Characteristics and Health Care Resource Use of Subjects with COPD in the Year Before Initiating LAMA Monotherapy or LAMA+LABA Combination Therapy: A U.S. Database Study

Saurabh Nagar, BPharm,[1*] Jeetvan Patel, PhD,[1*] Richard H. Stanford, PharmD, MS[1]

[1]GlaxoSmithKline

ABSTRACT

Purpose: To characterize subjects with chronic obstructive pulmonary disease (COPD) newly initiated on long-acting muscarinic antagonists (LAMA) or dual LAMA/long-acting β_2-adrenergic agonist (LABA) therapy.

Design: This pilot/preliminary analysis was a retrospective cross-sectional study of subjects with COPD from the Optum Impact National Managed Care Benchmark Database.

Methodology: Subjects with at least one LAMA prescription in the index period (July 2008–June 2009) were included and stratified by treatment. Data were collected in the year before the index date and included comorbidities, medication use, COPD-related costs, health care resource use, and exacerbations.

Results: Of 5,311 eligible subjects, 2,057 initiated LAMA therapy (LAMA cohort) and 191 initiated LAMA+LABA therapy (LAMA+LABA cohort). The Charlson comorbidity index was slightly lower in the LAMA+LABA cohort than the LAMA cohort (mean±SD: 0.63±1.13 vs. 0.66±1.28), but the number of prescriptions was higher (mean±SD: 42.9±23.2 vs. 30.5±27.2). The LAMA+LABA cohort had higher short-acting inhaled β_2 agonist (56.0% vs. 35.7%), oral corticosteroid (37.7% vs. 32.6%), and home oxygen therapy use (14.1% vs. 3.2%) than the LAMA cohort. Total medical costs were greater in the LAMA+LABA cohort than the LAMA cohort (mean±SD: $3,320.40±4085.9 vs. $1,226.20±3602.9), although emergency department ($11.00±66.8 vs. $30.70±259.2) and outpatient visit ($39.60±163.1 vs. $41.70±424.3) costs were lower. Resource use and exacerbation incidence were similar between cohorts.

Conclusion: In this first look, subjects with COPD initiating LAMA or LAMA+LABA therapy exhibited different clinical and resource use characteristics in the year before treatment. Subjects receiving LAMA+LABA were older, with higher COPD co-medication use, more prescriptions, and associated higher pharmacy costs compared with subjects initiating LAMA. These differences may reflect a higher severity of COPD in those starting LABA+LAMA treatment.

Key words: Chronic obstructive pulmonary disease, LAMA, LABA, tiotropium, salmeterol, formoterol

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive, life-threatening disease characterized by persistent airflow obstruction that is not fully reversible and can impact daily activities (GOLD 2018, Celli 2004). Globally, COPD is a leading cause of mortality; more than 3 million people died of COPD in 2015, which equates to 5% of all deaths in that year (WHO 2017). In the U.S., more than 11 million people have been diagnosed with COPD (ALA 2015). COPD places a large burden on individual subjects through increased morbidity (Barnes 2009) and reduced health-related quality of life (GOLD 2018). There is also a significant economic burden associated with COPD; COPD-related costs in 2010 in the United States were estimated at approximately $32.1 billion and were projected to increase to $49.0 billion by 2020 (Ford 2015).

Treatment of subjects with COPD focuses on delaying disease progression, limiting complications, and relieving symptoms to improve overall quality of life (GOLD 2018). Long-acting bronchodilators, which include long-acting muscarinic antagonists (LAMAs) and long-acting β_2-adrenergic agonists (LABAs), are central to the pharmacological management of COPD (GOLD 2018). A recent study demonstrated that subjects with COPD receiving long-acting bronchodilator monotherapy (76% of whom were receiving the LAMA tiotropium) continued to show significant symptoms and poor quality of life as well as taking high doses of short-acting inhaled β_2-agonist (SABA) rescue medication (Dransfield 2011). Combination therapy using two long-acting broncho-

* Nagar and Patel were employees of GlaxoSmithKline when this study was conducted. Nagar now works for RTI-Health Solutions and Patel for Amgen.

dilator treatments with distinct and complementary mechanisms of action can be prescribed to help address this unmet medical need (GOLD 2018, Cazzola 2010, Welte 2009, Maleki-Yazdi 2014, Celli 2014).

Treatment guidelines are in place to aid clinicians in their prescribing practices for COPD (GOLD 2018). However, it is unclear how strictly they are adhered to in real-world settings and which factors influence initiation or augmentation of existing COPD maintenance therapies.

The purpose of this study was to characterize the health care resource use, costs, and exacerbations among subjects in the 12 months preceding initiation on LAMA monotherapy or LAMA+LABA dual therapy.

METHODS

Study design

This pilot/preliminary analysis was a retrospective cross-sectional analysis of data from subjects diagnosed with COPD (GSK Study HO-12-6723) who received at least one prescription for a LAMA between July 1, 2008, and June 30, 2009, defined as the index period. Subject data were sourced from the Optum Impact National Managed Care Benchmark Database, a comprehensive, de-identified, U.S. health care claims database. These data were collected from 46 different health care plans serving members across nine consensus regions. The index date for subjects in the LAMA and LAMA+LABA cohorts was defined as the first prescription of LAMA therapy and LAMA+LABA therapy in the index period, respectively. Outcomes were assessed in a one-year period before the index date, defined as the pre-index period.

At the time of this study, the long-acting bronchodilators approved for treatment of COPD in the United States were the LAMA tiotropium and the two LABAs, formoterol and salmeterol. Subjects who were newly initiated on LAMA therapy during the index period were classified as the LAMA cohort. Subjects who initiated LAMA+LABA therapy during the index period were classified as the LAMA+LABA cohort. Subjects in the LAMA+LABA cohort could be new to LAMA+LABA or could have augmented from LAMA only. Therefore, the LAMA and LAMA+LABA cohorts were not mutually exclusive, as some of the LAMA+LABA users could be in both groups. Dual therapy was defined as the use of a LAMA and LABA (via separate inhalers) on the same day or overlapping days of supply at the index date.

Subjects

This analysis included adults ≥40 years of age during the index period, previously diagnosed with COPD (ICD-9 codes, 491.xx, 492.xx, and 496.xx), having at least one hospitalization claim, one emergency department (ED) claim, or one medical claim for a visit to the physician in the pre-index period that included a diagnosis of COPD in any recorded field and who were continuously eligible for inclusion in their health plan during the pre- and post-index periods. Subjects were excluded if they were diagnosed with the specific comorbid conditions listed in Supplementary Appendix 1 Table A1, page 48.

Abbreviations used in this study

ACO – accountable care organization
Ab – antibiotic
CCI – Charlson comorbidity index
COPD – chronic obstructive pulmonary disease
ED – emergency department
GSK – GlaxoSmithKline
ICS – inhaled corticosteroids
LABA – long-acting β_2-adrenergic agonists
LAMA – long-acting muscarinic antagonists
OCS – oral corticosteroid
Phy+Rx – COPD-related physician visit with a primary diagnosis of COPD and receipt of oral corticosteroid or antibiotic prescription within five days of physician visit
Rx – prescription
SABA – short-acting inhaled β_2-agonist

Outcomes and assessments

Demographics and clinical characteristics

Demographic and clinical characteristics, including comorbidities, were recorded during the pre-index period. Comorbidities were assessed by the number of unique prescription (Rx) classes based on Generic Product Identifier categorization, the number of prescriptions for drugs other than asthma drugs, the Charlson comorbidity index (CCI; calculated for each subject based on the presence of ICD-9-CM codes), and the number of subjects with unique three-digit diagnosis codes (a unique count of disease states beyond those used to calculate the CCI). Comorbidities of interest were identified by medical claims with a diagnosis or procedure code indicating the condition. These included asthma, depression, upper respiratory tract infection, lower respiratory tract infection, and cardiovascular disease (CVD). A binary indicator was used to designate the presence of the comorbidity (1=yes, 0=no).

Co-medication and maintenance drug use

The use of co-medications and maintenance drugs was assessed. Three co-medications were recorded: SABA, oral corticosteroids (OCS), and home oxygen therapy. The proportions of subjects with SABA and OCS use were recorded for both the LAMA and LAMA+LABA populations. The use of home oxygen therapy was defined

as a medical claim with a procedure code for home oxygen therapy and was recorded with a binary indicator variable (1=yes, 0=no). The number of subjects having a prescription for maintenance drug was recorded for both the LAMA and LAMA+LABA populations. Maintenance drug classes were inhaled corticosteroids (ICS), ICS+LABA, LAMA, and LABA.

COPD-related costs and health care resource use

COPD-related medical costs incurred during the pre-index period were defined as the costs for claims with a primary diagnosis of COPD. For hospitalization, all claims with a primary discharge diagnosis of COPD were used. COPD-related medical costs were classified into different components based on setting: in-patient hospital stay, ED visit, visit to the physician office, and outpatient visit. COPD-related pharmacy costs were defined as the costs for claims for both maintenance and rescue medications (Supplementary Appendix 1 Table A2, page 48). The total COPD-related cost was defined as the sum of COPD-related medical and pharmacy costs.

TABLE 1
Demographic and clinical characteristics among subjects initiating LAMA therapy and LAMA+LABA dual therapy in the 1-year period prior to initiation of therapy

	LAMA cohort (n=2,057)		LAMA+LABA cohort (n=191)	
	n	%	n	%
Mean age (SD)	60.6 (9.6)		64.8 (9.2)	
Gender				
Male	987	48.0	96	50.3
Female	1,070	52.0	95	49.7
Plan type				
Commercial	1,878	91.3	175	91.6
Medicaid	19	0.9	1	0.5
Medicare	160	7.8	15	7.9
Region				
Northeast	719	35.0	58	30.4
Midwest	333	16.2	34	17.8
West	196	9.5	33	17.3
South	790	38.4	65	34.0
Missing	19	0.9	1	0.5
Overall comorbid burden, mean (SD)				
Number of unique Rx classes	3.7 (3.8)		4.3 (3.6)	
Number of Rx	30.5 (27.2)		42.9 (23.2)	
Number of unique 3-digit diagnosis	11.3 (8.5)		10.9 (9.5)	
CCI	0.66 (1.28)		0.63 (1.13)	
Comorbidities of interest				
Asthma	346	16.8	39	20.4
Depression	202	9.8	19	10.0
URTI	365	17.7	32	16.8
LRTI	416	20.2	27	14.1
CVD	713	34.7	57	29.8

CCI=Charlson comorbidity index, CVD=cardiovascular disease, LABA=long-acting β_2-adrenergic agonists, LAMA=long-acting muscarinic antagonists, LRTI=lower respiratory tract infection, Rx= prescription, SD=standard deviation, URTI=upper respiratory tract infection.

The number of COPD-related visits was recorded for four types of health care resource use: ED visits, inpatient hospital stays, physician visits with receipt of OCS or antibiotic prescription (Ab Rx) within 5 days of the visit (Phy+Rx), and outpatient visits. An outpatient visit was defined as a visit in the outpatient setting for all other medical needs, including laboratory tests, procedures, diagnostic tests, and other ancillary services not accompanying a hospitalization, ED, or physician visit. Subjects receiving spirometry were recorded.

Exacerbations

Since exacerbations were based on visits, a visit was defined as a unique date of service for all visits except hospitalization, and as a unique admission and discharge date for a hospitalization. Three types of COPD exacerbations were defined: hospitalization with a primary discharge diagnosis of COPD, ED visit with a primary diagnosis of COPD, and Phy+Rx. Exacerbations were classified as severe (one COPD-related hospitalization) or moderate (COPD-related ED visit or a Phy+Rx). Exacerbations were considered as the same event if they occurred within 14 days of one another. Infrequent exacerbators and frequent exacerbators were defined as those subjects experiencing one and two or more exacerbations, respectively.

Statistical analysis

Due to the preliminary nature of the study and sample size considerations, no formal statistical comparisons were performed. Data are presented descriptively: continuous variables are presented as means and standard deviations; categorical variables were calculated and reported as sample sizes with the corresponding percentages.

RESULTS

Demographics

A total of 50,838 subjects were identified from the Optum database as receiving LAMA therapy, of whom 5,311 satisfied the inclusion criteria, had no exclusionary conditions, and were diagnosed with COPD. Of these, 2,057 subjects were new to LAMA monotherapy, i.e., had not received LAMA monotherapy in the pre-index period, and constituted the LAMA cohort. A total of 191 subjects initiated LAMA+LABA therapy during the index period; these subjects constituted the LAMA+LABA cohort. Out of 191 LAMA+LABA subjects, 157 (82.2%) subjects were included in both the LAMA cohort and the LAMA+LABA cohort.

Subject demographics and characteristics in the pre-index year are summarized in Table 1. The geographic distribution and plan coverage were broadly similar between the two cohorts. However, there were some differences in demographic characteristics. Subjects in the LAMA+LABA cohort were older than those in the LAMA cohort (mean±SD, 64.8±9.2 vs. 60.6±9.6 years, respectively). In addition, the LAMA+LABA cohort received more total prescriptions (mean±SD, 42.9±23.2 vs. 30.5±27.2) and more unique prescription classes (mean±SD, 4.3±3.6 vs. 3.7±3.8) than the LAMA cohort. However, assessment of comorbid burden by CCI revealed little difference between the groups, although there were differences observed in the comorbidities of interest. Overall, approximately

TABLE 2
Co-medication use among subjects initiating LAMA therapy and LAMA+LABA dual therapy in the 1-year period prior to initiation of therapy

	LAMA cohort (n=2,057)		LAMA+LABA cohort (n=191)	
	n	%	n	%
Co-medication use				
Proportion with SABA	734	35.7	107	56.0
Proportion with OCS	671	32.6	72	37.7
Proportion with home oxygen therapy	65	3.2	27	14.1
Maintenance drug use				
ICS only	155	7.5	88	46.1
ICS+LABA	471	22.9	27	14.1
LAMA	0	0.0	157	82.2
LABA	40	1.9	171	89.5

ICS=inhaled corticosteroids, LABA=long-acting β_2-adrenergic agonists, LAMA=long-acting muscarinic antagonists, OCS=oral corticosteroid, SABA=short-acting inhaled β_2-agonist.

TABLE 3
Baseline per-person COPD-related costs in the 1-year period prior to initiation of LAMA therapy or LAMA+LABA dual therapy

Component of care	Costs ($), mean (SD)	
	LAMA cohort (n=2,057)	LAMA+LABA cohort (n=191)
Medical	820.40 (3,495.50)	877.90 (3,685.10)
Inpatient hospital stay	687.20 (3,413.10)	710.60 (3,665.80)
ED	30.70 (259.20)	11.00 (66.80)
Visit to physician office	60.80 (108.20)	116.60 (160.70)
Outpatient	41.70 (424.30)	39.60 (163.10)
Pharmacy	405.80 (793.60)	2,442.00 (1,406.00)
Total	1,226.20 (3,602.90)	3,320.40 (4,085.90)

ED=emergency department, LABA= long-acting β_2-adrenergic agonists, LAMA=long-acting muscarinic antagonists.

a third of subjects had concomitant cardiovascular disease and 17%–20% had asthma (Table 1).

Co-medication and maintenance drug use

Co-medication was used as a proxy for severity of COPD. Subjects in the LAMA+LABA cohort had higher SABA (56.0% vs. 35.7%), OCS (37.7% vs. 32.6%), and home oxygen therapy (14.1% vs. 3.2%) use, as compared with the LAMA cohort in the year before initiating LAMA/LAMA+LABA therapy (Table 2).

The LAMA+LABA cohort also had a greater proportion of maintenance drug (ICS, ICS+LABA, LAMA, and LABA) use overall. Subjects in the LAMA+LABA cohort received ICS or LABA in 46.1% and 89.5% of cases, respectively, compared with 7.5% and 1.9% in the LAMA cohort. However, a greater proportion of the LAMA cohort received ICS+LABA in addition in this period: 22.9% compared with 14.1% in the LAMA+LABA cohort.

COPD-related costs and health care resource use

On a per-person basis, the LAMA+LABA cohort had greater medical costs ($877.90 vs. $820.40), inpatient costs ($710.60 vs. $687.20), costs for visits to physician offices ($116.60 vs. $60.80) and, most substantially, pharmacy costs ($2,442.50 vs. $405.80) in the pre-index year, as compared with the LAMA cohort (Table 3). The total health care–related cost was greater for subjects from the LAMA+LABA cohort as compared with subjects from the LAMA cohort ($3,320.41 vs. $1,226.20).

Health care resource use was generally comparable between the treatment cohorts. A slightly greater proportion of subjects in the LAMA+LABA cohort had Phy+Rx (6.3% vs. 4.9%) and outpatient visits (23.0% vs. 19.5%) compared with the LAMA cohort (Figure 1). In addition, more subjects in the LAMA+LABA cohort received spirometry during their interactions with health services (55.0% vs. 42.1%).

Exacerbation rates and treatment augmentation

In the pre-index period, the total number of exacerbations in the LAMA cohort was 237 (11.5%) compared with 25 (13.1%) in the LAMA+LABA cohort. The proportions of severe and moderate exacerbations, as well as frequent and infrequent exacerbators, were similar (Figure 2).

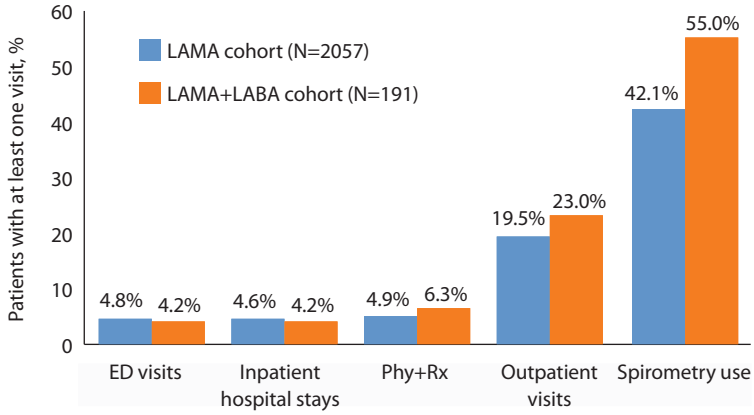
DISCUSSION

The clinical decision to initiate or augment existing COPD maintenance therapies is a complex one, based on factors including clinical history, presenting symptoms, and exacerbation risk. Therapeutic guidelines produced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend that a LAMA+LABA combination should be considered as an alternative treatment to LAMA alone for subjects with COPD classified as GOLD group B and C (GOLD 2018). Our study was conducted to assess the subject characteristics that may affect these treatment choices.

The current retrospective analysis used claims data from a large U.S. population to compare the demographics, COPD-related costs, and health care resource use for subjects with COPD who were new to LAMA monotherapy or LAMA+LABA therapy in the year prior to starting this treatment.

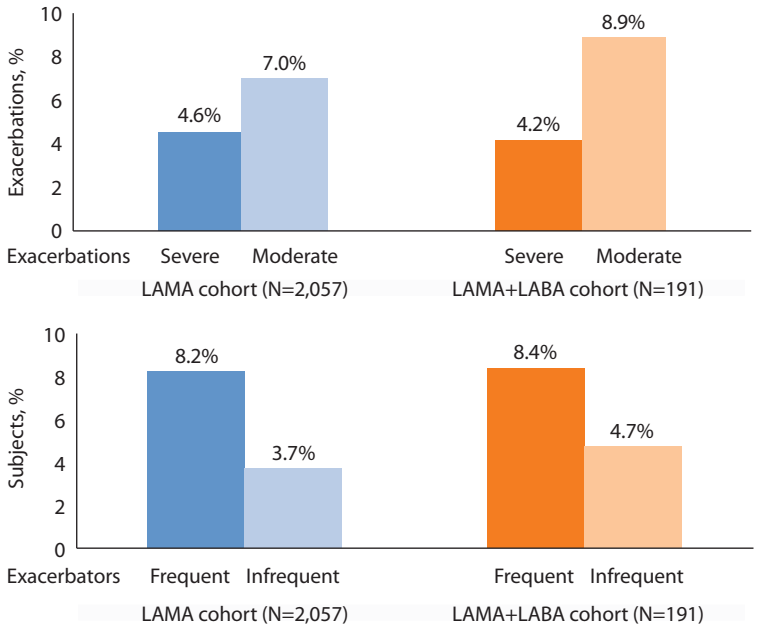
In our study, subjects newly prescribed LAMA+LABA had a higher use of co-medication and overall greater use of maintenance drugs in the pre-index period compared with subjects newly prescribed with LAMA therapy. The LAMA+LABA cohort also had a total COPD-related cost

FIGURE 1
Health care resource use in the pre-index period among subjects initiating LAMA therapy and LAMA+LABA dual therapy



ED=emergency department, LABA=long-acting β_2-adrenergic agonists, LAMA=long-acting muscarinic antagonists, Phy+Rx=physician visit with receipt of oral corticosteroid or antibiotic prescription within 5 days of the visit.

FIGURE 2
Exacerbations in the pre-index period among subjects initiating LAMA therapy or LAMA+LABA dual therapy stratified by (A) severe and moderate exacerbations and (B) frequent and infrequent exacerbators



LABA=long-acting β_2-adrenergic agonists, LAMA=long-acting muscarinic antagonists, Phy+Rx=physician visit with receipt of oral corticosteroid or antibiotic prescription within 5 days of the visit.

Severe exacerbation defined as a COPD-related hospitalization; moderate exacerbation defined as a COPD-related ED visit or a Phy+Rx. Infrequent exacerbators and frequent exacerbators were defined as those subjects experiencing one and two or more exacerbations, respectively. Exacerbations were considered as the same event if they occurred within 14 days of one another.

that was more than two and a half times greater than the LAMA cohort pre-index, with the most significant difference being in pharmacy costs.

The differences in costs between the two populations could be related to their underlying disease burden and age. The LAMA+LABA cohort was older and appeared to have more severe COPD. Even though the disease burden in terms of medication use was higher in the LAMA+LABA cohort, it is interesting to note that the CCI and mean number of disease states assigned to claims as identified by the unique three-digit diagnosis codes were similar between the cohorts. Analysis of comorbidities of interest provides a mixed picture; although incidence of asthma was higher in the LAMA+LABA cohort, respiratory tract infections and cardiovascular disease were higher in the LAMA cohort. As there are known links between COPD exacerbations and factors including comorbidities (Fumagalli 2015, Ho 2014), age, and COPD disease severity (Husebø 2014), it is possible that these underlying differences in baseline characteristics contributed to the reported differences in costs and exacerbations.

Other studies

Few database studies focus on health economics and outcomes data in the period before COPD maintenance treatment is prescribed, so comparisons with the existing literature to evaluate our results are somewhat limited. Notably, Kern (2014) conducted a study with a design similar to that reported here, assessing subject characteristics in the 12 months prior to initiation of the LABA-ICS combination budesonide-formoterol (BFC) or the LAMA tiotropium. This study used data from the HealthCore Integrated Research Database from March 2009 to January 2012. Comparisons of outcomes in the tiotropium group from Kern and the LAMA cohort

Corresponding author:

Richard H. Stanford, PharmD, MS
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
Phone: (919) 483-3779
Email: richard.h.stanford@gsk.com

Role of funding source:
GlaxoSmithKline (GSK) funded this study (HO-12-6723). The funders of the study had a role in study design, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data and the final responsibility to submit for publication. GSK manufactures Anoro Ellipta (umeclidinium/vilanterol) and Breo Ellipta (fluticasone/vilanterol). These combination products are indicated for treatment of patients with COPD and contain a LABA (vilanterol), but these combination products were not among the drugs taken by patients included in this current study.

Conflict-of-interest statements:
Nagar and Patel were employees of GSK and holders of GSK stock/shares at the time this study was undertaken. Nagar now is employed by RTI-Health Solutions and Patel by Amgen. Stanford is an employee of GSK and holds GSK stock.

Contributions: Patel was involved in the conception and design of the study, data analysis, and interpretation. Nagar was involved in the acquisition of data, data analysis, and interpretation. All authors contributed to the writing and reviewing of the manuscript and have given final approval to the version to be published.

Sources of support: Editorial support in the form of preparation of the first draft based on input from all authors, and collation and incorporation of author feedback to develop subsequent drafts, was provided by Joanne Ashworth, Susan Parker, PhD, and Elizabeth Jameson, PhD, of Fishawack Indicia Ltd, UK. The editorial support was funded by GSK.

Acknowledgements: The authors wish to thank Anand Dalal for his expertise in the study design, development of the protocol, and data analysis.

from our study (which consists of subjects who initiated tiotropium therapy) show broadly similar levels of use of some COPD-related health care resources (ED visit 8.6% vs. 4.8%, inpatient hospital stay 7.0% vs. 4.6%, respectively) with other factors being difficult to compare because of differences in how measures were assessed. However, the exacerbation rate (40.4%) was much higher in the Kern study than in our study (11.5%). Kern concluded that subjects starting BFC therapy had a different subject profile to those initiating tiotropium therapy and that these differences should be considered when comparing the effectiveness of different therapies.

A study by Wurst (2014) assessed baseline characteristics of subjects newly prescribed long-acting bronchodilator therapy. This study included subjects from the Truven Marketscan Commercial Database from January 2007 to December 2009 and enrolled a similar proportion of subjects in the relevant treatment groups (3,022 subjects started LAMA therapy, 53 subjects started LAMA+LABA therapy) to our study. The LAMA+LABA cohort may be larger in our study due to subjects switching to dual therapy during the index period and thus being included in both cohorts. Although Wurst did not report cost or resource utilization data for the pre-index period, comorbidity data show that subjects prescribed LAMA had a lower prevalence of asthma and depression but a slightly higher CCI, which is consistent with our study. In addition, Wurst found that subjects who added to or switched from LAMA therapy had more severe COPD in terms of more frequent exacerbations and more SABA prescriptions than those that did not add or switch. This finding also supports the results presented here.

It is interesting to note that in our study, of 5,311 subjects who fulfilled the inclusion criteria, only 191 subjects were receiving LAMA+LABA. This finding suggests this treatment combination is underutilized based on GOLD recommendations (GOLD 2018). This pattern is observed in other database studies and may indicate augmentation from LAMA monotherapy or LAMA+LABA therapy to LAMA+LABA+ICS (Wurst 2014, Kozma 2011).

Limitations

Strengths of the study include the large sample size and study design allowing insight into subject characteristics before treatment initiation. The limitations are primarily due to the nature of the data source. Any differences seen in this analysis are based on descriptive and not statistical comparisons. Consistent with the study objectives and a limited ability to adjust for potentially confounding factors along with low sample size, no formal statistical tests comparing results across cohorts are reported; nevertheless, the results section denotes observed variations in study measures across two cohorts where such differences appear notable.

In addition, the effect of the small sample size for the LAMA+LABA cohort and the fact that both the cohorts are non-mutually exclusive may make interpretation of the data difficult.

In future studies, it would be beneficial to carefully define the use of simultaneous LAMA/LABA versus staggered prescribing of LAMA/LABA to draw meaningful comparisons between the groups. Future studies with larger sample sizes may address this limitation and allow more formal statistical comparisons to be drawn across cohorts.

The presence of a claim of a filled prescription does not necessarily mean that the medication was consumed or was taken as prescribed.

Smoking status, a key factor in COPD disease progression, cannot

be ascertained from the claims data used in this study.

The population studied was U.S.-based, so our findings may not be generalizable outside of the United States.

CONCLUSION

Subjects with COPD initiating LAMA monotherapy and LAMA+LABA therapy had important differences in clinical characteristics, medication use, and COPD-related costs in the year before starting treatment. Subjects receiving LAMA+LABA were older, with higher COPD comedication use, more prescriptions, and associated higher pharmacy costs compared with subjects initiating LAMA. Differences were also seen in comorbidity profile, although the levels of comorbid burden were similar. These differences may reflect a higher severity of COPD in those starting LABA+LAMA treatment.

REFERENCES

ALA (American Lung Association). How Serious Is COPD. 2015. http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/copd/learn-about-copd/how-serious-is-copd.html. Accessed April 2018.

Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J.* 2009;33(5):1165–1185.

Cazzola M, Molimard M. The scientific rationale for combining long-acting beta$_2$-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther.* 2010;23(4):257–267.

Celli B, Crater G, Kilbride S. Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. *Chest.* 2014;145(5):981–991.

Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004;23(6):932–946.

Dransfield MT, Bailey W, Crater G, et al. Disease severity and symptoms among patients receiving monotherapy for COPD. *Prim Care Respir J.* 2011;20(1):46–53.

Ford ES, Murphy LB, Khavjou O, et al. Total and state-specific medical and absenteeism costs of chronic obstructive pulmonary disease among adults aged ≥18 years in the United States for 2010 and projections through 2020. *Chest*. 2015; 147: 31–45.

Fumagalli G, Fabiani F, Forte S, et al. INDACO project: COPD and link between comorbidities, lung function and inhalation therapy. *Multidiscip Respir Med.* 2015;10(1):4.

GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2018. http://www.goldcopd.com. Accessed April 2018.

Ho TW, Tsai YJ, Ruan SY, et al; HINT Study Group. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One.* 2014;9(12):e114866.

Husebø GR, Bakke PS, Aanerud M, et al. Predictors of exacerbations in chronic obstructive pulmonary disease—results from the Bergen COPD cohort study. *PLoS One.* 2014;9(10):e109721.

Kern DM, Williams SA, Tunceli O, et al. A US database study characterizing patients initiating a budesonide-formoterol combination vs. tiotropium bromide as initial maintenance therapy for chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2014;9:775–783.

Kozma CM, Paris AL, Plauschinat CA, et al. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: a database study. *BMC Pulm Med.* 2011;11:61.

Maleki-Yazdi MR, Kaelin T, Richard N, et al. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med.* 2014;108(12):1752–1760.

Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2009;180(8):741–750.

WHO (World Health Organization). Chronic obstructive pulmonary disease (COPD) Fact sheet 315. 2017. http://www.who.int/mediacentre/factsheets/fs315/en/. Accessed April 2018.

Wurst KE, St Laurent S, Mullerova H, Davis KJ. Characteristics of patients with COPD newly prescribed a long-acting bronchodilator: a retrospective cohort study. *Int J Chron Obstruct Pulmon Dis.* 2014;9:1021–1031.

Supplementary Appendix

TABLE A1
Exclusion criteria

Comorbid conditions	Pulmonary tuberculosis; sarcoidosis; respiratory cancer; cystic fibrosis; extrinsic allergic alveolitis; pneumoconiosis and other lung diseases due to external agents; empyema; pneumothorax; abscess of lung and mediastinum; pulmonary congestion and hypostasis; other alveolar and parietoalveolar pneumonopathy; lung involvement in conditions classified elsewhere; interstitial and compensatory emphysema; pulmonary eosinophilia; acute edema of lung; unspecified, pulmonary insufficiency following trauma and surgery; allergic bronchopulmonary aspergillosis; transfusion-related acute lung injury

TABLE A2
COPD-related medications of interest

Maintenance medications	
Inhaled corticosteroids 1. Beclomethasone 2. Budesonide 3. Flunisolide 4. Fluticasone 5. Triamcinolone	Inhaled corticosteroids + long-acting beta-agonist combination product 1. Fluticasone + salmeterol (all doses) 2. Budesonide + formoterol
Long-acting β_2-adrenergic agonists 1. Formoterol 2. Salmeterol 3. Arformoterol	Anticholinergics 1. Inhaled (non-nebulized) ipratropium or ipratropium/albuterol combination 2. Tiotropium
Xanthines 1. Aminophylline 2. Dyphylline 3. Oxtriphylline 4. Theophylline	Long-acting bronchodilator 1. Tiotropium 2. Tiotropium + any LABA
Rescue medications	
Short-acting inhaled β_2-agonists 1. Albuterol 2. Bitolterol 3. Isoetharine 4. Isoproterenol 5. Levalbuterol 6. Metaproterenol 7. Pirbuterol 8. Terbutaline	Anticholinergics 1. Nebulized ipratropium or ipratropium/albuterol combination
Oral corticosteroids 1. Betamethasone 2. Cortisone 3. Dexamethasone 4. Hydrocortisone 5. Methylprednisolone 6. Prednisone 7. Triamcinolone	Antibiotics 1. Macrolides (azithromycin, clarithromycin, dirithromycin, erythromycin) 2. Fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin) 3. Cephalosporin (cephalexin, cefaclor, cefadroxil, cefdinir, cefditoren, cefepime, cefixime, cefotaxime, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftriaxone, cefuroxime) 4. Trimethoprim-sulfamethoxazole 5. Tetracycline derivatives (doxycycline) 6. Penicillins (amoxicillin, ampicillin)