Personalised exhaled nitric oxygen fraction ($F_{\text{ENO}}$)-driven asthma management in primary care: a $F_{\text{ENO}}$ 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-105, 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 ($F_{\text{ENO}}$)-driven asthma management in primary care, based on prespecified subgroups with different levels of $F_{\text{ENO}}$.

Methods: We used data from 179 adults with asthma from a 12-month primary care randomised controlled trial with 3-monthly assessments of $F_{\text{ENO}}$, 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 $F_{\text{ENO}}$+symptom-driven strategy (FCa). In both groups, patients were categorised by their baseline level of $F_{\text{ENO}}$ as low (<25 ppb), intermediate (25–50 ppb) and high (>50 ppb). At 12 months, we compared, for each prespecified $F_{\text{ENO}}$ 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 $F_{\text{ENO}}$ level. No differences were found for asthma control, severe asthma exacerbations and asthma-related quality of life in patients with a low baseline $F_{\text{ENO}}$ level. Furthermore, in patients with intermediate or high level of $F_{\text{ENO}}$, no differences were found.

Conclusions: In primary care, $F_{\text{ENO}}$-driven asthma management is effective in patients with a low $F_{\text{ENO}}$ level, for whom it is possible to down-titrate medication, while preserving asthma control and quality of life.
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 (\(F_{\text{ENO}}\)) [4]. For diagnosing asthma, a \(F_{\text{ENO}}\) 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 \(F_{\text{ENO}}\) should be measured is still up for debate [8]. Several studies have shown that \(F_{\text{ENO}}\) 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 \(F_{\text{ENO}}\), or even that \(F_{\text{ENO}}\) resulted in worse outcomes [14–17].

A potential reason for these different findings might be that \(F_{\text{ENO}}\) measurements in the management of asthma, only have additional benefit in specific subgroups based on different levels of \(F_{\text{ENO}}\) 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 \(F_{\text{ENO}}\) subgroups also have their own set of required measurements, and that \(F_{\text{ENO}}\)-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 \(F_{\text{ENO}}\) 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 \(F_{\text{ENO}}\)-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 \(F_{\text{ENO}}\) at baseline, where \(F_{\text{ENO}}\) 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 \(F_{\text{ENO}}\) subgroups of patients who benefit (most) from \(F_{\text{ENO}}\)-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 \(F_{\text{ENO}}\) 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 \(F_{\text{ENO}}\) (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 \(\geq 12\%\) 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.
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 of FENO, 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 FENO 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 FENO subgroup. As a post hoc analysis we pooled the intermediate and high FENO subgroups (>25 ppb) because of the low number of

| Strategy | Level of asthma control | Ca strategy | Uncontrolled |
|----------|-------------------------|-------------|--------------|
|          | Controlled | Partly controlled | Step up: treatment choice | Step up: treatment choice |
| Ca strategy | 3 months: no change | 3 months: no change/change within current step to LABA | Step up: treatment choice |
| FCa strategy | Step down | 3 months: no change | Step up: LABA |
| Low FENO | No change | Step up: treatment choice | Step up: treatment choice |
| Intermediate FENO | 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; FENO: exhaled nitric oxide fraction; LABA: long-acting β-agonist; ICS: inhaled corticosteroid. #: <25 ppb; ¶: >50 ppb; *: until a maximum high dose is reached.

TABLE 1 Treatment strategy algorithms

Ca: controlled asthma; FCa: exhaled nitric oxide fraction-driven controlled asthma; FENO: exhaled nitric oxide fraction; LABA: long-acting β-agonist; ICS: inhaled corticosteroid. #: <25 ppb; ¶: >50 ppb; *: until a maximum high dose is reached.
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 | 852±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.
differ between the Ca strategy and FCA strategy. Therefore, our data suggest that down-titrating patients with low FENO 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 FENO-driven asthma management yields benefits in terms of costs, especially in patients with low FENO 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 FENO levels with FENO-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 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 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 FENO levels and, furthermore down-titrating medication in patients with FENO-driven asthma management also results in significantly 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 [32].

In the subgroups of patients with intermediate and high FENO levels, we found increased medication usage. Study populations with a high(er) representation of patients with intermediate to higher FENO levels could
Data are presented as mean±SD unless otherwise stated. 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. Ca: controlled asthma; FCA: FENO-driven controlled asthma; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire. *: Fisher’s exact test.

### Table 3 12-month outcomes per prespecified subgroup (based on exhaled nitric oxide fraction [FENO])

| FENO subgroup | Ca strategy | FCA strategy | Difference (95% CI) | p-value |
|---------------|-------------|--------------|---------------------|---------|
| **FENO <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 | 95±644 | 73±621 | 223 (6–439) | 0.04 |
| Cost of all medication US$ | 83±634 | 72±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* |
| **FENO 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* |
| **FENO >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* |
| **FENO >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* |

Strengths and limitations

In this study, the majority of patients in primary care (70%) were 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 levels 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 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 lead to contradictory findings showing that FENO-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 FENO levels [33]. In that setting, FENO-driven asthma management is likely to lead to more medication usage due to the higher representation of patients with intermediate and high FENO levels, even more so, if one considers that the cut-offs for intermediate and high FENO 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 FENO levels, but the decreased number of exacerbations suggest that it does; however, the study sample was small and no significant differences were found.

https://doi.org/10.1183/23120541.00351-2019
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. Snoek-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 PR, 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 specialty 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.