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# ASTHMA DRUG REGIMES IN ADULTS

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*Sex disparities in asthma drug regimes in adults and prescription patterns of Dutch general practitioners in prescribing asthma medication*

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## Abstract

About 10 per cent of the Dutch population suffers from asthma. To control and diminish asthma symptoms, inhalation medication can be used. In the Dutch Association of General Practitioners (NHG, Nederlandse Huisartsen Genootschap) standard, a treatment regime is drafted, describing the four steps in asthma treatment. In this longitudinal drug utilization study, the steps in the distribution of the steps and the changes in the steps of the asthma treatment regime of the adult asthma patient population in Dutch general practices are researched while comparing sexes. The data was acquired from the IADB (InterAction) database. The study population consisted of 38007 anonymized asthma patients. The Chronic obstructive pulmonary disease (COPD) patients were excluded by excluding Anatomical Therapeutic Chemical (ATC) codes of ipratropium and tiotropium. Around 39% (n=14668) of the patients were men, and 61% (n=23339) were women. Most patients were between 16 and 40 years old (67%, n=25385). The most used medication group was the short-acting beta-agonists (SABA) (36%, n= 14020) with runner-up inhaled corticosteroids (ICS) in combination with a long-acting beta-agonist (LABA) (30%, n=11528). Regarding the distribution of step up and step down in the treatment regime, most patients (temporarily) stopped their medication or stayed in the same step within one year. Over ten years, more patients were (temporarily) stopping their asthma treatment. There was no difference in men and women concerning asthma medication usage or changes in the treatment regime. In this study, the comparison with the NHG standard could not be made because of the limitations of this study considering the offered data and characterizing asthma patients.

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## Introduction

Asthma is a chronic illness consisting of an attack on the airways due to oversensitivity to allergic or non-allergic agents causing reversible bronchus obstruction and inflammation. <sup>1</sup> In the Netherlands, around 10% of the population has asthma. <sup>2</sup> In general practices, the incidence of asthma in Dutch adults is around 6 per 1000 patients per year and slowly decreases with age. <sup>2</sup> The prevalence in general practices regarding young adults (19-24 years) consists of 130 per 1000 patients: this decreases with age ( $\geq 25$  years old) to 94-97 per 1000 patients. <sup>2</sup> Asthma can be a day-to-day burden to patients due to the symptoms of wheezing, shortness of breath and coughing. <sup>3</sup> These symptoms can influence a patient's ability to engage in physical activities and impact the patient's quality of sleep. Then there is also the risk of exposure to allergens, causing exacerbations and the persistent airflow limitation. The treatment of asthma needs to be sufficient so that the symptoms and the risk of an asthma attack are under control and the chances of getting asthma symptoms or attacks are minimized. <sup>4</sup> Around 45% of asthma patients have insufficient asthma control. One out of three patients strays from their prescribed medication. <sup>5</sup> This shows over-prescription to those patients, meaning they are using less than advised, or the patients are underprescribed, meaning they are using more than advised.

This study's primary objective is to determine to what extent step-up and step-down treatment take place in adult asthma patients in the Dutch general practices. Secondly, there will be looked at how these different steps in asthma treatment are distributed among the adult asthma patient population. Since the incidence and prevalence of the prescription patterns of the inhalation medication for asthma are higher in adult women than in men, the difference between adult men and women will be researched. The prescription patterns are compared to the steps described in the Dutch guidelines, and they will be looked at if they are in concordance with each other. This could also be influenced by prescribing general practitioners. Therefore the differences in prescribing patterns between general practitioners (GP) will be analyzed.

The explorative objective of this research is to identify the prescription patterns of inhalation medication in adult asthma patients in Dutch general practices.

## Background

### Asthma treatment

The goal of asthma treatment is to gain control over asthma, meaning:

- no symptoms during the day and night
- no restrictions (for example, in physical activity)
- normal spirometry
- the dosage and administration as low as possible with the least adverse effects

The Asthma Control Questionnaire (ACQ) or the Asthma Control Test (ACT) is used to determine whether the treatment is sufficient for the patient. Depending on the score on either survey, the asthma control is altered or will stay the same. In the NHG guidelines, the treatment of asthma has five steps depending on the severity of the asthma symptoms, as seen in Table 1.

**Table 1: Step-by-step inhalation plan for adults** <sup>1</sup>

	Step 1 (optional) SABA or ICS- formoterol if necessary	Step 2 ICS	Step 3 Low dose ICS/LABA	Step 4 Intermediate to high dose ICS/LABA	Step 5 Referral
<b>(Maintenance) treatment</b>	Only SABA as-needed* or low dose ICS-formoterol as-needed* when symptoms occur, or immediately step 2	Low dose ICS or low dose ICS-formoterol, as-needed, when symptoms occur*	Low dose ICS + LABA or intermediate-dose ICS (without LABA)	Intermediate to (temporary) higher dose ICS + LABA or higher dose ICS (without LABA)	Consider referral to pulmonologist
<b>When symptoms occur*</b>	<ul style="list-style-type: none"> <li>• When ICS-formoterol is used: additional inhalation low dose of ICS-formoterol (maximum of 8 inhalations a day) * or additional SABA</li> <li>• Otherwise: SABA*</li> </ul>				
* When used > 2 times a week, the treatment is insufficient to maintain asthma control. Only formoterol-beclomethasone is registered to be used 'as needed' in addition to the maintenance treatment.					

### Step-up regimen

When patients show very few symptoms (less than two times a week during the daytime), the first step is to use a short-acting beta-2-agonist (SABA) as needed. The equivalent alternative of step 1 is to start with the lowest dose of inhalation corticosteroids (ICS) as needed or start the combination therapy of formoterol-budesonide or formoterol-beclomethasone as low as possible and as-needed. When these drugs are used over two times a week, and the symptoms occur more than two times a week or at night, the therapy needs to be re-evaluated, and the patient will go to the second step. <sup>1</sup>

The second step consists of maintenance treatment with a low dose of ICS or ICS combined with formoterol as needed. The ICS needs to be stepped down to the lowest dose possible. When ICS-formoterol is used, inhalation medication can be added, such as an additional low dose of ICS-formoterol or additional SABA. An alternative to the low dose of ICS is to prescribe a low dose of formoterol-budesonide or a low dose of formoterol-beclomethasone, both as needed. <sup>1</sup>

The third step is applied if the low dose of ICS is insufficient. The third step consists of maintenance treatment of a long-acting beta-2-agonist (LABA) added to a low dose of ICS. The LABA always needs to be combined with ICS in asthma treatment; if LABA is the monotherapy, the risk of hospitalization, severe asthma attacks and asthma-caused deaths increase. By combining ICS and LABA, these risks are not increased. If the LABA is causing too many adverse effects, tiotropium (long-acting muscarine agonist, LAMA) is an alternative for the LABA. <sup>1</sup>

The fourth step is applied if the third step does not achieve adequate asthma control, and it consists of maintenance treatment with LABA and an intermediate to a higher dose of ICS. If LABA gives too many adverse effects, it will be dropped, and monotherapy of a higher dose of ICS is applied. Tiotropium or montelukast could be added when this is still inadequate asthma control. If step four is ineffective in achieving asthma control, step five will be applied: referral to a pulmonologist. <sup>1</sup>

### Step-down regimen

In the NHG standard <sup>1</sup> and according to the Global Initiative for Asthma (GINA) guidelines <sup>5</sup>, there are no treatment schemes based on stepping down in inhalation medication. Most clinical practices are not familiar with stepping down. As seen above, stepping down is only mentioned when a patient starts with a certain step to achieve the lowest dose possible and if the asthma is under control for at least three months or to minimize the adverse effects. The review of Gionfriddo et al. showed that there could be a step-down regimen for asthma patients depending on the drugs patients take. <sup>6</sup> As seen in Table 2, the consideration of stepping down starts at the second step of the step-up regime. <sup>7</sup>

**Table 2: Step-down suggestions according to Gionfriddo et al. Leukotriene receptor antagonist (LTRA)**

Stepping from	down	Proposal	Effect
ICS		≥ 50% dose reduction of ICS	No increased risk of asthma exacerbation
		ICS as-needed	No increased risk of asthma exacerbation, but increased asthma symptoms
		LTRA instead of ICS	Stopping ICS increases the risk of asthma exacerbation
			Reduces the risk of asthma exacerbations when using LTRA as an addition to the step-down of ICS
		LABA instead of ICS	Reduces the risk of asthma exacerbations when using LTRA as an addition to the step-down of ICS
		Dose once a day instead of twice a day	It might be increasing the adherence when the dosing has a lower frequency
		Allergen immunotherapy	50% increased success in stepping down ICS
ICS with LABA		Discontinuation of ICS	Increased risk for asthma exacerbation
		Lower dose ICS-LABA with ICS-LABA as-needed	No increased risk of asthma exacerbation
LTRA		Lower dose ICS-LABA	No increased risk of asthma exacerbation
		Discontinuation of LTRA	It might increase the risk of asthma exacerbation

## The difference in COPD and asthma inhalation medication usage

The NHG standard of treating chronic obstructive pulmonary disorder (COPD) <sup>8</sup> and the pharmacotherapeutic compass (FK – farmacotherapeutisch Kompas) <sup>9</sup> show similarities and differences in drug usage when treating asthma and COPD. The difference in drug usage needs to be defined to separate the COPD patients from the asthma patients.

**Table 3: Differences and similarities in the treatment of Asthma and COPD based on the Pharmacotherapy Compass (FK)**

Drugs exclusively used in asthma treatment	Drugs exclusively used in COPD treatment	Drugs used in both COPD and asthma treatment
indacaterol/mometasone	olodaterol	formoterol
budesonide/salmeterol	indacaterol	salbutamol
formoterol/fluticasone	acetylcysteine	salmeterol
ciclesonide	aclidinium	terbutaline
cromoglycate acid	glycopyrronium	formoterol/beclomethasone
indacaterol/glycopyrronium/mometasone	umeclidinium	formoterol/budesonide
	aclidinium/formoterol	salmeterol/fluticasone
	fluticasone/umeclidinium/vilanterol	vilanterol/fluticasone furoate
	formoterol/glycopyrronium/budesonide	beclomethasone
	glycopyrronium/formoterol	budesonide
	indacaterol/glycopyrronium	fluticasone
	salbutamol/ipratropium	ipratropium
	tiotropium/olodaterol	tiotropium
		beclomethasone/formoterol/glycopyrronium
		fenoterol/ipratropium

As seen above, most LAMAs are advised to treat COPD.

According to the study by Lambooi et al., patients with asthma mostly use SABA's, ICS and ICS in combination with LABA. Patients with COPD mostly use LAMAs, SABA's and a combination of LABA and ICS. When comparing the asthma patients and COPD patients in the use of individual inhalation drugs, the SABA called salbutamol is twice as likely to be used in the treatment of asthma as in COPD.

## Sex differences

At a young age, boys develop twice as often asthma as girls. Around puberty, the prevalence switches. Asthma occurs more often in teenage girls than in teenage boys. Moreover, women suffer more frequently from severe asthma than men. <sup>2</sup>

## Anatomy

The parenchyma of the airways of girls grows during childhood and adolescence proportionally as opposed to the airways of boys. So, boys tend to have smaller lungs in their childhood than girls. This can explain why boys have asthma more often in childhood than girls.

Later in life, men have larger lungs and airways than women. This happens due to respiratory pressure. The respiratory pressure is higher in men than women, caused by the testosterone increase during puberty. <sup>10</sup> This could explain why women have asthma more often in their adult life than men.

## Sex hormones

### Men - Testosterone

Men, as mentioned above, are influenced by testosterone. Prepubescent boys are more prone to develop asthma. During puberty, testosterone increases, causing their lungs to grow and decrease the chances of developing asthma. However, when they grow older, the testosterone levels decrease, causing the prevalence of asthma to increase. <sup>10,11</sup>

### Women

#### Oestrogen and Progesterone

Many studies have shown that this can be explained by the fluctuations in hormone levels or changes in the hormone ratio between oestrogen and progesterone. <sup>11,12</sup> Townsend et al. and Baldaçara et al. noted that when the oestrogen levels drop, the asthma symptoms worsen, concluding that oestrogen might have a protective role in asthma. <sup>10,13</sup>

#### Menstruation

Women undergo menstruation, menopause and possibly pregnancy, which all cause hormone fluctuations and influence their bodies. Around 20% to 40% of women with asthma have experienced worsening symptoms in their pre-and peri-menstrual periods, leading to more hospitalizations, increased drug use, and healthcare. These women found relief when using oral contraceptives (OC). <sup>11,12</sup> However, Barbro et al. suggested that there could be a lag time in hormonal fluctuations and the perception of asthma symptoms. Which makes the hypothesis of worsening asthma due to hormone changes hard to believe. <sup>12</sup>

#### Pregnancy

During the pregnancy, oestrogen and progesterone rise and are at their highest concentration in the third trimester. Depending on the severity of asthma before the pregnancy, the symptoms may increase, decrease, or even stay the same. Women with severe asthma experienced their asthma worsening during pregnancy. Whereas women with mild to moderate asthma did not. Unfortunately, there is insufficient research to determine why this is the case. <sup>10,11</sup>



## Menopause

Around the 50<sup>th</sup> year of a woman's life, menopause will occur. Menopause causes a drop in oestrogen and progesterone and the increase of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Unfortunately, adult asthma exacerbations in women diagnosed with asthma in the past peak around menopause. However, menopausal women are less likely to become newly asthma patients compared to pre-menopausal women. <sup>10</sup>

## Sex differences in asthma treatment

According to Sexton et al. and Groeneveld et al., women visit their general practitioner more often than men. What can impact the prescriptions for women, causing them to switch more often from medication or increasing dosages and asking for a certain type of medication. With regards to asthma inhalation medication usage, Sexton et al. pointed out that there is no difference in the use of inhalation medication regarding inhaled  $\beta$ -agonists and corticosteroids. In contrast, women were more likely to use oral steroids than men. <sup>14,15</sup>

## Prescribing patterns of general practitioners

When a general practitioner has diagnosed the patient, they will go to the 'evoked set'. The evoked set is several medication treatments to treat the patient with, ranging from around 2 to 5 possible options and happens due to prior experience. To choose between these options, the GP will then think about what they normally prescribe (prescribing pattern and evoked set) and what is proven to be an effective treatment (evidence-based). <sup>16</sup>

## Methods

### Data source

The data will be obtained from the IADB. IADB is a database with information about provided medication in community pharmacies in the Netherlands initiated by the Groningen Research Institute Pharmacy (GRIP) from the Pharmacotherapy, -epidemiology & -economics (PTEE) department of the University of Groningen. The anonymous database contains around 120 community pharmacies and around 1.120.000 patients from 1996 to 2020. The IADB collaborates with the community pharmacies established in the north of the Netherlands and the University of Groningen. The drug data includes information on the ATC classification, prescription dates, duration of the therapy, defined daily doses and drug names.<sup>17</sup>

### Study design

This study is a longitudinal drug utilization study designed to gain information about the use of inhalation medication prescribed by general practitioners and its distribution among the Dutch asthma patient population. In this study, the patients were followed 10 years after receiving their first asthma inhalation prescription, determining how many patients stepped up, stepped down or stopped. The first year was divided into 4 quarters to research the step-up and step-down in the first person-year.

### Study population

The study population comprises all men and women aged 16 years or older. Among this population, the patients included were in the IADB.nl for at least 1 year before receiving their first asthma inhalation medication with the prescriptions and ATC codes below, dated until 2020. These patients also had to receive at least one more prescription(s) of the same asthma inhalation medication class within 365 days of the first start. The sample consisted of 38007 patients given the inclusion criteria described above.

These prescriptions with corresponding ATC codes were included to specify the patient population:

1. SABA: R03AC02, R03AC03
2. ICS: R03BA01, R03BA02, R03BA05, R03BA08
3. LABA: R03AC12, R03AC13
4. Combination ICS with LABA: R03AK06, R03AK07, R03AK08, R03AK10, R03AK11, R03AK12

The excluded patients were prior users of ipratropium or tiotropium and current users of ipratropium or tiotropium because these muscarinic antagonists are far more often prescribed in patients with COPD than with asthma. (9) There were other prescriptions excluded concerning excluding COPD patients, their ATC codes were: R03AL01, R03BB01, R03BB04, R03BB54, R03AL02, R03AL06 & R03AL10.

## Outcome

The NHG standard for asthma in adults is done as seen below<sup>1,18</sup>:

1. Only SABA as-needed\* or low dose ICS-formoterol as-needed\* when symptoms occur or immediately after step 2
2. Low dose ICS or low dose ICS-formoterol, as-needed, when symptoms occur
3. Low dose ICS + LABA or intermediate-dose ICS (without LABA)
4. Intermediate to (temporary) higher dose ICS + LABA or higher dose ICS (without LABA)
5. Consider referral to a pulmonologist

\* When used > 2 times a week, the treatment is insufficient to maintain asthma control.

However, for this study, the asthma treatment steps have been adjusted to those of the NHG to prevent overlapping treatment dosages and drugs. The steps are adjusted as follows:

Step 1a – SABA only

Step 1b – ICS only

Step 2 – ICS with SABA

Step 3a – LABA only

Step 3b – LABA with SABA

Step 3c – LABA with ICS

Step 4 – LABA, ICS and SABA all together

Step 0 – (temporary) discontinuation of asthma treatment

The terms are described to determine whether a patient is stepping up or down. When a patient moves from one step to the next, they could go a step up or a step-down. The patient is classified as a step 'up' if they move from a lower step towards a higher step, for example, from step 1 to step 3. A step 'down' is considered when patients go down in the steps, for example, from step 3c to step 2.

The definition of overlap/combination therapy is overlapping prescriptions of 2 or more different asthma inhalation medications collected simultaneously, within 3 months or a year.

When the asthma treatment is (temporarily) discontinued, or patients have not picked up any new medication within the timeframe, they are placed in step 0 and named stoppers.

In this study, the outcome is measured by step up, step down, the same step or stopped. The patients are followed for 10 years. Their first person-year is divided into 4 quarters of 3 months. Every 3 months, the used medication was categorized into the subsequent step to analyze how their treatment changed in the first year. The medication use of patients tracked over 10 years were investigated per person-year. The changes in the treatment of asthma among patients are distributed in the asthma population was determined.

## Analysis

The data were analyzed using Excel, R Studios and MySQL in IADB.nl. Numbers, percentages, medians and interquartile range over follow-up (person) time were calculated over:

- the frequency of the usage of each asthma inhalation medication by adult asthma patients in the Dutch asthma population.
- adult asthma patients in each step of asthma treatment
- adult asthma patients stepping up or down
- adult male asthma patients using asthma inhalation medication
- adult female asthma patients using asthma inhalation medication
- the frequency of the usage of each asthma inhalation medication in adult male and female asthma patients
- the frequency of newly added prescriptions of asthma inhalation medication in adult asthma patients
- every first prescription of a newly added asthma inhalation medication from general practitioners
- the frequency of each general practitioner prescribing each asthma inhalation medication

These will be visualized by graphs, and comparisons have taken place visually.

## Results

### Patient population

The asthma patient population mainly consisted of women. They had a median age on the index date (date of the start of the first asthma medication prescription) of 50 years. Also, 67% of the asthma patients were older than 40. The men were outnumbered by the women and were, on average, older than their female counterparts. The median age of both the male and female asthma patient population was close to the median age of the total asthma patient population of 50 years old.

**Table 4:** This table shows the number of patients and population percentage on different criteria.

	Number of patients	%
<b>Men</b>	14668	39
<b>Women</b>	23339	61
<b>16 - 40 years old</b>	12622	33
<b>&gt; 40 years old</b>	25385	67
<b>Total</b>	38007	100

**Table 5:** The median age of the asthma patients on the index date and divided by sex.

	Age in years
<b>The median age of the patient population on the index date</b>	50
<b>The median age of men on the index date</b>	51
<b>The median age of women on the index date</b>	49

### Asthma medication

#### Starters

The distribution of patients starting with each asthma inhalation medication is depicted in Figure 2. Most patients started with SABA, and the least number started with LABA in combination with SABA. The second most patients started with LABA combined with ICS, followed by only using ICS. The number of patients starting with SABA in combination with ICS, LABA or triple therapy of LABA in combination with ICS and SABA was much lower (> 3000 patients) than the rest of the starting medications (< 8000 patients).

In Figure 2, different groups of patients are portrayed, starting with various kinds of asthma inhalation medication. When comparing men and women, the women start more often with SABA ( $\approx 38\%$ ) in comparison to the men ( $\approx 34\%$ ), but the men start more often with LABA in combination with ICS ( $\approx 33\%$ ) than women ( $\approx 28\%$ ). When evaluating patients over 40 years old and younger than 40, fewer patients older than 40 start with SABA, but more patients older than 40 start with ICS and LABA in combination with ICS.

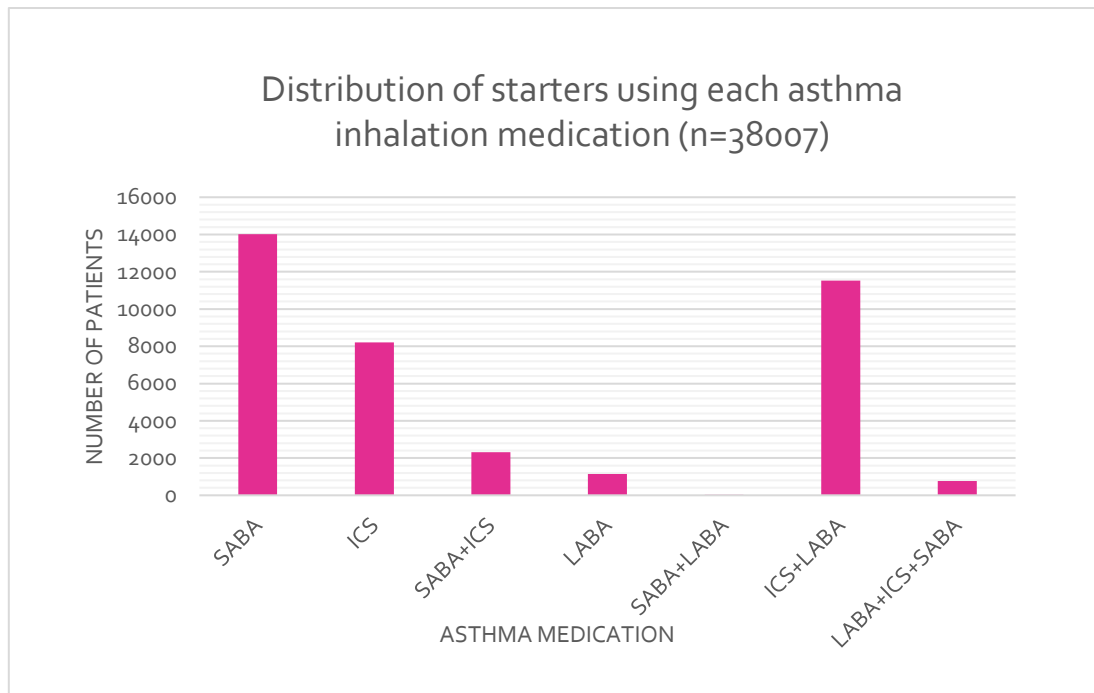


Figure 2: The general distribution of starters of each asthma medication. On the x-axis the different asthma medications and on the y-axis the number of patients starting with each asthma medication.

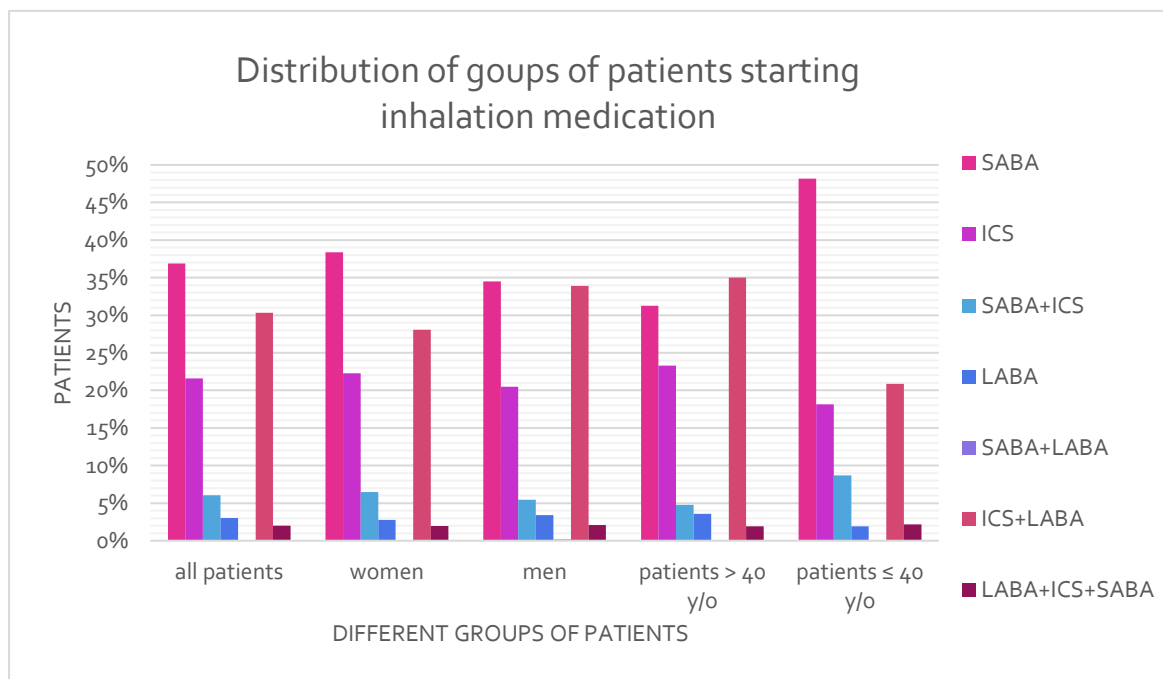


Figure 1: A bar chart comparing different groups of patients starting with different asthma medications. On the x-axis the different groups of patients are shown. On the y-axis, the percentage of patients in each group is presented.

## Asthma treatment regime

### Distribution of asthma medication steps in percentages of the patient population

Figure 3 is a bar chart showing all asthma patients (n=38007), female asthma patients (n=23339), male asthma patients (n=14668), patients aged 16-40 years old (n=25385) and patients aged older than 40 (n=12622) in different steps in the asthma regime on the index date. The bar chart shows that women are more likely to start in steps 1A, 1B and 2 than men (~4%). Nevertheless, when looking at the distribution of the patients starting in 3A and 3C, the percentage of the male population is higher than the women's patient percentages. When comparing the age groups, the patients younger than 40 mostly start in step 1A, whereas the most starters of patients older than 40 start in step 3C. Step 3B and step 4 were the lowest in all percentages of patient groups.

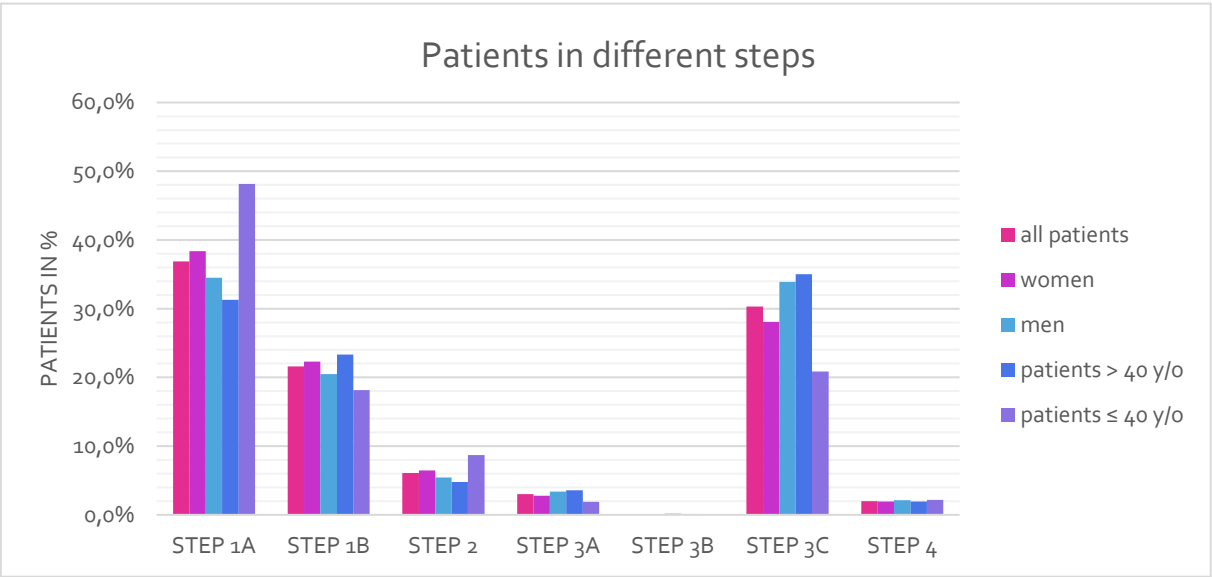


Figure 3: Distribution of patients in different steps on the index date. On the x-axis there are 7 different options presented: step 1A, step 1B, step 2, step 3A, step 3B, step 3C and step 4. \* On the y-axis the patient percentage is quantified.

\*The options are explained in the data and methods section.

### Step-up and step-down

Figure 4 is shown how the switchers (patients stepping up or down) are distributed among the sample size with different groups (men, women, and all patients). Every time interval, the bar of the women was higher than the men and all the patients (~ 3%). **Fout! Verwijzingsbron niet gevonden.** Figure 6 and Figure 5 show the progression of the asthma treatment over a year in diverse asthma patient populations. Both bar charts show that the longer the time passes, the more people discontinue their medication, as seen by the bars of 'stopped' getting higher than the 'same,' 'up' and 'down' bars. These figures also show that the percentage of the population in every category is stepping down and decreases over time. Figure 6 shows that the percentage of asthma patients staying in the same step decreases over time in all categories, while the percentage of asthma patients stepping up increases over time in all categories in one year. However, Figure 5 shows that only a temporary increase of patients stepping up occurs in the first 3 years. When comparing the men (n=14668) to the women (n=23339) in the first person-year (Figure 6), more men stay in the same step of asthma medication than women (~2%). Also, more women are stepping up compared to men (~2%), which happens in the first person-year as in 10 person-years.

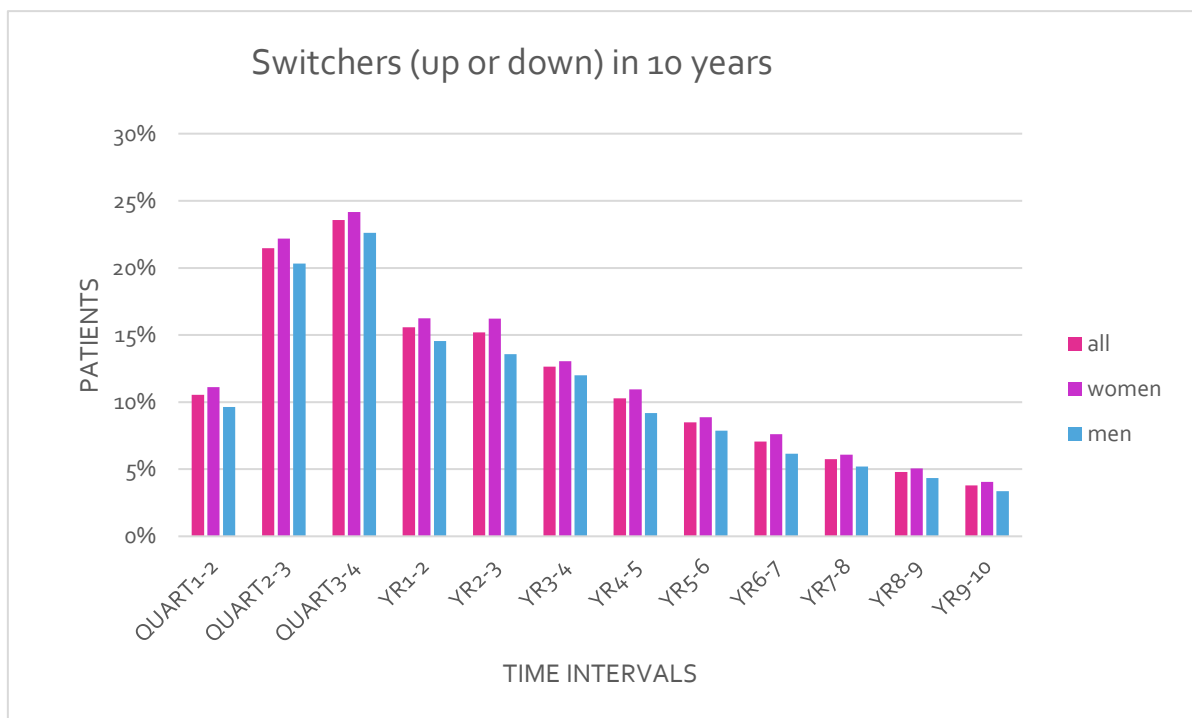


Figure 4: Switchers (step up and down) in 10 years. The first year divided into quarters (1 to 4) followed by every year (1 to 10). Switchers are all patients, only women and only men.



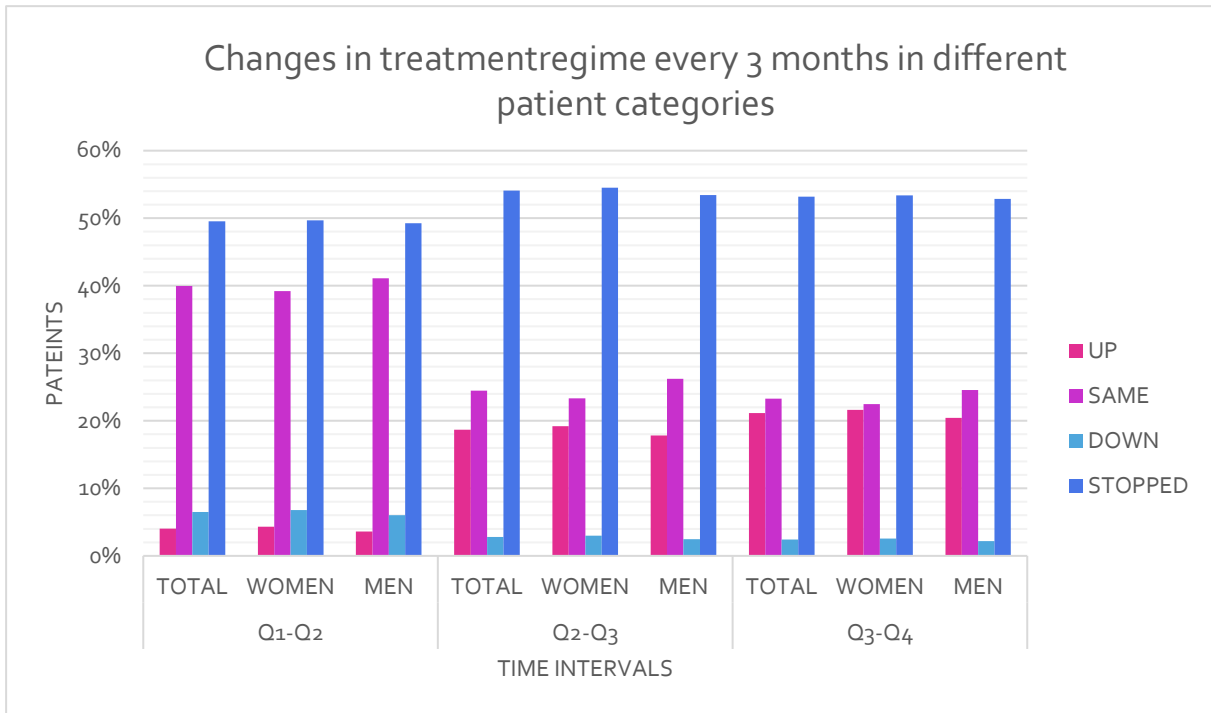


Figure 6: Bar chart showing the progression of the changes in the asthma regime every 3 months for 1 year in different asthma patient populations. On the x-axis the progression of time is shown. Q stands for quarter, matched with a number indicates the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> quarter of the year. The dash in between the Q-numbers specifies the changes made in between the quarters of the first person-year. On the y-axis the patients in percentages displayed.

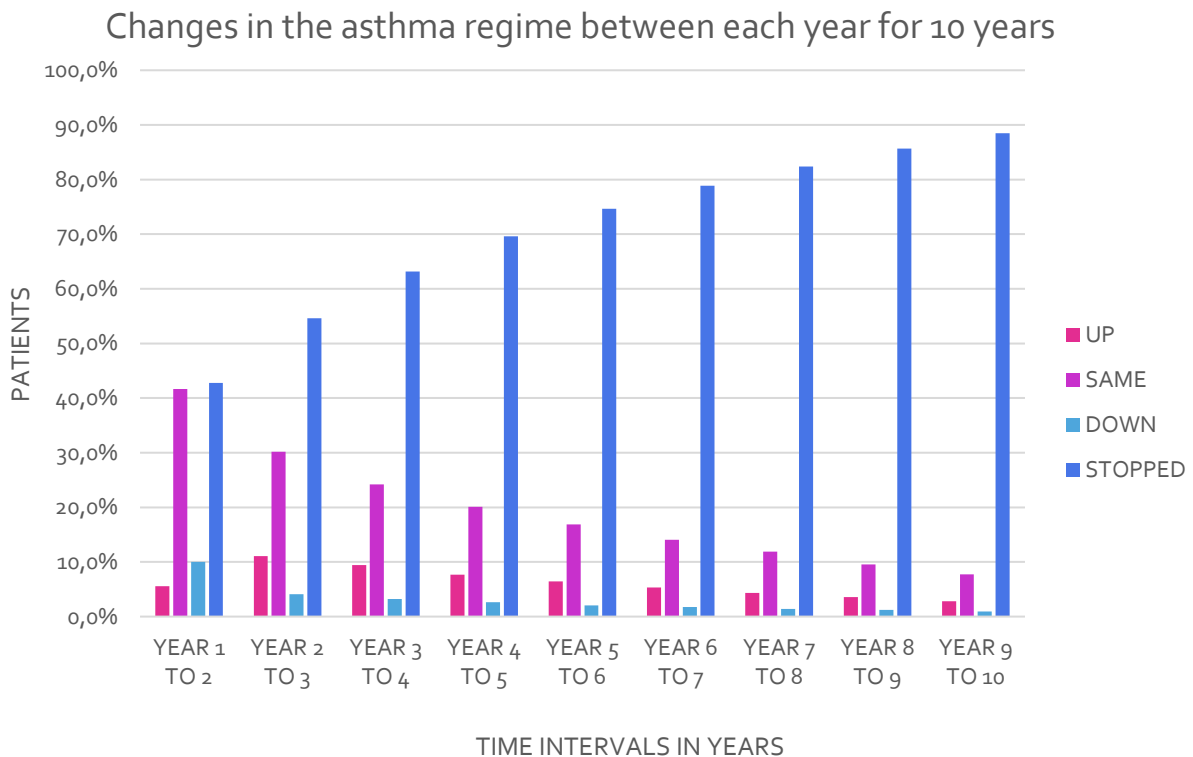


Figure 5: Bar chart showing the progression of the changes in the asthma regime every year for 10 years. On the x-axis the progression of time is shown. On the y-axis the patients in percentages displayed.

Figure 7 is a general visualization of the progression of the asthma treatment of all the asthma patients within their first person-year.

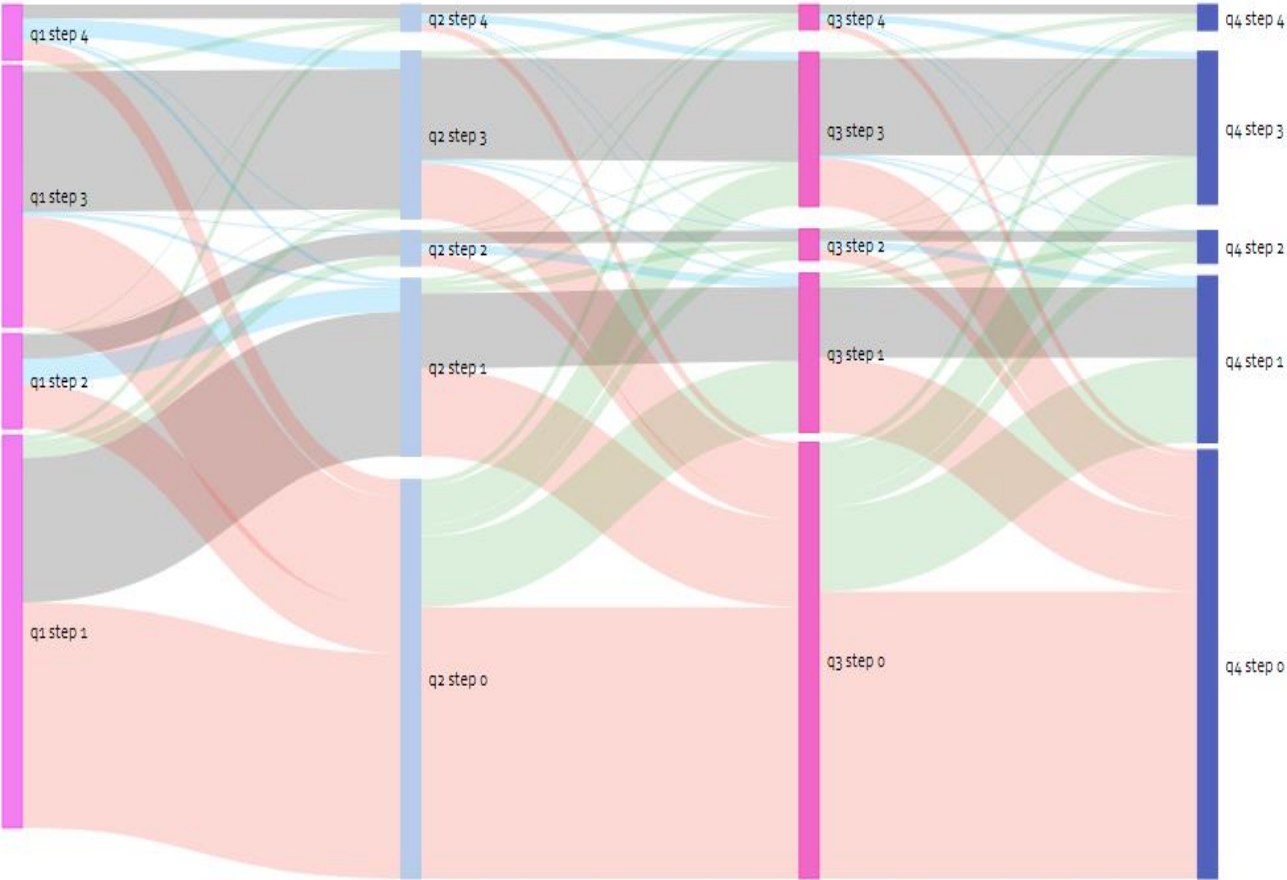


Figure 7: Sankey diagram of patients switching between steps in asthma regimen every three months of the year. Q stands for quarter, matched with a number indicates the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> quarter of the year. Next to every q# there is a step matched: step 0 (discontinuation of asthma treatment), step 1 (only SABA or only ICS use), step 2 (ICS in combination with or simultaneously used with SABA), step 3 (only LABA or LABA in combination with or simultaneously used with SABA/ICS) and step 4 (LABA in combination with or simultaneously used with SABA and ICS). The flows in between the bars are color coded as followed: red - discontinuation of the asthma treatment; green - step up; grey - same step; blue- step down

## Discussion

### Interpretation and comparison with the literature

This longitudinal drug utilization study was done to gain more insight into the asthma treatment regimes and how they are complied with in general practices compared with the theory. The primary objective was to determine to what extent step-up and step-down take place in treating adult asthma patients in the Dutch general practices. The answer to this objective is that step-up and step-down take place. However, step-up takes place more than stepping down (see Figures 4 and 5). This was also predicted in the literary part of the study. The remarkable outcome regarding the treatment progression over time is how many asthma patients discontinued their medication. As seen in Figure 6, most patients discontinuing their medication were those who were in step 1. These patients used only SABA or only ICS (probably) when necessary, as described in the NHG standard.<sup>8</sup> In addition, the inhaled medication used for asthma is also prescribed for patients with asthma-like symptoms, such as shortness of breath, but are not diagnosed with asthma. These patients use the beta-agonists sporadically or only for a short period. Also, there were more steps up than down, which was expected since the NHG standard does not mention stepping down in their asthma guidance.<sup>1,18</sup>

The secondary objective was to determine the distribution of these different steps in asthma treatment among the adult Dutch asthma patient population. When looking at the distribution of the patients in steps 1 through 4, steps 1 and 3 were the two most populated steps by the patients. (As seen in Figure 3 and Figure 7) According to the study of Lambooij et al., patients with asthma mostly use SABA's, ICS and ICS in combination with LABA.<sup>6</sup> The adjusted steps were step 1 (only ICS or only SABA) and step 3 (only LABA/LABA with SABA/LABA with ICS) this outcome was likely. However, Lambooij et al. also stated that patients with COPD mostly use LAMAs, SABAs and a combination of LABA and ICS. This could mean that the patients in the database were not only asthma patients but also COPD patients.

There are many similarities between asthma and COPD treatment regimes. Step 3c, using LABA in combination with ICS, is also prescribed in the second step of the COPD treatment regime. Most patients older than 40 were in this step (see Figure 3). Since the age of onset of COPD is 40 years old, there is a major possibility that those patients are also diagnosed with COPD.<sup>19</sup> In addition to this, the median age of the study sample is around 50 years old. When these patients are followed over 10 years, the median age increases to 60. The older patients are, the greater the chance of developing COPD after asthma and switching to COPD treatment.

Furthermore, the comparison between adult men and women in the inhalation medication prescription patterns for treatment of asthma was researched since the incidence and prevalence are higher in adult women than in men.<sup>2</sup> As seen in Table 5, the median age on the index date of men was 51. According to Chowdhury et al., as men grow old, their testosterone levels decrease, causing the prevalence of asthma to increase.<sup>14,20</sup> Which could explain why the median index date is so high. Also seen in table 2, the median age on the index date of women was 49. According to Townsend et al., adult women diagnosed with asthma in the past have asthma exacerbations at their peak around menopause.<sup>10</sup> This could explain why the median age of women is that high. Groeneveld et al. and Sexton et al. both claimed that women would switch more often by visiting the GP. As seen in Figure 4, the bar of the women in the switchers' sample was higher than the men's, meaning they switch more often than the men.

Sexton et al. pointed out that there is no sex difference in the use of inhalation medication regarding inhaled  $\beta$ -agonists and corticosteroids.<sup>14</sup> When looking at Figures 2 and 3, the largest proportion of women use SABA, and the largest proportion of men use LABA combined with ICS.

### Strengths and limitations

This study has its strength in being able to use live data from the IADB linking prescriptions to doctors as well as patients. The ability to track patients over a certain amount of time is especially helpful in this longitudinal drug utilization study when researching the usage of inhaled asthma medication.

The limitations of this study were the use of ATC codes and the inability to filter patients through diagnosis or indications. Only grouping patients by excluding and including ATC codes is not enough to specify the asthma study population. There were also inconsistent results regarding medication use, questioning whether the pharmacists and the general practitioner had tracked the data correctly. This could explain why asthma treatment discontinues so much (temporary). In addition, in this study, the only prescriptions included were those from the general practitioner. When a patient has severe asthma or an extremely dangerous asthma attack, the patient will visit the pulmonologist and receive a prescription. These prescriptions are not included in this study. This means that the situation is not representative of reality.

Furthermore, the treatment of asthma also consists of oral medication and can be influenced by oral medication, especially oral corticosteroids, and the use of the contraceptive. Another factor influencing asthma medication usage is the general practitioner's preference.<sup>15,21</sup>

### Future research

The recommendation of the future of this study is to account for the dosages instead of the drugs themselves since the NHG standard also mentions the dosage. Also, the age of the adult patients should be considered regarding COPD by adjusting the age limit to 16-40 years old to distinguish between asthma and COPD. Additionally, there should be the question as to why this many people stop using asthma medication.

## Conclusion

When summarizing the results, the study concludes that steps up and down occur in the treatment regime. Furthermore, there are no differences in asthma medication usage in men and women. However, there was a difference in the percentages of switchers, where the women switched more often than the men. There was also a difference in asthma inhaled drug use of patients younger than 40 (SABA) and patients older than 40 (ICS in combination with LABA). SABA was the most used when evaluating the frequency of asthma inhalation medication. In the future, more research must be done by adjusting the age limit and being more specific in selecting the study sample regarding daily defined dosages and how many people have stopped their asthma medication.

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