84	**0.000**
55-64 year	2.02	1.39-2.91	**0.000**
65+ year	2.38	1.64-3.45	**0.000**
Comedication (ref=none)			
1	2.42	1.73-3.39	**0.000**
2	3.43	2.47-4.75	**0.000**
>2	5.25	3.81-7.22	**0.000**
Comorbidity (ref=none)			
1	1.18	1.00-1.38	**0.044**
2	1.22	1.02-1.47	**0.028**
>2	1.20	1.00-1.44	**0.048**
GINA class[#] (2=ref)			
3	1.44	1.14-1.81	**0.002**
4	2.64	2.11-3.30	**0.000**
5	5.03	3.67-6.90	**0.000**

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA, and no ICS*

We have repeated this analysis for the adult group of patients (leaving out 918 children aged 12-17 years). This analysis gave similar results (see Appendix D, Table D1).

5.2.2 Characteristics associated with ICS adherence

ICS adherence has a skewed distribution (see also paragraph 4.1.1.). Therefore, we performed a multilevel logistic regression analysis with ICS adherence in two categories: adherent (>80%) versus nonadherent (≤80%) (see Table 5.5) and we investigated which characteristics are associated with being adherent to ICS.

Table 5.5 Percentage of patients classified as (non-)adherent to their ICS medication

ICS adherence	n	%
≤ 80% (nonadherent)	8,587	62.4
> 80% (adherent)	5,169	37.6
Total	13,756	100.0

The multilevel analysis revealed that having three OCS courses a year compared to none, up to 11 SABA prescriptions compared to none, being older than 40, having just one other chronic medication besides asthma medication, and being in a higher GINA class is associated with being adherent (odds ratio >1) (Table 5.6). Sex, having comorbidities, having more than one comedication, or receiving one, two or four OCS courses were not significantly associated.
About 29% of variance (indicated by the intra class correlation, ICC) can be attributed to patients belonging to the same general practice. Being adherent or not is clearly influenced by the general practice to whom the patient belongs.

*Table 5.6. Results of multilevel logistic regression analysis in which we investigate which variables (number of OCS courses, SABA use, sex, age, number of comedication, number of comorbidities and GINA class) **are associated with being adherent** (ICS adherence higher than 80%), while taking into account that patients (N=13,694) are nested within general practices.*

	Odds ratio	95% confidence interval	p-value
OCS course (ref=0)			
1 course	1.04	0.91-1.19	0.560
2 courses	1.12	0.86-1.46	0.411
3 courses	2.21	1.23-3.96	**0.008**
4 or more courses	1.94	0.90-4.19	0.091
SABA use (ref=0 prescriptions)			
1 SABA prescription	0.47	0.42-0.52	**0.000**
2-5 SABA prescriptions	0.62	0.56-0.68	**0.000**
6-11 SABA prescriptions	1.42	1.11-1.82	**0.005**
≥12 SABA prescriptions	1.71	0.89-3.29	0.109
Sex (ref=male)			
Female	1.04	0.95-1.13	0.386

- Table 5.6 to be continued -

Age (ref=12-17 year)			
18-39 year	0.88	0.73-1.07	0.193
40-54 year	1.28	1.06-1.54	**0.012**
55-64 year	1.64	1.34-2.02	**0.000**
65+ year	1.92	1.56-2.38	**0.000**
Comedication (ref=none)			
1	1.18	1.01-1.38	**0.034**
2	1.05	0.90-1.22	0.542
>2	1.11	0.96-1.29	0.163
Comorbidity (ref=none)			
1	1.03	0.92-1.16	0.634
2	1.09	0.95-1.25	0.242
>2	0.97	0.84-1.12	0.690
GINA class[#] (2=ref)			
3	1.16	1.01-1.34	**0.039**
4	1.33	1.15-1.53	**0.000**
5	1.81	1.37-2.38	**0.000**

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA and no ICS*

5.3 The association between SABA use, ICS adherence and asthma control

For 4,629 patients in our sample the ACQ score was available. However, since we were interested in the association between SABA use, ICS adherence and asthma control, we included those patients in our analysis for whom these variables were available. This was the case for 2,388 patients. The mean ACQ score for these patients was 0.95 (SD=0.8), with a range of 0-6. Asthma control can be classified into controlled asthma (ACQ score <0.75), partially controlled asthma (ACQ score between 0.75 and 1.5) and uncontrolled asthma (ACQ score >1.5). The mean ACQ score per subgroup of patients is shown in Table 5.7. Compared to the toal group, patients of whom an ACQ score was available were comparable for the distribution of sex, and the number of comedications and comorbidities, they were a bit younger and had a small but significant different distribution ver the GINA classes, more GINa class 2 and class 5.

Table 5.7 Patient characteristics of the subsample for whom both an ACQ score as well as an ICS adherence level was available (N=2,388)

	ACQ score
Sex	**M (SD)**
Male (n=924)	0.88 (0.80)
Female (n=1464)	1.00 (0.85)

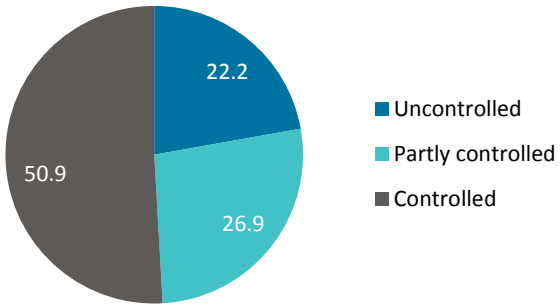
- Table 5.7 to be continued -

Age	
12-17 year (n=128)	0.91 (0.75)
18-39 year (n=503)	1.07 (0.88)
40-54 year (n=627)	1.02 (0.90)
55-64 year (n=491)	0.88 (0.81)
65+ year (n=639)	0.87 (0.76)
Comedication	
0 (n=265)	0.75 (0.72)
1 (n=451)	0.82 (0.74)
2 (n=548)	0.96 (0.86)
>2 (n=1,124)	1.05 (0.87)
Comorbidity	
0 (n=813)	0.92 (0.85)
1 (n=571)	0.94 (0.83)
2 (n=404)	0.94 (0.80)
>2 (n=600)	1.01 (0.84)
GINA class (n=2,376)[#]	
2 (n=283)	0.89 (0.77)
3 (n=889)	0.89 (0.83)
4 (n=1,161)	1.01 (0.84)
5 (n=43)	1.30 (1.02)

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA and no ICS*

Figure 5.2 shows the asthma control of our patient sample. About half of the patients in our study population have controlled asthma.

Figure 5.2 Percentage of patients having uncontrolled, partially controlled or controlled asthma according to the ACQ (n=2,388)



The multilevel analysis showed that an ICS adherence level of higher than 50% and being 65 years or older are significantly associated with controlled asthma (Table 5.8). Having more SABA prescriptions, having two or more other chronic medications and having more than two other chronic illnesses and being treated according to GINA class 4 and 5, on the other hand, significantly decrease the odds of being controlled. Sex was not associated with asthma control.
About 3% of variance (indicated by the intra class correlation, ICC) can be attributed to patients belonging to the same general practice.

*Table 5.8. Results of multilevel logistic regression analysis in which we investigate which variables (ICS adherence in categories, SABA use (number of prescriptions), sex, age, number of comedication, number of comorbidities and GINA class) are associated with **controlled asthma** compared to partially or uncontrolled asthma, while taking into account that patients (N=2,388) are nested within general practices (N=141)*

	Odds Ratio	95% Confidence interval	p-value
ICS adherence (ref=≤50%)			
51-60%	1.42	1.01-1.98	**0.042**
61-70%	1.51	1.06-2.15	**0.022**
71-80%	1.78	1.23-2.56	**0.002**
81-90%	1.71	1.15-2.55	**0.008**
91-100%	1.66	1.33-2.07	**0.000**
SABA use* (ref=0 prescriptions)			
1 SABA prescription	0.77	0.62-0.96	**0.019**
2-5 SABA prescriptions	0.48	0.38-0.60	**0.000**
6-11 SABA prescriptions	0.11	0.05-0.24	**0.000**
Sex (ref=male)			
Female	0.84	0.71-1.01	0.067
Age (ref=12-17 year)			
18-39 year	1.00	0.65-1.53	0.989
40-54 year	1.19	0.77-1.84	0.427
55-64 year	1.37	0.86-2.17	0.181
65+ year	1.74	1.08-2.80	**0.022**
Comedication (ref=none)			
1	0.81	0.58-1.13	0.221
2	0.69	0.50-0.95	**0.023**
>2	0.57	0.42-0.78	**0.000**
Comorbidity (ref=none)			
1	0.87	0.68-1.11	0.247
2	0.77	0.58-1.03	0.077
>2	0.60	0.44-0.82	**0.001**
GINA class[#] (2=ref)			
3	0.97	0.72-1.30	0.837
4	0.70	0.52-0.94	**0.018**
5	0.42	0.20-0.86	**0.018**

[*] *No patients in this subsample that have 12 or more SABA prescriptions*

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA, and no ICS*

6 Discussion and conclusion

In this study we aimed to provide insight into the medication use (ICS, ICS/LABA, SABA, OCS) of patients with asthma in primary care and its association with asthma outcomes (exacerbations and self-reported asthma control), using data from 2016 derived from the Nivel Primary Care Database which includes routine care data originating from electronic medical records from general practitioners across the Netherlands.

Main findings

Medication use and asthma outcomes

Our study population comprised 21,369 patients diagnosed with asthma (not COPD) in 2016, in which severe asthma was common with 46% of patients receiving treatment according to step 4 or 5 of the Global Initiative for Asthma (GINA). About 88% of patients used controller medication, ICS alone or in combination with LABA. Their adherence to this medication, computed over the whole year (2016) was on average 62%. Almost four out of ten patients had an adherence of 80% or higher. Regarding the as-needed reliever medication (SABA), 59% of all patients received at least one SABA prescription in 2016. More specifically, 23% received one, 20% received two and 16% received three or more SABA prescriptions. Chronic OCS treatment (part of GINA treatment step 5) was prescribed for about 1% of patients. LABA monotherapy, which is not recommended as treatment for asthma, was prescribed for 0.7% of mainly older patients. The majority of patients (87%) required no short OCS course in 2016, which was used as a proxy for moderate to severe exacerbations. About 10% of patients had one exacerbation in 2016, 3% had two or more exacerbations. For 2,388 patients, self-reported asthma control was available. About half of them had controlled asthma, 27% had partially controlled asthma and 22% had uncontrolled asthma.

Associations between SABA use, ICS adherence and asthma outcomes

Patients with no SABA prescriptions and patients with six or more prescriptions had higher adherence levels to ICS than patients with one to five SABA prescriptions. An increasing number of SABA prescriptions and increasing severity of asthma (higher GINA class) led to a higher risk of having one or more exacerbations, whilst ICS adherence was not clearly associated with the occurrence of exacerbations. Having six or more SABA prescriptions was significantly associated with being adherent to ICS (adherence >80%), whereas one up to five SABA prescriptions was significantly associated with being nonadherent (adherence ≤80%). Additionally, a higher GINA class was associated with being more adherent. Having an ICS adherence of higher than 50% was significantly associated with self-reported controlled asthma (ACQ score<0.75). On the other hand, an increasing number of SABA prescriptions and having severe asthma (GINA class 4 and 5) significantly decreased the change of having controlled asthma.

Reflection

Medication use and asthma outcomes

We found a higher percentage of patients treated according to GINA step 4 than other studies (Stridsman et al. 2020). This might be explained by our method to allocate patients to a GINA class. The prescription with the highest ICS dose in 2016 was leading in this allocation, regardless of how long the patient had followed this regimen (whether this was prescribed at the beginning or the end of the year). As such, we may have introduced an overestimation of patients treated according to the higher GINA steps.

Just like in our study, several studies have found a suboptimal adherence to controller medication in patients with asthma (e.g. Bårnes et al. 2015; Vähätalo et al. 2020).

In addition, the 62% average adherence over 2016 is similar to the adherence levels found over the years 2007 to 2013 in the Netherlands (www.TherapietrouwMonitor.nl), though these were based on pharmacy dispensing data.
If we look at the SABA use of patients in our study, we see that this appears to be in line with other European countries. A recent study investigating SABA over-use (defined as three or more SABA prescriptions per year) in the United Kingdom (UK), Germany, Italy, Spain and Sweden found percentages ranging from of 9% in Italy up to 38% in the UK (Janson et al. 2020). In our study, about 16% of patients received three or more SABA prescriptions in 2016.
The percentage of patients using LABA as monotherapy (0.7%) is low and comparable with France and the UK who have respectively 0.1% and 1.5% of patients with asthma using LABA only (Belhassen et al.2016). Notably, most patients in our study treated with this monotherapy are older patients (the majority being 55+), which might rise a question on the asthma diagnosis. COPD patients, usually an older population, do receive LABA as single treatment for their illness. However, for asthma patients, LABA monotherapy should be avoided because of the increased risk of asthma-related death (Morales et al. 2013).

Associations between SABA use, ICS adherence and asthma outcomes
In the univariate analysis, we found no linear association between ICS adherence and SABA use. Patients who do not use SABA and patients who use often SABA (six or more prescriptions per year) have a higher adherence to their ICS medication. This latter finding was also seen in a large American cohort study, showing that patients with an adherence level of 50% or higher were more likely to have six or more SABA prescriptions than patients with an adherence level lower than 50% (Makhinova et al. 2015). And the study of Elkout and colleagues, though amongst children, also showed higher adherence levels being associated with higher SABA use (Elkout et al. 2012). Also in the multivariate analysis, whilst taking into account several patient and clinical characteristics, we found that six or more SABA prescriptions was significantly associated with being adherent to ICS medication (adherence >80%) whereas up to five SABA prescriptions was significantly associated with being non-adherent (adherence ≤80%).

Several aspects can influence this finding. One aspect is the inhaler technique. A correct technique is crucial for the effectiveness of ICS medication, i.e. if patients do not use their inhalers correctly, the medication does not reach its target and cannot be optimally effective. Previous studies have revealed that many patients make critical errors in inhaling their medication, which has shown to worsen asthma outcomes (Price et al. 2017; Kocks et al. 2018). Another aspect might be that the ICS dosage is not adequate (too low) to control asthma symptoms, leading to an increased need of reliever medication whilst being adherent to the controller medication.

Many studies have shown that a higher ICS adherence decreased the risk of exacerbations (e.g. Williams et al. 2011; Engelkes et al. 2015). However, in our study, whilst taking into account SABA use and asthma severity, this association was not clearly found. It has been shown that ICS adherence fluctuates with an increase right before and after an exacerbation (Williams et al. 2011). With our operationalization of ICS adherence (medication availability computed over the whole year), these fluctuations could not be distinguished in the data.
We did find, in accordance with other studies (Amin et al. 2020; Van Ganse et al. 2019), that a higher number of SABA prescriptions increased the risk of exacerbations. A recent study revealed that patients perceive their SABA as a great support in treating asthma symptoms driven by its efficacy, whilst not realising that the frequent use of SABA indicates poorer asthma outcomes (Blakeston et al. 2020).

An ICS adherence of 50% or higher was significantly associated with having self-reported controlled asthma (ACQ score of lower than 0.75), having more SABA prescriptions and having severe asthma (GINA steps 4 and 5) decreased the likelihood of having self-reported asthma control. These results confirm that needing more reliever medication (SABA) and having severe asthma (higher GINA class) hinder asthma control.

Strengths & limitations

A strength of this study is that we were able to include data from a large cohort of patients with asthma. After data preparation steps, we were provided with robust and interpretable data for over 20,000 patients with asthma in 2016. We did lose patients for whom we could not calculate adherence to controller treatment, however, this was purely due to missing or incomplete information in the GP information system and not due to patient-related factors.

Our study also has limitations. This is a cross-sectional study, in which we only included exacerbations occurring in 2016, and as such disregarding whether patients have a long or short history with either few or many prior exacerbations. It would be interesting to investigate longer periods of time to investigate the effect of prior events. However, earlier studies already showed an association between consecutive exacerbations, since each exacerbation causes irreversible damage to the lungs. Furthermore, we used a short OCS course of more than 20mg daily as a proxy for an exacerbation. We did not have data on healthcare utilization, such as an emergency department visit, hospital admission, or an unscheduled visit to the GP, which often follow a severe exacerbation. Using a short OCS course as proxy might have led to more patients being wrongly identified as having had an exacerbation (also when the diagnosis accompanying the OCS prescription was unknown), which might have diluted the effect of our analyzed associations.

GINA recommendations for stepwise treatment were updated in 2018, leaving out SABA-only treatment and starting in step 1 with low dose ICS treatment. Using data from 2016, our results cannot be easily interpreted in the light of the most recent GINA recommendations.

The ACQ score was available for just a small subgroup of patients. The group of which ACQ was available was rather comparable to the total group, although they were a bit younger, and had a small different distribution over the GINA classes, more class 2 and class 5 compared to the total group. Yet, the results of this selected group for self-reported asthma control supports the results of the total group regarding asthma control expressed as exacerbations, namely that SABA (over)use and higher GINA class lead to more exacerbations and thus less controlled asthma.

There are many different ways to calculate adherence from administrative databases, such as a prescription database, all with its own strength and limitations (Hess et al. 2006) and each providing different estimates of adherence (Dima et al. 2017). For this study we used the Continuous multiple-interval Measures of medication Availability (CMA) to operationalize adherence, more specifically the CMA7. The CMA7 takes carry-over into account from before the observation window as well as within the observation window. By taking into account prescriptions that are issued before the observation window and for which the duration overlap with the start of this window (e.g. a prescription for 90 days issued at December 1, bringing 59 days into the window starting at January 1), CMA can be estimated more precisely. Disregarding the carry-over would underestimate the adherence rate. This is a clear advantage of CMA7. However, since CMA7 provides information about medication availability, overuse cannot be identified. Prescription patterns are an estimate for medication adherence, but lack information about actual intake. To actually monitor medication

intake behavior, other adherence measures are necessary, e.g. with electronic monitoring (Van Boven et al 2015).

Implications for practice and conclusion

The relation between ICS adherence and the number of SABA prescription with the risk of exacerbations and self-perceived asthma control is not a simple linear relationship. For GPs it is important to recognize that according to the SABA use of their patients with asthma, different approaches to achieving optimal asthma control (both symptom control as well as decreasing the occurrence of exacerbations) are needed. Our study revealed that a higher number of SABA prescriptions (six or more) was associated with a higher risk of exacerbations and a higher risk of having an uncontrolled asthma. Yet, a higher number of SABA prescriptions was also associated with being more adherent to ICS. So, improving ICS adherence in these patients is not the way to achieve better asthma control or reduce the risk of exacerbations. In these patients improvement in asthma control need to be sought in the technique a patient uses to take their controller medication, do they have the proper technique, and also whether the patient actually achieves asthma control with their controller medication dosage, or should it be increased. This information might guide the GP were to find room for improvement to reduce the occurrence of exacerbations and improve experienced asthma control.

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Appendix A List of comedication and comorbidity

Table A1. List of comedication used to define subgroups of patients with asthma

Medication	ATC-codes
Antihistaminergic agents	R06
Nasal decongestants	R01B
Systemic antibiotics	J01
Systematic corticosteroids	H02 (excl. H02AB06 & H02AB07)
Beta blockers	C07
Cardiac drugs	C01
Antidiabetic drugs	A10
NSAIDs	M01A
Paracetamol	N02BE01
GERD drugs	A03B
Tricyclic antidepressants	N06AA
Other antidepressants	N06A (other than N06AA)

Table A2. List of comorbidities used to define subgroups of patients with asthma

No	Chronic disease	ICPC-1# codes
1	Hypertension	K86, K87
2	Diabetes Mellitus	T90
3	Osteoarthritis	L89-L91
4	Coronary artery disease	K74-K76
5	Cancer	A79, B72-B74, D74-D77, L71, N74, R84, R85, S77, T71, U75-U77, W72, X75-X77, Y77, Y78
6	Chronic back or neck disorder	L83, L84, L86
7	COPD*	R91, R95
8	Visual disorder	F83, F84, F92-F94
9	Cardiac dysrhythmia	K78-K80
10	Depression (and psychosis)	P73, P76
11	Heart failure	K77
12	Asthma*	R96
13	Hearing disorder	H84-H86
14	Osteoporosis	L95
15	Stroke	K90
16	Rheumatoid arthritis	L88
17	Dementia (incl. Alzheimer's disease)	P70
18	Anxiety disorder	P74
19	Migraine	N89
20	Heart valve disorder	K83
21	Neuraesthenia/surmenage/burn-out	P78
22	Chronic alcohol abuse	P15
23	Parkinson's disease	N87
24	Epilepsy	N88

- Table A2 to be continued -

25	Personality disorder	P80
26	Schizophrenia	P72
27	Intellectual disability	P85
28	Congenital cardiovascular anomaly	K73
29	HIV/AIDS	B90

** Excluded from analyses*

Appendix B Detailed information GINA classification

In Table b1 and B2 detailed information regarding the GINA classification is presentend.

Table B1 Detailed GINA classificatie

Step 1	Step 2	Stap 3	Stap 4	Stap 5
Only SABA/SAMA 'as needed' - salbutamol (R03AC02) - terbutaline (R03AC03) - Ipratropium (R03BB01)	**Low dose ICS** - beclometason (MDI) (R03BA01): 100-200 mcg - budesonide (DPI) (R03BA02): 200-400 mcg - fluticason furoate (DPI) (R03BA09): 100 mcg - fluticason proprionate (DPI/MDI) (R03BA05): 100-250 mcg - ciclesonide (MDI) (R03BA08): 80-160 mcg	**Low dose ICS/LABA** - beclometason/formoterol (R03AK08) 100-200 mcg beclometason - budesonide/formoterol (R03AK07) 200-400 mcg budesonide - budesonide/salmeterol (R03AK12) 200-400 mcg budesonide - fluticasone/salmeterol (R03AK06) 100-250 mcg fluticason - fluticason/formoterol (R03AK11) 100-250 mcg fluticason <u>LABA with low dose ICS:</u> - salmeterol (R03AC12) - formoterol (R03AC13)	**Medium/high dose ICS/LABA** - beclometason/formoterol (R03AK08) >200 mcg beclometason - budesonide/formoterol (R03AK07) >400 mcg budesonide - budesonide/salmeterol (R03AK12) >400 mcg budesonide - fluticason/salmeterol (R03AK06) >250 mcg fluticason - fluticason/formoterol (R03AK11) > 250 mcg fluticason <u>LABA with medium/high dose ICS (see step 3):</u> - salmeterol (R03AC12) - formoterol (R03AC13)	**Add tiotropium mist inhaler** (R03BB04 product number 84808 or 128201)
	LTRA Only LTRA, without ICS - montelukast (R03DC03)	**Low dose ICS/LABA + LTRA**	**Medium/high dose ICS/LABA + tiotropium**	**Add anti-IgE** - omalizumab (R03DX05)
	Low dose theophylline[1] Only theophylline, without ICS - theophylline (R03DA04)	**Low dose ICS/LABA + theophylline**	**Medium/high dose ICS + LTRA**	**Add anti-IL5** - mepolizumab (R03DX09)

	Low dose ICS + LTRA	**Medium/high dose ICS + theophylline**	**Add low dose OCS**: <20mg prednisolon (H02AB06) Prednison (H02AB07)
	Low dose ICS + theophylline		
	Medium/high dose ICS - beclometason (R03BA01): >200 mcg - budesonide (R03BA02): >400 mcg - fluticason furoate (R03BA09): 200 mcg - fluticason propr. (R03BA05): >250 mcg - ciclesonide (R03BA08): >160 mcg		

Table B2: non-classifiable categories

GINA missing	
Missing value on ICS medication	492
*Medication that was not included in GINA	37
LABA monotherapy	160
LABA with SABA	62
SABA with tiotropium	46
Only tiotropium	98
Other combinations	5
Total	900

*List of medication that was not included in GINA

ATC	Name
R03AC18	Indacaterol
R03AC19	Olodaterol
R03AL01	Fenoterol met ipratropiumbromide
R03AL02	Salbutamol met ipratropiumbromide
R03AL03	Vilanterol met umeclidiniumbromide
R03AL04	Indacaterol met glycopyrroniumbromide
R03AL05	Formoterol met aclidiniumbromide
R03AL06	Olodaterol met tiotropiumbromide
R03BB06	Glycopyrroniumbromide
R03BC01	Cromoglicinezuur
R03BC03	Nedocromil

Appendix C Extra tables chapter 4

Categorized ICS adherence by sex, age, comorbidity, comedication and GINA class

Looking at ICS adherence in categories, Table C1 shows the percentage of patients per subgroup (sex, age categories, number of comedication and comorbidities, and GINA class) with an adherence level in the given category. Whilst more than half of patients younger than 40 has an ICS adherence of 50% or less, this applies to 29% of patients of 65 years and older. On the other hand, about four in ten patients aged 65 and older have an adherence between 91-100% compared to 23% of patients younger than 40. Of the patients with no other chronic medication, almost half has an adherence of 50% or less, compared to 35% of patients with two or more other chronic medications. About 36% of patients with two or more other chronic medications have an adherence level between 91-100%, compared to 23% of patients without any comedication. The same pattern can be seen for the number of comorbidities: patients with no comorbidities are less adherent than patients with two or more other chronic illnesses. About half of patients in GINA class 2 has a low adherence level (≤50%), whilst this is true for about three of ten patients in GINA class 5. Testing for a trend showed significant differences in categorized ICS adherence for all groups except for sex.

Table C1: ICS adherence in categories of patients with asthma (N=13,756) by sex, age, comedication, comorbidity and GINA class. Note: percentages are calculated per subgroup (per row)

	ICS adherence					
	≤50% (N=5,488)	51-60% (N=1,084)	61-70% (N=1,025)	71-80% (N=990)	81-90% (N=783)	91-100% (N=4,386)
Sex	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male (n=5,531)	2,267(41.0)	443 (8.0)	384 (6.9)	416 (7.5)	309 (5.6)	1,712 (31.0)
Female (n=8,225)	3,221 (39.2)	641 (7.8)	641 (7.8)	574 (7.0)	474 (5.8)	2,674 (32.5)
Age						
12-17 year (n=981)	530 (54.0)	68 (6.9)	57 (5.8)	59 (6.0)	38 (3.9)	229 (23.3)
18-39 year (n=2.919)	1,528 (52.4)	221 (7.6)	186 (6.4)	161 (5.5)	138 (4.7)	685 (23.5)
40-54 year (n=3.800)	1,531 (40.3)	308 (8.1)	300 (7.9)	290 (7.6)	226 (6.0)	1,145 (30.1)
55-64 year (n=2,692)	938 (34.8)	223 (8.3)	198 (7.4)	213 (7.9)	175 (6.5)	945 (35.1)
65+ year (n=3,364)	961 (28.6)	264 (7.9)	284 (8.4)	267 (7.9)	206 (6.1)	1,382 (41.1)
Comedication						
0 (n=1.618)	766 (47.3)	136 (8.4)	125 (7.7)	116 (7.2)	99 (6.1)	376 (23.2)
1 (n=2,768)	1,208 (43.6)	210 (7.6)	190 (6.9)	192 (6.9)	166 (6.0)	802 (29.0)
2 (n=2,978)	1,257 (42.2)	251 (8.4)	202 (6.8)	209 (7.0)	170 (5.7)	889 (29.9)
>2 (n=6,392)	2,257 (35.3)	487 (7.6)	508 (8.0)	473 (7.4)	348 (5.4)	2,319 (36.3)
Comorbidity						
0 (n=4,945)	2,352 (47.6)	373 (7.5)	352 (7.1)	312 (6.3)	262 (5.3)	1,294 (26.2)
1 (n=3,146)	1,251 (39.8)	262 (8.3)	239 (7.6)	223 (7.1)	197 (6.3)	974 (31.0)
2 (n=2,158)	783 (36.3)	172 (8.0)	140 (6.5)	178 (8.3)	126 (5.8)	759 (35.2)
>2 (n=3,507)	1,102 (31.4)	277 (7.9)	294 (8.4)	277 (7.9)	198 (5.7)	1,359 (38.8)

- Table C1 to be continued -

GINA class (n=13,694)[#]						
2 (n=1,743)	882 (50.6)	152 (8.7)	128 (7.3)	94 (5.4)	95 (5.5)	392 (22.5)
3 (n=4,886)	2,170 (44.4)	355 (7.3)	313 (6.4)	326 (6.7)	202 (4.1)	1,520 (31.1)
4 (n=6,672)	2,283 (34.2)	537 (8.1)	548 (8.2)	523 (7.8)	451 (6.8)	2,330 (34.9)
5 (n=393)	123 (31.3)	34 (8.7)	31 (7.9)	42 (10.7)	31 (7.9)	132 (33.6)

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA and no ICS medication*

SABA over-use according to the GINA 2018 guideline

*Table C2. From the **total group of patients** (N=21,369), the percentage of patients over-using SABA, categorised in three or more, seven or more, and 13 or more SABA prescriptions in 2016, by sex, age, comedication, comorbidity and GINA class.*

	≥3 SABA prescriptions (N=3,310)	≥7 SABA prescriptions (N=496)	≥13 SABA prescriptions (N=78)
	n (%)	n (%)	n (%)
Sex			
Male	1,389 (16.1)*	235 (2.7)*	30 (0.4)
Female	1,921 (15.1)*	261 (2.1)*	29 (0.2)
Age			
12-17 year	265 (17.2)*	31 (2.0)*	0 (0.0)*
18-39 year	958 (20.4)*	176 (3.7)*	24 (0.5)*
40-54 year	1,053 (17.8)*	180 (3.0)*	23 (0.4)*
55-64 year	524 (13.0)*	56 (1.4)*	9 (0.2)*
65+ year	510 (9.9)*	53 (1.0)*	3 (0.1)*
Comedication			
0	406 (15.8)	56 (2.2)	2 (0.1)
1	694 (16.0)	118 (2.7)	15 (0.4)
2	712 (15.3)	98 (2.1)	13 (0.3)
>2	1,498 (15.3)	224 (2.3)	29 (0.3)
Comorbidity			
0	1,332 (17.0)*	204 (2.6)*	20 (0.3)*
1	797 (16.1)*	143 (2.9)*	25 (0.5)*
2	499 (15.0)*	60 (1,8)*	6 (0.2)*
>2	682 (13.0)*	89 (1.7)*	8 (0.2)*
GINA class (n=20,469)			
1	584 (33.6)[#]*	88 (5.1)*	5 (0.3)
2	359 (14.0)*	48 (1.9)*	3 (0.1)
3	954 (13.9)*	140 (2.1)*	20 (0.3)
4	1,228 (14.0)*	195 (2.2)*	27 (0.3)
5	93 (16.8)*	13 (2.4)*	3 (0.5)

** significant at level p<0.05*

[#] *Due to our study's selection criterion of having minimally two prescriptions R03A or R03B in 2016, we induce a higher number of SABA prescriptions for patients in GINA class 1 and a high mean number of prescriptions as well.*

Figure C3 illustrates the distribution of the number of SABA prescriptions for the total group of patients.

Figure C3 Percentage of patients per number of SABA prescriptions for our total group (N=21,369). Categories of three or more, seven or more and 13 or more SABA prescriptions in 2016 are illustrated with the vertical lines.

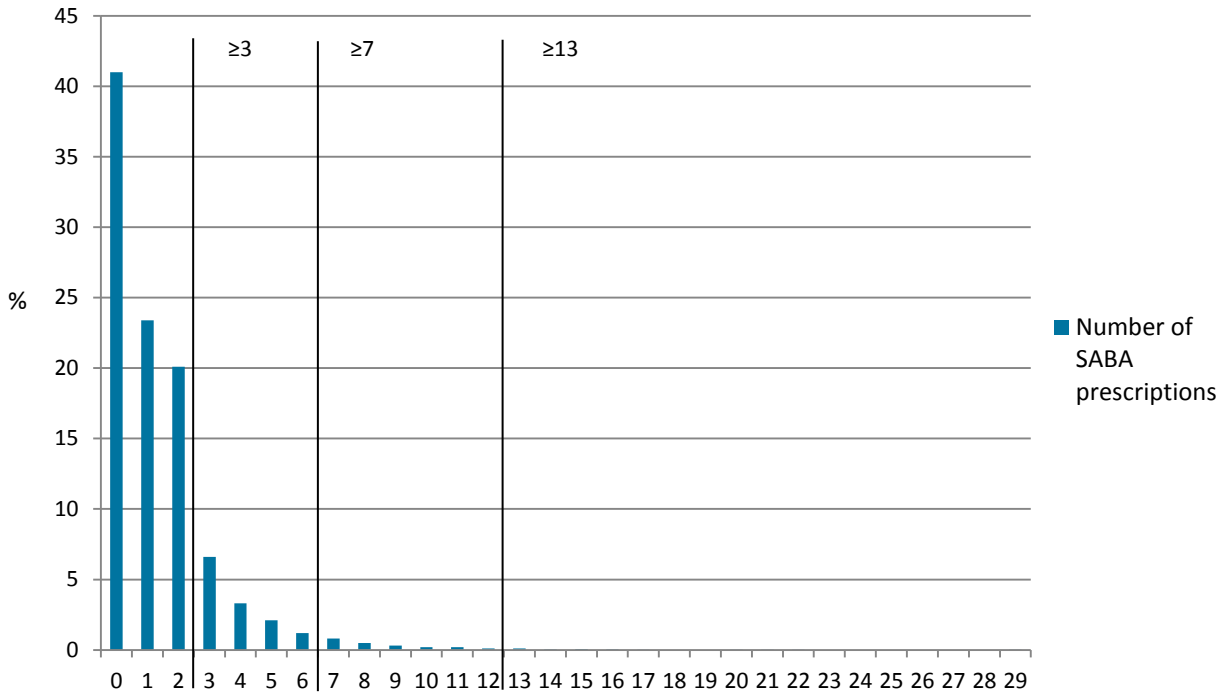

*Table C4. From the group of **patients receiving at least one SABA prescription** (N=12,609), the percentage of patients over-using SABA categorised in three or more, seven or more, and 13 or more SABA prescriptions in 2016, by sex, age, comedication, comorbidity and GINA class.*

	≥3 SABA prescriptions (n=3,310)	≥7 SABA prescriptions (n=496)	≥13 SABA prescriptions (n=59)
	n (%)	n (%)	n (%)
Sex			
Male (n=5,090)	1,389 (27.3)*	235 (4.6)*	30 (0.6)
Female (n=7,519)	1.921 (25.6)*	261 (3.5)*	29 (0.4)
Age			
12-17 year (n=1,323)	265 (20.0)*	31 (2.3)*	0 (0.0)*
18-39 year (n=3,544)	958 (27.0)*	176 (5.0)*	24 (0.7)*
40-54 year (n=3,694)	1,053 (28.5)*	180 (4.9)*	23 (0.6)*
55-64 year (n=2,066)	524 (25.4)*	56 (2.7)*	9 (0.4)*
65+ year (n=1,982)	510 (25.7)*	53 (2.7)*	3 (0.2)*
Comedication			
0 (n=5,475)	406 (24.7)*	56 (3.4)	2 (0.1)
1 (n=2,767)	694 (25.1)*	118 (4.3)	15 (0.5)
2 (n=2,796)	712 (25.5)*	98 (3.5)	13 (0.5)
>2 (n=5,405)	1,498 (27.7)*	224 (4.1)	29 (0.5)

- Table C4 to be continued -

Comorbidity			
0 (n=5,475)	1,332 (24.3)*	204 (3.7)*	20 (0.4)
1 (n=2,982)	797 (26.7)*	143 (4.8)*	25 (0.8)
2 (n=1,768)	499 (28.2)*	60 (3.4)*	6 (0.3)
>2 (n=2,384)	682 (28.6)*	89 (3.7)*	8 (0.3)
GINA class (n=12,202)			
1 (n=1,669)	584 (35.0)[#]*	88 (5.3)*	5 (0.3)
2 (n=1,841)	359 (19.5)*	48 (2.6)*	3 (0.2)
3 (n=3,950)	954 (24.2)*	140 (3.5)*	20 (0.5)
4 (n=4,482)	1,228 (27.4)*	195 (4.4)*	27 (0.6)
5 (n=260)	93 (35.8)*	13 (5.0)*	3 (1.2)

** significant at level p<0.05*

[#] Due to our study's selection criterion of having minimally two prescriptions R03A or R03B in 2016, we induce a higher number of SABA prescriptions for patients in GINA class 1 and a higher mean number of prescriptions as well.

Appendix D Sensitivity analyses

The association between SABA use, ICS adherence and exacerbations

Results from multilevel analysis to investigate which characteristics are associated with having 1 or more OCS courses with adults only (18+)

*Table D1. Results of multilevel logistic regression analysis in which we investigate which variables (ICS adherence in categories, SABA use (number of prescriptions), sex, age (**adults only**; 18+ years), number of comedication, number of comorbidities and GINA class) are associated with **having 1 or more OCS courses** (indicating an exacerbation) compared to no OCS courses, while taking into account that patients (N=12,715) are nested within general practices.*

	Odds Ratio	95% Confidence interval	p-value
ICS adherence (ref=≤50%)			
51-60%	0.79	0.63-0.99	**0.040**
61-70%	0.92	0.74-1.14	0.453
71-80%	0.90	0.72-1.13	0.380
81-90%	0.94	0.74-1.20	0.644
91-100%	1.12	0.97-1.29	0.116
SABA use (ref=0 prescriptions)			
1 SABA prescription	1.65	1.44-1.91	**0.000**
2-5 SABA prescriptions	2.26	1.98-2.58	**0.000**
6-11 SABA prescriptions	3.38	2.55-4.47	**0.000**
≥12 SABA prescriptions	3.08	1.53-6.22	**0.002**
Sex (ref=male)			
Female	1.12	1.00-1.25	0.055
Age (ref=18-39 year)			
40-54 year	1.14	0.96-1.34	0.133
55-64 year	1.15	0.95-1.38	0.142
65+ year	1.36	1.12-1.65	**0.002**
Comedication (ref=none)			
1	2.46	1.73-3.50	**0.000**
2	3.40	2.42-4.79	**0.000**
>2	5.33	3.82-7.43	**0.000**
Comorbidity (ref=none)			
1	1.19	1.01-1.40	**0.038**
2	1.23	1.03-1.48	**0.024**
>2	1.20	1.00-1.45	**0.049**

- Table D1 to be continued -

GINA class[#] (2=ref)			
3	1.41	1.10-1.80	**0.006**
4	2.65	2.10-3.35	**0.000**
5	5.04	3.65-6.96	**0.000**
Random part	**coef**	**SE**	
Between-practice variance	0.22	0.04	
	ICC (%)		
Practice level	6.2		

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA*

ICC intraclass correlation expressed as a percentage

Results from multilevel analysis to investigate which characteristics are associated with having 2 or more OCS courses with the total group

Table D2. Results of multilevel logistic regression analysis in which we investigate which variables (ICS adherence in categories, SABA use (number of prescriptions), sex, age, number of comedication, number of comorbidities and GINA class) are associated with having 2 or more OCS courses (indicating two or more exacerbations) compared to 1 or no OCS course, while taking into account that patients (N=13,694) are nested within general practices.

	Odds Ratio	95% Confidence interval	p-value
ICS adherence (ref=≤50%)			
51-60%	0.76	0.48-1.22	0.261
61-70%	1.11	0.74-1.67	0.608
71-80%	0.93	0.60-1.44	0.747
81-90%	1.34	0.89-2.03	0.164
91-100%	1.33	1.03-1.72	**0.029**
SABA use (ref=0 prescriptions)			
1 SABA prescription	1.48	1.12-1.97	**0.006**
2-5 SABA prescriptions	2.26	1.77-2.89	**0.000**
6-11 SABA prescriptions	3.56	2.22-5.71	**0.000**
≥12 SABA prescriptions	3.94	1.31-11.82	**0.014**
Sex (ref=male)			
Female	1.20	0.96-1.49	0.113
Age (ref=12-17 year)			
18-39 year	2.21	0.79-6.24	0.113
40-54 year	2.60	0.93-7.28	0.068
55-64 year	2.79	0.98-7.92	0.053
65+ year	2.94	1.03-8.38	**0.044**

- Table D2 to be continued -

Comedication (ref=none)			
1	2.47	1.02-5.95	**0.044**
2	3.62	1.55-8.45	**0.003**
>2	6.51	2.85-14.91	**0.000**
Comorbidity (ref=none)			
1	1.15	0.82-1.62	0.406
2	1.23	0.85-1.78	0.277
>2	1.45	1.01-2.08	**0.043**
GINA class[#] (2=ref)			
3	2.03	1.00-4.13	**0.049**
4	6.33	3.22-12.43	**0.000**
5	16.17	7.74-33.79	**0.000**
Random part	**coef**	**SE**	
Between-practice variance	0.22	0.08	
	ICC (%)		
Practice level	6.3		

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA, and no ICS*

ICC intraclass correlation expressed as a percentage

Results from multilevel analysis to investigate which characteristics are associated with having 2 or more OCS courses with adults only (18+)

*Table D3. Results of multilevel logistic regression analysis in which we investigate which variables (ICS adherence in categories, SABA use (number of prescriptions), sex, age (**only adults; 18+**), number of comedication, number of comorbidities and GINA class) are associated with **having 2 or more OCS courses** (indicating an exacerbation) compared to 1 or no OCS course, while taking into account that patients (N=12,715) are nested within general practices.*

	Odds Ratio	95% Confidence interval	p-value
ICS adherence (ref=≤50%)			
51-60%	0.76	0.47-1.22	0.251
61-70%	1.10	0.74-1.65	0.639
71-80%	0.93	0.60-1.43	0.731
81-90%	1.33	0.88-2.02	0.181
91-100%	1.29	0.99-1.67	0.057
SABA use (ref=0 prescriptions)			
1 SABA prescription	1.48	1.11-1.96	0.007
2-5 SABA prescriptions	2.24	1.75-2.86	0.000
6-11 SABA prescriptions	3.62	2.26-5.80	0.000
≥12 SABA prescriptions	3.95	1.32-11.84	0.014

- Table D3 to be continued -

Sex (ref=male)			
Female	1.20	0.96-1.50	0.109
Age (ref=18-39 year)			
40-54 year	2.45	1.02-5.92	0.045
55-64 year	3.42	1.46-8.00	0.005
65+ year	6.20	2.71-14.19	0.000
Comedication (ref=none)			
1	2.45	1.02-5.92	0.045
2	3.42	1.46-8.00	0.005
>2	6.20	2.71-14.19	0.000
Comorbidity (ref=none)			
1	1.15	0.82-1.63	0.412
2	1.24	0.85-1.79	0.264
>2	1.46	1.01-2.09	0.040
GINA class[#] (2=ref)			
3	1.90	0.94-3.85	0.076
4	5.90	3.01-11.57	0.000
5	15.17	7.28-31.63	0.000
Random part	**coef**	**SE**	
Between-practice variance	0.23	0.08	
	ICC[#] (%)		
Practice level	6.6		

[#] *GINA class 1 is not applicable, since patients in class 1 only use SABA*

ICC intraclass correlation expressed as a percentage