Reduction in Hospital Readmission Rates Among Medicare Beneficiaries With Chronic Obstructive Pulmonary Disease: A Real-world Outcomes Study of Nebulized Bronchodilators☆

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ABSTRACT

Purpose: Chronic obstructive pulmonary disease (COPD) is a common condition responsible for substantial morbidity, mortality, and costs in the United States. The economic burden of COPD is driven primarily by hospitalizations, with 1 in 5 hospitalized patients experiencing a 30-day readmission. Bronchodilators, delivered via handheld inhalers or nebulizers, are the mainstay of therapy for COPD. However, differences in outcomes between short- and long-acting therapies are unclear. We examined real-world differences in 30-day readmission and exacerbation rates between Medicare beneficiaries with COPD treated with a nebulized long-acting beta$_2$-agonist (arformoterol tartrate [ARF]) and beneficiaries treated with a nebulized short-acting beta$_2$-agonist (SABA) for maintenance therapy after hospital discharge.

Methods: Truven MarketScan Hospital Drug Database and Medicare files were probabilistically matched between 2009 and 2013 to identify beneficiaries who were aged ≥65 years and discharged from a hospital with a primary COPD diagnosis or a secondary COPD diagnosis and a primary diagnosis for another respiratory condition. Matching was performed by using COPD hospitalization date (±7 days) and source, length of stay (±1 day), discharge date and destination, and hospital region. After applying additional inclusion/exclusion criteria, 2 cohorts were created: nebulized ARF users (n = 953) and nebulized SABA users (n = 6939). Logistic regression analyses were used to examine 30-day readmission (all-cause and COPD related) and exacerbation rates. Odds ratios (ORs), 95% CIs, and *P* values were computed.

Findings: On average, nebulized SABA users had more comorbidities than nebulized ARF users, including diabetes, atrial fibrillation, renal disease, musculoskeletal disease, myocardial infarction, and cognitive impairment (all, $P < 0.0001$). However, nebulized ARF users had a higher average COPD severity score than nebulized SABA users (49.5 v. 38.0; $P < 0.001$). COPD therapies at baseline were similar in both cohorts and included systemic corticosteroids (≥65%), short-acting bronchodilators (≥33%), and inhaled corticosteroids + long-acting beta$_2$-agonists (30%). After adjusting for sociodemographic and hospital characteristics, concomitant medications, and case-mix, nebulized ARF users had 27% lower odds of an all-cause readmission (OR, 0.73; 95% CI, 0.59–0.92; $P = 0.008$) and 23% lower odds of a COPD-related readmission (OR, 0.77; 95% CI, 0.60–0.98; $P = 0.032$) at 30 days compared with users of a

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nebulized SABA. No difference was found in 30-day exacerbation rates between the cohorts.

Implications: Nebulized ARF users had lower 30-day readmission rates, greater COPD severity, and fewer comorbidities than nebulized SABA users. In this population, maintenance treatment with ARF reduced costly COPD outcomes. (*Clin Ther.* 2019;41:2283–2296)

Key words: arformoterol tartrate, exacerbations, hospital readmissions, long-acting beta$_2$-agonists, nebulized bronchodilators, short-acting beta$_2$-agonists.

INTRODUCTION

As the fourth leading cause of mortality in the United States,[1] chronic obstructive pulmonary disease (COPD) accounts for a substantial economic burden on the health care system. The estimated costs of COPD-related medical care are $50 billion annually, driven primarily by inadequately controlled symptoms that lead to nearly 700,000 hospitalizations each year.[2–8] COPD-related readmissions cost the US health care system more than $15 billion annually, with 1 in 5 hospitalized patients with COPD experiencing an early readmission within 30 days of discharge.[6–9]

Short- and long-acting bronchodilators (SABDs and LABDs, respectively) are the mainstay of treatment for COPD. These therapies can be delivered via handheld inhalers or nebulizers. SABDs are recommended as rescue medications to treat symptoms associated with an acute COPD exacerbation; LABDs, however, are recommended as maintenance COPD therapy.[10] Although the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report highlights the importance of prescribing LABD therapy to patients after a COPD-related hospitalization, only one half of these patients actually receive maintenance therapy in the 90 days following a hospital discharge.[11–13]

In the United States, COPD is most prevalent in individuals aged ≥65 years.[14] As such, it is not surprising that 12% of the Medicare population has been diagnosed with COPD.[15] Among patients hospitalized with COPD, 69% are Medicare beneficiaries.[16] Consequently, reducing the cost burden of COPD in the Medicare population is a priority for the Centers for Medicare & Medicaid Services (CMS), which has instituted financial penalties for hospitals with higher-than-expected 30-day readmission rates as part of the Affordable Care Act's Hospital Readmissions Reduction Program.[17]

Although much has been published on the clinical effectiveness of SABDs and LABDs,[10,18–20] little is known about the impact of nebulized delivery systems on early readmission and exacerbation rates. To address this knowledge gap, we examined real-world differences in all-cause and COPD-related 30-day readmission and exacerbation rates among Medicare beneficiaries with COPD who received arformoterol tartrate (ARF), a nebulized long-acting beta$_2$-agonist (LABA), compared with beneficiaries treated with a nebulized short-acting beta$_2$-agonist (SABA) for maintenance therapy following hospital discharge.

PATIENTS AND METHODS

Data Sources

Data were obtained from 2 sources between January 1, 2009, and December 31, 2013: the Truven MarketScan Hospital Drug Database (MS-HDD) and a 100% sample of Medicare fee-for-service administrative claims data for beneficiaries diagnosed with COPD. Access to Medicare data was subject to a Data Use Agreement with CMS. Inpatient service level and drug utilization information were extracted from the MS-HDD, including data from 593 hospitals across the United States.[21] Payer enrollment eligibility and duration, sociodemographic characteristics, and health service utilization patterns, including inpatient, outpatient, prescription drugs (Medicare Part D), skilled nursing, home health care, and durable medical equipment services, were extracted from Medicare files. Because the database was fully de-identified and compliant with the regulations of the Health Insurance Portability and Accountability Act of 1996, our study was exempt from institutional review board approval.

Study Sample and Cohort Selection

Medicare beneficiaries with hospitalizations who were discharged with a primary COPD diagnosis

(*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 491–492.xx, 496.xx) or a secondary COPD diagnosis and a primary diagnosis for another respiratory condition (ICD-9-CM codes 460.xx–519.xx) between January 1, 2010, and June 30, 2013, were identified in the MS-HDD and Medicare databases. After restricting the sample to beneficiaries aged ≥65 years, two cohorts emerged including 1,151,648 patients from the MS-HDD

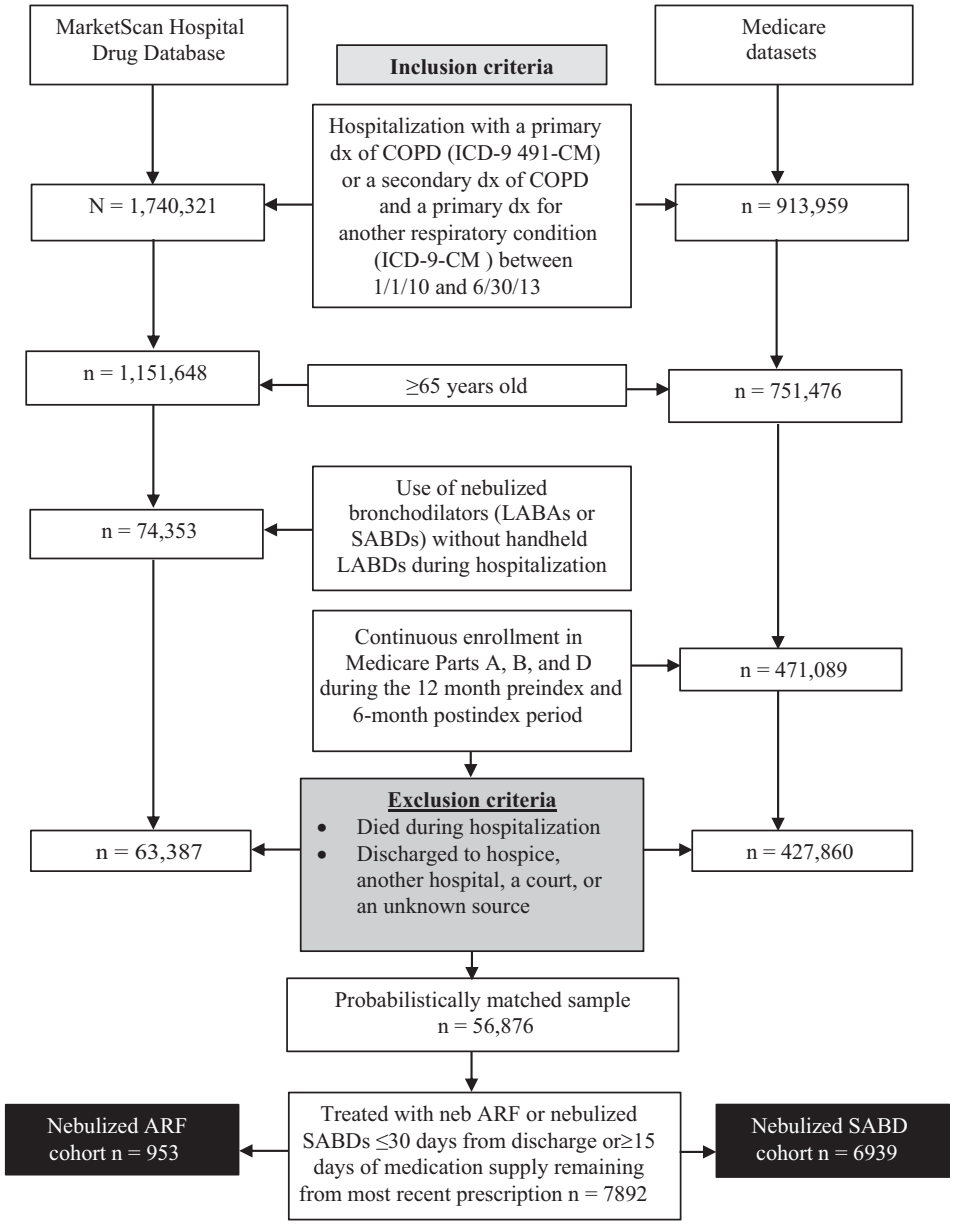

Figure 1. Cohort selection flow chart. ARF = arformoterol tartrate; COPD = chronic obstructive pulmonary disease; dx = diagnosis; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; LABA = long-acting beta$_2$-agonist; LABDs = long-acting bronchodilators; SABD = short-acting bronchodilator.

dataset and 751,476 beneficiaries from the Medicare files (Figure 1). After applying additional inclusion and exclusion criteria, probabilistic matching of the 2 cohorts was performed by using admission date (±7 days) and source, length of stay (±1 day), discharge date and destination, and hospital region. The matched sample was then stratified into 2 cohorts: (1) nebulized ARF users (n = 953) who received a nebulized LABD treatment as an inpatient (ie, with ARF or formoterol fumarate) and had an outpatient prescription for nebulized ARF within 30 days of hospital discharge, or had ≥15 days of ARF supply remaining from the most recent prescription before the index hospital admission; and (2) nebulized SABA users (n = 6939) who received a nebulized SABD treatment as an inpatient (albuterol, ipratropium, ipratropium/albuterol, or levalbuterol solutions) and had an outpatient prescription for a nebulized SABA, with no handheld or nebulized LABD treatment within 30 days of discharge, or those with ≥15 days of a nebulized SABA supply remaining from the most recent prescription before the index hospital admission.

Study Design and Measures

This retrospective observational study included 2 distinct periods (Figure 2): (1) a 12-month preindex period (ie, baseline), which was identified by using the index COPD hospitalization admission date; and (2) a 6-month treatment follow-up period, which was identified by using the index hospitalization discharge date.

Multiple independent variables were examined at baseline: (1) sociodemographic characteristics, including age, sex, race, and US region of residence; (2) dual-eligible status (ie, Medicare and Medicaid eligible); (3) smoking history (current/former); (4) oxygen therapy; (5) COPD medications based on drug refill rates, including SABDs such as short-acting muscarinic antagonists and SABAs, LABAs, long-acting muscarinic antagonists, inhaled corticosteroids (ICS), systemic corticosteroids (CS), methylxanthines, and anticholinergic agents; (6) hospital characteristics, including location (ie, urban/rural), type (ie, teaching vs nonteaching), and bed capacity (ie, 1−199, 200−299, 300−499, ≥500 beds); (6) length of stay during the index hospitalization; and (7) discharge destination (ie, self-care, transfer to another hospital or long-term care facility, home health care).

Several clinical measures related to comorbidities were also examined, including: (1) the Charlson Comorbidity Index[22,23]; (2) a COPD comorbidity score[24]; and (3) a COPD severity score.[25] The COPD

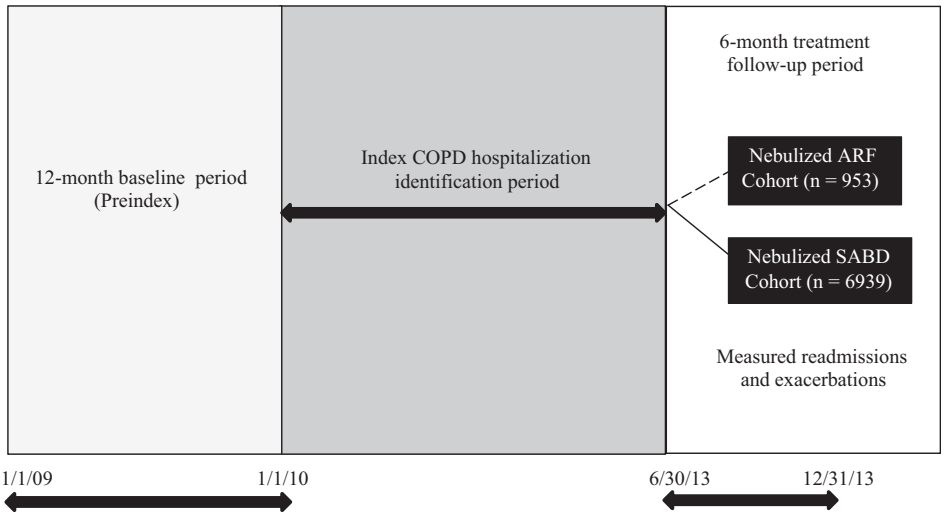

Figure 2. Study design. ARF = arformoterol tartrate; COPD = chronic obstructive pulmonary disease; SABD = short-acting bronchodilator.

comorbidity score was based on 14 comorbid conditions, including coronary heart disease, diabetes, congestive heart failure, stroke, osteoarthritis, osteoporosis, hypertension, high cholesterol, gastroesophageal reflux disease, stomach ulcers, obesity, sleep apnea, hay fever, and peripheral vascular disease. The COPD severity score was computed as a composite measure of 12 weighted claims–based components, with a higher score indicating greater COPD severity, using the following variables: hospitalizations or acute exacerbations due to chronic bronchitis, oxygen therapy, emphysema, claims for spirometry tests, pulmonologist visits, and use of COPD medications such as anticholinergic agents, ICS, oral CS, SABAs, LABDs, and the patient's age at mid-point of the diagnosis year.

Outcome measures examined at follow-up included: (1) 30-day all-cause hospital readmission rate; (2) 30-day COPD-related readmission rate; and (3) 30-day exacerbation rate. The 30-day exacerbation rate was defined as an occurrence of any one of the following events after discharge from the index hospital admission: (1) an inpatient, emergency department, or urgent care visit with a diagnosis of acute exacerbation of COPD (ICD-9-CM code 491.21 or 492.22) or a primary COPD diagnosis; or (2) a COPD-related office visit followed by a prescription for an oral or injectable CS or an antibiotic within 7 days of the visit.

Statistical Analyses

Univariate and bivariate analyses were conducted by using Student's t test and χ^2 tests to compare baseline characteristics and medication use between the nebulized ARF and nebulized SABA cohorts, including computing means, frequencies, and proportions. Logistic regression analysis was used to examine the likelihood of 30-day readmissions (all-cause and COPD-related) and exacerbations after treatment with nebulized ARF compared with nebulized SABAs, adjusting for potential confounders, including: (1) baseline demographic and clinical characteristics; (2) hospital characteristics; (3) dual-eligible status; (4) smoking history; (5) comorbidities; (6) concomitant COPD medications; and (7) length of stay. Odds ratios (ORs) and 95% CIs were computed. P values < 0.05 denoted statistical significance. All analyses were performed by using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Baseline Characteristics

The average age was similar between beneficiaries treated with nebulized ARF and nebulized SABA (77 [6.9] years vs 78 [7.7] years, respectively). Compared with the nebulized SABA cohort, a lower proportion of the nebulized ARF cohort was aged ≥85 years (23% vs 17%; $P < 0.001$) and dual eligible (15% vs 10%; $P < 0.001$) (Figure 3). However, a higher proportion of beneficiaries treated with nebulized ARF were white, non-Hispanic (96% vs 93%; $P < 0.001$) and had a history of smoking (59% vs 53%; $P < 0.001$) and asthma (29% vs 25%; $P < 0.01$) compared with the nebulized SABA cohort.

Compared with beneficiaries treated with nebulized ARF, beneficiaries treated with nebulized SABA had more comorbidities, including cognitive impairment (12% vs 6%; $P < 0.001$), musculoskeletal disease (15% vs 11%; $P < 0.001$), myocardial infarction (13% vs 9%; $P < 0.001$), atrial fibrillation (22% vs 19%; $P < 0.01$), renal disease (18% vs 13%; $P < 0.001$), diabetes (34% vs 26%; $P < 0.001$), and nutritional abnormalities (9% vs 6%; $P < 0.001$) (Figure 3). Based on a lower average Charlson Comorbidity Index score (1.9 vs 2.3; $P < 0.001$) and COPD comorbidity score (2.2 vs 2.4; $P = 0.001$), nebulized ARF users had a lower overall comorbidity burden than nebulized SABA users (Table). However, the nebulized ARF cohort had a higher COPD severity score than the nebulized SABA cohort (49.5 vs 38.0; $P < 0.001$).

An evaluation of medication use patterns at baseline revealed that ~30% of beneficiaries in both cohorts were being treated with dual-therapy ICS + LABA via a handheld inhaler, and ≥33% were being treated with either a handheld or nebulized SABA (Figure 4). Use of systemic CS was much more prevalent in both cohorts (75% nebulized ARF vs 65% nebulized SABA; $P < 0.001$) than handheld ICS (24% nebulized ARF vs 15% nebulized SABA; $P < 0.001$). Use of methylxanthines was higher in the nebulized ARF cohort than in the nebulized SABA cohort (10% vs 4%; $P < 0.001$). In addition, 69% of nebulized ARF users had received nebulized LABA therapy, and 48% had received a nebulized CS, whereas use of a nebulized LABA or nebulized CS was negligible for

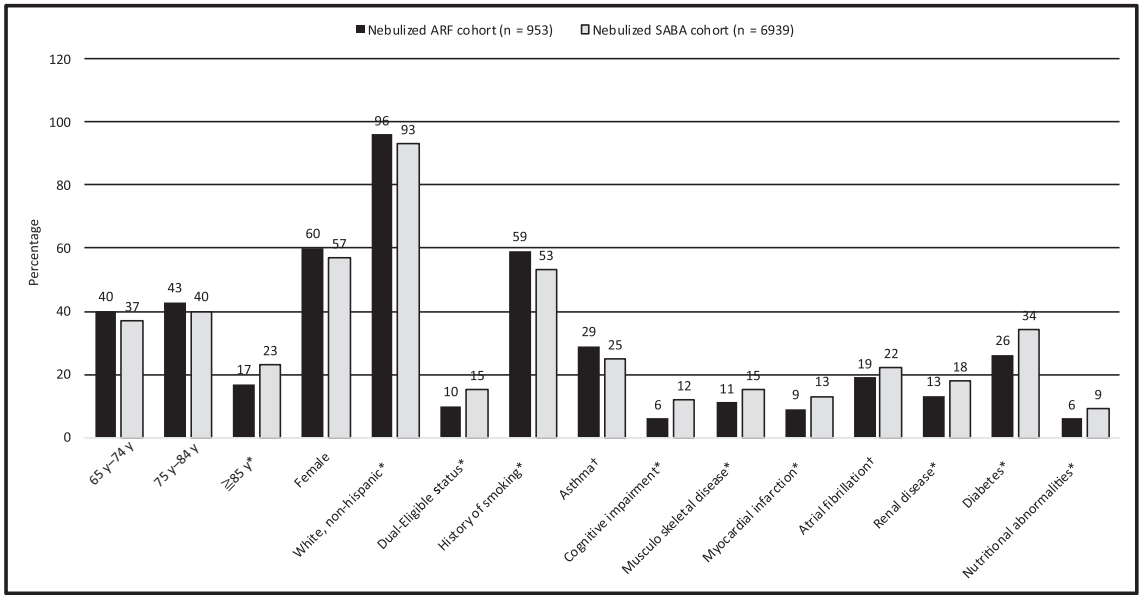

Figure 3. Baseline sociodemographic and clinical characteristics. ARF = arformoterol tartrate; SABA = short-acting beta$_2$-agonist.

users of nebulized SABAs. The prevalence of anticholinergic treatment was also significantly higher in the nebulized ARF cohort relative to the nebulized SABA cohort (38% vs 18%; $P < 0.001$).

30-Day Readmission and Exacerbation Rates

Unadjusted rates revealed that, compared with beneficiaries treated with nebulized SABA, nebulized ARF users had lower 30-day readmission rates for both all-cause (19.7% vs 15.2%, respectively; $P < 0.001$) and COPD-related causes (16.3% vs 13.6%, respectively; $P = 0.035$). These differences persisted after adjusting for potential confounders, with the nebulized ARF cohort having 27% lower odds of an all-cause readmission (OR, 0.73; 95% CI, 0.59−0.92; $P = 0.008$) and 23% lower odds of a COPD-related readmission (OR, 0.77; 95% CI, 0.60−0.98; $P = 0.032$) at 30 days compared with the nebulized SABA cohort (Figure 5). However, 30-day exacerbation rates were similar between the 2 cohorts in both the unadjusted and adjusted results.

DISCUSSION

This real-world observational study comparing maintenance treatment with nebulized ARF and nebulized SABA examined 30-day all-cause and COPD-related readmission and exacerbation rates in the Medicare population. We found that, despite having greater COPD severity, nebulized ARF users had 27% lower odds of an all-cause readmission and 23% lower odds of a COPD-related readmission at 30 days. Although this study is the first to be conducted in the Medicare population, our findings are comparable to previous studies in commercially insured patients with COPD. One such study reported 31% lower odds of an all-cause 30-day readmission in patients with COPD treated with nebulized ARF during an inpatient admission compared with patients treated with nebulized SABA.[26] A second study found that the adjusted risk of all-cause readmission at 6 months was 47% lower in patients with COPD who received a nebulized LABA (ie, ARF or formoterol) compared with patients treated with a nebulized SABA for maintenance therapy after having been discharged for a COPD-related hospitalization.[27]

The 30-day exacerbation rates were found to be comparable between nebulized ARF users and nebulized SABA users. There are several implications of this finding. First, because greater COPD severity

Table. Descriptive baseline and index hospitalization characteristics.

Characteristic	ARF Cohort (n = 953)		Nebulized SABD Cohort (n = 6939)		
	N/Mean	SD/%	N/Mean	SD/%	*P*
Age, y	77.22	6.88	78.21	7.73	<0.001
Age group*					
65–74 y	380	39.87	2554	36.81	0.066
75–84 y	413	43.34	2810	40.50	0.094
≥85 y	160	16.79	1575	22.70	<0.001
Sex*					
Female	575	60.34	3981	57.37	0.082
Male	378	39.66%	2958	42.63	0.082
Race*					
White	914	95.91%	6428	92.64	<0.001
Black	27	2.83%	339	4.89	0.005
Hispanic	5	0.52%	70	1.01	0.149
Other	7	0.73%	102	1.47	0.068
Region*					
Northeast	14	1.47%	87	1.25	0.579
Midwest	189	19.83%	1177	16.96	0.028
South	629	66.00%	4714	67.93	0.232
West	121	12.70%	960	13.83	0.338
Unknown	0	0.00%	1	0.01	0.711
Smoking*	558	58.55%	3652	52.63	0.001
Dual eligibility*	92	9.65%	1021	14.71	<0.001
Hospital characteristics*					
Hospital location					
Urban	809	84.89	5878	84.71	0.885
Rural	144	15.11	1061	15.29	0.885
Hospital setting					
Teaching	63	6.61	515	7.42	0.368
Nonteaching	890	93.39	6424	92.58	0.368
Hospital bed size					
1–199	249	26.13	1799	25.93	0.894
200–299	207	21.72	1305	18.81	0.032
300–499	252	26.44	1854	26.72	0.857
≥500 beds	245	25.71	1981	28.55	0.068
Discharge location					
Home	576	60.44	3792	54.65	<0.001
Home health	306	32.11	2042	29.43	0.090
Home (against medical advice)	2	0.21	16	0.23	0.900
Long-term care	69	7.24	1089	15.69	<0.001
Index hospitalization length of stay, d*	5.80	3.11	5.72	3.22	0.470
Index emergency admission*	637	66.84	4711	67.89	0.516
Index primary COPD diagnosis*	780	81.85	5078	73.18	<0.001

(*continued on next page*)

Table. (*Continued*)

Characteristic	ARF Cohort (n = 953)		Nebulized SABD Cohort (n = 6939)		
	N/Mean	SD/%	N/Mean	SD/%	*P*
Respiratory therapy during index hospitalization	68	7.14	476	6.86	0.753
Baseline comorbidity*					
COPD severity score	49.53	14.99	37.98	11.63	<0.001
No severe exacerbations	46.17	14.58	34.68	10.24	<0.001
1 Severe exacerbation	51.20	14.00	39.24	10.97	<0.001
≥2 Severe exacerbation	56.94	14.50	45.63	12.21	<0.001
COPD comorbidity score	2.21	1.90	2.43	2.05	0.001
Charlson Comorbidity Index	1.85	2.25	2.25	2.50	<0.001
Pulmonary comorbid conditions					
Asthma	274	28.75	1745	25.15	0.017
Respiratory infections	329	34.52	2615	37.69	0.058
Other lower respiratory disease	617	64.74	4453	64.17	0.731
Respiratory distress	254	26.65	1849	26.65	0.997
Pulmonary fibrosis	82	8.60	528	7.61	0.281
Lung cancer	64	6.72	438	6.31	0.632
Nonpulmonary comorbid conditions					
Cognitive impairment	56	5.88	797	11.49	<0.001
Depression	115	12.07	958	13.81	0.142
Anxiety	129	13.54	917	13.22	0.784
Osteoporosis	109	11.44	872	12.57	0.322
Skeletal muscle dysfunction	105	11.02	1053	15.18	0.001
Obesity	68	7.14	567	8.17	0.270
Stroke	115	12.07	996	14.35	0.057
Hypertension	605	63.48	4594	66.21	0.097
Coronary artery disease	346	36.31	2724	39.26	0.080
Myocardial infarction	81	8.50	878	12.65	<0.001
Atrial fibrillation	178	18.68	1530	22.05	0.018
Congestive heart failure	289	30.33	2322	33.46	0.054
Gastroesophageal reflux disease	200	20.99	1520	21.91	0.519
Renal disease	126	13.22	1211	17.45	0.001
Pulmonary hypertension	102	10.70	627	9.04	0.096
Diabetes	245	25.71	2353	33.91	<0.001
Nutritional abnormalities	59	6.19	650	9.37	0.001
Malignancy	144	15.11	1063	15.32	0.867
COPD medication use during the hospitalization (MS-HDD) or within 30 d of discharge*					
Inhaled maintenance medications (LABD)					
ICS/LABA	96	10.07	2	0.03	<0.001
LABA	7	0.73	4	0.06	<0.001
ICS	84	8.81	127	1.83	<0.001

Table. (*Continued*)

Characteristic	ARF Cohort (n = 953)		Nebulized SABD Cohort (n = 6939)		
	N/Mean	SD/%	N/Mean	SD/%	*P*
AC	231	24.24	239	3.44	<0.001
Nebulized maintenance medications (LABD)					
LABA	953	100.00	829	11.95	<0.001
CS	638	66.95	1,045	15.06	<0.001
Other maintenance medication (LABD): methylxanthines	60	6.30	47	0.68	<0.001
Inhaled rescue medications (SABD)					
SABA	176	18.47	900	12.97	<0.001
SABA/AC	75	7.87	564	8.13	0.784
Anticholinergic	186	19.52	1288	18.56	0.478
Nebulized rescue medications (SABD)					
SABA	914	95.91	6735	97.06	0.054
SABA/anticholinergic agent	193	20.25	4055	58.44	<0.001
Anticholinergic agent	678	71.14	5026	72.43	0.405
Other rescue medications					
Systemic corticosteroids	860	90.24	5989	86.31	<0.001
Oxygen use before and during the index hospitalization					
Before or during the index hospitalization	706	74.08	3869	55.76	<0.001
Before the index hospitalization	686	71.98	3703	53.37	<0.001
During the index hospitalization	283	29.70	1601	23.07	<0.001

ARF = arformoterol tartrate; COPD = chronic obstructive pulmonary disease; CS = corticosteroid; MS-HDD: MarketScan Hospital Drug Database; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LABD = long-acting bronchodilator; LAMA = long-acting anti-muscarinic agents; SABA = short-acting beta$_2$-agonist; SABD = short-acting bronchodilator; SAMA = short-acting anti-muscarinic agents.

*Variables were adjusted for in the logistic regressions.

has been shown to be strongly correlated with the occurrence of exacerbations,[23,28–32] and our analysis revealed that beneficiaries treated with nebulized ARF had significantly higher COPD severity scores than beneficiaries who received nebulized SABA, we expected to see more COPD exacerbations among the nebulized ARF cohort. Given that this expectation was not observed in the current findings, it is possible that the nebulized ARF cohort would have experienced more exacerbations if they had not received nebulized ARF as a maintenance therapy.

Second, an exacerbation is a risk factor for both an initial hospitalization as well as subsequent readmissions.[10,28,32,33] Because 30-day exacerbation rates were not significantly different between the nebulized ARF and nebulized SABA cohorts, yet all-cause and COPD-related 30-day readmission rates were, we assessed our findings against the literature to help inform our interpretation and its implications. Heterogeneity in the intensity of exacerbations (mild vs moderate vs severe) has been found to affect the risk of repeat exacerbations.[34,35] In the present study, the criteria used to define an exacerbation event could have combined mild, moderate, and severe exacerbations. An analysis of the revised classification of exacerbations in the 2017 GOLD treatment strategies showed that mild exacerbations are less important in determining COPD outcomes than moderate/severe exacerbations.[35] This study lacked this degree of granularity in differentiating exacerbation intensity, and the criteria applied to define

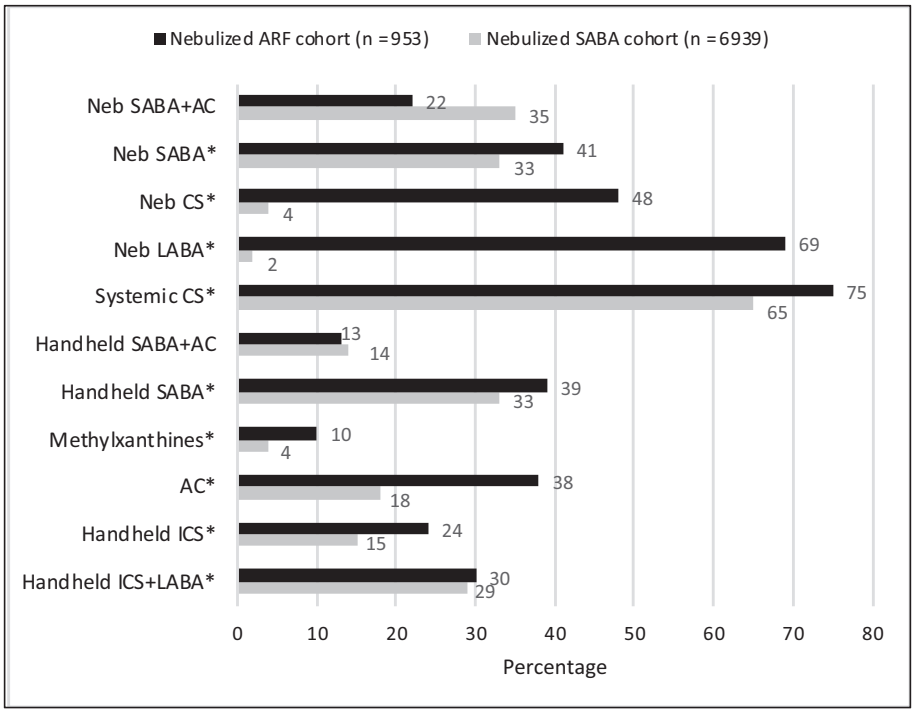

Figure 4. Baseline COPD treatment. ARF = arformoterol tartrate; COPD = chronic obstructive pulmonary disease; Neb SABA = nebulized short-acting beta$_2$-agonists; AC = anticholinergics; Neb CS = nebulized corticosteroid; Neb LABA = nebulized long-acting beta$_2$-agonist; ICS = inhaled corticosteroids; SABA = short-acting beta$_2$-agonist. *$P < 0.001$.

an exacerbation were not all indicative of moderate/severe cases. Thus, a potential lack of comparability between the nebulized ARF and nebulized SABA cohorts could have influenced our results.

Third, studies have found that certain patient and clinical factors are predictive of early readmission in patients with COPD, including greater COPD severity, lack of adherence to COPD bronchodilator medications, unstable comorbidity burden, dual-eligible status, having a discharge destination to a skilled nursing facility or home health care, and lack of adequate physician follow-up after the initial hospital discharge.[9,28,30,31,33,36–38] The regression models adjusted for many of these potential confounders but not all. It is therefore possible that certain unadjusted differences in case-mix, medication adherence, physician follow-up, or other potential confounders related to hospital systems influenced our findings.[39,40]

When hospitalized (particularly due to an acute exacerbation), patients are generally treated with SABDs, antibiotics, and systemic CS.[13,41,42] During inpatient stays, nebulized therapy is the preferred mode of medication delivery over handheld inhalers.[13,43,44] At discharge, initiation of maintenance therapy with LABDs is recommended,[10] with the primary goal of reducing repeated exacerbations and readmissions. However, a real-world study reported that as many as 43.12% of patients with COPD did not fill an LABD prescription within 180 days after a COPD-related hospitalization discharge.[11] The patient population selected for this study reflected a similar trend, in which a significant amount of these patients were undertreated with LABDs post-COPD hospitalization discharge. Our study adds new insights to these current treatment strategies by extending previous research beyond focusing solely on all-cause readmissions. By probabilistically matching commercial data to Medicare records, we were able to examine 30-day COPD-related readmissions in

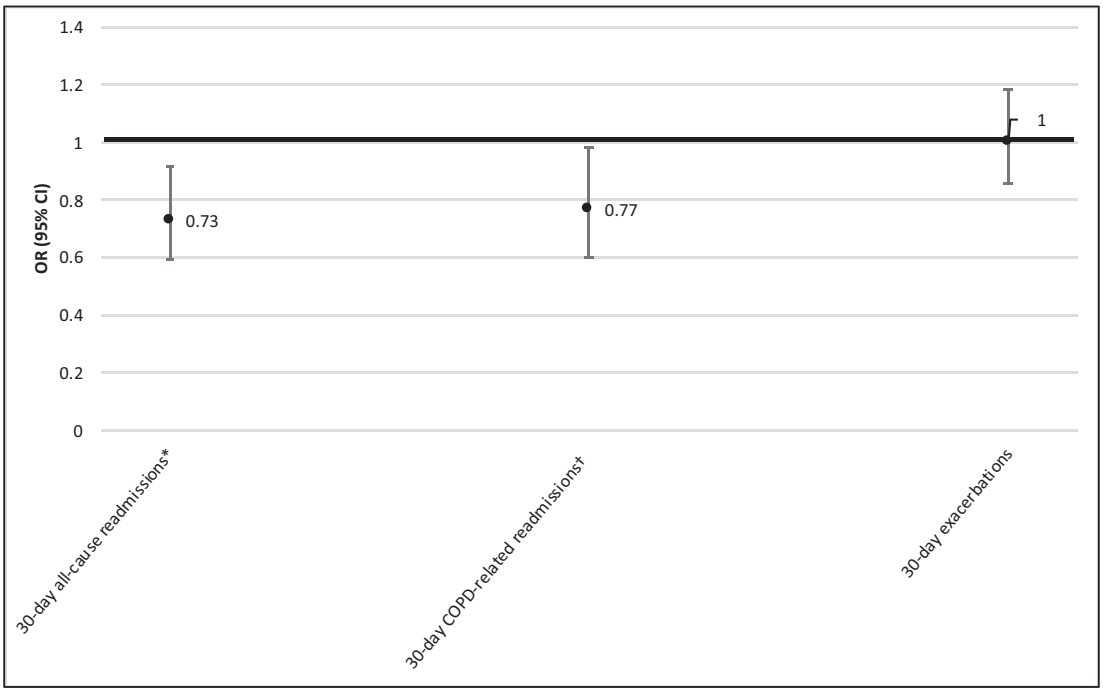

Figure 5. Logistic regression analysis depicting the odds of 30-day readmissions and exacerbations among Medicare beneficiaries treated with nebulized arformoterol. The model was adjusted for the following covariates: sociodemographic characteristics (ie, age, sex, race/ethnicity, region), dual-eligible status, smoking history, hospital characteristics (ie, urban/rural, teaching/nonteaching, bed capacity), discharge destination (eg, self-care, home health, another hospital), comorbidities, index hospitalization length of stay, chronic obstructive pulmonary disease (COPD) severity, and concomitant COPD medications. OR = odds ratio. *$P = 0.008$; †$P = 0.032$.

addition to a broader range of covariates. Finally, our study's findings are valuable in light of the efforts of CMS to curtail COPD readmissions under the Affordable Care Act's Hospital Readmissions Reduction Program. Because hospitals that fail to stay below their expected readmission rates can be penalized up to 3% of their Medicare reimbursement for all discharges,[28] our results provide useful information that can guide practice improvements in hospital and health system settings.

Our findings should be considered in light of certain limitations. This study was designed to examine the associations between outcomes and COPD treatment, and thus causal relationships cannot be evaluated. Given the nature of observational studies that rely on administrative claims, there may have been coding inaccuracies, missing information due to incorrect diagnosis or procedure codes, or other indicators affecting the reliability and validity of the data. Using data from 2009 to 2013, we were able to capture the recent trend of COPD treatment and associated clinical outcomes; however, COPD drugs that were approved after 2013 were not included, which may affect the results. In addition, the presence of a claim for a filled prescription does not necessarily indicate that the medication was consumed as prescribed. Moreover, medications filled over-the-counter or provided as samples by the physician would not have been included in the claims data. Although logistic regression with a comprehensive list of covariates was used, this study remains bound by the limitation of claims data; variables such as medications filled over-the-counter or provided as samples by the physician or potential variations in treatment and discharge protocols between hospitals are unavailable and thus were not controlled for in the model.

Beneficiaries who received nebulized ARF alone, and those who may have also received a nebulized SABD concomitantly after discharge, were grouped into the nebulized ARF cohort. Furthermore, no adjustment was made for the use of other forms of treatment for COPD.

Our analysis was based on fee-for-service Medicare data and limited to beneficiaries who were ≥65 years old; in addition, following hospital discharge, only patients prescribed ARF were included for the ARF cohort. Thus, our findings may not be generalizable to other populations with COPD. Furthermore, although several variables were selected for our probabilistic linkage analysis to match the outpatient and inpatient information of a particular patient, it is possible that more than one patient with similar hospitalization profiles could have led to potential mismatching across the two sources. Despite these limitations, claims data remain a valuable source of information because they reflect real-world practice patterns, patient behaviors, and outcomes.

CONCLUSIONS

This real-world observational study found that Medicare beneficiaries treated with nebulized ARF after being discharged following a COPD-related hospitalization had 27% lower odds of an all-cause readmission and 23% lower odds of a COPD-related readmission, at 30 days, compared with beneficiaries who received a nebulized SABA for maintenance therapy after discharge. Therefore, among this Medicare-insured population with a COPD-related hospitalization, use of nebulized ARF as maintenance therapy after a COPD-related hospitalization may potentially reduce the risk of readmission and unnecessary health resource utilization.

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Ms. Keshishian, Ms. Xie, and Dr. Yuce contributed to the conceptualization, study design, and data analysis phases of the study. Dr. Yuce was responsible for data curation and led data analysis and results reporting. Ms. Dembek contributed to the study design and data analysis. All authors contributed to drafting, revising, and approving the final manuscript.

DISCLOSURES

Ms. Keshishian and Ms. Xie are employed by STATinMED Research, which received funding from Sunovion Pharmaceuticals Inc to conduct this study. Ms. Dembek is employed by Sunovion Pharmaceuticals Inc, which sponsored this study. Dr. Yuce received consultation fees from STATinMED Research to participate in this study. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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