Tampere University

IIDA VÄHÄTALO

Medication in Adult-Onset Asthma

Focus on adherence, inhaled corticosteroids, and short-acting β_2-agonists

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ACADEMIC DISSERTATION
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ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Seinäjoki Central Hospital, Department of Respiratory Medicine
Finland

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PunaMusta Oy – Yliopistopaino
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To my grandmothers

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The following is a quote from the foreword of my master's thesis: "At the beginning of my studies, a picture was taken, where I hold two test tubes in my hands. The picture was labeled "Professional, one day," and I'm feeling that the day is getting closer."

Nokia, March 2024

Iida Vähätalo

ABSTRACT

Asthma is a chronic inflammatory disease affecting over 300 million people worldwide, presenting an enormous burden for society and individuals. As asthma rarely remits, especially in patients with adult-onset asthma, treating asthma involves long-term medication. Unfortunately, previous studies have shown that patients' adherence to treatment is suboptimal, with adherence rates usually being under 50%. However, studies evaluating adherence to asthma controller medication (inhaled corticosteroids) have typically been short-term follow-ups, and little is known about the variation of medication adherence between and within persons in long-term treatment.

The present study aims to evaluate medication use, adherence to controller medication (inhaled corticosteroids), and its variability in long-term treatment in real-life new-onset adult asthma patients. Further aims were to assess the factors associated with non-controlled asthma and investigate the relationship between patients' controller and reliever medications.

The present study examined patients in the Seinäjoki Adult Asthma Study (SAAS), a 12-year single-center follow-up study of patients with new-onset adult asthma (n=203). Patients' asthma-related visits and prescribed controller medication over the study were collected from medical records. The information on dispensed inhaled corticosteroids (ICS) (controllers) and short-acting β_2-agonists (SABA) (relievers) was obtained from the Finnish Social Insurance Institution, which records all reimbursed asthma medication purchases from any Finnish pharmacy. By comparing the prescribed doses to dispensed doses ([µg dispensed/µg prescribed]×100), assessing individual real-life ICS medication adherence annually and cumulatively during a 12-year follow-up period was possible. All doses of dispensed SABAs during the 12-year follow-up were counted; the sum was divided by 150 to express SABA use as standard canisters of 150 doses. High SABA use was defined as ≥36 canisters in 12 years, corresponding to an average of ≥3 dispensed canisters/year. Asthma control was evaluated after 12 years of treatment according to the Global Initiative for Asthma 2010 guideline.

The average 12-year adherence to ICS medication was relatively high (69%) in patients with new-onset adult asthma. When patients were grouped based on their

level of asthma control, higher ICS doses were prescribed to patients with uncontrolled asthma compared to patients with controlled and partially controlled asthma. The mean 12-year adherence to ICS was higher in patients with non-controlled asthma (76%) than in patients with controlled asthma (63%). Among patients with non-controlled asthma, those with a lower 12-year adherence (<80%) had more rapid decline in forced expiratory volume in 1 s than those with better adherence (≥80%). High SABA use was infrequent in patients with confirmed adult-onset asthma, as only 10% of the patients were classified as high SABA users during the study. Obesity (body mass index [BMI] ≥30) and high Airways Questionnaire 20 symptom scores at baseline predicted high long-term SABA use.

The current study's results show that patients with adult-onset asthma have moderate adherence to long-term ICS treatment, and high use of reliever medication is infrequent. Lower adherence (<80%) was associated with more rapid lung function decline in the long term, underscoring the importance of each patient's adherence to treatment. High adherence to high-dose ICS treatment was insufficient to improve asthma control among non-controlled patients. A possible explanation could be the lower degree of Type 2 inflammation, resulting in reduced efficacy of ICS. Therefore, tapering the ICS doses should be considered, and focusing on more individualized treatment approaches, pharmacological and non-pharmacological, must be emphasized in adult-onset asthma patients.

TIIVISTELMÄ

Astma on krooninen tulehduksellinen sairaus, jota esiintyy maailmanlaajuisesti yli 300 miljoonalla ihmisellä, muodostaen merkittävän taakan sekä yhteiskunnille että yksilöille. Aikuisiällä alkaneessa astmassa saavutetaan harvoin remissio, minkä vuoksi sitä hoidetaan pitkäaikaislääkityksellä. Aiemmat tutkimukset ovat osoittaneet, että potilaiden hoitoon sitoutuminen ei ole riittävää, sillä potilaat käyttävät alle 50 % heille määrätyistä hoitavista lääkkeistä (inhalaatiosteroidi). Sitoutumista inhalaatiosteroidihoitoon on kuitenkin aiemmin tutkittu vain lyhyissä seurantatutkimuksissa, minkä vuoksi ei tiedetä, miten yksilön lääkehoitoon sitoutuminen vaihtelee pitkäaikaisessa hoidossa tai toisaalta eroaako pitkäaikaiseen hoitoon sitoutuminen yksilöiden välillä.

Tämän väitöskirjatutkimuksen tavoitteena on selvittää aikuisiällä alkanutta astmaa sairastavien potilaiden lääkekäyttöä, heidän sitoutumistaan inhalaatiosteroidihoitoon ja hoitoon sitoutumisen vaihtelua pitkäaikaisessa seurannassa. Lisäksi tavoitteena on arvioida tekijöitä, jotka liittyvät huonossa hoitotasapainossa olevaan astmaan ja selvittää missä suhteessa potilaat käyttävät hoitavaa ja avaavaa astmalääkettä.

Väitöskirjan aineisto koostuu 12-vuotisen Seinäjoki Adult Asthma Study (SAAS) -seurantatutkimuksen potilaista (n=203), joilla diagnosoitiin uusi aikuisiällä alkanut astma. Potilaiden astmaan liittyvät käynnit ja lääkitystiedot kerättiin sairaskertomuksista. Apteekista toimitettujen hoitavien (inhalaatiosteroidi) ja nopeavaikutteisten avaavien (β_2-agonisti) lääkkeiden ostotiedot saatiin Kansaneläkelaitokselta, jonka rekisteriin tallentuvat kaikki suomalaisista apteekeista tehdyt korvatut astmalääkeostot. Vertaamalla potilaille määrättyjä annoksia potilaan apteekista hakemiin määriin ([ug toimitetut / ug määrätyt]x100) oli mahdollista arvioida yksittäisen potilaan sitoutumista inhalaatiosteroidihoitoon vuosittain sekä kumulatiivisesti 12 vuoden seurannan aikana. Potilaiden nopeavaikutteisten avaavien lääkkeiden ostot 12 vuoden seurannan ajalta laskettiin yhteen ja saatu summa jaettiin 150, jotta se ilmaisee vakioinhalaattorin kokoa, joka sisältää 150 annosta. Runsaan avaavan lääkkeen käytön raja-arvoksi määritettiin vähintään 36 ostettua vakioinhalaattoria 12 vuoden seurannan aikana, mikä vastaa keskimäärin vähintään kolmea inhalaattoria vuodessa. Potilaiden astman hoitotasapaino määritettiin

kansainvälisen astmahoitosuosituksen (the Global Initiative for Asthma 2010) mukaan.

Uutta aikuisiällä alkanutta astmaa sairastavat potilaat sitoutuivat suhteellisen hyvin (keskimäärin 69 %) 12 vuoden inhalaatiosteroidihoitoon. Kun potilaat ryhmiteltiin astman hoitotasapainon perusteella, huonossa hoitotasapainossa oleville määrättiin korkeampia inhalaatiosteroidiannoksia verrattuna osittaisessa tai hyvässä hoitotasapainossa oleviin potilaisiin. Potilaat, joiden astma ei ollut hoitotasapainossa, sitoutuivat inhalaatiosteroidihoitoonsa keskimäärin paremmin (76 %) 12 vuoden aikana kuin hyvässä hoitotasapainossa olevat potilaat (63 %). Potilaista niillä, joiden astma ei ollut hoitotasapainossa ja jotka sitoutuivat inhalaatiosteroidihoitoon huonommin (<80 %), keuhkofunktio (uloshengityksen sekuntikapasiteetti) laski nopeammin kuin paremmin hoitoon sitoutuneilla (≥80 %) potilailla. Aikuisiällä alkanutta astmaa sairastavista potilaista vain harva (10 %) käytti paljon nopeavaikutteista avaavaa lääkettä. Korkeat oirepisteet kansainvälisesti käytetyssä kyselyssä (Airways Questionnaire 20) ja lihavuus (painoindeksi ≥30) diagnoosikäynnillä ennustivat pitkäaikaista runsasta avaavan lääkkeen käyttöä.

Tämän väitöskirjatutkimuksen tulokset osoittavat, että aikuisiällä alkanutta astmaa sairastavien potilaiden sitoutuminen pitkäaikaiseen inhalaatiosteroidihoitoon oli kohtalaisen hyvällä tasolla ja toisaalta nopeavaikutteisen avaavan lääkkeen runsas käyttö oli harvinaista. Huonompi hoitoon sitoutuminen (<80 %) liittyi nopeampaan keuhkojen toiminnan heikkenemiseen pitkällä aikavälillä, mikä korostaa potilaan inhalaatiosteroidihoitoon sitoutumisen merkitystä. Toisaalta, vaikka huonossa hoitotasapainossa olevat potilaat sitoutuivat hyvin korkea-annoksiseen inhalaatiosteroidihoitoon, se ei ollut riittävä parantamaan näiden potilaiden astman hallintaa. Mahdollinen selitys voi olla matalampi tyypin 2 tulehduksen aste, minkä vuoksi vaste inhalaatiosteroideille jää vähäisemmäksi. Näin ollen tälle potilasryhmälle tulisi harkita inhalaatiosteroidiannoksien pienentämistä ja keskittyä yksilöllisempien farmakologisten ja ei-farmakologisten hoitovaihtoehtojen kehittämiseen.

CONTENTS

List of Figures

List of Tables

ABBREVIATIONS

AQ20	Airways questionnaire 20
ACT	Asthma control test
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BD	Bronchodilator
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
COPD	Chronic obstructive pulmonary disease
EMD	Electronic monitoring device
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
hsCRP	High sensitivity C-reactive protein
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
IQR	Interquartile range
IRR	Incidence rate ratio
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
$Max_{0\text{-}2.5}$	The point where the maximum lung function in FEV_1 during the first 2.5 years after the diagnosis of asthma was achieved
MPR	Medication possession ratio
OCS	Oral corticosteroid
PCD	Proportion of days covered
PEF	Peak expiratory flow
PKA	Protein kinase A
R03	Drugs for obstructive diseases
SAAS	Seinäjoki Adult Asthma Study

SABA	Short-acting β_2-agonist
SD	Standard deviation
SEM	Standard error of the mean
SII	Finnish Social Insurance Institution
Th2	T-helper type 2 lymphocytes

ORIGINAL COMMUNICATIONS

I Vähätalo I, Ilmarinen P, Tuomisto LE, Niemelä O & Kankaanranta H. (2018). Inhaled corticosteroids and asthma control in adult-onset asthma: 12-year follow-up study. *Respiratory Medicine*, *137*, 70–76. https://doi.org/10.1016/j.rmed.2018.02.025

II Vähätalo I, Ilmarinen P, Tuomisto LE, Tommola M, Niemelä O, Lehtimäki L, Nieminen P & Kankaanranta H. (2020). 12-year adherence to inhaled corticosteroids in adult-onset asthma. *ERJ Open Research*, *6*(1), 00324-2019. https://doi.org/10.1183/23120541.00324-2019

III Vähätalo I, Kankaanranta H, Tuomisto LE, Niemelä O, Lehtimäki L & Ilmarinen P. (2021). Long-term adherence to inhaled corticosteroids and asthma control in adult-onset asthma. *ERJ Open Research*, *7*(1), 00715-2020. https://doi.org/10.1183/23120541.00715-2020

IV Vähätalo I, Lehtimäki L, Tuomisto LE, Karjalainen J, Niemelä O, Ilmarinen P & Kankaanranta H. (2022). Long-Term Use of Short-Acting β_2-Agonists in Patients With Adult-Onset Asthma. *The Journal of Allergy and Clinical Immunology: In Practice*, *10*(8), 2074–2083.e7. https://doi.org/10.1016/j.jaip.2022.03.027

AUTHOR'S CONTRIBUTION

The author of this thesis was the main author in all publications (I-IV). The author's contributions in each publication were as follows:

I The author analyzed and interpreted the data and wrote the manuscript with the help of supervisors and co-authors. The author led the manuscript writing process and submission as the corresponding author.

II The author collected and analyzed the data and wrote the manuscript with the help of supervisors and co-authors. The author made the figures and led the manuscript writing process and submission as the corresponding author.

III The author collected and analyzed the data and wrote the manuscript with the help of supervisors and co-authors. The author interpreted the data, made the figures, and led the manuscript writing process and submission as the corresponding author.

IV The author collected and analyzed the data and wrote the manuscript with the help of supervisors and co-authors. The author made the figures and reviewed and edited the manuscript. The author led the manuscript writing process and submission as the corresponding author.

1 INTRODUCTION

Asthma is a heterogenous disease manifesting usually as chronic airway inflammation. Since over 300 million adults and children suffer from asthma worldwide, the disease burden on individuals' quality of life and the economic sustainability of society are enormous. Treating asthma is remarkable in preventing exacerbations, enhancing patients' quality of life, and decreasing health care resource utilization (Engelkes et al. 2015). As asthma is a disease with chronic inflammation, inhaled corticosteroids (ICS) are the basis of asthma treatment, reducing airway inflammation and hyperresponsiveness, improving lung function, controlling symptoms, and reducing exacerbations (Derendorf et al. 2006; GINA 2021; Ye et al. 2017). Unfortunately, the level of ICS use is not as good as it was hoped to be.

Regular use of ICS is the cornerstone for nearly all patients with asthma. However, adherence to the treatment has been suboptimal, meaning only 30%-70% of medication is taken as prescribed. Reductions in symptom control and quality of life, a decline in lung function, asthma-related exacerbations, and increased costs are possible consequences of poor adherence (Bidwal et al. 2017; Dima et al. 2019; Engelkes et al. 2015; Kandane-Rathnayake et al. 2009; Mäkelä et al. 2013; Suissa et al. 2001). Despite the chronic nature of the disease, most of the studies have evaluated patients' adherence to treatment only in short-term periods ranging from months to up to one year. Moreover, the medication use of patients with adult-onset asthma has rarely been studied. The disparity in measures used to determine adherence, the selection of study populations, the uncertainty of asthma diagnosis, and disease onset are factors being acknowledged as possible explanations of variations in reported adherence levels. For example, data settings such as insurance databases have not reached the whole asthma population, and the studies have usually ruled out smokers or patients with concomitant chronic obstructive pulmonary disease (COPD). There is a considerable need for long-term studies in general asthma populations to confirm how physicians follow the treatment guidelines and how longitudinal manners of medication use are associated with a patient's disease.

The present series of studies aimed to investigate long-term medication adherence in a clinical setting to real-life patients with adult-onset asthma. The study

also aimed to examine the factors related to poor long-term adherence to asthma medication and evaluate the relationship between patients' use of controller and reliever medications.

2 REVIEW OF THE LITERATURE

2.1 Description of asthma

Asthma is a chronic disease usually manifesting as the inflammation of airways in children and adults; asthma affects 1%-18% of the global population, the prevalence being around 10% in Finland (Honkamäki et al. 2019; Innes Asher et al. 2020; Pakkasela et al. 2020; To et al. 2012). Typical asthma symptoms are wheezing, dyspnea, cough, and mucus production, all of which vary in duration and intensity (GINA 2021). However, airway hyperresponsiveness to direct or indirect stimuli and chronic inflammation usually persist. Respiratory infections, exposure to irritant inhaled particles or allergens, weather change, and exercise often trigger variations in symptoms and bronchial obstruction. These variations may be absent for long periods, but patients with seemingly few or no symptoms are still at risk, even of severe exacerbations, which are episodic flare-ups of asthma. Moreover, subject-related factors such as poor adherence to treatment, poor inhaler technique(s), and comorbidities like obesity, rhinosinusitis or gastroesophageal reflux may induce variations in symptom control.

2.2 Asthma phenotypes

Asthma is a heterogeneous disease manifesting as various demographic, clinical and pathophysiological characteristics recognized as phenotypes. The prevalent perception has been that the onset of asthma in childhood strongly associated with allergic conditions. However, clustering has revealed that instead of asthma mainly being the disease of young boys with allergies, different clinical presentations distinguish many phenotypes of asthma, with the age of disease onset being an important discriminator of these variations (GINA 2021; Ilmarinen et al. 2015; Ilmarinen et al. 2017; Lefaudeux et al. 2017; Moore et al. 2010; Wenzel 2012). Besides adult- and childhood-onset asthma, other reported phenotypes are obesity-related asthma, allergic asthma, and smoking asthma (GINA 2021; Ilmarinen et al. 2017; Lefaudeux et al. 2017; Wenzel 2012). The phenotype of adult-onset (or late-onset)

asthma has been recognized as asthma that initially develops in the patient in their adult lives and typically manifests in non-atopic females with poorer response to ICS therapy (GINA 2021; Ilmarinen et al. 2017; Tuomisto et al. 2016). Current research from the USA and Finland has revealed that asthma diagnosed in adulthood is a common and dominant phenotype among women aged 35-40 (Honkamäki et al. 2019; Kankaanranta et al. 2017; Sood et al. 2013). Compared to childhood-onset asthma, adult-onset asthma rarely remits, and only 1.5%-11% of adult-asthma patients are shown to obtain remission (Almqvist et al. 2020; Honkamäki et al. 2021; Tuomisto et al. 2016).

Despite the distinct features of adult- and childhood-onset asthma, the genetic risk factors are seemingly shared and distinct, although the immune-mediated mechanism drives disease progression in both phenotypes (Pividori et al. 2019). However, no strong relationship between the clinical pattern and pathophysiological mechanism exists; further evaluation of phenotypes is essential to achieve more targeted and personalized approaches to asthma treatment. Non-rhinitic asthma, smoking-related asthma, late-onset eosinophilic asthma, obesity-related asthma and early-onset atopic adult asthma have been suggested to be the phenotypes among patients with adult-onset asthma (Ilmarinen et al. 2017; Lefaudeux et al. 2017; Wenzel 2012).

2.3 Pathophysiology of asthma

Chronic inflammation induced by different stimuli, including allergens, microbes, tobacco smoke, obesity, exercise, or cold air, causes the infiltration and activation of immune cells (e.g., as dendritic cells, eosinophils, neutrophils, lymphocytes, innate lymphoid cells, and mast cells) in asthmatic airways (Hammad and Lambrecht 2021). Inflammation leads to airway edema, mucus hypersecretion, mucus plugging and finally reduction in the diameter of the airways. Commonly, airflow obstruction is reversible, but in the most severe forms of asthma, the inflammation causes fixed airway obstruction and airway remodelling, which consists of airway smooth muscle hyperplasia, leading to increased smooth muscle mass and thickening of the bronchial wall (Camoretti-Mercado et al. 2021; Dunican et al. 2018; Hammad and Lambrecht 2021).

Characteristically, raised levels of cytokines include interleukin (IL)-4, IL-5, and IL-13 in traditional T-helper type 2 (Th2) driven inflammation (Figure 1). However, recent findings have revealed that eosinophilia may not always be allergy-driven but

due to innate immunity responses (e.g., group 2 innate lymphoid cell-mediated); therefore, the concept of Th2 high asthma is broadened to Type 2 high asthma (Ebbo et al. 2017; Sze et al. 2020). Moreover, Type 2 low asthma was suggested to even be as common as Type 2 high asthma, but the mechanisms are not well understood (Hammad and Lambrecht 2021). Potential pathobiological mechanisms for Type 2 low asthma are neutrophilic inflammation, paucigranulotic inflammation, or systemic inflammation in association with metabolic dysfunction and obesity (Hammad and Lambrecht 2021; Lachowicz-Scroggins et al. 2019; Peters et al. 2016; Tliba and Panettieri 2019).

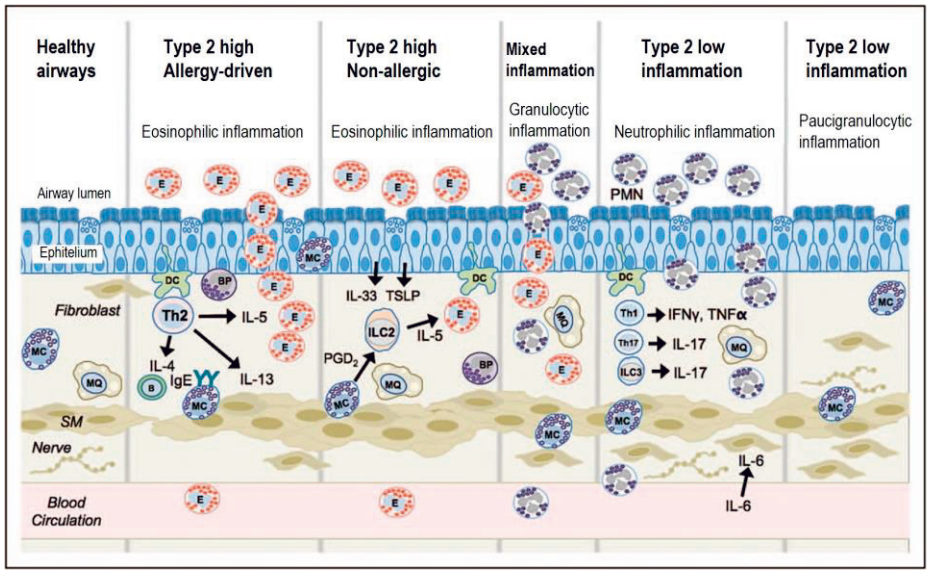

Figure 1. Representation of the pathobiological mechanisms of allergic, non-allergic, type 2 low and paucigranulocytic inflammation (Modified from Erjefält 2019)

2.4 Asthma diagnosis

In Finnish recommendations, an asthma diagnosis is based on identifying variability or reversibility in the expiratory airflow limitation of a patient and recognizing asthmatic respiratory symptoms (Current Care Guidelines 2022) (Table 1). The diagnostic criteria in the Global Initiative for Asthma (GINA) report are close to the Finnish recommendations but not exactly the same (Current Care Guidelines 2022; GINA 2021). In Finnish recommendations, lung function measurements are

typically performed with spirometry. Still, the diagnosis can also be made with peak expiratory flow (PEF) monitoring, bronchial challenge test, or indirect bronchial challenge test, such as an exercise challenge test.

Table 1. Diagnostic lung function tests and Finnish criteria for diagnostic result

Diagnostic feature	Test feature	Diagnostic result
Diurnal variability in PEF follow-up	Twice-daily PEF follow-up before and after bronchodilator over 2 weeks	At least three times ≥20% and ≥60 l/min variability before bronchodilator (comparing morning and evening measurements)
Repeated reversibility in PEF follow-up	Twice-daily PEF follow-up before and after bronchodilator over 2 weeks	At least three times ≥15% and ≥60 l/min response to bronchodilator
Reversibility in spirometry	Spirometry	Increase in FEV_1 or FVC ≥ 12% and ≥200 ml after bronchodilator
Bronchial hyperresponsiveness	Methacholine challenge test	Confirms moderate or strong hyperactivity (provocative dose causing 20% FEV_1 decline ≤ 0.6 mg)
	Exercise, mannitol or eucapnic voluntary hyperventilation challenge test	FEV_1 fall after test ≥15% from baseline
Reversibility in spirometry or PEF in response to a trial with oral or inhaled glucocorticoids	Anti-inflammatory treatment for example inhaled beclomethasone or budesonide 800-1600 µg for 8-12 weeks or oral prednisolone 20-40 mg/day for 5-7 days	Significant increase in lung function test after treatment. (In spirometry FEV_1 increases ≥15% and 200 ml, or average PEF increases ≥20% and ≥60 l/min when comparing between before and after treatment)

FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, PEF; peak expiratory flow, SABA; short-acting β_2-agonist (Current Care Guidelines 2022)

2.5 Asthma therapy

Asthma medication can be divided into controllers (medication contains ICS), relievers (symptom-relieving medication), and add-on therapies (for more difficult-to-control symptoms). Managing asthma consists of continuously assessing the patient's symptom control, comorbidities, inhaler technique, and adherence to treatment; adjusting the medication and non-pharmacological strategies based on the assessments; and, finally, reviewing the patient's symptoms, side effects, exacerbations, and lung function (GINA 2021). Based on the symptom control and evaluation of future risks for exacerbations, the treatment step is selected; with regular reviews of asthma, medication is increased or decreased as needed. Since smoking and obesity have been associated with more difficult-to-control asthma, non-pharmacological approaches such as smoking cessation, weight management, and physical activity should be part of asthma therapy (Ilmarinen et al. 2021; Peters et al. 2018; Polosa et al. 2011; Tommola et al. 2019). Moreover, instructing correct inhaler use, reviewing the inhalation technique, and adhering to medication are factors to consider regarding pharmacological treatment (GINA 2021; Haahtela et al. 2001).

ICS are the basis of asthma treatment, reducing airway inflammation; thus, ICS is part of all treatment steps of asthma management. Short-acting β_2-agonists (SABA), also known as rescue medication, relieve the acute symptoms of asthma and combined with the ICS, mild to moderate symptoms can be managed. Recent findings have also shown that a combination of formoterol (long-acting β_2-agonists [LABA]) and low-dose ICS taken as needed is as effective in controlling mild asthma as maintenance ICS therapy (GINA 2021; Reddel et al. 2021). In patients with mild asthma, low dose ICS-formoterol can be used as controller or reliever medication (GINA 2021). If symptoms persist despite an adequate amount of ICS or as-needed ICS-formoterol therapy, a regular ICS-LABA combination can be used. For patients with severe asthma and whose asthma remains out of control despite regular ICS-LABA combination therapy, add-on therapies can be considered. Leukotriene receptor antagonists (LTRA) and long-acting muscarinic antagonists (LAMA) are the most used add-on therapies, but for the most severe asthma, oral corticosteroids, azithromycin, theophylline, or biologic medications can be used (Current Care Guidelines 2022, GINA 2021).

2.5.1 Goals of asthma therapy

Asthma management aims to achieve good symptom control, minimize the risk of losing lung function, prevent/avoid exacerbations, and maintain normal activity levels (physical activity and everyday capability). Practical actions to assess asthma therapy are screening tools such as the Asthma Control Test (ACT), with higher scores indicating better asthma control (Nathan et al. 2004). In the GINA report, assessing asthma control is based on how asthma symptoms are controlled (well-controlled, partially controlled, and uncontrolled) and to evaluate possible risk factors increasing poor asthma outcomes (GINA 2021). When asthma is well-controlled, reducing the medication is recommended to detect the patient's lowest treatment that controls symptoms and exacerbations (GINA 2021, Hagan et al. 2014). Conversely, if asthma remains uncontrolled and adherence and inhaler technique have been assessed, stepping up should be considered for better asthma control.

2.5.2 Inhaled corticosteroids

ICS reduce airway inflammation and hyperresponsiveness, improve lung function, increase symptom control, and prevent or reduce exacerbations (Derendorf et al. 2006; Ye et al. 2017). The effect of glucocorticoids is mediated through mineralocorticoid (Type I) and glucocorticoid receptors (Type II), but ICS available on the market can bind uniquely to Type II receptors (Adcock and Mumby 2017; Matera et al. 2019). From Type II receptor forms, only glucocorticoid receptor alpha binds glucocorticoids and mediates the actions of glucocorticoids (Barnes 2011; Matera et al. 2019). Glucocorticoid binding to the receptor activates anti-inflammatory genes; suppresses inflammatory gene transcription, Th2 cells, and cytokines; and inhibits the expression of inflammatory genes (Barnes 2011). At the cellular level, corticosteroids induce apoptosis of immune cell types, reducing the number of eosinophils, T lymphocytes, mast cells, and dendritic cells (Adcock and Mumby 2017). The differences between glucocorticoids appear in receptor affinity and selectivity and the pharmacokinetic properties of the drugs (Matera et al. 2019).

The current evidence recommends using as low ICS doses as possible to manage symptoms effectively, yet to avoid the side effects (Table 2). Long-term use of ICS at high doses has been associated with more severe adverse events. Local side effects of pharyngitis, dysphonia, oropharyngeal candidiasis, and hoarseness may be prevented by rinsing the mouth after inhalation, changing the dosing, changing the

formulation from dry powder to aerosol or using a spacer (Ye et al. 2017). Potential systemic side effects depend on the amount of ICS absorbed into the systemic circulation appearing as reduced bone mineral density and osteoporosis, hypothalamic–pituitary–adrenal axis suppression, growth suppression in children, increased infections, increased bruising, psychiatric effects, cataracts, and glaucoma (Kelly and Nelso 2003; Savas et al. 2020; Suissa et al. 2013; Ye et al. 2017).

Table 2. Daily doses of ICS for adults and adolescents (12 years and older)

Formulation	Drug	Daily dose (µg)		
		Low	Medium	High
powder	Beclomethasone dipropionate	0-500	>500-1000	>1000
solution	Beclomethasone dipropionate*	0-200	>200-400	>400
powder	Budesonide	0-400	>400-800	>800
solution	Ciclesonide	0-160	>160-320	>320
powder	Fluticasone furoate	0-100	0-100	200
powder	Fluticasone propionate	0-250	>250-500	>500
suspension	Fluticasone propionate	0-250	>250-500	>500
powder	Mometasone furoate*	0-200	0-400	>400

*Daily doses are dependent on the used inhaler, causing variation in daily doses despite the same active substance (Current Care Guidelines 2022; GINA 2021)

2.5.3 β_2-agonists

β_2-agonists are effective bronchodilators, rapidly relieving asthma symptoms by relaxing airway smooth muscle. The bronchodilatory effects of β_2-agonists are mediated via G-protein-linked β_2-adrenergic receptors in airway smooth muscle cells (Barnes 2011; Cazzola et al. 2013). The binding of the β_2-agonist to the β_2-adrenergic receptor activates adenylyl cyclase via G protein, increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP), activating protein kinase A (PKA). PKA phosphorylates regulatory target proteins within the cell, causing inhibition of myosin light chain kinase, preventing contraction, and relaxing contracted smooth muscle. However, the classical cAMP signaling pathway seems more complex than considered, but relatively little is known regarding these new pathways in airway cells (Billington and Hall 2012).

β_2-agonists can be divided based on their pharmacodynamic half-lives into SABAs, LABAs, and ultra-LABAs (Billington et al. 2017; Cazzola et al. 2013). SABAs provide rapid as-needed symptom relief (onset of action <5 minutes); the duration of action is 4-6 hours. LABAs and ultra-LABAs act in 5-15 minutes but provide sustained relief of symptoms due to their long duration of action being 12 hours in LABAs and even 24 hours in ultra-LABAs.

Prolonged or repetitive use of β_2-agonists (SABA or LABA) attenuates bronchodilator response due to the downregulation of β_2-receptors, a phenomenon called desensitization, leading to losing some of the effects of β-agonists. However, corticosteroids compensate for the downregulation of β_2-receptors by increasing the β_2-receptor gene transcription, resulting in a higher expression of cell surface receptors (Barnes 2011). Monotherapy with LABA or over-reliance on SABA, i.e., high use of SABA with insufficient use of ICS, neglects the treatment of airway inflammation and the downregulation of β_2-receptors, increasing the risk for adverse outcomes of asthma. Monotherapy with LABAs and SABAs has been associated with an increased risk of severe exacerbations and asthma mortality; therefore, LABAs should be taken only with concomitant ICS therapy (Busse et al. 2018; Liao et al. 2010; Weatherall et al. 2010, Suissa and Ernst 1994, Nwaru et al. 2020, Stanford et al. 2012). Although the safety concerns towards β-agonists have been acknowledged for decades, steps to decrease the use of SABAs have been considered more recently; for instance, as-needed ICS-formoterol (ICS-LABA) has been recommended as a primary therapy instead of as-needed SABA for patients with mild asthma (GINA 2021; Hardy et al. 2019; Jenkins et al. 2020; O'Byrne et al. 2018).

2.5.4 High use of short-acting β_2-agonists

The rapid action and relief of symptoms are the preferred effects of SABAs, but patients may rely on SABAs instead of treating airway inflammation with ICS (Blakeston et al. 2021; Vervloet et al. 2020). Definitions such as "high use," "overuse," "excessive use," "inappropriate use," and "over-reliance" on SABA have been used to describe patients' reliance on SABA. Various thresholds have also been adopted to quantify the use of SABA, and there is room for more convergent definitions and terminologies (Amin et al. 2020). Increased risks for adverse asthma outcomes such as exacerbations, intensive care unit admissions, and poor asthma control have been associated with the annual use of ≥3 canisters of SABA, with the

risks becoming even likelier as the number of used SABA canisters increases annually (Figure 2) (Hull et al. 2016; Nwaru et al. 2020; Patel et al. 2014).

Some studies have shown that patients prefer SABA therapy instead of taking ICS, i.e., patients rely too much on SABA. However, in most of the previous research, the patients were categorized as SABA overusers solely based on their use of SABA. If the use of controller medication has not been assessed, all possible reasons leading to higher demand for SABA, like severe asthma or poor asthma control, have not been considered; therefore, overuse seems an inaccurate definition for these patients potentially being symptomatic and needing SABA, despite using controller medication. Moreover, high SABA use has recently been evaluated in register-based cross-sectional studies (Bloom et al. 2020; FitzGerald et al. 2017; Lugogo et al. 2021; Nwaru et al. 2020), where the diagnosis of asthma may not be clinically confirmed but based on a diagnosis code in the database or asthma medication purchases (e.g., two dispensed Anatomical Therapeutic Chemical (ATC) code R03 [Drugs for obstructive diseases] medications in a year). Thus, patients without confirmed diagnosis of asthma may be included in study populations potentially increasing the number of SABA canisters dispensed. Moreover, high SABA use has, in previous studies, been assessed from prescription data, thus potentially overestimating the use of SABA as the prescribed SABA does not guarantee that patient picks up the medication from pharmacy (Hull et al. 2016; Vervloet et al. 2020). No clinical studies with long-term follow-up showing the negative impact of high SABA use in patients with a confirmed diagnosis of asthma have been published.

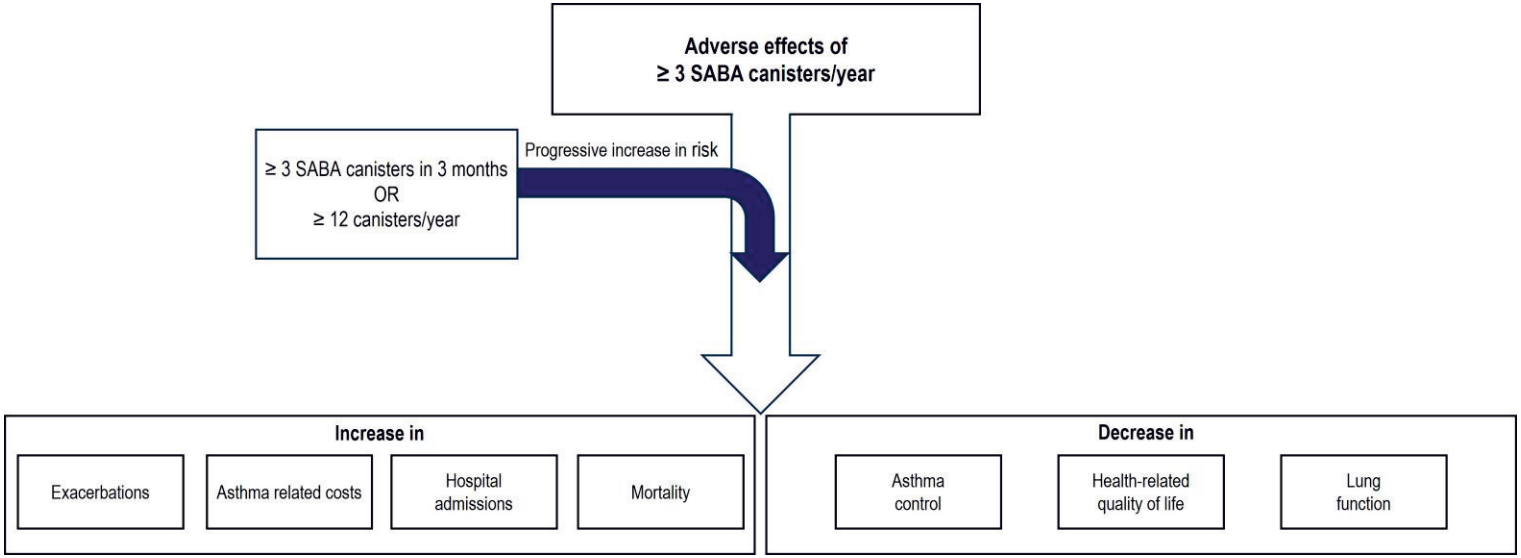

Figure 2. Adverse outcomes related to high use of SABA (Azzi et al. 2019; FitzGerald et al. 2017; Gerald et al. 2015; Gonem et al. 2019; Hull et al. 2016; Lugogo et al. 2021; Noorduyn et al. 2022; Nwaru et al. 2020; Patel et al. 2014; Quint et al. 2022; Silver et al. 2011; Suissa et al. 2000)

2.5.5 Formulations, inhalers, inhalation technique

The preferred route of administration in asthma is inhalation to avoid systemic side effects and enable the local action in airway surfaces. After inhalation, 10-60% of the inhaled drug is delivered to the lung (Derendorf et al. 2006; Dolovich and Dhand 2011; Leach et al. 2009; Ye et al. 2017). The particle size of the inhaled drug, the aerosol-generating system, the distribution of the inhaled aerosol, and the inhalation pattern impact the drug deposition in the airways (Dolovich and Dhand 2011; Longest et al. 2012; Usmani 2019). The most commonly used devices for pulmonary drug delivery are pressurized metered dose inhalers, dry powder inhalers, soft mist inhalers, and nebulizers (Usmani 2019). Despite numerous different inhalers on the market, inhaler errors are common in all devices, with critical errors ranging from 14% to 92% (Chrystyn et al. 2017). Therefore, teaching and regular counseling on correct inhaler techniques may lead to better asthma control, improvement in quality of life, and reduced costs and adverse effects of medication via decreased errors in inhalation techniques (Abdelrahman et al. 2021; Chrystyn et al. 2017; Elgendy et al. 2015; Usmani et al. 2018).

2.6 Prescribing practices in asthma

Control-based asthma management includes continuously evaluating asthma management, noting the patient's response to treatment, and minimizing future risks. Before the era of add-on therapies such as LABA and LTRA, the recommended step-up therapy was increasing the ICS dose, still an option today. However, clinicians' adherence to asthma guidelines is suboptimal, and improvements are required, such as in the prescribing of ICS. The study from the Netherlands reported that 4 out of 10 asthma patients did not have the co-prescription of ICS, only monotherapy with LAMA (Baan et al. 2021). Yet another study from Scotland evaluated that 17.7% of patients had monotherapy with LABA (Morales et al. 2013). Adherence to guidelines may also differ among general practitioners and specialists (Chou et al. 2015; Cloutier et al. 2018; Homaira et al. 2020).

Studies concerning asthma medication prescribing trends in adults and children showed signs of undertreating asthma and issuing inappropriate prescriptions for reliever medication (Cazzola et al. 2011; Elkout et al. 2012; Hull et al. 2016;

Sadatsafavi et al. 2017; Thomas et al. 2010). However, there is a lack of follow-up studies assessing medication use in patients with a confirmed asthma diagnosis and how the changes in therapy reflect the asthma control of the patients.

2.7 Medication adherence

Adherence, often used synonymously with compliance, persistence, and concordance, refers to a patient's behavior following a healthcare provider's agreed-upon recommendations (Dhruve and Jackson 2022; Horne 2006). Adherence consists of periods of persistence and non-persistence, including three key components: initiation, implementation, and discontinuation of medication (Vrijens et al. 2012). Persistence can be defined as the time from initiation until discontinuation (in register studies initiation is the time from prescription until first dispensation), meaning the duration that the patient remains on chronic therapy, whereas non-persistence is the time from patient discontinuing taking the medication to when the medication is no longer prescribed. Non-adherence can thereby occur when patient starts medication with a delay (late initiation) or does not start medication at all (primary non-adherence), the patient uses medication less or more than prescribed (suboptimal implementation/secondary non-adherence), or the treatment is discontinued too early (Blais et al. 2017; Vrijens et al. 2012; Weinstein 2015). Non-adherence can also be categorized as intentional or nonintentional. Non-adherence is deliberate when a patient actively decides not to take the medication as prescribed, such as due to concerns about its costs or side effects (Laba et al. 2019; Monteiro et al. 2022). In unintentional non-adherence, a patient intends to adhere but is prevented from taking the medication as recommended, such as due to misunderstanding the regimen or being incapable of using the inhaler properly.

2.7.1 Measurement of adherence

Many methods assess patients' adherence to asthma therapy, each having advantages and disadvantages (Table 3) (Dhruve and Jackson 2022). Subjective methods are easy to use for assessing adherence but may lack accuracy compared to objective methods, such as rates of prescription refills and electronic monitoring of medication administration. Depending on the method used, the time frame of assessed

adherence to asthma medication can vary from days (serum drug level), weeks (self-reported), months (electronic monitoring) to years (health database records). Despite asthma manifesting as a chronic disease, little is known about adherence over a one-year period. In studies assessing adherence via questionnaires or health database records, an asthma diagnosis is often self-reported, based on the International Classification of Diseases codes for asthma or asthma-related medications (e.g., at least two dispensed inhalers of ATC code R03 medications in a year), which may result in including patients without clinically confirmed asthma or those with other diseases (e.g., COPD).

The most widely used adherence measures are patient self-reports containing direct and written questionnaires and visual analog scales. The Morisky Medication Adherence Scale and Medication Adherence Report Scale are examples of the most used questionnaires in studies based on self-reports (Exarchos et al. 2022; Ivanova et al. 2008; Janežič et al. 2017; Lin et al. 2022; Orriëns et al. 2021; Roy et al. 2011). However, subjective recalling and reporting bias limit questionnaires and self-reporting-based adherence measures (Table 3) (Alahmadi et al. 2021; Krishnan et al. 2012; Patel et al. 2013).

From objective measures, health database records have been used extensively. Assessing adherence from electronic databases includes the assumption that prescription filling patterns reflect the patient's medication-taking behavior. A current systematic review addressed that 87% of literature concerning adherence measurement from pharmacy databases used the medication possession ratio (MPR) or proportion of days covered (PDC) formulas (Asamoah-Boaheng et al. 2021). Although the formulas are widely used, the calculation methods may still vary between studies. In MPR a "total day's supply" and in PDC "number of day's covered" are divided by the number of days in the observation period (DeClercq and Choi 2020; Peterson et al. 2007). However, a "day's supply" or "day's covered" are not easy to define in assessing asthma therapy since the dosing regimen can be flexible, e.g., one to two puffs twice daily, which leads to inaccuracy. The difference between the formulas is that MPR may exceed 100% if a patient has obtained medications too frequently during the observation period. In contrast, in PDC, overlapping fills are shifted to avoid double-counting, thus the value being always within the range of 0% to 100%. Patients with primary non-adherence are automatically excluded from the study populations since MPR- or PDC-based formulas cannot produce value for adherence when a patient is not collecting medication at all and most non-adherent patients are missing (Raebel et al. 2013). When using PDC and MPR formulas medication is assumed to be prescribed for

chronic daily use; therefore, sub-optimal prescribing may lead to underestimating adherence (Blais et al. 2011). A notable number of studies based on health records use insurance claims databases, meaning patients without insurance are excluded from the study population. Conversely, when adherence measure is based on health records, it does not cover the information the patient used the medication accurately, potentially leading to overestimating adherence.

Prescription records have also been used as an estimate for adherence to treatment (Covvey et al. 2014; d´Ancona et al. 2020; Engelkes et al. 2016; Papi et al. 2018). From the analysis of the Salford Lung Study, over 30% of prescriptions were not dispensed from the pharmacy, suggesting an overestimation of actual adherence (Tibble et al. 2020). Methodologically, prescription data is troublesome when measuring adherence since the prescription does not guarantee the drug's dispensation; however, without a prescription, a dispensation is impossible. For example, under-estimation of adherence is likely if a patient does not have a prescription to dispense from a pharmacy, i.e., suboptimal prescribing, possibly leading to poorer adherence (Blais et al. 2011). Despite these shortages, many studies based solely on prescription data have been published to describe patient adherence, although they tend to reflect a clinician's prescription manners more than a patient's adherence to treatment.

Electronic monitoring with electronic monitoring devices (EMDs) is the most reliable method to assess adherence, and many new devices are licensed for use or clinical trial evaluation (Dhruve and Jackson 2022). So far, the EMDs have been mostly used in research settings but are expanding to routine clinical care. EMDs would offer more accurate adherence data from general asthma populations, but issues regarding the costs, logistics of managing the data, and data privacy still exist and must be solved to enable longer follow-ups with EMDs in larger populations. Moreover, the malfunction of EMDs has been reported to be between 2% to 15%, decreasing the method's accuracy (Apter et al. 2011; Lee et al. 2018; Patel et al. 2013).

Due to the multiple measures for adherence, thresholds for optimal adherence levels also vary among studies (Asamoah-Boaheng et al. 2021; Engelkes et al. 2015). Adherence levels over >75% or >80% have been related to reduced exacerbations, with these cut-off values being the most used (Asamoah-Boaheng et al. 2021; Williams et al. 2011). However, conflicting results have also been shown (Lee et al. 2018); therefore, future studies should further investigate the proper thresholds.

Table 3. Usual methods to assess inhaler adherence

Method of assessment and examples	Outcome assessed	Strengths of the measure	Limitations of the measure
Self-reported questionnaire Morisky Medication adherence scale, Medication adherence report scale, Visual Analog scale	Pre-established cut-off point for certain questionnaire determines the level of adherence (e.g. low, medium or high adherence according to scores reached in Morisky scale)	Inexpensive and easy to use	Subjective method Poor accuracy due to recall and reporting bias
Health database records Medication possession ratio Proportion of days covered Continuous measure of medication gaps	Adherence percentage calculated based on mathematical formula (e.g. formula used in Medication possession ratio: percentage of days that the medication was filled divided by the follow-up period)	Objective inexpensive method Possible to measure adherence over a long period	Poor accuracy if used only prescription data OR only dispensing records Information about dispensed medication does not guarantee that medication was taken Not possible to ensure the correct administration
Serum drug level Serum corticosteroid concentration	Serum concentration	Objective	Costs Invasive Short-term data only
Dose counter Dose counter of inhaler automatically counts down the number of used doses e.g. Diskus®	Comparison of expected count to actual dose counter	Objective Easy to use	Poor accuracy due to possible dose dumping before the assessment of used doses Not all devices have a dose counter Short-term data only
Electronic monitoring devices Inhaler Compliance Assessment (INCA™), Respiro®	Frequency of inhaler use	Objective Inhaler technique check Reminders for patients	Costs Data availability Mechanical issues Relatively short-term data Data privacy (may not comply with General Data Protection Regulation)

(Dhruve and Jackson 2022)

2.7.2 Adherence to inhaled corticosteroids

As ICS are the cornerstone of asthma treatment, various studies have evaluated patients' adherence to ICS therapy. Unfortunately, results usually show levels of suboptimal adherence. The following studies of at least 12 months length and using objective method to collect data were identified and adherence to ICS ranged from 22% to 84% (Table 4, Table 5, and Table 6). The studies were conducted among adult (age ≥15 years) patient populations during the last decade. From those studies PDC was used in 40% of the studies (Table 4) (Atsuta et al. 2018; Barrecheguren et al. 2022; Cvietusa et al. 2019; Cyr et al. 2013; Gupte-Singh et al. 2015; Hadad et al. 2020; Jones et al. 2020; Oppenheimer et al. 2022; Raebel et al. 2020; Sadatsafavi et al. 2013; Serhal et al. 2020; Stanford et al. 2019), MPR was used in 27% of the studies (Table 5) (Bloom et al. 2019; Hong et al. 2019; Jensen et al. 2021; Kang et al. 2018; Papi et al. 2018; Pool et al. 2017; Sicras-Mainar et al. 2020; Voorham et al. 2017), and 33% of the studies that objectively measured adherence either reported alternative measures or did not provide a detailed description of the adherence calculation method (Table 6) (Dib et al. 2019; Eger et al. 2022; Erdogan et al. 2020; Hekking et al. 2015; Hyland et al. 2012; Murphy et al. 2012; Sá-Sousa et al. 2019; Van Steenis et al. 2014; von Bülow et al. 2018; Yang et al. 2018). The median adherence, if assessable, was 40% in studies utilizing PDC to measure adherence (n=10, Table 4), 59% in studies using MPR for adherence measurement (n=5, Table 5), and 77% in studies reporting adherence alternately or unclearly (n=4, Table 6).

Although data collection is approached objectively, this does not ensure a rigorous assessment of adherence (medication the patient is using as compared to what is prescribed). For example, several studies solely rely on prescribed drug data to assess adherence but do not include the dispended or bought medication data (Atsuta et al. 2018; Bloom et al. 2019; Hong et al. 2019; Hyland et al. 2012; Papi et al. 2018; Voorham et al. 2017). Furthermore, in certain studies, the data used for adherence calculations remains ambiguous or unclear (Table 6). The typical observed follow-up duration was one year, with only one study assessing adherence over a 5-year period but methodologically providing unclear details on adherence calculations (Hadad et al. 2020). Additionally, there is a lack of studies utilizing both prescribed and dispensed data with follow-up periods exceeding two years. Out of the 30 studies assessed, only four reported using a method that included both prescribed and dispensed data to measure adherence (Cyr et al. 2013; Murphy et al. 2012; Serhal et al. 2020; Yang et al. 2018). All these studies had short one-year follow-ups.

Information on patients' age of asthma onset or duration of asthma was missing in assessed studies (Table 4, Table 5, and Table 6). Patients were recruited from health care databases, and asthma was commonly defined as a diagnosis code in the database and/or with asthma medication purchases. As the criteria of diagnosis in previous studies do not guarantee an objectively confirmed diagnosis of asthma, the study populations may have included patients without a verification of asthma diagnosis by lung function tests, possibly affecting the results of the studies. Moreover, asthma onset may play a role in disease manifestation; therefore, the information concerning disease onset would be valuable but was often missing from the adherence studies. These factors may partially explain why adherence levels widely varied among the assessed studies (Table 4, Table 5, and Table 6). Furthermore, adherence calculations commonly utilized PDC or MPR formulas in various studies (Table 4 and Table 5). However, many of these studies presumed that additional information regarding the calculation method was unnecessary. These formulas were applied across studies assessing dispensation data and those solely relying on prescription data, despite the studies used otherwise the same measure for calculating adherence e.g., PDC. Sparse summaries of adherence calculations arouse the questions of how these formulas had been used in practice and how to repeat the measurement with the same methods.

Non-adherence to ICS treatment has been related to reductions in symptom control, lung function, and patient quality of life (Dima et al. 2019; Kandane-Rathnayake et al. 2009). Moreover, an increase in asthma exacerbations, health care costs, and even an increase in mortality and morbidity rates have been associated with suboptimal adherence (Engelkes et al. 2015; Jensen et a. 2021; Kang et al. 2018; Murphy et al. 2012; Suissa et al. 2000; Suissa et al. 2001; Zafari et al. 2014). Nearly two decades ago, Bender and Bender (2005) reviewed barriers to asthma treatment adherence, including concerns about drug safety, medication costs, and beliefs of not needing regular medication for their asthma. Although the factors related to non-adherent behavior were long acknowledged, the solutions addressing non-adherence still need further development. Someday, EMDs might become general outside the research settings and assist patients in correcting medication use, as done in recent studies (Boddy et al. 2021; Sulaiman et al. 2018; Taylor et al. 2018).

Table 4. Adherence studies published during the last 10 years using PDC adherence measure and utilizing at least one objective data source

Study	Length of adherence follow-up	Medication under study	Assessment method	Average adherence
Atsuta et al. Pulmonary Therapy 2018	12 months	FF/VI (once daily) versus FP/SAL diskus (twice daily)	Prescription rates*	Mean PDC was 27% for FF/VI (n=301) and 22% for FP/SAL (n=301)
Barrecheguren et al. NPJ Prim Care Respir Med 2022	12 months	MITT (multiple inhaler triple therapy) (ICS-LABA+ LAMA or ICS+LABA+ LAMA)	Medical records, prescribed medication#	Mean PDC 52% 196 patients (16.3%) had PDC >80%
Cvietusa et al. J Allergy Clin Immunol Pract 2019	24 months	ICS	Electronic healthcare records#	PDC was 39.5% in the year prior to intervention and 41.7% in the year following the intervention
Cyr et al. J Popul Ther Clin Pharmacol 2013	up to 12 months (average 309 days)	ICS	Prescriptions and refills prescribed and dispensed ICS	Patients with private drug insurance mean PDC 36.1% Patients with public drug insurance mean PDC 41.4%
Gupte-Singh et al. J Pharm Health Serv Res 2015	12 months	Controller medication	Prescription fills#	PDC≥50% in 27.6% of the patients
Hadad et al. Sci Rep 2020	6 years	ICS, LTRA, ICS-LABA, Theophylline	Prescription refills#	Refilled ≥3 canisters of relievers, average PDC of MART 27%, average PDC excluding MART 38% Refilled <3 relievers, average PDC of MART 15%, average PDC excluding MART 24%

Jones et al. ERJ Open Res 2020	12 months	FF/VI or usual care in deprivation quantiles	Electronic health records*#	Mean PDC for FF/VI in deprivation quantile 1 (the most deprived) was 78.2% and in deprivation quantile 5 (the least deprived) was 85.9% Mean PDC for usual care in deprivation quantile 1 was 78.9% and in deprivation quantile 5 was 75.8%
Oppenheimer et al. J Allergy Clin Immunol Pract 2022	12 months	ICS, LABA, LAMA and MITT (ICS+LABA +LAMA)	Claims data, pharmacy fills#	Overall mean PDC to MITT was 31% Mean PDC to individual components of the triple regimen was 54% to ICS, 53% to LABA and 41% to LAMA.
Raebel et al. Perm J 2020	12 months	ICS	Prescription refills#	Mean PDC 66% in those who provided preference on refill reminder and 52% in those who did not provide preference
Sadatsafavi et al. Chest 2013	12 months	ICS, ICS-LABA, any controller medication	Medication dispensations#	Mean PDC for ICS was 31% in the primary care group and 31.9% in the secondary care group
Serhal et al. Pharmacy (Basel) 2020	12 months	Preventer medication	Dispensed medication history from pharmacy dispensing software (includes participant´s prescribed dose)	PDC for preventative medication ≥80% in 28% of the patients
Stanford et al. J Allergy Clin Immunol Pract 2019	3-12 months	FF/VI, BUD/F	Pharmacy claims data#	Mean PDC 43% in FF/VI group Mean PDC 36% in BUD/F group

FF; fluticasone furoate, VI; vilanterol, MITT; multiple-inhaler triple therapy, FP; fluticasone propionate, SAL; salmeterol, PDC; proportion of days covered, ICS; inhaled corticosteroid, LABA; long-acting β_2-agonist, LAMA; long-acting muscarinic antagonist, LTRA; leukotriene receptor antagonist, MART; maintenance and reliever therapy, BUD; budesonide, F; formoterol, *; only prescription data, no dispensed or bought medication data, #; adherence calculation details or methodology unclear. The criterion to be included into table: studies measured adherence at least 12 months, studies included only adult patients (≥15yrs), studies were conducted in 2012 or after (last ten years).

Table 5. Adherence studies published during the last 10 years using MPR adherence measure and utilizing at least one objective data source

Study	Length of adherence follow-up	Medication under study	Assessment method	Average adherence
Bloom et al. Thorax 2019	12-24months	Maintanence inhaler adherence (ICS, LABA, LAMA, ICS-LABA, LAMA-LABA)	Electronic healthcare records (Prescription data)*	Preinhaler switch: median MPR 54.8% Postinhaler switch: median MPR 62.6%
Hong et al. J Allergy Clin Immunol Pract 2019	Follow-up was discontinued to first exacerbation or if treatment changed or max 3 years of follow-up	ICS, LTRA	Claims data, information on the prescribed medication*	ICS users' mean MPR 27% LTRA users' mean MPR 24%
Jensen et al. Asthma Res Pract 2021	12 months	ICS	Pharmacy redemption data#	Mean MPR 54%
Kang et al. BMJ Open 2018	12 months or the day before the first exacerbation	na	Claims data, information on the prescribed medication#	MPR<20% in 85.45% of the patients MPR 20-<50% in 6.01% of the patients MPR≥50 in 8.54% of the patients
Papi et al. J Allergy Clin Immunol Pract 2018	12 months	ICS	Electronic medical record data, ICS prescriptions issued*	MPR >80 in 19.4% of the patients MPR≤80 in 80.6% of the patients

Pool et al. PLoS One 2017	12 months	All asthma medication, asthma controller medications and reliever medications only	Insurance claims data#	Mean MPR for asthma controllers in intervention group baseline 77.5% and after 12 months 79.4% Mean MPR for asthma controllers in control group baseline 79.2% and after 12 months 82.7%
Sicras-Mainar et al. J Med Econ 2020	12 months	ICS-LABA	Drug dispensing records#	Mean MPR 70.4%
Voorham et al. Pragmat Obs Res 2017	12 months	FP/SAL	Prescription refill rates*	MPR≥80% in 34.3% of the payment cohort MPR≥80% in 34.9% of non-payment cohort

ICS; inhaled corticosteroid, LABA; long-acting β_2-agonist, LAMA; long-acting muscarinic antagonist, MPR; medication possession ratio, LTRA ; leukotriene receptor antagonist, FP; fluticasone propionate, SAL; salmeterol, *; only prescription data, no dispensed or bought medication data, #; adherence calculation details or methodology unclear. The criterion to be included into table: studies measured adherence at least 12 months, studies included only adult patients (≥15yrs), studies were conducted in 2012 or after (last ten years).

Table 6. Adherence studies published during the last 10 years using alternative measures than PDC or MPR and utilizing at least one objective data source

Study	Length of adherence follow-up	Medication under study	Assessment method	Adherence measure	Average adherence
Dib et al. Pharmacoepidemiol Drug Saf 2019	24 months	ICS or ICS-LABA	Prescription refills#	MRA	Intervention MRA>80 before program 7.1% after program 6.9% Unexposed group MRA>80 before 14.4% after 13.5%
Eger et al. Respiration 2022	12 months	ICS	Prescription fillings#	na	Questionnaire responders' median adherence 82% Questionnaire nonresponders' median adherence 67%
Erdogan et al. Clin Respir J 2020	12 months	Preventer therapy	Medication pick-up rates#	na	34.5% non-adherence (<80% adherence)
Hekking et al. J Allergy Clin Immunol 2015	12 months	ICS	Prescription records#	na	Questionnaire nonresponders' mean adherence 80% Questionnaire responders' mean adherence 84%
Hyland et al. Prim Care Respir J 2012	3 years	ICS	Prescription records*#	na	28% of patients had adherence ≥75%

Murphy et al. Thorax 2012	12 months	ICS, ICS-LABA, LTRA, antimuscarinic inhalers, theophylline	Prescription issue data and hospital´s dispensing computer system	Adherence ratio as the number of doses issued divided by the number of expected issues	Adherence <80% was 65.2% of ICS users, 62.4% of ICS-LABA users, and 85.7% of taking separate ICS and LABA inhales. Only 25.2% patients were found to be adherent (≥80%) to all prescribed medication.
Sá-Sousa et al. Clin Transl Allergy 2019	12 months	Maintenance treatment (ICS or ICS-LABA or LTRA or LAMA or LAMA-LABA or LAMA+ LABA)	Recording of all the prescription and dispensing data#	Percentage of packages of maintenance medication filled over the packages prescribed	Median adherence for maintenance treatment 66.7%
Van Steenis et al. Patient Prefer Adherence 2014	12 months	ICS, ICS-LABA	Pharmacy dispensing data#	Refill adherence	Mean adherence 79.1%
von Bülow et al. Respir Med 2018	12 months	na	Prescription fillings#	Number of doses issued divided by the number of doses expected * 100	Adherence ≥80% in 57.5% of the patients
Yang et al. NPJ Prim Care Respir Med 2018	12 months	ICS	Dispensing data linked to medical records	na	Among frequent exacerbator group (n=185) 46% had adherence <75%

ICS; inhaled corticosteroid, LABA; long-acting β_2-agonist, MRA; medication refill adherence, LTRA; leukotriene receptor antagonist, LAMA; long-acting muscarinic antagonist, *; only prescription data, no dispensed or bought medication data, #; adherence calculation details or methodology unclear. The criterion to be included into table: studies measured adherence at least 12 months, studies included only adult patients (≥15yrs), studies were conducted in 2012 or after (last ten years).

3 AIM OF THE STUDY

The present study aimed to evaluate long-term adherence to asthma medication in patients with adult-onset asthma by studying their characteristics and the prescribed and dispensed medications in the Seinäjoki Adult Asthma Study.

The detailed aims of the sub-works were as follows:

1. Evaluate medication use and adherence to long-term ICS treatment in patients with new-onset adult asthma over a 12-year period. (I and II)

2. Clarify whether a poor 12-year adherence to ICS treatment is related to non-controlled asthma in patients with adult-onset asthma. (III)

3. Examine the factors related to poor long-term ICS adherence. (II and III)

4. Evaluate the relationship between the patient's use of ICS and SABA medications and examine if the increased use of SABA is related to poor ICS adherence. (IV)

4 SUBJECTS AND METHODS

4.1 Study design and setting of Seinäjoki Adult Asthma Study

The present study is part of the Seinäjoki Adult Asthma Study (SAAS), a prospective single-center follow-up study of 257 patients with new-onset adult asthma (Kankaanranta et al. 2015). All new asthma patients 15 or older from 1999 to 2002 in Seinäjoki Central Hospital, Finland, were included. A respiratory physician diagnosed asthma based on typical symptoms of asthma and objective lung function measurements showing significant bronchial reversibility or variability. If considered necessary, an exercise provocation test was performed to ensure diagnosis. The study included patients with any comorbidities or a current or ex-smoking status and excluded patients who were younger than 15 or could not provide signed informed consent due to physical or mental inability. Over 94% of the patients diagnosed with novel asthma at the study site were recruited to the study (Tuomisto et al. 2016). In 2001, the study population represented >38% of all novel diagnoses of asthma made in adults in the whole geographical area (Ilmarinen et al. 2019).

The study was divided in two parts: collection of the original cohort (baseline) and the 12-year follow-up visit. At the baseline visit, data were collected on symptoms, lung function, and demographics. Most of the patients were therapy-naïve at the diagnosis, and ICS medication was started immediately after the diagnostic visit. During the follow-up, patients were actively treated according to the principles of the Finnish Asthma Program (Haahtela et al. 2001). From the original cohort of 257 patients, 203 (79%) returned to a control visit from 2012 to 2013 (mean follow-up of 12.2 years, range of 10.8–13.9 years). At the 12-year follow-up, blood samples were collected, lung function was measured, and structured questionnaires on background information, smoking history, asthma control, and medication use were used.

4.1.1 Lung function measurements

Lung function measurements were performed using a spirometer (Vmax Encore 22, Viasys Healthcare, Palm Springs, CA, USA) and calibrated daily, and Finnish reference values were used (Viljanen et al. 1982). Lung function measurement points were 1) baseline (i.e., time of asthma diagnosis); 2) the maximum lung function ($Max_{0\text{-}2.5}$) during the first 2.5 years after diagnosis (on average, 0.6 years post-diagnosis) (i.e., after starting anti-inflammatory therapy) based on the highest pre-bronchodilator forced expiratory volume in 1 s (FEV_1) % predicted and; 3) after 12 years of follow-up. Lung function measurements after the baseline visit were taken while patients were on medication, without pauses or withholding therapy. Diffusing capacity of the lung was measured at the baseline and follow-up. PEF monitoring was performed during two weeks at the baseline and the follow-up.

4.1.2 Laboratory measurements

The fraction of exhaled nitric oxide (FeNO) was measured with a portable rapid-response chemiluminescent analyzer according to American Thoracic Society standards (flow rate 50 mL·s−1; NIOX System, Aerocrine, Solna, Sweden) (ATS/ERS 2005). Venous blood samples were collected at the baseline and follow-up visits. Laboratory assays were performed in the Seinäjoki Central Hospital accredited laboratory (SFS-EN ISO/IEC 17025:2005 and ISO 15189:2007). White blood cell differential counts were determined. Total immunoglobulin E (IgE) levels were measured using ImmunoCAP (Thermo Scientific, Uppsala, Sweden)(ATS/ERS 2005). Serum levels of IL-6 were determined by ELISA (R & D Systems, Minneapolis, MN, USA), and hsCRP was measured using the particle-enhanced immunoturbidometric method on Roche Cobas 8000 automated clinical chemistry analyzer (Roche Diagnostics, Basel, Switzerland). Atopy was tested via skin-prick tests towards common aeroallergens at the baseline visit. At least one positive reaction toward an allergen (≥3 mm) was considered significant, and the patient was considered atopic.

4.1.3 Questionnaire data, medication use and health care

A structured questionnaire to collect background information was used. Patients reported their medication use on the questionnaire at the follow-up. Moreover, all asthma-related visits and medication information were collected from the 12-year follow-up from the patient records. Collected data included healthcare use, hospitalizations, and emergency department visits to primary care, occupational care, private clinics, and public hospitals. If the patient was moved to another hospital district area, the data on healthcare visits was collected from the departments the patient reported visiting.

4.1.4 Symptoms and asthma control

Patients completed the Airways Questionnaire 20 (AQ20) at the baseline visit, and symptoms were measured during the follow-up visit with AQ20 (Barley et al. 1998) and ACT (Nathan et al. 2004). The AQ20 is a short, well-validated questionnaire to measure and quantify disturbances in the airway-specific quality of life where higher scores indicate poor quality of life (Barley et al. 1998). ACT is a widely used self-administered tool for identifying those with poorly controlled asthma (low ACT scores) (Nathan et al. 2004). Patients were separated into three groups by asthma control at follow-up visits to define asthma control; these groups were defined according to the GINA 2010 report (GINA 2010). Patients with controlled asthma were defined by fewer symptoms, normal lung function, and rare usage of reliever medication. Patients with partially controlled asthma may have had one or two of the following features: day or night-time symptoms, need for reliever treatment more than twice weekly, decreased lung function (<80%), or limitation of activities due to asthma. When defining patients with uncontrolled asthma, three or more of those features were required. Patients were also evaluated in two subgroups based on their asthma control, controlled and non-controlled, when non-controlled included partially and uncontrolled asthma.

4.1.5 Comorbidities

Assessing comorbidities was based on self-reported medication or self-reported comorbidities. Unclear cases were confirmed from the patient records. Defining and classifying comorbidities was based Barnett et al.'s (2012) study. Comorbidities were

evaluated separately and as the sum of all comorbidities reported at the baseline and follow-up. Conditions included as comorbidities were bronchiectasis, cancer, hypertension, coronary heart disease, atrial fibrillation and other cardiac arrhythmias, heart failure, diabetes, thyroid disorders, rheumatoid arthritis and other inflammatory polyarthropathies and systematic connective disorders, irritable bowel syndrome, treated constipation, diverticular disease of the intestine, inflammatory bowel disease, treated dyspepsia (daily medication), viral hepatitis, chronic liver disease, chronic kidney disease, peripheral vascular disease, prostate disorders, glaucoma, stroke and transient ischemic attack, epilepsy, migraine, Parkinson's disease, multiple sclerosis, dementia, depression, schizophrenia/nonorganic psychosis or bipolar disorder, psoriasis, anxiety and other stress-related and somatoform disorders, painful conditions (daily use of analgesic medication), and COPD.

4.1.6 Ethical permission and study registration

Institutional permission (Seinäjoki Central Hospital, Seinäjoki, Finland) was obtained, and study participants gave written informed consent to the study protocol approved by the ethics committee of Tampere University Hospital (Tampere, Finland) (R12122). Seinäjoki Adult Asthma Study is registered at ClinicalTrials.gov with identifier number NCT02733016.

4.2 Adherence

4.2.1 Measurement of prescribed and dispensed inhaled corticosteroids

Prescribed ICS medication and ICS doses for each patient for each year of the follow-up were calculated based on medical records. All drugs (ICS in separate and combination inhalers) and dose changes were considered individually; finally, all doses were converted to budesonide equivalents (Table 7) (Bateman et al. 2011; Turner et al. 2022; Verbanck et al. 2010). If medication information was inadequate, it was calculated based on previous confirmed information. Medication gaps over nine days and medication changes over 14 days were considered. If prescribed, a flexible dose of the calculations was made using the smallest dosing possibility (e.g., one or two inhalations twice daily were calculated as one inhalation twice daily).

The dispensed ICS doses were obtained from the Finnish Social Insurance Institution (SII), which records all reimbursed medication purchases from any Finnish pharmacy. None of the evaluated medications in this study was available over the counter in Finland but needed a prescription. As with prescribed doses, all dispensed ICS doses were finally converted to budesonide equivalents. Since the medical records and data from SII were available over the 12-year follow-up, the prescribed and dispensed doses were determined annually and cumulatively.

Table 7. Dispensed inhalers containing ICS in SAAS study

Brand	Strength	Puffs per inhaler	Active substance (ICS)	Budesonide equivalent multiplier
Alvesco	160ug/dose	60	Ciclesonide	2.5
Alvesco	160ug/dose	120	Ciclesonide	2.5
Aerobec	100ug/dose	200	Beclometasone	2
Aerobec autohaler	50ug/dose	200	Beclometasone	2
Aerobec autohaler	100ug/dose	200	Beclometasone	2
Beclomet easyhaler	200ug/dose	200	Beclometasone	1
Beclomet easyhaler	400ug/dose	100	Beclometasone	1
Budesonid Easyhaler	200ug/dose	200	Budesonide	1
Cortivent	200ug/dose	200	Budesonide	1
Flixotide diskus	100ug/dose	60	Fluticasone	2
Flixotide diskus	250ug/dose	60	Fluticasone	2
Flixotide diskus	500ug/dose	60	Fluticasone	2
Flixotide evohaler	250ug/dose	120	Fluticasone	2
Novopulmon novolizer	200ug/dose	200	Budesonide	1
Pulmicort	0.5mg/ml	20x2ml (no puffs)	Budesonide	1
Pulmicort turbuhaler	200ug/dose	100	Budesonide	1
Pulmicort turbuhaler	200ug/dose	200	Budesonide	1
Pulmicort turbuhaler	400ug/dose	50	Budesonide	1
Pulmicort turbuhaler	400ug/dose	100	Budesonide	1
Pulmicort turbuhaler	400ug/dose	200	Budesonide	1
Seretide diskus	100ug/dose	60	Fluticasone	2
Seretide diskus	250ug/dose	60	Fluticasone	2
Seretide diskus	500ug/dose	60	Fluticasone	2
Seretide evohaler	50ug/dose	120	Fluticasone	2
Seretide evohaler	125ug/dose	120	Fluticasone	2
Seretide evohaler	250ug/dose	120	Fluticasone	2
Symbicort turbuhaler mite	100ug/dose	120	Budesonide	1
Symbicort turbuhaler	200ug/dose	120	Budesonide	1
Symbicort turbuhaler forte	400ug/dose	60	Budesonide	1

4.2.2 Annual and cumulative adherence

By comparing dispensed doses to prescribed ICS doses, evaluating the adherence of a single patient over the follow-up was possible. The 12-year adherence was calculated by comparing the total cumulative dispensed doses of ICS to the total cumulative 12 years of prescribed doses (Formula 1). Annual adherence was calculated for each patient individually for each calendar year by dividing yearly dispensed ICS doses by annually prescribed ICS doses (μg budesonide equivalents) (Formula 2) to obtain a view on the variability of adherence at long-term follow-up. Regarding the flexible doses prescribed (e.g., one or two puffs twice daily), we interpreted that patients were adherent when the minimum ICS doses were dispensed. The most used cut-off point (≥80%) in respiratory literature was used in this study to distinguish patients with better (≥80%) and poorer (<80%) 12-year adherence (Engelkes et al. 2015; Papi et al. 2018; Souverein et al. 2017). The extensive follow-up and continuously prescribed long-term ICS treatment enhanced the evaluation of 12-year ICS adherence, including the initiation of medication and periods of persistence and temporary non-persistence. Moreover, one recent publication used time-varying adherence to describe patients' adherence behavior; the present study adopted this method (Bijlsma et al. 2016).

$$\text{12-year adherence (\%)} = \frac{\text{12-year cumulative dispensed dose of ICS (μg)}}{\text{12-year cumulative prescribed dose of ICS (μg)}} \times 100$$

Formula 1.

$$\text{Annual adherence (\%)} = \frac{\text{yearly dispensed dose of ICS (μg)}}{\text{yearly prescribed dose of ICS (μg)}} \times 100$$

Formula 2.

4.3 Dispensed short-acting β_2-agonists

The dispensed SABA inhalers were obtained from the SII register (Table 8). SABA use was quantified as canisters collected annually (per calendar year) and cumulatively over the 12-year period. To account for different numbers of doses (range 60-400 puffs) in various types of canisters, we counted all doses of SABA dispensed during the 12-year follow-up and divided the sum by 150 to express SABA use as standard canisters of 150 doses.

Table 8. Dispensed inhalers containing SABA in SAAS study

Brand	Strength	Puffs per inhaler	Active substance
Airomir autohaler	0.1mg/dose	200	Salbutamol
Airomir	0.1mg/dose	200	Salbutamol
Atrovent comp eco	50ug/dose	200	Fenoterol
Bricanyl turbuhaler	0.25mg/dose	200	Terbutaline
Bricanyl	0.25mg/dose	400	Terbutaline
Bricanyl turbuhaler	0.5mg/dose	100	Terbutaline
Bricanyl turbuhaler	0.5mg/dose	200	Terbutaline
Buventol easyhaler	100ug/dose	200	Salbutamol
Buventol easyhaler	200ug/dose	60	Salbutamol
Buventol easyhaler	200ug/dose	200	Salbutamol
Salbutamol turbuhaler	50ug/dose	200	Salbutamol
Ventoline	0.2mg/dose	100	Salbutamol
Ventoline	1mg/ml	20x2.5ml (no puffs)	Salbutamol
Ventoline diskus	200ug/dose	60	Salbutamol
Ventoline evohaler	0.1mg/dose	200	Salbutamol
Ventoline rotadisk	0.2mg/dose	15x8 (no puffs)	Salbutamol

4.3.1 Definition of the high use of short-acting β_2-agonists

High SABA use was defined as ≥36 SABA canisters (with 150 puffs/canister) in 12 years, corresponding to an average of ≥3 dispensed canisters (with 150 puffs/canister) per year (corresponding to average SABA use more than daily) (GINA 2021). SABA over-reliance was classified into three categories: 1) high SABA use (≥36 canisters in 12 years) and no dispensed ICS canisters during the follow-up; 2) high SABA use and <36 dispensed canisters of ICS (corresponding to <3 dispensed canisters per year on average); 3) high SABA use and fewer ICS than SABA canisters dispensed. If a patient on maintenance ICS uses a lot of SABA, such indicates a need for a step-up in maintenance medication. Therefore, we also analyzed the number of patients with high use of SABA and who were on maintenance ICS but were not dispensed any second controllers (LABA [long-acting β_2-agonist] or LAMA [long-acting muscarinic antagonist]) to reveal signs of undertreatment.

4.4 Dispensed other asthma medication

Dispensed doses of oral corticosteroids (OCS) (mg) were obtained from SII and divided by the years of follow-up. Regarding dispensed OCS, only those prescribed as part of asthma treatment were considered. When the asthma indication was missing, information was verified from medical records; if no indication was available, the indication was assumed to be asthma. Differentiating whether the oral corticosteroids dispensed were used as short courses or as a daily treatment was impossible. Methyl prednisolone was converted into mg of prednisolone to calculate the total amount of purchased oral steroids during the entire follow-up as prednisolone mg. The total amount used during the whole follow-up was divided by the years the patients was followed up on to calculate their average annual use in mg.

Dispensed antibiotics were also obtained from the SII register and defined as a single purchase covering one course of antibiotics. The number of antibiotic courses were counted together to assess the patient's need for courses during the 12-year follow-up.

4.5 Statistical analysis

Statistical analyses were performed using IBM SPSS statistics software, version 27 (IBM SPSS, Armonk, NY, USA), and GraphPad Prism (version 7.03; GraphPad, LaJolla, CA, USA). A p-value of <0.05 was considered statistically significant. The normality of the data distribution was analyzed with the Kolmogorov-Smirnov's test or the Shapiro–Wilk test and by visually evaluating the distribution. Independent samples t-test, one-way ANOVA, or two-way ANOVA were used in group comparisons for normally distributed data. Tukey's post hoc test was used. Group comparisons in non-normally distributed continuous data were performed with the Mann–Whitney U or Kruskal-Wallis test. Pearson's Chi-squared or Fisher's exact test was used for categorical data. Baseline and follow-up values were compared using paired samples t-test (normally distributed data), related samples Wilcoxon signed rank test (skewed data) or the McNemar test (categorical data). The individual patient's area under the curve (AUC) was defined, and the mean AUC values were compared using paired-samples t-tests to analyze the differences cumulatively and annually between the prescribed and dispensed doses.

Multivariable linear and logistic regression analyses were performed to analyze the associations between independent variables and the dependent factor. The

correlation matrix was analyzed, and explanatory variables that were not strongly correlated ($r<0.7$) were included in the analyses. Before the regression analyses, the correlation matrix was analyzed, and forward, backward, and enter methods were used to select variables for the final model. In a linear regression analysis, outliers were removed to ensure homoscedasticity. R^2 in linear regression analysis and Nagelkerke's R^2 in logistic regression analysis were considered when selecting the best model. A negative binomial regression analysis was performed, predicting skewed continuous data. The incidence rate ratios (IRRs) with 95% CI were reported. Owing to overdispersion, we used negative binomial regression and adjusted the model with tested covariates. The natural logarithm of the length of follow-up was set as an off-set variable.

5 SUMMARY OF THE RESULTS

5.1 Description of the study population

The study population consisted of 203 patients with adult-onset asthma (patients who returned to the follow-up visit) (Studies I and IV). Most of the patients were female (58%), with a mean asthma onset age of 46 (SD 14) (Table 9). Altogether, 37% of the patients were atopic. Half were current or ex-smokers. At the 12-year follow-up, patients generally had a higher body mass index (BMI), better lung function and lower blood eosinophil counts than their baseline visit. During the diagnostic visit (baseline), 8% of the patients used ICS, whereas 76% reported being daily ICS users at the follow-up. Studies II and III excluded patients who were prescribed ICS only periodically (often GINA step 1 and ICS use during pollen season) at any point during the follow-up (n=22) to ensure that adherence calculations were as accurate as possible. Therefore, the study population consisted of 181 patients in Studies II and III, and the original communications have described the characteristics in detail.

Table 9. Characteristics of the study patients at baseline (asthma diagnosis) and 12-year follow-up visit (n=203)

	Baseline	Follow-up	p value
Age (y)	46 (14)	58 (14)	
Female gender n (%)	118 (58.1)	118 (58.1)	
BMI, kg/m^2	27.1 (24.2-29.8)	28.1 (24.4-31.3)	<0.001
Smokers (incl. ex) n (%)	103 (50.7)	107 (52.7)	0.125
Daily ICS use n (%)	16 (7.9)	155 (76.4)	<0.001
Pre-BD FEV_1% pred	83 (71-92)	86 (76-96)	<0.001
Pre-BD FVC% pred	90 (79-100)	96 (87-106)	<0.001
Pre-BD FEV_1/FVC	0.75 (0.69-0.80)	0.73 (0.66-0.79)	<0.001
Blood eosinophils (10^9/l)	0.28 (0.15-0.42)	0.16 (0.10-0.27)	<0.001
Total IgE (kU/l)	84 (35-174)	61 (24-163)	0.046
hsCRP	5 (5-5)	1.2 (0.57-2.5)	<0.001
Atopy n (%)	68 (37.2)		
AQ20 score	7 (4-10)	4 (2-7)	<0.001

BMI; body mass index, ICS; inhaled corticosteroid, BD; bronchodilator, FEV_1; Forced expiratory volume in one second; FVC; forced vital capacity, IgE; Immunoglobulin E, CRP; high-sensitivity C-reactive protein, AQ20; Airways questionnaire 20. Statistical significances were evaluated by related samples Wilcoxon signed rank test (if non-normally distributed) or McNemar test (categorical variables).

5.2 Prescribing of inhaled corticosteroids

5.2.1 Annual prescribed daily and cumulative inhaled corticosteroid doses

The average annual daily ICS doses and cumulative doses were calculated to visualize how anti-inflammatory medication for asthma was prescribed in this cohort of new-onset adult asthma patients from diagnosis to the 12-year follow-up. The mean cumulative prescribed dose of ICS for the 12-year follow-up was 3.4g (± SEM 0.1) (budesonide equivalents) per patient (Figure 3). The highest average annual ICS dose was 939 μg (± SEM 25) among the study population one-year post-diagnosis. For the remaining follow-up, the yearly daily average ICS dose remained at approximately 800 μg (Figure 3). Considering all dose changes, 649 increases or decreases occurred among the study population (median 3 [1-5] per patient). Of the increases (n=281), 38.4% were prescribed by a respiratory specialist and 61.6% by a general practitioner;

of the decreases (n=368), 56.5% were prescribed by a respiratory specialist and 43.5% by a general practitioner. In nine patients (4%), regular ICS was discontinued, and ICS was continued on an as-needed basis until the follow-up visit. Moreover, 13 patients (6.4%) were prescribed ICS periodically at any point during the follow-up, but later, regular daily ICS was continued.

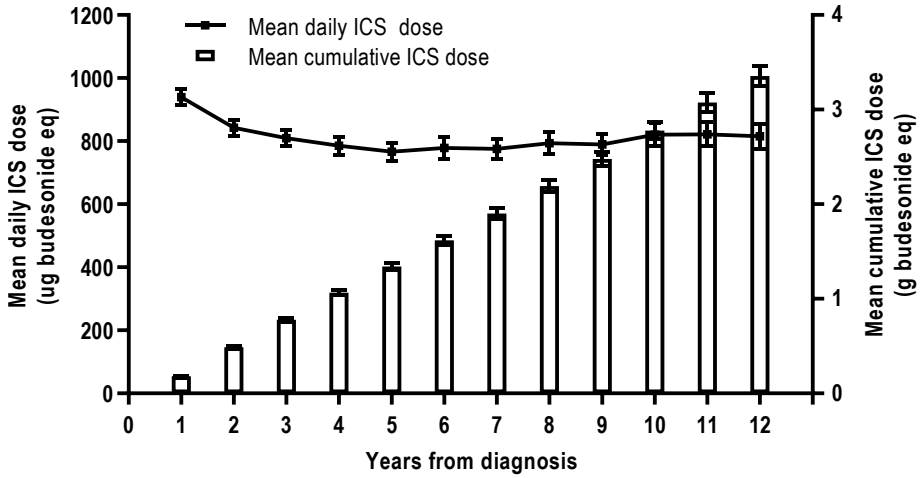

Figure 3. Mean and cumulative ICS doses prescribed to patients in SAAS over the 12-year follow-up period (Modified from Vähätalo et al. 2018)

5.2.2 Annual cumulative and daily inhaled corticosteroid doses in asthma control groups

From 203 patients, 69 had controlled, 74 had partially controlled, and 60 had uncontrolled asthma at the 12-year follow-up (Table 10). Patient groups with different levels of asthma control had significantly different prescribed cumulative doses of ICS during the 12-year follow-up ($p<0.0001$) (Figure 4). Patients with controlled asthma had the lowest total cumulative dose of ICS (2.9g ± SEM 0.2), whereas patients with uncontrolled asthma had the highest total cumulative dose of ICS (3.8g ± SEM 0.2) (Figure 4). The mean prescribed daily dose of ICS was higher in patients with uncontrolled asthma (937 µg [SD 367]) than in those with partially controlled (870 [SD 354]) or controlled asthma (760 [SD 278]) (Table 10). The median number of dose changes was four (IQR 2–6) per patient with uncontrolled

asthma and two (IQR 1–4) per patient with partially controlled and controlled asthma. A respiratory specialist significantly increased the dose of ICS more frequently with patients who had uncontrolled asthma than with those who had controlled asthma ($p<0.035$).

Table 10. Characteristics of the study patients according to their level of asthma control at 12-year follow-up visit (n=203)

	Controlled n=69	Partially controlled n=74	Uncontrolled n=60	p value
Age (y)	54 (14)	60 (12)	61 (13)	0.005
Female gender n (%)	48 (69.6)	42 (56.8)	28 (46.7)	0.030
BMI, kg/m^2	27.7 (4.8)	28.9 (5.8)	29.1 (6.1)	0.324
Smokers (incl. ex) n (%)	25 (36.2)	45 (60.8)	37 (61.7)	0.003
Pre-bd FEV_1% pred	92 (87-98)	86 (75-97)	75 (61-89)	<0.001
Pre-bd FVC% pred	103 (91-110)	96 (87-104)	90 (79-104)	<0.001
Pre-bd FEV_1/FVC	0.75 (0.71-0.80)	0.75 (0.67-0.79)	0.69 (0.57-0.76)	<0.001
Prescribed daily dose of ICS (ug budesonide equivalents)	760 (278)	870 (354)	937 (367)	0.019
Blood eosinophils (10^9/l)	0.16 (0.12–0.28)	0.18 (0.09–0.28)	0.19 (0.09–0.27)	0.870
Blood neutrophils (10^9/l)	3.7 (2.8-4.5)	3.6 (2.9-4.9)	4.2 (3.2-5.0)	0.169
Total IgE (kU/l)	47 (23-134)	76 (25-164)	72 (23-183)	0.349
FeNO (ppb)	12 (6-19)	10 (5-20)	11 (5-18)	0.533
AQ20 score	2 (0-4)	4 (2-6)	8 (5-11)	<0.001

BMI; body mass index, BD; bronchodilator, FEV_1; Forced expiratory volume in one second; FVC; forced vital capacity, ICS; inhaled corticosteroid, IgE; Immunoglobulin E, FeNO; fraction of exhaled nitric oxide, AQ20; Airways questionnaire 20. Statistical significances were evaluated by one-way ANOVA with Tukey's post hoc test, Pearson Chi-Square test or independent samples Kruskal-Wallis test.

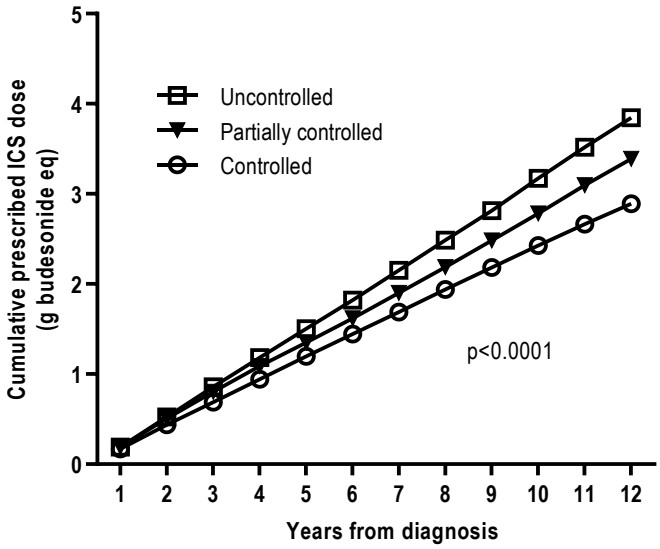

Figure 4. Cumulative prescribed ICS dose in patients with different level of asthma control. P-value indicates the difference between three slopes analyzed by two-way ANOVA (Modified from Vähätalo et al. 2018).

5.3 Adherence to inhaled corticosteroids

By utilizing dispensing data for reimbursed medication and data for prescribed medication, assessing adherence and its variability in long-term ICS treatment was possible in this study population during the 12-year follow-up. New-onset adult asthma patients with regularly prescribed ICS medication (n=181) had a mean 12-year ICS adherence of 69% (Figure 5). The mean annual adherence gradually declined from the first year of follow-up (81%) to year 12 (67%). Despite the mean adherence being moderate among the study population, the variance in annual ICS adherence was common since 37% of the patients had at least one year of non-adherence (annual adherence rate 0%) during the follow-up. Moreover, two (1%) patients failed to collect their first treatment prescription (initiation) and were fully non-adherent to ICS therapy during the entire 12-year follow-up. The prescribed annual daily ICS doses for study patients were high (on average, >800 μg budesonide

equivalents), but patients were dispensed significantly lower doses (on average, <800 μg budesonide equivalents) of ICS during the follow-up (Figure 6). If calculated using the maximum value of the dose range in the prescription instead of the lowest value of the range (e.g., in a subject prescribed budesonide/formoterol 200/6 μg, one to two puffs twice daily), maximum dose range affected the mean 12-year adherence by −4.4%. During the follow-up, 63% of the patients used ICS-LABA combination therapy at least once, and 43% used the ICS-LABA combination for six years or more.

To differentiate patients based on their 12-year adherence, they were categorized into groups with ≥80% (n=82) or <80% (n=99) adherence. Patients with ≥80% were more neutrophilic, used more daily add-on drugs and oral corticosteroid courses, and visited healthcare more often due to their asthma than patients with <80% adherence. However, the decline in lung function was steeper in patients with <80% adherence.

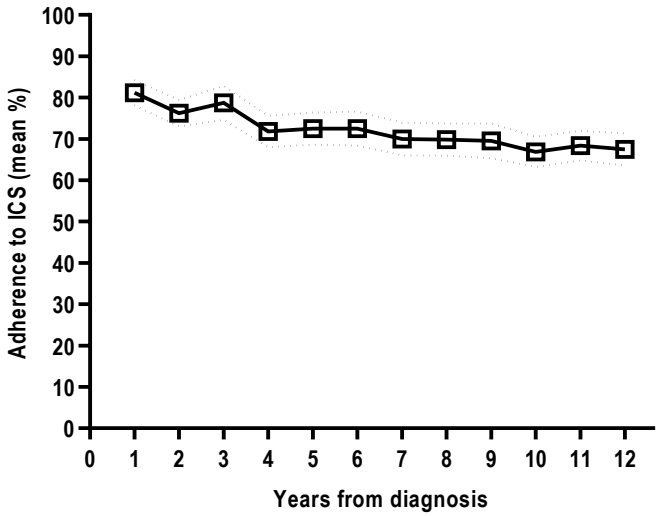

Figure 5. Mean yearly adherence to ICS of SAAS patients. Adherence was calculated by comparing yearly dispensed doses of ICS (ug) to yearly prescribed doses of ICS (ug) (Modified from Vähätalo et al. 2020).

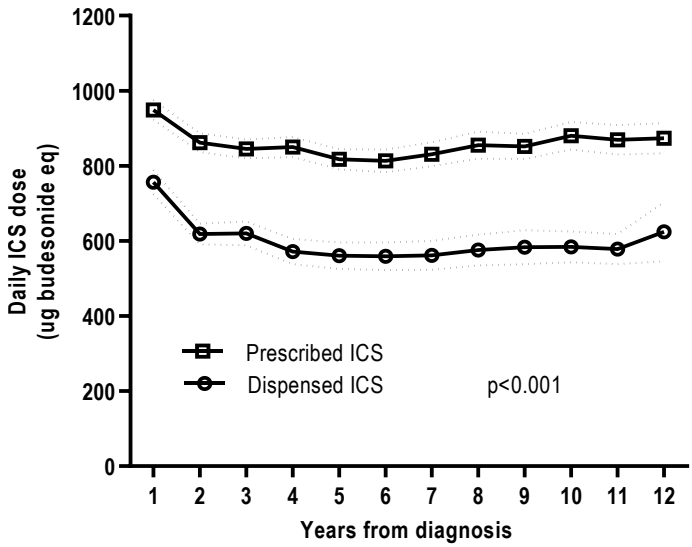

Figure 6. Prescribed and dispensed mean daily doses of ICS over the 12-year follow-up (Modified from Vähätalo et al. 2020)

At the 12-year follow-up, asthma control was evaluated, and the patients were divided into two groups: controlled (n=56) and non-controlled (n=125). Patients with non-controlled asthma were more often non-atopic males of older age, used more daily add-on drugs, spent more days in the hospital, and were dispensed higher doses of oral corticosteroids than patients with controlled asthma. The mean 12-year adherence to ICS was higher in patients with non-controlled asthma (76%) than in those with controlled disease (63%) (p=0.042) (Figure 7). From study patients having ≥80% adherence during the whole 12-year follow-up, 34% still had non-controlled asthma at the follow-up. The association between ≥80% adherence and non-controlled asthma remained in a binary logistic regression analysis, adjusting for age ≥60 years, sex, BMI ≥30 $kg \cdot m^{-2}$, COPD, and rhinitis.

From patients with non-controlled asthma, 61 (49%) had a mean 12-year adherence of ≥80%, whereas 64 (51%) had <80% 12-year adherence. The patients with non-controlled asthma and ≥80% adherence had a higher number of asthma-related contacts with health care, a more elevated blood neutrophil count, and used more long-acting β_2-agonists (LABA) or leukotriene receptor antagonists (LTRA) than patients with <80% adherence. From patients with controlled asthma 21, (38%)

had a mean 12-year adherence of ≥80%, whereas 35 (62%) had <80% 12-year adherence. Clinical differences between these groups existed in BMI and FEV_1 reversibility, which were lower in patients with ≥80% adherence. Total IgE and peripheral blood neutrophil counts were higher in patients with ≥80% adherence versus <80%.

We evaluated the change in lung function in patients with controlled and non-controlled asthma and with different adherence levels to assess the association of asthma control and adherence to lung function. Lung function did not differ in patients with ≥80% or <80% 12-year adherence and controlled asthma. However, the patients with non-controlled asthma and <80% 12-year adherence had more rapid decrease in lung function (FEV_1) than patients with ≥80% adherence (p=0.024) (Table 11). We conducted multiple linear regression analysis to find out whether poor adherence predicts accelerated lung function decline in patients with non-controlled asthma when adjusted for age, BMI at follow-up, sex, FeNO >20 ppb, ≥10 pack-years, and ΔFEV_1 (baseline−$max_{0–2.5}$). After adjustments, poorer adherence (<80%) remained a significant predictor for FEV_1 (mL) decline.

Table 11. Lung function change (ΔFEV_1 from max0-2.5 to 12-year follow-up visit) in patients with controlled and non-controlled asthma and different level of adherence (n=181)

	Adherence ≥80%	Adherence <80%	p value
Controlled asthma			
n=56			
ΔFEV_1 mL·year^{-1}	-39 (-59 to -24)	-35 (-67 to -25)	0.859
ΔFEV_1 % pred·year^{-1}	-0.31 (-0.76 to 0.54)	-0.34 (-1.10 to 0.07)	0.271
Non-controlled asthma			
n=125			
ΔFEV_1 mL·year^{-1}	-40 (-56 to -20)	-47 (-83 to -32)	0.024
ΔFEV1 % pred·year–1	-0.47 (-0.98 to 0.25)	-0.76 (-1.40 to -0.17)	0.029

ΔFEV_1= change in pre-bronchodilator-FEV_1 from the maximum value during the first 2.5 years after diagnosis and start of treatment to 12-year follow-up visit. Statistical significances were evaluated by independent samples Mann-Whitney U test.

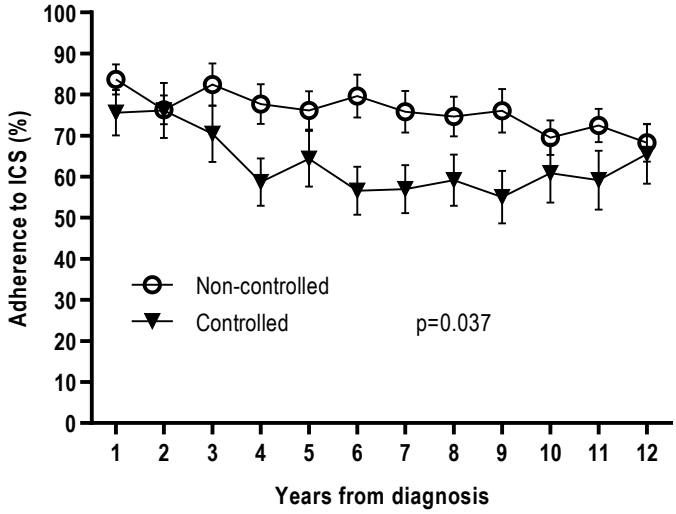

Figure 7. Mean adherence to ICS per year in patients with controlled and non-controlled asthma (Modified from Vähätalo et al. 2021)

5.4 Use of reliever medication

In the current study, purchases of SABA and ICS were collected individually from the 12-year follow-up and converted to standard canisters of 150 doses. The study patients were dispensed a median of six (IQR 3-16) canisters of SABA and 48 (IQR 18-67) canisters of ICS for 12 years, corresponding to the use of a median of two (IQR 1-4) SABA and 11 (IQR 5-16) ICS puffs per week (Figure 8). The categorization of high SABA use was based on the objective measurement of the SABA standard canisters dispensed. Of the study patients, 10% (n=21) were classified as high SABA users (≥36 canisters in 12 years, corresponding to ≥3 canisters dispensed per year, on average).

We conducted a negative binomial analysis to explore which factors or features during the asthma diagnosis predicted a higher use of SABA during the forthcoming 12 years. The final model included the age at diagnosis of asthma, sex, BMI at diagnosis, AQ20 scores at diagnosis, smoking status at the time of diagnosis and diagnostic FEV_1 (% predicted). After adjustments, BMI ≥30 at diagnosis and higher AQ20 scores at diagnosis predicted higher long-term SABA use (Table 12).

Patients with high SABA use (≥3 canisters/year) dispensed a median of 49 (IQR 39-69) canisters of SABA during the 12-year period, corresponding to 12 (IQR 9-16) puffs of SABA per week. Patients with low SABA use (<3 canisters/year) were dispensed a median of six (IQR 3-12) canisters of SABA during the 12-year period, corresponding to one (IQR 1-3) puff of SABA per week (Figure 9). However, high SABA users were also dispensed higher doses of ICS and had better 12-year adherence to ICS treatment than patients with low SABA use. There were no differences in lung function measurements or inflammatory markers except for blood neutrophil counts, which were higher for those who were dispensed ≥3 SABA canisters annually. Increased use of reliever medication was related to poorer asthma control since 86% of the high SABA users had non-controlled asthma, and over 25% of the patients had severe asthma according to ERS/ATS criteria. Moreover, patients with high SABA use had a higher BMI at follow-up, more comorbidities, used higher amounts of oral corticosteroids and antibiotics, and had more emergency department visits and asthma-related healthcare contacts than patients who were dispensed <3 SABA canisters annually.

Previous studies have indicated that high SABA users often have insufficient dispensing of controller medication, i.e., they are over-reliant on SABA. However, over-reliance on SABA was infrequent in this study population since all high SABA users were also dispensed ICS during the follow-up. Of these, only two patients were dispensed <3 canisters of ICS annually. Moreover, in 12 years of follow-up, five patients classified as high SABA users were dispensed fewer ICS canisters than SABA. By using any of the pre-defined criteria for SABA overreliance (1) high SABA use (≥36 canisters in 12 years) and no dispensed ICS canisters during the follow-up; 2) high SABA use and <36 dispensed canisters of ICS (corresponding to <3 dispensed canisters per year on average); and 3) high SABA use and fewer ICS than SABA canisters dispensed) only five of these patients (2%) had any signs of SABA over-reliance.

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

	Adjusted Incidence rate ratio (Adjusted 95% CI)	p value
Age of asthma onset	1.01 (0.99-1.02)	0.182
Female gender	1.10 (0.78-1.53)	0.574
Ex or current smoker	1.12 (0.83-1.52)	0.444
pre-BD FEV_1 % (baseline)	1.01 (0.99-1.01)	0.235
BMI <25	1	
BMI at diagnosis 25-29.9	1.19 (0.83-1.69)	0.334
BMI at diagnosis ≥30	1.53 (1.01-2.30)	0.043
AQ20 score	1.04 (1.00-1.08)	0.035

BD; bronchodilator, FEV_1; Forced expiratory volume in one second; BMI; Body mass index, AQ20; Airways questionnaire 20

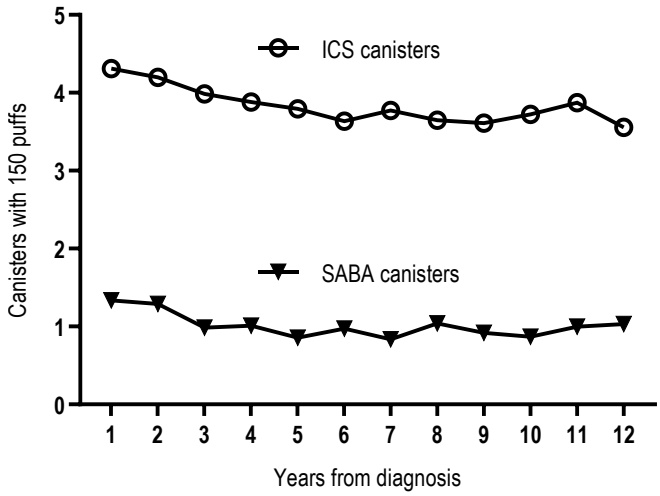

Figure 8. Mean ICS and SABA canisters dispensed per year during the 12-year follow-up (Modified from Vähätalo et al. 2022)

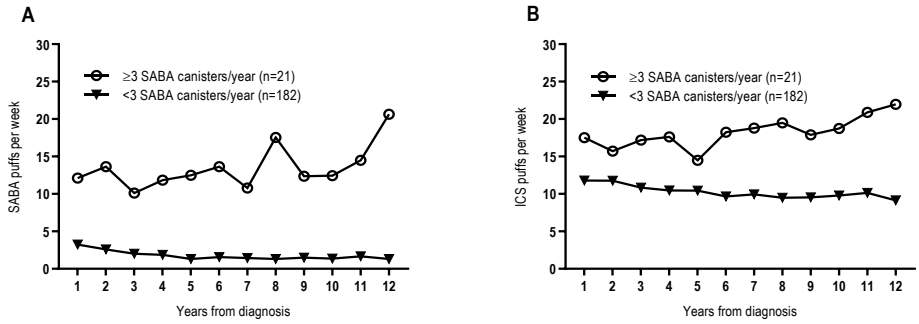

Figure 9. The mean number of dispensed SABA and ICS puffs per week among high and low SABA users during the 12-year follow-up (Modified from Vähätalo et al. 2022)

6 DISCUSSION

6.1 Methodology

The Seinäjoki Adult Asthma Study is a 12-year single-center retrospective follow-up study with real-life adult-onset asthma patients with information on prescribed and dispensed asthma medication from diagnosis to the 12-year follow-up visit. The long-term follow-up combined with individual medication and clinical data of the patients gives a unique perspective of real-life asthma patients by including patients with comorbidities and/or a history of smoking. Generally, studies regarding adherence to asthma medication are based on questionnaires or objective measures utilized in short-term follow-ups of medication use (most commonly, the 12-month follow-up) (Dima et al. 2019; Hekking et al. 2015; Jones et al. 2020; Munoz-Cano et al. 2017; Murphy et al. 2012; Oppenheimer et al. 2022). No studies on adherence were conducted with electronic monitoring devices in adult asthma populations over 12 months. However, several measures can be applied in adherence calculations completed with medication information, but definitions of different measures vary among studies, even along the same formula (Hess et al. 2006, Vrijens et al. 2012). In SAAS, all prescribed and dispensed ICS doses were converted to budesonide equivalents to ensure a comparison of the doses without a pre-defined adherence formula. Technically, the formula our adherence calculations used combined elements from MPR and PDC formulas, but those formulas were used inconsistently in previous studies; thus, claiming that our calculations were conducted like the previous studies was uncertain.

Longitudinal medical records and pharmacy dispensation data enabled the yearly individual evaluation of ICS adherence over a 12-year follow-up. We examined only patients with regular ICS medication and excluded patients whose ICS was prescribed only periodically at any point of the follow-up to improve the reliability of the adherence calculations. For example, in previous register-based studies, only patients with three medication purchases in previous year before the follow-up were included to exclude occasional medication users. However, this selection criteria does not guarantee that a physician will prescribe the medication during the the follow-up year. Moreover, in many register-based studies populations have been

included from healthcare organizations or insurance databases, meaning that patients outside these databases are excluded, and the cohort is selected (Cyr et al. 2013; Ivanova et al. 2008; Pool et al. 2017; Wu et al. 2015). For example, by using insurance data, those patients without insurance who often rely on public care are excluded. In the SAAS study, all patients over 14 years were included in the South Ostrobothnia region if they had asthma symptoms, and objective lung function measurements showed variability or reversibility of expiratory airflow limitation. Most register-based studies have reported asthma diagnoses based on patient self-reports or diagnostic codes in the database, limiting the reliability of the diagnosis. To summarize, the current study's major strengths in the field of adherence evaluation among asthmatics were as follows I) adherence was objectively evaluated over an extremely long follow-up; II) use of adherence calculation method which enabled true prescribed medication doses to be compared to dispensed doses; III) the national health registers were used, which covered all reimbursed asthma medication purchases in Finland; IV) only patients with clinically confirmed asthma diagnosis were included; and V) adherence data was combined with clinical examinations (e.g., lung-function measurements, blood samples, asthma control test).

The number of canisters used within a specific time, often defined as ≥3 canisters per year, has typically assessed the high use of SABA (Noorduyn et al. 2022; Nwaru et al. 2020; Stanford et al. 2012). At least in Finland, the SABA inhalers contain varying numbers of puffs ranging from 60 to 200, depending on the inhaler. Thus, categorizing high users from the Finnish population based solely on dispensed canisters would have been overestimating since patients with three or more 60-puff inhaler purchases would have been classified as high users. In some studies, there is an overestimation bias, as most of the SABA inhalers are assumed to contain 200 puffs (Bloom et al. 2020; Di Marco et al. 2021; Janson et al. 2020). However, we calculated all SABA puffs per year and divided the sum by 150 to interpret the standard SABA canister size with 150 puffs to avoid misclassifying the patients. In the GINA 2021 report, the over-use of SABAs is defined as SABA used, on average, more than daily (GINA 2021). For example, in a patient who used at least three SABA inhalers (with 150 puffs) in a year, the total daily average SABA use was more than one puff daily (1.2 puffs/day). Therefore, in SAAS, high SABA use was defined as ≥36 SABA canisters in 12 years, corresponding to an average of ≥3 canisters dispensed annually. A general limitation of the studies assessing SABA use based on the number of dispensed canisters is that inhalers may contain different active substances. In SAAS, 86% of the SABA inhalers contained salbutamol, and only 14% contained terbutaline.

As all medication purchases evaluated in the SAAS study were obtained from the national register, covering all reimbursed purchases made in Finnish pharmacies, we consider the dispensation data exceptionally comprehensive. Patients' medication use may have been under-evaluated if they had hospital admissions, as they may have received a new inhaler from the hospital, which was unaccounted for in this study. However, hospitalizations were infrequent in this study cohort, and medication use assessment was performed longitudinally, making possible under-evaluations irrelevant to the study's findings. Because the data concerning medication purchases included only reimbursed dispensations, not all asthma medication dispensations may have been captured in the data during the very first years of the follow-up. Purchases were not reimbursed if they did not exceed the 10€ deductible per dispensation before the change in the reimbursement system in 2006. However, in Figure 8, there was no increasing trend in medication use after 5 years of follow-up, suggesting that missing data is rare. It must be acknowledged that the medication dispensed does not guarantee the patient's medication intake, which is the primary limitation of studies that rely on register data. Although at the time of diagnosis, the specialized asthma nurse provided instructions on the inhaler technique, this study lacks information about the assessment of the inhaler technique during the follow-up. Some studies have evaluated that most of the patients make at least one error, and 14%-92% make at least one critical error when using their inhalers (Chrystyn et al. 2017; Usmani et al. 2018). Determining the role of possible inhaler errors in our findings was impossible.

Numerous studies have utilized prescription data to depict patients' adherence to treatment, although the prescription does not guarantee the medication's dispensation (Atsuta et al. 2018; Bloom et al. 2019; Covvey et al. 2014; d´Ancona et al. 2020; Engelkes et al. 2015; Hadad et al. 2020; Hong et al. 2019; Hyland et al. 2012; Papi et al. 2018; Voorham et al. 2017). We consider that an assessment of the medication prescribed reflects clinician's prescribing habits more than the patient's adherence to treatment, and when assessing the patient's adherence, the evaluation must include the patient's actions (dispensation). The study setting in SAAS enabled comparing the prescribed doses (from physician markings in medical records) to the doses patients had bought from the pharmacy. Sometimes, however, the medical records had only partial physician's markings. If the medication details were inadequate, the missing information was assumed to be the same as the last confirmed dosage recorded. As the study is a long-term follow-up, any inadequacy in medication information does not presumably have a major effect on the results.

The cut-off point of ≥80% was used in this study to identify patients with better and poorer 12-year adherence. Although the 80% cut-off point is frequently observed in respiratory literature, there is incomplete knowledge of how studies have concluded this particular value (Engelkes et al. 2015; Papi et al. 2018; Souverein et al. 2017). On the contrary, in diseases such as asthma, the symptoms vary in duration and intensity; arguably, a smaller quantity of an active substance might suffice (Asamoah-Boaheng et al. 2021). Therefore, we conducted a sensitivity analysis with an adherence cut-off set at 50% and noticed the results were broadly similar. However, more studies are needed to explore the potential cut-offs for assessing adherence to asthma medication.

As the study was conducted in one hospital district with a relatively small number of participants (n=203), and considering the uniqueness of the medication reimbursement system, generalizing the results to asthma populations worldwide should be approached with caution. In addition, the patients were diagnosed in secondary care, meaning that the study sample might include more severe asthmatics than the general asthma population. However, the follow-up period was exceptionally long, and the scope of information gained from patients increases the reliability of the results. Most importantly, patients' asthma diagnosis was confirmed through lung function measurements and evaluation by a respiratory physician, and the calculation method used in adherence assessment was detailed.

6.2 Use of medication

In the present study, patients with adult-onset asthma were prescribed medium to high doses of ICS (budesonide equivalents) during the 12-year follow-up (annual average ICS dose was between 775 and 939 ug). When patients were grouped based on their level of asthma control, higher doses were prescribed to patients with uncontrolled (12 y average daily dose 937 ug) than patients with controlled asthma (12 y average daily dose 760 ug). This dosing aligns with the GINA report and national current care guideline, which recommend dose titration according to symptom control and evaluation of future exacerbations (Current Care Guidelines 2022; GINA 2021). Patients with uncontrolled asthma also had more dose changes and daily add-on drugs in use than patients with controlled asthma, indicating that physicians have tried changing the treatment pattern to achieve better disease control. However, higher doses of ICS, more frequent dose changes and more use of add-on therapies did not improve the asthma control of those with uncontrolled

asthma. Poor disease control may be due to several long-term factors such as comorbidities, smoking, and obesity (Braido et al. 2016; Boulet and Franssen 2007; Polosa et al. 2011; Tuomisto et al. 2016). From the SAAS population, patients with uncontrolled asthma had more comorbidities and were more often current or ex-smokers than patients with controlled asthma, which may partially explain why patients with uncontrolled asthma were unresponsive to current therapeutic strategies. Moreover, incorrect inhaler usage, poor inhaling technique, and suboptimal adherence to treatment may decrease the disease control (Munoz-Cano et al. 2017).

6.3 Adherence to inhaled corticosteroids

The average 12-year adherence to ICS was 69% in the SAAS adult-onset asthma study population. Previous studies with remarkably shorter follow-ups (i.e., usually a one-year period) have suggested adherence levels to be between 22% and 84% (Tables 4-6 in the Results section). However, of the 30 studies during the last decade that objectively measured adherence, only three reported mean adherence levels of ≥80%. Similar findings have also been reported in the systematic review, which concluded adherence to asthma controller therapy to be generally low (Engelkes et al. 2015).

The factors related to a relatively high long-term adherence found in this study are diverse. A confirmed asthma diagnosis may be considered a major advantage of this study since all patients have needed continuous treatment. Moreover, adherence calculations were performed when a patient had regular ICS medication prescribed over the whole follow-up. Furthermore, factors related to costs such as reimbursement of asthma medicine expenses, relatively low medicine prices, free renewal of prescriptions, and the public health services being available for all may explain our results that indicate higher adherence than most of the previous studies. In long-term diseases such as asthma, the prescriptions are usually made for 1 year at a time in Finland, meaning that adherence to treatment is not dependent on the physician's adherence to prescribing the medication. Lung function measurements at asthma contacts and guidance to use inhalers correctly from health care providers such as specialized asthma nurses may have increased patients' adherence to treatment (Takala et al. 2020). Alongside the study, the Finnish asthma program was conducted to improve asthma care, which may have increased the ICS adherence rates in this study. We also consider our method to measure ICS adherence to be

straightforward as a patient's ICS purchases (dispensed ICS) were compared to the doses the doctor had prescribed. As all doses were converted to budesonide equivalents, the comparison of individual patients' doses as prescribed and dispensed ug levels yearly or cumulative manner was enhanced. On the contrary, database studies evaluating adherence often use terminology out of the clinical context, meaning formulas including concepts such as "defined daily doses" or "day's supply" (Cvietusa et al. 2019; Cyr et al. 2013; Gupte-Singh et al. 2015; Kang et al. 2018; Van Steenis et al. 2014). In these concepts, interpreting how individual patients have used medication, e.g., medium or high doses, is difficult to precisely predict.

In this study, patients with <80% adherence were dispensed lower doses of ICS than patients with ≥80% adherence, but the groups did not differ in prescribed doses, symptom control, or inflammatory markers (blood eosinophil counts, exhaled nitric oxide or IgE). However, patients with higher adherence (≥80%) had more OCS courses, daily add-on drugs in use, and asthma-related healthcare visits, supposing more severe asthma than patients with lower (<80%) adherence. Although such implies that suboptimal adherence did not affect the momentary condition of presumably milder asthma patients, the lung function change was steeper in a group of <80% adherence in the long term. When assessing self-reported adherence of clinical phenotypes in the SAAS population, the most common reason for not taking medication as prescribed in atopic and nonrhinitic clusters was a sense of improved asthma whereas in the obese cluster patients commonly reported financial matters (Ilmarinen et al. 2021). Riley et al. (2021) found in recent scoping review that reasons for nonadherence were diverse. Financial reasons and beliefs about medication were commonly reported as barriers to asthma medication adherence, aligning with the results in the SAAS study.

Suboptimal adherence has been associated with non-controlled disease, as previously discussed (Braido et al. 2016; Dima et al. 2019; Klok et al. 2014), as well as the logical continuum of events that the patient is not taking the medication as prescribed/instructed and gets more symptomatic. However, at the SAAS 12-year follow-up visit, 125 patients had non-controlled asthma, and 56 had controlled asthma and the mean 12-year adherence to ICS was higher in patients with non-controlled (76%) than in patients with controlled disease (63%). As suggested, based on the prescribed medication and cumulative doses of patients with uncontrolled asthma, these patients seemed to have more severe disease; even with high-dose treatment, these patients stayed uncontrolled. The explanation for poor asthma control could be hypothesized as suboptimal adherence, but as shown, mean adherence was higher in patients with non-controlled asthma confirming the

assumption of more severe disease. Interestingly, when non-controlled patients were divided based on their level of 12-year adherence, the groups were divided nearly equally to ≥80% adherent and <80% adherent. Therefore, those with non-controlled asthma due to low adherence also exist in the SAAS cohort, but surprisingly, non-controlled patients with higher adherence were more neutrophilic, used more add-on drugs (LABA, LTRA), and had a higher number of asthma-related contacts to health care. When evaluating the decline in lung function over a 12-year period in patients with non-controlled asthma, those with lower (<80%) adherence showed a faster decline in FEV_1 than those with ≥80% adherence. This distinction was unobserved in patients with controlled asthma. In conclusion, using ICS may have had a protective effect against lung function decline in patients with non-controlled asthma.

Patients with adult-onset asthma did not reach asthma control despite being highly adherent (≥80%) to long-term ICS treatment. Instead, patients with a higher 12-year adherence showed higher neutrophilic inflammation compared to patients with a lower level of adherence. These results may suggest a lower degree of Type 2 inflammation ("Type 2 low asthma") and, therefore, reduced efficacy to ICS. High exposure to corticosteroids has also been associated with many comorbidities, such as obesity and osteoporosis (Kankaanranta et al. 2023; Sullivan et al. 2018). Our results showed that high ICS doses were prescribed over the whole 12-year follow-up, exposing patients to possible adverse outcomes of the corticosteroid medication. In a worst-case scenario, a patient may have ended up using high ICS doses cumulatively leading to increased levels of blood neutrophils and comorbid conditions such as obesity. These factors may also increase insensitivity to treatment and possibly worsen asthma outcomes in the long term. Moreover, an increased number of comorbid conditions may complicate achieving asthma control. Therefore, tapering ICS doses should be considered, and focusing on more individualized treatment approaches, pharmacological and non-pharmacological manner, must be highlighted among adult-onset asthma patients (Mosbech et al. 2023; Pavord et al. 2023).

6.4 High use of short-acting β_2-agonist

Of the SAAS patients, 10% were classified as high SABA users (corresponding to ≥3 dispensed SABA canisters annually during the 12-year follow-up), and only 2.5% of patients showed a medication use behavior suggesting some degree of SABA

over-reliance. The prevalence of high SABA use in SAAS was lower than in most European countries studied in SABA use IN Asthma (SABINA) program, where high SABA use was shown to be 9% in Italy, 16% in Germany, 29% in Spain, 30% in Sweden, and 38% in the UK (Janson et al. 2020). When we evaluated the relationship between SABA and ICS use, we found that patients with high SABA use were dispensed higher doses of ICS (912 ug vs. 470 ug) and were more adherent to ICS treatment than patients using less SABA. The prevalent perception has been that patients underuse ICS, and when symptoms worsen, they rely on SABA. Vervloet et al. (2020) found that high use of SABA predicted lower ICS implementation. However, there has been a lack of clinical, long-term follow-up studies assessing medication use in patients with confirmed asthma diagnoses. Previous cross-sectional register-based studies have reported high rates of SABA overuse, but in those studies, SABA use has been evaluated based on prescription records, which probably overestimate SABA usage since a prescription does not guarantee the medication was dispensed (Bloom et al. 2020; Hull et al. 2016).

High SABA use has been associated with poor clinical outcomes such as increased hospital admissions, exacerbations, and a decrease in patients' quality of life (Bloom et al. 2020; FitzGerald et al. 2017; Nwaru et al. 2020). In SAAS, despite good adherence to treatment with high-dose ICS, high SABA users had more frequent exacerbations, emergency room visits, and courses of oral corticosteroids and antibiotics than low SABA users. Possible factors for higher demand for SABA were more frequent symptoms, poorer asthma control and more severe asthma than low SABA users. Poor asthma outcomes have been stated to be because of over-reliance on SABA and underuse of ICS; however, controversial results have also been published. Quint et al. (2022) found that high SABA use was independently associated with severe asthma exacerbations despite ICS therapy being prescribed or dispensed. In SAAS, obesity and higher symptom scores at diagnosis predicted higher SABA use during the follow-up. Currently, obesity treatment has received some new medications, as the indications of diabetes medications semaglutide and liraglutide have been extended to the treatment of obesity (Müller et al. 2022; O´Neil et al. 2018). These medications bring new ways to support the weight loss of obese asthma patients, as their treatment should prioritize weight loss. Future asthma research needs more studies in elderly populations with clinically confirmed asthma diagnoses and their dispensed medication data to discover more precise factors leading patients to high SABA use with poorly controlled asthma. Since high SABA use indicates more severe asthma, these patients must be recognized more carefully as they require more effective interventions.

6.5 Clinical implications and future directions

The present study showed that adult-onset asthma patients had a 69% adherence to long-term ICS therapy, but most patients' asthma was not controlled (partially or uncontrolled) after 12 years of treatment. Patients with non-controlled asthma also had higher adherence to ICS treatment than patients with controlled asthma. When only the patient group with non-controlled asthma was considered, half had an average 12-year adherence to ICS medication of <80%; these patients also had a more rapid decline in FEV_1 during the 12-year follow-up than patients with higher adherence (≥80%). These findings show the importance of treatment adherence in preventing poor long-term outcomes to patients' lungs. Therefore, a thorough evaluation of asthma control and treatment adherence enhances the identification of patients who are susceptible to their lung function rapidly declining over time. Furthermore, unhealthy lifestyle habits such as smoking, and obesity may induce insensitivity to ICS and reduce response to treatment (Ilmarinen et al. 2021; Lazarus et al. 2007; Peters et al. 2018; Tomlinson et al. 2005). These issues may explain why patients with ≥80% adherence stay more symptomatic and need more OCS courses and asthma-related visits to health care than patients with lower adherence. Prioritizing lifestyle aspects, such as smoking and weight management, in managing non-controlled adult asthma patients and developing new treatment approaches for these patients is essential.

Patients were treated with moderate to high doses of ICS on average over a 12-year follow-up period. During the time the study was conducted it was common to prescribe relatively high doses of ICS, in line with the current care guidelines that recommended doubling the ICS dose in asthma flare-ups. It is important to acknowledge that most patients had non-controlled asthma which possibly explains the prescribed high doses. However, patients with uncontrolled asthma had more add-on therapies in daily use and high-dose ICS treatment, yet they still did not achieve good control of the disease. These results suggest that the benefits of the used treatment should be assessed more regularly to avoid a prolonged corticosteroid load without effect on disease management (Beasley and Kankaanranta 2023; Pavord et al. 2023).

As asthma remission is rare in patients with adult-onset asthma, future research focusing on longer follow-ups would increase the understanding of adult-onset asthma phenotypes. The methods used to assess medication adherence should be more standardized. If such an assessment is impossible due to the diversity of different registers and databases, the methods sections in international asthma-

related journals could be broadened to clarify the data and/or adherence formula used in calculations to enhance the reliable comparison of the studies. Optimally, every study would include the following information or information the data was missing:

a) Age of asthma onset
b) Diagnosis of asthma
c) Data used in adherence calculations (prescribed, dispensed, both)
   -If both are unavailable, what is the reference?
d) Length of follow-up (adherence monitoring per patient)
e) Average used ICS ug per patient during the follow-up

In addition, when considering patients' adherence to long-term medication use, the data used in these studies should assess medication purchases, patient reports, or data from electronic monitoring devices. Future studies assessing prescribed medication should only be considered to describe the physician's prescribing practices or adherence to current care guidelines, but not patients' treatment adherence, to clarify the methods used in adherence assessment.

In the asthma treatment field, considerable steps have been taken toward the phenotype-specific treatment of the patients since biologic therapies have been available for patients with severe asthma and Type 2-driven inflammation. However, future studies should pay more attention to the pathophysiology of Type 2 low asthma since it remains poorly understood, and current treatment strategies seem insufficient, according to the study's results.

7 CONCLUSIONS

1. The average 12-year adherence to ICS medication was relatively high (69%) in patients with new-onset adult asthma. The prescribed doses for the patients were on average moderate to high over 12 years. When patients were grouped based on their level of asthma control, higher ICS doses were prescribed to patients with uncontrolled compared to patients with controlled and partially controlled asthma.

2. Patients with non-controlled (partially or uncontrolled) asthma had a higher average 12-year adherence to ICS treatment (76%) than patients with controlled asthma (63%). A high adherence to high-dose ICS treatment over a long-term period was insufficient to improve asthma control of the non-controlled patients. However, from non-controlled patients, those with <80% adherence had steeper lung function decline over the follow-up, underlining the poor consequences of poor adherence and non-controlled disease.

3. Patients with lower long-term ICS adherence were less neutrophilic, achieved asthma control more often, and had fewer hospital days or visits to healthcare due to their asthma than patients with higher adherence. These factors suggest that patients with lower adherence had milder asthma. Patients with lower adherence had a steeper change in lung function than patients with higher adherence, implying that better adherence to ICS treatment could have prevented these adverse lung outcomes, thus highlighting the importance of each patient's adherence to treatment.

4. High SABA use was infrequent in patients with confirmed adult-onset asthma. Patients with high SABA use had higher adherence to ICS treatment but used more oral corticosteroid and antibiotic courses than those with lower use of reliever medication. High reliever medication use indicates more problematic asthma and is associated with obesity at diagnosis, emphasizing the early recognition of these patients.

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ORIGINAL COMMUNICATIONS

PUBLICATION I

Inhaled corticosteroids and asthma control in adult-onset asthma: 12-year follow-up study

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Inhaled corticosteroids and asthma control in adult-onset asthma: 12-year follow-up study

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ABSTRACT

Background: Prescribed inhaled corticosteroid (ICS) doses in asthma have been studied in cross-sectional settings whereas long-term follow-up studies have not been carried out.
Objective: To evaluate prescribed medication longitudinally by calculating cumulative ICS doses and dose changes in a cohort of new-onset adult asthma during 12 years and in different groups of asthma control.
Methods: A total of 203 patients were followed for 12 years as part of Seinäjoki Adult Asthma Study (SAAS). All asthma-related visits and prescribed medication over the study period were collected from medical records.
Results: Total cumulative ICS dose for the 12-year follow-up period was 3.4g (± SEM 0.1) per patient. Both respiratory specialists and GPs prescribed step-ups and step-downs in ICS treatment and in total 649 dose changes were noted during the follow-up (median 3(1–5) per patient). Patients with uncontrolled asthma received higher ICS doses throughout the follow-up period, and therefore, cumulative 12-year ICS dose (3.8g ± SEM 0.2) in this group was higher than that in those with partially controlled (3.4g ± SEM 0.2) or controlled disease (2.9g ± SEM 0.2) ($p = 0.0001$). Patients with uncontrolled asthma were also prescribed a higher number of ICS dose changes than patients with controlled disease.
Conclusion: Despite frequent dose changes and high ICS doses during the 12-year follow-up, the level of asthma control remained poor in patients with uncontrolled asthma. This suggests that high ICS doses may not be effective enough for management of disease in patients with uncontrolled adult-onset asthma and novel targeted treatments are required.

1. Introduction

Asthma is a heterogenic disease occurring in both adults and children worldwide [1,2]. Age at disease onset has been shown to have a significant role in distinguishing the phenotypes of asthma [3,4]. Recent findings indicate that the majority of new-onset asthma cases occur in adults [5,6]. The early-onset (childhood-origin) and adult-onset asthma appear to be different with respect to several disease characteristics [3,4]. For example, over 70% of the early-onset asthma patients have been predicted to remit while only < 5% remission rates have been observed in patients with adult-onset asthma [7–9]. This suggests that data from studies among patients with asthma-onset at childhood may not be applicable to adult-onset forms of the disease.

Current guidelines recommend inhaled corticosteroids (ICS) as the basis of initial controller treatment [2]. Control-based management of asthma means that treatment is adjusted based on a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risks [2]. In patients with increased asthmatic symptoms and/or exacerbations of the disease, step-up of the treatment is recommended. Before the era of different add-on therapies such as long-acting bronchodilators or leukotriene antagonists, an increase in the dose of ICS was the recommended step-up in the therapy and this option remains an effective second line option even in the current guidelines [2] and especially if exacerbations of asthma prevail [2,10]. Several factors such as correct use of inhalers and adherence to the treatment affect the outcome of the disease and have been described to be major barriers for successful treatment [11,12]. Another factor less studied is adherence to treatment guidelines, i.e. whether correct treatment is prescribed. This has been examined in some register-based and cross-sectional studies which have indicated that the prescribing

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Abbreviations

ACT	Asthma control test
AQ20	Airways questionnaire 20
BD	Bronchodilator
BMI	Body mass index
FeNO	Fraction of NO in exhaled air
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HFA	Hydrofluoroalkane propellant
ICS	Inhaled corticosteroid
LABA	Long-acting β_2 agonist
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroids
SABA	Short-acting β2-agonist

practices of ICS may need further improvement [13–17]. It appears that the adherence to the guidelines may also be different between specialists and general practitioners (GPs) [16,17]. Discontinuation of the controller treatment has been reported to be common in children managed in primary care [18]. However, there is paucity of information concerning ICS therapy in long-term settings. It may, however, be expected that because the remission rate is low in patients with adult-onset asthma [8,9] the prescribed ICS dose should increase cumulatively over the years.

In light of the fact that the achievement of good disease control is the target of asthma management, relatively little is known on the long-term variability in asthma control. Even though some interventional studies have shown that good asthma control can be achieved by stepping up treatment or by follow-up interventions [19,20], surprisingly large proportion of patients remain uncontrolled after stepping up the therapy [12]. Factors such as smoking and concurrent chronic obstructive disease, obesity, male sex and rhinitis have been reported to associate with an increased risk of uncontrolled asthma [8,21]. This suggests that a poor disease control may result from several events occurring longitudinally. Therefore, it can be hypothesized that the status of current uncontrolled asthma can be traced back by following prescribed medication for asthma over the past years. Moreover, our aim was to assess the extent to which the initial ICS therapy is changed in real-life in new-onset adult-asthma patients.

2. Methods

2.1. Patients and study design

The current study was part of Seinäjoki Adult Asthma Study (SAAS), which is a prospective single-center (Seinäjoki Central Hospital, Seinäjoki, Finland) 12-year follow-up study containing 257 consecutive patients with diagnosis of new-onset adult asthma. All adult age (≥15 years) newly diagnosed patients were included during the period of 1999–2002. Institutional permissions were obtained and study participants gave written informed consent of the study protocol approved by the Ethics committee of Tampere University Hospital, Tampere, Finland.

The schematic presentation of the study is shown in Fig. 1. The study protocol has been published separately [22]. Patients were consecutively included in the study if all of the following criteria were fulfilled: 1) new-onset asthma diagnosed by respiratory specialist 2) confirmation of diagnosis by lung function measurements showing reversible obstruction 3) symptoms of asthma 4) age ≥15 years. Patients with comorbidities, other lung diseases, and history of smoking were included. The study was divided into two parts: collection of the original cohort and the 12-year follow-up visit (Fig. 1). At the baseline visit data was collected on symptoms, lung function, demographics and initial medication as previously described [23,24]. Patients were followed up for 12 years (mean 12.2 years, range 10.8–13.9 years) after the diagnostic visit. From the original cohort of 257 patients, 203 returned to the 12-year control visit in which asthma status, medication, control, and lung function were evaluated [8,23–25]. Asthma-related visits [24] and medication information were collected from the whole 12-year follow-up period from medical records (Fig. 1).

2.2. Medication information and ICS dose calculations

Prescribed medications and dose calculations were carried out based on the data obtained from all asthma-related visits (Fig. 1). Focus in this study was in ICS (including ICS-LABA combination inhalers). All ICS doses were converted into budesonide equivalents [2,26]. High dose was determined as daily dose over 800 μg and medium dose over 400–800 μg^2. If medication information was inadequate, it was calculated based on previous confirmed information. If the prescribed dose ranged the calculations were made by using the smallest dosing possibility (e.g. 1 or 2 inhalations twice daily was calculated as 1 inhalation twice daily). Medication gaps over 9 days and medication changes over 14 days were taken into consideration.

2.3. Asthma control

Patients were separated into three groups by their asthma control at follow-up visit which was defined according to the Global Initiative for Asthma (GINA) 2010 guideline [27] as previously reported [8]. Patients with controlled asthma were defined by fewer symptoms, normal lung

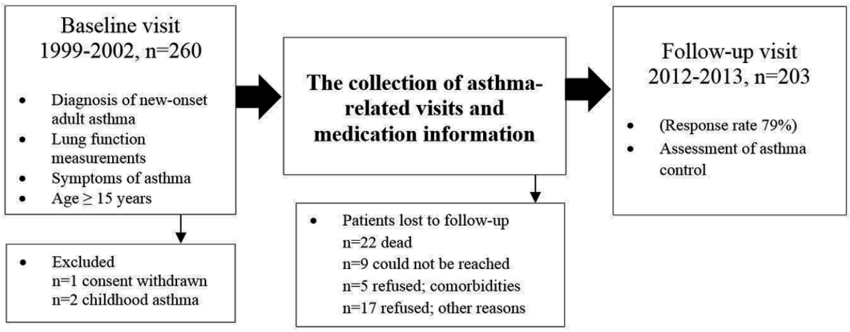

Fig. 1. Flow chart of Seinäjoki Adult Asthma Study (SAAS).

function and rare usage of reliever medication. Patients with partially controlled asthma may have had 1-2 of the following features: day or nighttime symptoms, need for rescue treatment, decreased lung function or limitation of activities due to asthma. When defining patients with uncontrolled asthma, three or more of those features were required.

2.4. Statistical analysis

The results are shown as mean ± SD, or median (interquartile range) but annual cumulative and daily doses are represented as mean ± SEM for clarity. Baseline and follow-up values were compared by using paired samples *t*-test, related samples Wilcoxon signed rank test or McNemar test. Comparison of three control groups were analyzed by using one-way ANOVA with Tukey's post hoc test, Pearson Chi-Square test or independent samples Kruskal-Wallis test. To analyze differences in cumulative dose of ICS and annual daily ICS dose between three control groups two-way ANOVA was used. A P-value < 0.05 was regarded as statistically significant. Statistical analysis were performed using SPSS software, version 24 (IBM SPSS, Armonk, NY, USA) and GraphPad Prism software, version 7.03 (GraphPad, La Jolla, CA, USA).

3. Results

3.1. Characteristics of the study patients

The main characteristics of the study population (n = 203) are shown in Table 1 [8]. The majority of patients were non-atopic (63%) and females (58%) and half of the patients were current or ex-smokers. Patients were more obese, had better spirometry values and lower blood eosinophil count at the 12-year follow-up visit than at baseline. Symptom score (AQ20) was lower at the follow-up visit than at baseline. During the diagnostic visit (baseline), 8% of the patients used inhaled corticosteroids (ICS) whereas 76% reported to be daily ICS users at the follow-up visit [8].

3.2. Annual prescribed daily and cumulative ICS doses

To visualize prescribed anti-inflammatory medication for asthma in the whole study population, the average annual daily inhaled corticosteroid (ICS) dose and cumulative dose were calculated (Fig. 2). The highest average annual ICS dose was 939 μg (± SEM 25) among the study population which was reached one year after the diagnosis (Fig. 2). The average total cumulative dose of ICS for the whole 12-year follow-up period was 3.4g (± SEM 0.1) per patient. The annual cumulative averages consist of individual patient profiles (eFigures 1–4) where each change in slope represents the change in dose of ICS and the steeper the change in slope the bigger the change in dose. Of the study cohort 87.2% (n = 177) had at least one change in ICS dose. Taking all increases and decreases into account 649 dose changes occurred among study population (median 3 (1–5) per patient) in 12-year study period. Of the increases (N = 281) 38.4% were prescribed by respiratory specialist and 61.6% by GP (general practitioner) and of the decreases (N = 368) 56.5% were prescribed by respiratory specialist and 43.5% by GP. Daily ICS was discontinued and ICS were continued on as needed basis until follow-up visit in 9 patients (4%). In addition, 13 patients (6.4%) had a period when ICS were used on as needed basis but later on regular daily ICS was prescribed again.

3.3. Asthma control

At the 12-year follow-up visit asthma control was evaluated and the patients were divided into three groups according to their asthma management level: controlled (n = 69), partially controlled (n = 74) and uncontrolled (n = 60) [8]. Characteristics of the groups are shown in Table 2. Patients with uncontrolled asthma were more often males, older and used higher dose of inhaled corticosteroids than patients with controlled asthma [8]. Daily add-on drugs were more often used in patients with uncontrolled than in patients with partially or controlled asthma. Lung function was higher in patients with controlled asthma than patients with partially or uncontrolled asthma. However, no difference was found in inflammatory parameters such as blood eosinophil counts, FeNO or total IgE between the three groups.

3.4. Annual cumulative and daily ICS doses in asthma subgroups

To evaluate how the level of asthma control affects prescribing of medication for the patient, we studied average annual cumulative and daily doses of ICS in the study subgroups. Patients with controlled, partially controlled and uncontrolled asthma had significantly different ($p < 0.0001$) cumulative doses of ICS during the 12-year study period (Fig. 3). Patients with controlled asthma had the lowest total cumulative dose of ICS (2.9g ± SEM 0.2) whereas patients with uncontrolled asthma had the highest total cumulative dose of ICS (3.8g ± SEM 0.2). Patients with uncontrolled asthma had higher annual daily dose of ICS versus patients with controlled asthma from 2 to 12 years after diagnosis ($p < 0.05$) (Fig. 4). When comparing patients with controlled and partially controlled asthma, the average annual daily ICS dose differed significantly only at two follow-up years (2 and 12- years after diagnosis). The highest annual daily average dose of ICS was 981 μg (± SEM 72) with uncontrolled asthma patients at tenth year after diagnosis and the lowest was 635 μg (± SEM 48) with controlled asthma patients 12 years after diagnosis. The current guideline [2] suggests that asthma therapy should be stepped down once good asthma control has been achieved and maintained for about 3 months. Even though current control-based treatment strategy was not in use during the early phase of this study, the decrease in the mean ICS dose in the second year in the group having currently well-controlled asthma suggest that in this group relatively good symptom control was achieved and the ICS dose was reduced (Fig. 4).

Table 1
Characteristic of the study patients (n = 203).[a]

	Baseline (n = 203)	Follow-up (n = 203)	p value
Age (y)	46 (14)	58 (14)	< 0.001
Female gender n (%)	118 (58.1)	118 (58.1)	
BMI, kg/m2	27.1 (24.2–29.8)	28.1 (24.4–31.3)	< 0.001
Smokers (incl. ex) n (%)	103 (50.7)	107 (52.7)	0.125
Post-bd FEV_1% pred	88 (77–99)	90 (80–98)	0.013
Post-bd FVC % pred	94 (82–102)	98 (88–107)	< 0.001
Post-bd FEV_1/FVC	0.79 (0.75–0.85)	0.75 (0.69–0.81)	< 0.001
Blood eosinophils (10^9/l)	0.28 (0.15–0.42)	0.17 (0.10–0.27)	< 0.001
Total IgE (kU/l)	84 (35–174)	61 (24–163)	0.046
AQ20 score	7 (4–10)	4 (2–7)	< 0.001
Daily ICS use n (%)	16 (8.0)	155 (76.4)	< 0.001
Daily ICS dose, μg budesonide equivalents of daily users		800 (400–1000)	
Daily LABA n (%)		96 (47.3)	
Daily add-on drug n (%)		103 (50.7)	
Daily LTRA n (%)		27 (13.4)	
Daily theophylline n (%)		4 (2)	
Daily tiotropium n (%)		8 (3.9)	

[a] A part of the data has been previously reported [8]. Data are presented as n (%), mean (SD) or median (interquartile range), unless otherwise stated. BMI = body mass index, ICS = inhaled corticosteroid, BD = bronchodilator, LABA = long-acting β2-agonist, LTRA = leukotriene receptor antagonist, FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, AQ20 = airways questionnaire 20.

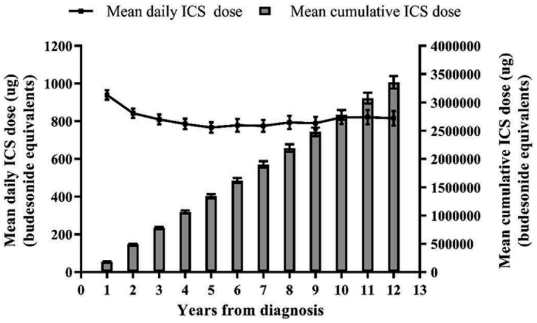

Fig. 2. Average prescribed annual daily inhaled corticosteroid (ICS) dose and cumulative dose among study population (n = 203). The data are presented as mean ± SEM.

3.5. Dose changes in asthma subgroups

To analyze other possible differences in prescribed ICS medication according to the status of asthma control, we compared the number of changes in ICS dose between the subgroups. Of the patients with uncontrolled asthma, 87% had at least one change in dose, and altogether 235 dose changes were needed to these patients within 12 year follow-up period. The differences between dose changes in control groups are shown in Fig. 5 where each change in slope indicates a change in ICS dose. The median number of dose changes was 4 (2–6) per patient with uncontrolled asthma and 2 (1–4) per patient with both partially controlled as well as controlled asthma. Statistically significant difference was seen in the number of dose changes between patients with uncontrolled and controlled asthma ($p = 0.016$) and also a similar tendency ($p = 0.055$) was observed between the patients showing uncontrolled and partially controlled disease. Respiratory specialist increased ICS dose significantly more often in patients with uncontrolled asthma than in controlled asthma (Table 3).

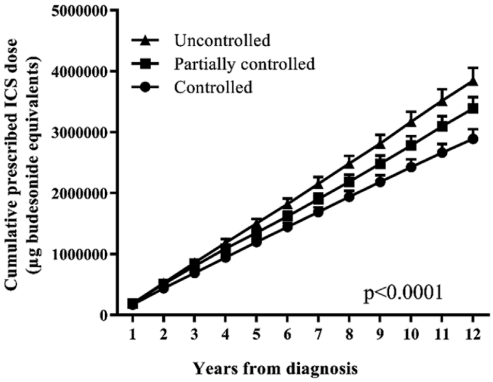

Fig. 3. Average of annual prescribed cumulative dose of inhaled corticosteroid (ICS) in asthma subgroups based on different level of asthma control. The data are presented as mean ± SEM. P-value indicates the difference between three slopes analyzed by two-way ANOVA.

4. Discussion

In this study we evaluated annual daily and cumulative doses of ICS from diagnosis to 12-year follow-up visit in patients with adult-onset asthma, in the total cohort and in patients having different levels of disease control. Concordant with the low rate of remission in adult-onset asthma the prescribed ICS dose increased in a cumulative manner. Cumulative and average annual daily dose of ICS were significantly higher in patients with uncontrolled asthma when compared to patients with controlled asthma through the 12-year study period. Patients with uncontrolled asthma also needed higher numbers of ICS dose changes. These results suggest that in adult-onset asthma the status of uncontrolled disease is not a momentary event but rather reflects poor asthma control long-term which may not be responsive to current therapeutic strategies.

Cross-sectional studies have revealed trends in ICS prescribing for adults and children [13–15,17,18] but follow-up studies concerning

Table 2
Characteristics of asthma patients at 12-year follow-up visit (n = 203).[a]

	Controlled n = 69	Partially controlled n = 74	Uncontrolled n = 60	p value
Age (y)	54 (14)	60 (12)*	61 (13)*	0.005
Female gender n (%)	48 (69.6)	42 (56.8)	28 (46.7)*	0.030
BMI, kg/m2	27.7 (4.8)	28.9 (5.8)	29.1 (6.1)	0.324
Smokers (incl. ex) n (%)	25 (36.2)	45 (60.8)*	37 (61.7)*	0.003
Daily ICS use n (%)	47 (68.1)	57 (77.0)	51 (85.0)	0.078
ICS daily dose µg budesonide equivalents of daily users	550 (400–1000)	800 (713–1000)	1000 (400–1350)*	0.016
Daily SABA n (%)	2 (2.9)	7 (9.5)	14 (23.3)*	< 0.001
Daily LABA n (%)	19 (27.5)	36 (48.6)*	41 (68.3)*	< 0.001
Daily add-on drug n (%)	20 (29)	38 (51.4)*	45 (75)*#	< 0.001
Daily LTRA n (%)	4 (5.8)	11 (14.9)	12 (20.3)*	0.049
Daily theophylline n (%)	0 (0)	2 (2.7)	2 (3.3)	0.338
Daily tiotropium n (%)	0 (0)	0 (0)	8 (13.3)*#	< 0.001
Use of oral corticosteroid courses for asthma n (%)	15 (22.1)	24 (32.4)	26 (44.8)*	0.025
Comorbidities	1 (0–2)	1 (0–2)	2 (1–3)*#	< 0.001
Post-bd FEV1% pred	96 (91–102)	89 (79–98)*	81 (64–94)*#	< 0.001
Post-bd FVC % pred	102 (93–110)	96 (85–105)	95 (83–105)*	0.007
Post-bd FEV1/FVC	0.77 (0.73–0.83)	0.76 (0.69–0.81)	0.71 (0.61–0.78)*#	< 0.001
Blood eosinophils (10^9/l)	0.16 (0.12–0.28)	0.18 (0.09–0.28)	0.19 (0.09–0.27)	0.870
FeNO (ppb)	12 (6–19)	10 (5–20)	11 (5–18)	0.533
AQ20 score	2 (0–4)	4 (2–6)*	8 (5–11)*#	< 0.001
ACT score	24 (22–25)	22 (20–24)*	18 (14–21)*#	< 0.001

[a] Part of the data has been previously reported [8]. Data is presented as n (%), mean (SD) or median (interquartile range).* indicates $p < 0.05$ versus controlled and# indicates $p < 0.05$ versus partly controlled. BMI = body mass index, ICS = inhaled corticosteroid, BD = bronchodilator, SABA = short-acting β2-agonist, LABA = long-acting β2-agonist, LTRA = leukotriene receptor antagonist, FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, FeNO = fraction of NO in exhaled air, AQ20 = airways questionnaire 20, ACT = asthma control test.

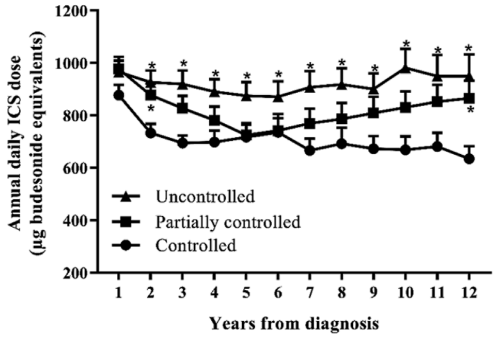

Fig. 4. Average of annual daily prescribed dose of inhaled corticosteroid (ICS) in asthma subgroups based on different level of asthma control. The data are presented as mean ± SEM. * indicates $p < 0.05$ versus controlled group analyzed by one-way ANOVA with Tukey's post hoc test or independent samples Kruskal-Wallis test.

individual patient's medication use longitudinally have not been carried out so far. The remission rate in childhood asthma have been evaluated and it appears to be significantly higher than in patients with adult-onset asthma [7,8]. Discontinuation of asthma medication has been reported to be common in children reflecting the low use of medication longitudinally in patients with early-onset asthma [18]. In our patients with adult-onset asthma cumulative dose of ICS increased during the 12 year follow-up and this combined with relatively low remission rate may indicate more persistent and difficult manifestations of the disease. Moreover, this is supported by the observed low rate (4%) of discontinuation of prescribed daily ICS treatment in all patients with adult-onset asthma.

Patients with uncontrolled asthma were treated with higher ICS doses than patients with partially and controlled asthma almost for the entire 12-year follow-up period, and therefore the cumulative dose of ICS increased most steeply in patients with uncontrolled disease. The average total cumulative prescribed dose of ICS 12 years after diagnosis in these patients was 33% higher than that in patients with controlled disease. In addition, the average annual daily dose was the highest in patients with uncontrolled asthma when compared to patients with controlled or partially controlled asthma 12 years from the diagnosis. The average annual daily dose ranged from 872 µg to 981 µg in patients with uncontrolled asthma, indicating that most patients were treated with high ICS dose throughout the 12-year study period. Partially controlled patients started with high dose of ICS but the dose declined during the first five years after diagnosis and then begun to increase. Treatment with high dose ICS was started also in controlled patients but the annual daily dose decreased to medium level during the first two years from diagnosis. These results are in line with guidelines [2] recommending to increase the controller medication if asthma remains uncontrolled by the current therapy and to decrease the dose when asthmatic symptoms have remained well-controlled for 3 months.

The need for high cumulative and average annual daily ICS doses in patients with uncontrolled asthma suggest that the status of disease control is not a momentary event but develops longitudinally as a result of several precipitating factors. The determinants which may contribute to inadequate asthma control include obesity, smoking and non-adherence to treatment [2,8,21]. Also incorrect use of inhaler devices and poor inhaling techniques are possible reasons leading to worsening of the asthma control [12]. It is commonly known that adherence to ICS treatment is unsatisfactory affecting management of asthma [11,28]. The risk factors for poor adherence have been studied and patients with milder asthma seem to be more non-adherent to the treatment compared with patients having moderate to severe symptoms of asthma [29,30]. This study was not planned to evaluate adherence to asthma treatment but to establish basis for these studies by observing prescribing practices of ICS in detail in long-term follow-up.

While assessing controller treatment and possible changes to ICS therapy the disease control, responsiveness to treatment and future risks must be taken into account for finding the appropriate step-up or

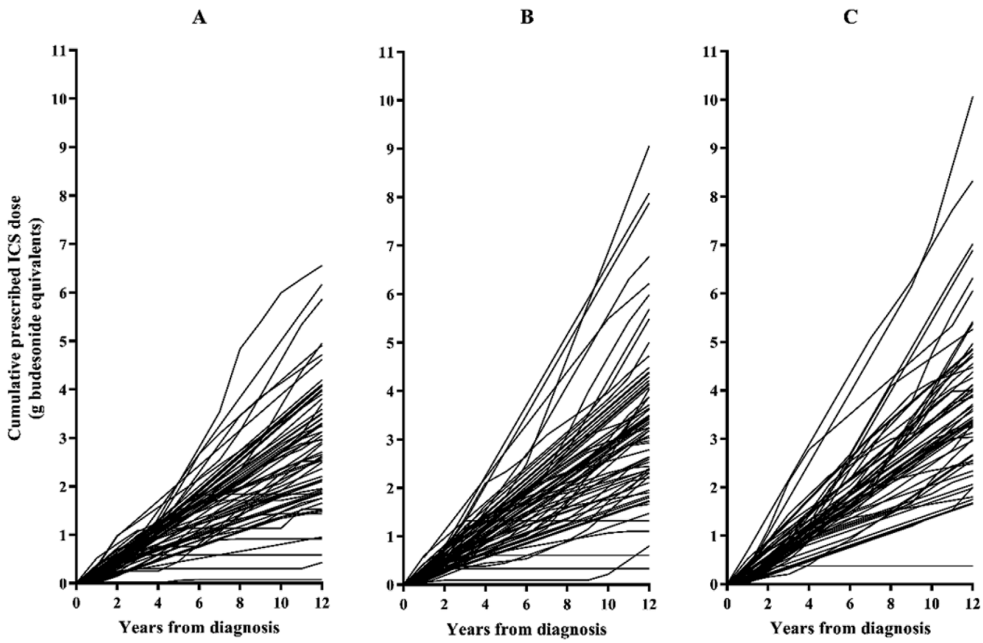

Fig. 5. Cumulative dose of prescribed inhaled corticosteroid (ICS) for individual patients in controlled A (n = 69), partially controlled B (n = 74) and uncontrolled C (n = 60) subgroups.

Table 3
Changes in ICS doses among patients with different level of asthma control and the proportion of changes made by respiratory specialist.

	Controlled n = 69	Partially controlled n = 74	Uncontrolled n = 60	p value
Dose changes N	195	219	235*	0.012
Increase in dose N (%)	77 (39)	98 (45)	106 (45)*	0.010
Increase in dose made by respiratory specialist N (%)	24 (31)	39 (40)	45 (42)*	0.035
Decrease in dose N (%)	118 (61)	121 (55)	129 (55)#	0.034
Decrease in dose made by respiratory specialist N (%)	60 (51)	81 (67)	67 (52)	0.470

Data are presented as N (%). * indicates $p < 0.05$ versus controlled and # indicates $p < 0.05$ versus partially controlled analyzed by one-way ANOVA with independent samples Kruskal-Wallis test. n, number of patients, N, number of dose changes.

step-down phases in treatment [2,15]. A previous study examined the effects of step-up treatment to uncontrolled adult asthma patients and showed that in spite of the optimization of the treatment most patients continued to show inadequately controlled asthma [12]. In our study patients with uncontrolled asthma had significantly more ICS dose changes and increases in ICS dose than patients with controlled asthma during 12-year follow-up period suggesting that physicians have tried to improve the management of asthma by changing the ICS dose of uncontrolled patients. On the other hand, in patients with stable asthma the reduction of medication has not been connected to increased risk to recurrence of symptoms and loss of asthma control [31–33]. In our study both respiratory specialists and general practitioners had prescribed reductions in ICS treatment for all study subgroups. Moreover, we showed that patients received more decreases than increases in dose during follow-up.

Seinäjoki Adult Asthma Study is a 12-year follow-up study of real-life new-onset adult asthma patients revealing information on prescribed ICS to consecutive adult asthma patients in a long-term follow-up setting. Many of the previous studies concerning prescribing practices are cross-sectional by nature. These studies included populations from different databases indicating that the cohort may be selected, and therefore patients or physicians outside these databases are excluded from the study cohort [13,16,18]. SAAS represents an extensive 12-year follow-up of patients including information on all asthma-related visits and prescribed medication over the years. Moreover, all new-onset adult asthmatics including patients with comorbidities, other lung disease, and history of smoking were included, and therefore the study cohort well represents the general adult population with asthma [8,23,24].

Our real-life setting establishes some possible sources of error into the results. Because physician's markings were not always complete in medical records, some shortage of information was observed. On the other hand, this kind of shortage is part of the treatment of every asthma patients in real-life. In case of inadequate information on medication, the calculations had to be made based on general assumptions. However, the study is a long-term follow-up, and therefore single shortcomings in medication information do not presumably have a major effect on the results. In the previous study concerning association between prescribing practices and uncontrolled asthma the level of asthma control was evaluated without lung function tests while we elucidated the level of asthma control with GINA 2010 recommendations where lung function tests were systematically a part of the disease assessment [27,34]. The questionnaire-based tests are clinically useful but when evaluating asthma control without lung function tests inaccuracy of assessment is possible [35,36].

Our findings show that prescribed longitudinal medication in patients with uncontrolled asthma differs markedly from partially and controlled patients. The annual average daily dose was significantly higher in patients with uncontrolled asthma than in patients with controlled asthma for almost the entire 12-year study period. Despite having many dose changes and treatment with high ICS dose during the 12-year follow-up, the level of asthma control remained poor in these patients at the 12-year follow-up visit. Current guidelines underline the adjustment of controller treatment to achieve good asthma control but our patients with poorly controlled asthma remained uncontrolled despite of high dose ICS treatment suggesting its limited benefit [2]. These findings indicate that general recommendations are not suitable for all patients with asthma. Our results also raise a question on the need for development of phenotype-specific drug treatment for those adult asthmatics being unresponsive to ICS. Steps towards phenotype-specific treatment of asthma have been recently taken since the uncontrolled allergic asthma patients have anti-IgE (omalizumab) as one of the treatment options and patients with severe eosinophilic asthma can be treated with anti-IL-5 antibodies (mepolizumab or reslizumab) [2,37–39]. In addition to allergic and eosinophilic asthma, our results suggest that the development of novel targeted therapies is needed also for other phenotypes to achieve good asthma control. Our previous cluster analysis concerning patients with adult-onset asthma showed that patients with phenotypes of obesity-related or smoking asthma had more often uncontrolled asthma as compared to patients with non-rhinitic, female or atopic asthma [24]. Step-up in treatment did not seem to improve the outcome of asthma in uncontrolled patients, therefore patients with obese-related or smoking asthma may benefit more of changes in lifestyle than increase in ICS dose [3,24,40]. Even though the benefits of higher dose of ICS have been shown to prevent exacerbations, the effects are shown to be limited in enhancing lung function and symptom-control [10]. This may be one of the explanations why high ICS dose seems to have only limited benefits in patients with uncontrolled asthma.

Taken together, we showed for the first time that in adult-onset asthma patients followed over a period of 12 years the prescribed ICS dose increased in a cumulative manner and prescription discontinuation was rare. This is in line with the low remission rate in adult-onset asthma. Patients with uncontrolled asthma received higher ICS doses throughout the follow-up period, and as a consequence, cumulative ICS dose 12 years after diagnosis was higher than in those with partially controlled and controlled disease. This suggest that the increase in ICS dose may not to be effective enough for the management of asthma in patients with uncontrolled adult-onset disease and novel targeted treatments are required. Consequently, the patients with uncontrolled asthma should receive special attention in asthma follow-ups.

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Competing interests

The authors report no conflict of interest related to this study.

Contributors

IV analyzed and interpreted the data, and wrote the manuscript. HK, LET and ON designed the study. PI contributed to the study design, interpretation of the data, writing of the manuscript and provided statistical advice. HK, PI, ON, and LET commented on drafts of the manuscript. All authors accept full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

Clinical Trials

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

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2018.02.025

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2018.02.025.

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PUBLICATION II

12-year adherence to inhaled corticosteroids in adult-onset asthma

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ORIGINAL ARTICLE
ASTHMA

12-year adherence to inhaled corticosteroids in adult-onset asthma

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ABSTRACT Adherence to inhaled corticosteroids (ICS) has been suggested to be poor but long-term follow-ups are lacking. The objective of the present study was to assess adherence to ICS treatment in patients with adult-onset asthma during 12-year follow-up.

A total of 181 patients with clinically confirmed, new-onset adult asthma were followed for 12 years as part of the Seinäjoki Adult Asthma Study. Adherence to ICS was assessed individually as the percentage of true dispensed ICS in micrograms per true prescribed daily ICS in micrograms over 12 years.

Mean 12-year adherence to ICS was 69% (mean±SD dispensed 2.5±1.8 g and prescribed 3.6±1.5 g budesonide equivalent per patient for 12 years), annual adherence varying between 81% (year 1) and 67% (year 12). Patients with good 12-year adherence (≥80%) used oral corticosteroids more often, and had add-on drugs in use and asthma-related visits to healthcare more often. In addition, they showed less reversibility in forced expiratory volume in 1 s and had higher peripheral blood neutrophil counts. However, lung function decline was steeper in patients with poorer adherence (<80%) and this association remained in multiple linear regression analysis. No difference was found in symptom scores, blood eosinophil counts, exhaled nitric oxide or immunoglobulin E between the patients with different levels of adherence.

In patients with adult-onset asthma, adherence to ICS was moderate. Poorer adherence (<80%) to ICS was associated with more rapid decline in lung function but was not associated to symptoms or markers of inflammatory endotypes.

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Mean long-term adherence to ICS treatment is 69% in patients with confirmed adult-onset asthma. While good ICS adherence (≥80%) is associated with features of more severe asthma, poorer adherence (<80%) predicts more rapid lung function decline. http://bit.ly/37mvh74

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Introduction

Inhaled corticosteroids (ICS) are the basis of asthma treatment, reducing airway inflammation, improving lung function, controlling symptoms and reducing exacerbations [1, 2]. When evaluating whether the patients take their medication as prescribed, one of the most settled terms is "medication adherence", consisting of three essential elements: initiation, implementation and persistence [3]. Objective methods, such as electronic monitoring and electronic health records, or subjective methods, like patient reports, can be used to address medication adherence. Whichever the method used, adherence to ICS treatment has been suggested to be poor [4].

The age of asthma onset has been shown to be a significant factor in distinguishing the phenotypes of asthma [5, 6]. Although a substantial proportion of asthma originates in childhood, recent data from the USA and Finland show that asthma diagnosed at adult age is common, and is in fact the dominant phenotype among women aged 35–40 years [7–9]. Patients with late-onset asthma are usually nonatopic and their response to corticosteroids is poorer than in patients with early-onset disease, and therefore they require more tailored medication [5, 6]. Moreover, asthma rarely remits in patients with adult-onset asthma [5, 6, 10, 11]. Even though many different characteristics of the adult-onset asthma phenotype have been described, adherence to medication remains unstudied.

Possible consequences of poor ICS adherence are decline in lung function, poorer symptom control and quality of life, and increase in asthma-related hospitalisations and costs [12–17]. Low adherence rates have also been associated with increased mortality and morbidity [4, 15, 18]. However, previous studies have usually been cross-sectional or short-term follow-ups and very little is known about the variation of medication adherence between and within persons in long-term treatment. In addition, to enhance reliable comparison of the results of adherence studies, variability in associated calculations and terms needs attention. Many studies based on medical records have used the best information available but the shortages in prescription or dispensation data have led to assumptions in adherence calculations [19–22]. In addition, previous studies have had shortages of information concerning diagnostic criteria, age of asthma onset and duration of asthma, which may all be factors influencing the results [22–25]. Though adherence to ICS has been <50% in recent studies, we hypothesised that when patients have a confirmed diagnosis of asthma and regular ICS in use, they would have better medication adherence than previously described. Therefore, our aim was to assess adherence and its variability in long-term ICS treatment in real-life new-onset adult asthma patients with confirmed diagnoses during 12-year follow-up by using full coverage dispensing data and true prescribed medication.

Methods

Study design and patients

This study is part of Seinäjoki Adult Asthma Study (SAAS), which is a prospective 12-year follow-up study of 257 patients with diagnoses of new-onset adult asthma. Patients were consecutively included in the study during the period 1999–2002 if all of the following criteria were fulfilled: 1) new-onset asthma diagnosed by a respiratory specialist; 2) confirmation of diagnosis by lung function measurements showing variable or reversible obstruction; 3) symptoms of asthma; and 4) age ⩾15 years (tables S1 and S2). Importantly, patients with comorbidities or smoking history were not excluded. Study participants gave written informed consent to the study protocol approved by the ethics committee of Tampere University Hospital, Tampere, Finland. More than 94% of the patients diagnosed with novel asthma at the study site were recruited to the study [11]. In 2001, the study population represented >38% of all novel diagnoses of asthma made in adults in the whole geographical area [26].

The study protocol has been published previously [27]. A schematic presentation of the study is shown in figure 1. The study was divided in two parts: collection of the original cohort (baseline) and the 12-year follow-up visit. At the baseline visit, data were collected on symptoms, lung function, demographics and initial medication [26]. Patients were followed for 12 years (mean 12.2 years, range 10.8–13.9 years) after the diagnostic visit. From the original cohort of 257 patients, 203 (79%) returned to the 12-year follow-up visit in which asthma status, medication, control and lung function were evaluated (supplementary material). All asthma-related visits and medication information were collected from the whole 12-year follow-up period from medical records. At the baseline visit, regular ICS medication was prescribed, and each patient received asthma education and self-management instructions according to Finnish Asthma Programme [28]. To ensure that the study population included only patients with regular ICS medication, we excluded patients for whom ICS was prescribed only as needed at any point in the follow-up period (figure 1).

Computation of adherence

The prescribed dose in each patient for the whole 12-year period was calculated based on medication records as previously described [29]. Shortly, we converted all prescribed ICS doses (ICS in both separate and

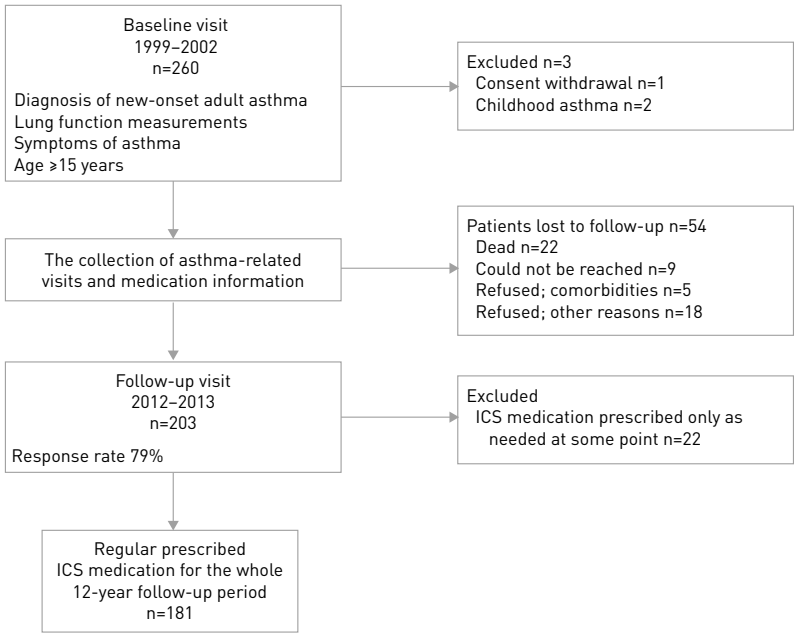

FIGURE 1 Flowchart of the study. ICS: inhaled corticosteroids.

combination inhalers) to budesonide equivalents and based on that information, calculated annual prescribed ICS medication for each patient. The dispensed ICS and oral corticosteroids were obtained from the Finnish Social Insurance Institution, which records all purchased medication from all Finnish pharmacies (supplementary material). Adherence to ICS was determined as previously described [3], consisting of initiation, implementation and persistence (supplementary material). The 12-year adherence was calculated by using formula 1 and annual adherence was calculated for each patient by using formula 2 (supplementary material). For comparing adherence groups, we used the most common cut-point of 80% [4, 21, 22].

$$\text{12-year adherence (\%)} = \frac{\text{12-year cumulative dispensed dose of ICS (μg)}}{\text{12-year cumulative prescribed dose of ICS (μg)}} \times 100 \quad (1)$$

$$\text{Annual adherence (\%)} = \frac{\text{yearly dispensed dose of ICS (μg)}}{\text{yearly prescribed dose of ICS (μg)}} \times 100 \quad (2)$$

Statistical analyses

The data are presented as mean±SD or median (interquartile range) except in figures, where annual cumulative and daily doses are represented as mean±SEM for clarity. Comparison of groups with ⩾80% or <80% adherence was analysed by using independent-sample t-tests and Mann–Whitney U-tests for normally and non-normally distributed continuous variables, respectively, and Pearson Chi-squared or Fisher's exact test for categorical variables. To analyse differences between prescribed and dispensed ICS doses in both cumulative and annual manners, the individual patient's area under curve (AUC) was defined and mean AUC values were compared by using paired-samples t-tests. A multivariable logistic regression was performed to predict oral corticosteroid use and multiple linear regression analysis was performed to analyse factors associated with forced expiratory volume in 1 s (FEV_1) decline as previously described [30]. The correlation matrix was analysed and explanatory variables not strongly correlated ($r<0.7$) were included in the analysis. In the linear regression analysis, outliers were removed to ensure homoscedasticity (supplementary material). A p-value <0.05 was regarded as statistically significant. Statistical analyses were performed by using IBM SPSS statistics software, version 24 (IBM SPSS, Armonk, NY, USA) and GraphPad Prism software, version 7.03 (GraphPad, La Jolla, CA, USA).

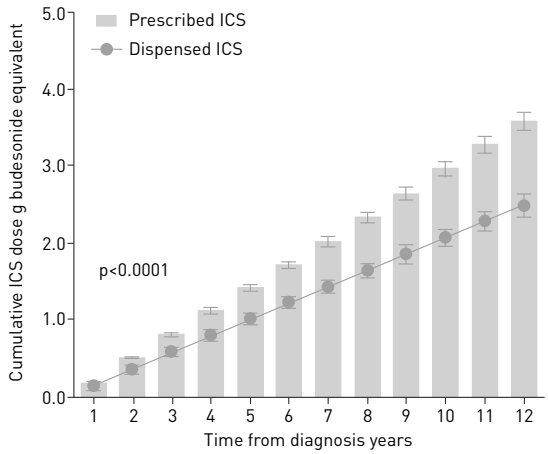

FIGURE 2 Annual prescribed and dispensed inhaled corticosteroids (ICS) shown as cumulative values (mean±SEM) (n=181). p-value re-presents difference between cumu-lative prescribed and dispensed ICS as defined by the area under the curve method and paired-sample t-test.

Results

Patient characteristics

The main characteristics of study patients are shown in table S3. The majority of the patients were female (60%) and half of the patients were current or ex-smokers. At the follow-up visit, patients had higher body mass index (BMI), FEV_1 and forced vital capacity (FVC), but lower blood eosinophil counts and symptom scores (Airway Questionnaire 20) than at the baseline.

Long-term adherence for 12 years

The mean 12-year adherence to ICS was 69% across all 181 patients (dispensed ICS 2.5±1.8 g and prescribed ICS 3.6±1.5 g budesonide equivalent per patient for 12 years) (figure 2). To visualise the variation in the long-term adherence in the whole study population, we determined annual adherence for each patient individually. The mean annual adherence gradually declined from year 1 (81%) to year 12 (67%) (figure 3). The prescribed annual daily ICS doses for study patients were high (on average, >800 µg) but patients dispensed significantly lower doses (on average, <800 µg budesonide equivalent) of ICS during the 12-year follow-up (figure 4). If calculated by using the maximum value of the dose range in the prescription instead of the mean value of the range (*e.g.* in a subject who was prescribed budesonide/formoterol 200/6 µg, one to two puffs twice a day), it affected the mean 12-year adherence by −4.4%. Smoking status or comorbidities did not affect the mean 12-year adherence values (data not shown).

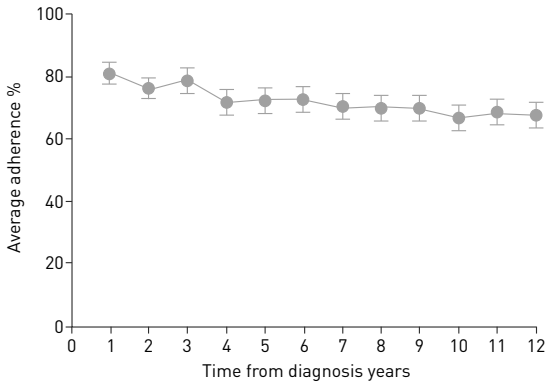

FIGURE 3 The average annual adherence (mean±SEM) during the 12-year follow-up period (n=181).

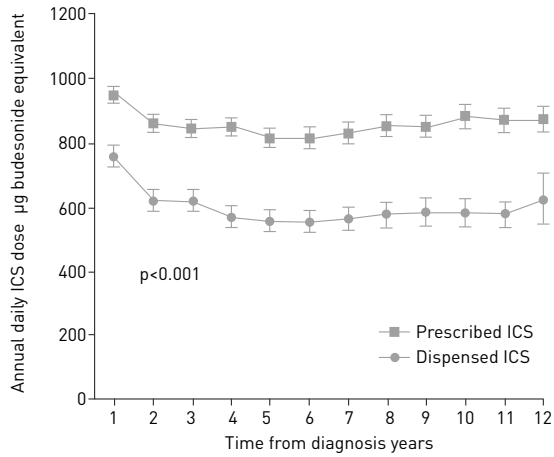

FIGURE 4 Average annual prescribed and dispensed daily doses of inhaled corticosteroids (ICS) in the 12-year follow-up periods (mean±SEM) (n=181). p-value represents difference between cumulative prescribed and dispensed ICS as defined by area under the curve method and paired-samples t-test.

Changes in adherence over 12 years

The proportion of adherent patients (⩾80%) was highest during the first year after the diagnosis (figure 5). Of the study patients, 17 (9%) had annual ICS adherence rates >80% during the whole 12-year follow-up period. In addition, 55 (30%) of the patients had annual adherence that was always >50%. Annual nonadherence (annual adherence rate 0%) ranged from 6.6% to 20.4% but on average, 14.5±4.6% of the patients were nonadherent during the 12 years (figure 5b). The total number of patients having an annual nonadherent period at least once was 67 (37%), and 1% of the patients failed to collect their first treatment prescription (initiation) [3] and were fully nonadherent to ICS therapy during the whole 12-year follow-up period.

Comparison of patients with good or poor 12-year adherence

Average prescribed ICS doses were similar in patients with better (⩾80%) and poorer (<80%) 12-year adherence but dispensed ICS doses were only one-third in patients with poorer adherence (table 1). Patients with good 12-year adherence (⩾80%) more often had a long-acting β_2-agonist (LABA) or any other add-on drug in use, more often reported oral corticosteroid courses and were dispensed higher amounts of oral corticosteroids during the follow-up (table 2 and supplementary material). In addition, they showed less FEV_1 reversibility, had higher peripheral blood neutrophils (table 3), had a higher number of asthma-related contacts to healthcare and tended to have more unplanned hospital in-patient days due to asthma (table 2). However, the decline in lung function was steeper in patients with poorer adherence (<80%). There was no difference in symptom scores or other inflammatory markers (blood eosinophils, exhaled nitric oxide fraction (F_{ENO}) or IgE) between the subgroups with different 12-year adherences (tables 2 and 3). If a lower cut-point for adherence was used, the results were largely similar.

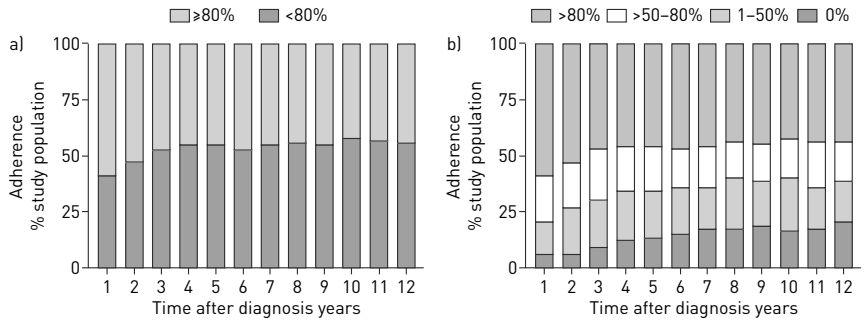

FIGURE 5 Annual adherence rates a) when using 80% adherence as a cut-off (n=181); and b) when dividing patients into high, moderate or low adherence, and non-adherence during the 12-year follow-up.

TABLE 1 Characteristics of patients at the 12-year follow-up visit and their medication according to their 12-year adherence

	12-year adherence		
	Good adherence[#]	Poor adherence[¶]	p-value
Age years mean±SD	61±12	58±14	0.065[§]
Female sex	52 (63.4%)	56 (56.6%)	0.365[f]
BMI kg·m^{-2}	28.1 (24.3–31.3)	28.4 (24.6–31.2)	0.640[##]
Smokers[+]	40 (48.8%)	51 (51.5%)	0.766[f]
Smoking history pack-years	18 (9–33)	17 (6–29)	0.407[##]
Smoking history ⩾10 pack-years and post-BD FEV_1/FVC <0.7	12 (30%)	21 (42%)	0.276[f]
Number of comorbidities	1 (0–3)	1 (0–2)	0.487[##]
Daily SABA	13 (15.9%)	8 (8.1%)	0.161[f]
Daily LABA	54 (65.9%)	41 (41.4%)	0.002[f]
Daily LTRA	18 (22%)	8 (8.2%)	0.011[f]
Daily theophylline	4 (4.9%)	0 (0%)	0.040[f]
Daily tiotropium	5 (6.1%)	3 (3.0%)	0.471[f]
Daily add-on drug	57 (69.5%)	44 (44.4%)	0.001[f]
Average prescribed ICS daily dose over 12 years µg budesonide equivalents	810 (611–1043)	805 (610–967)	0.496[##]
Average dispensed ICS daily dose over 12 years µg budesonide equivalents	803 (616–1075)	320 (146–472)	<0.001[##]

Data are presented as n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroid. [#]: ⩾80% adherence, n=82; [¶]: <80% adherence, n=99; [+]: including ex-smokers; [§]: independent-samples t-test; [f]: Fisher's exact test; [##]: Mann–Whitney U-test.

However, patients with ⩾50% adherence were more obstructive (lower FEV_1/FVC) but did not differ by lung function decline (table S4). Furthermore, we evaluated whether those with one or more completely nonadherent years differed from those without nonadherent years and the results were similar to the main results of the study (table S5).

Patients with ⩾80% adherence reported using oral corticosteroids more often during the follow-up and after adjusting this finding for age >50 years, sex, BMI >30 kg·m^{-2}, pre-FEV_1 at follow-up visit and COPD, the association remained (OR 1.99, 95% CI 1.02–3.87; p=0.043). In addition, we carried out multiple linear regression analysis to find out whether poor adherence predicts accelerated lung function decline when adjusted for age, ΔBMI during the follow-up period, sex, F_{ENO} >20 ppb, smoking history ⩾10 pack-years, blood eosinophils, use of oral corticosteroid courses, FEV_1 % pred at baseline and ΔFEV_1 (baseline−maximum$_{0-2.5}$) (table S6). After adjustments, poorer adherence (<80%) remained a significant predictor for FEV_1 (in millilitres) decline.

Discussion

In this study, we evaluated both annual and 12-year adherence to ICS from diagnosis to a 12-year follow-up visit in patients with adult-onset asthma. Mean 12-year adherence to ICS was 69%. Patients with good 12-year adherence (⩾80%) more often used LABA daily, and had more oral corticosteroid courses and asthma-related contacts to healthcare. In addition, they showed less reversibility of FEV_1 and had higher peripheral blood neutrophil counts. However, lung function decline during the follow-up period was steeper in patients with poorer long-term adherence (<80%). These results suggest that in patients with confirmed diagnoses of adult-onset asthma, the mean adherence to ICS is moderate but variance in annual ICS adherence is also common in long-term treatment. Even though good ICS adherence (⩾80%) was, overall, associated with features of more severe asthma, poorer adherence (<80%) predicted more rapid lung function decline.

Our study showed that the mean 12-year ICS adherence was 69%, which is in line with the previous studies where overall adherence to asthma treatment ranged 30–70% [4]. However, adherence was higher in our study than in other adherence studies based on electronic medical records, where adherence ranged 21–52% [23–25, 31–33]. Previous short-term studies have suggested a decline in lung function or reductions in symptom control and quality of life because of poor adherence [12, 13, 15, 16, 31]. In our study, for the first time, poorer adherence (<80%) was found to predict more rapid lung function decline long term. It might be

TABLE 2 Symptoms and burden due to asthma in patients according to their 12-year adherence

	12-year adherence		
	Good adherence[#]	Poor adherence[¶]	p-value
Symptoms of asthma			
AQ20 score	4 (2–7)	4 (1–8)	0.583
ACT score	21 (19–24)	21 (19–24)	0.790
CAT	12 (7–18)	11 (6–17)	0.473
Burden of asthma			
Self-reported use of oral corticosteroid courses for asthma	34 (42.5%)	26 (26.3%)	0.026[f]
Dispensed oral corticosteroid for asthma[+] mg·year^{-1}	101 (11–249)	51 (0–165)	0.019[##]
At least one hospitalisation due to asthma	14 (17.1%)	13 (13.1%)	0.532[f]
Three or more sick leaves during the past 2 years	3 (4.8%)	4 (5.2%)	>0.999[f]
Emergency department visits	0 (0–0)	0 (0–0)	0.708[##]
Fulfils severe asthma criteria according to ERS/ATS	6 (7.3%)	6 (6.1%)	0.772[f]
Hospital days, asthma-related[§]	0 (0–0)	0 (0–0)	0.051[##]
Range	0–64	0–12	
Hospital days, any respiratory reason[§]	0 (0–0)	0 (0–0)	0.072[##]
Range	0–64	0–37	
Asthma control visits	7 (4–11)	6 (3–9)	0.023[##]
Asthma-related visits to healthcare	19 (12–28)	11 (8–19)	<0.001[##]

Data are presented as median (interquartile range), unless otherwise stated. Symptoms of asthma were observed at the 12-year follow-up visit. Sick leaves were observed in the 2 years before the follow-up visit. Self-reported use of oral corticosteroids, hospitalisations and hospital days were examined during the whole 12-year follow-up period. AQ20: Airway Questionnaire 20; ACT: Asthma Control Test; CAT: COPD Assessment Test; ERS: European Respiratory Society; ATS: American Thoracic Society. [#]: ⩾80% adherence, n=82. [¶]: <80% adherence, n=99. [+]: data obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up (supplementary material); statistical significance considering symptoms of asthma were evaluated by independent-samples Mann–Whitney U-test. [§]: unplanned. [f]: Pearson Chi-squared test. [##]: independent-samples Mann–Whitney U-test.

argued whether the annual difference of 6 mL in median values is clinically significant but most patients had chronic asthma, which rarely remits, and therefore, the cumulative effect in the long term may have clinical significance. Even though patients with poorer adherence otherwise showed features of less severe disease (*e.g.* less use of add-on drugs and fewer healthcare visits), indicating that these patients may be less adherent because of the feeling of not needing medication, poor adherence seems to have harmful long-term effects on lung function. Given that reduced lung function is a risk factor for exacerbations [34], these patients might predispose themselves to exacerbations in the long term by not taking their medication. In our study as well as in the previous ones [30, 35], increased eosinophilic inflammation has been shown to associate with more rapid decline in lung function, but in our study, no difference was found in the level of blood eosinophils or F_{ENO} between the subgroups with different levels of adherence. However, the blood eosinophil and F_{ENO} values were based on a single time-point (12-year follow-up visit), leaving the possibility that the level of inflammation may have been higher for some period during the follow-up in these patients, providing a possible mechanism for steeper lung function decline in less adherent patients.

Despite the mean 12-year ICS adherence being as high as 69%, annual nonadherence was observed in 37% of the patients at least once during the 12-year follow-up period and only 9% of the patients had annual adherence that was always >80%. In summary, individual patients appeared to use ICS periodically under and over the prescribed doses but on average, patients adhered to ICS treatment well during long-term treatment. As symptoms of asthma and airway limitation vary over time [2], patients' adherence behaviour may reflect the nature of asthma as a disease. The reasons behind relatively high rates of adherence in Finnish adult asthma patients are various: 65% reimbursement of asthma medicine expenses, relatively low medicine prices, prescriptions for 1–2 years at time (medication available when needed), cost-free renewal of prescriptions, public health services available for all, lung function measurements at asthma contacts and guidance on correct inhaler use by, for example, specialised asthma nurses and the Finnish asthma programme [28].

Previous studies on adherence to asthma medication have been short-term follow-ups, the most common follow-up time being 12 months [23, 25, 31–33]. SAAS is a 12-year, real-life follow-up study of new-onset adult asthma patients giving information on adherence to ICS over an exceptionally long period. In addition, many

TABLE 3 Lung function and markers of inflammation in patients according to their 12-year adherence

	12-year adherence		
	Good adherence[#]	Poor adherence[¶]	p-value
Lung function at follow-up			
Pre-BD FEV_1 % pred	87 (75–99)	86 (75–94)	0.398
Pre-BD FVC % pred	97 (87–108)	96 (87–106)	0.374
Pre-BD FEV_1/FVC	0.73 (0.67–0.78)	0.74 (0.65–0.79)	0.730
Post-BD FEV_1 % pred	90 (79–99)	89 (81–96)	0.682
Post-BD FVC % pred	99 (85–108)	97 (88–105)	0.416
Post-BD FEV_1/FVC	0.74 (0.68–0.79)	0.76 (0.68–0.81)	0.320
FEV_1 reversibility mL	65 (7.5–123)	100 (40–170)	0.010
FEV_1 reversibility % initial FEV_1	2.7 (0.29–5.0)	3.8 (1.6–6.8)	0.039
Lung function change			
ΔFEV_1 % pred·year^{-1}	−0.39 (−0.88–0.40)	−0.54 (−1.2–0.0)	0.026
ΔFEV_1 mL·year^{-1}	−40 (−56–−22)	−46 (−81–−26)	0.050
ΔFVC % pred·year^{-1}	0.11 (−0.47–0.82)	−0.21 (−0.87–0.45)	0.034
ΔFVC mL·year^{-1}	−32 (−56–−10)	−36 (−64–−13)	0.329
ΔFEV_1/FVC year^{-1}	−0.005 (−0.008–−0.0001)	−0.005 (−0.008–−0.002)	0.316
Markers of inflammation			
Blood eosinophils ×10^9 L^{-1}	0.17 (0.09–0.28)	0.18 (0.10–0.27)	0.549
Total IgE kU·L^{-1}	71 (24–165)	56 (26–178)	0.956
F_{ENO} (ppb)	10 (5–19)	11 (5–18)	0.683
Blood neutrophils ×10^9 L^{-1}	4.2 (3.5–5.3)	3.5 (2.7–4.6)	0.001
IL-6 pg·mL^{-1}	1.9 (1.2–3.2)	1.8 (1.1–3.3)	0.537
hsCRP mg·L^{-1}	1.0 (0.48–2.3)	1.4 (0.62–2.9)	0.224

Data are presented as median (interquartile range) unless otherwise stated. Statistical significance was evaluated by independent-samples Mann–Whitney U-test. BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: exhaled nitric oxide fraction; IL: interleukin; hsCRP: high-sensitivity C-reactive protein. [#]: ⩾80% adherence, n=82; [¶]: <80% adherence, n=99.

studies only included populations from healthcare organisations or insurance databases, meaning that the patient cohort is selected and patients outside these databases are excluded [24, 31, 32]. SAAS has collected extensive 12-year follow-up data including information on all prescribed and dispensed asthma medication of the study patients. Moreover, all new-onset adult asthmatics, *i.e.* patients with comorbidities and a history of smoking, were included and therefore, the study cohort represents the general adult population with asthma well [26].

Information on the duration of asthma, age of asthma onset and diagnostic criteria used were missing from the previous adherence studies, all of which are factors that could influence adherence [23, 24, 31–33, 36]. In the studies using administrative or other register data only, asthma diagnosis has typically been based on International Classification of Diseases codes found from these records [25, 36, 37], causing unreliability and variation in the correctness of asthma diagnosis. For example, a study in the USA [23] identified that only 8.8% of the patients continued to refill their prescriptions from the index date to year's end, whereas in another study [38], ∼50% of the patients did not renew their initial prescription. In these studies, the average adherence to ICS was poor, which may be partly explained by the absence of strict diagnostic criteria and confirmed asthma diagnosis, leading to inclusion of nonasthmatic subjects in the study. Conversely, many studies based on health records have used the best information available but shortages in prescription or dispensation data have led to assumptions in adherence calculations [19–22]. For example, the total day's supply is often based on pharmacists' estimation, typically assuming the maximum use of prescribed doses (*e.g.* one to two puffs once or twice a day assumed to be four puffs a day), which can lead to underestimation of adherence [20]. Moreover, Blais *et al.* [39] noted that when one of the most commonly used measures adherence (proportion of days covered [37]) from administrative data is used, it assumes that the medication is prescribed for chronic daily use, and in cases of suboptimal prescribing, it may lead to underestimation of adherence. In our study, the diagnosis of asthma was made by a respiratory physician, and was based on both typical symptoms and variable or reversible airway obstruction in lung function measurements. Regarding adherence calculations, we examined all prescribed and refilled ICS doses and dose changes for 12 years based on individual patients' medical records and dispensation data, and all patients had regular prescribed ICS medication for the whole follow-up period (supplementary material).

Because our study was based on medical records and pharmacy dispensation data, it has some limitations. Firstly, the medical records were not always complete (shortage of physicians' notes, *e.g.* missing dose information) but prescribed medication was calculated based on previously confirmed information. Secondly, dispensing of a medicine does not guarantee patients' actual use of ICS nor good inhalation technique. Thirdly, some information on patients' behaviour regarding stepping medication up and down was not available in our study (*i.e.* patients may have used an action plan during influenza or an exacerbation and doubled the ICS dose). Despite these limitations, electronic medical records are preferred because they enable long observation periods in the assessment of adherence and they are commonly used in evaluation of adherence [4]. Moreover, electronic monitoring devices (EMDs), such as smart inhalers, are the gold standard in precise and reliable monitoring of adherence. Our results showed that adherence to ICS decreased most rapidly during the first 4 years of follow-up and this would potentially be an optimal point for EMD studies.

The results of earlier studies have shown many negative associations as a result of patients' poor ICS adherence [4, 12, 15]. In this study, patients with poorer long-term ICS adherence used remarkably lower ICS doses, less frequently used LABA on daily basis and were less often hospitalised compared to patients with better 12-year ICS adherence. This suggests that patients with poorer adherence (<80%) may have had milder asthma compared to patients with better adherence (⩾80%). Therefore, undesirable treatment outcomes should not be regarded only as consequences of poor adherence, since even patients with good adherence may suffer from these outcomes. Patients with better adherence had also higher blood neutrophil counts and showed features of more severe asthma, indicating that some patients may have had non-T2-mediated disease. Future studies should pay more attention to the reasons why undesirable outcomes emerge in patients with good adherence to ICS and whether there would be more effective treatment strategies for these patients [40].

Taken together, we show, for the first time, long-term, 12-year adherence data of patients with adult-onset asthma based on true prescribed and dispensed medication. Clinical patients with objectively confirmed diagnoses of new-onset adult asthma had, on average, moderate adherence to long-term ICS treatment. This suggests that when evaluating patients' adherence, it is important to ensure that study population includes only patients with reliable asthma diagnoses and need for regular ICS medication [36]. In addition, when assessing long-term adherence to ICS, major variability in annual rates of adherence should be considered and, therefore, follow-up periods should be set long enough. In future, adult- and childhood-onset asthma patients should be compared to gain better understanding of the characteristics of adherence in different phenotypes. The new information about adherence characteristics in phenotypes would enhance possibilities to intervene with patients who show signs of inefficient treatment. All in all, our results show that poor adherence to ICS treatment may lead to steeper decline in lung function, which may have negative consequences in the long term. Our findings, therefore, also support performing spirometry regularly, as recommended by the Global Initiative for Asthma. Otherwise, patients with good adherence showed features of more severe asthma in comparison to less adherent patients. These patients need new strategies for their asthma treatment when regular controller medication seems not to be effective enough.

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Conflict of interest: I. Vähätalo reports personal fees for a lecture from AstraZeneca outside the submitted work. P. Ilmarinen reports a grant for analysis and write-up of a study and a fee for a lecture from AstraZeneca, and personal fees for lectures from Mundipharma, GlaxoSmithKline and Orion, outside the submitted work. L.E. Tuomisto reports reimbursement of costs for attending international congresses from Chiesi, Boehringer Ingelheim, Orion Pharma and TEVA; reimbursement of costs for a lecture from AstraZeneca; and attendance of an advisory board meeting for Novartis, outside the submitted work. M. Tommola reports personal fees for lectures from AstraZeneca, Pfizer and Chiesi; personal fees for lectures and consultation from Boehringer Ingelheim; and grants from the Orion Research Foundation, outside the submitted work. O. Niemelä has nothing to disclose. L Lehtimäki reports personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Mundipharma, OrionPharma, SanofiGenzyme and Teva, outside the submitted work. P. Nieminen has nothing to disclose. H. Kankaanranta reports fees for lectures and consulting, costs for attending an international congress, and a research grant to their institution from AstraZeneca; fees for consulting from Chiesi Pharma AB, SanofiGenzyme and GlaxoSmithKline; fees for lectures and consulting, and costs for attending international congresses from Boehringer Ingelheim and Orion Pharma; fees for lectures and consulting from Novartis; and fees for lectures from Mundipharma, outside the submitted work.

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PUBLICATION III

Long-term adherence to inhaled corticosteroids and asthma control in adult-onset asthma

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ORIGINAL ARTICLE
ASTHMA

Long-term adherence to inhaled corticosteroids and asthma control in adult-onset asthma

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ABSTRACT

Background: In short-term studies, poor adherence to inhaled corticosteroids (ICS) has been associated with worse asthma control, but the association of long-term adherence and disease control remains unclear.

Objective: To assess the relationship between 12-year adherence to ICS and asthma control in patients with adult-onset asthma.

Methods: As part of the Seinäjoki Adult Asthma Study, 181 patients with clinically confirmed new-onset adult asthma and regular ICS medication were followed-up for 12 years. Adherence (%) to ICS was assessed individually ((µg dispensed/µg prescribed)×100) during the follow-up. Asthma control was evaluated after 12 years of treatment according to the Global Initiative for Asthma 2010 guideline.

Results: Asthma was controlled in 31% and not controlled (partly controlled or uncontrolled) in 69% of the patients. Patients with not-controlled asthma were more often male, older, nonatopic and used higher doses of ICS than those with controlled disease. The mean±SD 12-year adherence to ICS was 63±38% in patients with controlled asthma and 76±40% in patients with not-controlled disease (p=0.042). Among patients with not-controlled asthma, those with lower 12-year adherence (<80%) had more rapid decline in forced expiratory volume in 1 s (-47 mL·year^{-1}) compared to patients with better adherence (⩾80%) (-40 mL·year^{-1}) (p=0.024). In contrast, this relationship was not seen in patients with controlled asthma.

Conclusions: In adult-onset asthma, patients with not-controlled disease showed better 12-year adherence to ICS treatment than those with controlled asthma. In not-controlled disease, adherence <80% was associated with more rapid lung function decline, underscoring the importance of early recognition of such patients in routine clinical practice.

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Patients with not-controlled asthma and poor adherence show increased FEV_1 decline. Special emphasis should be placed on ICS adherence in subjects who do not have controlled asthma, as they seem to be at higher risk of developing fixed airway obstruction. https://bit.ly/2LOXL4f

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Introduction

Successful asthma treatment plays a pivotal role in preventing exacerbations, enhancing patients' quality of life and decreasing healthcare costs [1]. Asthma often remains poorly controlled despite effective pharmacological treatment strategies [2–4] and current guidelines emphasise the importance of finding out the reason behind not-controlled asthma in each patient [5]. Age of asthma onset has been shown to differentiate the phenotypes of asthma [6, 7], but very little information exists on the disease control characteristics of the late-onset asthma phenotype [3].

To gain optimal benefits from pharmacotherapy, patients should be adherent to treatment, which has been shown to be often suboptimal [1, 8]. Only two studies so far have evaluated long-term adherence to inhaled corticosteroids (ICS): the Childhood Asthma Management Program (CAMP) (4-year follow-up) [9] and the Seinäjoki Adult Asthma Study (SAAS) (12-year follow-up) [8]. In these studies, mean adherence to ICS was 52% and 69%, respectively. Previous studies assessing asthma control and adherence have been either cross-sectional or with short follow-up [10–18]. In addition, the evaluation of adherence and asthma control has mostly been questionnaire-based and information concerning diagnostic criteria, duration and age of onset of asthma are often missing, potentially influencing the results [4, 13, 15]. Poor asthma control has been associated with higher risk of exacerbations, lower quality of life and increased healthcare use [2, 4, 10, 19]. Previous studies have suggested that suboptimal adherence to pharmacological therapy impairs asthma control [4, 10–13, 20]. In contrast, a recent study identified that patients with uncontrolled asthma were more adherent to ICS treatment [21]. However, the adherence was determined from prescriptions issued, reflecting the physician's prescription manners, not the adherence of the patient. It should be noted that in previous studies medication possession ratio (MPR) and proportion of days covered (PDC) formulas have been used regularly for estimating adherence [1, 21]. Unfortunately, the data used in these formulas usually lack detail, such as did patients have continuous prescription for ICS and how were dose ranges and single maintenance and reliever therapy regarded, all being relevant issues in the treatment of asthma.

Inadequate use of preventer medication is suggested to be related to decline in lung function, but there are no data on the association between long-term adherence and lung function decline stratified by asthma control. An Australian study [22] found accelerated lung function in patients not taking adequate preventer therapy. Furthermore, in previous short-term (1-year) follow-up study conducted in the United Kingdom [23], patients with difficult-to-control asthma and suboptimal ICS adherence had reduced forced expiratory volume in 1 s (FEV_1). In our recent study, poorer 12-year adherence was related to lung function decline in the long-term, but patients with good adherence used more add-on drugs, oral corticosteroid courses, had more hospital days and used more healthcare services, *i.e.* had features suggesting not-controlled asthma [8]. Thus, we hypothesised that not-controlled asthma is not a direct consequence of poor adherence and that lung function decline does not depend on poor adherence only, but may be affected by asthma control. Hence this study aimed to assess the relationship between 12-year adherence to ICS and asthma control in patients with adult-onset asthma, especially concentrating on whether the effect of poor adherence on lung function decline is affected by asthma control. In this study, we used full-coverage dispensing data and information on prescribed ICS, offering the possibility to assess real-life adherence based on dispensed and prescribed amounts of ICS [8, 24].

Methods

Study design and patients

The current study is part of SAAS, which is a prospective 12-year follow-up study of patients with diagnosis of new-onset adult asthma. All new adult (age ⩾15 years) patients in Seinäjoki Central Hospital were included during the period 1999–2002. Diagnostic criteria, inclusion and exclusion criteria have been reported previously [25] (supplementary eTable 1). Patients with comorbidities or smoking history were not excluded. Study participants gave written informed consent to the study protocol approved by the ethics committee of Tampere University Hospital (Tampere, Finland).

The study was divided into two parts: baseline visit and 12-year follow-up visit (figure 1). At the baseline visit, data were collected on symptoms, lung function and demographics, as described previously [25]. Furthermore, regular ICS medication was prescribed and each patient received asthma education, advice on correct inhaler use and self-management instructions according to the Finnish asthma programme [26]. From the original cohort of 257 patients, 203 (79%) returned for the 12-year follow-up visit in which asthma control, medication and lung function were evaluated (supplementary material). All asthma-related visits and medication information were collected for the whole 12-year follow-up period from medical records [24]. To ensure that the study population included only patients with regular ICS medication, we excluded patients for whom ICS was prescribed only periodically (often Global Initiative for Asthma (GINA) step 1 and ICS use during pollen season) at any point of the follow-up (figure 1).

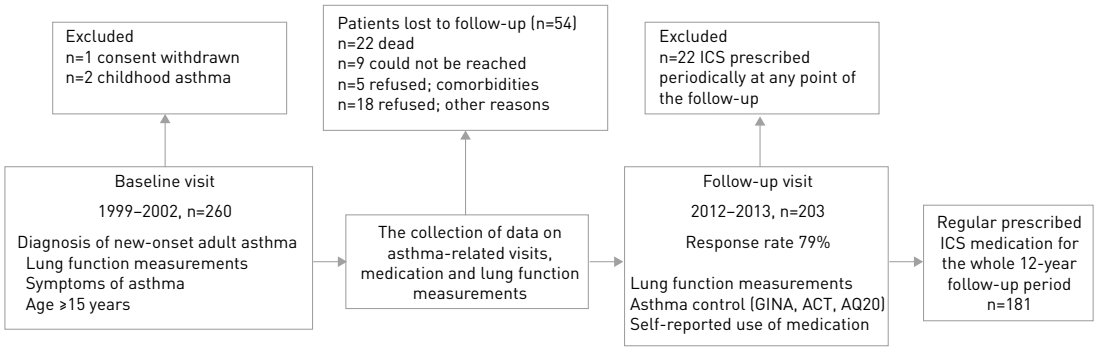

FIGURE 1 Flow-chart of the study. ICS: inhaled corticosteroids; GINA: Global Initiative for Asthma; ACT: Asthma Control Test; AQ20: Airway Questionnaire 20.

Asthma control and lung function

Asthma control was defined according to GINA 2010 [27] and "not-controlled" included both partially and uncontrolled asthma (supplementary material). Lung function measurement points were 1) baseline (diagnosis), 2) the maximum lung function ($max_{0-2.5}$) during the first 2.5 years after diagnosis (after start of therapy) and 3) 12-year follow-up visit (supplementary material). Decline in lung function during the 12-year follow-up period was defined as change in pre-bronchodilator FEV_1 from $max_{0-2.5}$ to the 12-year time point.

Assessment of adherence

The prescribed ICS dose in each patient for the 12-year period was calculated based on medication records, as described previously [24]. Briefly, we converted all prescribed ICS doses (ICS in both single and combination inhalers) to beclomethasone dipropionate equivalents, and based on that information, calculated annual prescribed ICS medication for each patient. The dispensed ICS doses were obtained from the Finnish Social Insurance Institution which records all medication purchased from any Finnish pharmacy. All drug and dose changes were taken into account individually. In the case of ranged doses prescribed (*e.g.* one or two puffs twice daily), we interpreted that patients were adherent when the minimum ICS doses were dispensed. Adherence to ICS was determined as described recently [8], consisting of initiation, implementation and persistence (supplementary material). The 12-year adherence was calculated by comparing cumulative dispensed doses of ICS (µg) to cumulative prescribed doses of ICS (µg) and annual adherence by comparing yearly dispensed doses of ICS (µg) to yearly prescribed doses of ICS (µg). This adherence calculation combines elements from both MPR and PCD formulas (supplementary material) [8, 28] and we estimated the time-variance of the adherence according to a recent publication [29].

Statistical analyses

The results are shown as mean±SD or median (interquartile range), but annual adherence is represented as mean±SEM for clarity. Comparison of groups with ⩾80% or <80% adherence to ICS were analysed by using independent samples t-test and Mann–Whitney U-test for normally and non-normally distributed continuous variables, respectively, and Pearson's Chi-squared or Fisher's exact test for categorical variables. To analyse differences in annual adherence over the 12-year period between controlled and not-controlled patients, annual adherence was plotted against time for individual patients, and mean area under curve values were compared using an independent samples t-test. A multivariable binary logistic regression analysis was performed to analyse factors associated with not-controlled asthma. A multiple linear regression analysis was performed to analyse factors associated with FEV_1 decline, as described previously [30]. The correlation matrix was analysed and covariates not strongly correlated ($r<0.7$) (age, sex, body mass index (BMI) at follow-up, exhaled nitric oxide fraction (F_{eNO}) >20 ppb, ⩾10 pack-years at follow-up, change (Δ) in FEV_1 (baseline−$max_{0-2.5}$) and average 12-year adherence (<80%) to ICS) were included in the analysis and outliers were removed to ensure homoscedasticity (supplementary material). A p-value <0.05 was regarded as statistically significant. Statistical analyses were performed using SPSS statistics software (version 24; IBM, Armonk, NY, USA) and GraphPad Prism (version 7.03; GraphPad, La Jolla, CA, USA).

Results

Patient characteristics

The majority of the study patients were female (60%), the average age was 59±13 years at the follow-up visit and half of the patients were current or ex-smokers (supplementary eTable 2). At the follow-up visit patients had higher BMI, better lung function, lower blood eosinophil counts and fewer symptoms (Asthma Questionnaire 20) compared to the baseline visit (supplementary eTable 2).

Asthma control

At the 12-year follow-up visit, asthma control was evaluated and the patients were divided into two groups: controlled (n=56) and not controlled (n=125). Group characteristics are shown in table 1. Patients with not-controlled asthma were more often male, older and were prescribed higher doses of ICS than

TABLE 1 Characteristics of asthma patients at 12 years after diagnosis according to their level of asthma control (n=181)[#]

	Controlled	Not-controlled	p-value
Patients	56	125	
Age years	56±14.6	61±12.4	0.011[++]
Female	41 (73.2)	67 (53.6)	0.014[§§]
BMI kg·m^{-2}	27.6±3.8	29.1±6.0	0.079[++]
Smokers (including ex-smokers)	18 (32.1)	73 (58.4)	0.001[§§]
Smoking history pack-years	7 (2–12)	20 (10–32)	<0.001[ff]
⩾10 pack-years and post-BD FEV_1/FVC <0.7[¶]	4 (7.1)	29 (23.4)	0.011[§§]
Pre-BD FEV_1% pred	92 (86–99)	82 (70–93)	<0.001[ff]
Pre-BD FEV_1/FVC	0.75 (0.70–0.79)	0.73 (0.64–0.78)	0.016[ff]
Post-BD FEV_1% pred	96 (90–101)	84 (75–96)	<0.001[ff]
Post-BD FEV_1/FVC	0.77 (0.73–0.83)	0.73 (0.65–0.79)	0.002[ff]
Blood eosinophils ×10^9·L^{-1}	0.17 (0.12–0.28)	0.18 (0.09–0.27)	0.353[ff]
Total IgE kU·L^{-1}	51 (28–161)	71 (24–172)	0.617[ff]
F_{eNO} ppb	12 (6–19)	10 (5–18)	0.392[ff]
Blood neutrophils ×10^9·L^{-1}	3.7 (3.0–4.6)	3.9 (2.9–4.9)	0.522[ff]
Prescribed daily dose of ICS µg BDP	751 (502–939)	838 (664–1023)	0.014[ff]
Dispensed daily dose of ICS µg BDP	411 (246–625)	602 (354–838)	0.002[ff]
Daily SABA[+]	2 (3.6)[###]	19 (15.2)	0.024[§§]
Daily LABA[+]	18 (32.1)	77 (61.6)	<0.001[§§]
Self-reported use of oral corticosteroid courses for asthma[§]	12 (21.4)	48 (39.0)	0.06[§§]
Dispensed oral corticosteroid for asthma per year mg[f]	44 (0–127)	92 (0–240)	0.013[ff]
Comorbidities	1 (0–2)	1 (0–3)	0.057[ff]
Co-medications (nonrespiratory)	1 (0–4)	2 (0–4)	0.124[ff]
AQ20 score	2 (0–4)	6 (3–9)	<0.001[ff]
ACT score	24 (22–25)	20 (17–23)	<0.001[ff]
Asthma-related visits to healthcare[§,##]	12 (6–19)	16 (10–26)	0.014[ff]
Atopy[¶¶]	27 (50.9)	34 (30.6)	0.016[§§]
⩾1 hospital in-patient periods, asthma-related (unplanned)[§]	1 (1.8)	15 (12.0)	0.024[§§]

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IgE: immunoglobulin E; F_{eNO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroid; BDP: beclomethasone dipropionate equivalents; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; AQ20: Airways Questionnaire 20; ACT: Asthma Control Test. [#]: the results of lung function and inflammatory parameters have been published previously in patients with controlled, partially controlled and uncontrolled asthma [3]; [¶]: baseline ⩾10 pack-years and post-BD FEV_1/FVC ratio <0.7 in patients with controlled asthma (n=2, 3.6%) and patients with not-controlled asthma (n=13, 10.7%) (p=0.150); [+]: self-reported daily use; [§]: examined during the whole 12-year follow-up period; [f]: values obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up; [##]: all respiratory-related scheduled and unscheduled contacts with healthcare due to asthma; [¶¶]: defined as ⩾1 positive response (⩾3 mm) in skin prick test towards common aeroallergens [31]; [++]: independent samples t-test; [§§]: Fisher's exact test; [ff]: independent samples Mann–Whitney U-test; [###]: these two patients were not dispensed SABA in the year when asthma control was determined and therefore they were considered to belong to the group of controlled patients. However, they self-reported daily use of SABA and more SABA was dispensed in preceding years of the follow-up.

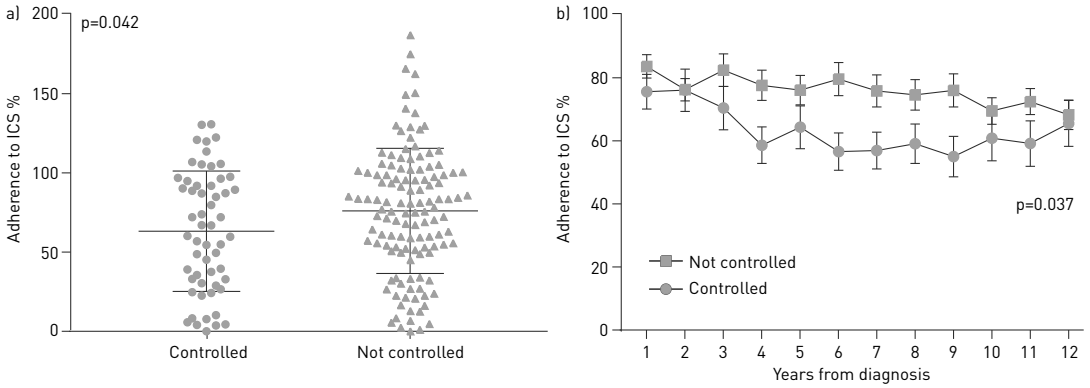

FIGURE 2 Long-term adherence to inhaled corticosteroids (ICS) in patients with controlled and not-controlled asthma. a) The average 12-year adherence to ICS in study subgroups (mean±SD). Adherence >100% means that patients were dispensed more than a regular individually prescribed minimum dose of ICS. b) The average annual adherence (mean±SEM) in patients with controlled and not-controlled asthma during the 12-year follow-up period. p-value represents difference in annual ICS adherence between not-controlled and controlled patients as defined by area under the curve method and independent-samples t-test. Significant difference was also seen when patients with COPD were excluded from the analyses (a) p=0.021 and b) p=0.019).

patients with controlled asthma. As reported previously, lung function was better and smoking was less common in patients with controlled asthma *versus* not-controlled asthma [3]. Patients with not-controlled asthma used more daily add-on drugs, had more days in hospital and were dispensed higher doses of oral corticosteroids (table 1). In addition, patients with not-controlled asthma were less often atopic and had a higher number of asthma-related contacts with healthcare. No difference was found in inflammatory parameters.

Adherence and asthma control

The mean±SD 12-year adherence to ICS was 63±38% in patients with controlled asthma and 76±40% in patients with not-controlled disease (p=0.042) (figure 2a). Patients with not-controlled asthma had significantly higher adherence (p=0.037) compared to patients with controlled asthma in the whole 12-year study period (figure 2b). Furthermore, 34% of the study patients had not-controlled asthma despite having ⩾80% adherence to ICS treatment during 12-year follow-up (table 2). The association between ⩾80% adherence and not-controlled asthma remained in binary logistic regression analysis adjusting for age ⩾60 years, BMI ⩾30 $kg \cdot m^{-2}$, sex, COPD and rhinitis. When evaluating long-term ICS use, it was found that 76.8% of the patients with not-controlled asthma and 60.7% of the patients with controlled asthma were >50% adherent to their ICS treatment each year during the 12-year follow-up (p=0.032).

Not-controlled asthma

A large variation in the ICS adherence was found in the not-controlled asthma group. Therefore, we considered that there may be two different groups of patients with suboptimal asthma control: 1) those having not-controlled asthma due to low adherence to ICS; and 2) those having not-controlled asthma despite good adherence to ICS. To see whether clinical differences exist between these groups, we evaluated asthma-related parameters in patients having not-controlled asthma and ⩾80% or <80% 12-year adherence (table 2 and supplementary eTable3). The patients having not-controlled asthma and ⩾80% adherence had a higher number of asthma-related contacts with healthcare, higher blood neutrophil count and used more often long-acting β_2-agonists (LABA) or leukotriene receptor antagonists (table 2).

Controlled asthma

Assessment of patients with good asthma control revealed that patients with ⩾80% adherence had lower BMI, higher total immunoglobulin E and peripheral blood neutrophil counts and lower FEV_1 reversibility (mL) than patients with <80% adherence and controlled asthma (table 3 and supplementary eTable 4). In addition, patients with controlled asthma and ⩾80% adherence reported using oral corticosteroids more often and had tendency to increased asthma-related visits to healthcare compared to <80% adherent patients.

TABLE 2 Characteristics of patients with not-controlled asthma at 12 years after diagnosis according to their level of 12-year adherence (n=125)

	Good adherence (⩾80%)	Poor adherence (<80%)	p-value
Patients	61	64	
Age years	62±12	60±13	0.242[f]
Female	36 (59.0)	31 (48.4)	0.283[##]
BMI kg·m^{-2}	28.4 (24.6–32.5)	28.5 (24.5–32.3)	0.286[¶¶]
Smokers (including ex-smokers)	35 (57.4)	38 (59.4)	0.857[##]
Smoking history pack-years	19 (9–34)	20 (12–30)	0.977[¶¶]
Pre-BD FEV_1 % pred	84 (71–99)	80 (70–90)	0.200[¶¶]
Pre-BD FEV_1/FVC	0.73 (0.65–0.78)	0.72 (0.63–0.78)	0.797[¶¶]
Post-BD FEV_1% pred	84 (75–99)	84 (75–92)	0.386[¶¶]
Post-BD FEV_1/FVC	0.73 (0.66–0.79)	0.73 (0.65–0.80)	0.888[¶¶]
Blood eosinophils ×10^9·L^{-1}	0.15 (0.08–0.25)	0.19 (0.10–0.29)	0.118[¶¶]
Total IgE kU·L^{-1}	61 (23–138)	79 (29–197)	0.140[¶¶]
Blood neutrophils ×10^9·L^{-1}	4.2 (3.4–5.2)	3.5 (2.7–4.6)	0.022[¶¶]
Prescribed daily dose of ICS µg BDP	841 (704–1062)	834 (642–995)	0.412[¶¶]
Dispensed daily dose of ICS µg BDP	831 (728–1+)	375 (210–520)	<0.001[¶¶]
Daily SABA[#]	13 (21.3)	6 (9.4)	0.082[##]
Daily LABA[#]	46 (75.4)	31 (48.4)	0.003[##]
Daily LTRA[#]	16 (26.2)	6 (9.5)	0.019[##]
Self-reported use of oral corticosteroid courses for asthma[¶]	26 (44.1)	22 (34.4)	0.355[##]
Dispensed oral corticosteroid for asthma per year mg[+]	125 (10–273)	70 (0–193)	0.176[¶¶]
Co-medications (non-respiratory)	2 (1–5)	2 (0–4)	0.116[¶¶]
AQ20 score	6 (3.5–8)	5.5 (2–10)	0.822[¶¶]
ACT score	21 (18–23)	20 (16–23)	0.795[¶¶]
Allergy and/or rhinitis	45 (73.8)	46 (71.9)	0.843[##]
Asthma-related visits to healthcare[¶,§]	19 (13–28)	13 (9–22)	0.005[¶¶]

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IgE: immunoglobulin E; ICS: inhaled corticosteroid; BDP: beclomethasone dipropionate equivalents; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; AQ20: Airways Questionnaire 20; ACT: Asthma Control Test. [#]: self-reported daily use; [¶]: examined during the whole 12-year follow-up period; [+]: dispensed doses of oral corticosteroids (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up; [§]: all respiratory-related scheduled and unscheduled contacts with healthcare due to asthma; [f]: independent samples t-test; [##]: Fisher's exact test; [¶¶]: independent samples Mann–Whitney U-test.

Decline in lung function

Next we evaluated the change in lung function in patients with controlled and not-controlled asthma and in groups of ⩾80% and <80% 12-year adherence. The patients with not-controlled asthma and <80% 12-year adherence had more rapid decrease in lung function (FEV_1) compared to patients with ⩾80% adherence (p=0.024) (table 4, figure 3). However, no difference was found in patients with controlled asthma between the adherence groups (table 4). We carried out multiple linear regression analysis to find out whether poor adherence predicts accelerated lung function decline in patients with not-controlled asthma when adjusted for age, BMI at follow-up, sex, F_{eNO} >20 ppb, ⩾10 pack-years and ΔFEV_1 (baseline−$max_{0–2.5}$) (table 5). After adjustments, poorer adherence (<80%) remained a significant predictor for FEV_1 (mL) decline.

Discussion

In this study we evaluated both annual and 12-year adherence to ICS from diagnosis to 12-year follow-up visit in patients with adult-onset asthma and different categories of asthma control. The mean adherence to ICS was better in patients with not-controlled than controlled asthma (76% *versus* 63%). Considering patients with not-controlled asthma, good 12-year adherence (⩾80%) was associated with daily use of LABA and higher number of peripheral blood neutrophils and asthma-related contacts to healthcare. Importantly, in patients with not-controlled asthma, <80% adherence predicted more rapid lung function decline in adjusted analyses.

TABLE 3 Characteristics of patients with controlled asthma at 12 years after diagnosis according to their level of 12-year adherence (n=56)

	Good adherence (⩾80%)	Poor adherence (<80%)	p-value
Patients	21	35	
Age years	58±11	54±16	0.266[f]
Female	16 (76.2)	25 (71.4)	0.764[##]
BMI kg·m^{-2}	26.3 (3.4)	28.3 (3.8)	0.045[f]
Smokers (including ex-smokers)	5 (23.8)	13 (37.1)	0.382[##]
Smoking history pack-years	10 (3.7–14.8)	5.3 (1.3–9.3)	0.383[¶¶]
Pre-BD FEV_1 % pred	91 (86–100)	92 (86–98)	0.939[¶¶]
Pre-BD FEV_1/FVC	0.74 (0.68–0.80)	0.75 (0.71–0.79)	0.460[¶¶]
Post-BD FEV_1% pred	96 (90–100)	96 (91–102)	0.826[¶¶]
Post-BD FEV_1/FVC	0.75 (0.71–0.82)	0.78 (0.73–0.83)	0.285[¶¶]
Blood eosinophils ×10^9·L^{-1}	0.25 (0.13–0.37)	0.15 (0.11–0.26)	0.095[¶¶]
Total IgE kU·L^{-1}	93 (39–214)	43 (23–95)	0.022[¶¶]
Blood neutrophils ×10^9·L^{-1}	3.9 (3.6–5.5)	3.6 (2.6–3.9)	0.016[¶¶]
Prescribed daily dose of ICS µg BDP	620 (488–1017)	800 (541–925)	0.565[¶¶]
Dispensed daily dose of ICS µg BDP	628 (476–983)	301 (90–402)	<0.001[¶¶]
Daily SABA[#]	0 (0)	2 (5.7)	0.523[##]
Daily LABA[#]	8 (38.1)	10 (28.6)	0.558[##]
Daily LTRA[#]	2 (9.5)	2 (5.7)	0.626[##]
Self-reported use of oral corticosteroid courses for asthma[¶]	8 (38.1)	4 (11.4)	0.040[##]
Dispensed oral corticosteroid for asthma per year mg[+]	48 (6–203)	0 (0–99)	0.060[¶¶]
Co-medications (nonrespiratory)	0 (0–4)	1 (0–4)	0.472[¶¶]
AQ20 score	2 (0–3.5)	2 (1–4)	0.724[¶¶]
ACT score	24 (22–25)	24 (22–25)	0.593[¶¶]
Allergy and/or rhinitis	14 (66.7)	24 (68.6)	>0.999[##]
Asthma-related visits to healthcare[¶,§]	17 (8–27)	9 (6–17)	0.062[¶¶]

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IgE: immunoglobulin E; ICS: inhaled corticosteroid; BDP: beclomethasone dipropionate equivalents; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; AQ20: Airways Questionnaire 20; ACT: Asthma Control Test. [#]: self-reported daily use; [¶]: examined during the whole 12-year follow-up period; [+]: dispensed doses of oral corticosteroids (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up; [§]: all respiratory-related scheduled and unscheduled contacts with healthcare due to asthma; [f]: independent samples t-test; [##]: Fisher's exact test; [¶¶]: independent samples Mann–Whitney U-test.

TABLE 4 Lung function change (change in pre-bronchodilator forced expiratory volume in 1 s (ΔFEV_1) from maximum lung function ($max_{0-2.5}$) during the first 2.5 years after diagnosis (after start of therapy) to 12-year follow-up visit) in patients with controlled and not-controlled asthma and different level of adherence (n=181)

	Good adherence ⩾80%	Poor adherence <80%	p-value
Not-controlled asthma n	125		
ΔFEV_1 mL·year^{-1}	−40 (−56–−20)	−47 (−83–−32)	0.024
ΔFEV_1 % pred·year^{-1}	−0.47 (−0.98–0.25)	−0.76 (−1.40–−0.17)	0.029
Controlled asthma n	56		
ΔFEV_1 mL·year^{-1}	−39 (−59–−24)	−35 (−67–−25)	0.859
ΔFEV_1 % pred·year^{-1}	−0.31 (−0.76–0.54)	−0.34 (−1.10–0.07)	0.271

Statistical significances were evaluated by independent-samples Mann–Whitney U-test. When patients with COPD were excluded from the analysis, ΔFEV_1 was −36 (−54–−18) mL·year^{-1} in patients with >80% adherence and −43 (−78–−28) mL·year^{-1} in patients with <80% adherence and not-controlled asthma (p=0.058).

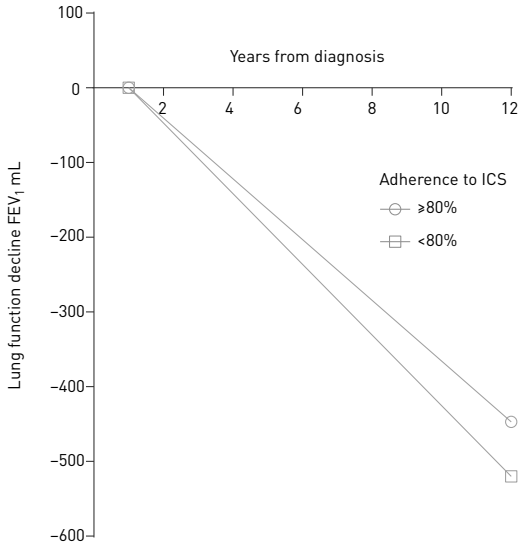

FIGURE 3 Schematic presentation of the changes in forced expiratory volume in 1 s (FEV_1) (mL) during 12 years of follow-up in patients with not-controlled asthma and ⩾80% or <80% adherence. Model based on group medians. At the year 0 patients were steroid-naïve and inhaled corticosteroid (ICS) treatment was initiated (diagnostic visit). Origin for lung function decline is the maximal point of lung function within 2.5 years after start of treatment.

Although previous studies have suggested better ICS adherence to be associated with good disease control [4, 11–13, 20], in this study patients with not-controlled asthma had higher 12-year adherence to long-term ICS treatment compared to patients with controlled disease. The higher proportion of adherent patients in the former group may be explained by more severe symptoms and associated need of medication [16, 21]. Conversely, patients with controlled asthma may have themselves stepped-down their ICS therapy after achieving disease control, which would appear as lower adherence rates during the follow-up. In group comparisons, 58% of the patients with not-controlled disease were current or ex-smokers and had significantly more pack-years than those with controlled asthma. This is in line with previous studies which have related smoking to worse asthma control [3, 4, 12, 32]. Furthermore, patients with not-controlled asthma were more often older, male and less often atopic compared to those with controlled disease. In addition, there was a tendency between poorer asthma control and higher BMI. In

TABLE 5 Predictors for annual decline of forced expiratory volume in 1 s (FEV_1) (mL) (ΔFEV_1 from maximum lung function ($max_{0–2.5}$) during the first 2.5 years after diagnosis (after start of therapy) to 12-year follow-up visit) in 12-year follow-up in patients with not-controlled asthma as evaluated by multiple linear regression analysis (n=100)

	Unstandardised B coefficient (95% CI)	p-value
Age at follow-up	−0.10 (−0.53–0.33)	0.638
Female	12.46 (1.03–23.89)	0.033
BMI at follow-up	−1.03 (−2.05–0.00)	0.049
⩾10 pack-years at follow-up	−7.92 (−19.01–3.16)	0.159
ΔFEV_1 mL (baseline−$max_{0–2.5}$)	−0.024 (−0.04–−0.01)	0.005
F_{eNO} >20 ppb	−23.48 (−35.99–−10.97)	<0.001
Average 12-year adherence (<80%) to ICS	−10.36 (−20.37–−0.36)	0.042

In univariate analysis, unstandardised B coefficient (95% CI) for average 12-year adherence (<80%) to ICS is −11.23 (−22.15–−0.32), p=0.044. BMI: body mass index; F_{eNO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroid.

patients with adult-onset asthma, phenotypes related to obesity and smoking are currently recognised, these phenotypes being at risk of poorer asthma outcomes and disease control [33–35]. Even though patients with not-controlled asthma had mean 12-year ICS adherence as high as 76%, factors such as smoking and obesity may induce insensitivity to ICS and poor response to treatment [34, 36, 37]. Furthermore, in recent studies the average age of patients has been lower in comparison to our study population [10, 13, 14] indicating that previous studies have included more patients with allergic asthma showing predominantly type 2 inflammation. Therefore, ⩾80% adherence to long-term ICS treatment appears not to be effective enough to control asthma, since these patients may have had non-type 2 inflammation or untreated comorbidities.

While it seems to have been taken for granted that poor adherence is one common reason behind not-controlled asthma, previous studies in this field have usually been cross-sectional or short-term follow-ups and no long-term studies have been conducted [10–17]. These cross-sectional studies mostly included patients having asthma diagnosis but the information on age of asthma onset, diagnostic criteria or duration of asthma were often lacking [10–12, 14, 16–18]. Moreover, in previous studies asthma control has been defined as asthma symptom control assessed by the Asthma Control Test or Asthma Control Questionnaire and not including both symptoms and lung function as defined by the GINA guideline. Furthermore, adherence has been evaluated with the Medication Adherence Rating Scale or Morisky (Morisky Medication Adherence Scale) questionnaires [4, 12, 14–16, 18]. Such self-reports are widely used for assessing adherence, but may be vulnerable to the shortcomings of these memory-dependent channels. We found one 3-month clinical trial on inhaler adherence in patients with uncontrolled asthma where control was assessed according to GINA guidelines and adherence monitored with an INCA (INhaler Compliance Assessment) device, in which 27% of patients stayed refractory despite being adherent to salmeterol/fluticasone treatment and having correct inhaler technique [38]. A similar result was found in the current study where 34% of the study patients remained not controlled despite having ⩾80% adherence to ICS treatment during 12-year follow-up. To our knowledge, this is the first study where asthma control is determined according to GINA guidelines in unselected patient population and adherence is confirmed longitudinally by comparing each patient´s dispensed ICS medication to truly prescribed doses of ICS [8]. Furthermore, all patients with objectively confirmed diagnosis of new-onset adult asthma were included, meaning patients with comorbidities and history of smoking, for example.

When assessing lung function decline during 12-year follow-up in patients with not-controlled asthma, those with lower (<80%) 12-year adherence had more rapid decline in FEV_1 compared to patients with ⩾80% adherence (p=0.024). This difference was not seen in patients with controlled asthma. In addition, the observed difference may be clinically meaningful since the patients with adult-onset asthma rarely remit and a level of 7 mL·year^{-1} would correspond to 140 mL in 20 years and 210 mL in 30 years. Smoking and exacerbations are also important factors associated with the decline in lung function [30]. Even though the two adherence groups with not-controlled asthma did not differ by smoking, we adjusted our analyses for smoked pack-years and found that poorer adherence (<80%) remained a significant predictor for FEV_1 decline in patients with not-controlled asthma. The finding underscores the importance of determining patients' asthma control by GINA guidelines and to assess treatment adherence. Early recognition of patients with not-controlled (partially or uncontrolled) asthma and suboptimal (<80%) adherence should allow us to detect those patients who may be at risk of steeper lung function decline in the long term. Moreover, it may allow the opportunity to motivate them towards better adherence and thereby avoid undesirable outcomes in lung function. Conversely, this may help to identify patients whose asthma is not controlled despite high adherence to treatment. These patients may show non-type 2 inflammation, since they have higher blood neutrophil counts and current medications may not be effective enough to control their disease. These results further suggest that patients with late-onset asthma and insufficient therapeutic response need new treatment strategies and possibly other interventions such as support in smoking cessation and weight loss.

In the current study, medical records and pharmacy dispensation data were used in adherence calculations, and therefore some limitations must be addressed. The dispensed medication is not a guarantee of inhaler use, and therefore patient´s adherence to treatment may be overestimated. Although patients had guidance to correct inhaler use when medication was initiated, the correct inhaler technique could not be ensured. Furthermore, asthma control was measured at follow-up visit and not regularly during the follow-up. However, the current study with an exceptionally long follow-up period is based on objectively calculated adherence data, and assessment of asthma control includes lung function according to GINA guidelines [3, 8]. It has been suggested [38] that an assessment of adherence using and electronic device could be beneficial in patients with severe asthma. According to our results such approaches could also be used in patients with not-controlled disease. Future studies should assess how guidance on adherence focused to subjects with poor adherence to ICS and not-controlled asthma affects long-term changes in lung function.

In conclusion, we combined, for the first time, long-term adherence to ICS with asthma control determined according to GINA guideline [27]. The mean 12-year adherence to this treatment was especially high in patients with not-controlled disease. New treatment strategies combining pharmacological and nonpharmacological approaches may be needed in patients with insufficient therapeutic response. Importantly, our results showed that patients with not-controlled asthma and poor adherence (<80%) had more rapid decline in FEV_1 during 12-year follow-up compared to patients with higher adherence (⩾80%), which must be recognised to avoid negative consequences. In clinical practice, careful evaluation of patient´s asthma control and adherence to treatment enhances the recognition of those patients at risk of rapid lung function decline in the long-term.

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PUBLICATION IV

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

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Original Article

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

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

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

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

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

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

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

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

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Conflicts of interest: I. Vähätalo reports personal fees from Astra Zeneca, outside the submitted work. L. Lehtimäki reports grants and personal fees from Orion Pharma; personal fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, Circassia, GSK, Mundipharma, Novartis, and Sanofi; and shares of Auscultthing Oy, outside the submitted work. L. E. Tuomisto reports personal fees from Boehringer Ingelheim, Astra Zeneca, and GlaxoSmithKline; and nonfinancial support from Chiesi, outside the submitted work. J. Karjalainen reports personal fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, Sanofi, GlaxoSmithKline, Novartis, and Orion Pharma, outside the submitted work. P. Ilmarinen is an employee of GlaxoSmithKline; and reports personal fees from GlaxoSmithKline, Novartis, Mundipharma, and Astra Zeneca, outside the submitted work. H. Kankaanranta reports personal fees from Astra Zeneca, Orion Pharma, Mundipharma, Boehringer Ingelheim, Chiesi Pharma AB, GlaxoSmithKline, MSD, Novartis, and Sanofi Genzyme, outside the submitted work. O. Niemelä declares that he has no relevant conflicts of interest.

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

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

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

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

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

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

METHODS

Study design and patients

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

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

Assessment of dispensed SABA and ICS

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

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

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

Evaluation of symptoms, asthma control, and dispensed oral corticosteroids

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

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

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

Statistical analyses

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

RESULTS

Patient characteristics

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

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

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

High use and over-reliance on SABA

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

Factors predicting high use of SABA

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

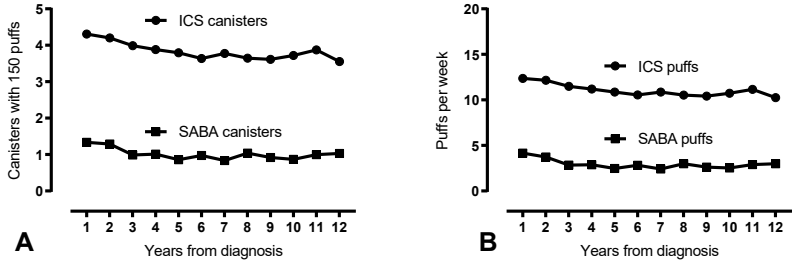

FIGURE 1. (**A**) Average SABA and ICS canisters dispensed per year during 12-year follow-up. (**B**) Average SABA and ICS puffs used per week during 12-year follow-up. Patients were dispensed mean 13 (SD 17) canisters of SABA and 48 (SD 33) canisters of ICS during 12 years corresponding to use of mean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

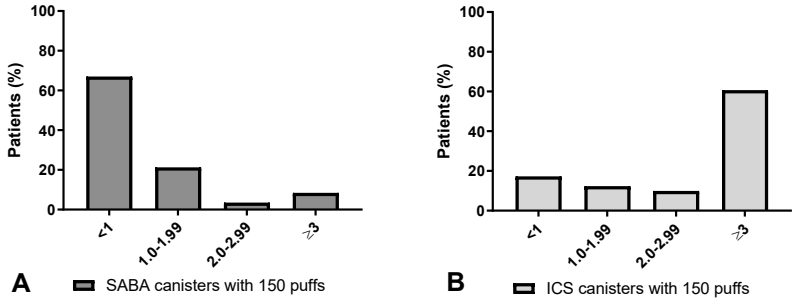

FIGURE 2. (**A**) The average annual dispensed number of SABA canisters during 12 years divided into 4 categories and (**B**) the average annual dispensed number of ICS canisters divided into 4 categories. In (**A**) and (**B**), the cutoff of 3 canisters is selected to show how many patients were dispensed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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

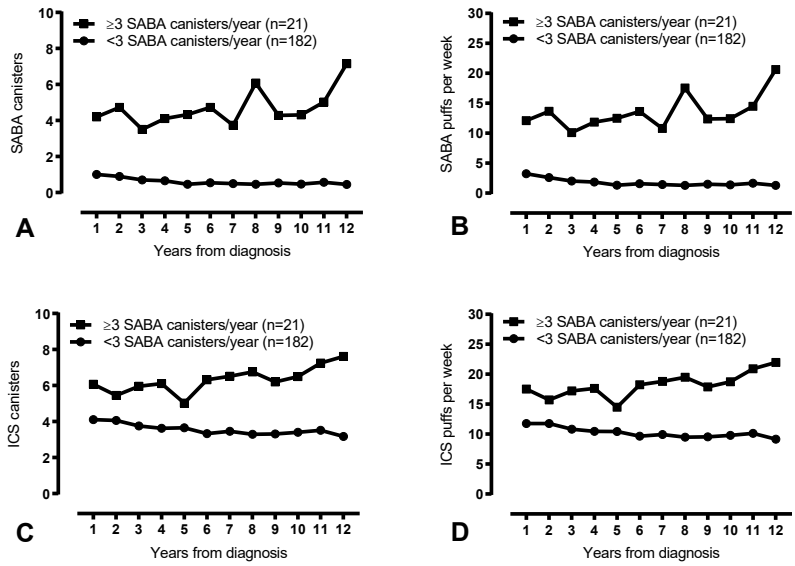

FIGURE 3. (**A**) The average annual dispensed number of SABA canisters; (**B**) SABA puffs per week; (**C**) average annual dispensed number of ICS canisters; (**D**) ICS puffs per week in patients with use of ≥3 or <3 SABA canisters annually during the 12-year follow-up. Patients with high SABA use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

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

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

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

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

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

Data are presented as n (%), mean (SD), or median (interquartile range). Adherence was calculated as total cumulative ICS dispensed (μg)/total cumulative ICS prescribed (μg) over 12 years. Number of comorbidities was evaluated separately and as the sum of all comorbidities reported at the 12-year follow-up visit.
BD, Bronchodilator; *BMI*, body mass index; *Control-to-total ratio*, dispensed inhaled corticosteroid canisters divided by the sum of dispensed short-acting β_2-agonist canisters and inhaled corticosteroid canisters; *Daily add-on drug*, self-reported daily use of long-acting β_2-agonist, leukotriene receptor antagonist, tiotropium, or theophylline; *Daily LABA*, self-reported daily use of long-acting β_2-agonist; *Daily SABA*, self-reported daily use of short-acting β_2-agonist; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *pack-y*, pack years of smokers; *SD*, standard deviation.
*Statistical significances were evaluated by the independent samples *t*-test.
†Statistical significances were evaluated by the Fisher exact test.
‡Statistical significances were evaluated by the independent samples Mann-Whitney *U* test.

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

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

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

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

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

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

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

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

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

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

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

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

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Lung function measurements

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

Laboratory measurements

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

Evaluation of SABA use

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

Computation of adherence

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

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

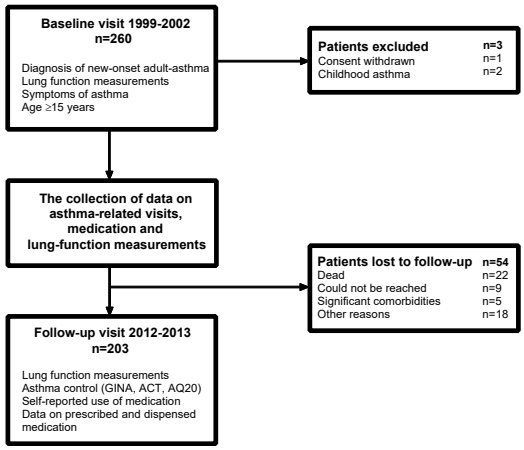

FIGURE E1. Flowchart of the study. *ACT*, Asthma Control Test; *AQ20*, Airways Questionnaire 20; *GINA*, Global Initiative for Asthma.

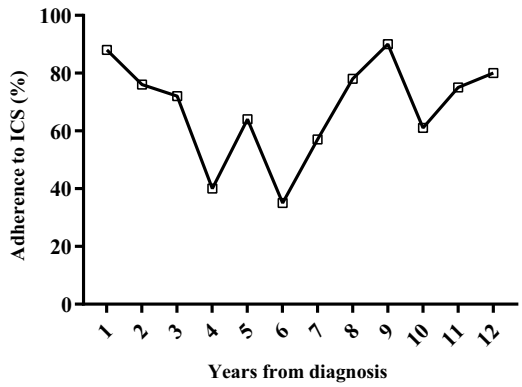

FIGURE E2. Twelve-year ICS adherence of 1 example patient. *ICS*, Inhaled corticosteroid.

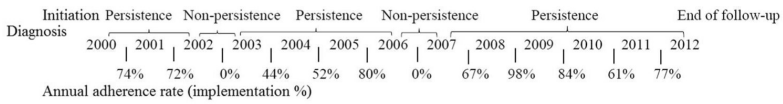

FIGURE E3. Time-varying adherence of 1 example patient (the average 12-year adherence of the example patient is 68%).

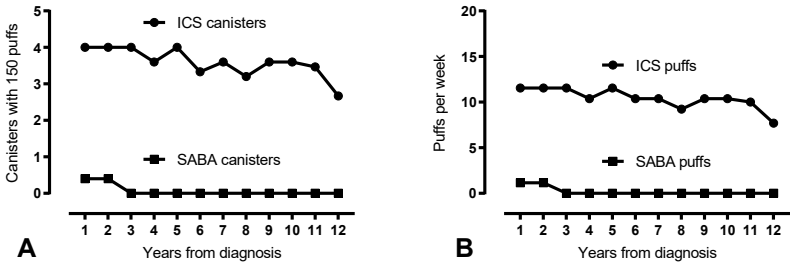

FIGURE E4. (**A**) Median SABA and ICS canisters per year dispensed during 12-year follow-up. (**B**) Median SABA and ICS puffs used per week during 12-year follow-up. *ICS*, Inhaled corticosteroid; *SABA*, short-acting β_2-agonists.

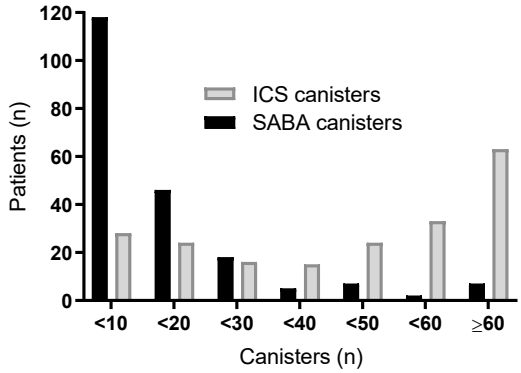

FIGURE E5. Cumulative dispensed ICS and SABA canisters during 12-year follow-up. *ICS*, Inhaled corticosteroid; *SABA*, short-acting β_2-agonists.

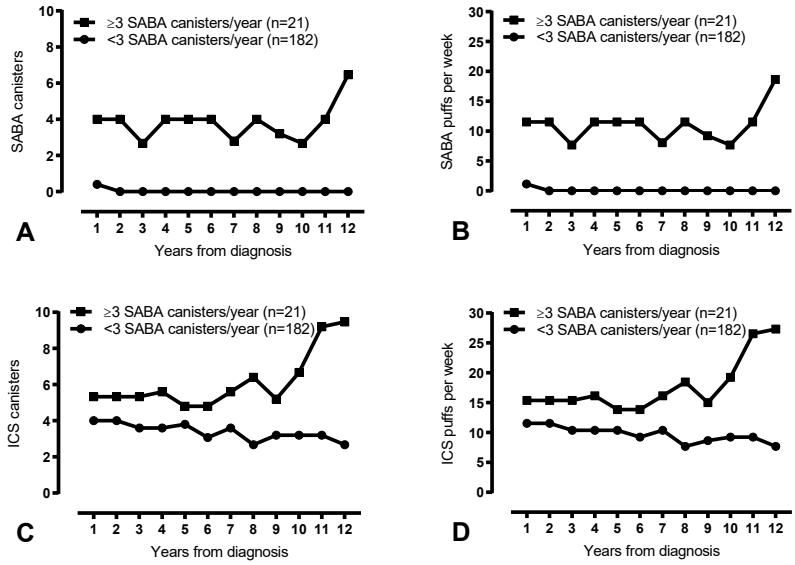

FIGURE E6. (**A**) The median annual dispensed number of SABA canisters; (**B**) SABA puffs per week; (**C**) median annual dispensed number of ICS canisters; (**D**) ICS puffs per week in patients with use of ≥3 or <3 SABA canisters annually during the 12-year follow-up. *ICS*, Inhaled corticosteroid;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

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

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

Published earlier: Kankaanranta et al 2015.[E13]

FEV_1, Forced expiratory volume in 1 second; *PEF*, peak expiratory flow, *SAAS*, Seinäjoki Adult Asthma Study.

TABLE E2. Inhalers containing SABA dispensed in the SAAS

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

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

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

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

AQ20, Airways Questionnaire 20; *BMI*, body mass index; *CRP*, C-reactive protein; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid.
*Statistical significances were evaluated by the related samples Wilcoxon signed-rank test (if non-normally distributed).
†Statistical significances were evaluated by the McNemar test (categorical variables).

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

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

Number of over-reliant patients was 5 (2.5%) by any definition.
ICS, Inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *SABA*, short-acting β_2-agonists.

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