

Daily Telemonitoring of Exhaled Nitric Oxide and Symptoms in the Treatment of Childhood Asthma

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Rationale: Asthma treatment might improve when inhaled steroids are titrated on airway inflammation. Fractional exhaled nitric oxide ($F_{E_{NO_{0.05}}}$), a marker of eosinophilic airway inflammation, can be measured at home.

Objectives: We assessed daily $F_{E_{NO_{0.05}}}$ telemonitoring in the management of childhood asthma.

Methods: Children with atopic asthma ($n = 151$) were randomly assigned to two groups: $F_{E_{NO_{0.05}}}$ plus symptom monitoring, or monitoring of symptoms only. All patients scored asthma symptoms in an electronic diary over 30 weeks; 77 received a portable nitric oxide (NO) analyzer. Data were transmitted daily to the coordinating centers. Patients were phoned every 3 weeks and their steroid dose was adapted according to $F_{E_{NO_{0.05}}}$ and symptoms, or according to symptoms. Children were seen at 3, 12, 21, and 30 weeks for examination and lung function testing. The primary end point was the proportion of symptom-free days in the last 12 study weeks.

Measurements and Main Results: Telemonitoring was feasible with reliable $F_{E_{NO_{0.05}}}$ data for 86% of days, and valid diary entries for 79% of days. Both groups showed an increase in symptom-free days, improvement of FEV_1 and quality of life, and a reduction in steroid dose. None of the changes from baseline differed between groups. The difference in symptom-free days over the last 12 weeks was 0.3% ($P = 0.95$; 95% confidence interval, -10 to 11%). There was a trend for fewer exacerbations in the $F_{E_{NO_{0.05}}}$ group.

Conclusions: Thirty weeks of daily $F_{E_{NO_{0.05}}}$ and symptom telemonitoring was associated with improved asthma control and a lower steroid dose. We found no added value of daily $F_{E_{NO_{0.05}}}$ monitoring compared with daily symptom monitoring only.

Keywords: airway inflammation; inhaled corticosteroid; symptom-free days; lung function; telemedicine

Treatment decisions in asthma are commonly made on the basis of symptoms and lung function (1). However, these parameters do not accurately reflect the underlying pathophysiology, which includes chronic airway inflammation. Inhaled corticosteroids (ICSs) are now the treatment of choice for asthma but have not been able to provide adequate asthma control for a majority of patients (2). Studies have suggested that taking airway inflammation into account can improve asthma outcome, resulting in fewer exacerbations, lower steroid requirement, reduced airway responsiveness, and improved lung function (3–7). For this

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Exhaled nitric oxide monitoring has shown limited benefits in titrating therapies for asthma. Better results might be obtained with more frequent fractional exhaled nitric oxide ($F_{E_{NO_{0.05}}}$) monitoring to assist in adjusting doses of inhaled steroids.

What This Study Adds to the Field

Daily home telemonitoring of symptoms and $F_{E_{NO_{0.05}}}$ for 30 weeks was feasible and well accepted by children with asthma, and was associated with marked improvement of symptoms and reduction in inhaled steroid dose. Taking $F_{E_{NO_{0.05}}}$ into account did not contribute to the observed improvements.

purpose, several surrogate markers of airway inflammation have been used, including eosinophils in induced sputum, and the fraction of nitric oxide in exhaled air ($F_{E_{NO_{0.05}}}$). The latter is by far the most feasible inflammometer, with excellent reproducibility and immediate results. $F_{E_{NO_{0.05}}}$ has been extensively validated and studied in relation to asthma management (8, 9). Dose titration studies employing $F_{E_{NO_{0.05}}}$ were dissimilar regarding patient selection, ICS dosing algorithms, and dose adjustments, and $F_{E_{NO_{0.05}}}$ was infrequently measured during clinic visits. We reasoned that more frequent monitoring of $F_{E_{NO_{0.05}}}$ could be even more effective. Portable $F_{E_{NO_{0.05}}}$ analyzers have become available that can be used at home (10). We hypothesized that frequent ICS dose adjustment guided by daily $F_{E_{NO_{0.05}}}$ and symptom monitoring as compared with a reference strategy in which ICS doses are adjusted on the basis of daily symptom scores alone would improve asthma control. Some of the data have been presented as an abstract at the 2008 American Thoracic Society conference (11).

METHODS

Study Design

In a prospective, open label, randomized, multicenter, parallel group study we monitored children with atopic asthma for 30 weeks, and ICS doses were adjusted every 3 weeks on the basis of either $F_{E_{NO_{0.05}}}$ and symptom scores, or symptom scores alone. Children were recruited from 5 academic centers and 12 general hospitals. Inclusion criteria were as follows: age, 6–18 years; stable mild–moderate asthma, diagnosed according to Global Initiative for Asthma (GINA) guidelines (1); treatment with 200–1,000 μg of inhaled budesonide or equivalent daily for 2 months before randomization; and RAST class 2 or higher or a positive skin prick test for at least one airborne allergen. Exclusion criteria were as follows: active smoking, previous admission to an intensive care unit for asthma, and concomitant disease that might

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affect $FE_{NO_{0.05}}$. All parents and children older than 12 years signed informed consent. Sample size, based on our earlier studies, aimed at a 30% difference between study arms in change from baseline of symptom-free days in the last 12 weeks. For a power of 80% and significance level of 5%, we needed 50 patients per group. To allow for dropouts, we included 150 children. Children were randomized at the first visit, stratified by center. The study protocol was approved by the medical ethics committees of all participating centers.

$FE_{NO_{0.05}}$ Measurements

Children in the $FE_{NO_{0.05}}$ group received an airway inflammation monitor (NIOX MINO; Aerocrine, Solna, Sweden) that measures $FE_{NO_{0.05}}$ (8). Measurements were performed daily. Measurement time was recorded by the device for later review. Data were transmitted to the coordinating center. All analyzers were checked for drift.

Symptom Scores

All children recorded asthma symptoms in a palmtop electronic diary (PalmOne Tungsten W PDA equipped with TrialMax software; CRF Inc., Helsinki, Finland). Entries were transmitted daily to the coordinating center. Symptom-free days were defined as days with a total symptom score of 0.

Clinic Visits and Telephone Contacts

Children of both groups were seen at randomization and at 3, 12, 21, and 30 weeks (Figure 1). Assessments included $FE_{NO_{0.05}}$, spirometry before and after salbutamol, and recording of adverse events. A Pediatric Asthma Caregiver Quality of Life Questionnaire with Standardized activities [PACQLQ(S)] was administered at the first and last visits (12). All parents were phoned every 3 weeks between visits, and medication was adapted according to geometric mean $FE_{NO_{0.05}}$ over the preceding 3 weeks and cumulative symptom scores (Table 1).

Statistical Evaluation

The study was divided into six periods of 3 weeks, and a final period of 12 weeks. The primary end point was change from baseline of percentage symptom-free days during the last 12 weeks. Only periods with at least 50% valid daily scores were analyzed. Secondary end points were cumulative symptom scores, ICS dose as budesonide equivalent (1), FEV_1 and reversibility, $FE_{NO_{0.05}}$, prednisone courses, emergency visits, hospitalizations for asthma, and PACQLQ scores. Changes in end points over time and differences between study arms were assessed by repeated measurements analysis of variance (RmANOVA) using SAS (SAS Institute, Cary, NC) PROC MIXED software. Categorical end points were compared by Fisher's exact test, and the Mann-Whitney test was used to compare changes from baseline in PACQLQ data and ICS dose. Intention-to-treat analysis was performed for all subjects who were enrolled. In addition, we performed a per protocol analysis. More detail is provided in the online supplement.

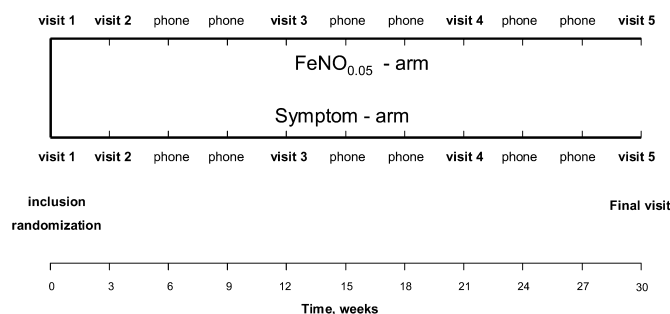


Figure 1. Study design. All subjects were contacted by phone every third week between clinic visits. In the fractional exhaled nitric oxide ($FE_{NO_{0.05}}$) arm, the inhaled corticosteroid (ICS) dose was adjusted according to FE_{NO} and symptoms; in the symptom arm, ICS dose was adjusted on the basis of symptom scores only. At each clinic visit, $FE_{NO_{0.05}}$ and FEV_1 were measured.

TABLE 1. ALGORITHM FOR ADJUSTING INHALED CORTICOSTEROID DOSE

Study Arm	Symptom Score*	$FE_{NO_{0.05}}$ †	Adjustment‡
$FE_{NO_{0.05}}$ group	High	High	Increase
	High	Low	No change
	Low	High	Increase
	Low	Low	Decrease or discontinue
Symptom group	Above range		Increase
	In range		No change
	Below range		Decrease or discontinue§

Definition of abbreviation: $FE_{NO_{0.05}}$ = fractional exhaled nitric oxide.
 * Cutoff level for high score: > 60, low score ≤ 60 cumulative in 3 weeks for $FE_{NO_{0.05}}$ group. For symptom group, the “normal range” was 10–60.
 † Cutoffs for $FE_{NO_{0.05}}$ were 20 ppb for children aged 6–10 years and 25 ppb for older children (21).
 ‡ Doses were changed according to predefined steps for each type of inhaled steroid, for example, budesonide at 100, 200, 400, 800, and 1,200 µg. Maximal allowed dose: 1,200 µg of budesonide or equivalent. If a combination of ICS and long-acting β-agonist (LABA) was used, the LABA was stopped whenever a decrease was required at the lowest ICS dose, before stopping ICS.
 § Steroids were stopped after 6 weeks with low symptom scores at the lowest steroid dose level.

RESULTS

We randomized 151 children, 77 in the $FE_{NO_{0.05}}$ group and 74 in the symptom group, within 3 months. Baseline characteristics did not differ significantly between study groups (Table 2). Four children (two in the symptom group, two in the $FE_{NO_{0.05}}$ group) were excluded from all analyses for reasons of severe non-compliance (n = 2), inappropriate inclusion (no allergy, n = 1), and moving abroad with impossibility to transfer data (n = 1). All others completed the study. Hence the total evaluable population was 147 children. Compliance with the study procedures was good, with 86% acceptable $FE_{NO_{0.05}}$ measurements, and 79% valid diary entries over the whole study period. There were 372 ICS dose changes in the $FE_{NO_{0.05}}$ group, as compared with 174 in the symptom group.

Symptom-free Days

Within each group the percentage of symptom-free days improved significantly (both $P < 0.001$ in RmANOVA; Figure 2).

TABLE 2. BASELINE CHARACTERISTICS OF STUDY POPULATION

	$FE_{NO_{0.05}}$ Group	Symptom Group	P Value
Sex, male: n (%)	46 (60)	54 (73)	0.12
Age, yr: mean (SD)	11.6 (2.6)	11.8 (4.3)	0.80
Weight, kg: mean (SD)	43.4 (12.5)	42.2 (14.5)	0.23
Height, cm: mean (SD)	150.3 (15.5)	147.2 (15.4)	0.44
White, n (%)	70 (91)	65 (88)	0.79
Medication, n (%)			
Antihistamine	36 (47)	28 (38)	0.32
Montelukast	21 (27)	13 (18)	0.17
Nasal steroid	25 (32)	24 (32)	1.00
Long-acting β-agonist	44 (57)	45 (61)	0.74
Initial ICS dose, µg · d ⁻¹ : mean (IQR)	400 (250–1,000)	400 (250–600)	0.43
Baseline $FE_{NO_{0.05}}$ ppb: median (IQR)	27.5 (15.0–54.0)	32.0 (15.0–59.0)	0.94
Baseline FEV_1 , % predicted: mean (SD)	88 (15)	88 (12)	0.68
Baseline reversibility of FEV_1 , % predicted: mean (SD)	+7 (11)	+6 (7)	0.28

Definition of abbreviations: ICS = inhaled corticosteroid; IQR = interquartile range.

Adjusted for baseline, there was no overall significant difference in percentage of symptom-free days during the whole study period between both groups ($P = 0.65$). The same applied for the primary end point, that is, the outcomes obtained during the last 12 weeks of the study. The baseline-adjusted overall difference of mean symptom-free days was +0.3% ($F_{E_{NO_{0.05}}}$ group minus symptom group, $P = 0.95$; 95% confidence interval for difference, -10 to +11%). Additional adjustment for center and sex gave similar results. ANOVA further showed that the treatment effect was not modified by baseline ICS dose ($P = 0.78$), center ($P = 0.62$), or sex ($P = 0.07$). Likewise, the use of long-acting β -agonist at baseline had no effect on these outcomes.

Medication

At baseline, median (interquartile range) daily doses of ICS in the $F_{E_{NO_{0.05}}}$ and symptom groups were similar: 400 (250–1,000) μg and 400 (250–600) μg , respectively. During the study, both groups showed a gradual reduction in ICS dose. At the end of the study, the $F_{E_{NO_{0.05}}}$ group used 200 (0–500) μg , and the symptom group 200 (100–500) μg , of budesonide equivalent per day ($P < 0.0001$ for both changes from baseline). The time course of ICS dose changes, and the change from baseline, did not differ significantly between groups ($P = 0.76$ at the end of the study for the changes from baseline). The ICS dose distribution at the end was similar in both groups. ICS could be stopped in 16 children in the $F_{E_{NO_{0.05}}}$ group, and in 12 in the symptom group ($P = 0.98$).

The median number of rescue β -agonist puffs per 3 weeks was similar at baseline (2, [range, 0–19] in the $F_{E_{NO_{0.05}}}$ group and 2 [range, 0–21] in the symptom group) and decreased to 0 (range, 0–19) and 1 (range, 0–19), respectively.

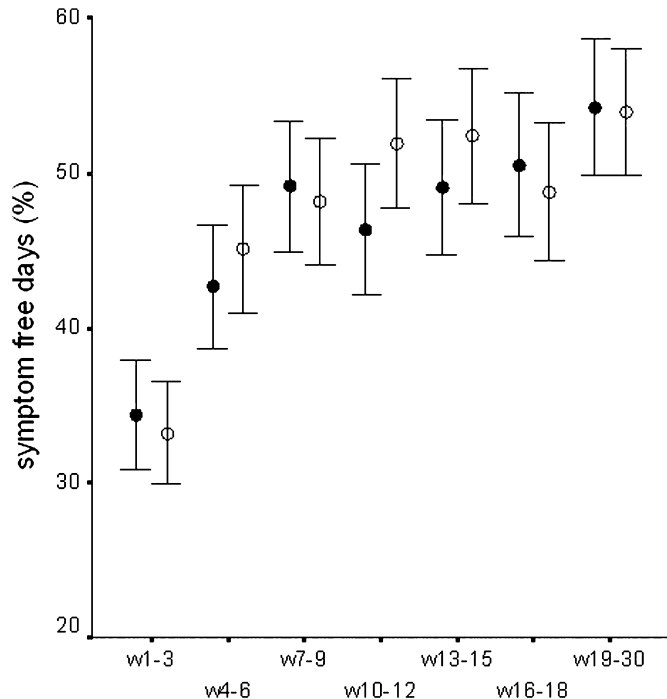


Figure 2. Symptom-free days. Solid symbols, $F_{E_{NO_{0.05}}}$ group; open symbols, control group. Horizontal axis shows time in weeks. Error bars represent standard errors. Both groups showed similar improvement. The baseline-adjusted difference in mean percentage of symptom-free days over the last 12 weeks was 0.3% ($F_{E_{NO_{0.05}}}$ group minus symptom group, $P = 0.95$; 95% confidence interval for difference, -10% to +11%).

Exacerbations

In the $F_{E_{NO_{0.05}}}$ arm, 9 patients were prescribed one or more prednisone courses, versus 12 in the symptom arm. Three in the $F_{E_{NO_{0.05}}}$ arm and six in the symptom arm got more than one prednisone course. Survival analysis by means of Kaplan-Meier curves of time to first prednisone course, emergency visit, hospitalization, or to any of these, whatever came first ($n = 31$) showed no significant differences ($P = 0.43, 0.68, 0.13$, and 0.13 , respectively). In the per protocol analysis the difference in time to first hospitalization reached borderline significance (Figure 3; $P = 0.10$).

Spirometry, Reversibility

At baseline, FEV_1 was similar in both groups: 88 (SD 15)% in the $F_{E_{NO_{0.05}}}$ group and 88 (13)% in the symptom group. Reversibility after salbutamol was 5 (5)% and 5 (6)%, respectively. At the end of the study, FEV_1 in the $F_{E_{NO_{0.05}}}$ group had improved to 95 (14)%, and in the symptom group to 94 (14)% and reversibility was 6 (6)% and 7 (6)%, respectively. There was no difference in change from baseline (RmANOVA, $P = 0.12$). The time course of FEV_1 and reversibility was similar between groups, with only baseline FEV_1 as significant predictor of outcome at any future time point ($P < 0.001$).

$F_{E_{NO_{0.05}}}$ Measurements

At clinic visits $F_{E_{NO_{0.05}}}$ values were similar at baseline in the $F_{E_{NO_{0.05}}}$ group (median, 27.5 ppb; interquartile range, 15.0–54.0 ppb) and the symptom group (median, 32.0 ppb; interquartile range, 15.0–59.0 ppb). There were no significant changes from baseline within both groups. At 30 weeks, the baseline-adjusted ratio of geometric means of $F_{E_{NO_{0.05}}}$ in the symptom and $F_{E_{NO_{0.05}}}$ groups was 1.01 (95% confidence interval, 0.78 to 1.33). Calibration of all NIOX MINOs after the study

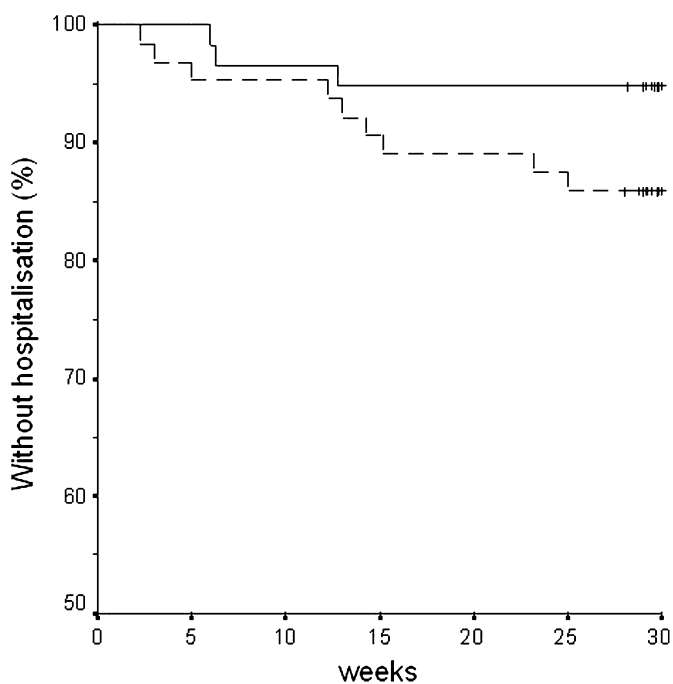


Figure 3. Time to first hospitalization. Survival analysis (Kaplan-Meier curves) of time to first hospitalization for the $F_{E_{NO_{0.05}}}$ group (solid line) and symptom group (dotted line), $P = 0.13$ for intention-to-treat analysis, shown here, and $P = 0.10$ for per protocol analysis. Tic marks indicate end of study for individual subjects.

showed drift outside the manufacturer's specifications in 11 of 77 instruments. In all cases we examined whether this could have affected treatment decisions due to $FE_{NO_{0.05}}$ values near the cutoff level. This was the case in only one subject.

Quality of Life

Initial mean total PACQLQ scores were similar in both groups: 5.8 (SD 0.8) in the $FE_{NO_{0.05}}$ group and 5.8 (1.0) in the symptom group. Both groups improved during the study with final total scores 6.2 (0.8) and 6.2 (0.7), respectively. Changes from baseline within groups were significant (both $P < 0.01$), but the changes from baseline of total scores and individual domains did not differ between study groups.

Adverse Events

Mild adverse events were reported 134 times in the $FE_{NO_{0.05}}$ group and 114 times in the symptom group, and included nonsevere respiratory symptoms of ear, nose, and throat; common colds; bronchitis; fever; cough; and seasonal allergy. None of the items differed significantly between groups. The single major adverse event (appendicitis) was unrelated to the study. Initial problems with study devices were rare (3 patients for NIOX MINO and 14 patients for e-diaries in the first week). During the study, a number of NIOX MINO devices had to be replaced as a risk of malfunctioning was detected. These devices were checked and no malfunctioning was detected. Also, some e-diaries occasionally had to be replaced because of malfunctioning.

Per Protocol Analysis

All analyses were repeated in the per protocol data set, comprising 58 children in the $FE_{NO_{0.05}}$ group and 64 in the symptom group. None of the findings in the per protocol analysis differed from those of the intention-to-treat analysis (data not shown).

DISCUSSION

We examined the added value of daily airway inflammation monitoring by means of $FE_{NO_{0.05}}$ and frequent ICS dose adjustments in the management of childhood asthma. Our results showed that 30 weeks of daily telemonitoring was feasible in the majority of children. Overall, children improved in symptom scores and at the same time could reduce their dose of steroids considerably. However, no added benefits of daily $FE_{NO_{0.05}}$ monitoring on symptoms, lung function, and airway inflammation were found. There was a tendency toward fewer exacerbations in the $FE_{NO_{0.05}}$ group. These data suggest that frequent monitoring and telephone contacts as such might have been responsible for marked improvements, which could not be further improved by taking $FE_{NO_{0.05}}$ into account.

Earlier studies have incorporated inflammation monitoring in asthma management. Different inflammometers have been used, including methacholine responsiveness, sputum eosinophils, and $FE_{NO_{0.05}}$ (3–7, 13). The results of earlier studies using $FE_{NO_{0.05}}$ suggested some benefit (4, 5, 14). Smith and colleagues treated adults with asthma according to an $FE_{NO_{0.05}}$ strategy or GINA guidelines (4). First, ICSs were down-titrated and the minimal dose needed for control was determined. During 1 year of follow-up, patients received a higher ICS dose in case of loss of control, defined on the basis of either $FE_{NO_{0.05}}$ or, in the control group, nighttime awakening, peak flow amplitude, bronchodilator use, and/or FEV_1 . Down-titration was not allowed. In the $FE_{NO_{0.05}}$ group, the exacerbation rate was 0.49 per patient per year, versus 0.90 in the control group (not significant). This study did not show better asthma control as a result of $FE_{NO_{0.05}}$ monitoring, but observed a significantly higher ICS dose in the control group than in the $FE_{NO_{0.05}}$ group

that might be the result of an imbalance in the study design (14). A pediatric study by Pijnenburg and coworkers used a protocol that was close to normal asthma management (5). Children with allergic asthma were monitored for 1 year and seen at 3-monthly intervals. ICSs were adapted on the basis of $FE_{NO_{0.05}}$ or symptoms, in a double-blind fashion. Significant improvement was seen in airway hyperresponsiveness as a result of the $FE_{NO_{0.05}}$ strategy. Exacerbations were more frequent in the control group than in the $FE_{NO_{0.05}}$ group (18 vs. 8; not significant). In a study by Shaw and coworkers, 103 adult with asthma were monitored for 1 year while their ICS dose was adapted on the basis of $FE_{NO_{0.05}}$ or conventional criteria, with 1- and 2-monthly intervals (7). This study found no difference in exacerbations between study groups, with 0.33 exacerbation per patient per year in the $FE_{NO_{0.05}}$ group and 0.42 in the control group. Retrospectively, this study was underpowered for exacerbations as the primary end point (7). Shaw and coworkers found higher ICS consumption in the $FE_{NO_{0.05}}$ group. So, there is agreement between these studies regarding a tendency toward fewer exacerbations with the $FE_{NO_{0.05}}$ strategy, but apparently none of them was sufficiently powered for this end point. Apart from power issues, a discrepancy between an effect on exacerbations and an effect on other aspects of asthma control might occur, as it has been shown that exacerbations are due mostly to viral infection and can occur irrespective of the previous level of asthma control (15).

We have earlier demonstrated that, in practice, ICS dose increments are ineffective in reducing high $FE_{NO_{0.05}}$ levels. This was not related to a faulty inhaler technique (16). Although it may be worthwhile to determine whether there are other factors that can explain this finding, including asthma severity and allergen exposure, we believe that there is at present little argument in favor of up-titrating ICS in patients who have elevated $FE_{NO_{0.05}}$ despite a conventional dose of ICS. Such a practice could easily lead to high doses of ICS solely because of high $FE_{NO_{0.05}}$, without clinical benefit. In contrast, down-titration of ICS in case of low $FE_{NO_{0.05}}$ is a sensible strategy, as loss of asthma control or exacerbation can be predicted by increases in $FE_{NO_{0.05}}$ (17, 18).

We compared $FE_{NO_{0.05}}$ -driven treatment with daily symptom telemonitoring and frequent contacts. Only by having the symptom group scoring and transmitting their symptoms with the same frequency, and contacting them as often as the $FE_{NO_{0.05}}$ group, could the actual added value of daily $FE_{NO_{0.05}}$ monitoring be assessed. In this respect it is important to determine whether taking $FE_{NO_{0.05}}$ into account made any difference in the number of dose changes. Indeed, there were almost twice as many dose changes in the $FE_{NO_{0.05}}$ group compared with the symptom group and this suggests sufficient opportunity to have a different study outcome between the groups. We speculate therefore that daily supervision and frequent phone contacts have produced an improvement that could not be beaten by additional monitoring of $FE_{NO_{0.05}}$, most likely because of a ceiling effect on treatment compliance. It will be important to determine whether the frequency of dose changes with daily telemonitoring would make a difference. We now adapt ICS doses every 3 weeks, and one could argue that more frequent dose adaptations would be more effective. Our data do not allow for such an analysis, as any dose change would affect subsequent $FE_{NO_{0.05}}$ and symptom scores, and thereby influence subsequent treatment.

Another possible explanation of our findings is provided by Haldar and colleagues, who reported asthma phenotypes that were either concordant or discordant with respect to eosinophilic airway inflammation and symptoms (19). Those in discord benefited most from a strategy that took eosinophilic inflammation into account for titrating ICS. Concordance for symp-

toms and FENO could explain our finding of no additive effect of FENO monitoring in the present study.

What are the implications of our results? In this hospital-based selection of children with atopic asthma, the addition of daily FENO_{0.05} monitoring to daily symptom monitoring and frequent contacts did not further improve asthma outcome. Daily FENO_{0.05} monitoring can therefore not be recommended for this purpose. We did not address other possible applications of frequent FENO_{0.05} monitoring, such as prediction of steroid effect, loss of control, prediction and prevention of exacerbations, and tapering of steroids in symptom-free children who wheezed in the past (17, 18, 20). We think that there is good reason to further study these potential applications. If FENO-driven treatment would indeed reduce exacerbations, children with more severe asthma and frequent exacerbations may be more likely to benefit from FENO monitoring. Our data show no effect modification by baseline ICS dose, a proxy for asthma severity. However, we did not include children with severe asthma. Hence, FENO_{0.05} monitoring in severe, troublesome asthma would be important to examine. Such a study in steroid-dependent adults is presently ongoing in the Netherlands. The present results show that such monitoring is feasible, well accepted, and does not reduce quality of life. Also, our findings highlight the promise of daily telemonitoring of symptoms as a potentially highly effective and feasible strategy to improve asthma care while reducing medication.

We conclude that daily telemonitoring of symptoms and FENO_{0.05} for 30 weeks was feasible and well accepted by children with asthma, and was associated with marked improvement of symptoms and at the same time with a reduction in inhaled steroid dose. Taking FENO_{0.05} measurements into account did not contribute to the observed improvements, but a tendency toward fewer exacerbations was seen. We speculate that the frequent telemonitoring as such was responsible for our findings, and most likely produced a ceiling effect on treatment compliance. Whether FENO_{0.05} monitoring in selected patients with more severe asthma is worthwhile remains to be shown.

Conflict of Interest Statement: J.C.d.J., in the past 3 years, has received travel grants and lectured at scientific meetings for GlaxoSmithKline, Merck Sharp & Dohme, Altana Pharma, Aerocrine, and Roche. The Department of Pediatrics/Erasmus MC Holding received research grants from GlaxoSmithKline, AstraZeneca, Aerocrine, Roche, Freisland Foods, Transave, Chiron, and Pfizer. S.C. received a research grant from Aerocrine and travel grants from Merck Sharp & Dohme and Chiesi. W.C.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.B. received a research grant from Aerocrine in the past 3 years and also received travel grants and lectured at scientific meetings for GlaxoSmithKline, Merck Sharp & Dohme, Abbott, and Valeas.

Participants of the CHARISM (Children with Asthma subjected to Respiratory Inflammatory Status Monitoring) study group represent the cooperation of 15 clinical research centers: Henk-Jan Aanstoot, M.D., Ph.D., Department of Pediatrics, IJsselland Hospital, Capelle aan de IJssel, The Netherlands; Eugenio Baraldi, M.D., Department of Pediatrics, University Hospital, Padua, Italy; Attilio Boner, M.D., Department of Pediatrics, University Hospital-Borgo Roma, Verona, Italy; Silvia Carraro, M.D., Department of Pediatrics, University Hospital, Padua, Italy; Fernando Maria de Benedictis, M.D., Department of Pediatrics, Salesi Hospital, Ancona, Italy; Sander W. W. Feith, M.D., Department of Pediatrics, St. Franciscus Hospital, Rotterdam, The Netherlands; Johan C. de Jongste, M.D., Ph.D., Department of Pediatrics, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands; Marquita H. Greijn, M.D., Department of Pediatrics, Walcheren Hospital, The Netherlands; Linda Landi, M.D., Department of Pediatrics, Mestre Hospital, Mestre, Italy; Gianluigi Marseglia, M.D., Department of Pediatrics, San Matteo Hospital, Pavia, Italy; Elio Novembre, M.D., Department of Pediatrics, Meyer Children's Hospital, Florence, Italy; Lydia Pescollerung, M.D., Department of Pediatrics, Bolzano Hospital, Bolzano, Italy; Giovanni Rossi, M.D., Department of Pediatrics, Giannina Gaslini Hospital, Genoa, Italy; Ruud Schornagel, M.D., Department of Pediatrics, Albert Schweitzer Hospital, Dordrecht, The Netherlands; Anja A. P. H. Vaessen-Verberne, M.D., Ph.D., Department of Pediatrics, Amphia Hospital Breda, Breda, The Netherlands; Leonieke N. van Veen, M.D., Department of Pediatrics, Reinier de Graaf Hospital, Delft, The Netherlands.

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