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ORIGINAL RESEARCH

Differences in health care outcomes between postdischarge COPD patients treated with inhaled corticosteroid/long-acting β_2-agonist via dry-powder inhalers and pressurized metered-dose inhalers

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Purpose: The aim of this study was to examine real-world differences in health care resource use (HRU) and costs among COPD patients in the USA treated with a dry powder inhaler (DPI) or pressurized metered-dose inhaler (pMDI) following a COPD-related hospitalization.

Methods: This retrospective analysis used the Truven MarketScan® databases. Eligibility criteria included 1) age ≥40 years, 2) COPD diagnosis, 3) inpatient admission with a diagnosis of COPD exacerbation, 4) inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) prescription within 10 days of hospital discharge (index date), and 5) continuous enrollment for 12 months preindex and 90 days postindex. Outcomes included pre- and postindex HRU and costs. DPI and pMDI groups were compared on postindex outcomes via multivariate models controlling for demographic and baseline characteristics.

Results: The sample included 1,960 DPI and 1,086 pMDI ICS/LABA patients. During the preindex period, pMDI patients were significantly more likely to be prescribed a short-acting β-agonist, experienced more COPD exacerbation-related hospital days, and had a greater number of pulmonologist visits compared to DPI patients ($P<0.05$), all suggestive of greater disease severity. However, multivariate models revealed that pMDI patients incurred 10% lower all-cause postindex costs (predicted mean costs [2016 US dollars]: $2,673 vs $2,956) and 19% lower COPD-related costs (predicted mean costs: $138 vs $169; $P<0.05$). Additionally, pMDI patients were 28% less likely to experience a COPD exacerbation-related hospital readmission within 60 days postdischarge compared to the DPI patients (OR: 0.72, 95% CI: 0.52–0.99, $P<0.05$).

Conclusion: Despite greater COPD-related HRU and costs preceding index hospitalization, US patients using a pMDI after hospital discharge incurred significantly lower all-cause and COPD-related health care costs compared with those using a DPI, in addition to a decreased likelihood of a COPD exacerbation-related hospital readmission. Results suggest that inhaler device type may influence COPD outcomes and that COPD patients may derive greater clinical benefit from treatment delivered via pMDI vs DPI.

Keywords: COPD, inhaler, inhaled corticosteroid, long-acting β_2-agonist, utilization, costs

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Introduction

COPD is a common, progressive pulmonary disease characterized by persistent airflow limitation.[1] The leading risk factor for COPD is extended inhalation of noxious particles or gases, usually from cigarette smoking, although pollution and occupational

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exposures can also be sources.[2] In 2014, COPD and other chronic lower respiratory diseases were the third leading cause of mortality in the USA,[3] with mortality rates increasing more than 30% between 1980 and 2014.[4]

Patients with COPD often have periods of acute worsening of symptoms or COPD exacerbations.[5] Moderate exacerbations require the use of antibiotics and/or systemic corticosteroids, whereas severe exacerbations result in hospitalization, which accounts for as much as 70% of COPD-related medical costs.[6–8] Reduction in exacerbation severity and frequency is a primary clinical objective. The total US national medical cost of COPD was estimated at $32.1 billion for 2010 and is projected to rise to $49 billion by 2020.[9]

Current COPD guidelines recommend treating symptomatic, stable COPD patients with inhaled long-acting bronchodilators, such as a long-acting β_2-agonist (LABA).[10] For the prevention of acute exacerbations in patients at risk for exacerbations, especially those with COPD-related hospitalizations, guidelines recommend the use of an inhaled corticosteroid (ICS) in combination with inhaled long-acting bronchodilators.[11] Selection of the specific pharmaceutical agent and delivery mechanism is left to the prescribing clinician based on patient preference, cost, and adverse effect profile.

For home use, inhaled COPD medications are most commonly delivered using either a dry powder inhaler (DPI) or a pressurized metered-dose inhaler (pMDI). These devices can be challenging to use for some patients, with administration errors commonly occurring and potentially resulting in inadequate dose delivery.[12,13] Each delivery system has requirements and limitations, making appropriate device selection and education a critical component of COPD care.[10,14]

Poor technique for various inhaler devices can be addressed with educational interventions; however, effective device usage is also dependent on patient physical characteristics.[15] For example, a systematic review found that 45% of pMDI users had suboptimal hand-breath coordination for optimal drug delivery.[16] Coordination limitations can be addressed by the use of holding chambers or spacers;[17] however, errors in handling, execution, and breath technique are still common.[16] Effective drug delivery via a DPI requires that the patient generates levels of inspiratory flow sufficient to overcome the resistance of the device.[18] In other words, the energy required to aerosolize a DPI medication comes from the user, and adequate DPI medication delivery relies on proper technique, sufficient effort from a patient, and a lack of medical conditions that might otherwise prevent adequate inspiratory flows. Importantly, peak inspiratory flow needed for DPI administration is often limited by lung hyperinflation, especially after an acute exacerbation. Recent studies of peak inspiratory flow after recovery from an acute exacerbation found that 19%–52% of COPD patients had insufficient peak inspiratory flow for effective DPI use, and those patients were more likely to be older and have more severe disease.[19–21]

Successful delivery of medication is required to achieve the desired benefit of reduced exacerbation and hospitalization frequency.[22] Poor inhalation technique has been estimated to increase direct medical costs of COPD by 2.2%–7.7%.[23] A randomized controlled trial of inhaled ICS/LABA combination therapy of fluticasone propionate/salmeterol xinafoate (FP/SAL) found no difference in clinical benefit between patients using a DPI or a pMDI.[24] However, patients enrolled in clinical trials are subject to strict inclusion criteria, receive more consistent training in inhaler use and are excluded if they are unable to effectively use a study device, have had a recent exacerbation, or suffer from very severe lung disease. In a real-world, retrospective matched cohort observational study of 236 patient pairs treated with a 500 μg/day dose of FP/SAL, those using a pMDI had fewer moderate-to-severe exacerbations compared with those using a DPI at equivalent dosage.[25]

This retrospective claims-based study examined real-world differences in all-cause and acute exacerbation of COPD (AECOPD)-related readmission rates within 30 and 60 days of discharge after hospitalization for an AECOPD among patients in the USA treated with an ICS/LABA combination delivered via DPI or pMDI. Treatment groups were also compared based on all-cause and COPD-related health care resource use (HRU), such as inpatient admissions, emergency room (ER) visits, outpatient office visits, and the associated costs. Results will provide much-needed evidence on the association between different types of inhaled medication delivery devices and health care outcomes in a real-world setting.

Methods

Data sources

This observational retrospective cohort analysis utilized de-identified US administrative claims data from the Truven Health Analytics MarketScan® Commercial Claims and Encounters database (Commercial) and MarketScan® Medicare Supplemental and Coordination of Benefits database (Medicare Supplemental) for the period from January 1, 2009, to July 29, 2016. Each database captures the inpatient medical, outpatient medical, and outpatient prescription drug

data for its respective covered population and together forms a nationally representative sample of insured individuals living in the USA.

Ethics approval and informed consent

All study data were accessed with protocols compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations (HIPAA). As the database is fully de-identified and compliant with the HIPAA, this study was exempted from Institutional Review Board approval.

Patient selection criteria

To be eligible for the current study, patients were required to have at least two nondiagnostic claims with a diagnosis of COPD (ICD-9-CM: 490.xx–492.xx and 496.xx; ICD-10: J40, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, and J44.9) between January 1, 2010, and April 30, 2016, and at least one prescription claim for an ICS/LABA combination therapy during the same period. Eligible therapies include budesonide and formoterol, fluticasone furoate and vilanterol, FP/SAL, and mometasone and formoterol. Patients had to be aged ≥40 years on the date of the first prescription claim for an ICS/LABA combination therapy, which must have been within 10 days after an inpatient discharge with a primary diagnosis of an AECOPD (ICD-9-CM: 491.21, 491.22, and 492.8; ICD-10: J44.1). The date of the prescription was set as the index date, and the date of the hospital discharge was set as the index discharge date.

Patients were required to fill a prescription for an ICS/LABA combination therapy dispensed by either a DPI or a pMDI, but not both, on the index date. Patients were required to have at least 15 months of continuous enrollment with medical and pharmacy benefits (12 months prior and 90 days following and including the index date). Patients were excluded if they had an asthma diagnosis during the 12-month preindex period or a diagnosis of cystic fibrosis, pulmonary fibrosis, bronchiectasis, or respiratory tract cancer anytime during the study period. Finally, patients with a prescription claim for any tiotropium medication within 90 days before or on the index date were excluded. Patients were not excluded based on short-acting β-agonist (SABA) usage in either the pre- or postindex periods, as these medications are commonly prescribed as rescue medications.[5]

Outcome measures

All-cause and AECOPD-related readmissions within 30 and 60 days after the index discharge date were assessed for all patients. Results were reported as the proportion of patients with one or more readmissions by the selected time point and as the time to the first readmission after the index discharge date.

All-cause and COPD-related HRU and costs were measured during both the 12-month pre-index and the 90-day postindex periods. HRU was reported for inpatient admissions, ER visits, physician office visits, outpatient laboratory and radiology services, outpatient prescriptions, and other outpatient services. Costs were calculated based on the paid amounts for adjudicated claims including portions paid by both insurers and the patient. All costs are reported as per person per month (PPPM) and were adjusted to 2016 US dollars using the medical care component of the consumer price index.[26]

Demographic and clinical characteristics

Patients' demographic characteristics were assessed on the index date and included age, age group, sex, geographic region, insurance plan type, payer type, and rural residence indicator. Urban or rural residence classification was based on whether the primary subscriber's address was located within a metropolitan statistical area.

Clinical characteristics were assessed during the 12-month preindex period and included the Deyo–Charlson comorbidity score, selected comorbid conditions (acute bronchitis and bronchiolitis, anxiety, asthma, cardiovascular disease, acute myocardial infarction, congestive heart failure, ischemic stroke, depression, diabetes, gastroesophageal reflux disease, hypertension, osteoporosis, osteoarthritis, and pneumonia), COPD severity indicators (hospitalization days due to AECOPD, pulmonologist visits, SABA prescription fills, and oral corticosteroid prescription fills), respiratory treatments (oxygen therapy, nebulizer use, and COPD medications), and medications for other common chronic conditions (antihypertensive, diabetes, and lipid-lowering medications).

Statistical analyses

Patients were segmented by their index device for all analyses. Descriptive statistics was calculated for demographics, clinical characteristics, and all outcome measures. For continuous variables, the mean and SD were calculated, with statistically significant differences between device groups assessed via Student's *t*-test. For categorical variables, the counts and percentages were calculated, with statistically significant differences between device groups assessed via Chi-squared test. The alpha level for all statistical tests was 0.05.

Logistic regression models were built to assess the association between inhaler type and binary outcomes including all-cause and AECOPD-related readmissions within 30 and 60 days in the postindex period. Cox proportional hazards models were used to assess the association between inhaler type and time to readmission (all-cause and AECOPD related) within 30 and 60 days of the index discharge date. Generalized linear models with gamma distributions were used to assess the association between inhaler type and costs (all-cause and AECOPD related) during the postindex period. The vector of covariates included in all models were as follows: age, sex, geographic region, insurance plan type, rural residence indicator, preindex myocardial infarction, preindex ischemic stroke, preindex SABA prescription, number of preindex AECOPD-related inpatient days, preindex experience with the index inhaler type, and number of preindex pulmonologist visits.

Results

Baseline patient characteristics

A total of 3,046 patients were eligible for study inclusion, with 64.3% (n=1,960) prescribed a DPI, and 35.7% (n=1,086) prescribed a pMDI (Figure 1). Demographic characteristics as assessed on the index date are listed in Table 1. DPI and pMDI groups did not differ with respect to age or sex, with approximately 46% of the sample being male and 53% aged 65 years or older. The majority of patients lived in urban areas (79%), and they were insured by a Medicare supplemental plan (55%). There were slight differences in the type of coverage between groups (±2%, $P<0.01$), with pMDI users being more likely to have comprehensive/indemnity, health maintenance organization, or consumer-driven/high-deductible health plans.

Clinical characteristics in the 12-month preindex period are listed in Table 1. Both cohorts had a mean Deyo-Charlson

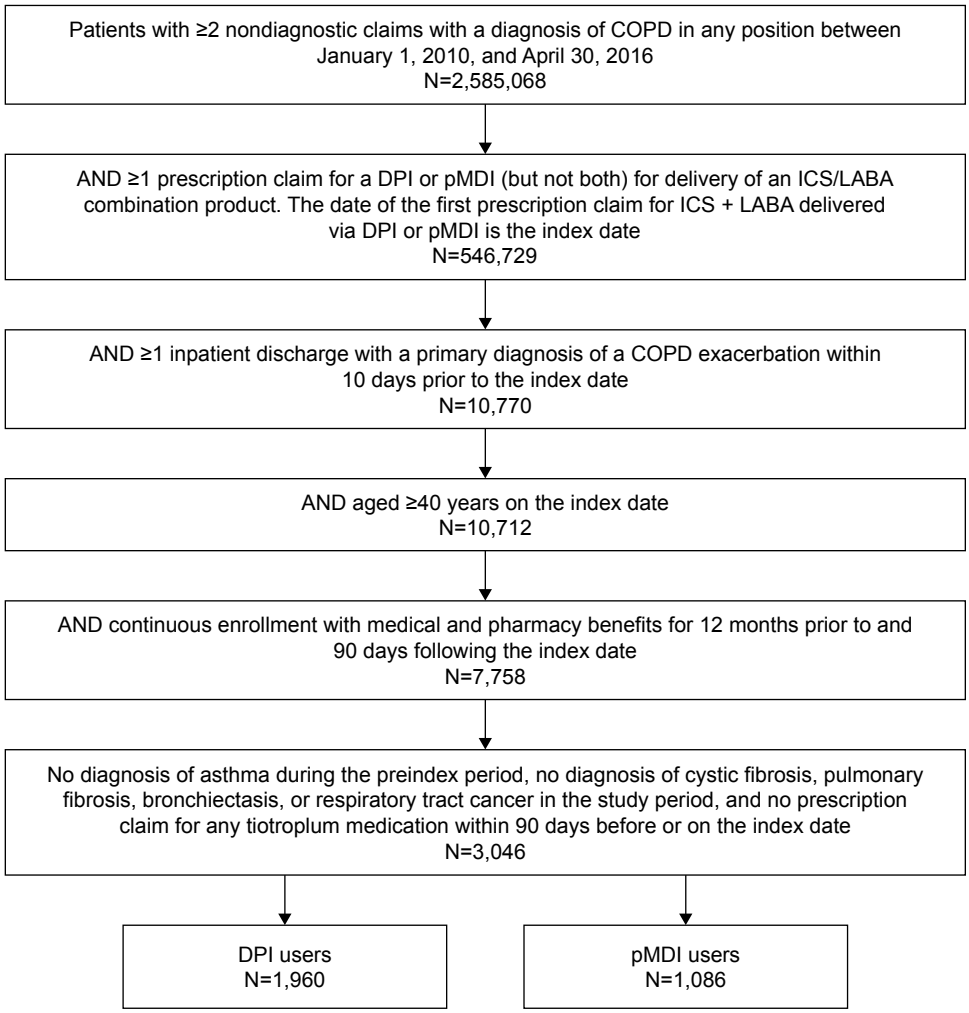

Figure 1 Patient selection.
Abbreviations: AECOPD, acute exacerbation of COPD; DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; pMDI, pressurized metered-dose inhaler.

Table 1 Demographic and clinical characteristics

	DPI (N=1,960)		pMDI (N=1,086)		*P*-value
	n/mean	%/SD	n/mean	%/SD	
Demographics[a]					
Age (years), mean, SD	67.7	12.1	67.5	11.9	0.60
Age (years) (n, %)					
40–44	27	1.4%	14	1.3%	0.74
45–49	84	4.3%	40	3.7%	
50–54	145	7.4%	94	8.7%	
55–59	280	14.3%	161	14.8%	
60–64	379	19.3%	197	18.1%	
65+	1,045	53.3%	580	53.4%	
Male (n, %)	903	46.1%	509	46.9%	0.67
Geographic region (n, %)					
Northeast	381	19.4%	160	14.7%	<0.0001
North Central	696	35.5%	443	40.8%	
South	638	32.6%	408	37.6%	
West	226	11.5%	65	6.0%	
Unknown	19	1.0%	10	0.9%	
Insurance plan type (n, %)					
Comprehensive/indemnity	636	32.4%	371	34.2%	<0.01
EPO/PPO	874	44.6%	457	42.1%	
POS/POS with capitation	120	6.1%	47	4.3%	
HMO	194	9.9%	129	11.9%	
CDHP/HDHP	62	3.2%	54	5.0%	
Unknown	74	3.8%	28	2.6%	
Payer (n, %)					
Commercial	884	45.1%	487	44.8%	0.89
Medicare supplemental	1,076	54.9%	599	55.2%	
Rural residence indicator (n, %)					
Urban	1,551	79.1%	849	78.2%	0.80
Rural	390	19.9%	227	20.9%	
Unknown	19	1.0%	10	0.9%	
Clinical characteristics[b]					
Deyo–Charlson comorbidity index, mean, SD	2.4	1.8	2.4	1.8	0.62
Comorbid conditions (n, %)					
Acute bronchitis and bronchiolitis	654	33.4%	370	34.1%	0.69
Anxiety	234	11.9%	139	12.8%	0.49
Cardiovascular disease	509	26.0%	286	26.3%	0.83
Acute myocardial infarction	78	4.0%	25	2.3%	0.01
Congestive heart failure	462	23.6%	250	23.0%	0.73
Ischemic stroke	33	1.7%	30	2.8%	0.045
Depression	301	15.4%	151	13.9%	0.28
Diabetes (type I or II)	524	26.7%	310	28.5%	0.28
Gastroesophageal reflux disease	233	11.9%	147	13.5%	0.19
Hypertension	1,282	65.4%	734	67.6%	0.22
Osteoarthritis	304	15.5%	159	14.6%	0.52
Osteoporosis	92	4.7%	41	3.8%	0.23
Pneumonia	681	34.7%	378	34.8%	0.97

(*Continued*)

Table 1 (*Continued*)

	DPI (N=1,960)		pMDI (N=1,086)		*P*-value
	n/mean	%/SD	n/mean	%/SD	
Antihypertensive medication (n, %)	1,332	68.0%	768	70.7%	0.12
Diabetes medication (n, %)	411	21.0%	240	22.1%	0.47
Lipid-lowering medication (n, %)	916	46.7%	534	49.2%	0.20
Respiratory treatments (n, %)					
Oxygen therapy	384	19.6%	191	17.6%	0.18
Nebulizer use	208	10.6%	127	11.7%	0.36
Maintenance medications[a]					
ICS	92	4.7%	58	5.3%	0.43
LABA	21	1.1%	15	1.4%	0.45
Long-acting muscarinic antagonist	118	6.0%	66	6.1%	0.95
Methylxanthines	20	1.0%	18	1.7%	0.13
Phosphodiesterase-4 inhibitors	2	0.1%	2	0.2%	0.55
SABA	714	36.4%	436	40.1%	0.04
Short-acting muscarinic antagonist	73	3.7%	50	4.6%	0.24
Systemic corticosteroids	842	43.0%	505	46.5%	0.06
Macrolide antibiotics	686	35.0%	406	37.4%	0.19
Single fill of a macrolide	464	67.6%	271	66.7	0.76
Multiple fills of a macrolide	222	32.4	135	33.3	
Leukotriene modifiers	76	3.9%	42	3.9%	0.99
Preindex use of index ICS/LABA inhaler type,[c,d] N, %	95	4.8%	411	37.8%	<0.0001
COPD severity, mean, SD					
Number of hospitalization days due to AECOPD	3.7	2.5	4.0	2.9	0.01
Number of pulmonologist visits	1.6	3.8	1.9	4.1	0.03
Number of SABA fills	1.0	2.4	1.2	2.6	0.09
Number of oral corticosteroid fills	0.9	1.8	1.0	1.7	0.22

Notes: [a]Assessed on the index date. [b]Assessed during the 12-month preindex period. [c]All patients with a preindex ICS + LABA had an index date in 2010. [d]Any ICS + LABA, ICS alone, LABA alone, or SABA medication delivered via DPI/pMDI.

Abbreviations: AECOPD, acute exacerbation of COPD; CDHP, consumer-driven health plan; DPI, dry powder inhaler; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; pMDI, pressurized metered-dose inhaler; POS, point of service; PPO, preferred provider organization; SABA, short-acting β-agonist.

comorbidity index of 2.4 and also a similar prevalence of the measured comorbid conditions, except for a higher prevalence of acute myocardial infarction in the DPI cohort (4.0% DPI vs 2.3% pMDI, $P<0.05$) and a higher prevalence of ischemic stroke in the pMDI cohort (1.7% DPI vs 2.8% pMDI, $P<0.05$). Rates of prescription medication fills for common chronic conditions (hypertension, diabetes, and high cholesterol) were similar for both groups. A significantly larger proportion of pMDI users filled a SABA prescription during the preindex period (36.4% DPI vs 40.1% pMDI, $P<0.05$), but otherwise there was no significant difference in respiratory treatments. Patients prescribed a pMDI had significantly more hospitalization days due to AECOPD (3.7±2.5 DPI vs 4.0±2.9 pMDI, $P<0.02$) and more outpatient pulmonologist visits (1.6±3.8 DPI vs 1.9±4.1 pMDI, $P<0.05$) in the preindex period. The pMDI group was significantly more likely than DPI users to have preindex experience with their index device type (4.8% DPI vs 37.8% pMDI, $P<0.0001$).

Baseline all-cause and COPD-related HRU and costs are listed in Table 2. During the 12-month preindex period, DPI users were more likely to visit the ER for both all-cause (48.0% DPI vs 43.6% pMDI, $P<0.05$) and COPD-related (19.4% DPI vs 15.7% pMDI, $P<0.02$) encounters. However, pMDI users had higher COPD-related HRU including longer in-patient hospitalizations (3.5±2.2 days DPI vs 3.7±2.3 days pMDI, $P<0.05$), more physician office visits (33.7% DPI vs 37.6% pMDI, $P<0.05$), and more prescriptions filled (5.3% DPI vs 6.0% pMDI, $P<0.05$). There were no statistically significant differences in all-cause or COPD-related costs during the 12-month preindex period.

Table 2 Health care resource utilization and costs in the 12-month preindex period

	DPI (N=1,960)			pMDI (N=1,086)			*P*-value
	n/mean	%/SD	Median	n/mean	%/SD	Median	
All-cause utilization							
Inpatient admissions (n, %)	1,956	99.8%		1,083	99.7%		0.69
Average number of admissions (mean, SD, median)	2.2	1.9	2.0	2.2	2.0	2.0	0.73
Average length of stay for inpatient admissions, days (mean, SD, median)	3.7	2.3	3.0	3.8	2.3	3.3	0.14
Outpatient ER visits (n, %)	941	48.0%		473	43.6%		0.02
Physician office visits (n, %)	1,796	91.6%		1,003	92.4%		0.48
Outpatient laboratory and radiology procedures (n, %)	1,446	73.8%		818	75.3%		0.35
Other outpatient services (n, %)	1,901	97.0%		1,065	98.1%		0.08
Outpatient pharmacy (n, %)	1,860	94.9%		1,041	95.9%		0.23
Average number of prescriptions (all medications) filled (mean, SD, median)	37.9	32.6	30.0	39.1	33.6	31.0	0.35
All-cause costs							
Total costs PPPM (mean, SD, median)	$2,705	$4,229	$1,637	$2,509	$2,515	$1,662	0.11
Total medical costs PPPM (mean, SD, median)	$2,383	$4,111	$1,345	$2,197	$2,415	$1,381	0.12
Inpatient	$1,459	$2,475	$847	$1,411	$1,659	$891	0.52
Outpatient	$923	$2,944	$357	$786	$1,441	$391	0.09
ER	$55	$170	$0	$53	$156	$0	0.69
Physician office visits	$76	$79	$55	$74	$66	$58	0.50
Outpatient laboratory and radiology procedures	$46	$163	$10	$59	$509	$10	0.43
Other outpatient services	$747	$2,840	$236	$601	$1,200	$242	0.05
Outpatient pharmacy costs PPPM (mean, SD, median)	$322	$560	$171	$311	$464	$165	0.57
COPD-related utilization							
Inpatient admissions (n, %)	1,954	99.7%		1,081	99.5%		0.50
Average number of admissions (mean, SD, median)	1.2	0.5	1.0	1.2	0.7	1.0	0.27
Average length of stay for inpatient admissions, days (mean, SD, median)	3.5	2.2	3.0	3.7	2.3	3.0	0.04
Outpatient ER visits (n, %)	380	19.4%		171	15.7%		0.01
Physician office visits (n, %)	660	33.7%		408	37.6%		0.03
Outpatient laboratory and radiology procedures (n, %)	268	13.7%		169	15.6%		0.15
Other outpatient services (n, %)	1,075	54.8%		610	56.2%		0.48
Outpatient pharmacy (n, %)	1,406	71.7%		802	73.8%		0.21
Average number of prescriptions (all medications) filled (mean, SD, median)	3.8	5.3	2.0	4.2	6.0	2.0	0.03
COPD-related costs							
Total costs PPPM (mean, SD, median)	$1,128	$1,076	$831	$1,180	$1,150	$861	0.23
Total medical costs PPPM (mean, SD, median)	$1,106	$1,069	$811	$1,155	$1,144	$838	0.24
Inpatient	$1,033	$1,031	$758	$1,079	$1,092	$795	0.26
Outpatient	$73	$190	$16	$77	$230	$13	0.61
ER	$13	$68	$0	$13	$75	$0	0.99
Physician office visits	$7	$16	$0	$8	$16	$0	0.16
Outpatient laboratory and radiology procedures	$4	$27	$0	$4	$27	$0	0.83
Other outpatient services	$48	$145	$2	$51	$193	$2	0.66
Outpatient pharmacy costs PPPM (mean, SD, median)	$23	$61	$3	$24	$62	$4	0.47

Note: All costs are presented in USD.

Abbreviations: DPI, dry powder inhaler; ER, emergency room; pMDI, pressurized metered-dose inhaler; PPPM, per person per month.

Postindex period outcomes

Postindex period all-cause and COPD-related HRU and costs are shown in Table 3. Bivariate analyses revealed that DPI users were more likely to initiate tiotropium use within 30 days of treatment index compared to the pMDI group (6.0% DPI vs 4.3% pMDI, $P<0.05$). Groups did not differ with respect to remaining HRU outcomes. Regarding health care expenditures, compared to the DPI group, pMDI patients incurred lower PPPM all-cause outpatient ($1,495±$3.641 DPI vs $1,222±$2,114 pMDI, $P<0.01$), COPD-related outpatient ($75±$232 DPI vs $58±$129 pMDI, $P<0.02$), COPD-related total medical ($112±$461 DPI vs $85±$247 pMDI, $P<0.05$), COPD-related total health care ($169±$467 DPI vs $136±$253 pMDI, $P<0.02$), and outpatient pharmacy costs ($57±$44 DPI vs $51±$40 pMDI, $P<0.0001$). Other health care expenditures did not differ between groups.

There was no significant difference in the frequency of all-cause or AECOPD-related readmissions within 30 days of discharge or all-cause readmission within 60 days of discharge between DPI and pMDI groups (Table 4). The bivariate analysis suggested that the pMDI group experienced a longer time to a COPD exacerbation-related hospital readmission within 30 days postdischarge compared to DPI patients ($P<0.05$). Results of logistic models of hospital readmissions, controlling for patient demographics and clinical characteristics, revealed that pMDI patients were 28% less likely to experience a COPD exacerbation-related hospital readmission within 60-day postdischarge compared to DPI patients (OR: 0.72, 95% CI: 0.52–0.99, $P<0.05$; Table 4). Kaplan–Meier plots for the time to 60-day all-cause and AECOPD-related readmissions are shown in Figure 2. Results of a Cox proportional hazards model confirmed that the time to AECOPD-related readmission within 60 days was significantly different between groups after multivariate adjustment (HR [pMDI vs DPI]: 0.73; 95% CI: 0.54–0.99). Increased age was associated with a greater likelihood of all-cause and COPD-related hospital readmissions in all models, whereas preperiod acute myocardial infarction and ischemic stroke were each associated with greater likelihood of 30- and 60-day all-cause readmissions.

Finally, results of the generalized linear gamma models of total health care costs controlling for patient demographics and clinical characteristics revealed that, compared to DPI patients, pMDI patients incurred lower all-cause ($2,673 vs $2,956) and COPD-related PPPM costs ($138 vs $169; $P<0.05$; Figure 3) during the postperiod. The presence of baseline acute myocardial infarction was associated with greater all-cause and COPD-related costs, whereas baseline SABA use and a greater number of visits to a pulmonologist were associated with increased COPD-related costs ($P<0.05$).

Discussion

This study demonstrated that patients prescribed a pMDI to deliver an ICS/LABA combination therapy after hospitalization for COPD had 10% lower all-cause health care costs and 18% lower COPD-related health care costs compared to patients prescribed a DPI. This was despite greater baseline disease severity of the pMDI cohort, as indicated by a greater number of AECOPD-related in-patient hospitalization days, outpatient pulmonologist visits, and SABA prescriptions filled prior to the index hospitalization. Mutivariate analysis was used to control for these baseline differences in indicators of disease severity. Notably, COPD-related prescription costs were lower for the pMDI cohort, potentially due to the lower percentage of pMDI patients being prescribed tiotropium-based medications. Patients using tiotropium alone delivered by soft-mist inhaler or DPI or in combination with olodaterol delivered by soft-mist inhaler (Respimat, Boehringer Ingelheim microParts GmbH, Dortmund, Germany) concurrent with their index hospitalization were excluded from the current analysis to avoid confounding the comparison between DPI and pMDI delivery of ICS/LABA.

The multivariate analysis revealed a lower frequency of AECOPD readmission within 60 days for the pMDI cohort, and this was confirmed by Kaplan–Meier curves and multivariate analysis comparing time to first readmission within 60-day postdischarge. Although the pMDI cohort had a lower frequency of readmission and longer times to readmission, the differences between groups were not statistically significant for any of the evaluated all-cause readmission outcomes or the AECOPD readmission outcomes evaluated at 30 days. We hypothesize that this is due to an inability to adequately control for the differences in COPD severity between groups without access to spirometry results. Several covariates (preindex SABA fills, AECOPD inpatient days, and pulmonologist visits) were chosen as surrogate markers of disease severity based on the descriptive analysis; however, none of these are a direct measure of lung function. Also, two variables controlling for differences in pre-existing cardiovascular disease between groups were included in the models. The observed lag in statistical significance of AECOPD readmission outcomes is consistent with the hypothesis that the selected covariates were unable to completely account for differences in disease severity and overall health.

In this study, patients in the pMDI cohort were significantly more likely to have had recent experience with their

Table 3 All-cause and COPD-related HRU and costs in the 90-day postindex period

	DPI (N=1,960)			pMDI (N=1,086)			*P*-value
	n/mean	%/SD	Median	n/mean	%/SD	Median	
All-cause utilization							
Inpatient admissions (n, %)	211	10.8%		119	11.0%		0.87
Average number of admissions (mean, SD, median)	0.1	0.5	0.0	0.1	0.5	0.0	0.88
Average length of stay for inpatient admissions (days) (mean, SD, median)	0.5	1.9	0.0	0.5	2.7	0.0	0.51
Outpatient ER visits (n, %)	356	18.2%		183	16.9%		0.36
Physician office visits (n, %)	1,785	91.1%		991	91.3%		0.87
Outpatient laboratory and radiology procedures (n, %)	1,006	51.3%		557	51.3%		0.98
Other outpatient services (n, %)	1,794	91.5%		998	91.9%		0.73
Outpatient pharmacy (n, %)	1,960	100.0%		1,086	100.0%		
Average number of prescriptions (all medications) filled (mean, SD, median)	15.9	9.5	14.0	16.1	9.7	14.0	0.55
Average number of ICS/LABA prescriptions filled (mean, SD, median)	1.6	0.8	1.0	1.6	0.8	1.0	0.99
All-cause costs							
Total costs PPPM (mean, SD, median)	$2,992	$6,461	$1,168	$2,623	$5,546	$1,147	0.10
Total medical costs PPPM (mean, SD, median)	$2,420	$6,389	$574	$2,056	$5,425	$538	0.10
Inpatient	$925	$4,878	$0	$834	$4,438	$0	0.60
Outpatient	$1,495	$3,641	$521	$1,222	$2,114	$486	0.009
ER	$96	$510	$0	$71	$312	$0	0.09
Physician office visits	$133	$117	$108	$129	$108	$105	0.38
Outpatient laboratory and radiology procedures	$59	$253	$0	$57	$276	$0	0.87
Other outpatient services	$1,208	$3,470	$335	$965	$1,935	$317	0.013
Outpatient pharmacy costs PPPM (mean, SD, median)	$572	$593	$420	$567	$714	$396	0.84
COPD-related utilization							
Inpatient admissions (n, %)	64	3.3%		32	2.9%		0.63
Average number of admissions (mean, SD, median)	0.0	0.2	0.0	0.0	0.2	0.0	0.57
Average length of stay for inpatient admissions, days (mean, SD, median)	0.1	0.8	0.0	0.1	0.6	0.0	0.45
Outpatient ER visits (n, %)	123	6.3%		56	5.2%		0.21
Physician office visits (n, %)	1,188	60.6%		650	59.9%		0.68
Outpatient laboratory and radiology procedures (n, %)	239	12.2%		128	11.8%		0.74
Other outpatient services (n, %)	1,243	63.4%		680	62.6%		0.66
Outpatient pharmacy (n, %)	1,960	100.0%		1,086	100.0%		
Average number of prescriptions filled (mean, SD, median)	4.4	2.6	4.0	4.2	2.6	4.0	0.16
Tiotropium use within 30 days after index date (n, %)	118	6.0%		47	4.3%		0.048
COPD-related costs							
Total costs PPPM (mean, SD, median)	$169	$467	$83	$136	$253	$73	0.011
Total medical costs PPPM (mean, SD, median)	$112	$461	$25	$85	$247	$20	0.037
Inpatient	$37	$382	$0	$27	$200	$0	0.34
Outpatient	$75	$232	$24	$58	$129	$20	0.010
Roomer	$7	$63	$0	$3	$24	$0	0.05
Physician office visits	$11	$14	$7	$10	$13	$7	0.16
Outpatient laboratory and radiology procedures	$2	$17	$0	$1	$7	$0	0.13
Other outpatient services	$56	$211	$8	$43	$120	$7	0.040
Outpatient pharmacy costs PPPM (mean, SD, median)	$57	$44	$43	$51	$40	$35	<0.0001

Note: All costs are presented in USD.

Abbreviations: DPI, dry powder inhaler; ER, emergency room; HRU, health care resource use; pMDI, pressurized metered-dose inhaler; PPPM, per person, per month.

Table 4 All-cause and AECOPD readmissions

	Bivariate results					Multivariate[a] results (DPI vs pMDI)			
	DPI		pMDI		*P*-value	OR	Lower 95% CL	Upper 95% CL	*P*-value
	n/mean	%/SD	n/mean	%/SD					
All-cause readmission within 30 days (n, %)	276	14.1%	139	12.8%	0.32	0.88	0.70	1.11	0.28
Days to the first all-cause readmission within 30 days (mean, SD, median)	8.0	9.3	8.9	9.2	0.35				
All-cause readmission within 60 days (n, %)	358	18.3%	188	17.3%	0.51	0.91	0.74	1.12	0.38
Days to the first all-cause readmission within 60 days (mean, SD, median)	16.1	17.6	18.5	18.7	0.14				
AECOPD readmission within 30 days (n, %)	109	5.6%	46	4.2%	0.11	0.72	0.50	1.04	0.08
Days to the first AECOPD readmission within 30 days (mean, SD, median)	5.0	7.6	8.2	9.5	0.028				
AECOPD readmission within 60 days (n, %)	140	7.1%	61	5.6%	0.10	0.72	0.52	0.99	0.045
Days to the first AECOPD readmission within 60 days (mean, SD, median)	13.2	17.3	17.0	18.1	0.16				

Note: [a]Logistic regression models.
Abbreviations: AECOPD, acute exacerbation of COPD; CL, confidence limit; DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler.

index device type. This may be due to the larger number of formulations available in this format, the lower cost of pMDI devices, or their common use in rescue inhalers.[27] Concurrent use of multiple device types has been shown to negatively impact patient outcomes as has nonconsensual switching of device types.[17,28,29] To control for the possibility that device continuity contributed to the improved outcomes observed in the pMDI cohort, preindex experience with the index inhaler type was included as a covariate in the multivariate modeling. It is notable that the difference in time to AECOPD

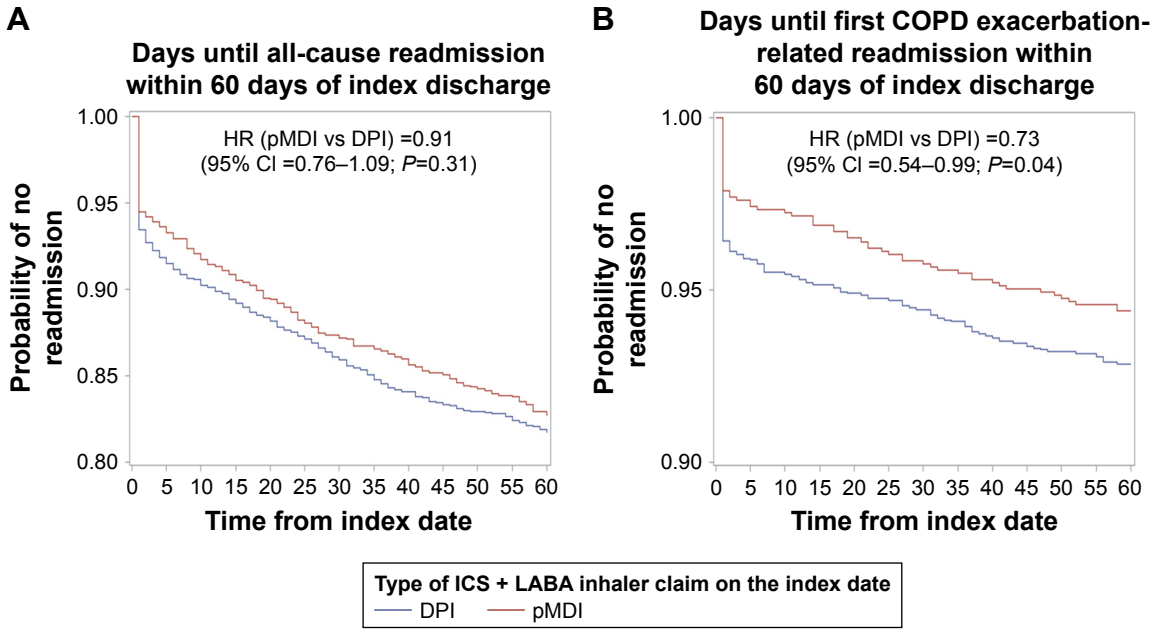

Figure 2 Kaplan–Meier curves comparing time (in days) from index date to first (**A**) all-cause readmission and (**B**) AECOPD-related readmission within 60 days postdischarge for DPI and pMDI cohorts.
Abbreviations: AECOPD, acute exacerbation of COPD; DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; pMDI, pressurized metered-dose inhaler.

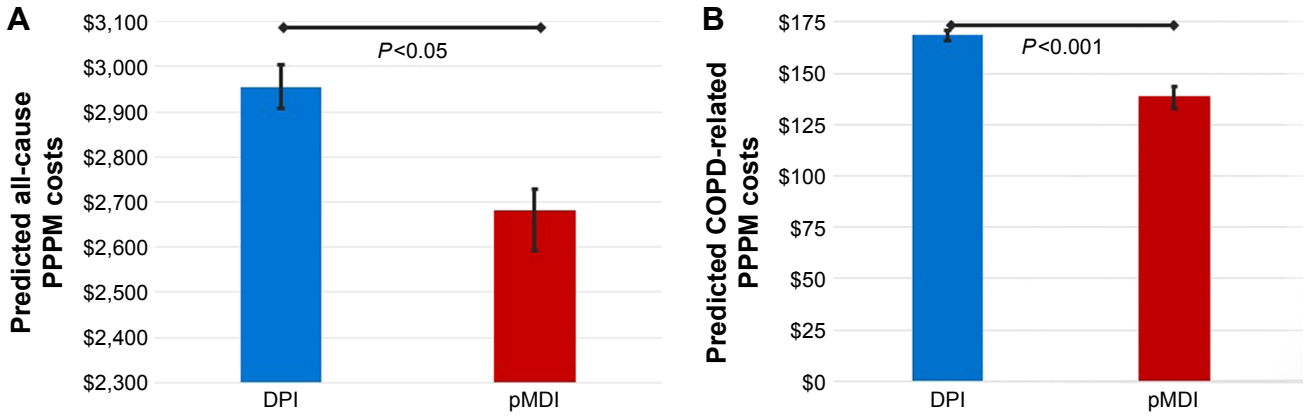

Figure 3 Predicted mean and 95% CIs of (**A**) all-cause and (**B**) COPD-related total health care costs (PPPM) in the 90-day postindex period.
Note: All costs are presented in USD.
Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; PPPM, per person per month.

readmission within 60 days did not become statistically significant until preindex device utilization was added as a covariate. This highlights the impact of real-world experience with an inhaler type on health outcomes.

One confounding factor to the above results is the difference in medication formulations between groups. Although we restricted our analysis to those patients newly prescribed an ICS/LABA combination therapy, manufacturer and regulatory restrictions created the scenario in which no formulations are available in the USA for the treatment of COPD in both device types. FP/SAL is available in both delivery devices; however, the pMDI format is only approved for use in asthma.[30] Although medications from the same class are anticipated to perform similarly,[24,31] the impact of the absence of formulations or combinations in either group is unknown. In addition, our analysis did not include patients using ICS and LABA monotherapies in combination. This decision was made to avoid additional confounding factors as LABA monotherapy is not available in a pMDI format, and ICS monotherapy is only available through off-label usage of asthma products. Furthermore, neither monotherapy is recommended for patients with previous hospitalizations for AECOPD.[14]

There are a number of studies that have examined the cost-effectiveness of various COPD medications, with the frequency of AECOPD-related hospitalizations being the primary driver of costs.[32–34] Analysis of the 3-year multicenter Towards a Revolution in COPD Health study of 6,112 participants found that the ICS/LABA combination of FP/SAL was more cost-effective than placebo or either treatment alone.[32] In that study, all medications were delivered via DPI.[35] A 2005 systematic review of COPD and asthma clinical trials by the American College of Chest Physicians and the American College of Asthma, Allergy, and Immunology, which relied heavily on data from LABA studies, found no significant difference in clinical outcomes between device types.[36] However, patients can only be included in clinical trials if they are able to use the study device correctly so these results cannot necessarily be extrapolated to real-world performance. Limited data exist from real-world practice regarding if and how the choice of inhalation device impacts outcomes in COPD; however, a 2011 retrospective matched cohort study of asthma patients (N=1,567 pairs) reported that pMDI users had significantly higher odds of achieving asthma control and treatment success (ie, no exacerbations and no change in therapy) compared to DPI users.[37] In addition, although it is known that use of inhalers containing ICS increases a patient's risk of developing oral thrush,[38] two recent real-world studies have reported that pMDI use is associated with a lower risk of thrush compared to DPI use.[39,40]

The findings of this study are consistent with those of the only other real-world observational study on the impact of inhaler type on ICS/LABA control of AECOPD.[25] In that matched cohort study by Jones et al, patients treated with a 500 µg/day dose of FP/SAL delivered via pMDI had fewer moderate-to-severe exacerbations than patients using a DPI. This effect was not present at the higher dose of 1,000 µg/day of FP/SAL. The authors hypothesized that the higher dosage compensated for any problems in minimum effective dose delivery due to suboptimal peak inspiratory flow for DPI usage. The study did not evaluate costs; however, hospitalization for AECOPD has been shown to be a leading driver of high costs in COPD treatment. Two possible reasons why pMDIs may be more effective than DPIs are that peak inspiratory flow rates have been shown to be lower during an AECOPD, which may reduce the efficacy of DPIs immediately following an exacerbation,[41] and some DPIs are sensitive to environmental moisture, which reduces the delivery of fine aerosol particles.[42,43]

Limitations

Studies based on administrative claims data, such as that found in the MarketScan® Research Databases, have several inherent limitations. First, these datasets are subject to miscoding and undercoding, which may introduce bias or measurement error. Previous studies have demonstrated that the claims-based approach of combining advanced age (≥40 or ≥55 years old) and a primary discharge diagnosis of AECOPD (ICD-9-CM 491.21) to identify patients hospitalized for AECOPD has a positive predictive value of 97% compared to manual chart review by a physician.[44,45] However, this selectivity for true-positive patients comes at the expense of excluding a large number of patients with the symptoms of an AECOPD but a different discharge code (sensitivity =12.5%). Stein et al[44] tested three other algorithms but found them to be inferior in performance and recommended the algorithm above for comparative effectiveness research.

Second, this study was limited to individuals in the US with commercial or employer-sponsored Medicare supplemental insurance; therefore, the results may not be generalizable to patients outside the USA, or US patients with other insurance coverage or no coverage who may experience different patterns of health care utilization and costs. Third, the costs represented in these databases reflect the paid amounts of adjudicated claims to individual hospitals and providers and do not include indirect costs, which are a substantial portion of the economic burden of COPD. Fourth, claims data only indicate that a prescription was filled and not that the medication was utilized as directed. Additionally, medication obtained without a concomitant insurance claim, such as samples from health care providers, or delivered in a clinical trial, would not be captured in the databases. Fifth, not all medication formulations were available with both inhaler types, so the comparisons are between different formulations and different devices. Additionally, the dosage of the ICS/LABA medication was not assessed in this study, and so unmeasured differences in medication dosage may have contributed to observed differences between groups. Sixth, only patients using DPIs or pMDIs were included in the analysis, so these results may not extend to patients using other types of inhalers such as a soft-mist inhaler. Inclusion of soft-mist inhalers would have complicated the analysis by both adding another device type and requiring inclusion of monotherapy combinations due to the lack of an ICS/LABA combination in this format. Seventh, this study excluded patients aged <40 years, those with asthma-COPD overlap syndrome, those with other major respiratory diseases, and those who had filled a prescription for a tiotropium medication in the 90 days leading up to the index date. The findings, therefore, may not extend to these populations. Finally, multivariate analysis was used to control for differences in baseline demographic and clinical characteristics and several known factors that influence device selection, such as spirometry results, are not captured in administrative claims and therefore could not be controlled for.

Conclusion

In this real-world retrospective cohort study, US patients initiating ICS/LABA combination therapy delivered by a pMDI after discharge from the hospital for an AECOPD had lower all-cause and COPD-related health care costs in the 90-day follow-up period despite having more severe disease during the preindex period, compared to those receiving a DPI. Reduced follow-up costs suggest that inhaler device type may influence COPD outcomes and that COPD patients may derive greater clinical benefit from treatment delivered via pMDI vs DPI, although this requires confirmation by future prospective studies.

Abbreviations

AECOPD, acute exacerbation of COPD; DPI, dry powder inhaler; ER, emergency room; FP/SAL, fluticasone propionate/salmeterol; HRU, health care resource use; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; pMDI, pressurized metered-dose inhaler; PPPM, per person per month; SABA, short-acting β-agonist.

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