

Asthma outcomes and costs of therapy with extrafine beclomethasone and fluticasone

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Background: Characteristics of inhaled corticosteroids (ICSs) differ, but data comparing the real-life effectiveness of various ICSs for asthma are lacking.

Objective: We sought to compare real-life asthma outcomes and costs of extrafine hydrofluoroalkane (HFA)–beclomethasone and fluticasone administered through a pressurized metered-dose inhaler.

Methods: This retrospective matched cohort study examined database markers of asthma control from a large US

longitudinal health care claims database over 1 baseline and 1 outcome year for 10,312 patients with asthma aged 12 to 80 years receiving their first ICS as HFA-beclomethasone or fluticasone and matched on baseline demographic characteristics and asthma severity.

Results: Patients started on HFA-beclomethasone had significantly higher odds (adjusted odds ratio, 1.19; 95% CI; 1.08-1.31) of achieving overall control (risk and impairment), which was defined as no hospital attendance for asthma, oral

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corticosteroids, or antibiotics for lower respiratory tract infection and less than 2 puffs per day of short-acting β -agonist; they also experienced a lower rate of respiratory-related hospitalizations or referrals (adjusted rate ratio, 0.82; 95% CI, 0.73-0.93) than patients started on fluticasone. Other database outcome measures were similar in the 2 cohorts. Prescribed HFA-beclomethasone doses were lower ($P < .001$) than fluticasone doses (median, 320 $\mu\text{g}/\text{d}$ [interquartile range, 160-320 $\mu\text{g}/\text{d}$] vs 440 $\mu\text{g}/\text{d}$ [interquartile range, 176-440 $\mu\text{g}/\text{d}$]). Adjusted respiratory-related health care costs were significantly lower for HFA-beclomethasone than fluticasone (mean, \$1869 [95% CI, \$1727-\$2032] vs \$2259 [95% CI, \$2111-\$2404]), representing a mean annual savings of \$390 (95% CI, \$165-\$620) per patient prescribed HFA-beclomethasone rather than fluticasone.

Conclusions: Asthma treatment outcomes were similar or better with HFA-beclomethasone prescribed at significantly lower doses and with lower costs than fluticasone. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Asthma control, beclomethasone dipropionate, extrafine particle, fluticasone propionate, observational study, United States

The prevalence of asthma in the United States (US) now exceeds 8%, and the proportion of patients with asthma in the US grew by 15% in the last decade.¹ Not surprisingly, the economic burden of asthma in the US is also substantial, estimated for 2007 at \$56 billion in direct medical costs and loss of productivity.² These facts underscore the need for not only effective but also cost-effective asthma treatments.

Inhaled corticosteroids (ICSs) are the preferred therapy for persistent asthma,³ acting directly on the pulmonary airways through topical anti-inflammatory effects.^{4,5} The formulation characteristics of ICSs, particularly particle size, can influence lung deposition and distribution and thus potentially ICS efficacy and safety.⁴ With the transition to hydrofluoroalkane (HFA) propellants for pressurized metered-dose inhalers (pMDIs), extrafine ICSs have been developed with smaller particle sizes and improved total airway deposition and penetration to the small peripheral airways.⁶⁻⁸ An area of active research in asthma is determining the role and prevalence of small-airways inflammation, as well as whether targeting small-airways inflammation with extrafine ICSs will improve asthma outcomes.^{6,9-11}

Beclomethasone dipropionate and fluticasone propionate are the 2 most commonly prescribed ICSs in the US. Although fluticasone is more potent *in vitro*,⁴ beclomethasone formulated in solution with extrafine particle size and HFA propellant has improved total and peripheral distribution relative to fluticasone, which has a larger particle size.^{7,12,13} In randomized trials HFA-beclomethasone provided comparable asthma control when administered at the same dose as fluticasone.¹⁴⁻¹⁶ These results prompted the recommendation that HFA-beclomethasone and fluticasone should be prescribed at a 1:1 dose ratio.³ However, comparisons of HFA-beclomethasone and fluticasone in short-term trials provide little information on the relative long-term benefits of these 2 ICSs.¹⁷ Rigorously conducted observational studies can examine longer-term outcomes, providing information to complement the results of randomized trials through inclusion of unselected representative patients managed in real-life clinical practice.¹⁸⁻²⁰ Our prior retrospective, observational,

Abbreviations used

ED:	Emergency department
HFA:	Hydrofluoroalkane
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
MPR:	Medication possession ratio
pMDI:	Pressurized metered-dose inhaler
SABA:	Short-acting β -agonist
UK:	United Kingdom
US:	United States

matched cohort study with a large primary care database in the United Kingdom (UK) found that patients prescribed HFA-beclomethasone had similar or better odds of achieving asthma control at lower prescribed doses than those managed with fluticasone.²¹

The objective of this study was to confirm the findings of our UK work in a US population and to extend the consequences of these findings by examining the costs of HFA-beclomethasone and fluticasone therapy. We hypothesized that better lung deposition with HFA-beclomethasone would result in improved asthma outcomes at a lower dose with cost savings.

METHODS

Study sample

This retrospective matched cohort study used deidentified patient data in the Ingenix Normative Health Information Database, now called the OptumInsight Research Database,²² a longitudinal health care claims database from primary and secondary (specialist and emergency) care for approximately 15 million patients per year from every US census region.

There were 2 patient populations studied. In both populations, patients eligible for inclusion were those aged 12 to 80 years with asthma. The initiation population included patients who received a first prescription of ICS through a pMDI on the index date from 2004 through 2009 as either HFA-beclomethasone (Qvar; Teva Pharmaceutical Industries, Petach Tikva, Israel) or fluticasone (Flovent or Flovent HFA; GlaxoSmithKline, Research Triangle Park, NC). The step-up population included patients who had received an ICS and who had received an increase (step-up) in ICS dose on the index date as either HFA-beclomethasone or fluticasone from a pMDI.

Eligible patients were included in the database for at least 1 year before (baseline year) and 1 year after (outcome year) the index date. Evidence of asthma was defined as a diagnostic code for asthma in the database or 2 or more prescriptions for asthma (reliever or controller medication) on at least 2 different dates. In addition, eligible patients had to have received 1 or more prescriptions for asthma during the outcome year as evidence of ongoing asthma care. We excluded patients with a diagnosis of any chronic respiratory disease other than asthma, patients who had received maintenance oral corticosteroid therapy during the baseline year, and smokers 60 years and older to minimize the inclusion of patients with chronic obstructive pulmonary disease misdiagnosed as asthma.

Institutional review board approval was waived for this noninterventional study.

Outcome measures

The 3 coprimary outcome measures were composites of key elements of asthma control derived from the database. The coprimary measure of *risk-domain asthma control* was defined as (1) no recorded hospital attendance for asthma, including admission, emergency department (ED) attendance, or outpatient hospital attendance; (2) no prescription for an acute course of oral corticosteroids; (3) no consultation, hospital admission, or ED

attendance for lower respiratory tract infection requiring antibiotics; and (4) no hospital admission or ED attendance for a lower respiratory tract reason. The coprimary measure of *overall control (risk and impairment)* incorporated limited short-acting β -agonist (SABA) use as a fifth criterion, namely average daily dose of 180 μg or less (≤ 2 puffs) albuterol. The coprimary measure of *severe exacerbation* was defined as unscheduled hospital admission or ED attendance for asthma or an acute course of oral corticosteroids.²³

Secondary outcome measures included 3 additional composite end points. First, *treatment success* was defined as risk-domain asthma control plus no change in asthma therapy (no increase in ICS dose, change in ICS, change in delivery device, or use of additional controller therapy for asthma as a long-acting β -agonist [LABA], leukotriene receptor antagonist, or theophylline). Second, in a *sensitivity analysis of treatment success* we further examined the latter measure, excluding changes in therapy that could have been motivated by cost savings, namely change in ICS or delivery device. Third, we also determined for each patient the number of *respiratory-related hospitalizations and referrals*, which was defined as unscheduled hospital admissions or ED attendance for lower respiratory tract reasons or planned hospital outpatient attendance for asthma.

The medication possession ratio (MPR) was defined as follows:

Number of days' supply of ICS/365 $\times$ 100%.²⁴⁻²⁶

The controller/total asthma medication ratio was defined as follows:

Units of controllers/(Units of controllers + relievers).^{27,28}

Statistical analyses

Outcome measures and analyses were established *a priori* according to standard operating procedures of the study group.²⁹ Analyses were performed with SPSS Statistics version 19 software (IBM SPSS Statistics, Feltham, Middlesex, United Kingdom), SAS version 9.2 software (SAS Institute, Marlow, Buckinghamshire, United Kingdom), and Microsoft Excel 2007 software (Microsoft Corp, Redmond, Was). Statistically significant results were defined as a *P* value of .05 or less. To account for multiple comparisons, we conducted false discovery rate-controlling procedures when primary outcome results showed significance.^{30,31}

Patients in the 2 treatment cohorts of each study population (ICS initiation and step-up) were matched before statistical analyses on 5 demographic and baseline criteria that could influence asthma control or that were predictive of asthma control in prior datasets examined by the study group, namely sex, age (± 3 years for age 12 years and ± 5 years for age ≥ 13 years) and, during the baseline year, mean SABA daily dose (0, 1-100, or ≥ 100 μg), number of oral corticosteroid prescriptions (0 or ≥ 1), and number of asthma consultations with no prescription for oral corticosteroids (0, 1, or ≥ 2). In addition, the step-up population was matched on mean ICS daily dose during the baseline year. Fewer patients in the dataset were prescribed HFA-beclomethasone than fluticasone (see Fig E1 in this article's Online Repository at www.jacionline.org); therefore to maximize both the cohort sizes and the number of matched groupings and thus the power of statistical tests, we matched patients in HFA-beclomethasone/fluticasone ratios of 1:3 and 1:2 for the initiation and step-up populations, respectively.

Summary statistics were used to assess all baseline and outcome variables. We investigated potential outliers and missing data (for type and reason for missingness). We handled skewed data using log transformation or, for heavily skewed data, categorization. Baseline variables and unadjusted outcome measures were compared between matched cohorts by using conditional logistic and Poisson regression models to account for the correlated data within the matched cohorts. Baseline variables significantly different at the 10% level were considered potential confounders. In addition, multivariate analyses were carried out by using the full dataset to identify baseline variables predictive ($P \leq .05$) of each outcome; these were considered additional potential confounders. Spearman correlation coefficients were calculated between all potential confounders to determine the strengths of linear relationships between variables; the correlation coefficients were considered, in conjunction with clinical interpretation, to identify possible collinearity issues. All primary and secondary outcomes were adjusted for appropriate noncollinear baseline confounders.

The adjusted odds of achieving risk-domain asthma control was compared between cohorts, with fluticasone as the reference treatment, using conditional logistic regression models, with the dichotomous outcome for risk-domain asthma control as the dependent variable and treatment and residual confounding factors as explanatory variables. The adjusted odds ratios for achieving the overall control (risk and impairment) and treatment success measures were calculated in similar fashion. The number of exacerbations in the outcome period was compared between cohorts by using a conditional Poisson regression model to obtain estimates of exacerbation rates relative to the fluticasone cohort. The model used empiric SEs for more robust CIs, and adjustments were made for potential baseline confounders. The adjusted rate ratio for respiratory-related hospitalizations was calculated by using the same model.

Total respiratory-related health care costs were summed, adjusted to 2010 prices, and compared between cohorts by using conditional logistic regression (see the Methods section in this article's Online Repository at www.jacionline.org for cost categories). To account for the switch to more expensive HFA inhalers in 2008, we used a standard 2010 price for SABA inhalers. We compared mean annual respiratory-related health care costs during the outcome period using generalized linear models with a log link and gamma distribution adjusted for baseline respiratory-related health care costs.

RESULTS

We identified 14,901 eligible patients initiating ICSs and 2,625 stepping up the dose of ICS who received a prescription for HFA-beclomethasone or fluticasone during the study period (see Fig E1). After matching, there were 10,312 patients initiating ICSs and 579 patients stepping up the ICS dose who were included in the analyses. Because of the small step-up sample size, interpretation of those results is limited; thus step-up results are summarized below and fully reported in the Results section in this article's Online Repository at www.jacionline.org.

Initiation population

Baseline demographic and clinical characteristics.

The 2578 and 7734 matched patients in the HFA-beclomethasone and fluticasone initiation cohorts, respectively, were similar at baseline (Table I and see Table E1 in this article's Online Repository at www.jacionline.org). A similar percentage of patients in the 2 cohorts met the risk-domain asthma control and overall control (risk and impairment) measures at baseline, with no baseline differences in the rates of severe exacerbations between the 2 cohorts.

Outcomes. The adjusted odds of achieving the coprimary asthma control measure (risk-domain asthma control) were similar for the 2 cohorts during the outcome year, but the HFA-beclomethasone cohort was significantly more likely to have achieved the measure of overall control (risk and impairment) that included limited SABA use (Table II). Overall control (risk and impairment) remained significantly different between cohorts after having controlled for the false discovery rate at the 0.05 level. Severe exacerbation rates were similar.

There were similar rates of treatment success for the HFA-beclomethasone and fluticasone cohorts, whereas the adjusted rate ratio of respiratory-related hospitalizations and referrals was significantly lower for the HFA-beclomethasone cohort. Patients prescribed HFA-beclomethasone were significantly less likely to use a SABA dose of greater than 180 $\mu\text{g}/\text{d}$, to have been hospitalized for asthma, or to have a change in therapy (Table II). For patients having a change in therapy, those in the HFA-beclomethasone cohort were significantly more likely to have

TABLE I. Matching criteria and other asthma control-related measures during the baseline year for matched cohorts of patients initiating ICSs administered through a pMDI (initiation population)

Characteristic*	Initiation population	
	HFA-beclomethasone (n = 2578)	Fluticasone (n = 7734)
Matching criteria		
Male sex	948 (37)	2844 (37)
Age (y), mean (SD)	37 (17)	37 (17)
Oral corticosteroid courses		
0	1977 (77)	5931 (77)
≥1	601 (23)	1803 (23)
Asthma consultations, no OCS		
0	969 (38)	2907 (38)
1	1016 (39)	3048 (39)
≥2	593 (23)	1779 (23)
Mean daily SABA dose		
0	1356 (53)	4068 (53)
1-100 µg	624 (24)	1872 (24)
101-200 µg	247 (10)	723 (9)
201-400 µg	165 (6)	509 (7)
≥400 µg	186 (7)	562 (7)
Risk-domain asthma control	1474 (57)	4343 (56)
Overall control (risk and impairment)	1179 (46)	3523 (46)
1 Severe exacerbation	453 (18)	1425 (18)
≥2 Severe exacerbations	220 (9)	682 (9)
≥1 Course of antibiotics for LRTI	476 (19)	1385 (18)
≥1 Hospitalization for asthma	64 (3)	288 (4)

LRTI, Lower respiratory tract infection; OCS, oral corticosteroids.

*Data are presented as numbers (percentages), unless otherwise specified. Percentages might not total 100 because of rounding.

either an increase in ICS dose or a change in ICS drug, whereas those in the fluticasone cohort were significantly more likely to have additional therapy.

Patients in the HFA-beclomethasone cohort were prescribed a significantly lower ($P < .001$) ICS dose on the index date than matched patients in the fluticasone cohort (median, 320 µg/d [interquartile range, 160-320 µg/d] vs 440 µg/d [interquartile range, 176-440 µg/d]). No patients in the HFA-beclomethasone cohort were prescribed more than 320 µg/d, whereas 18% of the patients in the fluticasone cohort were prescribed 880 µg/d or more (Fig 1).

The median MPR was low in both cohorts (16%, Table II); only 8% and 10% of patients in the HFA-beclomethasone and fluticasone cohorts, respectively, had an MPR of 80% or greater ($P = .051$ for the comparison). When outcomes were categorized by mean daily ICS dose consumed during the outcome year (ICS prescribed during the year divided by 365), patients who consumed the highest ICS doses tended to have a lower likelihood of achieving overall control (risk and impairment; Fig 2, A). When outcomes were categorized by MPR, a similar pattern was seen: patients with a lower MPR tended to have a higher likelihood of achieving the asthma control measures and a lower likelihood of a severe exacerbation (Fig 2, B-D). The exception was for an MPR of 81% to 100%, but this group represented a small percentage (2%) of the total patient population. Whichever way these dose-response relationships were viewed, either by MPR or calculated ICS dose, the differences in outcomes for the HFA-beclomethasone and fluticasone cohorts were consistent, with the clearest difference between cohorts seen for the patients with an MPR of 81% to 100%.

More patients in the HFA-beclomethasone cohort had a controller/total asthma medication ratio of 0.5 or greater (61% vs 57%, $P < .001$). Spacers were prescribed for 5% versus 7% of patients in the HFA-beclomethasone versus fluticasone cohorts ($P < .001$). The index dates were later for HFA-beclomethasone ($P < .001$), a finding potentially relevant to the cost analyses as prices increased over time.

Step-up population

There were no significant differences between treatment cohorts in baseline asthma control and exacerbation measures (see Table E1 in this article's Online Repository at www.jacionline.org). Full results for the step-up population are in Table E2 and Figs E1 to E3 in this article's Online Repository at www.jacionline.org. There were no statistically significant differences between the 2 treatment cohorts in the adjusted outcome measures (see Table E2). Patients in the HFA-beclomethasone cohort were prescribed significantly lower ($P < .001$) doses on the index date than matched patients in the fluticasone cohort (see Fig E2).

Respiratory-related health care costs

There were no significant baseline differences between treatment cohorts in total asthma and respiratory-related health care costs for the initiation or step-up population (data not shown).

There were no significant differences between treatment cohorts of the initiation population in unadjusted categorized or total respiratory-related treatment costs over the outcome period (Table III and see Table E3 in this article's Online Repository at www.jacionline.org). The adjusted total mean respiratory-related health care costs for the initiation population were significantly lower for the HFA-beclomethasone cohort than the fluticasone cohort (Table III), with a mean annual savings of \$390 (95% CI, \$165-\$620) per patient prescribed HFA-beclomethasone rather than fluticasone. Similarly, the adjusted total mean respiratory-related health care costs excluding ICS costs were significantly lower for the HFA-beclomethasone cohort (Table III), with a mean annual savings of \$306 (95% CI, \$80-\$535) per patient prescribed HFA-beclomethasone.

For the step-up population, there were no significant differences between cohorts in unadjusted or adjusted total mean respiratory-related treatment costs over the outcome period (see Tables E4 and E5 in this article's Online Repository at www.jacionline.org).

DISCUSSION

This large, retrospective, observational, real-life study included patients matched on baseline severity and demographic factors treated for asthma with either HFA-beclomethasone or fluticasone. For patients initiating ICSs, asthma-related outcomes were the same or better for the HFA-beclomethasone cohort than the fluticasone cohort, HFA-beclomethasone was prescribed at significantly lower doses than fluticasone, and adjusted total mean respiratory-related health care costs were significantly lower for the HFA-beclomethasone cohort than the fluticasone cohort.

A strength of this study is the use of multiple composite measures designed to reflect asthma control and exacerbations over 1 full baseline year and 1 full outcome year, mitigating the effect of seasonal variations. The inclusion of antibiotic

TABLE II. Unadjusted and adjusted results during the outcome year for the initiation population: matched cohorts

Outcome	HFA-BDP (n = 2578), no. (%)	Fluticasone (n = 7734), no. (%)	Adjusted odds or rate ratio for HFA-BDP (95% CI)
Coprimary outcome measures			
Risk-domain asthma control	1489 (58)	4419 (57)	1.05 (0.96-1.15)*
Overall control (risk and impairment)	1007 (39)	2650 (34)	1.19 (1.08-1.31)†
1 Severe exacerbation	422 (16)	1313 (17)	0.96 (0.88-1.06)‡
≥2 Severe exacerbations	232 (9)	706 (9)	
Secondary outcome measures			
Treatment success	1165 (45)	3380 (44)	1.09 (0.99-1.19)§
Sensitivity excluding cost-savings	1170 (45)	3425 (44)	1.07 (0.97-1.17)
≥1 Respiratory-related hospitalization or referral	445 (17)	1504 (19)	0.82 (0.73-0.93)¶
Disaggregated outcome measures			
			<i>P</i> value#
≥1 Oral corticosteroid course	572 (22)	1685 (22)	.66
≥1 Antibiotics for lower respiratory tract disease	445 (17)	1280 (17)	.40
SABA dose >180 µg/d	866 (34)	3204 (41)	<.001
≥1 Hospitalization for asthma	87 (3)	347 (5)	.015
Change in therapy	681 (26)	2305 (30)	.001
Increase in ICS dose	195 (8)	474 (6)	.010
Change in delivery device	83 (3)	232 (3)	.57
Change in ICS drug	160 (6)	354 (5)	.001
Additional therapy	552 (21)	1847 (24)	.010
MPR, median (IQR)	16 (8-41)	16 (8-41)	.11
MPR, mean (SD)	29 (27)	30 (28)	

The adjusted odds ratio/rate ratio for fluticasone was set at 1.0.

HFA-BDP, Hydrofluoroalkane-beclomethasone; IQR, interquartile range.

*Adjusted for gastroesophageal reflux disease, acetaminophen, number of non-asthma-related primary care consultations, and respiratory-related hospitalizations and referrals.

†Adjusted for gastroesophageal reflux disease, acetaminophen, number of prescriptions for asthma/allergies, respiratory-related hospitalizations and referrals, and year of index prescription.

‡Adjusted for rhinitis, gastroesophageal reflux disease, acetaminophen, number of asthma consultations, and respiratory-related hospitalizations and referrals.

§Adjusted for rhinitis, gastroesophageal reflux disease, number of non-asthma-related primary care consultations, number of prescriptions for asthma/allergies, and respiratory-related hospitalizations and referrals.

||Adjusted for rhinitis, gastroesophageal reflux disease, number of non-asthma-related primary care consultations, number of prescriptions for asthma/allergies, and respiratory-related hospitalizations and referrals.

¶Adjusted for gastroesophageal reflux disease, acetaminophen, number of non-asthma-related primary care consultations, number of SABA prescriptions, and respiratory-related hospitalizations.

#Conditional logistic regression.

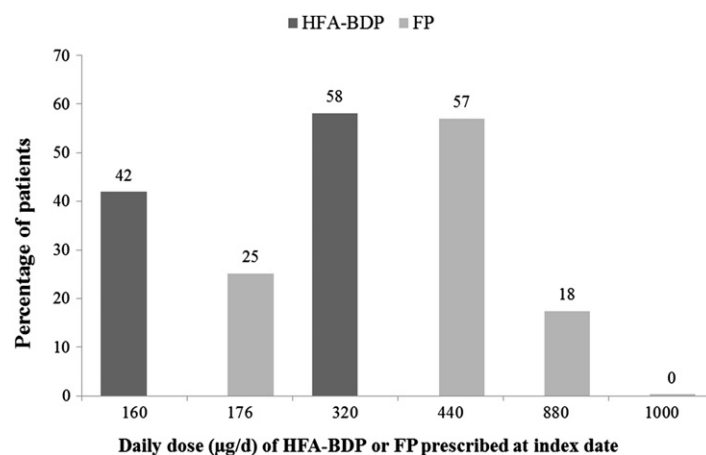
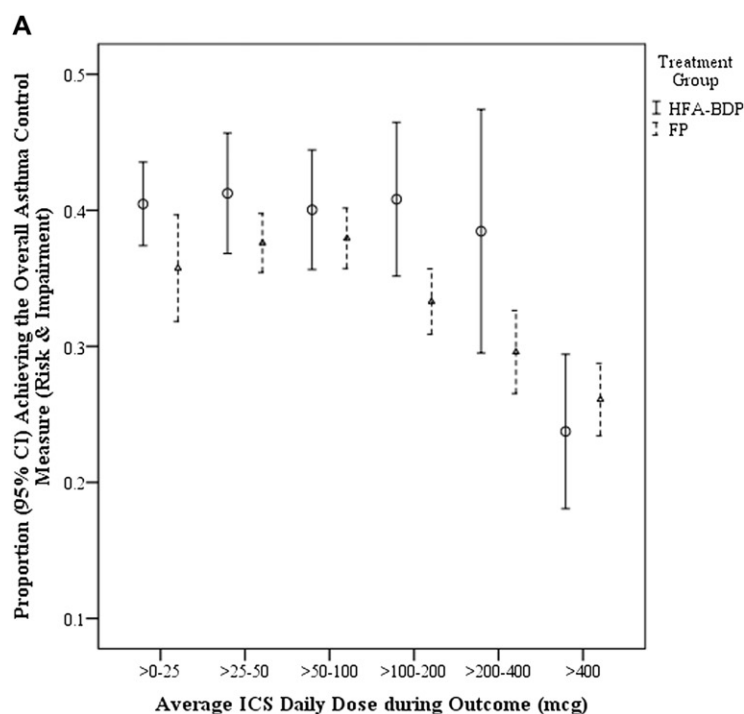


FIG 1. ICS dose for matched cohorts, as prescribed on the index date for the initiation population. All differences in dose between the extrafine HFA-beclomethasone and fluticasone cohorts were statistically significant ($P < .001$). FP, Fluticasone propionate; HFA-BDP, hydrofluoroalkane-beclomethasone dipropionate.

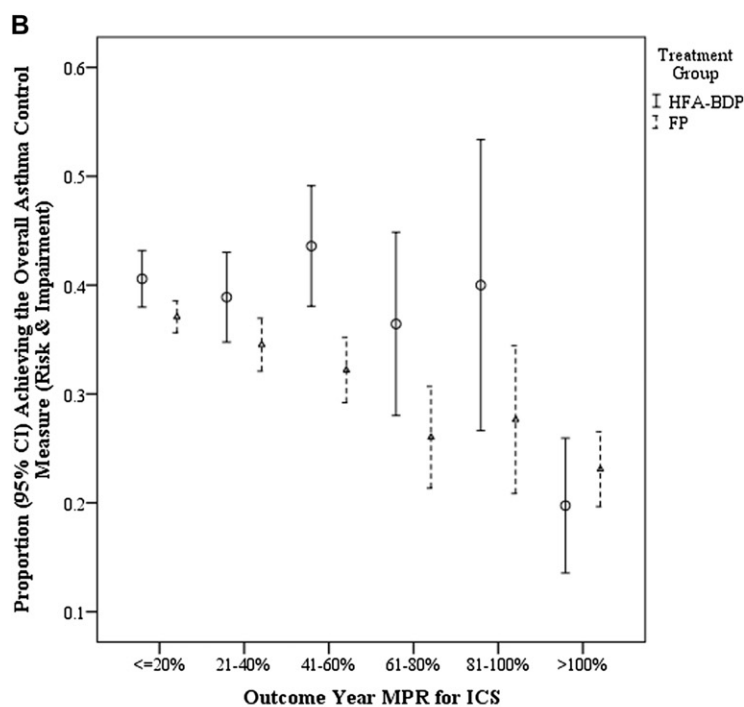
prescribing for lower respiratory tract infections in the asthma control measures adds robustness because asthma exacerbations can be confused in practice for respiratory infection.³²⁻³⁴ Additionally, the coprimary outcome measure of overall control (risk

and impairment) provides value because SABA use is an accepted marker of asthma symptom control and an important objective measure for individual patients.³⁵ We chose the average daily dose of 180 µg or less of albuterol (≤ 2 puffs) for this outcome



Patients, n (%):

	>0-25	>25-50	>50-100	>100-200	>200-400	>400
HFA-BDP	986 (38)	480 (20)	482 (20)	294 (11)	117 (5)	219 (8)
FP	579 (7)	1923 (25)	1845 (24)	1475 (19)	862 (11)	1050 (14)



Patients, n (%):

	≤20%	21-40%	41-60%	61-80%	81-100%	>100%
HFA-BDP	1380 (54)	540 (21)	312 (12)	129 (5)	55 (2)	162 (6)
FP	4227 (55)	1477 (19)	938 (12)	342 (4)	170 (2)	580 (8)

FIG 2. Proportion of patients in the initiation population by treatment cohort who achieved the overall control (risk and impairment) measure during the outcome year categorized by consumed ICS dose (ie,

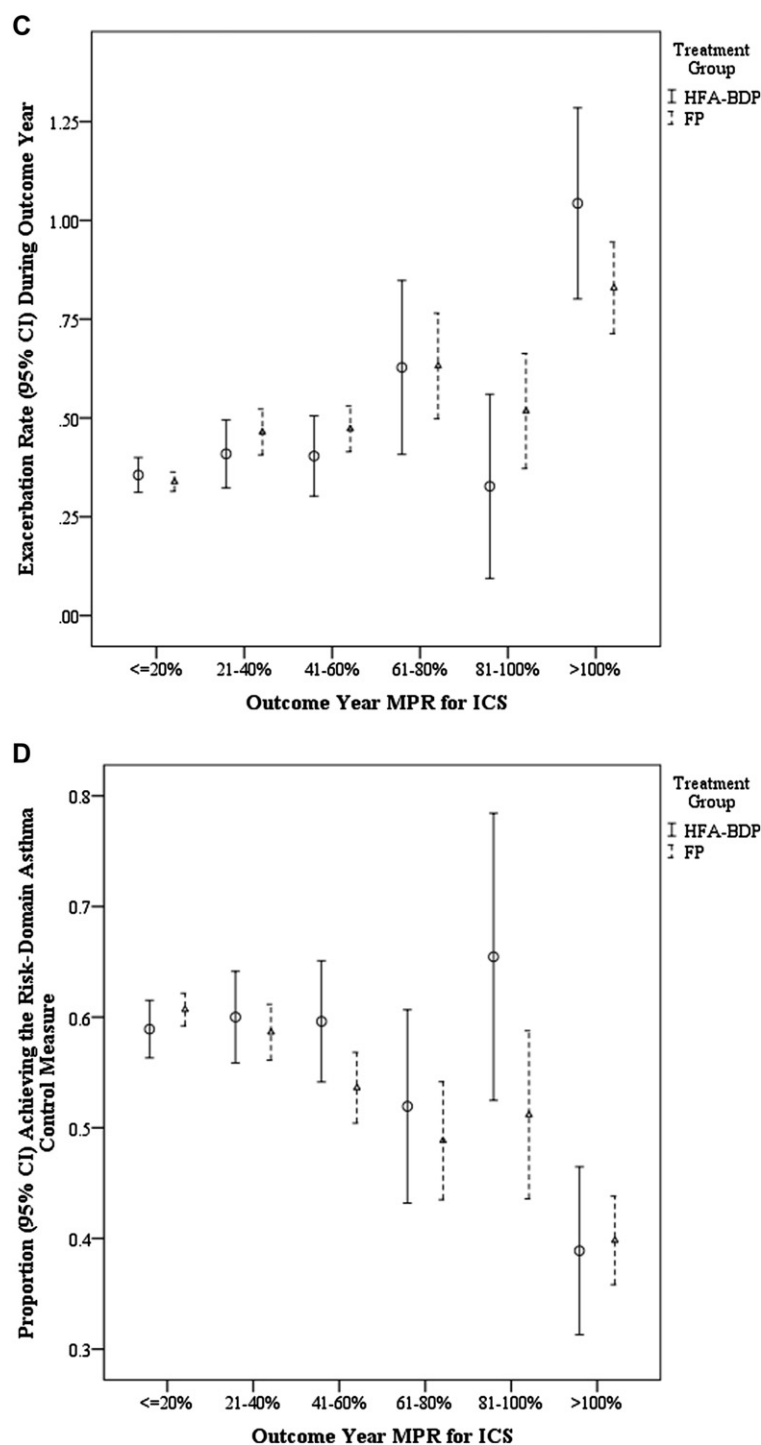


FIG 2. (Continued)

measure to take into account albuterol use for symptom relief, as well as priming the canister, preventing exercise-related difficulties, and dispensing of multiple canisters for home and travel.

The findings from this study are strengthened by the large sample sizes of the initiation cohorts and by the consistent benefits of HFA-beclomethasone in the initiation population

prescribed ICS divided by 365; **A**) and by MPR for ICSs (**B**). Exacerbation rates by MPR (**C**) and the proportion of patients who achieved the risk-domain asthma control measure by MPR (**D**) are shown also. Patient count percentages might not equal 100% because of rounding. *FP*, Fluticasone propionate; *HFA-BDP*, hydrofluoroalkane-beclomethasone dipropionate.

TABLE III. Mean respiratory-related medical resource costs (US\$)

Respiratory-related resource	Costs for the initiation population		
	HFA-beclomethasone (n = 2578)	Fluticasone (n = 7734)	P value*
Respiratory-related medication	800 (709)	840 (666)	.13
Respiratory-related primary care consultation	387 (1244)	328 (915)	.14
Total respiratory-related hospitalizations	765 (3816)	1201 (4191)	.15
Respiratory inpatient	428 (3152)	842 (8052)	.15
Respiratory outpatient	323 (1763)	328 (1935)	.95
Respiratory ED	15 (155)	31 (332)	.17
Lower respiratory, other medical	20 (188)	26 (335)	.66
Total asthma/respiratory primary and secondary care,† including ICS costs	1952 (4191)	2369 (8491)	.17
Total asthma/respiratory primary and secondary care, excluding ICS costs	1717 (4161)	2057 (8470)	.26
Total adjusted costs per patient‡ (95% CI)	1869 (1727-2032)	2259 (2111-2404)	—
Total adjusted costs per patient, excluding ICS costs‡ (95% CI)	1659 (1516-1823)	1965 (1817-2109)	—

Values are means (SDs), unless otherwise noted. Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policymakers and providers.

*Conditional logistic regression.

†Secondary care refers to specialist and emergency care.

‡Adjusted for baseline respiratory-related health care costs.

across clinically relevant primary and secondary outcome measures. The cohort treated with HFA-beclomethasone was more likely to achieve overall control (risk and impairment) and less likely to have respiratory-related hospitalizations and referrals. HFA-beclomethasone-treated patients were also less likely to require a change in therapy. Of interest, the patterns of change in therapy differed for the 2 treatment cohorts. Patients treated with HFA-beclomethasone who had a change in therapy were more likely than fluticasone-treated patients to have an increase in dose. This was possibly because HFA-beclomethasone was used at lower doses, providing more flexibility in dose titration upward. The fluticasone-treated patients, who received, on average, higher ICS doses, were more likely to have additional therapy. Although the smaller size of the step-up cohorts limits interpretation of findings, it is important to note that treatment outcomes for the HFA-beclomethasone and fluticasone step-up cohorts were similar even though the prescribed fluticasone doses were significantly higher than the HFA-beclomethasone doses.

This study was not designed to evaluate the mechanisms behind the real-life differences we observed. However, we speculate that formulation characteristics of HFA-beclomethasone might have played a role. The HFA-beclomethasone pMDI has been engineered to deliver a warm, soft, and long-duration aerosol spray with small particle sizes,^{7,13} making it relatively forgiving of poor inhaler technique, a common problem in clinical practice. Lung deposition of HFA-beclomethasone ranges from 37% with poor pMDI technique to 59% with good pMDI technique compared with values of 12% to 16% for fluticasone in patients with good pMDI technique. Moreover, the small-airways deposition of HFA-beclomethasone is greater than that of fluticasone.^{7,13} Thus HFA-beclomethasone therapy might particularly benefit those patients with poor inhaler technique and those with small-airways disease, who are difficult to identify clinically.¹⁰

Guidelines for the US recommend prescribing HFA-beclomethasone and fluticasone at a 1:1 dose ratio,³ but in practice fluticasone is dosed much higher both in the US and elsewhere,^{21,36-39} a discrepancy that could in part be explained by the availability of higher dose strengths for fluticasone (HFA pMDI canisters contain 44, 110, or 220 μ g per puff vs 40 or 80 μ g per puff for HFA-beclomethasone). The highest dose of HFA-beclomethasone in both the initiation and step-up cohorts

was 320 μ g/d, whereas 18% of fluticasone-treated patients were initiated on 880 μ g/d or greater, and 46% of fluticasone-treated patients were stepped up to 880 μ g/d or greater. Higher doses of fluticasone would be expected to have greater systemic effects. Treatment with 880 μ g/d fluticasone for 12 days has similar suppressant effects on 8 AM plasma cortisol levels as 10 mg/d oral prednisone.⁴⁰ A dose of 320 μ g/d HFA-beclomethasone does not significantly affect early-morning plasma cortisol levels but does reduce urinary cortisol secretion.⁴¹

The asthma control measures were achieved by a disappointingly low number of patients in both the HFA-beclomethasone and fluticasone cohorts. Fewer patients achieved risk-domain asthma control, and the rate of severe exacerbations was higher than in our previous, similarly designed UK study.²¹ Although this difference might result from differences between the US and UK health care systems, a more likely explanation is the pattern of asthma medication use in the US. Asthma guidelines recommend regular treatment with an ICS for persistent asthma.³ In database analyses this best practice approach is demonstrated by a controller/total asthma medication ratio of 0.5 or greater (reflecting reliance on regular use of ICSs rather than as-needed SABAs) and a controller MPR of greater than 0.8, indicating good adherence to ICSs.^{27,35} In the present study both the HFA-beclomethasone and fluticasone cohorts had an average controller/total medication ratio of 0.5 or greater. However, the MPR was low for both cohorts (median, 16%) and much lower than in our UK study (UK medians, 55% for HFA-beclomethasone and 33% for fluticasone).²¹

When we categorized MPR, 2 interesting patterns emerged. First, patients with lower MPRs had better risk-domain asthma control and fewer exacerbations and *vice versa*. The only exception to this pattern was for an MPR of 81% to 100%, but this group represented only 2% of the total population. This MPR pattern is compatible with a widespread belief that in the US patients do not use their ICSs when their asthma symptoms are tolerable and exacerbations are few but do use it when their symptoms are troublesome and exacerbations more frequent. Recent work supports this possibility: Williams et al⁴² found that adherence with ICSs was poor in general but increased after exacerbations. Moreover, in patients with moderate-to-severe persistent asthma, ICS use was significantly greater in those who had more frequent

exacerbations.⁴³ Second, across MPR values of 100% and less, patients treated with HFA-beclomethasone were more likely to achieve the overall asthma control measure than patients receiving fluticasone. Outcomes were steady for HFA-beclomethasone across MPRs of less than 80%, were consistently better for HFA-beclomethasone than fluticasone across MPRs of less than 80%, and were clearly better for HFA-beclomethasone than fluticasone for MPRs of 81% to 100%. This reassures us that the difference in outcomes, despite the low MPR, relates to the choice of ICS. Moreover, these observations reinforce the value of real-world effectiveness studies, which take into account how patients actually use their asthma medication.

Observational database studies might be limited by selection bias and residual confounding. Our goal in using a matched cohort design was to identify treatment cohorts of similar baseline asthma severity, as would occur in a randomized trial. Nevertheless, we cannot entirely exclude the possibility of differing severity in the 2 cohorts resulting from some unidentified baseline characteristic. Other study limitations include the possibility of misdiagnosis or miscoding and the lack of data on smoking status and lung function. Fluticasone administered by means of pMDI was introduced in the US in 1996 as a chlorofluorocarbon formulation and in 2005 as an HFA formulation. The chlorofluorocarbon-fluticasone product has similar particle size distribution as HFA-fluticasone.¹³ This reassures us that the observed differences in this study reflect both fluticasone pMDI products. Our analyses adjusted costs to 2010 prices, but the increasing costs over time for both HFA-beclomethasone and fluticasone might have biased comparative costs, namely the significantly later index dates of HFA-beclomethasone cohorts might have increased the cost of HFA-beclomethasone and decreased the cost-benefit relative to fluticasone.

In conclusion, characteristics of ICSs vary, but little information is available comparing the real-life effectiveness of various ICSs. In this analysis patients prescribed HFA-beclomethasone as an initial ICS had similar or better asthma outcomes at lower doses compared with those for patients prescribed fluticasone. We speculate that ICS formulation characteristics, including particle size and resulting action site within the lung, might be important in achieving effective asthma control in real life. Moreover, we found that HFA-beclomethasone was, on average, less costly than fluticasone for patients initiating ICSs.

We thank Muzammil Ali for his contributions to the statistical analyses.

Clinical implications: Initiating asthma controller therapy with extrafine-particle beclomethasone resulted in similar or better asthma control at lower doses and lower costs than seen with larger-particle fluticasone, suggesting there are differences among available ICSs.

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METHODS

Statistical analyses

Prior research in respiratory disease has identified a range of potential confounders that might affect study outcomes. These include a range of demographic, disease severity, treatment, and comorbid factors. The following variables were extracted, where available, for all patients.

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

- age;
- sex; and
- smoking status.

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

- date of first asthma diagnosis (where known) and
- other respiratory or other confounding diagnoses, including rhinitis, gastroesophageal reflux disease, and cardiac disease.

Potential confounders examined in the year before the index date:

- number of primary care consultations, both asthma related and not asthma related;
- number of hospital outpatient attendances for which asthma is recorded as the reason for referral;
- number of inpatient admissions for asthma;
- number of ED attendances for asthma;
- number of ED attendances or inpatient admissions for lower respiratory tract reasons;
- number of prescriptions for any antibiotic in which the reason for the prescription is lower respiratory tract infection;
- use of acute oral corticosteroids;
- other medications that might interfere with asthma control, such as β -blockers, nonsteroidal anti-inflammatory drugs, and acetaminophen;
- number of prescriptions for asthma, allergies, or both;
- SABA daily dosage;
- average ICS daily dose (step-up population only); and
- ICS dose at index date.

In addition:

- year of index date.

We summed total respiratory-related health care costs, adjusted to 2010 prices, and compared summary costs between treatment cohorts using conditional logistic regression. The following health care costs were calculated for each treatment group for the baseline and outcome periods:

- drug costs for:
 - SABAs;
 - leukotriene receptor antagonists;
 - LABAs;
 - ICSs;
 - fixed-dose combination (ICS-LABA) inhalers;
 - prednisolone;
 - antibiotics;
- Lower respiratory primary care consultation costs;
- total respiratory inpatient hospitalization costs;
- total respiratory ED attendance costs;
- total respiratory outpatient attendance costs; and
- other lower respiratory tract-related medical costs.

To account for the switch to more expensive HFA inhalers in 2008, we used a standard 2010 price for SABA inhalers. We compared mean annual respiratory-related health care costs during the outcome period adjusted for baseline respiratory-related health care costs.

RESULTS

Baseline demographic and clinical characteristics

Baseline characteristics of the 193 and 386 matched patients in the HFA-beclomethasone and fluticasone step-up cohorts, respectively, were similar (Table E1). No significant differences were found between cohorts for baseline asthma control and exacerbation measures. Approximately 90% of patients were stepped up in ICS dose by 50% or greater.

Outcomes

There were no statistically significant differences between the 2 treatment cohorts in any of the adjusted outcomes, including the adjusted odds ratios for asthma control measures or the adjusted rate ratio for exacerbations (Table E2).

Patients in the HFA-beclomethasone cohort were prescribed significantly lower ($P < .001$) doses on the index date than matched patients in the fluticasone cohort. The distribution of doses showed that all patients in the HFA-beclomethasone cohort were prescribed 320 $\mu\text{g}/\text{d}$, whereas 46% of patients in the fluticasone cohort were prescribed a dose of 880 $\mu\text{g}/\text{d}$ or greater (median dose, 440 $\mu\text{g}/\text{d}$ [interquartile range, 440-880 $\mu\text{g}/\text{d}$], Fig E2). Spacers were prescribed for 2% and 4% of patients, respectively ($P = .18$). The years of the index prescription date were later for the HFA-beclomethasone cohort ($P < .001$).

The median MPR was 41% and 26% in the HFA-beclomethasone and fluticasone cohorts, respectively (Table E2); 20% and 16% of patients in the HFA-beclomethasone and fluticasone cohorts, respectively, had an MPR of 80% or greater ($P = .27$). As with the initiation population, when outcomes were categorized by MPR, patients with a lower MPR were generally more likely to meet the risk-domain asthma control measure and to be less likely to have a severe exacerbation. The exception was for patients with MPRs of 81% to 100%, but again, these represented a very small percentage of the total population (Fig E3). The percentages of patients with a controller/total asthma medication ratio of 0.5 or greater were 65% in the HFA-beclomethasone and 59% in the fluticasone cohorts ($P = .13$).

Costs

There were no significant differences at baseline in total annual asthma and respiratory-related health care costs between the treatment cohorts in the step-up population (data not shown).

Respiratory-related drug prescriptions and costs and respiratory-related resource costs during the outcome year are summarized in Tables E4 and E5. Adjusted mean respiratory-related health care costs were not significantly different between the HFA-beclomethasone and fluticasone cohorts (Table E5; mean difference relative to fluticasone, \$68 [95% CI, $-\$571$ to $\$833$]). Similarly, the adjusted total mean respiratory-related health care costs excluding ICS costs were not significantly different between cohorts (Table E5; mean difference relative to fluticasone, $\$123$ [95% CI, $-\$564$ to $\$811$]).

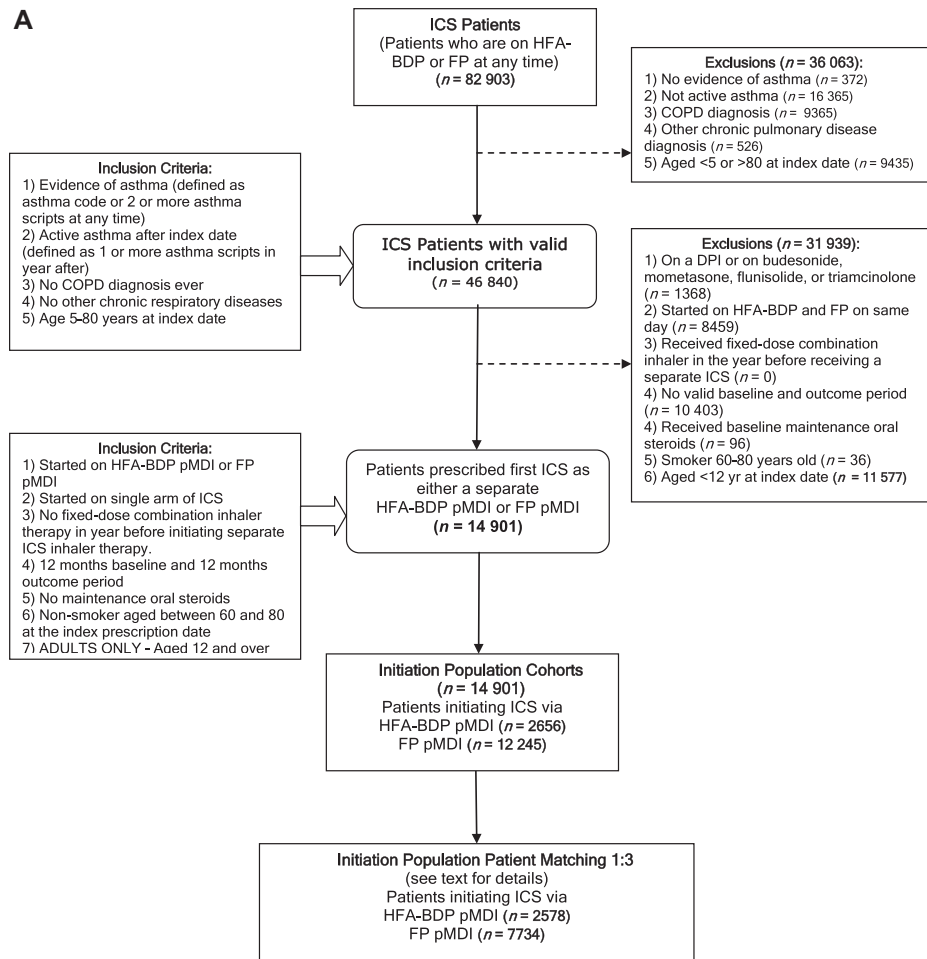
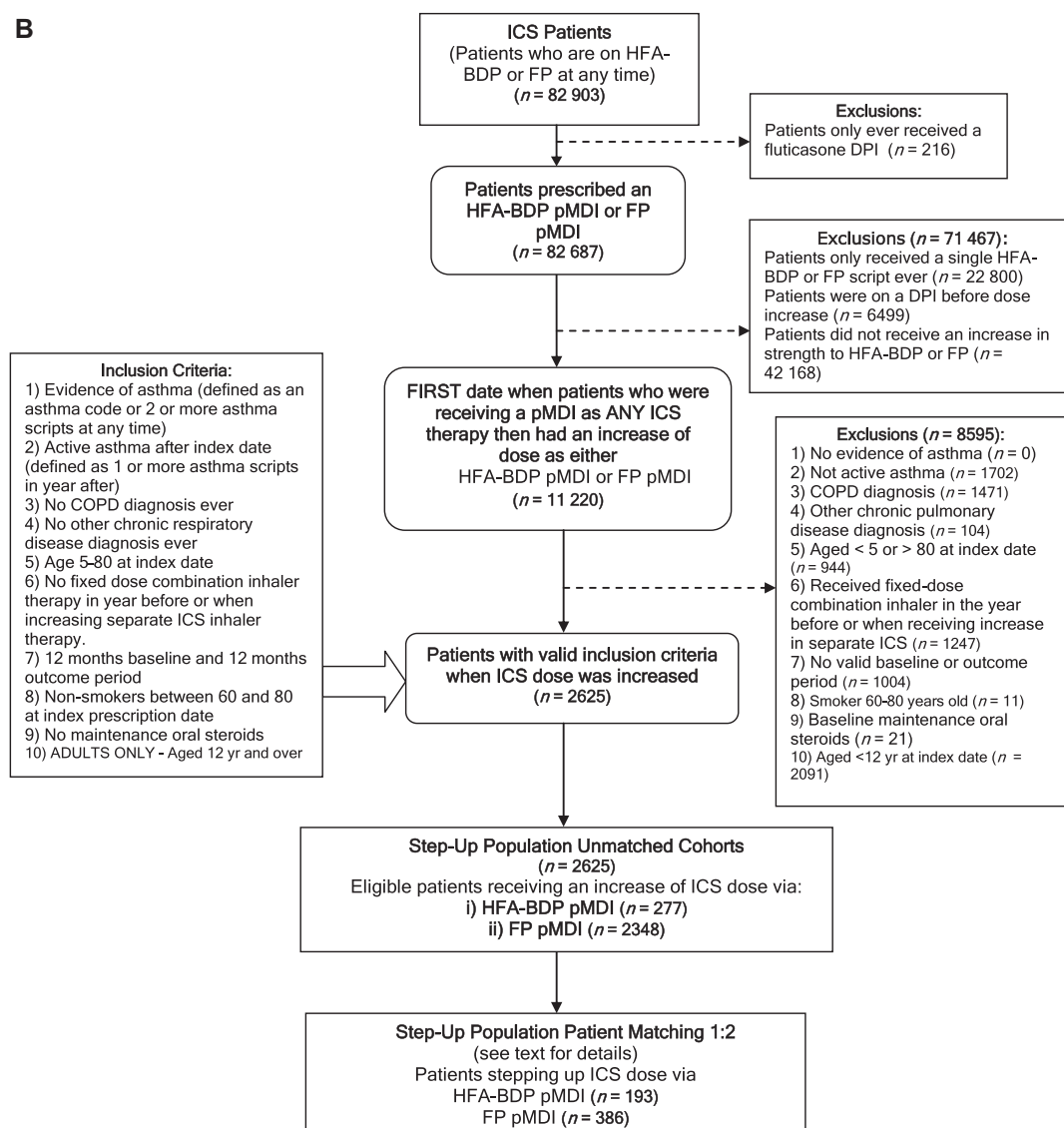


FIG E1. Identification of eligible patients from the database for the initiation (A) and step-up (B) populations. Patients in the 2 treatment cohorts (HFA-beclomethasone and fluticasone) of each study population were then matched on 5 demographic and baseline criteria that could be predictive of or influence asthma control. COPD, Chronic obstructive pulmonary disease; DPI, dry powder inhaler; FP, fluticasone propionate; HFA-BDP, hydrofluoroalkane-beclomethasone dipropionate.

B



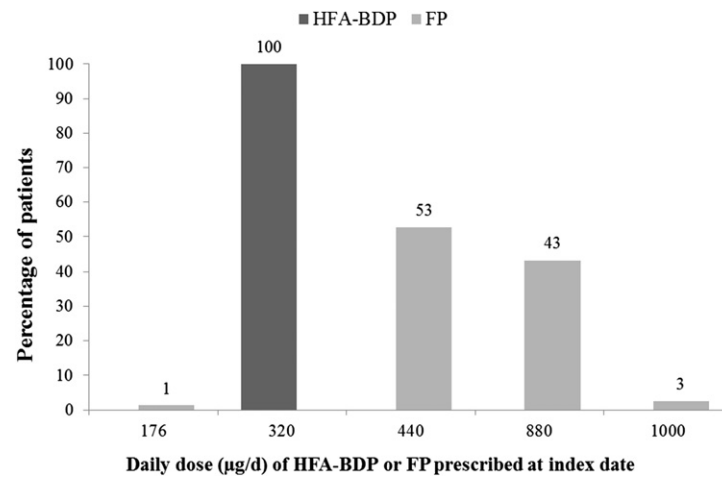
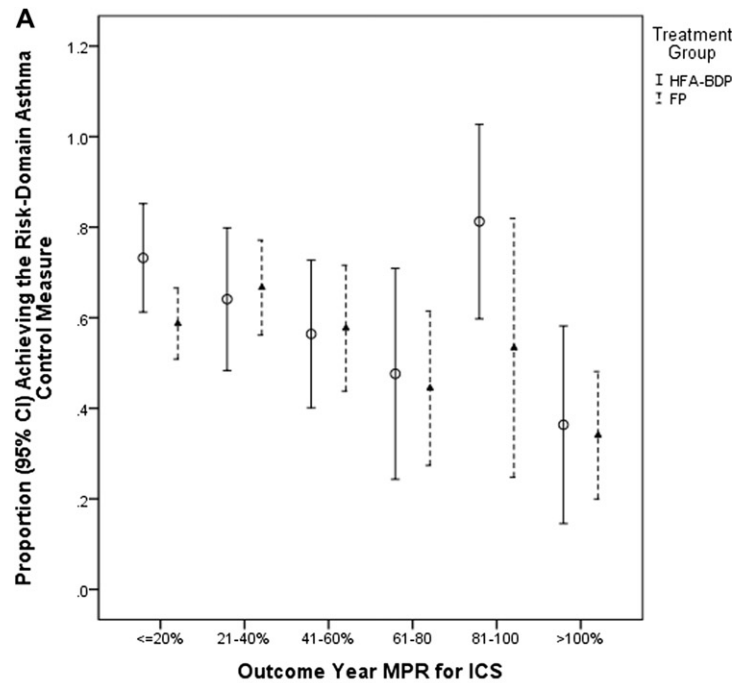
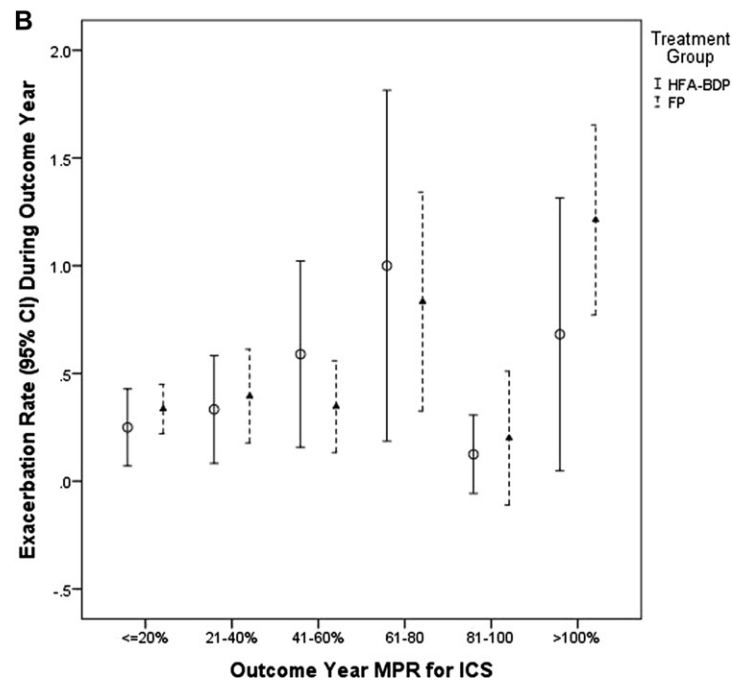


FIG E2. ICS dose for matched cohorts as prescribed on the index date for the step-up population. All differences in dose between the extrafine HFA-beclomethasone and fluticasone cohorts were statistically significant ($P < .001$). *FP*, Fluticasone propionate; *HFA-BDP*, hydrofluoroalkane–beclomethasone dipropionate.

Sample size, *n* (%)

	≤20%	21-40%	41-60%	61-80%	81-100%	>100%
HFA-BDP	56 (29.0)	39 (20.2)	39 (20.2)	21 (10.9)	16 (8.3)	22 (11.4)
FP	155 (40.2)	81 (21.0)	52 (13.5)	36 (9.3)	15 (3.9)	47 (12.2)

Sample size, *n* (%)

	≤20%	21-40%	41-60%	61-80%	81-100%	>100%
HFA-BDP	56 (29.0)	39 (20.2)	39 (20.2)	21 (10.9)	16 (8.3)	22 (11.4)
FP	155 (40.2)	81 (21.0)	52 (13.5)	36 (9.3)	15 (3.9)	47 (12.2)

FIG E3. Proportion of patients in the step-up population by treatment cohort who achieved risk-domain asthma control (**A**) and exacerbation rates (**B**) during the outcome year categorized by MPR for ICS. FP, Fluticasone propionate; HFA-BDP, hydrofluoroalkane-beclomethasone dipropionate.

TABLE E1. Clinical characteristics and asthma-related medical resource use during the baseline year for matched cohorts of patients initiating ICSs administered through a pMDI (initiation population) or receiving an increased dose of ICS through a pMDI (step-up population)

Characteristic*	Initiation population		Step-up population	
	HFA-beclomethasone (n = 2578)	Fluticasone (n = 7734)	HFA-beclomethasone (n = 193)	Fluticasone (n = 386)
Male sex†	948 (37)	2844 (37)	79 (41)	158 (41)
Age (y), mean (SD)	37.2 (17)	36.7 (17)	37.9 (18)	37.4 (18)
Recorded comorbidity				
Rhinitis coded	1817 (71)	4771 (62)	139 (72)	257 (67)
GERD coded/Rx‡	798 (31)	2175 (28)	59 (31)	117 (30)
Cardiac disease coded/Rx‡	729 (28)	2114 (27)	55 (29)	128 (33)
CCI score				
0	433 (17)	1428 (19)	33 (17)	63 (16)
1	1011 (39)	2894 (37)	75 (39)	131 (34)
≥2	1134 (44)	3412 (44)	85 (44)	192 (50)
≥1 Prescription in 12 mo				
NSAID	465 (18)	1280 (17)	29 (15)	55 (14)
Acetaminophen	667 (26)	1795 (23)	51 (26)	92 (24)
β-Blocker	134 (5)	387 (5)	4 (2)	18 (5)
Asthma diagnosis coded in database	2514 (98)	7561 (98)	189 (98)	381 (99)
Oral corticosteroid courses†				
0	1977 (77)	5931 (77)	145 (75)	290 (75)
≥1	601 (23)	1803 (23)	48 (25)	96 (25)
Asthma consultations, no OCS†				
0	969 (38)	2907 (38)	45 (23)	90 (23)
1	1016 (39)	3048 (39)	62 (32)	124 (32)
≥2	593 (23)	1779 (23)	86 (45)	172 (45)
Mean SABA dose†				
0	1356 (53)	4068 (53)	68 (35)	136 (35)
1-100 µg	624 (24)	1872 (24)	31 (16)	62 (16)
101-200 µg	247 (10)	723 (9)	26 (14)	44 (11)
201-400 µg	165 (6)	509 (7)	33 (17)	68 (18)
≥400 µg	186 (7)	562 (7)	35 (18)	76 (20)
Mean ICS dose during baseline year†				
1-10 µg	NA	NA	53 (28)	106 (28)
11-20 µg	—	—	28 (15)	56 (15)
21-50 µg	—	—	40 (21)	80 (21)
51-100 µg	—	—	26 (14)	52 (14)
101-200 µg	—	—	29 (15)	44 (11)
≥201 µg	—	—	17 (9)	48 (12)
Asthma consultations				
0	798 (31)	2427 (31)	32 (17)	70 (18)
1	1055 (41)	3151 (41)	67 (35)	122 (32)
2	376 (15)	1268 (16)	39 (20)	90 (23)
≥3	349 (14)	888 (12)	55 (29)	104 (27)
Asthma prescriptions				
0	655 (25)	2231 (29)	12 (6)	29 (8)
1	553 (22)	1649 (21)	10 (5)	38 (10)
2-3	529 (21)	1720 (22)	38 (20)	69 (18)
4-8	519 (20)	1373 (18)	65 (34)	136 (35)
≥9	322 (13)	761 (10)	68 (35)	114 (30)
Risk-domain asthma control	1474 (57)	4343 (56)	110 (57)	202 (52)
Overall control (risk and impairment)	1179 (46)	3523 (46)	64 (33)	122 (32)
1 Severe exacerbation	453 (18)	1425 (18)	36 (19)	68 (18)
≥2 Severe exacerbations	220 (9)	682 (9)	21 (11)	53 (14)
≥1 Course of antibiotics for LRTI	476 (19)	1385 (18)	29 (15)	63 (16)
≥1 Hospitalization for asthma	64 (3)	288 (4)	6 (3)	30 (8)

CCI, Charlson Comorbidity Index; GERD, gastroesophageal reflux disease; LRTI, lower respiratory tract infection; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroids; Rx, prescription.

*Data are presented as numbers (percentages), unless otherwise specified. Percentages might not total 100 because of rounding.

†Matching criterion.

‡Patient numbers for gastroesophageal reflux disease and cardiac disease include those with a coded diagnosis plus those receiving medication for these conditions.

TABLE E2. Unadjusted and adjusted results during the outcome year for the step-up population: matched cohorts

Outcome	HFA-beclomethasone (n = 193), no. (%)	Fluticasone (n = 386), no. (%)	Adjusted odds or rate ratio for HFA-beclomethasone (95% CI)
Coprimary outcome measures			
Risk-domain asthma control	119 (62)	215 (56)	1.09 (0.75-1.58)*
Overall control (risk and impairment)	78 (40)	122 (32)	1.39 (0.93-2.08)†
1 Severe exacerbation	28 (15)	50 (13)	0.98 (0.67-1.43)‡
≥2 Severe exacerbations	18 (9)	52 (14)	
Secondary outcome measures			
Treatment success	98 (51)	175 (45)	1.12 (0.78-1.59)§
Sensitivity excluding cost savings	99 (51)	185 (48)	1.03 (0.73-1.46)
≥1 Respiratory-related hospitalization or referral	39 (20)	88 (23)	1.14 (0.72-1.80)¶
Disaggregated outcome measures			
			<i>P</i> value#
≥1 Oral corticosteroid course	35 (18)	82 (21)	.36
≥1 Antibiotics for lower respiratory tract disease	22 (11)	64 (17)	.095
SABA dose >180 µg/d	79 (41)	187 (48)	.054
≥1 Hospitalization for asthma	10 (5)	22 (6)	.80
Change in therapy	45 (23)	100 (26)	.498
Increase in ICS dose	9 (5)	8 (2)	.086
Change in delivery device	6 (3)	13 (3)	.87
Change in ICS drug	13 (7)	27 (7)	.91
Additional therapy	34 (18)	78 (20)	.46
MPR, median (IQR)	41 (16-70)	26 (15-62)	.013
MPR, Mean (SD)	46 (32)	40 (32)	

The adjusted odds ratio/rate ratio for fluticasone was set at 1.0.

IQR, Interquartile range.

*Adjusted for cardiac disease, antibiotics, number of ICS prescriptions, and ED attendance for asthma.

†Adjusted for cardiac disease, SABA daily dose, and number of ICS prescriptions.

‡Adjusted for cardiac disease, number of ICS prescriptions, and number of exacerbations.

§Adjusted for cardiac disease, antibiotics, and number of prescriptions for asthma/allergies.

||Adjusted for cardiac disease, gastroesophageal reflux disease, antibiotics, and number of ICS prescriptions.

¶Adjusted for cardiac disease and respiratory-related hospitalizations and referrals.

#Conditional logistic regression.

TABLE E3. Mean respiratory drug prescriptions and unadjusted costs during the outcome year: initiation population

Respiratory-related medication	Medication use			Medication cost, \$		
	HFA-beclomethasone (n = 2578)	Fluticasone (n = 7734)	<i>P</i> value*	HFA-beclomethasone (n = 2578)	Fluticasone (n = 7734)	<i>P</i> value*
SABA inhalers	3.6 (5.4)	4.2 (5.4)	<.001	151 (215)	171 (215)	.009
FDC ICS-LABA inhalers	0.3 (1.1)	0.4 (1.2)	.071	64 (242)	75 (255)	.30
LTRA prescriptions	1.7 (3.2)	1.4 (2.8)	<.001	225 (396)	177 (350)	.001
LABA prescriptions	0.1 (0.9)	0.1 (0.8)	.057	21 (127)	16 (108)	.27
ICS prescriptions	3.2 (3)	3.1 (3)	.49	236 (251)	312 (304)	<.001
Oral corticosteroid prescriptions	0.4 (0.9)	0.3 (0.8)	.16	6 (29)	5 (16)	.086
Antibiotic prescriptions	0.2 (0.5)	0.2 (0.5)	.24	97 (213)	84 (160)	.065
Total mean medication costs	—	—	—	800 (709)	840 (666)	.13

Values are means (SDs), unless otherwise noted. Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policymakers and providers.

FDC, Fixed-dose combination; *LTRA*, leukotriene receptor antagonist.

*Conditional logistic regression.

TABLE E4. Mean respiratory drug prescriptions and unadjusted costs during the outcome year: step-up population

Respiratory-related medication	Medication use, mean (SD)			Medication cost, mean (SD) \$		
	HFA-beclomethasone (n = 193)	Fluticasone (n = 386)	P value*	HFA-beclomethasone (n = 193)	Fluticasone (n = 386)	P value*
SABA inhalers, mean (SD)	5.0 (7.9)	5.2 (6.4)	.81	210 (311)	214 (253)	.90
FDC ICS-LABA inhalers, mean (SD)	0.3 (1.0)	0.3 (1.3)	.41	68 (208)	87 (278)	.51
LTRA prescriptions, mean (SD)	1.7 (3.3)	1.7 (3.2)	.40	269 (447)	239 (392)	.55
LABA prescriptions, mean (SD)	0.4 (1.6)	0.2 (1.0)	.022	62 (224)	27 (132)	.089
ICS prescriptions, mean (SD)	4.8 (3.7)	4.2 (3.5)	.039	425 (335)	517 (476)	.042
Oral corticosteroid prescriptions, mean (SD)	0.3 (1.0)	0.4 (0.9)	.55	5 (24)	7 (28)	.51
Antibiotic prescriptions, mean (SD)	0.1 (0.4)	0.2 (0.5)	.043	83 (139)	68 (111)	.30
Total mean medication costs	—	—	—	1122 (778)	1158 (846)	.68

Values are means (SDs), unless otherwise noted. Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policymakers and providers.

FDC, Fixed-dose combination; LTRA, leukotriene receptor antagonist.

*Conditional logistic regression.

TABLE E5. Respiratory-related medical resource costs for the step-up population (US\$)

Respiratory-related resource	Costs for the step-up population		
	HFA-beclomethasone (n = 193)	Fluticasone (n = 386)	P value*
Respiratory-related medication	1122 (778)	1158 (846)	.68
Respiratory-related primary care consultation	351 (470)	294 (327)	.22
Total respiratory-related hospitalizations	900 (4057)	1065 (4869)	.78
Respiratory inpatient	599 (3856)	696 (4672)	.86
Respiratory outpatient	275 (977)	334 (1399)	.71
Respiratory ED	27 (212)	35 (244)	.79
Lower respiratory, other medical	22 (94)	23 (105)	.92
Total asthma/respiratory primary and secondary care,† including ICS costs	2374 (4178)	2517 (5045)	.81
Total asthma/respiratory primary and secondary care, excluding ICS costs	1948 (4155)	2000 (5009)	.90
Total adjusted costs (95% CI)‡	2396 (1875-2983)	2327 (1986-2690)	NS
Total adjusted costs per patient, excluding ICS costs‡ (95% CI)	1990 (1487-2601)	1867 (1511-2264)	NS

Values are means (SDs), unless otherwise noted. Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policymakers and providers.

NS, Not significant.

*Conditional logistic regression.

†Secondary care refers to specialist and emergency care.

‡Adjusted for baseline respiratory-related health care costs.