

Prescribing practices and asthma control with hydrofluoroalkane-beclomethasone and fluticasone: A real-world observational study

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Background: Long-term randomized trials comparing asthma outcomes between inhaled corticosteroids in real-world populations are lacking. As such, rigorously conducted observational studies to complement the findings of randomized trials are needed.

Objective: We sought to compare asthma-related outcomes over 1 year as recorded in a large primary care database for patients aged 5 to 60 years receiving a first prescription (initiation population) or dose increase (step-up population) of hydrofluoroalkane (HFA)-beclomethasone or fluticasone.

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Methods: We used a retrospective matched cohort study in which patients were matched on baseline demographic and disease severity measures. Coprimary outcomes were asthma control (a composite measure comprising no unplanned visit or hospitalization for asthma, oral corticosteroids, or antibiotics for lower respiratory tract infection) and exacerbation rate.

Results: More than 80% of patients in each population achieved asthma control; 10% and 16% of patients in the initiation and step-up populations, respectively, received add-on or combination therapy during the year. Fluticasone was prescribed at significantly higher doses than HFA-beclomethasone for both populations ($P \leq .001$). In the initiation population ($n = 1319$ in each cohort) the adjusted odds ratio for achieving asthma control with HFA-beclomethasone was 1.30 (95% CI, 1.02-1.65) relative to fluticasone. In the step-up population (cohorts: $n = 250$) the adjusted odds ratio for achieving asthma control with HFA-beclomethasone was 1.22 (95% CI, 0.66-2.26). Exacerbation rates were similar between cohorts.

Conclusions: In a real-world setting patients receiving HFA-beclomethasone had a similar or better chance of achieving asthma control at lower prescribed doses than with fluticasone. (*J Allergy Clin Immunol* 2010;■■■■:■■■■-■■■■.)

Key words: Asthma, database, fluticasone, hydrofluoroalkane-beclomethasone, inhaled corticosteroid, observational study

Asthma management guidelines recommend long-term treatment with inhaled corticosteroids (ICSs) to attenuate the chronic airway inflammation of persistent asthma.¹⁻³ The choice of ICS is typically guided by practical considerations, such as convenience and cost, rather than by differences in therapeutic effect because randomized controlled trials have not identified consistent and significant differences in outcomes among available ICSs.^{4,5} However, long-term trials comparing ICSs, particularly in real-world populations, are lacking. Most randomized trials of patients with asthma are short-term (≤ 3 months) and exclude patients failing to demonstrate predefined levels of airway reversibility or lung function impairment, as well as those who smoke or have other comorbidities. By 2 estimates, more than 90% of patients with asthma seen by general practitioners would not qualify for typical asthma trials.^{6,7}

Rigorously conducted observational studies can complement results from randomized controlled trials by examining long-term outcomes across the diverse spectrum of community-based

Abbreviations used

GPRD: General Practice Research Database
 HFA: Hydrofluoroalkane
 ICS: Inhaled corticosteroid
 MDI: Metered-dose inhaler
 UK: United Kingdom

patients with asthma.^{8,9} These studies might be particularly useful in comparing the clinical effectiveness of ICSs. For instance, the 2 most commonly prescribed ICSs in the United States, fluticasone and beclomethasone, have markedly different properties. Fluticasone is more potent, on a microgram basis, than beclomethasone,⁴ whereas beclomethasone, formulated as a hydrofluoroalkane (HFA) solution aerosol, has a smaller particle size, resulting in greater total and peripheral lung deposition than fluticasone.¹⁰⁻¹² Clinical trials have suggested that HFA-beclomethasone is equally effective as fluticasone in controlling asthma symptoms.^{1,13-15} However, these studies were of short duration and not adequately designed to determine whether the different properties of these ICSs might render one more effective than the other.

Therefore we hypothesized that differences in clinical effectiveness between these 2 ICSs might become apparent through a retrospective database analysis of 1-year outcomes for primary care patients with persistent asthma receiving a first prescription or a dose increase of either HFA-beclomethasone or fluticasone. Importantly, this study also enabled us to examine the effect of prescribing practices by general practitioners on asthma outcomes, an important assessment of guideline recommendations for asthma.

METHODS**Data source**

The General Practice Research Database (GPRD) is a large, well-maintained database administered as a not-for-profit by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency that contains deidentified longitudinal medical records from approximately 500 primary care practices in the UK.¹⁶⁻¹⁸ Patients' records in the GPRD total 13 million, and active records number 3.6 million, which is equivalent to 5.5% of the UK population. The demographic characteristics of patients included in the GPRD are considered broadly representative.

In the UK medical care is centralized in general practice, and thus the GPRD is a valuable source of long-term observational data. Patients' visit and clinical information collected in the GPRD includes diagnoses, symptoms, procedures, prescriptions issued, and referrals to secondary care.¹⁶ Prescribing information does not include whether medications are issued or taken as prescribed. Participating practice staff are trained in the use of computerized medical records and appropriate software. Periodic quality control checks are made to ensure up-to-standard data recording.

The GPRD Independent Scientific Advisory Committee approved data use for this study.

Study design and patients

This retrospective observational study used GPRD data from January 1, 1997, to June 30, 2007. Patients were evaluated over 2 consecutive years: a baseline period of 1 year for patient characterization and confounder identification before the index prescription date (index date) and an outcome period of 1 year after the index date.

Eligible patients were aged 5 to 60 years with asthma, and on the index date, they received a prescription for HFA-beclomethasone (QVAR; Teva

Pharmaceutical Industries Ltd, Petach Tikva, Israel) or fluticasone (HFA or chlorofluorocarbon formulation; Flixotide; Allen & Hanburys Ltd, Uxbridge, Middlesex, UK) delivered by means of metered-dose inhaler (MDI). Two patient populations were studied: those who received a first prescription for an ICS (initiation population) and those who received their first increase in dose of ICS (step-up population). Asthma was defined as a read code consistent with an asthma diagnosis or 2 or more prescriptions for asthma therapy, including 1 ICS prescription, at different time points during the outcome year. Patients in the step-up population had at least 1 prescription for ICS administered by means of an MDI during the baseline year and a minimum dose increase of 50% on the index date, which was captured in the database as an increase in prescribed number of puffs or formulation strength.

Patients had to be continuously registered at the same practice throughout the 2-year study period, with the practice judged as up-to-standard by the GPRD for both years. Patients with a recorded diagnosis of chronic obstructive pulmonary disease or chronic respiratory tract disease other than asthma were excluded, as were patients in the step-up population who received a combination inhaler or any add-on asthma controller agent during the baseline year.

Outcome measures

The 2 coprimary end points were the primary measure of asthma control and the exacerbation rate during the outcome year. The *primary measure of asthma control* was a composite measure defined as follows: (1) no recorded hospital attendance for asthma (including admission or emergency department visit, out of hours, or outpatient department attendance); (2) no prescription for oral corticosteroid; and (3) no consultation, hospital admission, or emergency department attendance for lower respiratory tract infection requiring antibiotics.

An *exacerbation* was defined as a course of oral corticosteroids, hospital admission, or emergency department attendance for asthma during the outcome year; exacerbations on the index date were included with the baseline data.

Secondary end points included 2 other composite measures, which were established *a priori* to evaluate different aspects of asthma control. *Asthma control plus short-acting β -agonist use* included an average prescribed daily dose of albuterol of 200 μ g or less or terbutaline of 500 μ g or less as a fourth outcome in addition to the 3 above-mentioned criteria defining asthma control. *Asthma control plus no additional or change in therapy* included the following 4 criteria: (1) no exacerbation (defined as above); (2) no increase in ICS dose; (3) no change in ICS or inhaler device; and (4) no use of any additional therapy for asthma.

Other secondary end points were the disaggregated outcomes comprising the composite measures. Ex-valve doses of ICSs are reported.

Statistical analyses

Outcome measures and analytic approaches were predefined before the analyses were performed; further detail on analytic methods and data gathering can be found in the Methods section of this article's Online Repository at www.jacionline.org and elsewhere.¹⁹

We performed a matched cohort analysis because of differences in key baseline characteristics between the HFA-beclomethasone and fluticasone cohorts of both initiation and step-up populations, as described in the Results section of this article's Online Repository at www.jacionline.org. The baseline variables for matching were prospectively chosen by using a pragmatic approach to include as many patients as possible while matching on demographic characteristics, as well as baseline disease severity and therapy variables. Patients in the 2 treatment cohorts of the initiation population were matched for age, sex, and prior (baseline year) mean daily dose of short-acting β -agonist and number of oral corticosteroid courses (as detailed in Table E1 in this article's Online Repository at www.jacionline.org). Patients in the step-up population were matched on these criteria, as well as on prior mean ICS daily dose. Other possible variables that were not used for matching were prior hospitalizations (very few) and asthma consultations, exacerbations, and asthma control, all of which showed collinearity with oral corticosteroid prescriptions. The Charlson comorbidity index was used to define the number and severity of comorbidities for each patient.²⁰

TABLE I. Baseline characteristics of the matched cohorts for both study populations, those initiating an ICS administered by means of an MDI (initiation population), and those receiving an increased dose of ICS administered by means of an MDI (step-up population), according to treatment cohort*

Characteristic	Initiation population			Step-up population		
	HFA-beclomethasone (n = 1319)	Fluticasone (n = 1319)	P value†	HFA-beclomethasone (n = 250)	Fluticasone (n = 250)	P value†
Male sex, no. (%)	588 (44.6)	588 (44.6)	NA‡	106 (42.4)	106 (42.4)	NA‡
Age (y)	28.1 ± 17.3	27.5 ± 18.1	NA‡	32.3 ± 17.6	32.0 ± 17.6	NA‡
5-12 y, no. (%)	344 (26.1)	439 (33.3)		41 (16.4)	54 (21.6)	
Weight (kg)§	66.7 ± 25.5	64.7 ± 26.8	.17	68.7 ± 26.1	69.1 ± 22.6	.82
Height (m)§	1.59 ± 0.22	1.56 ± 0.23	.03	1.61 ± 0.20	1.60 ± 0.19	.64
Body mass index (kg/m ²)§	25.0 ± 7.2	24.6 ± 7.5	≤.001	25.3 ± 7.4	25.9 ± 7.2	.81
Socioeconomic status, median (interquartile range)	16.2 (10.9-27.6)	17.6 (9.2-35.2)	.62	18.7 (11.8-30.8)	17.9 (9.0-36.3)	.88
Charlson comorbidity index,¶ no. (%)						
0	1237 (93.8)	1239 (93.9)	.96	230 (92.0)	227 (90.8)	.48
1	45 (3.4)	43 (3.3)		3 (1.2)	2 (0.8)	
2	26 (2.0)	25 (1.9)		11 (4.4)	12 (4.8)	
≥3	11 (0.8)	12 (0.9)		6 (2.4)	9 (3.6)	
Smoking status, no./total no. (%)						
Current	250/760 (32.9)	186/633 (29.4)	.15	54/175 (30.9)	35/128 (27.3)	.52
Former	113/760 (14.9)	110/633 (17.4)		29/175 (16.6)	20/128 (15.6)	
Never	397/760 (52.2)	337/633 (53.2)		92/175 (52.6)	73/128 (57.0)	
Recorded asthma diagnosis, no. (%)	1299 (98.5)	1279 (97.0)	.008	245 (98.0)	244 (97.6)	.76
Recorded comorbidity, no. (%)						
Rhinitis	203 (15.4)	252 (19.1)	.01	46 (18.4)	64 (25.6)	.06
Cardiac disease	25 (1.9)	39 (3)	.08	9 (3.6)	6 (2.4)	.41
Gastroesophageal reflux disease	74 (5.6)	93 (7.1)	.13	18 (7.2)	21 (8.4)	.62
≥1 Prescription in 12 mo, no. (%)						
Nonsteroidal anti-inflammatory drug	182 (13.8)	191 (14.5)	.60	45 (18.0)	43 (17.2)	.81
β-blocker	32 (2.4)	39 (3.0)	.41	13 (5.2)	7 (2.8)	.19
Acetaminophen	165 (12.5)	210 (15.9)	.01	43 (17.2)	50 (20.0)	.44
Mean SABA dose,¶ no. (%)						
0	618 (46.9)	618 (46.9)	NA‡	7 (2.8)	7 (2.8)	NA‡
1-100 μg/d	417 (31.6)	417 (31.6)		57 (22.8)	57 (22.8)	
101-200 μg/d	204 (15.5)	204 (15.5)		96 (38.4)	96 (38.4)	
201-300 μg/d	47 (3.6)	47 (3.6)		46 (18.4)	46 (18.4)	
301-400 μg/d	11 (0.8)	11 (0.8)		12 (4.8)	12 (4.8)	
>400 μg/d	22 (1.7)	22 (1.7)		32 (12.8)	32 (12.8)	
Oral corticosteroid courses, no. (%)						
0	1118 (84.8)	1118 (84.8)	NA‡	207 (82.8)	207 (82.8)	NA‡
1	171 (13.0)	171 (13.0)		31 (12.4)	31 (12.4)	
2	26 (2.0)	26 (2.0)		8 (3.2)	8 (3.2)	
≥3	4 (0.3)	4 (0.3)		4 (1.6)	4 (1.6)	
Mean ICS dose during baseline year, no. (%)	NA	NA				
1-99 μg/d				187 (74.8)	187 (74.8)	NA‡
100-199 μg/d				43 (17.2)	43 (17.2)	
200-299 μg/d				17 (6.8)	17 (6.8)	
300-399 μg/d				2 (0.8)	2 (0.8)	
400-599 μg/d				0	0	
600-799 μg/d				1 (0.4)	1 (0.4)	
≥800 μg/d				0	0	
Asthma consultations, no. (%)						
0	616 (46.7)	582 (44.1)	.008	64 (25.6)	49 (19.6)	.03
1	552 (41.8)	530 (40.2)		88 (35.2)	68 (27.2)	
2	118 (8.9)	159 (12.1)		50 (20.0)	75 (30.0)	
≥3	33 (2.5)	48 (3.6)		48 (19.2)	58 (23.2)	
Asthma consultations without OCS, no. (%)						
0	685 (51.9)	663 (50.3)	.030	79 (31.6)	65 (26.0)	.017
1	513 (38.9)	487 (36.9)		83 (33.2)	67 (26.8)	
2	94 (7.1)	133 (10.1)		50 (20.0)	68 (27.2)	
≥3	27 (2.0)	36 (2.7)		38 (15.2)	50 (20.0)	

(Continued)

TABLE I. (Continued)

Characteristic	Initiation population			Step-up population		
	HFA-beclomethasone (n = 1319)	Fluticasone (n = 1319)	P value†	HFA-beclomethasone (n = 250)	Fluticasone (n = 250)	P value‡
Courses of antibiotics for lower respiratory tract infection, no. (%)						
1	173 (13.1)	183 (13.9)	.74	37 (14.8)	45 (18.0)	.79
2	34 (2.6)	38 (2.9)		12 (4.8)	10 (4.0)	
≥3	16 (1.2)	7 (0.5)		4 (1.6)	4 (1.6)	
Asthma control status,** no. (%)	956 (72.5)	949 (71.9)	.67	172 (68.8)	161 (64.4)	.18

OCS, Oral corticosteroid prescription; SABA, short-acting β -agonist.

*Plus-minus values are means $\pm$ SDs. Because of rounding, percentages may not total 100%.

†P values were calculated with conditional logistic regression.

‡P value is not applicable for matching criteria.

§Not all patients had recorded weight and height data. For weight, the initiation populations were 1018 and 1048 for the HFA-beclomethasone and fluticasone cohorts, respectively; the step-up populations were 214 and 203, respectively. For height, the initiation populations were 1129 and 1135, respectively; the step-up populations were 231 and 222, respectively. For body mass index, the initiation populations were 999 and 1022, respectively; the step-up populations were 212 and 201, respectively.

||Socioeconomic status was that assigned, in quintiles, by the GPRD to each practice by using the Index of Multiple Deprivation as a proxy measure. The Charlson comorbidity index is a weighted index that accounts for the number and severity of comorbidities, each assigned a score depending on the associated risk of dying.²⁰

¶The SABA dose is the albuterol dose equivalent (standard dose in the UK is 100 μ g).

**The primary measure of asthma control was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection.

Conditional logistic regression was used for comparison of baseline characteristics between the matched cohorts. Baseline differences between treatment cohorts with *P* values of .10 or less were considered potential confounders. Conditional logistic regression was used to compare cohorts for binary outcomes, and a conditional Poisson regression model was used to derive the rate ratio for exacerbations.

In a *post hoc* sensitivity analysis, we repeated the matching process using the additional criterion of number of asthma consultations during the baseline period (0, 1, and ≥ 2). Patients were matched on the number of asthma consultations with no oral corticosteroid prescription within a 2-week window to avoid possible collinearity with oral corticosteroid prescriptions.

Data were analyzed with SPSS version 17 (SPSS, Inc, Chicago, Ill) and STATA 9.2 for Windows (StataCorp LP, College Station, Tex). A *P* value of .05 or less was used for primary end points, and a *P* value of .01 or less was used for secondary end points to denote statistical significance.

RESULTS

A first prescription of HFA-beclomethasone or fluticasone administered by means of an MDI was issued for 4411 patients; of these, 2638 were matched, resulting in 1319 patients in each treatment cohort of the initiation population. The median length of time patients were registered in the GPRD without a prior ICS prescription was 9.4 years (interquartile range, 5.1–15.4 years) for the HFA-beclomethasone cohort and 7.8 years (interquartile range, 4.6–13.0) for the fluticasone cohort.

Of 1,170 patients receiving an increased dose of ICS administered by means of an MDI, 500 were matched, for 250 patients in each cohort of the step-up population. Figures E1 to E3 (available in this article's Online Repository at www.jacionline.org) depict the matching process. Demographic and baseline clinical characteristics are summarized in Table I. In both the initiation and step-up populations, asthma control measures and exacerbations were similar in the baseline year. There were significant baseline differences between treatment cohorts (eg, height, body mass index, rhinitis, acetaminophen use, and asthma consultations), but these were small and not clinically meaningful.

Outcomes for the initiation population

On the index date, patients in the fluticasone cohort were prescribed a significantly higher dose of ICS (*P* $\leq$.001, Fig 1).

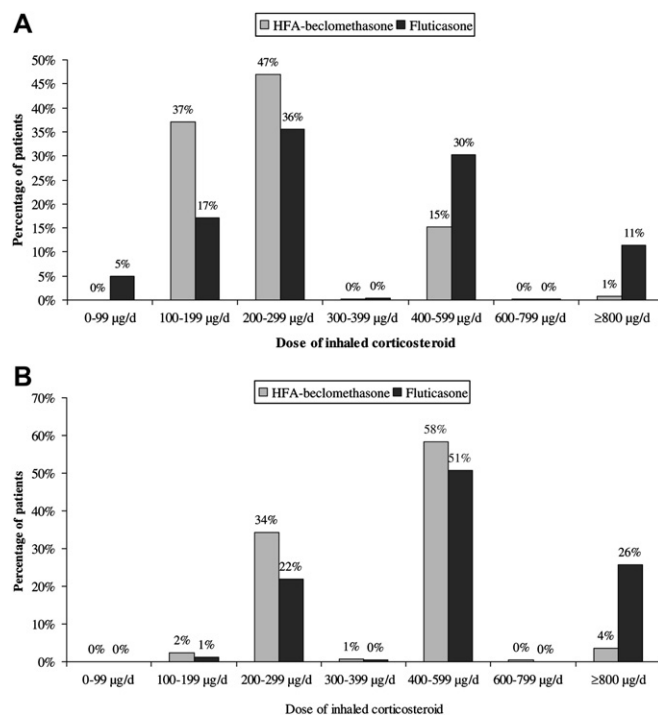


FIG 1. Distribution of prescribed doses at the index date for patients initiating an ICS (A) and patients receiving their first increase in ICS dose (B) administered by means of an MDI. Prescribed doses were significantly different between treatment cohorts in both the initiation and step-up populations (*P* $\leq$.001).

Patients achieving the primary measure of asthma control numbered 1134 (86.0%) and 1093 (82.9%) in the HFA-beclomethasone and fluticasone cohorts, respectively (Table II). The unadjusted and adjusted odds ratios for achieving asthma control were significantly higher for patients receiving HFA-beclomethasone (Fig 2). Exacerbation rates were not significantly different between cohorts.

Patients in the HFA-beclomethasone cohort had a significantly greater chance of meeting both secondary composite outcome

TABLE II. Outcomes for the matched cohorts for both study populations, those initiating an ICS and those receiving an increased dose of ICS, according to treatment cohort*

Outcome	Initiation population			Step-up population		
	HFA-beclomethasone (n = 1319)	Fluticasone (n = 1319)	P value†	HFA-beclomethasone (n = 250)	Fluticasone (n = 250)	P value‡
Asthma control status,‡ no. (%)						
Primary measure of asthma control	1134 (86.0)	1093 (82.9)		206 (82.4)	198 (79.2)	
Asthma control plus SABA use	844 (64.0)	780 (59.1)		113 (45.2)	109 (43.6)	
Asthma control plus no additional or change in therapy	1029 (78.0)	921 (69.8)		186 (74.4)	160 (64.0)	
Asthma exacerbations,§ no. (%)						
0	1218 (92.3)	1200 (91.0)		224 (89.6)	219 (87.6)	
1	72 (5.5)	94 (7.1)		17 (6.8)	19 (7.6)	
2	19 (1.4)	16 (1.2)		5 (2.0)	9 (3.6)	
≥3	10 (0.8)	9 (0.7)		4 (1.6)	3 (1.2)	
Disaggregated outcomes of the composite measures						
Change in therapy, no. (%)	229 (17.4)	340 (25.8)	≤.001	47 (18.8)	74 (29.6)	.006
≥1 Oral corticosteroid course, no. (%)	101 (7.7)	119 (9.0)	.52	26 (10.4)	31 (12.4)	.46
≥1 Hospital admission, no. (%)	7 (0.5)	15 (1.1)	.10	1 (0.4)	3 (1.2)	.34
≥1 Course of antibiotics for lower respiratory tract infection, no. (%)	105 (8.0)	121 (9.2)	.20	25 (10.0)	28 (11.2)	.64
Mean SABA dose >200 µg/d, no. (%)	369 (28.0)	410 (31.1)	.07	119 (47.6)	121 (48.4)	.82

SABA, Short-acting β-agonist.

*Because of rounding, percentages might not total 100%.

†P values were calculated with conditional logistic regression.

‡The primary measure of asthma control was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection. Asthma control plus SABA use was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection plus mean use of 200 µg/d or less of a SABA. Asthma control plus no additional or change in therapy was defined as no exacerbation, increase in ICS dose, change in ICS or inhaler device, or additional asthma controller therapy.

§An exacerbation was defined as a course of oral corticosteroids, hospital admission, or emergency department attendance for asthma; exacerbations on the index date were included in the baseline data.

||The SABA dose is the albuterol dose equivalent (standard dose in the UK is 100 µg).

measures (Fig 2). Other secondary outcome measures were not significantly different between cohorts, excepting change in therapy, which was less frequent in the HFA-beclomethasone than fluticasone cohort (Table II). Changes in therapy by type were generally similar between the 2 cohorts (Table III). Results of the sensitivity analysis supported those of the primary analysis (see Table E2 in this article's Online Repository at www.jacionline.org), as did the results of the unmatched analyses (detailed in Tables E3-E5 in this article's Online Repository at www.jacionline.org).

Outcomes for the step-up population

Patients in the fluticasone cohort were prescribed a significantly higher dose on the index date ($P \leq .001$, Fig 1).

Similar numbers of patients in the HFA-beclomethasone and fluticasone cohorts achieved the primary measure of asthma control (Table II). Adjusted odds ratios for the primary measure of asthma control and the exacerbation rates were not significantly different between cohorts during the outcome year (Fig 2).

The adjusted odds ratio for asthma control plus short-acting β-agonist use was not significantly different between cohorts, whereas the odds of achieving asthma control plus no additional or change in therapy were significantly greater for the HFA-beclomethasone cohort (Fig 2). There was a significantly lower proportion of patients with a recorded change in therapy in the HFA-beclomethasone cohort (Table II); the type and pattern of therapy change were similar for the 2 cohorts (Table III). Other disaggregated outcomes of the composite measures were not significantly different between cohorts (Table II). Trends in

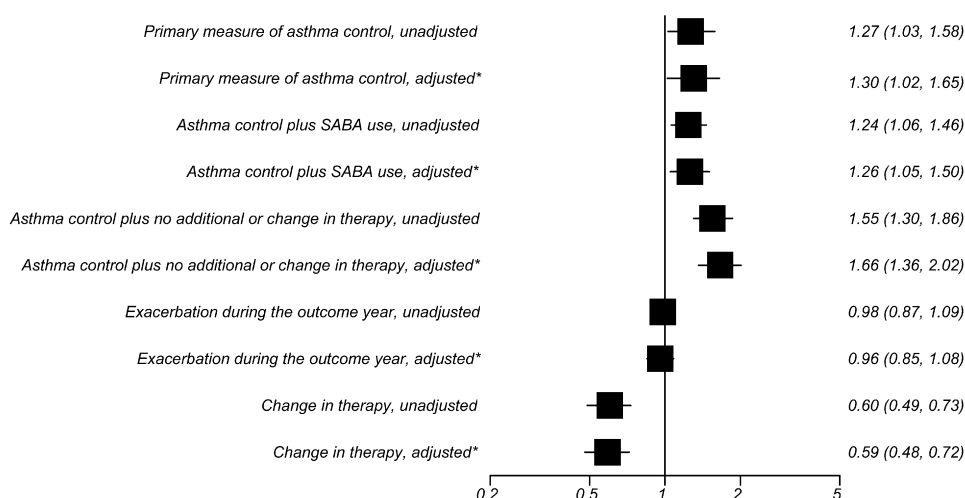
the sensitivity analysis supported those of the primary analysis (see Table E2 in this article's Online Repository at www.jacionline.org).

DISCUSSION

In this analysis of real-world asthma management in primary care, initiating treatment with either HFA-beclomethasone or fluticasone effectively improved asthma control, as per the predefined composite measures. In patients already taking ICSs and requiring a step-up in treatment, increasing the dose of either HFA-beclomethasone or fluticasone effectively reestablished asthma control. These real-world results reinforce guideline recommendations to start with ICS monotherapy and then step up, as necessary, to a higher dose.¹⁻³ This approach worked well when implemented in clinical practice. However, this long-term observational analysis demonstrated meaningful differences in outcomes for patients treated with these 2 different ICSs for asthma. Patients receiving HFA-beclomethasone had a similar or better chance of achieving asthma control at lower prescribed doses than those receiving fluticasone, a finding with important implications in clinical practice.

Outcomes in patients initiating ICSs in this observational study were similar to those reported in long-term controlled clinical trials.^{21,22} The overall percentage of patients meeting the proxy control measure increased from 72.2% at baseline to 84.4% over the 1-year outcome period, and exacerbations decreased from the baseline period. For patients with asthma requiring a step-up in therapy, guidelines recommend either increasing the dose of ICS or adding a long-acting β-agonist. Long-acting β-

Initiation Population



Step-Up Population

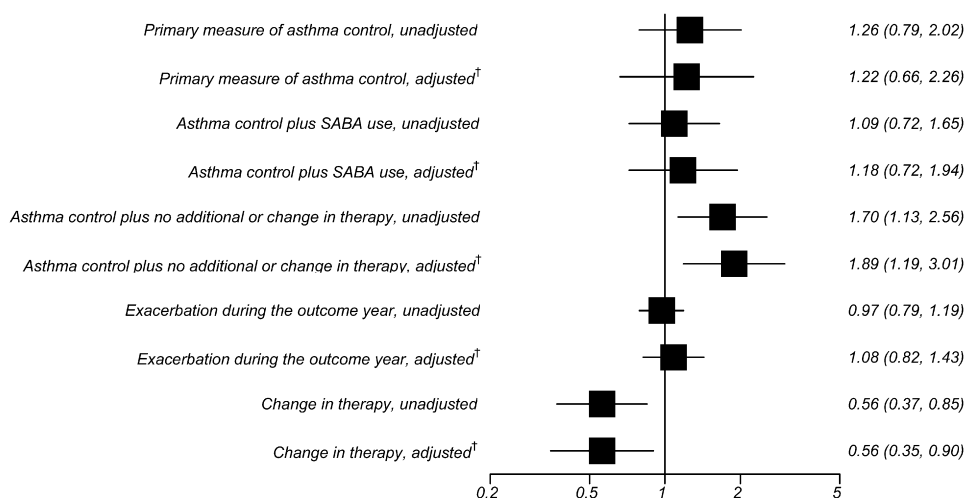


FIG 2. Odds ratios and rate ratios (95% CIs) for outcome measures for HFA-beclomethasone cohorts of initiation and step-up populations, with the fluticasone cohort set as the reference group (odds ratio/rate ratio = 1.0). SABA, Short-acting β -agonist. *Adjusted for year of index date, acetaminophen, asthma consultations, rhinitis diagnosis, recorded asthma diagnosis, and cardiac disease diagnosis. †Adjusted for year of index date, acetaminophen, asthma consultations, and rhinitis diagnosis.

agonists do not enhance anti-inflammatory effects,^{4,23} but they do improve symptom control and reduce exacerbations.^{4,24} However, there are concerns about the potential for increased asthma-related mortality associated with the use of long-acting β -agonists, both as monotherapy and in conjunction with ICSs.^{4,25,26} In this analysis 80.8% of patients receiving an increased dose of ICS as step-up therapy achieved asthma control, an increase from 66.6% at baseline; the rate of asthma exacerbations decreased, and only 12% to 19% of patients required a subsequent change to combination therapy or additional therapy, most commonly the addition of a long-acting β -agonist.

Although patients were well matched at baseline for demographic and asthma treatment variables, patients treated with

HFA-beclomethasone had consistently better outcomes. Patients started on HFA-beclomethasone were significantly more likely to achieve asthma control than those started on fluticasone. Patients receiving HFA-beclomethasone as step-up therapy were significantly more likely to achieve asthma control without the need for additional therapy than those given an increased dose of fluticasone. There were consistent, but not significant, advantages for HFA-beclomethasone treatment across all other measures of asthma control.

The better outcomes with HFA-beclomethasone treatment occurred despite differences in dosing patterns. High-dose prescribing was more common in the fluticasone cohorts: 42% and 76% of patients in the initiation and step-up populations,

TABLE III. Change in therapy by type for patients with a treatment change in both study populations, those initiating an ICS and those receiving an increased dose of ICS, according to treatment cohort*

Outcome	Initiation population		Step-up population	
	HFA-beclomethasone (n = 229)	Fluticasone (n = 340)	HFA-beclomethasone (n = 47)	Fluticasone (n = 74)
Increase in ICS dose	75 (32.8)	103 (30.3)	4 (8.5)	5 (6.8)
Change in inhaler device	56 (24.5)	63 (18.5)	10 (21.3)	4 (5.4)
Change in ICS	18 (7.9)	63 (18.5)	5 (10.6)	22 (29.7)
Change to combination therapy or additional therapy	105 (45.9)	158 (46.5)	31 (66.0)	47 (63.5)
Fluticasone + salmeterol	43 (18.8 [41.0])†	104 (30.6 [65.8])	14 (29.8 [46.7])	26 (35.1 [55.3])
Budesonide + formoterol	19 (8.3 [18.1])	11 (3.2 [7.0])	5 (10.6 [16.7])	4 (5.4 [8.5])
Long-acting β -agonist	52 (22.7 [49.5])	63 (18.5 [39.9])	18 (38.3 [58.1])	32 (43.2 [68.1])
Leukotriene receptor antagonist	24 (10.5 [22.9])	45 (13.2 [28.5])	10 (21.3 [32.3])	19 (25.7 [40.4])
Theophylline	1 (0.4 [1.0])	3 (0.9 [1.9])	0	8 (10.8 [17.0])

*Data are patient numbers (percentages of those with treatment change). Patients could have more than 1 change in therapy, and thus the numbers are not additive. Because of rounding, percentages might not total 100%.

†Percentages in brackets within parentheses refer to the subcohort receiving additional therapy.

respectively, were prescribed fluticasone doses of 400 $\mu\text{g}/\text{d}$ or greater (vs 16% and 62%, respectively, for HFA-beclomethasone), and 11% and 26%, respectively, were prescribed doses of 800 $\mu\text{g}/\text{d}$ or greater (vs 1% and 4%, respectively, for HFA-beclomethasone). High-dose fluticasone prescribing, previously reported by others,²⁷⁻³⁰ is of concern because the potential for systemic effects increases at higher doses with unclear therapeutic benefit. Fluticasone at a dose of 375 $\mu\text{g}/\text{d}$ (95% CI, 227-522 $\mu\text{g}/\text{d}$) is estimated to cause 30% adrenal suppression,³¹ and the efficacy dose-response curve for fluticasone regarding lung function is generally flat at greater than 200 $\mu\text{g}/\text{d}$, although there is individual variability, and some patients might benefit from further increases in dose.^{2,32}

Greater benefits found with HFA-beclomethasone treatment are possibly explained by formulation differences. Patients frequently use MDIs incorrectly.³³ The smaller particle size of HFA-beclomethasone, along with its softer and warmer spray and longer spray duration, results in good lung deposition characteristics, even in patients with demonstrated discoordinated inhaler technique.¹² Although fluticasone is a more potent molecule, HFA-beclomethasone has greater overall lung deposition and consistent deposition in both the large and small airways.^{10,11} HFA-beclomethasone significantly improves measures of small airway function, whereas large-particle ICSs do not.³⁴⁻³⁷ More effective control of small airway inflammation might contribute to better asthma control.^{38,39}

Almost one third of the patients in this study were current smokers. Although there were no significant differences between cohorts in the baseline prevalence of smoking, the proportions of current smokers were numerically higher in HFA-beclomethasone cohorts than in fluticasone cohorts. Of note, the intensity of smoking in these patients is not recorded in the GPRD.

Observational studies are limited by possible unmeasured or unrecognized confounding factors. However, a strength of this analysis was the matched cohort design, which ensured a comparison of patients with similar asthma severity matched at baseline for oral corticosteroid prescriptions, average short-acting β -agonist daily dose, and, for the step-up population, average ICS dose. The matching process endeavored to make comparisons analogous to a controlled clinical trial, with inclusion and

exclusion criteria applied to each matched pair of patients. In support of the value of the matching process was the internal consistency of the findings. The matched unadjusted and adjusted results were similar, indicating that confounding factors were eliminated to the extent it was possible to do so. Moreover, although we cannot rule out the possibility of residual confounders, the overall results were consistent regardless of which definition of control was used and regardless of which factors were included in the adjustment, indicating that the model is robust.

The analyses were by intention to treat, and the 12-month outcome period allowed for seasonal changes, as well as the recording of infrequent outcomes, such as exacerbations. The fact that treatment changes, when needed, were similar in all 4 treatment cohorts is reassuring because physician behavior was consistent and supports the validity of the findings.

The composite measures of control used in this study were constructed to provide different assessments of asthma control, incorporating database evidence of an asthma exacerbation (oral corticosteroid course or unscheduled care for asthma) and sub-optimal asthma control (increased use of reliever therapy or change in controller therapy). Although it can be argued that lung function parameters are important measures of successful treatment, in the end, measures of control and exacerbations are of practical importance, as well as predictors of future risk, and are consistent with goals of therapy, as delineated by guidelines and international consensus.^{1,40} However, it is likely that our estimation of control does not capture all symptoms resulting in the start of or increase in ICS therapy, as suggested by the proportions of patients categorized as controlled at baseline.

In summary, the results of this observational study support guideline recommendations on the management of persistent asthma to initiate ICS therapy and step-up as necessary to higher doses. This observational study also suggests a clinically meaningful difference in asthma outcomes depending on the choice of ICS. Patients prescribed HFA-beclomethasone, either as initial or step-up therapy, had a similar or better chance of achieving asthma control over 1 year than those receiving fluticasone, despite receiving lower prescribed doses. These findings might support the site of lung deposition of an ICS as being important in providing effective asthma control.

We thank Muzammil Ali for his assistance with the statistical analyses. The analysis was conducted according to Standard Operating Procedures of Research in Real Life Ltd. (<http://www.optimumpatientcare.org/downloads/documents/SOP%20observational%20database%20studies.pdf>).

Clinical implications: Initiating or increasing asthma controller therapy with HFA-beclomethasone results in similar or better asthma control than with fluticasone, suggesting that the choice of ICS might result in clinically meaningful differences.

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METHODS

Complete statistical analyses for both matched and unmatched populations

The 2 coprimary end points were the primary measure of asthma control and the exacerbation rate during the outcome year. All outcome measures and approaches to analysis were predefined before the analyses were performed according to standard operating procedures published by the study group (<http://www.optimumpatientcare.org/downloads/documents/SOP%20observational%20database%20studies.pdf>).

Examination of the original dataset for the 2 populations revealed several statistically significant and large clinical differences in baseline characteristics between the HFA-beclomethasone and fluticasone cohorts. These are described in the Results section of this article's Online Repository and led to the matched analyses described in the main body of the article. Of the unmatched populations, most demographic and baseline data were nonnormally distributed; treatment cohorts were thus compared by using the Mann-Whitney test for continuous variables and the χ^2 test for categorical variables. Any variables with baseline differences between cohorts having a *P* value of .10 or less were treated as potential confounders and were considered for inclusion in the regression model (assuming that they were not collinear with each other, in which case the one most likely to be clinically meaningful was used).

All end point analyses were specified *a priori* and took account of confounding variables by using multiple logistic regression. A binary logistic regression model was used to calculate odds ratios for the dichotomized primary end points, with asthma control as the dependent variable and cohort and potential confounding factors as explanatory variables (year of index date, age, sex, socioeconomic status, comorbidity, and treatment with medication that could affect respiratory outcomes). Variables that were heavily skewed were categorized as follows: short-acting β -agonist daily doses (0 μ g, 1-100 μ g, 101-200 μ g, 201-400 μ g, and >400 μ g); ICS daily doses prescribed on the index date and during the baseline year (0-100 μ g, 101-200 μ g, 201-400 μ g, 401-599 μ g, 600-799 μ g, and >800 μ g); and the number of oral corticosteroid prescriptions (0, 1, 2, and ≥ 3). A Poisson regression model was used to obtain estimates of exacerbation rates in the outcome period relative to the fluticasone cohort, and the model was adjusted for overdispersion by using robust standard errors and including adjustments for potential baseline confounders.

Although the baseline differences between treatment cohorts were adjusted for in the analyses described above, it was believed that a more robust evaluation of the data would require a matched analysis. The baseline variables were thus re-examined, and variables for matching were prospectively chosen without looking at outcomes by using a pragmatic approach to include as many patients as possible while matching on demographic characteristics and variables indicative of similar disease severity and therapy at baseline. The matching criteria are detailed in Table E1. Patients receiving their first ICS as HFA-beclomethasone or fluticasone (initiation population) were matched for age, sex, and prior (baseline year) mean daily dose of short-acting β -agonist and number of oral corticosteroid courses. Patients receiving an increased dose of ICS (step-up population) were matched on these criteria, as well as on prior mean daily dose of ICS, as detailed in Table E1. Other possible variables that were not used for matching were hospitalizations (very few) and asthma consultations, exacerbations, and asthma control, all of which showed collinearity with oral corticosteroid prescriptions. The Charlson comorbidity index was used to define the number and severity of comorbidities for each patient.^{E1}

For the matched populations, conditional logistic regression was used for comparison of baseline characteristics between the matched treatment cohorts. Any variable with baseline differences between treatment cohorts having a *P* value of .10 or less was considered a potential confounder. Conditional logistic regression was used to compare cohorts for binary outcomes, and a conditional Poisson regression model was used to derive the rate ratio for exacerbations.

In a *post hoc* sensitivity analysis, we repeated the matching process using the additional criterion of number of asthma consultations during the baseline

period (0, 1, or ≥ 2). Patients were matched on the number of asthma consultations with no oral corticosteroid prescription within a 2-week window to avoid possible collinearity with oral corticosteroid prescriptions.

For the primary outcomes, a *P* value of .05 or less was used to denote statistical significance. For secondary outcomes, a more stringent *P* value of .01 or less was used to denote statistical significance because of potential multiple testing and the associated increased chance of a type 1 error.

Data were analyzed with SPSS version 17 (SPSS, Inc) and STATA 9.2 for Windows (StataCorp LP) software.

RESULTS

Sensitivity analysis

After matching with the additional criterion of number of asthma consultations with no oral corticosteroid prescription at baseline, there were 592 patients in each cohort of the initiation population and 86 in each cohort of the step-up population (compared with 1,319 and 250, respectively, in our primary matched analysis).

Outcome measures are summarized in Table E2 for primary and sensitivity analyses. The trends and differences between cohorts in the sensitivity analysis results remained broadly the same as in the primary analysis, albeit with broader CIs because of the reduced population.

Unmatched populations**Baseline demographic and clinical characteristics.**

HFA-beclomethasone or fluticasone administered by means of an MDI was prescribed for a total of 4411 patients receiving their first ICSs (initiation population) and for 1170 patients receiving an increased dose of ICS (step-up population, Fig E1). In both populations patients in the fluticasone cohort, as compared with those in the HFA-beclomethasone cohort, were more likely to be younger, shorter, and less heavy and to have had more asthma consultations during the baseline year (*P* $\leq$.001 for all comparisons, Table E3). In the step-up population during the baseline year, those in the fluticasone cohort were less likely to have achieved asthma control and were more likely to have had an exacerbation, received an oral corticosteroid, and received a higher daily dose of short-acting β -agonist and ICS (*P* $\leq$.001 for all comparisons, Table E3).

Outcomes. The dose of fluticasone prescribed at the index date was significantly higher than the dose of HFA-beclomethasone for both initiation and step-up populations (*P* $\leq$.001 for both, Table E4).

The full results for the unmatched populations are summarized in Tables E4 and E5. The adjusted odds of asthma control were similar or better by all 3 measures for patients receiving HFA-beclomethasone in both initiation and step-up populations. The adjusted rate of exacerbations was similar in both treatment cohorts of the initiation population, whereas the rate of exacerbations was significantly higher for patients prescribed fluticasone in the step-up population. The adjusted odds ratio for change in therapy was significantly lower for the HFA-beclomethasone cohort.

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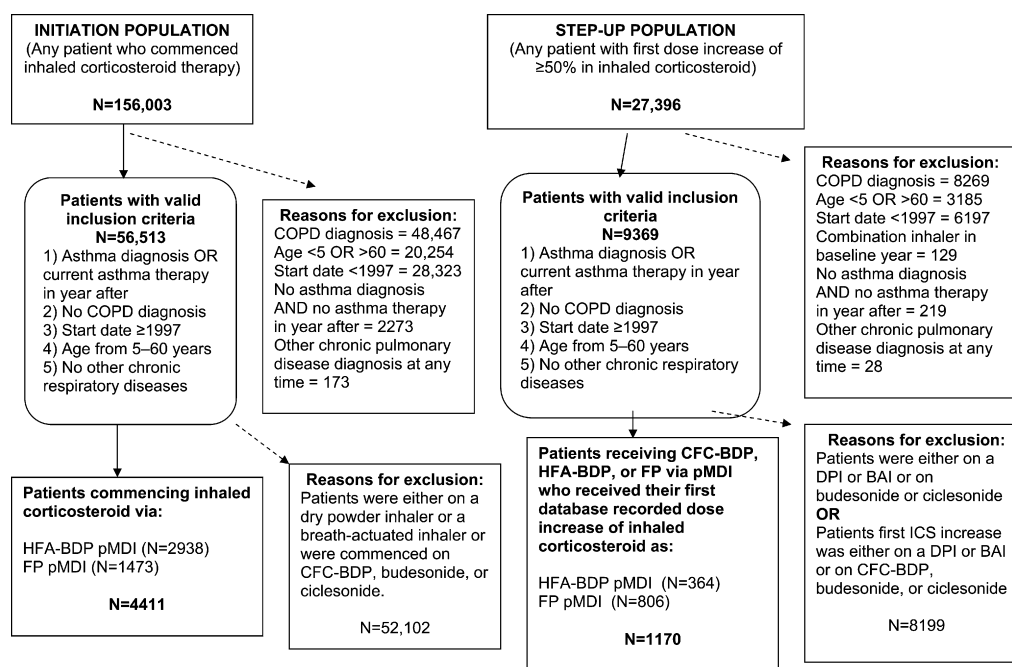


FIG E1. Selection of eligible patients in the database: unmatched cohorts. *BAI*, Breath-actuated inhaler; *BDP*, beclomethasone dipropionate; *CFC*, chlorofluorocarbon; *COPD*, chronic obstructive pulmonary disease; *DPI*, dry powder inhaler; *FP*, fluticasone propionate; *pMDI*, pressurized MDI.

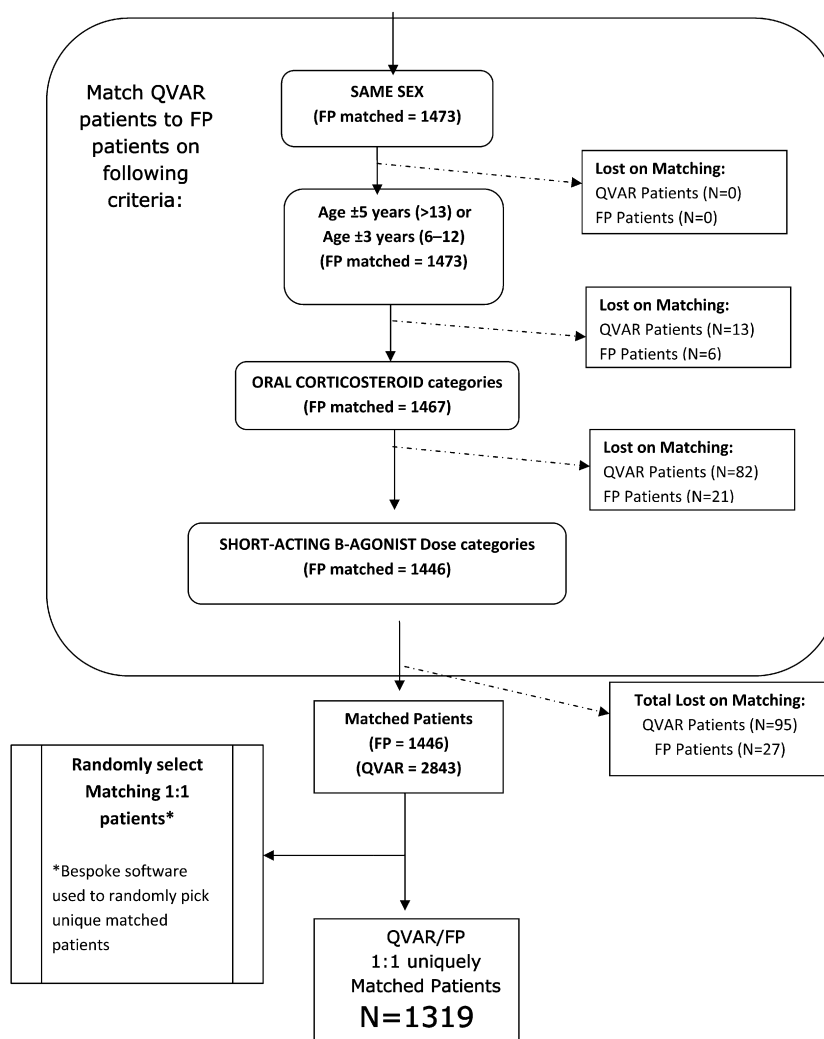


FIG E2. Selection of eligible patients in the database: matching of the cohorts initiating ICS therapy as HFA-beclomethasone or fluticasone administered by means of an MDI (initiation population). *FP*, Fluticasone propionate; *QVAR*, HFA-beclomethasone.

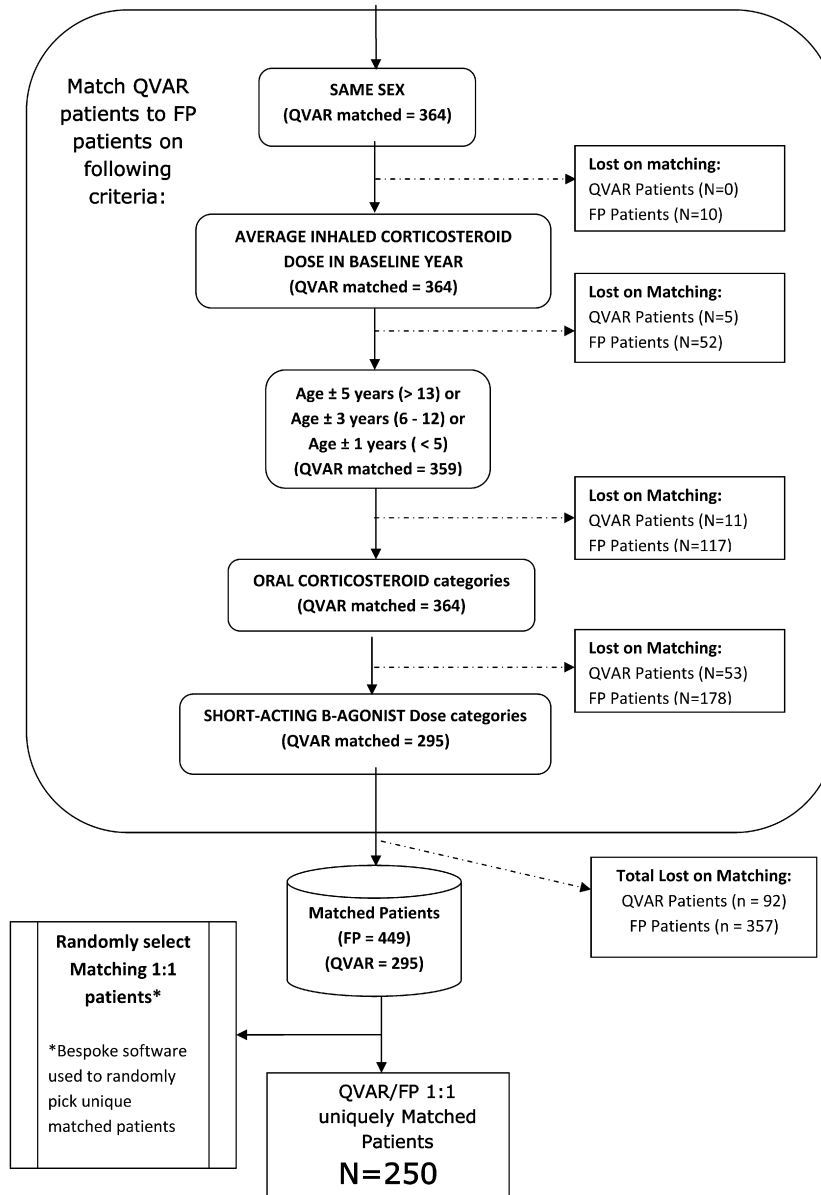


FIG E3. Selection of eligible patients in the database: matching of the cohorts receiving their first increase in dose of ICS as HFA-beclomethasone or fluticasone administered by means of an MDI (step-up population). FP, Fluticasone propionate; QVAR, HFA-beclomethasone.

TABLE E1. Details of the matching criteria used for the matched analyses

HFA-beclomethasone and fluticasone (both cohorts)	Categorizations
Oral corticosteroid prescriptions during baseline year	0, 1, 2, 3, ≥ 4
Age	Age ≥ 13 y: ± 5 y or 6-12 y: ± 3 y or 5 y: ± 1 y
Sex	Male/female
Mean SABA dose during the baseline year	0 $\mu\text{g}/\text{d}$ 1-100 $\mu\text{g}/\text{d}$ 101-200 $\mu\text{g}/\text{d}$ 201-300 $\mu\text{g}/\text{d}$ 301-400 $\mu\text{g}/\text{d}$ ≥ 400 $\mu\text{g}/\text{d}$
For step-up population only: mean ICS dose prescribed during the baseline year*	0-99 $\mu\text{g}/\text{d}$ 100-199 $\mu\text{g}/\text{d}$ 200-299 $\mu\text{g}/\text{d}$ 300-399 $\mu\text{g}/\text{d}$ 400-599 $\mu\text{g}/\text{d}$ 600-799 $\mu\text{g}/\text{d}$ ≥ 800 $\mu\text{g}/\text{d}$

SABA, Short-acting β -agonist.

*The defining of ICS dose categories at baseline for patients receiving an increase in dose of ICS was done because of differences in the index date prescribing doses between the HFA-beclomethasone and fluticasone cohorts.

TABLE E2. Outcome measures for HFA-beclomethasone cohorts of initiation and step-up populations, with the fluticasone cohort set as the reference group (OR/RR = 1.0): results of the primary analysis and the sensitivity analysis (in italics)

	Initiation population	Step-up population
	HFA-beclomethasone (n = 1319/592)	HFA-beclomethasone (n = 250/86)
Primary measure of asthma control, OR (95% CI)		
Adjusted for residual confounders	1.30 (1.02-1.65)*	1.22 (0.66-2.26)†
<i>Sensitivity analysis (adjusted as necessary)</i>	<i>1.60 (1.11-2.32)‡</i>	<i>1.25 (0.49-3.17)</i>
Exacerbation during the outcome year, RR (95% CI)		
Adjusted for residual confounders	0.96 (0.85-1.08)*	1.08 (0.82-1.43)†
<i>Sensitivity analysis (adjusted as necessary)</i>	<i>0.80 (0.51-1.26)§</i>	<i>1.00 (0.30-3.32)</i>
Asthma control plus no additional or change in therapy, OR (95% CI)		
Adjusted for residual confounders	1.66 (1.36-2.02)*	1.89 (1.19-3.01)†
<i>Sensitivity analysis (no adjustment necessary)</i>	<i>1.73 (1.34-2.23)</i>	<i>1.58 (0.77-3.26)</i>

OR, Odds ratio; RR, rate ratio.

*Adjusted for year of index date, acetaminophen, asthma consultations, rhinitis diagnosis, recorded asthma diagnosis, and cardiac disease diagnosis.

†Adjusted for year of index date, acetaminophen, asthma consultations, and rhinitis diagnosis.

‡Adjusted for year of index date.

§Adjusted for age group.

TABLE E3. Baseline characteristics of the unmatched cohorts for both study populations, those initiating ICS administered by means of an MDI and those receiving an increased dose of ICS administered by means of an MDI*

Characteristic	Initiation population			Step-up population		
	HFA-beclomethasone (n = 2938)	Fluticasone (n = 1473)	P value†	HFA-beclomethasone (n = 364)	Fluticasone (n = 806)	P value†
Male sex, no. (%)	1259 (42.9)	678 (46.0)	.05	158 (43.4)	355 (44.0)	.84
Age (y)	32.9 ± 15.8	25.7 ± 18.3	≤.001	33.9 ± 16.9	29.4 ± 18.6	≤.001
5-12 y, no. (%)	385 (13.1)	574 (39.0)		46 (12.6)	256 (31.8)	
13-18 y, no. (%)	328 (11.2)	130 (8.8)		50 (13.7)	53 (6.6)	
19-60 y, no. (%)	2225 (75.7)	769 (52.2)		268 (73.6)	497 (61.7)	
Weight (kg)‡	72.0 ± 23.1	62.5 ± 27.6	≤.001	71.4 ± 24.9	65.3 ± 27.8	.002
Height (m)‡	1.64 ± 0.18	1.53 ± 0.25	≤.001	1.63 ± 0.18	1.55 ± 0.23	≤.001
Body mass index (kg/m ²)‡	26.1 ± 7.1	24.3 ± 7.8	≤.001	26.1 ± 7.2	25.2 ± 8.5	.02
Socioeconomic status§						
Median	16.4	17.6	.79	18.2	17.9	.55
Interquartile range	11.2-28.8	9.2-35.2		11.4-32.1	9.7-37.1	
Charlson comorbidity index,§ no. (%)						
0	2733 (93.0)	1386 (94.1)	.03	337 (92.6)	736 (91.3)	.87
1	120 (4.1)	49 (3.3)		6 (1.6)	13 (1.6)	
2	65 (2.2)	25 (1.7)		14 (3.8)	34 (4.2)	
≥3	20 (0.7)	13 (0.9)		7 (1.9)	23 (2.9)	
Smoking status, no./total no. (%)						
Current	671/1912 (35.1)	194/672 (28.9)	.002	89/265 (33.6)	116/377 (30.8)	.73
Former	345/1912 (18.0)	111/672 (16.5)		42/265 (15.8)	65/377 (17.2)	
Never	896/1912 (46.9)	367/672 (54.6)		134/265 (50.6)	196/377 (52.0)	
Recorded asthma diagnosis, no. (%)	2706 (92.1)	1339 (90.9)	.17	356 (97.8)	788 (97.8)	.97
Recorded comorbidity, no. (%)						
Rhinitis	479 (16.3)	275 (18.7)	.05	81 (22.3)	189 (23.4)	.65
Cardiac disease	81 (2.8)	39 (2.6)	.83	14 (3.8)	29 (3.6)	.84
Gastroesophageal reflux disease	213 (7.2)	98 (6.7)	.47	26 (7.1)	63 (7.8)	.69
≥1 Prescription in 12 mo, no. (%)						
Nonsteroidal anti-inflammatory drug	481 (16.4)	202 (13.7)	.02	70 (19.2)	128 (15.9)	.16
β-blocker	97 (3.3)	39 (2.6)	.24	16 (4.4)	18 (2.2)	.04
Acetaminophen	392 (13.3)	247 (16.8)	.002	69 (19.0)	165 (20.5)	.55
Short-acting β ₂ -agonist dose (μg/d)						
Median	55	55	.59	110	164	≤.001
Interquartile range	0-55	0-55		55-274	110-329	
Oral corticosteroid courses, no. (%)						
0	2415 (82.2)	1225 (83.2)	.82	279 (76.6)	482 (59.8)	≤.001
1	415 (14.1)	195 (13.2)		51 (14.0)	183 (22.7)	
2	82 (2.8)	42 (2.9)		22 (6.0)	91 (11.3)	
≥3	26 (0.9)	11 (0.7)		12 (3.3)	50 (6.2)	
ICS dose during baseline year, μg/d						
Median	NA	NA	NA	55	82	.001
Interquartile range				28-110	33-165	
Asthma consultations, no. (%)						
0	1396 (47.5)	631 (42.8)	≤.001	86 (23.6)	143 (17.7)	.001
1	1201 (40.9)	586 (39.8)		120 (33.0)	212 (26.3)	
2	262 (8.9)	187 (12.7)		80 (22.0)	175 (21.7)	
≥3	79 (2.7)	69 (4.7)		78 (21.4)	276 (34.2)	
Asthma consultations without OCS, no. (%)						
0	1598 (54.4)	731 (49.6)	<.001	109 (29.9)	231 (28.7)	.052
1	1078 (36.7)	534 (36.3)		123 (33.8)	230 (28.5)	
2	205 (7.0)	157 (10.7)		73 (20.1)	161 (20.0)	
≥3	57 (1.9)	51 (3.5)		59 (16.2)	184 (22.8)	
Prescriptions for asthma						
Median	2	2	.009	5	6	≤.001
Interquartile range	1-3	1-3		3-8	4-9	
Courses of antibiotics for lower respiratory tract infection						
Median	0	0	.55	0	0	.77
Interquartile range	0-0	0-0		0-0	0-0	

(Continued)

TABLE E3. (Continued)

Characteristic	Initiation population			Step-up population		
	HFA-beclomethasone (n = 2938)	Fluticasone (n = 1473)	P value†	HFA-beclomethasone (n = 364)	Fluticasone (n = 806)	P value‡
Asthma control status,¶ no. (%)						
Primary measure of asthma control	2026 (69.0)	1028 (69.8)	.57	232 (63.7)	387 (48.0)	≤.001

NA, Not applicable; OCS, oral corticosteroid prescription.

*Plus-minus values are means $\pm$ SDs. Because of rounding, percentages might not total 100%.

†P values for continuous variables were calculated with the Mann-Whitney test and for categorical variables with the χ^2 test.

‡Not all patients had recorded weight, height, and body mass index data. For weight, the initiation populations were 2426 and 1132 for the HFA-beclomethasone and fluticasone cohorts, respectively; the step-up populations were 314 and 668, respectively. For height, the initiation populations were 2585 and 1249, respectively; the step-up populations were 337 and 717, respectively. For body mass index, the initiation populations were 2368 and 1101, respectively; the step-up populations were 310 and 652, respectively.

§Socioeconomic status was that assigned, in quintiles, by the GPRD to each practice by using the Index of Multiple Deprivation as a proxy measure. The Charlson comorbidity index is a weighted index that accounts for number and severity of comorbidities, each assigned a score depending on the associated risk of dying.^{E1}

||The short-acting β -agonist dose is the albuterol dose equivalent (standard dose in the UK is 100 μ g).

¶The primary measure of asthma control was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection.

TABLE E4. Outcomes for the unmatched cohorts for both study populations, those initiating an ICS and those receiving an increased dose of ICS*

Outcome	Initiation population			Step-up population		
	HFA-beclomethasone (n = 2938)	Fluticasone (n = 1473)	P value†	HFA-beclomethasone (n = 364)	Fluticasone (n = 806)	P value†
Asthma control status,‡ no. (%)						
Primary measure of asthma control	2444 (83.2)	1208 (82.0)		292 (80.2)	562 (69.7)	
Asthma control plus SABA use	1812 (61.7)	864 (58.7)		163 (44.8)	303 (37.6)	
Asthma control plus no additional or change in therapy	2222 (75.6)	1023 (69.5)		266 (73.1)	462 (57.3)	
Asthma exacerbations.§ no. (%)						
0	2651 (90.2)	1327 (90.1)		317 (87.1)	630 (78.2)	
1	201 (6.8)	115 (7.8)		33 (9.1)	91 (11.3)	
2	57 (1.9)	18 (1.2)		7 (1.9)	50 (6.2)	
≥3	29 (1.0)	13 (0.9)		7 (1.9)	35 (4.3)	
ICS dose at the index date, no. (%)						
0-99 µg/d	0 (0)	81 (5.5)	≤.001	0 (0)	0 (0)	≤.001
100-199 µg/d	875 (29.8)	276 (18.7)		6 (1.6)	13 (1.6)	
200-299 µg/d	1474 (50.2)	529 (35.9)		117 (32.1)	196 (24.3)	
300-399 µg/d	8 (0.3)	5 (0.3)		2 (0.5)	6 (0.7)	
400-599 µg/d	555 (18.9)	419 (28.4)		216 (59.3)	346 (42.9)	
600-799 µg/d	5 (0.2)	2 (0.1)		4 (1.1)	6 (0.7)	
≥800 µg/d	21 (0.7)	161 (10.9)		19 (5.2)	239 (29.7)	
Change in therapy, no. (%)	556 (18.9)	370 (25.1)	≤.001	72 (19.8)	239 (29.7)	≤.001
≥1 Oral corticosteroid course, no. (%)	287 (9.8)	146 (9.9)	.50	47 (12.9)	175 (21.7)	.01
≥1 Hospital admission, no. (%)	28 (1.0)	15 (1.0)	.84	2 (0.5)	22 (2.7)	.02
≥1 Course of antibiotics for lower respiratory tract infection, no. (%)	283 (9.6)	141 (9.6)	.53	36 (9.9)	115 (14.3)	.22
Mean SABA dose >200 µg/d, no. (%)	835 (28.4)	462 (31.4)	.04	173 (47.5)	420 (52.1)	.15

SABA, Short-acting β-agonist.

*Plus-minus values are means ± SDs. Because of rounding, percentages might not total 100%.

†P values for continuous variables were calculated with the Mann-Whitney test and for categorical variables with the χ^2 test.

‡The primary measure of asthma control was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection. Asthma control plus SABA use was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection plus mean use of 200 µg/d or less of SABA. Asthma control plus no additional or change in therapy was defined as no exacerbation, increase in ICS dose, change in ICS or inhaler device, or additional asthma controller therapy.

§An exacerbation was defined as a course of oral corticosteroids, hospital admission, or emergency department attendance for asthma; exacerbations on the index date were included in the baseline data.

||The SABA dose is the albuterol dose equivalent (standard dose in the UK is 100 µg).

TABLE E5. ORs (95% CIs) for measures of asthma control and change in therapy and rate ratios (95% CIs) for exacerbations in the HFA-beclomethasone cohorts of initiation and step-up populations during the outcome year, with the fluticasone cohort set as the reference group (OR = 1.0): Unmatched populations

	Initiation population	Step-up population
	HFA-beclomethasone (n = 2938)	HFA-beclomethasone (n = 364)
Primary measure of asthma control,* OR (95% CI)		
Unadjusted	1.09 (0.91-1.28)	1.75 (1.30-2.38)
Adjusted for residual confounders	1.15 (0.98-1.41) [†]	1.43 (1.03-1.96) [‡]
Asthma control plus SABA use, OR (95% CI)		
Unadjusted	1.14 (1.0-1.32)	1.33 (1.04-1.72)
Adjusted for residual confounders	1.18 (1.03-1.35) [†]	1.16 (0.88-1.54) [‡]
Asthma control plus no additional or change in therapy, OR (95% CI)		
Unadjusted	1.37 (1.19-1.56)	2.00 (1.54-2.63)
Adjusted for residual confounders	1.43 (1.23-1.64) [†]	1.75 (1.32-2.33) [‡]
Exacerbation during the outcome year, rate ratio (95% CI)		
Unadjusted	1.06 (0.81-1.41)	0.50 (0.31-0.83)
Adjusted for residual confounders	0.96 (0.74-1.27) [§]	0.62 (0.39-0.98)
Change in therapy, OR (95% CI)		
Unadjusted	0.70 (0.60-0.83)	0.58 (0.43-0.79)
Adjusted for residual confounders	0.70 (0.60-0.83) [§]	0.62 (0.45-0.84)

OR, Odds ratio; SABA, short-acting β -agonist.

*The primary measure of asthma control was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection. Asthma control plus SABA use was defined as no unscheduled or hospital care for asthma, oral corticosteroid course, or antibiotics for lower respiratory tract infection plus mean use of 200 μ g/d or less of SABA. Asthma control plus no additional or change in therapy was defined as no exacerbation, increase in ICS dose, change in ICS or inhaler device, or additional asthma controller therapy. An exacerbation was defined as a course of oral corticosteroids, hospital admission, or emergency department attendance for asthma; exacerbations on the index date were included in the baseline data.

[†]Adjusted for year of index date, age, oral corticosteroids, hospitalization for asthma, antibiotics, SABA dose, prescriptions for asthma, asthma consultations, rhinitis diagnosis, acetaminophen, and nonsteroidal anti-inflammatory drug.

[‡]Adjusted for year of index date, age, SABA dose, prescriptions for asthma, asthma consultations, β -blockers, and baseline ICS dose.

[§]Adjusted for age, body mass index, rhinitis diagnosis, acetaminophen, and nonsteroidal anti-inflammatory drug.

^{||}Adjusted for age, number of SABA prescriptions, ICS dose during the baseline year, asthma consultations, and primary measure of asthma control.