



Are we overlooking persistent small airways dysfunction in community-managed asthma?

William J. Anderson, MBChB ^{*}; Emma Zajda, BSc [†]; and Brian J. Lipworth, MD ^{*}

^{*} Asthma and Allergy Research Group, University of Dundee, Scotland, United Kingdom

[†] Health sciences, University of Abertay Dundee, Scotland, United Kingdom

ARTICLE INFO

Article history:

Received for publication May 2, 2012.

Received in revised form June 20, 2012.

Accepted for publication June 29, 2012.

ABSTRACT

Background: Whether small airways dysfunction persists in patients with asthma receiving standard community treatment is unknown. Impulse oscillometry (IOS) is a sensitive measure of small airways function.

Objective: To assess the degree of small airways dysfunction in a cross-section of patients with community-managed asthma.

Methods: We analyzed primary care referral data from patients with persistent asthma ($n = 378$) receiving standard community therapy, screened using spirometry and IOS. We compared patients by British Thoracic Society asthma treatment step (2–4).

Results: Step 2 patients were not different from step 3 patients receiving long-acting beta-agonist (LABA). Step 4 patients differed from step 2 by: higher inhaled corticosteroid (ICS) dose ($P < .0001$); lower forced expiratory volume in 1 second ($FEV_1\%$; $P = .02$) and forced mid-expiratory flow ($FEF_{25-75\%}$; $P = .001$); higher frequency of resonance (F_{res} ; $P = .02$) and peripheral airway resistance ($R5-R20$; $P = .006$); whereas for steps 3 vs 4 there were differences in F_{res} ($P < .05$) and $R5-R20$ ($P = .006$). There were high proportions of abnormality for $R5-R20$ (>0.03 kPa/L/s) at steps 2, 3, and 4, respectively: 64.6%, 63.5%, and 69.9%. Step 2 patients receiving extra-fine particle ICS demonstrated lower total airway resistance at 5Hz ($R5$) vs patients receiving standard ICS (124.1% vs 138.3%, $P < .05$), with no difference in FEV_1 . At step 4, $R5$ remained elevated at 141.3% despite concomitant LABA, with only 2.4% using extra-fine ICS.

Conclusion: Persistent small airways dysfunction occurs despite treatment at steps 2 through 4 of current asthma guidelines. Extra-fine ICS may reduce airway resistance at step 2. Prospective studies with extra-fine ICS $\pm$ LABA at steps 2 through 4 are required to discern whether improving small airways function might result in long-term improved control.

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Introduction

Asthma is widely regarded as a heterogeneous pulmonary disease in terms of its presentation, underlying pathophysiology, duration, severity, and response to treatment. In the United Kingdom asthma is largely managed in a community setting and standardized guidelines are well established, with inhaled corticosteroids (ICS) being the mainstay of asthma controller therapy. The British Thoracic Society (BTS) recommends a stepwise approach to treatment¹ ranging from inhaled bronchodilators alone (step 1) through low to moderate doses of ICS (step 2) $\pm$ long-acting beta-agonist (LABA), leukotriene receptor antagonists, and theophyllines (step 3); with higher-dose ICSs at step 4. However, despite the heterogeneity of asthma, these and other general guidelines² only take symptoms and spirometry into account to indicate when a change in asthma treatment may be necessary. This decision-making

process logically therefore further narrows to just symptom assessment when patients with “milder” disease have near normal spirometry.

The small peripheral airways (<2 mm diameter) are gaining greater recognition with regard to their involvement in the disease process of persistent asthma.³ Pathologic abnormality by way of small airway inflammation and that of surrounding alveolar tissue has been demonstrated regardless of asthma severity.^{4,5} These abnormalities also seem to persist even when asthma is said to be “stable” with regard to symptoms⁶; thus there is potential for the development of chronic airway remodeling because of unchecked disease.⁷ Historically these areas have been difficult to assess, with pathologic examination the main source of information. In addition to this, standard spirometric measurement mainly reflects more central airway dynamics; albeit some indication of small airway function can be gained from the expiratory flow-volume loop as the forced mid expiratory flow (FEF_{25-75}).⁸⁻¹⁰ Recent developments, including quantification of exhaled nitric oxide ($FeNO$) as a measure of overall airway inflammation¹¹ and the use of IOS¹² have provided new insights into the role of the small airways in

Reprints: Prof. Brian J. Lipworth, Asthma and Allergy Research Group, University of Dundee, Scotland, UK, DD1 9SY; E-mail: brianlipworth@gmail.com.

Disclosures: Authors have nothing to disclose.

Funding Sources: Internal departmental funds.

asthma.¹³ IOS measures airway resistance and reactance, with the ability to measure airway dynamics at multiple levels using different frequencies. To what degree these investigations and the small airways themselves relate to asthma severity and the associated stepwise treatment that accompanies this remain unclear, however. One study in children with asthma showed that, in those with uncontrolled asthma, there was an association with small airways dysfunction measured using IOS.¹⁴

After this recognition of small airways disease came the need to address the problem therapeutically. It was serendipitous that chlorofluorocarbon (CFC) propellants in pressurized metered dose inhalers (pMDI) had to be phased out by law because of ozone depletion, in that their replacement was a hydrofluoroalkane (HFA) propellant that when combined with beclomethasone dipropionate (HFA-BDP) in an aerosol solution formulation generated much smaller particle sizes compared with their CFC counterpart.^{15,16} Extra-fine particle pMDIs are being used in clinical practice both as single ICS therapy and combination ICS/LABA therapy for the reason that increased peripheral lung deposition could lead to improved lung function^{17,18} and symptom control as well as better treating underlying small airways inflammation.¹⁹ Moreover, Price et al²⁰ showed in a retrospective matched cohort study that HFA-BDP resulted in similar or better chances of achieving asthma control compared with fluticasone, and that at lower prescribed ICS doses.²⁰

In the present study we hypothesized that there might be an unmet need in terms of small airways dysfunction in community-treated asthma across a range of asthma treatment steps 2 through 4. We used IOS and FEF_{25–75} to measure small airway function. In this way we wished to provide information about where further targeted therapy with extra-fine ICS could be directed in future studies.

Methods

We performed a retrospective analysis of data from patient screening visits for clinical trials in our department, all of whom were receiving standard community treatment. We included patients with a diagnosis of persistent asthma, all receiving ICS between steps 2 and 4 of the BTS asthma guidelines, and stratified them into these groupings based on their ICS dose and LABA use. All patients were required to have had both spirometry and IOS at the same initial screening visit, along with recording of demographic parameters. FeNO measurements were also included for most pa-

tients, provided it had been performed at the same visit. All patients gave written informed consent for their data to be stored electronically for the sole use of the Asthma and Allergy Research Group, and we received ethical approval from the Tayside Committee for Medical Research Ethics for all the studies patients were being screened into. Trial-specific ethics reference numbers were 07/S1401/150; 08/S1402/35; 08/S1401/139; 10/S0501/13.

Measurements

Impulse oscillometry (Masterscreen IOS, Höchberg, Germany) was performed in triplicate in accordance with manufacturer's guidelines. A SuperSpiro spirometer (Micro Medical Ltd., Chatham, Kent, United Kingdom) was used to perform spirometry in triplicate in accordance with European Respiratory Society guidelines.²¹ FeNO was performed in duplicate using a handheld NIOX MINO machine (Aerocrine, Solna, Sweden) according to manufacturer's and American Thoracic Society guidelines²² at a standard flow rate of 50 mL/second.

Statistical analysis

All data were examined for normality of distribution, with non-Gaussian distributions logarithmically transformed to achieve normality before analysis. All ICS doses were converted to standard BDP potency equivalents for the purposes of statistical comparisons between treatment steps. Comparisons were performed with either Student's *t*-test for independent samples (2-tailed) or with analysis of variance (ANOVA) comparisons with Bonferroni correction when more than 2 means were being compared. Pearson's correlations were also performed between outcome measures. Statistical significance for all analyses was set at *P* < .05.

Results

We identified 378 patients with asthma who performed both IOS and spirometry at their initial screening visit. Stratification by BTS asthma treatment step (2, 3, and 4) was performed, and the categorized data are presented in Table 1. The numbers of patients at each treatment step were: step 2, *n* = 192; step 3, *n* = 63 and step 4, *n* = 123.

The highest usage of extra-fine ICS was seen in the step 2 group (34.9%) as compared with step 3 (9.5%) and step 4 (2.4%) (see eFig 1). As expected, combination inhalers of ICS/LABA were the most commonly prescribed asthma medication in steps 3 and 4. No

Table 1
Demographics, pulmonary function, and fractional exhaled nitric oxide (FeNO) by asthma treatment step

Variable	Step 2 (<i>n</i> = 192)	Step 3 (<i>n</i> = 63)	Step 4 (<i>n</i> = 123)	2 vs. 3 <i>P</i> -value	2 vs. 4 <i>P</i> -value	3 vs. 4 <i>P</i> -value
Age (years)	39 (37, 41)	41 (38, 45)	44 (42, 47)	.96	.011	.63
Sex M:F	71:121	26:37	46:77	—	—	—
BMI (kg/m ²)	27.1 (26.3, 27.8)	28.3 (27.0, 29.6)	28.6 (27.2, 29.9)	0.44	0.09	1.00
Current smokers (%)	11.5	6.3	12.2	—	—	—
ICS dose (μg/day)	459 (423, 495)	531 (474, 588)	1519 (1427, 1611)	.49	<.0001	<.0001
Extra-fine ICS (%)	34.9	9.5	2.4	—	—	—
LABA (%)	0	100	66.7	—	—	—
FEV ₁ (% predicted)	89.8 (87.5, 92.2)	86.3 (81.7, 90.8)	83.7 (79.6, 87.8)	.61	.017	1.00
FEF _{25–75} (% predicted)	65.9 (62.3, 69.5)	60.3 (54.2, 66.4)	54.6 (49.9, 59.4)	.40	.001	0.47
R5 ^a (% predicted)	133.1 (126.4, 140.2)	131.8 (120.3, 144.4)	137.3 (126.1, 149.5)	1.00	1.00	1.00
R20* (% predicted)	132.9 (127.4, 138.7)	132.8 (122.3, 144.1)	125.5 (117.3, 134.3)	1.00	.41	.81
R5-R20* (kPa/L/s)	0.089 (0.067, 0.093)	0.079 (0.045, 0.086)	0.123 (0.094, 0.151)	1.00	.006	.006
F _{res} * (Hz)	14.4 (13.6, 15.2)	14.0 (12.7, 15.5)	16.6 (15.1, 18.1)	1.00	.015	.046
FeNO* (ppb)	27.2 (24.0, 30.8)	21.5 (18.4, 25.0)	22.7 (19.4, 26.4)	.17	.19	1.00

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroid as beclomethasone dipropionate equivalent dose; LABA, long-acting beta agonist; FEV₁, forced expiratory volume in 1 second; FEF_{25–75}, forced expiratory flow between 25 and 75% of vital capacity; R5, total airway resistance at 5Hz; R20, central airway resistance at 20Hz; F_{res}, frequency of resonance; R5-R20, peripheral airways difference between total and central resistance at 5Hz and 20Hz (abnormal values > 0.03kPa/L/s).⁹ Data presented as arithmetic mean (95% CI) unless stated. Means comparisons using one-way analysis of variance (ANOVA) with Bonferroni correction. Significance set at *P* < .05. Those statistically significant differences are in bold.

^aGeometric mean (95% CI).

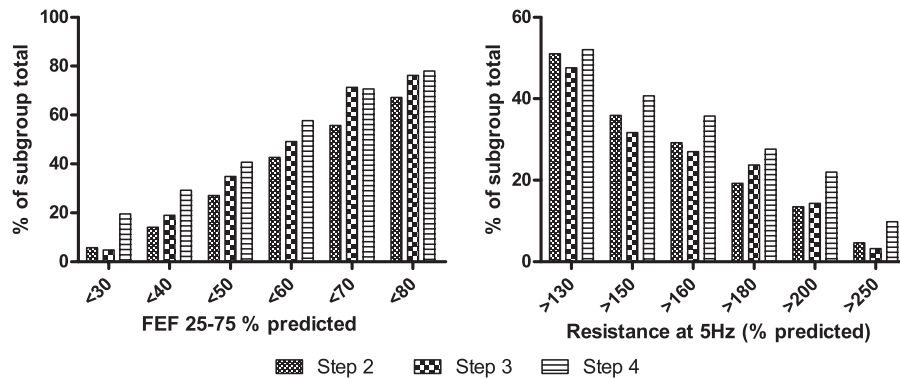


Fig. 1. Proportions of patients in each treatment step within set thresholds of $FEF_{25-75\%}$ (left) and $R5\%$ (right). Histograms show data as percentages of each of steps 2, 3, and 4 below or above each threshold. $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of vital capacity.

patients received extra-fine ICS/LABA combination inhalers, nor extra-fine LABA alone. Step 4 patients demonstrated the greatest differences overall in terms of percent predicted spirometry and IOS measures (Table 1). Within step 4 we found significantly lower mean forced expiratory volume in 1 second ($FEV_1\% = 83.7\%$, 95% CI: 79.6–87.8%) and mean $FEF_{25-75\%} = 54.6\%$ (95% CI: 49.9–59.4%) than step 2 patients; with significantly higher frequency of resonance (F_{res}) and peripheral airway resistance ($R5-R20$), than steps 2 and 3 patients. They were also receiving approximately 3 times as much ICS (mean = 1,519 $\mu\text{g/day}$, 95% CI: 1,427–1,611 $\mu\text{g/day}$) compared with steps 2 and 3 patients. There were no significant differences of any outcome measure between steps 2 and 3 other than the mutually exclusive use of LABA at step 3 (Table 1). There were proportionally more patients in step 4 at each threshold below 60% for $FEF_{25-75\%}$ and above 130% for total airway resistance $R5\%$ (Fig 1). Also there remained patients classed as step 2 or 3 who had $FEF_{25-75\%} < 40\%$ and $R5\% > 200\%$ (Fig 1).

We also evaluated the proportion of patients at each treatment step who had abnormal values for peripheral airways resistance $R5-R20$ (>0.03 kPa/L/s), which corresponds to values higher than the upper bound of the 95%CI in a previously reported group of healthy subjects.¹² This showed a high proportion of abnormal values at steps 2, 3, 4, respectively: 64.6%, 63.5%, and 69.9%, with mean $R5-R20$ values (including lower 95%CI) for each step also being greater than 0.03 kPa/L/s (Table 1, Fig 2).

Patients in step 2 who were prescribed extra-fine particle ICS ($n = 67$) had a significantly lower mean $R5\%$ (124.1%, 95% CI: 113.5–135.8%) compared with patients ($n = 125$) taking standard particle size ICS (138.3%, 95% CI: 130.0–147.0%), $P < .05$. Additionally, patients prescribed extra-fine ICS received a significantly

lower nominal dose of ICS than patients prescribed standard ICS (mean dose, 279 $\mu\text{g/day}$ vs. 406 $\mu\text{g/day}$, $P < .0001$) (Table 2). Comparisons of thresholds for $FEF_{25-75\%}$ and $R5\%$ at step 2 can be seen in eFigure 2.

Within step 4 according to LABA use, there were no significant differences in any outcome variables between those receiving LABA combined with ICS ($n = 82$) and those receiving ICS alone ($n = 41$) (Table 3). Both groups were receiving equally high doses of ICS (approximately 1,500 $\mu\text{g/day}$ BDP equivalent dose). $R5\%$ remained elevated (141.3%, 95% CI: 127.1–157.2%) despite the use of LABA at step 4, in addition to proportionally greater usage of LABA at each threshold for $FEF_{25-75\%}$ less than 60% and $R5\%$ greater than 130% (eFig 3).

We found significant correlations for all treatment steps between $R5\%$ and $FEV_1\%$ ($r = -0.47$, $P < .0001$) and between $R5\%$ and $FEF_{25-75\%}$ ($r = -0.39$, $P < .0001$), which remained almost identical when patients receiving LABA therapy were excluded from the correlation analysis (eFig 4). Correlations between $R5\%$ and $FEF_{25-75\%}$ were also present at steps 2 and 3, individually ($r = -0.35$, $P < .0001$ for both) and even greater at step 4 ($r = -0.44$, $P < .0001$).

Discussion

The results of the current study demonstrate a significant unmet need in terms of underlying small airways dysfunction in community-managed asthma despite the use of standard stepwise therapy according to guidelines. Patients at step 2 had the highest proportion of extra-fine ICS use, and these patients demonstrated significantly reduced airway resistance ($R5\%$), compared with patients receiving standard particle size ICS at step 2. Nonetheless, central airway resistance ($R20$) also trended toward being lower with

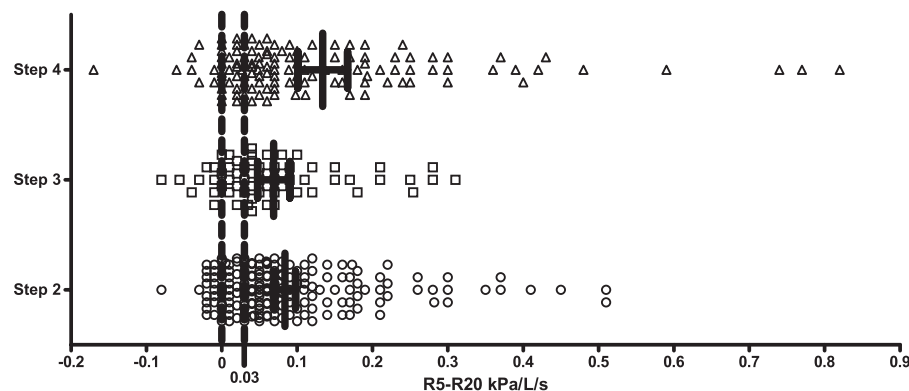


Fig. 2. Scatterplots of peripheral airways resistance ($R5-R20$) by asthma treatment step. Solid lines represent geometric mean and 95%CI error bars. Interrupted lines at 0 and at 0.03 kPa/L/s (the upper 95%CI in healthy volunteers⁹). Step 4 significantly different from each of steps 3 and 4 ($P = .006$ for both), using repeated-measures analysis of variance with Bonferroni correction.

Table 2

Comparisons of extra-fine particle solution formulation of inhaled corticosteroid (ICS) vs standard particle size (suspension CFC/HFA, or dry powder formulation) ICS outcomes at step 2

Variable	Extra-fine ICS (n = 67)	Standard ICS (n = 125)	P-Value
ICS dose ($\mu\text{g/day}$)	279 (249, 309)	406 (364, 447)	<.0001
FEV ₁ (% predicted)	88.9 (84.8, 92.9)	90.3 (87.5, 93.1)	.56
FEF ₂₅₋₇₅ (% predicted)	63.7 (57.5, 69.8)	67.1 (62.7, 71.5)	.38
R5 ^a (% predicted)	124.1 (113.5, 135.8)	138.3 (130.0, 147.0)	<.05
R20 ^a (% predicted)	126.0 (117.0, 135.8)	136.7 (130.0, 143.9)	.07
R5-R20 ^a (kPa/L/s)	0.069 (0.05, 0.088)	0.088 (0.071, 0.105)	.18
F _{res} ^a (kPa/L/s)	13.9 (12.6, 15.2)	14.6 (13.6, 15.7)	.36
FeNO ^a (ppb)	31.4 (24.9, 39.5)	25.3 (21.9, 29.2)	.11

Abbreviations: ICS dose, nominal inhaled corticosteroid dose; FEV₁, forced expiratory volume in 1 second; FEF₂₅₋₇₅, forced expiratory flow between 25 and 75% of vital capacity; R5, total airway resistance at 5Hz; R20, central airway resistance at 20Hz; F_{res}, frequency of resonance; R5-R20, peripheral airways resistance between 5Hz and 20Hz; FeNO, fractional exhaled nitric oxide.

Data presented as arithmetic means (95% CI) unless stated. Means comparison performed using Student's T-test for independent samples (two-tailed), significance $P < .05$.

^aGeometric mean (95% CI).

extra-fine ICS, which could explain why R5-R20 was not different at step 2. There were also no significant differences in spirometry (as FEV₁% and FEF₂₅₋₇₅%) between these subgroups. This confirms that IOS is likely to be a more sensitive airway outcome measure than spirometry as previously suggested,⁹ albeit this disconnect may only be seen in less severe step 2 patients. Moreover, this reduction was achieved using a significantly lower nominal dose exposure of ICS in the extra-fine group, as was demonstrated in a previous study comparing HFA-BDP and fluticasone,²⁰ alluding to increased peripheral deposition with the smaller particle size, which supports the findings of previous scintigraphic inhalation studies.^{15,16} Patients at step 4 showed no significant differences in any of spirometry, IOS, or FeNO, regardless of whether they were prescribed LABA in addition to ICS. However, there were markedly elevated values for R5-R20 and R5%, demonstrating persistent small airways dysfunction in such patients despite LABA. This might indicate that step 4 patients have already developed a degree of airway remodeling common to persistent asthmatics²³ and that inhaled therapies in these patients may be less effective in this regard. ICS treatment has been shown to prevent remodeling in milder patients^{24,25}; however, if the ICS particles are not reaching the lung periphery in patients with more severe asthma, then remodeling might continue unchecked because of ongoing peripheral airway inflammation.⁶ Pointedly, very few patients were receiving extra-fine ICS at step 4, with no patients receiving an extra-fine LABA or ICS/LABA combination.

We demonstrated widespread abnormality of the small airways across all treatment steps, using both IOS and FEF₂₅₋₇₅%. In other words, if IOS is not available then perhaps using FEF₂₅₋₇₅% could be a reasonable small airways surrogate.⁸⁻¹⁰ Using IOS, resistance at 5Hz (R5) reflects total airway resistance. Central airway resistance is approximated using resistance at 20Hz (R20) and is the largest component of R5. The peripheral or small airway component can thus be evaluated by calculating the difference between these 2 measurements, R5-R20. The coefficient of variability (Cv) for R5 has been reported between 4.0% and 7.3% in asthma,^{26,27} with a coefficient of repeatability (Cr) of 0.92 in 1 study²⁶ or 0.13kPa/L/s in absolute terms in another study that included a "normal subject" arm.²⁸ R20 has a reported Cv of 4.0% and Cr 0.74.²⁶ Low frequencies are more sensitive to change (ie, R5) than higher frequencies (R20)²⁸; therefore, R5 could be used on its own to describe changes in peripheral airway mechanics. There is greater variation in the calculated peripheral airways measurement: the closest referenced value is for R5-R15 in children, where the Cv was 10.8%.²⁷

However, in simple terms, when R5-R20 becomes a positive value, this means that peripheral resistance is becoming greater than central airways resistance (ie, the opposite of normal physiology), indicating abnormality of the peripheral airways. In the current study, mean values for R5% were all greater than 130% for each step, and for small airways resistance (as R5-R20) there were approximately two thirds of patients with abnormal values (>0.03 kPa/L/second)¹² within each step. It is particularly interesting that these abnormalities persist despite a much greater overall daily dose of ICS at step 4, further suggesting that this could be attributable to poor peripheral delivery of larger particle formulations of ICS. Although there were no overall significant differences in R20 between treatment steps, we did observe a trend toward a lower R20 value in step 4 patients, which conceivably could be attributable to effects of the higher ICS dose on larger airways. What is clear from our data is that the prescriptions of LABA do not provide any benefit in terms of treating the small airways in asthma, which could be for 2 possible reasons. First, step 2 and step 3 patients are statistically identical with regard to outcome measures apart from LABA use in step 3. Furthermore, LABA use in step 4 tallies with worse spirometry and IOS measures, which would suggest either that LABA therapy is not effective for small airways disease, or perhaps that this subgroup are simply more severe from the outset.

The heterogeneity of asthma makes it unlikely that standardized treatment protocols will benefit all patients. This has previously been proved with targeted therapy: using inflammatory markers in patients with asthma with an inflammatory asthma phenotype^{29,30} as well as in those patients who specifically demonstrate methacholine hyperresponsiveness³¹; showing greater benefits than standard care with personalized treatment. Given that symptoms of asthma can develop for multiple reasons, including inflammation and airway hyperresponsiveness, and the fact that spirometry is not a very sensitive marker of change, perhaps the time has come to develop either composite assessment from multiple sources, including the small airways, to determine treatment or more simply to treat by individual asthma phenotypes. The present study indicates that standard care does not control all aspects of asthma pathophysiology, in particular with regard to the small airways.

Extra-fine particle solution formulations of ICS were developed after the phase out of CFC-propelled pMDIs. HFA-BDP (Qvar, Teva, Castleford, United Kingdom) has a mass median aerodynamic diameter (MMAD) of approximately 1 μm , whereas CFC-BDP particles have a MMAD of approximately 3 μm . These extra-fine particles have also been shown to provide greater peripheral delivery of ICS, using radiolabeled scintigraphic studies comparing HFA-BDP

Table 3

Comparisons of long-acting beta agonist (LABA) use vs no LABA use at step 4

Variable	LABA (n = 82)	No LABA (n = 41)	P-Value
ICS dose ($\mu\text{g/day}$)	1,494 (1,392, 1,596)	1,568 (1,386, 1,751)	.45
FEV ₁ (% predicted)	81.8 (76.7, 86.9)	87.4 (80.9, 93.8)	.21
FEF ₂₅₋₇₅ (% predicted)	53.1 (47.3, 58.8)	58.0 (49.6, 66.3)	.35
R5 ^a (% predicted)	141.3 (127.1, 157.2)	129.1 (112.8, 147.8)	.33
R20 ^a (% predicted)	127.0 (116.5, 138.3)	122.5 (110.2, 136.2)	.63
R5-R20 ^a (kPa/L/s)	0.137 (0.099, 0.177)	0.091 (0.06, 0.122)	.07
F _{res} ^a (kPa/L/s)	17.3 (15.6, 19.2)	14.8 (12.5, 17.4)	.12
FeNO ^a (ppb)	22.0 (18.0, 26.8)	24.0 (19.1, 30.3)	.58

Abbreviations: ICS, inhaled corticosteroid as beclomethasone dipropionate equivalent dose; FEV₁, forced expiratory volume in 1 second; FEF₂₅₋₇₅, forced expiratory flow between 25 and 75% of vital capacity; R5, total airway resistance at 5Hz; R20, central airway resistance at 20Hz; F_{res}, frequency of resonance; R5-R20, peripheral airways resistance between 5Hz and 20Hz; FeNO, fractional exhaled nitric oxide.

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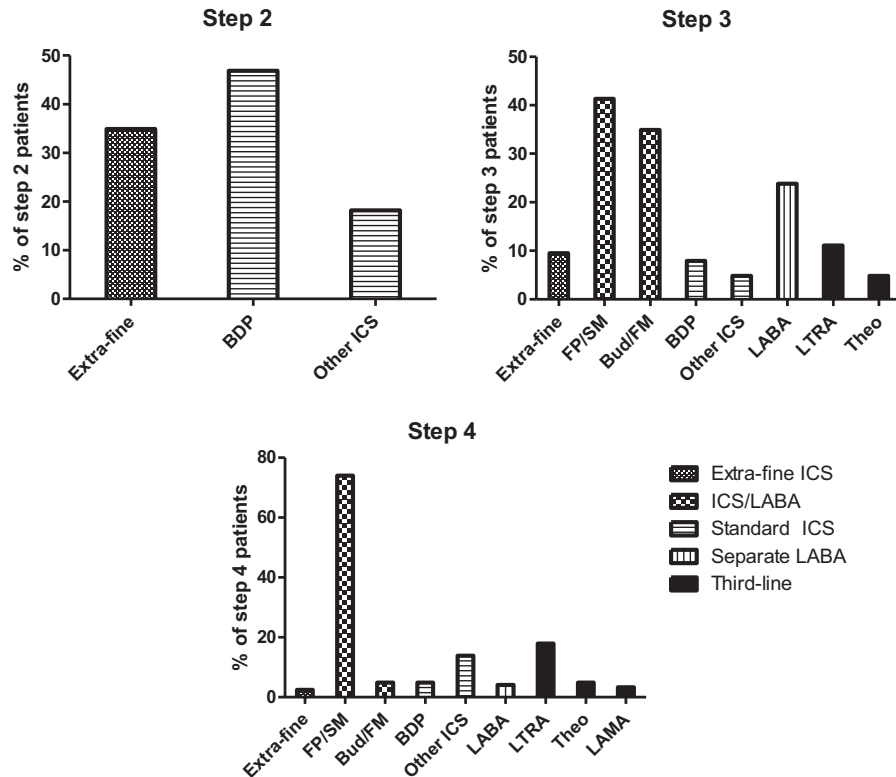
versus CFC-BDP pMDIs, of the order of 50 to 60% compared with 10 to 20%, respectively.¹⁶ Indeed, there is also an extra-fine solution-based formulation containing the combination of beclomethasone/formoterol with extra-fine particles for both moieties (Fostair, Chiesi, Cheadle, United Kingdom). Given the benefits seen in the step 2 patients receiving extra-fine ICS with regard to reduced airway resistance, perhaps the next logical interim step in asthma management is to convert uncontrolled patients onto an equivalent dose of extra-fine ICS rather than stepping up to the addition of a LABA, which appears to confer no benefit to the small airways. Indeed, one might speculate that adding extra-fine LABAs to extra-fine ICS also may be of benefit in this regard. Clearly, further randomized controlled trials are required to answer these questions based on outcome measures such as symptom control and exacerbations.

The limitations of this study are its retrospective design and reliance on patients' self-reporting of compliance to asthma medications. Also, we do not have formal data on symptom scores for these individuals, which would have allowed us to correlate our small airways findings with asthma control; nor do we have data on disease duration, exacerbations, or sensitization that would accurately reflect our study population. The strengths of the present study lie in the large numbers and wide cross-section of patients with asthma; as well as the presentation of "real-life" community prescribing practices that can help inform directions for future study.

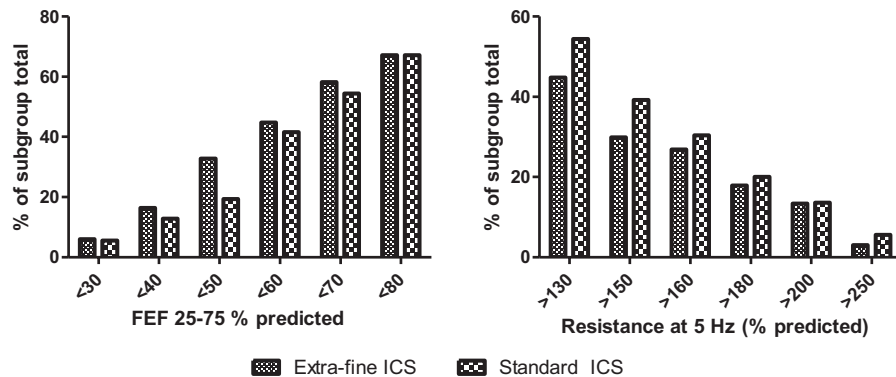
In conclusion, we have demonstrated a significant unmet need in terms of small airway dysfunction in asthma across a range of treatment steps that is present despite guideline-driven community asthma treatment. In particular, we have shown that extra-fine ICS may reduce airway resistance as measured by IOS, with the added benefit of lower ICS dose exposure compared with standard particle size ICS. Moreover, the addition of a LABA at any treatment step does not appear to impact in any way on small airways measures, generating the hypothesis that switching to extra-fine ICS or extra-fine ICS/LABA combination may be a more logical therapeutic step. Further prospective randomized controlled trials are required to further address these findings in addition to investigating relationships with asthma symptoms, control, and exacerbations.

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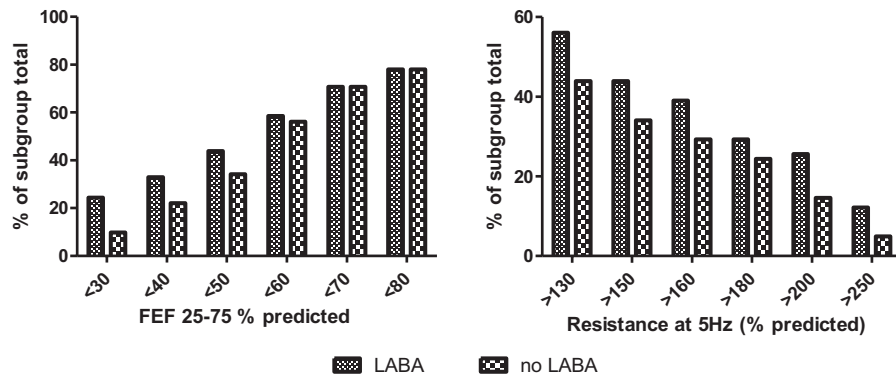
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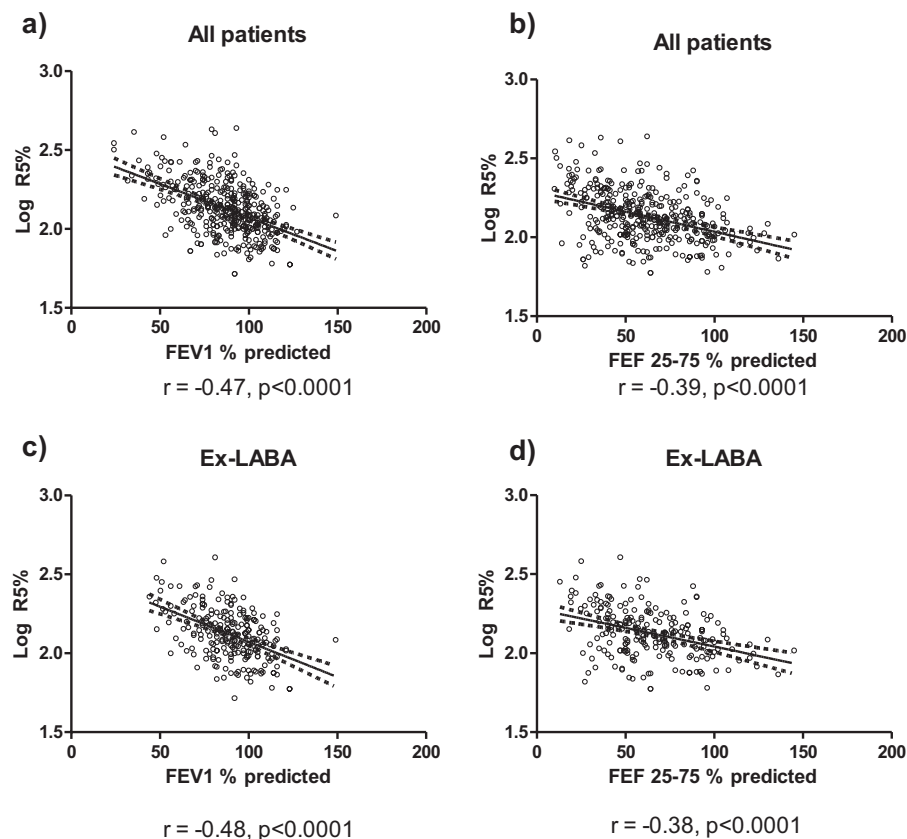
eFig. 1. Proportional usage of types of ICS alone, ICS/LABA combination, separate LABA, and third-line medications at each treatment step. Histogram bars represent percentage of patients receiving each medication at each treatment step. Extra-fine, extra-fine particle inhaled corticosteroid (ICS); BDP, beclomethasone dipropionate; FP/SM, fluticasone propionate/salmeterol combination inhaler; Bud/FM, budesonide/formoterol combination inhaler; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; Theo, theophylline; LAMA, long-acting muscarinic antagonist.



eFig. 2. Proportions of patients receiving extra-fine or standard particle size inhaled corticosteroids (ICS) within set thresholds of FEF25-75% (left) and R5% (right) at step 2. Histograms show data as a percentage of each subgroup within step 2 below or above each threshold. Patients receiving extra-fine ICS, n = 67; and standard ICS, n = 125. FEF₂₅₋₇₅, forced expiratory flow between 25-75% of vital capacity.



eFig. 3. Proportions of patients receiving or not receiving long-acting beta agonist (LABA) therapy within set thresholds of FEF25-75% (*left*) and R5% (*right*) at step 4. Histograms show data as a percentage of each subgroup within step 4 below or above each threshold. Patients receiving LABA, $n = 82$; not receiving LABA, $n = 41$. FEF₂₅₋₇₅, forced expiratory flow between 25-75% of vital capacity.



eFig. 4. Correlations between R5%, FEV1% and FEF25-75% for all patients (a, b) and patients not receiving long-acting beta agonist (Ex-LABA) therapy (c, d). Individual data points are represented as scatterplots. R5% values transformed using Log10. Pearson's test used for all correlations, r =correlation coefficient, significance set at $P < .05$. Solid line represents correlation line of identity, with interrupted lines representing the 95% confidence limits. All patients, $n = 378$; patients not receiving (ex) LABA, $n = 232$. R5%=resistance at 5Hz as percentage of predicted. FEV₁, forced expiratory volume in 1s; FEF25-75, forced expiratory flow between 25-75% of vital capacity.