

Original Article

Comparative Effectiveness of Step-up Therapies in Children with Asthma Prescribed Inhaled Corticosteroids: A Historical Cohort Study

Clare S. Murray, MBCHB, MD^{a,b}, Mike Thomas, PhD^{c,d}, Kathryn Richardson, PhD^e, David B. Price, FRCGP^{e,f}, and Steve W. Turner, MD^g *Manchester, Southampton, and Aberdeen, United Kingdom*

What is already known about this topic? In children with uncontrolled asthma prescribed low-dose inhaled corticosteroids (ICSs), various step-up options are available: fixed-dose combination ICS/long-acting β_2 -agonist (FDC), increasing ICS dose, or adding leukotriene receptor antagonist.

What does this article add to our knowledge? All the various step-up options in children with uncontrolled asthma prescribed low-dose ICS are likely to reduce severe exacerbations, but FDC may also improve asthma control.

How does the study impact current management guidelines? Based on current evidence, of the various step-up options in children with uncontrolled asthma prescribed low-dose ICS, FDC may be the best option to trial first.

^aDivision of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Science Centre, The University of Manchester, University Hospital of South Manchester, NHS Foundation Trust, Manchester

^bRoyal Manchester Children's Hospital, Central Manchester University Hospitals, NHS Foundation Trust, Manchester, Manchester

^cPrimary Care and Population Sciences, University of Southampton, Southampton

^dNIHR Southampton Respiratory Biomedical Research Unit, Southampton

^eObservational and Pragmatic Research Institute Pte Ltd, Singapore

^fAcademic Primary Care, University of Aberdeen, Aberdeen

^gChild Health, University of Aberdeen, Aberdeen

This work was supported by the Respiratory Effectiveness Group.

Conflicts of interest: C. Murray has received consultancy fees from Novartis; has received research support from North West Lung Research Centre Charity, JP Moulton Charitable Foundation, and the National Institute for Health Research; and has received lecture fees from Novartis and GlaxoSmithKline (GSK). M. Thomas has received consultancy fees from GSK, Novartis, Aerocrine, Boehringer Ingelheim, and Pfizer and has received lecture fees from GSK, Novartis, and Aerocrine. Neither he nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years, he has received speaker's honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Ingelheim, GSK, MSD, Teva, Novartis, Pfizer, and Sandoz. He has received honoraria for attending advisory panels with Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, and Novartis. He has received sponsorship to attend international scientific meetings from GSK and Astra Zeneca. He has received funding for research projects from GSK. He is a member of the British Thoracic Society/Scottish Intercollegiate Guidelines Network Asthma guideline group and the National Institute for Health and Care Excellence Asthma guideline group. At the time of the study analyses, K. Richardson was an employee of Research in Real-Life Ltd, which has conducted paid research in respiratory disease on behalf of the following organizations in the past 5 years: Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva. She has received research support from the Respiratory Effectiveness Group and Optimum Patient Care, Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva. D.B. Price is on the boards for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals (fees paid to Observational and Pragmatic Research Institute); has received consultancy fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Meda,

Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance (fees paid to Observational and Pragmatic Research Institute); has received grants and unrestricted funding for investigator-initiated studies (conducted through Research in Real-Life Ltd and Observational and Pragmatic Research Institute Pte Ltd) from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GSK, Meda, Merck, Mundipharma, Napp, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva Pharmaceuticals, and Zentiva; has received lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, Takeda, and Teva Pharmaceuticals (fees paid to Observational and Pragmatic Research Institute); has patents (planned, pending, or issued) from AKL Ltd; has received payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals (fees paid to Observational and Pragmatic Research Institute); has received payment for developing educational presentations from GSK, Novartis, and Mundipharma (fees paid to Observational and Pragmatic Research Institute); has stock/stock options from AKL Ltd, which produces phytopharmaceuticals; has received payment for travel/accommodations/meeting expenses from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals (fees paid to Observational and Pragmatic Research Institute); has received funding for patient enrollment or completion of research from Almirall, Chiesi, Teva Pharmaceuticals, Zentiva, and Novartis (fees paid to Observational and Pragmatic Research Institute); was a peer reviewer for grant committees of the Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), and Health Technology Assessment (2014); and owns 80% of Research in Real Life Ltd, 74% of the social enterprise Optimum Patient Care Ltd, UK, and 74% of Observational and Pragmatic Research Institute Pte Ltd, Singapore. S. W. Turner declares no relevant conflicts of interest.

Received for publication July 15, 2016; revised December 9, 2016; accepted for publication December 29, 2016.

Available online ■■

Corresponding author: Clare Murray, MBCHB, MD, Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, University of Manchester, Education and Research Building, University Hospital of South Manchester, Southmoor Rd, Manchester M23 9LT, UK. E-mail: Clare.murray@manchester.ac.uk.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.12.028>

*Abbreviations used**FDC*-fixed-dose combination*ICS*-inhaled corticosteroid*LABA*-long-acting beta-agonist*LTRA*-leukotriene receptor antagonist*OR*-odds ratio*SABA*-short-acting beta-agonist

BACKGROUND: In children with uncontrolled asthma prescribed low-dose inhaled corticosteroids (ICSs), various step-up options are available: fixed-dose combination ICS/long-acting β_2 -agonist (FDC), increasing ICS dose, or adding leukotriene receptor antagonist (LTRA). However, evidence of their relative effectiveness is limited.

OBJECTIVE: To compare the effectiveness of step-up treatment to FDC in children with asthma versus increased ICS dose, or LTRA.

METHODS: This matched cohort study used UK primary-care databases to study children prescribed their first step-up treatment to FDC, increased ICS dose, or LTRA. A year of baseline data was used for matching and identifying confounders. Outcomes over the following year were examined. The primary outcome was severe exacerbation rate; secondary outcomes included overall asthma control, derived from databases (no asthma-related admissions/hospital attendances/oral corticosteroids or antibiotics prescribed with a respiratory review, and average prescribed salbutamol ≤ 200 μ g/day).

RESULTS: There were 971 matched pairs in the FDC and increased ICS dose cohorts (59% males; mean age, 9.4 years) and 785 in the FDC and LTRA cohorts (60% males; mean age, 9.0 years). Exacerbation rates in the outcome year were similar between FDC and increased ICS (adjusted incidence rate ratio [95% CI], 1.09 [0.75-1.59]) and FDC and LTRA (incidence rate ratio, 1.36 [0.93-2.01]). Increased ICS and LTRA significantly reduced the odds of achieving overall asthma control, compared with FDC (odds ratios [95% CI], 0.52 [0.42-0.64] and 0.53 [0.42-0.66], respectively)—this was driven by reduced short-acting beta-agonist use.

CONCLUSIONS: FDC is as effective as increased ICS or LTRA in reducing severe exacerbation rate, but more effective in achieving asthma control. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Asthma; Child; Inhaled corticosteroid; Leukotriene receptor antagonist; Long-acting beta-agonist; Step-up therapy

Asthma is the commonest chronic disease in childhood, affecting about 1 in 11 children in the United Kingdom.¹ Although most children are well controlled on low-dose inhaled corticosteroids (ICSs), some will still experience symptoms and exacerbations, and physicians will recommend a step-up in treatment.² Current guidelines offer a number of different choices to physicians, including increasing the dose of ICS and addition of either long-acting beta-agonists (LABAs) or leukotriene receptor antagonists (LTRAs). Most guidelines, however, tend to put forward a first choice at this step: The British Thoracic Society guidelines advise the addition of LABA as the first step-up option³; the Global Initiative for Asthma recommends prescribing increased doses of ICS.⁴

The reason for these differences in guidance is that research on the comparative effectiveness of pediatric step-up therapies is limited. In the last few years, the evidence for which step-up treatment may be best has increased,⁵⁻¹⁰ in part, by the publication of a large randomized crossover trial evaluating differential responses over 16 weeks to 3 step-up strategies in 182 children aged 6 to 17 years with uncontrolled asthma on low-dose ICS.⁵ However, despite these important recent publications, a Cochrane review of the evidence published in 2014 still concluded that owing “to the paucity of pediatric trials,” the authors were “unable to draw firm conclusions about the best adjunct therapy in children.”¹¹ In addition, until recently, controversy regarding the safety of LABAs may have impacted on choice.^{12,13}

Notably, a large multicenter randomized controlled trial in the United Kingdom investigating whether adding LABA or LTRA to low-dose ICS in children could reduce the number of exacerbations closed early because of lack of recruitment.¹⁴ Despite increasing the recruitment time, only 63 children were randomized in this study from a target sample size of 450. Recruitment proved difficult in the main because children eligible for the trial were already prescribed add-on therapy. Consequently, no firm conclusions regarding the study medications could be drawn.

Although more evidence is required, large randomized controlled trials not only are expensive and time-consuming to conduct but also can be difficult to recruit for. The strengths of “real-world” studies have been highlighted in the “Brussels Declaration.”¹⁵ A Respiratory Effectiveness Group study was the first to report on initial step-up episodes in more than 10,000 children in the United Kingdom, and the first to describe the clinical characteristics of children who received different step-up options.¹⁶ Another Respiratory Effectiveness Group publication compared the effectiveness of extrafine-particle versus fine-particle ICS for children initiating or stepping up ICS therapy and ICS dose step-up with LABA.¹⁷ “Real-world” data about the clinical outcomes of asthma therapy can provide new information and hypotheses and complement data from controlled trials.¹⁸

Because of the paucity of pediatric trials, we are unable to draw firm conclusions about the best adjunct therapy in children.

The aim of this large population-based observational study was to compare the effectiveness of step-up therapies from low-dose ICS in a real-life pediatric population. In 2 matched cohorts, we compared the effect of a change to fixed-dose combination (FDC) versus an increase in ICS dose, and a change to FDC versus add-on LTRA, on asthma exacerbations and asthma control in the following year. We chose to compare the addition of LABA as an FDC inhaler rather than separate add-on LABA because current Global Initiative for Asthma guidelines recommend the use of combination inhalers,⁴ our own national guidelines recommend FDC as the optimal means of adding LABA,¹⁹ and we have recently published data from a similar historical cohort indicating that better asthma control was achieved with FDC inhalers than with separate inhalers.²⁰

METHODS

Study design

This was a historic observational database study of step-up therapy in children with asthma, consisting of a baseline year for

matching and identifying potential baseline confounders, preceding the date on which patients received treatment step-up (index date), followed by an outcome year for evaluating comparative effectiveness (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Data sources and permissions

Two UK primary-care databases were used to source medical and prescribing data, which include approximately 15% of UK children, and have previously been described in detail.^{16,17} First, the Clinical Practice Research Datalink is the world's largest database of de-identified records from primary care, and includes longitudinal data from more than 5 million active medical records from across the United Kingdom.^{21,22} It is a well-validated database that has been used in numerous observational studies.²³ Second, the Optimum Patient Care Research Database is a quality-controlled primary-care research database that contains anonymous routine medical record data and patient-reported outcomes from more than 550 practices in the United Kingdom.²⁴ Data were available from January 1, 1999, through April 2012 for the Clinical Practice Research Datalink, and to December 2012 for the Optimum Patient Care Research Database. Patient records were checked to avoid duplication of individuals in the analyses.

The study was conducted to standards recommended for observational research²⁵ and is registered with the European Network of Centres for Pharmacoeconomics and Pharmacovigilance (study registration ENCEPP/SDPP/10483). Data use was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink and the Trent Multi-Centre Research Ethics Committee. The study protocol was approved by the Anonymized Data Ethics Protocols and Transparency committee, the independent scientific advisory committee for the Optimum Patient Care Research Database.

Study population

Included children were aged 5 to 12 years with a diagnostic code for asthma or 2 or more asthma prescriptions, or both, in the previous 12 months, were receiving ICS at baseline, and had a 50% or more increase in ICS dose, switched to an FDC, or had an LTRA added at the index date. Included children were registered in the database for at least 1 year before and after the index date, and had to have received at least 1 asthma prescription in addition to the index date prescription during the outcome year. Children were excluded if they had ever received a diagnosis of any chronic respiratory disease other than asthma, maintenance oral corticosteroid therapy, multiple step-up therapies at the index date, or a previous add-on therapy.

Outcomes

The primary outcome was the number of severe asthma exacerbations in the year after the index date. Severe asthma exacerbations were defined according to American Thoracic Society/European Respiratory Society criteria, as an asthma-related emergency or hospitalization or oral corticosteroids with evidence of respiratory review.²⁶

Secondary outcomes included the following:

1. Risk-Domain Asthma Control: No emergency or hospital attendance for asthma-related events; no acute course of oral corticosteroids or antibiotics with evidence of respiratory consultation.
2. Overall Asthma Control: Risk-Domain Asthma Control and average daily prescribed dose of less than or equal to 200 μ g

salbutamol or less than or equal to 500 μ g terbutaline (equivalent to ≤ 2 puffs daily of reliever medication).

3. Treatment stability: Risk-Domain Asthma Control and no preventer treatment change in the year after the index date.
4. Acute Respiratory Events: Defined as the total number per patient, where an *event* is defined as asthma-related emergency or hospitalization, or oral corticosteroids with evidence of respiratory review, or antibiotics prescribed with evidence of respiratory review, in the year after the index date.

Other secondary outcomes including short-acting beta-agonist (SABA) use, prescriptions for oral thrush, and asthma-related hospitalizations are defined in detail in this article's Online Repository at www.jaci-inpractice.org.

Statistical analysis

Eligible children from the increased ICS dose and LTRA cohorts were separately matched (1:1) on key demographic and asthma-related characteristics during the baseline year to children from the FDC cohort. Matching variables were agreed by the steering committee *a priori* as the variables most likely to be associated with asthma outcomes and therefore potentially confound the results. The final matching variables were as follows:

1. Index date (± 3 years)
2. Age (in years)
3. Any severe asthma exacerbations during the baseline year
4. Previous ICS dose (0-150, 151-250, 251-500, >500 in budesonide equivalent μ g doses)
5. Average SABA daily doses during the baseline period (0, 1-200, or ≥ 201 μ g salbutamol or equivalent)

Baseline characteristics and outcome variables for unmatched patients were compared using chi-square test or Mann-Whitney test and, for matched patients, conditional logistic regression.

The total number of asthma exacerbations and acute respiratory events in the outcome year were compared between treatment cohorts separately using negative binomial regression to estimate the incidence rate ratio for exacerbations relative to the FDC group. General estimating equations were used to account for the correlation within matched pairs. The models used empirical standard errors (to calculate 95% CIs) and were adjusted for baseline confounders.²⁷ The other secondary outcomes were compared relative to the FDC group using conditional logistic regression models to estimate adjusted odd ratios (ORs) and 95% CIs.

For all multivariable models, variables showing a trend toward a difference ($P < .10$) between the matched treatment cohorts at baseline were included as potential confounding factors along with any strongly predictive variables of the outcome (see this article's Online Repository at www.jaci-inpractice.org). Variables were examined for collinearity and clinical importance and were then removed in a backward stepwise procedure, retaining confounding variables with a P value of less than .1. Analyses were performed using IBM SPSS Statistics Version 19 (SPSS Statistics, IBM, Somers, NY) and SAS versions 9.2 and 9.3 (SAS Institute, Marlow, Buckinghamshire, UK). Statistical significance was defined as a P value of less than .05.

RESULTS

Participants

The inclusion/exclusion criteria resulted in 1,390 children being selected into the FDC cohort, 9192 into the increased ICS

dose cohort, and 1275 into the LTRA cohort (see [Tables E1 and E2](#) in this article's Online Repository at www.jaci-inpractice.org). Following matching, there were 971 matched pairs in the FDC versus increased ICS dose analysis (see [Figure E2](#) in this article's Online Repository at www.jaci-inpractice.org), and 785 matched pairs in the FDC versus LTRA analysis (see [Figure E3](#) in this article's Online Repository at www.jaci-inpractice.org). [Tables E1 and E2](#) show the impact of matching at baseline on unmatched and matched cohorts for demographic variables and potential confounders.

Children were well matched on age, sex, and comorbidities, although rhinitis was more common in children stepped up to LTRA than to FDC ([Table I](#)). Acute respiratory events and antibiotics with respiratory consult were more common, and asthma general practice consultations less common, in the LTRA group. Average daily dose of ICS in the baseline year was significantly lower in those children who were stepped up to FDC compared with increased ICS dose (175 vs 203 μ g) and with LTRA (176 vs 188 μ g). However, ICS dose at time of index date was similar between the comparison groups. Overall, no child was on less than 150 μ g/day (beclomethasone equivalent) ICS and only 3.9% of all children were on more than 500 μ g/day ([Tables E1 and E2](#)). Children who stepped up to FDC had more general practice consultations for asthma compared with other groups at baseline.

Increased ICS dose versus FDC

The percentage of children experiencing 1 or more exacerbations fell from more than 11% during baseline to 6% during the outcome year in both cohorts. In the adjusted analysis, there was no significant difference in exacerbation rates for patients increasing the ICS dose compared with those stepping up to an FDC (incidence rate ratio = 1.09; 95% CI, 0.75-1.59; $P = .09$; [Figure 1](#)). Similarly, there was no difference in the odds of achieving risk-domain asthma control (OR = 0.91; 95% CI, 0.71-1.16; $P = .44$). However, children with increased ICS dose compared with those switching to FDC had significantly lower odds of achieving treatment stability (0.43; 95% CI, 0.35-0.53; $P < .001$), and significantly lower odds of achieving overall asthma control (0.52; 95% CI, 0.42-0.64; $P < .001$), likely driven by average daily SABA dose. Patients in the increased ICS dose cohort had a higher mean daily SABA dose than those in the FDC cohort (315 vs 233 μ g; [Table II](#)). Similar to the findings at baseline, asthma general practice consultations were still significantly higher in children who stepped up to FDC compared with those increasing the ICS dose, though both groups had reduced consultation rates ([Table II](#)). Further outcome differences (eg, estimates of adherence, emergency department visits, and spacer prescription) are reported in [Table E3](#) in this article's Online Repository at www.jaci-inpractice.org.

Add-on LTRA versus FDC

The percentage of children experiencing 1 or more exacerbations fell from 13% in both cohorts during the baseline year to 6% and 8% in the FDC and LTRA cohorts, respectively, during the outcome year. In adjusted analysis, there was no significant difference in the rate of severe exacerbations for children stepping up with add-on LTRA compared with changing to an FDC (incidence rate ratio = 1.36; 95% CI, 0.93-2.01; $P = .12$; [Table II](#) and [Figure 2](#)). Patients adding LTRA had lower odds of achieving risk-domain asthma control (OR = 0.77; 95% CI,

0.60-1.00; $P = .05$) and overall asthma control (OR = 0.53; 95% CI, 0.42-0.66; $P < .001$; [Figure 2](#)), compared with those switching to FDC, again likely driven by average daily SABA dose. Patients prescribed LTRA had significantly higher average daily SABA dosage, compared with FDC (315 vs 232 mg; $P < .001$; [Table II](#)). Further outcome differences are reported in [Table E3](#).

DISCUSSION

Main findings

In this historical, matched cohort study, we found no significant differences in the year following step-up treatment between either change to FDC and increased doses of ICS or change to FDC and add-on LTRA, in either the number of or the rate of severe asthma exacerbations (American Thoracic Society/European Respiratory Society definition). All cohorts achieved a reduction in the number of exacerbations in the year following step-up treatment. Children changing to FDC were more likely to achieve asthma control compared with children changing to step-up treatment with add-on LTRA or children changing to increased ICS dose. Children changing to FDC were more likely to achieve treatment stability than those who increased their ICS dose. Perhaps not surprisingly, those children who stepped up to FDC had less average daily SABA use than either of the 2 comparison groups. This is partly reflected in the overall asthma control findings. These results were observed after adjustment for all relevant factors in the data set.

Interpretation of findings

Very few studies comparing the addition of LABA to ICS with increased doses of ICS have investigated exacerbations requiring oral corticosteroids as an outcome,^{5,6,9,10} and even fewer compared this outcome for the addition of LABA to ICS or LTRA with ICS,⁵ despite exacerbations being highlighted as a core outcome for asthma trials in children.²⁸ None of these studies use exacerbations requiring oral prednisolone as the primary outcome of the study, although 1 large triple crossover study of 182 children included exacerbations requiring oral corticosteroids along with number of asthma control days and FEV₁ as a composite score for the primary outcome.⁵ In this crossover study, more children were likely to respond better to addition of LABA to ICS than either increased ICS or LTRA, although there was considerable individual subject heterogeneity in the differential responses to the 3 therapies. Studies reporting exacerbations as secondary outcomes report very few numbers of exacerbations and therefore results are difficult to interpret.^{6,9,10} A recent Cochrane review meta-analysis comparing exacerbation rates requiring oral steroid use in those adding LABA to ICS and those with increased ICS dose included just 3 studies^{6,9,10} (~290 children per group), and found that there was no significant difference in exacerbation rate between either group (OR = 1.69; 95% CI, 0.85-3.32).²⁹

Severe asthma exacerbations are relatively rare events, albeit important to patients and costly to the health service. Very large studies with a long follow-up period are required to investigate the effect of interventions on exacerbation rates. Real-life studies are ideally placed to answer such a research question, as typically they are of sufficient size and duration to assess the impact of exacerbations on health outcomes.³⁰ However, even in this large real-life study with a 12-month follow-up period, exacerbation rates were very low. We found no significant difference between

TABLE I. Matched baseline characteristics of children prescribed FDC inhalers versus increased dose in ICSs, and FDC inhalers versus add-on LTRAs

Baseline characteristic	FDC vs Increased ICS dose			FDC vs LTRA		
	FDC (n = 971)	Increased ICS dose (n = 971)	P value*	FDC (n = 785)	Add-on LTRA (n = 785)	P value*
Male sex, n (%)	573 (59)	579 (60)	.77	453 (58)	482 (61)	.12
Age at index date (y), mean $\pm$ SD†	9.4 $\pm$ 2.1	9.4 $\pm$ 2.1	NA	8.96 $\pm$ 2.2	8.96 $\pm$ 2.2	NA
Recorded comorbidity, n (%)						
Rhinitis diagnosis	227 (23)	234 (24)	.71	168 (21)	206 (26)	.03
Eczema diagnosis	483 (50)	464 (48)	.38	420 (54)	401 (51)	.34
GERD diagnosis/therapy	20 (2)	23 (2)	.64	15 (2)	25 (3)	.11
Year of index date, median (IQR)	2005 (2003-2007)	2004 (2002-2007)	<.001	2006 (2004-2008)	2006 (2004-2008)	.2
Average daily SABA dose (μ g/d), mean $\pm$ SD	248 $\pm$ 238	244 $\pm$ 224	.63	246 $\pm$ 219	256 $\pm$ 255	.23
Average daily ICS dose‡ (μ g/d), mean $\pm$ SD§	175 $\pm$ 155	203 $\pm$ 201	<.001	176 $\pm$ 142	188 $\pm$ 194	<.001
ICS dose before index date (μ g/d)						
Mean $\pm$ SD	361 $\pm$ 127	363 $\pm$ 134	.17	372 $\pm$ 188	368 $\pm$ 168	.16
Median (IQR)	400 (200,400)	400 (200,400)		400 (200,400)	400 (200,400)	
Severe asthma exacerbations, ATS/ERS definition, n (%)						
0†	863 (89)	863 (89)	.36	682 (87)	682 (87)	.59
1	85 (9)	79 (8)		81 (10)	84 (11)	
≥ 2	23 (2)	29 (3)		22 (3)	19 (2)	
Acute respiratory events, mean $\pm$ SD¶	0.44 $\pm$ 0.80	0.48 $\pm$ 0.81	.26	0.53 $\pm$ 0.89	0.63 $\pm$ 1.01	.02
Acute respiratory events, n (%)¶						
0	673 (69)	656 (68)	.13	508 (65)	490 (62)	.05
1	206 (21)	204 (21)		185 (24)	175 (22)	
≥ 2	92 (10)	111 (11)		92 (12)	120 (15)	
Risk-domain asthma control achieved, n (%)	668 (69)	655 (68)	.452	505 (64)	486 (62)	.245
Overall asthma control achieved, n (%)	367 (38)	356 (37)	.392	277 (35)	270 (34)	.54
Antibiotics with respiratory consult, mean $\pm$ SD	0.37 $\pm$ 0.73	0.41 $\pm$ 0.79	.215	0.43 $\pm$ 0.82	0.57 $\pm$ 0.98	.002
Antibiotics with respiratory consult, n (%)						
0	722 (74)	702 (72)	.2	559 (71)	519 (66)	.003
1	173 (18)	180 (19)		155 (20)	156 (20)	
≥ 2	76 (8)	89 (9)		71 (9)	110 (14)	
Asthma consultations before the index date, mean $\pm$ SD#	1.99 $\pm$ 1.67	1.44 $\pm$ 1.42	<.001	2.10 $\pm$ 1.73	1.73 $\pm$ 1.58	<.001
≥ 1 asthma-related hospital admission, n (%)	4 (0.4)	1 (0.1)	.22	9 (1)	7 (1)	.61
Asthma consultations before the index date, n (%)#						
0	172 (18)	297 (31)	<.001	128 (16)	199 (25)	<.001
1	270 (28)	274 (28)		211 (27)	197 (25)	
2	216 (22)	212 (22)		176 (22)	178 (23)	
≥ 3	313 (32)	188 (19)		270 (34)	211 (27)	

A&E, Accident and emergency; ATS/ERS, American Thoracic Society/European Respiratory Society; COPD, chronic obstructive pulmonary disease; ED, emergency department; GERD, gastroesophageal reflux disease; IQR, interquartile range; LTRI, lower respiratory tract infection; NA, not applicable.

Bold indicates statistical significance ($P < .05$).

Asthma-related hospitalizations consist of either a definite asthma A&E attendance or a definite asthma hospital admission; or a generic hospitalization Read code that has been recorded on the same day as a lower respiratory consultation; acute oral corticosteroid use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (eg, 6, 5, 4, 3, 2, 1 reducing, or 30 mg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation; evidence of a respiratory review consists of any lower respiratory consultation and any additional respiratory examinations, referrals, chest x-rays, or events; lower respiratory consultations consist of lower respiratory Read codes (including asthma, COPD, and LRTI Read codes); asthma/COPD review codes excluding any monitoring letter codes; lung function and/or asthma monitoring. Where ≥ 1 oral corticosteroid course/antibiotic/hospitalization occur within 2 wk of each other, these events were considered to be the result of the same exacerbation (and will be counted only once).

*Matched cohorts were compared using conditional logistic regression.

†Matching variable.

‡Average daily dose ICS over baseline year.

§The doses of ICS were standardized to equivalence with fine-particle beclomethasone; thus, the actual doses of budesonide were used, and doses of extrafine beclomethasone and fluticasone were doubled.

||An ATS/ERS severe asthma exacerbation is defined as an occurrence of the following: asthma-related hospital admissions or accident and emergency attendance, or an acute course of oral corticosteroids with evidence of respiratory review.

¶An acute respiratory event is asthma-related hospital admissions or A&E attendance, or an acute course of oral steroids with evidence of respiratory review, antibiotics prescribed with evidence of a respiratory review.

#Nonspecialist primary-care consultation where asthma was recorded.

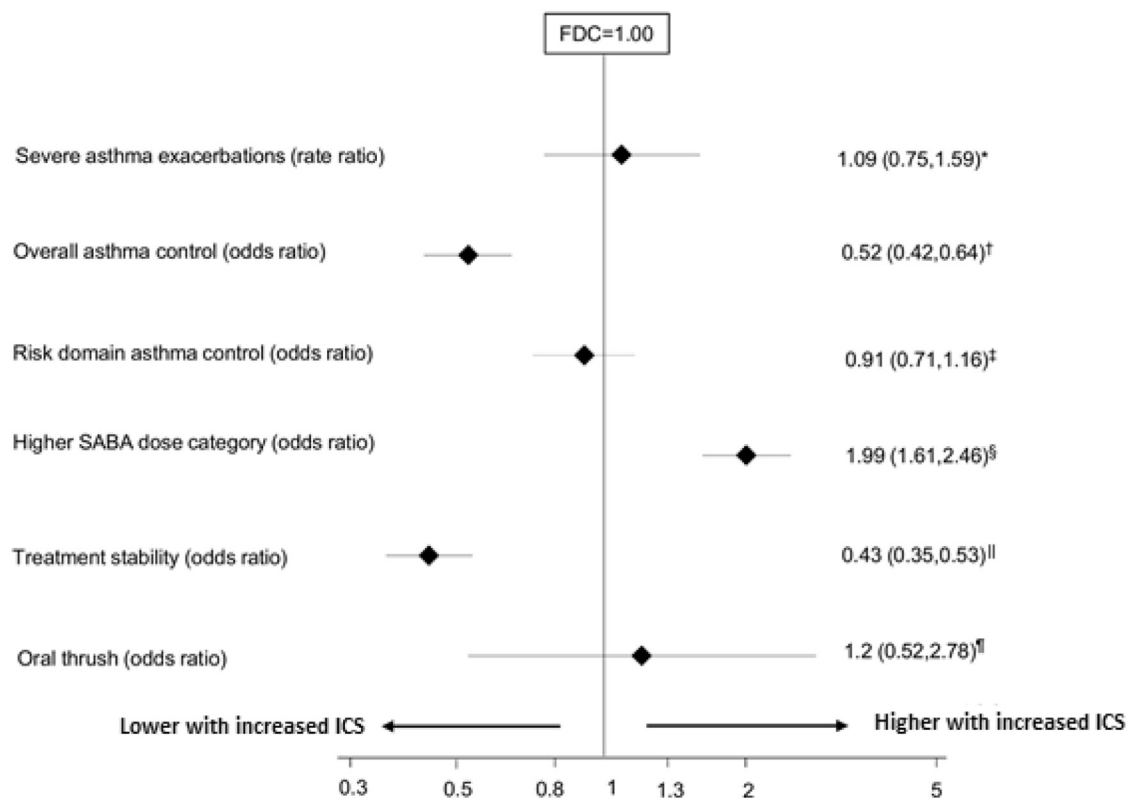


FIGURE 1. Adjusted rate ratio and OR during outcome year for FDC versus increased dose of ICS cohorts for primary and secondary outcomes (analysis 1). *Adjusted for rhinitis diagnosis/therapy, number of acute oral corticosteroid courses, and number of asthma consultations ($P = .09$). †Adjusted for acute oral corticosteroid courses ($P < .001$); ‡Adjusted for antibiotics with evidence of respiratory review and number of asthma consultations ($P = .44$). §Adjusted for rhinitis diagnosis/therapy and number of asthma consultations, and categorized as 0 to 200 or more than 200 μg ($P < .001$); ||Adjusted for antibiotics with evidence of respiratory review ($P < .001$); ¶Unadjusted ($P = .67$; conditional logistic regression).

the different step-up treatments in exacerbation rate. All step-up treatments assessed in this study were associated with reduced exacerbation rates, suggesting that all are effective in reducing exacerbations.

Randomized controlled trials have assessed asthma control in different ways, mostly with the use of symptom diaries for differing periods of time, documenting daytime and nighttime symptoms and reliever medication use. Two trials reported no difference in control between the groups^{6,9}; one reported better asthma control in the increased ICS group compared with the addition of LABA group¹⁰ and the other reported, in the form of a composite score, better outcomes in the addition of LABA group.⁵ In this real-life observational study, asthma control cannot be measured in the same way as in prospective trials. However, the results of our study suggest that control was more likely to be achieved in children who were stepped up to FDC, rather than by increasing ICS or by adding LTRA. When comparing FDC with increased ICS or addition of LTRA, overall asthma control was about twice as likely to be achieved, indicating that those individuals who stepped up to FDC had fewer unscheduled visits and less SABA usage. Although the differential effect between these step-up changes appears small, this large real-life study complements data from the largest of the randomized controlled trials cited in this study,⁵ and supports those guidelines that advise the addition of LABA as FDC as the first

step-up option,³ rather than those that advise prescribing increased doses of ICS.⁴

Strengths and limitations

A major strength of our study is the size, which was considerably larger than that in the Cochrane meta-analysis.²⁹ No prospective sample size calculation was estimated for the study; alternatively, we included all eligible children in the databases from January 1, 1999, who had the required data, to maximize study size. Data before 1999 were not extracted because LTRA and FDC inhalers were not licensed for use in the United Kingdom until 1998 and 1999, respectively. Data were extracted from well-maintained databases containing medical records of approximately 15% of all UK children. Furthermore, approximately 62% of those who stepped up to LTRA, and 70% of those who stepped up to FDC, were analyzed, although not all children who stepped up were selected. However, we believe that the matched children in this study were largely representative of those who initiate step-up treatment within primary-care settings in the United Kingdom. In addition, the study follows children for a full year following step-up treatment.

We conducted a thorough matching process,²⁵ resulting in cohorts with similar baseline characteristics and asthma severity. We adjusted for additional potential confounding factors, and collected and analyzed follow-up data for a full year after the

TABLE II. Outcome-year results for matched cohorts prescribed FDC inhalers vs increased dose ICSs (analysis 1), and FDC inhalers vs add-on LTRAs (analysis 2)

Outcome	FDC vs Increased ICS dose			FDC vs LTRA		
	FDC (n = 971)	ICS dose increase (n = 971)	P value*	FDC (n = 785)	Add-on LTRA (n = 785)	P value*
Average daily SABA dose ($\mu\text{g}/\text{d}$), mean $\pm$ SD	233 $\pm$ 234	315 $\pm$ 281	<.001	232 $\pm$ 227	315 $\pm$ 295	<.001
Average daily ICS dose ($\mu\text{g}/\text{d}$), mean $\pm$ SD†	247 $\pm$ 235	468 $\pm$ 333	<.001	257 $\pm$ 214	258 $\pm$ 241	.92
Severe asthma exacerbations, ATS/ERS definition, n (%)						
0	914 (94)	910 (94)	.81	737 (94)	718 (92)	.11
1	46 (5)	51 (5)		39 (5)	57 (7)	
≥ 2	11 (1)	10 (1)		9 (1)	10 (1)	
Acute respiratory events, mean $\pm$ SD	0.28 $\pm$ 0.66	0.29 $\pm$ 0.63	.78	0.31 $\pm$ 0.70	0.35 $\pm$ 0.65	.23
Acute respiratory events, n (%)						
0	772 (80)	757 (78)	.615	614 (78)	573 (73)	.049
1	149 (15)	167 (17)		123 (16)	160 (20)	
≥ 2	50 (5)	47 (5)		48 (6)	52 (7)	
Risk-domain asthma control achieved, n (%)	770 (79)	756 (78)	.44	614 (78)	569 (73)	.008
Overall asthma control achieved, n (%)	445 (47)	317 (33)	<.001	354 (45)	252 (32)	<.001
Antibiotics with respiratory consult, mean $\pm$ SD	0.25 $\pm$ 0.66	0.24 $\pm$ 0.58	.77	0.27 $\pm$ 0.71	0.29 $\pm$ 0.63	.52
Antibiotics with respiratory consult, n (%)						
0	796 (82)	788 (81)	.92	627 (80)	608 (77)	.19
1	132 (14)	150 (15)		109 (14)	138 (18)	
≥ 2	43 (4)	33 (3)		40 (5)	39 (5)	
Asthma GP consultations, mean $\pm$ SD	1.47 $\pm$ 1.62	1.20 $\pm$ 1.56	<.001	1.51 $\pm$ 1.58	1.50 $\pm$ 1.58	.92
≥ 1 asthma-related hospital admission, n (%)	4 (0.4)	2 (0.2)	.42	2 (0.3)	2 (0.3)	1
Oral thrush, n (%)‡	3 (0.3)	1 (0.1)	NA	1 (0.1)	4 (1)	.21
Treatment stability achieved, n (%)	552 (57)	377 (39)	<.001	431 (55)	446 (57)	.44

ATS/ERS, American Thoracic Society/European Respiratory Society; GP, general practice; NA, not applicable.

Bold indicates statistical significance ($P < .05$).

*Conditional logistic regression.

†The doses of ICS were standardized to equivalence with fine-particle beclomethasone; thus, the actual doses of budesonide were used, and doses of extra fine beclomethasone and fluticasone were doubled.

‡Oral thrush was defined as Read code for oral candidiasis or topical antifungal prescription definitely for treating oral candidiasis.

index date. However, we cannot exclude the possibility of residual confounding in this study; for example, the LTRA cohort had more antibiotics but fewer primary-care consultations in the baseline year, perhaps indicating more unstable asthma or different consulting behavior. There was, however, no evidence of significant difference in control at baseline (% of children who achieved Risk-domain and Overall control similar in baseline year). The LTRA cohort also had a higher incidence of rhinitis, which may have impacted on the severity of asthma symptoms but also may have affected physician choice of step-up treatment. We addressed this where possible, for example, investigating antibiotics and primary-care consultations as confounders in the multivariate models; they were used as adjusting variables in several of the outcome models (where thought to be important). It is also of note that when examining the year of index date, patients who stepped up to FDC tended to have later index dates than those who stepped up to increased ICS. This is probably likely because more FDC was used as time progressed as the practitioners became more familiar with its use (license granted in children only in 1999). However, we cannot reject the possibility that this may have caused bias within our study; perhaps physicians who adopted the approach of prescribing this shortly after being granted license were also more progressive in other ways and managed their patients differently.

We were not able to match on body mass index because much of these data were missing from the data set, and this may have introduced bias. Socioeconomic status and ethnicity information was not available to us. This may also have resulted in bias in our sample. Some incomplete patient records will have led to some individuals being excluded from this study, which may have introduced some selection bias.

Conventional methods of measuring asthma control include diary cards, daily SABA use, and the Asthma Control Test,^{31,32} but none is considered the “criterion standard.” Because of the historic nature of this study and its large size, we used indirect, surrogate measures of control derived from accurate markers of health care use (both primary and secondary) for respiratory conditions, prednisolone use, prescription of antibiotics, and SABA use, but it is recognized that some of these measures are quite different from those used in prospective studies where data on symptoms such as daily cough or wheeze may be collected. We found that overall control was significantly better in the FDC group.

It is important to note that in this population where treatment was stepped up by the primary-care physician, exacerbation rates at baseline were not high: 89% of the population had no exacerbations in the baseline year; also, SABA prescriptions were

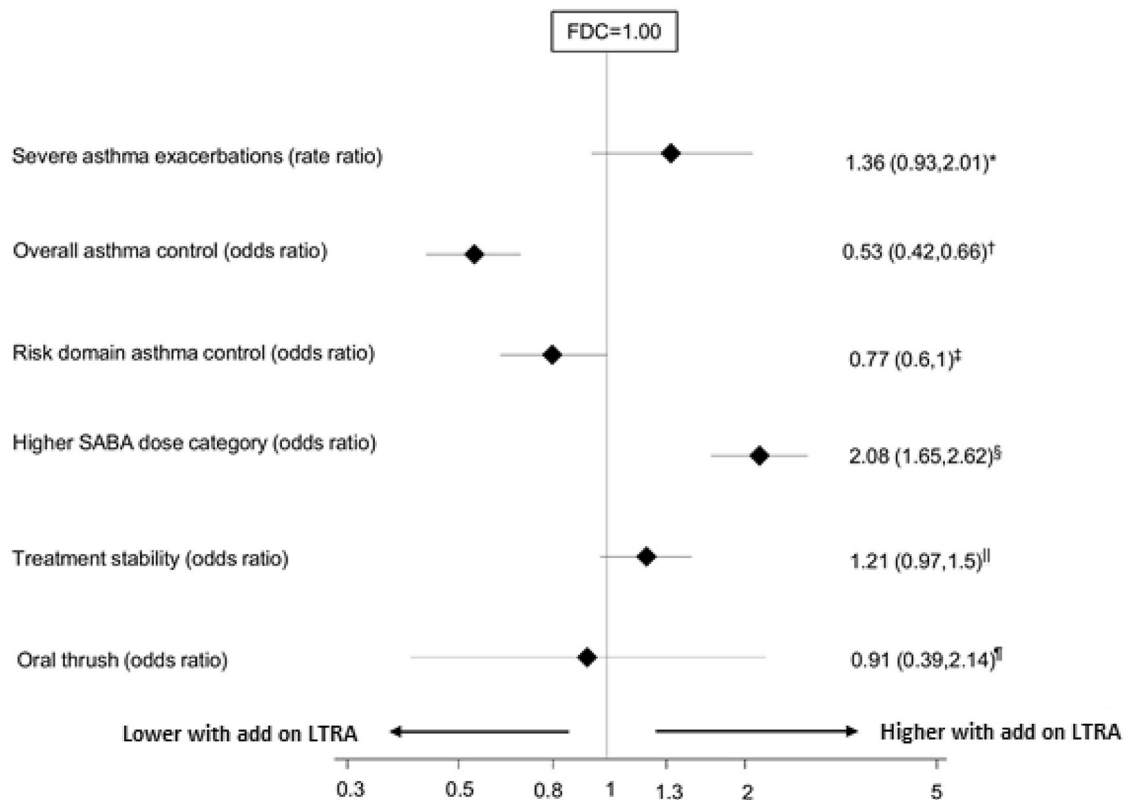


FIGURE 2. Adjusted rate ratio and OR during outcome year for FDC versus add-on LTRA cohorts for primary and secondary outcomes (analysis 2). *Adjusted for number of baseline exacerbations, antibiotics with evidence of respiratory review, and number of asthma consultations ($P = .116$). †Adjusted for rhinitis diagnosis/therapy and asthma consultations ($P < .001$). ‡Adjusted for number of baseline antibiotics with evidence of respiratory review ($P = .049$). §Adjusted for asthma-related outpatient department visits, nonasthma consultations and eczema, and categorized as 0 to 200 or more than 200 μg ($P < .001$). ||Adjusted for sex, rhinitis diagnosis/therapy, baseline antibiotics with evidence of respiratory review and data source ($P = .098$). ¶Unadjusted ($P = .828$; conditional logistic regression).

moderate, with a mean of 2.5 puffs of salbutamol or equivalent per day. It is important to note that the data we have collected are averaged over the previous year and it may have been that, for example, salbutamol use may have been excessive for a short period prompting the stepping up in treatment. Current UK guidelines suggest that control may be inadequate if SABA use is more than 3 times per week. This retrospective study cannot establish why it was felt necessary to step up treatment, but we assume that control was felt to be inadequate. However, because exacerbation rates were relatively low at baseline, this may have influenced our ability to show significant differences in the follow-up year.

It is increasingly recognized that asthma is not a single disease entity and different asthma phenotypes or different underlying gene defects will respond to these treatment options in different ways. Lemanske et al⁵ tried to examine whether patients who responded better to one or another treatment had any underlying characteristics, and showed that, for example, those of white race responded better to LABA step-up treatment, and those of black race were least likely to respond to LTRA. Children without a history of eczema may respond better to LABA step-up treatment, and race appears to differentiate responders to ICS from responders to LTRA.³³ The historic nature of this study prevented further investigation of responders and nonresponders.

CONCLUSIONS

To date, there is a lack of clarity in available evidence in asthma guidelines, concerning which step-up treatment should be used in children if asthma control is inadequate on low-dose ICS. The findings of our real-life study suggest that the 3 main step-up treatments have beneficial effects in children who are stepped up from low/moderate-dose ICS, and that the differential effect of any of these treatments is small. All treatments appear to produce long-term benefit in reducing exacerbation rates in children with uncontrolled asthma. Changing to FDC may result in better overall asthma control over LTRA or increased ICS, but this finding needs to be replicated in further studies using real-life data sets.

Acknowledgments

We thank the Respiratory Effectiveness Group for funding this work, Annie Burden for assistance with statistics, and Simon Van Rysewyk and Lisa Law for assistance with medical writing.

REFERENCES

1. Asthma UK. Asthma facts and FAQs 2015. Available from: <http://www.asthma.org.uk/asthma-facts-and-statistics>. Accessed May 16, 2016.
2. Turner S, Thomas M, von Ziegenweid J, Price D. Prescribing trends in asthma: a longitudinal observational study. *Arch Dis Child* 2009;94:16-22.
3. British Thoracic Society. British guideline on the management of asthma: a national clinical guideline (SIGN 141), updated 2014. Available from: <https://>

- www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/. Accessed May 16, 2016.
4. Global Initiative for Asthma (GINA). Pocket guide for asthma management and prevention, updated 2015. Available from: http://www.ginasthma.org/local/uploads/files/GINA_Pocket_2015.pdf. Accessed May 16, 2016.
 5. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez F, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975-85.
 6. de Blic J, Ogorodova L, Klink R, Sidorenko I, Valiulis A, Hofman J, et al. Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children. *Pediatr Allergy Immunol* 2009;20:763-71.
 7. Gappa M, Zachgo W, von Berg A, Kamin W, Stern-Strater C, Steinkamp G, et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAE). *Pediatr Pulmonol* 2009;44:1132-42.
 8. Murray CS, Custovic A, Lowe LA, Aldington S, Williams M, Beasley R, et al. Effect of addition of salmeterol versus doubling the dose of fluticasone propionate on specific airway resistance in children with asthma. *Allergy Asthma Proc* 2010;31:415-21.
 9. Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, Brackel HJ, Gerrits GP, Hop WC, et al. Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma. *Am J Respir Crit Care Med* 2010;182:1221-7.
 10. Verberne AAPH, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF, the Dutch Paediatric asthma group. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;156:688-95.
 11. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database Syst Rev* 2014;(1):CD003137.
 12. Stempel DA, Szeffler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. *N Engl J Med* 2016;375:840-9.
 13. Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med* 2016;374:1822-30.
 14. Lenney W, McKay AJ, Tudur Smith C, Williamson PR, James M, Price D, the MASCOT Study Group. Management of Asthma in School Age Children On Therapy (MASCOT): a randomised, double-blind, placebo-controlled, parallel study of efficacy and safety. *Health Technol Assess* 2013;17:1-218.
 15. Holgate S, Bisgaard H, Bjerner L, Haahtela T, Haughney J, Horne R, et al. The Brussels Declaration: the need for change in asthma management. *Eur Respir J* 2008;32:1433-42.
 16. Turner SW, Richardson K, Burden A, Thomas M, Murray C, Price D. Initial step-up treatment changes in asthmatic children already prescribed inhaled corticosteroids: a historical cohort study. *NPJ Prim Care Respir Med* 2015;25:15041.
 17. van Aalderen WM, Grigg J, Guilbert TW, Roche N, Israel E, Martin RJ, et al. Small-particle inhaled corticosteroid as first-line or step-up controller therapy in childhood asthma. *J Allergy Clin Immunol Pract* 2015;3:721-32.
 18. Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, et al. Integrating real-life studies in the global therapeutic research framework. *Lancet Respir Med* 2013;1:e29-30.
 19. National Institute for Health and Care Excellence. Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years (TA131); 2014. NICE Technology appraisal guidance 131. Available from: <http://www.nice.org.uk/guidance/TA131>. Accessed September 27, 2016.
 20. Turner S, Richardson K, Murray C, Thomas M, Hillyer EV, Burden A, et al; on behalf of the Respiratory Effectiveness Group. Long acting β -agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *J Allergy Clin Immunol Pract* 2017;5:99-106.
 21. Clinical Practice Research Datalink. Available from: <http://www.cprd.com/home/>. Accessed March 5, 2016.
 22. Boston Collaborative Drug Surveillance Program. The Clinical Practice Research Datalink. Available from: <http://www.bu.edu/bcdsp/gprd/>. Accessed March 5, 2016.
 23. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;54:413-9.
 24. Optimum Patient Care Research Database (OPCRD). Available from: http://www.optimumpatientcare.org/Html_Docs/OPCRD.html. Accessed March 5, 2016.
 25. Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, et al. Quality standards for real-world research: focus on observational database studies of comparative effectiveness. *Ann Am Thorac Soc* 2014;11:S99-104.
 26. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, 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.
 27. Whitehead J. The design and analysis of sequential clinical trials (Revised 2nd Edition). Chichester: John Wiley & Sons Ltd; 1992:48-50.
 28. Sinha IP, Gallagher R, Williamson PR, Smyth RL. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. *Trials* 2012;13:103.
 29. Chauhan BF, Chartrand C, Ni Chroinin M, Milan SJ, Ducharme FM. Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev* 2015:11.
 30. Belhassen M, De Blic J, Laforest L, Laigle V, Chanut-Vogel C, Lameze L, et al. Recurrent wheezing in infants: a population-based study. *Medicine* 2016;95:e3404.
 31. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
 32. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007;119:817-25.
 33. Malka J, Mauger DT, Covar R, Rabinovitch N, Lemanske RF Jr, Spahn JD, et al. Eczema and race as combined determinants for differential response to step-up asthma therapy. *J Allergy Clin Immunol* 2014;134:483-5.

METHODS

Post hoc sample size

Power for the primary outcome was conducted post hoc assuming a Poisson distribution and exacerbation rate of 0.18 in the matched FDC group.^{E1,E2} In matched add-on LTRA and increased ICS dose cohorts, we can detect a 37% and 34% reduction in exacerbation rates compared with the matched FDC cohort using a 2-sided test, respectively, with 80% power.

Outcomes

American Thoracic Society/European Respiratory Society severe asthma exacerbations and acute respiratory events are both defined in terms of asthma-related hospital admissions, acute course of oral corticosteroids with evidence of respiratory review, where *asthma-related hospitalizations* consist of either a definite asthma accident and emergency attendance or a definite asthma hospital admission; or a generic hospitalization Read code that has been recorded on the same day as a lower respiratory consultation; *acute oral corticosteroid* use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (eg, 6, 5, 4, 3, 2, 1 reducing, or 30 mg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation; *evidence of a respiratory review* consists of any lower respiratory consultation and any additional respiratory examinations, referrals, chest x-rays, or events; *lower respiratory consultations* consist of lower respiratory Read codes (including asthma, chronic obstructive pulmonary disease, and lower respiratory tract infection Read codes); asthma/chronic obstructive pulmonary disease review codes excluding any monitoring letter codes; lung function and/or asthma monitoring.

Where 1 or more oral corticosteroid course/antibiotic/hospitalization occur within 2 weeks of each other, these events were considered to result from the same exacerbation, and were counted once.

Average daily SABA dose during outcome year was calculated as the average number of puffs per day over the year multiplied by strength (in µg) and categorized as 0, 1 to 150, 151 to 300, and more than 300 µg.

Oral thrush was defined as topical antifungal prescriptions definitely for oral thrush, and/or coded for oral candidiasis.

Definitions

The medication possession ratio assesses adherence to prescribed therapy. In this study, the medication possession ratio for prescribed ICS therapy was defined as the number of days' supply of ICS/365 × 100%. A cutoff of 80% or more is generally strictly used in respiratory studies to represent adherent patients, versus less than 80% for nonadherent patients.^{E3,E4} This convention was adopted in this study.

Acute oral corticosteroid use associated with asthma exacerbation treatment is defined as all courses that are definitely not maintenance therapy, and/or all courses where dosing instructions suggest exacerbation treatment (eg, 6, 5, 4, 3, 2, 1 reducing, or 30 mg as directed), and/or all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, where "maintenance therapy" is defined as daily dosing instructions of less than

10 mg prednisolone or prescriptions for 1 mg prednisolone tablets.

Body mass index (BMI) is defined as the weight (in kg) divided by the square of the height (in meters), and is reported in kg/m². Age and sex-based BMI centiles were categorized, including a "missing" category where BMI was not available. All BMI centile values for individuals beyond ±5 SDs were excluded as likely outliers.

The International Obesity Task Force grade classifies BMI in children aged 2 to 18 years as thin, normal weight, overweight, or obese, depending on the child's age and sex, based on adult BMI cutoffs at 18 years. The BMI range at 18 years and corresponding grades are as follows: very thin, less than 16; moderately thin, 16 to less than 17; thin, 17 to less than 18.5; healthy, 18.5 to less than 25; overweight, 25 to less than 30; obese, 30+. Both BMI centiles and International Obesity Task Force grade were calculated using Microsoft Excel add-in *lmsGrowth*.

Potential confounding variables

A range of potential confounders have been identified in respiratory research, which may impact health outcomes.^{E5} These potential confounders include a range of demographic, disease severity, treatment, and comorbid factors. These variables were extracted, where available, for all patients.

Potential confounders examined at (or closest to) the index date were age of patient, sex of patient, smoking status of patient, BMI centile, and International Obesity Task Force grade.

Potential confounders examined regardless of when they occurred relative to the index date were date of first asthma diagnosis (where known); other respiratory or other confounding diagnoses, including rhinitis, gastroesophageal reflux disease, eczema, and cardiac disease.

Potential confounders examined in the year before the index date were number of primary-care consultations, both asthma- and non-asthma-related; number of hospital outpatient attendances where asthma is recorded as the reason for referral; number of inpatient admissions for asthma; number of emergency department attendances for asthma; number of emergency department attendances or inpatient admissions for lower respiratory reasons; number of prescriptions for antibiotics with evidence of respiratory review; acute oral corticosteroid use associated with asthma exacerbation treatment; prescriptions for other medications that might interfere with asthma control: beta-blockers, nonsteroidal anti-inflammatory drugs, and paracetamol; number of prescriptions for asthma and/or allergies; SABA daily dose; average ICS daily dose; ICS dose at index date. In addition, year of index date, previous step-up treatment recorded in the database, and time between first asthma prescription and the index date (0-1 years, >1 year) database were examined.

Baseline analysis

Summary statistics are provided for baseline and outcome variables by treatment groups. For variables measured on the interval or ratio scale, these include sample size (n), median, and interquartile range (25th and 75th percentiles).

For categorical variables, the summary statistics include sample size (n), range (if applicable), and count and percentage by category (distribution). Summary statistics highlight differences in baseline variable distributions between treatment groups. These differences are quantified using conditional logistic regression models. The

results of the baseline comparisons are presented as P values. As a conservative approach, differences between treatment groups were considered possibly important if P was less than .10. Variables meeting this criterion were examined for collinearity and clinical importance to select those used as potential confounders in the regression modeling of outcomes.

Predictors of outcomes

Multivariate analyses were carried out using the full data set to identify baseline variables that are predictive ($P < .05$) of each outcome variable during the outcome period. These were considered as potential confounders when modeling the outcome variables.

Correlations

Spearman correlation coefficients were calculated between all potential confounders to determine strengths of linear relationships between variables. The correlation coefficients were considered, in conjunction with clinical interpretation, to identify pairings of variables that might present collinearity issues at the modeling stage. In general, collinearity was considered an issue for relationships with rank correlation coefficients greater than 0.30.

Effectiveness analysis

A comparison of treatment cohorts using the matched data sets was conducted, making necessary minimal adjustments for other baseline confounders. Outcome results are provided unadjusted and adjusted for baseline residual confounders for each primary and secondary outcome.

Primary outcome analysis

The total number of *asthma exacerbations* (American Thoracic Society/European Respiratory Society definition) in the outcome period was separately compared between cohorts using a negative binomial regression model to obtain estimates of the exacerbation rates relative to the FDC cohort. General estimating equations were used to account for the correlation within matched pairs. The model uses empirical standard errors for more robust CIs and adjusts for potential baseline confounders.

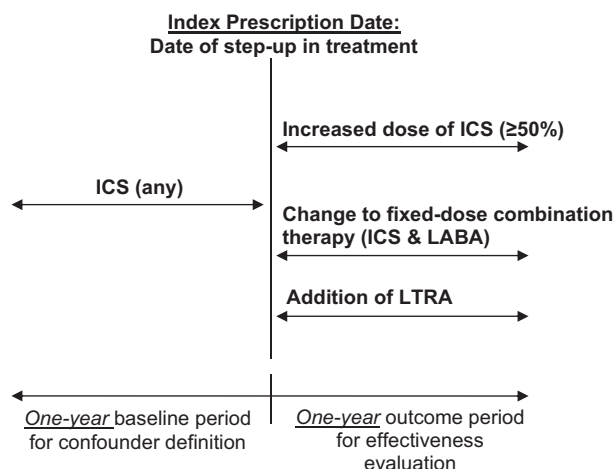


FIGURE E1. Summary of study design.

Secondary outcome analysis

The total number of *acute respiratory events* in the outcome period was separately compared between cohorts using a negative binomial regression model, and adjusted for baseline clinical exacerbations and number of non—asthma-related consultations. Secondary outcomes *risk-domain asthma control*, *overall asthma control*, and *treatment stability* were compared between treatment cohorts using conditional logistic regression models. Each secondary outcome was used as the dependent variable with treatment and potential confounding factors as independent variables.

For all multivariate models, those variables that are significantly different or show a trend toward a difference ($P < .10$) between the treatment groups at baseline were included as potential confounding factors along with any strongly predictive variables. Variables were examined for collinearity and clinical importance and then removed in a backward stepwise procedure until all confounding variables remaining in the multivariate model had a P value of less than .1.

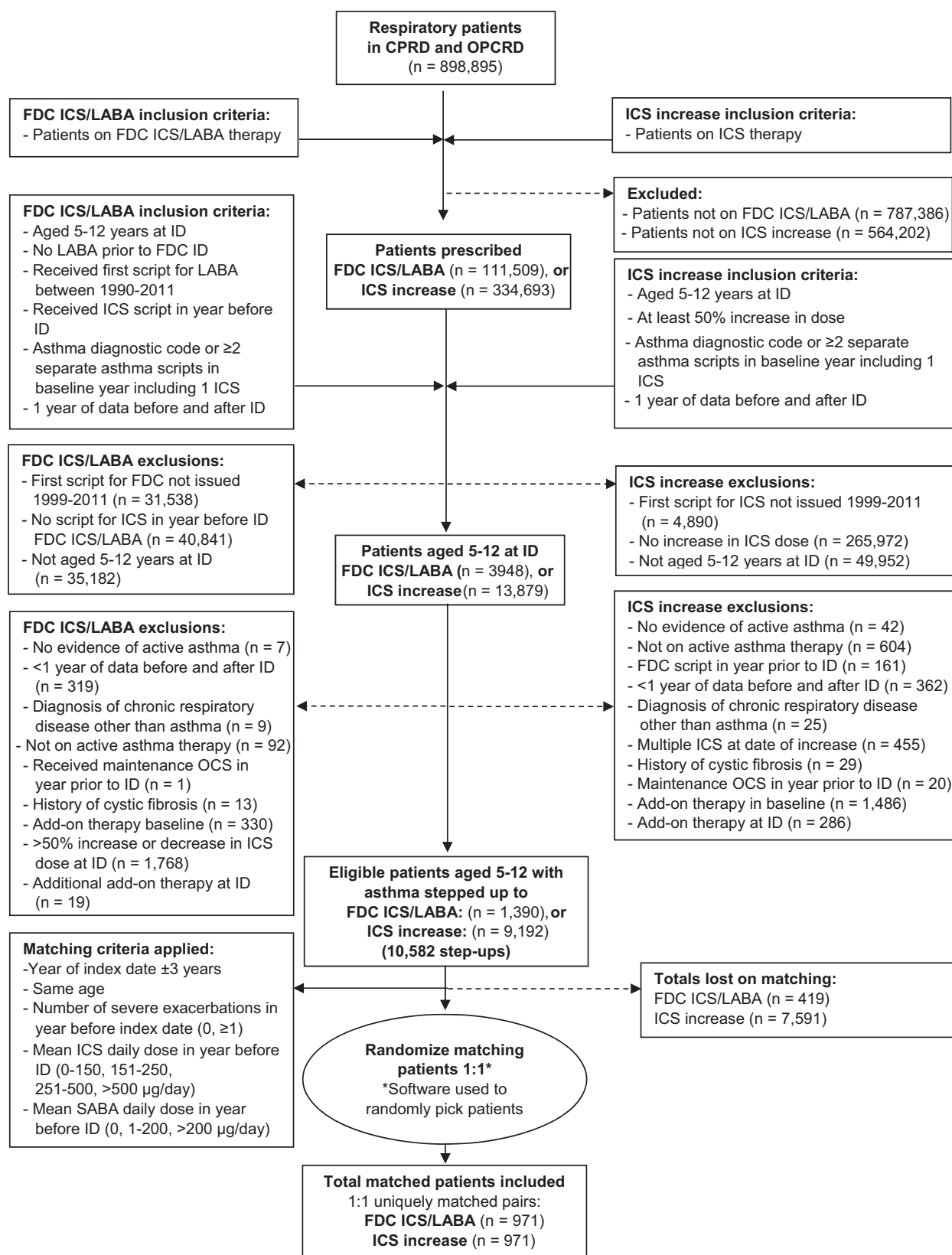


FIGURE E2. Patient selection and exact matching (1:1) for ICS dose increase versus FDC ICS/LABA step-up cohorts. Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. CPRD, Clinical Practice Research Datalink; DPI, dry powder inhaler; ID, index date; MDI, metered-dose inhaler; OCS, oral corticosteroid; OPCR, Optimum Patient Care Research Database; Script, prescription.

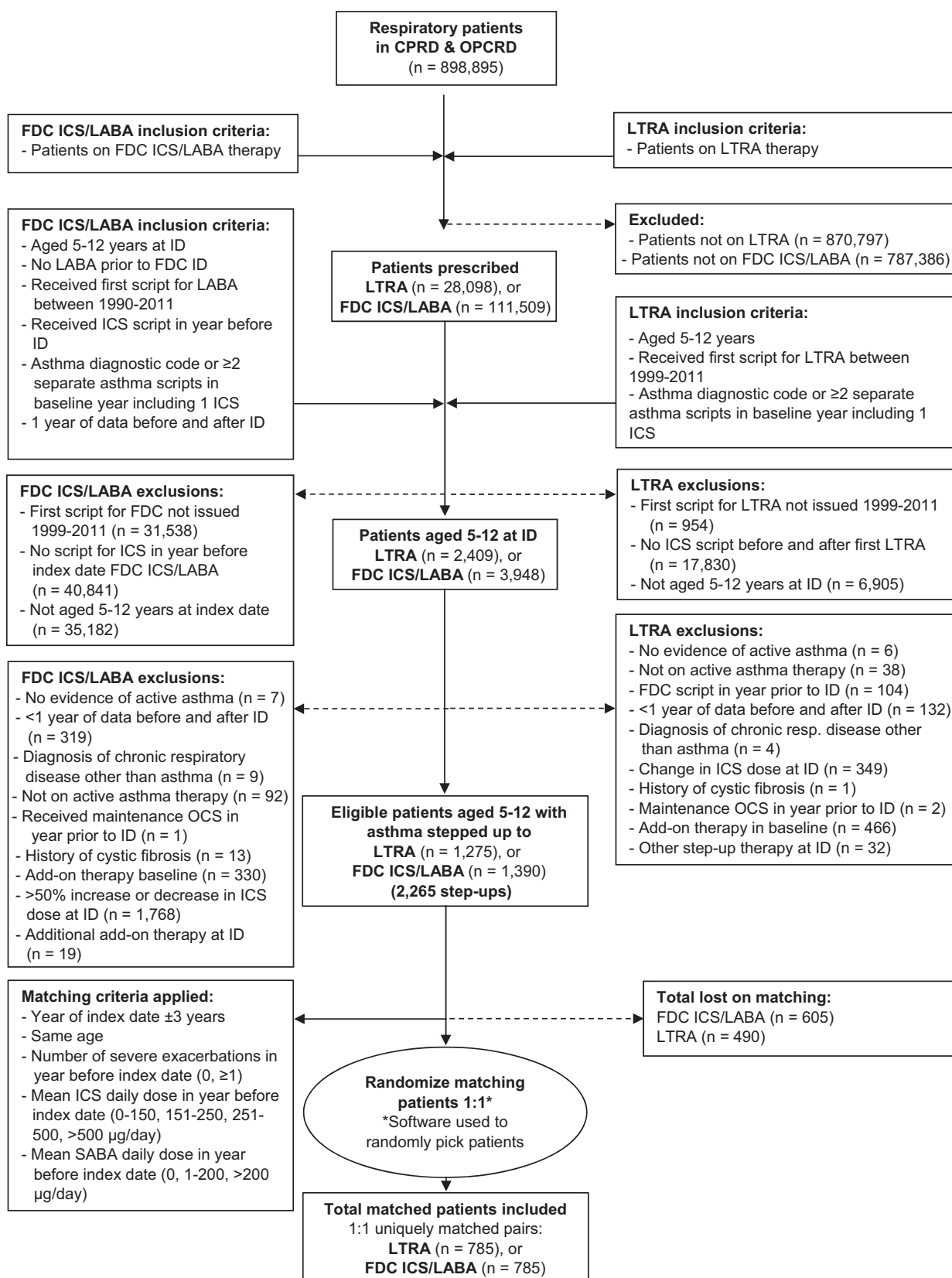


FIGURE E3. Patient selection and exact matching (1:1) for add-on LTRA versus FDC ICS/LABA cohorts. Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. *CPRD*, Clinical Practice Research Datalink; *ID*, index date; *OCS*, oral corticosteroid; *OPCRD*, Optimum Patient Care Research Database; *resp.*, respiratory; *Script*, prescription.

TABLE E1. Unmatched and exact matched (1:1) baseline characteristics of children prescribed FDC inhalers vs increased dose ICSs

Baseline characteristic	Unmatched cohorts (n = 10,972)			Matched cohorts (n = 1,942)		
	FDC (n = 1,390)	Increased ICS dose (n = 9,192)	P value*	FDC (n = 971)	Increased ICS dose (n = 971)	P value†
Age (y), median (IQR)‡	10 (8-11)	9 (7-11)	<.001§	10 (8-11)	10 (8-11)	NA
Sex, n (% male)	811 (58)	6,206 (60)	.36	573 (59)	579 (60)	.78
Year of index date, median (IQR)	2006 (2004-2008)	2001 (1997-2006)	<.001§	2005 (2003-2007)	2004 (2002-2007)	<.001
Recorded comorbidity, n (%)						
Rhinitis diagnosis/therapy	691 (50)	5,723 (55)	<.001	481 (50)	531 (55)	.02
Eczema therapy	702 (51)	4,966 (48)	.05	483 (50)	464 (48)	.38
GERD diagnosis/therapy	36 (3)	238 (2)	.48	20 (2)	23 (2)	.65
Other medication use, n (%)¶						
NSAIDs	82 (6)	369 (4)	<.001	57 (6)	45 (5)	.22
Paracetamol	209 (15)	1,529 (15)	.73	144 (15)	142 (15)	.90
Severe asthma exacerbations, ATS/ERS definition, n (%)‡#						
0	1,181 (85)	9,317 (90)	<.001	863 (89)	863 (89)	.36
1	161 (12)	866 (8)		85 (9)	79 (8)	
>2	48 (3)	226 (2)		23 (2)	29 (3)	
Risk-domain asthma control, n (%)**						
Controlled	895 (64)	7,064 (68)	.009	668 (69)	655 (68)	.45
Overall asthma control, n (%)††						
Controlled	485 (35)	4,201 (40)	<.001	367 (38)	356 (37)	.73
Acute oral corticosteroids, n (%)‡‡						
>1	196 (14)	1,021 (10)	<.001	105 (11)	104 (11)	.71
Previous ICS dose (µg), n (%)‡§§						
>0-150	0 (0.0)	1,507 (15)	<.001	0 (0.0)	0 (0.0)	NA
151-250	257 (19)	7,211 (69)		255 (26)	255 (26)	
251-500	1,046 (75)	1,596 (15)		695 (72)	695 (72)	
>501	87 (6)	95 (1)		21 (2)	21 (2)	
Medication possession ratio, n (%)						
≥80%	307 (22)	2,885 (28)	<.001	225 (23)	219 (23)	.72
SABA daily dose, n (%) (µg)‡						
0	28 (2)	705 (7)	<.001	19 (2)	19 (2)	NA
>0-200	685 (49)	5,390 (52)		495 (51)	495 (51)	
>201	677 (49)	4,314 (41)		457 (47)	457 (47)	
Antibiotics with respiratory consult, n (%)	390 (28)	2,838 (27)	.53	249 (26)	269 (28)	.28
Oral thrush, n (%)¶¶	10 (1)	73 (1)	.94	6 (1)	8 (1)	.59

ATS/ERS, American Thoracic Society/European Respiratory Society; GERD, gastroesophageal reflux disease; IQR, interquartile range; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; SABA, short-acting beta-agonist.

*Chi-square.

†Conditional logistic regression.

‡Matching variables.

§Mann-Whitney.

||Read code at any time and/or prescription during baseline or outcome analysis period.

¶Prescriptions received during the 1 y before index date or at index date.

#An ATS/ERS severe asthma exacerbation is defined as an occurrence of the following: asthma-related hospital admissions or accident and emergency attendance; or an acute course of oral corticosteroids with evidence of respiratory review.

**Risk-domain asthma control defined as absence of the following: asthma-related hospital admissions or accident and emergency attendance; or outpatient department attendance; and an acute course of oral corticosteroids with evidence of respiratory review, and antibiotics prescribed with evidence of respiratory review.

††Overall asthma control is defined as risk-domain asthma control plus average daily dose of ≤200 µg salbutamol/≤500 µg terbutaline.

‡‡Acute oral corticosteroid use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (eg, 6, 5, 4, 3, 2, 1 reducing, or 30 mg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation.

§§Beclometasone dipropionate equivalent doses.

|||Medication possession ratio is defined as the number of days supply of ICS/365 × 100.

¶¶Diagnosis for candidiasis and/or antifungals definitely for oral thrush.

TABLE E2. Unmatched and exact matched (1:1) baseline characteristics of children prescribed FDC inhalers vs add-on LTRAs

Baseline characteristic	Unmatched cohorts (n = 2665)			Matched cohorts (n = 1570)		
	FDC (n = 1,390)	Add-on LTRA (n = 1,275)	P value*	FDC (n = 785)	Add-on LTRA (n = 785)	P value†
Age (y), median (IQR)‡	10 (8-11)	8 (6-10)	<.001§	9 (7-11)	9 (7-11)	NA
Sex, n (% male)	811 (58)	768 (60)	.32	453 (58)	482 (61)	.12
Year of index date, median (IQR)	2006 (2004-2008)	2007 (2004-2008)	<.001§	2006 (2004-2008)	2006 (2004-2008)	.20
Recorded comorbidity, n (%)						
Rhinitis diagnosis/therapy	691 (50)	727 (57)	<.001	401 (51)	452 (58)	.00
Eczema therapy	702 (51)	662 (52)	.46	420 (54)	401 (51)	.34
GERD diagnosis/therapy	36 (3)	41 (3)	.34	15 (2)	25 (3)	.12
Other medication use, n (%)¶						
NSAIDs	82 (6)	79 (6)	.75	47 (6)	52 (7)	.61
Paracetamol	209 (15)	190 (15)	.92	127 (16)	118 (15)	.53
Severe asthma exacerbations, ATS/ERS definition, n (%)‡#						
0	1,181 (85)	1,105 (87)	.39	682 (87)	682 (87)	.59
1	161 (12)	135 (12)		81 (10)	84 (11)	
>2	48 (3)	35 (3)		22 (3)	19 (2)	
Risk-domain asthma control, n (%)**						
Controlled	895 (64)	751 (59)	.004	505 (64)	486 (62)	.25
Overall asthma control, n (%)††						
Controlled	485 (35)	442 (35)	.90	277 (35)	270 (34)	.54
Acute oral corticosteroids, n (%)‡‡						
>1	196 (14)	160 (13)	.24	95 (12)	98 (13)	.41
Previous ICS dose (µg), n (%)‡§§						
>0-150	0 (0.0)	41 (3)	<.001	0 (0.0)	0 (0.0)	NA
151-250	257 (19)	619 (49)		248 (32)	248 (32)	
251-500	1,046 (75)	535 (42)		490 (62)	490 (62)	
>501	87 (6)	80 (6)		47 (6)	47 (6)	
Medication possession ratio, n (%)						
≥80%	307 (22)	303 (24)	.30	186 (24)	165 (21)	.17
SABA daily dose, n (%) (µg)‡						
0	28 (2)	48 (4)	.02	9 (1)	9 (1)	NA
>0-200	685 (49)	640 (50)		391 (50)	391 (50)	
>201	677 (49)	587 (46)		385 (49)	385 (49)	
Antibiotics with respiratory consult, n (%)	390 (28)	467 (37)	<.001	226 (29)	266 (34)	.02
Oral thrush, n (%)¶¶	10 (1)	10 (1)	.85	5 (1)	6 (1)	.74

ATS/ERS, American Thoracic Society/European Respiratory Society; GERD, gastroesophageal reflux disease; IQR, interquartile range; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; SABA, short-acting beta-agonist.

*Chi-square.

†Conditional logistic regression.

‡Matching variables.

§Mann-Whitney.

||Read code at any time and/or prescription during baseline or outcome analysis period.

¶Prescriptions received during the 1 y before index date or at index date.

#An ATS/ERS severe asthma exacerbation is defined as an occurrence of the following: asthma-related hospital admissions or accident and emergency attendance; or an acute course of oral corticosteroids with evidence of respiratory review.

**Risk-domain asthma control defined as absence of the following: asthma-related hospital admissions or accident and emergency attendance; or outpatient department attendance; and an acute course of oral corticosteroids with evidence of respiratory review, and antibiotics prescribed with evidence of respiratory review.

††Overall asthma control is defined as risk-domain asthma control plus average daily dose of ≤200 µg salbutamol/≤500 µg terbutaline.

‡‡Acute oral corticosteroid use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (eg, 6, 5, 4, 3, 2, 1 reducing, or 30 mg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation.

§§Beclometasone dipropionate equivalent doses.

|||Medication possession ratio is defined as the number of days supply of ICS/365 × 100.

¶¶Diagnosis for candidiasis and/or antifungals definitely for oral thrush.

TABLE E3. Outcome-year results for matched (1:1) cohorts prescribed FDC inhalers vs increased dose ICSs, and FDC inhalers vs add-on LTRAs

Outcome	FDC vs ICS dose increase			FDC vs LTRA		
	FDC (n = 971)	ICS dose increase (n = 971)	P value*	FDC (n = 785)	Add-on LTRA (n = 785)	P value*
≥1 asthma-related ED attendance, n (%)	1 (0.1)	2 (0.2)	.57	1 (0.1)	3 (0.4)	NA
≥1 asthma-related OPD visit, n (%)	4 (0.4)	4 (0.4)	1.00	3 (0.4)	10 (1)	.06
1 acute course of oral corticosteroids, n (%)	41 (4)	50 (5)	.68	36 (5)	53 (7)	.12
≥2 courses of oral corticosteroids, n (%)	11 (1)	9 (1)		9 (1)	10 (1)	
SABA inhalers, mean ± SD	4 ± 4	6 ± 5	<.001	4 ± 4	6 ± 5	<.001
Hours/day β-agonist coverage, median (IQR)	11 (7-16)	2 (1-4)	<.001	10 (7-16)	2 (1-4)	<.001
Daily ICS dose, median (IQR)	197 (132-307)	384 (219-581)	<.001	197 (132-329)	219 (110-329)	.92
% Adherence to ICS, median (IQR)†	71 (48-100)	65 (42-95)	.01	74 (49-100)	82 (55-109)	.001
Medication possession ratio ≥80% for ICS, n (%)‡	319 (33)	298 (31)	.29	279 (36)	280 (36)	.95
Controller-to-total medication ratio ≥0.5, n (%)	793 (82)	679 (70)	<.001	645 (82)	670 (85)	.08
Change in therapy (any time), n (%)						
Increase in ICS dose (any time), n (%)	239 (25)	411 (42)	<.001	197 (25)	85 (11)	<.001
Additional therapy (any time), n (%)	98 (10)	156 (16)	<.001	81 (10)	116 (15)	<.001
Spacer prescription, n (%)	167 (17)	209 (22)	.01	138 (18)	184 (23)	.004

ED, Emergency department; IQR, interquartile range; NA, not applicable; OPD, outpatient department; SABA, short-acting beta-agonist.

*Conditional logistic regression.

†Defined as number of days per pack = number of actuations per pack/number of actuations per day; total pack days = Σ (number of days per pack); refill rate % = (total pack days/365) × 100.

‡(Number of days supply of ICS/365) × 100.

REFERENCES

- E1. Whitehead J. The design and analysis of sequential clinical trials (Revised 2nd Edition). Chichester: John Wiley & Sons Ltd; 1992:48-50.
- E2. van Aalderen WM, Grigg J, Guilbert TW, Roche N, Israel E, Martin RJ, et al. Small-particle inhaled corticosteroid as first-line or step-up controller therapy in childhood asthma. *J Allergy Clin Immunol Pract* 2015;3:721-32.
- E3. Erickson SR, Coombs JH, Kirking DM, Azimi AR. Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. *Ann Pharmacother* 2001;35:997-1003.
- E4. van Steenis MN, Driesenaar JA, Bensing JM, van Hulten R, Souverein PC, van Dijk L, et al. Relationship between medication beliefs, self-reported and refill adherence, and symptoms in patients with asthma using inhaled corticosteroids. *Patient Pref Adher* 2014;8: 83-91.
- E5. Price D, Hillyer EV, van der Molen T. Efficacy versus effectiveness trials: informing guidelines for asthma management. *Curr Opin Allergy Clin Immunol* 2013;13:50-7.