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.

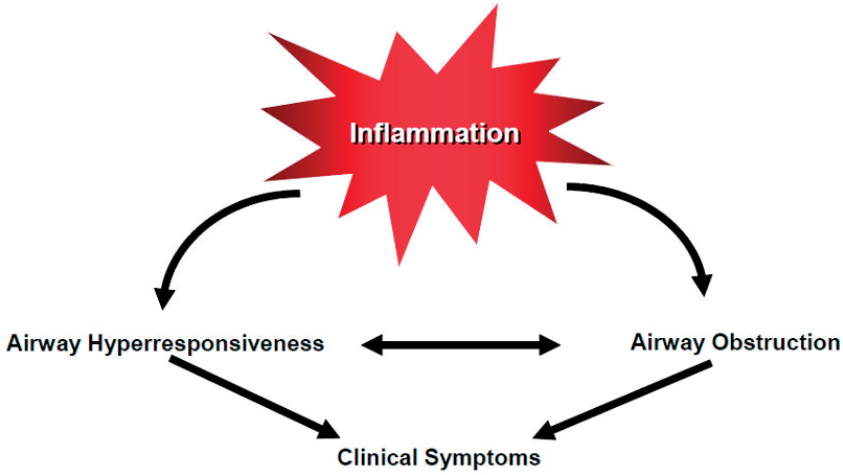

Figure 1.1. Interplay between airway inflammation and clinical symptoms.
Adapted from figure 2-1 of the NAEPP guideline 2007 [1].

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 ≥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 (FEV_1), 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

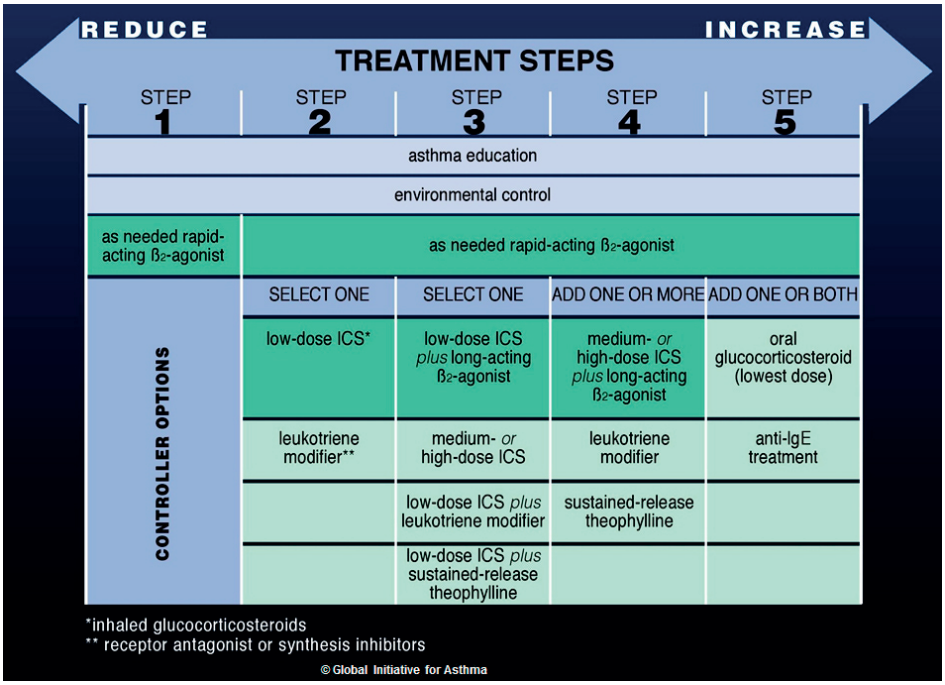

Figure 1.2. Medication at different treatment steps
Adapted from figure: Management approach based on control, chapter 4 of the GINA guideline 2012 [5].

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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