

# Real-world health care utilization in asthma patients using albuterol sulfate inhalation aerosol (ProAir<sup>®</sup> HFA) with and without integrated dose counters

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**Background:** Accurate tracking of the administered dose of asthma rescue inhalers is critical for optimal disease management and is related to reductions in rates of unscheduled health care utilization in asthma patients. There are few published data on the real-world impact of rescue inhalers with integrated dose counters (IDCs) on health care resource utilization (HRU) for asthma patients. This study evaluates HRU among users of ProAir<sup>®</sup> hydrofluoroalkane (HFA) (albuterol sulfate inhalation aerosol), with IDC versus without IDC, in asthma patients.

**Methods:** This was a retrospective administrative claims study of asthma patients receiving a new prescription for albuterol inhalation aerosol without IDC during 2 years (January 2011–December 2012) or with IDC during the first full year after IDC implementation in the USA (July 2013–July 2014). Six months of continuous enrollment with medical and prescription drug benefits were required before and after the first prescription during the study period. Data on respiratory-related hospitalizations and emergency department (ED) visits were collected during the follow-up period.

**Results:** A total of 135,305 (32%) patients used albuterol inhalation aerosol with IDC, and 287,243 (68%) patients received albuterol inhalation aerosol without IDC. After adjusting for baseline confounding factors, the odds ratio (OR) for experiencing a respiratory-related hospitalization (OR=0.92; 95% confidence interval [CI] 0.88–0.96) or ED visit (OR=0.92; 95% CI 0.90–0.94) was significantly lower among patients using albuterol inhalation aerosol with IDC versus without IDC.

**Conclusion:** In a real-world setting, asthma patients using ProAir HFA with IDC experienced significantly fewer hospitalizations and ED visits compared with patients using ProAir HFA without IDC. Dosage information provided by IDCs may allow providers to better understand patients' disease severity and aid in titrating controller medications and also decrease the likelihood that the canister will be empty when needed, thereby enhancing disease management and reducing HRU.

**Keywords:** asthma, ProAir, integrated dose counters, respiratory-related hospitalizations, emergency department visits, lower respiratory tract infections-related outpatient visits

## Introduction

Asthma is a major health problem that affects 26 million individuals in the USA.<sup>1</sup> Respiratory-related emergency department (ED) visits along with hospitalizations due to exacerbations impose significant health care resource utilization (HRU) burden among patients with asthma.<sup>2,3</sup> The economic burden of asthma is large and is attributable to patients with poorly controlled disease, highlighting the importance of maintaining disease control and minimizing the frequency of exacerbations.<sup>1,4</sup> Recent

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estimates suggest that the average cost per asthma-related hospital stay increased from \$5,200 to \$6,600 (2010 US dollars)<sup>5</sup> and for an outpatient (OP) ED visit averaged \$1,502 (2008 US dollars).<sup>6</sup> In addition, costs due to ED visits and hospitalization disproportionately account for a major portion of the total health care costs of asthma.<sup>4-7</sup>

The treatment goals for asthma are primarily driven by patient-centered outcomes such as relieving symptoms, preventing disease progression and exacerbations, and optimizing health status and quality of life.<sup>8,9</sup> Clinical practice guidelines for asthma emphasize the importance of using preventer/controllers with anti-inflammatory properties (e.g., inhaled corticosteroids [ICSs]) as first-line treatment in persistent asthma.<sup>8,9</sup> Despite guidelines, many patients may use their preventer/controller inhalers intermittently and wait for asthma flare ups to seek medication prescriptions.

ProAir<sup>®</sup> hydrofluoroalkane (HFA) (albuterol sulfate inhalation aerosol; Teva Pharmaceuticals, Inc., Frazer, PA) is a short-acting beta agonist (SABA) rescue/relief agent indicated for the treatment of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.<sup>10</sup> As a rescue/relief agent, albuterol sulfate inhalation aerosol is used to improve the symptoms of asthma while the preventer/controller agents are being titrated.<sup>11,12</sup> Accurate tracking of the administered dose is, therefore, critically important for optimal asthma control and for potentially reducing the rates of unscheduled health care utilization, and thus the cost of care, in patients with asthma.<sup>13-16</sup>

The advent of “integrated dose counters” (IDCs) led to a logistical shift in the effective management of patients with asthma.<sup>17-21</sup> IDCs may add value as they monitor rescue inhaler use; yet, they are not a standard feature across all rescue inhalers. IDCs indicate the number of actuations remaining in the canister, allowing patients to determine the number of doses available. The use of IDCs may contribute to improvements in the control of respiratory disease and respiratory-related health care utilization and costs. Results from a real-world study demonstrated reduced incidence of respiratory-related ED visits in patients using rescue inhalers with IDC compared to those with no dose counter on their inhalers.<sup>22</sup> However, there is paucity of data on the real-world impact of ProAir HFA equipped with dose counters on HRU among patients with asthma. Therefore, this study was conducted to evaluate health care resource use including hospitalizations, ED visits, and OP visits for lower respiratory tract infection (LRTI) among users of ProAir HFA with IDC compared to without IDC in patients with asthma.

## Methods

### Data source

A retrospective, observational study was conducted using patient-level administrative claims data from the Truven Health MarketScan<sup>®</sup> Commercial Claims and Encounters, and Medicare Supplemental and Coordinated Benefits Databases. The Commercial and Medicare Supplemental Databases contain administrative claims data for over 35 million covered lives (in 2013 alone) from ~150 large employers and health plans across the USA. Data included medical claims for health care services performed in both the inpatient and OP settings along with enrollment data including member demographic information, eligibility, and benefits data. The medical claims files included service dates, provider reimbursement amounts, patient copayment, and deductible amounts. Data are fully compliant with the Health Insurance Portability and Accountability Act of 1996, and because this study did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board review or approval was not required.

### Patient selection and study period

Patients between 4 and 64 years of age who received at least one new prescription for ProAir HFA with or without IDC and had at least one nonrule-out diagnosis indicative of asthma (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis code 493.xx except 493.20, 493.21, 493.22, 493.81) between January 1, 2011 through July 31, 2014, were included in the study. The date of the first ProAir HFA prescription was the index date. Patients having continuous enrollment with medical and prescription drug benefits for 6 months pre- and post-index (including the index date) period were included in the analysis, and patients with a ProAir HFA prescription in the 6 months pre-index period were not included in the results time frame. In addition, patients having a prescription for other brands of albuterol or SABAs during the pre- and post-index period were excluded. The index date was defined as the date of the first prescription fill for either ProAir HFA without IDC between January 1, 2011, and December 31, 2012 (a 2-year period “without IDC”), or for ProAir HFA with IDC between July 1, 2013 and July 31, 2014 (a 1-year period “with IDC”). The period from January 1, 2013 to June 30, 2013 (as IDC use was implemented for ProAir HFA) was not examined, because it was a time period when ProAir HFA was transitioning from not having an IDC to having an IDC. Therefore, patients included in the study utilized ProAir HFA (one or more prescriptions) during the 6-month post-index period.

## Study covariates

Patient demographic characteristics including age, gender, geographic location (US census division), population density (urban/rural), and type of health plan insurance were recorded on the index date. Clinical characteristics, including the comorbid conditions (based on the presence of ICD-9-CM diagnosis and procedure codes) and levels of utilization of oral/injectable corticosteroids and other asthma medications (based on Healthcare Common Procedure Coding System codes and National Drug Codes), were measured during the 6-month pre-admission period. In addition, the number and duration of inpatient hospitalizations and ED visits were examined.

## Outcome measures

Data on HRU, mainly respiratory-related hospitalizations and ED visits, were collected during the follow-up period. Hospitalizations were defined as respiratory-related if there was a claim with at least one of the following ICD-9-CM codes in the primary or secondary positions: 464, 466, 476, 480–488, 490–496, 500–508, or 510–519. The mean number and proportion of patients with hospital stays or ED visits, and the average number and percent of patients with OP visits for LRTI treated with antibiotics were determined. In addition, the mean number and proportion of patients with more than one albuterol inhalation aerosol prescription during the follow-up period were recorded.

## Statistical analysis

Descriptive statistics were used to test differences in demographic and clinical characteristics, as well as the health care utilization outcomes between users of albuterol inhalation aerosol with and without IDC, stratified by age. The means and standard deviations were reported for the continuous variables, and the counts and percentages were reported for the dichotomous or categorical variables. Chi-squared tests were used to evaluate the statistical significance of differences for dichotomous or categorical variables; Student's *t*-tests or Wilcoxon rank sum tests were used for comparison of continuous variables. An a priori  $p < 0.05$  was set as the threshold for statistical significance.

Multivariate generalized linear models (GLMs) and logistic regressions were used to control for potential confounding bias due to differences in pre-index patient demographics, clinical characteristics, and concomitant medications. GLMs with logit link and binomial error distribution were used to obtain the adjusted odds of post-index respiratory-related hospitalizations and ED visits among patients using albuterol

inhalation aerosol with and without IDC. Mean number of hospitalizations and ED visits was modeled using a GLM with log link and a negative binomial error distribution. Model covariates included age, gender, pre-index comorbid conditions, pre-index medication use (oral/injectable corticosteroids, ICS, long-acting beta agonists [LABAs], long-acting muscarinic antagonists [LAMAs], short-acting muscarinic antagonists [SAMAs], leukotriene receptor antagonists [LTRAs], and other medications), and pre-index all-cause health care costs. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

## Results

### Study population

A total of 422,548 patients with asthma were included in the analysis. Of these, 135,305 (32%) patients used albuterol inhalation aerosol with IDC, and 287,243 (68%) patients received albuterol inhalation aerosol without IDC (Figure 1).

### Patient characteristics

Baseline demographic and clinical characteristics stratified by cohorts and age are presented in Table 1. The mean age (32.9 vs 32.5 years) and the proportion of female patients (57.3% vs 57.9%) were similar across both cohorts. Females made up the majority in both cohorts with an exception of those in the  $\leq 17$  years subcohorts. The presence of rhinitis, gastroesophageal reflux disease (GERD), and eczema was modestly higher among the cohort with IDC compared to the cohort without IDC (all  $p < 0.05$ ). In general, baseline markers of asthma treatment were higher and all-cause hospitalizations and ED visits were lower in patients in the albuterol inhalation aerosol with IDC cohort compared to those in the cohort without IDC.

Overall, both cohorts contained an asthma population with a higher level of severity: 17.5%–20.5% of patients needed oral or injectable corticosteroids, 14.7%–15.4% had ED visits, and 3.1%–3.3% had hospitalizations in the pre-index 6 months even though they had not filled albuterol pre-index prescriptions. Only 28.2%–33.5% of patients were using maintenance ICS in any form (12.5%–14.7% were on LABAs with ICS) at baseline.

The proportion of patients in the albuterol inhalation aerosol cohort without IDC who were not receiving any asthma medications at baseline was higher than for the cohort with IDC (66.5% vs 59.8%;  $p < 0.05$ ). Patients in the IDC cohort had higher baseline use of oral or injectable corticosteroids (20.5% vs 17.5%), ICS (33.5% vs 28.2%), LABAs (14.7%



**Figure 1** Patient selection.

**Notes:** \*The date of first prescription for albuterol inhalation aerosol with IDC (albuterol with IDC cohort) and without IDC (albuterol without IDC cohort) was set as the index date.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; EIB, exercise-induced bronchoconstriction; HFA, hydrofluoroalkane; IDC, integrated dose counter; NDC, National Drug Code; SABA, short-acting beta agonist.

vs 12.5%), LAMAs (0.4% vs 0.3%), and other respiratory medications (16.1% vs 12.3%) (all  $p < 0.05$ ).

## Health care utilization

Table 2 summarizes the unadjusted health care utilization of study patients by treatment and age. The proportion of patients experiencing respiratory-related hospitalizations (2.1% vs 2.3%), ED visits (7.1% vs 8%), and LRTI-related OP visits treated with antibiotics (13.3% vs 13.7%) was significantly lower among patients using albuterol inhalation aerosol with IDC relative to the cohort without IDC. In addition, mean total numbers of respiratory-related hospitalizations and ED visits were significantly lower for the albuterol inhalation aerosol with IDC cohort compared to the cohort without IDC (all  $p < 0.05$ ) (Table 2). Those with

IDC also had a higher proportion of patients refill their albuterol prescription versus the cohort without IDC (35% vs 31.1%;  $p < 0.05$ ). These differences in health care utilization were generally seen across all age groups:  $\leq 17$ , 18–39, and 40+ (Table 2).

After adjusting for baseline confounding factors (pre-index patient demographics, clinical characteristics, and concomitant medications), the odds ratio (OR) for experiencing a respiratory-related hospitalization (OR=0.92; 95% confidence interval [CI] 0.88–0.96) or ED visit (OR=0.92; 95% CI 0.90–0.94) was significantly lower among patients using albuterol inhalation aerosol with IDC compared to those without IDC (Table 3). Similarly, the adjusted mean total numbers of respiratory-related hospitalizations and ED visits were significantly lower ( $p < 0.05$ ) among the cohort with IDC than

**Table 1** Patient demographic and clinical characteristics, by age group

Parameter	Albuterol inhalation aerosol with IDC				Albuterol inhalation aerosol without IDC			
	Age ≤17 years (N=39,826)	Age 18–39 years (N=39,358)	Age 40+ years (N=56,121)	Total (N=135,305)	Age ≤17 years (N=86,149)	Age 18–39 years (N=85,530)	Age 40+ years (N=115,564)	Total (N=287,243)
<b>Mean (SD) age, years</b>	11.0 (3.8)	28.5 (6.8)	51.6 (6.9)	32.9 (18.1)	11.0 (3.8) <sup>a</sup>	28.6 (6.7) <sup>b</sup>	51.5 (7.0) <sup>c</sup>	32.5 (18.0) <sup>d</sup>
<b>Gender, n (%)</b>								
Male	22,686 (57.0)	15,808 (40.2)	19,279 (34.4)	57,773 (42.7)	48,674 (56.5)	33,521 (39.2) <sup>b</sup>	38,630 (33.4) <sup>c</sup>	120,825 (42.1) <sup>d</sup>
Female	17,140 (43.0)	23,550 (59.8)	36,842 (65.6)	77,532 (57.3)	37,475 (43.5)	52,009 (60.8) <sup>b</sup>	76,934 (66.6) <sup>c</sup>	166,418 (57.9) <sup>d</sup>
<b>Comorbid conditions, n (%)</b>								
Rhinitis	8,417 (21.1)	5,953 (15.1)	9,784 (17.4)	24,154 (17.9)	15,045 (17.5) <sup>a</sup>	11,893 (13.9) <sup>b</sup>	18,533 (16.0) <sup>c</sup>	45,471 (15.8) <sup>d</sup>
GERD	558 (1.4)	1,365 (3.5)	4,037 (7.2)	5,960 (4.4)	1,018 (1.2) <sup>a</sup>	2,693 (3.1) <sup>b</sup>	7,676 (6.6) <sup>c</sup>	11,387 (4.0) <sup>d</sup>
Eczema	2,206 (5.5)	1,533 (3.9)	2,544 (4.5)	6,283 (4.6)	4,229 (4.9) <sup>a</sup>	3,042 (3.6) <sup>b</sup>	4,780 (4.1) <sup>c</sup>	12,051 (4.2) <sup>d</sup>
Ischemic heart disease	5 (0.02)	42 (0.1)	1,079 (1.9)	1,126 (0.8)	5 (0.01)	93 (0.1)	2,234 (1.9)	2,332 (0.8)
Other chronic respiratory diseases	85 (0.2)	69 (0.2)	244 (0.4)	398 (0.3)	122 (0.1) <sup>a</sup>	173 (0.2)	563 (0.5)	858 (0.3)
<b>Baseline medications, n (%)</b>								
Corticosteroids (oral/injectable)	5,187 (13.0)	7,206 (18.3)	15,338 (27.3)	27,731 (20.5)	9,538 (11.1) <sup>a</sup>	13,441 (15.7) <sup>b</sup>	27,367 (23.7) <sup>c</sup>	50,346 (17.5) <sup>d</sup>
Asthma drug therapy								
None	25,131 (63.1)	26,457 (67.2)	29,281 (52.2)	80,869 (59.8)	60,797 (70.6) <sup>a</sup>	62,867 (73.5) <sup>b</sup>	67,418 (58.3) <sup>c</sup>	191,082 (66.5) <sup>d</sup>
Other respiratory medications (SAMA, LTRA, other respiratory medications)	6,590 (16.5)	4,661 (11.8)	10,555 (18.8)	21,806 (16.1)	11,100 (12.9) <sup>a</sup>	7,008 (8.2) <sup>b</sup>	17,115 (14.8) <sup>c</sup>	35,223 (12.3) <sup>d</sup>
LABA <sup>e</sup>	2,514 (6.3)	5,161 (13.1)	12,184 (21.7)	19,859 (14.7)	4,551 (5.3) <sup>a</sup>	9,327 (10.9) <sup>b</sup>	22,015 (19.1) <sup>c</sup>	35,893 (12.5) <sup>d</sup>
ICS <sup>e</sup>	11,679 (29.3)	10,800 (27.4)	22,793 (40.6)	45,272 (33.5)	19,952 (23.2) <sup>a</sup>	19,535 (22.8) <sup>b</sup>	41,605 (36.0) <sup>c</sup>	81,092 (28.2) <sup>d</sup>
LAMA	6 (0.02)	49 (0.1)	480 (0.9)	535 (0.4)	9 (0.01)	90 (0.1)	812 (0.7) <sup>c</sup>	911 (0.3) <sup>d</sup>
<b>Baseline all-cause hospitalizations and ED visits</b>								
Patients with hospitalizations, n (%)	588 (1.5)	1,519 (3.9)	2,102 (3.7)	4,209 (3.1)	1,344 (1.6)	3,284 (3.8)	4,806 (4.2) <sup>c</sup>	9,434 (3.3) <sup>d</sup>
Number of hospitalizations, mean (SD)	0.017 (0.2)	0.046 (0.3)	0.044 (0.2)	0.037 (0.2)	0.018 (0.2)	0.045 (0.3)	0.049 (0.3) <sup>c</sup>	0.039 (0.2) <sup>d</sup>
Patients with ED visits, n (%)	5,629 (14.1)	6,754 (17.2)	7,482 (13.3)	19,865 (14.7)	12,995 (15.1) <sup>a</sup>	15,287 (17.9) <sup>b</sup>	15,866 (13.7) <sup>c</sup>	44,148 (15.4) <sup>d</sup>
Number of ED visits, mean (SD)	0.182 (0.5)	0.260 (0.7)	0.182 (0.6)	0.204 (0.6)	0.195 (0.5) <sup>a</sup>	0.266 (0.8)	0.188 (0.6)	0.213 (0.6) <sup>d</sup>

**Notes:** <sup>a</sup>*p*<0.05 versus patients aged ≤17 in the albuterol with IDC cohort; <sup>b</sup>*p*<0.05 versus patients aged 18–39 in the albuterol with IDC cohort; <sup>c</sup>*p*<0.05 versus patients aged 40+ in the albuterol with IDC cohort; <sup>d</sup>*p*<0.05 versus total patients in the albuterol with IDC cohort; <sup>e</sup>not mutually exclusive groups; includes combination LABA/ICS products.

**Abbreviations:** ED, emergency department; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids; IDC, integrated dose counter; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

the cohort without IDC (Figure 2). Other factors potentially leading to higher risk of hospitalizations (significant relative risk over 1.2) included older age groups (18–39 or 40+ vs <18 years), female gender, presence of ischemic heart disease, or other respiratory disease. For ED visits, the other primary risk factor was lack of asthma therapy. Potential protective factors (significant relative risks below 0.9) included presence of rhinitis (for hospitalizations and ED visits), eczema (for hospitalizations), ICS (for hospitalizations) or LABAs with ICS (for ED visits), LAMAs (for ED visits), and other respiratory medication use (for hospitalizations).

## Discussion

This study is the largest retrospective analysis to assess real-world respiratory-related health care utilization in asthma patients (N=422,548) indexed to albuterol sulfate inhalation aerosol with IDC compared to similar patients who received albuterol sulfate inhalation aerosol without IDC during a previous time period in the USA. The results of this analysis demonstrate that respiratory-related ED visits and hospitalizations were both ~8% lower in association with IDC after controlling for baseline characteristics. The mean numbers of total ED visits and total hospitalizations

**Table 2** Health care utilization among users of albuterol inhalation aerosol with and without IDC, by age group during 6 months of follow-up

Parameter	Albuterol inhalation aerosol with IDC				Albuterol inhalation aerosol without IDC			
	Age ≤17 years (N=39,826)	Age 18–39 years (N=39,358)	Age 40+ years (N=56,121)	Total (N=135,305)	Age ≤17 years (N=86,149)	Age 18–39 years (N=85,530)	Age 40+ years (N=115,564)	Total (N=287,243)
<b>Respiratory-related hospitalizations</b>								
Patients with hospitalizations, n (%)	405 (1.0)	919 (2.3)	1,452 (2.6)	2,776 (2.1)	940 (1.1)	2,190 (2.6) <sup>b</sup>	3,337 (2.9) <sup>c</sup>	6,467 (2.3) <sup>d</sup>
Number of hospitalizations, mean (SD)	0.01 (0.13)	0.03 (0.17)	0.03 (0.18)	0.02 (0.16)	0.01 (0.12)	0.03 (0.18) <sup>b</sup>	0.032 (0.20) <sup>c</sup>	0.02 (0.17) <sup>d</sup>
<b>Respiratory-related ED visits</b>								
Patients with ED visits, n (%)	2,475 (6.2)	3,685 (9.4)	3,484 (6.2)	9,644 (7.1)	6,320 (7.3) <sup>a</sup>	8,575 (10.0) <sup>b</sup>	7,994 (6.9) <sup>c</sup>	22,889 (8.0) <sup>d</sup>
Number of ED visits, mean (SD)	0.07 (0.28)	0.11 (0.38)	0.07 (0.30)	0.08 (0.32)	0.08 (0.31) <sup>a</sup>	0.12 (0.39) <sup>b</sup>	0.08 (0.31) <sup>c</sup>	0.09 (0.33) <sup>d</sup>
<b>LRTI OP visits treated with antibiotics</b>								
Patients with office visits, n (%)	3,954 (9.9)	4,942 (12.6)	9,119 (16.2)	18,015 (13.3)	9,984 (11.6) <sup>a</sup>	10,867 (12.7)	18,371 (15.9)	39,222 (13.7) <sup>d</sup>
Number of office visits, mean (SD)	0.12 (0.38)	0.15 (0.43)	0.20 (0.50)	0.2 (0.45)	0.13 (0.40) <sup>a</sup>	0.15 (0.43)	0.19 (0.49) <sup>c</sup>	0.16 (0.45) <sup>d</sup>
<b>Albuterol HFA prescriptions</b>								
Number of patients with >1 albuterol HFA Rx, n (%)	11,888 (29.8)	13,648 (34.7)	21,868 (39.0)	47,404 (35.0)	24,659 (28.6) <sup>a</sup>	25,522 (29.8) <sup>b</sup>	39,109 (33.8) <sup>c</sup>	89,290 (31.1) <sup>d</sup>
Mean (SD) albuterol HFA Rx among patients with >1 albuterol HFA Rx	2.45 (0.92)	2.99 (1.53)	2.87 (1.39)	2.80 (1.35)	2.37 (0.78) <sup>a</sup>	2.74 (1.32) <sup>b</sup>	2.72 (1.26) <sup>c</sup>	2.60 (1.18) <sup>d</sup>

**Notes:** <sup>a</sup>*p*<0.05 versus patients aged ≤17 years in the albuterol HFA with IDC cohort; <sup>b</sup>*p*<0.05 versus patients aged 18–39 years in the albuterol HFA with IDC cohort; <sup>c</sup>*p*<0.05 versus patients aged 40+ in the albuterol HFA with IDC cohort; <sup>d</sup>*p*≤0.05 versus total patients in the albuterol HFA with IDC cohort.

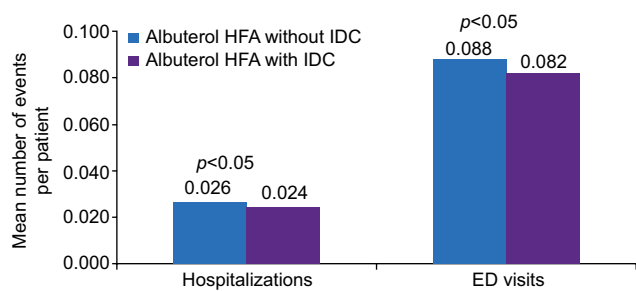
**Abbreviations:** ED, emergency department; HFA, hydrofluoroalkane; IDC, integrated dose counter; LRTI, lower respiratory tract infection; OP, outpatient; SD, standard deviation.

**Table 3** Multivariable logistic regression odds ratios for predicting respiratory-related hospitalizations and ED visits during 6-month follow-up<sup>a</sup>

Effect	Respiratory-related hospitalizations, odds ratio (confidence level)	Respiratory-related ED visits, odds ratio (confidence level)
Albuterol inhalation aerosol metered dose (ref=nonmetered dose)	0.92 (0.88–0.96) <sup>b</sup>	0.92 (0.90–0.94) <sup>c</sup>
<b>Demographic variables</b>		
Age group 18–39 years (ref=age <18 years)	1.74 (1.62–1.86) <sup>c</sup>	1.32 (1.29–1.37) <sup>c</sup>
Age group 40+ years (ref=age <18 years)	1.52 (1.42–1.63) <sup>c</sup>	0.87 (0.85–0.90) <sup>c</sup>
Female (ref=male)	1.23 (1.17–1.29) <sup>c</sup>	1.12 (1.09–1.14) <sup>c</sup>
<b>Clinical variables (ref=no)</b>		
Rhinitis	0.64 (0.60–0.68) <sup>c</sup>	0.73 (0.71–0.76) <sup>c</sup>
GERD	1.03 (0.95–1.11)	1.11 (1.05–1.18) <sup>b</sup>
Eczema	0.82 (0.74–0.92) <sup>b</sup>	0.97 (0.92–1.03)
Ischemic heart disease	1.26 (1.10–1.46) <sup>d</sup>	1.10 (0.98–1.25)
Other chronic respiratory disease	1.76 (1.40–2.20) <sup>c</sup>	1.03 (0.84–1.27)
Oral or injectable corticosteroids	1.06 (1.01–1.12) <sup>d</sup>	1.15 (1.11–1.18) <sup>c</sup>
ICS	0.78 (0.69–0.88) <sup>c</sup>	0.93 (0.87–1.01)
LABA (with ICS)	1.00 (0.92–1.08)	0.90 (0.86–0.95) <sup>c</sup>
LAMA	0.96 (0.72–1.30)	0.80 (0.63–1.03)
Other respiratory medications (SAMA, LTRA, and other)	0.87 (0.80–0.95) <sup>d</sup>	0.92 (0.88–0.98) <sup>d</sup>
No asthma drug therapy	1.13 (1.00–1.29)	1.32 (1.22–1.42) <sup>c</sup>
Pre-index all-cause total health care costs (log)	1.58 (1.56–1.60) <sup>c</sup>	1.08 (1.07–1.09) <sup>c</sup>

**Notes:** <sup>a</sup>Results were controlled for baseline demographics and pre-index clinical characteristics, medication use, and health care costs; all tests were statistically significant at <sup>b</sup>*p*<0.001; <sup>c</sup>*p*<0.0001; <sup>d</sup>*p*<0.05.

**Abbreviations:** ED, emergency department; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SAMA, short-acting muscarinic antagonist.



**Figure 2** Adjusted per-patient number of respiratory-related hospitalizations and ED visits during the 6-month follow-up period.

**Notes:** Utilization estimates based on the method of recycled predictions using the regression coefficient for albuterol HFA with IDC controlling for demographic and pre-index clinical characteristics and medication use.

**Abbreviations:** ED, emergency department; HFA, hydrofluoroalkane; IDC, integrated dose counter.

were also reduced significantly ( $p < 0.05$ ) in IDC users after controlling for potential confounders.

Baseline markers of asthma treatment were higher and all-cause hospitalizations and ED visits were lower in the IDC group. These findings likely represent differences in the two unique patient populations with respect to asthma severity and may also suggest that asthma care strategies may have changed from 2011–2012 to the later 2013–2014 period when patients received an albuterol inhalation aerosol prescription at the index date. In addition, it is important to note that the USA implemented the Affordable Care Act, which increased access for ~8 million patients beginning January 2014, which may have impacted these rates. Assessment of the patients' therapeutic profiles at baseline suggests that many selected patients may have had seasonal asthma or asthma triggered by infection as their predominant disease state.

Similar results were seen when patients in each treatment cohort were stratified by age, with patients using albuterol inhalation aerosol with IDC having significantly lower rates and mean numbers of hospitalizations and ED visits compared to their non-IDC counterparts. Consistent with our findings, a historical cohort study of 75,787 patients with asthma aged 4–64 years (53,964 using albuterol with a dose counter and 21,823 using albuterol without a dose counter) by Price et al demonstrated that patients using an inhaler with a dose counter had a 51% lower incidence of respiratory-related ED visits (adjusted rate ratio: 0.49; 95% CI 0.41–0.59).<sup>22</sup> The authors speculated that the albuterol dose counters may have enabled patients to determine when their rescue medication was empty, and/or when additional controller adherence was needed, thus preventing them from using an empty inhaler during an asthma exacerbation.<sup>22</sup> The addition of a dose counter can help to reduce ED visits, thereby reducing health care costs associated with asthma.

When using SABA metered-dose inhalers (MDIs) without IDCs, it may be difficult for the patient to gauge increasing use of rescue/relief medication as a sign of worsening asthma control, or to determine the remaining number of effective doses of rescue/relief medication.<sup>13,20,23</sup> This study was not designed to determine whether the utilization benefit of rescue/relief inhaled delivery devices tagged to an effective IDC is the result of increased patient insight into disease status (i.e., an early warning regarding impending loss of control), increased awareness of drug content (i.e., impending empty SABA inhaler), or both. Several study findings suggest, however, that the ability of an IDC to optimize controller therapy by targeting patients with increasing SABA use is at least a partial factor in the utilization benefit. These results include: 1) the finding at baseline of relatively low usage rates of ICS controller therapy (28.2%–33.5%) coupled with relatively high levels of acuity (14.7%–15.4% having ED visits); 2) the finding of “no asthma therapy” as a primary risk factor for ED visits; and 3) the finding that the use of an ICS controller is a potential protective factor for hospitalizations.

The small but significant utilization reduction associated with an IDC in this study should be understood in the context of the potentially low penetrance of IDC engagement by patients and providers in the “real-world” setting. For example, in a phone survey, only 36% of bronchodilator users reported ever having been told to keep track of MDI doses.<sup>14</sup> In the future, newer technologies may improve patient engagement with their asthma therapy, and gains in disease management may be possible if data for rescue dosing are better integrated into practice. In a recent study, telemonitoring of SABA use via a patient-facing smartphone application, with dose reporting to providers, was associated with decreased use of rescue medication and improved asthma control among those adults initially lacking asthma control.<sup>24</sup>

There are some aspects of the retrospective analysis design that may impact the study results. This study analyzed asthma patients newly treated with albuterol inhalation aerosol who had not received any other SABAs in the pre-index period; these criteria may have resulted in the selection of an intermittent, poorly adherent, or seasonally exacerbating asthma population. In addition, dose counters have become more commonly used in recent years. Baseline data showed somewhat increased use of asthma controllers (ICS, LABAs, and LAMAs) in the later 2013–2014 period compared to the earlier 2011–2012 cohort of patients, which may have reflected a national incentive for enhanced quality of care, as the Affordable Care Act, with widespread use of electronic medical records, and health quality tracking became

implemented during late 2013 and 2014. The inconsistent use of asthma medications, with only 28%–34% of patients utilizing ICS, may have influenced ED and hospitalization rates. Baseline medications were included in the multivariate models; therefore, the confounding effects of these variables were controlled in the analysis. Future prospective studies could evaluate patients enrolled at a single point in time and randomly assign patients to albuterol with or without IDC to prospectively monitor outcomes occurring over concurrent time frames.

There are a few additional limitations of this study. The MarketScan databases rely on administrative claims data for clinical detail; therefore, the data may be subject to data coding limitations and data entry error. This analysis was conducted over a relatively short follow-up time frame (e.g., 6 months post-index), and hospitalizations and ED visits in general are a relatively rare outcome. More pronounced results may be seen with longer follow-up. Finally, this study was limited to asthma patients who utilized health care services and continuously enrolled with commercial or private Medicare supplemental coverage, thereby limiting the generalizability of the findings to all asthma patients, especially those with other insurance or without health insurance coverage. The methodology of this study is not able to identify the degree to which the improvements seen reflect general improvements in health care delivery for asthma during 2011–2014 or the extent to which the use of an IDC device contributed to a reduction in health care utilization.

Notable strengths of this analysis include the fact that a very large patient population drawn from administrative claims data across the USA was evaluated. In addition, this study provides real-world data on respiratory-related health care utilization (hospitalizations, ED visits, and LRTI-related OP visits) among asthma patients indexed to albuterol inhalation aerosol with or without IDC in a geographically diverse population.

## Conclusion

In a real-world setting during 2013–2014, patients with asthma using albuterol sulfate inhalation aerosol with IDC experienced significantly fewer hospitalizations and ED visits compared to a cohort of patients using albuterol inhalation aerosol without IDC in 2011–2012. Dosage information provided by IDCs may improve treatment outcomes by decreasing the likelihood that the canister will be empty when needed, thereby enhancing disease management and reducing health care utilization, specifically respiratory-related hospitalizations and ED visits.<sup>3,13,15–17</sup> Therefore, IDCs may be of value for long-term health care cost savings, which is

in line with key national health policy objectives. Long-term studies in patients with all levels of asthma severity are warranted to validate the findings of this study.

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## Disclosure

Edward M Kerwin has served on advisory boards and speaker panels, or received travel reimbursement, from Amphastar, AstraZeneca, Forest, Ironwood, Merck, Mylan, Novartis, Pearl, Pfizer, Sanofi Aventis, Sunovion, Targacept, Teva, and Theravance, and has conducted multicenter clinical research trials for ~40 pharmaceutical companies including Teva. Thomas J Ferro, Rinat Ariely, and Ruchir Parikh are employees of Teva Pharmaceuticals. Debra E Irwin discloses that her institution receives funding from all major pharmaceutical companies to conduct research studies, but she does not personally receive any support. The authors report no other conflicts of interest in this work.

## References

- Centers for Disease Control and Prevention. National surveillance of asthma: United States, 2001–2010. Available from: [http://www.cdc.gov/nchs/data/series/sr\\_03/sr03\\_035.pdf](http://www.cdc.gov/nchs/data/series/sr_03/sr03_035.pdf). Accessed June 28, 2016.
- Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax*. 2000;55(7):566–573.
- Hasegawa K, Tsugawa Y, Brown DF, Camargo CA Jr. A population-based study of adults who frequently visit the emergency department for acute asthma. California and Florida, 2009–2010. *Ann Am Thorac Soc*. 2014;11(2):158–166.
- Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. *J Allergy Clin Immunol*. 2011;127(1):145–152.
- Barnett ML, Wier LM, Washington R. Trends in pediatric and adult hospital stays for asthma, 2000–2010: Statistical Brief #169. In: *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs* [Internet]. Rockville, MD: Agency for Health Care Policy and Research (US); 2014. Available from: <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb169-Asthma-Trends-Hospital-Stays.jsp>. Accessed June 28, 2016.
- Wang T, Srebotnjak T, Brownell J, Hsia RY. Emergency department charges for asthma-related outpatient visits by insurance status. *J Health Care Poor Underserved*. 2014;25(1):396–405.
- Stanford R, McLaughlin T, Okamoto LJ. The cost of asthma in the emergency department and hospital. *Am J Respir Crit Care Med*. 1999;160(1):211–215.
- National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Full report. 2007. Available from: <https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report>. Accessed June 28, 2016.



9. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2015.
10. ProAir® HFA (albuterol sulfate) [prescribing information] Horsham, PA: Teva Respiratory LLC; June 2016. Available from: [http://proair.com/hfa/library/docs/HFA\\_PI.pdf](http://proair.com/hfa/library/docs/HFA_PI.pdf). Accessed June 28, 2016.
11. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev*. 2012;64(3):450–504.
12. Lazarinis N, Jørgensen L, Ekström T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax*. 2014;69(2):130–136.
13. Conner JB, Buck PO. Improving asthma management: the case for mandatory inclusion of dose counters on all rescue bronchodilators. *J Asthma*. 2013;50(6):658–663.
14. Sander N, Fusco-Walker SJ, Harder JM, Chipps BE. Dose counting and the use of pressurized metered-dose inhalers: running on empty. *Ann Allergy Asthma Immunol*. 2006;97(1):34–38.
15. Hasegawa K, Brenner BE, Clark S, Camargo CA. Emergency department visits for acute asthma by adults who ran out of their inhaled medications. *Allergy Asthma Proc*. 2014;35(3):42–50.
16. Reznik M, Ozuah PO. Measurement of inhaled corticosteroid adherence in inner-city, minority children with persistent asthma by parental report and integrated dose counter. *J Allergy (Cairo)*. 2012;2012:570850.
17. Weinstein C, Staudinger H, Scott I, Amar NJ, LaForce C. Dose counter performance of mometasone furoate/formoterol inhalers in subjects with asthma or COPD. *Respir Med*. 2011;105(7):979–988.
18. Kaur I, Aggarwal B, Gogtay J. Integration of dose counters in pressurized metered-dose inhalers for patients with asthma and chronic obstructive pulmonary disease: review of evidence. *Expert Opin Drug Deliv*. 2015;12(8):1301–1310.
19. Sheth K, Wasserman RL, Lincourt WR, Locantore NW, Carranza-Rosenzweig J, Crim C. Fluticasone propionate/salmeterol hydrofluoroalkane via metered-dose inhaler with integrated dose counter: performance and patient satisfaction. *Int J Clin Pract*. 2006;60(10):1218–1224.
20. Wasserman RL, Sheth K, Lincourt WR, Locantore NW, Rosenzweig JC, Crim C. Real-world assessment of a metered-dose inhaler with integrated dose counter. *Allergy Asthma Proc*. 2006;27(6):486–492.
21. Shah S, White M, Uryniak T, O'Brien CD. The functionality of a budesonide/formoterol pressurized metered-dose inhaler with an integrated actuation counter. *Allergy Asthma Proc*. 2010;31(1):40–48.
22. Price DB, Rigazio A, Small MB, Ferro TJ. Historical cohort study examining comparative effectiveness of albuterol inhalers with and without integrated dose counter for patients with asthma or chronic obstructive pulmonary disease. *J Asthma Allergy*. 2016;9:145–154.
23. Holt S, Holt A, Weatherall M, Masoli M, Beasley R. Metered dose inhalers: a need for dose counters. *Respirology*. 2005;10(1):105–106.
24. Merchant RK, Inamdar R, Quade RC. Effectiveness of population health management using the propeller health asthma platform: a randomized clinical trial. *J Allergy Clin Immunol Pract*. 2016;4(3):455–463.

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