

Health-care utilization and costs with fluticasone propionate and fluticasone propionate/salmeterol in asthma patients at risk for exacerbations

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ABSTRACT

Although studies have established that adding long-acting beta agonists (LABA) to inhaled corticosteroid (ICS) monotherapy among patients with inadequately controlled asthma is associated with better outcomes than increasing ICS dosage, outcomes with ICS versus fixed-dose ICS/LABA combination among patients with recent asthma exacerbation or frequent use of rescue medication are unavailable. This study was designed to compare health-care utilization/costs among patients with recent asthma exacerbation or frequent rescue medication use who received fluticasone propionate (FP) alone versus fixed-dose FP/salmeterol combination (FSC). A retrospective cohort study was conducted using a large health insurance data set. Patients with one or more claims with asthma diagnosis, two or more prescriptions for FSC (250/50- or 100/50-mg formulations) or FP (220- or 110-mg formulations), and one or more asthma exacerbations or five or more short-acting beta agonist (SABA) prescriptions within 1 year before initial receipt of study medications were included. Health-care utilization/costs and controller therapy compliance were compared for patients receiving FSC versus FP using multivariate regression analysis controlling for FP dose and baseline characteristics. A total of 7779 patients met inclusion criteria (5769, FSC, and 2010, FP) with comparable mean follow-up (FSC, 685 days; FP, 670 days; $p = 0.151$). Controlling for FP dosage and baseline characteristics, FSC patients had lower risks of asthma-related exacerbations, fewer SABAs and systemic corticosteroids, higher costs of asthma medications and total asthma-related health care, and lower total asthma-related health-care costs excluding study medication cost. In asthma patients with recent exacerbation or frequent SABA use, receipt of FSC reduced asthma-related exacerbation risks and rescue medication use versus receipt of FP.

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The National Asthma Education and Prevention Program Expert Panel and the Global Initiative for Asthma recommend low-/medium-dose inhaled corticosteroids (ICSs) as the preferred initial treatment for patients with mild-to-moderate persistent asthma.^{1,2} Results of a meta-analysis of 12 randomized controlled trials with a total of 4576 subjects show that in patients with uncontrolled asthma, adding a long-acting β -agonist (LABA), such as salmeterol (SAL), to moderate doses of ICS (fluticasone propionate [FP] 200 μ g/day or equivalent) results in improved lung function, reduced daytime use of short-acting β -agonists (SABAs), and reduced frequency of moderate or severe exacerbations, compared with increasing the dose of ICS by twofold or more.³ Other evidence-based reviews of randomized controlled trials have shown greater im-

provements in symptom control and lung function with the combination of ICS and LABA compared with higher doses of ICS.⁴ However, evidence regarding outcomes with a higher-dose ICS versus a lower-dose ICS plus an LABA in a fixed-dose combination in patients who may or may not have received prior treatment with ICS, but still may be at risk for future asthma exacerbations, is not available. Patients with recent history of asthma exacerbations and/or with high use of albuterol have been identified as being at greater risk of experiencing a future asthma exacerbation.^{5,6} This study attempts to assess the effect of a fixed lower-dose combination of FP/SAL (FSC) and higher dose FP among asthma patients at risk for asthma exacerbations.

METHODS

Overview

A retrospective cohort study using a large health insurance claims data set was used to compare health-care usage and costs with FP alone versus lower doses of FP in fixed-dose combination with SAL (FSC) in patients with a recent asthma exacerbation or frequent use of rescue medications. Data were from the Pharmetrics Patient Centric Database and included claims

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Supplemental data available at www.IngentaConnect.com

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Figure 1. Study design. COPD, chronic obstructive pulmonary disease; FP, fluticasone propionate; FSC, fluticasone propionate + salmeterol in a single inhaler; ICS, inhaled corticosteroid; IgEB, immunoglobulin E blocker; IMCS, inhaled mast-cell stabilizer; LABA, long-acting β -agonist; LTRA, leukotriene receptor antagonist; MTHL, methylxanthine; Rx, outpatient prescription; SABA, short-acting β -agonist.

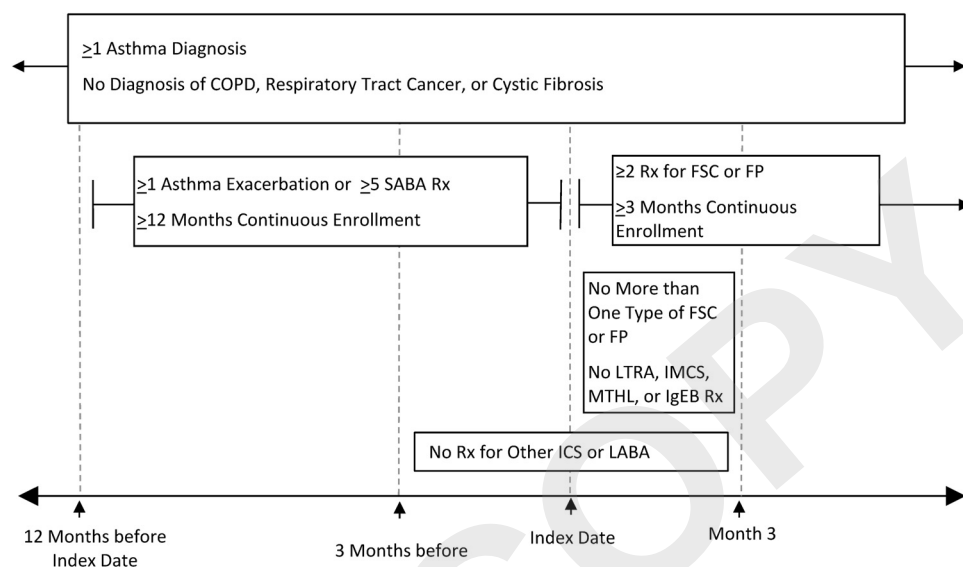


Table 1 Patient selection

Criteria	n
One or more diagnosis of asthma during study period	2,387,395
two or more FSC 250/50, FSC 100/50, FP 220, or FP 110 prescriptions during study period, and no study medications before July 1, 2005	289,918
One or more asthma exacerbations during preindex period	57,489
Exclusionary conditions	
More than one type of study medication within 3 mo of index date	2823
Had exclusionary asthma medications within 3 mo before or after index date	25,060
Had exclusionary diagnosis during study period	15,784
Had ipratropium or tiotropium during study period	15,643
Less than 12 mo of continuous enrollment on a plan before index date	20,609
Less than 3 mo of continuous enrollment on a plan post index date	1347
Age <12 or ≥65 yr on index date	18,385
Invalid data	1084
Total exclusions	49,710
Remaining	7779
FP 110	1541
FP 220	469
FSC 100/50	1971
FSC 250/50	3798

FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler.

from 2005 through 2010 ("study period"). The database contains information on enrollment files and medical and outpatient pharmacy claims from private health-care benefit plans covering ~78 million persons enrolled in >100 health plans across the United States and is fully de-identified and compliant with the Health Insurance Portability and Accountability Act of 1996. The database contains information on age, sex, and U.S. census region for all patients. Data on race, socioeconomic status, and anthropometrics are not

available. Health-care utilization/costs postindex were compared for patients receiving FP versus FSC using multivariable regression analysis to control for differences in baseline characteristics and ICS dosage.

Study Patients

Study patients had one or more claims with a diagnosis of asthma (ICD-9-CM 493.xx), and two or more claims for either FSC at 100/50 μ g, FSC at 250/50 μ g,

Table 2 Patient characteristics at index date

Characteristic	FP (n = 2,010)	FSC (n = 5,769)	p Value
Dose group, n (%)			
High dose	469 (23)	3798 (66)	<0.001
Low dose	1541 (77)	1971 (34)	
Year of index date, n (%)			
2005	107 (5)	509 (9)	<0.001
2006	311 (15)	825 (14)	
2007	428 (21)	1348 (23)	
2008	570 (28)	1585 (27)	
2009	568 (28)	1451 (25)	
2010	26 (1)	51 (1)	
Season on index date, n (%)			
Winter	547 (27)	1552 (27)	0.538
Spring	509 (25)	1492 (26)	
Summer	393 (20)	1193 (21)	
Fall	561 (28)	1532 (27)	
Age, yr, mean (SD)	34.9 (16.2)	38.6 (14.8)	<0.001
Males, n (%)	844 (42)	2354 (41)	0.352
Females, n (%)	1166 (58)	3415 (59)	
Region, n (%)			
Midwest	800 (40)	2349 (41)	<0.001
East	514 (26)	1668 (29)	
South	165 (8)	1037 (18)	
West	531 (26)	715 (12)	
Charlson index, mean (SD)	1.1 (0.7)	1.1 (0.7)	0.133
Most recent asthma exacerbation or 5+ SABA Rx during preindex period, n (%)			
Hospitalization	52 (3)	116 (2)	<0.001
ED visit	272 (14)	689 (12)	
SCS	1161 (58)	3651 (63)	
5+ SABA Rx	525 (26)	1313 (23)	
Time of last asthma exacerbation or last SABA Rx (if five or more) during preindex period, n (%)			
Within 3 mo	1438 (72)	3908 (68)	0.016
4–6 mo	267 (13)	862 (15)	
7–9 mo	203 (10)	682 (12)	
10–12 mo	102 (5)	317 (5)	
Medical care usage: Asthma-related			
Specialist visits, n (%)	264 (13)	1050 (18)	<0.001
Chest x rays, n (%)	674 (34)	2117 (37)	0.011
Airflow tests, n (%)	436 (22)	1567 (27)	<0.001
Oxygen therapy, n (%)	8 (0)	14 (0)	0.259
ICS prescriptions, n (%)	230 (11)	468 (8)	<0.001
ICS MPR, mean (SD)	2.7 (9.5)	2.0 (8.2)	<0.001
LABA prescriptions, n (%)	25 (1)	160 (3)	<0.001
SABA prescriptions, n, mean (SD)	3.9 (3.7)	3.7 (3.9)	<0.001
SCS prescriptions and procedures, n (%)	1385 (69)	4232 (73)	<0.001
Antibiotic prescriptions, n (%)	722 (36)	2089 (36)	0.815
Other medications, n, mean (SD)	16.1 (21.8)	16.0 (19.7)	0.023
1+ ED visits, n (%)	282 (14)	715 (12)	0.059
1+ inpatient hospitalizations, n (%)	52 (3)	116 (2)	0.126
Physician office/hospital outpatient visits, n, mean (SD)	1.2 (1.4)	1.4 (1.8)	<0.001

Table 2 Continued

Characteristic	FP (n = 436)	FSC (n = 1567)	p Value
Medical care cost: Asthma-related, \$, Mean (SD)			
ED visits	96 (345)	86 (350)	0.062
Hospitalizations	138 (1,015)	132 (1,331)	0.130
Physician office/hospital outpatient visits	168 (674)	171 (317)	0.002
Outpatient prescriptions	188 (645)	181 (305)	0.022
Other health-care services	10 (50)	13 (87)	0.351
Total costs	600 (1,456)	583 (1,485)	0.967
Medical care usage: Nonasthma-related			
1+ ED visits, n (%)	504 (25)	1,492 (26)	0.486
1+ inpatient hospitalizations, n (%)	98 (5)	322 (6)	0.228
Physician office/hospital outpatient visits, n, mean (SD)	11 (13)	11 (12)	0.476
Medical care cost: Nonasthma-related, \$, mean (SD)			
ED visits	261 (794)	247 (716)	0.489
Hospitalizations	624 (4,117)	794 (5,322)	0.205
Physician office/hospital outpatient visits	2015 (4,235)	2205 (5,234)	0.599
Outpatient prescriptions	993 (2,198)	1147 (2,584)	<0.001
Other health-care services	506 (3,201)	378 (1,374)	0.599
Total costs	4398 (8,989)	4772 (9,815)	0.002
Duration of follow-up, days, mean (SD)	670 (419)	685 (425)	0.151

The *p* values calculated using chi-square test, Fisher's exact test, Student's *t*-test, or Wilcoxon rank sum test.

ED = emergency department; FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler; ICS = inhaled corticosteroids; LABA = long-acting β -agonists; MPR = medication possession ratio; SABA = short-acting β -agonists; SCS = systemic corticosteroids.

FP at 110 μ g, or FP at 220 μ g during the study period. The date of the first prescription for such medicines was designated the "index date." Patients must have also had one or more "asthma exacerbations" or five or more prescriptions for SABAs within 1 year before the index date ("preindex period"). These patients were determined to be at risk for future asthma exacerbations. An asthma exacerbation was defined as an asthma-related emergency department (ED) visit, an asthma-related hospitalization, or an asthma-related treatment with systemic corticosteroid (SCS). The study design is summarized in Fig. 1.

Hospitalizations were considered asthma-related if the primary discharge diagnosis on the hospital inpatient claim was for asthma. Because primary and secondary diagnoses can not be distinguished on outpatient claims, they were considered asthma-related if there was any diagnosis of asthma on the claim and all of the other diagnosis codes on the claim date were respiratory related or there was one or more asthma-related procedure code on the claim. Claims for SCS were considered asthma-related if there was one or more claim with asthma diagnosis within 7 days of the SCS claim.

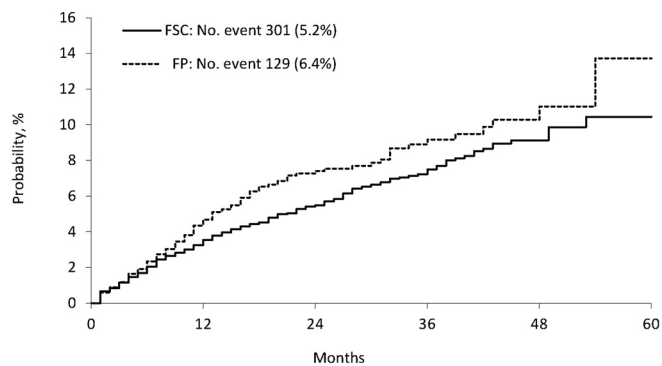
Persons who met any of the following criteria were excluded: (1) more than one study medication during

the 3-month period after index date; (2) one or more claims for an ICS or LABA other than the study medication within 3 months pre-/postindex date; (3) one or more claims of leukotriene receptor antagonist, inhaled mast-cell stabilizer, methylxanthine, or immunoglobulin E blocker during the 3-month period after index date; (4) any claims with a diagnosis of chronic obstructive pulmonary disease, respiratory tract cancer, or cystic fibrosis during the study period; (5) any claims for ipratropium or tiotropium during the study period; (6) <12 months of complete claims history before index date; (7) <3 months of follow-up; and (8) age <12 years or ≥ 65 years at index date.

Patient Characteristics

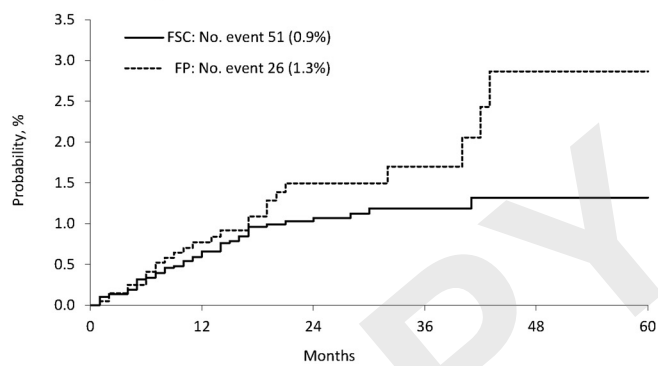
Patient characteristics included age at index date, gender, census region, and measures assessed over the preindex period: Charlson-Deyo comorbidity index⁷; evidence of visits to allergist or pulmonologist and services for chest x rays, airflow tests, and oxygen therapy; number of prescriptions for ICS, LABA, SABA, asthma-related SCS, antibiotics, and other medications; and ICS medication possession ratio (MPR) for patients who received ICS. MPR was defined as the sum of preindex ICS therapy days, not

A. Asthma-related ED visit



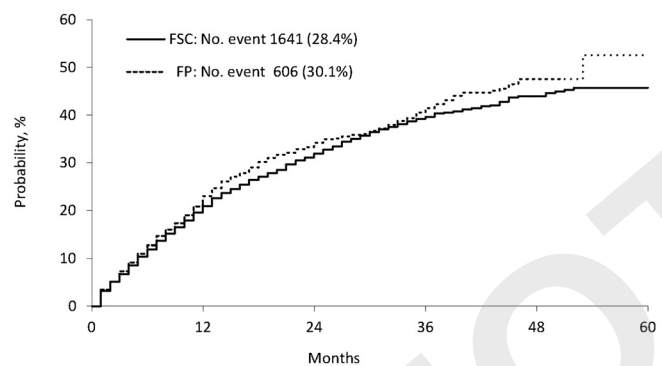
N at risk						
FSC	5,769	4,111	2,282	1,021	407	0
FP	2,010	1,408	746	355	122	0

B. Asthma-related hospitalization



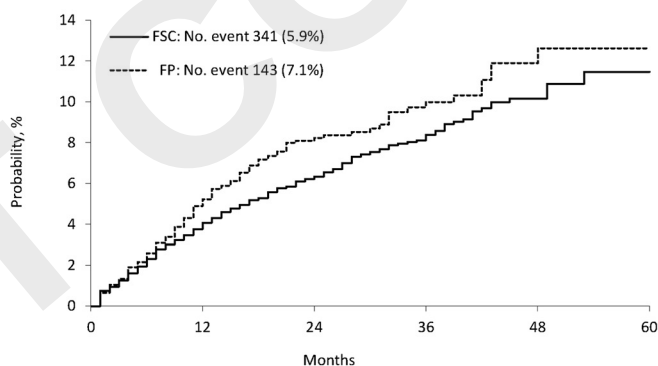
N at risk						
FSC	5,769	4,235	2,382	1,075	435	0
FP	2,010	1,466	787	376	124	0

C. Claim for systemic corticosteroids



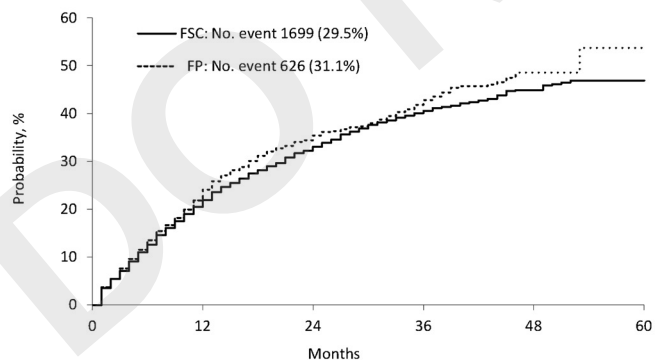
N at risk						
FSC	5,769	3,395	1,660	700	262	0
FP	2,010	1,145	541	239	69	0

D. Asthma-related ED visit or hospitalization



N at risk						
FSC	5,769	4,090	2,263	1,012	404	0
FP	2,010	1,400	742	351	120	0

E. Asthma-related ED visit, hospitalization or claim for systemic corticosteroids



N at risk						
FSC	5,769	3,349	1,632	689	258	0
FP	2,010	1,129	527	233	68	0

Figure 2. Kaplan-Meier estimates of time to first asthma-related events by treatment group. (A) Asthma-related ED visit; (B) asthma-related hospitalization; (C) claim for systemic corticosteroids; (D) asthma-related ED visit or hospitalization; and (E) asthma-related ED visit, hospitalization, or claim for systemic corticosteroids. ED, emergency department; FP, fluticasone propionate; FSC, fluticasone propionate + salmeterol in a single inhaler.

including the portion of supplies carried forward beyond preindex period, divided by the number of days between the first date with ICS supply and the index date.

Also ascertained during the preindex period were a number of asthma-related and nonasthma-related ED visits, hospitalizations, and physician office/hospital outpatient visits, and the costs of asthma-related and

nonasthma-related hospitalizations, ED visits, physician office/hospital outpatient visits, outpatient prescriptions, and other services. Costs were estimated using the amount plans allow for a particular service, which is typically the paid amount plus copay, deductible, and coinsurance.

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. Asthma-related exacerbation was the combined end point of experiencing an asthma-related ED visit, an asthma-related hospitalization, or a receipt of asthma-related SCS. Other measures of interest included numbers of SABA prescriptions, asthma-related SCS claims, and asthma-related office/outpatient visits; costs of study medications, asthma-related medications, asthma-related medications excluding costs of study medications, asthma-related ED visits or hospitalizations, and other asthma-related encounters; total asthma-related costs with/without costs of study medications; and MPR and refill rate for study medication. MPR was defined as the sum of therapy days supplied on all FSC or FP prescriptions during follow-up divided by the sum of the number of days between the first and last such prescription and the number of days on the last such prescription. Refill rate was defined as the number of prescriptions for FSC or FP during follow-up divided by the duration of follow-up.

Statistical Analyses

Preindex characteristics were compared using chi-square or Fischer's exact test for categorical variables and Student's *t*-test or Wilcoxon's rank sum test for continuous variables. Patients were censored at the end of follow-up in analyses of time-to-event measures. Hazard ratios (HRs) for FSC versus FP were calculated using Cox proportional hazards regression analysis with all baseline characteristics included as covariates.

Other outcome measures were analyzed using multivariable generalized linear model regression with all patient characteristics included as covariates.⁸ Measures representing counts were evaluated with a log link and negative binomial distribution. Costs measures were analyzed using log link with a γ -distribution. Because MPR is heavily skewed toward and truncated at 100%, we analyzed 1-MPR as the dependent variable using a log link with normal distribution. The duration of follow-up entered as an offset term to control for differences in follow-up.

Table 3 Results of Cox regression analysis on time to asthma-related exacerbation in patients with asthma receiving FSC vs FP

Outcome	HR	(95% CI)	<i>p</i> Value
ED visit			
FSC vs FP	0.83	(0.64–1.06)	0.134
High dose vs low dose	1.03	(0.82–1.29)	0.784
Hospitalization			
FSC vs FP	0.55	(0.31–0.97)	0.038
High dose vs low dose	1.18	(0.66–2.12)	0.583
SCS			
FSC vs FP	0.82	(0.74–0.91)	<0.001
High dose vs low dose	1.24	(1.13–1.36)	<0.001
ED visit or hospitalization			
FSC vs FP	0.80	(0.64–1.02)	0.068
High dose vs low dose	1.09	(0.88–1.36)	0.414
ED visit, hospitalization, or SCS			
FSC vs FP	0.83	(0.75–0.92)	<0.001
High dose vs low dose	1.22	(1.12–1.34)	<0.001

CI = confidence interval; ED = emergency department; FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler; HR = hazard ratio; SCS = systemic corticosteroid.

For both proportional hazards and generalized linear model regression, baseline characteristics, treatment group (FSC versus FP), and a covariate representing the dose of FP were included as covariates. FSC at 100/50 μ g and FP at 110 μ g were considered low dose, and FSC at 250/50 μ g and FP at 220 μ g were considered high dose. It should be noted that because FP is typically administered as two inhalations twice daily whereas FSC is administered as one inhalation twice daily, the effective dose of FP in FP110 is approximately double that in FSC at 100/50 μ g, and the effective dose of FP in FP220 is approximately double that in FSC at 250/50 μ g. The coefficient for treatment group thus provides a measure of the average treatment effect over all doses of FP after adding SAL (FSC) versus using a higher dose FP. Two additional models were also estimated for each outcome: a simpler model including all of the covariates listed previously except for the FP dose group and a more complex model including all of the covariates listed previously as well as a covariate representing the interaction of the treatment group and the FP dose group. The interaction term in the complex model provides a test of whether this treatment effect is modified by referent dose of FP in FSC. Adjusted means and 95% confidence intervals (CIs) were reported for each measure. All analyses were conducted using SAS Proprietary Software, Release 9.2 (SAS Institute, Inc., Cary, NC).

Table 4 Results of generalized linear model regression analysis on asthma-related health-care utilization, costs, and adherence to ICS therapies in patients with asthma receiving FSC vs FP

Outcome	Estimate	(95% CI)	p Value
No. of SABA*			
FSC vs FP	−0.21	(−0.26, −0.15)	<0.001
High dose vs low dose	0.03	(−0.01, 0.08)	0.169
No. of SCS*			
FSC vs FP	−0.20	(−0.31, −0.08)	<0.001
High dose vs low dose	0.27	(0.17, 0.37)	<.001
No. of physician office or hospital outpatient visits*			
FSC vs FP	−0.03	(−0.11, 0.05)	0.493
High vs low dose	0.08	(0.01, 0.16)	0.024
Cost of study medications, \$#			
FSC vs FP	0.45	(0.41, 0.49)	<0.001
High vs low dose	0.16	(0.12, 0.20)	<0.001
Cost of other asthma medications \$#			
FSC vs FP	−0.08	(−0.18, 0.02)	0.140
High vs low dose	0.12	(0.03, 0.20)	0.008
Cost of all asthma medications, \$#			
FSC vs FP	0.33	(0.29, 0.37)	<0.001
High vs low dose	0.15	(0.11, 0.18)	<0.001
Cost of asthma-related hospitalizations and ED visits, \$#			
FSC vs FP	−0.88	(−1.10, −0.66)	<0.001
High vs low dose	0.43	(0.23, 0.63)	<0.001
Cost of other asthma-related visits, \$#			
FSC vs FP	−0.07	(−0.21, 0.07)	0.317
High vs low dose	0.21	(0.09, 0.34)	<0.001
Asthma-related total cost, \$#			
FSC vs FP	0.25	(0.21, 0.29)	<0.001
High vs low dose	0.18	(0.14, 0.22)	<0.001
Asthma-related total cost excluding study medications, \$#			
FSC vs FP	−0.11	(−0.20, −0.01)	0.026
High vs low dose	0.23	(0.15, 0.31)	<0.001
Noncomplicance: 100-MPR*			
FSC vs FP	−0.15	(−0.22, −0.07)	<0.001
High vs low dose	0.04	(−0.03, 0.11)	0.253
Refill rate per year*			
FSC vs FP	0.34	(0.28, 0.40)	<0.001
High vs low dose	−0.05	(−0.10, 0.00)	0.046

*The dependent variable was log transformed and negative binomial distribution was used in generalized linear model regression.

#The dependent variable was log transformed and γ -distribution was used in generalized linear model regression.

CI = confidence interval; ED = emergency department; FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler; ICS = inhaled corticosteroids; MPR = medication possession ratio; SABA = short-acting β -agonists; SCS = systemic corticosteroids.

RESULTS

Study Sample

There were 57,489 patients who had one or more claims with asthma diagnosis, two or more claims for one of the study medications on or after July 1, 2005, and one or more asthma exacerbations or five or more SABA claims during the preindex period (Table 1). A total of 7779

patients met all inclusion and exclusion criteria, including 1971 patients with FSC 100/50, 3798 patients with FSC 250/50, 1541 patients with FP110, and 469 patients with FP220. The largest sources of attrition (not mutually exclusive) were receipt of other asthma medications within 3 months before/after the index date (43.6%), <12 months of continuous health plan enrollment before in-

Table 5 Adjusted means on asthma-related healthcare use, costs, and adherence to ICS therapies in patients with asthma receiving FSC vs FP

Outcome	FP	FSC	FSC-FP (95% CI)
Selected asthma-related health-care utilization			
No. of SABA	5.4	4.4	−1.01 (−1.33, −0.73)
No. of SCS	0.6	0.5	−0.11 (−0.17, −0.04)
No. of physician office or hospital outpatient visits	1.5	1.4	−0.04 (−0.20, 0.10)
Asthma-related costs, \$			
Study medications	758	1190	432 (398, 471)
Other medications	351	326	−26 (−58, 3)
All medications	1091	1519	428 (384, 481)
Hospitalizations and ED visits	1289	536	−754 (*, −72)
Other	225	210	−15 (−51, 15)
Total	1458	1868	410 (336, 493)
Total excluding study medications	738	664	−74 (−155, −2)
ICS adherence			
Noncompliance: 100-MPR	50.7	43.8	−6.9 (−9.4, −4.3)
Refill rate per year	3.4	4.7	1.4 (1.1, 1.6)

The 95% CIs were calculated by nonparametric bootstrap method.

* $< -100,000$.

CI = confidence interval; ED = emergency department; FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler; ICS = inhaled corticosteroids; MPR = medication possession ratio; SABA = short-acting β -agonists; SCS = systemic corticosteroids.

dex date (35.9%), age <12 years or ≥ 65 years on index date (32.0%), with one or more claims with diagnoses of chronic obstructive pulmonary disease, respiratory tract cancer, or cystic fibrosis (27.5%), and receipt of ipratropium or tiotropium (27.2%).

Patient Characteristics

Mean age was 39 and 35 years in FSC and FP groups ($p < 0.001$), respectively (Table 2). Compared with the FP group, the FSC group was more likely to receive high-dose FP on index date (66% versus 23%; $p < 0.001$), more likely to be in the South (18% versus 8%; $p < 0.001$), less likely to be in the West (12% versus 26%), and more likely to receive SCS as their most recent qualifying event (63% versus 58%; $p < 0.001$). Mean duration of follow-up was comparable between FSC and FP groups (685 days versus 670 days; $p = 0.151$). Patients in the FSC group had higher rates of use of medical services during the preindex period, including physician office/hospital outpatient visits; specialist visits; chest x rays; airflow tests; SABA, LABA, and ICS prescriptions; and SCS claims. FSC patients also had higher mean preindex ICS MPR.

Outcome Measures

Unadjusted Kaplan-Meier estimates for time-to-event outcomes are reported in Fig. 2. Corresponding Cox proportional hazards regression analyses are reported in Table 3. The receipt of FSC was associated

with reduced risk of asthma-related hospitalization (HR = 0.55; 95% CI = 0.31–0.97; $p = 0.038$); reduced risk of receipt of SCS (HR = 0.82; 95% CI = 0.74–0.91; $p < 0.001$); and reduced risk of asthma-related ED visit, hospitalization, or SCS (HR = 0.83; 95% CI = 0.75–0.92; $p < 0.001$).

Patients in the FSC group had fewer claims for SABAs (coefficient for FSC = -0.21 $p < 0.001$) and fewer claims for SCS (coefficient = -0.20 ; $p < 0.001$; Table 4), and FSC was associated with a significant mean reduction of 1.01 (95% CI, 0.73–1.33) SABA claims and 0.11 (95% CI, 0.04–0.17) SCS claims on average over the follow-up period (Table 5).

Compared with patients in the FP group, patients in the FSC group had lower noncompliance (coefficient = -0.15 ; $p < 0.001$) and higher refill rate (coefficient = 0.34; $p < 0.001$).

The results of the additional models are reported in Appendices A–C (www.IngentaConnect.com), and they were similar to those reported previously in this study.

DISCUSSION

This was a retrospective comparison of health-care utilization with FP alone (110- or 220- μ g formulations) versus FSC (100/50 and 250/50 formulations) in asthma patients with recent exacerbation or frequent use of rescue medications (five or more canisters in a year). Based on Cox regression analysis controlling for

baseline characteristics and ICS dosage, FSC patients had lower risks of asthma-related hospitalization; receipt of SCS; and the composite measure of ED visit, hospitalization, or SCS when compared with FP monotherapy at a twofold greater ICS dose. Controlling for baseline characteristics and dosage, FSC patients also had fewer claims for SABAs and fewer claims for SCS than double-dose FP monotherapy. FSC patients had higher costs of asthma medications and higher total asthma-related health-care costs. However, total asthma-related health-care costs excluding the costs of study medications were lower with FSC. Our findings are similar to those of prior studies. In a randomized, double-blinded, parallel-group study, FP 100 and FSC 100/50 were compared over a 24-week period among asthma patients who were ICS naïve and with mild uncontrolled asthma.⁹ It was reported that the FSC group showed favorable results in terms of mean morning peak expiratory flow, percentage of symptom-free days, and asthma exacerbation-related health-care utilization. Also, there are retrospective studies reporting superiority of lower risks of asthma exacerbations with FSC when compared with FP.^{10,11} Unlike the studies referenced previously, which compared FSC and FP in patients with mild asthma or among an unselected group of asthma patients, the current study focused on patients with recent exacerbation of asthma or frequent use of rescue medication.

Limitations of this study should be noted. As with any observational study, because treatment was not randomly assigned, it is possible that differences between FSC and FP groups in study outcomes were caused by differences in patient characteristics rather than the treatments *per se*. Although we attempted to control for confounding using multivariable regression, because this study relied on health insurance claims, information on some clinical parameters that may be independently predictive of outcomes in asthma patients (*e.g.*, frequency and severity of symptoms) were unavailable, and the possibility of residual confounding must be recognized. It should be noted that such confounding might also explain the failure to find differences between groups for some outcomes. The database used in this study is based on a large convenience sample. Because the sample is not random, it may not be generalizable to other populations. In particular, the database is geographically diverse but not geographically representative of the U.S. pop-

ulation. Also, Medicaid patients are not represented. Finally, it should also be noted that this study did not consider differences between groups in loss of school and work time, progression and worsening of disease, or the health-related quality of life.

CONCLUSIONS

Results of this observational health insurance claims-based study suggest that in patients with asthma who had experienced an asthma exacerbation or received five or more SABA prescriptions within 1 year, receipt of FSC versus FP at twofold greater dosing of ICS is associated with a lower risk of asthma-related exacerbations and reduced use of rescue medications but increased asthma-related health-care costs related to the greater cost of the medication of interest.

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Appendix A Results of Cox regression analysis on time to asthma-related exacerbation in patients with asthma receiving FSC vs FP

Outcome	Model 1			Model 2			Model 3		
	HR	(95% CI)	p Value	HR	(95% CI)	p Value	HR	(95% CI)	p Value
ED visit									
FSC vs FP	0.84	(0.67–1.05)	0.129	0.83	(0.64–1.06)	0.134	0.91	(0.68–1.22)	0.533
High vs low dose	—			1.03	(0.82–1.29)	0.784	1.30	(0.85–2.00)	0.230
FSC high dose	—			—			0.74	(0.45–1.21)	0.225
Hospitalization									
FSC vs FP	0.59	(0.36–0.97)	.038	0.55	(0.31–0.97)	0.038	0.58	(0.28–1.21)	0.147
High vs low dose	—			1.18	(0.66–2.12)	0.583	1.29	(0.48–3.48)	0.616
FSC high dose	—			—			0.88	(0.27–2.88)	0.831
SCS									
FSC vs FP	0.90	(0.81–0.99)	.025	0.82	(0.74–0.91)	<0.001	0.79	(0.69–0.90)	<0.001
High vs low dose	—			1.24	(1.13–1.36)	<0.001	1.14	(0.95–1.37)	0.161
FSC high dose	—			—			1.12	(0.91–1.39)	0.293
ED visit or hospitalization									
FSC vs FP	0.84	(0.67–1.03)	.099	0.80	(0.64–1.02)	0.068	0.89	(0.67–1.18)	0.420
High vs low dose	—			1.09	(0.88–1.36)	0.414	1.38	(0.92–2.05)	0.115
FSC high dose	—			—			0.74	(0.47–1.17)	0.191
ED visit, hospitalization, or SCS									
FSC vs FP	0.90	(0.82–0.99)	.031	0.83	(0.75–0.92)	<0.001	0.80	(0.70–0.91)	<.001
High vs low dose	—			1.22	(1.12–1.34)	<0.001	1.13	(0.94–1.35)	0.204
FSC high dose	—			—			1.12	(0.91–1.38)	0.295

Model 1, treatment variable (FSC vs FP) and baseline covariates; model 2, treatment variable (FSC vs FP), dose variable (high dose vs low dose), and baseline covariates; model 3, treatment variable (FSC vs FP), dose variable (high dose vs low dose), treatment dose interaction term, and baseline covariates.

CI = confidence interval; ED = emergency department; FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler; HR = hazard ratio; SCS = systemic corticosteroids.

Appendix B Results of generalized linear model regression analysis on asthma-related health-care utilization, costs, and adherence to ICS therapies in patients with asthma receiving FSC vs FP

Outcome	Model 1			Model 2			Model 3		
	Estimate	(95% CI)	p Value	Estimate	(95% CI)	p Value	Estimate	(95% CI)	p Value
No. of SABA*									
FSC vs FP	-0.19	(-0.24, -0.14)	<0.001	-0.21	(-0.26, -0.15)	<0.001	-0.23	(-0.30, -0.17)	<0.001
High vs low dose	—			0.03	(-0.01, 0.08)	0.169	-0.03	(-0.13, 0.07)	0.578
FSC high dose	—			—			0.08	(-0.03, 0.20)	0.164
No. of SCS*									
FSC vs FP	-0.09	(-0.19, 0.02)	0.100	-0.20	(-0.31, -0.08)	<0.001	-0.21	(-0.35, -0.07)	0.003
High dose vs low dose	—			0.27	(0.17, 0.37)	<0.001	0.23	(0.04, 0.43)	0.021
FSC high dose	—			—			0.05	(-0.18, 0.27)	0.692
No. of physician office or hospital outpatient visits*									
FSC vs FP	0.00	(-0.08, 0.08)	0.940	-0.03	(-0.11, 0.05)	0.493	0.00	(-0.10, 0.11)	0.935
High dose vs low dose	—			0.08	(0.01, 0.16)	0.024	0.16	(0.01, 0.31)	0.041
FSC high dose	—			—			-0.10	(-0.27, 0.07)	0.265
Cost of study medications, \$#									
FSC vs FP	0.51	(0.47, 0.55)	<0.001	0.45	(0.41, 0.49)	<0.001	0.53	(0.47, 0.58)	<0.001
High dose vs low dose	—			0.16	(0.12, 0.20)	<0.001	0.33	(0.25, 0.41)	<0.001
FSC high dose	—			—			-0.22	(-0.30, -0.13)	<0.001
Cost of other asthma medications \$#									
FSC vs FP	-0.03	(-0.12, 0.07)	0.591	-0.08	(-0.18, 0.02)	0.140	-0.15	(-0.27, -0.03)	0.012
High dose vs low dose	—			0.12	(0.03, 0.20)	0.008	-0.08	(-0.26, 0.10)	0.406
FSC high dose	—			—			0.25	(0.04, 0.45)	0.018
Cost of all asthma medications, \$#									
FSC vs FP	0.39	(0.35, 0.42)	<0.001	0.33	(0.29, 0.37)	<0.001	0.36	(0.31, 0.41)	<0.001
High dose vs low dose	—			0.15	(0.11, 0.18)	<0.001	0.22	(0.15, 0.29)	<0.001
FSC high dose	—			—			-0.10	(-0.18, -0.01)	0.024
Cost of asthma-related hospitalizations and ED visits, \$#									
FSC vs FP	-0.73	(-0.94, -0.51)	<0.001	-0.88	(-1.10, -0.66)	<0.001	-0.76	(-1.01, -0.51)	<0.001
High dose vs low dose	—			0.43	(0.23, 0.63)	<0.001	0.77	(0.36, 1.18)	<0.001
FSC high dose	—			—			-0.44	(-0.90, 0.01)	0.057

Appendix B Continued		Model 1			Model 2			Model 3		
Outcome		Estimate	(95% CI)	p Value	Estimate	(95% CI)	p Value	Estimate	(95% CI)	p Value
Cost of other asthma-related visits, \$#										
FSC vs FP		0.01	(-0.12, 0.15)	0.826	-0.07	(-0.21, 0.07)	0.317	-0.04	(-0.21, 0.12)	0.602
High dose vs low dose		—			0.21	(0.09, 0.34)	<0.001	0.28	(0.01, 0.54)	0.040
FSC high dose		—			—			-0.08	(-0.38, 0.21)	0.585
Asthma-related total cost, \$#										
FSC vs FP		0.32	(0.28, 0.36)	<0.001	0.25	(0.21, 0.29)	<0.001	0.29	(0.24, 0.34)	<0.001
High dose vs low dose		—			0.18	(0.14, 0.22)	<0.001	0.27	(0.19, 0.35)	<0.001
FSC high dose		—			—			-0.11	(-0.20, -0.03)	0.010
Asthma-related total cost excluding study medications, \$#										
FSC vs FP		-0.01	(-0.10, 0.07)	0.764	-0.11	(-0.20, -0.01)	0.026	-0.11	(-0.22, 0.00)	0.052
High dose vs low dose		—			0.23	(0.15, 0.31)	<0.001	0.22	(0.05, 0.39)	0.012
FSC high dose		—			—			0.01	(-0.18, 0.21)	0.887
Noncompliance: 100-MPR*										
FSC vs FP		-0.13	(-0.20, -0.06)	<0.001	-0.15	(-0.22, -0.07)	<0.001	-0.17	(-0.26, -0.07)	<0.001
High dose vs low dose		—			0.04	(-0.03, 0.11)	0.253	-0.01	(-0.15, 0.13)	0.909
FSC high dose		—			—			0.06	(-0.10, 0.22)	0.456
Refill rate per year*										
FSC vs FP		0.32	(0.26, 0.37)	<0.001	0.34	(0.28, 0.40)	<0.001	0.34	(0.27, 0.41)	<0.001
High dose vs low dose		—			-0.05	(-0.10, 0.00)	0.046	-0.05	(-0.16, 0.06)	0.399
FSC high dose		—			—			-0.01	(-0.13, 0.12)	0.932

Model 1, treatment variable (FSC vs FP) and baseline covariates; model 2, treatment variable (FSC vs FP), dose variable (high dose vs low dose), and baseline covariates; model 3, treatment variable (FSC vs FP), dose variable (high dose vs low dose), treatment dose interaction term, and baseline covariates.

*The dependent variable was log transformed and negative binomial distribution was used in generalized linear model regression.

#The dependent variable was log transformed and γ distribution was used in generalized linear model regression.

CI = confidence interval; ED = emergency department; FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler; ICS = inhaled corticosteroids; MPR = medication possession ratio; SABA = short-acting β -agonists; SCS = systemic corticosteroids.

Appendix C Adjusted means on asthma-related health-care utilization, costs, and adherence to ICS therapies in patients with asthma receiving FSC vs FP

Outcome	Model 1			Model 2			Model 3		
	FP	FSC	FSC-FP (95% CI)	FP	FSC	FSC-FP (95% CI)	FP	FSC	FSC-FP (95% CI)
Selected asthma related health-care utilization									
No. of SABA	5.4	4.4	-0.9 (-1.2, -0.7)	5.4	4.4	-1.0 (-1.3, -0.7)	5.3	4.4	-0.9 (-1.3, -0.6)
No. of SCS	0.6	0.5	0.0 (-0.1, 0.0)	0.6	0.5	-0.1 (-0.2, 0.0)	0.6	0.5	-0.1 (-0.2, 0.0)
No. of physician office or hospital outpatient visits	1.4	1.4	0.0 (-0.1, 0.1)	1.5	1.4	0.0 (-0.2, 0.1)	1.5	1.4	-0.1 (-0.3, 0.1)
Asthma-related costs, \$									
Study medications	725	1207	482 (448, 518)	758	1190	432 (398, 471)	805	1193	389 (347, 431)
Other medications	338	330	-9 (-39, 18)	351	326	-26 (-58, 3)	330	325	-5 (-37, 24)
All medications	1045	1539	495 (450, 543)	1091	1519	428 (384, 481)	1119	1521	402 (350, 457)
Hospitalizations and ED visits	1307	631	-676 (*, 1,370)	1289	536	-754 (*, -72)	1623	538	-1,085 (*, 160)
Other	211	214	3 (-31, 30)	225	210	-15 (-51, 15)	231	210	-21 (-73, 18)
Total	1383	1899	516 (432, 587)	1458	1868	410 (336, 493)	1506	1871	365 (269, 461)
Total excluding study medications	687	678	-9 (-85, 54)	738	664	-74 (-155, -2)	735	664	-71 (-167, 18)
ICS adherence									
Noncompliance: 100-MPR	50.1	44.0	-6.1 (-8.5, -3.8)	50.7	43.8	-6.9 (-9.4, -4.3)	49.9	43.8	-6.2 (-9.0, -3.4)
Refill rate per year	3.4	4.7	1.3 (1.0, 1.6)	3.4	4.7	1.4 (1.1, 1.6)	3.4	4.7	1.4 (1.1, 1.7)

Model 1, treatment variable (FSC vs FP) and baseline covariates; model 2, treatment variable (FSC vs FP), dose variable (high dose vs low dose), and baseline covariates; model 3, treatment variable (FSC vs FP), dose variable (high dose vs low dose), treatment-dose interaction term, and baseline covariates. The 95% CIs were calculated by nonparametric bootstrap method.

* $< -100,000$.

CI = confidence interval; ED = emergency department; FP = fluticasone propionate; FSC = fluticasone propionate + salmeterol in a single inhaler; ICS = inhaled corticosteroids; MPR = medication possession ratio; SABA = short-acting β -agonists; SCS = systemic corticosteroids.

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