

Assessment of Adherence and Asthma Medication Ratio for a Once-Daily and Twice-Daily Inhaled Corticosteroid/Long-Acting β -Agonist for Asthma



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What is already known about this topic? The efficacy and safety of once-daily fluticasone furoate/vilanterol (FF/VI) and twice-daily budesonide/formoterol (BUD/F) have been shown in prospective trials with strict patient monitoring.

What does this article add to our knowledge? The evaluation of adherence, persistence, and asthma-related emergency department/inpatient risk among users of once-daily FF/VI and twice-daily BUD/F in a real-world setting.

How does this study impact current management guidelines? This study suggests that patients initiating treatment with once-daily FF/VI have higher adherence and are at lower risk for future asthma-related emergency department/inpatient events than patients initiating treatment with twice-daily BUD/F after controlling for baseline differences.

BACKGROUND: Although efficacy and safety of fluticasone furoate/vilanterol (FF/VI) and budesonide/formoterol (BUD/F) have been demonstrated in clinical studies, real-world comparisons of utilization have not been performed.

OBJECTIVE: To compare similar patients with asthma initiating FF/VI or BUD/F on measures of adherence, persistence, and the asthma medication ratio (AMR).

METHODS: This was a retrospective cohort study of commercial and Medicare Advantage with Part D enrollees initiating FF/VI or BUD/F for asthma. Adult patients (≥ 18 years) with at least 15-month (12-month preindex and 3-month postindex) continuous enrollment and 1 or more asthma diagnosis code were eligible for the study. Patients with a history of fixed-dose inhaled corticosteroid/long-acting β -agonist and other respiratory disorders (chronic obstructive pulmonary disease, cystic fibrosis, acute respiratory failure) in the baseline period were excluded. Propensity-score matching was used to balance cohorts on baseline characteristics. Logistic regression

and Cox-proportional hazard models were used to assess differences.

RESULTS: A total of 9951 patients met all criteria. After propensity-score matching, 1725 patients were matched in each cohort. Subjects who initiated FF/VI had a significantly higher mean proportion of days covered ($P < .001$), had 86% greater odds of having a proportion of days covered value of greater than or equal to 0.80 (adjusted odds ratio, 1.86; 95% CI, 1.51-2.30), 26% lower risk of discontinuation (adjusted hazard ratio, 0.74; 95% CI, 0.69-0.79), and 36% greater odds of an AMR of greater than or equal to 0.50 (adjusted odds ratio, 1.36; 95% CI, 1.23-1.50) compared with BUD/F.

CONCLUSIONS: Adherence and treatment persistence were low in both cohorts; however, patients initiating once-daily FF/VI were more likely to be adherent, have an AMR of greater than or equal to 0.5, and were less likely to discontinue therapy compared with patients initiating twice-daily BUD/F (GlaxoSmithKline Study HO1617302/206482). © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1488-96)

Key words: Asthma; Adherence; Discontinuation; Asthma medication ratio; Fluticasone furoate; Vilanterol; Budesonide; Formoterol; ICS/LABA

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hypersensitivity and episodes of bronchospasm in response to various stimuli.¹ According to 2015 data, it is estimated that more than 18 million adults and more than 6 million children in the United States suffer from asthma.^{2,3} Asthma is a major cause of morbidity in the United States and imposes a substantial burden on patients and payers,

Abbreviations used

AMR- asthma medication ratio
BUD/F- budesonide/formoterol
ED- emergency department
FF/VI- fluticasone furoate/vilanterol
HEDIS- Healthcare Effectiveness Data and Information Set
ICS- inhaled corticosteroid
IP- inpatient
LABA- long-acting β -agonist
MAPD- Medicare Advantage with Part D
PDC- proportion of days covered
PSM- propensity-score matching
SAMA- short-acting muscarinic antagonist
Std Diff- standardized differences

with total direct costs of \$18 billion (2008 dollars) estimated in patients 18 years or older from Medical Expenditure Survey Data.⁴

Therapy includes the use of short-acting bronchodilator medication to treat acute episodes and controller medications to reduce airway inflammation, control symptoms, and lower the risk of future exacerbations.¹ Exacerbations can be life-threatening and often require costly medical services, including emergency department (ED) visits and hospitalizations.⁵ Optimizing asthma treatment provides opportunities for significant cost savings as well as improvements in patients' functioning and quality of life.

Current treatment guidelines recommend a stepwise treatment approach to achieve and maintain asthma control.¹ Inhaled corticosteroids (ICSs) are the cornerstone of asthma treatment recommendations, as the preferred first-line strategy for all but the most mild cases of asthma, which are treated with rescue medications only.^{1,6} Treatment intensification or escalation for inadequately controlled asthma involves increasing the ICS dose and/or add-on therapy with long-acting β_2 -agonists (LABAs) or leukotriene modifiers.

Despite the recent development of a range of therapies, as many as half the patients treated with intensive therapy have uncontrolled asthma.⁷⁻⁹ Uncontrolled asthma is due to suboptimal therapy and/or treatment nonadherence and is associated with higher total medical cost and increased risk of exacerbation.^{10,11}

It has been shown that the addition of a LABA to an ICS-based regimen reduces the use of rescue medications, such as albuterol, and reduces the risk of asthma exacerbations.^{11,12} Based on the Healthcare Effectiveness Data and Information Set (HEDIS), the National Committee for Quality Assurance created a measure to assess the relationships between asthma treatment and risk of future asthma-related ED/inpatient (IP) events.¹³ The components of the HEDIS score include adherence to controller medication, and the asthma medication ratio (AMR)—the ratio of controller medication use to total asthma medication (ie, controller plus short-acting β -agonist) use.^{13,14} Patients who achieve an AMR of greater than or equal to 0.5 have been observed to have a lower risk of future asthma-related ED/IP visits, as well as better patient-reported control and quality-of-life outcomes.¹⁴⁻¹⁶

Budesonide/formoterol (BUD/F) is a twice-daily inhaled combination ICS/LABA in a metered dose inhaler, whereas

fluticasone furoate and vilanterol (FF/VI) is a once-daily inhaled ICS/LABA combination in dry powder Ellipta device.^{17,18}

Although the efficacy and safety of BUD/F and FF/VI have been demonstrated, payers and providers in the United States are interested in data that assess the real-world treatment patterns for each combination therapy. The purpose of this retrospective study was to assess adherence, as measured by proportion of days covered (PDC), persistence, and AMR, in patients initiating treatment with either BUD/F or FF/VI.

METHODS

Study design and setting

We conducted a retrospective observational cohort study of commercial and Medicare Advantage with Part D (MAPD) plan enrollees using the Optum Research Database, a proprietary research database containing enrollment, medical, and pharmacy claims data (GSK Study HO1617302 and 206482). For 2014, data relating to approximately 12.3 million individuals with both medical and pharmacy benefit coverage were available from commercial health plans as well as 5 million enrollees in MAPD plans.

Study population

All patients initiating FF/VI 100 μ g/25 μ g or BUD/F 160 μ g/4.5 μ g between January 01, 2014, and June 30, 2016, were identified. Index was defined as the date of the first prescription fill for either treatment. To be included in the study, patients had to meet the following criteria: 18 years or older, diagnosis of asthma, and continuous enrollment for at least 12 months preindex and at least 3 months postindex date, up to a maximum of 12 months. Patients were excluded from the study if they had a history of fixed-dose ICS/LABA use, or diagnosis of cystic fibrosis, acute respiratory failure on medical claims at any time during the study period, or chronic obstructive pulmonary disease on a medical claim in the 12-month preindex period. Patients meeting all study eligibility criteria were assigned to a cohort on the basis of index medication: FF/VI 100 μ g/25 μ g (FF/VI cohort) or BUD/F 160 μ g/4.5 μ g (BUD/F cohort) (Figure 1). See Table E1 in this article's Online Repository at www.jaci-inpractice.org for diagnosis codes related to inclusion and exclusion criteria.

Measures and outcomes

The outcomes of interest were adherence, measured by PDC; persistence, measured by time to index treatment discontinuation; and the AMR. Each study outcome was measured during the variable follow-up period (3-12 months) after initial prescription fill. PDC is a commonly used proxy measure of medication adherence and is calculated by dividing the total number of days on which medication was available based on filled prescriptions, by the length of each subject's observation period.¹⁹ In alignment with the HEDIS measure, mean PDC and the proportion of patients who achieved PDC values of greater than or equal to 0.5 and PDC values of greater than or equal to 0.8 were assessed. PDC was calculated from the index date.

Persistence was measured as total time between the index date and the time of therapy discontinuation. Patients were determined to have discontinued therapy if there was a gap of at least 45 days (commercial pharmacy) or 115 days (mail-order) between prescription fill dates. Once subjects met discontinuation criteria they were no longer followed, so sample sizes for both groups approach 0 overtime.

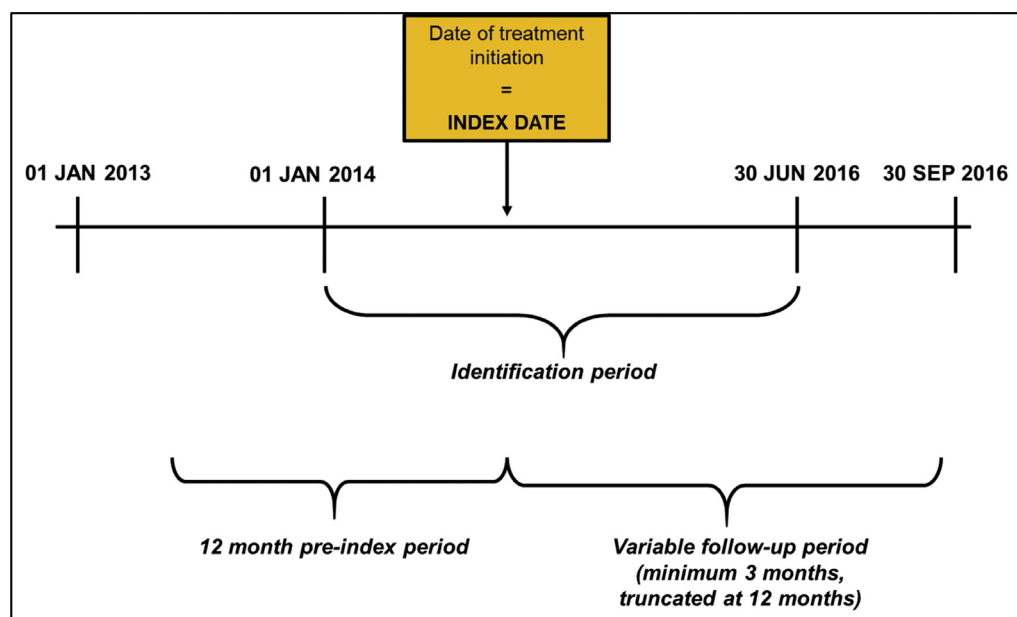


FIGURE 1. Study schematic.

The 2 cohorts were also compared on the AMR. The AMR is a validated, national quality measure and has been shown to predict future asthma-related emergency room (ED) visits and IP hospitalizations.¹⁴⁻¹⁶ AMR was calculated by dividing the number of controller medication fills (ICS/LABA, ICS, LABA, mast cell stabilizers, leukotriene modifiers, xanthines, and xanthine combinations) over the sum of controller medications and rescue medications (short-acting beta-agonist fills). An AMR may range from 0 to 1. A lower AMR would mean few controller treatments were filled relative to rescue inhalers and indicates a greater future asthma-related ED/IP event risk. Conversely, an AMR closer to 1 indicates more controller fills relative to rescue fills and would indicate a lower risk of future asthma-related ED/IP events. In calculating AMR, patients who switched to a non-index ICS/LABA had follow-up time censored at treatment switch. Mean AMR and the proportion of patients achieving AMR value of greater than or equal to 0.5 were also evaluated.

Baseline asthma-related exacerbations were assessed. Moderate asthma-related exacerbations were defined as an asthma-related ED visit, physician office or urgent care visit (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 493.0, 493.1, 493.8, or 493.9 or *International Classification of Diseases, Tenth Revision, Clinical Modification* code J45.x in any position) along with a prescription for or an administration of a systemic corticosteroid within 5 days. Severe asthma-related exacerbations were defined as hospitalizations with an asthma-related diagnosis code present on the inpatient claim. Time to first asthma-related exacerbation and annual asthma-related costs during the follow-up period were also assessed as exploratory end points.

A post hoc sensitivity analysis was conducted on subjects with a minimum of 6 months of follow-up. This subgroup was restricted to matched pairs where both patients had at least 6 months follow-up to ensure similar baseline characteristics.

Statistical analysis

In this retrospective cohort study, propensity-score matching (PSM) methods were used to address the issue of confounding

inherent in nonrandomized studies; this is done under the assumption that balancing the cohorts on observed measures will lead to balanced cohorts on unobserved measures approximating a randomized experimental design.²⁰ Patients were matched in a 1:1 ratio and were hard-matched on baseline oral corticosteroid use and insurance type. The success of the matching procedure was evaluated by comparing standardized differences (Std Diffs) in patient characteristics and were considered matched if the Std Diffs between the cohorts on a variable were less than or equal to 10%.²¹ Pre- and post-match propensity score distribution by cohort are reported in [Figures E1 and E2](#), respectively (available in this article's Online Repository at www.jaci-inpractice.org). Select asthma-related variables included in the propensity-score model are presented in [Table I](#), whereas all variables included in the PSM are reported in [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org.

All study variables, including baseline and outcome measures, were analyzed descriptively using SAS version 9.3 (SAS Institute, Inc, Cary, NC). Descriptive techniques that accounted for length of observation time were used where appropriate. Bivariate comparisons of baseline measures in the matched population used Std Diffs. To account for possible correlations due to matching, a Rao-Scott test was used to test for differences between cohorts on binary measures and Z test using robust (sandwich) standard errors was used to test for differences between cohorts on continuous measures.

Multivariable models for PDC, persistence, and AMR were also used after PSM to adjust for possible residual confounding. Logistic regression models were used to estimate treatment adherence with PDC values of greater than or equal to 50% and PDC values of greater than or equal to 80% and to estimate AMR values of greater than or equal to 0.50. To measure persistence, Cox-proportional hazards regression was used to model discontinuation. Variables included in the postmatch multivariable models, regardless of Std Diffs observed after matching, were limited to the number of moderate asthma exacerbation events, and the number of severe asthma exacerbations (inpatient events) in the baseline period. Use of

TABLE I. Baseline demographic and clinical characteristics: Pre- and post-PSM

Variable description	Prematch			Postmatch		
	FF/VI 100/25 µg (n = 2276)	BUD/F 160/4.5 µg (n = 7675)	Std Diff (%)	FF/VI 100/25 µg (n = 1725)	BUD/F 160/4.5 µg (n = 1725)	Std Diff (%)
Age (y), mean	51.3	53.5	−13.76	52.4	52.6	−1.35
Sex: male, %	36.3	35.8	1.07	35.7	37.4	−3.62
Medicare Advantage Prescription Drug,* %	19.3	33.5	−32.52	24.7	24.7	—
Baseline AMR	0.275	0.261	3.87	0.276	0.273	0.93
ICS usage, %	16.8	15.3	4.05	17.1	17.5	−0.95
LABAs, %	1.23	0.87	3.50	1.16	1.10	0.57
Long-acting muscarinic agents (LAMAs),† %	3.16	2.64	3.09	3.19	3.13	0.35
Leukotriene receptor antagonists, %	33.7	32.1	3.36	33.3	32.5	1.73
Xanthines, %	0.70	0.90	−2.74	0.70	0.81	−1.28
Asthma biologic, %	0.53	0.47	0.83	0.46	0.34	1.65
Oral corticosteroids (OCSs) (at least 1 dispensing),* %	63.4	63.4	−0.01	66.3	66.3	—
Count of SABA canisters, mean	2.96	2.89	1.54	3.08	3.03	1.03
Baseline SAMA or SAMA/SABA, %	8.88	9.81	−3.22	9.68	9.22	1.59
Count of unique medications in baseline	11.5	11.8	−5.64	11.8	11.8	0.30
Charlson score, %						
0	78.4	77.3	2.73	77.7	77.5	0.70
1-2*	6.37	7.00	−2.51	6.61	6.61	—
3-4	12.1	12.4	−1.02	12.2	12.5	−0.71
5+	3.16	3.34	−0.97	3.42	3.48	−0.33
CDS score	3600	3860	−7.57	3740	3708	0.93
Baseline asthma-related ambulatory visit count, mean	1.73	2.15	−16.04	1.72	1.78	−2.09
Baseline asthma-related ED count, mean	0.06	0.10	−9.54	0.06	0.07	−2.15
Baseline asthma-related IP stay count, mean	0.03	0.05	−8.26	0.03	0.04	−2.76
Baseline count of asthma exacerbations, mean	0.59	0.65	−6.56	0.63	0.64	−1.03
Baseline count of moderate asthma exacerbations,† mean	0.55	0.59	−4.29	0.59	0.59	−0.40
Baseline count of severe asthma exacerbations, mean	0.04	0.06	−9.11	0.04	0.05	−2.40
Patient OOP cost of index fill (log \$), mean	3.66	3.74	−5.81	3.67	3.68	−0.88
Provider specialty, %						
Primary care	47.2	55.3	−16.33	49.6	49.9	−0.70
Respiratory specialist	35.1	23.6	25.38	30.7	30.8	−0.38
Unknown	17.7	21.0	−8.45	19.8	19.3	1.32

CDS, Chronic Disease Score; OOP, out-of-pocket; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist.

*Cohorts were hard-matched on these variables.

†Not included in the PSM analysis.

mail-order pharmacy on the index prescription fill was also included in the discontinuation model.

RESULTS

Sample selection

Sample attrition is shown in Figure 2. We identified 149,903 patients with 1 or more claim for FF/VI 100 µg/25 µg or BUD/F 160 µg/4.5 µg during the identification period. Of these, 78,325 patients met continuous enrollment criteria. Patients were excluded if they had evidence of any fixed-dose ICS/LABA use in the preindex period (n = 36,795) or a diagnosis of chronic obstructive pulmonary disease (n = 22,763), cystic fibrosis (n = 12), or acute respiratory failure (n = 178), or were younger than 18 years at the index date (n = 776). After exclusions, the final population eligible for this study was 9951 patients, with 2276 in the FF/VI cohort and 7675 in the BUD/F cohort. After PSM, a total of 1725 patients initiating treatment

with FF/VI were matched to 1725 patients initiating treatment with BUD/F (Table I). Controller and rescue medications included in the AMR are displayed in Table E4 and respiratory medications accounted for in the baseline period are displayed in Table E5 (available in this article's Online Repository at www.jaci-inpractice.org). A comparison of the baseline characteristics in the unmatched sample can be seen in Table E6 of this article's Online Repository at www.jaci-inpractice.org.

Overall, asthma-related events, including exacerbations, and other patient characteristics in the preindex period were well matched (Table I), with all baseline variables after PSM having Std Diffs of less than 10%. The mean age was 52.4 ± 16.31 years and 52.6 ± 15.92 years in the FF/VI and BUD/F cohorts, respectively. Sixty-four percent of patients in the FF/VI cohort and 63% of patients in the BUD/F cohort were female; 25% were enrolled in MAPD insurance. In both cohorts, the practice setting of the prescribing provider was 50% primary care and 31% respiratory specialist. The mean baseline exacerbation rate

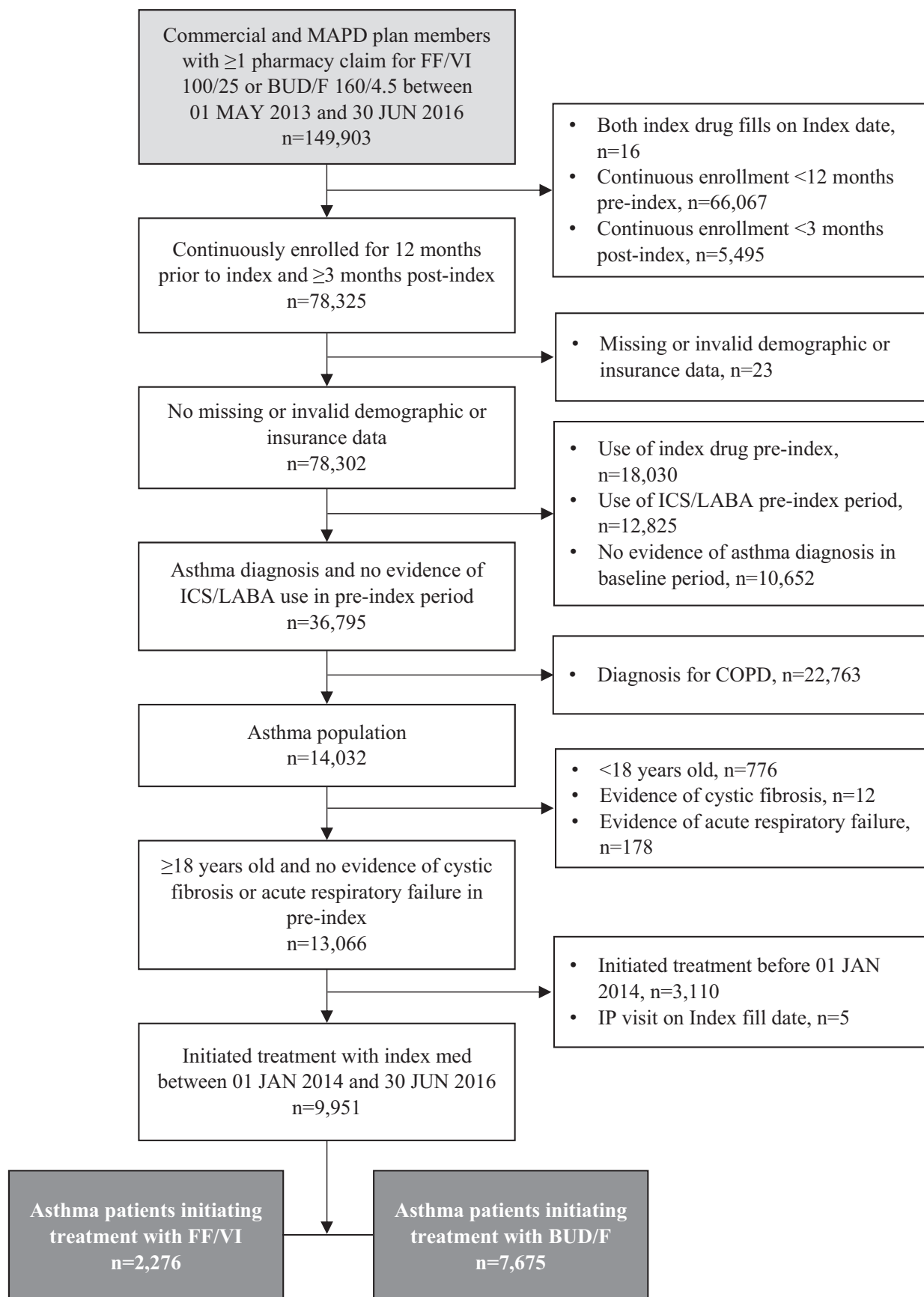
FIGURE 2. Sample attrition. *med*, Medicine.

TABLE II. Means and percent that achieved each threshold for FF/VI vs BUD/F

Endpoint	FF/VI 100/25 µg (n = 1725)	BUD/F 160/4.5 µg (n = 1725)	P value
PDC, mean ± SD	0.43 ± 0.30	0.36 ± 0.27	<.001
≥0.5, %	38.3	26.6	<.001
≥0.8, %	17.5	10.2	<.001
Treatment discontinuation (within 12 mo), %	88.4	93.2	<.001
AMR, mean ± SD	0.63 ± 0.40	0.57 ± 0.42	<.001
≥0.5, %	68.6	62.3	<.001

was 0.63 ± 0.90 for the FF/VI cohort and 0.64 ± 0.93 for the BUD/F cohort. In the postindex follow-up period, mean follow-up time was 255.7 ± 99.14 days and 255.1 ± 104.06 days in FF/VI and BUD/F cohorts, respectively. Baseline treatment with asthma biologics was rare (<1%); however, because treatment with an asthma biologic may indicate greater asthma severity, the percent of patients with preindex biologics was included in the PSM. After matching, the cohorts were well balanced, with 0.46% and 0.34% of patients in the FF/VI and BUD/F cohorts, respectively, receiving an asthma biologic. The proportion of patients receiving mail-order prescriptions was also low in both cohorts (<5%) but could potentially impact treatment persistence. Although not included in the PSM, this variable was subsequently added into discontinuation model post hoc. Table I reports both the prematch and the postmatch baseline demographic and clinical characteristics.

Outcomes

After PSM, the mean PDC over the entire follow-up period was significantly ($P < .001$) higher for FF/VI, 0.43 ± 0.30 , compared with BUD/F, 0.36 ± 0.27 (Table II). In addition, a significantly higher proportion of patients on FF/VI achieved a PDC of greater than or equal to 0.50 and greater than or equal to 0.80 (38.3% and 17.5%) compared with those initiating BUD/F (26.6% and 10.2%; all $P < .001$). After multivariable logistic regression analysis, patients initiating treatment with FF/VI had 72% greater odds (adjusted odds ratio, 1.72; 95% CI, 1.48-2.00; $P < .001$) of achieving a PDC of greater than or equal to 0.5 and 86% greater odds of achieving a PDC of greater than or equal to 0.8 (adjusted odds ratio, 1.86; 95% CI, 1.51-2.30; $P < .001$) (Table III).

The mean AMR for patients who initiated FF/VI was 0.63 ± 0.40 compared with 0.57 ± 0.42 in those initiating BUD/F ($P < .001$). Furthermore, a significantly ($P < .001$) higher proportion of patients treated with FF/VI achieved an AMR of greater than or equal to 0.5 compared with patients on BUD/F (68.6% and 62.3% for FF/VI and BUD/F, respectively; $P < .001$). Patients in the FF/VI cohort had 36% greater odds of achieving an AMR of greater than or equal to 0.5 compared with patients in the BUD/F cohort (adjusted odds ratio, 1.36; 95% CI, 1.23-1.50; $P < .001$). The mean number of albuterol canisters dispensed was similar ($P = .323$) for FF/VI, 2.21 ± 4.7 , and BUD/F, 2.44 ± 6.7 .

In a multivariable proportional hazards model assessing medication persistence (Figure 3), patients were 26% less likely to discontinue FF/VI compared with BUD/F (adjusted hazard ratio, 0.74; 95% CI, 0.69-0.79; $P < .001$). In addition, the

TABLE III. Likelihood and risk assessment for each end point FF/VI vs BUD/F

Endpoint	Adjusted OR	95% CI	P value
PDC			
≥0.5	1.72	1.48-2.00	<.001
≥0.8	1.86	1.51-2.30	<.001
AMR			
≥0.5*	1.36	1.23-1.50	<.001
Adjusted hazards ratio 95% CI P value			
Time to discontinuation (hazards ratio)	0.74	0.69-0.79	<.001

OR, Odds ratio.

Note: Multivariable analysis controlled for count of baseline asthma-related moderate exacerbations and baseline asthma-related severe exacerbations. Time to discontinuation analysis was also adjusted for use of mail-order pharmacy.

*AMR censored at ICS/LABA switch.

exploratory end points of asthma-related costs and time to first exacerbation in the follow-up period were not significantly different between the 2 groups (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Results were consistent in the sensitivity analysis. A total of 795 matched pairs with greater than or equal to 6 months of follow-up were identified. All primary and secondary outcomes were similar to the overall analysis. Complete results of the sensitivity analyses can be seen in this article's Online Repository at www.jaci-inpractice.org (Tables E7 and E8).

DISCUSSION

The introduction of FF/VI allowed for a unique opportunity to assess differences in adherence, persistence, and AMR between a once-daily ICS/LABA, FF/VI, and twice-daily BUD/F. In this study of 3450 patients with asthma using FF/VI or BUD/F and matched on demographic and clinical characteristics, differences in adherence, persistence with treatment, and AMR, which has been shown previously to be related to future asthma-related ED/IP event risk, were evaluated. The results of this study provide evidence of how adherence, persistence, and AMR differ between patients initiating treatment with a once-daily versus twice-daily ICS/LABA.

Greater adherence to once-daily inhalers compared with twice-daily inhalers in the real-world setting has previously been shown for patients on ICS monotherapy.²²⁻²⁴ Navaratnam et al²³ found that patients receiving once-daily mometasone furoate via a metered dose inhaler had PDC values of 0.24 compared with 0.15 for patients taking twice-daily fluticasone propionate via a metered dose inhaler ($P < .0001$), which translated into approximately 33 extra days of treatment per year when using a once-daily product over the course of a year.²³ In the study by Wells et al,²⁴ comparing the effect of once-daily ICS with 2 or more doses per-day schedules on adherence, found that adherence as measured by a continuous multiple-interval measure of medication availability was 61% and 41%, respectively ($P = .001$), or 73 more days of treatment on average for the once-daily therapy. The 26-day improvement in treatment days we observed in the FF/VI cohort relative to BUD/F provides further evidence to support that a once-daily treatment may lead to improved therapy adherence compared with twice-daily

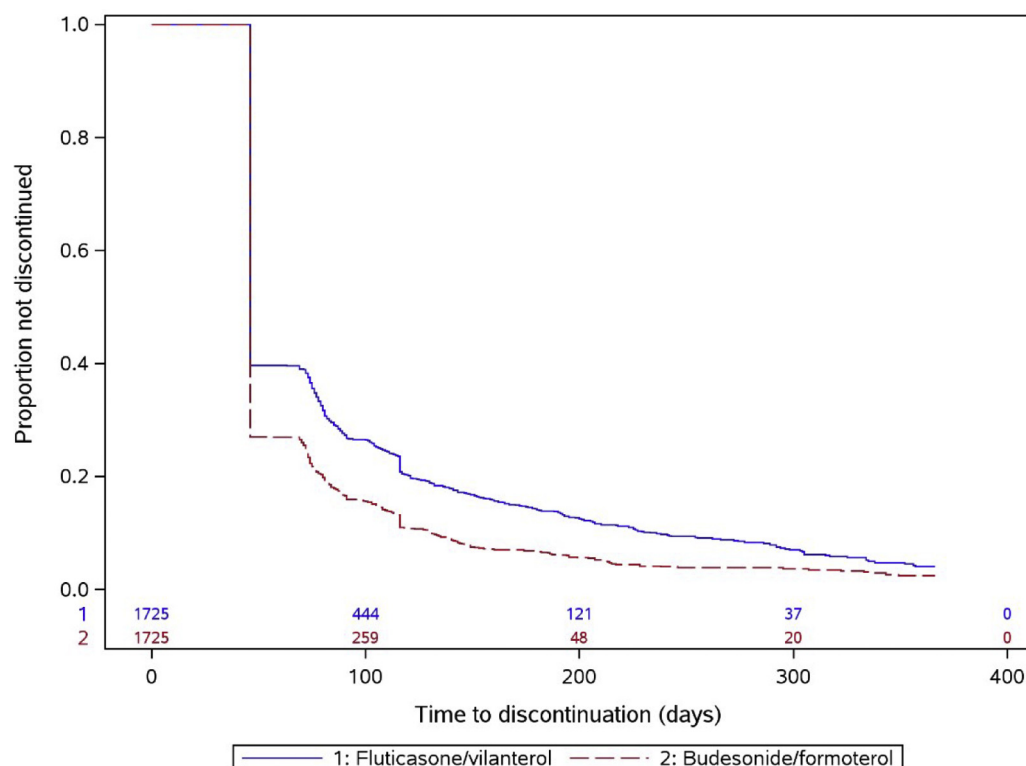


FIGURE 3. Kaplan-Meier survival estimate for time to discontinuation. Note: Discontinuation was defined as a gap of at least 45 days (commercial pharmacy) or 115 days (mail-order) between fill dates. Index prescription fills from mail-order pharmacies made up 4.17% of the FF/VI cohort compared with 2.49% of the BUD/F cohort. Cox-proportional hazards regression was adjusted for preindex count of asthma-related moderate and severe exacerbations, and mail-order pharmacy.

inhaler therapy in patients with asthma. The greater adjusted odds of surpassing the prespecified PDC threshold of at least 80% while on a once-daily controller therapy as observed in this study are supported by Wells et al²⁴ who showed that patients on once-daily treatments had more than 3 times greater adjusted odds of reaching an adherence threshold of 75% ($P = .001$) as measured by a continuous multiple-interval measure of medication availability.²⁴

The high percentage of patients in this study who had discontinued ICS/LABA within 12 months of initiation is consistent with previous literature in patients with asthma on inhalation therapy.^{25,26} Both Marceau et al²⁵ and Breekveldt-Postma et al²⁶ reported that significantly more patients were persistent with therapy at 12 months when a simpler treatment regimen was used. Even though these authors used different methods to determine discontinuation, their findings are consistent with what was observed in the current analysis.

The use of AMR as a predictor of asthma exacerbation risk is part of the current HEDIS asthma quality measure endorsed by the National Committee for Quality Assurance.¹³ The complex nature of asthma treatment makes predicting events difficult. Risk of asthma-related exacerbation increases as rescue medication use increases.^{12,15,27} In addition it has been shown that an AMR of greater than or equal to 0.5 is related to a reduction in the risk of future asthma-related ED/IP visits.¹⁴ Research has suggested that increasing the use of ICS/LABA is also associated with a greater likelihood of achieving an AMR of greater than or equal to 0.5 and reducing the need for albuterol.²⁸ In addition,

Stanford et al¹⁶ assessed AMR in this same database and estimated that patients achieving AMR values of greater than or equal to 0.5 had an observed 47% lower odds of having an asthma-related ED visit in the following year and 43% lower odds of having an asthma-related hospitalization in the following year. This is the first study to assess the difference in achieving the AMR greater than or equal to 0.5 threshold between a once-daily ICS/LABA and a twice-daily ICS/LABA. In this analysis, patients starting FF/VI, a once-daily therapy, were significantly more likely to achieve an AMR of greater than or equal to 0.5 compared with those starting BUD/F, a twice-daily therapy.

To mitigate factors that are correlated with nonadherence to medication therapy, we designed the study with inclusion/exclusion criteria and statistical methods to ensure that any differences between cohorts on factors related to future adherence would be balanced and not confound our results. Some patient-level factors that are likely related to poor adherence include asthma-related severity, insurance status, and patient out-of-pocket costs.^{24,29-31} Out-of-pocket prescription costs for FF/VI and BUD/F were matched at baseline to ensure similar out-of-pocket burden for each cohort. In addition, differences in demographic factors and comorbidities such as age, sex, and asthma severity were assessed in the propensity matching and were similar at baseline.²¹ Different methods for defining the eligible treatment cohort, such as prevalent or incident users and look-back periods of various lengths, have been shown to create bias in adherence measures.³² To mitigate these biases, our study

was restricted to new users of FF/VI and BUD/F, and excluded patients with a history of any ICS/LABA combination treatment in the 12-month baseline period while matching on baseline AMR. Overall, the FF/VI and BUD/F cohorts were well matched on factors related to future adherence, which increases the likelihood that the improved PDC and AMR values observed in this study are related to once-daily FF/VI treatment regimen rather than other observable factors.

A total of 75.8% members of the FF/VI sample were matched 1:1 to BUD/F. Although there was considerable loss of sample size in the BUD/F cohort, this was mainly due to the much larger sample for BUD/F and the limit of a 1:1 match. This limits the number of the final matched population to the lowest sample, which would be the FF/VI cohort. The unmatched populations were similar on most characteristics; however, there were several baseline variables that were not similar and support the choice of the PSM procedure.

Patients were required to have at minimum 3 months continuous enrollment in the health plan to be included in the study population. This 3-month cutoff was chosen to maximize the number of patients available for analysis while retaining sufficient follow-up time for the outcomes of interest. Although there were no restrictions on minimum adherence or persistence, a sensitivity analysis was conducted among matched pairs with a minimum of 180 days to test whether the results were robust to continuous enrollment requirements (see this article's Online Repository at www.jaci-inpractice.org).

Study limitations

Certain limitations must be considered in drawing conclusions regarding observational studies using health care claims data. Some information cannot be captured through claims data alone; for example, the presence of a claim for a filled prescription does not indicate that the medication was taken as prescribed and physician samples are not observed in claims data. Furthermore, administrative claims data are collected for payment rather than research purposes, and are susceptible to coding errors, which do not confirm proof of disease. Clinical characteristics related to asthma severity and possible factors related to asthma adherence such as asthma symptoms and asthma control assessment were not available. This study used PSM to control for potential biases. However, the inability to measure and control for certain known and unknown factors using claims data may impact the interpretation of findings in this and similar studies. Generalizability beyond this matched population may be limited. In addition, treatment discontinuation and cessation of medication at the end of a treatment episode was determined using pharmacy dispensing data, and reasons for discontinuation are not known.

As observed in other studies, the treatment discontinuation analysis excludes subjects who meet the predefined discontinuation definition from the at-risk population, such that the number of patients still at risk for discontinuation in each group approaches 0 over the 1-year follow-up. This may overestimate true treatment discontinuation if patients continue therapy after the predefined discontinuation gap.

The generalizability of the results of this study are limited to patients with continuous commercial and/or MAPD enrollment. Therefore, results are most applicable to patients with asthma in

stable managed care settings. Nonetheless, the health plans in this study represent patients across a wide US geographic distribution, and therefore, provide for generalization on a national level. In addition, these data have the advantage of large sample sizes composed of patients with diverse medical histories. Despite possible limitations, claims data are a rich data source for examining real-world patterns of care and health outcomes.

CONCLUSIONS

This study examined controller adherence, persistence, and AMR in patients using either once-daily FF/VI or twice-daily BUD/F. The most important finding from these analyses is that patients initiating treatment with once-daily FF/VI had better treatment adherence as measured by PDC and had a lower risk of asthma-related ED/IP events based on the relationship previously found between AMR and exacerbations. Although discontinuation rates were high in both cohorts, persistence was significantly better in the FF/VI cohort compared with the BUD/F cohort as measured by time to discontinuation. These findings illustrate how once-daily therapy could improve adherence and future asthma-related ED/IP event risk relative to a twice-daily alternative. Future research could explore how patient preferences for treatment regimens and delivery devices are related to treatment adherence and outcomes as well as treatment effectiveness in certain subgroups.

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TABLE E1. ICD-9/10-CM Diagnosis codes

Diagnosis	Diagnosis code (ICD-9/10-CM)
Asthma	ICD-9-CM: 493.xx ICD-10-CM: J45.3, J45.4, J45.5, J45.9
Acute respiratory failure	ICD-9-CM: 518.81 ICD-10-CM: J96.0, J96.2
Cystic fibrosis	ICD-9-CM: 277.0ICD-10-CM: E84.0-E84.9
COPD	ICD-9-CM: 491.xx, 492.xx, 496.xx ICD-10-CM: J41, J42, J43, J44

COPD, Chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

TABLE E2. Variables included in the propensity-score analysis

Description
Index date in 2014 Jan-Mar
Index date in 2014 Apr-Jun
Index date in 2014 Jul-Sep
Index date in 2014 Oct-Dec
Index date in 2015 Jan-Mar
Index date in 2015 Apr-Jun
Index date in 2015 Jul-Sep
Index date in 2015 Oct-Dec
Index date in 2016 Jan-Mar
Age
Sex
Midwest region
South region
West/Other region
Business line—commercial (vs Medicare)*
Baseline AMR—including index date
Baseline ICSs—including index date
Baseline long-acting muscarinic agents (LAMAs)—including index date
Baseline LAMA/LABA combination—including index date
Baseline count of LAMA units—including the index date
Any LAMA on index date
Baseline LABAs—including index date
Baseline leukotriene modifiers—including index date
Baseline methylxanthines—including index date
Baseline asthma biologic—including index date
Baseline count of any SABA units—including index date
Any SABA on index date
Baseline SAMA or SAMA/SABA—including index date
Baseline systemic corticosteroids (OCS)—including index date*
Baseline number of medications—including the index date
Number of medications on the index date
Log of patient-paid cost of index medication fill
Baseline Charlson score of 1—including index date
Baseline Charlson score of 3-4—including index date
Baseline Charlson score of 5+—including index date
Baseline chronic disease score—including index date
Baseline dyslipidemia—including index date
Baseline substance-related disorder—including index date
Baseline other lower respiratory disease—including index date
Baseline developmental disorder and/or ADHD
Baseline diabetes
Provider specialty: Primary care
Provider specialty: Respiratory specialist
Baseline asthma-related ambulatory visit count—including index date
Baseline asthma-related ER count—including index date
Baseline asthma-related IP count—including index date
Asthma-related ambulatory visit on index date
Asthma-related ER exacerbation event on index date
Asthma-related ambulatory exacerbation event on the index date
Baseline count of asthma-related exacerbations—including index date
Baseline count of asthma-related severe exacerbations—including index date

ADHD, Attention deficit/hyperactivity disorder; *ER*, emergency room; *OCS*, oral corticosteroid; *SABA*, short-acting beta-agonist; *SAMA*, short-acting muscarinic antagonist.

*Hard-matched variables.

TABLE E3. Estimated annualized asthma-related costs and time to first asthma-related exacerbation

Adjusted yearly asthma costs per patient			
Costs	FF/VI 100/25 µg	BUD/F 160/4.5 µg	P value
Total medical and pharmacy	\$1980	\$1868	.55
Medical	\$572	\$861	.096
Asthma-related exacerbations FF/VI vs BUD/F			
	Adjusted hazard ratio (95% CI)		P value
Any exacerbation	0.989 (0.85-1.15)		.884
Severe exacerbation	0.69 (0.48-0.99)		.045

Costs and time to exacerbations were adjusted for baseline asthma-related exacerbations and baseline severe asthma-related exacerbations. Any exacerbation = outpatient, ED, or urgent visit for asthma + systemic corticosteroid use within 5 d or asthma-related hospitalization. Severe exacerbation (post hoc analysis) = asthma-related hospitalization.

TABLE E4. Controller and rescue medications included in the AMR

Drug class	Subclass	Medication
Controller medications	ICSs	Beclomethasone
		Betamethasone
		Budesonide (both inhaler and nebulizer)
		Ciclesonide
		Flunisolide
		Fluticasone
	ICS/LABA combinations	Mometasone
		Triamcinolone
		Budesonide/formoterol
		Fluticasone/vilanterol
	Mast cell stabilizers	Fluticasone/salmeterol
		Mometasone/formoterol
		Nedocromil
	Leukotriene modifiers and Xanthine combinations	Cromolyn
		Montelukast
		Zafirlukast
Rescue medications	Short-acting β-agonists (SABAs)	Zileuton
		Methylxanthines
		Aminophylline
		Dyphylline
		Oxtriphylline
		Theophylline
		Theophylline/guaifenesin
		Albuterol
		Bitolterol
		Isoetharine
		Isoproterenol
		Levalbuterol
		Metaproterenol
		Pirbuterol
		Terbutaline

TABLE E5. Respiratory medications accounted for in the baseline period

Drug class	Subclass	Medication
Maintenance/controller medications	Long-acting muscarinic antagonist/long-acting anticholinergic aka “LAMA” or “anticholinergic”	Tiotropium
		Acclidinium
		Umeclidinium
		Glycopyrronium
	ICSs	Beclomethasone
		Budesonide (inhaler and nebulizer)
		Ciclesonide
		Flunisolide
		Fluticasone
		Mometasone
		Triamcinolone
	LABAs	Arformoterol
		Formoterol
		Salmeterol
		Olodaterol
	ICS/LABA fixed combination	Indacaterol
		Fluticasone/salmeterol
		Budesonide/formoterol
		Fluticasone/vilanterol
	Mast cell stabilizers	Mometasone/formoterol
		Nedocromil
		Cromolyn
	Anticholinergic/LABA combination	Tiotropium/olodaterol
		Glycopyrrolate/indacaterol
		Vilanterol/umeclidinium
	Leukotriene modifiers	Montelukast
		Zileuton
		Zafirlukast
	Methylxanthines aka xanthines	Aminophylline
		Dyphylline
		Oxtriphylline
		Theophylline
	Anti-IgE treatment	Omalizumab
	IL-5 inhibitors	Mepolizumab
		Reslizumab
	Xanthine combinations	Theophylline/guaifenesin
	Phosphodiesterase inhibitors	Roflumilast
Rescue medications	SAMAs	Ipratropium
	SABA	Albuterol
		Pirbuterol
		Levalbuterol
		Metaproterenol
		Terbutaline
	SAMA/SABA	Ipratropium/albuterol
	Oral corticosteroids (OCSs) aka “systemic corticosteroids”	Betamethasone
		Cortisone
		Dexamethasone
		Hydrocortisone
		Methylprednisolone
		Prednisolone
		Prednisone
		Triamcinolone

SABA, Short-acting β -agonist; SAMA, short-acting muscarinic antagonist.

TABLE E6. Baseline demographic and clinical characteristics: Unmatched FF/VI and unmatched BUD/F

Variable description	Unmatched cohorts		Std Diff (%)
	FF/VI 100/25 µg (n = 551)	BUD/F 160/4.5 µg (n = 5950)	
Age (y), mean	47.99	53.80	−38.27
Sex: male, %	38.29	35.31	6.19
Medicare Advantage Prescription Drug, %	2.36	35.97	−94.41
Baseline AMR	0.272	0.257	3.97
ICS usage, %	15.8	14.7	3.11
LABAs, %	1.45	0.81	6.10
Long-acting muscarinic agents (LAMAs), %	3.09	2.50	3.52
Leukotriene receptor antagonists, %	34.66	31.95	5.76
Xanthines, %	0.726	0.992	−2.88
Asthma biologic, %	0.726	0.504	2.83
Oral corticosteroids (OCSs) (at least 1 dispensing), %	54.08	62.50	−17.13
Count of SABA canisters, mean	2.59	2.85	−6.04
Baseline SAMA or SAMA/SABA, %	6.35	9.98	−13.28
Count of unique medications in baseline	10.33	11.85	−23.14
Charlson score, %			
0	80.40	77.19	7.85
1-2	5.63	7.11	−6.07
3-4	11.62	12.40	−2.42
5+	2.36	3.29	−5.64
CDS score	3163	3904	−22.16
Baseline asthma-related ambulatory visit count, mean	1.73	2.26	−20.86
Baseline asthma-related ED count, mean	0.06	0.11	−11.40
Baseline asthma-related IP stay count, mean	0.04	0.06	−7.17
Baseline count of asthma exacerbations, mean	0.46	0.65	−21.76
Baseline count moderate asthma exacerbations, mean	0.43	0.56	−18.87
Baseline count of severe asthma exacerbations, mean	0.04	0.07	−13.30
Patient OOP cost of index fill (log \$), mean	3.64	3.76	−8.63
Provider specialty, %			
Primary care	39.75	56.89	−34.81
Respiratory specialist	49.00	21.55	59.95
Unknown	11.25	21.56	−28.10

CDS, Chronic Disease Score; OOP, out-of-pocket; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist.

TABLE E7. Means and percent that achieved each threshold for FF/VI vs BUD/F: Sensitivity analysis (patients with ≥ 6 -mo follow-up)

Endpoint	FF/VI100/25 μg (n = 795)	BUD/F 160/4.5 μg (n = 795)	P value
PDC, mean $\pm$ SD	0.41 $\pm$ 0.29	0.30 $\pm$ 0.25	<.001
≥ 0.5 , %	35.5	18.2	<.001
≥ 0.8 , %	14.6	6.3	<.001
Treatment discontinuation (within 12 mo), %	91.19	97.11	<.001
AMR, mean $\pm$ SD	0.64 $\pm$ 0.39	0.54 $\pm$ 0.42	<.001
≥ 0.5 , %	70.7	60.5	<.001

TABLE E8. Likelihood and risk assessment for each end point FF/VI vs BUD/F: Sensitivity analysis (patients with ≥ 6 -mo follow-up)

Endpoint	Adjusted OR	95% CI	P value
PDC			
≥ 0.5	2.45	1.94-3.09	<.001
≥ 0.8	2.59	1.83-3.66	<.001
AMR			
≥ 0.5 (OR)*	1.69	1.36-2.09	<.001
	Adjusted hazards ratio	95% CI	P value
Time to discontinuation (hazards ratio)	0.67	0.61-0.75	<.001

OR, Odds ratio.

Note: Multivariable analysis controlled for count of baseline asthma-related exacerbations (any type) and baseline asthma-related severe exacerbations.

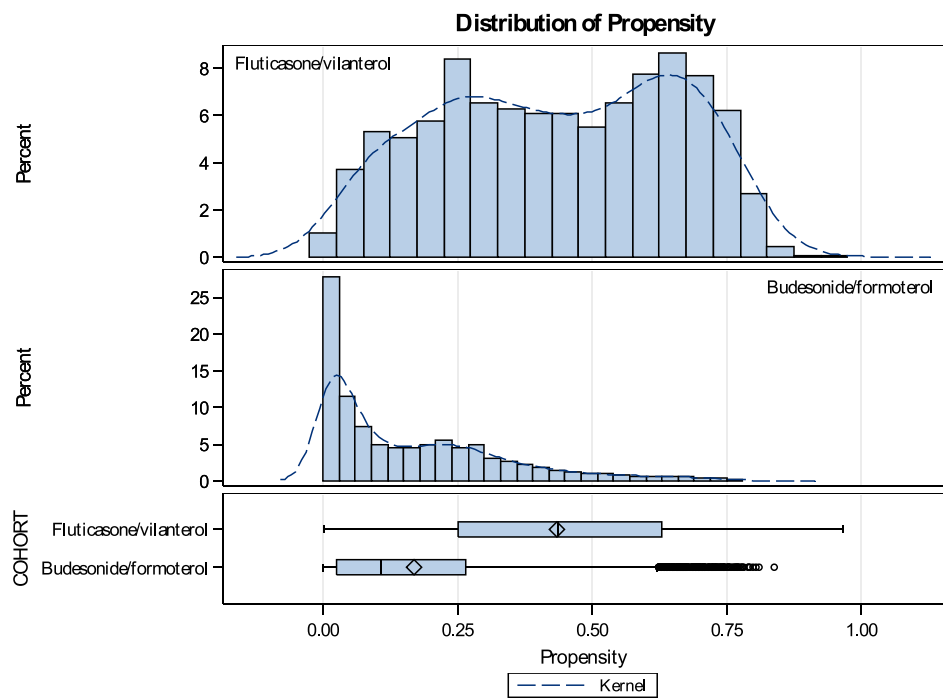


FIGURE E1. Prematch propensity scores by cohort.

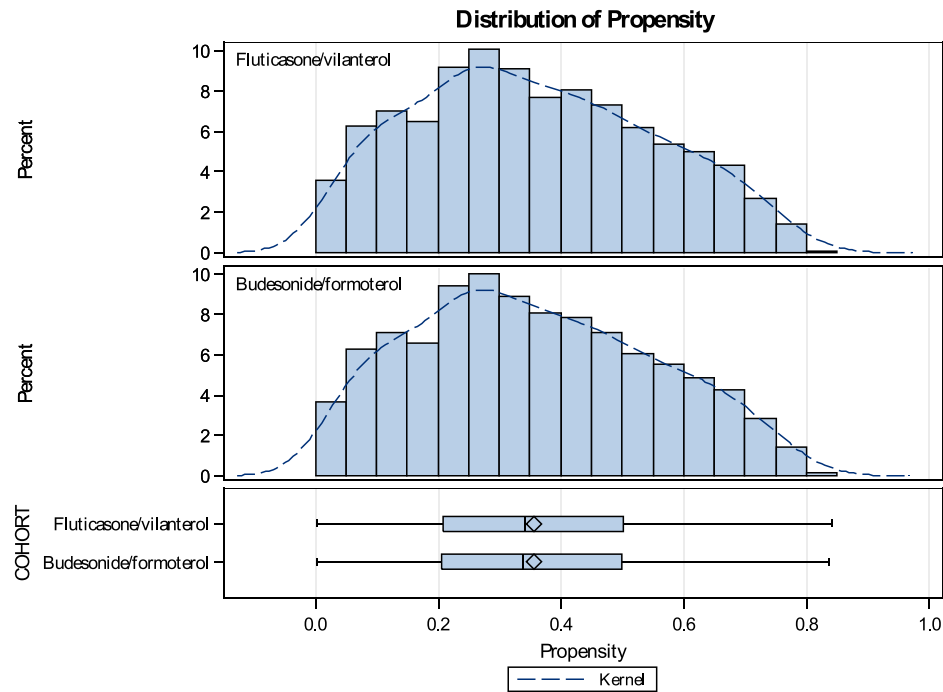


FIGURE E2. Postmatch propensity scores by cohort.

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