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. 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 (ACQ>1.5), while FeNO was low (FeNO<25), in ≥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 advices 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 predictedan 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.smartinhaler.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 advices 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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