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ORIGINAL RESEARCH

Burden of Exacerbations in Patients Newly Initiating an Inhaled Regimen for COPD: A Claims Analysis

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Background: Chronic obstructive pulmonary disease (COPD) is a progressive disease that has a great impact on healthcare resource utilization (HRU). Large-scale real-world evidence studies evaluating the clinical and economic impact of current maintenance inhaler therapies are scarce.

Objective: To assess annual exacerbation rate and COPD-related HRU in patients with COPD before and after initiation of an inhaled treatment regimen.

Methods: The Optum Clinformatics® Data Mart database was used to identify inpatient, outpatient, and pharmacy claims from patients aged ≥40 years with COPD in the United States from January 2016 to June 2023. The index date was the date of the first prescription claim for a new inhaled maintenance therapy after a 12-month maintenance treatment-free baseline period. The primary outcome was the proportion of patients with ≥1 moderate/severe exacerbation within 12 months post-index. The average number of moderate/severe exacerbations per patient and the proportion of patients with inpatient, emergency department (ED), office, and outpatient visits within 12 months post-index were also assessed.

Results: Of the 137,691 included patients, 51.5% were female and 74.6% were White, with a mean (standard deviation [SD]) age of 70.9 (9.49) years and a mean (SD) Elixhauser Comorbidity Index of 5.67 (3.29). Most (48.3%) patients were initiated on long-acting beta-agonists/inhaled corticosteroids (LABA/ICS). The proportions of patients with exacerbations significantly decreased overall (pre-index, 45.5%; post-index, 37.0%; $P < 0.001$). However, more than one-third of patients still experienced an exacerbation 12 months after initiating treatment. The proportion of patients with COPD-related HRU generally decreased; however, 5.0% and 2.9% of patients had inpatient and ED care post-index, respectively.

Conclusion: Despite use of inhaled treatments for COPD, patients continue to experience exacerbations and HRU. Better implementation of guideline-based COPD care and novel therapies for persistent exacerbation burden are needed to improve care of the COPD population in real-world settings.

Keywords: chronic obstructive pulmonary disease, healthcare resource utilization, outcomes research, real-world data, exacerbations

Introduction

Chronic obstructive pulmonary disease (COPD), a progressive disease characterized by airflow obstruction and inflammation that causes tissue damage over time,[1] is a leading cause of morbidity and mortality worldwide.[2] The prevalence of COPD has increased substantially in the last 30 years and currently affects around 16 million adults in the US.[3,4] The American Lung Association reports that COPD is associated with substantial healthcare resource utilization (HRU), with approximately 1 million COPD-related emergency department (ED) visits in the US in 2020.[5] The primary driver of COPD-related HRU is exacerbations, defined as an acute worsening of respiratory symptoms that may occur through infection or environmental pollutants and may prompt modification of treatment.[1,2,6]

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Current standard-of-care treatment paradigms for COPD aim for symptom control and reduction of the frequency and severity of exacerbations. Until recently, the most common treatment options for COPD have included long-acting muscarinic antagonists (LAMA), long-acting beta-agonists (LABA), and inhaled corticosteroids (ICS).[2] The 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report recommends that initial therapy be based on symptoms and exacerbation history, beginning with single or dual bronchodilator therapy (LABA/LAMA) and only escalating to triple therapy if exacerbations persist or in patients with high blood eosinophil counts.[2] Previous studies have examined exacerbations and HRU associated with various COPD treatment regimens.[7–9] However, many of these previous studies included data collected prior to the COVID-19 pandemic and did not report the impact of treatment on exacerbations or HRU in a patient population newly initiating common inhaled maintenance therapies for COPD. Given that the burden of disease has likely shifted in the post-pandemic era in addition to the sustained prevalence of COPD and its growing HRU, further analysis in a large, real-world, longitudinal sample is needed to elucidate the current value that each of these inhaled COPD maintenance therapies hold for payers, providers, and patients.

The Optum Clinformatics® DataMart (CDM) database is a large US commercial and Medicare insurance database that has been used extensively for research regarding the demographic and clinical characteristics of patients with COPD and clinical and economic outcomes associated with COPD.[9,10] The objective of this observational study was to assess the annual moderate/severe exacerbation rate and COPD-related HRU in a population of patients with COPD before and after initiating a new inhaled treatment regimen.

Methods

Study Design and Data Sources

This retrospective observational cohort study was conducted using the Optum CDM dataset, which contains deidentified inpatient, outpatient, and pharmacy claims from patients in the US from January 2016 to June 2023 (Figure 1). Optum CDM contains claims data derived from 81 million patients who are covered by commercial and Medicare Advantage plans across all 50 US states.[10] As all analyses were conducted on anonymized retrospective patient data, this research is exempt from institutional review board (IRB) review and approval. The datasets analyzed were licensed by the study sponsor from Optum®, with permission obtained from Optum to access and use these non-publicly available data.

Study Population

Patients with a diagnosis of COPD (defined by ≥1 International Classification of Diseases, Tenth Revision [ICD-10] diagnosis code for COPD in any position during baseline; Supplemental Table 1) who newly initiated inhaled maintenance therapy with LABA, LAMA, LABA/LAMA, LABA/ICS, or LABA/LAMA/ICS (single inhaler or multiple inhalers; Supplemental Table 2) during the data window were identified from Optum CDM. In cases where a patient initiated an inhaler within the study

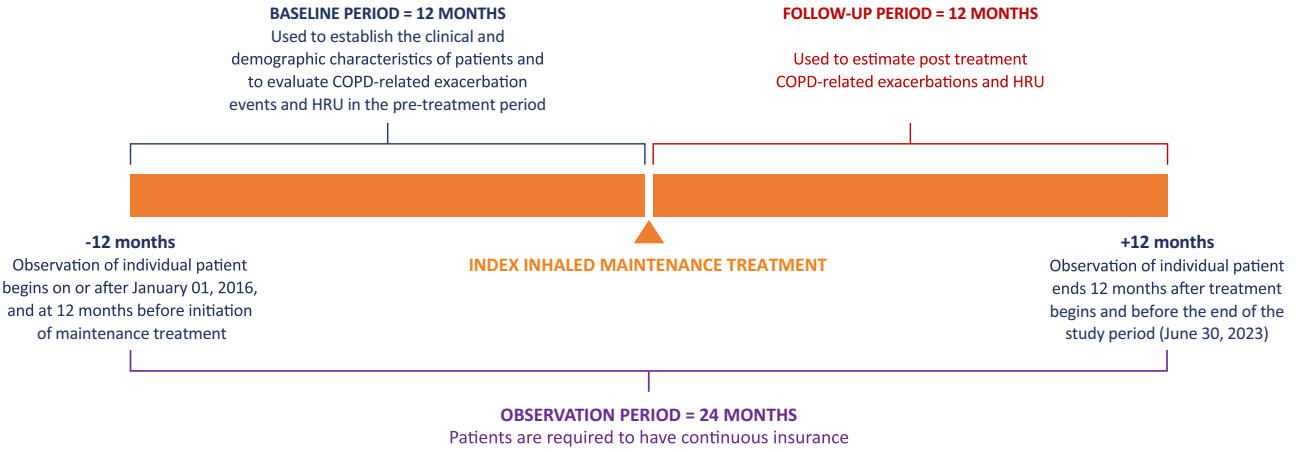

Figure 1 Study design of Optum Clinformatics® Data Mart database.
Abbreviations: COPD, chronic obstructive pulmonary disease; HRU, healthcare resource utilization.

timeframe, discontinued it for over 12 months, and then restarted therapy, they were not re-entered into the database as a new case; there was one record per patient in this analysis. The date of the first prescription for a new inhaled maintenance therapy was set as the index date. The baseline period was defined as the 12 months prior to the index date. Patients were required to be aged ≥40 years and have a pre-index and post-index period of ≥365 days. Patients with a pharmacy claim for an inhaled COPD maintenance therapy in the 12 months prior to the index date (ie, the baseline period) were excluded. Additionally, patients with a diagnosis of asthma, interstitial lung disease, cystic fibrosis, and/or lung cancer during the 12-month baseline period were excluded from the analysis.

Patient Characteristics and Comorbidity Profile

Baseline demographics and comorbidities were assessed in the 12-month baseline period prior to the index date. Patient baseline demographics included age, gender, race/ethnicity, and the type of health insurance plan at the time of entry into the cohort. Comorbidities were assessed using the Elixhauser Comorbidity Index, which is composed of a comprehensive set of 30 comorbidities defined using the ICD-10 codes from administrative data.[11,12] Patient characteristics by class of maintenance therapy (LABA, LAMA, LABA/LAMA, LABA/ICS, or LABA/LAMA/ICS) were examined. The proportion of patients with Elixhauser conditions and the total Elixhauser Comorbidity Index score during the 12-month baseline period were also assessed. Index prescription refills and treatment duration were also captured. Yearly trends in the initial inhaled COPD maintenance therapy were captured for 2016 to 2022.

Exacerbations and Healthcare Utilization

The primary outcome was the proportion of patients with ≥1 moderate or severe exacerbation within 12 months after the index date. A moderate exacerbation was defined as one necessitating an ambulatory (ie, office or outpatient) visit with a COPD diagnosis code plus a pharmacy claim for an oral corticosteroid and/or a COPD guideline–recommended antibiotic prescription (Supplemental Table 3) within 7 days before or after the office/outpatient visit. A severe exacerbation was defined as one necessitating an inpatient admission or an ED visit with a primary COPD diagnosis code, a diagnosis code for acute respiratory failure in the primary position plus a COPD diagnosis code in any position, or an inpatient admission or ED visit with a diagnosis code for acute respiratory failure in the primary position plus an inpatient admission or ED visit with a COPD diagnosis code in any position within 7 days before or after the inpatient admission or ED visit. Exacerbations occurring within 14 days of each other were considered a single exacerbation and were classified according to the event of the highest severity. If a patient initiated an inhaler during or immediately after an acute exacerbation, only the exacerbations that began ≥1 day prior to treatment initiation were counted in the pre-index period.

Secondary outcomes included the average number of moderate or severe exacerbations and the proportion of patients with ≥1 COPD-related inpatient, ED, office (ie, all the visits at a doctor's office, including primary care, specialty care, nurse practitioner, and physician assistant visits), and outpatient visits (ie, outpatient care in hospital settings including diagnostic, laboratory, radiology, and surgery visits) during the 12-month post-index period. The average annual number of exacerbations per patient as well as the average annual number of moderate or severe exacerbations per patient were compared between the pre-index and post-index period for the overall patient population, as well as by initial inhaled maintenance therapy type. In this analysis, COPD-related HRU was also assessed, including inpatient admissions, ED visits, office visits, and outpatient visits. A visit was defined as COPD-related if a COPD diagnosis was listed in the primary position of the claims data (ie, the primary reason for the visit was attributed to COPD).

Statistical Analyses

Descriptive analyses were used to assess the baseline characteristics of the population of patients with COPD initiating maintenance therapy. Continuous variables were summarized using means with standard deviations and median with minimum and maximum values; discrete variables were summarized via counts and proportions. The proportions and annual number of moderate, severe, and all (both moderate and severe) COPD exacerbations were reported in the 12-month pre-index and post-index periods. Additionally, the annual COPD-related HRU by setting of care was estimated. The associations between receiving treatment, exacerbation rates, and HRU were tested within each treatment cohort separately and for the entire sample via pre-index and post-index comparisons using paired *t* tests for numerical variables

and McNemar's tests for categorical variables, with $P < 0.05$ considered significant. Data were analyzed using R 4.1.2 and Presto SQL statistical software.

Results

Patient Demographics and Clinical Characteristics, Comorbidities, and Treatment Patterns

A total of 137,691 patients met the study inclusion criteria (Figure 2). Baseline clinical and demographic characteristics are shown in Table 1. Overall, 51.5% of patients were female, and the majority (74.6%) were White, with a mean (SD) age of 70.9 (9.49) years. During the 12-month baseline period, three-quarters of patients (76.9%) had uncomplicated hypertension (Supplemental Table 4). Other common comorbidities included peripheral vascular disorders (31.7%), cardiac arrhythmias (30.7%), uncomplicated diabetes (29.2%), depression (27.9%), and complicated hypertension (25.1%). Approximately half of patients (56.5%) had an Elixhauser Comorbidity Index score ≥5 (mean [SD]: 5.67 [3.29]). Tobacco use was reported in 67.2% of patients, and coronary artery disease was reported in 31.6% of patients.

Most patients (48.3%) initiated maintenance therapy with LABA/ICS on the index date, followed by LAMA (19.5%), LABA/LAMA (19.1%), LABA/LAMA/ICS in a single inhaler (9.1%), LAMA/LABA/ICS in multiple inhalers (3.0%), and LABA (1.0%; Figure 3). Most inhalers were not initiated by specialists (72.0%), whereas a minority (18.8%) of patients were prescribed their initial therapy by a pulmonologist. From 2016 to 2022, LABA/ICS remained the most common initial maintenance therapy, despite gradual reductions in utilization from 2016 to 2022 (Figure 4). The proportion of patients whose initial maintenance therapy was LAMA/LABA/ICS in a single inhaler steadily increased

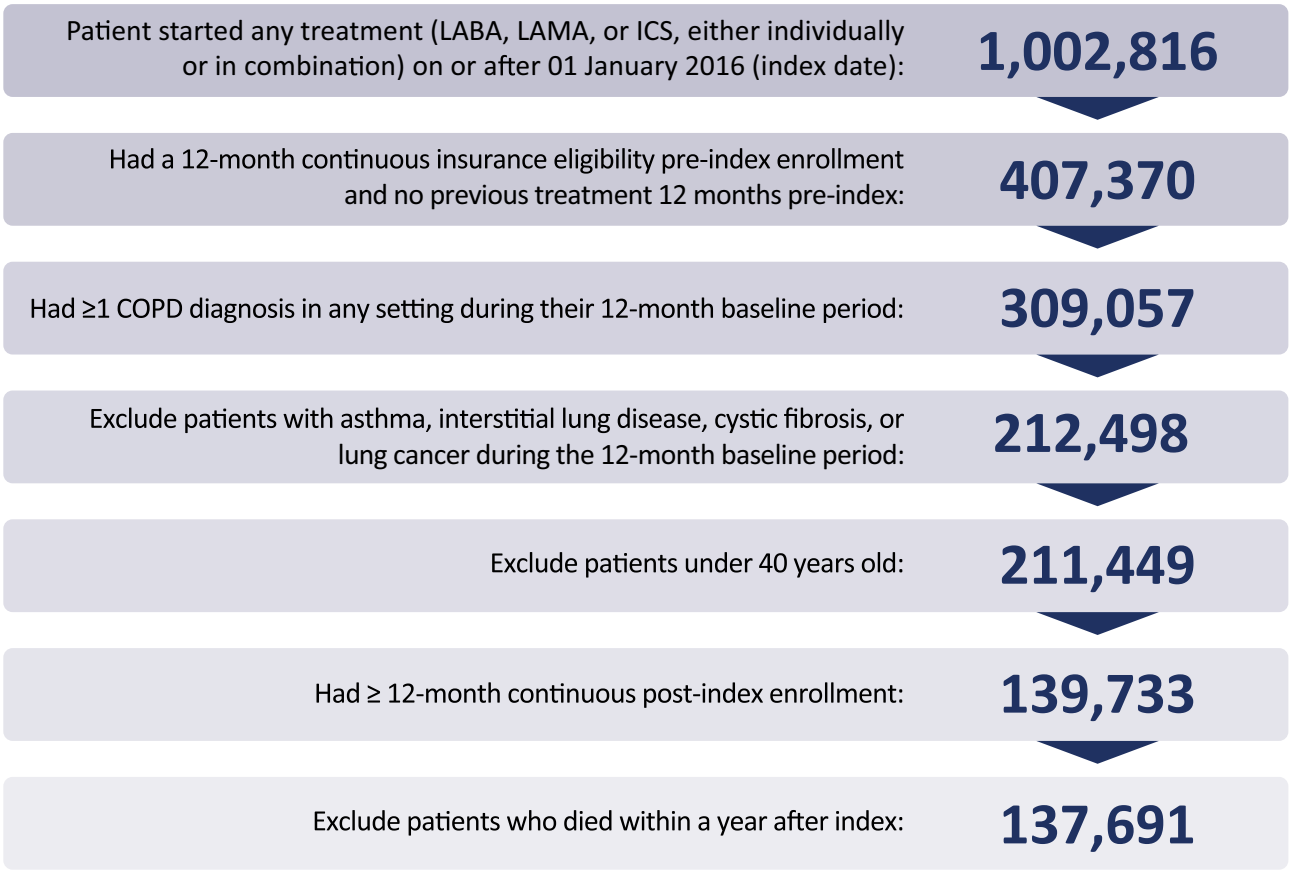

Figure 2 Patient flow for overall analysis.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

Table 1 Demographic and Clinical Characteristics for Patients with COPD by Type of Treatment Initiation

	LABA (n = 1414)	LABA/ICS (n = 66493)	LABA/LAMA (n = 26243)	LAMA (n = 26883)	TTM (n = 4176)	TTS (n = 12482)	Overall (n = 137,691)
Demographics, n (%)							
Gender							
Female	761 (53.8)	35,494 (53.4)	12,866 (49.0)	13,768 (51.2)	2054 (49.2)	6009 (48.1)	70,952 (51.5)
Male	653 (46.2)	30,993 (46.6)	13,376 (51.0)	13,113 (48.8)	2122 (50.8)	6472 (51.9)	66,729 (48.5)
Unknown	0 (0)	6 (0.0)	1 (0.0)	2 (0.0)	0 (0)	1 (0.0)	10 (0.0)
Age							
Mean (SD)	74.0 (9.31)	70.6 (9.78)	70.9 (9.22)	71.2 (9.28)	70.7 (9.17)	71.2 (8.97)	70.9 (9.49)
Median [Min, Max]	74.0 [41.0, 89.0]	71.0 [40.0, 89.0]	71.0 [40.0, 89.0]	72.0 [40.0, 89.0]	71.0 [40.0, 89.0]	72.0 [40.0, 89.0]	71.0 [40.0, 89.0]
Race/ethnicity							
White	1095 (77.4)	48,564 (73.0)	19,995 (76.2)	20,436 (76.0)	3147 (75.4)	9498 (76.1)	102,735 (74.6)
Asian	10 (0.7)	1127 (1.7)	431 (1.6)	443 (1.6)	66 (1.6)	181 (1.5)	2258 (1.6)
African American	150 (10.6)	7780 (11.7)	3010 (11.5)	3110 (11.6)	511 (12.2)	1334 (10.7)	15,895 (11.5)
Hispanic	86 (6.1)	5730 (8.6)	1637 (6.2)	1622 (6.0)	272 (6.5)	752 (6.0)	10,099 (7.3)
Unknown	73 (5.2)	3292 (5.0)	1170 (4.5)	1272 (4.7)	180 (4.3)	717 (5.7)	6704 (4.9)
Region							
Midwest	264 (18.7)	13,463 (20.2)	5091 (19.4)	5827 (21.7)	787 (18.8)	2112 (16.9)	27,544 (20.0)
Northeast	195 (13.8)	7009 (10.5)	2882 (11.0)	3398 (12.6)	573 (13.7)	1260 (10.1)	15,317 (11.1)
South	601 (42.5)	31,711 (47.7)	13,110 (50.0)	9981 (37.1)	1839 (44.0)	7002 (56.1)	64,244 (46.7)
West	353 (25.0)	14,193 (21.3)	5114 (19.5)	7618 (28.3)	971 (23.3)	2082 (16.7)	30,331 (22.0)
Other	0 (0)	67 (0.1)	32 (0.1)	38 (0.1)	3 (0.1)	25 (0.2)	165 (0.1)
Missing	1 (0.1)	50 (0.1)	14 (0.1)	21 (0.1)	3 (0.1)	1 (0.0)	90 (0.1)
Type of insurance							
Commercial	101 (7.1)	8724 (13.1)	3332 (12.7)	3292 (12.2)	512 (12.3)	1157 (9.3)	17,118 (12.4)
Medicare	1313 (92.9)	57,769 (86.9)	22,911 (87.3)	23,591 (87.8)	3664 (87.7)	11,325 (90.7)	120,573 (87.6)
Prescriber of initial therapy							
Non-specialist	973 (68.8)	51,460 (77.4)	16,301 (62.1)	19,809 (73.7)	2602 (62.3)	7973 (63.9)	99,118 (72.0)
Pulmonologist	276 (19.5)	8099 (12.2)	8398 (32.0)	4593 (17.1)	787 (18.8)	3753 (30.1)	25,906 (18.8)
Other specialist[a]	165 (11.7)	6934 (10.4)	1544 (5.9)	2481 (9.2)	787 (18.8)	756 (6.1)	12,667 (9.2)
Index prescription treatment duration, months							
Mean (SD)	19.2 (20.0)	21.7 (21.7)	23.8 (21.1)	23.3 (22.4)	25.8 (23.2)	16.4 (13.6)	22.1 (21.3)
Median [Min, Max]	14.0 [0, 89.0]	16.0 [0, 89.0]	19.0 [0, 89.0]	18.0 [0, 89.0]	20.0 [0, 89.0]	14.0 [0, 62.0]	17.0 [0, 89.0]

Notes:[a]Includes primary care physicians, nurse practitioners, and physician assistants.

Abbreviations: COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-agonist; LABA/ICS, long-acting beta-agonist/inhaled corticosteroid; LABA/LAMA, long-acting beta-agonist/long-acting muscarinic antagonist; SD, standard deviation; TTM, triple therapy in multiple inhalers; TTS, triple therapy in single inhaler.

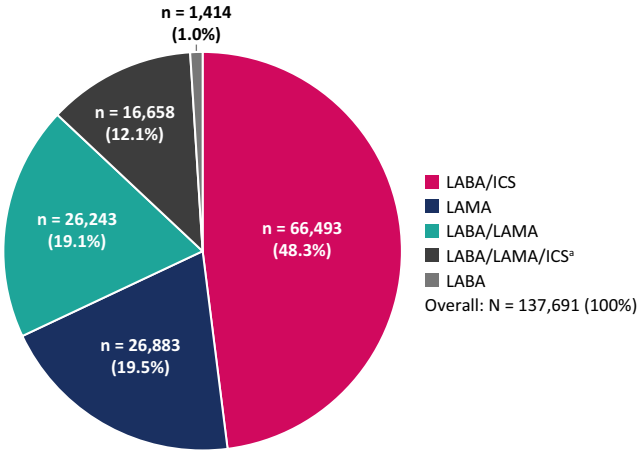

Figure 3 Proportion of patients by inhaled COPD maintenance therapy at index (2016–2023). [a]Includes triple therapy in multiple inhalers and triple therapy in single inhalers.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

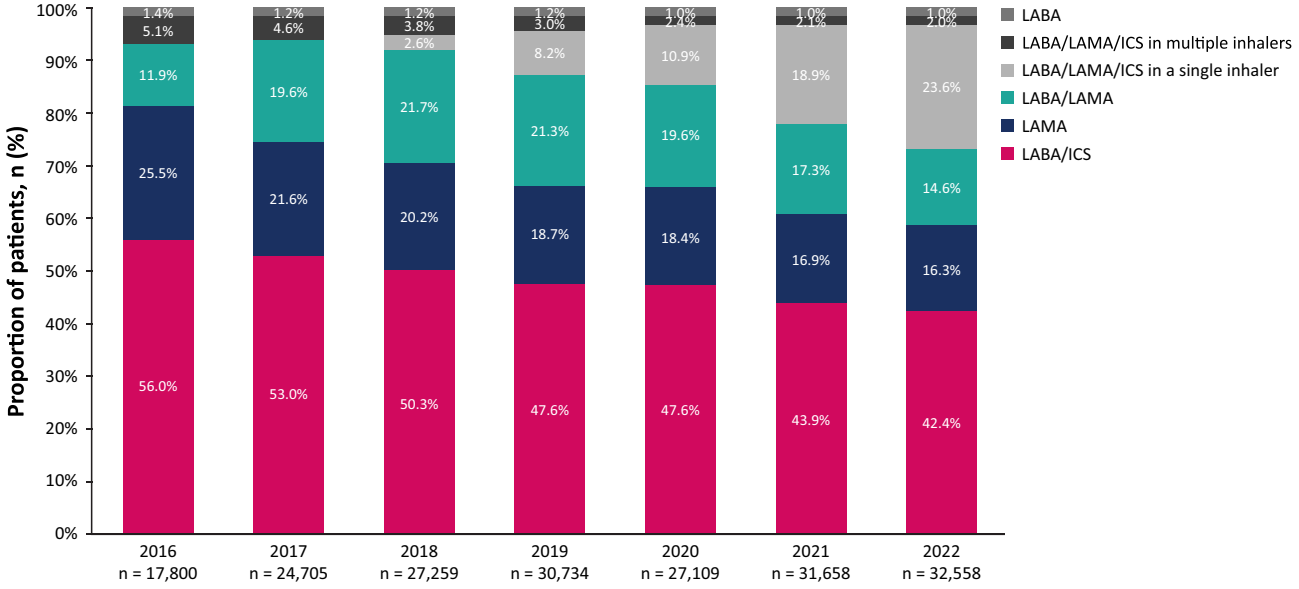

Figure 4 Yearly trends in the initial inhaled COPD maintenance regimens prescribed.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

since approval of this class in 2017,[13] with 23.6% of patients initiating treatment with single-inhaler LAMA/LABA/ICS in 2022. The mean index prescription treatment duration was >12 months in all treatment groups.

Exacerbations Overall and by Treatment Type

The proportions of patients who experienced a moderate or severe COPD exacerbation pre-index versus post-index in the overall population and according to treatment type are shown in Figure 5. The proportion of patients who experienced a moderate or severe exacerbation was significantly reduced from the pre-index to the post-index period overall (pre-index, 45.5%; post-index, 37.0%; $P < 0.001$); this was consistent across all treatment groups.

The proportion of patients who experienced a moderate exacerbation decreased significantly overall (pre-index, 35.7%; post-index, 32.0%; $P < 0.001$), except in patients initiating triple therapy in multiple inhalers (TTM) or LAMA, where a similar proportion of patients exacerbated from the pre-index to the post-index periods (TTM: pre-index, 37.4%; post-index, 37.9%; $P = 0.600$; LAMA: pre-index, 31.3%; post-index, 30.7%; $P = 0.083$). The proportion of patients who

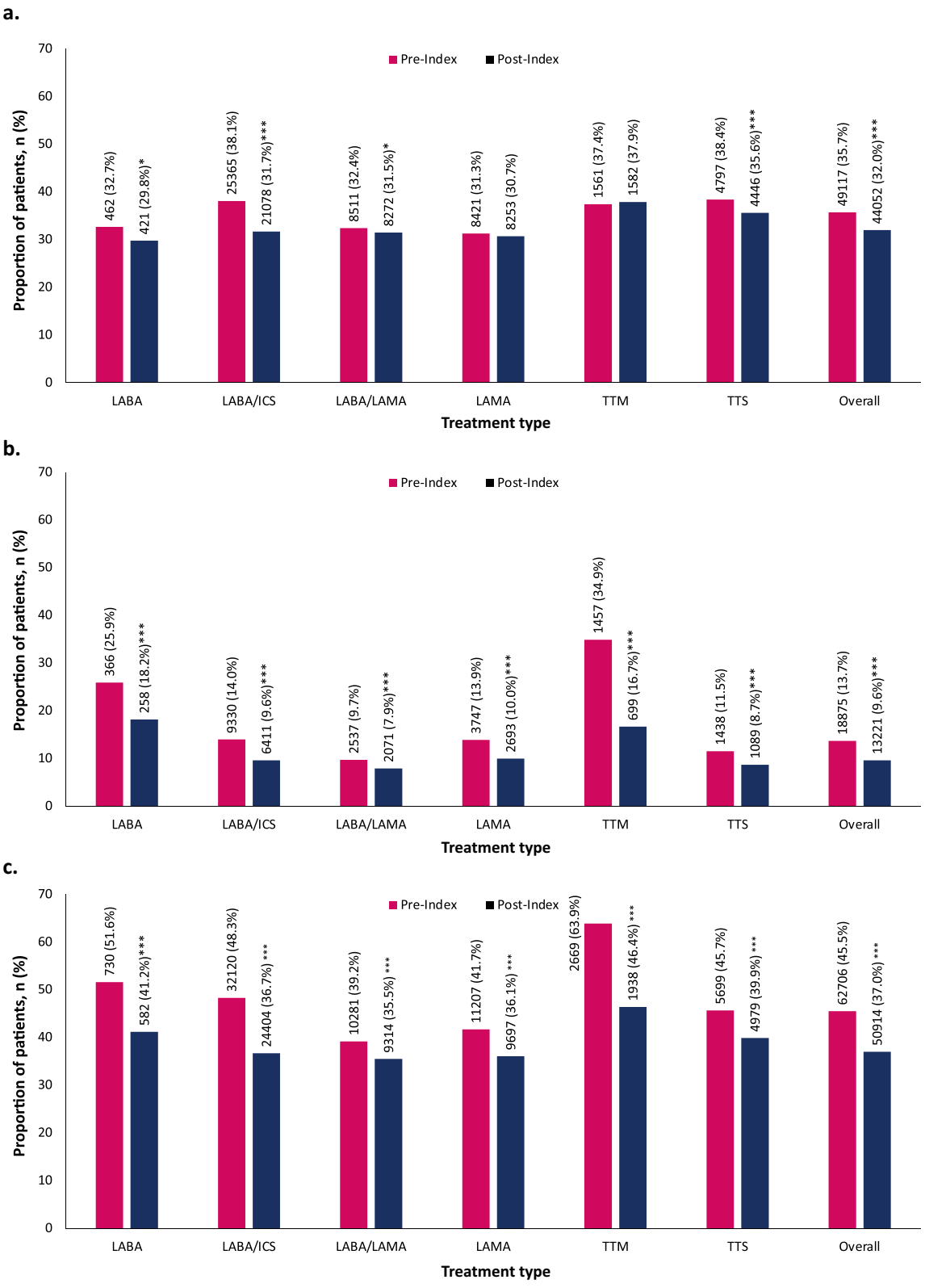

Figure 5 Proportion of patients with (**a**) moderate, (**b**) severe, and (**c**) moderate or severe exacerbations pre- and post-index treatment initiation. ***$P < 0.001$ pre-index versus post-index. *$P < 0.05$ pre-index versus post-index.

Abbreviations: LAMA, long-acting muscarinic antagonist; LABA, long-acting β2 agonist; LABA/ICS, long-acting beta-agonist/inhaled corticosteroid; LABA/LAMA, long-acting muscarinic antagonist/long-acting beta-agonist; TTM, triple therapy in multiple inhalers; TTS, triple therapy in a single inhaler.

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experienced a severe exacerbation significantly decreased ($P < 0.001$) from the pre-index to the post-index period both overall and across all treatment groups.

The average number of moderate or severe exacerbations during the 12-month pre- and post-index treatment initiation periods in the overall population and according to treatment type are shown in Table 2. In the overall sample, the average annual number of moderate or severe exacerbations per patient decreased significantly from the pre-index to the post-index period (pre-index, 0.666; post-index, 0.652; $P < 0.001$). Patients initiating TTM had the highest average annual number of moderate or severe exacerbations per patient both pre- and post-index (mean [SD]: 0.968 [1.05] and 0.895 [1.34], respectively). The average annual number of moderate or severe exacerbations per patient was significantly reduced ($P < 0.001$) from the pre-index to the post-index period in the LABA/ICS and TTM treatment groups, while the average annual number of moderate or severe exacerbations significantly increased for the LABA/LAMA (mean [SD]: pre-index, 0.560 [0.880]; post-index, 0.602 [1.06]; $P < 0.001$) and LAMA treatment groups (mean [SD]: pre-index, 0.602 [0.937]; post-index, 0.634 [1.13]; $P < 0.001$). No significant differences between the pre-index and post-index periods were observed in the LABA or TTS treatment groups.

The average annual number of moderate exacerbations per patient increased significantly ($P < 0.001$) from the pre-index to the post-index period in the overall population and in the LABA/LAMA, LAMA, and TTM treatment groups; however, significant decreases were observed in the LABA/ICS treatment group ($P < 0.001$). There were no differences between the pre-index and post-index periods in the LABA and TTS treatment groups. Contrary to the increases observed among patients with moderate exacerbations in many treatment groups, there were consistent reductions in the average annual number of severe exacerbations per patient from the pre-index to the post-index period overall and across all treatment groups.

COPD-Related HRU

In the overall sample, the proportion of patients utilizing COPD-related ED care, hospitalizations, and office visits decreased from the pre-index to the post-index period, while the proportion of patients with outpatient visits increased (Table 3). The proportions of patients with ED care or hospitalizations decreased in all treatment groups from the pre-index to the post-index period. Among those patients with a COPD-related hospitalization, the proportion of patients that had a COPD-related readmission within 90 days increased from the pre-index to the post-index timepoints (pre-index, n = 419/6125 [6.8%]; post-index, n = 672/4030 [16.7%]); this was also consistent across treatment groups. Proportions of patients with outpatient visits increased from the pre-index to the post-index period overall (pre-index, n = 23,550/137,691 [17.1%]; post-index, n = 25,604/137,691 [18.6%]) and across all treatment groups. Proportions of patients with office visits decreased from the pre-index to the post-index period overall (pre-index, n=63,631/137,691 [46.1%]; post-index, n=62,872/137,691 [45.5%]) but increased in the LABA, LAMA, and TTM groups.

Discussion

This Optum CDM database analysis provides real-world evidence that despite patients initiating approved inhaled treatment regimens, exacerbations continue to persist, and the HRU burden remains high in the US. The number of patients newly initiating inhaled treatment for their COPD steadily increased between 2016 and 2022, and despite GOLD recommendations discouraging the use of LABA/ICS in patients with COPD,[2] LABA/ICS remains the most prescribed initial maintenance therapy (48.3%). Data from this analysis supports findings from other assessments. In another real-world study utilizing the Inovalon database of US administrative claims data, the authors found that despite recommendations against the use of ICS as part of the initial treatment regimen, 62% of patients with a new diagnosis of COPD received LABA/ICS at the time of their diagnosis.[14] Patients increasingly initiated single-inhaler triple therapy (TTS) with ICS as time progressed after the approval of this treatment class for COPD in 2017.[13] This finding is notable, as the GOLD 2024 report recommends that single bronchodilator or dual LABA/LAMA treatment be used as the initial treatment for COPD and that triple therapy be considered in specific patient populations that are most likely to benefit from the addition of ICS (ie, those with persistent exacerbations and/or high eosinophil counts).[2] Moreover, analyses from similar claims-based datasets have demonstrated that ICS-containing therapies for COPD are associated with an

Table 2 Annualized Exacerbation Rates by Treatment Type and Overall Population (Overall and by Severity)

	LABA			LABA/ICS			LABA/LAMA			LAMA		
	Pre-Index	**Post-Index[a]**	***P* value**	**Pre-Index**	**Post-Index[a]**	***P* value**	**Pre-Index**	**Post-Index[a]**	***P* value**	**Pre-Index**	**Post-Index[a]**	***P* value**
	(n = 1414)	**(n = 1414)**		**(n = 66,493)**	**(n = 66,493)**		**(n = 26,243)**	**(n = 26,243)**		**(n = 26,883)**	**(n = 26,883)**	
Overall												
Mean (SD)	0.952 (1.39)	0.884 (1.52)	0.0726	0.698 (0.961)	0.647 (1.14)	<0.001 ***	0.560 (0.880)	0.602 (1.06)	<0.001 ***	0.602 (0.937)	0.634 (1.13)	<0.001 ***
Moderate												
Mean (SD)	0.537 (1.03)	0.549 (1.13)	0.66	0.529 (0.833)	0.504 (0.935)	<0.001 ***	0.450 (0.792)	0.498 (0.924)	<0.001 ***	0.429 (0.773)	0.482 (0.911)	<0.001 ***
Severe												
Mean (SD)	0.415 (0.983)	0.335 (0.989)	0.003 **	0.170 (0.503)	0.143 (0.572)	<0.001 ***	0.111 (0.375)	0.104 (0.426)	0.0204 *	0.173 (0.536)	0.151 (0.597)	<0.001 ***
	TTM			**TTS**			**Overall**					
	Pre-Index	**Post-Index[a]**	***P* value**	**Pre-Index**	**Post-Index[a]**	***P* value**	**Pre-Index**	**Post-Index[a]**		***P* value**		
	(n = 4176)	**(n = 4176)**		**(n = 12,482)**	**(n = 12,482)**		**(n = 137,691)**	**(n = 137,691)**				
Overall												
Mean (SD)	0.968 (1.05)	0.895 (1.34)	<0.001 ***	0.720 (1.05)	0.717 (1.18)	0.812	0.666 (0.962)	0.652 (1.14)		<0.001 ***		
Moderate												
Mean (SD)	0.557 (0.900)	0.654 (1.09)	<0.001 ***	0.585 (0.954)	0.600 (1.05)	0.131	0.500 (0.832)	0.512 (0.948)		<0.001 ***		
Severe												
Mean (SD)	0.410 (0.653)	0.241 (0.678)	<0.001 ***	0.136 (0.418)	0.117 (0.456)	<0.001 ***	0.166 (0.497)	0.140 (0.553)		<0.001 ***		

Notes: [a]Requiring 12 months of follow-up during post-index. ****P* < 0.001 pre-index versus post-index. ** *P* < 0.01 pre-index versus post-index. * *P* < 0.05 pre-index versus post-index.

Abbreviations: LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-agonist; LABA/ICS, long-acting beta-agonist/inhaled corticosteroid; LABA/LAMA, long-acting muscarinic antagonist/long-acting beta-agonist; SD, standard deviation; TTM, triple therapy in multiple inhalers; TTS, triple therapy in a single inhaler.

Table 3 COPD-Related HRU (Overall Treated Population)[a]

	LABA			LABA/ICS			LABA/LAMA			LAMA		
	Pre-Index (n = 1414)	**Post-Index[b] (n = 1414)**	***P* value**	**Pre-Index (n = 66,493)**	**Post-Index[b] (n = 66,493)**	***P* value**	**Pre-Index (n = 26,243)**	**Post-Index[b] (n = 26,243)**	***P* value**	**Pre-Index (n = 26,883)**	**Post-Index[b] (n = 26,883)**	***P* value**
Type of HRU, n (%)												
Emergency department visits	145 (10.3)	111 (7.9)	0.018*	5321 (8.0)	3399 (5.1)	<0.001***	1427 (5.4)	1124 (4.3)	<0.001***	1964 (7.3)	1387 (5.2)	<0.001***
Hospitalizations	107 (7.6)	88 (6.2)	0.14	3108 (4.7)	1967 (3.0)	<0.001***	758 (2.9)	598 (2.3)	<0.001***	1185 (4.4)	807 (3.0)	<0.001***
−90-day readmissions (n, % of hospitalizations)	14 (13.1)	12 (13.6)	0.8	222 (7.1)	333 (16.9)	<0.001***	35 (4.6)	87 (14.5)	<0.001***	86 (7.3)	143 (17.7)	<0.001***
Office visits[c]	690 (48.5)	706 (49.6)	0.5	27,948 (41.9)	27,305 (40.9)	<0.001***	14,205 (54.1)	13,528 (51.5)	<0.001***	11,983 (44.4)	12,451 (46.2)	<0.001***
OP visits[d]	342 (24.2)	378 (26.7)	0.067	10,682 (16.1)	11,353 (17.1)	<0.001***	4396 (16.8)	4758 (18.1)	<0.001***	4899 (18.2)	5449 (20.3)	<0.001***
	TTM			**TTS**			**Overall**					
	Pre-Index (n = 4176)	**Post-Index[b] (n = 4176)**	***P*value**	**Pre-Index (n = 12,482)**	**Post-Index[b] (n = 12,482)**	***P* value**	**Pre-index (n = 137,691)**		**Post-index[b] (n = 137,691)**		***P* value**	
Type of HRU, n (%)												
Emergency department visits	713 (17.1)	363 (8.7)	<0.001***	833 (6.7)	551 (4.4)	<0.001***	10,403 (7.6)		6935 (5.0)		<0.001***	
Hospitalizations	572 (13.7)	265 (6.3)	<0.001***	395 (3.2)	305 (2.4)	<0.001***	6125 (4.4)		4030 (2.9)		<0.001***	
−90-day readmissions (n, % of hospitalizations)	38 (6.6)	47 (17.7)	0.4	24 (6.1)	50 (16.4)	0.00361**	419 (6.8)		672 (16.7)		<0.001***	
Office visits[c]	1797 (42.8)	2352 (56.0)	<0.001***	7008 (56.1)	6530 (52.3)	<0.001***	63,631 (46.1)		62,872 (45.5)		<0.001***	
OP visits[d]	918 (22.0)	1211 (29.0)	<0.001***	2313 (18.5)	2455 (19.7)	0.0232*	23,550 (17.1)		25,604 (18.6)		<0.001***	

Notes: [a]Based on claims with COPD as the primary diagnosis. [b]Requiring 12 months of follow-up during post-index. [c]Office visits include all the visits at doctor's office, including primary care, specialty care, nurse practitioners and physician assistant visits. [d]OP visits include diagnostic, laboratory, radiology, and surgery visits. ****P* < 0.001 pre-index versus post-index. ** *P* < 0.01 pre-index versus post-index. **P* < 0.05 pre-index versus post-index.

Abbreviations: COPD, chronic obstructive pulmonary disease; HRU, healthcare resource utilization; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-agonist, LABA/ICS, long-acting beta-agonist/inhaled corticosteroid; LABA/LAMA, long-actingbeta-agonist/long-acting muscarinic antagonist; OP, outpatient; SD, standard deviation; TTM, triple therapy in multiple inhalers; TTS, triple therapy in single inhaler.

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increased risk of pneumonia and a modest reduction in the rate of first moderate or severe exacerbations compared with LABA/LAMA.[15,16] These findings should prompt further investigation into the appropriate use of ICS in COPD.

In this study, the proportion of patients who experienced a moderate or severe exacerbation reduced from the pre-index to the post-index treatment initiation period. However, 37.0% of patients continued to experience exacerbations in the overall population post-index period. This is similar to the findings of the IMPACT study, which showed that despite a reduction in exacerbations among the triple therapy group, nearly 50% had a moderate exacerbation in the 12 months after therapy initiation.[17,18] Additionally, the magnitude of reduction in annual exacerbation rates after initiating standard-of-care inhaled maintenance therapies, though statistically significant in some groups, may not translate to clinical significance for patients and/or the healthcare system. Interestingly, we found a decrease in severe exacerbations, and an increase in moderate exacerbations for most treatment groups. Confounding by indication may have contributed to the paradoxical observation of increased moderate exacerbations following maintenance medication initiation in some treatment groups; a "downgrading" effect of otherwise severe exacerbations may also be responsible for the increase in moderate exacerbations.[19] Whether differences in the direction of response in moderate exacerbations by treatment type are reproducible should be further explored in independent cohorts. While statistical analyses were not performed to compare the differences in moderate versus severe exacerbation rate reduction, these data do suggest that initiating these inhaled maintenance treatments may reduce the severity of exacerbations. It should be noted that there is heterogeneity of exacerbation rates depending on treatments.

Similarly, although COPD-related HRU also decreased from the pre-index to the post-index period overall and in most treatment initiation groups, a substantial proportion of patients with COPD continued to experience HRU burden post-index while on treatment. Data from this study support findings from other assessments, which indicate that the HRU burden associated with COPD remains high.[20,21] It is worth mentioning that 5.0% and 2.9% of patients had inpatient and ED care, respectively, in the post-index period. This finding underscores not only the need for broader implementation of guideline-driven care and potentially earlier referral to pulmonologist care, which has been shown to reduce HRU in COPD, but that there is also a need for novel therapies to reduce the COPD disease burden.[22]

There are several novel therapies for COPD that have been approved or are in advanced- to late-stage clinical trials in recent years, and which may be key to curtailing overuse of ICS as well as HRU and exacerbations experienced in this patient population. Roflumilast is an oral phosphodiesterase 4 (PDE4) inhibitor indicated as a treatment to reduce the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[23] Another PDE inhibitor is ensifentrine, a first-in-class inhaled dual selective inhibitor of PDE3 and PDE4, which was approved in 2024 for the maintenance treatment of COPD.[24] Dupilumab was also recently approved as the first-ever biologic treatment for patients with inadequately controlled COPD and high eosinophil counts (≥300 cells/L).[25,26] In addition, the dry powder inhaler tanimilast has been shown to significantly reduce inflammatory mediators in sputum compared with placebo and is currently being studied in two Phase 3 studies as an add-on to triple maintenance therapy LAMA/LABA/ICS.[27–30] Thus, until recently, available therapies for COPD have traditionally been limited to bronchodilators and ICS. There exists a need for additional studies exploring the effectiveness of these recently approved therapies, their effects on HRU and COPD exacerbations, and their associated real-world clinical outcomes.

There are a number of strengths and limitations associated with this analysis, particularly those inherent to claims data. The data are limited to those patients with insurance. The database captured claims that were fully or partially paid by the patient's insurer; only some insurers may have allowed partial reimbursement of out-of-network pharmacy costs. Therefore, not all important clinical outcomes are captured by these claims data, given that the database may not capture non-reimbursable HRU. Furthermore, while a strength of the pre-post design is that it inherently removes any confounding variables associated with fixed patient characteristics, residual confounding—including confounding due to changes in a patient's health status from the pre- to post-index period—remains possible. Certain baseline characteristics commonly observed in studies of patients with COPD were not accounted for in this database analysis. Claims data do not reliably capture inhaler type or treatment adherence, nor do they capture clinical measures such as spirometric lung function, symptoms, or eosinophil counts, which could be used to further quantify inappropriate ICS use and its lack of effect on exacerbation rates. Additionally, robust smoking status and pack-year data are not available, and patients are categorized only as either tobacco users or not. The study did not distinguish between patients who were initiating their

first-ever prescription treatment for COPD and those who may have been prescribed a treatment for COPD in the past (prior to the 12-month baseline period), and reasons for any delay in maintenance treatment initiation were uncertain given the nature of claims data. These findings are in line with other real-world studies, which show that a significant proportion of patients with diagnosed COPD are not currently on any maintenance treatment.[14,31] The study was limited to the US population, and therefore, results may not be generalizable to other countries. In addition, this study is not necessarily reflective of treatment patterns after June 2023. Future analyses should reflect current treatment patterns. Moreover, some of the reported differences, while statistically significant, may have minimal clinical relevance. For example, in the overall population, the small difference in the pre-index (0.67) and post-index (0.65) acute exacerbation rates (a 0.02 difference) may not have a clinically meaningful impact. We recommend focusing on differences that have more substantial effects on treatment decisions and patient care. Paired *t* tests were used given the large sample size. However, the strength of this analysis and study lies in the up-to-date, real-world HRU data from patients with COPD and the insight it provides into the dynamic changes associated with initiating inhaled treatments. This study uses a large longitudinal sample, which increases the generalizability of our research to real-world populations. A particularly unique aspect of this study is the wide range of treatment regimens captured within the Optum CDM dataset.

Conclusions

Using a large national US sample, this study provides a comprehensive landscape assessment of the types and trends in inhaled maintenance therapies for COPD and evaluates changes in exacerbation rates and HRU associated with these treatments. Overall, there continues to be a need for implementation of guideline-based care and new therapies to alleviate the persistent COPD exacerbation burden.

Data Sharing Statement

Data from Optum Clinformatics® Data Mart database are outside of Verona Pharma's data sharing policy and are unavailable for sharing.

Ethical Conduct of Research

An institutional review board (IRB) local to the corresponding author's affiliation institution (IRB 20250333) determined that this research using only deidentified patient data from the Optum Clinformatics® Data Mart database does not involve human subjects as defined by the Department of Health and Human Services and the United States Food and Drug Administration regulations, and therefore is exempt from IRB review and approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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