

Anti-inflammatory Treatment of Atopic Asthma Guided by Exhaled Nitric Oxide: A Randomized, Controlled Trial

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What is already known about this topic? Previous randomized controlled trials on the fraction of exhaled nitric oxide ($F_{\text{E}}\text{NO}$) guided asthma management has been conducted within secondary care or on asthma subpopulations (pregnant women); the outcomes have been mixed.

What does this article add to our knowledge? This is the first randomized controlled study on $F_{\text{E}}\text{NO}$ -guided asthma management within primary care. $F_{\text{E}}\text{NO}$ -guidance resulted in improved asthma symptom control and reduced exacerbation frequency in adults with atopic asthma followed-up for 1 year.

How does this study impact current management guidelines? $F_{\text{E}}\text{NO}$ -guided anti-inflammatory treatment improved asthma outcomes and thus appears potentially useful in the long-term management of patients with atopic asthma.

BACKGROUND: Atopic asthma is characterized by Th2 cytokine-driven inflammation of the airway mucosa, which is signaled by the fraction of exhaled nitric oxide ($F_{\text{E}}\text{NO}$). **OBJECTIVE:** We tested whether an $F_{\text{E}}\text{NO}$ -guided anti-inflammatory treatment algorithm could improve asthma-related quality of life and asthma symptom control, and reduce exacerbations in atopic asthmatics within primary care.

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METHODS: Altogether, 187 patients with asthma and who were nonsmokers (age range, 18-64 years) with perennial allergy and who were on regular inhaled corticosteroid treatment were recruited at 17 primary health care centers, randomly assigned to 2 groups and followed up for 1 year. For the controls ($n = 88$), $F_{\text{E}}\text{NO}$ measurement was blinded to both operator and patient, and anti-inflammatory treatment was adjusted according to usual care. In the active group ($n = 93$), treatment was adjusted according to $F_{\text{E}}\text{NO}$. Questionnaires on asthma-related quality of life (Mini Asthma Quality of Life Questionnaire) and asthma control (Asthma Control Questionnaire) were completed, and asthma events were noted.

RESULTS: The Asthma Control Questionnaire score change over 1 year improved significantly more in the $F_{\text{E}}\text{NO}$ -guided group (-0.17 [interquartile range {IQR}, -0.67 to 0.17] vs 0 [-0.33 to 0.50]; $P = .045$), whereas the Mini Asthma Quality of Life Questionnaire score did not (0.23 [IQR, 0.07 - 0.73] vs 0.07 [IQR, -0.20 to 0.80]; $P = .197$). The change in Asthma Control Questionnaire was clinically important in subpopulations with poor control at baseline ($P = .03$). Furthermore, the exacerbation rate (exacerbations/patient/y) was reduced by almost 50% in the $F_{\text{E}}\text{NO}$ -guided group (0.22 [CI, 0.14 - 0.34] vs 0.41 [CI, 0.29 - 0.58]; $P = .024$). Mean overall inhaled corticosteroid use was similar in both groups ($P = .95$). **CONCLUSION:** Use of $F_{\text{E}}\text{NO}$ to guide anti-inflammatory treatment within primary care significantly reduced the exacerbation rate and improved asthma symptom control without increasing overall inhaled corticosteroid use. © 2013 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2013;1:639-48)

Key words: Asthma; Atopy; Breath test; $F_{\text{E}}\text{NO}$; Quality of life; Exacerbation; Corticosteroid; Leukotriene receptor antagonist; Primary care

Asthma is by definition a chronic inflammatory disorder of the airway mucosa. A majority of the cases are atopic asthma,

Abbreviations used

ACQ- Asthma Control Questionnaire
 BMI- Body mass index
 F_ENO- Fraction of exhaled nitric oxide
 FEV₁- Forced expiratory volume in 1 second
 FVC- Forced vital capacity
 GQLI- Gothenburg Quality of Life Instrument
 ICS- Inhaled corticosteroid
 IgE- Immunoglobulin E
 IQR- Interquartile range
 LABA- Long-acting β -2 agonist
 LTRA- Leukotriene receptor antagonist
 mAQLQ- Mini Asthma Quality of Life Questionnaire
 NO- Nitric oxide
 SABA- Short-acting β -2 agonist
 SD- Standard deviation

initiated by IgE sensitization to aeroallergens. Atopic asthma is characterized by Th2 lymphocyte-driven inflammation with recruitment and activation of eosinophilic granulocytes and mast cells, and inhaled corticosteroids (ICS) represent the most-effective maintenance therapy for this group of patients. Current asthma guidelines recommend that anti-inflammatory treatment should be based on the patient's symptoms, the need for short-acting β -2-agonists (SABA), and lung function. However, several studies have pointed out that asthma control in the population remains suboptimal despite guidelines and the introduction of long-acting β -2 agonists (LABA).¹⁻³ There also is evidence for overtreatment of asthma with ICS, which introduces an unnecessary risk of adverse effects.⁴ Thus, care of the patient with asthma needs to improve.

Exhaled nitric oxide (NO) has appeal as a marker to guide adjustment of anti-inflammatory treatment in patients with atopic asthma because it signals allergen-triggered Th2 cytokine-driven inflammatory mechanisms within the bronchial mucosa,⁵ gives reproducible results, and is responsive to changes in ICS doses.⁶ The use of exhaled NO as a complement to conventional monitoring of asthma based on symptoms has been studied in several randomized controlled trials, so far with equivocal results.⁷⁻¹² However, possible limitations in the design and methodology of these studies have been identified.¹³ For example, the treatment algorithms used must allow the fraction of exhaled NO (F_ENO) to have an impact on treatment decisions in the active group. Otherwise, no difference in asthma outcomes can be expected.¹³ Furthermore, previous studies have not been performed within primary health care, in which most patients with asthma are generally managed. Thus, to our knowledge, this is the first point-of-care study on F_ENO-guided asthma treatment. The study has a pragmatic approach, which leaves the control group as close to usual care as possible, which further increases the generalizability of the study. For the purposes of this study, usual care is defined as routine clinical assessment according to the Swedish Medical Product Agency guidelines. Because F_ENO is a marker of airway inflammation, we focused on anti-inflammatory treatment, and LABAs were not allowed.¹¹ The objectives of this study were to investigate if F_ENO guidance could improve asthma-related quality of life, asthma symptom control, and/or the exacerbation rate in patients with atopic asthma over a study period of 1 year. We also wanted to examine in what way F_ENO-based

TABLE I. F_ENO algorithm

F _E NO (ppb)		Treatment step change
Women	Men	
<19	<21	↓ 1 step
19-23	21-25	No change
≥24	≥26	↑ 1 step*
≥30	≥32	↑ 2 steps†

*No change in the treatment step if on step 4 or 5 and when using ≤ 2 inhalations of SABA/wk.

†Only if on treatment step 1.

TABLE II. Treatment steps

	1	2	3	4	5*	6*
Budesonide (μ g/d)	0	200	400	800	800 + LTRA	1600 + LTRA
Fluticasone (μ g/d)	0	100	250	500	500 + LTRA	1000 + LTRA
Mometasone (μ g/d)	0	100	200	400	400 + LTRA	800 + LTRA

*LTRA, montelukast 10 mg.

monitoring would change therapy, which has not been described in great detail previously.

METHODS

Study design and participants

This multicenter, open-label, parallel-group, randomized controlled study was conducted at 17 primary health care centers in 7 different autonomous health care regions in central and southern Sweden from November 2006 to March 2010 (the NOAK study [optimization of anti-inflammatory asthma treatment using exhaled NO to improve asthma-related quality of life within primary health care]) (the investigators are presented in this article's Online Repository at www.jaci-inpractice.org). A total of 187 participants were randomized to the F_ENO-guided treatment or the control group. Eligible participants had a physician's diagnosis of asthma, had been on prescribed ICS treatment for at least 6 months, and had confirmed IgE sensitization to at least 1 major airborne perennial allergen (dog, cat, or mite). In addition, they were 18 to 64 years old, nonsmokers since at least 1 year earlier and with a smoking history of <10 pack years (see Methods in this article's Online Repository at www.jaci-inpractice.org). The study was approved as a multicenter study by the regional ethics committee in Stockholm (Dnr: 2006/185-31). All the participants provided written informed consent.

Procedures

At visit 1 (screening), eligibility was confirmed and informed consent collected. Capillary blood was sampled to confirm perennial allergy by using ImmunoCAP Rapid Wheeze/Rhinitis Child (Phadia AB, Uppsala, Sweden). All the patients currently being treated with combination inhalers (corticosteroid plus LABA) were required to switch to the corresponding single corticosteroid inhaler and to withdraw the LABA component. All patients switched SABA to a salbutamol inhaler (Buventol Easyhaler; Orion Corp, Espoo, Finland), which incorporates a dose counter. The examination at visit 2 (2-4 weeks later) included F_ENO measurement (NIOX MINO; Aerocrine AB, Solna, Sweden),¹⁴ spirometry with reversibility, asthma-related

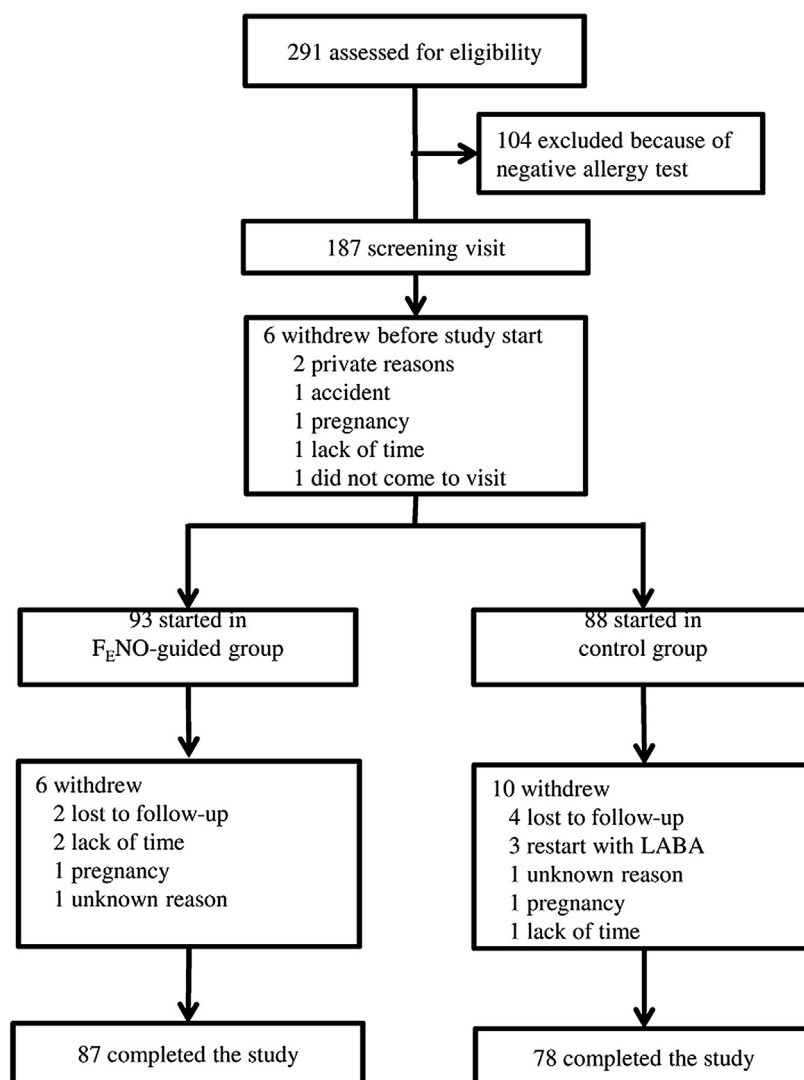


FIGURE 1. Trial profile.

quality of life (Juniper Mini Asthma Quality of Life Questionnaire [mAQLQ]),¹⁵ generic quality of life (the Gothenburg Quality of Life Instrument),¹⁶ asthma control (Juniper 6-item Asthma Control Questionnaire [ACQ]),¹⁷ and a questionnaire on allergen exposure (see F_ENO measurement, mAQLQ, the Gothenburg Quality of Life Instrument, and ACQ in this article's Online Repository at www.jaci-inpractice.org). Venous blood was sampled for serum IgE analysis. In the F_ENO-guided group, the anti-inflammatory treatment (ICS and leukotriene receptor antagonist [LTRA]) was adjusted according to an algorithm based on exhaled NO levels (Table I) and 6 fixed treatment steps (Table II). Cutoff levels were based on data that showed that most healthy subjects had F_ENO levels below 20 ppb and on the suggestion that levels above approximately 25 ppb are associated with eosinophilic inflammation.^{18,19} Also, the cutoff levels took into consideration the fact that men have slightly higher values than women, and a gray zone of 5 ppb was applied to avoid frequent dose changes.¹⁸ In the control group, F_ENO measurement was done but was blinded to both operator and patient, and treatment was adjusted according to usual care,

that is, based on patient-reported symptoms, SABA use, physical examination, and results of pulmonary function tests. The goal of the asthma treatment was to achieve and maintain clinical control, which implies that the patient should be free from symptoms; maintain normal activity levels, including physical exercise; maintain pulmonary function as close to normal as possible; avoid adverse effects of asthma medication; and have little or no need for reliever medication, all according to the Swedish Medical Product Agency recommendations (issued in 2002). In the control group, only the treatment steps described in Table II were allowed, but changes in treatment steps were entirely at the discretion of the treating physician, and immediate changes over several steps were allowed. Permissible treatment steps, shown in Table II, basically followed the prevailing national guidelines at the time of study start, issued in 2002 by the Swedish Medical Product Agency, with the exception that only LTRA was used as an add-on treatment. At visit 3 (2 months), the ACQ was filled in, exhaled NO was measured, and treatment was adjusted as described above. Visit 4 (4 months) also included mAQLQ and ACQ. Visit 5 (8 months) was

identical to visit 3. Visit 6 (12 months) was identical to visit 2 (see text and Table E1 in this article's Online Repository at www.jaci-inpractice.org for more information about procedures and study design). All the participants received a logbook to take home, in which they noted contacts with health care, changes in drug therapy, sick leave, or other problems between scheduled visits.

Clinical outcomes

The primary outcome was the change in mAQLQ score during the study. Secondary outcomes were changes in ACQ score, exacerbation frequency, lung function, generic quality of life score, and overall medication use. Exacerbations met the American Thoracic Society/European Respiratory Society Task Force criteria,²⁰ and we defined moderate exacerbations as deterioration in symptoms with the need to step up controller treatment for at least 2 days, with or without a concomitant clinic visit or contact. Prophylactic increase in controller treatment before the pollen season was disregarded. Severe exacerbations were defined as worsening in asthma that necessitated a course of oral corticosteroids.

Randomization and masking

Randomization was done by lottery; the participant picked 1 lot from an envelope. The envelope was prepared in advance by a study coordinator outside the primary health care center. The first envelope contained 8 lots, and subsequent envelopes (if needed) contained 6 lots. Lots were distributed at a 1:1 ratio in all envelopes. All the participants exhaled into the NO measurement apparatus, but the instrument's display was masked for the control group and thus not available to either the operator or the patient. All results were saved on smart cards and were extracted after the study was concluded.

Statistical methods

The sample size was calculated with a 2-sided 5% significance level and a power of 80%. A total of 64 participants per group was needed to detect a mean difference of 0.5 in mAQLQ between groups by assuming an SD of 0.7 (based on a pilot study).²¹ The data were analyzed on an intention-to-treat basis. Two-sided tests with *P* values less than .05 were considered significant. The primary end point and most of the secondary end points were analyzed by comparing changes between visit 2 and visit 6 according to the objectives of the study.

Results were analyzed with the Mann-Whitney *U* test for comparison between groups and the Wilcoxon signed rank test for analysis of change within groups between visits, or the corresponding Student *t* tests. Categorical data were analyzed with the χ^2 test or the Fisher exact test when applicable. Exacerbation rates were analyzed by using Poisson regression with group as an independent variable and time as an offset. The time to first exacerbation was analyzed by using the log-rank test and was graphically presented in Kaplan-Meier plots. In addition, the hazard ratios were estimated by using a Cox proportional hazards model adjusted for LABA use before study entry, age, sex, and body mass index. Statistical analyses were performed with Stata/IC11 version 2.14.1 (Stata Corp, College Station, Tex) and R (Foundation for Statistical Computing, Vienna, Austria). We followed the CONSORT reporting policy. This study is registered with ClinicalTrials.gov (identifier NCT00421018).

TABLE III. Patient characteristics at baseline*

	Control (N = 88)	FE _{NO} guided (N = 93)
Demographic characteristics		
Men	46/88 (52.3)	48/93 (51.6)
Age (y)	41.1 ± 12.9	40.9 ± 11.8
Height (cm)	173.6 ± 9.8	172.9 ± 10.4
BMI (kg/m ²)	26.1 ± 4.79	27.0 ± 5.08
Education (rank 1-3)†	3 (2-3)	2 (2-3)
Employed	75/87 (86.2)	79/89 (88.8)
Married or cohabiting	71/85 (83.5)	78/90 (86.7)
Asthma and atopy characteristics		
Years since diagnosis (rank 1-5)‡	4 [3-5]	5 [3-5]
No. of positive allergens (maximum 9)§	4 [3-6]	4 [3-5]
Sensitized to a seasonal allergen	65/87 (75)	67/92 (73)
Total IgE (kU/L)	102 [54-260]	135 [63-307]
Sum of IgE – perennial allergens (kU/L)	11 [3.4-26]	12 [3.7-44]
FE _{NO} (ppb), geometric mean [95% CI]	21.6 (18.7-25.0)	22.0 (19.3-25.2)
Budesonide equivalent ICS dose (μg/d)	400 [400-800]	400 [400-800]
LABA use before study entry	30/88 (34.1)	24/93 (25.8)
ACQ	0.83 [0.33-1.5]	0.83 [0.5-1.5]
Quality of life		
mAQLQ	5.93 [5.07-6.53]	5.93 [5.27-6.73]
GQLI	5.31 [4.89-5.83]	5.44 [4.83-5.80]
Spirometry		
FEV1 (% predicted)	83.7 ± 12.5	84.3 ± 14.1
FVC (% predicted)¶	87.4 ± 11.3	88.7 ± 12.5
FEV1/FVC¶	0.79 ± 0.08	0.78 ± 0.08
Reversibility (mL)	203 ± 178	221 ± 192
Significant reversibility#	14/86 (16.3)	21/92 (23.0)

BMI, Body mass index; GQLI, Gothenburg Quality of Life Instrument.

*Data are median [IQR], mean ± SD, or no./N (%), unless otherwise indicated; all *P* values are >.10; statistical tests used: Student *t* test, Mann-Whitney *U* test, and χ^2 test.

†Compulsory, 1; secondary, 2; university, 3.

‡1, 0-2 y; 2, 3-5 y; 3, 6-10 y; 4, 11-20 y; 5, >20 y.

§Analyzed allergens: cat, dog, birch, timothy, horse, mite (2 different mites), mugwort, and cladosporium.

||Perennial allergens tested were cat, dog, horse, mite, and cladosporium.

¶For FVC, spirometry measures are after bronchodilation.

#Measured as ≥12% improvement of FEV₁ and ≥200 mL.

RESULTS

In all, 187 participants were included at 17 primary health care centers from November 2006 to March 2009, and the study ended in March 2010. A total of 54 participants stopped LABA treatment at study entry. Six participants withdrew before randomization. Thus, 181 participants (48% women) came to the baseline visit (visit 2), and 165 completed the study (Figure 1). Participants who withdrew before the end of the study had significantly worse asthma control and lower scores in the activity domain of the mAQLQ than those who completed the study (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Those who stopped using LABA did not withdraw more than those who did not use LABA before study entry (*P* = .999). There was no significant difference

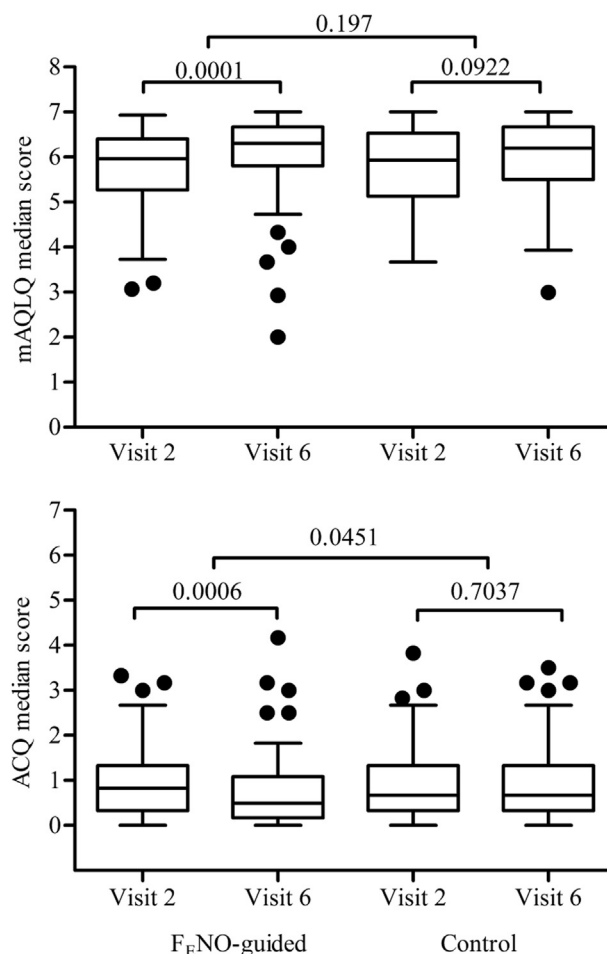


FIGURE 2. Comparison within and between groups. Median scores on mAQLQ and ACQ at visits 2 and 6.

between study groups in terms of participants who withdrew from the study (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). At baseline, the mean (SD) age was 41 ± 12.4 years, the median daily ICS dose was 400 $\mu\text{g}/\text{d}$ (interquartile range [IQR], 400-800 $\mu\text{g}/\text{d}$) budesonide equivalents, mean (SD) FEV₁ was $84.0\% \pm 13.3\%$, geometric mean FENO value of 20.4 ppb (95% CI, 18.5-22.5 ppb), the median mAQLQ score of 5.93 (IQR, 5.20-6.47), and median ACQ score of 0.83 (IQR, 0.33-1.50) (Table III). The mean (SD) study treatment period was 387 ± 48.4 days in the FENO-guided group and 377 ± 36.7 days in the control group ($P = .13$). Adherence to the FENO algorithm was 85%-88% in the FENO-guided group, whereas the treatment decisions in the control group mimicked the FENO algorithm in less than 30% of decision points, with a trend to lower congruence toward the end of the study (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). The most common reason not to follow the algorithm in the FENO-guided group was declining to use a lower treatment step because of the approaching pollen season.

The median overall mAQLQ score changed significantly within the FENO-guided group ($P = .0001$), but the change was not significantly larger than that in the control group ($P = .197$) (Figure 2, A). However, analysis of the domains of the mAQLQ revealed that improvement of the symptom domain was

TABLE IV. The number of patients with a clinically important change in the ACQ score during the study

	ACQ score change	Control group, no./N (%)	FENO-guided group, no./N (%)	<i>P</i> *
All participants	<0.5	55/74 (74)	52/81 (64)	
	≥ 0.5	19/74 (26)	29/81 (36)	.17
ACQ >1.25 at baseline	<0.5	12/22 (55)	5/22 (23)	
	≥ 0.5	10/22 (45)	17/22 (77)	.03
ACQ >1.5 at baseline	<0.5	8/15 (53)	3/17 (18)	
	≥ 0.5	7/15 (47)	14/17 (82)	.03

* χ^2 test.

significantly larger in the FENO-guided group than in the control group ($P = .041$) (see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

Asthma control rated with ACQ showed that patients were generally well controlled at study start (Table III). A significantly larger improvement of the ACQ score was noted in the FENO-guided group compared with the control group ($P = .045$) (Figure 2, B). The effect on ACQ and the symptom domain of

TABLE V. Efficacy results over a 1-year study period*†

	Control	No. controls	F _E NO guided	No. F _E NO guided patients	P‡
Quality of life					
mAQLQ	0.07 [−0.20 to 0.80]	77	0.23 [0.07-0.73]	80	.197
GQLI	0 [−0.39 to 0.39]	78	0.06 [−0.22 to 0.28]	85	.666
Exacerbations					
Moderate (≥1 event)	20/88 (22.7)	88	8/93 (8.6)	93	.009
Severe (≥1 event)	6/88 (6.8)	88	8/93 (8.6)	93	.654
Any (≥1 event)	25/88 (28.4)	88	15/93 (16.1)	93	.047
No. of exacerbations/patient/y (95% CI)	0.41 (0.29-0.58)	88	0.22 (0.14-0.34)	93	.024
Asthma control					
ACQ	0 [−0.33 to 0.50]	74	−0.17 [−0.67 to 0.17]	81	.045
F _E NO (ppb), arithmetic mean	−1.46 ± 23.86	76	−2.57 ± 20.94	87	.75
Lung function					
FEV ₁ (l)	−0.006 ± 0.28	78	−0.034 ± 0.28	88	.648
FVC (l)§	−0.019 ± 0.29	78	−0.084 ± 0.35	88	.185
FEV ₁ /FVC§	0.002 ± 0.054	78	0.009 ± 0.057	88	.396
Reversibility (mL)	1.54 ± 178	78	18.3 ± 186	88	.652
Treatment					
Budesonide equivalent ICS dose (μg/d)	0 [−200 to 200]	78	0 [−400 to 400]	86	.945
Participants with LTRA	19/85 (22.4)	85	33/92 (35.9)	92	.069
Months on LTRA	1.81 ± 3.89	85	2.87 ± 4.42	92	.094

GQLI, Gothenburg Quality of Life Instrument; l, litre.

*Values presented in the table represent the change between visits 2 and 6 unless otherwise indicated.

†Data are shown as median [IQR], mean ± SD, or no./N (%), unless otherwise indicated.

‡Student *t* test and Mann-Whitney *U* test. Estimated “No. of exacerbations/patient/y” is based on Poisson regression with time as offset.

§For FVC, spirometry measures are after bronchodilation.

||At any time during the study.

mAQLQ was only significant when changes over the whole study period were compared (see text and Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In an analysis of the proportion of patients that showed a clinically important improvement of the ACQ score (≥0.5), a higher proportion was noted in the F_ENO-guided group, but this was not significant. In a subgroup analysis in patients with inadequately controlled asthma at baseline (ACQ score, >1.25 or >1.5), this proportion was significantly larger in the F_ENO-guided group (Table IV).

The use of SABA did not differ significantly between the groups at any time point and did not change over time within any group (see Table E6 in this article's Online Repository at www.jaci-inpractice.org). The groups did not differ significantly in terms of mean F_ENO (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org) or measures of lung function (FEV₁, FVC, FEV₁/FVC, and reversibility) during the study (Table V). Generic quality of life was measured with the Gothenburg Quality of Life Instrument, but no significant differences between the groups were noted.

We recorded a total of 52 exacerbations (35 moderate and 17 severe), and they were distributed as follows: January-March (14), April-June (12), July-September (8), and October-December (18). A significantly lower cumulative incidence of exacerbations was found in the F_ENO-guided group versus the control group (*P* = .029) (Figure 3). This was dependent on the fact that moderate exacerbations were reduced in the F_ENO-guided group (*P* = .006) (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org): 9 exacerbations in 8 participants compared with 26 exacerbations in 20 participants

in the control group. The proportion of patients who experienced at least one exacerbation was significantly lower in the active group (*P* = .047) (Table V). In a Cox proportional hazards model adjusted for confounding factors, the hazard ratio for having a moderate exacerbation still showed a significant difference between the study groups (0.349 [CI, 0.152-0.798]; *P* = .013). The number needed to treat was 9. We found no significant difference in the number of severe exacerbations between the groups (Table V) (see Figure E4 in this article's Online Repository at www.jaci-inpractice.org).

A change in treatment step was more common in the F_ENO-guided group than in the control group at visits 2-4, but this difference had disappeared by visit 5 due to a gradual decline in the proportion of patients who changed treatment steps in the active group. The number of changes between treatment steps was generally lower in the control group and remained relatively stable throughout the study (see Table E7 in this article's Online Repository at www.jaci-inpractice.org). The mean ICS dose did not differ between groups (Figure E2). However, clear differences developed between the groups over time when concerning the distribution of treatment steps (Figure 4). This distribution changed significantly between visits 2 and 6 in both the F_ENO-guided (*P* < .0001) and the control group (*P* = .024). There was no difference between the groups in the distribution of treatment steps at visit 2 (*P* = .83) but the difference was significant at visit 6 (*P* = .035), mainly due to more patients ending up at the lowest and highest treatment steps in the F_ENO-guided group (Figure 4). These changes in treatment resulted in slightly more LTRA use in the F_ENO-guided group, but the difference was not statistically significant (Table V).

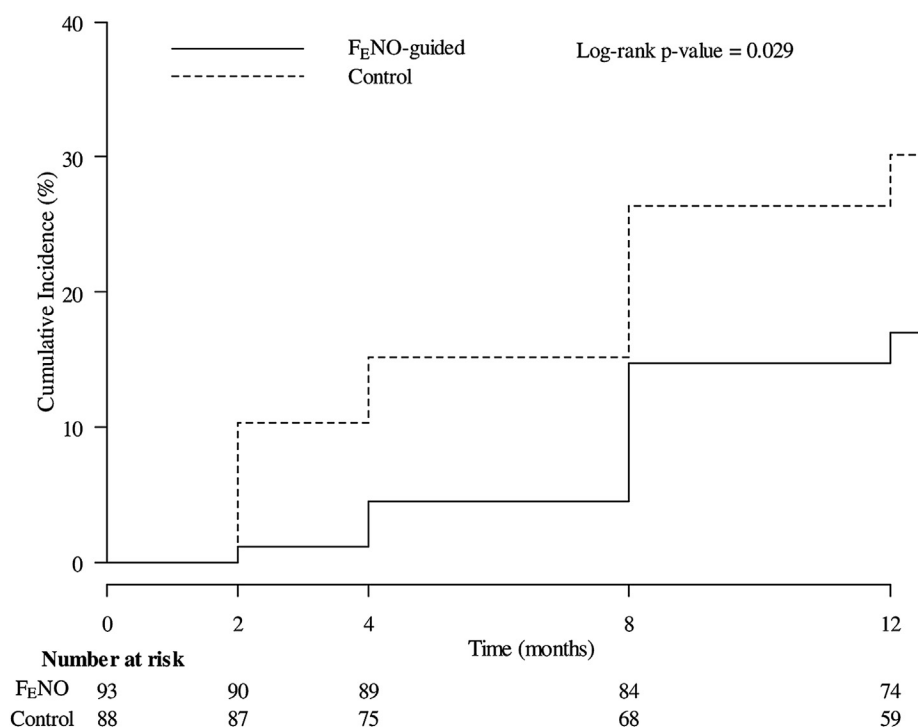


FIGURE 3. Time to any exacerbation.

DISCUSSION

To our knowledge, this is the first randomized controlled trial that has assessed the value of using $F_{E}NO$ to guide asthma treatment in a primary health care setting. In this multicenter study, anti-inflammatory treatment was adjusted according to $F_{E}NO$ over a 1-year period in patients with atopic asthma, and the outcome was compared with that of patients treated according to the clinics' standard procedure. The main findings were that guiding anti-inflammatory treatment by means of $F_{E}NO$ slightly improved asthma symptom control as shown by the ACQ instrument, and this was clinically important for ACQ subpopulations with inadequately controlled asthma at baseline. Moreover, $F_{E}NO$ guidance reduced the rate of exacerbations. These benefits were probably attained because the $F_{E}NO$ treatment algorithm shifted the distribution of treatment steps, with more participants at the lowest (no treatment) and highest step of anti-inflammatory treatment compared with the control group. However, this occurred without increasing overall ICS use.

Some previous studies in adults have not been able to show a reduction in reported symptoms in the $F_{E}NO$ -guided group,^{10,11,22} whereas Powell et al²³ reported that the use of $F_{E}NO$ measurement significantly improved the ACQ score in a subpopulation of pregnant women with asthma. We saw a small but statistically significant effect on ACQ in our study, even though the effect may be considered not clinically important when looking at the whole population. The effect on ACQ was supported by a similar effect on the symptom domain of mAQLQ in our material, in line with the strong relationship between these two instruments in previous primary care studies.²⁴ The total mAQLQ score was not significantly affected in our study, similar to other studies on biomarker-guided asthma treatment.^{23,25} The patients in this study had mild or moderate

asthma. When judging from their quality of life and asthma control scores at baseline, they were generally well treated at study entry, better than the general asthma population managed within primary health care in Sweden.² This is probably an effect of the investigators being experienced general practitioners with a special interest in asthma. Furthermore, all the patients had to be having ICS treatment to be included in the study. In spite of using a study group that in all probability provided less room for improvement than the general asthma population (ceiling effect), significant improvements in asthma control were seen in the $F_{E}NO$ -guided group. Also, and in line with the reasoning above, the proportion of patients who showed a clinically important improvement of their ACQ score was significantly higher in the $F_{E}NO$ -guided group when analyzing subpopulations with inadequately controlled asthma at baseline. It is interesting to note that these results were achieved solely by optimizing anti-inflammatory treatment, without the step-up of bronchodilatory agents. It also is noteworthy that the effect on asthma symptom control was incremental over the study period in the $F_{E}NO$ -guided group, whereas a transient effect on these end points was seen in the control group (see this article's Online Repository at www.jaci-inpractice.org). This is probably explained by more and more patients in the active group reaching an optimal level of anti-inflammatory treatment during the course of the study, whereas increased attention brought along transient improvements among the controls. Furthermore, the treatment algorithm probably favored the control group in the beginning of the study because there were no restrictions on the increase in treatment level in this group. The nonlinear effect on these end points together with the fact that these variables showed strongly skewed distribution indicate that analysis by using mixed linear models is not optimal, and such analyses did turn out to be

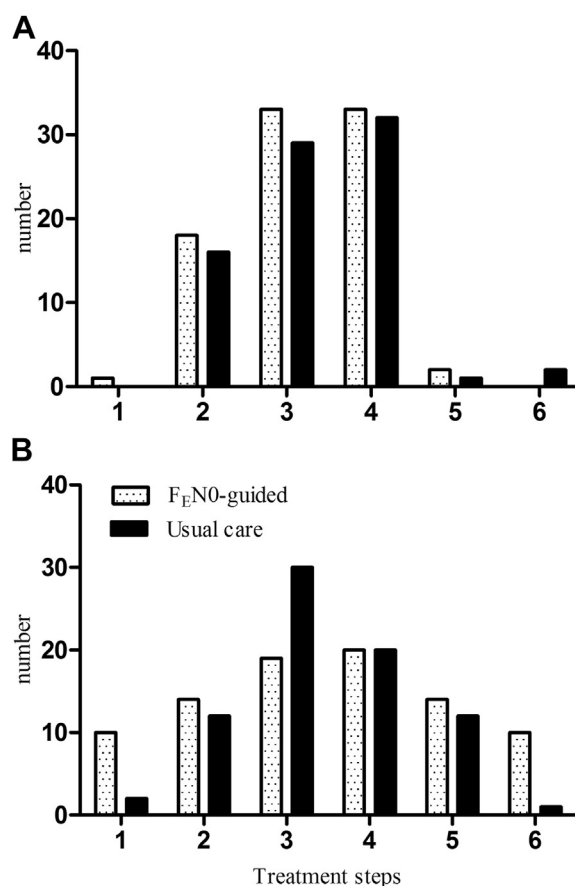


FIGURE 4. Distribution of treatment steps at (A) visit 2 and (B) visit 6. There was no difference between the groups in the distribution of treatment steps at visit 2 ($P = .83$) but the difference was significant at visit 6 ($P = .035$). Statistics: Fisher exact test.

nonsignificant as would be expected. Moreover, to be able to see the full effect of F_ENO guidance, it might have been more appropriate to titrate more frequently at the beginning of the study, or, alternatively, to follow up the patients for a longer period than 1 year. These potential problems with F_ENO algorithm studies were recently highlighted by Gibson.¹³

We also were able to show a significant reduction in asthma exacerbations among those in this population of patients with asthma in primary care whose treatment was guided by F_ENO. The effect was related to a reduction in moderate exacerbations, whereas the rate of severe exacerbations (prednisolone courses) was unchanged. Severe exacerbations were few in this study, fewer than in the general asthma population in our country,² which reduced our possibility of showing a significant effect on this end point. Furthermore, in a *post hoc* analysis of a study of daily monitoring of F_ENO in children with asthma, an increase in exhaled NO could predict moderate but not severe exacerbations.²⁶ However, we could not find a relationship between preceding F_ENO values and moderate exacerbations, which is probably due to the comparatively long measurement intervals in our study. A possible explanation for our results is that severe exacerbations are primarily caused by rhinovirus infections,^{27,28} and it is well recognized that stepping up ICS treatment has little effect on virus-induced exacerbations.²⁹ Moderate exacerbations may be more closely related to allergen exposure with a buildup of inflammation, which F_ENO signals for early on.^{26,30} The

reduction in the rate of moderate exacerbations was probably a result of intensified anti-inflammatory treatment in patients with persistently high F_ENO levels, which also led to higher use of LTRA in the F_ENO-guided group, although nonsignificant. The proportion of patients who used any LTRA was 60% higher in the F_ENO group, and this could have added to the effect on exacerbations as well as on symptom control.^{31,32} However, the addition of LTRA to treatment with intermediate-to-high doses of ICS only causes a minor further reduction in F_ENO in patients with asthma,³³ which is consistent with F_ENO being similar in the 2 groups in our study. Four previous randomized controlled trials on F_ENO guidance had exacerbations^{10,11,23} or treatment failure³⁴ as primary end point, but only the study by Powell et al²³ was able to show a significant effect. Two other studies^{10,11} were smaller than our study and the one by Powell et al,²³ and probably had a lack of sufficient power. The fourth study³⁴ was larger than ours but included only patients with asthma that was well controlled on low doses of ICS, which probably left very little room for improvement in the F_ENO-guided arm compared with the other arms. A limitation of our study was the lack of historic data on exacerbations because moderate exacerbations, as defined by American Thoracic Society/European Respiratory Society criteria, were impossible to retrieve from medical records.²⁰

There recently was a call for effectiveness studies in the real-world setting, including primary health care.³⁵ An earlier

uncontrolled study in primary care showed a significant increase in the proportion of patients with well-controlled asthma, although ICS use was slightly reduced, after asthma management based on a $F_{E}NO$ algorithm.³⁶ In our study, we aimed at determining the real-world effectiveness of $F_{E}NO$ -guided treatment algorithms by using the randomized controlled trial design applied in a pragmatic way entirely within primary health care. For example, the control group was as close to usual care as possible. Thus, a structured algorithm was not used in this group, which might have increased the risk of bias. However, we could not detect any sign of mismanagement of the control group. Rather, asthma symptom control also increased slightly in this group. Furthermore, it might not be appropriate to introduce an end point variable such as symptom control in the treatment algorithm. The patient sample was representative, with only minor limitations. We did not use strict objective criteria for asthma diagnosis. In this way, our study resembles several previous studies in the field.^{10,11,23} Use of objective criteria, eg, spirometry with a reversibility test, would greatly reduce the external validity of the study because reversibility is seen in only a fraction of treated patients with asthma.³⁷ Smokers were excluded from the study, but only 10% of patients with asthma in the Swedish population regularly smoke.² Also, only patients with atopic asthma were included. However, subjects who were atopic constitute the bulk of patients with asthmas in our country, up to approximately 75% of adult patients as evidenced by broad IgE determination.³⁸ Thus, we believe that our study is highly generalizable for the primary care sector. The rationale for using exhaled NO as a marker of asthmatic inflammation is that it indicates bronchial Th2 cytokine-driven inflammation,⁵ and, by selecting subjects with atopic asthma, we ensure that increased disease activity is reflected by $F_{E}NO$.³⁹ Thus, these patients should be suitable for a trial on the $F_{E}NO$ -based adjustment of ICS dose, whereas patients who are not atopic, at least the subgroup with noneosinophilic asthma, would be less suitable.⁴⁰

In conclusion, we have shown in a primary care study with high external validity, that anti-inflammatory asthma therapy guided by $F_{E}NO$ measurement compared with usual care, reduced exacerbation rate and improved asthma symptom control without increasing overall ICS use. The improvement of asthma symptom control was clinically important in a subpopulation with poor control at baseline.

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METHODS

Inclusion criterion

Ability to read and understand the Swedish language.

Exclusion criteria

Ongoing pregnancy or breastfeeding, participation in another study, medical treatment solely with montelukast or in combination with an ICS in budesonide equivalent dose 0-400 µg (dose step 1-3 in the study), and unstable asthma, defined as ≥ 4 oral corticosteroid courses during the past year or hospitalization in the past 6 months. Smokers were excluded because they have lower $F_{E}NO$ values than nonsmokers and the reduction is related to smoking history.^{E1} At the time of study start, there was not enough data available to allow the adjustment of cutoffs according to smoking history. Excluding smokers also reduced the risk of including patients with mixed asthma and chronic obstructive pulmonary disease.

Procedures

$F_{E}NO$ was measured with a standardized method according to American Thoracic Society/European Respiratory Society guidelines.^{E2} Participants inhaled to total lung capacity and then immediately exhaled into the nitric oxide (NO) analyzer (NIOX MINO; Aerocrine AB, Solna, Sweden) for 10 seconds at a flow rate of 50 mL/s. The mean of 2 measurements was used. A third measurement was added if the 2 first differed $>10\%$.

The Gothenburg Quality of Life Instrument was used to assess generic quality of life. The Gothenburg Quality of Life Instrument has 18 questions about social, physical, and mental health. Social well-being was rated on the basis of answers to questions about home and family situation, housing, work situation, personal finances, health, and leisure time. Physical well-being was rated on the basis of answers to questions about hearing, vision, memory, fitness, and appetite. Mental well-being was rated on the basis of answers to questions about mood, energy, patience, self-confidence, and sleep.^{E3} All items were rated on a 7-point Likert scale from "very poor" (1 point) to "excellent, could not be better" (7 points).

Elizabeth Juniper's mAQLQ was used to assess asthma-related quality of life. There are 15 questions in the mAQLQ within 4

different domains (symptoms [5 items], activity limitation [4 items], emotional function [3 items], and environmental stimuli [3 items]). Participants score their experience during the past 2 weeks on a 7-point scale (7, not impaired at all; 1, severely impaired). The overall AQLQ score is the mean of all 15 responses, and the individual domain scores are the means of the items in those domains. A change in the score of 0.5 is considered the minimal clinically important difference. A cutoff that defines poor asthma-related quality of life has not been described.^{E4}

Elizabeth Juniper's ACQ with 6 questions ($FEV_1\%$ predicted was not included) was used to assess asthma control. Participants score their experience during the past week on a 7-point scale (0, no impairment to 6, maximum impairment). The ACQ score is the mean of the 6 questions. A change in the score of 0.5 is considered the minimal clinically important difference.^{E5} A score of >1.25 or >1.5 can be used to define not well-controlled asthma with a high positive predictive values.^{E6}

Patients with birch pollen sensitization were not to start the study during the birch pollen season and, if possible, avoid appointments during the season. Participants with a respiratory infection were asked not to come in until they were asymptomatic but not more than 4 weeks past the scheduled appointment. Participants whose asthma condition deteriorated were asked to turn primarily to the physician in charge of the study at the primary health care center. Asthma exacerbations were primarily treated with an increase in ICS or, if necessary, with oral corticosteroids. Participants who did not tolerate LTRA and those who did not have satisfactory control of their asthma with ICS and LTRA treatment, and needed to add LABA, were withdrawn from the study.

Statistical methods

ACQ and mAQLQ (including its separate domains) showed strongly skewed distributions that could not be transformed into bell-shaped distribution and were consequently analyzed nonparametrically. End points with at least 3 repeated measurements were analyzed with a linear mixed model with measurements after baseline as dependent variable and group, time, and baseline value as independent fixed factors. Subject was included as a random factor in the model.

RESULTS

Patients were recruited consecutively (50%), by letter or telephone call (20%), and by advertisement (30%), without significant difference between groups. The effect on the symptom domain of mAQLQ and ACQ was incremental over the study year in the $F_{E}NO$ -guided group, whereas a transient effect was seen on these end points in the control group (Figure E1). Also, in the control group, there was a trend toward a larger proportion of the treatment changes at visit 2 being increases in treatment level compared with the $F_{E}NO$ -guided group (74% vs 54%; $P = .07$). No significant effect of active treatment was seen when analyzing these end points by using the linear mixed model.

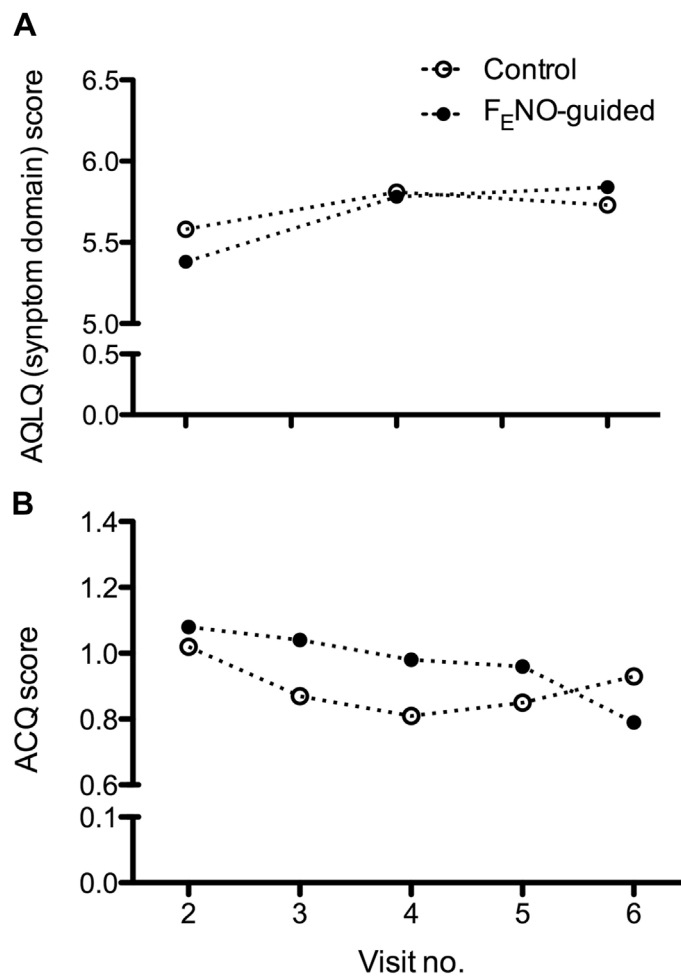


FIGURE E1. Changes in (A) AQLQ (symptom domain) and (B) ACQ scores during the study.

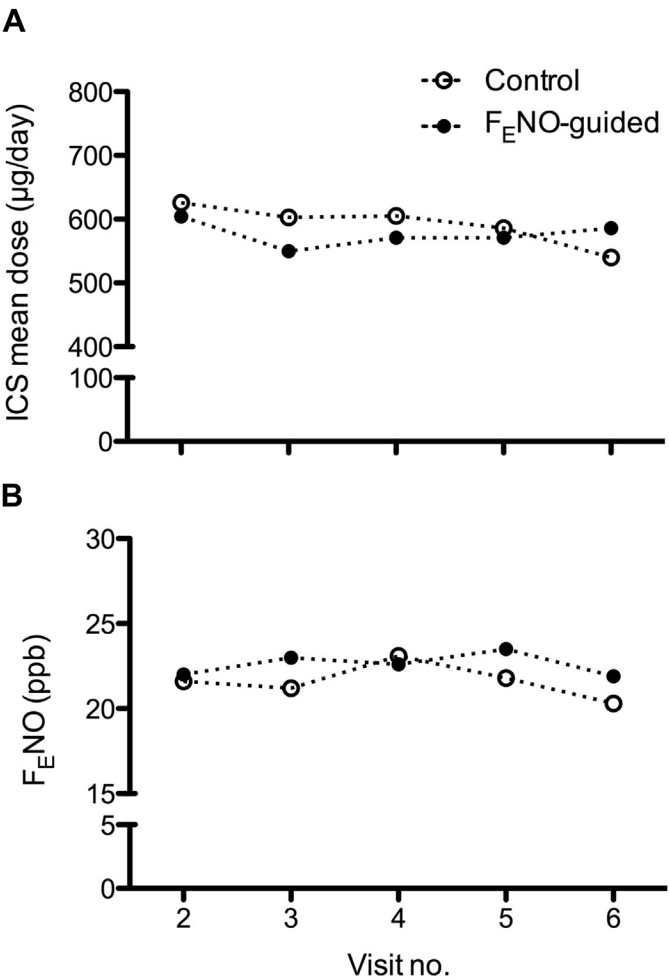


FIGURE E2. Changes in (A) mean daily ICS dose and (B) $F_{E}NO$ during the study.

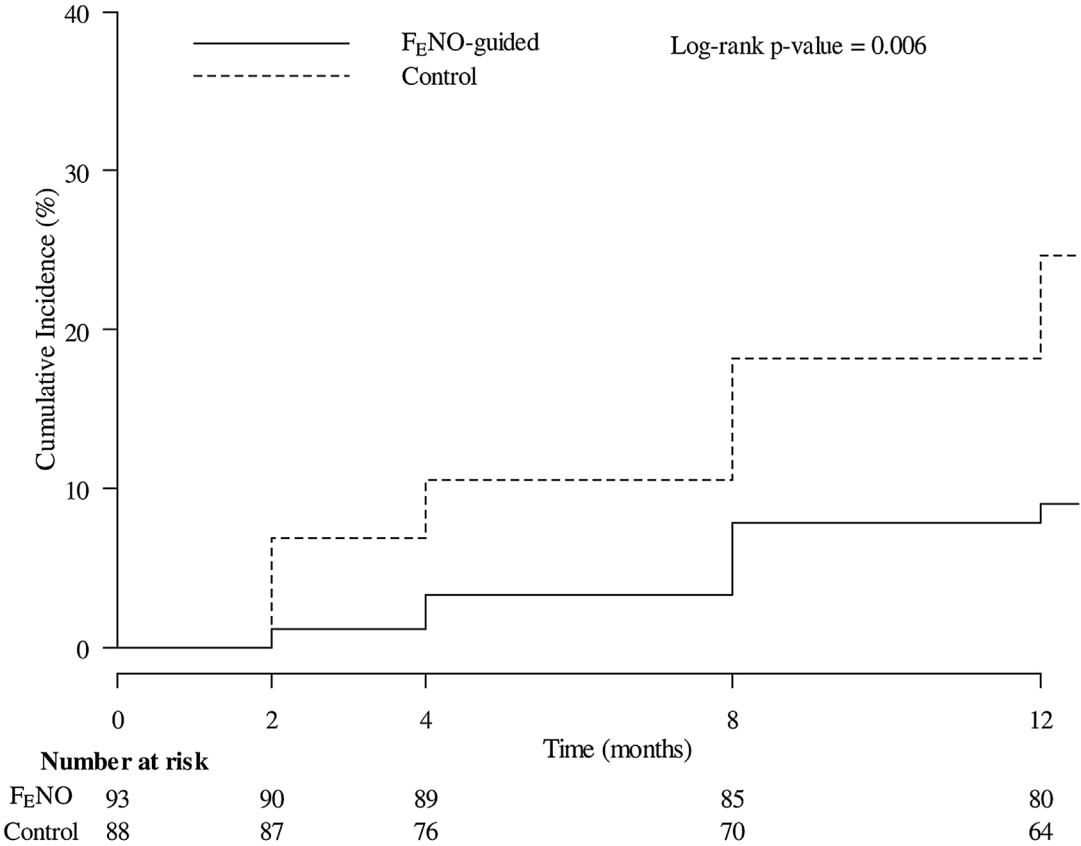


FIGURE E3. Time to moderate exacerbations.

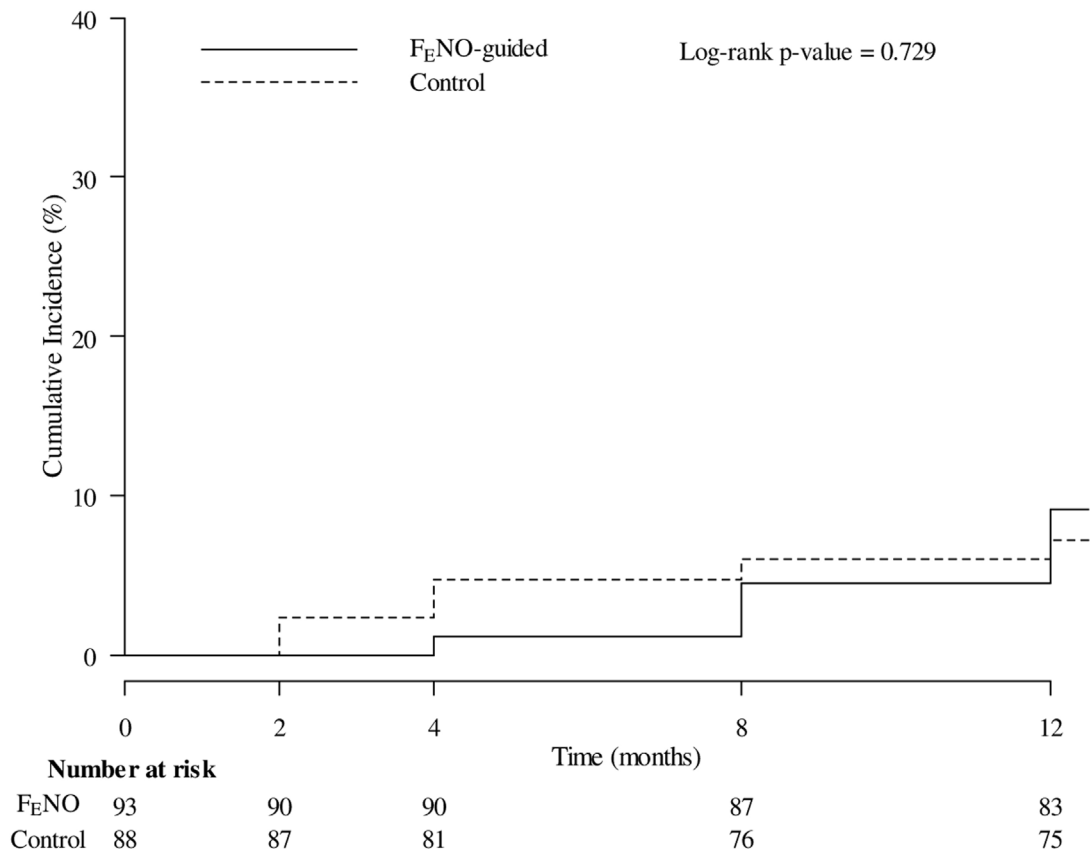


FIGURE E4. Time to severe exacerbations.

TABLE E1. Study design

	Visit 1, screening	Visit 2, baseline	Visit 3, 2 mo	Visit 4, 4 mo	Visit 5, 8 mo	Visit 6, 12 mo
ImmunoCAP Rapid capillary blood test, eligibility check for inclusion	×					
FE(NO)		×	×	×	×	×
Spirometry and reversibility test		×				×
mAQLQ		×		×		×
ACQ		×	×	×	×	×
GQLI		×		×		×
Registration of exacerbations, SABA and ICS use		×	×	×	×	×

GQLI, Gothenburg quality of life instrument.

TABLE E2. Patient characteristics at baseline for those who withdrew from the study and those who completed the study*

	No. withdrew	Withdrew	No. completed	Completed	P†
Demographic characteristics					
Men	16	9/16 (56.2)	165	85/165 (51.5)	.717
Age (y)	16	40.62 ± 13.2	165	41 ± 12.3	.908
Height (cm)	14	171.8 ± 12.1	164	173.4 ± 10.0	.579
BMI (kg/m ²)	14	26.2 ± 4.0	162	26.6 ± 5.0	.797
Education (rank 1-3)‡	13	2 (2-3)	160	3 (2-3)	.051
Employed	13	10/13 (76.9)	163	137/163 (84.0)	.452
Married or cohabiting	14	12/14 (85.7)	161	137/161 (85.1)	.950
Asthma and atopy characteristics					
Years since diagnosis (rank 1-5)§	15	5 [3-5]	165	4 [3-5]	.786
No. of positive allergens (maximum 9)	14	3.5 [2-4]	164	4 [3-5]	.087
Total IgE (kU/L)	14	123 [76.7-220]	164	108 [59.6-301]	.791
Sum of IgE — perennial allergens (kU/L)¶	14	5.88 [2.39-20.3]	164	14.2 [3.76-38.4]	.232
FE _{NO} (ppb), geometric mean [95% CI]	12	16.2 [10.0-26.0]	165	22.3 [20.2-24.6]	.100
Budesonide equivalent ICS dose (µg/d)	15	800 [400-800]	162	400 [400-800]	.094
LABA use before study entry	15	3/15 (20)	165	51/165 (31)	.377
ACQ, mean (0-6)	14	1.58 [1.33-2.0]	164	0.83 [0.33-1.33]	.005
Quality of life					
mAQLQ total (1-7)	13	5.50 [5.07-5.93]	165	5.93 [5.20-6.47]	.078
mAQLQ symptom	13	5.40 [4.20-5.60]	164	5.60 [4.80-6.40]	.330
mAQLQ emotional	13	5.33 [3.67-6.67]	165	6.00 [4.67-6.67]	.356
mAQLQ environment	13	5.50 [5.00-6.33]	162	6.00 [5.00-6.67]	.377
mAQLQ activity	13	5.50 [5.00-6.25]	162	6.50 [5.75-6.75]	.015
GQLI, mean (1-7)	14	4.97 [4.33-5.61]	164	5.39 [4.89-5.83]	.114
Spirometry					
FEV ₁ (% predicted)	12	85.5 ± 13.5	164	83.9 ± 13.3	.697
FVC (% predicted)#	12	91.2 ± 13.5	164	87.8 ± 11.8	.342
FEV ₁ /FVC#	12	0.80 ± 0.77	165	0.79 ± 0.76	.723
Reversibility (mL)	13	296 ± 197	165	206 ± 183	.089
Significant reversibility**	13	5/13 ± 0.38	165	30/165 ± 0.18	.077

BMI, Body mass index; CI, confidence interval; GQLI, Gothenburg Quality of Life Instrument.

*Data are median [IQR], mean ± SD, or no./N (%), unless otherwise indicated.

†Mann-Whitney *U* test, Student *t* test, and χ^2 test.

‡Compulsory, 1; secondary, 2; and university, 3.

§1, 0-2 y; 2, 3-5 y; 3, 6-10 y; 4, 11-20 y; 5, >20 y.

||Analyzed allergens: cat, dog, birch, timothy, horse, mite (2 different mites), mugwort, and cladosporium.

¶Perennial allergens: cat, dog, horse, mite, and cladosporium.

#For FVC, spirometry measures are after bronchodilatation.

**Measured as ≥12% improvement of FEV₁ and ≥200 mL.

TABLE E3. Baseline characteristics of patients who withdrew from the study*

	No.	Control	No.	F _E NO-guided	P†
Demographic characteristics					
Men	10	6/10 (60)	6	3/6 (50)	.696
Age (y)	10	39.4 ± 12.8	6	42.7 (14.8)	.550
Height (cm)	9	176 ± 9.97	5	165 (13.3)	.109
BMI (kg/m ²)	9	25.4 ± 4.52	5	27.7 (2.82)	.463
Education (rank 1-3)‡	6	2.5 (2-3)	6	2 (2-2)	.164
Employed	9	6/9 (67)	4	4/4 (100)	.768
Married or cohabiting	8	6/8 (75)	6	6/6 (100)	.186
Asthma and atopy characteristics					
Years since diagnosis (rank 1-5)§	10	5 (3-5)	5	4 (3-5)	.558
No. of positive allergens (maximum 9)	9	3 (2-4)	5	4 (3-4)	.779
Total IgE (kU/L)	9	195 [77.3-260]	5	84.6 [76.7-135]	.257
Sum of IgE — perennial allergens (kU/L)¶	9	3.57 [2.39-20.3]	5	8.18 [3.29-9.44]	.842
F _E NO (ppb), geometric mean [95% CI]	6	14.6 (6.40-33.5)	6	17.9 (7.99-40.0)	.810
Budesonide equivalent ICS dose (µg/d)	9	800 [800-1200]	6	600 [400-800]	.151
LABA use before study entry	9	3/6 (50)	6	0/6 (0.00)	.114
ACQ, mean (0-6)	8	1.67 [0.67-2.75]	6	1.58 [1.50-1.83]	.999
Quality of life					
mAQLQ total (1-7)	8	5.50 [4.77-6.10]	6	5.50 [5.33-5.73]	.846
mAQLQ symptom	8	5.60 [4.10-6.60]	6	5.40 [5.20-5.40]	.296
mAQLQ emotional	8	5.83 [4.00-6.83]	6	5.00 [3.67-6.00]	.516
mAQLQ environment	8	5.50 [5.00-6.50]	6	5.50 [5.33-6.33]	.999
mAQLQ activity	8	5.50 [4.88-6.00]	6	5.75 [5.00-6.75]	.604
GQLI, mean (1-7)	8	4.67 [4.14-5.86]	6	5.28 [4.44-5.55]	.948
Spirometry					
FEV ₁ (% predicted)	7	84.5 ± 10.6	5	86.9 (18.2)	.570
FVC (% predicted)#	7	90.1 ± 6.69	5	92.8 (20.7)	.685
FEV ₁ /FVC#	8	0.79 ± 0.88	4	0.81 (0.06)	.932
Reversibility (mL)	8	295 ± 213	5	298 (191)	.884
Significant reversibility**	8	3/8 (38)	5	2/5 (0.40)	.928

BMI, Body mass index; CI, confidence interval; GQLI, Gothenburg Quality of Life Instrument.

*Data are median [IQR], mean ± SD, or no./N (%), unless otherwise indicated.

†Mann-Whitney *U* test and χ^2 test.

‡Compulsory, 1; secondary, 2; and university, 3.

§1, 0-2 y; 2, 3-5 y; 3, 6-10 y; 4, 11-20 y; 5, >20 y.

||Analyzed allergens: cat, dog, birch, timothy, horse, mite (2 different mites), mugwort, and cladosporium.

¶Perennial allergens: cat, dog, horse, mite, and cladosporium.

#For FVC, spirometry measures are after bronchodilatation.

**Measured as ≥12% improvement of FEV₁ and ≥200 mL.

TABLE E4. Adherence to F_ENO-guided algorithm

Visit	2	3	4	5
F _E NO guided, no./N (%)	76/86 (88)	78/90 (87)	74/87 (85)	72/84 (86)
Control, no./N (%)*	23/76 (30)	17/78 (22)	18/78 (23)	14/75 (19)

*Data are provided only for comparison because the algorithm was not applied in the control group; the data show that different decisions were taken in the groups concerning anti-inflammatory treatment.

TABLE E5. Effect of F_ENO-guided asthma treatment on mAQLQ domains*

	Control (No. = 77-85)			F _E NO-guided (No. = 78-86)			Between groups
	Visit 2	Visit 6	P†	Visit 2	Visit 6	P†	P†
Symptoms	5.70 (4.80-6.40)	6.00 (5.20-6.40)	.254	5.60 (4.80-6.20)	6.00 (5.60-6.60)	<.0001	.041
Activity limitation	6.25 (5.50-7.00)	6.50 (5.75-7.00)	.109	6.50 (5.75-6.75)	6.75 (6.00-7.00)	.380	.544
Emotional function	6.00 (4.67-6.67)	6.00 (5.33-6.67)	.042	6.00 (4.67-6.67)	6.33 (5.67-7.00)	.002	.596
Environmental stimuli	5.67 (5.00-6.67)	6.33 (5.33-6.67)	.037	6.00 (5.00-6.67)	6.33 (5.67-6.67)	<.0001	.193

*Data are median (IQR).

†Wilcoxon signed rank test and Mann-Whitney *U* test.**TABLE E6.** SABA use per week*†

Period	Visits 2 to 3	Visits 3 to 4	Visits 4 to 5	Visits 5 to 6
F _E NO guided	1.88 (0.25-6.87)	2.25 (0.12-7.12)	1.56 (0.31-6.25)	1.56 (0.06-5.18)
Control	1.25 (0.06-4.06)	1.0 (0-3.25)	0.94 (0-3.38)	0.94 (0.03-2.81)

*Data are median (IQR).

†SABA use was measured with an inhaler dose counter and was reported at every visit and averaged per week since the last visit.

TABLE E7. Change in treatment step*†

Visit	2		3		4		5	
F _E NO guided	65/85 (76)		53/90 (59)		41/87 (47)		31/86 (36)	
Control	27/78 (35)	<i>P</i> < .0001‡	15/81 (18)	<i>P</i> < .0001‡	18/79 (23)	<i>P</i> = .001‡	21/78 (27)	<i>P</i> = .240‡

*Data are no./N (%).

†The proportion of participants who took a treatment step up or down.

‡Statistical analysis between groups was by using the Fisher exact test.

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