Things change: The early identification of patients with an unfavourable prognosis

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Chapter 6

Personalized FeNO-driven asthma management in primary care: a FeNO-subgroup analysis of the ACCURATE trial

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ABSTRACT

Background

The aim of this study was to identify patients who benefit most from FeNO-driven asthma management in primary care, based on prespecified subgroups with different levels of FeNO.

Methods

We used data of 179 adult asthmatics from a 12-month primary care RCT with three-monthly assessments of FeNO, asthma control, medication usage, costs of medication, severe asthma exacerbations and quality of life. In the original study patients were randomised to either a symptom driven treatment strategy (Controlled asthma (Ca-strategy)) or FeNO + symptoms driven strategy (FCa). In both groups, patients were categorized by their baseline level of FeNO as low (<25 ppb), intermediate (25-50 ppb) and high (>50 ppb). At twelve months, we compared, for each prespecified FeNO-subgroup, asthma control, asthma-related quality of life, medication usage, and costs of medication between the Ca and FCa-strategy.

Results

We found a difference between the Ca- and FCa-strategy for the mean dosage of beclomethasone strategy of 223 mcg (6;439), p = 0.04) and for the total costs of asthma medication a mean reduction of $159 (33;285), p = 0.03) in patients with a low baseline FeNO level. No differences were found for asthma control, severe asthma exacerbations and asthma-related quality of life in patients with a low baseline FeNO level. Furthermore, in patients with intermediate or high level of FeNO no differences were found.

Conclusions

In primary care, FeNO-driven asthma management is effective in patients with a low FeNO level, for whom it is possible to down-titrate medication, while preserving asthma control and quality of life.

Trial registration

NTR 1756 at www.trialregister.nl

Kewords

Fractional exhaled nitric oxide, feno, asthma management, primary care

BACKGROUND

Asthma is a heterogeneous disease with different underlying components interacting in each individual patient.[1,2] An important component of asthma is eosinophilic airway inflammation, which can even be present in the absence of severe symptoms.[3] Until recently, assessing the severity of eosinophilic airways inflammation proved hard and required more invasive measurements. However, the assessment of airways inflammation became available with the advent of relatively inexpensive equipment for the measurement of the concentration of nitric oxide (NO) in exhaled breath, the so-called fractional exhaled nitric oxide (FeNO).[4] For diagnosing asthma, a FeNO measurement is now recommended as part of the diagnostic algorithm in several guidelines, alongside clinical evaluation, spirometry, and symptom assessments.[5-7]

However, in monitoring asthma after the diagnosis of asthma has been established, whether or not FeNO should be measured is still up for debate.[8] Several studies have shown FeNO could be of use in the monitoring of symptoms, resulting in improved asthma control, reduced exacerbation rate, improvement of quality of life and that it could aid in optimizing titration of inhaled steroid treatment.[9-13] Others have shown opposing results, showing no advantage of FeNO or even that FeNO resulted in worse outcomes.[14-17]

A potential reason for all these different findings might be that FeNO measurements in the management of asthma, only have additional benefit in specific subgroups based on different levels of FeNO at baseline. Several recent landmark papers suggest a shift in the management of asthma towards the treatment of treatable traits, indicating a need for a more precise determination of a person's airways disease.[2,18] It is imaginable that each of these prespecified FeNO-subgroups, have their own set of required measurements as well, and FeNO-driven asthma management might only be of use for a selection of these.

This is also why the Global Initiative of Asthma (GINA) states there is no role for FeNO in asthma management at this point in time and further studies are needed to identify the populations most likely to benefit, and the optimal frequency of monitoring.[8] Additionally, there are also costs to be considered. Although the ACCURATE study showed FeNO-driven asthma management already proved to be cost-effective in primary care, a more targeted deployment could improve upon that.[19]

Ideally, we would like to identify specific subgroup of patients, based on different levels of FeNO at baseline, where FeNO measurement would be of benefit, and simultaneously

subgroups where it does not contribute to improved outcomes. Therefore, the aim of the present study was to identify specific FeNO-subgroups of patients who benefit (most) from FeNO-driven asthma management in primary care, in terms of asthma control, asthma-related quality of life, medication usage and (asthma) medication costs.

METHODS

Study design

This study concerns a subgroup analysis of a dataset from a three-arm pragmatic cluster-randomized trial (RCT) assessing patient preferences and cost-effectiveness of three asthma management strategies in primary care. The first strategy aimed to achieve well-controlled asthma, by making treatment decisions based on conventional control measures of asthma, including the Asthma Control Questionnaire (ACQ) and spirometry (Ca-strategy). The second strategy also aimed for well controlled asthma, but it included an additional FeNO-measurement upon which treatment decisions were based alongside conventional measures (FCa-strategy). In this subgroup analysis we omitted the third strategy, which was aimed to achieve only partly controlled asthma; and therefore treatment plan allowed for more variation in asthma control. During the trial, maintenance asthma medications were adjusted at 3-month intervals, based on 6-item Asthma Control Questionnaire (ACQ) and spirometry with or without FeNO (table 1). A detailed description of study procedures and participants of the Asthma Control Cost-Utility RAndomized Trial Evaluation (ACCURATE) has been published elsewhere (registered at www.trialregister.nl (NL1658 (NTR1756))).[19,20]

TABLE 1. *Treatment strategy algorithms*

	Levels of asthma control		
Strategy	***Controlled***	***Partly controlled***	***Uncontrolled***
Ca-strategy	- 3 mo: no change - > 3 mo: step-down	step-up: treatment choice	step-up: treatment choice
FCa-strategy			
- *Low FeNo level (< 25 ppb)*	step-down	- 3 mo: no change/ change within current step to LABA - > 3 mo: step-down ICS	step-up: LABA
- *Intermediate FeNo level*	no change	step-up: treatment choice	step-up: treatment choice
- *High FeNo level (> 50 ppb)*	step-up/change within current step to ICS	step-up: 1 x ICS	step-up: 2xICS*

Ca = Controlled asthma
FCa = Feno-driven controlled asthma
LABA = Long-Acting Beta-Agonist
ICS = Inhaled Corticosteroids

Study population

Patients were aged 18-50 years, with a doctor's diagnosis of asthma and prescribed inhaled corticosteroids. In primary care the diagnosis of asthma is based on the presence of a characteristic clinical history, which includes recurrent episodes of dyspnoea, wheezing and/or cough.[21] An additional measurement of lung function can enhance diagnostic confidence, if it shows reversibility, which is defined as an increase of ≥12% and 200 ml in FEV1 after bronchodilator therapy.[22,23] Follow-up was 12 months and patients filled out online questionnaires at approximately three-monthly intervals. We included all patients where data of all outcome measurements was available at 12 months as a secondary complete case analysis.

Baseline prespecified FeNO subgroups

We distinguished between three prespecified subgroups, based on different levels of FeNO at baseline, which were classified as low (< 25 ppb), intermediate (25-50 ppb) and high (> 50 ppb). Classification cut-offs were based on the American Thoracic Society.[24,25] At baseline, FeNO level was measured in general practice for all patients in both strategies, according to international guidelines with the NIOX-MINO (Aerocrine, Solna, Sweden).[26,27]

Outcome measurements

The three specific subgroups, based on different baseline levels FeNO, were evaluated on five different outcomes after twelve months of treatment; level of asthma control, asthma-related quality of life, medication usage, total medication costs, asthma specific medication costs and the occurrence of at least one severe exacerbation.

The level of asthma control was measured with the ACQ, which can be subdivided into low (ACQ < 0.75), medium (ACQ 0.75-1.50) and high (ACQ > 1.50) level of asthma contr[ol.28] Asthma-related quality of life was measured by the Dutch version of the Asthma Quality of Life Questionnaire (AQLQ)-Juniper. The Asthma Quality of Life Questionnaire was able to detect changes in patients who responded to treatment or who had natural fluctuations in their asthma ($p < 0.001$) and to differentiate these patients from those who remained stable ($p < 0.001$).[29] The usage of inhaled corticosteroid medication was recalculated into the beclomethasone equivalent based on recommendations by the Dutch pharmaceutical guidelines and a panel of respiratory experts.[19, 30] Medication costs (in dollars) were assessed based on medication prescriptions obtained from electronic patient records, completed with the patient's report on medication purchased elsewhere, separate for total medication usage and asthma medication only.[27] Benefit could for example either be defined as a reduction in medication usage, while asthma

control, quality of life and exacerbation rate remained similar, or as an improvement of asthma control or quality of life. The minimal important difference (MID) is defined as 0.5 points in asthma control (ACQ) and asthma-related quality of life (AQLQ). A severe asthma exacerbation was defined as a course of oral prednisolone prescribed for worsening asthma for three or more days, or an emergency department visit/ hospitalisation due to asthma.[31]

Analysis

First, baseline levels were calculated for asthma control, asthma quality of life and medication usage per FeNO-subgroup and per treatment strategy (Ca and FCa). Second, the mean level of all outcome measurements was assessed at twelve months: asthma control, asthma quality of life, medication usage, total costs of medication, asthma specific medication costs and the occurrence of at least one severe asthma exacerbation. Whether there was a difference in baseline values and/or outcomes at twelve months between the Ca and FCa-strategy was assessed by Mann-Whitney U test (method of choice especially due to the low number of patients) or by Fisher's exact test for occurrence of at least one severe exacerbation (a binary variable) ($p < 0.05$). All analyses were performed separately per FeNO-subgroup. As a post-hoc analysis we pooled the intermediate and high FeNO-subgroups (> 25 ppb) because of the low number of patients in these FeNO-subgroups separately. STATA statistical software version 14 (Statacorp, College Station, Texas, USA) was used for all analyses.

RESULTS

Patient characteristics

We included 179 patients in this study, patients of whom data of all outcome measurements was available at 12 months (so-called complete case analysis), 94 in the Ca-strategy and 85 in the FCa-strategy (table 2). In patients within the Ca-strategy the mean age was 41.6 (SD 6.8) years and 68% was female, and the mean asthma duration was 18.2 (SD 13.3) years. In patients within the FCa-strategy the mean age was 41.2 (SD 8.1) and 74% was female, and the mean asthma duration in years was 19.7 (SD 14.2).

Prespecified FeNO-Subgroups

At baseline, no significant differences were found for asthma control (ACQ-score), quality of life (AQLQ-score) and medication usage (beclomethasone equivalent) for any FeNO-subgroup between the Ca- and FCa-strategy (table 1; *online supplement*).

TABLE 2. *Patient Characteristics*

	Ca-strategy	FCa-strategy
Continuous variables		
Patients (n)	94	85
Mean age (SD)	41.6 (6.8)	41.2 (8.1)
BMI (SD)	25.9 (4.7)	26.3 (5.6)
Asthma duration in years (SD)	18.2 (13.3)	19.7 (14.2)
Baseline FeNO in ppb (SD)	20.5 (21.3)	23.1 (22.9)
Beclomethasone equivalent dose in mcg (SD)	853 (702)	824 (634)
Mean baseline ACQ (SD)	0.91 (0.76)	0.94 (0.68)
Mean baseline AQLQ (SD)	5.87 (0.88)	5.80 (0.93)
Categorical variables		
Sex % F	68	74
Long Acting Beta Antagonist (LABA) use (%yes)	61	51
Current smokers (% yes)	10	11
Previous smokers (% yes of current non-smokers)	33	36
ACQ-subgroup (%)		
Low (< 0.75)	50	39
Medium (0.75-1.50)	34	45
High (> 1.50)	16	17

Ca = Controlled asthma
SD = standard deviation
PPB = parts per billion
ACQ = Asthma Control Questionnaire
AQLQ = Asthma Quality of Life Questionnaire
FCa = Feno-driven controlled asthma
BMI = body mass index
MCG = microgram
%F =percentage female

At twelve months, in the low FeNO-subgroup there were no differences in ACQ-score and AQLQ-score between the Ca- and FCa-strategy. However, the dosage of inhaled corticosteroid medication (converted to beclomethasone equivalent) and total costs of asthma medication were reduced in the FCa- as compared to the Ca-strategy by 223 mcg (6;439), p = 0.04) and $159 (33;285), p = 0.03), respectively (figure 1; table 3a). At twelve months mean dosage of beclomethasone for patients with a low FeNO-level increased with 80 mcg within the Ca-strategy and decreased with more than 150 mcg within the FCa-strategy. Furthermore, no significant differences were found for the experience of at least one severe asthma exacerbations.

At twelve months, in patient with intermediate or high FeNO levels no differences were found between the strategies (table 3b and 3c). For patients with an intermediate and high FeNO level the beclomethasone dosages decreased in the Ca-strategy, where there was an increase for patients within the FCa-strategy. Pooled analysis of the intermediate and high FeNO-subgroups did not result in a significant difference at twelve months between the Ca-strategy and FCa-strategy either (table 3d).

TABLE 3. *12-months outcomes per prespecified subgroup (based on FeNO-level)*

A. Subgroup with low level (< 25 ppb)

	Ca-Strategy (N = 71)	**FCa-Strategy (N = 63)**	**Difference (95% CI)**	**p-value**
ACQ	0.90 (0.75)	1.01 (0.80)	-0.11 (-0.38;0.15)	0.40
AQLQ	5.97 (0.87)	5.85 (0.95)	0.12 (-0.20;0.43)	0.66
Beclomethasone equivalent (mcg)	954 (644)	731 (621)	223 (6;439)	0.04
Cost of all medication ($)	836 (634)	723 (761)	113 (-126;351)	0.17
Cost of asthma medication ($)	568 (406)	409 (322)	159 (33;285)	0.03
≥ 1 severe exacerbation (n) ††	14 (20%)	8 (13%)	-	0.35

B. Subgroup with intermediate level (25-50 ppb)

	Ca-Strategy (N = 14)	**FCa-Strategy (N = 13)**	**Difference (95% CI)**	**p-value**
ACQ	0.73 (0.69)	0.58 (0.47)	0.15 (-0.32;0.62)	0.71
AQLQ	6.28 (0.57)	6.28 (0.64)	0.00 (-0.48;0.48)	1.00
Beclomethasone equivalent (mcg)	621 (591)	754 (533)	-132 (-580;315)	0.38
Cost of all medication	511 (451)	587 (580)	-76 (-486;334)	0.80
Cost of asthma medication	323 (408)	428 (461)	-105 (-449;239)	0.66
≥ 1 severe exacerbation (n) ††	2 (14%)	2 (15%)	-	1.00

C. Subgroup with high level (50 ppb)

	Ca-Strategy (N = 9)	**FCa-Strategy (N = 9)**	**Difference (95% CI)**	**p-value**
ACQ	0.90 (0.65)	0.98 (1.10)	-0.08 (-0.98;0.82)	0.79
AQLQ	6.09 (0.75)	6.32 (0.98)	-0.23 (-1.09;0.65)	0.20
Beclomethasone equivalent (mcg)	556 (662)	756 (613)	-200 (-837;437)	0.42
Cost of all medication	334 (193)	511 (279)	-177 (-416;63)	0.35
Cost of asthma medication	247 (172)	301 (170)	-54 (-225;116)	0.54
≥ 1 severe exacerbation (n) ††	1 (11%)	2 (22%)	-	1.00

D. Combined subgroups with intermediate/high level (>25 ppb)

	Ca-Strategy (N = 23)	**FCa-Strategy (N = 22)**	**Difference (95% CI)**	**p-value**
ACQ	0.80 (0.67)	0.74 (0.79)	0.05 (-0.38;0.49)	0.58
AQLQ	6.21 (0.64)	6.30 (0.77)	-0.09 (-0.52;0.34)	0.39
Beclomethasone equivalent (mcg)	596 (606)	755 (553)	-159 (-508;190)	0.19
Cost of all medication	442 (376)	556 (473)	-114 (-370;142)	0.44
Cost of asthma medication	293 (332)	376 (369)	-83 (-294;128)	0.42
≥ 1 severe exacerbation (n) ††	3 (13%)	4 (18%)	-	1.00

Ca = Controlled asthma FCa = Feno-driven controlled asthma
ACQ = Asthma Control Questionnaire AQLQ = Asthma Quality of Life Questionnaire
† As a post-hoc analysis we pooled the intermediate and high FeNO-subgroups (> 25 ppb) because of the low number of patients in these FeNO-subgroups separately. †† Fisher's exact test

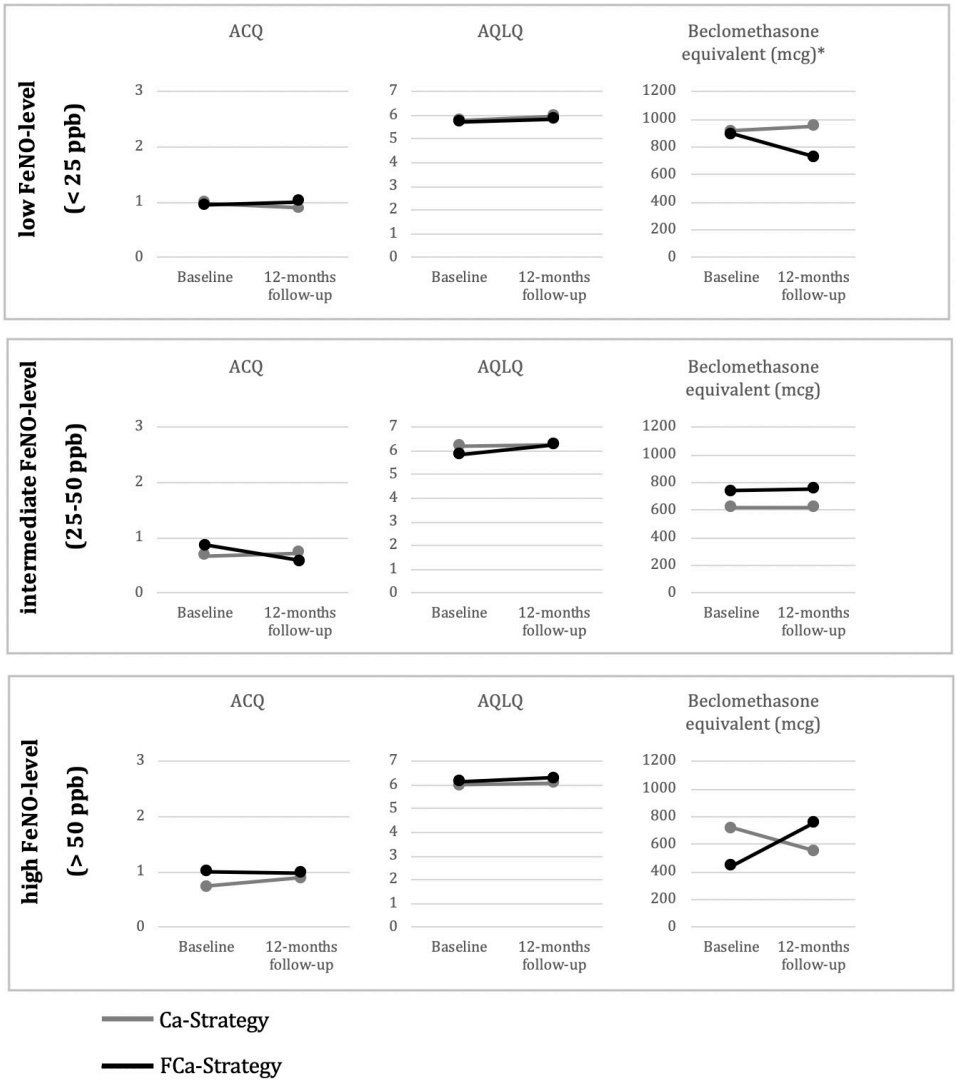

FIGURE 1. *Mean-differences between the Ca-stratefy and the FCa-strategy over a 12-months period for Asthma Control Quistionaire (ACQ), Asthma Quality of Life Questionaire (AQLQ) and Beclomethasone equivalent; per prespecified subgroup (based on FeNO-level)*

** p = 0.04*

DISCUSSION

Our aim was to identify a specific FeNO-subgroup of patients who may benefit (most) from FeNO-driven asthma management in primary care. We found patients presenting with a low FeNO level at baseline, benefit from a FeNO and symptom-based treatment algorithm compared to only symptom based, in terms of a reduction in asthma medication usage and costs, while asthma control and quality of life do not differ between the Ca-strategy and FCa-strategy. Therefore, our data suggest that down-titrating in patients with low FeNO level is possible and safe.

This finding is in line with other studies. First of all, as a deepening study of Honkoop et al. (2015) we showed the FeNO-driven asthma management yields benefits in terms of costs especially in patients with a low FeNO level at baseline.[19] Also, even with less medication use with this strategy compared to conventional asthma management, asthma control and quality of life remain similar. Therefore, our results showed the possibility of safely down-titrating in patients with low FeNO-level with FeNO-driven asthma management.[32] Note that our findings showed no down-titrating in patients with conventional asthma management; although both patient-groups weren't any different at baseline.

We cannot conclude that patients with a low FeNO level benefit from FeNO-driven asthma management in terms of clinical outcomes. However, use of as little medication as possible without the loss of asthma control or quality of life is worsening of as it is an important treatment goal according to international asthma guidelines.[8] Our results show that this can be achieved in patients with low baseline FeNO-level and, furthermore down-titrating medication in patients with FeNO-driven asthma management also results in significant lower asthma medication (costs), compared to patients with the same FeNO levels in conventional asthma management. This adds to the ongoing discussion of appropriate prescribing, for example in the Choosing Wisely campaign: an initiative that seeks to advance a dialogue on avoiding unnecessary medical tests, treatments and procedures.[33]

In the subgroups of patients with intermediate and high FeNO-levels, we found increased medication usage. Study populations with a high(er) representativeness of patients with intermediate to higher FeNO-levels could lead to contradictory findings showing that FeNO-driven asthma management will lead to increased medication usage.[34,35] For example, study populations based on patients treated in secondary care, it was shown that 45% of the patients has intermediate to high FeNO-levels.[35] In that setting FeNO-

driven asthma management is likely to lead to more medication usage due to the higher representativeness of patients with intermediate and high FeNO-levels. Even more so, if one considers that the cut-offs for intermediate and high FeNO, and therefore a decision to increase treatment, has been as low as 10 to 20 ppb before the publication of the current guidelines in 2014.[36] Unfortunately, in the intermediate and high subgroups we did not assess any benefit or harm in the comparison between asthma treatment based on FCa versus Ca-strategy. It could still be questioned if increased medication usage is necessary in patients with high FeNO-level, but the decreased number of exacerbations suggest it does, however, the study sample is small and no significant differences were found.

Strengths and limitations

In this study, the majority of patients in primary care (70%) are classified as having a low FeNO level, with less patients classified as having an intermediate or high level of FeNO. This does not affect our concluding remarks about the possibility of down-titrating medication in patients with low FeNO level in primary care. However, due to lack of power for the intermediate and high FeNO levels we cannot state our concluding remarks about both with confidence. Unfortunately, it was not possible to explore whether specific groups based on the frequency of severe asthma exacerbations benefit most from FeNO-driven, as suggested by Petsky et al. (2016).[13] Our data provided only information about the presence of previous severe exacerbations as a dichotomous variable. A potential limitation of our study is that the GP's diagnosis of asthma was not reassessed. However, Lucas et al.[37] 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.

Clinical implication

Many patients in primary care have low FeNO level. Therefore, using FeNO-driven asthma management for those patients supports a safe reduction of ICS use without loss of asthma control and quality of life. Symptoms of asthma can be caused by a lot of different factors. Sometimes these symptoms will remain even if no inflammation is present (for example in obese asthma patients). In those cases asthma management relying on symptoms tends to maintain or even increase medication usage. FeNO-driven asthma management showing no signs of inflammation allows for down titrating. Additionally physicians and patients are reluctant to decrease medication usage and a measurement showing no inflammation reassures them that decreasing is safe. Consequently, this strategy results in a reduction in medication costs, with a cost-

efficient intervention.[19]

Conclusion

With FeNO-driven asthma management down-titrating medication in primary care patients with low FeNO level is possible and safe, while preserving asthma control and quality of life. FeNO-driven asthma management can be of substantial aid in reducing the use of inhaled corticosteroid.

ABBRIVATIONS

ACQ. Asthma Control Questionnaire

AQLQ. Asthma Quality of Life Questionnaire

BMI. Body mass index

Ca-strategy. Controlled asthma strategy

CI. confidence interval

FCa-strategy. Fractional exhaled nitric oxide-driven controlled asthma strategy

FeNO. Fractional exhaled nitric oxide

ICS. Inhaled Corticosteroids

LABA. Long-Acting Beta-Agonist

MCG. Microgram

NO. Nitric oxide

PPB. Parts per billion

SD. Standard deviation

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ONLINE SUPPLEMENT

TABLE 1. *Baseline characteristics per prespecified subgroup (based on FeNO-level)*

A. Subgroup with low level (< 25 ppb)

	Ca-Strategy (N = 71)	**FCa-Strategy (N = 63)**	**Difference (95% CI)**	**p-value**
ACQ	0.98 (0.80)	0.95 (0.73)	0.04 (-0.23;0.30)	0.93
AQLQ	5.78 (0.92)	5.74 (0.93)	0.04 (-0.28;0.35)	0.80
Beclomethasone equivalent (mcg)	915 (716)	895 (619)	20 (-210;250)	0.72

B. Subgroup with intermediate level (25-50 ppb)

	Ca-Strategy (N = 14)	**FCa-Strategy (N = 13)**	**Difference (95% CI)**	**p-value**
ACQ	0.68 (0.69)	0.87 (0.28)	-0.19 (-0.61;0.24)	0.14
AQLQ	6.26 (0.72)	5.85 (0.98)	0.41 (-0.27;1.08)	0.16
Beclomethasone equivalent (mcg)	621 (683)	738 (762)	-117 (-690;456)	0.56

C. Subgroup with high level (50 ppb)

	Ca-Strategy (N = 9)	**FCa-Strategy (N = 9)**	**Difference (95% CI)**	**p-value**
ACQ	0.74 (0.46)	1.01 (0.83)	-0.27 (-0.94;0.40)	0.48
AQLQ	5.99 (0.71)	6.17 (0.88)	-0.17 (-0.97;0.63)	0.35
Beclomethasone equivalent (mcg)	722 (570)	444 (407)	228 (-217;772)	0.26

D. Combined subgroups with intermediate/high level (>25 ppb)

	Ca-Strategy (N = 23)	**FCa-Strategy (N = 22)**	**Difference (95% CI)**	**p-value**
ACQ	0.70 (0.60)	0.92 (0.56)	-0.22 (-0.57;0.13)	0.16
AQLQ	6.16 (0.71)	5.98 (0.93)	0.18 (-0.32;0.67)	0.68
Beclomethasone equivalent (mcg)	661 (629)	618 (646)	43 (-341;426)	0.87

Ca = Controlled asthma
FCa = Feno-driven controlled asthma
ACQ = Asthma Control Questionnaire
AQLQ = Asthma Quality of Life Questionnaire
CI = confidence interval
† As a post-hoc analysis we pooled the intermediate and high FeNO-subgroups (> 25 ppb) because of the low number of patients in these FeNO-subgroups separately.