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Management of Asthma in primary care

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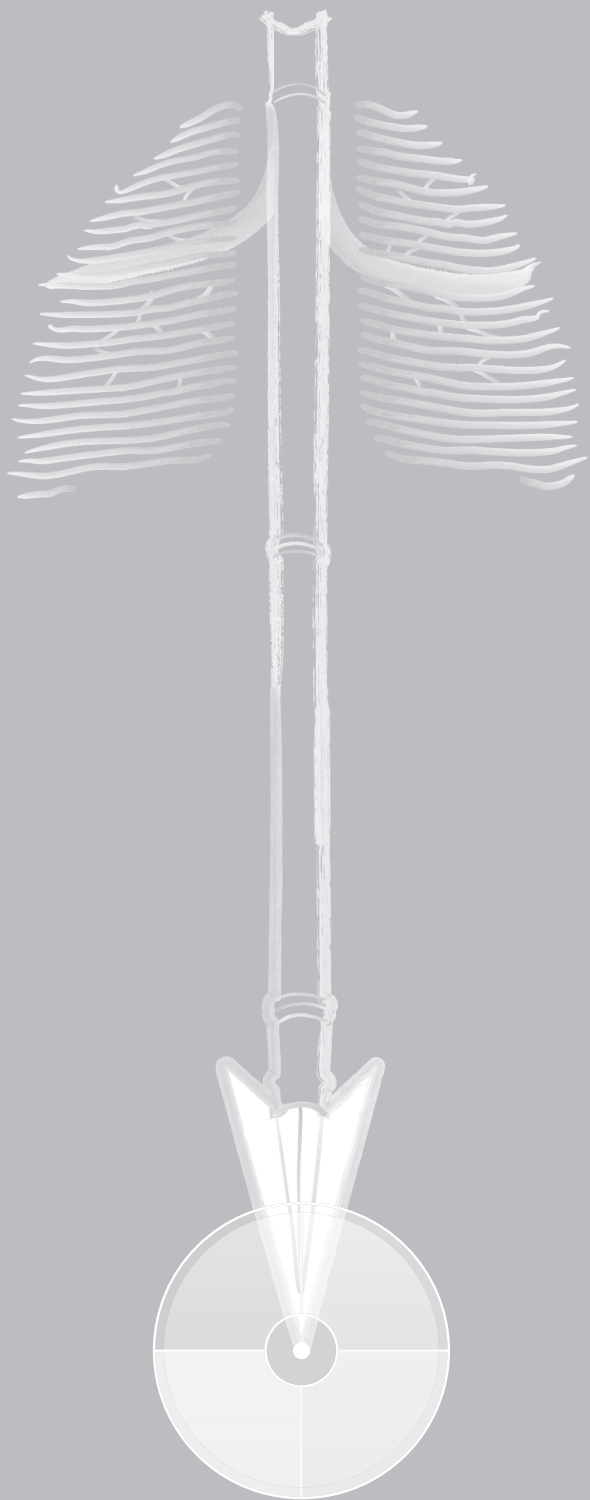
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Chapter 1

General introduction and
aims of the study

Definitions

Asthma is a common non-communicable respiratory disease, characterised by episodic shortness of breath and wheezing. The US National Heart Lung and Blood Institute (NHLBI) defines asthma as follows in their National Asthma Education and Prevention Program NAEPP [1]: 'Asthma is a common chronic disorder of the airways that is complex and characterised by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment'. Symptoms of asthma include recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with airflow obstruction within the lung that is often reversible, either spontaneously or with treatment.

Asthma symptoms can gradually increase over time, slowly increasing the burden of asthma on daily life. Asthma symptoms can also increase more rapidly, sometimes within a day, and this is referred to as an asthma attack, or asthma exacerbation. Exacerbations are characterised by a combination of an increase in shortness of breath, cough, wheezing and chest tightness and they are potentially life threatening, depending on their severity.

Organisation of healthcare

The Accurate trial, on which most chapters in this manuscript are based, was performed in the Netherlands with patients with asthma currently being treated in primary care. In the Dutch healthcare system primary care serves as a gatekeeper. This means that all patients and all illnesses are diagnosed and treated in primary care, unless the primary care physician refers a patient to secondary care for analysis or treatment. Therefore, in contrast to other countries, most patients with asthma in the Netherlands are treated in primary care, while patients with severe or difficult-to-treat asthma, or patients in whom the diagnosis is uncertain, will be treated in secondary or tertiary care. Another difference with some other countries is that in recent years primary care physicians have employed practice nurses to aid in the management of chronic diseases. Traditionally, practice nurses primarily assessed patients for cardiovascular disease management and for diabetes. Nowadays, COPD management is also largely performed by practice nurses and there is a significant increase in the management of asthma as well. Usually a practice nurse will assess a patient regularly and discuss outcomes and possible treatment changes with the primary care physician. Intercurrent worsening of disease, such as an asthma exacerbation, is still treated by the primary care physician.

Trials

The chapters in this manuscript are based on data from several different trials. Chapters 2, 4 and 6 and most of Chapter 3 are based on the Accurate trial [2]. Part of chapter 3 is based on a cohort of patients who were referred by their GP for lung function testing in a primary care diagnostic centre in the Nijmegen area. Chapter 5 is based on the data from two trials that were originally conducted in New Zealand [3,4].

Epidemiology

Asthma is a worldwide problem, and globally, the prevalence ranges from 1-24% of the population in different countries and races [5]. The prevalence is still increasing in most countries, especially in children, along with a similar increase in other atopy-related diseases such as eczema and rhinitis [5-8]. In the Netherlands the prevalence is roughly 28 per 1000 persons and the number of newly diagnosed adult asthma patients in Dutch primary care is 6 per 1000 per year [9]. The prevalence of asthma changes with age, from more than 30 per 1000 in young adults to approximately 20 per 1000 in the elderly [9]. In primary care males are diagnosed with asthma 1.5 times as often as females. Most importantly, even though asthma is a relatively well-manageable disease, asthma still accounts for approximately 1 in every 250 deaths worldwide, especially in areas with low access to healthcare [5,6].

Mechanisms of asthma

As has been outlined above, asthma is characterised by several processes: airway inflammation, airway hyper responsiveness and airway obstruction. The interaction between these processes will determine the frequency and severity of the symptoms a patient will experience [figure 1.1].

Central to asthma is the continuous presence of underlying airway inflammation, which is caused by an inappropriate response to environmental stimuli, such as allergens, cigarette smoke, certain drugs or air pollutants [10]. Although airway inflammation varies in intensity, it remains persistent in asthma, even when symptoms are not present. Therefore, there is no clearly established relationship between the severity of asthma symptoms and the intensity of inflammation [11,12]. Inflammation affects the calibre of the airways leading to airway obstruction and in addition affects (hyper)responsiveness of airways to stimuli, which leads to an increased sensitivity to bronchospasm [11]. The relationship between bronchospasm and patients' symptoms is more clear, especially when bronchospasm occurs acutely.

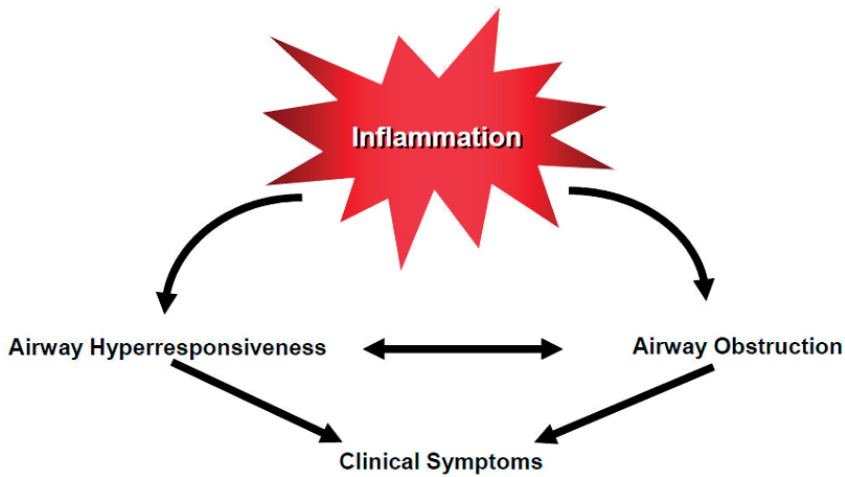


Figure 1.1. Interplay between airway inflammation and clinical symptoms. Adapted from figure 2-1 of the NAEPP guideline 2007 [1].

Diagnosis

In primary care the diagnosis of asthma is based on the presence of a characteristic clinical history, which includes recurrent episodes of dyspnoea, wheezing and/or cough [10]. An additional measurement of lung function can enhance diagnostic confidence, if it shows reversibility, which is defined as an increase of $\geq 12\%$ and 200 ml in FEV_1 after bronchodilator therapy [13,14]. If the sole symptom is recurrent cough, without dyspnoea or wheezing, reversibility is obligatory to diagnose asthma, to differentiate it from other diagnostic possibilities such as eosinophilic bronchitis, gastroesophageal reflux, postnasal drip, chronic sinusitis, and vocal cord dysfunction [15]. Other findings in history taking and physical examination include a family history of asthma or allergies, atopy, fatigue, deterioration of physical abilities, wheezing on auscultation and prolonged expiratory time. Increased breathing frequency, and use of accessory muscles can also occur if asthma symptoms are more severe. Typically the symptoms in asthma are variable and intermittent, they may be exacerbated by exercise, viral infections, exposure to irritants or allergens, changes in weather, strong emotional expressions and menstrual cycles [1, 16]. Based on symptom frequency, there is a distinction between intermittent (symptoms ≤ 2 times a week) and persistent (symptoms > 2 times a week) asthma. A special subcategory of intermittent asthma is exercise-induced asthma, in which symptoms only occur during or shortly after physical exercise.

Treatment

An important and integral part of asthma treatment consists of lifestyle advices. Smoking-cessation is the key component, since smoking results in a more rapid decline of forced expiratory volume in one second (FEV₁), worsens the natural course of asthma and decreases the effectiveness of inhaled corticosteroids (ICS) [17]. Physical activity should be encouraged, since it increases oxygen uptake and expiratory volume [18]. The exposure to allergens should be limited, especially for relevant allergies. With regards to domestic mite allergy there is no convincing evidence that reducing exposure benefits patients with asthma [19]. However, based on experienced improvements of asthma control in clinical practice, Dutch guidelines state that in patients with difficult to control asthma and a proven allergy, an integrated approach including barrier methods, dust removal and reduction of microhabitats favourable to mites might improve symptoms [13, 20, 21].

The mainstay of asthma treatment is medication. In the management of asthma two types of medication exist, namely 'controllers' and 'relievers'. Controllers are daily medications, developed to keep asthma under clinical control, mainly through their anti-inflammatory effects. They include inhaled and systemic corticosteroids, leukotriene modifiers, combinations between inhaled corticosteroids and long-acting beta agonists (LABA), theophylline, cromones, anti-IgE, and other systemic steroid-sparing therapies. Relievers are medications used on an as-needed basis and designed to reverse bronchoconstriction and thereby relieve its symptoms. They include rapid-acting inhaled beta-agonists, inhaled anticholinergics and short-acting theophylline. As stated before, the relationship between bronchoconstriction and asthma symptoms is more clear than between inflammation and symptoms. Therefore patients perceive more direct benefit from reliever medication which address bronchospasm (i.e. bronchodilators) than from medications that are aimed at controlling the underlying inflammation, for which (inhaled) corticosteroids (or leukotriene modifiers) are the medications of choice. However, although patients will not perceive direct benefit, especially in the long-term, controller medication are the most important component of treatment, since they address underlying inflammation. These differences in expected perceived advantages of medication need to be addressed in consultation to improve patient adherence.

Costs and cost-effectiveness

The Dutch governmental organisation for health and environment 'Rijksinstituut voor Volksgezondheid en Milieu' (RIVM) has assessed costs for asthma in the Netherlands in 2007 [22]. Total healthcare costs were € 287 million per year, which amounts to € 530 per

patient per year. Costs for asthma medication account for nearly 70% of total healthcare costs for asthma. Other costs constitute physiotherapy (10.8%), regular monitoring in secondary care (9.5%), hospitalisation (5.7%), and regular monitoring in primary care (4.5%). Furthermore, there are additional costs for loss of productivity, which range from € 340 per year for employed patients between 15-25 years, to € 2000 per year for employed patients between 55-65 years. Loss of productivity can be mainly ascribed to inability to work due to asthma exacerbations. Therefore, to achieve a reduction in costs for asthma, medication-usage and exacerbation frequency are the most appropriate targets. A more patient tailored approach of medication prescription, instead of a one-size-fits-all approach, would ideally reduce total medication use, without loss of control on asthma symptoms. Another effective measure to reduce costs would be to decrease the asthma exacerbation rate, since this would decrease both costs for hospitalisations and costs due to loss of productivity.

Asthma management

In the Netherlands 80% of patients with asthma are managed in primary care, 10% are managed solely by a pulmonary physician and 10% are managed by both [22]. In primary care the recommended frequency of assessment of current asthma control is once to twice a year when asthma is controlled, to as often as every two weeks when asthma remains uncontrolled [1,8,13,23]. In clinical practice, the actual frequency of assessment may vary widely between different general practitioners and between individual patients. This can be caused by several factors, such as lack of patient or doctor adherence to the recommended monitoring frequency, which may be explained by a perceived lack of benefit. However, with the advent of integrated disease management [IDM] programs, a more uniform approach to asthma management is arising [23]. IDM programs are commonly used for COPD and include individualised targets, exercise programs, regular monitoring and self-management [24]. For asthma, these programs are currently initiated by large conglomerates of primary care practices. The content is based on recent guidelines and reviewed by several stakeholders, such as primary care physicians, pulmonary physicians and health insurance companies [13, 21].

When monitoring asthma, the aim is to achieve and maintain control of clinical manifestations for prolonged periods of time. Additional aims include prevention of exacerbations, minimising side-effects of medication, and keeping asthma costs as low as possible [1,8,13,25]. The severity of clinical manifestations of asthma is generally classified into controlled, partly controlled and uncontrolled asthma [1,8]. This classification is based on several clinical parameters: presence/absence of daytime symptoms, limitations in activity, nocturnal symptoms/awakening, the need for reliever therapy

and lung function [1,8,13]. Current control on asthma can be measured by the Asthma Control Questionnaire (ACQ), which is a composite questionnaire that incorporates all these parameters [26]. According to international guidelines, the current aim of asthma management, is to achieve controlled asthma [1,8,13]. However, in practice, 45% of patients are partly controlled and 30% of patients are uncontrolled [27-29]. In these patients a step-up of asthma medication is advocated to achieve controlled asthma [1,8,13,25]. However, for patients who are considered partly controlled, the benefits of stepping up treatment might be limited and should be weighed against potential harms, because the dose-response relationship of inhaled corticosteroids (ICS) flattens at higher levels, while the risk of side-effects such as cough, pneumonia and adrenal insufficiency increases [30,31]. This dilemma in asthma management is captured in the notion that patient preferences/goals should be taken into account before stepping up treatment when asthma is partly controlled [8,13]. To clarify this dilemma, we performed a trial, in which we compared a treatment strategy aiming for controlled asthma, with a strategy that accepted partly controlled asthma, using asthma control, asthma related quality of life, exacerbation rate, medication prescription levels and costs as outcome-comparators. **Chapter 2** contains the published version of the protocol for this study, describing study procedures, measurements and algorithm, while study results are presented in **chapter 4**.

Another dilemma in current guidelines involves the choice of type of medications in a step-up or step-down of treatment. Guidelines do not give clear advice on whether to increase/decrease inhaled corticosteroids (ICS) or add/remove long-acting beta-agonists (LABA) [1,8,13]. Some guidelines also include the options of adding/removing leukotriene modifiers or theophylline at certain treatment levels (See figure 1.2).

There is a need to identify which individual patients would benefit most from a step-up/step-down in ICS and which would benefit most from a step-up/step-down in LABA. If medication prescriptions are tailored to an individual patient's needs, the lowest possible effective dosage can be prescribed, thereby maximizing asthma control and minimising therapy-related side-effects and costs. Currently it is recommended to assess symptoms and lung function in asthma management. However, these measurements do not provide sufficient information to appropriately choose between different types of medication in an individual patient. An additional measurement of airways inflammation would enable a more tailored decision making, since inflammation is the underlying process in asthma and it is the main target for inhaled corticosteroids. Recent studies showed that biomarkers, such as fractional exhaled nitric oxide (FeNO), might provide the required additional information on bronchial inflammation [32]. However, the use of FeNO in asthma management has led to contradicting results. Some studies on tailoring treatment based on FeNO showed an increased proportion of patients with 'controlled asthma' [33] and a reduction in ICS dosage [4]. In contrast, other studies showed an

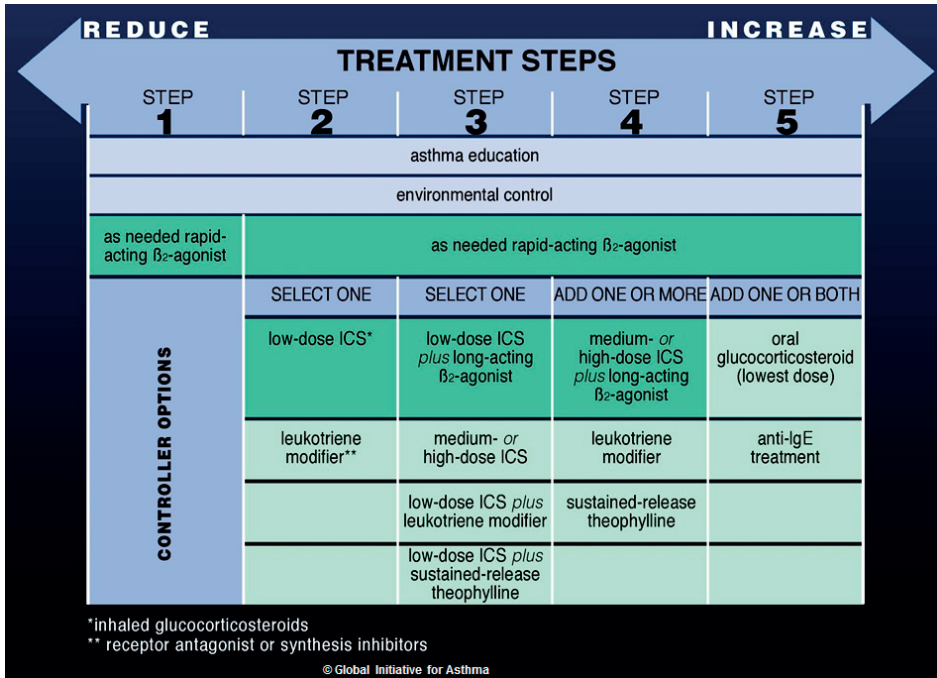


Figure 1.2. Medication at different treatment steps
 Adapted from figure: Management approach based on control, chapter 4 of the GINA guideline 2012 [5].

increase in ICS use [34-36]. However, most of these studies have been performed in secondary care patients, which have more severe asthma. Also, the choice of cut-off points for FeNO and the role the FeNO-measurement had in asthma management decisions differed between these studies. To date, it remains unclear, whether FeNO is a useful adjunct test to symptom assessment and lung function, when assessing asthma control in adult patients in primary care. Therefore, we address this topic in **chapter 3**.

Furthermore, it is unknown whether the pursuit of controlled asthma with additional guidance by a measure of airway inflammation (FeNO) improves our aim to achieve and maintain controlled asthma, and/or leads to a more tailored medication prescription, an improved asthma related quality of life, lower exacerbation-rates and/or reduced costs of treatment. To that end, we added a third strategy that aimed for controlled asthma additionally driven by Fractional exhaled Nitric Oxide (FeNO), to our previously described study that compared aiming for partly controlled asthma with aiming for controlled asthma. In **chapter 2** we describe the study protocol and the specific measurements regarding the use of FeNO. **Chapter 4** describes the results of our study.

Reduction of future risk, defined as the occurrence of (severe) exacerbations, or prolonged periods of loss of control, is another important aim in the management of asthma. Obviously, improving control on asthma symptoms by regular monitoring and finding

the optimal management strategy, should result in a reduced frequency of exacerbations and prolonged periods of loss of control. Therefore, we also addressed the exacerbation frequency in our comparison of the three treatment strategies in **chapter 4**.

In addition to regular control visits, patients are provided with the option to use an (online) self-management plan to improve control on asthma and detect and prevent imminent exacerbations. Self-management preferably includes creating an individualised Written Asthma Action Plan (WAAP) [37]. Multiple different types of WAAPs exist, but generally patients are provided with a diary in which they daily record their asthma symptoms, or a lung function measurement, or both. As a measure of lung function, Peak Expiratory Flow (PEF) is usually used, since it can be easily assessed at home using a handheld device (PIKO-1 device). In the WAAP several threshold levels of symptoms and/or PEF are pre-specified and if the daily measurements exceed these threshold levels, the patient is advised to take a particular action. Hence these thresholds are called 'action points'. Examples of action points are that a patient can be advised to increase his inhaled corticosteroids when he starts experiencing breathlessness during activity, or a patient can be advised to immediately see a doctor if his PEF measurement is below 50% of his personal best value. In order to be effective, an action point should detect an imminent exacerbation accurately and well before its onset. Although a number of different candidate action points have been proposed in the literature, most currently recommended action points have not been validated [1,8,13,38-41]. Furthermore, in most guidelines, thresholds for symptoms or PEF are not even specified and should be determined empirically by a physician (in conjunction with the patient), lacking any evidence base [8, 13]. Also, the optimum time point at which changes in symptoms or PEF may be detected prior to an exacerbation is largely unknown. If action points are inaccurately selected, this potentially leads to over treatment (false-positive action points) or missed opportunities for early intervention (false-negatives). Therefore in **chapter 5**, we aimed to develop optimal action points, based on symptoms and/or PEF threshold levels for early detection of asthma exacerbations which allow timely intervention (with oral prednisone) in patients with mild-moderate asthma.

The Internet

The world is changing rapidly and already a large proportion of our time is spent online. Unsurprisingly, simultaneously we see the appearance of all sorts of online tools to monitor chronic diseases, such as apps and patient portals, and future self-management plans will be mainly online [42-44]. Often it is assumed that the results of measurements of questionnaires online will be similar to pen & paper versions, and outcomes will therefore be interchangeable. For the Asthma Control Questionnaire, which had a

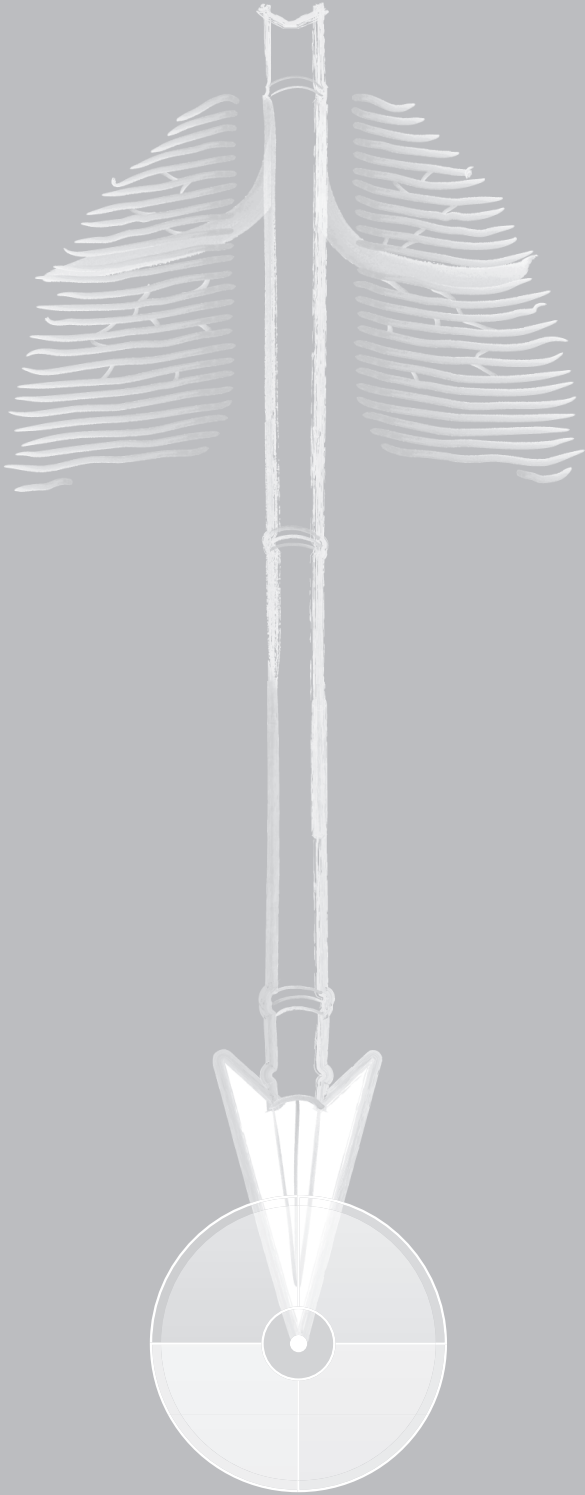
central role in our study in chapters 2,3 and 4, Juniper *et al.* have shown that a paper version of the questionnaire and an electronic version on a handheld device have similar results [26,45]. However, this might be different for an online assessment, since several other studies on other questionnaires have shown different results between offline and online applications [46,47]. Therefore, in **chapter 6** we assessed the agreement between an online self-administered version of the ACQ and an interviewer-administered ACQ by a practice nurse during a routine control visit.

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Chapter 2

Asthma control cost-utility randomised trial evaluation (ACCURATE): the goals of asthma treatment

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Abstract

Background Despite the availability of effective therapies, asthma remains a source of significant morbidity and use of health care resources. The central research question of the ACCURATE trial is whether maximal doses of (combination) therapy should be used for long periods in an attempt to achieve complete control of all features of asthma. An additional question is whether patients and society value the potential incremental benefit, if any, sufficiently to concur with such a treatment approach. We assessed patient preferences and cost-effectiveness of three treatment strategies aimed at achieving different levels of clinical control:

1. sufficiently controlled asthma
2. strictly controlled asthma
3. strictly controlled asthma based on exhaled nitric oxide as an additional disease marker

Design 720 Patients with mild to moderate persistent asthma from general practices with a practice nurse, age 18-50 year, daily treatment with inhaled corticosteroids (more than 3 months usage of inhaled corticosteroids in the previous year), will be identified via patient registries of general practices in the Leiden, Nijmegen, and Amsterdam areas in The Netherlands. The design is a 12-month cluster-randomised parallel trial with 40 general practices in each of the three arms. The patients will visit the general practice at baseline, 3, 6, 9, and 12 months. At each planned and unplanned visit to the general practice treatment will be adjusted with support of an internet-based asthma monitoring system supervised by a central coordinating specialist nurse. Patient preferences and utilities will be assessed by questionnaire and interview. Data on asthma control, treatment step, adherence to treatment, utilities and costs will be obtained every 3 months and at each unplanned visit. Differences in societal costs (medication, other (health) care and productivity) will be compared to differences in the number of limited activity days and in quality adjusted life years (Dutch EQ5D, SF6D, e-TTO, VAS). This is the first study to assess patient preferences and cost-effectiveness of asthma treatment strategies driven by different target levels of asthma control.

Trial registration Netherlands Trial Register (NTR): NTR1756

Background

Despite the availability of effective therapies, asthma remains a source of significant morbidity and use of health care resources [1,2]. The societal costs of asthma are considerable. Asthma negatively affects work productivity as well as labour force participation. Furthermore, a survey showed that in the Netherlands 30% of asthmatics needed urgent care in the past year, which was on average 8% more than in other European countries [3]. Under a system designed for acute rather than chronic care, patients are not adequately taught to care for their own illness. Sixty-two percent of patients visit their pulmonary specialists or general practitioners only if they have an acute health problem. Only 15% of Dutch asthmatics had a doctor-written action plan for their asthma [3]. In addition, there is a major discrepancy between patients' perceived control of asthma and symptom severity [4]. National and international guidelines define the goal of treatment as to achieve and maintain clinical asthma control [5,6]. Daily treatment with inhaled corticosteroids is recommended on a long-term basis as first-line therapy to keep asthma under clinical control in patients with persistent asthma. Short-term bronchodilators are used on an as-needed basis to reverse bronchoconstriction and relieve symptoms. The 2006 updated international guidelines [6] introduced a management approach based on asthma control. According to the Global Initiative for Asthma (GINA) guidelines the levels of asthma control are defined as follows:

- 1) Partly controlled asthma is defined as the presence of any of the following: daytime symptoms \geq twice per week, limitations of activities, nocturnal symptoms, need for reliever treatment, reduced lung function and exacerbations (further referred as sufficiently controlled).
- 2) Controlled asthma is defined as daytime symptoms that are present \leq twice per week and the absence of limitations of activities, nocturnal symptoms, need for reliever treatment, reduced lung function and exacerbations (further referred as strictly controlled).
- 3) Uncontrolled asthma is defined as \geq 3 features of partly controlled or the presence of an exacerbation.

The level of asthma control can be assessed using composite measures such as the validated Asthma Control Questionnaire (ACQ) [7]. Each patient should be assessed to establish the current treatment regimen, adherence to the current regimen, and the level of asthma control. If asthma is uncontrolled on the current treatment regimen, treatment should be stepped up until control is achieved. If asthma is partly controlled, the guidelines recommend that a step-up in treatment should be considered.

Strictly controlled asthma can be achieved in the majority of patients with uncontrolled asthma by a treatment strategy with (high dose) inhaled corticosteroids alone or with combination therapy of an inhaled corticosteroid and a long-acting bronchodilator

[8]. Symptoms and lung function will improve and the number of awakenings and severe exacerbation rate will reduce [9]. However, this is in marked contrast with the levels of control observed in community studies, where patients tend to be partly controlled [4]. Current guidelines show some ambiguity whether the treatment target should be controlled or partly controlled [6]. Another question is not only whether maximal doses of (combination) therapy should be used for long periods in an attempt to achieve complete control of all features of asthma, but also whether patients would value the potential incremental benefit sufficiently to concur with such a treatment approach [10]. In addition, there is only limited data available on the cost-effectiveness of treatment strategies aimed at different levels of asthma control [11,12].

Recently, the fraction of exhaled nitric oxide (FeNO) has been introduced as a non-invasive marker of airway inflammation in asthma. The role of FeNO in titrating anti-inflammatory treatment to the most effective dose of inhaled corticosteroids in asthma is still controversial [13]. Addition of FeNO as an indicator of control of asthma has led to higher [14] as well as lower [15] doses of inhaled corticosteroids without a difference in symptomatic asthma control. Adjustments to medication dose based on FeNO measurements seem to reduce the number of exacerbations, but recent studies had insufficient power to reach statistical significance when adjusting for multiple exacerbations within patients [16]. Therefore, it is not yet determined whether FeNO measurements may indicate whether a step-up in treatment is effective or a step-down can be achieved without loss of asthma control and thereby contribute to the efficiency of asthma care.

Therefore, we aim to investigate whether a treatment strategy aimed at strict asthma control is more (cost-)effective as compared to a treatment strategy aimed at achieving sufficiently controlled asthma. In addition we postulate that a treatment strategy aimed at strict asthma control is more (cost-)effective when the treatment step is additionally guided by measurements of exhaled nitric oxide (FeNO) as compared to a treatment strategy aimed at achieving strictly controlled asthma or sufficiently controlled asthma without the addition of FeNO.

Preliminary results

Monitoring control

An internet application will be used to assist the physician/nurse practitioner/physician assistant in adjusting the treatment step according to the 3 treatment algorithms. In the Self-Management of Asthma Supported by Hospitals, Information and communication technology, Nurses and General practitioners (SMASHING) -project we have already used an internet application for monitoring Forced Expiratory Volume in 1 second (FEV₁) and the asthma control questionnaire (ACQ) [17]. Furthermore, in this project we have

set-up electronic versions <http://www.netquestionnaires.nl> of the majority of questionnaires. In the OPPAS-project (UMCN) we have already explored the distribution of levels of asthma control in general practice patients with asthma [18].

Design

The study is a cluster-randomised parallel trial with 3 arms and 12 months follow-up (Figure 2.1). In order to avoid recruitment bias the identification of potential patients from the general practice information system will be performed before the allocation of a general practice cluster to a treatment strategy [19,20]. The 3 treatment strategies are defined as:

- 1 SUFF-strategy: achieving sufficiently controlled asthma based on conventional asthma control measures
- 2 STRICT-strategy: achieving strictly controlled asthma based on conventional asthma control measures
- 3 FeNO-strategy: achieving strictly controlled asthma based on conventional asthma control measures and an indirect marker of airways inflammation (FeNO).

General practices will be randomly assigned to the 3 groups using a computer generated permuted block scheme, ensuring concealment of allocation. Treatment assignment will be stratified according to characteristics of general practices (solo/duo/etc practice, rural/urban). The patients will visit the general practice for an introduction visit and control visits at baseline, 3, 6, 9, and 12 months. In case of asthma exacerbations patients pay an additional visit to the general practice or chest physician.

Intervention

The level of asthma control will be based on a 3-monthly assessment of asthma symptoms, number and severity of exacerbations, FEV₁, with or without the level of FeNO. Asthma symptoms will be assessed with the ACQ, which is closely associated with the level of asthma control from the GINA guidelines (Table 2.1). Step-ups in medication will be adjusted (Table 2.2), using specific algorithms for the 3 treatment strategies (Table 2.3). The step-up in medication in the FeNO-strategy will be additionally guided by the level and change in FeNO according to recent recommendations and the latest available evidence [21]. This allows adjustment of the dosage of inhaled corticosteroids based on information of airways inflammation whilst the dosage of additional reliever medication is based on asthma control measures [21]. At each planned and unplanned visit during the 12 months follow-up maintenance, therapy will be adjusted according to the relevant algorithm, using the internet-based asthma monitoring system by either the

FLOWCHART
 ACCURATE: Asthma Control Cost-Utility RAnimized Trial Evaluation

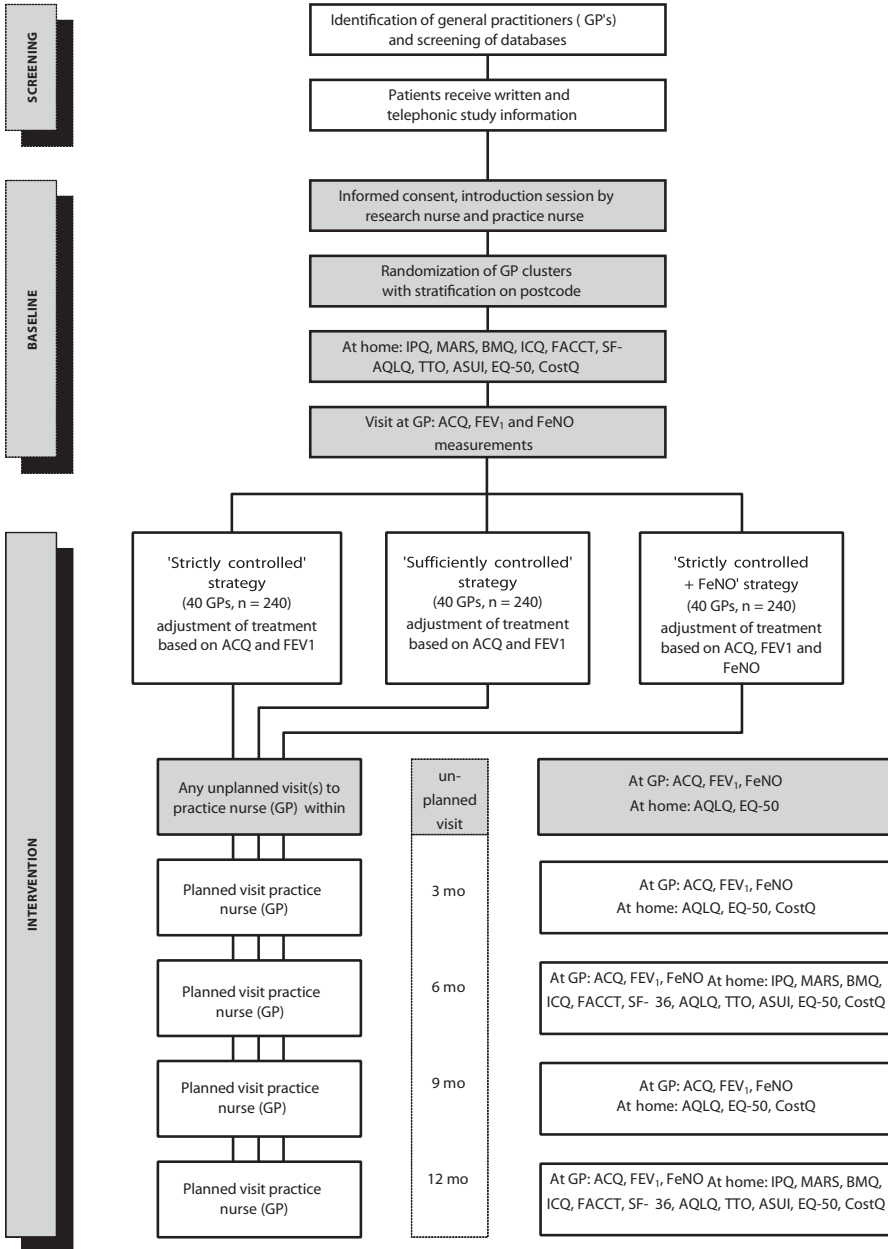


Figure 2.1. Flowchart of the Accurate trial.

Table 2.1. Levels of Asthma Control

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (FEV ₁)	Normal	< 80% predicted	
Exacerbations*	None	1 st moderate exacerbation	≥ 2 moderate exacerbation [†] or severe exacerbation

*modified from the GINA guidelines; the presence of an exacerbation influences the level of asthma control at baseline or at an exacerbation. If one or more exacerbations have led to an adjustment in treatment, this category starts at 0 again. At baseline: treatment levels only will be adjusted when exacerbations were present ≤ 3 months prior to the study; [†] during the same treatment regime.

nurse practitioner or general practitioner [17]. This allows the supervision of this process by a central coordinating nurse specialist.

Patients

720 Patients with mild to moderate persistent asthma (prevalent cases) will be recruited from general practices via patient registries in three regions in The Netherlands:

- Leiden University Medical Center (LUMC) general practice network LEON (240 patients, 40 general practices)

Table 2.2. Management approach based on control (GINA guidelines)

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
As needed rapid-acting β₂-agonist	As needed rapid-acting β₂-agonist			
	Select one	Select one	Add one or more	Add one or both
	Low-dose ICS*	Low-dose ICS plus long-acting β ₂ -agonist	Medium- or high dose ICS plus long-acting β ₂ -agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier	Medium- or high dose ICS Low-dose ICS plus Leukotriene modifier [†]	Leukotriene modifier	Anti-IgE treatment
	Asthma education Environmental control			

*ICS=inhaled corticosteroids

Table 2.3. Treatment strategy algorithms

Strategy	Levels of asthma control		
	Controlled	Partly controlled	Uncontrolled
STRICT-strategy	– 3 mo: no change – > 3 mo: step-down	step-up: treatment choice	step-up: treatment choice
SUFF-strategy	step-down	no change	step-up: treatment choice
FeNO-strategy			
- Low FeNo level	step-down	– 3 mo: no change/ change within current step to LABA – > 3 mo: step-down ICS	step-up: LABA
- Intermediate FeNo level	no change	step-up: treatment choice	step-up: treatment choice
- High FeNo level	step-up/change within current step to ICS	step-up: 1 x ICS	step-up: 2xICS*

A raised FeNO level is indicative of eosinophilic airway inflammation; ICS=inhaled corticosteroids; LABA=long-acting β_2 -agonist. *until a maximum high dose of ICS is reached

- Radboud University Nijmegen Medical Centre general practice network (240 patients, 40 general practices)
- Amsterdam Medical Center (AMC) general practice network (240 patients, 40 general practices)

Only general practices with a practice nurse (or nurse practitioner/or physician assistant, further referred to as 'practice nurse') will participate (70% of general practices in the Netherlands currently have a employed such a professional [22]). Based on previous research experience in patients with asthma in general practice (SMASHING-project CME number P05.136), we estimate a response rate of 40% with an inclusion of 6 patients per 'standard' practice (i.e. practice with 2,300 patients) and 40 'standard' general practices per treatment strategy.

Inclusion criteria

(all of the following criteria)

- age 18-50 yr
- doctor's diagnosis of asthma
- patients who need inhaled corticosteroids as controller medication (step 2-4 GINA guidelines)
- inhaled corticosteroids \geq 3 months in the previous year
- written informed consent
- no exacerbation of asthma within 1 month before entry

Exclusion criteria

- daily or alternate day oral corticosteroid therapy for at least 1 month before entering into the study
- inability to understand written and oral Dutch instructions
- active diseases likely to interfere with the purpose of the study, such as end-stage disease or inability to visit the general practitioner

Methods of measurements

At baseline, patient characteristics will be assessed including questions on atopy, smoking and symptom free days. In line with the Dutch national guidelines for general practitioners [3], patients are invited to visit their general practice every 3 months in order to titrate medication to the lowest level that is needed to achieve or maintain control. 3-Monthly care by the nurse practitioner will be organized similar to the advise in the national guidelines for general practitioners [5], including questions on asthma control, medication, adverse events and measurement of lung function. At all planned and unplanned visits questionnaires will be performed at home (Table 2.4). In addition, the ACQ will be performed at home monthly as an outcome measure. Peripheral blood will be obtained at baseline. Both paper and electronic versions will be used to collect the data, depending on the preference of a patient. Electronic versions in the ACCURATE project will be similar to those from the SMASHING project <http://www.netquestionnaires.nl> . A coordinating nurse specialist will supervise the nurse practitioners.

Table 2.4. Instrument Table

	Assessment of level of asthma control: driving treatment step						Outcomes						
	airway inflammation			Patient preferences			Quality of life		Patient utilities			Costs	
	lung function	asthma control	illness perception	adherence	beliefs about medicines	patient satisfaction	generic	asthma related	patient perspective	asthma related	societal perspective	health care + other costs	
	FeNO	FEV1	ACQ	IPQ	MARS	BMQ	FACCT	SF-36	AQLQ	TTO	ASUI	EQ-5D	CostQ
Baseline	X	X	X	X	X	X	X	X	X	X	X	X	X
Unplanned visit	F	X	X						X		X	X	
3 months	F	X	X						X		X	X	X
6 months	F	X	X	X	X	X	X	X	X	X	X	X	X
9 months	F	X	X						X		X	X	X
12 months	X	X	X	X	X	X	X	X	X	X	X	X	X

X in all treatment strategies, F only in FeNO strategy

Assessment of level of asthma control

At each planned and unplanned visit to the general practice a nurse practitioner will assess the level of asthma control with:

1. asthma control questionnaire (ACQ-score) [7]
2. lung function level (FEV₁)
3. FeNO (only in the FeNO-strategy)
4. presence of exacerbations, now or in previous weeks

Asthma control questions

Asthma control will be assessed every 3 months with the Asthma Control Questionnaire (ACQ), which consists of 6 items with a 7-point scale (0 = totally controlled, 6 = severely uncontrolled) [7]. In addition, the ACQ will be completed monthly at home. The ACQ contains questions on respiratory symptoms over the previous week. The patients will be asked whether these symptoms were representative for the last 4 weeks. If not, the ACQ will be assessed from the most representative of the last 4 weeks. The optimal cut-point for 'strictly controlled' asthma is defined as a mean ACQ score ≤ 0.75 and a score of ≥ 1.50 confirms 'uncontrolled' asthma [23]. We regard control to be sufficient if $0.75 < \text{mean ACQ} < 1.50$.

Lung function measurements

Spirometry will be performed in the general practices according to national [5] and international guidelines [24]. For the baseline visit patients will be instructed to refrain from bronchodilator use for a specified number of hours before the scheduled spirometry test. Reversibility of airways obstruction will be measured 20 min. after administering 4 single puffs of 100 μg salbutamol per metered dose-inhaler connected to a spacer (Volumatic®). The response will be expressed as ml and percentage change in predicted value of FEV₁.

Exhaled nitric oxide

Fraction of exhaled Nitric Oxide (FeNO) will be measured in the general practices according to international guidelines [25] with the NIOX-MINO (Aerocrine, Solna, Sweden) [26]. At baseline and at the last visit all patients will perform FeNO measurement, whereas at 3, 6, and 9 months, FeNO only will be assessed in the FeNO Group. FeNO will be measured before spirometric manoeuvres, at an exhaled rate of 50 ml/sec maintained for 10 seconds. Patients are not allowed to smoke at least one hour before the measurements. Results are expressed as the NO concentration in ppb (equivalent to nanolitres/litre) based on the first approved measurement. FeNO levels will be categorized into low when $\text{FeNO} \leq 25$ ppb (absence of inflammation), intermediate $25 \text{ ppb} < \text{FeNO} < 50$ ppb

and high FeNO ≥ 50 ppb (presence of airway inflammation) [13]. Results will be adjusted for smoking (yes/no), gender and height [27].

Exacerbations

Patients will be instructed to pay an additional visit to their general practice if they experience worsening of asthma symptoms. In line with the national [5] and GINA guidelines [6] exacerbations of asthma are defined as acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness, or some combination of these symptoms [28] and will be treated by the general practitioner [5]. FeNO will be performed only in the FeNO strategy. Additional questionnaires and lung function will be performed at home (Table 2.4).

After an exacerbation is resolved the patient visits the nurse practitioner who will assess the current level of asthma control. GINA advises to incorporate the occurrence of exacerbations in the assessment of current asthma control, but is not entirely clear as to how to do that. Therefore, in the present study exacerbations are handled as follows. Questions will be asked on new respiratory symptoms, medication change and hospitalisation [28]. The exacerbation will be classified according to severity as based on the presence of respiratory symptoms, prescribed medication and/or hospitalisation. A moderate exacerbation is defined as a (sub)acute deterioration in symptoms and/or lung function with increased rescue bronchodilator use (or ICS) which lasts 2 days or more, not severe enough to warrant oral steroids (for 3 days or more) or hospitalisation. A severe exacerbation is defined as (sub)acute deterioration in asthma resulting in the need for oral steroids for 3 days or more or hospitalisation (as judged by the physician) [29]. Subsequently, the level of control will be assessed as based on Table 2.1 and maintenance therapy will be assigned according to the treatment algorithm after exacerbation treatment is finished.

Assessment of cost-utilities and patient preferences

Costs

- cost questionnaires: health care consumption; absenteeism and productivity loss (CostQ) [30]

Patient preferences

- the Foundation for Accountability (FACCT) [31]
- the Brief Illness Perception Questionnaire (Brief IPQ) [32]
- the Beliefs about Medicines Questionnaire (BMQ) [33]
- Medication Adherence Report Scale (MARS) [34,35]

Quality of life, patient utilities

- quality of life: Asthma Quality of Life Questionnaire (AQLQ) [36] and Short-Form 36 (SF-36) [37]
- patient utilities: the Asthma Symptom Utility Index (ASUI) [38]. Patient utilities will additionally be assessed by the time-trade-off method by telephonic interview and a web-page (e-TTO) at each planned and unplanned period (exacerbation) [39]
- indirect utilities from the general public will be obtained using the SF-6D [37,34] and EQ-5D [40,41]. This allows the calculation of quality adjusted life years (QALYs).
- number of limited activity days by questionnaire

Analysis

The analysis will be carried out on an intention to treat basis. The data set will consist of all included patients from randomised practices.

Sample-size calculation

A minimally important change in patient utility (EQ-5D) has been defined as 0.074 point [42]. With 150 patients per treatment strategy we are able to detect at least a change of 0.06 points by net health benefit analysis [43] between the arms with a SD = 0.175 EQ-5D points (baseline data SMASHING-project; trial registry number NTR826: SD = 0.17) and a SD of €1000 for costs (SD = €816, usual care strategy [44]) and an increase in costs of €250 when a treatment strategy is not only more effective but also more costly, for a willingness-to-pay (WTP) of €30K (alpha = 0.05, one sided [43], beta = 0.20, one sided, rho costs-effects = 0) (Figure 2.2). With 40 clusters (general practices) per arm and assuming an intra-cluster correlation of 0.01, 0.07 and 0.11 the number of patients per cluster is 4, 5, and 6, and the total number of patients is 480, 600 and 720, respectively [45].

Data-analysis and presentation/synthesis

At baseline, data from all planned and unplanned contact will be collected according to the scheme in Table 2.4. The instruments include variables of:

- patient characteristics: age, sex, socioeconomic status, smoking status and smoking history
- medical outcomes: FEV₁, FeNO, ACQ, current treatment step, asthma medication
- patient preferences: FACCT, IPQ, BMQ, MARS
- quality of life: AQLQ, SF-36
- patient utilities: ASUI, SF-6D and EQ-5D, QALYs, e-TTO, number of limited activity days
- costs: health care consumption; CostQ

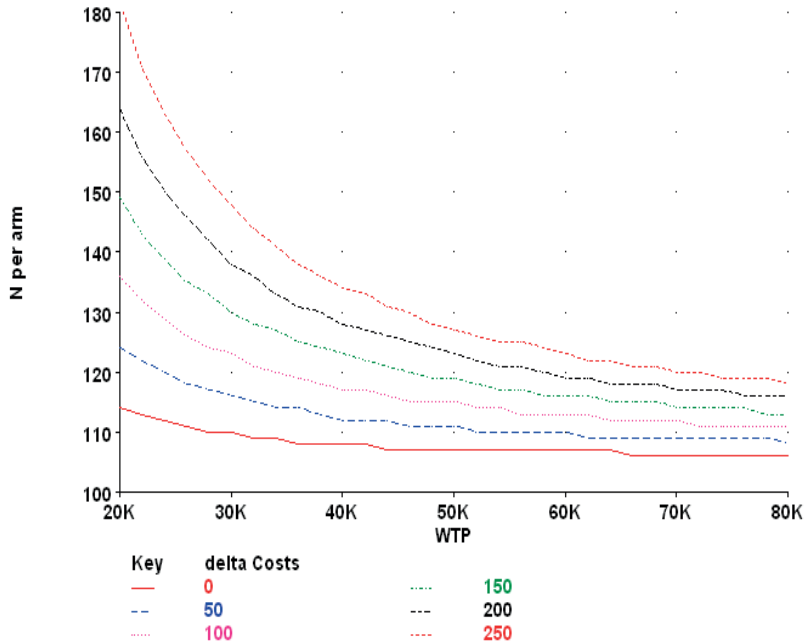


Figure 2.2. Power curve of the required sample-size per treatment arm as a function of willingness-to-pay (WTP) for a range of increases in costs (delta Costs) when a treatment strategy is not only more effective but also more costly. The presented +sample-size is unadjusted for intra-cluster correlation.

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With 40 clusters (general practices) per arm and assuming an intra-cluster correlation of 0.01, 0.07 and 0.11 the number of patients per cluster is 4, 5, and 6, and the total number of patients is 480, 600 and 720, respectively.

Economic evaluation

General considerations

The economic evaluation will compare differences in societal effects and costs to differences in the number of limited activity days (cost-effectiveness analysis, CEA) and quality adjusted life years (cost-utility analysis, CUA). The analysis will have a 12-months' time horizon, without discounting. Group averages will be statistically compared using two-sided bootstrapping and net-benefit analysis will be used to relate costs to patient outcome. Sensitivity analyses will be performed on the perspective (societal versus health care) and the applied utility measure (Dutch EQ5D, SF6D, e-TTO, AQLQ-5D).

Cost-effectiveness

The primary end-point is the evaluation of the cost-effectiveness of treatment strategies by incremental net-benefit analysis [43]. Net health benefit addresses cost-effectiveness ratios by assuming values for the willingness-to-pay per unit of effectiveness.

Cost analysis

The cost analysis will include both medical (medication, visits, and hospitalizations) and non-medical costs (productivity losses, informal care). Purchased medication will be assessed from electronic patient records (with written patient permission), complemented with the patient's report on medication purchased elsewhere [46]. Other costs will be estimated using quarterly cost questionnaires (CostQ) [30]. Costs will be valued according to standard prices charges [47] including time and travel costs.

Analysis of effectiveness

The differences in levels and changes in utilities based on EQ-5D, SF-6D, VAS, e-TTO and the number of limited activity days will be compared between the treatment strategies using a random-effects analysis accounting for within-patient repeated measurements and clustering on general practice.

Patient outcome analysis

Utilities will be assessed every three months. In the base case analysis, quality-adjusted life years (QALYs) will be estimated using societal utilities obtained using the Dutch EQ-5D tariff [48]. As sensitivity analyses, QALYs will be estimated using the SF-6D and individual utilities obtained using the e-TTO and visual analogue scale (transformed using a power transformation).

Ethical approval

Ethical approval was obtained from the Medical Ethics Committee of the Leiden University Medical Center (ABR no: 24488).

Discussion

The aim of the ACCURATE trial is to compare the cost-effectiveness and patient preferences of three asthma treatment strategies: 1) sufficiently controlled strategy, aiming to achieve sufficiently controlled asthma based on conventional asthma control measures (ACQ and lung function); 2) strictly controlled strategy, aiming to achieve controlled asthma also based on asthma conventional control measures; and 3) FeNO-strategy, aimed at achieving strictly controlled asthma based on conventional asthma control

measures plus an indirect marker of airways inflammation. For this purpose we will implement an internet-based programme, to be used by care providers in general practices.

To our knowledge, this is the first study to assess patient preferences and cost-effectiveness of asthma treatment strategies aimed at different levels of control on asthma. Notably, the current study is fully investigator driven, granted by governmental funding rather than pharmaceutical funding. Current guidelines advise clinicians to ensure that asthma is strictly controlled, i.e. patients should not experience any symptoms. However, in daily practice, a considerable proportion of asthma patients continuously experience symptoms without consulting their physician [49]. This raises the question of patient's preferences with regard to treatment aims. It is not yet known whether patients are willing to conform to the stringent treatment aim of strictly controlled asthma, especially if it results in high doses of asthma medication and an increased likelihood of concurrent side effects. These uncertainties hamper implementation of current guidelines and therefore a great diversity in treatment exists. Furthermore, discordance in patient's and medical treatment goals might result in unnecessary asthma symptoms and health care use.

A recent meta-analysis showed that FeNO guided treatment of asthma does not reduce the number of exacerbations; however it did reduce the daily dose of inhaled corticosteroids [50]. Our study may extend these findings by providing further understanding of the cost-effectiveness and patient preferences of FeNO guided treatment of asthma.

We hypothesize that:

- 1) a treatment strategy aimed at achieving strictly controlled asthma is more (cost-)effective as compared to a treatment strategy aimed at sufficiently controlled asthma;
- 2) a treatment strategy aimed at achieving strictly controlled asthma is (cost-)effective when the treatment step is additionally guided by measurements of fractional exhaled nitric oxide (FeNO) as compared to a treatment strategy aimed at strictly controlled asthma or sufficiently controlled asthma.

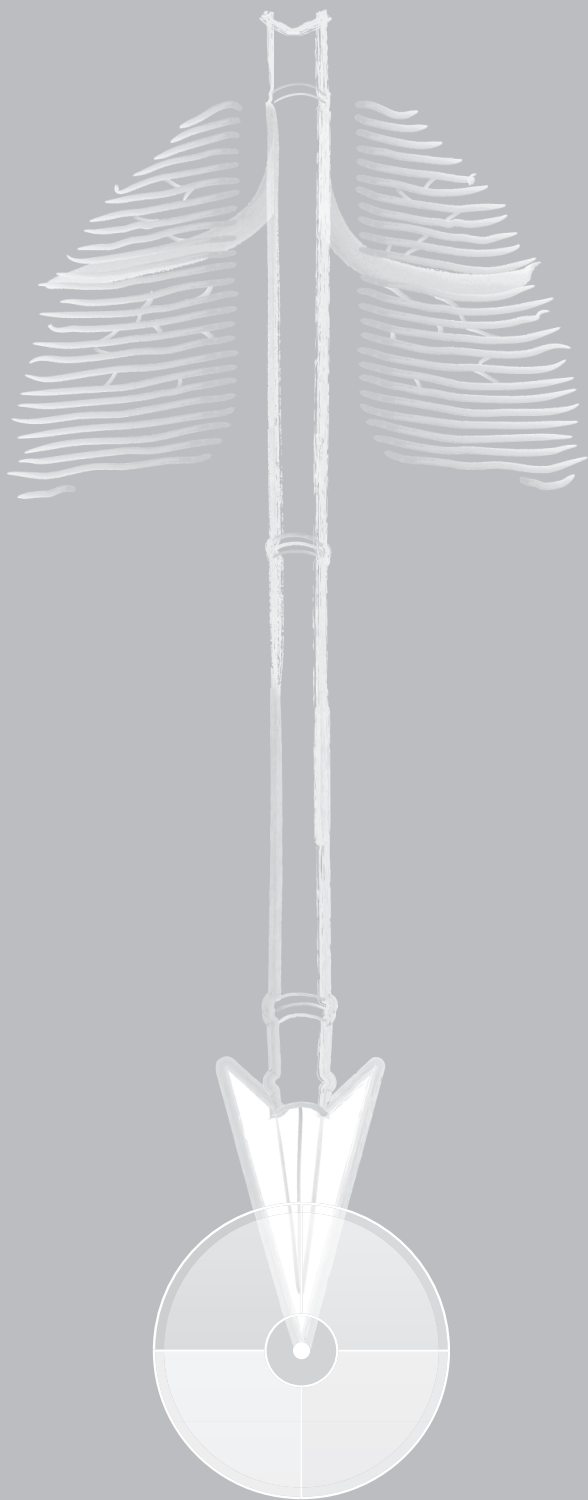
During the course of the trial the definition of asthma exacerbations has been changed. In our analysis we will use the definitions as proposed by the ATS/ERS task force [51]. By incorporating internet-based graphic feedback on a patients' asthma control status and internet-based decision support based on current guidelines, we will enhance the feasibility and standardization of the treatment advice. The results of this study will provide insight into the potential discordance between patient's and medical treatment goals and the effect on health care costs from the societal perspective. The internet-based decision support methodology and results of our study may facilitate cost-effective implementation of future tailored treatment strategies for patients with mild to moderate asthma in primary care.

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Chapter 3

Fractional exhaled Nitric Oxide: a useful adjunct test when assessing asthma control in adult patients in primary care? A cross-sectional exploratory study

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Abstract

Objective Established markers of asthma control, i.e. asthma symptoms and lung function, do not measure underlying bronchial inflammation and their results can contradict each other. Measuring fractional exhaled nitric oxide (FeNO) as a marker of eosinophilic airway inflammation may have added value for primary care asthma management. The aim of this study was to explore the added value of FeNO as an adjunct to symptoms and lung function when assessing asthma control in primary care.

Methods Cross-sectional analysis of two primary care adult asthma cohorts. We measured FeNO levels, lung function, and Asthma Control Questionnaire (ACQ) scores. Pearson correlation coefficients were calculated between FeNO, ACQ, FEV₁%predicted, and reversibility. In a decision tree analysis patients' asthma control was categorized according to the two established control markers, and subsequently with FeNO as an additional marker.

Results We included 307 patients (63% females). Correlations between FeNO, symptoms and lung function were weak (max. $r=0.240$). In 25.7% of patients all three markers were consistent in their interpretation of asthma control. In 28.1% the two established markers were consistent, but FeNO showed a contradictory result. In 46.3% the two established markers contradicted each other.

Conclusions We observed weak correlations between FeNO, symptoms and lung function in adults with asthma in primary care, which confirms that FeNO is an independent marker of asthma control. In almost half the study population the results of symptoms and lung function contradicted each other; in this group FeNO might fine-tune assessment of asthma control and tailor therapy choices.

Background

Asthma is a prevalent chronic airways disease that is mainly diagnosed and managed in primary care. It is characterised by recurrent respiratory symptoms, airflow obstruction, airway hyperresponsiveness and an underlying airways inflammation. Although airways inflammation varies in intensity, it remains persistent in asthma, even when symptoms are not present. Asthma can place severe limitations on daily life, and may even lead to life-threatening exacerbations. In order to reduce these complications, and to improve prognosis, it is important to achieve control of asthma, which is one of the main targets in asthma management according to different international guidelines [1-4]. On the other hand it is also important to avoid overtreatment and concomitant side-effects as much as possible. Therefore asthma control should be achieved with the lowest possible medication dosage and the choice between different types of asthma medication should be targeted to individual needs.

The management of asthma control in primary care is mainly guided by the severity of clinical symptoms as manifested in experienced limitations and ability to perform everyday life activities. It can be measured using short questionnaires like the Asthma Control Questionnaire (ACQ) [5]. Symptoms assessment is supplemented by spirometric measurement of airway obstruction and its reversibility after administering a bronchodilator [1]. However, both symptoms and lung function do not reflect the severity of the underlying chronic airway inflammation.

For several reasons, measuring airway inflammation and incorporating it as a marker of asthma control in asthmatic patients could be interesting for general practitioners (GPs). Firstly, it provides independent information in the assessment of asthma so it can be considered a separate domain of asthma control, just like symptoms and lung function are [6]. Secondly, asthma symptom control can be achieved with pharmacotherapy while underlying inflammation may still be present but 'masked', which may lead to an increased frequency of exacerbations [7,8]. Finally, airway inflammation is the target for inhaled corticosteroids (ICS), the cornerstone of pharmacotherapy in asthma.

During the last two decades, fractional exhaled nitric oxide (FeNO) has emerged as a more direct marker of eosinophilic airway inflammation [9]. Nitric oxide (NO) is produced in the bronchial epithelial cells as part of the inflammatory process [10]. It is measured in a simple, non-invasive manner in exhaled air and can therefore easily be applied in primary care, especially with the advent of small handheld NO-meters. Several studies have been performed to test the usefulness, accuracy and implications of measuring FeNO in managing asthma. They found that FeNO could predict asthma exacerbations [8] and response to ICS [11], was cost-effective [12] and could aid in optimizing titration of inhaled steroid treatment [12-14]. Besides, FeNO can predict changes in asthma control [15]. Other studies found no additional value when using FeNO [16-19]. These

differences in results might depend on cut-off values for FeNO, study populations, and how influential FeNO results were in therapy management-decisions. Since most studies have been performed in secondary care settings, the added value of FeNO needs to be studied in a primary care population, which is more heterogenous and differs in asthma severity. Furthermore, there is a need to identify how FeNO could aid in the assessment of current asthma control, and which patients could benefit most from a FeNO measurement. Therefore, the aim of this study was to explore the added value of FeNO as an adjunct to symptoms and spirometry when assessing asthma control in primary care patients.

Methods

Design and study population

The study was a cross-sectional analysis of two available primary care cohorts of adult patients with asthma in the Netherlands. Cohort A consisted of patients who were referred by their GP for lung function testing in a primary care diagnostic centre in the period October 2008 until July 2010. Cohort B consisted of patients who were recruited from 128 general practices between June 2009 and July 2010 to participate in a longitudinal multicentre trial (Clinical Trial number: NTR1756)[20]. Table 3.1 shows the inclusion and exclusion criteria for both cohorts.

All patients underwent FeNO measurement, followed by spirometry. The ACQ [5] was completed during the same session. Several patient characteristics that may influence FeNO levels were recorded: gender, age, height, smoking status, allergy status, and upper respiratory infection in the previous week. Both studies were approved by our local ethics committee and all subjects gave informed consent.

Measurement of asthma control markers

Asthma symptom control

Symptom control was measured using the six-item ACQ [5], a validated questionnaire that uses a 7-point scale (0=totally controlled, 6=severely uncontrolled). The ACQ has been shown to be an effective instrument to measure asthma control in general practice [21]. The six items comprise: nocturnal symptoms; symptoms when waking up; limitations of daily activity; shortness of breath; wheeze; and use of bronchodilator rescue medication. Level of asthma symptom control was categorized as *controlled* (mean ACQ score ≤ 0.75) or *uncontrolled* (mean ACQ score >0.75) [22].

Table 3.1. Inclusion and exclusion criteria for the two asthma cohorts

	Cohort A	Cohort B
Source	Consecutive patients with asthma referred to primary care diagnostic centre for lung function testing as a periodical control or because of asthma symptoms	Trial population
Inclusion criteria	Selection of patients: GPs diagnosis of asthma according to patients history OR at least once $\geq 12\%$ reversibility according to available database in diagnostic centre 16-40 years	Selection of patients: diagnosis asthma according to medical records GP AND ICS use at least three months within past year AND No exacerbation within one month before entry AND No serious comorbidity such as end-stage disease or inability to visit GP 18-50 years
Exclusion criteria	No successful FeNO-measurement or spirometry No available information about height, smoking status, allergy status, upper respiratory infection preceding week	No successful FeNO-measurement or spirometry No available information about height, smoking status, allergy status, upper respiratory infection preceding week

GP: general practitioner

ICS: inhaled corticosteroids

FeNO: fractional exhaled nitric oxide

Lung function

Spirometry was performed in accordance with international guidelines [23]. Reversibility was assessed after administration of 400 micrograms of aerosolized salbutamol and expressed as the percentage increase in FEV₁. A cut-off of $\geq 12\%$ was used for presence of reversibility. Airway obstruction was defined as prebronchodilator FEV₁ % predicted $< 80\%$ [1].

Fraction exhaled nitric oxide

FeNO was measured with a portable NIOX MINO® Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). Patients exhaled 10 seconds at a flow rate of 50 ml/s, in accordance with international recommendations [24]. FeNO levels were corrected for gender, height, smoking, allergy and recent upper respiratory infection by applying appropriate factors for adjustment [25]. A FeNO level of ≤ 25 parts per billion (ppb) was regarded as normal, > 25 FeNO ≤ 50 ppb as intermediate, and FeNO > 50 ppb as high [26]. In this study we defined FeNO > 25 ppb as an indicator of uncontrolled asthma.

Analysis

First, correlations between FeNO, ACQ, percentage reversibility, and prebronchodilator FEV₁ (forced expiratory volume in one second) percentage of predicted were calculated.

Table 3.2. Patient characteristics for cohorts A, B, and overall. Numbers are means (SD) unless stated otherwise

	Cohort A	Cohort B	Overall
n (%)	147 (100%)	160 (100%)	307 (100%)
Females, n (%)	77 (52.4%)	115 (71.9%)	192 (62.5%)
Age, years^a	29.7 (7.0)	40.7 (9.1)	35.4 (9.8)
Current smokers^a, n (%)	44 (29.9%)	21 (13.1%)	65 (21.2%)
Allergic symptoms, n (%)	118 (80.3%)	129 (80.6%)	247 (80.5%)
Asthma medication use, n (%)			
None	26 (17.7%)	16 (10.0%)	42 (13.7%)
Bronchodilator only	31 (21.1%)	11 (6.9%)	42 (13.7%)
ICS only	9 (6.1%)	12 (7.5%)	21 (6.8%)
ICS and bronchodilator	81 (55.1%)	121 (75.6%)	202 (65.8%)
Mean ACQ-score^b	1.00 (0.33-1.83)	0.67 (0.33-1.33)	0.83 (0.33-1.67)
Controlled (mean ACQ \leq 0.75)	58(39.5%)	81 (50.6%)	139(45.3%)
Uncontrolled (mean ACQ $>$ 0.75)	89 (60.5%)	79 (49.4%)	168 (54.7%)
FEV₁ % predicted^a	77.7 (13.6)	86.3 (17.9)	82.2 (16.5)
Obstruction ($<$ 80%)	85 (57.8%)	42 (26.2%)	127 (41.4%)
Reversibility, %^b	6.8 (3.6-14.1)	4.0 (1.4-9.5)	5.43 (2.3-10.9)
Reversibility (\geq 12%), n (%)	42 (28.6%)	29 (18.1%)	71 (23.1%)
Uncorrected FeNO values, ppb^b	12.0 (8.0-22.0)	16.0 (12.0-27.0)	15.0 (9.0-26.0)
Normal level (\leq 25 ppb), n (%)	111 (75.5%)	81 (50.6%)	192 (62.5%)
Intermediate level (25 $<$ FeNO \leq 50 ppb)	21 (14.3%)	51 (31.9%)	72 (23.5%)
High level ($>$ 50 ppb)	15 (10.2%)	28 (17.5%)	43 (14.0%)
Corrected FeNO values, ppb^{b d}	18.9 (10.0-43.0)	25.6 (14.9-48.2)	22.4 (11.9-44.9)
Normal level (\leq 25 ppb), n (%)	87 (59.2%)	76 (47.5%)	163 (53.1%)
Intermediate level (25 $<$ FeNO \leq 50 ppb)	31 (21.1%)	49 (30.6%)	80 (26.1%)
High level ($>$ 50 ppb)	29 (19.7%)	35 (21.9%)	64 (20.8%)

^a Parametric data: mean and standard deviation (SD)

^b Non-parametric data: median and interquartile range (IQR)

^c Ex-smokers were regarded as non-smokers if they had stopped at least four weeks before the date of the measurements

^d For smokers FeNO levels were corrected by multiplying by 0.627, for males by 1.174, for allergic symptoms by 1.496, for upper respiratory infection by 1.235 and for height by 1.113^{(height in cm-170)/10}

FEV₁: forced expiratory volume in one second

ACQ: asthma control questionnaire

ppb: parts per billion

Because FeNO values were not normally distributed according to a histogram and Kolmogorov-Smirnov test, they were log₁₀-transformed for this part of the analysis. Pearson correlation coefficients were calculated with log₁₀-FeNO levels for the two cohorts separately. Next, patients were categorized according to their level of asthma control using the established markers of asthma control (i.e., symptom control and lung function),

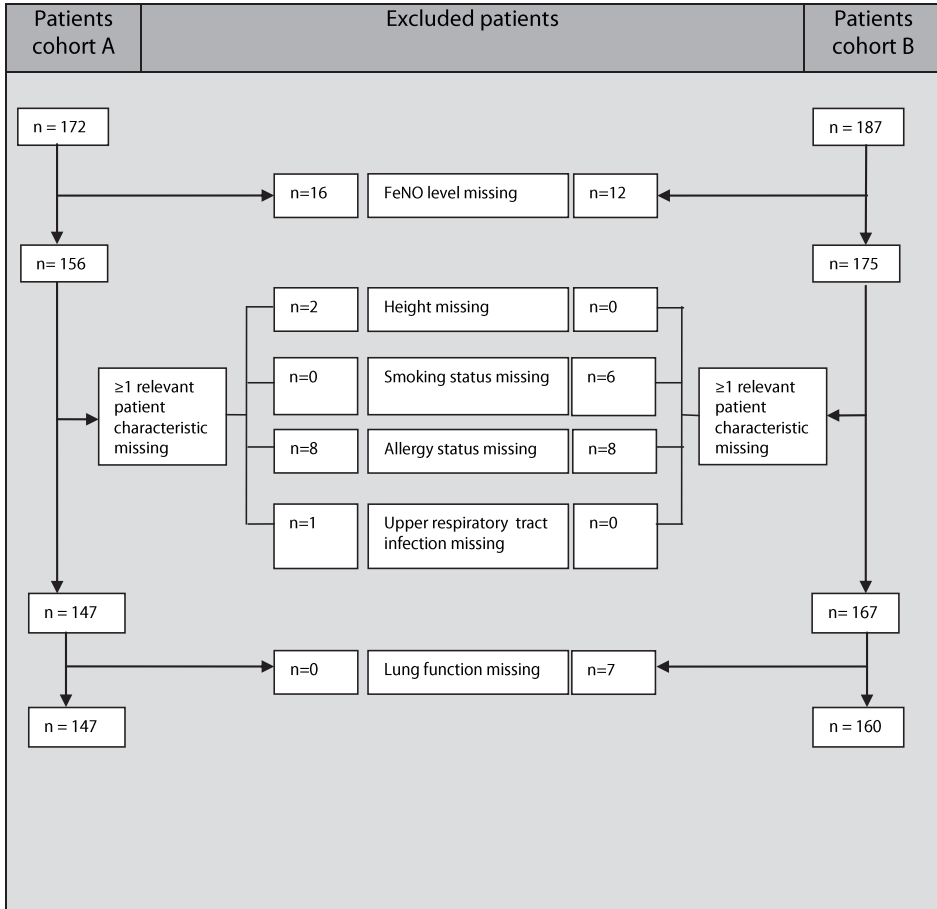


Figure 3.1. Flow diagram of the study population

with FeNO added as a third marker. This resulted in eight categories (see Figure 3.2). In the analysis of the flow diagram, the two cohorts were combined. Sensitivity analyses were performed using uncorrected instead of corrected FeNO values and using less strict cut-off values for uncontrolled symptom score (mean ACQ >1.50) and for uncontrolled FeNO level (FeNO>50ppb). The Statistical Package for the Social Sciences (SPSS) version 16.0 was used for the statistical analyses. P-values <0.05 indicated statistical significance.

Results

Patient characteristics

147 patients in cohort A and 160 in cohort B could be analysed (Figure 3.1). Table 3.2 describes characteristics for both cohorts. Most characteristics showed different distri-

Table 3.3. Pearson correlation coefficients for the established markers of asthma control and FeNO for both cohorts

	ACQ (score)		Reversibility (%)		log ₁₀ -FeNO (ppb)**	
	Cohort A (n=147)	Cohort B (n=160)	Cohort A (n=147)	Cohort B (n=160)	Cohort A (n=147)	Cohort B (n=160)
ACQ (mean)	1	1			0.15 p=0.07	-0.04 p=0.61
Reversibility %	0.28 p=0.001*	0.17 p=0.036*	1	1	0.16 p=0.05	0.24 p=0.002*
FEV₁%pred	-0.31 p<0.001*	0.01 p=0.94	-0.63 p<0.001*	-0.50 p<0.001*	-0.02 p=0.85	-0.21 p=0.009*

As the correlation coefficient is a standardized ratio, its interpretation is independent whether variables are log-transformed or not.

*= correlation is statistically significant at the 0.05 level (2-tailed)

**= log₁₀-FeNO level corrected for gender, height, smoking, allergy and upper respiratory infection

butions for the two cohorts. In both cohorts the majority of patients were treated with ICS (61.2% in cohort A and 83.1% in cohort B, respectively).

Correlations between markers of asthma control

Table 3.3 shows that correlations between log₁₀-FeNO values and ACQ scores, FEV₁ values, and reversibility were weak (maximum of $r=0.24$ for correlation between log₁₀-FeNO and % reversibility in cohort B; $p=0.002$). The two spirometric markers of asthma control (i.e., % FEV₁ predicted and % reversibility) showed moderate correlation ($r= -0.63$ and -0.50 in the respective cohorts; $p<0.001$).

Classification of asthma control levels

Figure 3.2 depicts the distribution of patients according to the two established markers of asthma control (i.e., ACQ and lung function), with FeNO as an additional marker. In total 144 (46.9%) patients were considered to be uncontrolled in terms of airway inflammation. In 25.7% of patients (13.0% in category 1 and 12.7% in category 8) all three control markers were consistent in their interpretation of asthma control. Furthermore, in 28.1% of patients, the two established markers were consistent in their interpretation of asthma control, but FeNO was contradicting (13.4% in category 2 and 14.7% in category 7). In category 3 until 6 of figure 3.2 the results of the two established markers showed disagreement: asthma was controlled according to one marker and uncontrolled according to the other. This comprised 46.3% of the total study population (142/307).

Sensitivity analyses

Using uncorrected FeNO values, only 25.7% of patients had uncontrolled FeNO levels. More patients ended up in categories 1 and 5, less in categories 2 and 6 (see footnote

d in figure 3.2). Adopting 50 ppb as the cut-off for uncontrolled FeNO led to only 20.9% of patients being considered uncontrolled. More patients ended up in categories 1, 3, 5, and 7, and less in categories 2, 4, 6, and 8 (see footnote e). Use of a less strict ACQ score cut-off (1.50 instead of 0.75) led to more patients ending up in categories 1, 2, and 3 but fewer patients in categories 5, 6, and 7 (see footnote f). Irrespective of these different

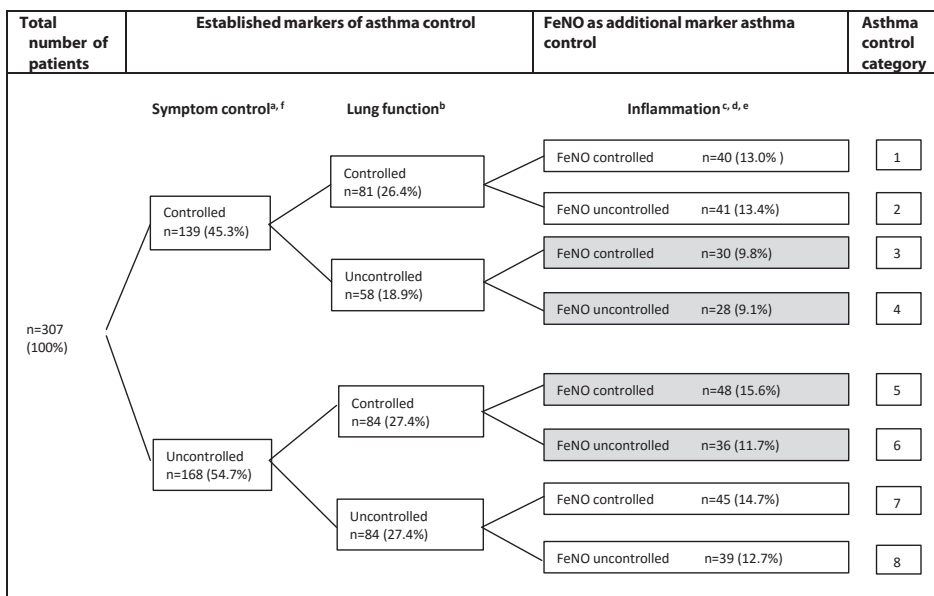


Figure 3.2. Flow diagram for classification of asthma control based on the established markers, with FeNO as an additional, independent marker

Marked boxes indicate patients with conflicting asthma control according the two GINA markers.

^a Being controlled= mean ACQ \leq 0.75; being uncontrolled= mean ACQ $>$ 0.75

^b Being controlled= no obstruction or reversibility; being uncontrolled= obstruction and/or reversibility. Obstruction= FEV₁ $<$ 80% predicted;

Reversibility = (FEV₁-postbronchodilator minus FEV₁-prebronchodilator)/ FEV₁-prebronchodilator \geq 12%

^c Being controlled= FeNO \leq 25; being uncontrolled= FeNO $>$ 25 (corrected FeNO)

^d Sensitivity analyses: uncorrected FeNO levels lead to the following % in the 8 categories: 19.5%; 6.8%; 13.0%; 5.9%; 23.1%; 4.2%; 18.6%; 8.8%, respectively

^e Sensitivity analyses: being controlled= FeNO \leq 50; being uncontrolled= FeNO $>$ 50 (corrected FeNO) lead to the following % in the 8 categories: 21.2%; 5.2%; 14.3%; 4.6%; 24.1%; 3.3%; 19.5%; 7.8%

^f Sensitivity analyses: being controlled= mean ACQ $<$ 1.50; being uncontrolled= mean ACQ \geq 1.50 lead to the following % in the 8 categories: 22.8%; 19.2%; 15.0%; 12.7%; 5.9%; 5.9%; 9.4%; 9.1%

percentages of patients ending up in the separate categories, in all sensitivity analyses the overall percentages of patients with either three consistent markers of control, two consistent established markers but contradicting FeNO, or two contradicting established markers remained more or less the same.

Discussion

Main findings

We aimed to explore the added value of FeNO as an adjunct to symptoms and spirometry when assessing asthma control in primary care. We observed only weak cross-sectional relationships between symptoms, lung function (the two established markers of asthma control) and FeNO. This lack of correlation confirmed that FeNO can be considered to be an independent marker of asthma control in primary care patients. The analysis of the flow chart in figure 3.2 revealed that in 46.3% of the adult asthma patients in primary care, symptoms and lung function yielded contradicting results regarding the interpretation of asthma control. FeNO might serve as a third decisive marker of asthma control in those instances, since it is an independent marker measuring airways inflammation, which is the central process to airway obstruction and hyperresponsiveness and the target for inhaled corticosteroid therapy. In 28.1% of patients the two established markers were consistent in their interpretation, but FeNO was contradictory.

Strengths and limitations of this study

This is the first study executed in a large heterogenous primary care sample where the added value of FeNO when assessing asthma control was examined for individual patients. By combining two primary care cohorts of patients, data from a larger study population could be analysed. As the cohorts consist of heterogeneous populations, including smokers, patients with recent upper respiratory infections, ICS use and allergies, this greatly enhances generalizability of the results. Cohort A consisted of a more heterogeneous group of asthma patients, including milder asthmatics and some patients who had been referred for spirometry by their GP because of worsening of their symptoms. This might explain the lower ICS use and the lower lung function values in this cohort. In cohort B the ACQ was completed not solely by the patient him- or herself, but together with a practice nurse [27]. Despite the differences between both cohorts, we combined them in our analysis, to assess the additional value of measuring FeNO when assessing asthma control in all types of asthma and in different circumstances. Final limitations are our cross-sectional design (i.e., we could not study the utility of FeNO when monitoring asthma), and the fact that our data did not contain detailed information about the dose of asthma medication for all patients, which would have

enabled us to look at possible modifications of pharmacotherapy in the patients in the respective asthma control categories when FeNO is added to their assessment.

It is not easy to define an 'uncontrolled' or increased FeNO in a particular patient. Although some prefer using a 'personal best' value [28], using fixed cut-off points is more widely accepted. Several studies have been performed in the general population [29,30] as well as in specialist care settings [31], to generate normal values. Based on these studies, we chose to use the 25 ppb cut-off. We are aware of the problem that, as shown in our sensitivity analysis, we might overestimate the percentage of patients being uncontrolled compared to using the less strict 50 ppb cut-off, which is also mentioned as a justified cut-off in the literature [26]. To date it is unclear what the longitudinal consequences of normalizing FeNO are; therefore it is difficult to predict whether it is most important to demonstrate controlled disease by using a lower cut-off (and to avoid under treatment), or to prove uncontrolled disease by using a higher cut-off (and to avoid over treatment). However, even when using the less strict 50 ppb cut-off, the proportion of patients where FeNO provided additional information remained similar.

A final limitation of using FeNO in primary care are the high costs when purchasing a device, which currently has a refractory life of three years only, and the need of acquiring a new costly sensor every twelve months. However, Honkoop et al have shown that due to decreased medication usage and costs, adding FeNO is a cost-effective strategy [12].

Interpretation of findings in relation to previously published work

Most studies on FeNO have analysed whether FeNO could be used as a replacement for conventional asthma control markers. Only few studies have been performed about the relation between FeNO and other asthma control markers, and their results are inconsistent. Some studies indicate that increased FeNO levels are associated with uncontrolled asthma [32] or are significantly related to changes in ACQ scores over time [33]. On the other hand, one study showed that FeNO was not associated with ACQ scores [34]. In the primary care setting, one study found a modest correlation between FeNO and a non-validated symptom score ($r=0.4$, $p<0.05$) [35] which disappeared when treatment with ICS was taken into account. In this same study the correlation between FeNO and FEV₁ was weak ($r=0.2$, $p=0.03$). Another study found very weak correlations between FeNO, the ACQ and lung function, cross-sectional as well as longitudinal [36]. Finally, Hewitt et al showed that by adding FeNO to conventional markers they were able to lower ICS usage [18].

Our finding of only weak cross-sectional associations confirms that FeNO might serve as an independent, distinctive marker when assessing asthma control [37]. This weak cross-sectional association on its own is naturally no conclusive proof of added value. However, combined with results from previous longitudinal studies where the additional use of FeNO resulted in lower ICS usage [12,14,18], this points towards its added value

in the assessment of asthma control. In other words, FeNO does indeed seem to reflect another domain of asthma control than the current markers do: underlying inflammation rather than symptoms or (reversible) airway obstruction.

Implications for future research, policy and practice

Since asthma has a multi-dimensional nature, FeNO could provide GPs with additional information, especially in those patients where symptoms and lung function provide conflicting results. GPs might in the future define asthma control not only by symptoms and spirometry, but also by level of inflammation.

As presented in the flow chart analysis in figure 3.2, in a substantial percentage of patients (46.3%) the GP will be confronted with patients whose asthma is controlled according to one of the established markers (e.g. symptoms) but uncontrolled according to the other (lung function), or vice versa. Although currently clinical symptoms are considered to be more important than lung function when assessing asthma control [1], it may still confuse the GP when these two markers contradict each other. In these patients, adding FeNO as a third marker could be decisive when judging the patient's asthma control. In another 28.1% it is FeNO that gives contradicting results compared to the two established markers. As to date it is unclear which of the three markers should be the dominant one and future research should focus on establishing an order. The ultimate goal of improving the assessment of a patient's asthma control level by adding FeNO are the therapeutic consequences. With this additional measurement, decisions regarding treatment could be guided on the actual pathophysiology. For instance, in circumstances where both symptoms and lung function show uncontrolled asthma and FeNO is controlled, patients should be prescribed LABAs, whereas ICS would be preferred if FeNO is uncontrolled. On the other hand, when symptoms are controlled, a GP might be more reluctant to prescribe high-dosed ICS when there is no sign of active bronchial inflammation. In case of uncontrolled FeNO and after checking compliance and inhaler technique, ICS could be started or increased as the risk of exacerbation should be considered [8]. Follow up of the patient remains necessary though, as not all elevated FeNO levels seem to respond to ICS [38]. Also, if symptoms and lung function are uncontrolled, it could be harmful for the patient to stop or reduce (ICS-) treatment in response to normal FeNO levels, as there are phenotypes of asthma that never have an increased FeNO level.

If FeNO is to be used as a new marker of asthma control in primary care, some important barriers remain. One important issue is whether FeNO testing is 'robust' enough to be applicable for all patients and in all circumstances. Levels of FeNO appear to be gender, age, and height dependent [25,29], which hampers interpretation of FeNO results in individual patients. Furthermore, raised FeNO levels are not exclusively due to asthma, but are also seen in atopic subjects [29], in patients with an upper respiratory

infection [39], after bronchodilation [40] and after a nitrate rich meal [41]. Conversely, levels are reduced by smoking [42], ICS use [43], and spirometry manoeuvres [40]. More recent studies concluded therefore that FeNO should be corrected for its main influencing factors, gender, height, smoking, allergy and recent upper respiratory infection [25,29,30]. Therefore, we chose to correct FeNO using the established adjustments for these influencing factors [25]. In our sensitivity analysis, however, we showed that results of categorizing patients differed only slightly if FeNO values are not corrected.

Conclusions

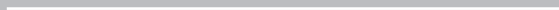
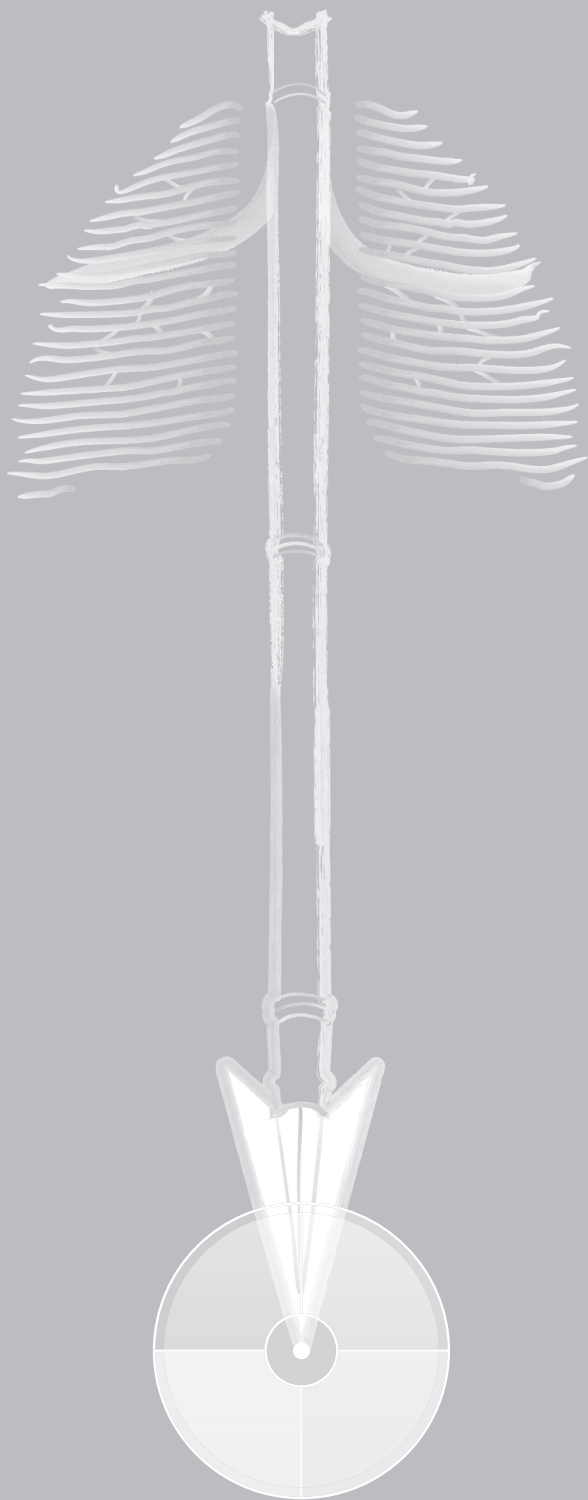
In conclusion, our cross-sectional study of adult patients with asthma in primary care demonstrated that FeNO correlates weakly with respiratory symptoms and lung function, which confirms that it might serve as an independent marker for assessing asthma control. If, in the future, FeNO would be incorporated as a marker of asthma control in primary care, it will enable 'fine-tuning' when categorizing asthma control in almost half of the patients. Although for the time being measuring FeNO is rather impractical and provides additional work, it is likely that these obstacles will resolve over time, especially since FeNO has been shown to be cost-effective. Prospective research on the impact of the additional use of FeNO in the subgroup of patients with conflicting symptom and lung function results on long-term results such as asthma control and exacerbation rate is needed, to be able to tailor asthma management in primary care.

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Chapter 4

Symptom- and fraction of exhaled nitric oxide— driven strategies for asthma control: A cluster- randomised trial in primary care

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Abstract

Background Aiming at partly controlled asthma (PCa) instead of controlled asthma (Ca) might decrease asthma medication use. Biomarkers, such as the fraction of exhaled nitric oxide (FeNO), allow further tailoring of treatment.

Objective We sought to assess the cost-effectiveness and clinical effectiveness of pursuing PCa, Ca, or FeNO-driven controlled asthma (FCa).

Methods In a nonblind, pragmatic, cluster-randomised trial in primary care, adults (18-50 years of age) with a doctor's diagnosis of asthma who were prescribed inhaled corticosteroids were allocated to one of 3 treatment strategies: (1) aiming at PCa (Asthma Control Questionnaire [ACQ] score <1.50); (2) aiming at Ca (ACQ score <0.75); and (3) aiming at FCa (ACQ score <0.75 and FeNO value <25 ppb). During 12 months' follow-up, treatment was adjusted every 3 months by using an online decision support tool. Outcomes were incremental cost per quality-adjusted life year gained, asthma control (ACQ score), quality of life (Asthma Quality of Life Questionnaire score), asthma medication use, and severe exacerbation rate.

Results Six hundred eleven participants were allocated to the PCa ($n = 219$), Ca ($n = 203$), or FCa ($n = 189$) strategies. The FCa strategy improved asthma control compared with the PCa strategy ($P < .02$). There were no differences in quality of life ($P \geq .36$). Asthma medication use was significantly lower for the PCa and FCa strategies compared with the Ca strategy (medication costs: PCa, \$452; Ca, \$551; and FCa, \$456; $P \leq .04$). The FCa strategy had the highest probability of cost-effectiveness at a willingness to pay of \$50,000/quality-adjusted life year (86%; PCa, 2%; Ca, 12%). There were no differences in severe exacerbation rate.

Conclusion A symptom- plus FeNO-driven strategy reduces asthma medication use while sustaining asthma control and quality of life and is the preferred strategy for adult asthmatic patients in primary care.

Introduction

Globally, an estimated 300 million persons have asthma [1], representing a considerable and increasing burden to patients, health care, and society at large. Asthma has a significant effect not only on an individual patient's health-related quality of life but also on society and the economy through work absence, premature retirement, and high costs for asthma treatment [2-6]. Cost-effective treatment strategies are required to face the burden of asthma.

According to guidelines, the aim of asthma treatment is to achieve and maintain control of clinical manifestations for prolonged periods of time. Patient safety, including prevention of exacerbations and side effects of medication, and keeping in check the cost of treatment are also important goals [7-11]. The severity of clinical manifestations of asthma is classified into controlled asthma (Ca), partly controlled asthma (PCa), and uncontrolled asthma categories to direct treatment decisions [8]. In practice, symptoms in up to 75% of patients are controlled suboptimally (partly controlled or uncontrolled) [12-14]. In these patients a step up of asthma medication is advocated to achieve controlled asthma. Because the dose-response relationship flattens at higher levels of inhaled corticosteroids (ICSs) and the risk of side effects increases [15,16], the benefits of stepping up treatment to achieve Ca might be limited.

Recent studies have shown that biomarkers, including fractional exhaled nitric oxide (FeNO), help to distinguish between patients who benefit more from adding a long-acting β -agonist (LABA) and those requiring a change in ICS dosage by providing additional information regarding the level of bronchial inflammation [17-20]. However, in primary care the current recommendation is to guide treatment decisions based solely on controlling the clinical features of disease because assessments of biomarkers are unavailable, likely to increase health care costs because of expensive equipment, or both [8]. Recently, easy-to-use and cheaper handheld FeNO devices have been introduced [21]. To date, it is unknown whether in primary care the pursuit of improving asthma control through assessment of airway inflammation by using FeNO measurements is helpful to achieve and benefit from controlled asthma with regard to the patient's quality of life, exacerbation rates, and cost of treatment.

To that end, we performed a 3-armed cluster-randomised trial comparing 3 strategies aiming at either PCa, Ca, or FeNO-driven controlled asthma (FCa).

Methods

This was an entirely investigator-designed and investigator-driven study. A detailed description of study procedures, sample size calculation, and measurements has been published elsewhere [22].

Setting and participants

General practices from both rural and urban areas in The Netherlands were invited to participate. Inclusion criteria were age of 18 to 50 years, doctor-diagnosed asthma according to the Dutch national guidelines [10], a prescription for ICS for at least 3 months in the previous year, and asthma being managed in primary care. Exclusion criteria were significant comorbidity (at the general practitioner (GP)'s discretion), inability to understand Dutch, and a prescription for oral corticosteroids in the previous month. The trial was approved by the Medical Ethics Committee of Leiden University Medical Center. All included patients provided written informed consent. The trial was registered at www.trialregister.nl (NTR 1756).

Design overview

This was a nonblind, 3-arm, pragmatic, cluster-randomised trial with 12 months' follow-up of adult asthmatic patients in primary care. Cluster randomization was performed at the general practice level instead of the patient level to prevent intervention contamination within practices. No specific eligibility criteria applied to clusters. At local information meetings, study procedures were explained to participants, and afterward, informed consent was obtained. When the list of participants for each practice had been completed, the general practices were randomly allocated to one of 3 treatment strategies by an independent researcher using a computer-generated permuted block scheme for groups of 3 general practices stratified according to region (Amsterdam, Leiden, and Nijmegen), urbanization grade (rural vs urban), and the practice nurse (PN)'s level of experience with asthma management (≥ 1 year vs < 1 year). Allocation concealment applied to both the cluster and participant levels (Figure 4.1).

Interventions

The 3 treatment strategies targeting different levels of asthma control were defined as follows: (1) aiming at partly controlled asthma (PCa strategy), (2) aiming at controlled asthma (Ca strategy), and (3) aiming at FeNO-driven controlled asthma (FCa strategy). In all 3 strategies patients visited the PN of their general practice every 3 months over the course of 1 year. During these visits, the PN assessed current medication use and asthma control status by using the 7-item Asthma Control Questionnaire (ACQ) that includes lung function [23]. In addition, a FeNO measurement was performed in the FCa strategy.

FeNO values were expressed as the concentration in parts per billion and automatically adjusted for smoking, when applicable [24]. At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score ≤ 0.75), partly controlled ($0.75 < \text{ACQ score} \leq 1.5$), or uncontrolled (ACQ score > 1.5) and additionally in the FCa strategy as 3 subcategories of FeNO: low/absence of airway inflammation for values at 25 ppb or less, intermediate at 26 to 50 ppb, and high/presence of airway inflammation at greater than 50 ppb [19]. Treatment decisions were based on a dedicated algorithm for each strategy (Table 4.1). To increase the feasibility of implementing our strategies, we designed an online decision support tool. Current medication use and all measurements were entered into this decision support tool, which subsequently auto-

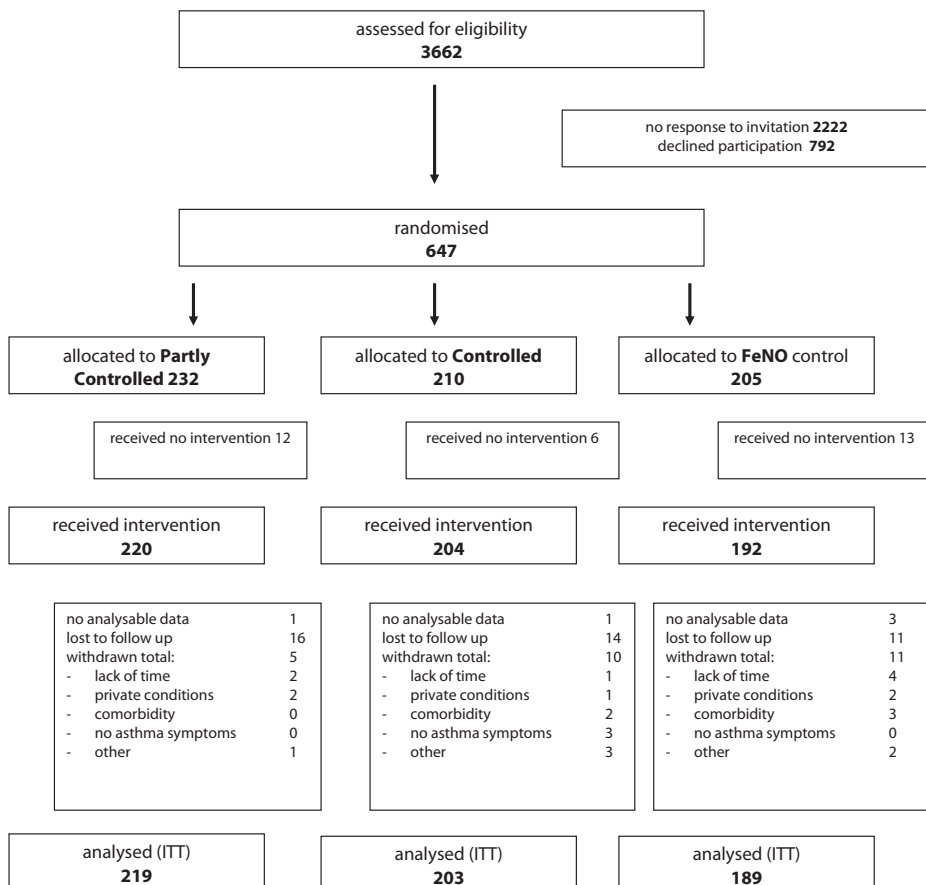


Figure 4.1. Consort Flow diagram ACCURATE trial.

647 patients provided informed consent, of which 31 withdrew before the first visit to the general practice and before filling out online questionnaires. Since randomisation was performed at group level they were randomized, but they were unaware of their strategy before withdrawal. 5 participants visited their general practice once, but no analysable data was available since they never filled out online questionnaires.

matically generated treatment advice based on the appropriate algorithm for each of the 3 treatment strategies (Table 4.1). Patients' current medication use was classified as an asthma treatment step ranging from 0 (only short-acting β -agonists) to 5 (oral prednisone) based on the US National Asthma Education and Prevention Program guideline [7]. When treatment was to be adjusted, in the PCa and Ca strategies professionals and patients could choose any (combination of) type or types of asthma medication they preferred within a certain treatment step (for all possibilities, see Table 4.E1 in this article's supplement), whereas the FCa strategy offered more guidance toward adding/removing LABAs or ICSs (Table 4.1).

Table 4.1. Treatment advice for the three strategies at possible levels of asthma control

Strategy aimed at	Asthma control status		
	Controlled (ACQ= <0.75)	Partly Controlled ($0.75 > \text{ACQ} = <1.5$)	Uncontrolled (ACQ >1.5)
PCa	step-down open †	no change	step-up: treatment choice open †
Ca	– 3 mo: no change – > 3 mo: step-down	step-up: treatment choice open †	step-up: treatment choice open †
FCa			
Low FeNO (<25 ppb)	step-down open †	– 3 mo: no change/ change within current step to LABA – > 3 mo: step-down ICS §	– 3mo: step-up: LABA – >3 mo: Revise asthma diagnosis
Intermediate FeNO (25-50 ppb)	no change	step-up: treatment choice open †	step-up: treatment choice open †
High FeNO (>50 ppb)	step-up/change within current step to ICS ‡	step-up: 1 \times ICS	step-up: 2 \times ICS ¶

* Adjusted for smoking

† When the treatment advice was open, Nurse Practitioners (General Practitioners) could choose which types of medication were increased/decreased or added/removed. With the exception of solely treating with LABA, which was not allowed, according to the guidelines [1-4].

‡ If the participant did not use ICS, or used ICS in combination with LABA, the advice was to change treatment by starting ICS or to replace LABA by a higher dose of ICS. This effectively kept patients in the same treatment step [1]. Otherwise the advice was to step up treatment by increasing ICS dosage.

§ If the participant did not use LABA and used a medium to high dose of ICS, the advice was to reduce ICS dosage and add LABA, which effectively kept patients in the same treatment step [1]. Otherwise the advice was to remain on current treatment. If FeNO results of patients remained low at different visits to the Nurse Practitioner, the advice was to step down ICS-usage if possible (solely LABA was not allowed).

|| Patients were advised to add LABA to their current treatment. If they already used LABA, the advice was to step-up treatment open. If patients remained uncontrolled with a normal FeNO we advised to review the asthma diagnosis and assess concomitant diseases such as gastro-oesophageal reflux or depression.

¶ Increase ICS usage from low to high. If this was not possible increase ICS usage and add LABA/montelukast.

All unplanned doctor's office visits for increased symptoms of asthma were treated at the GP's discretion, irrespective of the participant's experimental assignment. When symptoms had normalized, patients additionally visited the PN's office, where asthma control was reassessed and therapy was adjusted by using the assigned treatment strategy.

Outcomes and follow-up

The primary outcome was the societal costs per quality-adjusted life year (QALY) gained. Patients filled out online questionnaires at home every 3 months to assess QALYs and costs from a societal perspective. QALYs were obtained by calculating the area under the health state utility curve based on the Dutch tariff of the EuroQol classification system (EQ-5D) [25]. Total costs were obtained by adding the costs of 3 relevant categories: all health care costs, productivity loss, and intervention costs, including additional costs for the measurement of FeNO [26]. Costs in Euros were converted to dollars by using the purchasing parity index [27].

Secondary outcomes were asthma control, asthma-related quality of life (Asthma Quality of Life Questionnaire [28]), number of days with (asthma-related) limitations of activity, medication adherence (Medication Adherence Report Scale (MARS) [29]), severe exacerbation rate, lung function, FeNO value, and total medication use.

Severe exacerbations were defined as hospitalizations or emergency care visits because of asthma, or systemic use of oral corticosteroids for 3 or more consecutive days [11]. Unplanned doctor's office visits for increased asthma symptoms were recorded, as were experienced symptoms and received treatment, allowing severe exacerbations to be distinguished from moderate exacerbations and periods of loss of control.

Total medication use was assessed by obtaining all medication prescriptions from local pharmacy records and from the Dutch Foundation for Pharmaceutical Statistics [30]. All ICS prescriptions were expressed as beclomethasone equivalent values based on recommendations by the Dutch pharmaceutical guidelines [31] and a panel of respiratory experts to allow comparisons between strategies.

Statistical analysis

Patients were analysed according to the intention-to-treat methodology. Statistical uncertainty of the cost-effectiveness ratio was analysed by using the net benefit approach [32]. The net benefit is defined as follows:

$$\lambda \times \Delta \text{QALY} - \Delta \text{costs},$$

where λ is the willingness to pay for a gain of 1 QALY. This way, the observed QALY difference is reformulated into a monetary difference. The probability of cost-effectiveness at

different λ levels was assessed in an acceptability curve. All outcomes pertained to the individual participant's level and were adjusted for clustering within general practices. Outcomes from the clinical perspective were analysed with the Stata 11.0 xtmixed command for multilevel linear regression, adjusting for clusters at the practice level, repeated measurements within patients, and baseline values (StataCorp, College Station, Tex). For a detailed description of statistical procedures, see the Methods section in this article's Supplement.

Results

Recruitment and baseline characteristics

Figure 4.1 provides the flowchart of the study. Between September 2009 and January 2012, 611 asthmatic patients participated, of whom 219 (in 44 clusters) were allocated to the PCa strategy, 203 (43 clusters) to the Ca strategy, and 189 (44 clusters) to the FCa strategy. All initially started general practices (clusters) completed the study.

Participants' baseline characteristics were similar for the 3 strategies (Table 4.2). Table 4.E2 in this article's Supplement shows a comparison between participants and those who declined participation. Participants were slightly older, and their asthma was less controlled.

Process outcomes

Asthma control during the study, as measured by using the ACQ, was significantly better in the FCa strategy than in the PCa strategy (Δ ACQ score, -0.12 ; 95% CI, -0.23 to -0.02 ; $P = .02$; see Table 4.E3 in this article's Supplement). No significant differences were found between the PCa and Ca strategies or between the FCa and Ca strategies ($P \geq .15$; see Fig E1, A, in this article's Supplement). The percentage of participants who achieved Ca at 12 months' follow-up was 55% for the PCa strategy, 68% for the Ca strategy, and 61% for the FCa strategy (1-way ANOVA for different outcomes at 12 months: PCa vs Ca, $P = .01$; PCa vs FCa: $P = .28$; and FCa vs Ca: $P = .75$).

During the study, 41 (6.7%) patients withdrew, and 6 (1.0%) were lost to follow-up (Figure 4.1). One participant in the Ca strategy died during the study because of a non-study-related cause. Rates of withdrawal and loss to follow-up were similar between the strategies.

The study treatment algorithm was effective in leading to markedly different treatment advice for the 3 strategies ($P < .001$, Pearson χ^2 test; see Table 4.E4 in this article's Supplement). Overall, participants did not adhere to the treatment algorithm 30% of the time: 66% of the advice given was to decrease treatment, 32% was to increase treat-

Table 4.2. Baseline characteristics

	Partly Controlled	Controlled	FeNO
Patients (n)	219	203	189
Clusters	44	43	44
Sex % F	68.4	65.8	72.3
Mean age (SD)	38.9 (9.3)	39.9 (9.8)	39.5 (9.3)
Asthma duration in years (SD)	18 (13)	16 (12)	20 (14)
BMI (SD)	26.8 (5.9)	26.0 (4.9)	26.1 (5.1)
Allergy (defined as total IgE >100) in %	56	52	55
FEV1 (SD) in % predicted	92.4 (17.2)	93.0 (17.0)	93.1 (17.0)
Baseline FeNO in ppb (SD)	27.3 (30.4)	24.7 (29.8)	24.5 (21.7)
Beclomethason equivalent dose in mcg (SD)	831 (701)	825 (639)	853 (642)
Long Acting Beta Agonist (LABA) use (% yes)	49	52	47
Mean baseline ACQ (SD)	1.08 (0.84)	0.93 (0.80)	0.99 (0.73)
Current Smokers (% yes)	13	16	14
Previous Smokers (% yes of current non-smokers)	32	35	31

SD = standard deviation FEV1 = Forced Expiratory Volume in one second
 %F = percentage female Ppb = parts per billion
 BMI = Body Mass Index Mcg = microgram
 IgE = immunoglobulin E ACQ = Asthma Control Questionnaire

ment, and 2% was to remain on current treatment (see the Results section in this article's Supplement for more detail).

Primary outcome

There were no significant differences in QALYs between the strategies ($P \geq .36$, Table 4.3). Costs per patient for asthma medication were significantly less in the strategies aimed at PCa and FCa compared with Ca (PCa, \$452; Ca, \$551; and FCa, \$456). Costs for asthma-related contacts with health care professionals, costs because of loss of productivity, and annual societal costs showed no significant differences (Table 4.3). The FCa strategy showed the highest probability of cost-effectiveness over a wide range of willingness-to-pay values (\$0-\$125,000/QALY). Specifically, at a willingness-to-pay threshold of \$50,000/QALY [31], the FCa strategy was 86% likely to be the most cost-effective (PCa strategy, 2%; Ca strategy, 12%; Figure 4.2).

Secondary outcomes

There were no differences in asthma-related quality of life between the strategies (Asthma Quality of Life Questionnaire differences, $P \geq .60$; see Fig E1, B). Neither the number of days with asthma-related limitations of activity per year nor the adherence to medication (MARS) showed significant differences between the strategies (see Table

Table 4.3. Outcomes from the health economic perspective

	Partly Controlled (n=219)	Controlled (n=203)	FeNO (n=189)	Ca vs Pca	Fca vs Pca	Fca vs Ca
QALY (EQ-5D) ‡ (95% CI)	0.89 (0.88 to 0.90)	0.91 (0.90 to 0.91)	0.90 (0.89 to 0.90)	0.01 (-0.02 to 0.04)	0.01 (-0.01 to 0.03)	0.01 (-0.02 to 0.03)
Intervention costs (in dollars)	0	0	105 ¶			
Asthma related visits † (95% CI) (in dollars)	269 (234 to 304)	281 (257 to 308)	224 (205 to 242)	12 (-87 to 112)	-45 (-127 to 38)	-57 (-116 to 1)
Asthma Medication † (95% CI) (in dollars)	452 (427 to 479)	551 (526 to 588)	456 (429 to 482)	99 (5 to 202) *	4 (-75 to 81)	-96 (-183 to -17) **
Other healthcare costs † § (95% CI) (in dollars)	979 (894 to 1,063)	1,065 (837 to 1,292)	1,005 (919 to 1,092)	86 (-459 to 653)	25 (-182 to 234)	-59 (-594 to 474)
Productivity loss (95% CI) (in dollars)	2463 (2,166 to 2,761)	2641 (2,266 to 3,017)	2099 (1833 to 2,366)	178 (-879 to 1,305)	-364 (-1,227 to 654)	-542 (-1,658 to 659)
Total Societal costs (95% CI) (in dollars)	4,180 (3,818 to 4,543)	4,591 (4,123 to 5,060)	3,893 (3,584 to 4,203)	411 (-904 to 1,797)	-287 (-1,240 to 847)	-698 (-1,985 to 699)

* Significant difference, p=0.04

** Significant difference, p=0.02. All other results were non-significant

† Asthma related visits; Asthma Medication and Other healthcare cost added make up Healthcare costs

‡ Values are summary estimates of the 5 datasets obtained by multiple imputation, combined using Rubin's rules [44].

§ Including non-asthma related medication and visits to healthcare professionals

|| Intervention + Healthcare + Productivity loss (numbers do not add up exactly, because bootstrap analysis was repeated at each level).

¶ The unit price per FeNO measurement depends on the capacity of acquired sensors, from 11.65 dollar/measurement for a sensor with 1000 measurements, to 26.25 dollar/measurement for a sensor with 100 measurements. In the cost-analysis the most expensive sensor was assessed, since a sensor with 100 measurements is the most feasible option in primary care.

4.E5 in this article's Supplement). An additional analysis on the adherence to treatment advice after the visit to the PN also showed no significant differences between the strategies (see the Results section in this article's Supplement). The total number of severe asthma exacerbations was 63 for the PCa strategy (0.29 exacerbations/patient/y), 58 for the Ca strategy (0.29/patient/y), and 37 for the FCa strategy (0.19/patient/y), and the odds ratios for experiencing 1 or more severe exacerbations between the strategies showed no significant differences (see Table 4.E6 in this article's Supplement).

In accordance with the significant differences in asthma medication costs between

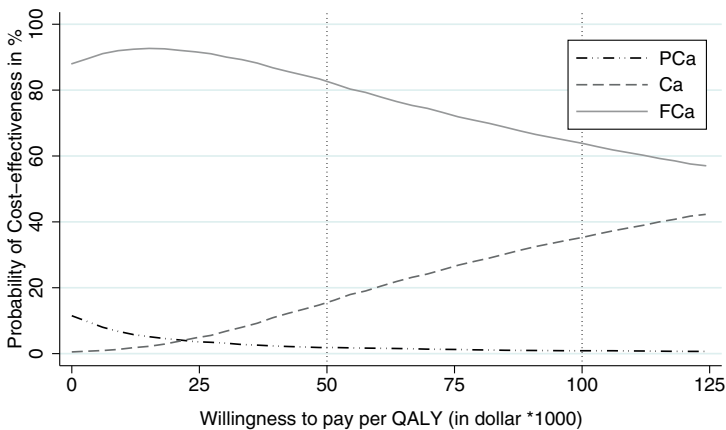


Figure 4.2. Cost-effectiveness acceptability curve.

This figure shows the probability that a strategy is the most cost-effective compared to the other two strategies at different willingness-to-pay per QALY levels from a societal perspective, which includes all health-care costs and costs due to loss of productivity.

the PCa and Ca strategies and between the FCa and Ca strategies, asthma medication prescriptions at 12 months were highest in the Ca strategy for ICSs, LABAs, and montelukast (Table 4.3 and see Figure 4.E2, A, in this article's Supplement).

Discussion

In this pragmatic cluster-randomised trial in patients with mild to moderately severe asthma in primary care, we found that a treatment approach aiming at PCa instead of Ca significantly decreases asthma medication use and associated costs, whereas asthma control, quality of life, and severe exacerbation rates remain similar. However, a strategy aiming at Ca that is additionally driven by a FeNO measurement seems to be the preferred strategy because it also reduces asthma medication use and associated costs, has

the highest probability of cost-effectiveness, and improves asthma control compared with the PCa strategy.

To our knowledge, this is the first study in which asthma treatment strategies pursuing different levels of control are compared from a comprehensive health economic, patient, and clinical perspective. With respect to patient utilities based on the EQ-5D, there was no additional gain in the Ca and FCa strategies compared with the PCa strategy, which is in line with a previous study comparing utility scores between the Ca and PCa strategies [33]. Interestingly, total societal costs were lowest for the FCa strategy, including lower costs for asthma medications. As a result, the FCa strategy had a greater than 86% chance of being the most cost-effective strategy for a willingness to pay up to the commonly cited threshold of \$50,000 per QALY [32].

An important clinical finding is that by using FeNO as a biomarker, medication could be better tailored to an individual patient's needs. Therefore compared with aiming for Ca as such, the FCa strategy decreased the cumulative daily dose of ICS and the daily use of LABAs and montelukast. In addition, although not statistically significant, we observed the lowest severe exacerbation rate and the lowest use of prednisone in the FCa strategy (see Fig E2). Therefore our results are in line with studies in secondary care showing that tailoring treatment based on FeNO values reduced corticosteroid exposure, exacerbation rates (in pregnant women), and possibly long-term corticosteroid-related side effects [15,20,34].

In previous studies the use of FeNO as an adjunct to primary care management has led to an increased proportion of patients with controlled asthma [35], a similar reduction in ICS dosage as in our study [18], or no differences [36]. In contrast to our results in studies by Szeffler et al [17], De Jongste et al [37], and Shaw et al [38] and in a meta-analysis by Petsky et al [39], the addition of FeNO measurement did not reduce or even increase ICS use. These differences might be attributed to the choice of FeNO cutoff points for dose increase because cutoff points are critical in asthma treatment algorithm studies [40]. In our study a relatively high cutoff point (50 ppb vs 20 ppb (Szeffler et al [17]), 25 ppb (De Jongste et al [37]), and 26 ppb (Shaw et al [38])) was used, leading to fewer step ups of treatment in response to FeNO measurements. In addition, low FeNO values in our study led to advice to step down treatment, even when symptoms were present.

In terms of a patient's perspective and for clinical outcomes, the present study showed no additional benefit for pursuing Ca compared with accepting PCa as a sufficient treatment goal, whereas it did increase asthma medication use and associated costs. In our study approximately 60% of all patients achieved Ca compared with 65% to 71% in the Gaining Optimal Asthma Control (GOAL) trial, whereas exacerbation rates and asthma-related quality of life are similar between the studies [41]. In the GOAL trial 57% to 88% of patients required the highest ICS dose (ie, 2000 µg of beclomethasone equivalent), and in half of their study, the population received LABA supplementation.

Furthermore, 5% to 11% of patients required daily oral corticosteroid therapy of 0.5 mg/kg for 4 weeks [41]. Therefore even though aiming for Ca might be successful in the majority of patients, as was shown in the GOAL trial, the comparison with our results shows that it is accompanied by much higher daily medication use, offers no additional benefits compared with accepting PCa as a sufficient goal, and is also not beneficial from a societal perspective because of increased costs.

In our study the Ca strategy had the lowest percentage of uncontrolled patients but was still the most expensive strategy. Interestingly, Accordini et al [42] showed that uncontrolled asthma is approximately 4 times 'more expensive' and Gold et al [13] showed that PCa might be associated with increased use of health care resources. However, both studies were based on cross-sectional analyses. Therefore increased use of health care resources by patients with PCa either did not occur longitudinally in our study or was compensated by the increased costs for medication and health care use in the Ca strategy.

The results of this study do not seem to be negatively influenced by study design or selection bias. Randomization was performed after inclusion of patients, thereby preventing selection bias. This study had a pragmatic approach with regard to in and exclusion criteria and included a wide spectrum of patients in the full range of asthma control from both rural and urban areas, including smokers. The absence of differences for most of the outcomes on effectiveness does not seem to be explained by missing data. We observed that 14.8% of data were missing overall. However, the frequency of missing values was not associated with a particular intervention arm, and sensitivity analyses with different methods of imputation all showed similar results (see this article's Supplement).

The power calculation for this study was based on the cost-utility measurements, and our study was underpowered for some secondary outcomes, including severe exacerbations. Because the severe exacerbation rate was lowest in the FCa strategy (see Table 4.E6), we do not expect that another preferred strategy would be found when the study was adequately powered for exacerbations.

A potential limitation of our study is that the GP's diagnosis of asthma was not reassessed. However, Lucas et al [43] showed that asthma was correctly classified in 73% of primary care patients of all ages in The Netherlands. Furthermore, in real life, these patients are being treated for asthma, and this will affect the clinical usefulness of any treatment strategy. A difference in adherence to treatment might also exist between the strategies, especially in the FCa strategy, because an additional measurement can provide more insight and subsequent adherence. However, the MARS questionnaire regarding adherence and 2 additional analyses (see this article's Supplement) showed no significant differences between the strategies. Therefore we expect that results cannot be ascribed to differences in adherence.

Another limitation is that the magnitude of the differences in effectiveness was small and of limited clinical relevance. For instance, the effect sizes for asthma-related quality of life within the strategies were very similar, and differences between the strategies were well below the clinically important range of 0.5 points [44]. Moreover, the 95% confidence limits were generally incompatible with the existence of clinically important differences.

In this study all patients were treated similarly, irrespective of the baseline phenotypic characteristics of their asthma. Recent studies have shown that distinct phenotypes might preferentially benefit from more personalized treatment approaches [45,46], and future research should focus on which phenotypes benefit most from a strategy aimed at a Ca, FCa, or PCa approach.

In conclusion, treatment aimed at achieving and maintaining Ca as such offers no additional benefits from the health economic, patient, and clinical perspective over aiming for PCa. Therefore in primary care it seems justifiable to aim for PCa instead of Ca because asthma medication costs and use are lower, with no apparent loss in terms of clinical outcomes.

However, if feasible, the preferred strategy for achieving and maintaining Ca is to additionally guide treatment with a FeNO value as a biomarker because this strategy appears to be the most cost-effective and leads to more tailored asthma medication prescription while clinical asthma control improves.

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Methods

Interventions

Lung function measurements were based on percentage predicted pre-bronchodilator FEV₁, as determined by using routine practice-based spirometry, according to international guidelines [E1]. FeNO measurements were performed before spirometry by using the NIOX-MINO (Aerocrine, Solna, Sweden), according to international guidelines [E2].

Outcomes

During the study, several identical parameters were measured with different questionnaires. In this article the most common questionnaires are mentioned. For a detailed overview of all outcomes, please contact the authors.

Health economic outcomes

Participants reported their use of health care resources and hours of absence from work every 3 months in the cost questionnaire [E3]. Health care costs included emergency department visits, hospital admissions, medication use (all drugs), and all contacts with health care professionals, complementary care, and paramedical professionals. Productivity costs consisted of hours of absence from work multiplied by standardized average hourly wages for the participant's sex and age [E3]. Actual costs of medication prescriptions were obtained from pharmacy records [E4]. Costs for FeNO were based on the current price of FeNO measurements. Finally, all prices were converted to the price level of 2013 according to the general Dutch consumer price index [E5].

Clinical and patient outcomes

For the online assessment of the ACQ at home, percentage predicted FEV₁ was assessed by means of handheld spirometry (PIKO-1, NSpire Health, Oberthulba, Germany).

Statistical analysis

For the cost analyses, missing cost questionnaires, EQ-5Ds, and pharmacy records were imputed by using multiple imputation, creating 5 data sets, with the UVIS command from Stata 11.0 (StataCorp). A QALY was calculated by assessing the area under the utility curve from the outcomes of the 3-month EQ-5D over a period of 1 year [E6]. Differences and statistical uncertainty of QALYs and costs were calculated by using nonparametric bootstrap estimation with 5000 random samples (1000 for each of the 5 data sets), combining the 5 multiple imputation sets by using Rubin's rules [E7]. Subsequently, the net benefit approach was applied to reformulate the QALY difference into a monetary difference and include statistical uncertainty [E8].

The net benefit is defined as follows:

$$\lambda \times \Delta\text{QALY} - \Delta\text{costs}$$

where λ is the willingness to pay for a gain of 1 QALY. On the basis of these monetary differences, a model of net monetary benefit was constructed to assess the probability of cost-effectiveness for the 3 strategies. This probability was calculated across a range of different values of society's willingness to pay (λ) for an incremental outcome gain. This allowed the generation of a cost-effectiveness acceptability curve, plotting the probability of cost-effectiveness for each of the strategies at different willingness-to-pay values.

All outcomes from the patient and clinical perspective were analysed by using the Stata `xtmixed` command for multilevel linear regression, adjusting for clusters at the GP level, repeated measurements within a patient, and baseline values. Strategy-time interactions were assessed to detect any differences between the groups in particular time periods. If these interactions had no significant influence on results, the assessment was repeated without the strategy-time interactions. In a subanalysis the effect of missing data on results was analysed by means of imputation of results using the last observation carried forward or cluster means.

For exacerbations, we assessed mean exacerbation ratios, and for comparisons between treatment strategies, we used a multilevel mixed-effects logistic regression. This way we determined for each 3-month study period whether either an exacerbation had or had not occurred, thereby ensuring independence of events and diminishing the influence of frequent exacerbators on outcomes [E9].

Sample size calculation

The sample size calculation was based on a minimally important change in patient utility (EQ-5D), which has been defined as 0.074 points [E10]. With 150 patients per treatment strategy, we are able to detect a change of at least 0.06 points by net health benefit analysis [E11] between the arms with an SD of 0.175 EQ-5D points (baseline data SMASHING project: SD, 0.17), an SD of €1000 for costs (SD, €816; usual care strategy [E12]), and an increase in costs of €250 when a treatment strategy is not only more effective but also more costly, for a willingness-to-pay value of €30,000 ($\alpha = .05$, one sided [E11]; $\beta = .20$, one sided; ρ costs effects = 0). With 40 clusters (general practices) per arm and assuming an intracluster correlation of 0.01, 0.07, and 0.11, the number of patients per cluster is 4, 5, and 6, and the total number of patients is 480, 600, and 720, respectively [E13]. The mean cluster size of 4.7 patients per cluster was lower than the anticipated 6 in the study protocol. The number of clusters was extended from 120 to 131 to preserve power.

Results

Noncompliance

Because of the pragmatic design of the trial, PNs were allowed to discuss the treatment advice offered by the algorithm to make a final (shared) decision on a treatment change. Randomization of practices should have led to an equal distribution of PNs who tend to choose more (or less) aggressive treatments (or deviations from the protocol) across the 3 trial arms. However, it is possible that participants might wish to deviate more from the algorithm in a certain treatment strategy. Therefore in an exploratory analysis the frequency and reasons for noncompliance with treatment advice were assessed. There were no significant differences in deviations from protocol. When the advice was to step down treatment, 49% of patients were afraid of an increase in symptoms, in 33% of cases the GP/NP was afraid of loss of control, in 10% of cases asthma medication had recently been switched and patients did not want to step down too quickly, and 8% of patients had a variety of other reasons. When the advice was to step up treatment, 29% of patients or physicians refused the use of prednisolone or a referral to a pulmonary physician (which was advised when patients were already taking high-dose ICSs with LABAs), in 28% GPs/NPs did not want to increase medication, in 14% the medication had recently been stepped up and patients did not want to step up too quickly, in 11% patients were worried about side effects, and in 11% patients had not been sufficiently adherent on the current dosage, and other reasons were present in 7% of patients. To explore the sensitivity of our results to adherence with treatment advice, we repeated the main analysis including only the patients with an adherence rate to treatment decisions of at least 75%. The results of this sensitivity analysis were very similar to those for the whole group (results not shown).

Also, at the start of each visit to the PN, participants were asked which medications they had actually used in the previous months, and sometimes these levels did not correspond with the prescribed medication level from the previous visit. To assess whether a difference in adherence existed, we analysed the correspondence between the prescribed medication and the medication the participants had used. In 66% of cases these levels matched, in 18% patients were using less medication than they were supposed to use, and in 16% they were using more. There were no significant differences in deviations from medication adherence between the treatment strategies.

Missing data

There were no significant differences in odds ratios for missing data between the strategies: Ca versus PCa, 0.95 (0.69-1.31, $P = .77$); FCa versus PCa, 0.96 (0.69-1.33, $P = .80$); and Ca versus FCa, 0.99 (0.71-1.39, $P = .97$); 14.8% of all measurements in the study were missing. An exploratory reanalysis of all questionnaires was performed after imputation

by using either last observation carried forward or cluster means. No significantly different outcomes were obtained (data not presented).

Supplement Tables

Table 4.E1: Medication equivalent dosages

Medication Level	Medication	Total daily dosage
Level 0	Short Acting Beta Agonists as necessary:	na
	Ventolin	
	Atrovent	
	Bricanyl	
	Airomir	
Level 1	Beclomethason powder	400mcg
	Beclometason aerosol	200mcg
	Beclomethason extrafine	200mcg
	Budesonide powder	400mcg
	Budesonide aerosol	200mcg
	Fluticason powder	200mcg
	Fluticason aerosol	200mcg
	Ciclesonide aerosol	160mcg
	Montelukast	10mg
Level 2	Beclometason powder	800mcg
	Beclometason aerosol	500mcg
	Beclomethason extrafine	400mcg
	Budesonide powder	800mcg
	Budesonide aerosol	400mcg
	Fluticason powder	500mcg
	Fluticason aerosol	500mcg
	Ciclesonide aerosol	320mcg
	Formoterol/budesonide powder	400/12mcg
	Salmeterol/fluticason powder	200/100mcg
	Salmeterol/fluticason aerosol	250/50mcg
	Formoterol/beclomethasone aerosol	200/12mcg
	Beclometason powder + LABA	400mcg + laba
	Beclometason aerosol + LABA	200mcg + laba
	Beclomethason extrafine + LABA	200mcg + laba
	Budesonide powder + LABA	400mcg + laba
	Budesonide aerosol + LABA	200mcg + laba
	Fluticason powder + LABA	200mcg + laba
	Fluticason aerosol + LABA	200mcg + laba
	Ciclesonide aerosol + LABA	160mcg +laba
	Montelukast + LABA	10mg +laba
	Beclometason powder + Montelukast	400mcg +mont
	Beclometason aerosol + Montelukast	200mcg +mont
	Beclomethason extrafine + Montelukast	200mcg +mont
	Budesonide powder + Montelukast	400mcg +mont

Table 4.E1: Medication equivalent dosages (continued)

Medication Level	Medication	Total daily dosage
	Budesonide aerosol + Montelukast	200mcg +mont
	Fluticason powder + Montelukast	200mcg +mont
	Fluticason aerosol + Montelukast	200mcg +mont
	Ciclesonide aerosol + Montelukast	160mcg +mont
Level 3	Formoterol/budesonide powder	800/24mcg
	Salmeterol/fluticason powder	500/100mcg
	Salmeterol/fluticason aerosol	500/100mcg
	Formoterol/beclomethasone aerosol	400/24mcg
	Beclometason powder + LABA	800mcg + laba
	Beclometason aerosol + LABA	500mcg + laba
	Beclomethason extrafine + LABA	400mcg + laba
	Budesonide powder + LABA	800mcg + laba
	Budesonide aerosol + LABA	400mcg + laba
	Fluticason powder + LABA	500mcg + laba
	Fluticason aerosol + LABA	500mcg + laba
	Ciclesonide aerosol + LABA	320mcg + laba
	Beclometason powder + Montelukast	800mcg + mont
	Beclometason aerosol + Montelukast	500mcg + mont
	Beclomethason extrafine + Montelukast	400mcg + mont
	Budesonide powder + Montelukast	800mcg + mont
	Budesonide aerosol + Montelukast	400mcg + mont
	Fluticason powder + Montelukast	500mcg + mont
	Fluticason aerosol + Montelukast	500mcg + mont
	Ciclesonide aerosol + Montelukast	320mcg + mont
	Formoterol/budesonide powder + Montelukast	400/12mcg + mont
	Salmeterol/fluticason powder + Montelukast	200/100mcg + mont
	Salmeterol/fluticason aerosol + Montelukast	200/100mcg + mont
	Formoterol/beclomethasone aerosol + Montelukast	200/12mcg + mont
	Beclometason powder + LABA + Montelukast	400mcg + laba + mont
	Beclometason aerosol + LABA + Montelukast	200mcg + laba + mont
	Beclomethason extrafine + LABA + Montelukast	200mcg + laba + mont
	Budesonide powder + LABA + Montelukast	400mcg + laba + mont
	Budesonide aerosol + LABA + Montelukast	200mcg + laba + mont
	Fluticason powder + LABA + Montelukast	200mcg + laba + mont
	Fluticason aerosol + LABA + Montelukast	200mcg + laba + mont
	Ciclesonide aerosol + LABA + Montelukast	160mcg +laba +mont
Level 4	Formoterol/budesonide powder	1600/48mcg
	Salmeterol/fluticason powder	1000/100mcg
	Salmeterol/fluticason aerosol	1000/100mcg
	Formoterol/beclomethasone aerosol	-
	Beclometason powder + LABA	1600mcg + laba

Table 4.E1: Medication equivalent dosages (continued)

Medication Level	Medication	Total daily dosage
	Beclometason aerosol + LABA	1000mcg + laba
	Beclomethason extrafine + LABA	800mcg + laba
	Budesonide powder + LABA	1600mcg + laba
	Budesonide aerosol + LABA	800mcg + laba
	Fluticason powder + LABA	1000mcg + laba
	Fluticason aerosol + LABA	1000mcg + laba
	Formoterol/budesonide powder + Montelukast	800/24mcg + mont
	Salmeterol/fluticason powder + Montelukast	500/100mcg + mont
	Salmeterol/fluticason aerosol + Montelukast	500/100mcg + mont
	Formoterol/beclomethasone aerosol + Montelukast	400/24mcg + mont
	Beclometason powder + LABA + Montelukast	800mcg + laba + mont
	Beclometason aerosol + LABA + Montelukast	500mcg + laba + mont
	Beclomethason extrafine + LABA + Montelukast	400mcg + laba + mont
	Budesonide powder + LABA + Montelukast	800mcg + laba + mont
	Budesonide aerosol + LABA + Montelukast	400mcg + laba + mont
	Fluticason powder + LABA + Montelukast	500mcg + laba + mont
	Fluticason aerosol + LABA + Montelukast	500mcg + laba + mont
	Ciclesonide aerosol + LABA + Montelukast	320mcg + laba + mont
Level 4.5	Formoterol/budesonide powder + Montelukast	1600/48mcg + mont
	Salmeterol/fluticason powder + Montelukast	1000/100mcg + mont
	Salmeterol/fluticason aerosol + Montelukast	1000/100mcg + mont
	Beclometason powder + LABA + Montelukast	1600mcg + laba + mont
	Beclometason aerosol + LABA + Montelukast	1000mcg + laba + mont
	Beclomethason extrafine + LABA + Montelukast	800mcg + laba + mont
	Budesonide powder + LABA + Montelukast	1600mcg + laba + mont
	Budesonide aerosol + LABA + Montelukast	800mcg + laba + mont
	Fluticason powder + LABA + Montelukast	1000mcg + laba + mont
	Fluticason aerosol + LABA + Montelukast	1000mcg + laba + mont
Level 5	Oral prednisone	na

LABA = Long acting beta agonist Mont = montelukast

Table 4.E2. Comparison of baseline characteristics of participants and asthma patients who declined their invitation (non-participants)

	Non participants	Participants
Total (n)	788	644
Mean age (in yr)	35.7	38.3
% Females	68.5	68.1
Mean ACQ	0.62	0.97
% Strict control	68.2	48.4
% Partial control	18.0	27.2
% Uncontrolled	13.9	24.4

Table 4.E3. Clinical outcomes

	Outcome at 12 monthst		Differences between strategies#		
	Partly Controlled	Controlled	FeNO	CavsPCa	FCavsPCa
ACQ-7	0.91 (0.80 to 1.03)	0.69 (0.59 to 0.78)	0.78 (0.67 to 0.88)	-0.08 (-0.18 to 0.03)	-0.12* (-0.23 to -0.02)
FEV ₁ (% predicted)	90.6 (88.1 to 93.1)	90.3 (87.9 to 92.6)	92.4 (89.9 to 94.8)	0.25 (-1.2 to 1.7)	0.29 (-1.2 to 1.7)
ACQ category					
Controlled	54.8	68.0	61.4	P=0.01*	P=0.28
Partly Controlled	28.0	24.8	21.6		
Uncontrolled	17.2	7.2	17.0		
FeNO	25.5	25.7	24.0	§	

* Significant difference, p<0.05

† Mean results at the final visit per strategy. Numbers in parentheses are 95% confidence intervals, unless otherwise stated.

‡ Results were based on multilevel linear regression analysis of assessments at 3, 6, 9 and 12 months, adjusted for baseline assessment, time and clusters.

§ Multilevel linear regression analysis was not possible since FeNO was only measured at baseline and 12 months in the PCa and Ca strategies.

|| Comparison assessed by Oneway Anova analysis

ACQ-7= Asthma Control Questionnaire, including spirometry. Results are between zero and six and lower results represent better control on asthma symptoms
 ACQ-category: the results of the ACQ can be subdivided into controlled (ACQ=<0.75), partly controlled (ACQ>0.75 and ACQ =< 1.5) and uncontrolled (ACQ>1.5)

Table 4.E4. Difference in treatment advice between the three strategies:

	PCa	Ca	FeNO
Step-up treatment	20%	39%	20%
No change or change within current treatment step	43%	39%	39%
Step-down treatment	37%	30%	41%

Pearson Chi Squared p<0.001

Table 4.E5. Outcomes from the patient perspective

	Outcome at 12 months*			Differences between strategies†		
	Partly Controlled	Controlled	FeNO	CavsPCa	FCavsPCa	FCavsCa
AQLQ (95% CI)	5.9 (5.8 to 6.0)	6.0 (5.9 to 6.2)	6.0 (5.8 to 6.1)	0.03 (−0.08 to 0.13)	0.03 (−0.08 to 0.14)	0.001 (−0.11 to 0.11)
Number of limited activity days per year (95% CI)	4.5 (2.2 to 6.8)	5.2 (1.1 to 9.3)	3.6 (1.9 to 5.2)	1.2 (−3.1 to 5.5)	0.04 (−4.3 to 4.3)	1.1 (−3.4 to 5.6)
MARS (95% CI)	3.6 (3.5 to 3.7)	3.7 (3.6 to 3.7)	3.5 (3.4 to 3.6)	0.07 (−0.02 to 0.15)	0.01 (−0.08 to 0.08)	−0.06 (−0.15 to 0.03)

*Mean results at the final visit per strategy. Numbers in parentheses are 95% confidence intervals, unless otherwise stated.

† Results were based on multilevel linear regression analysis of assessments at 3, 6, 9 and 12 months, adjusted for baseline assessment, time and clusters.

AQLQ= Asthma-related Quality of life Questionnaire. Results are between zero and seven and higher results represent a better quality of life

MARS = the Medication Adherence Report Scale. Results are between one and five and higher results represent a better adherence to medication.

Table 4.E6. Asthma exacerbations

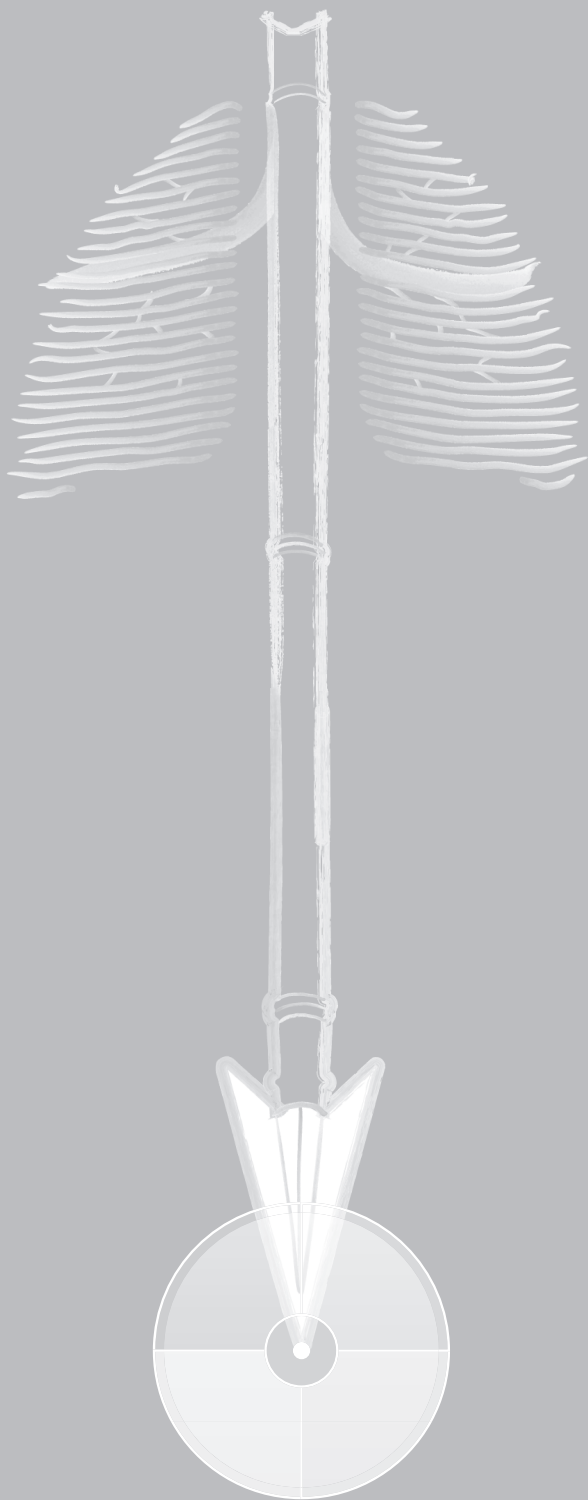
	Outcome at 12 months*			Odds ratio for differences between strategies†		
	PCa	Ca	FeNO	CavsPCa	FCavsPCa	FCavsCa
Mean severe exacerbation rate per patient per year (95% CI)	0.29 (0.15 to 0.43)	0.29 (0.17 to 0.40)	0.19 (0.11 to 0.29)	1.26 (0.54 to 2.92)	0.79 (0.32 to 1.93)	0.64 (0.27 to 1.56)
Courses of prednisone (n)	54	53	34			
Hospitalizations (n)	6	2	1			
Emergency department visits (n)	3	3	2			

* The mean severe exacerbation rate per strategy (sum of courses of prednisone, hospitalisations and emergency department visits). If a patient visited the hospital or ED and also received prednisone, the exacerbation was counted only once in the (arbitrarily) most severe category (1 hospitalisation, 2 ED visit, 3 course of prednisone)

† Odds ratios were assessed using a multilevel mixed effects logistics regression. For each three month study period an exacerbation had or had not occurred, thereby ensuring independence of events and diminishing the influence of frequent exacerbators on outcomes. Odds ratios were not assessed for subtypes of severe exacerbations

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Chapter 5

Early detection of asthma exacerbations by using action points in self-management plans

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Abstract

Background Our aim was to validate optimal action points in written action plans for early detection of asthma exacerbations.

Methods We analysed daily symptoms and morning peak expiratory flows (PEFs) from two previous studies. Potential action points were based on analysis of symptom scores (standard deviations), percentage of personal best PEF, PEF variability in relation to a run-in period, or combinations of these measures. Sensitivity and specificity for predicting exacerbations were obtained for each action point. The numbers needed to treat to prevent one exacerbation and the time interval between reaching action point criteria and the start of the exacerbation were calculated. Based on these parameters, the optimal action points for symptoms, PEF and PEF plus symptoms were determined, and their performance compared with published guidelines' action points.

Results The optimal action points were, for symptoms, statistical variability (standard deviations) and, for PEF, <70% of personal best. The combination of PEF plus symptoms performed best, with improved specificity and earlier detection. The main benefits associated with using these action points was to reduce false positive rates for detecting exacerbations.

Conclusion Early detection of asthma exacerbations can be improved using a composite action point comprising symptoms and PEF measurements over 1 week.

Introduction

Exacerbations of asthma are common and, even when asthma is mild, constitute a significant health risk [1]. Assessing future risk of adverse events, including exacerbations, and educating patients to use a self-management plan is recommended [2–6].

Self-management includes developing individualized Written Asthma Action Plans (WAAPs). WAAPs specify the level of symptoms or peak expiratory flow (PEF) (called action points, APs) at which to adjust medication (usually starting oral corticosteroids) in order to either prevent or reduce the severity of exacerbations. To ensure effective intervention, an AP should detect an imminent exacerbation well before its onset.

Gibson et al. [7] and Gibson and Powell [8] have previously validated several APs using quality control analysis (QCA). However, in the Global Initiative for Asthma (GINA) guidelines and the Dutch national guidelines, thresholds for symptoms or PEF are not specified [3, 9]. Although APs in the current British Thoracic Society (BTS) and US National Heart Lung and Blood Institute (NHLBI) guidelines are more specific, these APs have not been validated [2, 5, 6]. The optimum time point at which changes in either symptoms or PEF may be detected, or the relevant thresholds reached prior to an exacerbation are largely unknown. This lack of validation means that physicians often determine APs for individual patients empirically. If APs are inaccurately selected, this potentially leads to over treatment (false-positive APs) or missed opportunities for early intervention (false-negative APs).

In this study, our aim was to develop optimal APs based on symptoms and/or PEF threshold levels for early detection of asthma exacerbations that allow timely intervention in patients with mild-to-moderate asthma. Subsequently, we aimed to validate the performance of the optimized APs in a similar but separate study population

Methods

We analysed asthma symptoms, morning PEFs, the occurrence of exacerbations and the use of prednisone using data from written daily diaries from two previous studies [10, 11]. The development dataset was obtained from a randomised controlled trial designed to compare the effects of 6 months of treatment with regular inhaled salbutamol, salmeterol or placebo [10]. The validation dataset was obtained from a single-blind placebo-controlled trial that explored the use of fractional exhaled nitric oxide (FeNO) to guide treatment in chronic asthma [11]. The follow-up period was 1 yr.

Subjects

There were 165 patients in the development dataset and 94 in the validation dataset, all with stable mild-to-moderate chronic asthma [10, 11].

Daily diaries

In both studies, daily diary recordings included symptoms of daytime and night-time chest tightness/wheeze/dyspnoea, cough, sputum production, exercise impairment, and either appearance of or increased frequency of nocturnal awakening. All were scored on a 0–3 scale or by a yes/no response where appropriate. The best of three PEF measurements was also recorded each morning and evening. Missing data were interpolated using the mean of the recordings from the previous and following days.

Exacerbations

Exacerbations were defined in both studies using a composite daily asthma score. The scoring criteria were similar between the two studies, but differed regarding the use of a β -agonist ‘reliever’ and nocturnal awakening (table 5.1 in Taylor et al. [10] and table 5.2 in Smith et al. [11]). In brief, major exacerbations were defined as a visit to the emergency department, a PEF <40% personal best (pb) for ≥ 1 day, a PEF <60% pb for ≥ 2 days plus an increase in symptoms, or a PEF <60% pb for ≥ 1 day and PEF <75% pb for ≥ 2 days with an increase in symptoms.

During the study, courses of prednisone were administered in response to deteriorating symptoms and/or peak flows, or at the discretion of patients or clinicians independently of diary data. Prednisone use for ≥ 3 days is widely used as a definition for exacerbations [4]. Therefore, as a sensitivity analysis, we also assessed the predictive utility of APs using this alternative definition

Table 5.1. Baseline characteristics of patients in the two studies.

	Development Dataset [10]	Validation Dataset [11]
Number of patients (n)	164	94
Mean age (years)	38 (range 18-64)	44 (range 12-73)
Sex	Male = 73 (45%) Female = 91 (55%)	Male = 35 (37%) Female = 59 (63%)
Taking regular inhaled corticosteroids (%)*		
None	8%	0%
1-400 μ g/day	34%	53%
401-1000 μ g/day	36%	45%
>1000 μ g/day	22%	2%
Mean symptom score during run-in period (maximum = 6.0)	0.55 (range 0-2.06)	0.56 (range 0-2.65)
Mean personal best PEF during run-in (l/min)	508 (range 305-755)	448 (range 230-705)

* Beclomethasone equivalent.

Action points

A range of pre-specified APs was evaluated. For symptoms, we assessed APs used in currently recommended WAAPs: the occurrence of nocturnal awakening or the appearance of any symptoms [2, 3, 6, 9]. Additionally, we evaluated APs based on QCA of symptoms using standard deviations from the mean symptom score during run-in for each patient. To this end, we developed a composite daily symptom score (range 0–6), which combined all daily recorded individual symptoms and ‘reliever’ β -agonist use, with higher scores representing more severe symptoms (table 5.5a,b in this Article’s Supplement). The mean score and its standard deviation were determined per patient during the run-in period when asthma was well controlled. Subsequently, occasions characterised by deviation from the mean by more than one, two or three standard deviations were evaluated as potential APs. In patients without any symptoms during the run-in, the mean symptom score and standard deviation was 0. In these cases, the one, two and three standard deviation thresholds were set at 0.17, 0.34 and 0.50, respectively, representing the minimal possible changes in composite symptom score.

For PEF, the APs were derived from percentages of personal best morning PEF measurement obtained during the run-in period (% pb), or QCA based on the approach outlined by Gibson et al. [7] and Gibson and Powell [8]. We also analysed whether combining PEF and symptoms as a composite AP might perform better, since using single outliers of PEF or symptoms alone might result in relatively high false positive rates for exacerbation prediction. Therefore, we assessed whether a combination of symptom and PEF thresholds were reached on the same day, and also within a 1-week time window. Finally, we assessed the performance of the APs currently recommended by the NHLBI, which are based on both symptoms and PEF (‘yellow zone’) [2]. As it is not clear whether reaching the threshold for either symptoms or PEF alone is sufficient or both are required, we analysed both options.

For each patient, every week in the diary recordings was coded as either a ‘stable week’, when no exacerbation occurred, or ‘pre-exacerbation week’ for the week prior to an exacerbation. For all stable and pre-exacerbation weeks, we assessed whether the AP(s) either predicted a future exacerbation (when one or more of the daily recordings in that week fulfilled criteria for that specified AP), or predicted that a future exacerbation would not occur (when daily recording(s) did not reach the defined thresholds) (figure 5.1).

Analysis

All analyses were performed with STATA (release 11; StataCorp, College Station, TX, USA). Contingency tables for each AP threshold were constructed to calculate performance characteristics including sensitivity, specificity, accuracy and area under the receiver operating characteristic (AUC) curve for predicting an exacerbation. In addition, for each AP threshold we assessed the (potential) number needed to treat (NNT) in order to

prevent one exacerbation, given a hypothetical perfect treatment and early detection, defined as the number of days before the onset of an exacerbation the AP was reached for the first time in a pre-exacerbation week. NNT was calculated by dividing the total number of times an AP was reached (true positives and false positives) by the number of times it accurately predicted a future exacerbation (true positives).

The APs that performed optimally were grouped within four categories: 1) symptoms solely; 2) PEF solely; 3) symptoms and PEF on the same day; and 4) symptoms and PEF within 1 week prior to an exacerbation, using the development dataset. Optimal performance was defined as a sensitivity of $\geq 75\%$ combined with the best trade-off between early detection and potential NNT. To determine this outcome, we plotted the number of days on which an exacerbation was predicted before its occurrence against the NNT for a series of different APs (figure 5.2).

To assess the external validity of the optimal APs derived from the development dataset, their performance was assessed and compared with several published APs using the validation dataset [11].

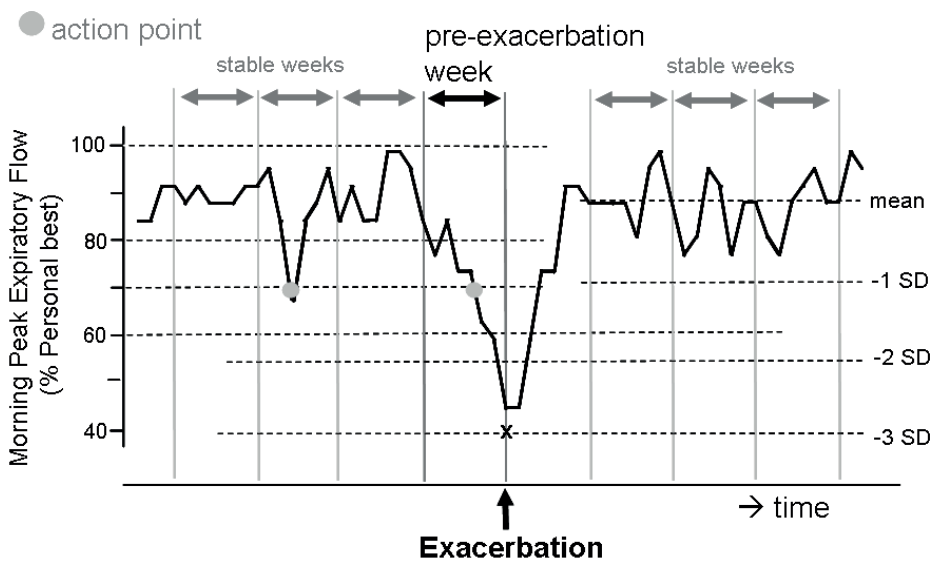


Figure 5.1. The use of action points in an 8-week peak flow chart with an exacerbation at the half-way point. The dotted lines indicate the thresholds of potential action points, on the left based on % of personal best (pb) peak expiratory flow (PEF), and on the right based on individual standard deviations for PEF. The observation period is divided into weeks before and during the exacerbation, and weeks of normal control, respectively coded as pre-exacerbation weeks and stable weeks. In this example, we have highlighted the action points PEF 70% pb and PEF -3 SD. The action point PEF 70% pb is reached twice, once as a false positive in a stable week and once accurately 2 days before the exacerbation in the pre-exacerbation week. The action point PEF -3 SD is never reached in this example, representing a false negative prediction for the pre-exacerbation week (marked X).

Results

The development dataset consisted of daily recordings from 164 patients. 88 exacerbations, defined using diary data, occurred during 18 months of follow-up. Exacerbations occurred in 39 different patients, a mean rate 1.8 per patient per year, ranging from 1 to 13. 147 exacerbations, defined as the use of a course of oral prednisone, occurred during the follow-up interval.

In the validation dataset, 94 patients provided daily recordings. 22 exacerbations occurred. Exacerbations occurred in 17 patients and the mean rate was 1.5 per patient per year (range 1 to 5). Oral prednisone was used on 75 occasions.

The characteristics of patients from both studies are listed in table 5.1.

Action points

The performance of 25 potential APs was analysed (a complete overview of results is presented in tables 5.4a–d of the Supplement). Six APs were based on symptoms, eight on PEF, nine on combinations of symptoms and PEF on the same day, and two on combinations of symptoms and PEF within 1 week. In general, APs based on standard deviations of symptom scores performed better than pre-defined absolute levels of symptoms. This judgment was based on lower NNTs for the former approach. PEF using % pb resulted in considerably lower NNTs than using standard deviations.

The optimal symptom AP was a score that increased by more than two standard deviations more than the run-in mean, and this detected exacerbations 2.9 days before occurrence with 88.5% sensitivity, 86.3% specificity and a NNT of 24. For PEF, the optimally performing AP was a PEF <60% pb, which is also currently proposed by the BTS as the threshold for commencing oral prednisone treatment [5]. It had a sensitivity of 78.2%, specificity of 98.7% and a NNT of 3. However, it detected exacerbations only 1 day before their occurrence. The optimal combination (symptoms and PEF) comprised a symptom score increase of more than two standard deviations plus PEF decrease to <70% pb. This combination detected exacerbations 1.4 days before their occurrence with 80.5% sensitivity, 98.3% specificity and a NNT of 4. Within a 1-week window, this symptom–PEF combination detected exacerbations 4.1 days (mean) before their occurrence with a sensitivity of 85.1%, specificity of 97.2% and a NNT of 6 (table 5.2).

The performance characteristics of optimal APs in the validation dataset are presented in table 5.3. In general, the sensitivities for each of the optimal APs differed somewhat from those obtained using the developmental dataset, whereas specificities remained similar. For each optimal AP, the number of days before the onset of an exacerbation at which the AP predicted future exacerbations was better in the validation dataset, *i.e.* between 0.4 and 1.0 day earlier.

For both versions of the AP recommended by the NHLBI, the combination of 'appearance of any symptoms' plus PEF <80% pb performed best (table 5.3). It detected exacerbations 4.9 days before onset, with a sensitivity of 100% and specificity of 86.8%. However, the NNT is 43, whereas it is 12 for the optimal AP from the development dataset (figure 5.2).

Table 5.2. Performance characteristics in the development dataset of the optimal action points per category.

Action point category and optimal criteria	Definition of exacerbation	Early Detection (days)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	NNT
<i>Symptoms (>2SD)</i>	Symptoms PEFs	2.9	88.5	86.3	86.3	0.87	24
	Use of prednisone	2.7	76.9	86.6	86.5	0.82	17
<i>PEF (<70% pb)</i>	Symptoms PEFs	2.9	90.8	93.9	93.9	0.92	11
	Use of prednisone	2.6	61.2	93.9	93.5	0.78	10
<i>PEF (<60% pb)*</i>	Symptoms PEFs	1.0	78.2	98.7	98.6	0.88	3
	Use of prednisone	1.2	38.1	98.7	98.0	0.68	4
<i>Symptoms + PEF: same day†</i>	Symptoms PEFs	1.4	80.5	98.3	98.2	0.89	4
	Use of prednisone	1.4	47.6	98.3	97.7	0.72	4
<i>Symptoms + PEF: within 1 week†</i>	Symptoms PEFs	4.1	85.1	97.2	97.1	0.91	6
	Use of prednisone	3.5	54.4	97.2	96.7	0.76	5

Early Detection is a description of how many days before the onset of an exacerbation this action point will predict the future occurrence of the event. It was assessed by calculating the mean number of days that this action point's thresholds were reached for the first time in the week preceding the exacerbation, from all predicted exacerbations.

Sensitivity, specificity and accuracy refer to this action point's ability to correctly predict an exacerbation and how often exacerbations are missed or falsely predicted.

AUC is a measure of the overall accuracy of a prediction, with 1.0 representing a perfect prediction with 100% sensitivity and 100% specificity, and 0.5 representing a random guess and therefore the model has no predictive properties. In general, AUC values of less than 0.7 do not have clinical significance.

NNT is the number of times this action point is positive per predicted exacerbation. It is a measure of how often an intervention is applied unnecessarily to prevent one exacerbation.

‡ For Symptoms and PEF on the same day the optimal combination consisted of a composite symptom score >2SDs of the mean *plus* PEF <70% of personal best

† For Symptoms and PEF within one week the optimal combination consisted of a composite symptom score >2SDs of the run-in mean *plus* PEF <70% of personal best, with a seven day time window being allowed for either threshold to become positive.

* Action Point advised by the British Thoracic Society [5]

Table 5.3 Performance characteristics in the validation dataset of optimal action points derived from the development dataset and of the NHLBI action point [2].

Action point category and optimal criteria	Definition of exacerbation	Early Detection (days)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	NNT
<i>Symptoms (>2SD)</i>	Symptoms PEFs	3.3	75.0	86.2	86.2	0.81	59
	Use of prednisone	4.1	60.0	86.9	86.6	0.73	19
<i>PEF (<70%pb)</i>	Symptoms PEFs	4.2	100	92.5	92.6	0.96	24
	Use of prednisone	3.6	53.3	93.0	92.5	0.73	12
<i>PEF (<60% pb) *</i>	Symptoms PEFs	1.8	100	97.6	97.6	0.99	8
	Use of prednisone	2.3	18.7	97.5	96.6	0.55	12
<i>Symptoms + PEF: same day</i>	Symptoms PEFs	1.7	75.0	98.3	98.2	0.87	8
	Use of prednisone	2.1	29.3	98.5	97.6	0.64	5
<i>Symptoms + PEF: within 1 week</i>	Symptoms PEFs	5.1	75.0	97.4	97.3	0.86	12
	Use of prednisone	4.8	33.3	97.6	96.8	0.65	7
<i>NHLBI criteria changes in Symptoms AND in PEF†</i>	Symptoms PEFs	4.9	100	86.8	86.9	0.93	43
	Use of prednisone	4.0	70.7	87.5	87.3	0.79	16
<i>NHLBI criteria changes in symptoms OR in PEF†</i>	Symptoms PEFs	6.5	100	47.5	47.6	0.74	176
	Use of prednisone	6.1	100	48.2	48.8	0.74	46

Descriptions are similar to the ones provided below Table 5.2

* Action point advised by the British Thoracic Society [5]

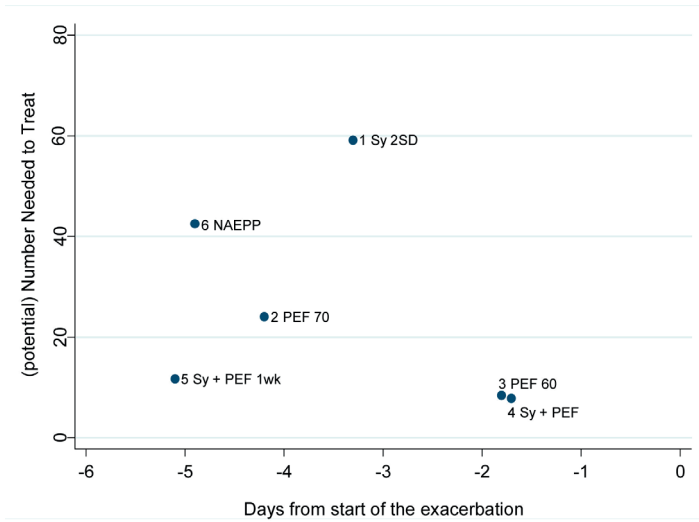
Since the NHLBI action point can be interpreted in two ways, we provided both: † appearance of any symptoms plus PEF <80% pb; ‡ appearance of any symptoms or a PEF <80%.

The comparable data using the alternative definition of ‘use of oral prednisone’ are also reported in tables 5.2 and 5.3, and tables 5.4a–d in this article’s Supplement. In general, sensitivities were considerably lower, overall accuracies were similar, early diagnosis was slightly later, but the NNTs were better.

Discussion

The present study provides the most comprehensive data to date of the performance characteristics of a range of symptom and/or PEF thresholds at which patients might intervene to abort an asthma exacerbation or to reduce its severity. For symptoms, a change of more than two standard deviations in a composite symptom score provided optimum outcomes. For PEFs, a decrease to <60% pb was optimal. However, an AP based on a combination of changes in symptom score (more than two standard deviations) and PEF (<70% pb) occurring during a 1-week period performed even better. This combination predicted exacerbations 5 days before their occurrence, thus allowing sufficient time to intervene, whilst the NNT remained low.

A



B

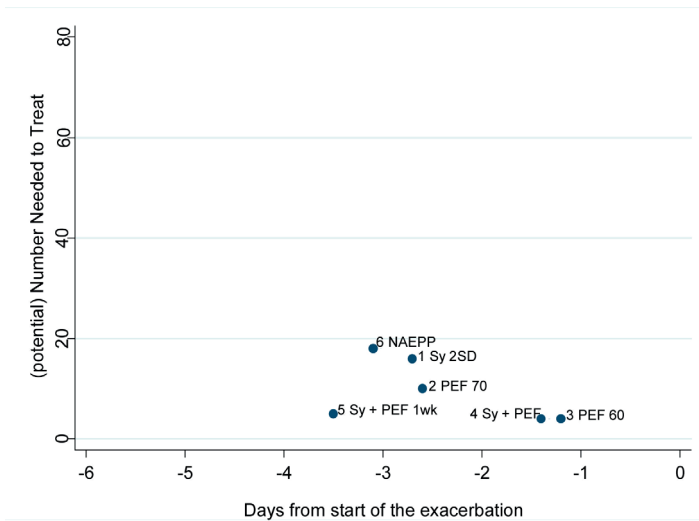
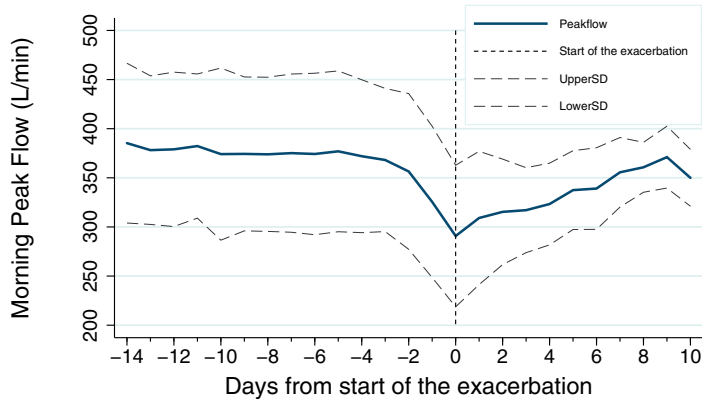
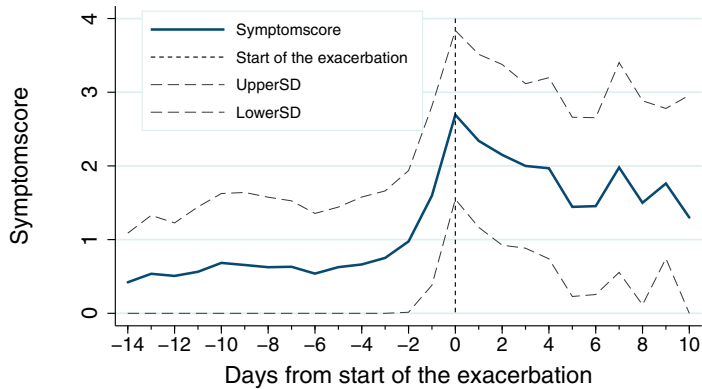


Figure 5.2 a, b. The number of days that the exacerbation is predicted before its occurrence is plotted against the (potential) number needed to treat (NNT) in order to prevent one exacerbation, for a series of different action points. The lower left corner represents the optimal action point, i.e. early prediction and low NNT. a) Exacerbations are defined using the definition described in the Methods section. b) Exacerbations are defined as a “use of oral prednisone”. Action point 1: symptoms (Sy) 2 SD; 2: peak expiratory flow (PEF) 70% personal best (pb); 3: PEF 60% pb; 4: Sy 2 SD + PEF 70% pb; 5: Sy 2 SD + PEF 70% pb within 1 week; 6: National Heart Lung and Blood Institute (NHLBI). a) and b) similar results are shown, although the differences are larger in a). Action points 3, 4 and 5 perform similarly, with a slight increase in NNT for each day the exacerbation is diagnosed earlier. The optimum depends on the trade-off between NNT and early detection. To allow sufficient time to successfully intervene, we opted for number 5. Action points 1, 2 and 6 perform considerably worse, due to the high NNTs.

A



B



Figures 5.3a and 3b. Changes in PEF (a) and symptom scores (b) from day -14 to day +10 before and after an exacerbation, using the mean PEF and symptom score data from each exacerbation in the development dataset.

Previously, in a Cochrane review, Powell and Gibson [12] compared the use of WAAPs based on symptoms with those based on PEF [12]. Results showed that these were equivalent with regard to outcomes, *i.e.* hospitalisations or unscheduled doctor visits. Our data indicate that combining symptoms and PEFs provide added value. Clearly, it is not practical for patients to do the necessary calculations and therefore, in practice, an AP based solely on PEF <60% pb might be optimal. Nevertheless, with the advent of internet-based applications ('Apps'), the use of seemingly complex APs is now feasible [13]. Although compliance with paper diary recordings is generally poor [14], such an approach is feasible with electronic recordings [15] and is of particular relevance in patients with difficult or brittle asthma.

The fact that a 'both/and' combination of symptoms and PEF performed better than single APs is not surprising. Even with good asthma control, symptoms and PEFs may

vary discordantly, and one of these parameters may change in isolation, especially in 'poor perceivers'. APs with threshold levels based solely on either symptoms or PEF are susceptible to these variations. Using a more stringent threshold, such as PEF <60% pb, can solve this issue, but has the disadvantage of late detection of an imminent exacerbation. Therefore, using a 1-week window for the symptoms plus PEF provided the best AP as it detected exacerbations 5.1 days before occurrence, at only a slight cost in specificity and NNT. To assess whether symptoms or PEF drive earlier detection using the AP with a one week time window, we performed a subgroup analysis of the 74 predicted exacerbations. There was no consistent pattern as to whether changes in symptoms preceded PEFs or *vice versa*. Symptoms occurred earlier in 25 subjects, the threshold for PEF changes was reached earlier in 23, and in 26 there was no discordance.

Previously, Gibson et al. [7] analysed nine different APs and showed that QCA of daily PEFs performs better than percentages of personal best PEF (in contrast to the present data) or percentage predicted of PEF. Gibson et al. [7] reported that the optimal QCA AP detected 91% of exacerbations and falsely predicted an exacerbation in 23% of periods of normal control. Tattersfield et al. [16] analysed the false positive rate of APs based on the median values of PEF and symptoms at 2 days before the start of an exacerbation. They found a false-positive rate of 6.4% using the advent of night-time symptoms, 26% for morning PEF and 30% for daytime symptoms. Thamrin et al. [17] analysed daily fluctuations in PEF and, by calculating conditional probabilities of future decreases in lung function, predicted the risk of exacerbations with a sensitivity of 68.8% and specificity of 67.4%. The AUC was 0.85, which is only slightly lower than AUCs of most optimal APs in this study [17].

The time course of changes in symptoms and PEF that constitute an asthma exacerbation is important in determining the optimum time for intervention. If changes can only be identified after the time at which intervention is likely to be effective, then the rationale for using WAAPs would be weak. Previous data suggest that symptoms and PEF start declining 5–10 days before exacerbations [16, 18]. The changes in PEFs and symptom scores associated with exacerbations in our patients are illustrated in figure 5.3a and b. Based on these findings, we systematically analysed the 7-day period preceding exacerbations. We found that changes in the optimal APs occurred between 1.7 and 5.1 days before the defined onset of an exacerbation (table 5.S4). The onset of action of systemic corticosteroid is within 12–24 h, and so the APs would be reached in sufficient time to allow for steroids to have a modifying effect. The effectiveness of quadrupling the dose of inhaled corticosteroids was recently investigated by Osborne et al. [19], and might have resulted in greater clinical benefits if commenced at the times calculated to be optimal in our study

Our study has several possible limitations. First, we selected criteria for acceptable sensitivity and specificity (see Statistical analysis section), as we aimed to balance early detection of exacerbations against potential overdiagnosis. Secondly, the composite symptom score(s) used in the two studies were not externally validated. It is not certain whether applying QCA to alternative scoring systems such as the Asthma Control Questionnaire or the Asthma Control Test would give similar results [20, 21]. However, given the overall similarity between results using both of our datasets, there is reason to believe that QCA is a valid approach to optimising APs independently of the exact scoring system used. Thirdly, APs were based on parameters that were incorporated in the definition of an exacerbation. Our study was not designed to be explanatory but rather to model predictive performance, and as such is methodologically sound. Our definition of major exacerbations, *i.e.* either emergency room visits or changes in PEF plus symptoms for ≥ 2 days, is in accordance with recent criteria for severe exacerbations [4]. Furthermore, in modified forms, our definition has been used in several previous studies [10, 11, 22, 23]. However, accepting that the definition of an exacerbation is important in the interpretation of our data, we performed additional analyses using 'use of oral prednisone' as the definition of an exacerbation (tables 5.2 and 5.3 and table 5.4 of the Supplement). The order of optimal APs was similar with regard to early detection and NNT (fig. 5.2b). Using this definition, the sensitivity to detect exacerbations was considerably lower when using PEF either solely or in combination with symptoms, whereas it was only slightly lower using symptoms alone (table 5.4). This implies that the decision to administer prednisone depended more on symptoms than on PEF. Given that the sensitivity was $<75\%$, and the NNT was high, we concluded that the analysed APs did not perform well enough to predict exacerbations defined as 'use of oral prednisone'. Such events were generally less severe than the exacerbations defined *a priori* using composite symptom scores and PEFs. It is therefore arguable that our APs performed well in predicting events of higher severity and in which earlier intervention is clinically desirable.

In conclusion, the optimal AP for the early detection of asthma exacerbations consists of a greater than two standard deviations increase in a composite symptom score and a fall in PEF to $<70\%$ pb, occurring within a 1-week window. With the advent of handheld computer technology, there is potential to use these criteria more readily in day-to-day practice, and thus reduce the impact of exacerbations, particularly in patients with a history of frequent exacerbations. Prospective studies or further analyses using other published datasets should be carried out to confirm the present findings, and together they should be used to revise and improve the empirical recommendations offered in current guidelines.

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Supplement Tables

Table 5.4a. Performance characteristics of all action points based solely on Symptoms.

The action point 'nocturnal awakening' was considered positive whenever a patient had awoken due to asthma symptoms; 'appearance of any symptoms' was positive whenever a patient had experienced any breakthrough symptoms; 'severe symptoms' whenever the composite symptom score was two or more, or yes in case of nocturnal awakening. The action points based on SD are positive whenever the result of a composite symptom score was higher than respectively 1, 2, or 3 standard deviations from a mean symptom score calculated from data obtained during the run in period.

Action point criteria	Definition of exacerbation	Early diagnosis (days)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	NNT
<i>Nocturnal awakening</i>	Symptoms PEFs	2.5	83.9	86.3	86.3	0.85	26
	Use of prednisone	2.6	77.6	86.7	86.6	0.82	16
<i>Appearance of any symptoms</i>	Symptoms PEFs	5.4	100	42.0	42.4	0.71	94
	Use of prednisone	5.2	97.7	42.3	42.9	0.70	57
<i>Severe symptoms</i>	Symptoms PEFs	3.0	90.8	79.5	79.6	0.85	36
	Use of prednisone	3.2	91.2	79.9	80.0	0.86	21
<i>Symptom score >1SD</i>	Symptoms PEFs	3.6	95.4	77.3	77.4	0.86	38
	Use of prednisone	3.4	91.8	77.7	77.8	0.85	23
<i>Symptom score >2SD</i>	Symptoms PEFs	2.9	88.5	86.3	86.3	0.87	24
	Use of prednisone	2.7	76.9	86.6	86.5	0.82	17
<i>Symptom score >3SD</i>	Symptoms PEFs	2.7	74.7	90.9	90.8	0.83	19
	Use of prednisone	2.6	61.9	91.1	90.8	0.77	14

Table 5.4b. Performance characteristics of action points based solely on Peak Flow.

'PEF 2 days 85% of personal best' was considered positive whenever PEF was lower than 85% of the personal best PEF on two consecutive days; 'PEF % of personal best' whenever PEF was lower than the designated percentage of that patients personal best PEF score; 'PEF SD' whenever PEF was lower than respectively 1, 2, or 3 standard deviations from the mean PEF obtained during the run in period.

Action point criteria	Definition of exacerbation	Early diagnosis (days)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	NNT
<i>PEF 85% pb on 2 consecutive days</i>	Symptoms PEFs	4.4	87.4	78.8	78.8	0.83	38
	Use of prednisone	3.7	82.3	79.0	79.1	0.81	24
<i>PEF <80% pb</i>	Symptoms PEFs	4.4	94.3	80.4	80.5	0.87	33
	Use of prednisone	3.5	87.1	80.6	80.7	0.84	21
<i>PEF <70% pb</i>	Symptoms PEFs	2.9	90.8	93.9	93.9	0.92	11
	Use of prednisone	2.6	61.2	93.9	93.5	0.78	10
<i>PEF <60% pb</i>	Symptoms PEFs	1.0	78.2	98.7	98.6	0.88	3
	Use of prednisone	1.2	38.1	98.7	98.0	0.68	4
<i>PEF <1SD</i>	Symptoms PEFs	4.4	95.4	71.3	71.4	0.83	49
	Use of prednisone	3.7	87.1	71.5	71.6	0.79	32
<i>PEF <2SD</i>	Symptoms PEFs	3.3	89.7	85.3	85.3	0.87	26
	Use of prednisone	2.5	76.9	85.5	85.4	0.81	18
<i>PEF <3SD</i>	Symptoms PEFs	2.7	70.1	92.6	92.5	0.81	17
	Use of prednisone	2.6	54.4	92.8	92.3	0.74	13

Table 5.4c. Performance characteristics of all action points that combined thresholds for both Symptoms and PEF, where *both* thresholds were reached on the same day. For example 'symptoms 1SD and PEF 80%' was positive whenever the composite symptom score was higher than 1 standard deviation from the mean symptom score and PEF was lower than 80% of that patients personal best. For a further description see table 4a and 4b.

Action point criteria	Definition of exacerbation	Early diagnosis (days)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	NNT
<i>Symptoms >1SD and PEF <80% pb</i>	Symptoms PEFs	2.6	89.7	92.1	92.1	0.91	14
	Use of prednisone	2.3	77.6	92.4	92.2	0.85	10
<i>Symptoms >2SD and PEF <70% pb</i>	Symptoms PEFs	1.4	80.5	98.3	98.2	0.89	4
	Use of prednisone	1.4	47.6	98.3	97.7	0.72	4
<i>Symptoms >2SD and PEF <60% pb</i>	Symptoms PEFs	0.3	67.8	99.6	99.4	0.84	2
	Use of prednisone	0.5	30.6	99.5	98.7	0.65	2
<i>Symptoms >3SD and PEF 60% pb</i>	Symptoms PEFs	0.3	55.2	99.8	99.5	0.77	2
	Use of prednisone	0.5	23.1	99.7	98.8	0.61	2
<i>Appearance of symptoms and PEF <80% (NAEPP)</i>	Symptoms PEFs	3.9	94.3	83.3	83.4	0.89	28
	Use of prednisone	3.1	85.0	83.5	83.6	0.84	18
<i>Appearance of symptoms and PEF <70% pb</i>	Symptoms PEFs	2.7	90.8	94.4	94.4	0.93	10
	Use of prednisone	2.4	60.5	94.4	94.1	0.78	9
<i>Appearance of severe symptoms and PEF <70% pb</i>	Symptoms PEFs	1.6	81.6	97.4	97.3	0.90	6
	Use of prednisone	1.6	51.0	97.5	97.0	0.74	5
<i>Nocturnal awakening and PEF <70% pb</i>	Symptoms PEFs	1.3	75.9	98.1	97.9	0.87	5
	Use of prednisone	1.2	44.2	98.1	97.5	0.71	5
<i>Symptoms >1SD and PEF >1SD</i>	Symptoms PEFs	2.6	92.0	89.0	89.0	0.90	19
	Use of prednisone	2.7	75.5	89.2	89.1	0.82	14
<i>Symptoms >2SD and PEF >2SD</i>	Symptoms PEFs	1.8	81.6	95.5	95.4	0.89	9
	Use of prednisone	1.8	60.5	95.6	95.2	0.78	7
<i>Symptoms >3SD and PEF >3SD</i>	Symptoms PEFs	1.7	56.3	97.9	97.7	0.77	6
	Use of prednisone	2.1	41.5	98.0	97.4	0.70	5

Table 5.4d. Performance characteristics of action points that used a Time Window for thresholds of Symptoms and PEF. For example '7 day timeframe 2SD symptoms, 70% personal best PEF' was positive whenever the composite symptom score was higher than two standard deviations above the mean symptom score on a certain day and the PEF result was lower than 70% of that patients personal best PEF on that day, or on any of the preceding or following seven days.

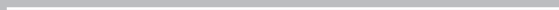
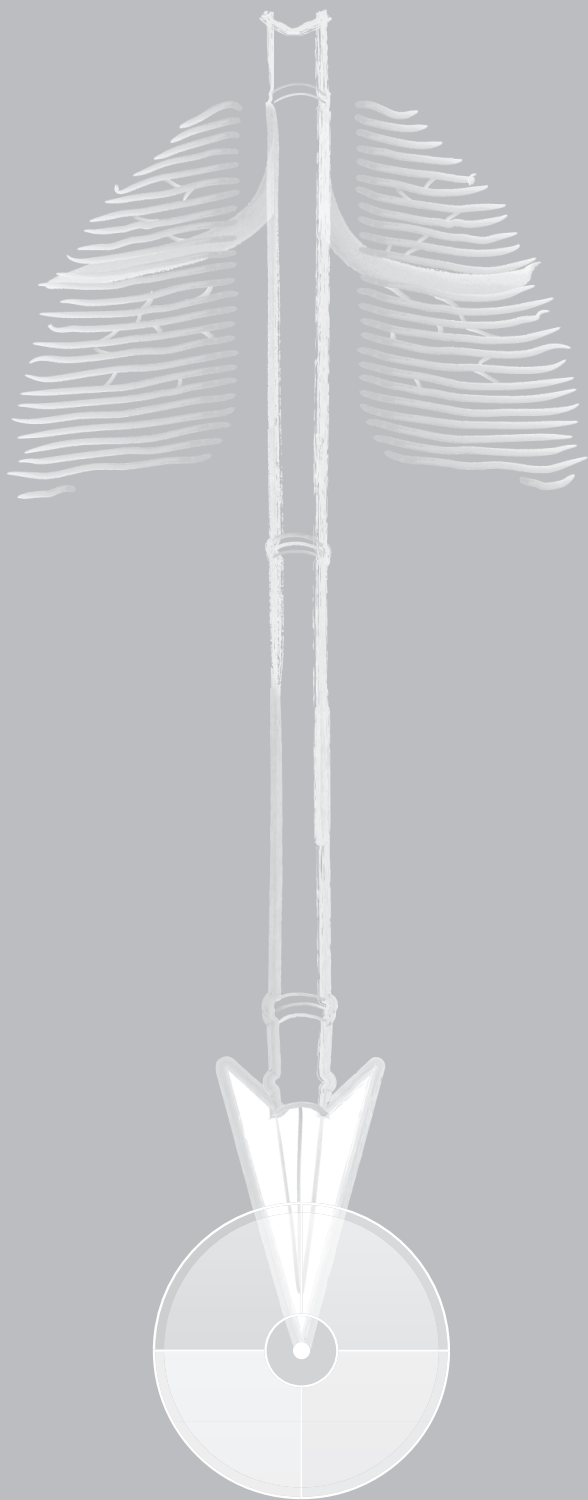
TIME WINDOW							
Action point criteria	Definition of exacerbation	Early diagnosis (days)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	NNT
3 day timeframe	Symptoms PEFs	3.4	81.6	97.7	97.6	0.90	5
Symptoms 2SD PEF <70% pb	Use of prednisone	2.6	51.0	97.6	97.1	0.74	5
7 day timeframe	Symptoms PEFs	4.1	85.1	97.2	97.1	0.91	6
Symptoms 2SD PEF <70% pb	Use of prednisone	3.5	54.4	97.2	96.7	0.76	5

Table 5.5a. Symptom score used in developmental dataset [8]. Each symptom was scored between 0 and 1. Zero meant that symptom was not experienced, and 1 was the maximum score for that symptom. For symptoms scored between 0-3, i.e. chest tightness, we adjusted results (0=0, 1=0.33, 2=0.66, 3=1). B2-usage was scored as 0 when no 'reliever' medication was used; 0.16 for 1 or 2 puffs; 0.33 for 3 or 4; 0.5 for 5-8; 0.66 for 9-12; 0.83 for 13-16; and 1 for >16 uses of reliever medication per day. Nocturnal awakening scored 0 if it had not occurred that day and 1 if the patient had awoken due to symptoms.

Symptom	Score
Morning and evening chest tightness	0-1
Morning and evening cough	0-1
Nocturnal awakening	0-1
Sputum production	0-1
Exercise limitations	0-1
B2-usage	0-1
Total daily composite symptom score	0-6

Table 5.5b. Symptom score in the validation dataset [9]. Symptoms were scored between 0-5. 0 = no symptoms, 1 = symptoms for one short period, 2 = symptoms for two or more short periods, 3 = symptoms most of the time that did not affect normal daily activities, 4 = symptoms most of the time that did affect normal daily activities, and 5 = symptoms so severe as to disrupt daily activities. This score between 0 and 5 was recalculated between 0-3 (i.e. 0=0, 1=0.6, 2=1.2, 3=1.8, 4=2.4, 5=3). Nocturnal awakening and B2-usage were scored similarly as in the development dataset (see description Table 5a).

Symptom	Score
Limitations and symptoms	0-3
Nocturnal awakening	0-1
B2-usage	0-1
Total daily composite symptom score	0-5



Chapter 6

Comparison between an online self-administered and an interviewer-administered version of the Asthma Control Questionnaire: a cross-sectional validation study

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Abstract

Background Online self-management programmes for asthma have recently become available. International guidelines suggest that the Asthma Control Questionnaire (ACQ) can be used in these programmes. In order to assess the current level of control and guide therapy, the same cut-off values are being used as in conventional asthma management. However, results might differ between different types of administration of the ACQ.

Aims To assess the agreement between an online self-administered version of the ACQ and an interviewer-administered version at a routine visit.

Methods Cross-sectional data from primary care asthma patients in the Asthma Control Cost Utility Randomised Trial Evaluation (ACCURATE) trial aged 18–50 years and prescribed inhaled steroids were analysed. We selected patients who self-administered an ACQ online and subsequently had an ACQ completed by a nurse practitioner within 7 days at a trial-related control visit. ACQ scores were calculated and agreement assessed by paired t-tests, Pearson's correlation coefficient and a Bland-Altman plot.

Results A total of 351 patients were eligible (68% female, mean age 40 years). The time interval between the two versions was 3.2 days. There was a significant difference of 0.14 (95% CI 0.09 to 0.20; $p < 0.001$) between the results of the online self-administered ACQ (mean 1.04 ± 0.04) and the interviewer-administered ACQ results (0.90 ± 0.04). The Pearson correlation coefficient was 0.79. The limits of agreement ($-0.86, 1.14$) exceeded the predefined minimal clinically important difference between results (± 0.5). The Bland-Altman plot therefore showed insufficient agreement.

Conclusions Assessment of asthma control by the ACQ is influenced by the type of administration. Our results suggest that better control of asthma is perceived when interacting with a caregiver than by online self-assessment.

Introduction

Online monitoring of asthma symptoms provides an opportunity of optimising patient-centred daily control. Online self-management programmes have therefore been developed which offer similar questionnaires to those being used in daily practice for assessment of asthma control. This policy is advocated in current guidelines which state that composite symptom scores such as the Asthma Control Questionnaire (ACQ) can be used in different settings by both patients and care providers to assess current asthma control [1-4].⁴ As a consequence, even though the ACQ was originally developed and validated for guided self-administration, it is now administered in a variety of ways — for example, in self-management plans using pen and paper or internet applications [5,6], self-administered but under guidance of a professional during regular control visits, or interviewer-administered by a practice nurse (PN), general practitioner or chest physician based on patients' responses [1-3]. Recent studies did not show statistically significant differences between paper and electronic versions of the ACQ [7] or between a postal-administered version and a version under guidance of a healthcare professional [8]. However, little is known about the agreement between online self-administered and interviewer-administered versions of the ACQ.

The aim of this study was to assess the agreement between an online self-administered version of the ACQ and an interviewer-administered ACQ by a PN during a routine control visit in adults with asthma.

Methods

Patients

The ACQ results of patients collected in the Asthma Control Cost Utility Randomised Trial Evaluation (ACCURATE) trial were used [9]. The trial was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands, and compares three different treatment strategies for asthma in primary care. Patients were included in the study if they were aged 18–50 years, had a doctor's diagnosis of asthma, and had received a prescription for inhaled corticosteroids in the previous year. Patients were excluded if they suffered from significant co-morbidity, if they were unable to understand written or oral Dutch instructions, or if they had been prescribed oral corticosteroids in the previous month.

Observations

In the ACCURATE trial, patients visited the general practice where ACQs were administered by a PN (interviewer-administered ACQ). Appointments were scheduled at approximately three-monthly intervals at a convenient time for both practices and participants. In addition, patients completed online questionnaires monthly at home, including the ACQ (online self-administered ACQ). Since the time between completion of the two versions of the ACQ was variable, we only selected observations from patients who self-administered an ACQ online and subsequently visited the PN for a trial-related control visit within 7 days. This time window was selected because it lies well within the advised range of 2–14 days for assessing reproducibility of instruments [10]. We excluded measurements where online self-administered ACQs were completed after the visit to the PN because trial-related medication changes might influence asthma control. We used a cross-sectional design to ensure that each participant was included only once.

Asthma Control Questionnaire (ACQ)

The ACQ consists of six questions on symptoms and one on pre-bronchodilator percentage predicted forced expiratory volume in one second (FEV₁% predicted). In the present study, FEV₁% predicted was assessed with a hand-held spirometer (PIKO-1) in the online self-administered ACQ and by routine spirometry in the interviewer-administered ACQ. In the online self-administered version, patients completed the questionnaire online at home without supervision, whereas in the interviewer-administered version the PN completed all questions based on patient responses. An overview of all methods of ACQ assessment is shown in Table 6.1. All questions were scored on a 7-point scale from 0 to 6 (where 0=good control, 6=poor control), and the composite ACQ7 score is the mean of the seven responses. The minimal important difference (MID) between results is 0.5 [11]. Current control of asthma was divided into three levels: controlled (ACQ <0.75); partly controlled (0.75 ≥ ACQ <1.5); uncontrolled (ACQ ≥ 1.5) [1,3].

Statistical analysis

Paired t-tests were used to assess whether there were systematic differences between online self-administered and interviewer-administered ACQ results. The strength of the relationship was assessed using Pearson correlation coefficients. A Bland-Altman plot was used to assess the agreement between the two versions. In order to interpret a Bland-Altman plot, a clinically significant difference had to be predefined and results agreed sufficiently if they remained within this limit [12]. In the present study the MID of 0.5 was used for this purpose.

Linear regression and correlation analysis were performed to assess whether the time between self-administered and interviewer-administered questionnaires, age of

Table 6.1. Different types of assessment of the Asthma Control Questionnaire

Types of assessment	Description
Pen & Paper self-administration	Filled out by patients themselves on a paper format
Postal administration	Filled out by patients themselves on a paper format, after it was sent to them by mail
Electronic administration	Filled out by patients themselves on a PDA electronic device
Online self-administration*	Filled out by patients themselves online using a link sent to them by email
Administration under guidance of a professional	Filled out by patients themselves at the office of a professional. Afterwards the professional discusses results with the patient
Interviewer-administration*	Filled out by professionals based on patients' responses on the different questions of the ACQ during an interview

* Used in the current study

participants, smoking behaviour, years of asthma history, or differences in sex between patients and PNs influenced ACQ results. All analyses were performed with STATA Version 11 (StataCorp LP).

Results

Of 611 patients participating in the ACCURATE trial, 351 visited the PN within one week after completion of the online questionnaire at home and were therefore eligible for the current analysis. Their mean age was 40.0 years, 68% were female, the mean inhaled corticosteroid dose was 861mcg beclomethasone equivalent, and 50% used a long-acting bronchodilator (Table 6.2). There was a statistically significant difference between the online self-administered (mean±SE 1.04±0.04, range 0–4.1) and interviewer-administered ACQ results (mean±SE 0.90±0.04, range 0–4.3) (difference 0.14; 95% CI 0.09 to 0.20; $p < 0.001$). The Pearson correlation coefficient was 0.79.

Table 6.2. Baseline characteristics of participants of the current study and a comparison with the baseline characteristics of non-participants of the current study out of the entire sample of 611 patients in the ACCURATE trial

	ACCURATE		
	Participants current study	Non-participants	p
Number of patients	n=351	n=260	
Interviewer-administered ACQ baseline	0.95 (95%ci 0.87-1.03)	0.99 (95% CI 0.88-1.09)	0.58
Mean age (in yr)	39.8 ± 9.2 (range 18-51)	39.5 ± 8.6 (range 18-50)	0.66
Gender, % female	68%	70%	0.69
Inhaled corticosteroid dose (mcg) *	849.3±38.8 (range 0-4000)	811.0±40.2 (range 0-4000)	0.51
Use of long-acting β-agonists (in %)	47.2%	52.5%	0.20

* in Beclomethasone equivalent

When comparing the level of control, in 23% of patients the online self-administered version indicated a worse current level of control than the interviewer-administered version. This would lead to a step-up in maintenance treatment if the online self-administered ACQ were to be used to guide treatment decisions, which would not occur with the interviewer-administered ACQ. In 6% of patients the level of control was better, potentially triggering a step-down in medication. Overall kappa was 0.54, indicating moderate agreement (see Table 6.3 and Figure 6.1).

Table 6.3: Comparison between the levels of control of the online self-administered and the interviewer administered ACQ-results.

ACQ Levels of control		Interviewer Administered		
		Controlled (n, %)	Partly Controlled (n, %)	Uncontrolled (n, %)
Online Self-Administered	Controlled	139 (39.6)	11 (3.1)	3 (0.8)
	Partly Controlled	49 (14.0)	62 (17.7)	8 (2.3)
	Uncontrolled	8 (2.3)	23 (6.5)	48 (13.7)

Kappa= 0.54, representing moderate agreement.

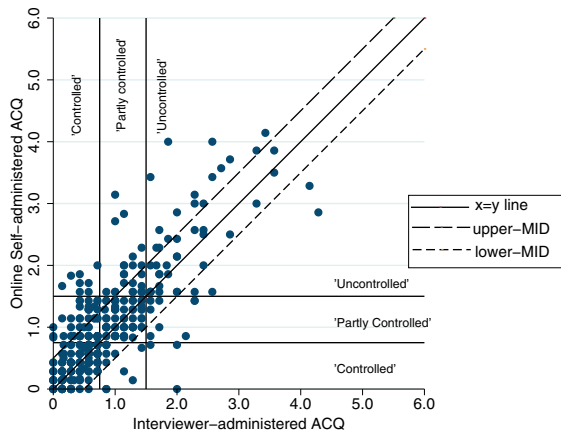


Figure 6.1. Results of online self-administered Asthma Control Questionnaire (ACQ) results plotted against the results of the interviewer-administered version. On the x=y line of identity the results are identical and they agree sufficiently when they lie within the upper and lower minimal important difference (MID=0.5). The three categories of current asthma control (controlled, partly controlled, and uncontrolled) are also depicted. Treatment decisions will differ if the asthma control category by the online self-administered and the interviewer-administered versions of the ACQ do not concur.

The Bland-Altman plot showed a mean difference of 0.14 between the two versions and the 95% limits of agreement (at $\pm 1.96SD$ from the mean) were at -0.86 and 1.14 points. Both limits of agreement were beyond the predefined acceptable difference of (-0.5) and therefore there was insufficient agreement between the two versions (Figure 6.2). Since the dispersion of the difference increased as the mean increased, we repeated the Bland-Altman analysis after log transformation and obtained similar results: mean log-transformed difference 0.16 (95% CI 0.10 to 0.22, $p < 0.001$), 95% limits of agreement -0.98 and 1.31 .

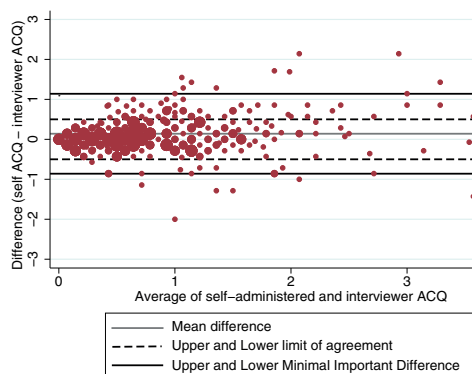


Figure 6.2. Bland Altman plot showing the average scores of the online self-administered and interviewer-administered ACQ plotted on the x-axis against the difference between both results on the y-axis. The mean difference between the versions was 0.14. The predefined limits of sufficient agreement between both versions were the minimal important difference (MID) at +0.5 and -0.5 (dotted lines). The limits of agreement (± 2 SD) are also shown at 1.14 and -0.86 (solid lines). Both limits of agreement lie outside the MID and therefore there is not sufficient agreement between both versions.

The difference between the two versions of the ACQ exceeded the MID of 0.5 in 25.1% of patients, of which 79.5% had a higher result in the online self-administered version and 20.5% in the interviewer-administered version. The differences were especially prominent in uncontrolled asthma. Furthermore, when questions in the ACQ were assessed separately, each question was significantly higher in the online self-administered version ($p < 0.03$), except the question on FEV1 % predicted which showed no significant difference ($p = 0.39$, Table 6.4).

The mean time between completion of the two versions of the ACQ was 3.2 days (95% CI 2.9 to 3.5). Linear regression and correlation analyses showed no significant association between the difference in ACQ scores and the time between visits (Pearson correlation coefficient (r)=0.03, $p = 0.54$), age of participants ($r = 0.02$, $p = 0.73$), smoking behaviour (yes or no) ($r = 0.06$, $p = 0.23$), history of allergy (yes or no) ($r = 0.03$, $p = 0.54$), years of asthma history ($r = 0.04$, $p = 0.52$), and sex differences between patient and healthcare professional ($r = 0.01$, $p = 0.81$).

Table 6.4: Comparison between results of the self-administered and interviewer-administered ACQ

	Online Self-administered	Interviewer-administered	Mean difference (95% CI)	P-value
Total ACQ score#	1.04	0.90	0.14 (0.09 to 0.20)	<0.001
ACQ Q1 (awoken)	0.61	0.50	0.11 (0.03 to 0.19)	0.01
ACQ Q2 (morning)	1.21	1.04	0.17 (0.08 to 0.26)	<0.001
ACQ Q3 (limitations)	1.04	0.93	0.11 (0.01 to 0.21)	0.03
ACQ Q4 (shortness of breath)	1.57	1.41	0.16 (0.05 to 0.26)	0.003
ACQ Q5 (wheeze)	0.97	0.78	0.19 (0.10 to 0.28)	<0.001
ACQ Q6 (B2-use†)	0.66	0.39	0.26 (0.19 to 0.34)	<0.001
ACQ Q7 FEV1 in % predicted	92.7	91.9	0.83 (-1.05 to 2.72)	0.39
in l/min	3.16	3.13	0.03 (-0.03 to 0.09)	0.35

The total score is the mean of all 7 questions divided by seven. Each individual ACQ question (Q1-Q7) ranges between 0 and 6.

† Use of short-acting beta-agonists

Discussion

Main findings

This study shows that the level of current asthma control is influenced by the type of administration of the instrument to assess control status. More severe symptoms were reported with the online self-administered questionnaire than with the interviewer-administered questionnaire by a PN based on patients' responses. This difference is of particular relevance due to the increasing use of questionnaires in clinical practice [13] and the appearance of online self-management programmes for asthma [5,6]. These programmes adjust therapy based on the same cut-off points of asthma control as those used in conventional asthma management, which may lead to different treatment advice in 29% (95% CI 24.6% to 34.1%) of cases.

Strengths and limitations of the study

Since we included patients from both rural and urban areas with the full range of uncontrolled to well-controlled asthma and less than 1% of all eligible patients for the ACCURATE trial were excluded due to exclusion criteria other than age, the strength of our study is that the 351 patients included comprise a representative sample of adult asthma patients aged 18–50 years. Also, the interviewer-administered ACQs were assessed by PNs in 119 different general practices so selection bias seems unlikely. A limitation of our study is that the results may perhaps not be applied straightforwardly to patients aged >50 years who were excluded because of the increased prevalence of chronic obstructive pulmonary disease and fixed airways obstruction in this group. Furthermore, online self-administered versions were always completed before the interviewer-administered version, which might have introduced an order bias. However, an analysis of 68 patients who self-administered an online ACQ within one week after a trial-related visit and in whom no trial-related change in asthma medication was prescribed confirmed the higher ACQ results in the online self-administered version (difference 0.17, 95% CI 0.04 to 0.29, $p=0.01$). The time difference between administrations of the two versions probably did not influence the results since the correlation analysis of difference in ACQ results and time between both administrations showed no significant association ($r=0.03$, $p=0.54$) (data not shown).

The online self-administered ACQ was used in a previous study [6] and validated in a preceding pilot study (which was not formally published). We showed that the repeatability was very good (intraclass correlation coefficient (ICC) 0.86) and the agreement was also very good (ICC 0.88). The obtained validation sample of subjects was a relatively homogeneous population with low mean scores for the ACQ (0.60) and no high results. Even though the ICC of 0.88 is slightly below the required 0.9 for validation [3], we considered the online version validated since the ICC is highly dependent on

between-subject variability. In our population sample the between-subject variation was relatively low and, therefore, the ICC of 0.88 underestimates the actual agreement. On the other hand, assessment by a PN based on patient responses is a non-validated method of assessment, albeit widely used. Therefore, in the present study we compared a validated method of assessment with a non-validated method of assessment which could (partly) explain the difference in results.

Interpretation of findings in relation to previously published work

Two previous studies compared a postal-administered version of the ACQ with a version under guidance of a healthcare professional [8], and an electronic version with a paper self-administered version [7]. In both studies the ICC and Pearson's correlation were high and paired t-tests showed no statistically significant differences. Juniper et al. selected a more homogeneous group of only patients with uncontrolled asthma, whereas we included patients with the full range of asthma control. Furthermore, in the same study, Juniper et al. did find a significant difference between the electronic and paper versions of two other questionnaires with a more favourable outcome (i.e. fewer symptoms) with the paper version [7]. Also, in these studies, all assessments of the ACQ were completely self-administered while in our study it was completed by the PN based on patients' responses. Therefore, the actual person administering the questionnaire might explain the difference in ACQ results. In a review of different methods of administration of questionnaires, Bowling showed that patients reported more symptoms in self-administered than in interviewer-administered questionnaires in a number of fields of medicine, although not consistently [14]. For certain asthma symptoms, McDonald et al. recently showed that patients and healthcare professionals rate the importance differently [15]. Hence, the differences may be explained by a different interpretation of the question between patients and healthcare professionals, or PNs may weigh patients' answers and score their own interpretation. Finally, patients may express their symptoms more freely online or under-report symptoms when answering a PN due to social desirability, a known phenomenon when assessing highly sensitive personal behaviour [16].

Several previous papers have shown that patients reported more symptoms in an online self-administered questionnaire than in a paper self-administered version [14,17,18], suggesting that the format of an online questionnaire might have an effect. However, this was not a consistent finding [14,18,19] and we also showed very good agreement between the online self-administered version and a paper self-administered version in our pilot study.

Implications for future research, policy and practice

Our results suggest that, during face-to-face contact with a healthcare professional, on average, symptoms of asthma are reported as less severe than with self-assessment of symptoms when the same questionnaire (i.e. the ACQ) is used. It remains to be seen if asthma is better controlled if guided by online self-administered (risking overtreatment) or by healthcare professional-administered measurement scales (risking undertreatment). In order to guide treatment by the level of asthma control, the type of assessment — even when using standardised tools — should therefore be taken into account.

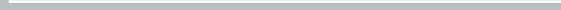
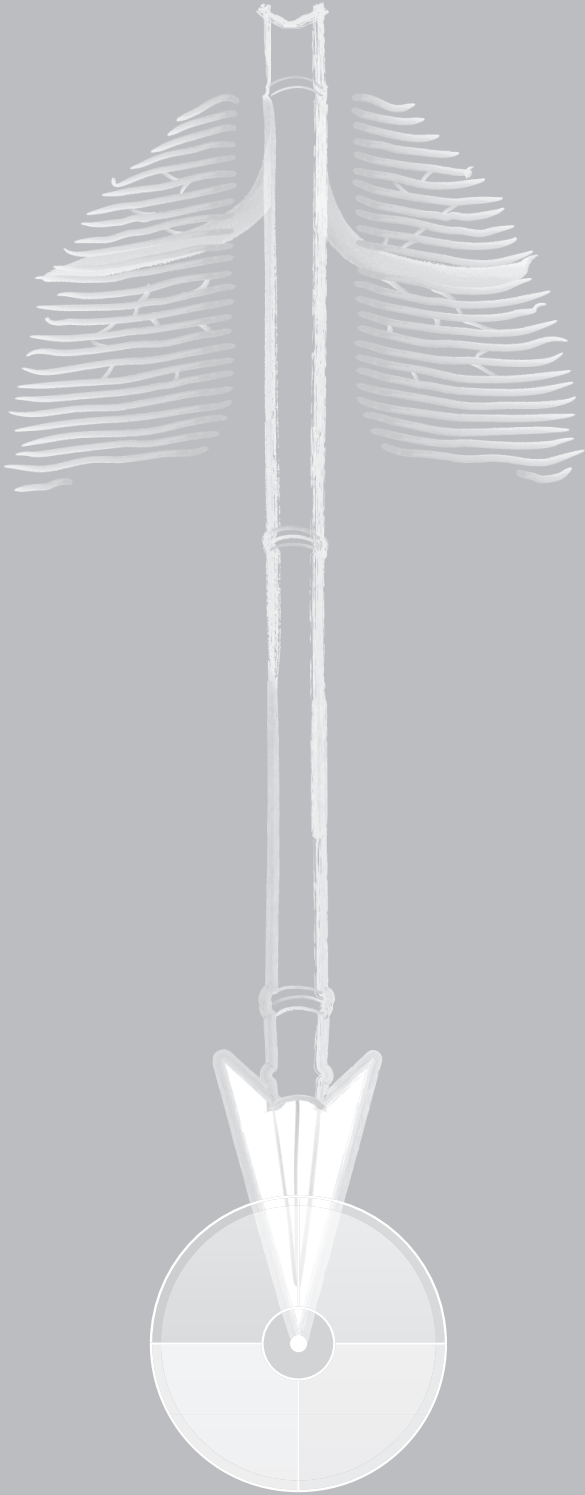
Our study also underscores the relevance of validating new methods of assessment of questionnaires before using them in clinical practice.

Conclusions

The level of asthma control measured by the ACQ depends on the type of administration. Symptoms of asthma are reported as less severe in the interaction with a healthcare professional compared with online self-assessment at home

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Chapter 7

General discussion

Assessment of asthma control: aim, parameters and cost-effectiveness

The aim of asthma management

In the presented ACCURATE trial in chapter 4 one of the main research questions was to identify the optimal aim of asthma management in primary care, with regard to control of asthma symptoms. Current guidelines suggest to aim for controlled asthma and to consider increasing treatment when asthma is partly controlled [1-5]. However, aiming for controlled asthma can lead to high doses of daily medication and associated costs and a less stringent aim, such as partly controlled asthma, might better balance pros and cons. Therefore, we assessed whether a strategy aimed at partly controlled asthma, instead of controlled asthma, proved superior when comparing cost-effectiveness, clinical outcomes and patient preferences. Our results showed that aiming for partly controlled asthma is similar to aiming for controlled asthma in terms of asthma control, quality of life, asthma exacerbations and patient preferences, while it reduced asthma medication use and costs. The reduction in asthma medication prescription was achieved by both reducing the frequency that treatment was stepped-up during control visits (39% vs 20%, respectively for Controlled asthma (Ca)-strategy vs Partly Controlled asthma (PCa) strategy) and by increasing the frequency of stepping-down treatment (30% vs 37%, respectively for Ca vs PCa). As stated before, the currently recommended aim of guidelines is controlled asthma [1-5]. We showed that if we maintain this aim, instead of accepting both controlled and partly controlled asthma, it will lead to similar clinical outcomes, but at a higher treatment burden and associated costs, which effectively results in many patients being over treated in primary care. A possible explanation is that most trials have been performed in secondary or even tertiary care centers. In general, patients in these centers have more severe asthma, therefore more room for improvement and so they may benefit more from treatment. When management aims based on these secondary care studies are applied to primary care, where patients generally have less severe asthma, the risk of overtreatment ensues, with associated increased costs and side-effects such as cough, pneumonia and adrenal insufficiency. [6-8] Although this may appear surprising, a likewise development was seen in the last decade for another major non-communicable disease, diabetes. In the management of diabetes several more recent trials have assessed aiming for strict glycemic control (HbA1C <6%), i.e. achieving completely normal glycemic levels, similarly to the concept of total control/no symptoms of asthma [9-11]. Although normoglycemia could be achieved and led to lower diabetes related cardiovascular complications, the resulting side-effects such as hypoglycemia led to significant morbidity and some subgroups even had higher mortality rates than the group aiming for less stringent control. In diabetes management this has led to a less stringent aim for most of the patients with diabetes (HbA1C<7%) and additionally different aims for certain subgroups. By aiming for partly controlled asthma

instead of controlled asthma, a similar transition could occur in primary care asthma management.

The use of FeNO in the assessment of asthma control

When treatment decisions are based on levels of asthma control, it is very important what kind of instruments are used to define asthma control. Using a composite control score, such as the ACQ7, has the advantage of providing one single score which can be monitored over time. Furthermore, it takes into account asthma symptoms, limitations in activity, quick reliever use and lung function in one measurement. However, it is a 'one size fits all' approach and disregards (subtle) differences in disease severity on the separate domains between individuals with asthma. Also, if asthma symptoms and lung function show conflicting results when assessing current control on asthma, some debate on whether asthma is sufficiently controlled or not remains. Although clinical symptoms are currently considered to be more important than lung function, it may still confuse the physician when these two markers contradict each other. Furthermore, both of these markers give no direct information on inflammation, which is the underlying central process to airway obstruction, hyperresponsiveness and symptoms. Additionally, airway inflammation is the target of inhaled corticosteroids, the most important type of medication in asthma. Therefore, we chose to evaluate a third marker of asthma control that could give an indication of airways inflammation, and could aid decision making when the conventional markers contradict each other. The measurement of the biomarker Fractional exhaled Nitric Oxide (FeNO) has this potential, since it is a non-invasive measure of airways inflammation in exhaled breath. In Chapter 3 we showed in a cross-sectional analysis that FeNO-results are non-concordant with either lung-function or symptoms. Therefore, it might have the potential to serve as adjunct to conventional markers of asthma control, especially since in 46% of asthma control assessments the results of symptoms and lung function are conflicting. Additionally, FeNO showed a different level of control than the other, conventional, markers in another 28% of cases. The relevance of these results is that we can conclude that FeNO has no strong correlation with any of the conventional markers. If that had been the case, additionally using FeNO would give no clear benefit over conventional markers of asthma control. However, these results give no clear indication of an actual benefit of using FeNO, since it could also point towards FeNO being an inadequate marker of asthma control. Therefore a longitudinal assessment, using FeNO as an additional marker of asthma control, was required to assess whether FeNO has added value, which is partly why we performed the ACCURATE study described in Chapters 2 and 4.

FeNO in therapy decision making

Other than serving as an additional marker of asthma control, another benefit of FeNO could be to guide the decision between different types of asthma medication. Currently commonly prescribed asthma maintenance medications in primary care are inhaled corticosteroids (ICS), long-acting beta agonists (LABA) and leukotriene modifiers (LTRA). Guidelines recommend a stepwise increase or decrease in medication [1-4]. The first step is to start with solely short-acting beta-agonists (SABA), in the second step ICS or LTRA are added to SABA. The third step has a wider range of options: either ICS is increased, or LABA is added to ICS or LTRA, or ICS and LTRA are combined, or a patient could additionally start using theophylline [2]. There is little or no evidence that one type of maintenance therapy is clearly superior over another, especially in the second and third treatment steps, which are predominant in primary care. Since FeNO is a marker of airways inflammation, it could help distinguish between patients requiring therapy aimed at reducing inflammation (i.e. ICS or LTRA) and patients requiring symptom relief (i.e. LABA). Therefore, the second main research question of the ACCURATE trial aimed to identify the usefulness of additionally measuring FeNO in therapy decision making. Our results show that the FeNO-guided Controlled asthma strategy (FCa), in contrast to the Controlled asthma (Ca) strategy, reduces asthma medication use. Asthma medication levels are reduced to a similar level, as is achieved by the Partly Controlled asthma strategy (PCa). However, it does so at significantly higher levels of asthma control in the FCa strategy than in the PCa strategy, indicating a more targeted use of asthma medication. The additional measurement of FeNO only led to a treatment advice that differed from that in the conventional Ca strategy, when FeNO was considered low (<25 ppb) or high (>50 ppb). This was the case in 77% of treatment advices in the FCa-strategy. The additional benefits of a FCa strategy could be further improved if patients that have a stable intermediate FeNO score could be identified in advance and subsequently treated according to either the Ca or the PCa strategy, without the need to reassess FeNO.

Several other trials have shown conflicting results on the use of FeNO, such as an increase in ICS dosage [12-14], or no differences in asthma medications [15]. There are a number of explanations for these differences. First, in our study, we used the cut-off point of a FeNO outcome of 50 parts per billion to increase treatment, which was recently assessed as the most appropriate cut-off point [16]. This is relatively high compared to the cut-off points used in research in earlier stages of FeNO's development. Second, we decided to include smokers in our study, and adjusted FeNO results for smoking, whereas smokers were usually excluded in other studies [12-14]. Third, patient adherence might be higher if an additional, new measurement is performed, although results from the medication adherence questionnaire (MARS) [17] in our study do not support this theory. Fourth, in our study FeNO was used as an adjunct to conventional markers, whereas previous studies often assessed FeNO versus these conventional markers.

Fifth, in our FCa strategy several possibilities to step-down treatment were built into the algorithm (as well as step-up options) in contrast to various previous studies where the algorithm was mostly driven towards keeping medications levels similar or towards higher use of medication [12,13]. The final advantage of our FCa strategy was that it led to a different treatment approach for a specific subgroup of patients that tend to be overtreated when using solely symptoms and lung function measurements to determine current control on asthma [18]. Haldar et al. identified this subgroup of patients, who continuously experience uncontrolled asthma, due to consistently high levels of symptoms, while there is no concomitant airways inflammation. These high levels of symptoms will invariably lead to a step-up in treatment in both the Ca and the PCa strategy, even though this will not reduce the experienced symptom load [18]. In contrast, the algorithm for treatment decisions in the FCa strategy added a FeNO measurement and if the FeNO result showed no signs of airways inflammation (i.e. $\text{FeNO} < 25$), ICS use in these patients was down-titrated. In the ACCURATE study (chapter 4) 8.7% of participants in the FCa strategy belonged to this subgroup (defined as those patients that scored 'uncontrolled asthma' according to symptom and lung function measurements ($\text{ACQ} > 1.5$), while FeNO was low ($\text{FeNO} < 25$), in $\geq 50\%$ of all assessments). Therefore, for 8.7% of participants, the FCa strategy led to an opposite treatment advice compared to the PCa and Ca strategy, safely down-titrating medication instead of increasing it. Consequently, we can conclude that the addition of FeNO in the assessment of current asthma control results in a targeted, more individualized, approach to asthma medication therapy.

Cost-effectiveness

With ever increasing healthcare costs, treatment should provide value for money and therefore studies on management of disease should be accompanied by an economic evaluation. To this purpose we calculated the societal costs per Quality-Adjusted Life Year (QALY) gained for each of the three strategies in the ACCURATE trial. This allowed a direct comparison of costs and utilities between the three strategies. Furthermore, since point estimates of costs and utilities are rather uncertain we used the net benefit approach, which allowed us to give a probability of cost-effectiveness at different societal Willingness-To-Pay (WTP) levels for one QALY [19].

Our cost-effectiveness acceptability curve (figure 4.2, chapter 4) shows that a strategy additionally guided by FeNO has the highest probability of cost-effectiveness throughout a wide range of WTP levels. At the commonly cited threshold of €40,000 per QALY per year [19] the FeNO guided strategy had a probability of 83% of being the most cost-effective strategy. Some issues regarding this result need to be addressed. First, the costs for the use of FeNO were based on the use of a specific sensor that can perform a maximum of 100 measurements, which is the most expensive version. For

an individual general practice this is the most realistic sensor. However, for spirometry and blood sampling, conglomerates of general practitioners nowadays employ specific organisations or companies to perform these measurements. These organisations or companies could also perform FeNO-measurements and upscale to cheaper sensors with 1000 measurements, which would further reduce costs. Second, the only clear conclusion that can be drawn is that the FeNO guided control strategy is the most likely to be cost-effective. Which strategies come second and third is hard to say due to the design of this overall analysis. It seems that the PCa strategy performed worst. However, the PCa strategy performed better than the Ca strategy with regard to costs. Thus, in a direct comparison between the two, the PCa strategy would have a higher probability of cost-effectiveness. However, since the costs in the FCa strategy were even lower, this effect is nullified by the FCa strategy when analyzing all three together. Third, even though a 83% probability of cost-effectiveness is high and the differences in costs between the strategies are quite substantial, both the direct comparison in utilities and in costs showed no significant differences between the strategies, other than significantly lower asthma medication costs. These non-significant results can partly be ascribed to the wide confidence intervals in the different assessments of costs, which is inherent to this type of research and further increased in our study by the large heterogeneity in patient characteristics in this pragmatic trial. Fourth, since costs in primary care are generally low, results can be substantially influenced by outliers. However, by using a non-parametric bootstrap estimation with 5000 random samples and subsequently applying the net benefit approach we tried to minimise this effect. The reduction in asthma medication use, the similar levels of asthma control and quality of life, and the high probability of being the most cost-effective strategy, all suggest that the FCa strategy is the superior strategy and therefore a FeNO-measurement deserves to be implemented as an adjunct in the management of asthma in primary care.

Secondary outcomes of the ACCURATE trial

The primary outcome of the ACCURATE trial was the comparison of cost-effectiveness of the three strategies and our study was powered using these parameter. However, to decide on an optimal management strategy for asthma in primary care, other outcomes are important as well. Therefore, we also assessed current asthma control, patient preferences, asthma related quality of life and severe exacerbation rate. It is important to note that we observed no differences between the strategies for most of these outcomes, and that the magnitudes of even the statistically significant differences were small and of limited clinical relevance. On the other hand, we found that in all strategies participants had improved asthma control when comparing baseline values to results at twelve months. Furthermore, differences *within* a strategy (from baseline to 12 months) were usually higher than differences *between* strategies (at a certain point). The similarity of

improvement from baseline parameters in the three strategies can partly be ascribed to so-called regression to the mean, especially since participants had worse baseline asthma control than non-participants (chapter 4, Table 4.E2). Another explanation is that most likely in all three strategies patients were being more regularly assessed and treated than before the study. Two recent large primary care studies regarding the treatment of patients with mild to moderate asthma, showed no significant differences between different treatment strategies in multiple outcomes. However, similarly to our results, patients had improved compared to baseline [15,20]. Therefore, for patients with mild to moderate asthma the most important aspect of asthma management might be regular monitoring, which in itself has the largest effect on the improvement of asthma control. In addition to regular monitoring, distinctive asthma management strategies are likely to lead to only small fine-tuning effects on asthma management, rather than causing drastic effects on asthma control, patient preferences, quality of life and exacerbations.

With regard to patient preferences, there were no clear differences between the strategies, as measured by several questionnaires. On individual level though, when assessed with the Beliefs about Medication Questionnaire (BMQ) [21], some patients preferred remaining on the safe side and minimising the risk of exacerbations and loss of control, thereby risking overtreatment, while other patients preferred to minimise medication usage and side-effects. Assessing these preferences regularly in individual patients and subsequently selecting the appropriate target of asthma control and concomitant medication usage based on these preferences, might greatly enhance patient satisfaction.

How to address future risk?

Written Asthma Action Plans

In addition to measuring markers which indicate current asthma control, an asthma control assessment should also include measurements enable the prediction of the risk of future adverse events [1-4, 22]. Currently the most commonly used method to predict future risk, is the exacerbation frequency in the past year. If patients are defined as being at risk, controller-therapy can be increased as a preventive measure, which should reduce the chance of experiencing an exacerbation [22]. An alternative approach to predict future risk and subsequently minimise the chance of future exacerbations, is providing these patients with a Written Asthma Action Plan (WAAP). In a WAAP patients report their symptoms and/or lung function on a regular basis (daily/weekly) and receive feedback when control on asthma is deteriorating or an asthma exacerbation is imminent. The advantage of this approach over increasing asthma controller therapy, is that medication is only increased when asthma control of that person is actually de-

teriorating. To adequately detect imminent exacerbations and simultaneously prevent unnecessary overtreatment when no exacerbation is imminent, the level of symptoms and/or lung function at which feedback is given to the patient, is of vital importance. This threshold level is called an Action Point and in our study we assessed the optimal characteristics of the Action Point that advises to start oral corticosteroids or to immediately visit your GP/pulmonary physician. Previous research on optimal Action Points mainly assessed the sensitivity and specificity of predicting exacerbations [23-26]. We added two additional analyses in our research in Chapter 5. First, the (potential) Number Needed to Treat (NNT), which assessed how often an Action Point gives a false positive signal for each correctly identified imminent exacerbation. Second, we analysed all the daily results in the week before an exacerbation and assessed when an Action Point was positive for the first time. This is an important measure because the higher the number of days between the positive signal of the Action Point and the start of the exacerbation, the more time a patient has to take appropriate measures.

We discerned four ways of identifying Action Points, based on the type of information used. For each of these ways, we defined the appropriate threshold(s) that indicated the optimal Action Points. The four ways and their optimal thresholds were:

- Solely symptoms: symptom increase > 2 standard deviations above mean symptom score (>2SD)
- Solely peak flow: below 60% of personal best value (<60% pb)
- Symptoms and peak flow: symptom increase >2SD and peak flow <70% pb
- Symptoms and peak flow within one week: symptom increase >2SD and peak flow <70% pb, occurring within 1 week from each other

Overall, the Action Point that combined a symptom increase of >2SD and a peak flow decline to <70% pb within one week performed best. It predicts an imminent exacerbation 4.1 days before its occurrence, with a sensitivity of 85.1%, specificity of 97.2% and a number needed to treat (NNT) of 6. We also assessed the predictive characteristics of several Action Points that are currently advised by international guidelines. The NHLBI advises the use of 'appearance of any symptoms *plus* peak flow <80%pb', which resulted in a much higher NNT of 28 [1]. The British Thoracic Society uses a peak flow <60%pb, which performed really well with regard to sensitivity, specificity and NNT, but its main disadvantage was that it predicted an exacerbation only one day before its occurrence [4]. Several guidelines give no direction as to what an Action Point should consist of, and solely state a WAAP with Action Points should be used [2,3]. This leaves the choice of threshold values for Action Points to the discretion of the physician. Theoretically, a physician-driven Action Points might be superior to our optimal Action Point, since it can be individualised to the asthma exacerbation characteristics of a specific patient. However, by using standard deviations from a mean symptom score and percentages of personal best, our Action Points also include individualised measurements. Therefore, it

is unlikely a non-validated Action Point will perform better, especially since we further validated our optimal Action Points in a different dataset.

The most feasible Action Points are those that consist solely of symptom scores, since they require no additional measurements. Unfortunately these Action Points had the worst performance characteristics and led to a huge number of false positive signals. Therefore a measure of lung function should be included. If that is not feasible, it is probably better not to use a Written Asthma Action Plan, than to use one that is quite seriously flawed.

In a pen & paper WAAP, calculation of a combined Action Point with a one week time-window is complex and non-feasible and assessing a mean symptom score and standard deviations similarly requires difficult calculations. Fortunately, there are now online self-management programs and mobile phone application (Apps), that can do the necessary calculations automatically. Another common problem with using a WAAP is patient non-adherence to filling in diary recordings. Apps could also improve this, by using automatic reminders when patients forget to fill in questions. However, even when using an App, patients still need to perceive enough benefit compared to all the effort required. Especially, if an Action Point with a peak flow measurement is used, which requires patients to have a peak flow device available when filling out the questionnaire. Therefore, the most feasible solution will be to prescribe a WAAP only to patients with a high risk of asthma exacerbations, those with a very severe course of previous exacerbations, or those keen on self-management.

Online assessment of current asthma control

In the management of chronic non-communicable diseases validated questionnaires play a pivotal role to monitor disease status. Usually patients visit their physician or practice nurse and fill in these questionnaires preceding or during the consultation visit. In recent years we have seen the advent of online self-management programs. In those programs patients fill in a questionnaire online and sometimes even receive immediate feedback without intervention of their physician or practice nurse [27-29]. In online asthma self-management programs, the Asthma Control Questionnaire (ACQ) by Juniper is a frequently used questionnaire [30]. The ACQ was originally designed and validated to be self-administered under guidance of a healthcare professional. Therefore, even though the questions are exactly the same, when the ACQ is used online, this represents a different method than it was originally validated for. Of course this issue arises with many other questionnaires in online programs. In Chapter 6 we showed that when patients fill out an online questionnaire at home they report significantly more symptoms than when the ACQ is assessed by a practice nurse. Previous research on

questionnaires for certain psychiatric disorders also showed that patients report more symptoms in self-administered than in interviewer-administered questionnaires [31-33]. Possibly patients express their symptom frequency and severity more freely during self-administration than when talking with a healthcare professional, especially in an online format. It seems preferable that a patient expresses his symptoms as freely as possible, because that gives the clearest indication of the burden of the disease for that patient. That would indicate a preference for the use of self-administration. However, the problem of validation remains. If non-validated online versions of questionnaires are used to guide treatment, and treatment decisions are based on the same cut-off points as are used in (interviewer-administered) validated versions, the possibility of overtreatment looms large. Therefore, even though self-management and online assessment is the way forward, we should remain vigilant and validate new types of administration of questionnaires.

Directions for future research

Research in primary care

The results of our ACCURATE trial described in chapters 2 and 4 showed different results, with regard to levels of asthma control, exacerbation frequency, the use of FeNO and asthma related quality of life, in comparison to previous research [5,6,12-14, 22-26]. An important aspect explaining at least part of these differences in results, seems to be related to the choice of study population. The ACCURATE trial was a pragmatic trial, performed in primary care and included a wide variety of patients in the full range of asthma control, from both rural and urban areas and even including smokers. In contrast, a large proportion of previous research was performed in secondary or tertiary care centers, on selected subsets of patients, even though in the United States only roughly 10% of all patients are treated in secondary care and less than 1% in tertiary care [34,35]. Since the healthcare system in the Netherlands is more oriented towards primary care, these percentages may be even lower in the Netherlands. While most clinical guidelines assume that results from studies in secondary or tertiary care centers can be applied to all patients with asthma, it is quite likely they can not, as the disease spectrum of patients in primary care may differ strongly from those in secondary and tertiary care. Since the majority of patients with asthma, and of most other diseases for that matter, are being treated in primary care, future research should be aimed at performing more large pragmatic trials in primary care, with as few in- and exclusion criteria as possible.

Phenotypes of asthma

In our trial described in Chapters 2 and 4, participants were randomised to have their treatment goals set at either 'partly controlled asthma', 'controlled asthma', or 'FeNO guided controlled asthma'. We showed that in general, FeNO guided controlled asthma is preferable, followed by partly controlled asthma. However, subgroups of patients may benefit from more stringent control on asthma, for example those with more frequent exacerbations. Therefore, future research should focus on the optimal aim of asthma management for subgroups of patients with different clinical phenotypes of asthma. Additionally, future research should take into account personal preferences regarding medication usage, side-effects, risks of asthma exacerbations and goals for asthma treatment. Also, according to our study algorithm, management decisions were the same for the FCa and the Ca strategy, if the FeNO score was intermediate (i.e. between 25-50). Therefore in future research, patients with a stable intermediate FeNO score, may be managed without continuation of FeNO, since it is a costly measurement, which has no added value for these patients. Furthermore, in our research we decided to measure FeNO at every visit, independent of previous FeNO scores, current asthma control and current medication usage. Possibly, in the management of asthma, FeNO could be measured less often, and future research should identify the optimal frequency of assessment. Another alternative use of FeNO would be as a diagnostic tool, to determine an individual patient's asthma profile. Future research should analyse whether FeNO has the potential to differentiate between phenotypes of asthma, similarly as another inflammometer, the enose, has been used for that purpose in COPD [36].

Action Points

In chapter 5 we showed the best Action Point for Written Asthma Action Plans (WAAP). That Action Point requires calculations that are nearly impossible to implement in a pen & paper WAAP. Therefore future research should focus on creating and using online platforms and IT-solutions for measurements and calculations. The feasibility of the use of a WAAP may be further increased by peak flow measurement devices that can automatically communicate with the patient's smartphone or be inserted into it (for example, My Spiroo-device, www.myspiroo.com). Alternatively, intelligent inhalers with sensors that automatically register peak flow (derivatives) while inhaling may signal the smartphone when medication is forgotten (for example smartinhalers, www.smartinaler.com).

A WAAP normally contains several different Action Points in an increasing order of disease severity. The first warns patients, because they are experiencing more symptoms than normal. The second indicates a loss of control on asthma and advises to temporarily step-up ICS treatment. The third indicates an exacerbation is imminent and that a patient should take immediate action, such as starting oral corticosteroids, or immediately visit a GP/Pulmonary physician. In our study in Chapter 5 we have assessed the optimal

threshold levels for the third type of Action Point. Future research should assess the optimal thresholds for the other two types of Action Points. This future research will require a different balance between accuracy and NNT for each type of Action Point, since a false positive signal in an Action Point that solely gives a warning, is less detrimental than when it results in a course of oral prednisone.

Future research into different Action Points should also take into account that the level of asthma control may differ, depending on which criteria you use. As we showed in chapter 3, symptoms and lung function result in a different level of control in almost half of the patients. Individualised WAAPs might therefore be improved if FeNO would be included as an additional home monitoring device, although this will only be feasible if FeNO measurements will become a lot cheaper in the future.

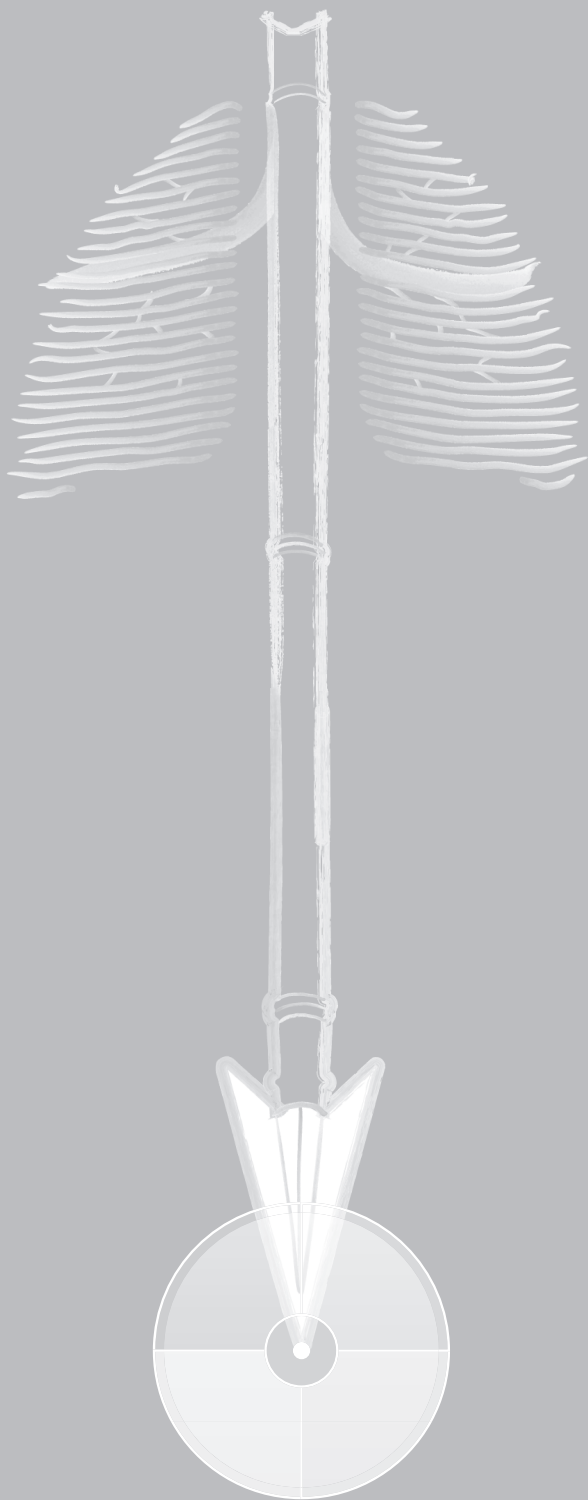
Conclusion

In conclusion, we have provided the optimal Action Point for an (Written) Asthma Action Plan, which new Action Plans should incorporate. We also showed the disadvantages of copying questionnaires to a new format without proper validation and physicians should be aware of these differences when using new formats of questionnaires. Finally, we have shown that accepting 'partly controlled asthma' may be a strategy that is superior to aiming for 'controlled asthma'. In addition, we have demonstrated the benefits of the additional use of a FeNO-measurement in asthma control assessments. For adult patients with asthma in primary care, our results should lead to the implementation of FeNO as an aid in the assessment of current control on asthma and to guide asthma therapy choices. If a FeNO measurement is not yet available, aiming for partly controlled asthma is a worthy alternative.

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Chapter 8

Summary

This thesis aimed to contribute to the improvement of several components of the management of asthma in primary care. The main part of this thesis consists of the AC-CURATE trial. In this trial we compared three different management strategies for adult patients with asthma in primary care. In the first management strategy, we targeted 'Controlled asthma', which is the currently recommended aim in clinical guidelines. 'Controlled asthma' means patients should experience hardly any symptoms of their asthma. A downside of this strategy is that it usually requires relatively high doses of medication. The second management strategy, targeted 'Partly Controlled asthma' and in this strategy some symptoms were allowed. This should lead to a lower requirement to step-up treatment in response to symptoms, which would lead to less medication usage and thus less side-effects. The third management strategy evaluated the use of adding a measurement of Fractional exhaled Nitric Oxide (FeNO), a possible indicator of airways inflammation. In the other two strategies, assessment of current control on asthma, was based on the conventional markers lung function and symptoms. Adding FeNO could aid in assessing current control and help guide therapy choices. In order to establish the best management treatment strategy, we assessed as many relevant indicators as possible. Therefore we not only assessed clinical parameters, such as asthma control and exacerbations, but we also assessed the societal perspective, by performing a cost-effectiveness analysis and the patient's perspective by measuring relevant issues such as quality of life and adherence. The conclusions from our trial can be summarized as follows:

- From a societal perspective, as well as a patient's and a clinical perspective, a symptom- plus FeNO-driven strategy is the preferred management strategy for adult asthma patients in primary care.
- Treatment aimed at 'FeNO guided Controlled asthma' improves asthma control with a high probability of cost-effectiveness and without increasing medication use and costs compared to aiming at 'Partly Controlled asthma'.
- Treatment aiming at 'Controlled asthma' leads to increased asthma medication use and costs, without a significant improvement in asthma control, quality of life or exacerbation rate, compared to aiming at 'Partly Controlled asthma' or to aiming at 'FeNO guided Controlled asthma'.
- FeNO shows a weak correlation with respiratory symptoms and lung function
- If FeNO is incorporated as a marker of asthma control in primary care, it enables 'fine-tuning' when categorizing asthma control in almost half of the patients

Additionally we performed two other studies. In the first study, we aimed to improve the usefulness of asthma action plans. In an asthma action plan a certain threshold level of symptoms or peak flow is defined, called an Action Point. If a patient's symptoms or peak flow exceed that threshold level, the patient is advised to take immediate action. Usually

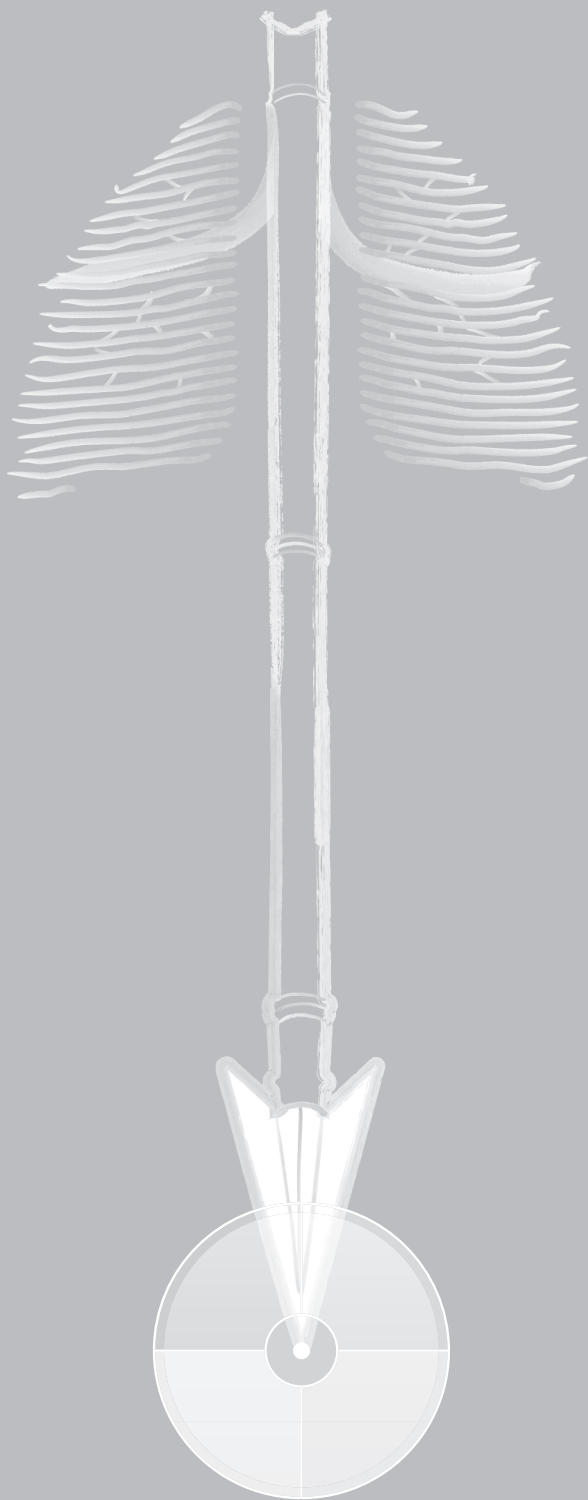
there are several different Action Points within one asthma action plan, each with their own threshold levels and with different actions to be taken. The most important Action Point is the one that indicates a severe exacerbation is imminent and advises to start oral corticosteroids or immediately visit a physician/hospital. In our study we aimed to identify the best threshold-levels for this Action Point. In order to decide the best threshold levels it is important that they provide a good sensitivity and specificity with regard to detecting exacerbations. Furthermore, it is also important that an exacerbation is detected well in advance to allow appropriate treatment. Finally, it is also important that an Action Point has a low Number Needed to Treat, since false positive predictions will result in over treatment. Our results show that the optimal action point for the early detection of asthma exacerbations consists of two components:

- A ≥ 2 standard deviations increase in a composite symptom score from a mean symptom score acquired during a baseline, combined with a fall in PEF to $< 70\%$ of personal best, both occurring within a one week window.

This Action Point detected exacerbations 4.1 days before occurrence, with a sensitivity of 85.1%, specificity of 97.2% and a number needed to treat (NNT) of 6.

Finally we explored the potential hazards of using a questionnaire in a different setting than it was originally validated for. To this purpose we compared the results of an assessment of the Asthma Control Questionnaire online, with the results of that same questionnaire assessed by a practice nurse together with the patient. Both questionnaires were completed within one week of each other. We concluded that:

- Assessment of asthma control by the Asthma Control Questionnaire is influenced by the type of administration. Control over asthma symptoms is perceived as higher when interacting with a caregiver than in an online self-assessment



Chapter 9

Nederlandse samenvatting

Inleiding

Astma is een veel voorkomende chronische aandoening van de luchtwegen. De kenmerkende klachten zijn periodes van kortademigheid en een piepende ademhaling. Deze klachten zijn bij de meeste astmapatiënten niet continu aanwezig: astma kenmerkt juist zich door periodes van veel klachten afgewisseld met periodes van amper tot geen klachten. Daarnaast kunnen astma patiënten acuut (heel) ernstig kortademig worden. Dit wordt een astma-aanval of 'exacerbatie' genoemd. De klachten van astma worden veroorzaakt door een vernauwing van de luchtwegen, waardoor het moeilijker wordt om in en uit te ademen. Deze vernauwing is weer het gevolg van een chronische ontstekingsreactie in de luchtwegen. Deze ontsteking wordt niet veroorzaakt door bacteriën of virussen, maar is het gevolg van een reactie op allerlei allergische en niet-allergische prikkels in de lucht, zoals huisstofmijt, haren van huisdieren, pollen, sigarettenrook en mist. Om de klachten van astma onder controle te krijgen is het daarom erg belangrijk deze prikkels zoveel mogelijk te vermijden. Stoppen met roken is daarbij de eerste stap. Daarnaast is het goed om te weten of iemand ergens allergisch voor is, zodat dit ook zoveel mogelijk gemeden kan worden. Ook bestaan er verschillende soorten medicijnen voor astma. De belangrijkste twee soorten zijn 'ontstekingsremmers' en 'luchtwegverwijders'. Ontstekingsremmers richten zich op het onderliggende ontstekingsproces en proberen dit proces zoveel mogelijk te verminderen, terwijl luchtwegverwijders de luchtwegen open zetten. Mensen met astma merken vrijwel direct het nut van luchtwegverwijders en geven daarom vaak de voorkeur aan deze medicijnen. Het bestrijden van de onderliggende ontsteking is echter minstens net zo belangrijk.

Controle over astma in de huisartsenpraktijk

Om astma goed te kunnen behandelen en de klachten goed onder controle te houden, is het de bedoeling dat patiënten regelmatig voor een consult langskomen bij de huisartsenpraktijk. Tijdens dat consult wordt onder andere gevraagd naar het medicatiegebruik en naar de klachten die astma geeft, soms aan de hand van een vragenlijst. Daarnaast wordt er vaak ook een longfunctie-meting verricht. Tezamen geven deze metingen een beeld van hoeveel last iemand van zijn astma heeft. In de behandeling van astma gebruiken we hiervoor de term mate van controle over astma. In principe is het natuurlijk de bedoeling dat iemand geen of zo min mogelijk klachten heeft van zijn astma, ofwel 'goed gecontroleerd' astma heeft. Daarnaast bestaat er ook 'voldoende gecontroleerd' astma, waarbij een patiënt enige klachten van zijn astma ervaart, en 'slecht gecontroleerd' astma, waarbij een patiënt veel klachten van zijn astma ervaart. Uit eerdere onderzoeken is gebleken dat goed gecontroleerd astma voor de meeste

patiënten een haalbaar doel is. Er zit echter wel het nadeel aan dat de meeste patiënten (hele) hoge doseringen medicatie moeten gebruiken om goede controle over astma te krijgen en sommigen hebben zelfs een kuur prednison nodig. Hoge doseringen medicatie geven een verhoogd risico op bijwerkingen en brengen hoge kosten met zich mee. Het is mogelijk dat streven naar voldoende controle in plaats van naar goede controle een betere afweging geeft tussen de klachten van astma zo goed mogelijk onder controle houden enerzijds versus bijwerkingen en kosten anderzijds. In hoofdstuk 2 en 4 hebben we daarom deze twee streefdoelen, 'goede controle' en 'voldoende controle', met elkaar vergeleken.

In hoofdstuk 4 wordt ook nog een derde streefdoel geanalyseerd en dat is 'goede controle met behulp van een Fractional exhaled Nitric Oxide (FeNO) meting'. Om het nut hiervan uit te leggen is het belangrijk terug te gaan naar het consult bij de huisartsenpraktijk. Tijdens dat consult wordt gevraagd naar klachten, deze zeggen iets over de hinder die een patiënt ervaart, en wordt de longfunctie gemeten, en dat geeft een beeld van de ernst van de vernauwing van de luchtwegen. Zoals gesteld in de inleiding speelt echter ook het ontstekingsproces in de longen een belangrijke rol in de ontwikkeling van klachten en zowel klachten als longfunctie geven onvoldoende aanwijzing over hoe ernstig het gesteld is met dat onderliggende ontstekingsproces. Een FeNO-meter is een apparaat dat de concentratie van stikstof monoxide in de uitgeademde lucht meet. Uit eerdere onderzoeken is gebleken dat dit mogelijk aanvullende informatie geeft over de mate van ontsteking in de luchtwegen. In hoofdstuk 3 hebben wij eerst gekeken of deze FeNO-meting inderdaad aanvullende informatie geeft. Hiervoor hebben wij de klachten, longfunctie en FeNO uitslagen van 307 volwassen astma patiënten met elkaar vergeleken. Als maat voor de ernst van de klachten werd gebruikt gemaakt van de Asthma Control Questionnaire (ACQ), een vragenlijst bestaande uit 6 vragen over de ernst van de astmaklachten. Voor de longfunctie uitslagen werd gebruikt gemaakt van een spirometer. Dit is een apparaat waarin een patiënt op bepaalde manier moet uitblazen en de uitslagen geven informatie over de longinhoud en de doorgankelijkheid van de luchtwegen. Uit het onderzoek in hoofdstuk 3 bleek dat de uitkomsten van de klachtenvragenlijst ACQ en van de longfunctie in 46% van de gevallen tegenstrijdige informatie gaven. De vragenlijst over ervaren klachten gaf dan bijvoorbeeld aan dat iemand weinig of geen klachten ervaart, terwijl de longfunctie meting liet zien dat de luchtwegen sterk vernauwd zijn. FeNO kan in dat geval van aanvullende waarde zijn. In nog eens 28% van de gevallen gaf FeNO een ander signaal dan zowel de klachten als de longfunctie. Als de FeNO meting verhoogde ontstekingswaardes laat zien, terwijl zowel longfunctie als de klachten vragenlijst aangeven dat astma goed onder controle is, kan FeNO als waarschuwing dienen dat er mogelijk meer klachten kunnen gaan komen in de toekomst. Aan de andere kant kan FeNO mogelijk richting geven in de medicatie keuze als er weinig of geen onderliggende ontsteking is, maar patiënten wel veel klachten en

een slechte longfunctie hebben. In dat geval zal een patiënt meer baat hebben bij de luchtwegverwijdende medicijnen, dan bij ontstekingsremmers. In hoofdstuk 4 hebben we vervolgens de uitkomsten van 'goede controle met behulp van een FeNO meting' vergeleken met de eerdergenoemde streefdoelen 'goede controle' en 'voldoende controle'.

We hebben voor de vergelijking van de drie streefdoelen 611 volwassen astma patiënten tussen de 18-50 jaar uit 131 verschillende huisartsenpraktijken gedurende een jaar gevolgd. Via loting werden alle huisartsenpraktijken samen met de deelnemende patiënten, verdeeld over de drie verschillende behandel streefdoelen. Alle patiënten van één huisartsenpraktijk hadden dus hetzelfde streefdoel. De patiënten kwamen vervolgens elke drie maanden langs bij de praktijk, in de meeste gevallen bij de praktijkondersteuner. De ernst van de klachten werd gemeten met de ACQ vragenlijst, de huidige medicatie werd vastgesteld, er werd een longfunctietest verricht en in de FeNO groep werd ook een FeNO meting verricht. De praktijkondersteuner vulde al de uitslagen in een internetprogramma in, waarna automatisch een behandeladvies volgde dat gebaseerd was op het streefdoel van die patiënt en ook rekening hield met de huidige medicatie. De verschillen tussen de drie behandelstrategieën waren dat: bij 'goede controle' de medicatie werd opgehoogd tot goede astma controle was bereikt; bij 'voldoende controle' de medicatie alleen werd opgehoogd bij slechte astma controle en geprobeerd werd de medicatie te verminderen bij goede astma controle; bij 'goede controle m.b.v. FeNO' de uitslag van de FeNO meting mede bepalend was voor de keuze om wel of niet de medicatie op te hogen of te verminderen en daarnaast een leidende rol had in welk soort medicijn (luchtwegverwijders of ontstekingsremmers) werd gegeven. De belangrijkste uitkomsten van het onderzoek waren de volgende:

- Er was geen significant verschil in (astma-gerelateerde) kwaliteit van leven, therapietrouw en aantal ernstige astma-aanvallen tussen de drie strategieën
- Streven naar 'voldoende controle' zorgt ervoor dat patiënten minder medicatie gebruiken en dat de kosten lager zijn dan bij het streven naar 'goede controle', zonder dat dit ervoor zorgt dat een patiënt meer klachten ervaart
- Ook streven naar 'goede controle m.b.v. FeNO' leidt tot minder medicatie gebruik en lagere kosten dan streven naar 'goede controle'
- Streven naar 'goede controle m.b.v. FeNO' leidt daarnaast tot significant minder symptomen van astma dan streven naar 'voldoende controle'
- Streven naar 'goede controle m.b.v. FeNO' is het meest kosteneffectief

Wanneer alle uitkomsten van het onderzoek samen worden genomen blijkt dat de beste behandelstrategie van astma in de huisartsenpraktijk degene is waarbij gestreefd wordt naar goede controle met behulp van een FeNO meting. Het is de meest kosteneffectieve manier om astma te behandelen en het leidt tot het minste medicatie gebruik, terwijl astma wel goed onder controle blijft. Dit wijst er op dat de astma-medicatie gericht

wordt gebruikt. Het streefdoel 'goede controle m.b.v. FeNO' moet dan ook ingevoerd gaan worden in de dagelijks praktijk. Aangezien een apparaat om FeNO te meten nog niet overal beschikbaar is, is een goed alternatief om te streven naar 'voldoende controle' zonder FeNO-meting. Ook bij deze strategie is er duidelijk minder medicatie nodig dan bij de huidige gangbare 'goede controle', terwijl de controle over astma niet verminderd.

Astma-aanvallen

Naast het behouden van controle over astma is het bestrijden en voorkomen van astma-aanvallen een van de belangrijkste onderdelen van de behandeling van astma. Een astma-aanval leidt regelmatig tot ziekenhuisopnames, langdurig ziek thuis zijn en nog steeds sterven er jaarlijks zelfs nog mensen als gevolg hiervan, ook in Nederland. De mogelijke ernstige afloop van een astma-aanval en de impact die het heeft op de gezondheid, zijn redenen om mensen die frequente of ernstig verlopende astma-aanvallen hebben, extra goed in de gaten te houden. Daarom wordt hen vaak een astma-actie-plan meegegeven. In een astma-actie-plan wordt aan patiënten gevraagd om regelmatig (lieft dagelijks) de ervaren klachten op te schrijven in een dagboek. In de modernere versies kan dit ook online bijgehouden worden op een website, of op de smartphone in een App. Daarnaast wordt in sommige bestaande astma-actie-plannen gevraagd om ook een longfunctie meting te verrichten. Vaak gebeurt dit met een piekstroom meter, waarbij patiënten moeten uitblazen in een klein apparaatje. In het actie plan staat vervolgens beschreven bij welke hoeveelheid klachten, of bij welke waarde van een longfunctie meting, deze persoon in actie moet komen. Vaak wordt gebruik gemaakt van een kleurencode, bijvoorbeeld:

- Groen. Uw astma is goed onder controle
- Geel. U heeft enige klachten, vermijdt prikkels die uw astma kunnen verergeren
- Oranje. U heeft meer klachten dan normaal, verhoog (tijdelijk) uw medicatie
- Rood. Ga direct naar uw arts of start een prednisonkuur

Wil een astma-actie-plan goed werken, is het van belang dat de hoeveelheid klachten en de longfunctie waardes die bij een bepaalde kleur horen, een toekomstige astma-aanval goed voorspellen. Als namelijk het astma-actie-plan geen signaal afgeeft terwijl iemand wel een astma-aanval krijgt, heeft het actie plan gefaald. En aan de andere kant bestaat het gevaar dat iemand teveel medicijnen krijgt als er een signaal wordt gegeven dat er een astma aanval aankomt, terwijl dit achteraf beschouwd niet waar is. In hoofdstuk 5 hebben wij voor het actiepunt dat hoort bij de rode kleur (ga direct naar uw arts, of start een prednisonkuur) uitgezocht welke hoeveelheid klachten en welke waarde van een longfunctie meting het beste gebruikt kunnen worden. Hiervoor hebben wij een dataset geanalyseerd van 164 volwassen astma-patiënten die gedurende

anderhalf jaar dagelijks hun klachten en piekstroom meting invulden in een dagboek. Daarnaast werd bijgehouden wanneer zij een astma-aanval doormaakten. Door de klachten en piekstroom in de week voorafgaand aan een astma-aanval te vergelijken met de klachten en piekstroom in alle weken dat er geen astma-aanval optrad, werd gezocht naar een specifiek patroon voorafgaand aan astma aanvallen. Nadat we dit hadden gevonden, werd dit patroon bevestigd in een dataset van 94 andere volwassen astma patiënten, die een jaar lang een soortgelijk dagboek hadden ingevuld. Het meest geschikte actiepunt maakt gebruik van meerdere metingen in de tijd en is alleen geschikt als de berekeningen automatisch uitgevoerd kunnen worden (zoals in een App, of in een online programma). Voor het geval dit niet beschikbaar is, en voor gevallen waarbij alleen klachten of juist alleen een piekstroom waarde kunnen worden gemeten, zijn ook nog 3 andere geschikte actiepunten in hoofdstuk 5 gepresenteerd.

Online vragenlijsten

Met de toenemende invloed van het internet op ons leven, zal ook de gezondheidszorg zich meer en meer online gaan afspelen. Op dit moment bestaan er bijvoorbeeld al meerdere patiëntenportalen. Hierin kunnen patiënten hun klachten bijhouden en extra informatie over hun ziekte vinden. Vaak hebben ook artsen toegang en kunnen zij direct zien hoe het met de ziekte van één van hun patiënten gesteld is. Ook zijn er al veel Apps waarin je de controle over een ziekte kan vervolgen, waaronder Apps die specifiek op astma gericht zijn. In al deze online tools wordt vaak gebruik gemaakt van vragenlijsten om de ernst van astma klachten in te schatten, bijvoorbeeld de al eerder genoemde ACQ vragenlijst. Er wordt hierbij vanuit gegaan dat de uitkomst van een vragenlijst die bij de huisarts wordt ingevuld, precies hetzelfde is als de uitkomst van diezelfde vragenlijst als die thuis achter de computer/telefoon wordt ingevuld. In hoofdstuk 6 hebben wij voor de ACQ vragenlijst uitgezocht of dit inderdaad het geval is. Hiervoor hebben wij van 351 volwassen astma-patiënten de uitkomst van een online thuis ingevulde ACQ vergeleken met een ACQ die werd ingevuld op de huisartsenpraktijk bij de praktijkondersteuner. Beide versies werden binnen een week van elkaar ingevuld, zodat eventuele verschillen in uitkomst niet konden worden verklaard doordat de astma klachten in de tussentijd erg veranderd waren. Online bleken patiënten significant meer klachten aan te geven dan bij de huisarts. Daarnaast zou in 25% van de gevallen het gebruik van de online versie in plaats van de versie bij de praktijkondersteuner hebben geleid tot een ander behandeladvies. Voordat een reeds bestaande vragenlijst online gebruikt kan worden, is het dus belangrijk om opnieuw te testen of de uitkomsten wel hetzelfde zijn. Zo nodig moeten er nieuwe grenswaardes worden bepaald van wat als een normale score en wat als een afwijkende score moet worden beschouwd.

Algemene discussie

In hoofdstuk 7 worden alle uitkomsten van de verschillende onderzoeken nog eens op een rij gezet. Vervolgens worden er aanbevelingen gedaan hoe deze uitkomsten de behandeling van astma zouden moeten veranderen, waarbij er ook rekening wordt gehouden met de uitkomsten van eerdere onderzoeken door andere onderzoekers. Op het einde van deze discussie worden ook suggesties gedaan voor toekomstig onderzoek. Zo is het belangrijk om in toekomstig onderzoek niet alleen te kijken naar astma patiënten als een groep en te bepalen wat gemiddeld voor hen het beste streefdoel is, maar ook te kijken naar individuele astma patiënten en te achterhalen wat voor hen persoonlijk het beste streefdoel is. Ook moet er meer onderzoek in de huisartsenpraktijk gebeuren, omdat veel van de huidige richtlijnen gebaseerd zijn op gegevens van onderzoeken uit het ziekenhuis terwijl die patiënten niet goed vergelijkbaar zijn met patiënten die worden behandeld in de huisartsenpraktijk. Voor wat betreft de astma-actie-plannen moet nog onderzocht worden wat het beste 'gele' en 'oranje' actiepoint is, omdat wij alleen naar 'rood' hebben gekeken. En als laatste staat de ontwikkeling van IT in de gezondheidszorg nog in de kinderschoenen en zouden er meer goede en veilige oplossingen voor het gebruik hiervan onderzocht moeten gaan worden.

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Curriculum Vitae

Persijn Honkoop was born on June 18th 1980 in Goes, the Netherlands. After graduating in 1998 from secondary school, the Calvijn College Goes, he started studying Medicine at the University of Antwerp. After one year he continued his study at the Leiden University Medical Center and graduated in 2006. After his graduation, he worked as attending physician at the department of Internal Medicine, Cardiology and Pulmonology at the Groene Hart Ziekenhuis in Gouda. In 2007 he started his vocational training for General Practitioner, which he combined from 2008 onward with his PhD project at the department of Medical Decision Making at Leiden University Medical Center (under supervision of dr. J.K. Sont, prof. W.J.J. Assendelft and prof. J. Kievit). In 2010 he received a Research Fellowship grant from the Lung Foundation Netherlands, which he used to work as a honorary research fellow at the Dunedin School of Medicine in New Zealand (under supervision of prof. D.R. Taylor). In 2012 he received an Aiosko grant from the Leiden University Medical Center, which he used to continue his PhD.

From 2010-2012 he was a board member of the National Organisation for Family Doctor Trainees (LOVAH) and of the Dutch National Organisation for Family Doctor Trainees and PhD-students (Aiotho-netwerk). From 2012 until present he has been the Dutch representative in the Europe Council of the Vasco Da Gama Movement, the WONCA Europe network for new and future General Practitioners and from 2013-2015 he has also been the liaison Research of the Executive Board of the Vasco Da Gama Movement.

In 2014 and 2015 he has worked as scientific employee of the Dutch College of General Practitioners (NHG), where he was involved in the development of Quality Indicators for chronic diseases and co-authored the book 'Protocollaire astma en COPD zorg'.

In 2012 he finished his vocational training as General Practitioner and since then he has worked part-time as a locum General Practitioner. In 2016 he plans to start his own practice within the Wantveld Healthcare Centre in Noordwijk.

In 2015 he has started as a senior researcher at the Leiden University Medical Center, where he works on a project regarding the use of mHealth in the management of asthma.

