

# Long-acting bronchodilators with or without inhaled corticosteroids and 30-day readmission in patients hospitalized for COPD

Raju Bishwakarma<sup>1</sup>Wei Zhang<sup>1</sup>Yong-Fang Kuo<sup>2,3</sup>Gulshan Sharma<sup>1,3</sup>

<sup>1</sup>Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, <sup>2</sup>Office of Biostatistics, <sup>3</sup>Sealy Center of Aging, University of Texas Medical Branch, Galveston, TX, USA

**Background:** The ability of a long-acting muscarinic antagonist (LAMA) and long-acting beta 2 agonists (LABAs; long-acting bronchodilators, LABDs) with or without inhaled corticosteroids (ICSs) to reduce early readmission in hospitalized patients with COPD is unknown.

**Methods:** We studied a 5% sample of Medicare beneficiaries enrolled in Medicare parts A, B and D and hospitalized for COPD in 2011. We examined prescriptions filled for LABDs with or without ICSs (LABDs±ICSs) within 90 days prior to and 30 days after hospitalization. Primary outcome was the 30-day readmission rate between “users” and “nonusers” of LABDs±ICSs. Propensity score matching and sensitivity analysis were performed by limiting analysis to patients hospitalized for acute exacerbation of COPD (AECOPD). Among 6,066 patients hospitalized for COPD, 3,747 (61.8%) used LABDs±ICSs during the specified period. The “user” and “nonuser” groups had similar rates of all-cause emergency room (ER) visits and readmissions within 30 days of discharge date (22.4% vs 20.7%, *P*-value 0.11; 18.0% vs 17.8%, *P*-value 0.85, respectively). However, the “users” had higher rates of COPD-related ER visits (5.3% vs 3.4%, *P*-value 0.0006), higher adjusted odds ratio (aOR) 1.47 (95% CI, 1.11–1.93) and readmission (7.8% vs 5.0%, *P*-value <0.0001 and aOR 1.48 [95% CI, 1.18–1.86]) than “nonusers”. After propensity score matching, the aOR of COPD-related ER visits was 1.45 (95% CI, 1.07–1.96) and that of readmission was 1.34 (95% CI, 1.04–1.73). The results were similar when restricted to patients hospitalized for AECOPD.

**Conclusion:** Use of LABDs±ICSs did not reduce 30-day readmissions in patients hospitalized for COPD.

**Keywords:** COPD, readmission, long-acting bronchodilators, Medicare

## Introduction

The natural history of COPD includes progressive expiratory air flow limitation interrupted by exacerbations.<sup>1–4</sup> Most exacerbations can be managed in outpatient settings.<sup>3</sup> However, severe exacerbations require acute care hospitalizations.<sup>3</sup> Exacerbations are associated with a decline in lung function,<sup>4–7</sup> reduced quality of life,<sup>5,7,8</sup> increased mortality,<sup>9,10</sup> increased risk of further exacerbations<sup>7,11,12</sup> and increased financial burden to the health-care system.<sup>13,14</sup> Reducing exacerbations – particularly severe exacerbations – requiring hospitalization is the goal for improving patient care and reducing health-care expenditures.

In the US, of patients aged 65 years and older hospitalized for COPD, one in five were readmitted within 30 days,<sup>15–17</sup> but less than half of those readmissions were COPD-related.<sup>17</sup> Due to the high cost to Medicare of readmission, in 2014, the Center for Medicare and Medicaid Services (CMS) added readmission for COPD as

Correspondence: Raju Bishwakarma  
Division of Pulmonary, Critical Care and Sleep Medicine, University of Texas Medical Branch, 301 University Boulevard, 5.140 John Sealy Annex, Galveston, TX 77555-0561, USA  
Tel +1 409 772 2436  
Fax +1 409 772 9532  
Email [rajucentury@gmail.com](mailto:rajucentury@gmail.com)

a condition for which it would penalize hospitals with higher than expected rates.<sup>15</sup>

COPD readmission represents a complex interplay of patient, provider and system factors. Interventions such as self-management, education, medication reconciliation, early follow-up, patient navigator, transition coach and home visits have been shown to reduce early readmission,<sup>18–21</sup> but none of these interventions target patients with COPD. A recent systematic review of five randomized controlled trials specially targeting the COPD population failed to show any intervention that impacted readmission.<sup>22</sup> A single-center randomized controlled trial targeting smoking cessation, inhaler education, screening for gastroesophageal reflux disease and anxiety, and a postdischarge follow-up call failed to show a reduction in readmission.<sup>23</sup>

The Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of long-acting bronchodilators (LABDs), such as long-acting muscarinic antagonist (LAMA) and long-acting beta 2 agonists (LABAs) with or without inhaled corticosteroids (ICSs) in patients with moderate to severe disease and those with frequent exacerbations.<sup>3</sup> Use of these medications has been shown to increase the number of symptom-free days, improve quality of life, decrease moderate to severe exacerbations, decrease hospitalizations and slow the decline in lung function.<sup>3,24–26</sup> Roflumilast, a phosphodiesterase-4 inhibitor, was shown to reduce moderate to severe exacerbations and also all-cause readmissions within 30 days in a select group of patients with COPD.<sup>27,28</sup>

The purpose of this study is to examine the rate of 30-day readmission in patients who received LABDs with or without LABDs±ICSs within 90 days prior to and 30 days after the index hospitalization for COPD. Our hypothesis is that use of maintenance drugs is associated with a reduction in the 30-day readmission rate.

## Methods

### Data source

This study uses files from the 5% national Medicare sample in 2011 provided by the Research Data Assistance Center (ResDAC). Data from the following files were used: 1) Denominator File (Medicare enrollment information and demographic data); 2) Medicare Provider Analysis and Review file (claims for hospital inpatient and skilled nursing facility stays); 3) Outpatient Standard Analytic File (hospital outpatient services); 4) 100% Physician/Supplier File (physician and other medical services); 5) Part D drug event data; and 6) Durable Medical Equipment (DME) File. ResDAC

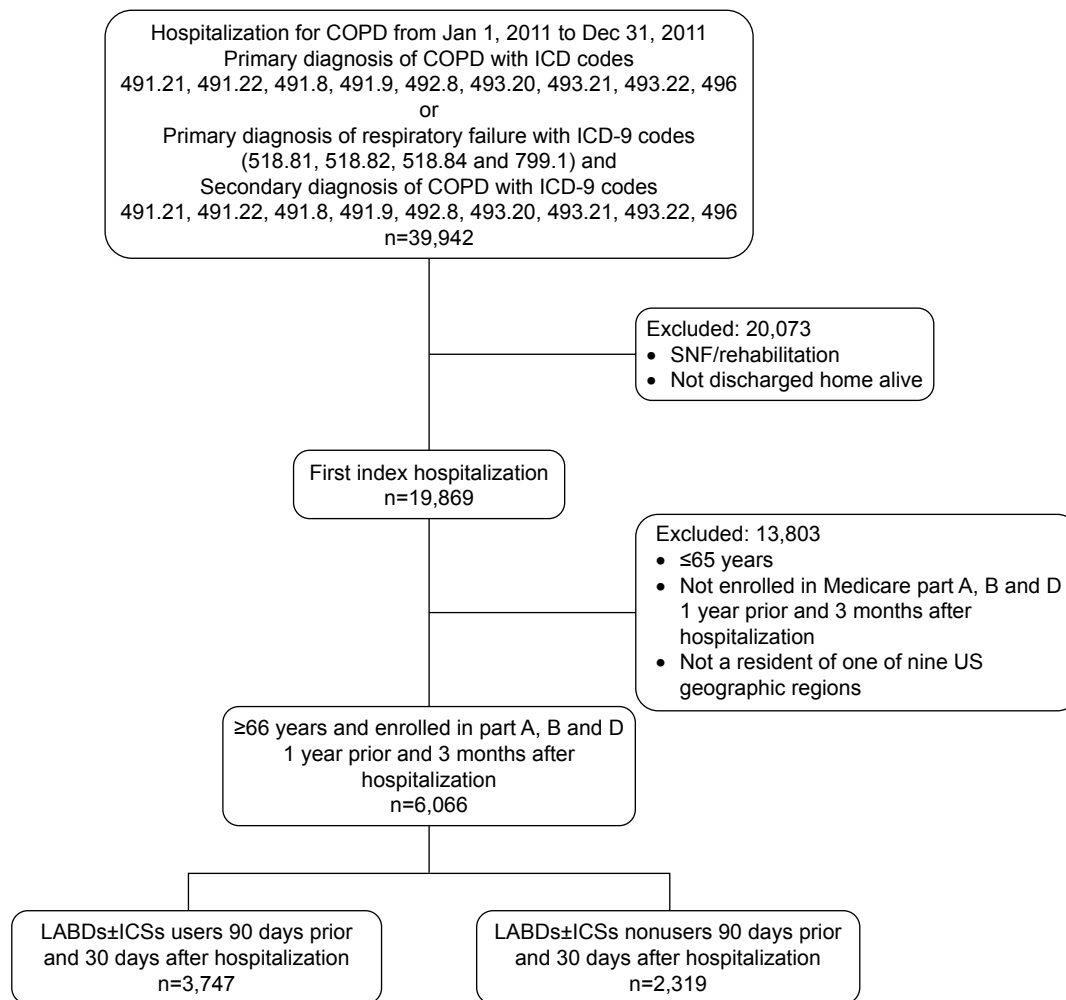
provides deidentified data for research purposes, and, due to the nature of the study, the University of Texas Medical Branch IRB deemed that patient consent was not required for this study. The study was approved by the University of Texas Medical Branch Institutional Review Board (IRB Project 09-054).

### Study cohort

Establishment of the study cohort is shown in Figure 1. In 2011, 6,066 patients aged 66 years or older with COPD had an index hospitalization, were discharged home alive, enrolled in Medicare parts A, B and D, but not in a health maintenance organization (HMO), from 1 year prior to 3 months after the index hospitalization, and resided in one of nine US geographic regions. Patients were enrolled from January 1, 2011, to December 31, 2011, and we looked back 1 year prior to index hospitalization (up to January 1, 2010) for baseline characteristics and 30 days after discharge (up to January 31, 2012) for readmission. COPD hospitalization was defined as, 1) hospitalization with a primary International Classification of Diseases, Ninth Revision (ICD-9) code for COPD (491.21, 491.22, 491.8, 491.9, 492.8, 493.20, 493.21, 493.22 and 496), or 2) primary ICD-9 codes for respiratory failure (518.81, 518.82, 518.84 and 799.1) and secondary ICD-9 codes for COPD, as described earlier. All other hospitalizations were classified as non-COPD related. An “index hospitalization” was defined as the first COPD hospitalization of the year.

### Variables

Subject demographic characteristics were obtained from the Denominator File and included the following: age (66–74 years, 75–84 years and ≥85 years), gender (male and female), race (non-Hispanic white, black and others), region (New England, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific) and socioeconomic status. Low socioeconomic status was based on the eligibility for at least 1 month during the index year for state buy-in coverage provided by the Medicaid program. The index hospitalization characteristics included admission type and number of Elixhauser comorbidities (0, 1, 2 and >2). Hospital characteristics included number of hospital beds and medical school affiliation. The following parameters were included as surrogates for severity of baseline disease: number of any hospitalizations, oxygen therapy and pulmonary specialist visits in the year before the index hospitalization; intensive care unit (ICU) or coronary care unit (CCU) use; mechanical ventilation; length of hospital stay and pulmonary specialist visit during index hospitalization.



**Figure 1** Establishment of study cohort.

**Abbreviations:** ICD, International Classification of Diseases; ICD-9, ICD, Ninth Revision; LABDs, long-acting bronchodilators; ICSs, inhaled corticosteroids; Jan, January; Dec, December; SNF, skilled nursing facility.

## Exposure

We defined the “user” group as those who filled a prescription of LABDs±ICSs, such as LAMA and LABAs with or without ICSs, from 90 days prior to the index hospitalization to 30 days after the discharge date (Figure 2). We chose the time period of 90 days prior to index hospitalization and 30 days after discharge to classify exposure appropriately. Most prescriptions (73.8%) were filled as a 30-day supply; however, a mail-in order can be for a 90-day supply. In order

to capture the latter, we extended the look back period to 90 days prior to hospitalization. Those with no prescription filled for these medications within this period were included in the “nonuser” group.

Among “users”, we also calculated medication adherence as the proportion of days covered (PDC), defined as the proportion of days out of 120 days that a patient had maintenance medication available. For overlap prescription of maintenance medication, an average PDC was calculated.



**Figure 2** Prescription for long-acting bronchodilators, with or without ICSs, filled by patients with COPD 90 days prior to index hospitalization to 30 days after the discharge in 2011.

**Abbreviation:** ICSs, inhaled corticosteroids.

## Outcomes

Our primary outcome of interest was health-care utilization, defined as emergency room (ER) visit and readmission within 30 days after discharge from the acute care hospital. We calculated the unadjusted cost associated with a 30-day readmission stay after index discharge in “users” and “nonusers” based on CMS methodology.

## Statistical analysis

Characteristics were expressed as mean  $\pm$  standard deviation for continuous variables and as percentages for categorical variables. Categorical variables were compared using the chi square test. Logistic regression model was used to estimate odds ratios, adjusted for the variables in Table 1.

**Table 1** Baseline characteristics of LABDs with or without ICSs user and nonuser patients hospitalized with COPD in 2011

Demographic characteristics	LABDs $\pm$ ICSs		P-value
	Users <sup>a</sup>	Nonusers <sup>b</sup>	
Total	3,747 (61.77)	2,319 (38.23)	
Age (mean $\pm$ SD)	76.50 $\pm$ 7.04	77.50 $\pm$ 7.49	<0.0001
Age group, years			<0.0001
66–74	1,676 (44.73)	941 (40.58)	
75–84	1,510 (40.30)	922 (39.76)	
$\geq$ 85	561 (14.97)	456 (19.66)	
Gender			0.32
Female	2,539 (67.76)	1,543 (66.54)	
Male	1,208 (32.24)	776 (33.46)	
Race			0.02
White	3,147 (83.99)	1,974 (85.12)	
Black	375 (10.01)	244 (10.52)	
Others	225 (6.00)	101 (4.36)	
Low socioeconomic status			<0.0001
No	2,071 (55.27)	1,414 (60.97)	
Yes	1,676 (44.73)	905 (39.03)	
Region			<0.0001
New England	222 (5.92)	123 (5.30)	
Middle Atlantic	514 (13.72)	261 (11.25)	
East North Central	719 (19.19)	446 (19.23)	
West North Central	223 (5.95)	120 (5.17)	
South Atlantic	814 (21.72)	548 (23.63)	
East South Central	370 (9.87)	295 (12.72)	
West South Central	408 (10.89)	295 (12.72)	
Mountain	123 (3.28)	71 (3.06)	
Pacific	354 (9.45)	160 (6.90)	
Number of hospital beds			0.05
<250	1,652 (44.09)	1,091 (47.05)	
250–499	1,327 (35.41)	797 (34.37)	
$\geq$ 500	768 (20.50)	431 (18.59)	
Medical school affiliation			0.06
Major	659 (17.59)	356 (15.35)	
Minor	850 (22.68)	525 (22.64)	
None	2,238 (59.73)	1,438 (62.01)	
Type of hospital			0.0002
Government	460 (12.28)	359 (15.48)	
For-profit	2,637 (70.38)	1,524 (65.72)	
Nonprofit	650 (17.35)	436 (18.80)	

(Continued)

**Table 1** (Continued)

Demographic characteristics	LABDs $\pm$ ICSs		P-value
	Users <sup>a</sup>	Nonusers <sup>b</sup>	
Admission type			0.04
Emergency	2,825 (75.39)	1,683 (72.57)	
Urgent	624 (16.65)	443 (19.10)	
Others	298 (7.95)	193 (8.32)	
Number of comorbidities			0.08
0	373 (9.95)	233 (10.05)	
1	574 (15.32)	340 (14.66)	
2	667 (17.80)	360 (15.52)	
$\geq$ 3	2,133 (56.93)	1,386 (59.77)	
Number of hospitalizations in the 1 year before index hospitalization			0.37
0	1,789 (47.74)	1,147 (49.46)	
1	936 (24.98)	548 (23.63)	
$\geq$ 2	1,022 (27.28)	624 (26.91)	
ICU/CCU stay during hospitalization			0.04
No	2,521 (67.28)	1,620 (69.86)	
Yes	1,226 (32.72)	699 (30.14)	
Mechanical ventilation during hospitalization			0.32
No	3,658 (97.62)	2,273 (98.02)	
Yes	89 (2.38)	46 (1.98)	
Oxygen therapy use 1 year before index hospitalization			<0.0001
No	1,907 (50.89)	1,476 (63.65)	
Yes	1,840 (49.11)	843 (36.35)	
Pulmonary specialist visits in the 1 year before index hospitalization			<0.0001
No	2,323 (62.00)	1,767 (76.20)	
Yes	1,424 (38.00)	552 (23.80)	
Length of hospital stay in days (mean $\pm$ SD)	4.32 $\pm$ 2.93	4.02 $\pm$ 2.55	0.0001
Pulmonary specialist visit during hospitalization			0.0002
No	2,978 (79.48)	1,932 (83.31)	
Yes	769 (20.52)	387 (16.69)	

**Notes:** Data presented as number (%) unless otherwise stated. <sup>a</sup>Users defined as those who had a prescription filled for LABDs with or without ICSs within 90 days prior to and 30 days after hospitalization. <sup>b</sup>Nonusers are those who did not have a prescription filled for LABDs with or without ICSs within 90 days prior to and 30 days after hospitalization.

**Abbreviations:** LABDs, long-acting bronchodilators; ICSs, inhaled corticosteroids; ICU, intensive care unit; CCU, coronary care unit.

We performed the following sensitivity analyses to explain the robustness of our findings. First, we limited the analysis to patients discharged with a principal diagnosis of acute exacerbation of COPD (AECOPD; primary ICD-9 code 491.21 or primary ICD-9 codes 518.81, 518.82, 518.84 and 799.1 with secondary ICD-9 code 491.21). Second, we performed propensity score matching. We did 1:1 match for every “nonuser” to a “user” based on estimated propensity scores from a logistic regression model adjusted for all variables in Table 1. The matching was based on nearest Mahalanobis distance. Finally, we examined the impact of medication adherence during the 120 days studied. Adherence was defined as low, moderate or high based on <50%, 50%–79% or  $\geq$ 80% of days covered, respectively.

All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA). All reported *P*-values were two-sided, and *P*<0.05 was considered statistically significant.

## Results

In 2011, 6,066 patients with COPD who had a hospitalization were included in the study. Of these, 3,747 (61.8%) filled a prescription for LABDs±ICSs from 90 days prior to the index hospitalization to 30 days after discharge.

The baseline characteristic of “users” and “nonusers” of LABDs±ICSs is presented in Table 1. Patients who received a prescription for LABDs±ICSs were younger, more likely to have lower socioeconomic status and had more emergency admissions. They were more likely to be admitted to for-profit hospitals. The “user” and “nonuser” groups had a similar distribution of comorbidities. However, LABDs±ICSs “users” were more likely to be on oxygen therapy in the year prior to hospitalization and were more likely to be under the care of a pulmonary physician, suggesting more severe disease. Length of stay for the index hospitalization was longer for the “user” group than for the “nonuser” group (4.32 days vs 4.02 days, *P*-value 0.0001). A larger proportion of “users” were seen by a pulmonary physician during the index hospitalization (20.5% vs 16.7%, *P*-value 0.0002) compared to “nonusers”.

Health-care utilization in terms of ER visits and readmissions is presented in Table 2. The “user” and “nonuser” groups had similar rates of all-cause ER visits and readmissions within 30 days of discharge date (22.4% vs 20.7%, *P*-value 0.11; 18.0% vs 17.8%, *P*-value 0.85, respectively). However, compared to “nonusers”, LABDs±ICSs “users” had higher rates of COPD-related ER visits (5.3% vs 3.4%, *P*-value 0.0006) and COPD-related readmissions (7.8% vs 5.0%, *P*-value <0.0001). After adjusting for all variables in Table 1, “users” had 1.47 greater odds of a COPD-related

ER visit (95% CI, 1.11–1.93) and 1.48 greater odds of a readmission (95% CI, 1.18–1.86) than “nonusers”.

Restricting patients to those with AECOPD (ICD-9 code 491.21, n=3,925) did not change our results. For example, the risk of a COPD-related ER visit was 6.0% vs 3.9% (*P*-value 0.004) and of a COPD-related readmission was 8.5% vs 5.4% (*P*-value 0.0003) in LABDs±ICSs “users” vs “nonusers” (Table S1).

Based on the propensity score, we were able to match 95.5% of “nonusers” with LABDs±ICSs “users” (n=2,214 in each group). Figure 3 shows the distribution of propensity score of the two groups before and after matching. As shown, the propensity score overlaid well after matching, and no significant differences in patient characteristics were found between the matched groups. Outcomes were similar, with “users” having an adjusted 1.45 increased risk of a COPD-related ER visit (95% CI, 1.07–1.96) and 1.34 adjusted greater odds of readmission (95% CI, 1.04–1.73) compared to “nonusers” (Figure 4 and Table S2). Medication adherence rates based on PDC during the 120-day period were not associated with risk of all-cause or COPD-related readmission. Among “users”, 966 patients had 30-day readmission (all-cause and COPD-related) and average cost was US\$11,499.56 (median \$7,835, quartile (Q)1=\$5,826, Q3=\$12,307). Total 30-day readmission among “nonusers” was 527 with an average cost of US\$10,829.84 (median \$7,139, Q1=\$5,428.5, Q3=\$11,378). There was no difference in cost between the “user” and “nonuser” groups.

## Discussion

Our study found that the use of LABDs±ICSs as maintenance therapy in COPD patients during 90 days prior to and 30 days after hospitalization did not reduce the rate of 30-day readmission. The rates of all-cause ER visits and readmissions were similar between the “user” and “nonuser” groups.

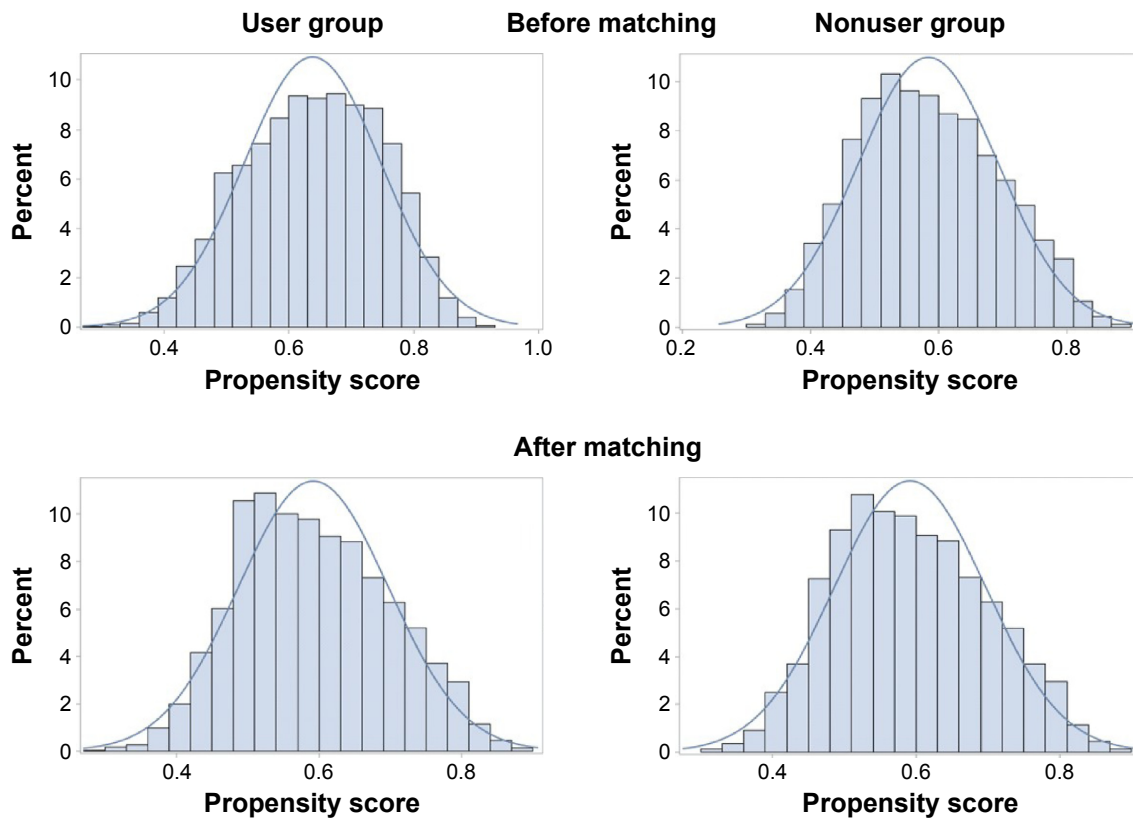
**Table 2** Health-care utilization within 30 days of discharge by LABDs±ICSs with or without LABDs±ICSs users and nonusers groups

Outcomes	LABDs±ICSs		Adjusted OR (95% CI) <sup>e</sup> , ref = nonuser
	Nonusers <sup>a</sup> , 3,747, n (%)	Users <sup>b</sup> , 2,319, n (%)	
All-cause ER visit	480 (20.7)	840 (22.4)	1.07 (0.94–1.23)
COPD-related ER visit	78 (3.4)	197 (5.3) <sup>d</sup>	1.47 (1.11–1.93) <sup>d</sup>
All-cause readmission	412 (17.8)	673 (18.0)	0.96 (0.83–1.11)
COPD-related readmission	115 (5.0)	293 (7.8) <sup>d</sup>	1.48 (1.18–1.86) <sup>d</sup>

**Notes:** <sup>a</sup>Nonusers are those who did not have a prescription filled for LABDs±ICSs with or without LABDs±ICSs from 90 days prior to and 30 days after hospitalization.

<sup>b</sup>Users defined as those who had a prescription filled for LABDs with or without ICSs from 90 days prior to and 30 days after hospitalization. <sup>c</sup>Logistic regression model was used to estimate odds ratio, adjusted by age, gender, race, region, Medicaid eligibility, comorbidity score, number of hospital beds, medical school affiliation, type of hospital, type of admission, hospitalization in the 1 year before index hospitalization, ICU/CCU during hospitalization, MV during hospitalization, oxygen therapy and pulmonary specialist visit in the 1 year before index hospitalization, LOS and pulmonary specialist visit during hospitalization. <sup>d</sup>*P*-value <0.05.

**Abbreviations:** LABDs, long-acting bronchodilators; ICSs, inhaled corticosteroids; ICU, intensive care unit; CCU, coronary care unit; ER, emergency room; LOS, length of stay; MV, mechanical ventilation.



**Figure 3** Propensity score distribution plot comparing LABDs±ICSs users vs nonusers before and after matching.

**Notes:** Propensity score matching adjusting for age, gender, race, region, Medicaid eligibility, comorbidity score, number of hospital beds, medical school affiliation, type of hospital, type of admission, hospitalization 1 year before index hospitalization, ICU/CCU during index hospitalization, MV during index hospitalization, oxygen therapy 1 year before index hospitalization, pulmonary specialist visit 1 year before index hospitalization, length of index hospitalization stay and pulmonary specialist visit during index hospitalization.

**Abbreviations:** LABDs, long-acting bronchodilators; ICSs, inhaled corticosteroids; ICU, intensive care unit; CCU, coronary care unit; MV, mechanical ventilation.

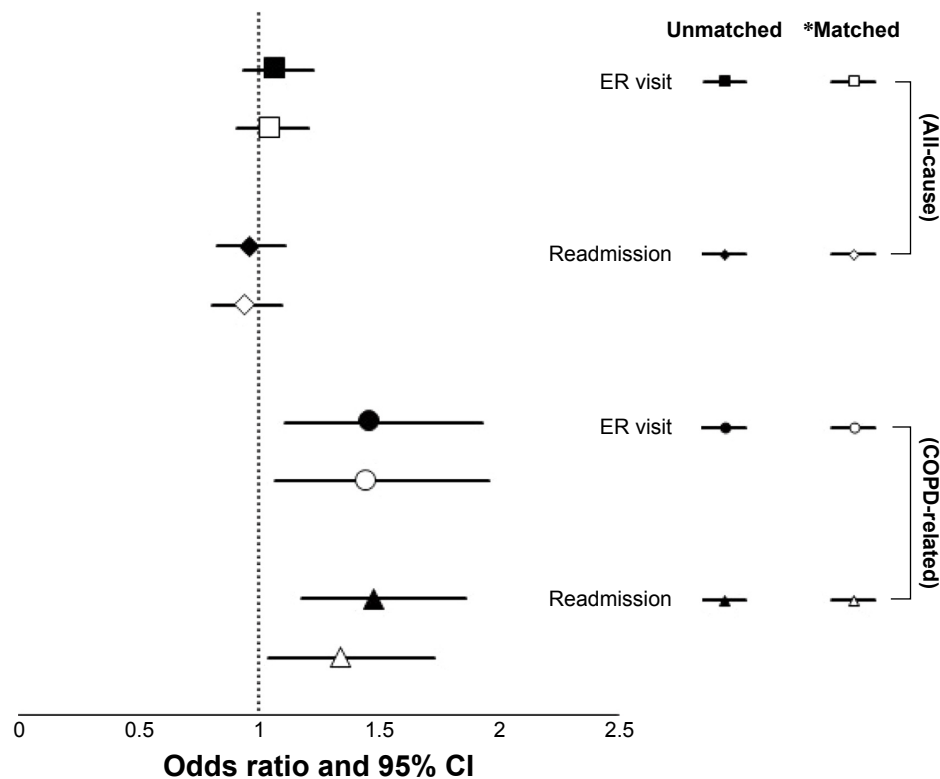
Higher rates of COPD-related ER visits and 30-day readmissions in patients on maintenance drugs are likely related to illness severity rather than causal. LABAs with or without ICSs and LAMA use in stable patients with COPD have been shown to prevent exacerbations, reduce hospitalizations and improve both lung function and quality of life.<sup>3,24–26</sup> Our study showed that the use of maintenance medication did not reduce early readmission.

More than half of readmissions in patients hospitalized for COPD are non-COPD related and not all COPD-related readmissions are related to AECOPD.<sup>17</sup> Numerous factors related to patient disease severity, comorbidity and health-care delivery play a role in 30-day readmission.<sup>29–31</sup> LABDs±ICSs has a role in preventing exacerbations in stable patients with COPD<sup>3,24–26,32,33</sup> but not per se in reducing 30-day readmissions.

The findings of our study are similar to prior reports. Lindenauer et al<sup>34</sup> showed that the use of LABDs in patients hospitalized for AECOPD was not associated with better

outcomes. Instead, 30-day LABDs-related readmission rates were higher in patients treated with LABDs when compared with those who received short-acting bronchodilators for AECOPD (3.1% vs 2.6%,  $P$ -value<0.001).<sup>34</sup> Baker et al<sup>35</sup> showed that the use of LABDs after hospitalization for COPD was associated with higher rates of ER visits (17.8% vs 14.1%,  $P$ -value<0.0001) and hospitalization (16.0% vs 12.6%,  $P$ -value<0.001) within 90 days compared to nonusers of LABDs±ICSs.

These findings taken together could merely reflect that sicker individuals are on maintenance drugs and sicker people get rehospitalized. The other explanation could be related to the differential mechanism of these drugs during exacerbation and recovery phase, which makes patients prone to poor symptoms control after discharge, requiring readmission. Functional antagonism and receptor downregulation can occur during exacerbations due to strong cholinergic tone, and prolonged use of long-acting agents may necessitate an increased need for short-acting beta agonist.<sup>36–38</sup> Excessive



**Figure 4** Odds of ER visit and readmission within 30 days after index hospitalization related to COPD in patients using LABDs±ICSs 90 days prior to hospitalization and/or 30 days after discharge.

**Notes:** \*Matched: propensity score matching adjusted for age, gender, race, region, Medicaid eligibility, comorbidity score, number of hospital beds, medical school affiliation, type of hospital, type of admission, hospitalization 1 year before index hospitalization, ICU/CCU during index hospitalization, MV during index hospitalization, oxygen therapy 1 year before index hospitalization, pulmonary specialist visit 1 year before index hospitalization, length of index hospitalization stay and pulmonary specialist visit during index hospitalization.

**Abbreviations:** LABDs, long-acting bronchodilators; ICSs, inhaled corticosteroids; ICU, intensive care unit; CCU, coronary care unit; ER, emergency room; MV, mechanical ventilation.

use of beta agonist and antimuscarinic agents can predispose patients to adverse cardiovascular side effects such as tachycardia, arrhythmias and congestive heart failure, resulting in an increase in all-cause ER visits and readmissions.<sup>29</sup>

Our findings should be considered in the context of our study's limitations. First, our study is limited to fee-for-service Medicare beneficiaries who had Medicare Parts A, B and D. Second, we used ICD-9 codes to establish a diagnosis of COPD, and these codes may not reflect disease severity. However, we were able to control for other surrogates of disease severity such as prior hospitalization, oxygen use, ICU/CCU and mechanical ventilation use during index hospitalization, whether the patient was under the care of a pulmonary physician in the year prior to the hospitalization and whether the patient was seen by a pulmonary provider during the index hospitalization. Third, we defined LABDs/LABDs±ICSs users as those who had a prescription filled within the 90 days prior to the index hospitalization and 30 days after discharge; however, these data may not capture actual use. Even though high medication adherence measured as PDC was not associated with reduced risk of all-cause or COPD-related readmission, the

reasons for readmissions in this chronically ill population are multifactorial and may not be amenable to the use of maintenance medication. Fourth, we did not examine the role of early follow-up, pulmonary rehabilitation or disease management in our study. To date, none of these approaches has been shown to reduce readmission, in well-designed studies.

## Conclusion

We found that the use of maintenance drugs LABDs±ICSs 90 days prior to and 30 days after hospitalization for COPD did not reduce 30-day readmission.

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## Disclosure

Dr Sharma serves on the advisory board of Theravance Biopharma, Mylan and Sunovion pharmaceutical companies. The authors report no other conflicts of interest in this work.

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## Supplementary materials

**Table S1** Health-care utilization within 30 days of discharge by LABDs with or without ICSs users and nonusers group for AECOPD<sup>a</sup>, N=3,925

Outcomes	LABDs±ICSs		Adjusted OR (95% CI) <sup>d</sup> , ref = nonuser
	Nonusers <sup>b</sup> , n=2,504, n (%)	Users <sup>c</sup> , n=1,421, n (%)	
All-cause ER visit	302 (21.25)	593 (23.68)	1.11 (0.94–1.31)
COPD-related ER visit	55 (3.87)	151 (6.03) <sup>e</sup>	1.42 (1.02–1.98) <sup>e</sup>
All-cause readmission	269 (18.93)	493 (19.69)	1.00 (0.84–1.19)
COPD-related readmission	76 (5.35)	213 (8.51) <sup>e</sup>	1.48 (1.14–1.99) <sup>e</sup>

**Notes:** <sup>a</sup>AECOPD is defined as hospitalization with a primary ICD-9 code (491.21) or primary ICD-9 codes for respiratory failure (518.81, 518.82, 518.84 and 799.1) with secondary ICD-9 code (491.21). <sup>b</sup>Nonusers are those who did not have a prescription filled for LABDs with or without ICSs from 90 days prior to and 30 days after hospitalization. <sup>c</sup>Users defined as those who had a prescription filled for LABDs with or without ICSs from 90 days prior to and 30 days after hospitalization. <sup>d</sup>Logistic regression model was used to estimate odds ratio, adjusted by age, gender, race, region, Medicaid eligibility, comorbidity score, number of hospital beds, medical school affiliation, type of hospital, type of admission, hospitalization in the 1 year before index hospitalization, ICU/CCU during hospitalization, MV during hospitalization, oxygen therapy and pulmonary specialist visit in the 1 year before index hospitalization, LOS and pulmonary specialist visit during hospitalization. <sup>e</sup>P-value <0.05.

**Abbreviations:** LABDs, long-acting bronchodilators; ICSs, inhaled corticosteroids; AECOPD, acute exacerbation of COPD; ICD-9, International Classification of Diseases, Ninth Revision; ER, emergency room; ICU, intensive care unit; CCU, coronary care unit; LOS, length of stay; MV, mechanical ventilation.

**Table S2** Health-care utilization within 30 days of discharge by LABDs with or without ICSs users and nonusers group after propensity matching, N=4,428

Outcomes	LABDs±ICSs		Adjusted OR (95% CI) <sup>c</sup> , ref = nonuser
	Nonusers <sup>a</sup> , n=2,214, n (%)	Users <sup>b</sup> , n=2,214, n (%)	
All cause ER visit	452 (20.42)	469 (21.18)	1.05 (0.91–1.21)
COPD-related ER visit	75 (3.39)	107 (4.83) <sup>d</sup>	1.45 (1.07–1.96) <sup>d</sup>
All cause readmission	393 (17.75)	375 (16.94)	0.94 (0.81–1.10)
COPD-related readmission	110 (4.97)	145 (6.55) <sup>d</sup>	1.34 (1.04–1.73) <sup>d</sup>

**Notes:** <sup>a</sup>Nonusers are those who did not have a prescription filled for LABDs with or without ICSs from 90 days prior to and 30 days after hospitalization. <sup>b</sup>Users defined as those who had a prescription filled for LABDs with or without ICSs from 90 days prior to and 30 days after hospitalization. <sup>c</sup>Logistic regression model was used to estimate odds ratio, adjusted by age, gender, race, region, Medicaid eligibility, comorbidity score, number of hospital beds, medical school affiliation, type of hospital, type of admission, hospitalization in the 1 year before index hospitalization, ICU/CCU during hospitalization, MV during hospitalization, oxygen therapy and pulmonary specialist visit in the 1 year before index hospitalization, LOS, and pulmonary specialist visit during hospitalization. <sup>d</sup>P-value <0.05.

**Abbreviations:** LABDs, long-acting bronchodilators; ICSs, inhaled corticosteroids; ICU, intensive care unit; CCU, coronary care unit; ER, emergency room; LOS, length of stay; MV, mechanical ventilation.

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