

Adherence and usage patterns of inhaled corticosteroids–long-acting beta-agonists by using inhaler-monitoring technology

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ABSTRACT

Background: Results of previous research indicate that adherence to prescribed inhaled corticosteroid–long-acting beta₂-agonist (ICS-LABA) asthma controller medications is suboptimal, yet actual daily-use patterns are unclear and may be influenced by regimen complexity or dosing frequency.

Objective: To investigate real-world use of asthma medications by using inhaler sensors for the ICS-LABA controllers: twice-daily fluticasone propionate (FP) plus salmeterol (SAL) and once-daily fluticasone furoate (FF) plus vilanterol (VI); and albuterol rescue medication.

Methods: This longitudinal, two-phase, observational study included adults with asthma-prescribed FP-SAL (phase I) or FF-VI (phase II), and albuterol metered-dose inhalers. The participants completed baseline and follow-up surveys, and used clip-on inhaler sensors to monitor real-time inhaler use over the 6-month study period. Pharmacy claims data for the 6-month follow-up period were used to assess refills of ICS-LABA and albuterol inhalers.

Results: Patients who used twice-daily FP-SAL received a sufficient dose (≥ 2 actuations/day) approximately one third of the time, those on once-daily FF-VI received a sufficient dose (≥ 1 actuation/day) $\sim 60\%$ of the time. Patients who used once-daily FF-VI were more likely to take their medication as prescribed versus those who used twice-daily FP-SAL. There were no significant differences in the percentage of albuterol-free days (FP-SAL, 68.06% [$n = 241$]; FF-VI, 72.67% [$n = 127$]; $p = 0.230$). Exploratory outcomes are reported in this article's Online Supplemental Material. Claims-based measures of adherence were higher than sensor-based measures, hence claims data may have overestimated adherence, whereas sensors may have more accurately measured patients' medication use.

Conclusion: These data supported the use of inhaler sensors as tools to directly and accurately measure ICS-LABA adherence and rescue medication use, and the adherence benefits of once-daily versus twice-daily ICS-LABA regimens.

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Long-term goals of asthma treatment include achieving good 24-hour symptom control; minimally using rescue medication; maintaining normal activities; and minimizing the future risk of exacerbations, fixed airflow limitation, and side effects.¹ Short-acting β_2 -agonist “rescue” medications (e.g., albuterol) quickly relieve asthma bronchospasm, whereas patients with moderate–severe asthma depend on inhaled corticosteroids (ICS) plus long-acting β_2 -agonists (LABA) for maintenance therapy.¹ Fluticasone propionate (FP) and salmeterol (SAL), delivered by DISKUS (GlaxoSmithKline plc., Research

Triangle Park, NC) dry powder inhaler (DPI) is indicated for twice-daily asthma treatment in those patients ages ≥ 4 years (available as FP-SAL 100–50 μg , 250–50 μg , and 500–50 μg). Fluticasone furoate (FF) plus vilanterol (VI), delivered by ELLIPTA (GlaxoSmithKline plc., Research Triangle Park, NC) DPI, is available as FF-VI 100–25 μg and 200–25 μg for once-daily asthma treatment in individuals ≥ 18 years.^{2,3}

Although results of clinical studies show that asthma control can be achieved in most patients,^{4–10} results of surveys suggest that this is not the case in real life.^{11–15}

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Night-time symptoms and absence from work or school show that asthma control in everyday life is far from optimal and that many patients require acute interventions.¹² Nonadherence and poor inhaler technique are associated with suboptimal asthma control; up to 50% of patients do not use controller medication as prescribed, others use inhalers incorrectly or over-use rescue medication.^{12,16}

Assessing adherence has several challenges. Self-reporting is open to bias and can be burdensome for patients and physicians. Less-intrusive, indirect measures of adherence (e.g., pharmacy records) are incomplete, indicating prescription refills and not capturing medication use. Furthermore, because pharmacy records are intended for administrative purposes, there is significant delay between data capture and availability. Technologic advances provide insight into the actual use of therapies in real time, with easy-to-use, accurate data-collection tools.¹⁷ Inhaler sensors capture adherence in real-world settings, and, coupled with patient feedback, may provide a means to improve adherence.^{18,19} We examined patterns of use and adherence to once-daily and twice-daily ICS-LABA controller medications and rescue medications by using clip-on inhaler sensors versus pharmacy-claims data, as two different measures of adherence, in patients with asthma from a real-world U.S. health-care setting.

METHODS

Study Design

This longitudinal, observational study combined retrospective and prospective data collection to assess inhaled medication usage and asthma control in patients with asthma over a 6-month period (GlaxoSmithKline plc. study 206477). The study had two phases (further details are provide in the Online Supplemental Material):

- Phase I (FP-SAL cohort): Adults with ≥ 1 FP-SAL (ADVAIR DISKUS; GlaxoSmithKline plc.) and albuterol metered-dose inhaler (MDI), dispensing during the most recent 6 months of the claims identification period were identified in the Optum Research Database (Optum, Eden Prairie, MI) in December 2016, by using medical and pharmacy claims between November 1, 2015, and October 31, 2016.
- Phase II (FF-VI cohort): Adults with one or more FF-VI DPI (BREO ELLIPTA; GlaxoSmithKline plc.) and albuterol MDI dispensing were identified in the Optum Research Database in July 2017, by using medical and pharmacy claims from June 1, 2016 to May 31, 2017.

During each phase, potentially eligible patients were mailed a baseline survey, which included demographics

(age, gender, race), clinical characteristics (smoking status, body mass index, duration of asthma), general health status, and asthma control scores by using the Asthma Control Test (ACT; GlaxoSmithKline plc., Brentford, UK).²⁰ ACT scores reflect a patient's assessment of his or her asthma control, asthma-symptom frequency, rescue medication use, and daily-life asthma impact over the previous month.^{21,22}

Patients who returned the baseline survey and who met eligibility requirements were then invited to use inhaler sensors with their compatible controller (FP-SAL or FF-VI) and rescue medications for the 6-month study period. Those who opted in received a Propeller Health Kit (Propeller Health, Madison, WI), which contained a sensor (which captured the time, date, number of actuations in real time of the controller and rescue albuterol) and a hub (which enabled wireless data transmission from the sensor to the Propeller platform). An index date was assigned as the date that the sensor was first connected to the FP-SAL DPI or FF-VI DPI or to the rescue albuterol MDI (whichever was sooner). Pharmacy-claims data for the 6-month follow-up period were assessed to determine the number of refills of the ICS-LABA and albuterol inhaler to characterize treatment patterns. The study was approved by the New England Institutional Review Board (IRB) Newton, Massachusetts (IRB120160975), on December 1, 2016, the study sponsor (GlaxoSmithKline plc.), Optum, and the affiliated health plan. All the patients provided informed consent.

Study Population

Fully insured adult members (ages ≥ 18 years) of Optum-affiliated commercial health plans with a self-reported asthma diagnosis and evidence of asthma medication use in the past 6 months of the claims identification period were included. Patients with one or more *International Classification of Diseases, Tenth Revision*²³ codes for chronic obstructive pulmonary disease were excluded. Continuous enrollment in Optum-affiliated health plans during the 12-month preindex (baseline) and 6-month postindex (follow-up) periods was required for assessment of claims-based outcomes in the subset of patients who met this criterion. Further details are provided in the Online Supplemental Material. The patients received financial incentives of up to \$275 for participation after survey completion and for each month of inhaler-sensor attachment.

Objectives

The primary objective was to examine patient adherence to the inhaled controller, measured by using inhaler sensors. *Post hoc* objectives included comparing adherence between FP-SAL and FF-VI cohorts by using inhaler-

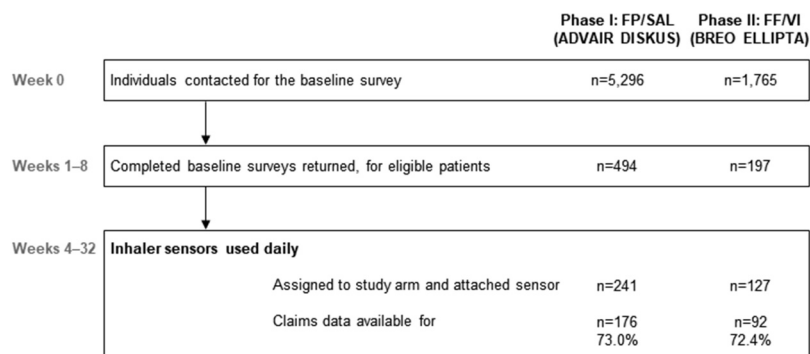


Figure 1. Patient disposition. FF = Fluticasone furoate; FP = fluticasone propionate; SAL = salmeterol; VI = vilanterol.

sensor and pharmacy-claims data in an unadjusted and adjusted analysis of controller and albuterol use.

End Points

The primary end point was the pattern of inhaled controller (FP-SAL and FF-VI) use during the 6-month follow-up period. Measures included the number of days with a sufficient dose of inhaled controller (≥ 2 actuations/day for FP-SAL, ≥ 1 actuation/day for FF-VI), inhaled controller correct dose count adherence (for FP-SAL, the number of days with exactly one actuation at two distinct time points; for FF-VI, the number of days with exactly one actuation), and the daily inhaled controller use count. Secondary and exploratory end points are described in the Online Supplemental Material; however, the exploratory end point of claims-based proportion of days covered (PDC) is described below for comparison with the sensor-based inhaler use and/or adherence primary end point.

The FP-SAL and FF-VI cohorts were compared, including days with medication used as prescribed and the proportion of patients with $\geq 50\%$ and $\geq 80\%$ of days with medication used as prescribed. Asthma control was also an exploratory end point, as measured by the total mean ACT scores of the participants with complete ACT scores at baseline and the 6-month end point (Online Supplemental Material). The study was not initially designed to statistically evaluate differences in outcomes between the cohorts.

Post hoc analyses statistically compared the end points between cohorts and adjusted covariates by using inverse probability treatment weighting (IPTW), described below. This was an observational study that involved retrospective and prospective data collection from participants that did not solicit adverse event data (nor were any adverse events spontaneously reported); as such, data on adverse events were not available and were thus not presented in this article.

Data Analysis

All measures were assessed descriptively, expressed as mean $\pm$ standard deviation for continuous variables

and as number (percentage) for dichotomous and/or polychotomous variables. *Post hoc* analyses included comparing adherence measures between FP-SAL and FF-VI by using both inhaler sensors and claims (albuterol use and the asthma medication ratio), and are described in the Online Supplemental Material.

IPTW was applied to reduce confounding on observed clinical, demographic, and sociodemographic characteristics, and to balance the distribution of covariates that would have occurred if participants had been randomly assigned to treatment cohorts *a priori*.²⁴ Weightings were based on each individual's probability of receiving a specific treatment given the confounders, known as the propensity score, as previously demonstrated (details in the Online Supplemental Material).^{25–27} Statistical analyses were conducted by using SAS (Marlow, UK) statistical software (v 9.4).

RESULTS

Participant Flow and Characteristics

In phase I, 5296 patients satisfied the identification criteria for the FP-SAL cohort (Fig. 1). By using the American Association for Public Opinion Research response rate calculation no. 4, the informed consent and baseline survey response rate for eligible patients was 14.2%. All the participants who were provided with sensors connected them to their inhalers ($n = 241$), most had claims data available in the follow-up period ($n = 176$ [73.0%]). In phase II, 1765 patients were identified for the FF-VI cohort (Fig. 1). The phase II American Association for Public Opinion Research response rate was 14.6%. Overall, 127 patients who used FF-VI connected the sensors to their inhalers, most had available claims data ($n = 92$ [72.4%]).

Before IPTW adjustment, the FP-SAL and FF-VI cohorts were generally well balanced for demographics and clinical characteristics (Table 1; Online Supplemental Material). For both, $\sim 65\%$ were female and $\sim 90\%$ were white; the mean baseline ACT scores were 19.0–19.1; and 54.3–54.4% had well-controlled asthma. For FP-SAL, 66.0% of the patients reported never smoking, and 64.3% had an asthma duration of ≥ 20 years. For FF-VI, 74.8%

Table 1 Demographics and clinical characteristics of the FP-SAL and FF-VI cohorts after IPTW adjustment

Characteristics	IPTW-Adjusted Data for All Patients			IPTW-Adjusted Data for Patients with Baseline and Follow-up Claims Data		
	FP-SAL (n = 241)	FF-VI (n = 127)	Stand. Diff., %	FP-SAL (n = 176)	FF-VI (n = 92)	Stand. Diff., %
Age, mean $\pm$ SD, y	48.01 $\pm$ 12.33	48.17 $\pm$ 12.61	-1.22	48.96 $\pm$ 11.98	49.06 $\pm$ 10.95	-0.84
Female, n (%)	156 (64.85)	82 (64.29)	1.18	117 (66.52)	62 (67.07)	-1.18
Ethnicity, n (%) [*]						
American Indian or Alaska native	3 (1.15)	0 (0.00)	15.22	3 (1.71)	0 (0.00)	18.67
Asian	8 (3.40)	2 (1.57)	11.77	5 (2.83)	4 (3.97)	-6.31
Black or African American	13 (5.22)	9 (6.77)	-6.53	8 (4.82)	5 (5.52)	-3.14
Native Hawaiian or other Pacific Islander	1 (0.38)	2 (1.57)	-12.13	1 (0.45)	4 (3.97)	-24.11
White	216 (89.80)	113 (88.88)	2.98	158 (89.52)	82 (88.97)	1.76
Other	6 (2.56)	4 (2.77)	-1.34	6 (3.21)	1 (1.54)	11.02
Mean BMI, mean $\pm$ SD, kg/m ² #	30.53 $\pm$ 7.17	30.43 $\pm$ 8.38		30.07 $\pm$ 6.21	29.81 $\pm$ 7.46	
Baseline ACT score, mean $\pm$ SD	19.05 $\pm$ 3.98	19.01 $\pm$ 3.87	1.01	19.03 $\pm$ 3.90	19.22 $\pm$ 3.64	-5.12
ACT score, n (%)						
5-15 (poorly controlled)	43 (17.80)	24 (18.65)	-2.22	30 (17.00)	17 (18.17)	-3.08
16-19 (somewhat controlled)	66 (27.54)	36 (28.32)	-1.74	48 (27.09)	24 (25.77)	2.99
20-25 (well controlled)	132 (54.66)	67 (53.03)	3.29	98 (55.91)	52 (56.06)	-0.29
Years with asthma, n (%)§						
<1 y	11 (4.41)	7 (5.53)	-5.18	6 (3.19)	5 (5.07)	-9.43
1-5 y	30 (12.48)	18 (14.23)	-5.15	22 (12.63)	14 (15.75)	-8.96
6-10 y	23 (9.42)	12 (9.46)	-0.14	13 (7.16)	8 (8.51)	-5.00
11-19 y	37 (15.29)	16 (12.75)	7.32	28 (16.08)	12 (12.70)	9.64
≥ 20 y	141 (58.40)	74 (58.02)	0.76	107 (60.94)	53 (57.98)	6.03
Smoking history, n (%)						
Never smoked and no one in household smoked	157 (65.28)	83 (65.32)	-0.09	117 (66.68)	61 (66.15)	1.12
Never smoked and someone in household smoked	9 (3.66)	8 (6.69)	-13.70	6 (3.26)	6 (6.55)	-15.25
Former smoker	59 (24.51)	30 (23.49)	2.37	43 (24.30)	22 (23.56)	1.73
Current smoker	16 (6.56)	6 (4.50)	9.02	10 (5.75)	3 (3.74)	9.50
Dispensing counts (claims data), mean $\pm$ SD						
Controller medication	N/A	N/A	N/A	5.54 $\pm$ 3.34	5.44 $\pm$ 3.20	3.12
Rescue (albuterol) medication	N/A	N/A	N/A	2.97 $\pm$ 2.63	2.93 $\pm$ 2.72	1.77

FP = Fluticasone propionate; SAL = salmeterol; FF = fluticasone furoate; VI = vilanterol; IPTW = inverse probability treatment weighting; Stand. Diff = standardized difference; SD = standard deviation; BMI = body mass index; ACT = Asthma Control Test; N/A = not available.

^{*}Sum of percentages may exceed 100%, because patients could select more than one response.

#BMI was imputed for three patients on FP-SAL with missing data for IPTW modeling.

§Asthma duration was imputed for one patient on FF-VI with missing data for IPTW modeling.

Sensor-derived data

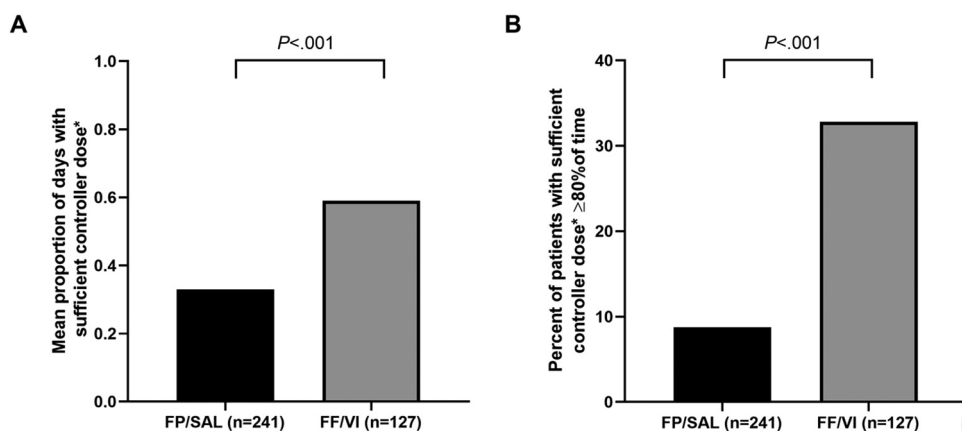


Figure 2. IPTW-adjusted (A) mean proportion of days with sufficient controller dose and (B) proportion of patients with sufficient controller dose for $\geq 80\%$ of the time, for the FP-SAL and FF-VI cohorts over the 6-month follow-up period. IPTW = Inverse probability treatment weighting; FP = fluticasone propionate; SAL = salmeterol; FF = fluticasone furoate; VI = vilanterol. *Sufficient controller dose: ≥ 2 actuations/day for FP-SAL; ≥ 1 actuation/day for FF-VI.

reported never smoking and 45.2% had an asthma duration of ≥ 20 years.

IPTW adjustment to assess inhaler-sensor data resulted in more-balanced characteristics (Table 1) for FP-SAL and FF-VI cohorts, respectively: female (64.9 versus 64.3%), asthma duration ≥ 20 years (58.4 versus 58.0%), and well-controlled asthma (54.7 versus 53.0%). IPTW adjustment was also conducted for patients with baseline and follow-up claims data (Table 1). Thereafter, the FP-SAL and FF-VI cohorts, respectively, were better balanced for mean baseline ACT scores (19.0 versus 19.2; additional data at Online Supplement Material), mean asthma duration (≥ 20 years, 60.9 versus 58.0%), mean baseline dispensing counts of controller medication (5.5 versus 5.4), and rescue medication (3.0 versus 2.9).

IPTW-Adjusted Adherence, Inhaled Controller, and Rescue Medication Use Patterns during the 6-Month Follow-up Period

Sensor-Based Data. The mean (median [interquartile range]) number of controller actuations per day was 1.04 (0.98 [0.52–1.60]) for patients on FP-SAL and 0.62 (0.65 [0.36–0.89]) for patients on FF-VI. In the FP-SAL cohort, the mean proportion of days on which sufficient controller dose (≥ 2 actuations/day) was observed by using inhaler sensors was 0.33 versus 0.59 (≥ 1 actuation/day) in the FF-VI cohort (Fig. 2A); 8.7% of patients on FP-SAL and 32.8% of patients on FF-VI had sufficient controller dose for $\geq 80\%$ of days (Fig. 2B). The mean proportion of days that the patients used medication with the correct dose count (1 actuation/day at two time points for FP-SAL, and 1 actuation/day for FF-VI) was 0.24 for FP-SAL and 0.57 for FF-VI (Fig. 3A). For FP-SAL, 4.1% of the patients had $\geq 80\%$ of days of medication use with the correct dose count, whereas the corresponding value for FF-VI was 30.6% (Fig. 3B). The patients prescribed FP-SAL used rescue medication on more days than did

the patients prescribed FF-VI: 53.7 and 45.9 mean days, respectively (Table 2), although this difference was not statistically significant ($p = 0.230$). The proportion of days without rescue medication use was 68.1% for FP-SAL and 72.7% for FF-VI.

Claims-Based Data. In separate analyses of controller medication use from claims data, the patients in the FP-SAL cohort had a slightly lower, albeit not statistically significant, mean PDC than those prescribed FF-VI (0.59 versus 0.66, respectively [Fig. 4]). There was also no significant difference between the cohorts for the mean number of rescue medication prescription refills (FP-SAL, 1.0; FF-VI, 0.9).

DISCUSSION

Our results showed that inhaler sensor monitoring of real-time treatment use and adherence may be an improved measure of adherence than retrospective assessment of pharmacy dispensing claims. Inhaler sensors showed daily controller medication use as prescribed; corresponding dispensing claims only assessed medication possession. In particular, the number of days for which sufficient and correct daily dose was obtained *via* sensors was significantly higher with once-daily FF-VI than with twice-daily FP-SAL; however, PDC values (an accepted proxy for adherence) when using pharmacy-claims data were not significantly different.

The sensor-based adherence was 44% lower than the claims-based measure for the twice-daily controller and 11% lower for the once-daily controller, which suggested that claims-based PDC measures of medication possession may overestimate true adherence. Inhaler-sensor technology is a more objective and reliable measure that provides direct and accurate data on patterns of treatment use and adherence, which enables discrete measures of adherence to the prescribed dose to be calculated. Conversely, despite being less intrusive, claims-based data from pharmacy dispensing

Sensor-derived data

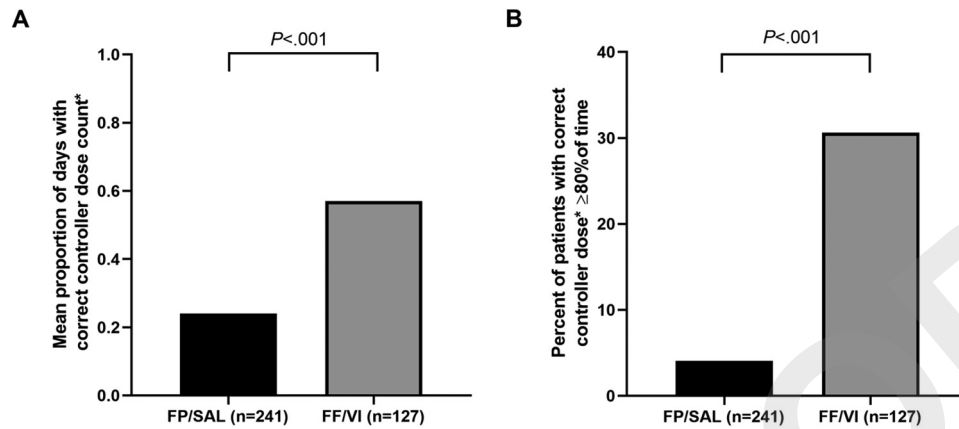


Figure 3. IPTW-adjusted (A) mean proportion of days with the correct controller dose count and (B) proportion of patients with correct controller dose count for $\geq 80\%$ of the time, for the FP-SAL and FF-VI cohorts over the 6-month follow-up period. IPTW = Inverse probability treatment weighting; FP = fluticasone propionate; SAL = salmeterol; FF = fluticasone furoate; VI = vilanterol. *Correct controller dose: exactly one actuation at two distinct time points per day for FP-SAL; exactly 1 actuation/day for FF-VI.

Table 2 IPTW-adjusted rescue MDI use and asthma medication ratio in the FP-SAL cohort (n = 241) and the FF-VI cohort (n = 127) over the 6-month follow-up period

End point, mean $\pm$ SD*	FP-SAL Cohort	FF-VI Cohort	p
Inhaler sensor data, n	241	127	
Rescue actuations per day, mean $\pm$ SD	1.04 $\pm$ 1.46	1.01 $\pm$ 1.85	0.882
No. days with rescue actuations, mean $\pm$ SD	53.65 $\pm$ 49.64	45.91 $\pm$ 46.62	0.230
Days with no rescue use, %	68.07	72.67	
Asthma medication ratio, mean $\pm$ SD#	0.53 $\pm$ 0.31	0.56 $\pm$ 0.29	0.499
Claims data, n	176	92	
Total no. rescue prescription fills, mean $\pm$ SD	1.03 $\pm$ 1.39	0.88 $\pm$ 1.36	0.482
Asthma medication ratio, mean $\pm$ SD§	0.69 $\pm$ 0.34	0.74 $\pm$ 0.33	0.341
≥ 0.5 , n (%)	143 (81.12)	78 (85.32)	0.494

IPTW = inverse probability treatment weighting; MDI = metered-dose inhaler; FP = fluticasone propionate; SAL = salmeterol; FF = fluticasone furoate; VI = vilanterol; SD = standard deviation.

*Unless otherwise stated.

#Calculated by using inhaler-sensor data as follows: days with controller actuations divided by the sum of days with controller actuations and the number of rescue actuations.

§Defined as the number of claims for controller medication divided by the sum of claims for controller and rescue medication, set to 0 for patients with claims for neither controller nor rescue medications.

records may be incomplete, not capture actual medication use as prescribed, and have delayed availability of captured refill data.

Adherence to asthma treatments can be affected by regimen complexity, including the number of agents, dosing frequency, and ease of use.^{28,29} We found improved adherence in those patients prescribed once-daily FF-VI versus twice-daily ICS-LABAs, consistent with other studies.^{30,31} In a recent claims-based study,³⁰ patients with asthma who initiated once-daily FF-VI were more adherent and less likely to discontinue therapy than the patients who initiated twice-daily budesonide-formoterol

or FP-SAL. Patients with improved controller adherence are also reported to use fewer rescue medications.³² Herein, we found no significant difference in rescue medication use or asthma medication ratio between FP-SAL and FF-VI, despite the observed adherence difference.

Similarly, an exploratory analysis found no significant difference between ACT scores (Online Supplemental Material), although sample-size calculations conducted after completion of the study suggest that this exploratory analysis was not sufficiently powered to detect a statistically significant difference, unlike in the real-world asthma Salford Lung Study,³³ which reported

Claims-derived data

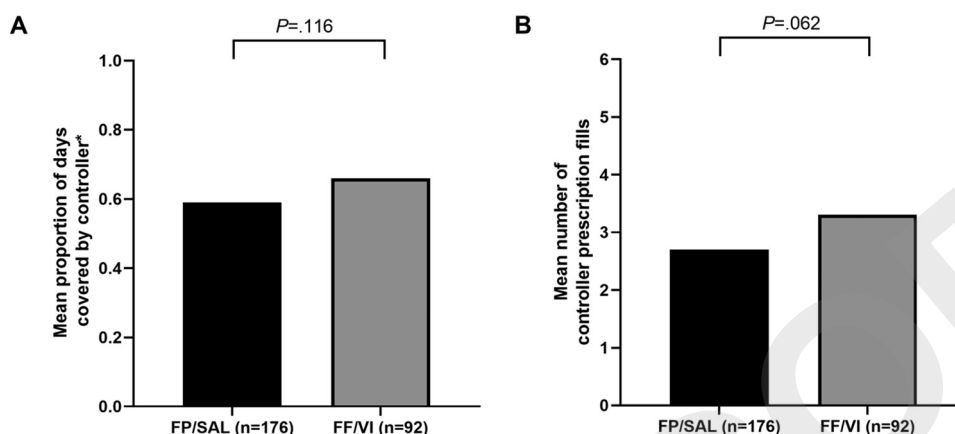


Figure 4. IPTW-adjusted (A) mean proportion of days covered by controller medication and (B) mean number of controller prescription fills, for the FP-SAL and FF-VI cohorts over the 6-month follow-up period. IPTW = Inverse probability treatment weighting; FP = fluticasone propionate; SAL = salmeterol; FF = fluticasone furoate; VI = vilanterol. *The proportion of days covered was calculated as the number of days that the medication was available, based on days of supply reported on pharmacy claims, divided by the number of days in the follow-up period; because the index date was based on sensor attachment and not on a pharmacy claim, the numerator included the days of supply from fills on or after the index date as well as of the days of supply available from fills before the index date.

improved ACT scores 24 weeks after treatment initiation with FF-VI versus FP-SAL. Interestingly, the difference in PDC values between the groups in the asthma Salford Lung Study (FF-VI, 82.4%; FP-SAL, 76.6%)³³ was similar to our findings. Because our study was not designed to evaluate causal relationships between adherence to controller medication and asthma control, it was difficult to infer from our data the potential impact on outcomes.

Real-time inhaler use and medication adherence in this study were monitored by using clip-on inhaler sensors that comprised the adherence component of the Propeller Health system, a digital-health asthma management tool that also offers a mobile phone application for patients. When used in full, the system may aid patient self-management because the additional features (such as the mobile application and digital feedback) will likely have benefits for patient adherence, similar to the described benefits on outcomes.^{34,35} Additional feeding back of inhaler sensor data to physicians could also be of benefit in monitoring adherence in patients with asthma.³⁶ This evidence of the system's effectiveness, along with providing an accurate record of use, which may be used to aid informed decision-making, facilitate treatment discussions between physicians and patients, and improve asthma control overall, address key concerns for healthcare providers when considering the use of such systems in practice.³⁷ Practicalities of data handling and interpretation, device usage in practice (such as whether actuation is recorded, despite the attached inhaler canister being empty), and the development of appropriate regulatory standards for these technologies

remain critical features to be demonstrated for healthcare provider confidence in implementing such electronic monitoring systems,^{37,38} in parallel with further studies of effectiveness.

A key study strength was the novel real-world data collection that combined inhaler-sensor use with retrospective and prospective strategies. Observational studies with voluntary survey participation commonly have small numbers of participants,³⁹ and, subsequently, the small number of participants in our analyses was a potential limitation. Further limitations included the potential for sampling, coverage, and/or measurement errors inherent to survey data, and possible observer-effect influences, all of which may not have reliably represented real-world findings from patients with asthma. The patients who chose to participate may have been more likely to be adherent (not assessed), which future studies could address by randomizing inhaler-sensor allocation; however, here, a significant difference in controller use was observed with once-daily versus twice-daily therapy, consistent with other studies of inhaler adherence and dosing frequency.^{30,31}

It is also possible that the relatively high baseline ACT scores in both cohorts (mean of ~19; the majority of patients in each cohort reported well-controlled asthma at baseline)^{21,22} did not allow for large ACT improvements in this population and that patients who believed that their asthma was controlled at baseline may have felt less need to adhere to controller regimens. The 6-month duration of follow-up in our study may not have

been a long enough timescale to observe clinical benefits of improved adherence, and, regardless, the study was not designed to determine causal relationships between adherence to controller medication and asthma control. Claims-based measures are subject to coding errors, and a pharmacy claim does not equate to the use of the medication as prescribed. Patients could also receive medications outside of the health plan (e.g., purchasing medication out-of-pocket). Eligible patients were initially identified *via* claims records, but inclusion in the study was based on self-reported medication use, which may have been inaccurate.

An inhaler with a built-in sensor could potentially provide more reliable data on adherence than the clip-on sensors in our study did. Sensor data were captured only if the inhaler was connected to the device; whereas patients were given incentives to do this; whether they remained attached throughout the study was not monitored or required. Sensor data may have resulted in underestimated actual medication use because only data from the inhaler attached to the device were captured, and some patients may have used multiple inhalers (e.g., albuterol). However, this bias would occur equally in both cohorts. Included participants were selected from a large U.S. health plan and may not have represented the general asthma population; study findings may also not be generalizable to non-U.S. health-care settings, which may be further limitations, along with the seasonal nature of asthma and when undertaking measurements for each cohort at different times of the year. Although the intention was to describe the two cohorts, use of IPTW adjustment to control for differences in baseline characteristics was *post hoc* rather than preplanned.

CONCLUSION

Clip-on inhaler sensors revealed that controller asthma medications are often not taken as prescribed and that adherence was higher in patients who received once-daily versus twice-daily ICS-LABA. Claims-based measures of adherence to ICS-LABA were higher than sensor-based adherence measures; claims-based measures may thus overestimate medication adherence, whereas sensor-derived measures may improve accuracy when measuring adherence. Our findings supported inhaler sensors as direct, real-time, accurate measures of adherence to inhaled asthma medications. Further research is needed to corroborate these findings in different health-care settings, prospectively evaluate the relationship to outcomes, and further develop inhaler sensors and other treatment-monitoring strategies in asthma.

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