Elsevier Editorial System(tm) for Journal of Allergy and Clinical Immunology: In Practice
Manuscript Draft

Manuscript Number: INPRACTICE-D-15-00416R3

Title: Long-acting beta-agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids

Article Type: Original Article

Section/Category: Asthma and Lower Airway Disease

Keywords: asthma; child; inhaled corticosteroid; long-acting beta-agonist; step-up therapy

Corresponding Author: Dr. Stephen William Turner, MD

Corresponding Author's Institution: University of Aberdeen

First Author: Stephen William Turner, MD

Order of Authors: Stephen William Turner, MD; Kathryn Richardson; Clare Murray; Mike Thomas; Elizabeth Hillyer; Anne Burden; David Price

Manuscript Region of Origin: UNITED KINGDOM

Abstract: Background Adding a long-acting β2-agonist (LABA) to inhaled corticosteroids (ICS) using a fixed-dose combination (FDC) inhaler containing ICS and LABA is the UK guideline-recommended step-up option for children aged >4 years with uncontrolled asthma on ICS monotherapy. The evidence of benefit of FDC inhalers over adding a separate LABA inhaler to ICS therapy is limited.
Objective: Our aim was to compare outcomes for FDC versus separate LABA+ICS inhalers for children by analyzing routinely-acquired clinical and prescribing data.
Methods This matched cohort study used large UK primary care databases to study children prescribed their first step-up from ICS monotherapy at 5-12 years of age as add-on LABA, either via separate LABA inhaler or FDC inhaler. A baseline year was examined to characterize patients and identify potential confounders; outcomes were examined during the subsequent year. The primary outcome was adjusted odds ratio for overall asthma control, defined as no asthma-related hospital admission, emergency room visit prescription for oral corticosteroids and ≤200 µg/day salbutamol.
Results After matching, there were 1330 children in each cohort (mean age [SD] 9 [2] years; 59% male). All measures of asthma exacerbations and control improved during the outcome year in both cohorts. In the separate ICS+LABA cohort, the odds of achieving overall asthma control were lower (adjusted odds ratio, 0.77 [95% CI 0.66-0.91] P = 0.001) compared with the FDC cohort.
Conclusion Our results demonstrate a small but significant benefit of add-on LABA therapy as FDC over separate inhaler and support current recommendations.

Sir,

We are very grateful for the chance to submit a revision of our work. We would also like to thank the reviewers and the editorial team for their very helpful suggestions. We have made considerable changes to the previous version submitted in response to the comments raised after our most recent submission. Our point by point response follows this message.

Yours faithfully

Steve Turner (on behalf of all authors)

EDITOR'S SPECIFIC COMMENTS:
We appreciate your patience with our review process, but there are several additional issues that need to be addressed which before it is completed. The revision will improve the readability of the manuscript for our readers.

1. The manuscript needs to be written in better scientific style with more easily to read sentences. In addition, please assure that American English spelling is used throughout the manuscript, i.e., hospitalization instead of hospitalisation. Please check the paper carefully as there are many punctuation errors. Also many sentences are too long and can easily be shortened or divided into two sentences to improve readability. Just 2 of many examples: Lines 300-305, 322-326. Step up should be hyphenated: step-up.

Complete edit of writing style has been carried out.

2. Please be consistent in terminology: suggest whenever ICS+LABA is noted it should be more precise and writing as separate ICS+LABA. See line 246 which notes, "ICS+LABA as separates cohort."

Terminology amended to be consistent

3. Tables and Figures should be capitalized throughout the text. Numbering should be in increasing roman numbers, e.g., Table I, Table II. For the online repository tables should written as Table E1, Table E2, etc.

Done

4. Lines 61-62: This definition of asthma control used for the study appears incomplete: Table 1 notes "All of the following: 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>g/day salbutamol or ≤500 <mu>g/day terbutaline (equivalent to ≤2 puffs daily of reliever medication)." I suggest the following change: defined as no asthma-related hospital admission, emergency room visit, prescription for oral corticosteroids or antibiotic with evidence of respiratory consultation, and ≤2 puffs of short-acting beta-agonist daily.

Suggested change made (lines 71-73 in revised document with tracked changes)

5. Lines 64-65: Please remove exacerbations since the abstract should emphasize the primary outcome: control. I suggest changing the sentence to "Asthma control improved during the outcome year in both cohorts."

Suggested change made (lines 77-78)

6. Lines 70-71: Suggest modifying to: The study demonstrates a small but significant benefit in achieving asthma control form add-on LABA therapy as FDC with ICS compared to a separate inhaler with ICS which supports current guideline recommendations.

Suggested change made (lines 81-83)

7. Line 127: The readers are not familiar with your study databases and other terms and it is suggested that they not be abbreviated throughout. Moreover several are cited infrequently in the text. Please also remove them from the abbreviation section. CPRD, OPCRD, ADEPT.

Changed to full wording and removed from list of abbreviations

8. Line 131: Reference in parenthesis needs to be added to citations: ref ENCEPP/SDPP/10483

Number written is registration number for study. So this has been kept in, but a new reference has now also been added for the website of ENCEPP (line 146, ref 19)

9. Lines 155-159: Please add back the primary outcome definition since it should be in the text. It can also be in Table I.

Done (lines 180-183)

10. Line 224: Please define what is meant by OOPCRD and do not abbreviate.

Done (line 256)

11. Lines 226 and elsewhere: data should be written with the words 95% CI, as : 0.77 (95% CI, 0.66-0.91; P = 0.001).

Changed to be consistent with the rest

12. Line 237: achieving not achieve

Changed (line 270)

13. Lines 270-271: Please provide the % of patients in addition to the number that switched drug categories.

Done (lines 307-310)

14. Line 287: inhalers should be plural.

Changed (line 317)

15. Line 297: Do you mean 1 additional child gain control?

Yes – wording changed to avoid ambiguity (line 335)

16. Lines 300-305: Sentence too long, please improve its presentation.

Addressed in general edit of writing style

17. Line 309: Please add short duration rather than just short.

Changed (lines 352)

18. Lines 318-324: Purely speculative and should be deleted.

Done (lines 361-368)

19. Line 346: Is there a better word than 'covert'?

Word now omitted (line 393)

20. Line 360: The 'SMART' regimen has not been described previously in the manuscript and needs to be noted if it is to be discussed.

Brief description and new reference (Chapman 2010) has been added. (lines 403-404, ref 40)

21. Lines 411-413: Please delete as not an important new finding from this study.

Line has been re-phrased to have it read as a method rather than a finding (lines 454-456)

22. Line 414: Why is the term whole population needed in this sentence?

Removed(line 457)

23. Table 1: Title seems inaccurate as it includes the primary outcome for this manuscript. Perhaps more accurate would be "Definitions of database-derived primary and secondary study outcomes."

Suggested change made

24. The following should be added footnote to the table: "Definitions of oral corticosteroid use and respiratory consultation are provided in the supplement."

Added as footnote

COMMENTS FROM REVIEWER #1:
The authors have responded well to the previous comments. The revised manuscript is improved and reads well.

COMMENTS FROM REVIEWER #2:
I have again re-reviewed your paper entitled 'Long-acting beta-agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids' and still have some questions/concerns:

1. Line 607: Please comment on the following: since extra-fine ICS has much greater lung deposition than standard ICS an equivalent dose would be 1/2, not double.

Changed to “halved” (footnote, table II)

2. As with my previous reviews I find disturbing that the various outcome measures not to improve much by either preparation in the post year presumably because adherence as measured by MPR, which has been reported not to be as rigorous as the AMR by Schatz in this journal recently, was extremely poor. This certainly does not explain the difference in the 2 cohorts. One would think 1 device would result in better adherence than 2. Need to explain this finding. I suspect these cohorts would have done well on Step 2 with improved adherence. To me these results are consistent with primary care management in general where patient education is poor, guidelines are not followed, and most important continuity of care by the same physician is sorely lacking. I would think this would merit some thought and comment.

New sentence (with reference) has been added to clarify point: "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 guidelines[3] recommend that before initiating a new drug therapy, adherence to existing therapies should be considered, as well as inhaler technique and the elimination of trigger factors. The adherence in our study suggests that this may not be happening routinely." -- (lines 337-343, ref 30)

COMMENTS FROM THE EDITORIAL OFFICE:
** Please submit separate Conflict of Interest Disclosure statements for each author who is listed on the title page, using the form found on the Journal's submissions site. You can download the form directly from http://ees.elsevier.com/inpractice/img/forms.html. The documents should be uploaded alongside the revised manuscript. If necessary, the forms can be sent to the Editorial Office by email to Dawn Angel at InPractice@aaaai.org, or by fax to319-467-7583.

Your revision must include the following items: (1) point-by-point responses to the Editor and reviewer comments, (2) a marked copy of your revision showing the changes made, and (3) a clean (unmarked) copy of your revised manuscript. If your manuscript has any figures, tables, or Online Repository material in separate files, please be sure these are included in the revision as well. For further information regarding formatting of these elements, please consult the Guidelines for Submitting a Revision (found on the Elsevier Editorial System (EES) homepage in the Guide for Authors). To avoid a delay in a final decision on your manuscript, please follow these instructions carefully.

Revised documents for online material have been submitted without tracked changes, as changes were minor – table names changed from Table S1 to Table E1, for example.

Long-acting beta-agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids

Steve Turner MD[1], Kathryn Richardson PhD[2], Clare Murray MD[3], Mike Thomas PhD[4], Elizabeth V. Hillyer, DVM[2], Anne Burden, MSc[2], David B. Price, FRCGP[2,5], on behalf of the Respiratory Effectiveness Group

[1]Department of Child Health, University of Aberdeen, UK

[2]Research in Real-life Ltd, Cambridge, UK

[3]Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester, NHS Foundation Trust

[4]Primary Care and Population Sciences, University of Southampton, UK. NIHR Wessex CLAHRC and NIHR Southampton Biomedical Research Unit.

[5]Academic Primary Care, University of Aberdeen, UK

Corresponding author: Dr Steve Turner, Child Health, Royal Aberdeen Children's Hospital, Aberdeen, UK AB25 2ZG. Tel: +44 1224 438470; s.w.turner@abdn.ac.uk

Key words: asthma, child, inhaled corticosteroid, long-acting beta-agonist, step-up therapy

Abbreviations:

aOR Adjusted Odds Ratio

aRR Adjusted Rate Ratio

BTS/SIGN The British Thoracic Society and Scottish Intercollegiate Guidelines Network

FDA Food and Drug Administration

FDC Fixed Dose Combination inhaler

ICS Inhaled Corticosteroids

LABA Long Acting Beta Agonist

OCS Oral Corticosteroids

NICE National Institute for Health and Care Excellence

SABA Short Acting Beta Agonist

Funding. This study was funded by the Respiratory Effectiveness Group

Word count: 4001.

What is already known about this topic?

Current asthma guidelines recommend that children prescribed long-acting β_2-agonist (LABA) should receive treatment as a fixed-dose combination inhaler, rather than as an additional, separate inhaler alongside inhaled corticosteroids (ICS). 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 to a fixed-dose combination inhaler.

How does this study impact current management guidelines?

These findings support recommendations from British Thoracic Society, NICE asthma guideline and Food and US Drug Administration, to prescribe add-on LABA as a fixed-dose combination inhaler with ICS in children.

ABSTRACT

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 >4 years with uncontrolled asthma. The evidence of benefit of adding a FDC inhaler over a separate LABA inhaler is limited.

Objective Our aim was to compare effectiveness of LABA added as a 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 two-year follow-up period. We included children prescribed their first step-up from ICS monotherapy. Two cohorts were formed for children receiving add-on LABA as FDC inhaler, or 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 control (defined as; 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 beta-agonist daily).

Results The final study consisted of 1330 children in each cohort (mean age 9 years [SD, 2]; 59% male). In the separate ICS+LABA cohort, the odds of achieving overall asthma control were lower (adjusted odds ratio, 0.77 [95% CI, 0.66-0.91] *P* = 0.001) compared with the FDC cohort.

Conclusion The study demonstrates a small but significant benefit in achieving asthma control from add-on LABA as FDC, compared to a separate inhaler which supports current guideline recommendations.

INTRODUCTION

Asthma is common amongst children in the UK, with an estimated 8%, 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. 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.[3-6] 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.[2] However, some children continue to be prescribed separate inhalers. One risk of prescribing 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 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 months [8] and 6 months[9], when comparing groups randomized to LABA as 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 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 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 LABA as 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 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 two large primary care databases including ~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 over 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 over 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 Clinical Practice Research Datalink and through December 2012 for the Optimum Patient Care Research Database.

The study was conducted to standards recommended for observational research[18] and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.[19] (ref 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 Optimum Patient Care Research Database 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 (ADEPT) committee - the independent scientific advisory committee for the Optimum Patient Care Research Database. Further background information is available in the online supplementary material.

Inclusion and exclusion criteria

Our study included a two-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: either a read code diagnosis of asthma or 2 or more inhaler prescriptions (at least 1 of which was for ICS in the previous 12 months) - the latter comprise 2% of the study population[10]; 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: cystic fibrosis or any chronic respiratory disease other than asthma; receipt of add-on therapy (including combination inhaler) at any time prior to the index date; treatment with oral corticosteroids (OCS) for more than 7 consecutive days during the baseline year; multiple step-up therapies on the index date; ≥50% increase or decrease in ICS dose on the index date (the latter ensured that we studied outcomes of 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 two 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 Society[23] definition, i.e. the level of clinical asthma control (as evidenced here by short acting beta agonist use) and the risk of future adverse events (as evidenced here by a history of adverse events including hospitalisation, 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 µg/day salbutamol or ≤500 µg/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 absence of 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:

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

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:

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

Individuals were categorized as either non-adherent (MPR<80%), or adherent (MPR≥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 two treatment cohorts were matched sequentially 1:1 on the following criteria, which were known to differ at baseline[4]: 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 µg/day), and mean daily SABA dose (0, 1–200, >200 µg/day) during baseline year. Bespoke software was used to randomly select unique matched patient pairs when more than one match was possible.

Data were prepared for analysis by investigating potential outliers, transforming skewed data (e.g., 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 adjusted odds ratios (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 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 confidence intervals.

For all multivariable models, those variables that were significantly different or showed a trend towards a difference ($P < 0.10$) between the treatment cohorts at baseline were included as potential confounding factors, along with any strongly predictive variables. Potential confounders examined are listed in the online supplementary material (Table E1). Variables were examined for collinearity and clinical importance and were then removed in a backwards stepwise procedure until all confounding variables remaining in the multivariable model had $P < 0.1$ (see online supplementary material for further details).

All analyses were done on an intention-to-treat basis, i.e. children remained in their original cohort even if their treatment method changed during the outcome year. Statistical significance was set at the 5% level, i.e. $P < 0.05$. No prospective power calculation was carried out since our sample size was determined by the number of eligible children in the Clinical Practice Research Datalink and Optimum Patient Care Research Database.

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

RESULTS

Patients

Overall, 1390 and 3771 children were eligible for the FDC ICS/LABA and separate ICS+LABA cohorts, respectively (see Figure E1 in supplementary file). Ninety seven percent of children had a diagnosis of asthma and 70% were from the Optimum Patient Care Research Database. After matching there were 1330 children in each cohort, of mean age 9 years (SD, 2), and 59% were male (Table II). The two 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 one year earlier (i.e. 2005 versus 2006) compared to the FDC cohort (Table II and Table E2).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% afterwards. Equivalent proportions in the separate ICS+LABA cohort were 35% and 37% (Table III). The adjusted odds ratio (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; $P = 0.001$; Figure I).

Secondary outcomes

The number of acute respiratory events was greater among the separate ICS+LABA cohort compared to the FDC ICS/LABA cohort (Table III). The adjusted rate ratio (aRR) was 1.21 (95% CI, 1.04–1.39; $P = 0.012$; Figure I). 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; $P = 0.056$). 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; $P = 0.003$) and achieving

248 treatment stability (aOR 0.67; 95% CI, 0.57–0.79; *P* < 0.001; Figure I). There were no
249 significant differences between cohorts for adherence (MPR>80%) or for severe
250 exacerbations. In the outcome year there were 6 hospitalizations for asthma in each cohort.
251 There were 16 children in the FDC ICS/LABA cohort and 3 in the separate ICS+LABA cohort
252 treated for thrush (*P* = 0.008, Table E2). Compared to the baseline year, more children in
253 the separate ICS+LABA cohort (29.9% in baseline year and 22.5% in follow up year)
254 received treatment with antibiotics during the follow-up year than in the FDC cohort (28.6%
255 and 19.6% respectively, *P* = 0.041). There was a trend which approached significance for a
256 greater proportion of the separate ICS+LABA cohort to receive OCS compared to the FDC
257 ICS/LABA cohort during the outcome year (8.8% versus 6.5%, p=0.084).
258 Asthma prescribing during outcome year
259 Asthma therapy prescribed during the outcome year, as well as changes in therapy, are
260 summarized in Table IV. Children in the FDC ICS/LABA cohort typically received one fewer
261 SABA inhalers in the outcome year compared with those in the separate ICS+LABA cohort
262 (3 vs. 4 inhalers; *P* < 0.001). Children in the FDC ICS/LABA cohort were more likely to have
263 an increase in ICS dose compared with those in the separate ICS+LABA cohort (10% vs.
264 4%; *P* < 0.001), but no more likely to have LTRA added. The proportion of children achieving
265 adherence (MPR>80%) was 33% in the FDC ICS/LABA cohort and 31% in the separate
266 ICS+LABA cohort (aOR 0.87; 95% CI, 0.72–1.06). During the outcome year the median daily
267 ICS dose was 219 μg for both cohorts. Further, during the outcome year 231 (18%) children
268 in the separate ICS+LABA cohort switched to FDC, and 17 (1%) children in the FDC
269 ICS/LABA cohort switched to a separate LABA inhaler. LTRA treatment was started in 122 in
270 the FDC ICS/LABA cohort (9%) and 112 in the separate ICS+LABA cohort (8%).
271

DISCUSSION

The aim of this matched cohort study was to provide evidence to support guideline recommendations that children receiving LABA as an add-on to ICS treatment should be prescribed a fixed-dose combination inhaler (FDC) and not an additional, separate LABA inhaler. It is an important point to establish as prescription of separate inhalers remains very common in UK clinical practice, despite recommendations.[2,3] The main finding was that children prescribed add-on LABA with ICS as separate inhalers had a 23% reduced odds of having controlled asthma compared with children prescribed FDC. Additionally 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 LABA to be prescribed as FDC, and not as a separate, inhaler.[2,3]

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 to 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 guidelines[3] recommend that before initiating a new drug therapy, adherence to existing therapies should be considered, as well as inhaler technique and the elimination of trigger factors. The 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 add-on LABA, yet many thousands of children are prescribed LABA each year. Outcomes were similar with FDC versus separate inhalers for children in two double-blind, double-dummy trials with relatively short duration,[8,9] although one trial did observe a greater increase in peak expiratory flow in children receiving FDC compared to separate inhalers.[9] These studies might have been underpowered to detect differences between two effective treatments, and additionally 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 two 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 there may be a biochemical synergy between ICS and LABA with their co-deposition in the airways.[33,34] Moreover, an important advantage of combining ICS and LABA in one inhaler is the prevention of LABA use as monotherapy, which carries potential increased risk of asthma-related mortality. Since 2005 LABA monotherapy is accompanied by a Food and Drug Administration (FDA) “black box” warning in the US.[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 use of a single FDC ICS/LABA inhaler rather than two separate inhalers is generally acknowledged.[2] 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 to the separate ICS+LABA cohort might suggest increased adherence with ICS in the FDC cohort, but may reflect a lower proportion using a spacer device compared to 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 one 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 al.[39] 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 elsewhere[38] suggest that FDC is associated with superior outcomes. Potentially, this may be explained by different taking behavior, e.g. taking more separate inhalers when symptomatic.

Treatment with a “SMART” regimen[40] (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 excerbations in any age group, but since antibiotics are commonly prescribed for childhood asthma

355 exacerbations,[24-26] failure to consider antibiotic prescribing will result in missing a large
356 number of exacerbations. One study of 60 million asthma exacerbations reported that one in
357 six pediatric exacerbations were treated with antibiotics. Only 26% of those treated with
358 antibiotics received corticosteroid treatment (i.e. 12% of all exacerbations)[26] and would not
359 be identified as an exacerbation.

360 This study has several strengths. We drew on well-maintained and stable datasets
361 containing medical record information for approximately 15% of children in the UK through
362 2012. A full baseline year was used for confounder definition. By using a full outcome year,
363 we could capture infrequent asthma-related events such as exacerbations, and also
364 eliminate the effect of seasonal variations in allergy. A rigorous matching process was used,
365 which was informed by our previous work that identified differences between children
366 receiving LABA as separate inhaler or FDC.[10] Matching resulted in two cohorts with similar
367 demographic characteristics and baseline indicators of asthma severity and control.
368 Adjustments were made for minor residual confounding. We studied children receiving their
369 first therapy step-up with add-on LABA, thereby reducing potential effects of declining
370 persistence with therapy over time.[14]

371 Our study has a number of limitations. First, as in all studies of this nature the patient
372 outcomes were inferred from prescribing information. This brings the benefits of a large
373 representative sample size, but it cannot capture aspects of asthma control such as
374 nocturnal or exertional symptoms, though it can capture use of relieving medication - a valid
375 index of asthma control. We cannot rule out the possibility of undetected residual
376 confounding in this study, although our matching and analytic methods were designed to
377 minimize this possibility. Despite matching for index date the FDC ICS/LABA cohort was
378 identified one year after the separate ICS+LABA cohort, reflecting the later introduction of
379 FDC to clinical practice compared to separate LABA inhaler, but we do not believe that this
380 difference has substantially affected the outcome. Our matching ensured that the children in
381 each cohort were prescribed the same ICS dose (400 µg) but we acknowledge that the
382 separate ICS+LABA cohort had received less ICS during the baseline year compared to the

FDC cohort (143 versus 164 µg). Due to 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 add-on LABA inhaler choice. This could in turn influence outcomes. Missingness was present but was equally distributed across the two cohorts, e.g. only 60% of children had height and weight data available. The children with the most severe asthma, i.e. 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 concluding, we used routinely acquired healthcare 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.

401 **Competing interests**

402 MT. Neither MT nor any member of his close family has any shares in pharmaceutical
403 companies. In the last 3 years he has received speaker's honoraria for speaking at
404 sponsored meetings or satellite symposia at conferences from the following companies
405 marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Inglehiem,
406 GSK, MSD, Teva. He has received honoraria for attending advisory panels with; Aerocrine,
407 Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Novartis. He has received sponsorship to
408 attend international scientific meetings from: GSK, Astra Zeneca, Mundipharma. He has
409 received funding for research projects from: GSK, Almirall. He is chief medical adviser to the
410 charity Asthma UK, a member of the BTS SIGN Asthma guideline group and the NICE
411 Asthma guideline group.

412 DP. Board Membership: Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim,
413 Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva. Consultancy: Almirall, Amgen,
414 AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp,
415 Novartis, Pfizer, and Teva. Grants/Grants Pending: UK National Health Service, British
416 Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly,
417 GlaxoSmithKline, Meda, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory
418 Effectiveness Group, Takeda, Teva, and Zentiva. Payments for lectures/speaking: Almirall,
419 AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck,
420 Mundipharma, Novartis, Pfizer, SkyePharma, Takeda, and Teva. Payment for manuscript
421 preparation: Mundipharma and Teva. Patents (planned, pending or issued): AKL Ltd

422 Payment for the development of educational materials: GSK, Novartis. Stock/Stock options:
423 Shares in AKL Ltd which produces phytopharmaceuticals and owns 80% of Research in
424 Real Life Ltd and its subsidiary social enterprise Optimum Patient Care. Payment for
425 travel/accommodations/meeting expenses: Aerocrine, Boehringer Ingelheim, Mundipharma,
426 Napp, Novartis, and Teva. Funding for patient enrolment or completion of research: Almirall,

Chiesi, Teva, and Zentiva. Peer reviewer for grant committees: Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), HTA (2014). Unrestricted funding for investigator-initiated studies: Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva.

At the time of the study analyses, AB and KR were employees of RiRL, 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, Zentiva.

ST and CM have no conflicts of interest to declare.

Contributorship

ST, CM, MT and DP conceived the idea for the analysis. KR and AB analyzed the data. EVH and ST wrote the first draft of the paper. All authors made contributions to the final paper.

Acknowledgements

The authors thank Prof Stanley Szefler for his comments on the paper, and Lisa Law for help with editing.

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558 **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 OCS or antibiotic with evidence of respiratory consultation; average daily prescribed dose of ≤200 µg/day salbutamol or ≤500 µg/day terbutaline (equivalent to ≤2 puffs daily of reliever medication).
Secondary endpoints *(determined over 12 months)*
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.
Rate of 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, ***and*** no prescription for acute course of oral corticosteroids with evidence of a respiratory consultation, ***and*** 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.

559 Definitions of oral corticosteroid use and respiratory consultation are provided in the
560 supplement.
561

562 **Table II Baseline characteristics of children prescribed add-on LABA as FDC ICS/LABA inhaler or separate ICS+LABA inhalers:**

563 **matched cohorts**

Characteristic		**FDC ICS/LABA (n=1330)**	**Separate ICS + LABA (n=1330)**	**p value for difference between cohorts**
Male sex, n (%)		780 (58.6)	779 (58.6)	0.97†
Age at index date, mean (SD)		9.4 (2.2)	9.4 (2.2)	n/a†
Weight categories‡	Not obese or overweight (i.e. <91th BMI centile)	571 (42.9)	542 (40.8)	0.11
	Overweight (i.e. 91–97th BMI centile)	118 (8.9)	111 (8.3)	
	Obese (i.e. ≥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)	0.083

(%)	Eczema diagnosis	664 (49.9)	658 (49.5)	0.81
Year of index date, median (IQR)		2006 (2004–2008)	2005 (2003–2007)	<0.001
Year since first asthma script, median (IQR)		3 (1–5)	3 (1–6)	0.29
Median (IQR) annualized daily ICS dose, µg/d¶		143 (82–247)	164 (99–274)	0.001
ICS dose prescribed before index date, n (%)	≤150 µg/d	0 (0)	0 (0)	n/a†
	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 (%)¶	0 µg/d	21 (1.6)	21 (1.6)	n/a†
	≤200 µg/d	652 (49.0)	652 (49.0)	

	>200 µg/d	657 (49.4)	657 (49.4)	

564 †Matching variable.

565 ‡ Cut offs for overweight and obese recommended by the Royal College of Paediatrics and Child Health.[41]

566 ¶The doses of ICS and SABA were averaged over the baseline year using the formula [number of inhalers x doses per inhaler] divided by 365

567 x strength (in µg). ICS doses were standardized to equivalence with standard-particle beclomethasone; thus, the actual doses of budesonide

568 were used, and doses of extrafine beclomethasone and fluticasone were halved.

569 BMI, body mass index; CPRD, Clinical Practice Research Datalink; FDC, fixed-dose combination; ICS, inhaled corticosteroid; IQR, interquartile

570 range; LABA, long-acting β-agonist; n/a, not applicable; OPCRD, Optimum Patient Care Database; SD, standard deviation.

571

572 **Table III** Study endpoints, and their components, during the baseline and outcome years. Negative binomial logistic regression models which
573 yield adjusted. Unadjusted p values are presented here. Adjusted Odds Ratio and Rate Ratio with p values are presented in Figure I.

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 difference between groups during the follow up years relative to baseline year without adjustment**
Achieve overall asthma control	469 (35.3)	464 (34.7)	0.59	543 (43.1)	495(37.2)	0.001
Acute respiratory events, mean (SD)	0.49 (0.84)	0.54 (0.92)	0.084	0.32 (0.71)	0.39 (0.75)	0.011

Acute respiratory events, n (%)	0	883 (66.4)	857 (64.4)	0.21	1031 (77.5)	966 (72.6)	0.003
	1	300 (22.6)	316 (23.8)		217 (16.3)	256 (19.2)	
	≥2	147 (11.1)	157 (11.8)		82 (6.2)	108 (8.1)	
Severe exacerbations, n (%)	0	1157 (87.0)	1157 (87.0)	0.54†	1237 (93.0)	1205 (90.6)	0.056
	1	136 (10.2)	131 (9.8)		68 (5.1)	98 (7.4)	
	≥2	37 (2.8)	42 (3.2)		25 (1.9)	27 (2.0)	
Achieved risk-domain asthma control, n (%)		846(65.1)	820480 (63.9)	0.21	999 (77.4)	973 (72.5)	0.003
Achieved treatment stability, n (%)		n/a	n/a	n/a	842 (65.6)	947 (56.9)	<0.001

†Matching variable. Note: severe exacerbations were matched as 0 or ≥1.

FDC, fixed-dose combination; GP, general practice; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; n/a, not applicable; SABA, short-acting β-agonist.

577 **Table IV** Asthma therapy prescribed during the outcome year

Outcome	FDC ICS/LABA (n=1330)	Separate ICS + LABA (n=1330)	p value for difference between groups
SABA inhalers, median (IQR)	3 (2–6)	4 (2–7)	<0.001
Change in therapy (any time), n (%)	244 (18.3)	326 (24.5)	<0.001
Increase in ICS dose ≥50% (any time)	133 (10.0)	58 (4.4)	<0.001

578 †The doses of ICS and SABA were averaged over the outcome year using the formula
579 [number of inhalers x doses per inhaler] divided by 365 x strength (in µg). SABA doses were
580 converted to puffs using the formula 100 µg = 1 puff. The doses of ICS were standardized to
581 equivalence with standard-particle beclomethasone; thus, the actual doses of budesonide
582 were used, and doses of extrafine beclomethasone and fluticasone were doubled.
583 FDC, fixed-dose combination; ICS, inhaled corticosteroid; IQR, interquartile range; LABA,
584 long-acting β-agonist; n/a, not applicable (comparison not possible because of 0 or low
585 number); SABA, short-acting β_2-agonist.
586

587 **FIGURE LEGEND**

588

589 **Figure I.** Adjusted asthma-related outcome measures comparing matched treatment cohorts
590 during 1 outcome year. adjOR/adjRR, adjusted odds ratio/rate ratio; FDC, fixed-dose
591 combination; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting
592 β_2-agonist
593 *p=0.002. Adjusted for nonsteroidal anti-inflammatory drugs
594 †p=0.012. Adjusted for baseline acute respiratory events and paracetamol prescription
595 ‡p=0.057. Adjusted for baseline severe exacerbations and number of asthma and non-
596 asthma consultations
597 §p=0.001. Adjusted for paracetamol prescription
598 ¶p=0.001. Adjusted for data source

Figure No.

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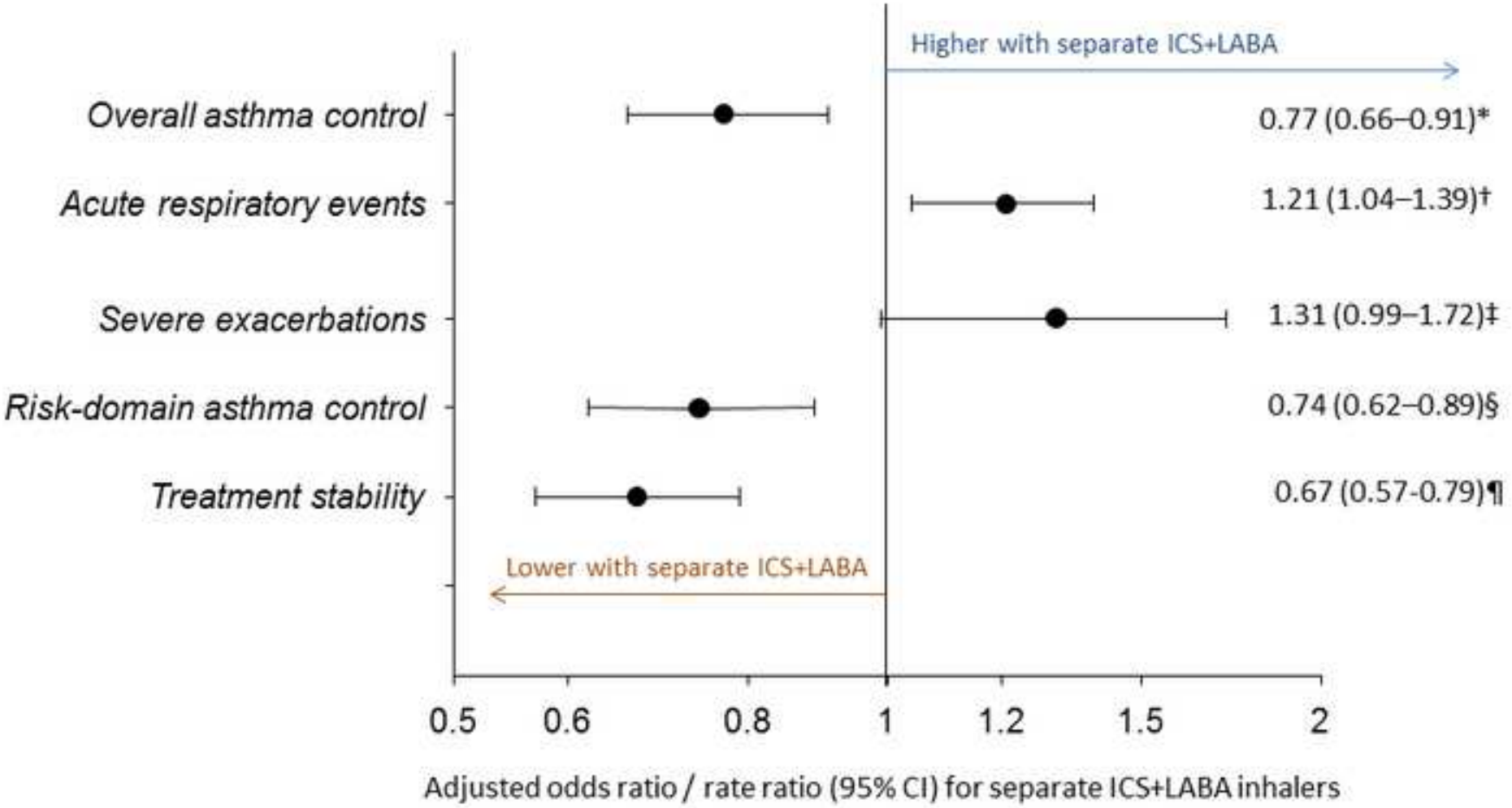

Long-acting beta-agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids

Steve Turner MD[1], Kathryn Richardson PhD[2], Clare Murray MD[3], Mike Thomas PhD[4], Elizabeth V. Hillyer, DVM[2], Anne Burden, MSc[2], David B. Price, FRCGP[2,5], on behalf of the Respiratory Effectiveness Group

[1]Department of Child Health, University of Aberdeen, UK

[2]Research in Real-life Ltd, Cambridge, UK

[3]Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester, NHS Foundation Trust

[4]Primary Care and Population Sciences, University of Southampton, UK. NIHR Wessex CLAHRC and NIHR Southampton Biomedical Research Unit.

[5]Academic Primary Care, University of Aberdeen, UK

Corresponding author: Dr Steve Turner, Child Health, Royal Aberdeen Children's Hospital, Aberdeen, UK AB25 2ZG. Tel: +44 1224 438470; s.w.turner@abdn.ac.uk

Key words: asthma, child, inhaled corticosteroid, long-acting beta-agonist, step-up therapy

Abbreviations:

~~ADEPT Anonymized Data Ethics Protocols and Transparency~~

aOR Adjusted Odds Ratio

aRR Adjusted Rate Ratio

BTS/SIGN The British Thoracic Society and Scottish Intercollegiate Guidelines Network

~~CPRD Clinical Practice Research Database~~

FDA Food and Drug Administration

FDC Fixed Dose Combination inhaler

ICS Inhaled Corticosteroids

LABA Long Acting Beta Agonist

OCS Oral Corticosteroids

~~OPCRD Optimum Patient Care Research Database~~

NICE National Institute for Health and Care Excellence

SABA Short Acting Beta Agonist

Funding. This study was funded by the Respiratory Effectiveness Group

Word count: ~~3499~~4001.

What is already known about this topic?

Current asthma guidelines~~Clinical trials provide no evidence to support~~ recommend~~ations~~ that children ~~with asthma~~ prescribed long-acting β_2-agonist (LABA) should receive treatment as a fixed-dose combination inhaler, rather than ~~and not by~~ as an additional, ~~of a~~ separate inhaler ~~to~~ alongside inhaled corticosteroids (ICS). 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 ~~and increased risk for exacerbation~~ compared to a fixed-dose combination inhaler.

How does this study impact current management guidelines?

These findings support recommendations from British Thoracic Society, NICE asthma guideline and Food and US Drug Administration, ~~recommendations~~ to prescribe add-on LABA as a fixed-dose combination inhaler with ICS in children.

ABSTRACT

Background Adding a long-acting β_2-agonist (LABA) to inhaled corticosteroids (ICS) using a fixed-dose combination (FDC) inhaler ~~containing ICS and LABA~~ is the UK guideline ~~-~~ recommend~~ation~~ed ~~step-up option~~ for children aged >4 years ~~with uncontrolled asthma on ICS monotherapy~~with uncontrolled asthma. The evidence of benefit of adding a FDC inhaler~~s~~ over ~~adding~~ a separate LABA inhaler ~~to ICS therapy~~ is limited.

Objective~~:~~ Our aim was to compare effectiveness of LABA added as a FDC inhaler, and as a separate inhaler, in children with uncontrolled asthma. ~~Our aim was to compare outcomes for FDC versus separate LABA+ICS inhalers for children by analyzing routinely-acquired clinical and prescribing data.~~

Methods Two UK primary care databases were used to create a~~This~~ matched cohort study with a two-year follow-up period. We included ~~used large UK primary care databases to study~~ children prescribed their first step-up from ICS monotherapy. Two cohorts were formed~~,~~ ~~at 5–12 years of age,~~ ~~as add-on LABA, either via separate LABA inhaler or FDC inhaler.~~ for children receiving add-on LABA as FDC inhaler, or separate LABA inhaler. Matching variables and confounders were identified by comparing characteristics during a~~A~~ baseline year of follow-up.~~was examined to characterize patients and identify potential confounders;~~ O~~o~~utcomes were examined during the subsequent year. The primary outcome was an adjusted odds ratio for overall asthma control ~~,~~ (defined as; 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 beta-agonist daily).~~defined as no asthma-related hospital admission, emergency room visit prescription for oral corticosteroids and ≤200 µg/day salbutamol.~~

Results ~~After matching, there were~~The final study consisted of 1330 children in each cohort (mean age 9 years [SD~~]~~ 9, ~~[~~2] ~~years~~; 59% male). ~~All measures of asthma exacerbations and control improved during the outcome year in both cohorts.~~ In the separate ICS+LABA cohort, the odds of achieving overall asthma control were lower (adjusted odds ratio, 0.77 [95% CI, 0.66-0.91] *P* = 0.001) compared with the FDC cohort.

Conclusion ~~Our results~~The study demonstrates a small but significant benefit in achieving asthma control from~~of~~ add-on LABA ~~therapy~~ as FDC, ~~over~~compared to a separate inhaler~~.~~ which supports current guideline recommendations.

INTRODUCTION

Asthma is common amongst children in the UK, with an estimated 8%, 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. Inhaled corticosteroids (ICS), prescribed at step 2 of the current BTS/SIGN guideline, are effective controller medications for most children with persistent asthma. For ~~although from~~ 10–25% of children with asthma, ~~require~~ additional therapy is required.[3-6] For children aged 5-12 years on ICS monotherapy, a~~A~~dding a long-acting β_2-agonist (LABA) ~~to ICS~~ is the preferred step-up option (step 3) recommended by the BTS/SIGN when asthma is uncontrolled.~~for children ages 5-12 years with uncontrolled asthma on ICS monotherapy.~~[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.[2] However, ~~preferred over adding LABA as a separate inhaler,[2] but~~ some children continue to be prescribed separate inhalers. One risk of prescribing LABA as a separate inhaler is its use without concomitant ICS therapy. ~~and~~This is a major concern discussed in the National Review of Asthma Deaths ~~recommended that LABA "should be prescribed with an inhaled corticosteroid in a single combination inhaler"~~.[7]

The benefit of FDC over 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 months [8] and 6 months[9] ~~treatment~~, when comparing ~~between~~ groups randomized to LABA as separate inhaler or FDC. However, patient behavio~~u~~r~~s~~ 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 LABA as an FDC compared ~~with additional~~with a separate inhaler.[4] ~~but importantly~~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 LABA as a separate inhaler are younger and on a lower dose of ICS compared with those stepped up to FDC~~.~~,[10] ~~and~~ T~~t~~hese baseline differences might explain the apparent superiority of FDC over LABA as 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 ~~evaluate whether~~compare outcomes ~~differ~~ between children ~~with asthma~~ stepped up to add-on LABA as separate ~~vs.~~inhalers, versus those receiving FDC inhalers. Our hypothesis was that children stepped up to separate inhalers would have ~~increased~~ reduced odds for ~~poor~~ 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 two large primary care databases including ~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), which 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 over 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 over 400 UK practices caring for approximately half a million patients with asthma.[17] thatAs well as contains anonymous routine medical records, the database contains data and patient-completed questionnaire data. from over 400 practices throughout the UK caring for approximately a half million patients with asthma.[17] Data were available from January 1990 through April 2012 for the Clinical Practice Research DatalinkCPRD and through December 2012 for the OPCRDOptimum Patient Care Research Database.

The study was conducted to standards recommended for observational research[18] and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.[19] (ref 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 Optimum Patient Care Research Database has been approved by the Trent Multi Centre Research Ethics Committee for clinical research use, and. Tthe protocol for this study was approved by the Anonymized Data Ethics Protocols and Transparency (ADEPT) committee, - the independent scientific advisory committee for the Optimum Patient Care Research DatabaseOPCRD. Further background information is available in the online supplementary material.

Inclusion and exclusion criteria

Our study included a two-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: either a ~~Read~~ read code diagnosis of asthma or ~~with ≥2~~2 or more inhaler prescriptions (at least 1 of which~~including ≥1 for~~ was for ICS in the previous 12 months) - (~~the~~ the latter comprise 2% of the study population[10]~~)~~; ~~prescribed~~ prescription of~~a~~ step-up with LABA, from ICS monotherapy at 5–12 years of age; registered in the database for ~~≥2~~at least 2 sequential years, including 1 baseline year before the date of therapy step-up (~~the~~ index date). Exclusion criteria were: cystic fibrosis or any chronic respiratory disease other than asthma; receipt of add-on therapy (including combination inhaler) at any time prior to the index date; treatment with ~~>7 consecutive days~~ oral corticosteroids (OCS) for more than 7 consecutive days during the baseline year; multiple step-up therapies on the index date; ≥50% increase or decrease in ICS dose on the index date (the latter ensured that we studied outcomes of addition of LABA independent of change in ICS).

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Study Outcomes

The primary endpoint, previously described[~~19-21~~20-22], was an adjusted odds ratio (aOR) for overall asthma control. This compared two 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). ~~(expressed as an adjusted odds ratio, aOR)~~ ~~and this~~The definition of asthma control includes both components of the American Thoracic Society/European Respiratory Society[~~22~~23] definition ~~of asthma control~~, i.e. the level of clinical asthma control (as evidenced here by short acting beta agonist use) and the risk of future adverse events (as evidenced here by a history of adverse events including hospitalisation, ~~ED~~ emergency visits and receipt of OCS). ~~Overall~~ The criteria for overall asthma control, as defined ~~is defined~~ in T~~t~~able ~~1~~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 µg/day

salbutamol or ≤500 µg/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 absence of same in the definitions of asthma control) because in clinical practice antibiotics may be prescribed for an asthma exacerbation.[23-25][24-26] Secondary outcomes were acute respiratory events, severe exacerbations,[26][23] risk-domain measure of asthma control (to give insight into risk for future exacerbation)[19-21][20-22] and treatment stability (see Table 1 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:

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

~~as the [number of inhalers x doses per inhaler] divided by 365 multiplied by strength (in µg).~~

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~~nd~~ 2:~~1~~ 1 ratio for extrafine beclomethasone (Qvar):~~-~~BDP. The ICS medication possession ratio (MPR) was calculated as:

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

~~the number of days coverage of the drug prescribed divided by 365 multiplied by 100 and expressed as~~ Individuals were ~~<80%~~ categorized as either~~(~~ non-adherent (MPR<80%), ~~)~~ ~~and~~or adherent (~~-~~MPR≥80% ~~(adherent~~).[27,28] The separate LABA inhalers that were available during the study period contained salmeterol or formoterol~~;~~ T~~t~~he FDC ICS/LABA inhalers contained fluticasone-salmeterol (Seretide), budesonide-formoterol (Symbicort), and extrafine beclomethasone-formoterol (Fostair).

Statistical analyses and sample size

Children in the two treatment cohorts ~~(separate ICS+LABA and FDC ICS/LABA)~~ were matched sequentially 1:1 on the following criteria, which were ~~either~~ known to differ at baseline~~base line~~[4]: year of index date (±3 years), age (exact year), ~~baseline year~~ number of severe exacerbations (0 or ≥1) during baseline year, prior ICS daily dose (≤150, 151–250, 251–500, or >500 µg/day), and ~~baseline year~~ mean daily SABA dose (0, 1–200, >200 µg/day) during baseline year. Bespoke software was used to randomly select unique matched patient pairs when more than one match was possible.

Data were prepared for analysis by investigating potential outliers, transforming skewed data (e.g., log transformation), and categorizing heavily skewed data.~~;~~ M~~m~~issing data were investigated for type and reason for missingness. ~~All matched unadjusted baseline and outcome data were tabulated using summary~~ Summary statistics were computed, by cohort, for baseline characteristics and outcome events. ~~and~~ They were compared using conditional logistic regression (unadjusted) ~~and an intention-to-treat analysis, whereby all children were included in the outcome year analyses.~~.

Conditional logistic regression models were used to estimate adjusted odds ratios (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 ~~to. estimate a~~ Adjusted ~~ratio~~ rate ratios (aRR) were computed ~~and~~ with 95% CIs, with 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 confidence intervals ~~(CIs) and adjusted for potential baseline confounders.~~ .

~~Conditional logistic regression models were used to estimate adjusted odds ratios (aOR) and 95% CIs for the dichotomous outcomes, e.g. overall asthma control, with FDC ICS/LABA as the reference, and adjusted for potential confounding factors.~~

For all multivariable models, those variables that were significantly different or showed a trend towards a difference ($P < 0.10$) between the treatment cohorts at baseline were included as potential confounding factors, along with any strongly predictive variables. Potential confounders examined are listed in the online supplementary material (Table ~~S1~~E1). Variables were examined for collinearity and clinical importance and were then removed in a backwards stepwise procedure until all confounding variables remaining in the multivariable model had $P < 0.1$ (see online supplementary material for further details).

All analyses were done on an intention-to-treat basis, i.e. children remained in their original cohort even if their treatment method changed during the outcome year. Statistical significance was set at the 5% level, i.e. $P < 0.05$.

~~———~~ No prospective power calculation was carried out since our sample size was determined by the number of eligible children in ~~CPRD~~ the Clinical Practice Research Datalink and ~~OPCRD~~Optimum Patient Care Research Database.

The analyses were carried out using IBM SPSS Statistics version 21 (SPSS Statistics, IBM, Somers, NY, USA), SAS version 9.3 (SAS Institute, Marlow, Buckinghamshire, UK), and Microsoft Excel 2007 (Microsoft, Bellevue, WA, USA)~~;~~ ~~statistically significant results were defined as $P < 0.05$.~~.

RESULTS

Patients

Overall, 1390 and 3771 children were eligible for the FDC ICS/LABA and separate ICS+LABA cohorts, respectively (see Ffigure E1 in supplementary file). Ninety seven percent of children had a diagnosis of asthma and 70% were from OOPCRDthe Optimum Patient Care Research Database. After matching there were 1330 children in each cohort, of mean age (SD) 9 (2) years (SD, 2), and 59% were male (Ttable II2). The two cohorts were similar in characteristics apart from the separate ICS+LABA cohort having: higher dose of ICS at baseline,–; higher annualized ICS dose, and; and the LABA step--up occurring one year earlier (i.e. 2005 versus 2006) compared to the FDC cohort, (Ttable 2 II and Ttable ES2).The cohorts were well-matched for indicators of baseline asthma severity and control (Ttable 3III).

Outcomes

Primary outcome

TIn the FDC ICS/LABA cohort, the proportion of children who achieved overall asthma control was 35% before the index datea and 43% afterwards. among Equivalent proportions in the FDC cohort and corresponding proportionsseparate ICS+LABA cohort were 35% and 37% among the ICS+LABA cohort(Table III).: The adjusted odds ratio (aOR) for children in the separate ICS+LABA cohort achievinge control relative to the FDC ICS/LABA cohort was 0.77 (95% CI, 0.66–0.91; *P* = 0.001;), table 3, Ffigure I)1.

Secondary outcomes

The rate number of acute respiratory events was greater among the separate ICS+LABA cohort compared to the FDC ICS/LABA cohort (Table III).group The (adjusted rate ratio ([aRR) was] 1.21; (95% CI, 1.04–1.39; *P* = 0.012; table 3, Ffigure I1). 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 among the children prescribed

~~ICS+LABA relative to FDC~~ was 1.31 (95% CI~~,~~; 0.99–1.72; *P* = 0.056~~; table 3, figure 1~~). Relative to the FDC ICS/LABA cohort, children in the separate ICS+LABA ~~as separates~~ cohort ~~were at~~had reduced ~~-~~odds for~~-~~ achieving risk-domain asthma control (aOR 0.74; 95% CI, 0.61–0.89; *P* = 0.003) and achieving treatment stability (aOR 0.67; 95% CI, 0.57–0.79; *P* < 0.001~~), table 3, ; F~~figure ~~1~~). There were no significant differences between cohorts for adherence (MPR>80%) ~~medication possession ratio being >80%~~ or for severe exacerbations. In the ~~follow up~~outcome year there were 6 hospitalizations for asthma in each cohort ~~(*P* = 0.99)~~. There were 16 children in the FDC ICS/LABA cohort and 3 in the separate~~s~~ ICS+LABA cohort treated for thrush ~~during the follow up year~~ (*P* = 0.008, ~~see on line supplement~~Table E2). Compared to the baseline year, more children in the separate ICS+LABA~~s~~ cohort (29.9% in baseline year and ~~19.6~~22.5% in follow up year) received treatment with antibiotics during the follow~~-~~up year than in the FDC cohort (28.6% and ~~22.5~~19.6% respectively, ~~p~~*P* = 0.041). There was a trend which approached significance for a greater proportion of the ~~separates~~ separate ICS+LABA cohort to receive ~~oral corticosteroid~~OCS~~s~~ compared to the FDC ICS/LABA cohort during the outcome ~~follow up~~ year (8.8% versus 6.5%, p=0.084). ~~but no difference in the number with asthma-related hospital admissions and GP consultations for asthma.~~

Asthma prescribing during outcome year

Asthma therapy prescribed during the outcome year, as well as changes in therapy, are summarized in T~~t~~able ~~4~~IV. Children in the FDC ICS/LABA cohort typically received one fewer SABA inhaler~~s~~ in the outcome year ~~(3 versus 4, table 4)~~ compared with those in the separate ICS+LABA cohort (3 vs. 4 inhalers; *P* < 0.001)~~as separates~~. 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~~as separates~~ (10% vs. 4%; *P* < 0.001), but no more likely to have LTRA added. ~~Seventeen percent of children in the ICS+LABA as separates cohort were started on an FDC during the outcome year.~~ The proportion of children achieving adherence~~with~~ (~~-~~MPR>80%) was 33% in the FDC ICS/LABA cohort and ~~was~~ 31% ~~for~~ in the separate ICS+LABA~~- as separates~~ 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~~s~~ cohort ~~-~~switched to FDC, and 17 (1%) children ~~-~~in the FDC ICS/LABA cohort ~~-~~switched to a separate LABA inhaler.~~s~~ ~~and~~ LTRA treatment was started in 122 in the FDC ICS/LABA cohort (9%) and 112 in the separate~~s~~ ICS+LABA cohort (8%).

DISCUSSION

The aim of this matched cohort study was to provide evidence to support guidelines ~~recommending~~ recommendations that children receiving LABA as an add-on to ICS treatment should be prescribed a fixed-dose combination inhaler (FDC) and not an additional, separate LABA inhaler. ~~,~~ It is an important point to establish as ~~prescribing~~ prescription of separate inhalers ~~remains~~ very common in UK clinical practice, despite recommendations ~~.~~[2,3] The main finding was that children prescribed add-on LABA with ICS as separate inhalers had a ~~30~~23% reduced odds of having controlled asthma compared with children prescribed FDC. Additionally the use of separate inhalers was associated with a 21% greater ~~exacerbation~~ 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. ~~, but o~~Our data suggest that the trial should be with FDC in the first instance. Our results provide additional evidence that supports guideline recommendations for LABA to be prescribed as FDC, and not as a separate, inhaler.[2,3]

Although significant, the improvement in outcomes for those treated with FDC was only ~~improved~~ by a small degree compared with treatment with separate ICS and LABA inhalers. ~~(figure 1).~~ We used an intention-to-treat analysis, but ~~know that~~as 17% of the separate ICS+LABA cohort received FDC during the follow up, ~~and~~ 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 to 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 ~~to mean~~for one additional child to achieve ~~d~~ 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 guidelines[3] recommend that before initiating a new drug therapy, adherence to existing therapies should be considered, as well as inhaler technique and the elimination of trigger factors. The adherence in our study suggests that this may not be happening routinely.~~An additional factor may be that adherence was relatively poor for all participants (22-33%). Overall, relatively few children prescribed LABA in our study achieved overall asthma control (35-43%), and whilst this is partly related to the moderate severity of their disease this study highlights the burden of respiratory morbidity in children with asthma which can be at least partly improved by FDC prescription in place of ICS and LABA separates, typically one fewer SABA canister per annum.~~

There is little prior published work comparing outcomes with FDC versus separate inhalers for children prescribed add-on LABA, yet many thousands of children are prescribed LABA each year. Outcomes were similar with FDC versus separate inhalers for children in two ~~relatively short~~ double-blind, double-dummy trials with relatively short duration,[8,9] although one trial did observe a greater increase in peak expiratory flow in children receiving FDC compared ~~with ICS+LABA as~~to separate inhaler~~s~~.[9] These studies[8,9] might have been underpowered to detect differences between two effective treatments, and additionally 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. ~~and T~~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] ~~One possible explanation for the findings of Elkout et al.[4] is that the apparent benefit of FDC is due to children receiving separates being at increased risk for adverse outcomes *per se* and our previous work confirms that younger children are more likely to be prescribed separate inhalers[10] and are also more likely to have exacerbations.[30] The present study applied a matched cohort analysis and although there were small differences between~~

~~cohorts in ICS dose at baseline where any effect would minimize any benefit of step up to FDC we are able to conclude that the benefit of FDC over separates is not explained by differences at baseline.~~

The use of an FDC ICS/LABA inhaler has several theoretical benefits over two 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 there may be a biochemical synergy between ICS and LABA with their co-deposition in the airways.[33,34] Moreover, an important advantage of combining ICS and LABA in one inhaler is the prevention of LABA use as monotherapy, which carries potential increased risk of asthma-related mortality. ~~and S~~since 2005 LABA monotherapy is accompanied by a Food and Drug Administration (FDA) "black box" warning in the US.[35,36] ~~A~~ In 2010, the FDA recommended the use of FDC products to ensure compliance with concomitant therapy in pediatric and adolescent patients.~~ation was that "a FDC product…be used 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 use of a single FDC ICS/LABA inhaler rather than two separate inhalers is generally acknowledged.[2] We found no evidence for improved ICS adherence between cohorts, in terms of refill prescription rates., ~~but~~ However, the increased number of children treated for thrush in the FDC ICS/LABA compared to the separate ICS+LABA cohort~~s~~ might suggest increased adherence with ICS in the FDC cohort, ~~-~~ but may reflect a lower proportion using a spacer device compared to the separate~~s~~ 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 one randomized controlled trial (patients ~~ages~~ aged 16–65 years) where ~~covert~~ 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 al.[39] found that MPR was similar for children prescribed separate ICS and +LABA inhalers and FDC LABA/ICSonly. Further, and it is possible that although separate ICS and LABA inhalers are issued with equal frequency, adherence with ICS is higher compared with separate LABA separateinhalers. Clearly more research is needed in this area but the limited data from children presented here and from adults elsewhere[38] suggest that FDC is associated with superior outcomes compared with ICS plus LABA as separates and . Potentially, this difference may be explained by different taking behavior, e.g. taking more separates inhalers when symptomatic.

Treatment with a "SMART" regimen[40] (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[4041] but this work has not been confirmed elsewhere or incorporated into guidelines to date.

Antibiotics are not recommended for the treatment of acute asthma excerbations in any age group, but since antibiotics are commonly prescribed for childhood asthma exacerbations,[23-2524-26] failure to consider antibiotic prescribing will result in missing a large number of exacerbations. One study of 60 million asthma exacerbations reported that one in six pediatric exacerbations were treated with antibiotics., and Oonly 26% of those treated with antibiotics received corticosteroid treatment (i.e. 12% of all exacerbations)[2526] 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 and using a full outcome year for examining asthma-related outcomes to , 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 LABA as separate inhaler or FDC.,[10] and thisMatching resulted in two cohorts with similar demographic characteristics and baseline indicators of asthma severity and control.; Aadjustments were made for minor residual confounding. We studied children receiving their first therapy step-up with 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. whichThis brings the benefits of a large representative sample size, but which but it cannot capture aspects of asthma control such as nocturnal or exertional symptoms, however we are able tothough it can capture use of relieving medication which is 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 data date the FDC ICS/LABA cohort was identified one year after the separate ICS+/LABA cohort, reflecting the later introduction of FDC to clinical practice compared to 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 separates separate ICS+LABA cohort had received less ICS duringever the previous baseline year compared to the FDC cohort (143 versus 164 µg). Due to the small size of this difference and the fact the cohorts are well-matched elsewhere, and we do not believe that this difference has affected the difference seen between cohorts. Moreover, as in any observational study there was the potential for bias, for example,Another potential source of bias is in differential prescribing with regard to add-on LABA inhaler choice. This that could in turn influence outcomes. Missingness was present but was equally distributed across the two cohorts, e.g. only 60% of children had height and weight data available. The children with the most severe asthma, i.e. maintenance oral corticosteroids, were excluded from the analysis and our results cannot necessarily be extrapolated to this very small group of patients. Children with small changes

~~in ICS dose than recommended (i.e. <50%) were also excluded from our analysis meaning that our results cannot be extrapolated to this clinical setting.~~ 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. ~~so~~ It is unlikely that our~~the~~ inclusion criteria for asthma diagnosis ~~are not likely to~~ affected the results.

In concluding, we used routinely acquired healthcare data ~~are a valuable source for determining~~to evaluate asthma treatment benefits in a real world setting ~~and complement results from clinical trials.~~. Our results, which are based on data collected from 2660 children, provide evidence that ~~for the whole population~~ LABA treatment in children should be administered as an FDC and not as a separate inhaler.

Competing interests

MT. Neither MT 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 Inglehiem, GSK, MSD, Teva. He has received honoraria for attending advisory panels with; Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Novartis. He has received sponsorship to attend international scientific meetings from: GSK, Astra Zeneca, Mundipharma. He has received funding for research projects from: GSK, Almirall. He is chief medical adviser to the charity Asthma UK, a member of the BTS SIGN Asthma guideline group and the NICE Asthma guideline group.

DP. Board Membership: Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva. Consultancy: Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva. Grants/Grants Pending: UK National Health Service, British Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, and Zentiva. Payments for lectures/speaking: Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyePharma, Takeda, and Teva. Payment for manuscript preparation: Mundipharma and Teva. Patents (planned, pending or issued): AKL Ltd

Payment for the development of educational materials: GSK, Novartis. Stock/Stock options: Shares in AKL Ltd which produces phytopharmaceuticals and owns 80% of Research in Real Life Ltd and its subsidiary social enterprise Optimum Patient Care. Payment for travel/accommodations/meeting expenses: Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva. Funding for patient enrolment or completion of research: Almirall,

Chiesi, Teva, and Zentiva. Peer reviewer for grant committees: Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), HTA (2014). Unrestricted funding for investigator-initiated studies: Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva.

At the time of the study analyses, AB and KR were employees of RiRL, 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, Zentiva.

ST and CM have no conflicts of interest to declare.

Contributorship

ST, CM, MT and DP conceived the idea for the analysis. KR and AB analyzed the data. EVH and ST wrote the first draft of the paper. All authors made contributions to the final paper.

Acknowledgements

The authors thank Prof Stanley Szefler for his comments on the paper, and Lisa Law for help with editing.

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630 **Table I~~1~~** Definitions of database-derived primary and~~study~~ secondary study outcomes.
631 ~~Definitions of oral corticosteroid use and respiratory consultation are provided in the~~
632 ~~supplement.~~

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 OCS or antibiotic with evidence of respiratory consultation; average daily prescribed dose of ≤200 µg/day salbutamol or ≤500 µg/day terbutaline (equivalent to ≤2 puffs daily of reliever medication).	
Secondary endpoints *(determined over 12 months)*	
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.	
Rate of 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, ***and*** no prescription for acute course of oral	

corticosteroids with evidence of a respiratory consultation, ***and*** 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.

633 Definitions of oral corticosteroid use and respiratory consultation are provided in the
634 supplement.
635

Table II2 Baseline characteristics of children prescribed add-on LABA as 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 difference between cohorts
	Male sex, n (%)	780 (58.6)	779 (58.6)	0.97†
	Age at index date, mean (SD)	9.4 (2.2)	9.4 (2.2)	n/a†
Weight categories‡	Not obese or overweight (i.e. <91th BMI centile)	571 (42.9)	542 (40.8)	0.11
	Overweight (i.e. 91–97th BMI centile)	118 (8.9)	111 (8.3)	
	Obese (i.e. ≥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)	0.083

(%)	Eczema diagnosis	664 (49.9)	658 (49.5)	0.81
Year of index date, median (IQR)		2006 (2004–2008)	2005 (2003–2007)	<0.001
Year since first asthma script, median (IQR)		3 (1–5)	3 (1–6)	0.29
Median (IQR) annualized daily ICS dose, µg/d¶		143 (82–247)	164 (99–274)	0.001
ICS dose prescribed before index date, n (%)	≤150 µg/d	0 (0)	0 (0)	n/a†
	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 (%)¶	0 µg/d	21 (1.6)	21 (1.6)	n/a†
	≤200 µg/d	652 (49.0)	652 (49.0)	

	>200 µg/d	657 (49.4)	657 (49.4)	

†Matching variable.

‡ Cut offs for overweight and obese recommended by the Royal College of Paediatrics and Child Health.[41]

¶The doses of ICS and SABA were averaged over the baseline year using the formula [number of inhalers x doses per inhaler] divided by 365 x 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 ~~doubled~~halved.

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; OPCRD, Optimum Patient Care Database; SD, standard deviation.

Table III~~3~~ Study endpoints, and their components, during the baseline and outcome years. Negative binomial logistic regression models which yield adjusted. Unadjusted p values are presented here. Adjusted Odds Ratio and Rate Ratio with p values are presented in ~~figure~~ Figure ~~one~~l.

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 difference between groups during the follow up years relative to baseline year without adjustment**
Achieve overall asthma control	469 (35.3)	464 (34.7)	0.59	543 (43.1)	495(37.2)	0.001
Acute respiratory events, mean (SD)	0.49 (0.84)	0.54 (0.92)	0.084	0.32 (0.71)	0.39 (0.75)	0.011

Acute respiratory events, n (%)	0	883 (66.4)	857 (64.4)	0.21	1031 (77.5)	966 (72.6)	0.003
	1	300 (22.6)	316 (23.8)		217 (16.3)	256 (19.2)	
	≥2	147 (11.1)	157 (11.8)		82 (6.2)	108 (8.1)	
Severe exacerbations, n (%)	0	1157 (87.0)	1157 (87.0)	0.54†	1237 (93.0)	1205 (90.6)	0.056
	1	136 (10.2)	131 (9.8)		68 (5.1)	98 (7.4)	
	≥2	37 (2.8)	42 (3.2)		25 (1.9)	27 (2.0)	
Achieved risk-domain asthma control, n (%)		846(65.1)	820480 (63.9)	0.21	999 (77.4)	973 (72.5)	0.003
Achieved treatment stability, n (%)		n/a	n/a	n/a	842 (65.6)	947 (56.9)	<0.001

†Matching variable. Note: severe exacerbations were matched as 0 or ≥1.

FDC, fixed-dose combination; GP, general practice; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; n/a, not applicable; SABA, short-acting β-agonist.

Table IV4 Asthma therapy prescribed during the outcome year

Outcome	FDC ICS/LABA (n=1330)	Separate ICS + LABA (n=1330)	p value for difference between groups
SABA inhalers, median (IQR)	3 (2–6)	4 (2–7)	<0.001
Change in therapy (any time), n (%)	244 (18.3)	326 (24.5)	<0.001
Increase in ICS dose ≥50% (any time)	133 (10.0)	58 (4.4)	<0.001

†The doses of ICS and SABA were averaged over the outcome year using the formula [number of inhalers x doses per inhaler] divided by 365 x strength (in µg). SABA doses were converted to puffs using the formula 100 µg = 1 puff. The doses of ICS were standardized to equivalence with standard-particle beclomethasone; thus, the actual doses of budesonide were used, and doses of extrafine beclomethasone and fluticasone were doubled.

FDC, fixed-dose combination; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist~~; LTRA, leukotriene receptor antagonist~~; n/a, not applicable (comparison not possible because of 0 or low number); SABA, short-acting β_2-agonist.

661 **FIGURE LEGEND**

662

663 **Figure ~~1~~1.** Adjusted asthma-related outcome measures comparing matched treatment
664 cohorts during 1 outcome year. adjOR/adjRR, adjusted odds ratio/rate ratio; FDC, fixed-dose
665 combination; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting
666 β_2-agonist
667 *p=0.002. Adjusted for nonsteroidal anti-inflammatory drugs
668 †p=0.012. Adjusted for baseline acute respiratory events and paracetamol prescription
669 ‡p=0.057. Adjusted for baseline severe exacerbations and number of asthma and non-
670 asthma consultations
671 §p=0.001. Adjusted for paracetamol prescription
672 ¶p=0.001. Adjusted for data source

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Online data repository

Long-acting beta-agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids

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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 categorised 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 non-obese/non-overweight*†

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 (GERD), 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 in-patients admissions for asthma;
- Number of ER attendances for asthma;
- Number of ER attendances or in-patient 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: beta-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 years, > 1 year)
- Database (OPCRD vs. CPRD)

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

† Non-overweight/non-obese was defined as BMI index <91st. Overweight was defined as BMI centile ≥91st and <98th. Obese was defined as BMI centile ≥98th.

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)	0.18
≥1 asthma-related OPD visit, n (%)	15 (1.1)	11 (0.8)	0.44	5 (0.4)	7 (0.5)	0.57
Total GP consultations, median (IQR)	6 (3–9)	6 (3–9)	0.77	5 (3–8)	5 (2–8)	0.38
GP consultation not for asthma, median (IQR)	3 (2–6)	4 (2–6)	0.86	3 (1–6)	3 (1–5)	0.19
Spacer device prescribed, n (%)	366 (27.5)	379 (28.5)	0.57	257 (19.3)	334 (25.1)	<0.001
Thrush, n (%)†	10 (0.8)	9 (0.7)	0.81	16 (1.2)	3 (0.2)	0.008

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

Repository - Unmarked Text

Online data repository

Long-acting beta-agonist in combination or separate inhaler as step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids

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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 one 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 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.

emergency room; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist.

Statistical analyses

Variables that differed between treatment groups with $p<0.10$ were examined for collinearity and clinical importance to select those used as potential confounders in the regression modelling of outcomes. In addition, multivariable analyses were used to identify baseline variables that were predictive (at $p<0.05$) of each outcome variable during the outcome period; these were considered as potential confounders when modelling 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 modelling stage. In general, collinearity was considered an issue for relationships with rank correlation coefficients >0.30. Potential confounders examined are listed in Table E1.

Figure Legend

Figure E1 Patient selection and matching: Patients in the two treatment cohorts were matched on clinically and demographically important characteristics.

CPRD, Clinical Practice Research Datalink; FDC, fixed-dose combination ICS/LABA; 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.

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