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 < ACQ score ≤ 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-

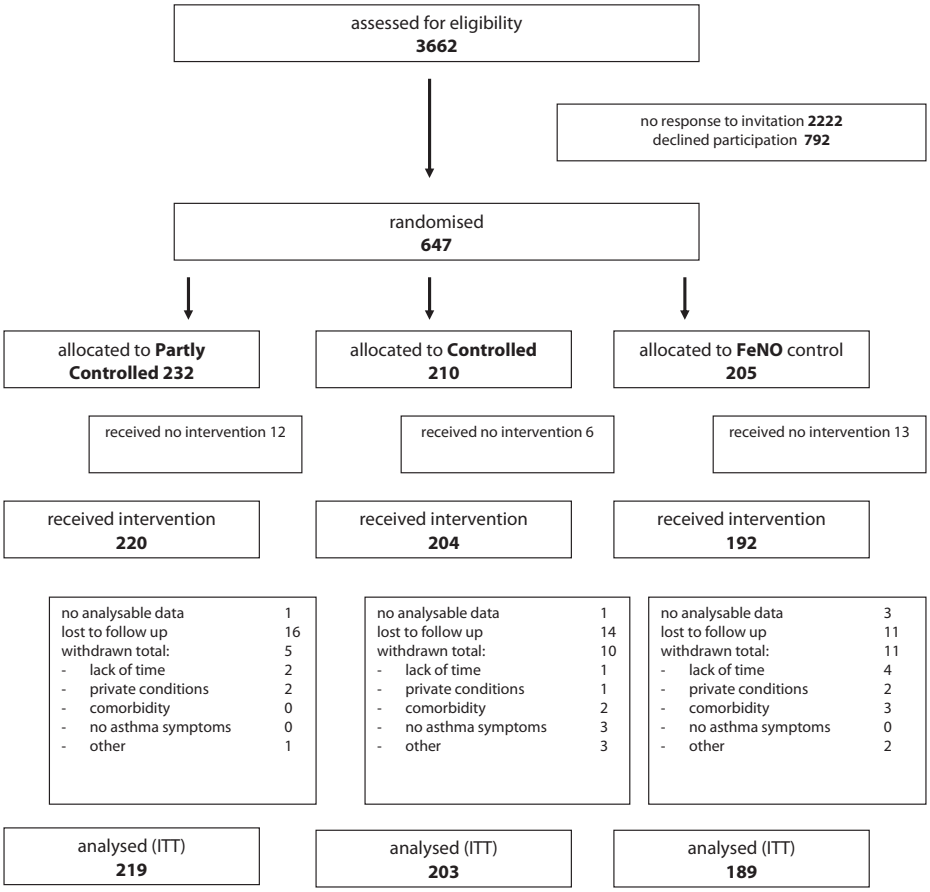

Figure 4.1. Consort Flow diagram ACCURATE trial.
647 patients provided informed consent, of which 31 withdrew before the first visit to the general practice and before filling out online questionnaires. Since randomisation was performed at group level they were randomized, but they were unaware of their 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>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 × ICS	step-up: 2 x 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:

$$\lambda \times \Delta QALY - \Delta costs,$$

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 (ΔACQ 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
%F = percentage female
BMI = Body Mass Index
IgE = immunoglobulin E
FEV1 = Forced Expiratory Volume in one second
Ppb = parts per billion
Mcg= microgram
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

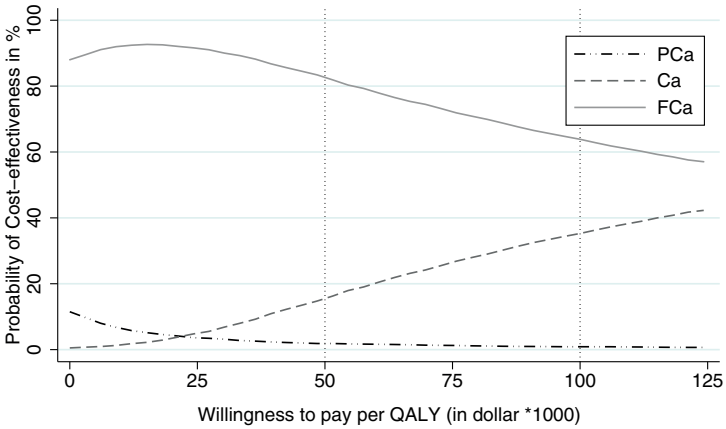

Figure 4.2. Cost-effectiveness acceptability curve.
This figure shows the probability that a strategy is the most cost-effective compared to the other two strategies at different willingness-to-pay per QALY levels from a societal perspective, which includes all healthcare costs and costs due to loss 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 Szefler 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 (Szefler 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 FEV_1, 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 the general Dutch consumer price index [E5].

Clinical and patient outcomes

For the online assessment of the ACQ at home, percentage predicted FEV_1 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:

$\lambda \times \Delta QALY - \Delta costs$

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; rho 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 months†			Differences between strategies‡		
	Partly Controlled	Controlled	FeNO	CavsPCa	FCavsPCa	FCavsCa
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)	−0.05 (−0.15 to 0.06)
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)	0.04 (−1.4 to 1.5)
ACQ category						
Controlled	54.8	68.0	61.4	P=0.01*‖	P=0.28‖	P=0.75‖
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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