

Does this mean that there was no benefit in patients with higher risk thresholds? Using fractional exhaled nitric oxide to guide step down treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis

Abstract

Introduction

Use of fractional exhaled nitric oxide (FeNO) is recommended for asthma diagnosis but its role in guiding safe reduction of inhaled corticosteroids (ICS) is unclear.

Aims and objectives

To assess the value of FeNO in identifying asthma patients in whom ICS can be safely reduced.

Methods

We performed a systematic electronic database search to identify studies which recruited asthma patients aged ≥ 12 years maintained on low to moderate dose ICS in whom FeNO was measured at baseline before subsequently stepping down ICS treatment, irrespective of what the baseline FeNO value was. We performed multi-level mixed-effects logistic regression in relation to absence or presence of acute exacerbations up to 12 weeks after stepping down ICS, accounting for within-study clustering, age, sex and FeNO as baseline covariates. FeNO was categorised as low (≤ 20 ppb [parts per billion]), intermediate (>20 ppb to <50 ppb) or high (≥ 50 ppb). Net benefit values were calculated for ICS step-down guided by FeNO versus stepping down ICS in all patients or no patients for baseline exacerbation risk thresholds up to 30%.

Results

We obtained individual patient data from seven studies (393 patients; acute exacerbation, $n=44$). After adjustment for all baseline covariates in our regression model, exacerbation risk was significantly higher in patients with high FeNO (odds ratio [OR] 2.70, 95% confidence interval 1.16 to 6.26, $p=0.021$) than low FeNO. FeNO-guided step-down decisions had greater net benefit than stepping down treatment in all patients or no patients at baseline exacerbation risk thresholds between 6% and 16%.

Conclusion

Patients with mild-to-moderate asthma whose FeNO is ≥ 50 ppb are at greater risk of exacerbation following ICS reduction than patients whose FeNO is in the low or intermediate range. Assessment of FeNO is therefore important in guiding safe clinical decisions about stepping down treatment in asthma patients who appear to be symptomatically controlled on low or moderate dose ICS.

Introduction

Inhaled corticosteroids (ICS) are the mainstay of treatment to prevent acute exacerbations of asthma.(1) However, around 30% of patients receiving ICS in primary care are prescribed these without any clear indication,(2) and around one-third of patients with clinician-diagnosed asthma do not experience deterioration in symptoms, reversible airflow obstruction or bronchial hyper-responsiveness after being withdrawn from all asthma medications.(3) Inappropriate treatment with ICS not only generates unnecessary prescribing costs, but can also cause potential harm by increasing patients' risk of steroid-related adverse effects, including dyspepsia, obesity, hypertension and pneumonia.(4, 5)

Clinical practice guidelines therefore recommend that clinicians should aim to maintain asthma patients on the lowest possible dose of ICS and consider stepping down treatment in patients who have been clinically stable for at least three months.(1) However, previous systematic reviews of randomised controlled trials (RCTs) comparing fixed dose ICS strategies with reduction or withdrawal of ICS have reported inconsistent findings. One review found that stopping ICS in children and adults whose asthma has been stable for at least four weeks was associated with significantly increased risk of exacerbations.(6) However, another review concluded that reducing ICS dose by 50% or more did not significantly increase risk of exacerbations.(7) A recent Cochrane review(8) also did not demonstrate clinically or statistically significant differences in exacerbations, symptom control or quality of life between adults whose ICS dose was reduced by 50 to 60% versus individuals whose ICS dose was maintained, but found that data were limited and of low quality.

Basing step down treatment decisions on symptom control is unlikely to be reliable in asthma patients in whom there is discordance between symptom expression and eosinophilic airway inflammation.(9) Furthermore, it is estimated that around half of patients with mild-to-moderate asthma have persistent non-eosinophilic airway inflammation, which responds poorly to ICS.(10) In around two-thirds of patients with non-eosinophilic asthma, ICS may be reduced or withdrawn without subsequent worsening in exacerbation rates or symptom control.(11) Stepping down ICS in these patients may even be associated with improvement in asthma control and quality of life.(12) However, using sputum eosinophil counts to identify patients with non-eosinophilic asthma(11) and guide reductions in their treatment(9) is invasive and not feasible in primary care settings, where most monitoring of asthma treatment occurs.

Fractional exhaled nitric oxide (FeNO) is a non-invasive breath test which is strongly correlated with sputum eosinophils(13) and is both technically feasible and acceptable to patients and staff in primary care asthma clinic settings.(14) A previous RCT demonstrated that FeNO-guided management resulted in lower ICS use without compromising asthma control.(15) Nevertheless, clinicians remain hesitant about using FeNO to guide step down treatment decisions in patients with asthma. One primary care study reported that protocol deviations from a FeNO-guided management algorithm occurred in 25% of decisions, mostly in relation to reducing treatment.(16) Additionally, asthma treatment was only reduced in 9% of patients with FeNO measurements consistent with low levels of steroid-responsive airway inflammation in US specialist asthma clinics.(17) There is therefore a clear need for pragmatic, evidence-based guidance to help clinicians use and interpret FeNO measurements to minimise risk of exacerbations when making step-down treatment decisions in primary care asthma patients who appear to be symptomatically well controlled on low to moderate dose ICS.

Methods

Our study protocol is registered on the PROSPERO International prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017071826).

Data sources and searches

We performed systematic electronic database searches of Medline and Medline In Process (OvidSP) [1946-], EMBASE (OvidSP)[1974-], Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) and Web of Science Core Databases (Web of Science, Thomson Reuters) until 7th November 2016 with no language restrictions. Appendix 1 summaries our search strategy. We supplemented our electronic search by screening the reference lists of included studies and relevant systematic and narrative reviews to identify potentially suitable studies and asking experts in the field to review our list of included studies and highlight any obvious omissions.

Study selection

One reviewer (KW) screened the titles of articles retrieved by our search and excluded those which were obviously irrelevant. Two reviewers (KW and JV) independently assessed article abstracts and full text articles for eligibility and inclusion, and resolved any disagreements by discussion. Studies eligible for inclusion were prospective observational studies or randomised controlled trials which included participants aged 12 years and over with clinician-diagnosed asthma treated with low or medium dose inhaled corticosteroids (ICS) and recruited from community health care settings (e.g. primary care, hospital outpatient clinic). Included studies measured fractional exhaled nitric oxide (FeNO) in study participants before either reducing or withdrawing ICS, but did not use FeNO measurements to inform decisions about stepping down treatment. We excluded studies which recruited highly selected study populations (e.g. occupational asthma). We also excluded studies where ICS was replaced with an alternative treatment after being stepped down or which did not collect data on acute exacerbations of asthma based on our study definition (see below).

Definition of acute exacerbations

We defined acute exacerbations of asthma as acute asthma-related episodes requiring treatment with systemic corticosteroids or antibiotics, hospital admission or unscheduled health care visits due to asthma during the 12-week period after stepping down ICS. Study authors were asked to provide data on these outcome events as separate variables where possible. However, composite outcome data on acute exacerbations were also accepted if definitions of these were consistent with our pre-specified study definition.

Data extraction and quality assessment

Authors whose studies met eligibility criteria were approached for provision of individual patient data (IPD) including baseline characteristics (age, sex, smoking status, body mass index, atopy), baseline FeNO measurements and ICS dose, and acute exacerbations of asthma (see definition above).

Original IPD were kept on a secure server and prepared in a consistent format for all studies. Overall ethical approval was not required as this study did not require use of patient identifiers. Collaborating groups gained individual approval for data sharing where necessary.

Study quality was independently assessed by two reviewers (JB and AF-N) using a modified version of the Quality in Prognosis Studies (QUIPS) tool(18) presented in Appendix 2. Any discrepancies were resolved by discussion involving a third reviewer (KW). Study level data were summarised and compared with published findings. Study authors were contacted for assistance with clarifying any discrepancies identified.

Data synthesis and analysis

We conducted a one-stage IPD meta-analysis using mixed effects multi-level logistic regression in relation to absence or presence of acute exacerbations of asthma during the 12-week period after stepping down ICS. Our regression models accounted for within-study clustering and included age,

sex, and FeNO as baseline covariates. FeNO was classified as low (≤ 20 parts per billion [ppb]), intermediate (> 20 and < 50 ppb) or high (≥ 50 ppb) based on American Thoracic Society Taskforce guidelines on interpreting FeNO measurements.(19)

We conducted subgroup analyses according to age (12 to 59 years inclusive versus 60 years and older), smoking status, and baseline ICS dose before stepping down treatment. Baseline ICS dose was classified as being within or outside of the range associated with greatest therapeutic benefit (100 to 250 micrograms fluticasone propionate [FP] equivalent per day).(20)

Where possible, we estimated the net benefit of our models for FeNO-guided step-down of ICS compared to strategies involving stepping down ICS in all patients or no patients across a range of baseline exacerbation risk thresholds considered to be relevant to community-based asthma populations.(21, 22)

Statistical software and presentation

Logistic regression analyses were conducted using STATA version 14 using the melogit command. Results were presented as adjusted odds ratios with 95% confidence intervals.

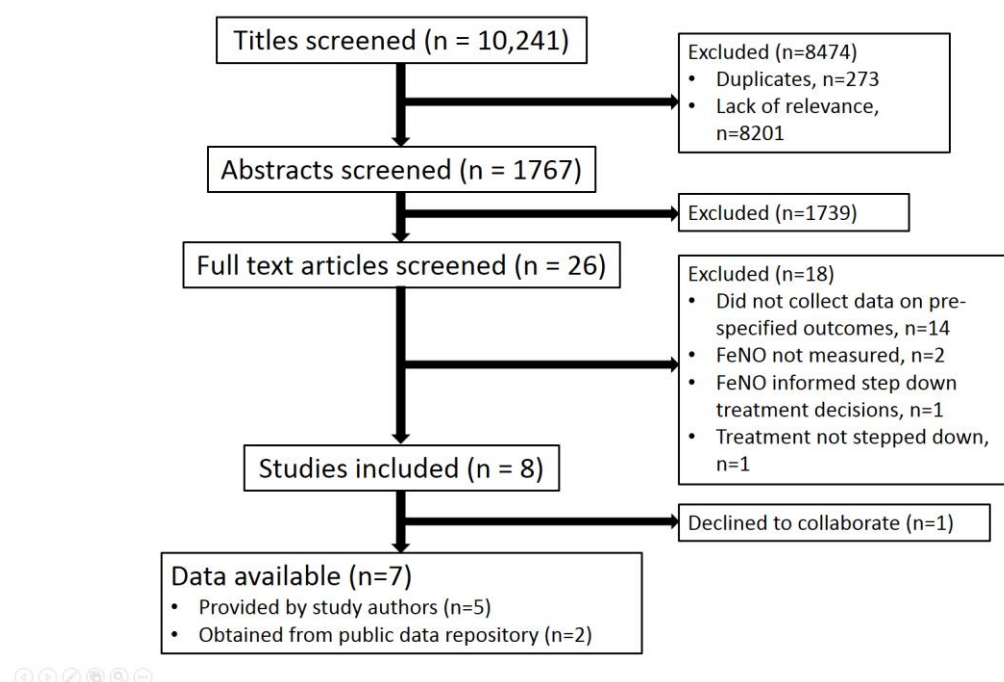
Calculation of the net benefit of our logistic regression models was performed using the rmda package in R version 3.3.3 (<https://www.r-project.org/>). This package calculates decision curves, which summarise net benefit estimates at any given probability threshold (i.e. the threshold above which patients are considered at 'high risk' of an acute exacerbation). For each threshold we calculated sensitivity, specificity, net benefit, number of net true positives (exacerbations) per 100 patients and number needed to prevent one additional exacerbation compared to stepping down ICS in all patients using the ClassificationPlot package (available on GitHub via <https://github.com/BavoDC/ClassificationPlot>). These results were tabulated and presented below the x-axis of the decision curve.

Results

Selection of included studies

Figure 1 summarises the results of our electronic database search, which retrieved 9968 articles excluding duplicates. We assessed 26 full text articles of which eight were identified as being suitable for inclusion.(23-30) The authors of four studies provided individual patient data (IPD) for all participants who met our eligibility criteria.(24, 27, 28, 30) The authors of one study(29) were unable to provide IPD from participants recruited at one recruitment centre due to internal reasons, but provided IPD for all other participants. Data from a further two studies(25, 26) were obtained from the National Heart, Lung, and Blood Institute (NHLBI) BioLINCC repository (Biologic Specimen and Data Repository Information Coordinating Center, <https://biolincc.nhlbi.nih.gov/home/>). The authors of the remaining study(23) declined to provide IPD.

Figure 1: Study selection



Overview of studies which provided IPD

Studies whose authors agreed to provide IPD were published between 2001 and 2016. Table 1 summarises the characteristics of studies included in our IPD meta-analysis.

Three studies were conducted in hospital outpatient clinics,(24, 28, 29) one in primary care,(30) one in university-based ambulatory care centres,(25) and one in clinical centres in the US.(27) One study recruited patients from communities surrounding testing and referral centres in an Asthma Clinical Research Network.(26)

We included data from two prospective observational studies which halved ICS doses in all participants(29, 30) and two open label randomised controlled trials (RCTs)(24, 28) which included treatment arms in which participants' ICS dose was halved. In one study, LABA dose was also halved alongside the ICS dose.(29) We also included data from the placebo groups of three blinded RCTs which involved an initial period of regular ICS treatment after which participants were provided with placebo inhalers.(25-27) For one RCT,(27) we also included data from participants randomised to the "rescue beclometasone" group, whose ICS dose was reduced from regular use to use on a rescue basis only.

Four studies included participants whose asthma had been well controlled for at least three months.(24, 28-30) Three RCTs included participants whose asthma had been well controlled for six weeks(25, 26) or four weeks(27) and included some participants who had not previously used controller treatment before the initial ICS treatment phase.

Two studies defined well controlled asthma based on GINA criteria,(28, 29) one based on US National Asthma Education and Prevention Program asthma care guidelines,(27) and three according to clinical criteria including FEV1 >80% of predicted value and average peak flow variability ≤20% during the final two weeks of the ICS treatment period,(25) Asthma Control Test (ACT) score of >19,(24) and Asthma Control Questionnaire 5-item version score of ≤1.5 and absence of exacerbations requiring oral corticosteroids.(30) One study did not provide an explicit definition of

well controlled asthma(26) but did state that participants who experienced a significant asthma exacerbation during the initial 6-week ICS treatment phase were withdrawn before randomisation.

Two studies provided IPD on exacerbations as a single variable including acute asthma-related episodes requiring treatment with systemic corticosteroids or antibiotics, hospital admission or unscheduled health care visits.(28, 29) Other included studies provided exacerbation data as separate variables for exacerbations requiring treatment with systemic corticosteroids,(24-27, 30) hospital admissions,(24, 25) unscheduled health care visits,(25) or antibiotics.(30)

Table 1: Characteristics of included studies

Study	Design	Setting	Method of FeNO measurement	Participant eligibility criteria	Method of stepping down ICS	Definition of acute exacerbations of asthma
Harada 2016(24)	Open label RCT	Hospital outpatient clinic, Japan	NOA 280i, Sievers, Boulder, Colorado; flow rate: 50 ml/s	Mild persistent asthma aged 20 years or older, well controlled for at least 3 months. No COPD or other respiratory disorder, history of near fatal asthma, treatment with oral corticosteroids, hospitalisation due to asthma in previous 6 months, treatment with other asthma medications during previous three months.	ICS dose halved	Requirement for treatment with systemic steroid. Hospitalisation or visit to emergency department reported as separate outcome.
Lazarus 2001(25)	Blinded placebo-controlled RCT	University-based ambulatory care centres, USA	NOA 280, Sievers, Boulder, Colorado	Aged 12 to 65 years, persistent asthma, non-smokers, no serious medical illness other than asthma, no respiratory tract infection or asthma exacerbation within 6 weeks of ICS run-in period.	ICS withdrawn	Requirement for prednisone, emergency department or urgent care visit or hospitalisation.
Martin 2007(26)	Blinded placebo-controlled RCT	Communities surrounding testing and referral centres in ACRN, USA	As per previous ACRN studies, but no further details given in published paper. Study protocol refers to ACRN General Manual of Procedures.	Aged 18 to 55 years, non-smokers, no ICS or systemic corticosteroids at least 4 weeks before study enrolment, no respiratory infection within 6 weeks before study screening period, no other respiratory disease or significant medical illness.	ICS withdrawn	Requirement for systemic corticosteroids.
Martinez 2011(27)	Blinded placebo-controlled	Clinical centres, USA	No details given.	Aged 6 to 18 years, mild persistent asthma during previous 2 years, symptomatically well controlled,	ICS withdrawn (placebo group) or used as	Requirement for 12 puffs of albuterol in 24 hours (excluding preventive use)

	RCT			Exclusions: FEV1 < 60% predicted, hospitalised for asthma in previous year, asthma exacerbation in previous 3 months or more than 2 exacerbations in previous year, history of life-threatening asthma exacerbations.	rescue treatment only (rescue beclometasone group)	before exercise), a peak expiratory flow of less than 70% of reference value before each albuterol use, symptoms that led to inability to sleep or do daily activities for 2 or more consecutive days, a peak expiratory flow of less than 50% of reference value despite relief treatment, or worsening asthma symptoms requiring an emergency room visit or treatment with prednisone.
Mori 2016(28)	Open label RCT	Hospital outpatient clinic, Japan	FeNO measured using NIOX MINO (Aerocrine AB, Solna, Sweden) according to American Thoracic Society/European Respiratory Society recommendations	Aged >18 years with asthma treated with budesonide/formoterol 320/9 mg twice a day for at least 3 months; well controlled based on GINA criteria for at least 3 months, agreed to receive step-down treatment. Exclusions: changed asthma treatment less than 3 months before beginning of study, current smokers or had a smoking history of >10 pack-years, other chronic pulmonary disease.	ICS dose halved	Requirement for unexpected or emergency visit to hospital, hospitalisation, or systemic corticosteroid treatment for more than 3 days.
Shirai 2014(29)	Prospective observational study	Hospital outpatient clinic, Japan	FeNO measured using NIOX MINO; Aerocrine AB, Solna, Sweden) according to American Thoracic Society/European	Age > 18 years, asthma for at least 6 months, symptomatically well controlled on formoterol/budesonide 4.5/160 micrograms twice daily for at least 3 months. Exclusions: current	ICS dose halved	Requirement for hospitalisation, emergency department visit, systemic corticosteroid treatment, or >12 puffs of short-acting beta 2-agonist

			Respiratory Society recommendations	smokers or smoking history of more than 10 pack-years, other chronic respiratory condition, previous exacerbation requiring hospitalisation within the last year or emergency department visit or systemic corticosteroid within the last 3 months.		for 3 days due to asthma symptoms
Wilson 2014(30)	Prospective observational study	Primary care, UK	FeNO measured using Flex Flow (Aerocrine, Solna, Sweden); flow rate 50 ml/s	Aged 18 to 75 years with recorded asthma diagnosis and received at least one ICS prescription in the last year, non smokers (< 10 pack years). Exclusions: Poorly compliant participants, previous exacerbation requiring oral steroids in last 12 weeks, ACQ-5 score >1.5 (poor control).	ICS dose halved	Requirement for course of antibiotics or oral steroids

FeNO = Fractional exhaled nitric oxide

ICS = Inhaled corticosteroids

ACRN = Asthma Clinical Research Network

GINA = Global Initiative for Asthma

ACQ-5 = Asthma Control Questionnaire 5-item version

Risk of bias

Table 2 summarises risk of bias assessments for our included studies. Risk of bias was generally low in relation to study participation, study attrition, and measurement of acute exacerbations. Risk of bias for study participation was only felt to be high in one study,(25) which only collected baseline FeNO measurements in 26 of 56 participants randomised to the placebo group (46%). Risk of bias for measurement of FeNO was also generally low but two studies did not report any detail on the devices or methods used to measure FeNO.(26, 27)

The findings of one study(29) were felt to be at high risk of confounding, as the analysis did not stratify or adjust for differences in baseline characteristics between participants with high (≥ 37 ppb) or low (< 37 ppb) FeNO. Another study stated that differences in FeNO and clinical measurements between participants who remained stable versus those who had exacerbations after ICS treatment was stepped down were not statistically significant, but did not present data or formal statistical comparisons to substantiate this.(30) Risk of bias was therefore felt to be unclear in relation to confounding, statistical analysis and reporting.

Table 2: Risk of bias assessments

Study	Study participation	Study attrition	Measurement of FeNO	Measurement of acute exacerbations	Confounding	Statistical analysis and reporting
Harada 2016(24)	Low	Low	Low	Low	Low	Low
Lazarus 2001(25)	High	Low	Low	Low	Low	Low
Martin 2007(26)	Low	Unclear	Unclear	Low	Low	Low
Martinez 2011(27)	Low	Low	Unclear	Low	Low	Low
Mori 2016(28)	Low	Low	Low	Low	Low	Low
Shirai 2014(29)	Low	Low	Low	Low	High	Moderate
Wilson 2014(30)	Low	Low	Low	Low	Unclear	Unclear

Characteristics of included participants

IPD were provided for 426 participants, of which 33 (7.7%) were excluded from our dataset due to missing data on baseline FeNO measurements before ICS treatment was stepped down (Lazarus 2001(25), n=30; Wilson 2014(30), n=2; Mori 2016(28), n=1). Among the 393 participants included in our dataset, 44 had an acute exacerbation within 12 weeks of stepping down ICS dose (11.2%).

Table 3 summarises the baseline characteristics of participants included in our dataset. Around three-quarters of participants had never smoked, nearly two-thirds had a history of atopy and just over three-fifths received treatment with low dose ICS before treatment was stepped down. Data on baseline FeNO measurements taken before treatment was stepped down were positively skewed. FeNO was 20 parts per billion (ppb) or less in around half of participants.

Table 3: Participant characteristics

	Number (%), mean (SD) or median (range)							
Characteristic	All (n=393)	Harada 2016(24) (n=20)	Lazarus 2001(25) (n=26)	Martin 2007(26) (n=35)	Martinez 2011(27) (n=47)	Mori 2016(28) (n=42)	Shirai 2014(29) (n=34)	Wilson 2014(30) (n=189)
Age (years)	46.6 (19.0)	56.5 (15.6)	31.3 (9.7)	33.2 (9.5)	13.9 (1.5)	54.5 (15.2)	58.0 (14.8)	54.5 (13.0)
Sex - male	174 (44.3)	9 (45.0)	8 (30.8)	18 (51.4)	26 (55.3)	17 (40.5)	14 (41.2)	82 (43.4)
Smoking status								
• Never smoked	292 (74.3)	15 (75.0)	16 (61.5)	27 (77.1)	47 (100.0)	34 (81.0)	27 (79.4)	126 (66.7)
• Ex smoker	101 (25.7)	5 (25.0)	10 (38.5)	8 (22.9)	0 (0.0)	8 (19.1)	7 (20.6)	63 (33.3)
History of atopy	251 (63.9)	16 (80.0)	22 (84.6)	33 (94.3)	44 (93.6)	31 (73.8)	23 (67.7)	82 (43.4)
Body Mass Index (kg/m ²)*	26.2 (5.9)	21.2 (3.4)	NC	NC	23.0 (5.2)	25.1 (5.9)	23.6 (6.4)	28.3 (5.4)
ICS dose (micrograms per day FP equivalents)**								
Low dose (<=200)	236 (60.1)	20 (100.0)	26 (100.0)	0 (0.0)	47 (100.0)	0 (0.0)	34 (100.0)	109 (57.7)
Moderate dose (>200 to <1000)	157 (39.9)	0 (0.0)	0 (0.0)	35 (100.0)	0 (0.0)	42 (100.0)	0 (0.0)	80 (42.3)
FeNO (ppb)	20 (3.1 to 129)	42.4 (14.8 to 129)	14.3 (7.5 to 41)	13.6 (3.5 to 44.5)	18.8 (4.9 to 68.7)	24.5 (8 to 117)	26.5 (9 to 109)	19.3 (3.1 to 121.8)
FeNO categories								
• Low (<=20 ppb)	202 (51.4)	1 (5.0)	16 (61.5)	28 (80.0)	26 (55.3)	17 (40.5)	13 (38.2)	101 (53.4)
• Intermediate (>20 ppb to <50 ppb)	148 (37.7)	13 (65.0)	10 (38.5)	7 (20.0)	18 (38.3)	18 (42.9)	16 (47.1)	66 (34.9)
• High (>=50 ppb)	43 (10.9)	6 (30.0)	0 (0.0)	0 (0.0)	3 (6.4)	7 (16.7)	5 (14.7)	22 (11.6)

*Based on available data from 332 participants

** Categorisation of ICS doses based on British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines(1)

SD = Standard deviation; ICS = Inhaled corticosteroids; FP = Fluticasone propionate; ppb = parts per billion; NC = not collected

Logistic regression analysis

Table 4 summarises odds ratios with 95% confidence intervals for predictors of an acute exacerbation within 12 weeks of stepping down ICS treatment. After accounting for age, sex, and within-study clustering, the risk of an acute exacerbation was significantly greater in participants with high FeNO versus low FeNO (adjusted Odds Ratio [OR] 2.70, 95% confidence interval [CI] 1.16 to 6.26, $P=0.021$). However, there was no significant difference in exacerbation risk between participants with intermediate FeNO versus low FeNO (OR 0.63, 95% CI 0.29 to 1.35, $P=0.231$).

The findings of our subgroup analyses in participants who had never smoked or whose baseline ICS dose was not within the optimal therapeutic range were consistent with the findings of our main analysis. However, our subgroup analysis in participants aged 60 years and over found that participants whose FeNO was in the intermediate range before ICS treatment was stepped down were significantly less likely to have a subsequent exacerbation than participants with low FeNO (OR 0.14, 95% CI 0.03 to 0.74, $P=0.02$). However, high FeNO was not associated with significantly greater likelihood of exacerbation than low FeNO (OR 2.40, 95% CI 0.68 to 8.52, $P=0.175$).

Our subgroup analyses did not demonstrate a statistically significant association between FeNO and acute exacerbations after stepping down ICS in participants who were ex-smokers, under 60 years of age, or receiving ICS doses within the optimal therapeutic range before treatment was stepped down.

Net benefit analysis

Figure 2 summarises net benefit values associated with FeNO-guided step down treatment decisions versus stepping down ICS in either all or no patients. FeNO-guided step down decisions have higher net benefit than “step down all” and “step down none” strategies for baseline exacerbation risks between 6% and 16%, and higher net benefit than stepping down treatment in no patients at baseline exacerbation risks between 16% and 26%.

For exacerbation risk thresholds below 6%, FeNO-guided step down decisions are no better than stepping down treatment in all patients. For risk thresholds above 26%, FeNO-guided step down decisions are no better than stepping down treatment in no patients.

At a risk threshold of 10%, FeNO-guided step down of ICS in 37 patients would prevent one additional acute exacerbation versus stepping down treatment in all patients. This number needed to treat increases to 73 at a risk threshold of 15% and 175 at a risk threshold of 20%.

Table 4: Predictors of acute asthma exacerbation within 12 weeks of stepping down inhaled corticosteroids

Participants	Number of patients with acute exacerbation	Predictor	Odds Ratio (95% confidence interval)	P-value
All participants (n=393)	44	Age	1.00 (0.98 to 1.02)	0.947
		Sex	1.78 (0.94 to 3.40)	0.078
		FeNO (ppb)*		
		<ul style="list-style-type: none"> >20 to <50 >=50 	0.63 (0.29 to 1.35) 2.70 (1.16 to 6.26)	0.231 0.021
Never smoked (n=292)	33	Age	1.00 (0.98 to 1.02)	0.799
		Sex	1.56 (0.73 to 3.30)	0.250
		FeNO (ppb)*		
		<ul style="list-style-type: none"> >20 to <50 >=50 	0.62 (0.26 to 1.49) 2.84 (1.03 to 7.82)	0.285 0.043
Ex smoker (n=101)	11	Age	0.98 (0.93 to 1.04)	0.537
		Sex	4.78 (0.85 to 26.9)	0.076
		FeNO (ppb)*		
		<ul style="list-style-type: none"> >20 to <50 >=50 	0.66 (0.13 to 3.38) 2.29 (0.44 to 12.0)	0.621 0.327
Baseline ICS dose within optimal therapeutic range** (n=209)	19	Age	0.99 (0.96 to 1.02)	0.572
		Sex	1.97 (0.74 to 5.23)	0.171
		FeNO (ppb)*		
		<ul style="list-style-type: none"> >20 to <50 >=50 	0.48 (0.15 to 1.48) 1.09 (0.27 to 4.42)	0.200 0.903
Baseline ICS dose not within optimal therapeutic range** (n=184)	25	Age	1.01 (0.99 to 1.03)	0.439
		Sex	1.80 (0.73 to 4.44)	0.201
		FeNO (ppb)*		
		<ul style="list-style-type: none"> >20 to <50 >=50 	0.80 (0.28 to 2.32) 5.50 (1.74 to 17.5)	0.680 0.004
Age 12 to <60 years (n=265)	27	Age	0.99 (0.97 to 1.02)	0.655
		Sex	1.70 (0.76 to 3.83)	0.197
		FeNO (ppb)*		
		<ul style="list-style-type: none"> >20 to <50 >=50 	1.13 (0.46 to 2.77) 2.89 (0.90 to 9.28)	0.789 0.075
Age >=60 years (n=128)	17	Age	0.91 (0.79 to 1.04)	0.166
		Sex	2.67 (0.86 to 8.26)	0.089
		FeNO (ppb)*		
		<ul style="list-style-type: none"> >20 to <50 >=50 	0.14 (0.03 to 0.74) 2.40 (0.68 to 8.52)	0.020 0.175

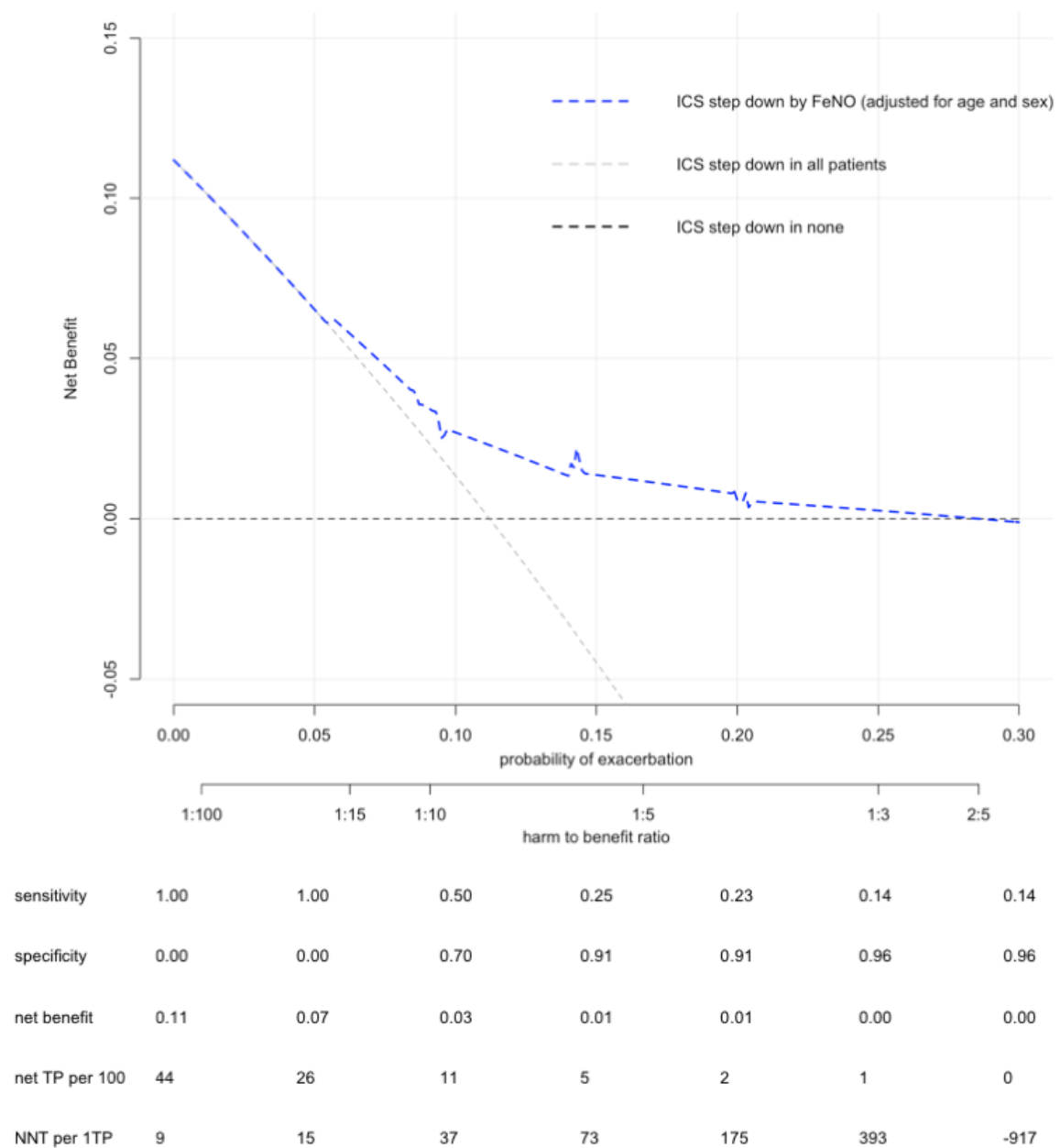
FeNO = fractional exhaled nitric oxide

ppb = parts per billion

*FeNO ≤20 ppb was reference category

**Optimal therapeutic range for baseline ICS dose defined as 100 to 250 micrograms per day fluticasone propionate equivalents

Figure 2: Decision curve showing net benefit for different step-down treatment strategies in asthma patients on low to moderate doses of inhaled corticosteroids



ICS = inhaled corticosteroids
 TP = True Positives
 NNT = Number Needed to Treat

Discussion

Summary of main findings

The risk of an acute exacerbation after stepping down ICS treatment is significantly increased in asthma patients with FeNO ≥ 50 ppb who appear to be symptomatically well controlled on low or moderate dose ICS. FeNO-guided step down treatment decisions have greater net benefit than stepping down treatment in all patients or no patients when baseline exacerbation risk is between 6% and 16%. At an exacerbation risk threshold of 10%, one additional exacerbation can be prevented for every 37 asthma patients for whom FeNO is used to guide step-down treatment decisions instead of stepping down treatment in all patients.

Comparison with existing literature

BTS/SIGN guidance suggests that low FeNO (<25 ppb in adults; <20 ppb in children under 12 years of age) may have a role in identifying patients who can step down corticosteroid treatment safely.(1) However, these decision thresholds are largely based on those recommended in relation to diagnosis of asthma, which are based on general population data rather than data from asthma patients already receiving ICS.(31)

In children whose asthma has been stable for at least two months, a FeNO level of 22 ppb or higher is reported to be a significant predictor of future exacerbations.(32) Additionally, a study in adults with well-controlled moderate asthma concluded that halving ICS/LABA doses was safe in patients with FeNO of 28 ppb or less since no significant differences in numbers of exacerbations were observed during the periods before and after treatment was reduced.(33) However, neither study compared exacerbation risk between participants with intermediate versus low FeNO.

Our finding that risk of exacerbation was not significantly higher in patients with intermediate versus low FeNO could suggest that patients with intermediate FeNO also have low levels of eosinophilic airway inflammation, which are not yet reflected by their FeNO levels. This is consistent with the findings of a small longitudinal study which found that decreases in FeNO were only reflected in sputum eosinophil counts after a 6-month period of well-controlled symptoms.(34)

Our finding that FeNO of 50 ppb or higher was a significant predictor of exacerbations in patients who had never smoked but not in ex-smokers is consistent with reports of a non-significant trend for lower FeNO thresholds predicting sputum eosinophilia in smokers.(35) Smokers are also reported to be less responsive than non-smokers to low dose ICS but equally responsive to high dose ICS.(36)

Strengths and limitations

Our study focused on a well-defined population of patients with mild-to-moderate well-controlled asthma, in whom current clinical practice guidelines recommend empirical trials of stepping down treatment.(1) We were able to obtain individual patient data from seven out of eight relevant studies identified by our systematic review. Data on baseline FeNO measurements were missing from less than 8% of participants, justifying a complete case analysis. Availability of IPD also allowed us to use data from all studies to consistently define acute asthma exacerbation events, create pragmatic categories for low, intermediate or high FeNO, and examine clinically relevant subgroups. Additionally, to compare utility of FeNO-guided step-down decisions versus stepping down treatment in all patients or no patients, we estimated net benefit values for all three strategies over a range of exacerbation risk thresholds relevant to community asthma populations.

Although it has been shown that previous acute exacerbations(21) and raised blood eosinophil counts(37) within the last year are important risk factors for future exacerbations, these variables were not available for us to include in our regression model. We were also unable to examine the predictive value of follow-up FeNO measurements after stepping down treatment, as not all of our

included studies obtained follow-up measurements, and there was considerable variation in timings of these measurements among those studies that did.

The findings of our subgroup analyses should be interpreted with caution due to low numbers of acute exacerbation events. This also precluded construction of net benefit decision curves according to subgroup. We had intended to perform a secondary analysis using acute exacerbations resulting in treatment with systemic corticosteroids as the outcome. However, we could not perform this analysis because we were unable to reliably identify outcome events meeting this definition. We were able to identify 14 acute exacerbations requiring systemic corticosteroids from five studies (Wilson 2014(30) n=3; Martinez 2011(27) n=6; Martin 2007(26) n=2; Lazarus 2001(25) n=3; Harada 2016(24) n=0). However, authors of the other two studies(28, 29) were only able to provide aggregate data on exacerbations, and were unable to specify which of these resulted in treatment with systemic corticosteroids. We were also unable to estimate pooled sensitivities and specificities in relation to specific FeNO thresholds because one study had no exacerbation events based on the definition used in this review.(24)

Implications of findings for clinical practice and future research

In the UK, around 5.4 million people receive treatment for asthma,(38) of whom at least 90% are treated with low or moderate doses of ICS.(39) The exacerbation rate which we observed is similar to that reported among asthmatic trial participants receiving low dose ICS, which was either maintained or changed to montelukast or an ICS/LABA combination.(40) Therefore, based on our estimates of numbers needed to treat and assuming a baseline exacerbation risk of 10%, use of FeNO to guide step-down treatment decisions would prevent around 130,000 additional exacerbations (27% reduction) compared to stepping down ICS in all asthma patients who appear to be symptomatically well controlled. Even with a baseline exacerbation risk of 15%, we estimate that FeNO-guided step-down decisions would prevent around 66,000 additional exacerbations (14% reduction).

Our findings therefore suggest that clinicians should avoid stepping down ICS treatment in asthma patients with FeNO of 50ppb or higher, even if they appear to be symptomatically well controlled on low or moderate dose ICS. Instead, medication adherence and inhaler technique should be carefully evaluated and optimised in these patients to minimise their risk of future exacerbations. Clinicians may, however, consider stepping down ICS in participants whose FeNO is less than 50 ppb. Further reductions in exacerbation risk may be achieved by consideration of other risk factors, especially history of previous exacerbations(21) and raised blood eosinophil counts of 400 cells per μ L or greater during the last year.(37)

Future research should determine the predictive value of follow-up FeNO measurements taken after ICS treatment has been stepped down. Marked variability in FeNO has been demonstrated around the time when exacerbations requiring treatment with systemic corticosteroids occur.(41) Additionally, a small study conducted in children found that FeNO at four weeks after withdrawal of ICS was a strong predictor of deterioration in exacerbation frequency, requirement for beta-agonists and peak flow variability, and was a better predictor of deterioration than the ratio between FeNO measurements at four weeks and baseline.(42)

The predictive value of FeNO alongside other biomarkers of steroid-responsive airway inflammation should also be investigated in patients with mild-to-moderate asthma. Composite biomarker strategies are already being explored in patients with severe asthma.(43) However, these patients only account for 5 to 10% of the asthma population.(39) Concurrently raised FeNO and blood eosinophil counts are associated with poorer symptomatic control in children and young adults with

asthma.(44) However, more research is needed to establish whether these biomarkers are also associated with increased risk of exacerbations.

Additionally, further research is needed to improve understanding of barriers and facilitators to using FeNO to guide step-down treatment decisions. This will in turn inform development of strategies to address clinicians' concerns about stepping down treatment, even in patients whose FeNO values suggest low levels of airway inflammation and low exacerbation risk.(16, 17) The potential cost-effectiveness of using FeNO to guide step-down decisions should also be examined, particularly in relation to its contribution to overall cost savings and cost-effectiveness in community health care settings.(45, 46)

Conclusions

Our findings demonstrate that FeNO can help guide safer and more accurate step-down treatment decisions in patients with mild-to-moderate asthma who appear to be symptomatically well controlled. Clinicians should avoid stepping down treatment in patients whose FeNO is 50 ppb or higher, as risk of exacerbations is highest in this group. However, ICS dose reductions may be considered in patients whose FeNO is less than 50 ppb, particularly if overall exacerbation risk is felt to be low. Future research should aim to establish the predictive value of follow-up FeNO measurements after treatment has been stepped down, and to inform strategies to improve uptake of FeNO to guide step-down treatment decisions in routine clinical settings.

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