

PHARMACOTHERAPY

Risk of Asthma Exacerbation, Asthma-Related Health Care Utilization and Costs, and Adherence to Controller Therapy in Patients with Asthma Receiving Fluticasone Propionate/Salmeterol Inhalation Powder 100 µg/50 µg Versus Mometasone Furoate Inhalation Powder

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Objective. National asthma treatment guidelines recommend low/medium-dose inhaled corticosteroids (ICSs) as initial therapy in mild asthma patients. However, low doses of a fixed-dose combination of ICS and long-acting β -agonists are sometimes used. This study compares asthma-related outcomes and health care utilization and costs in clinical practice in patients starting fluticasone propionate 100 µg and salmeterol 50 µg via Diskus (FSC) or mometasone furoate (MF). **Methods.** A retrospective cohort study was conducted to compare asthma-related outcomes in asthma patients who received FSC or MF, using a large health insurance claims dataset spanning January 2004–December 2008. Patients with ≥ 1 claim with an asthma ICD-9-CM diagnosis code and ≥ 2 FSC or MF prescriptions were included, stratified into FSC or MF groups by study drug received first and matched using propensity score. **Results.** A total of 18,283 patients met inclusion criteria (14,044 FSC and 4239 MF); 3799 matched pairs were identified (mean follow-up: FSC 548 days, MF 537 days). FSC patients had lower risk of asthma-related exacerbation (Hazard ratio = 0.88, 95% CI 0.81–0.95, $p = .002$), defined as either asthma-related emergency department (ED) visits/hospitalizations or receipt of systemic corticosteroids (SCSs); fewer SCS claims (mean 0.28 vs. 0.33, $p = .021$); and fewer asthma-related physician office (PO) and hospital outpatient (HO) visits (mean 1.17 vs. 1.63, $p < .001$). However, asthma-related ED visits were higher with FSC ($p = .004$), and FSC patients had higher total costs of asthma-related health care (\$953 vs. \$862, $p = .002$). **Conclusions.** In asthma patients initiating ICS therapy, MF had lower asthma-related ED visits. However, FSC may reduce the use of SCS and asthma-related PO/HO visits.

Keywords asthma, exacerbation, fluticasone propionate, inhaled corticosteroids, mometasone, retrospective study, salmeterol

INTRODUCTION

The National Asthma Education and Prevention Program (NAEPP) Expert Panel and the Global Initiative for Asthma (GINA) both recommend low- to medium-dose inhaled corticosteroids (ICSs) as the preferred initial treatment for patients with mild-to-moderate persistent asthma (1, 2). Results from numerous studies have shown that compliance with ICS may be improved by reducing the frequency of dosing (3–7). Other studies have demonstrated that improved compliance with ICS in turn may result in improved outcomes and reduced health care utilization and costs (8–10).

Mometasone furoate (MF) inhalation powder is an ICS that has been approved in the United States for once-daily maintenance treatment of asthma in patients 4 years of age or older; it is available in two formulations (110 and 220 µg). MF is the only ICS currently approved in the United States for once-daily administration. However, other ICS products are often used once daily. While there is evidence that once-daily administration of other ICS may be as effective as twice-daily administration (11), there are also data suggesting that once-daily administration of these medications are not as effective as twice-daily

dosing (12). The extent to which outcomes differ in clinical practice for patients who receive MF once daily versus other available treatments for asthma is limited (13, 14).

The fixed-dose combination of fluticasone propionate and salmeterol administered via a dry powder inhaler with dose counter is available in three formulations (100 µg/50 µg [“FSC 100/50”], 250 µg/50 µg [“FSC 250/50”], and 500 µg/50 µg [“FSC 500/50”]). The use of twice-daily FSC 100/50 is typically used for patients with less severe disease and who are more likely to be candidates for (off-label) once-daily administration of FSC. This study compared the risk of asthma exacerbation, asthma-related health care utilization and costs, and adherence to controller therapy in patients with asthma who received FSC 100/50 versus MF in clinical practice, using health insurance claims data.

METHODS

Overview

A retrospective cohort study was employed to compare the risk of asthma exacerbation, asthma-related health care utilization and costs, and adherence to controller therapy in asthma patients who received FSC 100/50 or MF in clinical practice (GSK study ADA112604). Data were from a large health insurance claims dataset spanning

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January 2004–December 2008. Subjects included patients with ≥ 1 claim with an ICD-9-CM diagnosis code for asthma and ≥ 2 prescriptions for FSC 100/50, MF 220, or MF 110. Patients were stratified into an FSC or MF group based on the study drug received first. Propensity score matching was used to control for possible differences in baseline characteristics.

Data Source

Data for this study were obtained from the IHCIS National Managed Care Benchmark Database. The database is comprised of information from enrollment files, and medical and outpatient pharmacy claims from a variety of private, health care-benefit plans covering (at that time this study was initiated) approximately 17 million persons enrolled in over 30 health plans across eight US census regions. The database contains information on age, sex, US census region, and dates of claims for all patients. Data on race, socioeconomic status, and anthropometrics are not available. Each medical claim includes the dates of service and International Classification of Diseases 9th Edition, Clinical Modification (ICD-9-CM) diagnosis codes, and may include revenue codes (e.g., on hospital claims) or Current Procedural Terminology, Version 4 (CPT-4) and Healthcare Common Procedure Coding System (HCPCS) procedure codes (e.g., on professional service claims). Each outpatient pharmacy claim includes the drug dispensed (in National Drug Code format), the dispensing date, and the quantity and number of therapy-days dispensed. All claims include an estimated standardized cost, calculated based on an algorithm designed to yield allowable payments (including member deductibles and copayments) for health care services normalized across health plans, geographic areas, and calendar time. All claims for an individual patient can be linked using a unique encrypted patient identifier. The database is fully de-identified and HIPAA (Health Insurance Portability and Accountability Act of 1996) compliant. Data for this study included claims for the period from January 2004 through December 2008 (i.e., the most recent 5 years for which claims data are available) (“study period”).

Study Patients

Study patients were selected by first identifying all those in the database who had one or more medical claims with a diagnosis (primary or secondary) of asthma (ICD-9-CM 493.xx) during the study period. Among these persons, we then selected all those who had two or more outpatient pharmacy claims for FSC 100/50, MF 110, or MF 220 during the study period; patients were stratified into treatment groups based on the study drug received first. These patients constituted the “base sample.” The date of the first prescription for FSC 100/50, MF 110, or MF 220 was designated the “index date.” The 12-month (365-day) period prior to the index date was designated the “pre-index period.” The 90-day period beginning with the index date was designated the “treatment identification period.”

Persons who met any of the following criteria were excluded: (1) no asthma diagnosis on index date or during

pre-index period; (2) one or more ICS prescriptions during pre-index period (to control for the difference in indications for MF, which is recommended for both mild and moderate persistent asthma, and FSC, which is recommended for moderate persistent asthma and after a failure to control with an ICS monotherapy); (3) < 12 months of complete and uninterrupted claims history prior to index date; (4) < 3 months of complete and uninterrupted claims history on or after index date; (5) any medical claims during the study period with a diagnosis of chronic obstructive pulmonary disease (COPD) (ICD-9-CM CD-9-CM 491, 492, 494, or 496), or respiratory tract cancer (ICD-9-CM 160–164, or 231); (6) any pharmacy claims during the study period for ipratropium; tiotropium; or dornase alpha; (7) one or more prescriptions during the treatment identification period for leukotriene receptor antagonist (LTRA), inhaled mast-cell stabilizer (IMCS), methylxanthine (MTHL), IgE blocker (IgEB), or non-study ICS or long-acting β -agonists (LABAs) (i.e., other than FSC 100/50 or MF); (8) for patients with FSC 100/50 on the index date, one or more prescriptions for MF 110 or MF 220 during the treatment identification period; (9) for patients with MF 110 on the index date, one or more prescriptions for FSC 100/50 or MF 220 during the treatment identification period; (10) for patients with MF 220 on the index date, one or more prescriptions for FSC 100/50 or MF 110 during the treatment identification period; (11) age < 12 years or ≥ 65 years as of index date; (12) index date prior to 1 January 2005; (13) on Medicaid or Medicare; (14) missing or invalid data for demographic or plan characteristics; and (15) missing or invalid data on claims required to calculate pre-index characteristics or study outcomes (e.g., days supply on pharmacy claims, payments information on asthma-related claims). Remaining patients were designated the “base sample.”

Patients who switched their study therapy or had received prescriptions for LTRA, IMCS, MTHL, IgEB, non-study ICS, or LABA after the treatment identification period were censored as of the day prior to date of receipt of such therapy. The period beginning with the index date and ending with either the last date for which complete claims data are available or the date of censoring, whichever occurs first, was designated the “follow-up period.”

Patient Characteristics

Demographic and plan information captured for each patient included year of index date, season associated with index date, age (years) at index date, gender, census region (Midwest, New England, South, West), and plan type (health maintenance organization [HMO], preferred provider organization [PPO], point of service plan [POS], and others). Professional service claims were scanned to identify persons with specialist (allergist or pulmonologist) visits during the pre-index period. Diagnosis codes on medical claims during the pre-index period were also scanned to calculate the Charlson–Deyo comorbidity index for each patient (15). Procedure codes on professional service claims during the pre-index period were scanned to identify persons receiving the following asthma

and other respiratory-related services, including chest X-rays, airflow tests, and oxygen therapy. Results of pulmonary function tests (e.g., spirometry) are unavailable in the dataset. Pharmacy claims during the pre-index period were scanned to ascertain the number of prescriptions for short-acting β -agonists (SABAs), asthma-related systemic corticosteroids (SCSs) (defined in the next paragraph), antibiotics, and other medications.

Also, ascertained were number of hospitalizations, emergency department (ED) visits, and physician office (PO)/hospital outpatient (HO) visits that were considered asthma-related and non-asthma-related, and costs of hospitalizations, ED visits, PO/HO visits, outpatient prescriptions, other services, and the total cost that were considered asthma-related and non-asthma-related. Hospitalizations were considered asthma-related if the primary discharge diagnosis on the hospital inpatient claim is for asthma. Because primary and secondary diagnoses cannot be distinguished on outpatient claims (including claims for ED visits), claims for ED visits and other outpatient services were considered asthma-related only if there was a diagnosis of asthma on the claim and all the other diagnosis codes on the claim date were respiratory-related or there was one or more asthma-related procedure code on the claim date. Chest X-rays, airflow tests, and oxygen therapy were considered asthma-related procedures. Claims for SCS were considered asthma-related if there was at least one claim with a diagnosis code for respiratory diseases during the 7-day period ending with the day of the SCS claim. In calculating asthma-related costs, medical claims occurring during inpatient stays ("confinements") were classified based on the associated inpatient stay. Outpatient pharmacy claims for SABAs, ICS, LTRAs, LABAs, MTHL, IMCS, and IgEB were also considered asthma-related.

In calculating baseline patient characteristics, all pharmacy claims other than study medications and all medical claims occurring on the index date were assumed to have occurred prior to the index prescriptions for FSC 100/50 or MF and therefore were counted in the pretreatment period.

Costs were estimated using a standardized cost, calculated by I3 Ingenix UHC/IHCIS based on an algorithm designed to yield allowable payments (including member deductibles and copayments) for health care services normalized across health plans, geographic areas, and calendar time.

Matching

To control for differences in observed characteristics at baseline, matched samples of patients receiving FSC 100/50 and MF were identified. Each patient in the FSC 100/50 group was matched to one patient in the MF group using propensity score techniques (16, 17). Propensity scores were calculated for all patients in the base sample by estimating a logistic regression model with treatment group (MF vs. FSC 100/50) as the dependent variable, and patient characteristics as of the index date as independent variables. Propensity scores for each patient were defined as the predicted probability (range: 0–1) of

receiving MF, conditional on the observed values of the other baseline characteristics. Matched pairs of MF and FSC 100/50 patients were then identified using nearest neighbour matching based on the propensity score. When patient characteristics were not well matched after propensity score matching (p -value for comparison greater than .05), these characteristics were added to the matching criteria in stepwise fashion based on the p -value for the comparison between groups. Characteristics were added to the matching algorithm, until groups were well balanced on all baseline characteristics.

Outcome Measures

Outcome measures were evaluated over the follow-up period and included time to first asthma-related ED visit, asthma-related hospitalization, asthma-related ED visit or hospitalization, receipt of asthma-related SCS, and asthma-related exacerbation, defined as an asthma-related ED visit, asthma-related hospitalization, or receipt of asthma-related SCS. Deaths and utilization of ICU services were not considered as such information was not available in the PharMetrics database. The other measures of interest included number of SABA prescriptions, asthma-related SCS claims, asthma-related office/outpatient visits, costs of asthma-related medications, costs of asthma-related ED visits or hospitalizations, other asthma-related costs, total costs of asthma-related care, costs of asthma-related medications excluding FSC 100/50 or MF, total costs of asthma-related care excluding FSC 100/50 or MF, medication possession ratio (MPR) for study therapy (FSC 100/50, MF), and refill rate for study therapy. The designation of asthma-related health care services is found in the patient characteristics section. The MPR was defined as the sum of the number of therapy-days supplied on all FSC 100/50, MF 110, or MF 220 dispensed from the index date to the end the follow-up period divided by the sum of the number of days between the first and last such prescription during follow-up and the number of days on the last such prescription. The refill rate was defined as the number of prescriptions for FSC 100/50, MF 110, or MF 220 dispensed from the index date to the end of the follow-up period divided by the duration of follow-up.

Statistical Analyses

Pre-index characteristics among unmatched patients were compared across FSC 100/50 and MF groups using chi-square test or Fischer's exact test for categorical variables, and Student's t -test or Wilcoxon's rank sum test for continuous variables. For comparisons of matched samples for pre-index characteristics and post-index health care utilization and cost measures, the McNemar test or Bowker symmetry test were used for categorical variables, and paired t -test was used for continuous variables. For all time to event outcomes, patients were censored at the end of follow-up in these analyses. Hazard ratios (HRs) for FSC 100/50 versus MF were calculated using Cox proportional hazards regression analysis (18). All analyses were conducted using SAS[®] Proprietary Software, Release 9.2 (SAS Institute Inc., Cary, NC). Cox proportional hazard

model analyses were performed using PROC PHREG. A p -value of .05 was used in all tests of statistical significance. No adjustments were made for multiple comparisons.

RESULTS

Study Sample

There were 224,608 patients with at least one claim with asthma diagnosis who also had at least two FSC 100/50, or two MF 220 or MF 110 prescriptions. Of these, 206,325 patients were excluded (92%). The largest sources of attrition (not mutually exclusive) were less than 12 month of continuous enrollment prior to index date (51.5%), no claims with asthma diagnosis on index date or during pre-index period (35.8%), index date prior to 1 January 2005 (34.8%), one or more prescriptions during treatment identification period for LTRA, IMCS, MTHL, IgEB, or non-study ICS or LABA (28.4%), ICS prescriptions during pre-index period (26.8%), and age <12 or ≥ 65 at index date (21.9%). A total of 18 283 patients met study inclusion criteria, including 14,044 FSC 100/50 and 4239 MF patients.

Patient Characteristics Prior to Matching

Among unmatched patients, the mean ages for FSC 100/50 and MF groups were 36 years and 38 years ($p < .001$), respectively (Table 1). For both groups, about 40% of the patients were male. Patients who received FSC 100/50 were more likely to receive the first therapy in calendar year 2005 (44% versus 4%, $p < .001$), more likely to receive the first therapy in winter or spring (59% versus 51%, $p < .001$), more likely to be located in New England and less likely to be located in South (40% versus 36% for New England, and 28% versus 34% for South, $p < .001$), more likely to be on HMO (25% versus 16%, $p < .001$), and had lower mean Charlson index than MF patients (0.95 vs. 1.03 with $p < .001$). MF patients had significantly higher rates of utilization of specialist visits, chest X-rays, airflow tests, oxygen therapies, and significantly higher mean number of SCS claims, and asthma-related PO/HO visits. FSC patients were more likely to have asthma-related ED visits (5.7% for FSC vs. 4.3% for MF, $p < .001$).

Matching

Using propensity scores, 3799 pairs of FSC 100/50 and MF patients were identified that were well matched on all pretreatment characteristics (Table 1) and had comparable mean duration of follow-up (548 vs. 537 days, $p = .105$).

Time to Event Measures

Compared with MF, receipt of FSC 100/50 was associated with reduced risk of receipt of SCS (HR = 0.85, 95% confidence interval [CI] 0.78–0.92, $p < .001$) and reduced risk of the composite outcome of asthma-related ED visit, inpatient hospitalization, or receipt of SCS (HR = 0.88,

95% CI 0.81–0.95, $p = .002$). Time to asthma-related inpatient hospitalization was not statistically different between the groups (HR = 0.29, 95% CI 0.08–1.02, $p = .053$). However, receipt of FSC 100/50 was associated with increased risk of asthma-related ED visit (HR = 1.40, 95% CI 1.11–1.76, $p = .038$), and combined asthma-related ED visit/hospitalization (HR = 1.35, 95% CI 1.08–1.68, $p = .009$) (Table 2, Figure 1). A total of 821 patients in the MF group and 744 patients in the FSC group experienced the composite outcome of asthma exacerbation. Of the three possible causes of asthma exacerbations, asthma-related hospitalizations, and ED visits occurred relatively infrequently: eight patients in the MF group and five patients in the FSC group experienced asthma-related hospitalizations, while 95 patients in the MF group and 116 patients in the FSC group had claims for asthma-related ED visits (Table 2).

Asthma-Related Health Care Utilization

Compared with the MF group, patients in the FSC 100/50 group had fewer claims for SCS (0.28 vs. 0.33, $p = .021$), and fewer asthma-related PO and HO visits (1.17 vs. 1.63, $p < .001$) (Table 3). FSC patients also had lower asthma-related outpatient pharmacy costs excluding the costs of study medications (\$54 vs. \$62, $p < .001$), lower other asthma-related health care services costs (\$192 vs. \$249, $p = .016$), and lower total costs of asthma-related health care excluding the costs of study medications (\$279 vs. \$342, $p = .014$). FSC patients had higher total asthma-related outpatient pharmacy costs (including study medications) (\$728 vs. \$583, $p < .001$), and higher total costs of asthma-related health care (\$953 vs. \$862, $p = .002$).

Compliance with Controller Therapy

Compared to MF patients, patients who received FSC 100/50 had lower ICS medication possession ratio (57.2 vs. 59.3, $p < .001$) and lower ICS refill rate (4.1 vs. 4.4, $p < .001$).

Sensitivity Analyses

Mean copay on all prescriptions during the pre-index period was lower for FSC than that for MF. This variable was not identified a priori as part of matching criteria, so a sensitivity analysis was conducted with this variable included among the covariates used to estimate propensity scores. The results of these additional analyses were qualitatively similar to the base case.

DISCUSSION

This was a retrospective observation study comparing risk of asthma-related exacerbations and health care utilization and costs in asthma patients who received FSC 100/50 or MF in clinical practice. Data were obtained from a large health insurance claims database. Patients in the FSC cohort had a lower risk of receipt of SCS for asthma treatment as well as a

TABLE 1.—Patient characteristics at index date for unmatched and matched samples, by treatment group.

Characteristic	Unmatched			Matched		
	FSC 100/50 (N = 14044)	MF (N = 4239)	<i>p</i>	FSC 100/50 (N = 3799)	MF (N = 3799)	<i>p</i>
Year of index date, No. (%)						
2005	6192 (44)	154 (4)	<.001	142 (4)	154 (4)	.393
2006	3490 (25)	1348 (32)		1264 (33)	1279 (34)	
2007	2685 (19)	1495 (35)		1351 (36)	1344 (35)	
2008	1677 (12)	1242 (29)		1042 (27)	1022 (27)	
Season on index date, No. (%)						
Winter	4160 (30)	1057 (25)	<.001	978 (26)	987 (26)	.129
Spring	4073 (29)	1111 (26)		962 (25)	1008 (27)	
Summer	2837 (20)	969 (23)		883 (23)	854 (22)	
Fall	2974 (21)	1102 (26)		976 (26)	950 (25)	
Age, years, Mean (SD)	36.1 (15.4)	38.2 (14.8)	<.001	38.0 (15.1)	37.9 (14.9)	.763
Males, No. (%)	5656 (40)	1639 (39)	.061	1468 (39)	1497 (39)	.493
Region, No. (%)						
New England and other	5638 (40)	1541 (36)	<.001	1508 (40)	1397 (37)	.175
Midwest	2525 (18)	785 (19)		641 (17)	695 (18)	
South	3897 (28)	1426 (34)		1218 (32)	1247 (33)	
West	1984 (14)	487 (11)		432 (11)	460 (12)	
Plan type, No. (%)						
POS	6424 (46)	2379 (56)	<.001	1985 (52)	2090 (55)	.222
PPO	3962 (28)	1164 (27)		1096 (29)	1049 (28)	
HMO	3498 (25)	666 (16)		689 (18)	631 (17)	
Other	160 (1)	30 (1)		29 (1)	29 (1)	
Charlson Index, Mean (SD)	0.95 (0.75)	1.03 (0.76)	<.001	1.02 (0.76)	1.02 (0.77)	.916
Health care utilization: Asthma-related						
Specialist visits, No. (%)	3169 (23)	1995 (47)	<.001	1539 (41)	1590 (42)	.092
Chest X-rays, No. (%)	3524 (25)	1293 (31)	<.001	1140 (30)	1138 (30)	.960
Airflow tests, No. (%)	4680 (33)	2400 (57)	<.001	1998 (53)	1998 (53)	1.000
Oxygen therapy, No. (%)	42 (0.30)	23 (0.54)	.020	17 (0.45)	19 (0.50)	.739
No. of SABA prescriptions, Mean (SD)	1.78 (2.58)	1.69 (2.36)	.720	1.82 (2.56)	1.71 (2.41)	.076
No. of SCS claims, Mean (SD)	0.35 (0.77)	0.43 (0.83)	<.001	0.44 (0.88)	0.41 (0.80)	.241
No. of antibiotics, Mean (SD)	0.31 (0.75)	0.32 (0.70)	.134	0.32 (0.74)	0.31 (0.70)	.736
No. of other medications, Mean (SD)	13.5 (17.8)	15.6 (19.7)	<.001	15.0 (18.5)	15.1 (19.5)	.912
Inpatient hospitalizations, No. (%)	59 (0.42)	13 (0.31)	.301	11 (0.29)	10 (0.26)	.827
ED visits, No. (%)	794 (5.7)	183 (4.3)	<.001	164 (4.3)	166 (4.4)	.910
No. of physician office/hospital outpatient visits, Mean (SD)	1.26 (1.93)	1.53 (1.80)	<.001	1.52 (2.12)	1.45 (1.55)	.090
Health care cost: Asthma-related, \$, Mean (SD)						
Hospitalizations	20.6 (342)	20.1 (416)	.303	13.8 (275)	13.3 (279)	.933
ED visits	32.0 (241)	35.4 (277)	.001	29.5 (215)	33.5 (248)	.460
Physician office or hospital outpatient visits	190 (760)	294 (547)	<.001	301 (1397)	271 (560)	.206
Outpatient prescriptions	90 (195)	108 (233)	<.001	107 (216)	104 (234)	.594
Other healthcare services	3.6 (32)	7.8 (189)	.003	4.2 (37)	8.3 (200)	.207
Total costs	335 (902)	466 (905)	<.001	456 (1458)	430 (819)	.340
Health care utilization: Non-asthma-related						
Inpatient hospitalizations, No. (%)	745 (5.3)	226 (5.3)	.946	224 (5.9)	199 (5.2)	.218
ED visits, No. (%)	3,288 (23.4)	1010 (23.8)	.577	934 (24.6)	915 (24.1)	.611
No. of physician office/hospital outpatient visits, Mean (SD)	10.6 (12.3)	12.4 (13.3)	<.001	12.1 (13.6)	12.2 (13.2)	.763
Health care cost: Non-asthma-related, \$, Mean (SD)						
Hospitalizations	551 (3727)	552 (3398)	.936	671 (4460)	546 (3407)	.174
ED visits	198 (716)	241 (1090)	.251	237 (830)	223 (738)	.445
Physician office or hospital outpatient visits	2282 (4217)	2647 (4783)	<.001	2670 (4631)	2594 (4782)	.484
Outpatient prescriptions	1091 (2420)	1229 (2312)	<.001	1241 (2730)	1188 (2323)	.361
Other healthcare services	436 (8820)	374 (1423)	.133	468 (3049)	355 (1396)	.037 ^a
Total costs	4557 (11851)	5043 (8074)	<.001	5286 (9713)	4907 (7964)	.063
Propensity score, Mean (SD)	0.18 (0.18)	0.41 (0.18)	<.001	0.38 (0.17)	0.38 (0.17)	.136
Duration of follow-up, days, Mean (SD)	730 (415)	525 (295)	<.001	548 (304)	537 (297)	.105

Notes: For unmatched population, *p*-values calculated using Chi-square test, Fisher's exact test, Student's *t*-test, or Wilcoxon rank sum test. For matched population, *p*-values calculated using McNemar test, Bowker test, or paired *t*-test. FSC, Fluticasone propionate + salmeterol in a single inhaler; MF, Mometasone furoate inhalation powder; POS, Point of Service; HMO, Health maintenance organization; PPO, Preferred provider organization; Short-acting β -agonists; ICS, Inhaled corticosteroids; SCS, Systemic corticosteroids; LTRA, Leukotriene-receptor antagonists; ED, Emergency department; SD, Standard deviation.

^a Categorical version of the variable was used for matching.

lower risk of asthma-related exacerbation, defined as either asthma-related ED visits or hospitalizations, or receipt of SCS for asthma treatment. They also had fewer claims for SCS and

fewer asthma-related physician office and hospital outpatient visits. However, patients in the MF group had a lower risk of asthma-related ED visits.

TABLE 2.—Cox regression analysis on time to asthma-related ED visit, hospitalization, ED visit or hospitalization, and ED visit, hospitalization or claim for systemic corticosteroids, among propensity-matched patients receiving FSC100/50 versus MF.

Outcome	FSC 100/50 (N = 3799)		MF (N = 3799)		HR	(95% CL)	p
	No.	%	No.	%			
Asthma-related ED visit	116	(3.1)	95	(2.5)	1.40	(1.11–1.76)	.004
Asthma-related hospitalization	5	(0.1)	8	(0.2)	0.29	(0.08–1.02)	.053
Asthma-related ED visit or hospitalization	120	(3.2)	100	(2.6)	1.35	(1.08–1.68)	.009
Receipt of SCS	688	(18.1)	780	(20.5)	0.85	(0.78–0.92)	<.001
Asthma-related ED visit, hospitalization, or receipt of SCS	744	(19.6)	821	(21.6)	0.88	(0.81–0.95)	.002

FSC, Fluticasone propionate + salmeterol in a single inhaler; MF, Mometasone furoate inhalation powder; ED, Emergency department; SCS, Systemic corticosteroids; HR, Hazard ratio for FSC vs. MF; CI, Confidence interval.

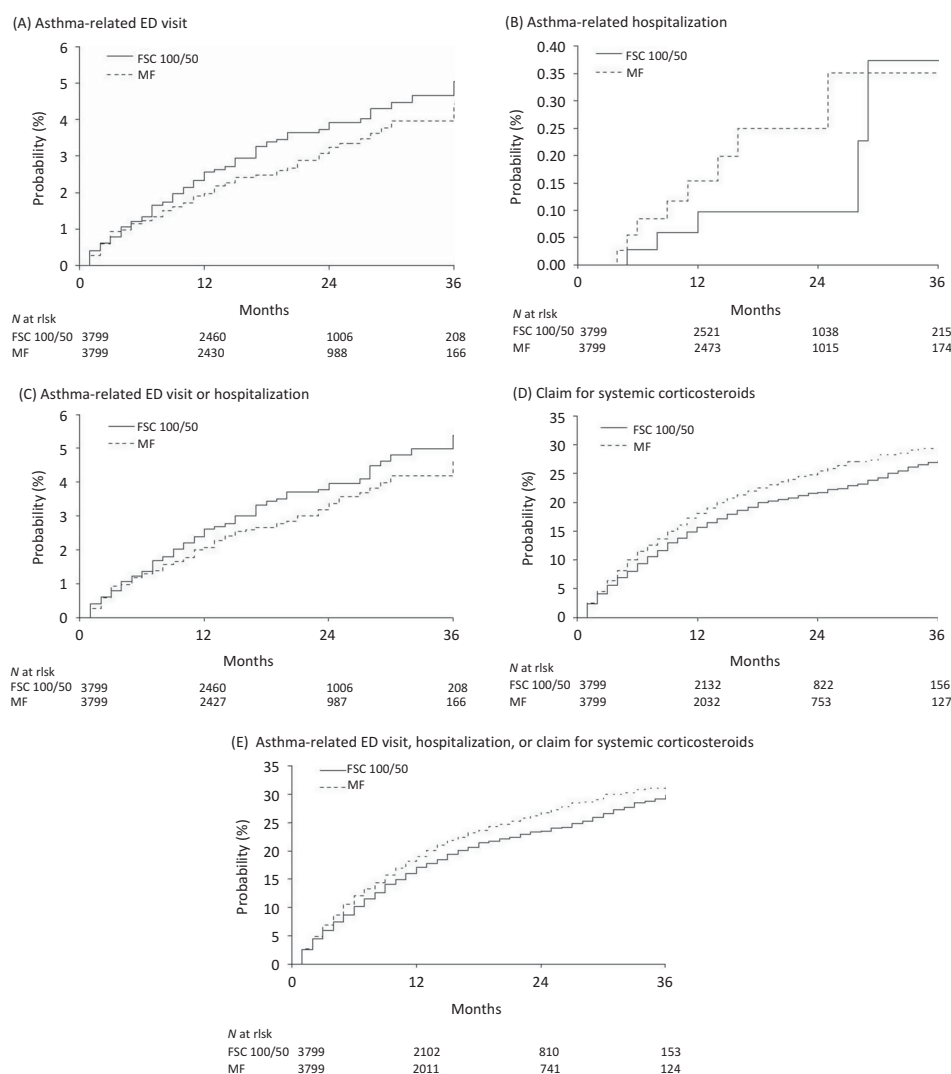


FIGURE 1.—Kaplan–Meier estimates of time to first asthma-related events among propensity-matched patients, by treatment group: (A) Asthma-related ED visit; (B) Asthma-related hospitalization; (C) Asthma-related ED visit or hospitalization; (D) Claim for systemic corticosteroids (SCSs); and (E) Asthma-related ED visit, hospitalization, or claim for SCSs.

Navaratnam et al. used data from a large administrative claims dataset to examine asthma-related health care utilization and costs and adherence to controller therapy in patients with mild asthma who initiated treatment with MF versus FSC (14). Patients were matched for pre-index characteristics using propensity scores and

compared using multivariate generalized linear regression models. Results reported here are similar to those reported by Navaratnam et al. in terms of total asthma-related costs, asthma-related outpatient pharmaceutical costs, and adherence to controller medication. However, unlike the study by Navaratnam et al., the incidence of exacerbation in the

TABLE 3.—Descriptive statistics on asthma-related health care utilization and costs and adherence to ICS during the follow-up among propensity-matched patients, by treatment group.

Measure	FSC 100/50 (N = 3799)	MF (N = 3799)	<i>p</i>
Asthma-related medical care utilization, Mean (SE)			
No. of SABA prescriptions	1.48 (0.04)	1.60 (0.04)	.069
No. of SCS claims	0.28 (0.01)	0.33 (0.01)	.021
No. of physician office/hospital outpatient visits	1.17 (0.05)	1.63 (0.07)	<.001
Asthma-related cost, \$, Mean (SE)			
ED visits	26 (229)	18 (199)	.137
Hospitalizations	8 (243)	12 (289)	.475
ED visits and hospitalizations	33 (339)	31 (356)	.711
Outpatient pharmacy	728 (633)	583 (562)	<.001
Outpatient pharmacy excluding MF and FSC 100/50	54 (101)	62 (124)	<.001
Other healthcare services	192 (916)	249 (1132)	.016
Total costs	953 (1192)	862 (1357)	.002
Total costs excluding MF and FSC 100/50	279 (996)	342 (1213)	.014
Adherence to ICS therapy			
MPR, <i>N</i> (%)	57.2 (27.2)	59.3 (27.1)	<.001
Refill rate per year	4.1 (2.9)	4.4 (3.1)	<.001

Notes: P-values calculated using McNemar test, Bowker test, or paired *t*-test. FSC, Fluticasone propionate + salmeterol in a single inhaler; MF, Mometasone furoate inhalation powder; SABAs, Short-acting β -agonists; SCSs, Systemic corticosteroids; ED, Emergency department; ICS, Inhaled corticosteroids; MPR, Medication possession ratio.

study reported here, defined as asthma-related ED visit, hospitalization, or claim for SCS, was lower in patients receiving FSC 100/50. The reasons for these differences in findings between the two studies are difficult to ascertain but may relate to differences in the study subjects, outcome definitions, and methods of analysis. Navaratnam et al. did not exclude patients based on receipt of ICS, attempted to focus on patients with mild asthma, and compared MF to all dosage strengths of FSC, whereas the current study excluded patients who received other ICS prior to MF or FSC, and compared MF to low-dose FSC 100/50 only. Also, unlike in the current study, in the study by Navaratnam et al., asthma exacerbations were defined to include outpatient visits in which patients received nebulization. While the study by Navaratnam et al. controlled for a variety of patient pre-index characteristics, including age, sex, comorbidities, pre-index asthma charges, SABA use, total number of asthma-related records, and asthma-related days, the study reported here controlled for a variety of additional potentially confounding factors including plan type, region, year and season of index prescription, numbers of chest X-rays and airflow tests, specialist visits, oxygen therapy, number of SCS claims, and receipt of antibiotics.

There are data suggesting that the frequency of asthma exacerbations is lower among patients receiving ICS/LABA combination therapy versus ICS monotherapy. For example, Pauwels et al. reported that the addition of formoterol to low-dose budesonide therapy resulted in a 26% and 40% reduction in the rates of severe and mild asthma exacerbations, respectively (19).

Although the US FDA recommends that ICS/LABA combination therapies be prescribed for patients not adequately controlled on a long-term asthma control medication, or whose asthma disease severity warrants the need for ICS and LABA, only 27% of patients in this study

received ICS within one year prior to the first receipt of FSC or MF. It is possible that the remaining 73% had ICS more than one year prior to index date. It was outside the scope of our study to investigate possible reasons for the seemingly high rate of utilization of FSC in patients without recent ICS utilization.

FDA-approved prescribing information for FSC states that people with asthma who take LABAs have an increased risk of death from asthma problems and it is unknown whether FP reduces the risk of death from asthma problems seen with salmeterol. This study did not examine survival and therefore does not provide information with respect to potential mortality effects of FSC versus MF.

Additional limitations of our study should be noted. First, there are differences between MF and FSC in terms of the patient populations for which they are recommended. MF is recommended for treatment of both mild and moderate asthma, while FSC is recommended for patients with moderate asthma only. While we attempted to control for differences between the patients receiving MF versus FSC in observed patient characteristics using propensity score matching, the possibility of residual confounding by unobserved factors must be recognized. In particular, because our study relied on health-insurance claims, we lacked information on some clinical parameters that may be independently predictive of outcomes in asthma patients (e.g., frequency and severity of symptoms, pulmonary function tests). It should be noted that such confounding might also explain the failure to find differences between groups in some outcomes.

Second, the database lacked information on race and socioeconomic status. In the Salmeterol Multicenter Asthma Research Trial (SMART), the increased risk of respiratory-related and asthma-related deaths or life-threatening experiences with salmeterol versus placebo

occurred largely in the African American subpopulation (20). In this trial, African Americans were reported to have a lower peak expiratory flow, a less ICS use, and higher percentages of hospitalizations and ED visits at baseline compared with Caucasians. If clinicians avoid prescribing FSC to African Americans, and outcomes are otherwise less favorable for African Americans versus other patients, then this might have biased the comparison of FSC versus MF.

A third limitation of the study is that the database does not include information on physicians' instructions to patients for the dosing of asthma medications and that estimates of adherence may therefore be biased. In particular, MPR was calculated based on the number of therapy days supplied written on each prescription. If patients are instructed to use the medication at a different dosage than that implied by the days and quantity supplied information on each claim then estimates of MPR may be biased. For example, if a patient is written a prescription for mometasone 220 µg twice daily but instructed to only take one inhalation daily (to reduce patient copayment), then this would not be reflected in the days supply information in the database and the estimate of MPR for this patient would be downwardly biased. This bias may apply to patients receiving FSC as well.

The finding of lower risk of asthma-related ED visit and higher risk of asthma-related exacerbation among the patients in the MF cohort versus those in the FSC 100/50 cohort is counterintuitive, as one would expect both outcomes to be correlated with disease severity and control. The higher risk of asthma-related exacerbations in the MF group versus the FSC 100/50 group was primarily due to greater utilization of SCS in the former. If receipt of SCS is a competing risk for asthma-related ED visits (because patients who receive SCS no longer require ED visits), it is possible that the lower frequency of ED visits in the MF group was due at least in part to the greater utilization of SCS among those patients. Another possibility is that there are one or more unobserved factors that are associated with receipt of FSC 100/50 that predispose patients to receive the treatment of asthma exacerbations in the ED rather than by SCS. While this possibility must be recognized, results were qualitatively similar; however, when we compared cohorts in subgroups of patients defined on whether they received SCS during the pre-index period, there were insufficient numbers of patients with ED visits during the pre-index period to stratify on this factor. It is also possible that this result was a consequence of confounding resulting from the methods used to select the study population. For example, patients with prescriptions for the other study medication during the treatment identification period were excluded from the analysis. If patients on ICS monotherapy with worsening asthma are more likely to be prescribed an ICS/LABA combination than those with stable disease, this might have biased the comparison in favor of ICS monotherapy. Because the numbers of asthma-related ED visits were small, this outcome might be especially susceptible to such confounding. Note that the rate of asthma ED visits in

the follow-up period (2.5% for MF and 3.1% for FSC 100/50 over mean follow-up of 1.5 years for both the groups) was lower than the rate in 12-month pre-index period (4.4% for MF and 4.3% for FSC 100/50) for both the groups.

CONCLUSIONS

The use of low-dose FSC 100/50 compared with the use of once-daily administration of ICS such as MF may reduce the use of SCS and asthma-related physician office and hospital outpatient visits in patients with asthma initiating ICS therapy. The decision to use either a once-daily ICS administration or a twice-daily low-dose ICS/LABA administration should be determined by the physicians and patients at the time of clinical presentation.

DECLARATION OF INTEREST

The authors alone are responsible for the content and writing of the paper.

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