Initiation of Inhaled Corticosteroid and Long-Acting β_2-adrenergic Agonist (ICS/LABA) in Asthma

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ABSTRACT

Objectives: To examine the proportion of patients with asthma appropriately initiated on inhaled corticosteroid/long-acting β_2-adrenergic agonist (ICS/LABA) combination therapies—fluticasone propionate/salmeterol combination (FSC) versus budesonide/formoterol fumarate dihydrate combination (BFC) using guideline-based healthcare utilization measures.

Study Design: The current study is a retrospective cohort analysis of patients with asthma, aged 12 to 64 years, new to ICS/LABA combination therapy, using—US healthcare claims data between June 1, 2007, and December 31, 2010.

Methods: Patients with asthma controller medication or asthma exacerbation high risk criteria in the 12 months prior to ICS/LABA combination treatment initiation were considered appropriately treated (Expert Panel Report-3 [EPR-3] guidelines). Regression analysis was used to identify factors associated with BFC or FSC initiation.

Results: A total of 11,718 BFC, 38,697 FSC, and 126 mometasone/formoterol fumarate dihydrate combination (MFC) patients were identified; MFC was not included in analysis due to low market presence. Over the study period, 32% of patients in each cohort met asthma exacerbation high risk criteria; however, a significantly greater percentage of BFC patients had asthma maintenance therapy (41% vs 31%) in the prior year (adjusted OR: 1.43, P <.0001). Overall, a higher proportion of BFC patients were initiated appropriately (57% vs 52%) and had a higher odds of appropriate initiation after adjustment for potential confounding variables (adjusted OR: 1.21; P <.0001). The majority of the difference occurred initially in the study with a decrease in the BFC-appropriate initiation rate over the study period while the rate was fairly consistent for FSC.

Conclusions: The odds of appropriate BFC initiation were significantly higher after controlling for selected confounders/baseline differences. This result could be driven by the higher appropriate initiation of BFC versus FSC cohort at the beginning of the study period.

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Asthma is a chronic respiratory condition characterized by inflammation in the air passages, which narrows the airways and impedes respiration.[1,2] While some patients have genetic predispositions to asthma,[3,4] the condition is also linked to well-known environmental triggers such as inhaled allergens and irritants,[1,2] which can increase inflammation and cause asthma attacks. Asthma affects approximately 8.2% (24.6 million) of people in the United States,[5] and more than 300 million worldwide.[3] Prevalence is greater among children (8.9%) compared with adults (7.2%) in the United States.[6] Each year, about 4000 deaths are directly attributable to asthma.[6] In 2007, asthma-related emergency department (ED) visits and hospitalizations were estimated at 1.75 million and 456,000, respectively.[5] The total costs directly applicable to asthma treatments in 2007 were estimated at $37.2 billion in the United States.[7]

The current Expert Panel Report-3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma state that the preferred treatment for persistent asthma is long-term controller medication, usually an inhaled corticosteroid (ICS).[8] For patients 12 years or older with moderate to severe asthma whose asthma is not well controlled on a low to medium dose of ICS alone, the EPR-3 guidelines suggest the addition of a long-acting β_2-adrenergic agonist (LABA). The guidelines also suggest the addition of LABAs in cases with high levels of impairment, or when patients are at risk for asthma exacerbation. LABAs are not recommended for monotherapy due to evidence associating the LABA salmeterol with asthma-related deaths.[9] A subsequent FDA-mandated class black-box warning (2005) resulted in updated product labeling, which now includes a reference to this association for all products containing LABAs.[10] For ICS/LABA combination treatments, the current labeling indicates usage in patients who are not adequately controlled with other asthma controller medications, or for patients whose disease severity warrants the use of 2 maintenance therapies.[11,12]

Three ICS/LABA combination therapies are currently approved for asthma treatment in the United States: fluticasone propionate/salmeterol combination (FSC) therapy approved August 2000; budesonide/formoterol fumarate dihydrate combination (BFC) approved July 2006 (launched June 2007); and mometasone/formoterol fumarate dihydrate (MFC) approved June 2010.[11-13] The current study includes all 3 agents in the total but focuses on BFC and FSC, given the very small number of MFC study patients due to low market presence (n = 126).

In clinical asthma studies, ICS/LABA combination treatments have proved efficacious and are associated with improved outcomes among patients with asthma.[14,15] Evidence from retrospective studies utilizing large commercial insurance claims databases have suggested, however, that combination therapies were being prescribed inappropriately with respect to both the EPR-3 and Canadian Asthma Guidelines requirements.[16,17] One retrospective cohort study by Ye and colleagues utilizing medical and pharmacy data from a large commercially insured US population between January 1, 2006, and December 31, 2007, demonstrated that 38% of 24,231 patients in the study sample initiated BFC or FSC therapy according to EPR-3 guideline recommendations. The study found, however, that the proportion of patients considered appropriately initiated on ICS/LABA combination therapy was significantly greater for BFC patients (n = 993) than for those receiving FSC therapy (n = 23,238; 58.4% vs 36.7%, respectively; $P < .0001$).[18]

Blanchette and colleagues utilized medical and pharmacy claims data for US patients (PharMetrics Patient-Centric Database) between July 1, 2006, and June 30, 2008, in a retrospective cohort study identifying patients aged 12 to 64 years who appropriately initiated FSC or BFC therapies. Overall, only 39% of study subjects (n = 16,205) initiated therapy in accordance with guideline recommendations.[19] Data presented by Ye and Blanchette also showed that the likelihood of BFC being appropriately prescribed for patients (n = 1417) was, at 55.6%, significantly higher than it was for FSC patients (n = 14,788), at 37.7% ($P < .001$).[18,19]

The objective of this study was to investigate the extent to which initiation of the ICS/LABA combination therapies—BFC versus FSC—were associated with the guideline recommendations, using the most recently available claims data from a large US commercial health insurance plan over a 3-year period.

PRACTICAL IMPLICATIONS

- In the current study, more than 50% of patients met the criteria corresponding to the Expert Panel Report-3 guidelines for appropriate initiation of ICS/LABA combination therapy.
- A significantly higher proportion of patients initiated budesonide/formoterol combination (BFC) treatment appropriately compared with fluticasone propionate/salmeterol combination (FSC)-treated patients, with higher odds of appropriate initiation for BFC-treated patients versus FSC-treated patients.
- There was, however, an apparent decrease over time in the appropriate initiation rate for BFC, while the rate was fairly consistent for FSC.

METHODS

Data Source and Study Design

This retrospective observational cohort study queried the HealthCore Integrated Research Database (HIRD) to identify patients with asthma who were initiated on ICS/LABA therapy between June 1, 2007, and December 31, 2010. HIRD contains clinically rich and geographically diverse longitudinal claims data for 45 million researchable lives covered by health insurance plans in US Northeast, Midwest, Southern and Western regions. Data acquisition and handling in this outcomes study complied with all state and federal privacy regulations including the Health Insurance Portability and Accountability Act.

Study Population

Patients initiating ICS/LABA combination therapies anytime between June 1, 2007, and December 31, 2010 with no prescription fill for an ICS/LABA combination at least once in the prior year or more were considered ICS/LABA combination–naïve and were eligible for study inclusion. The start of the index period (June 1, 2007) was chosen to coincide with the date that BFC became available in the United States. Patients were assigned to BFC and FSC cohorts based on their first prescription fill. The first prescription date for BFC or FSC was the index date. *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes were used to identify patients based on medical claims; generic product identifier (GPI) codes were employed for pharmacy claims.

Patients aged 12 to 64 years on the index date were considered to have asthma if they had at least 1 medical claim with an *ICD-9* code for asthma (493.0x, 493.1x, or 493.9x) in any position (primary or secondary) and any setting (inpatient, outpatient, ED, or physician office) within 12 months of the index date. Patients were also required to have at least 12 months of continuous health plan enrollment prior to the index date.

Patients with ICS/LABA combination therapy prescriptions within 12 months of the index date were excluded.

Also excluded were patients initiating 1 or more types of ICS/LABA combination therapies on the index date because assignment to a single cohort was not possible. Patients with any claims for chronic obstructive pulmonary disease, cystic fibrosis, lung cancer, or tuberculosis during the entire study period were excluded, as were those with diagnoses for exercise-induced asthma with no other asthma diagnosis.

Patients who filled prescriptions for ICSs or leukotriene receptor antagonist (LTRA) asthma controller medications within 12 months of ICS/LABA combination treatment initiation, or who were identified as high risk for asthma exacerbation (defined as having an asthma-related ED visit or asthma-related hospital admission or 2 or more oral systemic corticosteroids [OSC] prescription fills with days of supply of ≤21 days, or dispensed ≥6 short-acting β_2-adrenergic agonist [SABA] canisters), were considered appropriately initiated on ICS/LABA combination treatment.

Statistical Analysis

Statistical analyses were conducted for the total study population and each BFC and FSC treatment cohort separately. Univariate analyses were conducted for the 12-month pre-index period on demographic and clinical characteristics as well as previous medication use. Means, medians, standard deviations, relative frequencies, and proportions were calculated for the population as a whole (including all 3 BFC, FSC, and MFC treatment groups) and by BFC and FSC cohorts. Demographic and baseline clinical characteristics were summarized for BFC and FSC cohorts using descriptive statistics only. Subgroup comparisons with statistical testing and *P* values were calculated for the BFC and FSC cohorts for the following outcomes during the 12-month pre-index period: prior asthma controller medication use (ICS or LTRA); high-risk status (the occurrence of asthma-related hospitalizations); ED visits, hospitalizations, or both; 2 or more prescription claims for OCS with days of supply of ≤21 days or ≥6 SABA canisters. Logistic regression was used for each outcome to assess differences between the BFC and FSC cohorts. The FSC cohort was considered as the reference group for both the unadjusted and adjusted statistical models. A stepwise selection algorithm was utilized to determine covariates (demographic and baseline characteristics) to include in the final logistic regression model of each outcome. ORs, 95% CIs, and *P* values were reported for all covariates included in the model. As the current study had a longer follow-up time, which overlapped the time periods covered in the previous studies,[18,19] a post-hoc analysis was performed to gain an understanding of BFC- and FSC-appropriate initiation over time within each calendar year of the study period. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). A statistical significance level of 0.05 was utilized.

RESULTS

Patient Disposition

Among 27,185,050 health plan enrollees, 1,538,077 patients had at least 1 asthma diagnosis code between June 1, 2007, and December 31, 2010, and 578,751 patients had at least 1 eligible ICS/LABA combination therapy prescription fill during the same period. Overall, 50,541 BFC, FSC, and MFC patients satisfied all study inclusion/exclusion criteria (**Figure**).

Baseline Demographics and Clinical Characteristics

Of patients included in the study, 11,718 were in the BFC cohort and 38,697 in the FSC cohort. **Table 1** summarizes the demographics and baseline characteristics for the BFC and FSC cohorts. Differences observed between the cohorts included mean age, where FSC patients (38 years) were slightly younger than BFC patients (40 years). More BFC patients had preferred provider organization (PPO) insurance coverage compared with FSC patients (73.6% vs 70.8%). Patient distribution by index year differed between the treatment cohorts, with 8.2% of BFC patients versus 21.3% of FSC patients initiating therapy during 2007. Allergic rhinitis was the most commonly observed comorbidity in each cohort, with a greater proportion of BFC patients diagnosed with allergic rhinitis (41.4% vs 31.6%) and sinusitis (28.9% vs 25.1%). The distribution of prescribing physician specialty also differed between cohorts, driven mostly by a greater proportion of allergists/immunologists and pulmonologists prescribing BFC (30.5%) versus FSC (17.5%).

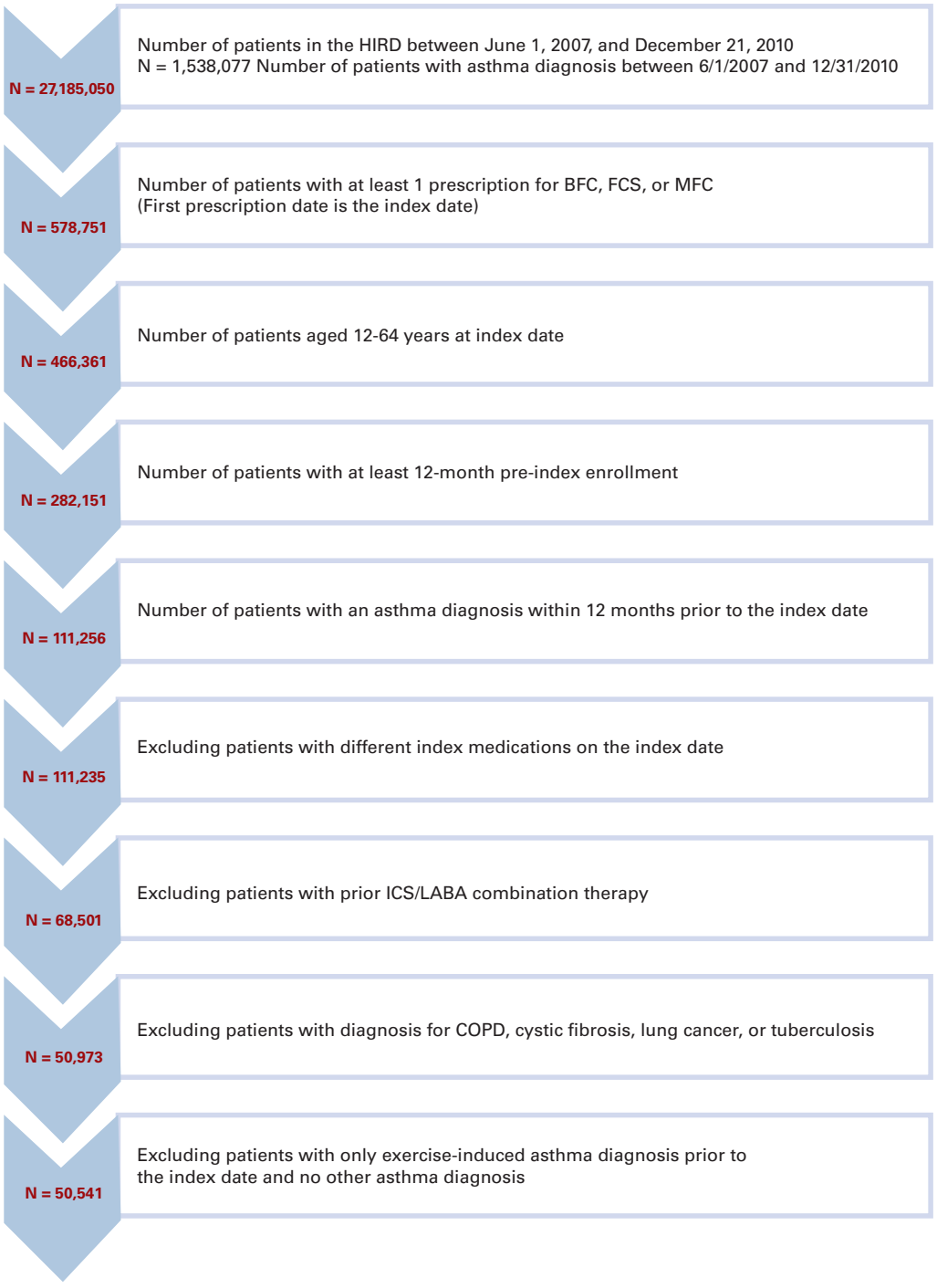
Concomitant Asthma Medication Usage

Concomitant asthma medication use was defined as at least 1 fill of the medication of interest during the 12-month pre-index period, as shown in **Table 2**. Previous asthma medication use was consistently higher in the BFC group across all classes (ICS, LTRA, SABA, and OCS) and for individual medications in each class. The largest difference in prior asthma medication use was for ICS medication use, with 24.9% of BFC patients versus 14.8% of FSC patients taking those medications.

Appropriate Use of Combination Therapies

In both BFC and FSC cohorts, approximately 32% of patients met asthma exacerbation high-risk criteria within the

Figure. Overall Study Design and Flow Chart



BFC indicates budesonide/formoterol combination; COPD, chronic obstructive pulmonary disorder; FSC, fluticasone propionate/salmeterol combination; HIRD, HealthCore Integrated Research Database; ICS/LABA, inhaled corticosteroid/long-acting β_2-adrenergic agonist; MFC, mometasone/formoterol fumarate dihydrate combination.

1 year prior to initiating combination therapies (**Table 3**). Prior controller therapy (ICS and/or LTRA) was prescribed to 42% of BFC and 31% of FSC patients. Compared with FSC patients (52%), a higher percentage of BFC patients (57%) appropriately initiated ICS/LABA therapy.

After controlling for selected confounders, as shown in the footnotes to Table 3, the odds that the BFC cohort of patients with asthma appropriately initiated ICS/LABA combination therapy was 1.21 times higher compared with those who initiated FSC (adjusted OR 1.21; $P<.0001$).

Table 1. Baseline Demographic and Clinical Characteristics by Treatment Cohort

	Total Sample[a]		FSC (Launched 2000)		BFC (Launched 2007)	
	N/Mean	%/Std	N/Mean	%/Std	N/Mean	%/Std
Number of patients (N)	50,541	–	38,697	–	11,718	–
Male	18,393	36.4	14,005	36.2	4336	37.0
Age (mean ± SD)	38.7	14.9	38.4	15.0	39.5	14.7
Geographic region at index date, N (%)						
Northeast	10,300	20.4	7996	20.7	2294	19.6
Midwest	12,773	25.3	9553	24.7	3179	27.1
South	13,588	26.9	10,306	26.6	3253	27.8
West	13,880	27.5	10,842	28.0	2992	25.5
Index year[b] N (%)						
2007	9201	18.2	8241	21.3	960	8.2
2008	16,190	32.0	12,761	33.0	3429	29.3
2009	14,107	27.9	10,144	26.2	3963	33.8
2010	11,043	21.8	7551	19.5	3366	28.7
Health plan type at index date, N (%)						
HMO	10,268	20.3	8090	20.9	2161	18.4
PPO	36,097	71.4	27,379	70.8	8619	73.6
POS	2468	4.9	1960	5.1	503	4.3
All other[c]	1708	3.4	1268	3.3	435	3.7
Pre-index period comorbidities, N (%)						
Insomnia	1711	3.4	1321	3.4	383	3.3
Allergic rhinitis	17,134	33.9	12,215	31.6	4845	41.4
Sinusitis	13,143	26.0	9716	25.1	3386	28.9
GERD	4989	9.9	3646	9.4	1319	11.3
Anxiety	3726	7.4	2841	7.3	876	7.5
Depression	5194	10.3	4070	10.5	1113	9.5
Prescribing physician specialty, N (%)						
Allergist/immunologist	7062	14.0	4515	11.7	2496	21.3
Pulmonologist	3354	6.6	2267	5.9	1080	9.2
Family/general practice	18,364	36.3	14,557	37.6	3767	32.2
Internal medicine	10,972	21.7	8757	22.6	2199	18.8
Other specialty[d]	10,674	21.1	8499	22.0	2163	18.5
Unknown	115	0.2	102	0.3	13	0.1
DCI score (mean ± SD)	0.3	0.8	0.3	0.8	0.3	0.8

BFC indicates budesonide/formoterol combination; DCI, Deyo-Charlson Comorbidity Index; FSC, fluticasone/salmeterol combination; GERD, Gastroesophageal reflux disease; HMO, health maintenance organization; PPO, preferred provider organization; POS, point of service.
[a]Total sample includes BFC, FSC, and MFC (N = 126) patients.
[b]Index year 2007 only includes June through December, but all other years include the full 12 months.
[c]Includes fee for service, other commercial and unknown.
[d]Other specialty includes anesthesiology/pain management, cardiology, dermatology, emergency medicine, endocrinology/metabolism, gastroenterology, geriatrics, hematology, infectious disease, nephrology, neurology, nuclear medicine, ob/gyn, oncology, ophthalmology, otolaryngology, pediatrics, physical medicine/rehab, podiatry, psychiatry, radiology, rheumatology, surgery, urology.

An asthma-related hospitalization during the 12-month pre-index period was considered a proxy of high risk for asthma exacerbations. Asthma-related hospitalizations were determined from the occurrences of any asthma-related claims during an event. This entailed using any occurrence of asthma diagnosis (primary or secondary positions) as a proxy for identifying asthma-related hospitalizations, which could lead to overestimation. To address this, a post hoc sensitivity analysis was performed to explore if study outcomes were sensitive to the definition

Table 2. Concomitant Medication Use by Treatment Cohort During the 12-Month Pre-Index Period

	Total Sample[a]		FSC		BFC	
	N	%	N	%	N	%
Number of patients (N)	50,541	–	38,697	–	11,718	–
Any inhaled corticosteroids	8680	17.2	5709	14.8	2919	24.9
Any leukotriene receptor antagonist	11,474	22.7	8288	21.4	3135	26.8
Any short-acting beta-2 adrenergic agonist	30,797	60.9	23,195	59.9	7509	64.1
Any oral corticosteroids	20,627	40.8	15,399	39.8	5164	44.1

BFC indicates budesonide/formoterol combination; FSC, fluticasone/salmeterol combination.
[a]Total sample includes BFC, FSC, and MFC (N = 126) patients.

of asthma-related inpatient visits by using occurrences of asthma diagnoses in the primary position only. The results showed that the proportion of patients with asthma-related hospitalizations decreased by more than 50% for each cohort (6.3% to 2.8% for FSC, 4.9% to 2.3% for BFC). The overall effect on the proportion of patients who appropriately initiated ICS/LABA combination therapy, however, decreased only slightly for both cohorts, and the direction of the relationships remained unchanged (51.6% to 49.7% for FSC, 57.3% to 56.1% for BFC). The new definition had a slightly higher impact on FSC than BFC, as reflected in the model that showed the crude OR for appropriate initiation of BFC to FSC, increasing from 1.26 to 1.30 and the adjusted OR changed from 1.21 to 1.24.

The evaluation of appropriate initiation by calendar year showed a decline over the entire study period in the percentage of patients considered appropriately initiated on BFC, but showed fairly consistent results over the study period for FSC patients (**Table 4**). These results were based on crude percentages, not adjusted for covariates, and need to be interpreted within the context of these limitations.

DISCUSSION

The current study evaluated the appropriateness of ICS/LABA treatment initiation among commercially insured patients with asthma in accordance to EPR-3 guideline recommendations.

Over the 3.5-year study period, greater than 50% of patients met the appropriate initiation criteria outlined in this study. Compared with FSC patients (52%), BFC patients (57%) were significantly more likely to initiate ICS/LABA therapy appropriately (adjusted OR, 1.21; $P<.0001$).

A prior study, also utilizing a large retrospective US insurance claims database, demonstrated a significant difference in the percentage of patients appropriately initiating BFC and FSC therapies during the study period of January 2007 to December 2007 (58.4% vs 36.7%, respectively; $P<.0001$).[18] In another analysis of US insurance claims data, Blanchette and colleagues reported 39.2% of patients met at least 1 criterion for appropriate initiation of ICS/LABA combination therapy, with a significantly larger percentage of patients in the BFC group (55.6%) initiating treatment appropriately versus 37.7% in the FSC group ($P<.001$) during the study period of July 2007 to June 2008.[19]

This study provides an updated perspective on the appropriate initiation of ICS/LABA by utilizing the extensive HIRD claims database for 3.5 years (June 2007-December 2010) after BFC became available in the United States. The findings of the current study were consistent with those of Ye and Blanchette, all of which showed higher appropriate initiation rates for BFC patients versus FSC patients over the time periods investigated in the respective studies.[18,19] The greater difference observed between the treatment cohorts in the earlier published literature may be due to the higher appropriate initiation of therapy coinciding with the time of BFC launch. Additional post-hoc analysis was performed to investigate appropriate initiation rates for BFC and FSC within each calendar year of the study period (Table 4). This evaluation showed a decline over the entire study period in the percentage of patients considered appropriately initiated on BFC, but the results over the study period were fairly consistent for FSC patients. These results were based on crude percentages, not adjusted for covariates, and need to be interpreted within the context of these limitations of the study period, which could have been influenced by physician specialty. The greater difference observed between the 2 cohorts may also be due to the level of physician education during marketing of the drug or safety concerns around LABA use which may affect the prescribing behavior.

In our study population, BFC patients were more likely than FSC patients to have allergic rhinitis, sinusitis, and higher previous asthma controller medication use across all medication classes and for individual medications in those classes. The difference was greatest for prior ICS use, which could be the driver for the differences in appropriate initiation of BFC and FSC therapies.

Table 3. High Risk/Prior Controller Use Status During 12-Month Pre-Index Period by Treatment Cohort

	Total Sample[a]		FSC		BFC					
	N	%	N	%	N	%				
All patients	50,541	–	38,697	–	11,718	–				
Prior controller use during 12-month pre-index period							Adjusted OR[2]	95% Lower	95% Upper	Adjusted *P*
Use of ICS or LTRA	17,010	33.7	12,075	31.2	4858	41.5	1.43	1.37	1.49	<.0001
ICS use	8680	17.2	5709	14.8	2919	24.9	1.77	1.68	1.86	<.0001
LTRA use	11,474	22.7	8288	21.4	3135	26.8	1.23	1.17	1.29	<.0001
High risk criteria during 12-month pre-index period	16,162	32.0	12,400	32.0	3715	31.7	1.01	0.97	1.06	0.6348
An asthma-related ED visit or hospital admission	8406	16.6	6758	17.5	1630	13.9	0.84	0.79	0.90	<.0001
ED visits	5835	11.5	4677	12.1	1143	9.8	0.88	0.82	0.94	0.0003
Hospitalizations	3025	6.0	2448	6.3	574	4.9	0.81	0.74	0.89	<.0001
≥2 prescription claims of OCSs with a day's supply of ≤21 days	7714	15.3	5649	14.6	2036	17.4	1.15	1.08	1.22	<.0001
≥6 SABA canisters	3703	7.3	2721	7.0	969	8.3	1.28	1.19	1.39	<.0001
Prior controller use OR High risk criteria during 12-month pre-index period	26,774	53.0	19,966	51.6	6714	57.3	1.21	1.16	1.27	<.0001

BFC indicates budesonide/formoterol combination; ED, emergency department; FSC, fluticasone propionate/salmeterol combination; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; OCS, oral systemic corticosteroid; OR, odds ratio; SABA, short-acting β_2-adrenergic agonist.

[a]Total sample includes BFC, FSC, and MFC (N = 126) patients.

Covariates included in the logistic regression model for each outcome:

Use of ICS or LTRA: gender, age, geographic region, physician specialty, number of non-asthma concomitant medications, Deyo-Charlson Comorbidity Index (DCCI), and pre-index comorbidity (allergic rhinitis, sinusitis, anxiety, and depression)

Use of ICS: age, geographic region, health plan type, physician specialty, number of non-asthma concomitant medications, DCCI, and pre-index comorbidity (allergic rhinitis, anxiety, and depression)

Use of LTRA: gender, age, geographic region, physician specialty, number of non-asthma concomitant medications, DCCI, and pre-index comorbidity (allergic rhinitis, sinusitis, anxiety, and depression)

High-risk criteria: age, geographic region, physician specialty, health plan type, number of non-asthma concomitant medications, DCCI, and pre-index comorbidity (allergic rhinitis, sinusitis, anxiety, and insomnia)

An asthma-related ED visit or hospital admission: gender, age, geographic region, health plan type, physician specialty, number of non-asthma concomitant medications, DCCI, and pre-index comorbidity (allergic rhinitis, insomnia, sinusitis, anxiety, gastroesophageal reflux disease [GERD], and depression)

ED visits: gender, age, geographic region, health plan type, physician specialty, number of non-asthma concomitant medications, DCCI, and pre-index comorbidity (allergic rhinitis, insomnia, sinusitis, GERD, and anxiety)

Hospitalizations: gender, age, geographic region, health plan type, physician specialty, number of non-asthma concomitant medications, DCCI, and pre-index comorbidity (allergic rhinitis, sinusitis, GERD, anxiety, and depression)

≥2 prescription claims of OCS each with a supply of ≤21 days: gender, geographic region, health plan type, physician specialty, number of non-asthma concomitant medications, DCCI, and pre-index comorbidity (allergic rhinitis, insomnia, sinusitis, GERD, and depression)

≥6 short-acting β_2-adrenergic agonist (SABA) canisters: gender, age, health plan type, physician specialty, DCCI, and pre-index comorbidity (allergic rhinitis, insomnia, sinusitis, and GERD)

Prior controller use OR high-risk criteria: age, geographic region, health plan type, physician specialty, number of non-asthma concomitant medications, DCCI, and pre-index comorbidities (allergic rhinitis, sinusitis, and insomnia)

The appropriate initiation of ICS/LABA was evaluated based on selected criteria in the EPR-3 guidelines, per claims data availability such as prior asthma controller medication use. For this study, 1 or more prescription fills for ICS or LTRA during the 12-month pre-index period was considered an indicator of persistent asthma. Patients with 1 or more prescription fill for ICS or LTRA during the 12-month pre-index period were considered appropriately initiated on ICS/LABA combination regardless of whether they met any other high-risk criteria during that time period. Overall, 21% of study patients (10,612 of 50,541; 19.6% FSC, 25.6% BFC) received ICS or LTRA monotherapy before initiating ICS/LABA combination treatment, but had no other study-defined high-risk criteria. In addition, 17.2% of the patients in the total sample—14.8% in the FSC cohort and 24.9% in the BFC cohort—received any ICS during the 12-month pre-index period. Substantially larger proportions of patients received OCS during the pre-index period: 40.8% in the total sample, 39.8% in the FSC cohort, and 44.1% in the BFC cohort (Table 2). Nonetheless, it is not known whether or how many of those patients were well controlled on ICS or LTRA alone before initiating ICS/LABA combination, as disease severity could not be assessed from the claims data due to lack of availability of information on asthma symptoms and lung function. Thus, overall, 38% (7566 of 19,966) of FSC and 45% (2999 of 6714) of BFC patients identified in this study as appropriately initiating ICS/LABA therapy did not have simultaneous high-risk criteria, and it is not known whether they were controlled on their ICS or LTRA monotherapy prior to stepping up to ICS/LABA combination.

Table 4. Summary of Patients Appropriately Initiating ICS/LABA Combination Therapy by Treatment Cohort and by Index Date Year During the Study Period

	Total Sample			FSC			BFC		
	N[a]	n[b]	%	N[a]	n[b]	%	N[a]	n[b]	%
2007	9201	5069	55.1	8241	4408	53.5	960	661	68.9
2008	16,190	8648	53.4	12,761	6583	51.6	3429	2065	60.2
2009	14,107	7357	52.2	10,144	5166	50.9	3963	2191	55.3
2010	11,043	5700	51.6	7551	3809	50.4	3366	1797	53.4

BFC indicates budesonide/formoterol combination; FSC, fluticasone/salmeterol combination; ICS, inhaled corticosteroid; LABA, long-acting β_2-adrenergic agonist.
N[a] = total number of patients initiating ICS/LABA combination therapy during a given calendar year.
n[b] = number of patients determined to have appropriately initiated ICS/LABA during a given calendar year.
2007 includes only 7 calendar months; 2008, 2009, 2010 each include 12 calendar months.

In this study, a higher percentage of patients had BFC prescribed by a specialist physician (allergists/immunologists and pulmonologists) compared with the FSC patients. The specialty of the prescribing physician should be considered when interpreting differences in appropriate initiation between BFC and FSC, as this may play a role in the appropriateness of the initial therapy selected; in general, specialists are more likely to treat more severely affected patients who are in need of ICS/LABA treatment. It is likely that specialists will be more aware of and adhere to treatment guidelines. Physician specialty was controlled for in the statistical models as a covariate in this study.

Limitations

The results should be interpreted within the context of limitations inherent to administrative claims data, including the absence of clinical indicators of disease severity or progression, which may have underestimated the appropriateness of ICS/LABA combination therapy initiation. The absence of data on lung function and asthma symptoms does not allow a full assessment of disease severity. It is therefore likely that appropriate initiation of therapy was underestimated, as only proxies for disease severity were used from the database. Further, limiting the study to ICS/LABA treatment-naïve patients and the exclusion of patients with compromised and/or reduced lung function is likely to have contributed to an underestimation of appropriateness of treatment initiation.

Given that the same criteria were used for both patient cohorts, this misclassification is likely to be nondifferential and should not impact the comparisons between treatment cohorts. Asthma-related utilization in this study was based on the occurrence of asthma claim codes, which could lead to erroneous estimates of the actual utilization levels for any patient or population. Study medications were identified based on pharmacy claims for each medication, which indicate medication dispensing but remain uncertain on whether treatment was initiated, and on what date. This study was conducted among commercially insured subjects aged between 12 and 64 years in a managed care setting. Thus, the ability to generalize these results may be limited to similar patient groups. Patients older than 64 years were not included in this analysis because data in the HIRD were collected from a commercially insured population, generally younger than 65 years. Nonetheless, because the majority of patients with asthma are younger than 65 years, the exclusion of patients who are 65 years and older resulted in the loss of only a minimal number of true asthmatics, while likely excluding a large number of possible COPD patients.

CONCLUSIONS

Over the 3.5-year study period, greater than 50% of patients were appropriately initiated on ICS/LABA combination therapy criteria as defined in this study to correspond with EPR-3 guidelines.

The percentage of patients considered appropriately initiated was significantly higher among BFC-treated patients than among FSC-treated patients. After controlling for selected potential confounders/baseline differences, the odds of patients with asthma initiating BFC appropriately were 1.21 times greater compared with patients initiating FSC. However, there was a decrease over the study period in the appropriate initiation rate for BFC, while the rate was fairly consistent for FSC. While these results were consistent with earlier reported patterns, further evidence, including a more accurate assessment of disease severity using multiple data sources with additional clinical information, could provide a more reliable estimation of appropriate treatment initiation.

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