

High-dose inhaled corticosteroids versus add-on long-acting β -agonists in asthma: An observational study

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Background: Guidelines recommend that for patients uncontrolled on inhaled corticosteroids (ICSs), step-up options include an increase in ICS dosage or addition of a long-acting β -agonist (LABA). Controversy persists about the best option in routine practice.

Objective: To compare asthma outcomes in patients whose first step-up from ICS monotherapy was by addition of LABA (LABA cohort) or increase in ICS dosage or formulation (ICS cohort).

Methods: Observational study using the General Practice Research Database, comparing outcomes in the following 12 months with regression modeling allowing for baseline cohort differences: age, sex, socioeconomic status, body mass index, comorbidity (rhinitis, heart disease), smoking status, short-acting β -agonist (SABA) use, oral corticosteroid use, and use of asthma complicating medication.

Results: We found 46,930 patients in the ICS and 17,418 in the LABA cohort. In adjusted analysis, the odds ratio (95% CI) of successful treatment (no hospitalization, no oral corticosteroid use, average daily SABA use <1 dose/d) was lower in the ICS cohort (0.75; 0.72-0.79). The adjusted odds ratio of needing rescue SABA prescriptions was higher in the ICS cohort (1.67; 1.59-1.76). However, the adjusted odds of using any oral corticosteroids were lower (0.75; 0.71-0.78), particularly of using 3 or more courses (0.50, 0.46-0.55), and the adjusted odds of respiratory hospitalization were lower (0.69; 0.59-0.81).

Conclusion: Although symptomatic control and rescue bronchodilator use may be improved by the addition of a LABA to ICS, there may be a lower risk of severe exacerbations and hospitalizations from ICS dose increase. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, long-acting β -agonist, inhaled corticosteroid, safety, inflammation, observational study

Asthma is a common chronic illness characterized by airways inflammation and is principally treated with inhaled anti-inflammatory and bronchodilator medication.¹ Pharmacotherapy for asthma is generally effective, and many patients achieve control with inhaled corticosteroids (ICSs) plus rescue short-acting β -agonist (SABA) bronchodilators. Most patients who remain uncontrolled can achieve guideline-specified control either by increasing the dose of ICS or by adding second pharmacotherapeutic agents,² yet currently many patients remain uncontrolled.³⁻⁵ Patients with persistent symptoms should be prescribed maintenance therapy with ICS at low to moderate doses,^{6,7} which in the United Kingdom (UK) is defined as up to 800 μ g/d beclomethasone dipropionate or equivalent for adults.⁷ Although higher doses of ICS were previously recommended,⁸ recent evidence suggests that the addition of a long-acting β -agonist (LABA) is a better option for most. High doses of ICS are not without problems and have been associated with a dose-related increase in risk of corticosteroid-related adverse outcomes.⁹⁻¹² In addition, for many, the maximum clinical benefits will occur at low doses.¹³ Asthma control is a complex concept encompassing different physiological and patient-centered factors including exacerbation frequency, and different therapies may have differential effects on aspects of control such as lung function, exacerbation frequency, and day-to-day symptom minimization.¹⁴

Initial fears that the increasing use of long-acting bronchodilators could mask untreated inflammation and lead to a higher risk of adverse outcomes,^{15,16} particularly severe exacerbations and deaths, were allayed by the data from head-to-head studies comparing the addition of a LABA to the same dose of ICS to increasing the dose of ICS. These studies reported reduced overall symptoms in those given LABAs, and suggested that the asthma exacerbation risk was even reduced by LABA add-on therapy.¹⁷ Concerns have re-emerged recently after the premature closure of a large US randomized double-blind observational study comparing the safety of salmeterol, a LABA, with placebo in addition to usual care¹⁸ after a higher death rate was found in the LABA arm. An older, double-blind randomized safety study comparing the safety of LABA with SABAs had also found a nonstatistically significant increase in deaths in the LABA arm, with a comparable number needed to harm.¹⁹ These studies have prompted a re-

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Abbreviations used

BMI:	Body mass index
GINA:	Global Initiative for Asthma
GPRD:	General Practice Research Database
ICS:	Inhaled corticosteroid
IQR:	Interquartile range
LABA:	Long-acting β -agonist
OR:	Odds ratio
SABA:	Short-acting β -agonist
UK:	United Kingdom

evaluation of the risk-benefit profile of inhaled β -agonists in asthma with an ongoing debate^{20,21} regarding their safety profile. This has prompted US regulators to issue patient safety warnings with all LABA containing preparations,^{22,23} and other regulators internationally to re-evaluate safety data.

Fortunately, life-threatening asthma attacks and deaths are rare events, but because of this, differences between arms will not emerge clearly from randomized controlled trials unless very large numbers of patients are studied. Recent meta-analyses pooling data from randomized controlled studies have continued to raise concerns.²⁴ The patient characteristics and the behavior of patients and clinicians in everyday clinical practice are often different from those observed in a controlled trial setting.²⁵ We compared markers of efficacy and safety in cohorts of patients stepped up from ICS monotherapy to either a higher dose of ICS or the addition of a LABA in routine clinical practice, using a large and well validated UK clinical and prescribing database.

METHODS

This was a retrospective observational study using deidentified individual patient clinical and prescribing information routinely collected by UK general practitioners subscribing to the General Practice Research Database (GPRD), a large, well validated UK database extensively used in pharmaco-epidemiologic studies and described elsewhere.²⁶

Cohorts of patients with asthma were identified whose first step-up detailed in the database in regular preventative pharmacotherapy was from ICS monotherapy (with or without SABAs) to either the addition of a LABA (addition of a separate LABA inhaler or switch to a combination ICS-LABA preparation containing the same ICS molecule and dose)—the LABA cohort—or to a higher dose of ICS (either by an increase in the daily beclomethasone equivalent microgram dose on the prescribing instructions, or if prescribing instructions were unclear, to a higher strength inhaler)—the ICS cohort. Subjects with a minimum of 12 months of clinical and prescribing data before the index event date were included. For the purposes of dose comparison, potency ratios for different ICS molecules were assumed as beclomethasone: budesonide: fluticasone: mometasone: ciclesonide: ultrafine particle beclomethasone (Qvar, Tera Ltd.) as 1:1:1:2:2:2:2, and doses are expressed as beclomethasone equivalent.

(Details of the search strategy and Read codes used for diagnostic, consultation, and pharmacotherapy searches are shown in the Appendix in this article's Online Repository at www.jacionline.org.)

Cohort membership was defined by the following:

- Membership of the database for a minimum period of 3 complete years from 1991 to 2004.
- Previous prescription for any ICS monotherapy preparation (with no other antiasthma regular therapy other than a SABA), with registration with practice and clinical details present for at least 12 months before first-ever recorded ICS prescription.
- Coded asthma diagnosis and lack of coded chronic obstructive pulmonary disease diagnosis.

- Full clinical details for at least 12 months after the index date, defined as the date of first increase in asthma therapy after initiation of ICS therapy.
- ICS cohort: an increase in ICS therapy occurs on the index date (either by an increase in daily dose prescribed based on prescribing instructions and inhaler strength or, in the absence of prescribing instructions, by an increase in the strength of inhaler, device, or molecule) to a higher equivalent ICS dose.
- LABA cohort: a change in therapy occurs on index date by the addition of a LABA preparation with or without an increase in ICS dose (either as addition of a separate inhaler or by a switch to a combination preparation using the same ICS molecule and delivery device).

Data were collected on cohort members on demography, comorbidity, and surrogate markers of asthma severity and control for the 12 months before and the 12 months after the index date. The primary outcome was treatment success in the 12-month period after the index date, which was a composite measure assessed from Global Initiative for Asthma (GINA) guidelines-based definitions of success and formally defined by the following:

- Successful outcome: no recorded hospital attendance for asthma including admission or emergency department attendance, no prescriptions of oral corticosteroid, and an average daily dose of SABA (calculated from issued prescriptions) of no more than 100 μ g salbutamol or 250 μ g terbutaline.
- Partial success outcome: not meeting successful outcome definition, but no recorded asthma-related hospital attendance as stated, a maximum of 2 prescriptions for oral corticosteroids, and an average daily dose of SABA (calculated from issued prescriptions) of no more than 400 μ g salbutamol or 1000 μ g terbutaline.
- Unsuccessful outcome: 1 or more asthma-related hospital attendances, or more than 2 prescriptions for oral corticosteroids or an average daily dose of SABA (calculated from issued prescriptions) of more than 400 μ g salbutamol or 1000 μ g terbutaline.

Secondary outcomes were surrogate markers of asthma exacerbations (oral corticosteroid courses and hospitalizations) and of asthma symptoms (SABA prescriptions).

Statistical methods

The GPRD data were entered into an electronic database (MySQL 5.0, Sun Microsystems, Santa Clara, Calif) and the search algorithm applied (see Appendix in the Online Repository). Data were analyzed in SPSS version 15 (SPSS Inc, Chicago, Ill). Descriptive statistics (Mann-Whitney test and χ^2 test) were used to compare baseline factors between the 2 cohorts. All analyses were specified a priori. Odds ratios (ORs; 95% CIs) for 2 dichotomized definitions of successful treatment were calculated by using a binary logistic regression model with treatment success as the dependent variable and cohort together with potential confounding factors (year of step-up, age, sex, socioeconomic status, comorbidity, SABA daily dose, and treatment with medication that may affect asthma outcomes) as explanatory variables. Sensitivity analyses were performed by further including potentially confounding factors for which incomplete data were present (body mass index [BMI], smoking status, and baseline ICS dosage) in the regression model. Multiple logistic regression was also used to determine the independence of cohort on each of the secondary outcomes after adjustment for a range of potential confounders. A nominal regression model was constructed with either receipt of oral steroid courses or average daily dose of SABA in the outcome period as the dependent variable and cohort membership, year of step-up, and potential confounding factors as explanatory variables. The analyses of the primary and secondary outcomes was then stratified by age group (19 years or less, 20-39 years, 40-59 years, 60 years or more) and oral corticosteroid use in the baseline period (see Table E1 in this article's Online Repository at www.jacionline.org).

The logistic models described all give adjusted ORs and their 95% CIs, although some clinicians prefer to think in terms of relative risks. Because the outcomes in the current study are all common, the OR is not a good approximation of the relative risk. Therefore, we used a conditional standardization method as described by Localio et al²⁷ to calculate relative risks for the primary and secondary outcomes (see Table E2 in this article's Online Repository at www.jacionline.org).

TABLE I. Baseline characteristics of the 2 cohorts

	ICS cohort (N = 46,930 unless indicated)	LABA cohort (N = 17,418 unless indicated)	P value
Male sex (%)	46.3	41.0	<.001
Age at index date (y), median (IQR)	25 (10-49)	42 (20-58)	<.001
BMI, number with data (kg/m ²), median (IQR)	N = 34,102 23.87 (19.61-28.10)	N = 13,781 25.40 (21.90-29.21)	<.001
Recorded rhinitis (%)	21.1	21.4	.371
Socioeconomic status, median (IQR)	18.41 (9.55-33)	17.59 (9.27-30.93)	.001
Recorded gastroesophageal reflux disease (%)	1.4	2.0	<.001
Recorded cardiovascular disease (%)	19.1	25.7	<.001
SABA use			
Taking none (%)	25.8	15.6	<.001
Among takers only, median doses/d (IQR)	0.82 (0.55-1.64)	1.10 (0.55-2.19)	<.001
Inhaled corticosteroid daily dose prescribed on latest prescription for those with clearly defined prescribing instructions (µg/d), median (IQR)	N = 38,099 400 (200-400)	N = 13,566 400 (400-800)	<.001
Oral steroid prescription for asthma in previous 12 mo (%)	23.2	32.4	<.001
Antibiotics prescription for respiratory indication in previous 12 mo (%)	29.1	27.9	.004
One or more general practitioner asthma consultations in previous 12 mo (%)	57.6	63.4	<.001
One or more respiratory hospital admissions in previous 12 mo (%)	1.9	1.5	.001
Prescription for β-blockers in previous 12 mo (%)	2.1	3.0	<.001
Prescription for nonsteroidal anti-inflammatory drug in previous 12 mo (%)	15.7	21.5	<.001
Prescription for acetaminophen in previous 12 mo	22.4	24.7	<.001
Smoking status: number with data	N = 36,422	N = 15,451	
Never smoked, no. (%)	55.4 (20,175)	55.7 (8,601)	<.001
Passive smoker, no. (%)	6.0 (2,185)	3.4 (527)	
Exsmoker, no. (%)	5.2 (1,899)	6.0 (926)	
Current smoker, no. (%)	33.4 (12,163)	34.9 (5,397)	

Ethical approval

Ethical approval of the study was provided by the Scientific and Ethical advisory group linked to GPRD.

Funding

Costs for accessing the GPRD database were met by Schering-Plough, but this pharmaceutical company had no involvement in the protocol, data analysis, or manuscript preparation, and no funding was received from any other source for this study.

RESULTS

A total of 46,930 patients with asthma were identified whose first increase in therapy was to a higher dose or different formulation of ICS (ICS cohort) and 17,418 patients whose first increase in therapy was by the addition of a LABA (LABA cohort), either by the addition of a second LABA inhaler or by switch to a combination ICS-LABA inhaler. The proportion of patients stepped up by the addition of a LABA as first increase in maintenance therapy rose from 22.5% in 1991 to 57% in 2003 (see this article's [Table E3](#) in the Online Repository at www.jacionline.org). The median (interquartile range [IQR]) time from the commencement of ICS monotherapy to the step-up was 663 (196-1449) days in the ICS cohort and 1412 (741-2443) days in the LABA cohort.

The baseline characteristics of the 2 cohorts are shown in [Table I](#). It should be noted that because of the large numbers of subjects in the database, statistically significant differences may be apparent even when only minor differences in cohort characteristics

occur; however, it was found that those prescribed LABAs tended to be older, were more likely to be female, and were more likely to have comorbid cardiovascular disease. The LABA cohort had greater SABA use, oral steroid use, and general practitioner consultations in the previous 12 months and had a slightly higher proportion of current smokers. Note that smoking, BMI, and ICS dose data were not recorded for all patients.

Primary outcome: successfully treated patients

In unadjusted analysis, although a similar proportion of patients achieved successful treatment in the ICS and the LABA cohorts, a higher proportion was unsuccessful in the LABA cohort ([Table II](#)). However, when adjustments were made for the baseline differences in potential confounders that existed between the cohorts, more successful outcomes were consistently seen in the LABA cohort in all models, including those from the sensitivity analyses of models with BMI, smoking, and ICS dose before setup as covariates ([Table III](#)).

Further stratified analyses were performed on subcohorts defined by age group (19 years or less, 20-39 years, 40-59 years, 60 years or more) and by the presence or absence of oral corticosteroid use in the baseline period and are presented in the on-line supplement; these adjusted analyses confirmed significantly improved success in the LABA cohort in all age bands for subjects who had not required oral corticosteroids in the baseline period, and for some age bands in subjects who had required oral steroids in the baseline period (see this article's [Tables E1, E4 and E5](#) in the Online Repository at www.jacionline.org).

TABLE II. Unadjusted proportions of patients achieving successful, partially successful, and unsuccessful treatment in the ICS and LABA cohorts

	Successful treatment	Partially successful treatment	Unsuccessful treatment
ICS cohort, % (n)	26.2 (12,299)	48.0 (22,524)	25.8 (12,107)
LABA cohort, % (n)	26.3 (4,581)	43.9 (7,652)	29.8 (5,185)

Secondary outcomes

Oral corticosteroid use. In the 12-month outcome period, 1 or more courses of short burst oral corticosteroid treatment were prescribed to a lower proportion of the ICS cohort than of the LABA cohort (22.2% [n = 10,428] vs 27.0% [n = 4702]; $P < .001$). After multiple logistic regression analyses, and after adjustment for baseline confounders including the year of step-up, there remained a significantly lower likelihood of receipt of 1 or more oral corticosteroid courses associated with the ICS cohort compared with the LABA cohort (OR, 0.75; 95% CI, 0.71-0.78).

A nominal regression model was then constructed with the number of oral corticosteroid courses received in the outcome period (categorized as none, 1 course, 2 courses, or 3 or more courses) as the dependent variable and cohort membership as the explanatory variable (unadjusted analysis) and then with the inclusion of potential confounding factors (including year of switch and demographic factors; Table IV). Both analyses indicated that the membership of the ICS cohort was associated with a significantly lower use of oral corticosteroid use irrespective of number of courses prescribed.

In the stratified analyses, the ICS cohort was associated with significantly lower oral steroid use in all age bands in subjects who had required oral steroids in the baseline period, but only in the older age bands (40-59 and 60+ years) in subjects who had not used oral steroids in the baseline period (see this article's Tables E6 and E7 in the Online Repository at www.jacionline.org).

Respiratory hospitalization. Codes indicating respiratory-related hospitalization were present in the year after the step-up date in 596 patients in the ICS cohort (1.3%) and in 291 patients in the LABA cohort (1.7%). In a binary logistic regression model including potentially confounding baseline factors (year of change in therapy, age, sex, socioeconomic status, baseline oral corticosteroid and SABA use, comorbidity, and use of asthma-affecting medication), the adjusted OR for a respiratory admission was significantly lower in the ICS cohort compared with the LABA cohort (OR, 0.69; 95% CI, 0.59-0.81). When the ICS dose before the step-up was included in the model, the odds of admission remained significantly lower in the ICS cohort (OR, 0.81; 95% CI, 0.66-0.98). In the stratified age-group and oral steroid use analyses, because of the smaller numbers, wide confidence intervals were seen with few statistically significant ORs (Tables E6 and E7).

Short-acting bronchodilator prescriptions. The number of patients requiring no SABA prescriptions in the 12 months after the step-up date was 8727 in the ICS cohort (18.6%) and 3676 in the LABA cohort (21.1%). In a binary logistic regression model including potentially confounding baseline factors (year of switch, age, sex, socioeconomic status, baseline oral corticosteroid and SABA use, comorbidity, and use of asthma-affecting medication), the multiple-adjusted OR for needing any SABA prescriptions was significantly higher in the ICS cohort compared

with the LABA cohort (OR, 1.67; 95% CI, 1.59-1.76). Including the ICS dose before the step-up in the model did not greatly affect the magnitude of these odds (OR, 1.54; 95% CI, 1.45-1.64).

A nominal regression model was constructed with the average number of doses of SABA used (based on issued prescriptions and categorized as none, as many as 0.5 doses/d, 0.5-1.0 doses/d, 1.01-1.5 doses/d, 1.51-2 doses/d, 2.01-3 doses/d, 3.01-4 doses/d, and >4 doses/d) over the 12-month outcome period as the dependent variable and cohort membership as the explanatory variable (unadjusted analysis), and then with the inclusion of the potential confounding factors (including year of switch, demographic and comorbidity factors; see this article's Table E8 in the Online Repository at www.jacionline.org). In the adjusted analyses, the ICS cohort was significantly more likely to have required SABA prescriptions than the LABA cohort. This was maintained across all categories of SABA prescription frequencies. Furthermore, in the age-group and oral steroid use stratified analyses, LABA cohort membership was consistently associated with significantly lower SABA use (Tables E6 and E7).

Because the amount of SABA used at baseline was significantly less in the ICS group, a sensitivity analysis was performed that examined the odds of the primary outcome across quartiles of baseline SABA doses per day (0-0.27, 0.271-0.55, 0.551-1.64, and >1.64). A successful outcome was significantly more likely in the LABA cohort across all quartile groups (see this article's Table E9 in the Online Repository at www.jacionline.org). A similar sensitivity analyses was performed on the primary outcome across strata of baseline ICS dose (<200, 200-400, 401-800 $\mu\text{g}/\text{d}$). Again, the conclusion of significantly more successful treatment in the LABA group was maintained across each stratum (see this article's Table E10 in the Online Repository at www.jacionline.org).

Finally, conditional standardization was used to estimate adjusted relative risks and bootstrap estimated 95% CIs for the primary and secondary outcomes. One thousand simulations were run for each model. In comparison with the adjusted ORs, the adjusted relative risks for the primary outcome tended to be slightly higher (approximately 0.9 compared with 0.75) but were all statistically significant in the same direction as previously. A similar picture was seen for the 3 secondary outcomes (see this article's Table E2 in the Online Repository at www.jacionline.org).

DISCUSSION

This observational study compared surrogate markers of efficacy and safety in patients with asthma whose asthma therapy was increased for the first time from ICS alone to either higher doses of ICS or to the addition of a LABA. We found some differences in the characteristics of those prescribed either a LABA or high-dose ICS in that the LABA cohort participants were on average older, were more likely to be female, and had indications of having more severe or less well controlled asthma. Although these baseline differences were seen between cohorts, these were not too major to preclude comparison between groups, and regression models were constructed to adjust for these differences, with sensitivity analyses run to examine the robustness of the findings. When potential confounding factors were modeled, we observed that, in comparison with increasing ICS dose, LABA use was associated with a higher proportion of patients meeting the successful treatment criteria based on a composite definition derived from GINA guidelines-specified aims of asthma management encompassing exacerbation frequency

TABLE III. OR (95% CI) for successful treatment for ICS cohort versus LABA cohort in unadjusted and multiple-adjusted logistic regression models

	ICS cohort (n) LABA cohort (n)	Successful vs partial/ unsuccessful treatment	Successful/partial vs unsuccessful treatment
Unadjusted	46,930 17,418	1.00 (0.96-1.04)	1.22 (1.17-1.27)
Adjusted for initial confounders*	46,771 17,339	0.75 (0.72-0.79)	0.96 (0.91-1.00)
Adjusted for initial confounders* plus BMI	34,017 13,733	0.75 (0.72-0.80)	0.96 (0.90-1.01)
Adjusted for initial confounders* plus smoking status	36,314 15,396	0.76 (0.72-0.80)	0.92 (0.88-0.97)
Adjusted for initial confounders* plus BMI and smoking status	29,756 12,939	0.76 (0.72-0.80)	0.94 (0.88-0.99)
Adjusted for initial confounders* plus ICS dose before step-up	37,966 13,502	0.75 (0.71-0.79)	0.87 (0.82-0.92)

*Year of step-up, age, sex, socioeconomic status, SABA daily dose, comorbid cardiac disease and rhinitis, β -blocker prescription, nonsteroidal anti-inflammatory drug prescription, acetaminophen prescription, and oral corticosteroid prescription.

and rescue bronchodilator use and reduced rescue bronchodilator requirements, a marker for improved asthma related morbidity.²⁸ The complexity and multidimensional nature of asthma is increasingly appreciated, and an American Thoracic Society–European Respiratory Society task force on asthma outcomes has recently recommended the use of composite outcome measures.¹⁴ There was a small but significant increase in markers of severe exacerbations (oral corticosteroid use and hospitalization) in the LABA cohort. Exacerbations, although relatively infrequent, are of great importance to patients, clinicians, and health care providers because they mark the time of greatest impact on quality of life and mortality risk and the highest medical resource use, so they may be of greater significance than the level of rescue bronchodilator use. Although hospitalizations were infrequent, they are associated with the most severe asthma and with the highest asthma-related costs, so they are of clinical and health economic significance. As in any observational research in which nonrandom allocation of subjects to different therapies or exposures occurs, it is possible that unrecognized and unmeasured confounding factors may have influenced the observed associations, although we have entered all known and measured potentially confounding factors into the regression models. Other statistical approaches such as propensity scoring are also possible in analyzing such data, but have their own limitations, and we feel that the statistical methodology used, presenting both OR and relative risk analysis with sensitivity analyses incorporating stratified analyses and modeling including parameters for which full data were lacking, is the most appropriate.

The studied subjects had clinical records included in the GPRD database from 1991 to 2004. Low to moderate doses of ICS have remained the first-line recommended UK treatment for persistent asthma throughout this time, but the relative strength of endorsement of different options in those uncontrolled on ICS monotherapy has changed; in earlier periods increasing the dose of ICS was the preferred option,²⁹ and currently the addition of a LABA is favored, whereas both strategies have been cited as possible options in intermediate times.³⁰ Although there have been differences over time in the proportion of patients using these alternatives, both have been commonly used. Clear guidance to general practitioners on which option to use has been lacking. In any nonrandomized analysis, factors unrelated to the outcome being considered may confound observed associations, and in this

TABLE IV. Unadjusted and multiple-adjusted ORs (95% CIs) of needing 1, 2, or 3 or more courses of oral corticosteroids in outcome period for patients in ICS versus LABA step-up groups

Oral steroid outcome	Unadjusted	Multiple-adjusted*
0 (Reference group)	1.0	1.0
1 course	0.88 (0.84-0.92)	0.85 (0.81-0.90)
2 courses	0.77 (0.72-0.84)	0.69 (0.64-0.76)
≥ 3 courses	0.54 (0.51-0.59)	0.50 (0.46-0.55)

*Year of step-up, age, sex, socioeconomic status, SABA daily dose, comorbid cardiac disease and rhinitis, β -blocker prescription, nonsteroidal anti-inflammatory drug prescription, acetaminophen prescription, and oral corticosteroid prescription.

analysis we collected as many data on potentially confounding factors in the demography, comorbidity, asthma severity, and co-prescribed medication between cohorts as possible. A number of regression models were constructed to adjust, as far as possible, for the baseline differences between cohorts, and numerous stratified analyses were undertaken. A consistent pattern emerged, with symptomatic control better in those prescribed a LABA, but with a small increase in the risk of exacerbations and hospitalizations over those prescribed higher doses of ICS.

This disconnection between bronchodilator use and exacerbation frequency is consistent with other studies. A recent meta-analysis of randomized controlled studies comparing different step-up strategies found a disconnect between the effects on exacerbations and on symptomatic control from the addition of a LABA to ICS,³¹ although it did not find a significant difference in the exacerbation rates. A potential masking effect of LABA therapy on the symptomatic response to increasing inflammation levels has been reported,¹⁵ and a study comparing a strategy targeting control of inflammation with symptom-based management in severe asthma found that the inflammation strategy resulted in a major reduction in exacerbations, but no significant difference in symptomatic control.³² The results of our study are consistent with the hypothesis that LABA treatment improves symptoms of asthma, but that in a subpopulation, it may mask the symptoms resulting from ongoing inflammation and increase exacerbation risk. Alternatively, the association between LABA treatment and increased exacerbation frequency may be explained by an as yet unidentified confounding factor. Do these data give us information on which is the best option in everyday practice? The

National Institutes of Health guidance on step-wise asthma pharmacotherapy³³ states that combination ICS-LABA therapy is an equally preferred option to increasing the dose of ICS in step 3 care, balancing the established benefits of combination therapy with the possible increased risk of severe exacerbations with daily LABA use, and our data are consistent with this. We feel that until more definitive prospective data are provided, this is a matter of interpretation for the individual clinician faced by the individual patient; however, our findings suggest that in patients deemed at risk of exacerbations (such as those with previous exacerbations), increasing anti-inflammatory medication may be most appropriate, whereas in those with persistent need for bronchodilators, a LABA may be more successful.

The database used is well validated²⁶ and contains a high level of clinical and demographic data that can be used in modeling the outcomes. The weakness of this study, inherent in observational research, lies in the nonrandom allocation of patients to the different treatment options investigated. It is possible that there could be some unidentified patient-related or physician-related factor influencing the choice of therapy and outcome. It is possible that the choice of one or other treatment strategy may act as a marker for better asthma care in the practice; however, it seems to us unlikely that a higher exacerbation frequency in the LABA cohort could be explained by this mechanism. This study recorded only prescribing instructions on issued prescriptions. It cannot be assumed that patients were compliant with these instructions, and low adherence is associated with poor outcomes in asthma³⁴; future studies should assess compliance with different asthma prescribing regimens (including comparisons between ICS and LABA therapy given by a single fixed-dose inhaler or by separate inhalers) and the influence this factor has on outcomes.

In summary, this observational study used routine clinical and prescribing data on more than 65,000 UK patients with asthma whose first step-up of from ICS monotherapy was either to addition of a LABA or to a higher dose of ICS, and observed that, after adjusting for differences in baseline factors, LABA therapy was associated with a higher proportion of patients achieving GINA-specified control driven by lower rescue bronchodilator use, but there was a significant increase in the more serious adverse outcomes of need for oral corticosteroid use and hospitalization.

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Clinical implications: Control of inflammation is needed in asthma to reduce exacerbation frequency.

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TABLE E1. Oral corticosteroid use in the baseline (pre–step-up) 12-month period stratified by age group

Age group	ICS cohort		LABA cohort	
	No use (n, % of cohort age group)	One or more course (n, % of cohort age group)	No use (n, % of cohort age group)	One or more course (n, % of cohort age group)
≤19 y	16,782 (79.5)	4,330 (20.5)	3,142 (74.2)	1,090 (25.8)
20–39 y	7,367 (78.9)	1,967 (21.1)	2,536 (68.0)	1,195 (32.0)
40–59 y	7,150 (73.2)	2,620 (26.8)	3,431 (63.7)	1,958 (36.3)
≥60 y	4,751 (70.9)	1,954 (29.1)	2,666 (65.6)	1,400 (34.4)
Total	36,059 (76.8)	10,871 (23.2)	11,775 (67.6)	5,643 (32.4)

TABLE E2. Relative risk (95% CI) for primary and secondary outcomes for ICS cohort vs LABA cohort

	ICS cohort (n) LABA cohort (n)	Successful vs partial/un-successful treatment	Oral corticosteroid use†	Respiratory hospitalization	SABA prescriptions‡
Unadjusted	46,930 17,418	1.00 (0.99-1.01)	—	—	—
Adjusted for initial confounders*	46,771 17,339	0.89 (0.87-0.91)	0.96 (0.95-0.97)	0.98 (0.97-0.99)	1.34 (1.31-1.37)
Adjusted for initial confounders* plus BMI	34,017 13,733	0.90 (0.88-0.92)	—	—	—
Adjusted for initial confounders* plus smoking status	36,314 15,396	0.90 (0.87-0.92)	—	—	—
Adjusted for initial confounders* plus BMI and smoking status	29,756 12,939	0.90 (0.87-0.92)	—	—	—
Adjusted for initial confounders* plus ICS dose before step-up	37,966 13,502	0.89 (0.86-0.91)	—	0.98 (0.97-0.99)	1.30 (1.25-1.35)

*Year of step-up, age, sex, socioeconomic status, SABA daily dose, rhinitis, β -blockers, nonsteroidal anti-inflammatory drugs, paracetamol, cardiac disease, and oral corticosteroid prescription.

†Year of step-up, age, sex, socioeconomic status, SABA daily dose, rhinitis, β -blockers, nonsteroidal anti-inflammatory drugs, paracetamol, cardiac disease.

‡Year of step-up, age, sex, socioeconomic status, rhinitis, β -blockers, nonsteroidal anti-inflammatory drugs, paracetamol, cardiac disease, and oral corticosteroid prescription.

TABLE E3. Number (%) of patients stepped up from ICS monotherapy to higher-dose ICS or to addition of LABA treatment in each year from 1991 to 2003

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
High-dose ICS	1978 (77.5)	2553 (87.2)	3356 (86.3)	3939 (85.9)	4217 (85.9)	4539 (84.5)	5122 (80.2)	4700 (78.4)	3957 (72.4)	3660 (66.3)	3630 (60.9)	3153 (53.9)	2126 (43.0)
LABA	574 (22.5)	376 (12.8)	534 (13.7)	645 (14.1)	691 (14.1)	834 (15.5)	1266 (19.8)	1295 (21.6)	1506 (27.6)	1858 (33.7)	2329 (39.1)	2692 (46.1)	2818 (57.0)

TABLE E4. Primary outcome: OR (95% CI) for successful treatment vs partial/unsuccessful in ICS cohort vs LABA cohort stratified by age group in subjects with no oral steroid use in baseline (pre-step-up) 12-month period

Primary outcome	≤19 y	20-39 y	40-59 y	≥60 y
ICS-LABA unadjusted	0.91 (0.84-0.99)	0.88 (0.80-0.97)	0.95 (0.87-1.03)	1.01 (0.91-1.12)
Adjusted for initial confounders*	0.69 (0.63-0.76)	0.76 (0.68-0.86)	0.74 (0.66-0.82)	0.79 (0.70-0.90)
Adjusted for initial confounders plus BMI	0.70 (0.62-0.79)	0.77 (0.67-0.87)	0.73 (0.65-0.81)	0.79 (0.69-0.91)
Adjusted for initial confounders plus smoking status	0.72 (0.64-0.81)	0.77 (0.68-0.87)	0.73 (0.66-0.81)	0.80 (0.70-0.91)
Adjusted for initial confounders plus BMI and smoking status	0.71 (0.62-0.83)	0.77 (0.68-0.88)	0.72 (0.64-0.81)	0.79 (0.69-0.90)
Adjusted for initial confounders plus ICS dose before step-up	0.72 (0.64-0.80)	0.76 (0.66-0.88)	0.71 (0.63-0.81)	0.84 (0.72-0.97)

*Year of step-up, sex, socioeconomic status, SABA daily dose, rhinitis, β -blockers, nonsteroidal anti-inflammatory drugs, paracetamol, and cardiac disease.

TABLE E5. Primary outcome: OR (95% CI) for successful treatment vs partial/unsuccessful in ICS cohort vs LABA cohort stratified by age group in subjects with 1 or more courses of oral steroid use in baseline (pre–step-up) 12-month period

Primary outcome	≤19 y	20-39 y	40-59 y	≥60 y
ICS-LABA unadjusted	1.06 (0.89-1.27)	0.94 (0.78-1.14)	0.86 (0.74-1.00)	0.99 (0.83-1.19)
Adjusted for initial confounders*	0.86 (0.71-1.05)	0.80 (0.64-0.99)	0.74 (0.62-0.87)	0.83 (0.68-1.02)
Adjusted for initial confounders plus BMI	0.83 (0.65-1.07)	0.87 (0.69-1.11)	0.75 (0.62-0.89)	0.82 (0.66-1.02)
Adjusted for initial confounders plus smoking status	0.89 (0.69-1.15)	0.79 (0.63-0.98)	0.73 (0.62-0.86)	0.83 (0.67-1.02)
Adjusted for initial confounders plus BMI and smoking status	0.88 (0.65-1.19)	0.87 (0.68-1.10)	0.75 (0.63-0.90)	0.80 (0.64-1.00)
Adjusted for initial confounders plus ICS dose before step-up	0.82 (0.64-1.03)	0.80 (0.63-1.02)	0.72 (0.59-0.87)	0.91 (0.72-1.15)

*Year of step-up, sex, socioeconomic status, SABA daily dose, rhinitis, β -blockers, nonsteroidal anti-inflammatory drugs, paracetamol, and cardiac disease.

TABLE E6. Secondary outcomes: unadjusted and multiadjusted* ORs and 95% CIs of secondary outcomes in ICS cohort vs LABA cohort stratified by age group in subjects with no oral steroid use in baseline (pre-step-up) 12-month period

Secondary outcome	≤19 y	20-39 y	40-59 y	≥60 y
≥1 course oral steroid				
Unadjusted	1.07 (0.96-1.19)	0.93 (0.83-1.05)	0.89 (0.80-0.99)	0.92 (0.81-1.05)
Multiadjusted	1.02 (0.91-1.15)	0.90 (0.79-1.02)	0.84 (0.75-0.94)	0.86 (0.75-0.99)
Respiratory hospitalization				
Multiadjusted	1.08 (0.72-1.62)	0.66 (0.40-1.11)	0.74 (0.44-1.23)	0.75 (0.44-1.28)
Multiadjusted including baseline ICS dose	1.32 (0.79-2.21)	0.94 (0.52-1.69)	0.67 (0.37-1.23)	0.78 (0.40-1.53)
≥1 SABA prescription				
Multiadjusted	1.80 (1.63-2.00)	1.83 (1.61-2.09)	1.61 (1.44-1.80)	1.48 (1.30-1.70)
Multiadjusted including baseline ICS dose	1.67 (1.48-1.90)	1.65 (1.41-1.92)	1.61 (1.40-1.84)	1.27 (1.08-1.45)

*Year of step-up, sex, socioeconomic status, SABA daily dose, rhinitis, β-blockers, nonsteroidal anti-inflammatory drugs, paracetamol, and cardiac disease.

TABLE E7. Secondary outcomes: unadjusted and multiadjusted* ORs and 95% CIs of secondary outcomes in ICS cohort vs LABA cohort stratified by age group in subjects with 1 or more course of oral steroid use in baseline (pre-step-up) 12-month period

Secondary outcome	≤19 y	20-39 y	40-59 y	≥60 y
≥1 course oral steroid				
Unadjusted	0.99 (0.87-1.13)	0.81 (0.70-0.93)	0.81 (0.72-0.91)	0.93 (0.81-1.07)
Multiadjusted	0.94 (0.81-1.08)	0.78 (0.67-0.91)	0.79 (0.69-0.89)	0.86 (0.74-1.00)
Respiratory hospitalization				
Multiadjusted	0.87 (0.59-1.27)	0.51 (0.33-0.78)	0.70 (0.45-1.09)	0.94 (0.57-1.56)
Multiadjusted plus previous ICS dose	0.79 (0.49-1.28)	0.70 (0.40-1.20)	0.75 (0.44-1.27)	1.02 (0.54-1.94)
≥1 SABA prescription				
Multiadjusted	1.52 (1.24-1.86)	1.60 (1.28-2.00)	1.69 (1.43-1.99)	1.62 (1.32-2.00)
Multiadjusted plus previous ICS dose	1.42 (1.11-1.81)	1.33 (1.03-1.72)	1.65 (1.25-2.00)	1.32 (1.04-1.69)

*Year of step-up, sex, socioeconomic status, SABA daily dose, rhinitis, β -blockers, nonsteroidal anti-inflammatory drugs, paracetamol, and cardiac disease.

TABLE E8. Unadjusted and multiple-adjusted ORs and 95% CIs of using categorised average daily doses of SABAs in outcome period for patients in ICS vs LABA step-up groups

Average SABA daily dose in outcome period	Unadjusted	Multiple-adjusted*
0 (Reference group)	1.0	1.0
0.01-0.50	1.27 (1.19-1.35)	1.69 (1.57-1.81)
0.51-1.0	1.29 (1.22-1.36)	1.74 (1.64-1.85)
1.01-1.5	1.22 (1.14-1.29)	1.69 (1.58-1.82)
1.51-2	1.16 (1.08-1.25)	1.64 (1.52-1.77)
2.01-3	1.01 (0.95-1.08)	1.47 (1.37-1.59)
3.01-4	1.05 (0.97-1.14)	1.55 (1.42-1.70)
≥4.01	0.98 (0.91-1.06)	1.38 (1.27-1.49)

*Year of step-up, age, sex, socioeconomic status, SABA daily dose, comorbid cardiac disease and rhinitis, β -blocker prescription, nonsteroidal anti-inflammatory drug prescription, acetaminophen prescription, and oral corticosteroid prescription.

TABLE E9. OR (95% CI) for successful treatment for ICS cohort vs LABA cohort (in unadjusted and multiple-adjusted logistic regression models) stratified by quartiles of baseline SABA use

Quartile of baseline SABA	Unadjusted	Multiple-adjusted*
0-0.27	0.79 (0.74-0.84)	0.74 (0.69-0.79)
0.271-0.55	0.72 (0.66-0.80)	0.74 (0.66-0.82)
0.551-1.64	0.64 (0.59-0.70)	0.65 (0.59-0.72)
> 1.641	0.46 (0.39-0.55)	0.48 (0.40-0.58)

*Year of step-up, age, sex, socioeconomic status, comorbid cardiac disease and rhinitis, β -blocker prescription, nonsteroidal anti-inflammatory drug prescription, acetaminophen prescription, and oral corticosteroid prescription.

TABLE E10. OR (95% CI) for successful treatment for ICS cohort vs LABA cohort in unadjusted and multiple-adjusted logistic regression models) stratified by baseline ICS dose

ICS dose ($\mu\text{g}/\text{d}$)	Unadjusted	Multiple-adjusted*
<200	1.03 (0.97-1.11)	0.74 (0.69-0.80)
201-400	0.97 (0.91-1.04)	0.78 (0.73-0.85)
401-800	1.00 (0.92-1.09)	0.79 (0.72-0.88)

*Year of step-up, age, sex, socioeconomic status, comorbid cardiac disease and rhinitis, β -blocker prescription, nonsteroidal anti-inflammatory drug prescription, acetaminophen prescription, SABA daily dose, and oral corticosteroid prescription.