

Long-Acting β -Agonist in Combination or Separate Inhaler as Step-Up Therapy for Children with Uncontrolled Asthma Receiving Inhaled Corticosteroids



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What is already known about this topic? Current asthma guidelines recommend that children prescribed a long-acting β_2 -agonist (LABA) should receive treatment as a fixed-dose combination (FDC) inhaler, rather than as an additional, separate inhaler alongside inhaled corticosteroids (ICS). The current literature, however, does not provide evidence to support this.

What does this article add to our knowledge? In a matched cohort study, LABA treatment as a separate inhaler was associated with poorer asthma control compared with an FDC inhaler.

How does this study impact current management guidelines? These findings support recommendations from British Thoracic Society, National Institute for Health and Care Excellence asthma guideline, and US Food and Drug Administration, to prescribe an add-on LABA as an FDC inhaler with ICS in children.

BACKGROUND: Adding a long-acting β_2 -agonist (LABA) to inhaled corticosteroids (ICS) using a fixed-dose combination (FDC) inhaler is the UK guideline recommendation for children aged more than 4 years with uncontrolled asthma. The evidence of benefit of adding an FDC inhaler over a separate LABA inhaler is limited.

OBJECTIVE: The objective of this study was to compare the effectiveness of a LABA added as an FDC inhaler, and as a separate inhaler, in children with uncontrolled asthma.

METHODS: Two UK primary care databases were used to create a matched cohort study with a 2-year follow-up period. We included children prescribed their first step-up from ICS monotherapy. Two cohorts were formed for children receiving an add-on LABA as an FDC inhaler, or a separate LABA inhaler. Matching variables and confounders were identified by comparing characteristics during a baseline year of follow-up. Outcomes were examined during the subsequent year. The primary outcome was an adjusted odds ratio for overall asthma

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*Abbreviations used**aOR*-Adjusted odds ratio*aRR*-Adjusted rate ratio*BDP*-Beclomethasone dipropionate*BTS/SIGN*-The British Thoracic Society and Scottish Intercollegiate Guidelines Network*CI*-Confidence interval*CPRD*-Clinical Practice Research Datalink*FDA*-Food and Drug Administration*FDC*-Fixed-dose combination*ICS*-Inhaled corticosteroids*LABA*-Long-acting β -agonist*LTRA*-Leukotriene receptor antagonist*MPR*-Medication possession ratio*OCS*-Oral corticosteroids*OPCRD*-Optimum Patient Care Research Database*NICE*-National Institute for Health and Care Excellence*SABA*-Short-acting β -agonist*SMART*-Single maintenance and reliever therapy

control (defined as follows: no asthma-related hospital admission or emergency room visit, prescription for oral corticosteroids or antibiotic with evidence of respiratory consultation, and ≤ 2 puffs of short-acting β -agonist daily).

RESULTS: The final study consisted of 1330 children in each cohort (mean age 9 years; 59% male). In the separate ICS + LABA cohort, the odds of achieving overall asthma control were lower (adjusted odds ratio, 0.77 [95% confidence interval, 0.66-0.91]; $P = .001$) compared with the FDC cohort.

CONCLUSION: The study demonstrates a small but significant benefit in achieving asthma control from an add-on LABA as an FDC, compared with a separate inhaler and this supports current guideline recommendations. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:99-106)

Key words: Asthma; Child; Inhaled corticosteroid; Long-acting β -agonist; Step-up therapy

Asthma is common amongst children in the UK, with an estimated 7%, or 1.1 million, children prescribed current asthma therapy.^{1,2} The British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) guideline for the management of asthma recommends a stepwise approach to therapy, to maintain symptom control and minimize future risk of exacerbations.³ Inhaled corticosteroids (ICS), prescribed at step 2 of the current BTS/SIGN guideline, are effective controller medications for most children with persistent asthma. For 10%-25% of children with asthma, additional therapy is required.⁴⁻⁶ For children aged 5-12 years on ICS monotherapy, adding a long-acting β_2 -agonist (LABA) is the preferred step-up option (step 3) recommended by the BTS/SIGN when asthma is uncontrolled.³

Guidance from the UK National Institute for Health and Care Excellence (NICE) identifies a fixed-dose combination (FDC) inhaler containing ICS and LABA as the optimal means of adding a LABA.¹ However, some children continue to be prescribed separate inhalers. One risk of prescribing a LABA as a separate inhaler is its use without concomitant ICS therapy. This is a major concern discussed in the National Review of Asthma Deaths.⁷

The benefit of FDC over the addition of a separate LABA inhaler to ICS treatment for children with uncontrolled asthma is unclear. Two clinical trials, where adherence was closely monitored, found no difference in symptoms after 3 months⁸ and 6 months,⁹ when comparing groups randomized with a LABA as a separate inhaler or FDC. However, patient behavior and clinical outcomes are often different in the context of a clinical trial as opposed to “real-life” usual clinical care. One database study using real-life data observed a reduced need for short-acting β_2 -agonist (SABA) and oral corticosteroid (OCS) treatment in children treated with a LABA as an FDC compared with a separate inhaler.⁴ These results are limited, however, as there was no matching at baseline for factors known to be different between groups, including age and obesity.¹⁰ We have recently reported that children stepped up to a LABA as a separate inhaler are younger and on a lower dose of ICS compared with those stepped up to FDC.¹⁰ These baseline differences might explain the apparent superiority of FDC over a LABA as a separate inhaler.

Rigorously conducted observational research can provide information about outcomes of asthma therapy under conditions of usual clinical practice, to complement information from controlled trials.¹¹ Results of prior retrospective observational studies suggest that adherence and refill persistence may be better with a combination inhaler, at least among adults and adolescents.¹²⁻¹⁴ In turn, better adherence and persistence could lead to better outcomes. The aim of this large population-based observational study was to compare outcomes between children stepped up to an add-on LABA as separate inhalers, versus those receiving FDC inhalers. Our hypothesis was that children stepped up to separate inhalers would have reduced odds for achieving asthma control compared with matched children stepped up to FDC.

METHODS

Data source and permissions

In a matched cohort study, we sourced medical records and prescribing data from 2 large primary care databases including approximately 15% of children in the UK, as previously described.¹⁰ Duplicate records from individual children were identified and removed. The Clinical Practice Research Datalink (CPRD; formerly General Practice Research Database) is well validated and used frequently for observational research. It is the world's largest repository of anonymized longitudinal data from primary care, drawing from more than 600 subscribing practices throughout the UK.^{15,16} The Optimum Patient Care Research Database (OPCRD) is a quality-controlled primary care research database, containing information from more than 400 UK practices caring for approximately half a million patients with asthma.¹⁷ As well as anonymous medical records, the database contains patient-completed questionnaire data. Data were available from January 1990 through April 2012 for the CPRD and through December 2012 for the OPCRD.

The study was conducted to standards recommended for observational research¹⁸ and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.¹⁹ (study reference ENCEPP/SDPP/10483) Use of the data was approved in 2010 by the Independent Scientific Advisory Committee of the (then) General Practice Research Database. The OPCRD has been approved by the Trent Multi Centre Research Ethics Committee for clinical research use. The protocol for this study was approved by the Anonymized Data Ethics Protocols and Transparency committee—the independent scientific advisory committee for the OPCRD.

TABLE I. Definitions of database-derived primary and secondary study outcomes

Study endpoints
Primary endpoint
Overall asthma control. All of the following: no asthma-related hospital admission; no emergency room or outpatient attendance for asthma; no prescription for oral corticosteroid or antibiotic with evidence of respiratory consultation; average daily prescribed dose of ≤ 200 $\mu\text{g/day}$ salbutamol or ≤ 500 $\mu\text{g/day}$ terbutaline (equivalent to ≤ 2 puffs daily of reliever medication).
Secondary endpoints (determined over 12 mo)
Acute respiratory events
Acute course of oral corticosteroids (with associated evidence of a respiratory consultation) or asthma-related hospitalization or emergency room attendance or antibiotic prescription with evidence of a respiratory consultation.
Severe exacerbations
Acute course of oral corticosteroids (with associated evidence of a respiratory consultation) or asthma-related hospitalization or emergency room attendance.
Risk-domain asthma control
No asthma-related hospital admission, emergency room attendance, or unscheduled outpatient department attendance, <i>and</i> no prescription for acute course of oral corticosteroids with evidence of a respiratory consultation, <i>and</i> no antibiotic prescription with evidence of a respiratory consultation.
Treatment stability
Risk-domain asthma control achieved (see above) and no additional therapy during the outcome year.

Definitions of oral corticosteroid use and respiratory consultation are provided in the [Supplementary Methods](#) in this article's Online Repository at www.jaci-inpractice.org.

Further background information is available in the [Supplementary Methods](#) section in this article's Online Repository at www.jaci-inpractice.org.

Inclusion and exclusion criteria

Our study included a 2-year period of follow-up, consisting of a baseline year and an outcome year, on either side of an index date. The index date was the point at which step-up LABA therapy was initiated. General patient information and events during the baseline year were used to determine which individuals entered the study sample. Inclusion criteria were as follows: either a Read code diagnosis of asthma or 2 or more inhaler prescriptions (at least one of which was for ICS in the previous 12 months)—the latter comprise 2% of the study population¹⁰; prescription of step-up with LABA, from ICS monotherapy at 5-12 years of age; registered in the database for at least 2 sequential years, including 1 baseline year before the date of therapy step-up (index date). Exclusion criteria were as follows: cystic fibrosis or any chronic respiratory disease other than asthma; receipt of add-on therapy (including combination inhaler) at any time before the index date; treatment with OCS for more than 7 consecutive days during the baseline year; multiple step-up therapies on the index date; a $\geq 50\%$ increase or decrease in ICS dose on the index date (the latter ensured that we studied outcomes of the addition of LABA independent of change in ICS).

Study outcomes

The primary endpoint, previously described,²⁰⁻²² was an adjusted odds ratio (aOR) for overall asthma control. This compared 2 study cohorts: those who received step-up LABA as an FDC inhaler (FDC ICS/LABA cohort) and those who received a separate LABA inhaler (separate ICS+LABA cohort). The definition of asthma control includes both components of the American Thoracic Society/European Respiratory Society²³ definition, that is, the level of clinical asthma control (as evidenced here by SABA use) and the risk of future adverse events (as evidenced here by a history of adverse events including hospitalization, emergency visits, and receipt of OCS). The criteria for overall asthma control, as defined in [Table I](#), include no asthma-related hospital admission; no emergency room or outpatient attendance for asthma; no prescription for OCS or antibiotic with evidence of respiratory consultation; average daily

prescribed dose of ≤ 200 $\mu\text{g/day}$ salbutamol or ≤ 500 $\mu\text{g/day}$ terbutaline (equivalent to ≤ 2 puffs daily of reliever medication). Hospital admission, emergency room attendance, and unscheduled outpatient attendance were coded from discharge diagnosis. A prescription for antibiotics in conjunction with a respiratory consultation was included in the definition of an acute respiratory event (and the absence of the same in the definitions of asthma control) because in clinical practice antibiotics may be prescribed for an asthma exacerbation.²⁴⁻²⁶ Secondary outcomes were acute respiratory events, severe exacerbations,²³ risk-domain measure of asthma control (to give insight into risk for future exacerbation),²⁰⁻²² and treatment stability (see [Table I](#) for definitions). Medication use during the 12 months after the index date was also compared between cohorts.

Calculations of medication use

We calculated the average daily doses of SABA and of ICS during the baseline and outcome years in the following way:

$$\frac{\text{number of inhalers} \times \text{doses per inhaler}}{365} \times \text{strength of dose } (\mu\text{g})$$

For ICS doses, we used the beclomethasone dipropionate (BDP)-equivalent doses for the calculations, thus, a 1:1 ratio for budesonide:BDP; a 2:1 ratio for fluticasone propionate:BDP; and a 2:1 ratio for extrafine beclomethasone (Qvar):BDP. The ICS medication possession ratio (MPR) was calculated as

$$\frac{\text{number of days coverage of prescribed drug}}{365} \times 100$$

Individuals were categorized as either nonadherent (MPR < 80%) or adherent (MPR $\geq 80\%$).^{27,28} The separate LABA inhalers that were available during the study period contained salmeterol or formoterol. The FDC ICS/LABA inhalers contained fluticasone-salmeterol (Seretide), budesonide-formoterol (Symbicort), and extrafine beclomethasone-formoterol (Fostair).

Statistical analyses and sample size

Children in the 2 treatment cohorts were matched sequentially 1:1 on the following criteria, which were known to differ at baseline⁴: year of index date (± 3 years), age (exact year), number of severe exacerbations (0 or ≥ 1) during baseline year, prior ICS daily

dose (≤ 150 , 151-250, 251-500, or > 500 $\mu\text{g/day}$), and mean daily SABA dose (0, 1-200, > 200 $\mu\text{g/day}$) during baseline year. Bespoke software was used to randomly select unique matched patient pairs when more than 1 match was possible.

Data were prepared for analysis by investigating potential outliers, transforming skewed data (eg, log transformation), and categorizing heavily skewed data. Missing data were investigated for type and reason for missingness. Summary statistics were computed, by cohort, for baseline characteristics and outcome events. They were compared using conditional logistic regression (unadjusted).

Conditional logistic regression models were used to estimate aOR and 95% confidence intervals (CIs) for the dichotomous outcomes, such as the primary endpoint—overall asthma control. The reference cohort was the FDC ICS/LABA cohort.

The rates of adverse respiratory events and severe exacerbations during the outcome year were compared using a negative binomial regression model. Adjusted rate ratios (aRR) were computed with 95% CIs, with the FDC ICS/LABA cohort as the reference cohort. General estimating equations were used to account for the correlation within matched pairs.²⁹ The model used empirical standard errors for more robust CIs.

For all multivariable models, those variables that were significantly different or showed a trend toward a difference ($P < .10$) between the treatment cohorts at baseline were included as potential confounding factors, along with any strongly predictive variables. Potential confounders examined are listed in Table E1 (available in 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 until all confounding variables remaining in the multivariable model had $P < .1$ (Supplementary Methods, available in this article's Online Repository at www.jaci-inpractice.org).

All analyses were done on an intention-to-treat basis, that is, children remained in their original cohort even if their treatment method changed during the outcome year. Statistical significance was set at the 5% level, that is, $P < .05$. No prospective power calculation was carried out because our sample size was determined by the number of eligible children in the CPRD and OPCR. D.

The analyses were carried out using IBM SPSS Statistics version 21 (SPSS Statistics, IBM, Somers, NY), SAS version 9.3 (SAS Institute, Marlow, Buckinghamshire, UK), and Microsoft Excel 2007 (Microsoft, Bellevue, Wash).

RESULTS

Patients

Overall, 1390 and 3771 children were eligible for the FDC ICS/LABA and separate ICS+LABA cohorts, respectively (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). A total of 97% of children had a diagnosis of asthma and 70% were from the OPCR. After matching there were 1330 children in each cohort, of mean age 9 years (SD, 2), and 59% were male (Table II). The 2 cohorts were similar in characteristics apart from the separate ICS+LABA cohort having higher dose of ICS at baseline; higher annualized ICS dose; and LABA step-up occurring 1 year earlier (ie, 2005 vs 2006) compared with the FDC cohort (Table II and Table E2 [available in this article's Online Repository at www.jaci-inpractice.org]). The cohorts were well matched for indicators of baseline asthma severity and control (Table III).

Outcomes

Primary outcome. In the FDC ICS/LABA cohort, the proportion of children who achieved overall asthma control was 35% before the index date and 43% afterward. Equivalent proportions in the separate ICS+LABA cohort were 35% and 37% (Table III). The aOR for children in the separate ICS+LABA cohort achieving control relative to the FDC ICS/LABA cohort was 0.77 (95% CI, 0.66-0.91; $P = .001$; Figure 1).

Secondary outcomes. The number of acute respiratory events was greater among the separate ICS+LABA cohort compared with the FDC ICS/LABA cohort (Table III). The aRR was 1.21 (95% CI, 1.04-1.39; $P = .012$; Figure 1). The percentage of children with ≥ 1 severe exacerbations was 13% during the baseline year for both cohorts, and in the outcome year was 7% for the FDC ICS/LABA cohort and 9% for the separate ICS+LABA cohort. The aRR for severe exacerbations was 1.31 (95% CI, 0.99-1.72; $P = .056$). Relative to the FDC ICS/LABA cohort, children in the separate ICS+LABA cohort had reduced odds for achieving risk-domain asthma control (aOR 0.74; 95% CI, 0.61-0.89; $P = .003$) and achieving treatment stability (aOR 0.67; 95% CI, 0.57-0.79; $P < .001$; Figure 1). There were no significant differences between cohorts for adherence (MPR $> 80\%$) or for severe exacerbations. In the outcome year, there were 6 hospitalizations for asthma in each cohort. There were 16 children in the FDC ICS/LABA cohort and 3 in the separate ICS+LABA cohort treated for thrush ($P = .008$, Table E2 [available in this article's Online Repository at www.jaci-inpractice.org]). Compared with the baseline year, more children in the separate ICS+LABA cohort (29.9% in the baseline year and 22.5% in the follow-up year) received treatment with antibiotics during the follow-up year than in the FDC cohort (28.6% and 19.6%, respectively, $P = .041$). There was a trend that approached significance for a greater proportion of the separate ICS+LABA cohort to receive OCS compared with the FDC ICS/LABA cohort during the outcome year (8.8% vs 6.5%, $P = .084$).

Asthma prescribing during the outcome year. Asthma therapy prescribed during the outcome year, as well as changes in therapy, is summarized in Table IV. Children in the FDC ICS/LABA cohort typically received one fewer SABA inhalers in the outcome year compared with those in the separate ICS+LABA cohort (3 vs 4 inhalers; $P < .001$). Children in the FDC ICS/LABA cohort were more likely to have an increase in ICS dose compared with those in the separate ICS+LABA cohort (10% vs 4%; $P < .001$), but no more likely to have leukotriene receptor antagonist (LTRA) added. The proportion of children achieving adherence (MPR $> 80\%$) was 33% in the FDC ICS/LABA cohort and 31% in the separate ICS+LABA cohort (aOR 0.87; 95% CI, 0.72-1.06). During the outcome year, the median daily ICS dose was 219 μg for both cohorts. Further, during the outcome year 231 (18%), children in the separate ICS+LABA cohort switched to FDC, and 17 (1%) children in the FDC ICS/LABA cohort switched to a separate LABA inhaler. LTRA treatment was started in 122 in the FDC ICS/LABA cohort (9%) and 112 in the separate ICS+LABA cohort (8%).

DISCUSSION

The aim of this matched cohort study was to provide evidence to support guideline recommendations that children receiving a

TABLE II. Baseline characteristics of children prescribed add-on LABA as an FDC ICS/LABA inhaler or separate ICS+LABA inhalers: matched cohorts

Characteristic	FDC ICS/LABA (n = 1330)	Separate ICS + LABA (n = 1330)	P value for the difference between cohorts
Male sex, n (%)	780 (58.6)	779 (58.6)	.97*
Age at index date, mean (SD)	9.4 (2.2)	9.4 (2.2)	n/a*
Weight categories†			.11
Not obese or overweight (ie, <91th BMI centile)	571 (42.9)	542 (40.8)	
Overweight (ie, 91th-97th BMI centile)	118 (8.9)	111 (8.3)	
Obese (ie, ≥98th BMI centile)	101 (7.6)	136 (10.2)	
Missing BMI data	540 (40.6)	541 (40.7)	
Recorded comorbidity, n (%)			
Rhinitis diagnosis	295 (22.2)	333 (25.0)	.083
Eczema diagnosis	664 (49.9)	658 (49.5)	.81
Year of index date, median (IQR)	2006 (2004-2008)	2005 (2003-2007)	<.001
Year since first asthma script, median (IQR)	3 (1-5)	3 (1-6)	.29
Median (IQR) annualized daily ICS dose, µg/d‡	143 (82-247)	164 (99-274)	.001
ICS dose prescribed before index date, n (%)			n/a*
≤150 µg/d	0 (0)	0 (0)	
151-250 µg/d	248 (18.6)	248 (18.6)	
251-500 µg/d	1000 (75.2)	1000 (75.2)	
>500 µg/d	82 (6.2)	82 (6.2)	
Median ICS (IQR) ICS dose at index date (µg/d)	400 (400, 400)	400 (400, 400)	n/a*
Mean daily SABA dose, n (%)‡			n/a*
0 µg/d	21 (1.6)	21 (1.6)	
≤200 µg/d	652 (49.0)	652 (49.0)	
>200 µg/d	657 (49.4)	657 (49.4)	

BMI, Body mass index; CPRD, Clinical Practice Research Datalink; FDC, fixed-dose combination; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; n/a, not applicable; OPCR, Optimum Patient Care Database; SABA, short-acting β-agonist; SD, standard deviation.

*Matching variable.

†Cutoffs for overweight and obese recommended by the Royal College of Paediatrics and Child Health.³⁰

‡The doses of ICS and SABA were averaged over the baseline year using the formula (number of inhalers × doses per inhaler) divided by 365 × strength (in µg). ICS doses were standardized to equivalence with standard-particle beclomethasone; thus, the actual doses of budesonide were used, and doses of extrafine beclomethasone and fluticasone were halved.

TABLE III. Study endpoints, and their components, during the baseline and outcome years

Characteristic	Baseline year			Outcome year		
	FDC ICS/LABA (n = 1330)	Separate ICS + LABA (n = 1330)	P value for difference between groups	FDC ICS/LABA (n = 1330)	Separate ICS + LABA (n = 1330)	P value for the difference between groups during the follow-up years relative to baseline year without adjustment
Achieve overall asthma control	469 (35.3)	464 (34.7)	.59	543 (43.1)	495 (37.2)	.001
Acute respiratory events, mean (SD)	0.49 (0.84)	0.54 (0.92)	.084	0.32 (0.71)	0.39 (0.75)	.011
Acute respiratory events, n (%)						.003
0	883 (66.4)	857 (64.4)		1031 (77.5)	966 (72.6)	
1	300 (22.6)	316 (23.8)		217 (16.3)	256 (19.2)	
≥2	147 (11.1)	157 (11.8)	.21	82 (6.2)	108 (8.1)	
Severe exacerbations, n (%)						.056
0	1157 (87.0)	1157 (87.0)		1237 (93.0)	1205 (90.6)	
1	136 (10.2)	131 (9.8)		68 (5.1)	98 (7.4)	
≥2	37 (2.8)	42 (3.2)	.54*	25 (1.9)	27 (2.0)	
Achieved risk-domain asthma control, n (%)	846 (65.1)	820 (63.9)	.21	999 (77.4)	973 (72.5)	.003
Achieved treatment stability, n (%)	n/a	n/a	n/a	842 (65.6)	947 (56.9)	<.001

FDC, Fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; n/a, not applicable; SD, standard deviation.

Unadjusted P values are presented here. Adjusted odds ratio and rate ratio with P values are presented in Figure 1. Severe exacerbations were matched as 0 or ≥1.

*Matching variable.

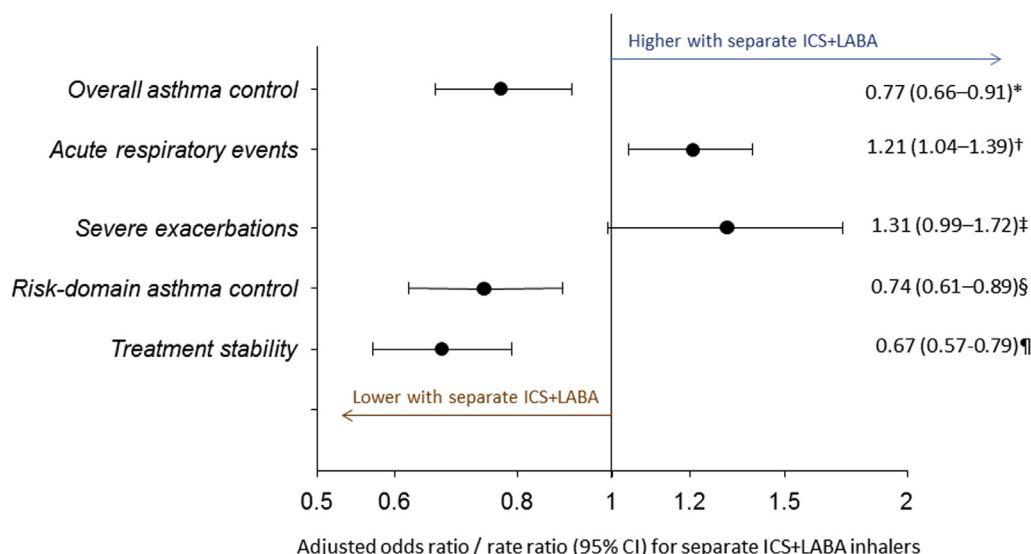


FIGURE 1. Adjusted asthma-related outcome measures comparing matched treatment cohorts during 1 outcome year. * $P = .001$, adjusted for nonsteroidal anti-inflammatory drugs; † $P = .012$, adjusted for baseline acute respiratory events and paracetamol prescription; ‡ $P = .057$, adjusted for baseline severe exacerbations and number of asthma and nonasthma consultations; § $P = .001$, adjusted for paracetamol prescription; ¶ $P = .001$, adjusted for the data source. *CI*, Confidence interval; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist.

TABLE IV. Asthma therapy prescribed during the outcome year

Outcome	FDC ICS/LABA (n = 1330)	Separate ICS + LABA (n = 1330)	P value for the difference between groups
SABA inhalers, median (IQR)	3 (2-6)	4 (2-7)	<.001
Change in therapy (any time), n (%)	244 (18.3)	326 (24.5)	<.001
Increase in ICS dose ≥50% (any time)	133 (10.0)	58 (4.4)	<.001

FDC, Fixed-dose combination; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *LABA*, long-acting β_2 -agonist; *SABA*, short-acting β_2 -agonist.

LABA as an add-on to ICS treatment should be prescribed a FDC and not an additional, separate LABA inhaler. This is an important point to establish as prescription of separate inhalers remains very common in UK clinical practice, despite recommendations.^{1,3} The main finding was that children prescribed an add-on LABA with ICS as separate inhalers had a 23% reduced odds of having controlled asthma compared with children prescribed FDC. In addition, the use of separate inhalers was associated with a 21% greater rate of acute respiratory events compared with those who received FDC. The fact that 17% of children in the separate ICS+LABA cohort were prescribed an FDC inhaler during the outcome year suggests that prescribers may be trialing LABA as a separate inhaler. Our data suggest that the trial should be with FDC in the first instance. Our results provide additional evidence that supports guideline recommendations for a LABA to be prescribed as an FDC, and not as a separate, inhaler.^{1,3}

Although significant, the improvement in outcomes for those treated with FDC was only by a small degree compared with

treatment with separate ICS and LABA inhalers. We used an intention-to-treat analysis, but as 17% of the separate ICS+LABA cohort received FDC during the follow-up, this will underestimate the true clinical benefit of FDC over separate ICS+LABA inhalers. We present our results as odds ratios, and the effect size is small when presented as a likelihood ratio for achieving control (0.9 for the separate ICS+LABA cohort compared with the FDC ICS/LABA cohort), or as the number needed to treat (17 children would require treatment with FDC instead of a separate inhaler in order for one additional child to achieve asthma control). This small effect may be partly explained by improvement in all outcomes in both groups as the children became older. An additional factor may be that adherence was relatively poor for all participants (22%-33%) and poor adherence is associated with poor control.³⁰ This may have led to the decision to step-up and also to a relatively disappointing response to treatment. National guidelines³ recommend that before initiating a new drug therapy, adherence to existing therapies should be considered, as well as an inhaler technique and the elimination of trigger factors. The low adherence in our study suggests that this may not be happening routinely.

There is little prior published work comparing outcomes with FDC versus separate inhalers for children prescribed an add-on LABA, yet many thousands of children are prescribed a LABA each year. Outcomes were similar with FDC versus separate inhalers for children in 2 double-blind, double-dummy trials with relatively short duration,^{8,9} although 1 trial did observe a greater increase in peak expiratory flow in children receiving FDC compared with separate inhalers.⁹ These studies might have been underpowered to detect differences between 2 effective treatments, and, in addition, it is well recognized that clinical trials recruit individuals whose disease is exceptionally stable and whose adherence behavior is not generalizable to the whole population. This potentially reduces the ability of clinical trials to

detect a difference in outcome between treatment groups.¹⁸ A recent retrospective observational database study observed that children prescribed FDC inhalers received fewer acute oral corticosteroid courses and, in 2 of the 4 years studied, also less reliever medication than those prescribed separate inhalers.⁴

The use of an FDC ICS/LABA inhaler has several theoretical benefits over 2 separate inhalers. The concurrent delivery of a bronchodilator (LABA) may provide a symptomatic benefit with use of FDC inhalers that promotes inhaler use, and thus may lead to improved adherence with treatment and increased consumption of concomitant ICS.^{31,32} Other authors have hypothesized that there may be a biochemical synergy between ICS and LABA with their codeposition in the airways.^{33,34} Moreover, an important advantage of combining ICS and LABA in 1 inhaler is the prevention of LABA use as monotherapy, which carries potential increased risk of asthma-related mortality. Since 2005, LABA monotherapy has been accompanied by a Food and Drug Administration (FDA) “black box” warning in the United States.^{35,36} In 2010, the FDA recommended the use of FDC products to ensure compliance with concomitant therapy in pediatric and adolescent patients.³⁷ Conversely, an advantage of prescribing separate inhalers is the ability to titrate ICS dose independently of the LABA.

The assumption of better LABA adherence with the use of a single FDC ICS/LABA inhaler rather than 2 separate inhalers is generally acknowledged.¹ We found no evidence for improved ICS adherence between cohorts, in terms of refill prescription rates. However, the increased number of children treated for thrush in the FDC ICS/LABA compared with the separate ICS+LABA cohort might suggest increased adherence with ICS in the FDC cohort, but may also reflect a lower proportion using a spacer device compared with the separate cohort. Some retrospective observational studies find that FDC inhalers are associated with better adherence and refill persistence by both adults and adolescents with asthma,¹²⁻¹⁴ but this finding is not seen in all studies. For example, in 1 randomized controlled trial (patients aged 16-65 years) where electronic monitoring was used to measure adherence, similar adherence was found with FDC and separate inhaler therapy.³⁸ In a retrospective observational study, and consistent with our findings, Elkout et al³⁹ found that MPR was similar for children prescribed separate ICS and LABA inhalers and FDC only. Further, it is possible that although separate ICS and LABA inhalers are issued with equal frequency, adherence with ICS is higher compared with separate LABA inhalers. Clearly more research is needed in this area, but the limited data from children presented here and from adults elsewhere³⁸ suggest that FDC is associated with superior outcomes. Potentially, this may be explained by different taking behavior, for example, taking more separate inhalers when symptomatic.

Treatment with a “Single maintenance and reliever therapy (SMART)” regimen⁴⁰ (which utilizes a combination inhaler with both preventer and reliever medication) has never been recommended for children in the UK, and our study cannot give insight into the potential benefits of this practice. There is evidence of reduced exacerbations in children randomized to a “SMART” regimen compared with FDC,⁴¹ but this work has not been confirmed elsewhere or incorporated into guidelines to date.

Antibiotics are not recommended for the treatment of acute asthma exacerbations in any age group, but because antibiotics are commonly prescribed for childhood asthma exacerbations,²⁴⁻²⁶

failure to consider antibiotic prescribing will result in missing a large number of exacerbations. One study of 60 million asthma exacerbations reported that 1 in 6 pediatric exacerbations were treated with antibiotics. Only 26% of those treated with antibiotics received corticosteroid treatment (ie, 12% of all exacerbations)²⁶ and would not be identified as an exacerbation.

This study has several strengths. We drew on well-maintained and stable datasets containing medical record information for approximately 15% of children in the UK through 2012. A full baseline year was used for confounder definition. By using a full outcome year, we could capture infrequent asthma-related events such as exacerbations, and also eliminate the effect of seasonal variations in allergy. A rigorous matching process was used, which was informed by our previous work that identified differences between children receiving a LABA as a separate inhaler or FDC.¹⁰ Matching resulted in 2 cohorts with similar demographic characteristics and baseline indicators of asthma severity and control. Adjustments were made for minor residual confounding. We studied children receiving their first therapy step-up with an add-on LABA, thereby reducing potential effects of declining persistence with therapy over time.¹⁴

Our study has a number of limitations. First, as in all studies of this nature, the patient outcomes were inferred from prescribing information. This brings the benefits of a large representative sample size, but it cannot capture aspects of asthma control such as nocturnal or exertional symptoms, though it can capture use of relieving medication—a valid index of asthma control. We cannot rule out the possibility of undetected residual confounding in this study, although our matching and analytic methods were designed to minimize this possibility. Despite matching for index date, the FDC ICS/LABA cohort was identified 1 year after the separate ICS+LABA cohort, reflecting the later introduction of FDC to clinical practice compared with a separate LABA inhaler, but we do not believe that this difference has substantially affected the outcome. Our matching ensured that the children in each cohort were prescribed the same ICS dose (400 µg), but we acknowledge that the separate ICS+LABA cohort had received less ICS during the baseline year compared with the FDC cohort (143 vs 164 µg). Because of the small size of this difference and the fact the cohorts are well matched elsewhere, we do not believe that this difference has affected the difference seen between cohorts. Another potential source of bias is in differential prescribing with regard to the add-on LABA inhaler choice. This could in turn influence outcomes. Missingness was present but was equally distributed across the 2 cohorts, for example, only 60% of children had height and weight data available. The children with the most severe asthma, that is, maintenance oral corticosteroids, were excluded from the analysis and our results cannot necessarily be extrapolated to this very small group of patients. We acknowledge that the definition of asthma used may have resulted in inclusion of children without asthma and exclusion of children with (unrecognized) asthma, but the aim of this study was to compare outcomes between groups of children with asthma and not outcomes between groups with and without asthma. It is unlikely that our inclusion criteria for asthma diagnosis affected the results.

In conclusion, we used routinely acquired health care data to evaluate asthma treatment benefits in a real-world setting. Our results, which are based on data collected from 2660 children, provide evidence that LABA treatment in children should be administered as an FDC and not as a separate inhaler.

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ONLINE REPOSITORY

Supplementary Methods

The study was conducted to standards suggested for observational studies, including an independent advisory group (all authors), use of an a priori analysis plan, study registration with commitment to publish, and well-maintained and monitored study databases.¹ Funding for the analyses was provided by the Respiratory Effectiveness Group (REG),² and the study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).³ The analyses and the dissemination of the results were conducted in accordance with the REG standards and the ENCePP Code of Conduct.⁴

Definitions of outcomes. For the severe exacerbation and acute respiratory event definitions, any criteria occurring within 2 weeks of each other were counted as 1 exacerbation/event.

An acute course of oral corticosteroids was defined as (i) prescribing instructions that suggested an exacerbation (reducing dose over time or 30 mg prednisolone as directed), (ii) a course without prescribing instructions but unlikely to be maintenance therapy and with a code for asthma or lower respiratory event, (iii) not maintenance therapy (defined as a prescribed daily dose of <10 mg prednisolone or prescription for 1 mg prednisolone tablets).

Evidence of a respiratory consultation was defined as any lower respiratory Read codes (asthma, chronic obstructive pulmonary disease, or lower respiratory infection codes) or codes

for any additional respiratory examinations, referrals, chest radiographs, or events.

Statistical analyses. Variables that differed between treatment groups with $P < .10$ were examined for collinearity and clinical importance to select those used as potential confounders in the regression modeling of outcomes. In addition, multivariable analyses were used to identify baseline variables that were predictive (at $P < .05$) of each outcome variable during the outcome period; these were considered as potential confounders when modeling the outcome variables. 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 >0.30 . Potential confounders examined are listed in Table E1.

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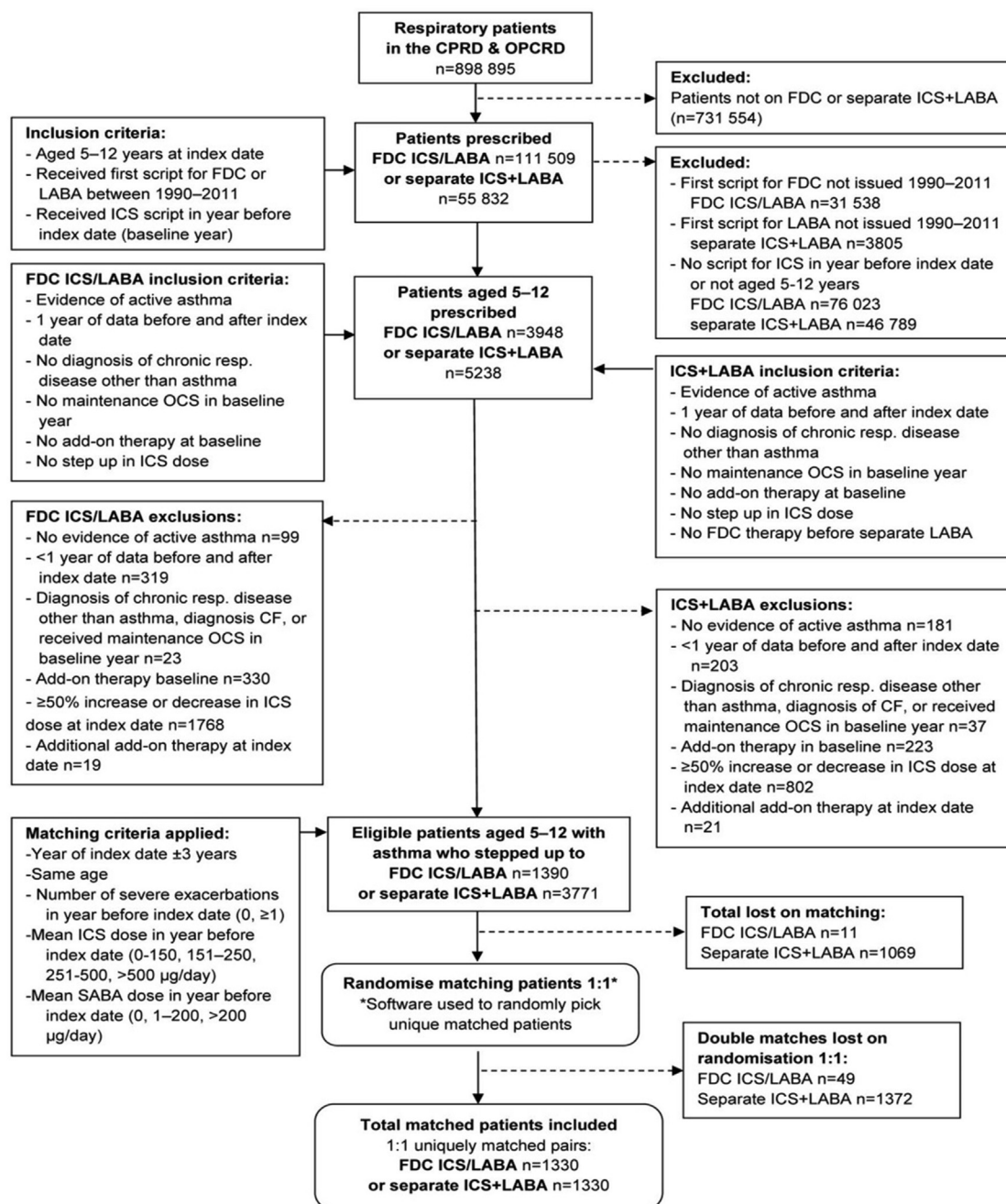


FIGURE E1. Patient selection and matching: patients in the 2 treatment cohorts were matched on clinically and demographically important characteristics. *CPRD*, Clinical Practice Research Datalink; *FDC*, fixed-dose combination; *ICS*, inhaled corticosteroid; *index date*, date of first prescription for FDC ICS/LABA or separate ICS+LABA; *LABA*, long-acting β_2 -agonist; *OCS*, oral corticosteroid; *OPCRD*, Optimum Patient Care Research Database; *SABA*, short-acting β_2 -agonist.

TABLE E1. Potential confounding factors considered in this study

Potential confounders examined at (or closest to) the relevant index date:

- Age
- Sex
- Smoking status
- Body mass index (BMI) centile categorized including a “missing” category where BMI was not available. All BMI centile values for individuals beyond ± 5 standard deviations were excluded as likely outliers.*
- Weight category (obese, overweight, or nonobese/nonoverweight)*,†

Potential confounders examined regardless of when they occurred relative to the index date:

- Date of first asthma diagnosis (where known)
- Other respiratory or other confounding diagnoses, including rhinitis, gastro-oesophageal reflux disease, eczema, and cardiac disease

Potential confounders examined in the year before the index date:

- 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 inpatients admissions for asthma
- Number of ER attendances for asthma
- Number of ER attendances or inpatient admissions for lower respiratory reasons
- Number of prescriptions for antibiotics with evidence of respiratory review
- Acute oral steroid use associated with asthma exacerbation treatment
- Prescriptions for other medications that might interfere with asthma control: β -blockers, NSAIDs, and paracetamol
- Number of prescriptions for asthma and/or allergies
- SABA daily dosage
- Average ICS daily dose
- ICS dose at index date

In addition:

- Year of index date
- Previous step-up recorded in the database
- Time between first asthma prescription and the index date (0-1 y, >1 y)
- Database (OPCRD vs CPRD)

CPRD, Clinical Practice Research Datalink; ER, emergency room; ICS, inhaled corticosteroid; IOTF, International Obesity Task Force; NSAID, nonsteroidal anti-inflammatory drug; OPCR, Optimum Patient Care Database; SABA, short-acting β -agonist.

*Both BMI centiles and IOTF grade were calculated using Imsgrowth macro software; Microsoft Excel add-in, version 1.12.

†Nonoverweight/nonobese was defined as BMI <91st. Overweight was defined as BMI centile ≥ 91 st and <98th. Obese was defined as BMI centile ≥ 98 th.

TABLE E2. Additional study outcomes during the baseline and outcome years

Characteristic	Baseline year			Outcome year		
	FDC ICS/LABA (n = 1330)	Separate ICS + LABA (n = 1330)	P value*	FDC ICS/LABA (n = 1330)	Separate ICS + LABA (n = 1330)	P value*
≥ 1 asthma-related ED attendance, n (%)	6 (0.5)	6 (0.5)	1.0	2 (0.2)	6 (0.5)	.18
≥ 1 asthma-related OPD visit, n (%)	15 (1.1)	11 (0.8)	.44	5 (0.4)	7 (0.5)	.57
Total GP consultations, median (IQR)	6 (3-9)	6 (3-9)	.77	5 (3-8)	5 (2-8)	.38
GP consultation not for asthma, median (IQR)	3 (2-6)	4 (2-6)	.86	3 (1-6)	3 (1-5)	.19
Spacer device prescribed, n (%)	366 (27.5)	379 (28.5)	.57	257 (19.3)	334 (25.1)	<.001
Thrush, n (%)†	10 (0.8)	9 (0.7)	.81	16 (1.2)	3 (0.2)	.008

ED, Emergency department; FDC, fixed-dose combination; GP, general practice; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β -agonist; OPD, outpatient department.

*Matched cohorts were compared using conditional logistic regression.

†Thrush was defined as a Read code for oral candidiasis or topical antifungal prescription definitely for treating oral candidiasis.

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