ORIGINAL ARTICLE
ASTHMA

Personalised exhaled nitric oxygen fraction (F_{ENO})-driven asthma management in primary care: a F_{ENO} subgroup analysis of the ACCURATE trial

Suzanne Boer[1,2], Persijn J. Honkoop[1], Rik J.B. Loijmans[3], Jiska B. Snoeck-Stroband[1], Willem J.J. Assendelft[4], Tjard R.J. Schermer[4] and Jacob K. Sont[1]

Affiliations: [1]Dept of Biomedical Data Sciences, Section of Medical Decision Making, Leiden University Medical Centre, Leiden, The Netherlands. [2]Dept of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands. [3]Dept of General Practice, Academic Medical Centre, Amsterdam, The Netherlands. [4]Dept of Primary and Community Care, Radboud University Medical Centre, Nijmegen, The Netherlands.

Correspondence: Jacob K. Sont, Leiden University Medical Centre, Postzone J-10S, Albinusdreef 2, 2300 RC Leiden, The Netherlands. E-mail: j.k.sont@lumc.nl

ABSTRACT

Background: The aim of this study was to identify patients who benefit most from exhaled nitric oxide fraction (F_{ENO})-driven asthma management in primary care, based on prespecified subgroups with different levels of F_{ENO}.

Methods: We used data from 179 adults with asthma from a 12-month primary care randomised controlled trial with 3-monthly assessments of F_{ENO}, 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 a F_{ENO}+symptom-driven strategy (FCa). In both groups, patients were categorised by their baseline level of F_{ENO} as low (<25 ppb), intermediate (25–50 ppb) and high (>50 ppb). At 12 months, we compared, for each prespecified F_{ENO} 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 µg (95% CI 6–439), p=0.04) and for the total costs of asthma medication a mean reduction of US$159 (95% CI US$33–285), p=0.03) in patients with a low baseline F_{ENO} level. No differences were found for asthma control, severe asthma exacerbations and asthma-related quality of life in patients with a low baseline F_{ENO} level. Furthermore, in patients with intermediate or high level of F_{ENO}, no differences were found.

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

@ERSpublications
In primary care, F_{ENO}-driven asthma management is effective in patients with a low F_{ENO}, for whom it is possible to down-titrate medication while preserving asthma control and quality of life https://bit.ly/2wC25N7d

Cite this article as: Boer S, Honkoop PJ, Loijmans RJB, *et al*. Personalised exhaled nitric oxygen fraction (F_{ENO})-driven asthma management in primary care: a F_{ENO} subgroup analysis of the ACCURATE trial. *ERJ Open Res* 2020; 6: 00351-2019 [https://doi.org/10.1183/23120541.00351-2019].

This article has supplementary material available from openres.ersjournals.com

Received: 7 Jan 2020 | Accepted after revision: 24 March 2020

Copyright ©ERS 2020. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

Introduction

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 difficult 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 in exhaled breath, the so-called fractional exhaled nitric oxide (F_{ENO}) [4]. For diagnosing asthma, a F_{ENO} measurement is now recommended as part of the diagnostic algorithm in several guidelines, alongside clinical evaluation, spirometry, and symptom assessments [5–7].

However, when monitoring asthma after the diagnosis of asthma has been established, whether or not F_{ENO} should be measured is still up for debate [8]. Several studies have shown that F_{ENO} 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 optimising titration of inhaled steroid treatment [9–13]. Others have shown opposing results, showing no advantage of F_{ENO}, or even that F_{ENO} resulted in worse outcomes [14–17].

A potential reason for these different findings might be that F_{ENO} measurements in the management of asthma, only have additional benefit in specific subgroups based on different levels of F_{ENO} 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 F_{ENO} subgroups also have their own set of required measurements, and that F_{ENO}-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 F_{ENO} 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 that F_{ENO}-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 F_{ENO} at baseline, where F_{ENO} 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 F_{ENO} subgroups of patients who benefit (most) from F_{ENO}-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 randomised controlled trial 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 F_{ENO} 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, the treatment plan allowed for more variation in asthma control. During the trial, maintenance asthma medications were adjusted at 3-monthly intervals, based on the six-item ACQ and spirometry with or without F_{ENO} (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].

Study population

Patients were aged 18–50 years, with a doctor's diagnosis of asthma and were prescribed inhaled corticosteroids (ICSs). 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 at 12 months and patients filled out online questionnaires at approximately 3-monthly intervals. We included all patients where data of all outcome measurements was available at 12 months as a secondary complete case analysis.

TABLE 1 Treatment strategy algorithms

Strategy	Level of asthma control		
	Controlled	Partly controlled	Uncontrolled
Ca strategy	3 months: no change>3 months: step down	Step up: treatment choice	Step up: treatment choice
FCa strategy			
Low F_{ENO}[#]	Step down	3 months: no change/change within current step to LABA>3 months: step down ICSs	Step up: LABA
Intermediate F_{ENO}	No change	Step up: treatment choice	Step up: treatment choice
High F_{ENO}[¶]	Step up/change within current step to ICSs	Step up: 1×ICS	Step up: 2×ICS[+]

Ca: controlled asthma; FCa: exhaled nitric oxide fraction-driven controlled asthma; F_{ENO}: exhaled nitric oxide fraction; LABA: long-acting β-agonist; ICS: inhaled corticosteroid. [#]: <25 ppb; [¶]: >50 ppb; [+]: until a maximum high dose is reached.

Baseline prespecified F_{ENO} subgroups

We distinguished between three prespecified subgroups, based on different levels of F_{ENO} 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, F_{ENO} 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 of F_{ENO}, were evaluated on five different outcomes after 12 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) levels of asthma control [28]. Asthma-related quality of life was measured by the Dutch version of the Asthma Quality of Life Questionnaire (AQLQ)-Juniper. The AQLQ 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 ICS 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 US 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 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 3 days or more, 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 F_{ENO} subgroup and per treatment strategy (Ca and FCa). Second, the mean level of all outcome measurements was assessed at 12 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 12 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 F_{ENO} subgroup. As a *post hoc* analysis we pooled the intermediate and high F_{ENO} subgroups (>25 ppb) because of the low number of

patients in these F_{ENO} 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 for 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, 68% were 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 years (SD 8.1), 74% were female, and the mean asthma duration was 19.7 years (SD 14.2).

Prespecified F_{ENO} 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 F_{ENO} subgroup between the Ca and FCa strategy (table 1 and supplementary material).

At 12 months, in the low F_{ENO} subgroup there were no differences in ACQ score and AQLQ score between the Ca and FCa strategy. However, the dosage of ICS medication (converted to beclomethasone equivalent) and total costs of asthma medication were reduced in the FCa strategy compared to the Ca strategy by 223 µg (95% CI 6–439 µg), p=0.04) and US$159 (95% CI $33–285), p=0.03), respectively (figure 1 and table 3). At 12 months, mean dosage of beclomethasone for patients with a low F_{ENO} level increased by 80 µg within the Ca strategy and decreased by more than 150 µg within the FCa strategy. Furthermore, no significant differences were found for the experience of at least one severe asthma exacerbations.

At 12 months, in patients with intermediate or high F_{ENO} levels no differences were found between the strategies (table 3). For patients with an intermediate and high F_{ENO} level, 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 F_{ENO} subgroups also did not result in a significant difference at 12 months between the Ca strategy and FCa strategy (table 3).

Discussion

Our aim was to identify a specific F_{ENO} subgroup of patients who may benefit (most) from F_{ENO}-driven asthma management in primary care. We found that patients presenting with a low F_{ENO} level at baseline, benefit from a F_{ENO} and symptom-based treatment algorithm compared to only symptom-based, in terms of a reduction in asthma medication usage and costs, whereas asthma control and quality of life did not

TABLE 2 Patient characteristics

	Ca strategy	FCa strategy
Continuous variables		
Patients	94	85
Age years	41.6±6.8	41.2±8.1
BMI kg·m^{-2}	25.9±4.7	26.3±5.6
Asthma duration years	18.2±13.3	19.7±14.2
Baseline F_{ENO} ppb	20.5±21.3	23.1±22.9
Beclomethasone-equivalent dose µg	853±702	824±634
Baseline ACQ score	0.91±0.76	0.94±0.68
Baseline AQLQ score	5.87±0.88	5.80±0.93
Categorical variables		
Females %	68	74
Long-acting β-agonist use %	61	51
Current smokers %	10	11
Previous smokers % of current nonsmokers	33	36
ACQ subgroup %		
Low[#]	50	39
Medium[¶]	34	45
High[+]	16	17

Data are presented as mean±SD unless otherwise stated. Ca: controlled asthma; FCa: exhaled nitric oxide fraction-driven controlled asthma; BMI: body mass index; F_{ENO}: exhaled nitric oxide fraction; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire. [#]: <0.75; [¶]: 0.75–1.50; [+]: >1.50.

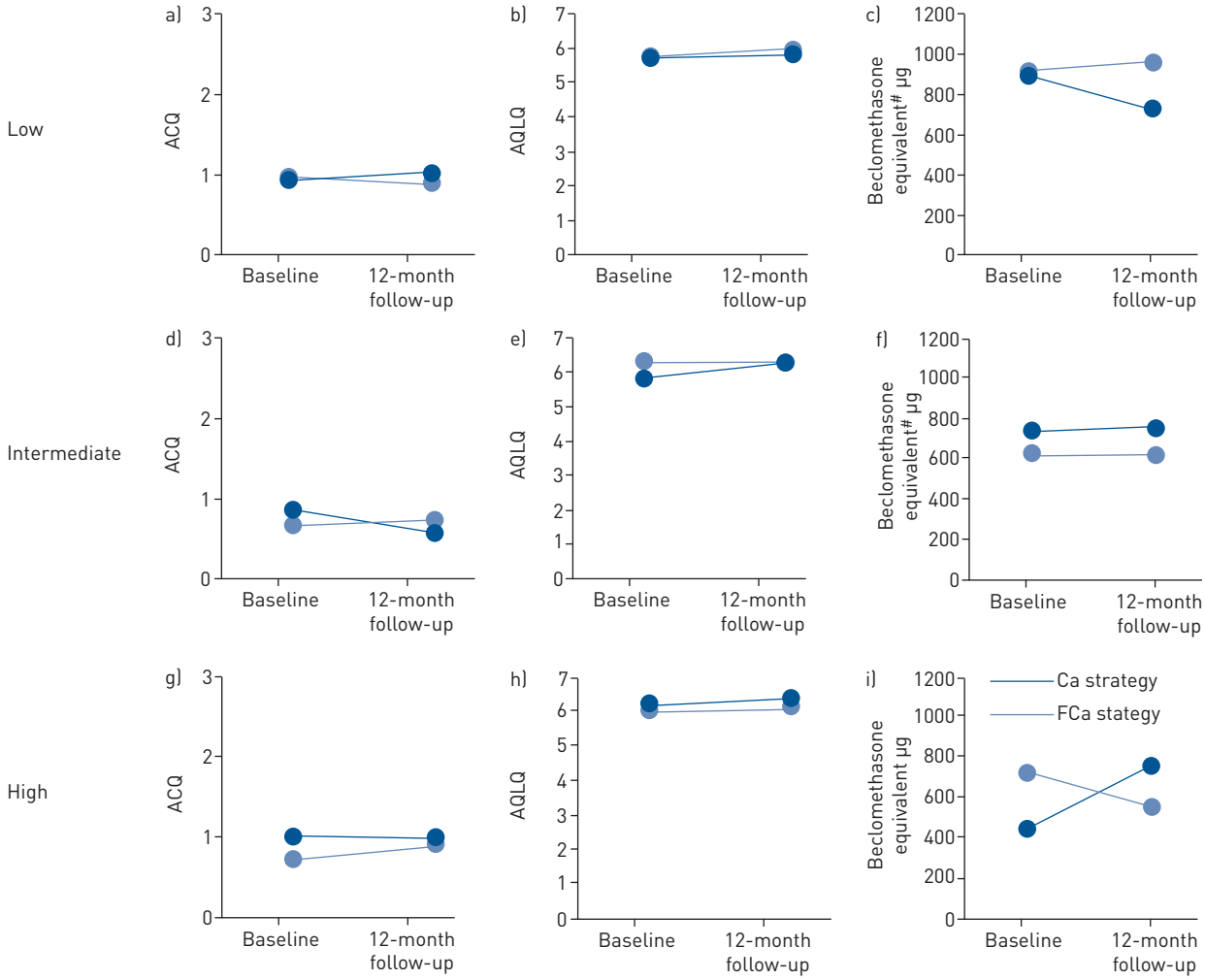

FIGURE 1 Mean differences between the controlled asthma (Ca) strategy and the exhaled nitric oxide fraction (F_{ENO})-driven controlled asthma (FCa) strategy over a 12-month period for Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ) and beclomethasone equivalent; per prespecified subgroup (based on F_{ENO} level). a–c) Low F_{ENO}; d–e) intermediate F_{ENO}; f–h) high F_{ENO}. #: p=0.04.

differ between the Ca strategy and FCa strategy. Therefore, our data suggest that down-titrating patients with low F_{ENO} levels is possible and safe.

This finding is in line with other studies. First of all, as a deepening study of Honkoop *et al.* [19] we showed that F_{ENO}-driven asthma management yields benefits in terms of costs, especially in patients with a low F_{ENO} level at baseline. 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 show the possibility of safely down-titrating patients with low F_{ENO} levels with F_{ENO}-driven asthma management [10]. Note that our findings showed no down-titrating in patients with conventional asthma management, although both patient groups were not any different at baseline.

We cannot conclude that patients with a low F_{ENO} level benefit from F_{ENO}-driven asthma management in terms of clinical outcomes. However, use of as little medication as possible without the loss of asthma control or worsening of quality of life is an important treatment goal according to international asthma guidelines [8]. Our results show that this can be achieved in patients with low baseline F_{ENO} levels and, furthermore down-titrating medication in patients with F_{ENO}-driven asthma management also results in significantly lower asthma medication (costs), compared to patients with the same F_{ENO} 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 [32].

In the subgroups of patients with intermediate and high F_{ENO} levels, we found increased medication usage. Study populations with a high(er) representation of patients with intermediate to higher F_{ENO} levels could

TABLE 3 12-month outcomes per prespecified subgroup (based on exhaled nitric oxide fraction (F_{ENO}))

	Ca strategy	FCa strategy	Difference (95% CI)	p-value
F_{ENO} <25 ppb				
Patients	71	63		
ACQ score	0.90±0.75	1.01±0.80	−0.11 (−0.38; 0.15)	0.40
AQLQ score	5.97±0.87	5.85±0.95	0.12 (−0.20–0.43)	0.66
Beclomethasone-equivalent dose µg	954±644	731±621	223 (6–439)	0.04
Cost of all medication US$	836±634	723±761	113 (−126–351)	0.17
Cost of asthma medication US$	568±406	409±322	159 (33–285)	0.03
⩾1 severe exacerbation	14 (20%)	8 (13%)		0.35#
F_{ENO} 25–50 ppb				
Patients	14	13		
ACQ score	0.73±0.69	0.58±0.47	0.15 (−0.32–0.62)	0.71
AQLQ score	6.28±0.57	6.28±0.64	0.00 (−0.48–0.48)	1.00
Beclomethasone-equivalent dose µg	621±591	754±533	−132 (−580–315)	0.38
Cost of all medication US$	511±451	587±580	−76 (−486–334)	0.80
Cost of asthma medication US$	323±408	428±461	−105 (−449–239)	0.66
⩾1 severe exacerbation	2 (14%)	2 (15%)		1.00#
F_{ENO} >50 ppb				
Patients	9	9		
ACQ score	0.90±0.65	0.98±1.10	−0.08 (−0.98–0.82)	0.79
AQLQ score	6.09±0.75	6.32±0.98	−0.23 (−1.09–0.65)	0.20
Beclomethasone-equivalent dose µg	556±662	756±613	−200 (−837–437)	0.42
Cost of all medication US$	334±193	511±279	−177 (−416–63)	0.35
Cost of asthma medication US$	247±172	301±170	−54 (−225–116)	0.54
⩾1 severe exacerbation	1 (11%)	2 (22%)		1.00#
F_{ENO} >25 ppb				
Patients	23	22		
ACQ score	0.80±0.67	0.74±0.79	0.05 (−0.38–0.49)	0.58
AQLQ score	6.21±0.64	6.30±0.77	−0.09 (−0.52–0.34)	0.39
Beclomethasone-equivalent dose µg	596±606	755±553	−159 (−508–190)	0.19
Cost of all medication US$	442±376	556±473	−114 (−370–142)	0.44
Cost of asthma medication US$	293±332	376±369	−83 (−294–128)	0.42
⩾1 severe exacerbation	3 (13%)	4 (18%)		1.00#

Data are presented as mean±SD unless otherwise stated. As a *post hoc* analysis, we pooled the intermediate and high F_{ENO} subgroups (>25 ppb) because of the low number of patients in these F_{ENO} subgroups separately. Ca: controlled asthma; FCa: F_{ENO}-driven controlled asthma; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire. #: Fisher's exact test.

lead to contradictory findings showing that F_{ENO}-driven asthma management will lead to increased medication usage [15, 33]. For example, study populations based on patients treated in secondary care, showed that 45% of patients had intermediate to high F_{ENO} levels [33]. In that setting, F_{ENO}-driven asthma management is likely to lead to more medication usage due to the higher representation of patients with intermediate and high F_{ENO} levels, even more so, if one considers that the cut-offs for intermediate and high F_{ENO} levels, and therefore a decision to increase treatment, has been as low as 10–20 ppb before the publication of the current guidelines in 2014 [34]. Unfortunately, in the intermediate and high subgroups, no benefit or harm was assessed in the comparison between asthma treatments based on the FCa *versus* Ca strategy. It could still be questioned whether increased medication usage is necessary in patients with high F_{ENO} levels, but the decreased number of exacerbations suggest that it does; however, the study sample was small and no significant differences were found.

Strengths and limitations

In this study, the majority of patients in primary care (70%) were classified as having a low F_{ENO} level, with less patients classified as having an intermediate or high level of F_{ENO}. This does not affect our concluding remarks about the possibility of down-titrating medication in patients with low F_{ENO} levels in primary care; however, due to lack of power for the intermediate and high F_{ENO} 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 F_{ENO}-driven management, as suggested by Petsky *et al.* [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 a general practitioner diagnosis of asthma was not reassessed. However, Lucas *et al.* [35]. 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 a low F_{ENO} level. Therefore, using F_{ENO}-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 patients with asthma). In those cases, asthma management relying on symptoms tends to maintain or even increase medication usage. F_{ENO}-driven asthma management showing no sign 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].

Conclusions

With F_{ENO}-driven asthma management down-titrating medication in primary care patients with low F_{ENO} levels is possible and safe, while preserving asthma control and quality of life. F_{ENO}-driven asthma management can be of substantial aid in reducing the use of ICSs.

Author contributions: S. Boer analysed and interpreted the data, and wrote the manuscript. J.K. Sont and P.J. Honkoop were major contributors to the analysis and writing the manuscript. J.K. Sont and P.J. Honkoop contributed substantially to the conception and design of the original study (ACCURATE) and the acquisition of data, as well as R.J.B. Loijmans, J.B. Snoek-Stroband, W.J.J. Assendelft and T.R.J. Schermer. All authors provided critical revision of the article and provided final approval of the version to publish.

This Asthma Control Cost-Utility Randomized Trial Evaluation (ACCURATE) is registered at www.trialregister.nl with identifier number NL1658 (NTR1756). The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: S. Boer has nothing to disclose. P.J. Honkoop has nothing to disclose. R.J.B. Loijmans has nothing to disclose. J.B. Snoeck-Stroband has nothing to disclose. W.J.J. Assendelft has nothing to disclose. T.R.J. Schermer reports projects grants for the study from the Netherlands Organisation for Health Research and Development, and the Dutch Lung Foundation, during the conduct of the study. J.K. Sont reports an unrestricted research grant from GSK Netherlands outside the submitted work.

References

1 Lötvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127: 355–360.
2 Agusti A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47: 410–419.
3 Sont JK, van Krieken HJM, Evertse CE, *et al.* Relationship between the inflammatory infiltrate in bronchial biopsy specimens and clinical severity of asthma in patients treated with inhaled steroids. *Thorax* 1996; 51: 496–502.
4 Arnold RJG, Layton A, Massanari M. Cost impact of monitoring exhaled nitric oxide in asthma management. *Allergy Asthma Proc* 2018; 39: 338–344.
5 British Thoracic Society. Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2014; 69: 1–192.
6 NICE. Asthma: diagnosis, monitoring and chronic asthma management NICE guideline 2017. Last accessed: June 2020. Last updated: February 2020. www.nice.org.uk/guidance/ng80/.
7 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
8 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2018 Last accessed: June 2020. Last updated: 2018. www.ginasthma.org.
9 Jones SL, Kittelson J, Cowan JO, *et al.* The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med* 2001; 164: 738–743.
10 Smith AD, Cowan JO, Brassett KP, *et al.* Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005; 352: 2163–2173.
11 Pijnenburg MW, Bakker EM, Hop WC, *et al.* Titrating steroids on exhaled nitric oxide in children with asthma: a randomised controlled trial. *Am J Respir Crit Care Med* 2005; 172: 831–836.
12 Donohue JF, Jain N. Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. *Respir Med* 2013; 107: 943–952.
13 Petsky HL, Kew KM, Turner C, *et al.* Exhaled nitric oxide levels to guide treatment for adults with asthma. *Cochrane Database Syst Rev* 2016; 9: 1–3.
14 Shaw DE, Berry MA, Thomas M, *et al.* The use of exhaled nitric oxide to guide asthma management: a randomised controlled trial. *Am J Respir Crit Care Med* 2007; 176: 231–237.
15 Szefler SJ, Mitchell H, Sorkness CA, *et al.* Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008; 372: 1065–1072.

16 De Jongste JC, Carraro S, Hop WC, *et al.* Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009; 179: 93–97.
17 Hewitt RS, Modrich CM, Cowan JO, *et al.* Outcomes using exhaled nitric oxide measurements as an adjunct to primary care asthma management. *Prim Care Respir J* 2009; 18: 320–327.
18 Shrimanker R, Choo XN, Pavord ID. A new approach to the classification and management of airways diseases: identification of treatable traits. *Clin Sci* 2017; 131: 1027–1043.
19 Honkoop PJ, Loijmans RJ, Termeer EH, *et al.* Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: a cluster-randomized trial in primary care. *J Allergy Clin Immunol* 2015; 135: 682–688.
20 Honkoop PJ, Loijmans RJ, Termeer EH, *et al.* Asthma Control Cost-Utility Randomized Trial Evaluation (ACCURATE): the goals of asthma treatment. *BMC Pulm Med* 2011; 11: 53.
21 Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet* 2006; 368: 780–793.
22 The Dutch General Practice Society (NHG). 2015. Asthma in Adults. Huisarts en Wetenschap. Utrecht.
23 Killian KJ, Watson R, Otis J, *et al.* Symptom perception during acute bronchoconstriction. *Am J Respir Crit Care Med* 2000; 162: 490–496.
24 Pavord ID, Shaw D. The use of exhaled nitric oxide in the management of asthma. *J Asthma* 2008; 45: 523–531.
25 Dweik RA, Boggs PB, Erzurum SC, *et al.* An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (F_{ENO}) for clinical applications. *Am J Respir Crit Care Med* 2011; 184: 602–615.
26 American Thoracic Society and European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005; 171: 912–930.
27 Alving K, Janson C, Nordvall L. Performance of a new hand-held device for exhaled nitric oxide measurement in adults and children. *Respir Res* 2006; 7: 67.
28 Juniper EF, Bousquet J, Abetz L, *et al.* Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006; 100: 616–621.
29 Juniper EF, Guyatt GH, Ferrie PJ, *et al.* Measuring quality of life in asthma. *Am Rev Respir Dis* 1993; 147: 832–838.
30 College voor Zorgverzekeringen. Farmacotherapeutisch Kompas. Last accessed: June 2020. Last updated: 2020. https://www.zorgwijzer.nl/zorgwijzers/medicijnen.
31 Reddel HK, Taylor DR, Bateman ED, *et al.* An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180: 59–99.
32 Choosing Wisely. Promoting conversations between patients and clinicians. Last accessed: June 2020. Last updated: 2020. www.choosingwisely.org.
33 Stone B, Davis JR, Trudo F, *et al.* Characterizing patients with asthma who received Global Initiative for Asthma steps 4–5 therapy and managed in speciality care setting. *Allergy Asthma Proc* 2018; 39: 27–35.
34 Grob NM, Dweik RA. Exhaled nitric oxide in asthma. From diagnosis, to monitoring, to screening: are we there yet? *Chest* 2008; 133: 837–839.
35 Lucas AE, Smeenk FJ, Smeele IJ, *et al.* Diagnostic accuracy of primary care asthma/COPD working hypotheses, a real-life study. *Respir Med* 2012; 106: 1158–1163.