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ORIGINAL RESEARCH

Characteristics and Outcomes of People With COPD Who Experience Exacerbations While on Inhaled Triple Therapy: Results of the SIRIUS I Cohort Study in the US (2015–2019)

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Purpose: Many people with chronic obstructive pulmonary disease (COPD) continue to experience frequent moderate/severe exacerbations despite treatment with inhaled triple therapy (TT). We evaluated the baseline characteristics and outcomes (exacerbation rate, mortality, and healthcare resource utilization [HCRU]) of this COPD population, overall and by smoking status.

Patients and methods: A retrospective real-world cohort study of US patients was conducted using Optum's deidentified Market Clarity Data, an integrated claims and electronic health record database (study period: 2015–2019). Patients eligible for inclusion were aged ≥40 years, with a COPD diagnosis, continuous 12-month (baseline) period of treatment with TT, and record of ≥2 moderate or ≥1 severe exacerbation during baseline. Follow-up was either variable (from end of baseline to death, loss to follow-up, or end of 2019) or fixed (12 months). Baseline characteristics and treatment patterns, crude incidence rates (IRs) for exacerbations and mortality (per 100 person-years [PYs]; variable follow-up), and HCRU and costs (12-month follow-up) were summarized descriptively.

Results: Of 4,920 patients in the TT cohort, mean (SD) age was 62.3 (9.7) years, 60.9% were female, and 68.0% were white; 46.5% of TT cohort patients with a history of smoking were current smokers. Hypertension (92.7%), ischemic heart disease (52.1%), and heart failure (40.1%) were the most prevalent cardiovascular comorbidities. Most patients received oral corticosteroids (89.6%) or antibiotics (92.8%) for exacerbation management during baseline. Add-on therapies included phosphodiesterase-4 inhibitors (10.4%) and leukotriene receptor antagonists (26.4%). During follow-up, IRs (95% CI) were 108.2 (104.7–111.8) per 100 PY for any moderate/severe exacerbation and 8.0 (7.4–8.6) per 100 PY for mortality. Exacerbation risk was similar by smoking status. During the 12-month follow-up, mean (SD) all-cause and COPD costs were $63,178 ($77,061) and $26,153 ($47,085), respectively.

Conclusion: There is high mortality and considerable HCRU and healthcare costs incurred by people with COPD experiencing frequent moderate/severe exacerbations while on TT. Optimization of COPD management and new therapies are needed to reduce disease burden in this population.

Keywords: COPD, burden of illness, exacerbation, inhaled triple therapy, mortality, healthcare resource utilization

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity globally, with a substantial and increasing economic and societal burden.[1–5] According to 2019 global estimates, there were 212 million people living with COPD, with 3.3 million COPD-related deaths.[4] In the US, COPD affects an estimated 14.2 million adults, and it is the sixth leading cause of death with 144,752 COPD-related fatalities reported for 2019.[6,7] COPD-related healthcare expenses are expected to increase globally over the next few years and are projected to cost $60.5 billion in the US in 2029.[8,9] Exacerbations are a key feature of COPD and present a clinical and healthcare challenge worldwide;

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most people with COPD experience exacerbations of varying severity and frequency, with worsening symptoms and declining lung function over their lifetime.[10,11] Exacerbations also vary in severity and can be categorized as mild (requiring treatment with short-acting bronchodilators only), moderate (requiring add-on medication), and severe (requiring hospitalization or an emergency room [ER] visit).[2] Frequent exacerbators are defined as those that experience ≥2 exacerbation events within a year or ≥1 exacerbation requiring hospitalization, while super exacerbators are defined as those with ≥3 exacerbations in a year.[2,12,13]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends management of COPD with single or multiple maintenance inhaled therapies, depending on exacerbation patterns and dyspnea intensity.[2] In people with ≥2 moderate and/or ≥1 severe exacerbation within a year, initial treatment with inhaled dual therapy (long-acting muscarinic antagonist [LAMA] and long-acting β_2-agonist [LABA]) is recommended; inhaled triple therapy (LAMA +LABA with inhaled corticosteroids [ICS]) is also recommended as the initial treatment option for patients with high eosinophil count (≥300 cells/μL) or as step-up therapy for those with an eosinophil count of ≥100 cells/μL who continue to experience exacerbations.[2] Beyond inhaled medications, add-on therapies (eg, long-term macrolides, N-acetylcysteine, long-term oral glucocorticoids, phosphodiesterase 3 and 4 inhibitors, or mucolytics) are also considered; however, these have limited risk/benefit profiles.[2,14,15] In addition to pharmacological therapy, smoking cessation is a priority in COPD management, and, yet, observational studies suggest that up to 30% to 40% of people with COPD remain current smokers.[2,16,17] Despite these available therapeutic options, and challenges association with smoking cessation, it is estimated that 30% to 60% of patients continue to experience moderate to severe exacerbations while receiving dual or triple inhaled therapy, highlighting an unmet medical need for more effective treatment options for the management of COPD exacerbations.[18–23]

Several monoclonal antibodies targeting different inflammatory pathways are currently under development, and one has been recently approved, aimed at decreasing exacerbation risk and improving symptoms in people with COPD who continue to experience exacerbations while on inhaled dual or triple therapy.[24–27] However, the patients enrolled in clinical trials may differ from the heterogenous real-world population[28] and little is known about the characteristics and clinical outcomes of this COPD population in routine clinical practice. The primary aim of this study was to describe clinical characteristics, healthcare resource utilization (HCRU) and costs, and exacerbation and mortality rates in people with COPD who experienced moderate or severe exacerbations despite being on maintenance maximal inhaled triple therapy, overall and stratified by smoking status.

Methods

Study Design and Data Source

The SIRIUS I study was a retrospective real-world cohort study using Optum's deidentified Market Clarity Data (Market Clarity) in the US (2015–2019). Market Clarity deterministically links medical and pharmacy claims with electronic health record data from providers across the continuum of care.[29] The base study population was people with COPD who experienced ≥2 moderate or ≥1 severe COPD exacerbation while on maintenance inhaled dual or triple therapy (Figure 1). People with COPD were defined as those with ≥1 inpatient or outpatient visit claim with a COPD diagnosis code (using *International Classification of Diseases, 9th* or *10th Revision* [*ICD-9/10*]; Table S1) between January 1, 2015, and December 31, 2018, and aged ≥40 years at the first COPD diagnosis. Use of maintenance inhaled dual or triple therapy was defined as (1) ≥2 prescriptions for single or multiple inhaled dual or triple therapy (LAMA/ICS; LABA/ICS; LAMA/LABA; LAMA/LABA/ICS) within a 90-day period, with the first prescription (start of the 12-month baseline period) occurring after COPD diagnosis and (2) another dispensation of inhaled dual/triple therapy in the 30 days before the end of the 12-month baseline period. For multiple inhaler therapy, an overlap of ≥30 days between 2 different inhalers was required. Exacerbation history during the baseline period was characterized by either ≥2 moderate exacerbations (defined as an ER visit with a primary diagnosis code for COPD or an outpatient visit with a primary diagnosis code for COPD and dispensation of systemic corticosteroids and/or GOLD-recommended antibiotics within 7 days of the visit) or ≥1 severe exacerbation (defined as a hospitalization with ≥1 overnight stay with a primary diagnosis code for COPD).[2]

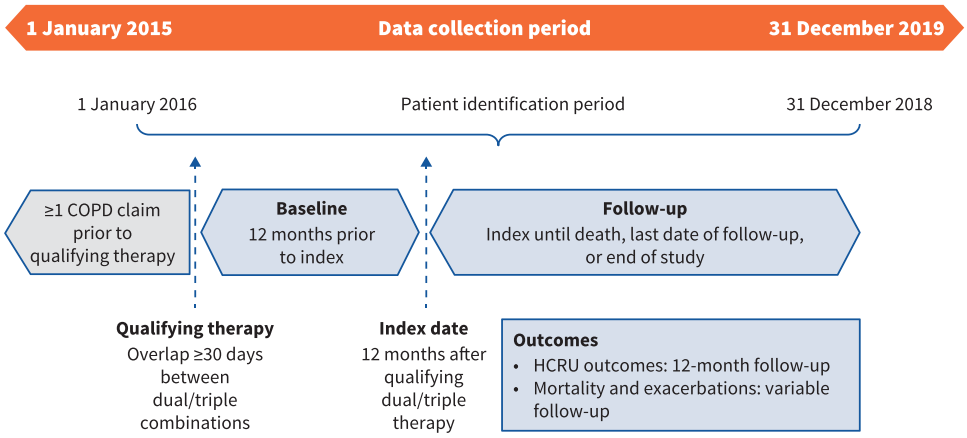

Figure 1 Study Design and Observation Period.
Abbreviations: COPD, chronic obstructive pulmonary disease; HCRU, healthcare resource utilization.

Patients were excluded if they had incomplete data availability during baseline; had a diagnosis of cystic fibrosis, interstitial lung disease, or alpha-1 antitrypsin deficiency; or were participating in a clinical trial (Figure 2).

The primary population of interest was patients on maintenance inhaled triple therapy during baseline ("triple therapy cohort"), defined as ≥1 dispensation of inhaled triple therapy during baseline. Patients in the triple therapy cohort with information on smoking history were further stratified according to smoking status (current or former smokers). The secondary population of interest was patients who received either inhaled dual or triple therapy ("dual/triple therapy cohort").

Day 1 following the end of the baseline period constituted the start of the follow-up period, which ended at the earliest of death, disenrollment, or December 31, 2019. For HCRU and direct healthcare cost measures, a 12-month follow-up was required.

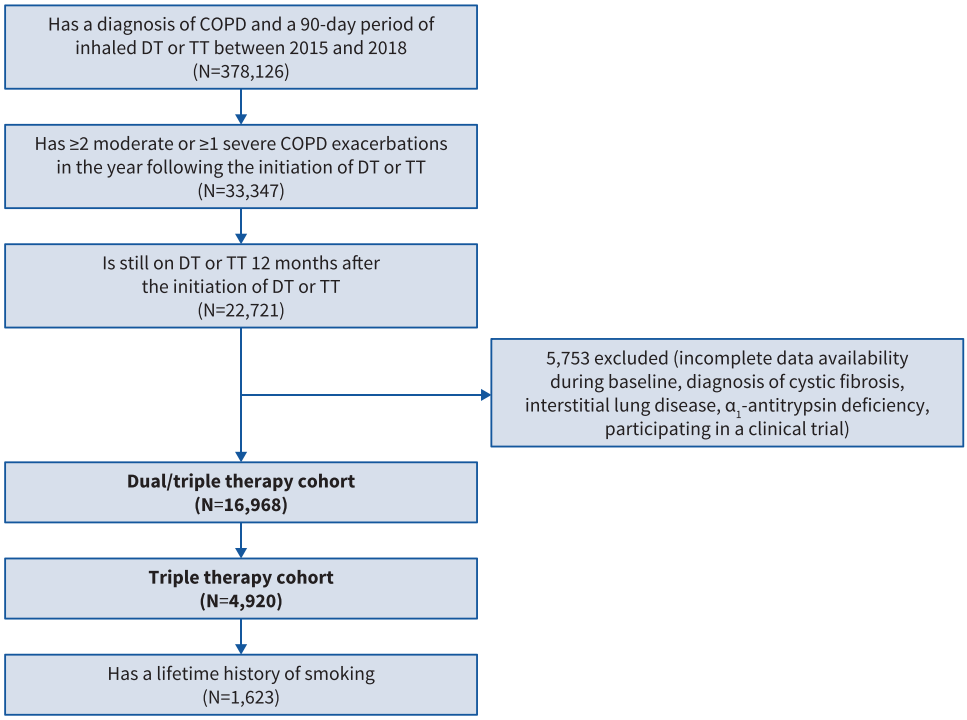

Figure 2 Study Population.
Abbreviations: COPD, chronic obstructive pulmonary disease; DT, dual therapy; TT, triple therapy.

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Study Variables

Baseline characteristics included age, sex, payer type (commercial, managed Medicare, Medicaid, multiple, unknown), smoking status (current/former/never smoked), body mass index, and number and severity of exacerbations (moderate or severe). Comorbidity burden was assessed through Charlson Comorbidity Index (CCI) scores[30] and prevalence of prespecified comorbidities of interest (ischemic heart disease, heart failure, arrhythmia, type 2 diabetes, chronic kidney disease [CKD], and asthma).

Medical specialties of the initial inhaled treatment prescriber (within the baseline period) and patterns of COPD and other medication use (long-acting and short-acting inhalers, oral corticosteroids [OCS], GOLD-recommended antibiotics, methylxanthines, phosphodiesterase 4 [PDE4] inhibitors, and leukotriene receptor antagonists [LTRAs]) were also described.

COPD exacerbation (any severity) and all-cause mortality were recorded during follow-up. HCRU and healthcare costs, including all-cause and COPD-related outpatient visits, ER visits, and hospitalizations, were identified using Current Procedural Terminology/Healthcare Common Procedure Coding System codes and reported for baseline and the first 12 months of follow-up. Costs per patient-year (PPY) were reported and adjusted to 2021 US dollars using the annual medical care component of the Consumer Price Index.[31]

Statistical Analysis

Baseline characteristics and outcomes were described for the triple therapy cohort (overall and stratified by smoking status [current or former smokers]). Baseline characteristics, HCRU, and costs were summarized using descriptive statistics. Crude incidence rates (IRs) of a first exacerbation (any severity, moderate, severe) and mortality rates were calculated as the ratio between the number of first events during follow-up and the number of 100 person-years (PY) of follow-up; 95% CIs were estimated using the exact Poisson method. IRs were also stratified by sex and age. IRs of all-cause mortality were calculated without considering the competing risk of an exacerbation. Missing codes for a given comorbidity or healthcare event were not measurable or imputed. Results were also summarized for the dual/triple therapy cohort.

Results

A total of 16,968 patients comprised the dual/triple therapy cohort, including 4,920 (29.0%) in the triple therapy cohort (Figure 2). Of the triple therapy cohort, 144 (2.9%) received fixed (ie, single inhaler) triple therapy.

Characteristics of the Triple Therapy Cohort

Among the patients in the triple therapy cohort, 1,623 (33.0%) had a recorded history of smoking; of these, 755 (46.5%) were current smokers and 868 (53.5%) were former smokers (Table 1). Sociodemographic characteristics of patients in the triple therapy cohort and current and former smoker subsets were broadly comparable. Most of the triple therapy cohort were female (60.9%); this proportion was slightly higher among current smokers (62.8%) (Table 1). Mean (SD) age was 62.3 (9.7) years for the triple therapy cohort and younger in current smokers (59.4 [8.7] years).

With respect to comorbidities, 52.1% of patients had ischemic heart disease, 49.7% had asthma, 40.1% had heart failure, 38.8% had type 2 diabetes, and 13.0% had CKD (Table 1). The prevalence of cardiovascular disease was greater in former vs current smokers, in particular, arrhythmia (50.1% vs 44.7%, respectively) and heart failure (44.7% vs 35.8%, respectively). During the 12-month baseline period, 55.6% of patients had ≥2 moderate exacerbations (and no severe) and 44.4% had ≥1 severe exacerbation; the proportion who had ≥1 severe exacerbation was 44.5% in current smokers and 49.1% in former smokers. Baseline characteristics of the dual/triple therapy cohort are described in Table S2.

Prescriber and Treatment Patterns in the Triple Therapy Cohort

Prescribers and treatment patterns at baseline are described for the triple therapy cohort in Table 2. In addition to inhaled triple therapy, the mean (SD) cumulative durations of exposure to other COPD-related medications (in patients receiving

Table 1 Baseline Sociodemographics and Comorbidities of Patients in the Triple Therapy Cohort and Stratified by Smoking Status[a]

	Triple Therapy (N=4,920)	Current Smokers (n=755)	Former Smokers (n=868)
Female sex	2,998 (60.9)	474 (62.8)	493 (56.8)
Age, mean (SD), years	62.3 (9.7)	59.4 (8.7)	64.9 (10.0)
Age category, n (%)			
40–49 years	395 (8.0)	81 (10.7)	45 (5.2)
50–64 years	2,690 (54.7)	492 (65.2)	408 (47.0)
65–74 years	1,205 (24.5)	136 (18.0)	241 (27.8)
≥75 years	630 (12.8)	46 (6.1)	174 (20.1)
Race, n (%)			
White	3,347 (68.0)	585 (77.5)	717 (82.6)
African American	589 (12.0)	131 (17.4)	106 (12.2)
Asian/other/unknown	984 (20.0)	39 (5.2)	45 (5.2)
Region in the US, n (%)			
Northeast	1,014 (20.6)	107 (14.2)	157 (18.1)
Midwest	2,063 (41.9)	403 (53.4)	432 (49.8)
South	1,242 (25.2)	174 (23.1)	161 (18.6)
West	376 (7.6)	50 (6.6)	87 (10.0)
Other/unknown	225 (4.6)	21 (2.8)	31 (3.6)
Payer, n (%)			
Commercial only	1,058 (21.5)	157 (20.8)	188 (21.7)
Medicare Advantage only	2,150 (43.7)	273 (36.2)	460 (53.0)
Medicaid only	1,210 (24.6)	246 (32.6)	127 (14.6)
Multiple known	206 (4.2)	24 (3.2)	32 (3.7)
None/unknown	296 (6.0)	55 (7.3)	61 (7.0)
Smoking status, n (%)			
Current smoker	755 (15.4)	755 (100.0)	N/A
Former smoker	868 (17.6)	N/A	868 (100.0)
Never smoked	75 (1.5)	N/A	N/A
Unknown	47 (1.0)	N/A	N/A
Missing	3,175 (64.5)	N/A	N/A
Charlson Comorbidity Index score, n (%)			
≤2	2,392 (48.6)	386 (51.1)	383 (44.1)
3–4	1,593 (32.4)	239 (31.7)	285 (32.8)
≥5	935 (19.0)	130 (17.2)	200 (23.0)

(*Continued*)

Table 1 (Continued).

	Triple Therapy (N=4,920)	Current Smokers (n=755)	Former Smokers (n=868)
Charlson Comorbidity Index score, mean (SD)	2.82 (2.10)	2.72 (2.11)	3.03 (2.20)
Cardiovascular conditions, n (%)[b]	**n=4,415**	**n=684**	**n=795**
Hypertensive disease	4,093 (92.7)	633 (92.5)	727 (91.5)
Ischemic heart disease[c]	2,299 (52.1)	352 (51.5)	429 (54.0)
Arrhythmias	2,014 (45.6)	306 (44.7)	398 (50.1)
Heart failure	1,771 (40.1)	245 (35.8)	355 (44.7)
Cardiomyopathy	1,229 (27.8)	186 (27.2)	237 (29.8)
Pulmonary embolism	293 (6.6)	56 (8.2)	64 (8.1)
Other conditions, n (%)			
Hyperlipidemia	3,452 (70.2)	523 (69.3)	604 (69.6)
Asthma	2,446 (49.7)	385 (51.0)	411 (47.4)
Type 2 diabetes	1,908 (38.8)	292 (38.7)	322 (37.1)
Obesity (BMI ≥30 kg/m^2)[d]	1,775 (36.1)	317 (42.0)	386 (44.5)
Chronic kidney disease	641 (13.0)	90 (11.9)	143 (16.5)
Lung cancer	308 (6.3)	43 (5.7)	66 (7.6)
Exacerbation pattern, n (%)			
≥2 moderate exacerbations	2,737 (55.6)	419 (55.5)	442 (50.9)
≥1 severe exacerbation	2,183 (44.4)	336 (44.5)	426 (49.1)
Follow-up time, mean (SD), months	21.2 (12.4)	20.2 (12.6)	20.2 (12.4)

Notes: [a]A total of 1,623 patients in the triple therapy cohort had a recorded history of smoking; the stratified analyses were conducted in this subset of the triple therapy cohort. [b]The n values for the "Cardiovascular conditions" category represent the number of patients with available data in each analysis group. [c]Ischemic heart disease includes coronary artery diseases, acute myocardial infarction, and unstable angina. [d]Obesity was defined as BMI ≥30 kg/m^2 or using diagnosis code.
Abbreviations: BMI, body mass index; N/A, not applicable.

Table 2 Prescriber and Treatment Patterns During Baseline for Patients in the Triple Therapy Cohort and Stratified by Smoking Status[a]

	Triple Therapy (N=4,920)	Current Smokers (n=755)	Former Smokers (n=868)
Initial treatment prescriber specialty, n (%)			
Primary care physician	2,352 (47.8)	359 (47.6)	456 (52.5)
Pulmonology	1,196 (24.3)	147 (19.5)	240 (27.7)
Other[b]	60 (1.2)	12 (1.6)	9 (1.0)
Missing/unknown	1,312 (26.7)	237 (31.4)	163 (18.8)

(*Continued*)

Table 2 (Continued).

	Triple Therapy (N=4,920)	Current Smokers (n=755)	Former Smokers (n=868)
Inhaled maintenance therapy medications			
Any LAMA (free dose or combination)			
≥1 Dispensation, n (%)	4,854 (98.7)	742 (98.3)	860 (99.1)
Cumulative number of days, mean (SD)[c]	296.2 (112.8)	287.4 (111.5)	299.0 (113.1)
LAMA (free dose)			
≥1 Dispensation, n (%)	4,533 (92.1)	691 (91.5)	794 (91.5)
Cumulative number of days, mean (SD)[c]	289.5 (113.8)	282.2 (112.2)	290.8 (115.9)
LAMA/LABA (single inhaler combination)			
≥1 Dispensation, n (%)	533 (10.8)	71 (9.4)	109 (12.6)
Cumulative number of days, mean (SD)[c]	178.8 (127.9)	182.9 (126.1)	189.6 (138.7)
Triple therapy (fixed dose)			
≥1 Dispensation, n (%)	144 (2.9)	21 (2.8)	29 (3.3)
Cumulative number of days, mean (SD)[c]	214.6 (140.0)	260.5 (128.5)	195.9 (141.1)
Any LABA (free dose or combination)			
≥1 Dispensation, n (%)	4,920 (100.0)	755 (100.00)	868 (100.00)
Cumulative number of days, mean (SD)[c]	337.7 (100.8)	332.3 (96.1)	334.9 (92.6)
LABA (free dose)			
≥1 Dispensation, n (%)	124 (2.5)	15 (2.0)	28 (3.2)
Cumulative number of days, mean (SD)[c]	127.0 (119.0)	170.0 (161.4)	127.0 (128.8)
ICS/LABA (single inhaler combination)			
≥1 Dispensation, n (%)	4,742 (96.4)	726 (96.2)	825 (95.1)
Cumulative number of days, mean (SD)[c]	321.9 (104.4)	318.2 (100.5)	317.2 (100.3)
Any ICS (free dose or combination)			
≥1 Dispensation, n (%)	4,907 (99.7)	754 (99.9)	863 (99.4)
Cumulative number of days, mean (SD)[c]	330.6 (106.2)	325.8 (101.0)	326.9 (101.5)
ICS (free dose)			
≥1 Dispensation, n (%)	498 (10.1)	68 (9.0)	94 (10.8)
Cumulative number of days, mean (SD)[c]	147.2 (131.0)	155.9 (139.8)	167.3 (145.9)
Patterns of add-on COPD medications			
GOLD-recommended antibiotics			
≥1 Dispensation, n (%)	4,566 (92.8)	704 (93.3)	796 (91.7)
Cumulative number of days, mean (SD)[c]	44.8 (71.0)	41.2 (63.0)	49.4 (78.8)

(*Continued*)

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Table 2 (Continued).

	Triple Therapy (N=4,920)	Current Smokers (n=755)	Former Smokers (n=868)
Oral corticosteroids			
≥1 Dispensation, n (%)	4,408 (89.6)	690 (91.4)	775 (89.3)
Cumulative number of days, mean (SD)[c]	72.5 (102.0)	63.1 (90.6)	79.4 (109.9)
Phosphodiesterase 4 inhibitors			
≥1 Dispensation, n (%)	509 (10.4)	88 (11.7)	98 (11.3)
Cumulative number of days, mean (SD)[c]	222.6 (139.4)	207.0 (134.1)	223.0 (150.7)
Leukotriene receptor antagonists			
≥1 Dispensation, n (%)	1,301 (26.4)	170 (22.5)	200 (23.0)
Cumulative number of days, mean (SD)[c]	265.7 (130.5)	252.4 (128.2)	265.0 (126.8)
Methylxanthines[d]			
≥1 Dispensation, n (%)	269 (5.5)	36 (4.8)	53 (6.1)
Cumulative number of days, mean (SD)[c]	246.3 (141.4)	241.4 (142.5)	256.9 (136.4)
Short-acting β-agonists, ≥1 dispensation, n (%)			
Free dose or in combination	4,631 (94.1)	734 (97.2)	790 (91.0)
Alone	4,454 (90.5)	710 (94.0)	752 (86.6)
In combination with short-acting antimuscarinic agents	1,586 (32.2)	265 (35.1)	276 (31.8)

Notes: [a]A total of 1,623 patients in the triple therapy cohort had a recorded history of smoking; the stratified analyses were conducted in this subset of the triple therapy cohort. [b]"Other" category includes allergy/immunology, gastroenterology, and otolaryngology specialists. [c]In patients with ≥1 dispensation. [d]Formulation type (sustained release or fast acting) not specified.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.

these medications), were 222.6 (139.4) days for PDE4 inhibitors and 265.7 (130.5) days for LTRAs. Most patients received antibiotics (92.8%) and OCS (89.6%), which were prescribed for mean (SD) cumulative durations of 44.8 (71.0) days and 72.5 (102.0) days, respectively. Mean (SD) duration of exposure was higher among the former vs current smokers for PDE4 inhibitors (223.0 [150.7] days vs 207.0 [134.0] days), LTRAs (265.0 [126.8] days vs 252.4 [128.2] days), and exacerbation-management medication (OCS, 79.4 [109.9] days vs 63.1 [90.6] days; antibiotics, 49.4 [78.8] days vs 41.2 [63.0] days) (Table 2). Prescriber and treatment patterns for the dual/triple therapy cohort are described in Table S3.

Outcomes of Exacerbations and Death

During a mean (SD) follow-up of 21.2 (12.4) months, 71.8% of patients in the triple therapy cohort had ≥1 exacerbation of any severity (IR: 108.2 [95% CI 104.7–111.8] per 100 PY), 64.2% had ≥1 moderate exacerbation (IR: 83.4 [95% CI 80.5–86.4] per 100 PY), and 32.3% had ≥1 severe exacerbation (IR: 23.8 [95% CI 22.6–25.0] per 100 PY) (Figure 3A–C). When stratified by sex and age, exacerbation rates trended toward being higher in females (Table S4). Among the current and former smoker subgroups, 70.6% and 71.3%, respectively, had ≥1 exacerbation of any severity during follow-up; IRs for first exacerbation were similar in both groups (Figure 3A–C, Table S4, and Figure S1A). Exacerbations in the dual/triple therapy cohort are reported in Table S4, Figures S1B, and S2.

During the follow-up period, 13.9% of patients in the triple therapy cohort died (IR: 8.0 [95% CI 7.4–8.6] per 100 PY). Mortality rates were higher in former smokers (IR: 11.3 [95% CI 9.6–13.2] per 100 PY) than current smokers (IR:

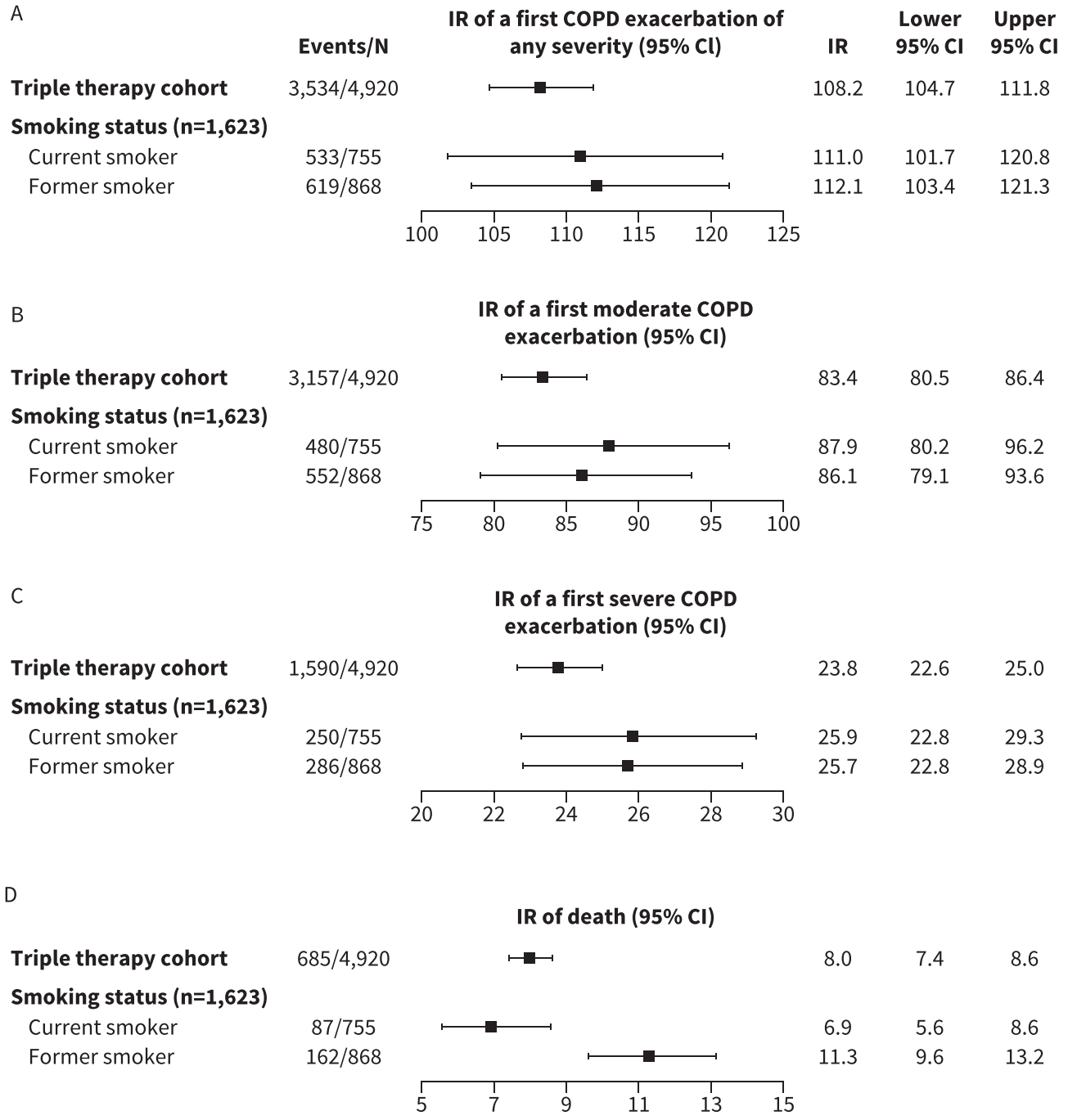

Figure 3 Incidence Rates of a First COPD Exacerbation, for (**A**) Exacerbations of Any Severity, (**B**) Moderate Exacerbations, and (**C**) Severe Exacerbations, and (**D**) Death During Follow-up in the Triple Therapy Cohort.

Notes: IRs were calculated as the ratio between the number of first events during follow-up and the number of 100 person-years of follow-up. A total of 1,623 patients in the triple therapy cohort had a recorded history of smoking; the stratified analyses were conducted in this subset of the triple therapy cohort.

Abbreviations: COPD, chronic obstructive pulmonary disease; IR, incidence rate.

6.9 [95% CI 5.6–8.6] per 100 PY) (Figure 3D and Figure S3A) and increased with age and male sex (Table S5). Results for the dual/triple therapy cohort are shown in Table S5, Figures S2, and S3B.

HCRU and HCRU-Related Costs

At the end of the 12-month follow-up, 3,290 patients (66.9%) in the triple therapy cohort remained alive and had continuous enrollment. Almost all patients had ≥1 ambulatory visit at baseline (98.9%) and during the 12-month follow-

Table 3 Healthcare Resource Utilization in Patients in the Triple Therapy Cohort During Baseline and the First 12 Months of Follow-up

	Triple Therapy (N=3,290)			
	All-Cause HCRU		COPD-Related HCRU	
	Baseline (12 Months)	Follow-up (12 Months)	Baseline (12 Months)	Follow-up (12 Months)
HCRU				
≥1 Ambulatory visit, n (%)	3,254 (98.9)	3,206 (97.5)	3,049 (92.7)	2,705 (82.2)
Mean (SD) number of visits	30.7 (26.4)	28.7 (27.3)	6.0 (6.9)	4.6 (5.4)
≥1 ER visit, n (%)	2,524 (76.7)	2,166 (65.8)	1,552 (47.2)	1,099 (33.4)
Mean (SD) number of visits	3.2 (5.1)	2.9 (6.7)	1.0 (1.6)	0.7 (1.7)
≥1 Hospitalization, n (%)	1,646 (50.0)	1,112 (33.8)	1,423 (43.3)	773 (23.5)
Mean (SD) number of hospitalizations	0.9 (1.4)	0.7 (1.5)	0.6 (1.0)	0.4 (0.9)
Mean (SD) PPY costs, $				
Ambulatory visits	12,350 (21,713)	12,083 (20,991)	1,578 (4,979)	1,321 (4,515)
ER visits	4,588 (8,270)	4,117 (9,407)	975 (2,255)	780 (2,723)
Hospitalizations	25,409 (54,342)	19,884 (55,136)	19,068 (45,830)	12,793 (43,917)
Office visits	4,426 (8,478)	4,435 (10,202)	622 (1,515)	566 (2,803)
Outpatient visits	7,924 (18,910)	7,647 (16,989)	956 (4,728)	756 (3,362)
Other medical services	12,548 (21,052)	12,161 (20,122)	3,041 (6,335)	2,938 (7,646)
Pharmacy	17,404 (21,931)	14,934 (18,724)	9,983 (4,620)	8,321 (4,954)
Total cost	72,299 (77,241)	63,178 (77,061)	34,645 (47,334)	26,153 (47,085)

Notes: Standardized costs were adjusted to 2021 US dollars using the annual medical care component of the Consumer Price Index to reflect inflation.[31]

Abbreviations: COPD, chronic obstructive pulmonary disease; ER, emergency room; HCRU, healthcare resource utilization; PPY, per patient-year.

up (97.5%), and most had ≥1 ER visit (baseline, 76.7%; follow-up, 65.8%); mean (SD) total all-cause costs were $72,299 ($77,241) PPY and $63,178 ($77,061) PPY, respectively (Table 3). COPD-related costs represented 47.9% of all-cause costs at baseline and 41.4% of all-cause costs during the 12-month follow-up (mean [SD] total cost: $34,645 [$47,334] PPY vs $26,153 [$47,085] PPY) (Table 3). COPD-related ER visits occurred in 47.2% of patients at baseline and 33.4% of patients during follow-up, and COPD-related hospitalizations occurred in 43.3% and 23.5%, respectively. Similar trends in HCRU and HCRU-related costs were observed in the dual/triple therapy cohort (Table S6).

Discussion

In this real-world data analysis of people with COPD who experience frequent moderate or severe exacerbations while receiving inhaled triple therapy, we identified a substantial clinical and healthcare burden. Mortality was high in this population, with death reported in approximately 8% of the cohort in a 12-month period and of those who survived, most experienced a subsequent exacerbation during follow-up. Trends in outcomes were similar among former and current smokers within this cohort, highlighting the overall disease burden experienced by this COPD population regardless of smoking status.

More than 1 in 10 people in the triple therapy cohort in this study died during the follow-up period of less than 2 years. These observations align with a recent UK study reporting a mortality rate of 7.5 per 100 PY in a COPD cohort

who experienced ≥2 exacerbations over a 12-month period.[32] People in this study were also at high-risk of a subsequent exacerbation, with more than 70% experiencing an exacerbation during follow-up; the exacerbation rate was lower in this study (108 events per 100 PY) than in a previous US study using Medicare data, in which people who experienced ≥2 moderate exacerbations over a 12-month period had an exacerbation rate of 135 per 100 PY.[33] However, the higher exacerbation rates reported were likely attributable to the older age (mean age: 69.8 years) and greater comorbidity burden (mean CCI: 3.6) in that study cohort, and we would therefore consider these findings to broadly corroborate our own.

Individuals with COPD who experience exacerbations while receiving inhaled triple therapy experience a high comorbidity burden, with metabolic and cardiovascular diseases, such as hypertension, ischemic heart disease, type 2 diabetes, and CKD, being common comorbidities. A similar comorbidity profile was reported for a real-world COPD population receiving fixed inhaled triple therapy, in which high prevalence of cardiovascular comorbidities was also observed.[34] Treatments for COPD exacerbations aim to improve symptoms and resolve current exacerbations. In this study, the use of add-on COPD medications was very high with approximately 90% of patients receiving OCS and antibiotics for exacerbation management; however, these medications may be associated with adverse effects. A previous study has shown that people with COPD who were exposed to OCS had significantly higher risk of multiple adverse outcomes, including hypertension, type 2 diabetes, and CKD, compared with those not exposed to OCS.[35] Risk of osteoporosis was also 80% greater with exposure to OCS (vs no exposure),[35] which is an important factor for consideration noting the high average age of people affected by COPD. In this study, antibiotics were also received for an average of 41 days per year; this could lead to increased risk of antimicrobial resistance, which is a public health concern.[36]

Aside from exacerbation-management medications, the COPD population in this study also frequently received oral add-on medications, such as LTRAs and PDE4 inhibitors, similar to prior studies.[37] However, LTRAs are not currently indicated in COPD, and use of some PDE4 inhibitors are associated with gastrointestinal adverse effects.[2] These suggest the lack of suitable therapies for this COPD population, highlighting an unmet medical need.

In this study, HCRU and related costs were largely sustained from baseline to follow-up; the lower values observed during follow-up are likely due to either regression to the mean effects from high baseline HCRU and costs or the decreased exacerbation risk following treatment as previously reported.[38] Other US studies have reported similarly high healthcare costs; one reported an average expenditure of $16,085 PPY for adults with COPD and another reported mean annual total healthcare costs of $22,130 for people with COPD, with costs increasing with disease severity (ranging $22,217–$31,148 for GOLD stage 1–4).[8,39] While differences in methodology and time periods may account for absolute differences in healthcare costs, these results reflect the high healthcare and economic burden of COPD, especially in those with comorbidities and severe disease.

In this study, 47% of patients receiving inhaled triple therapy with a history of smoking were current smokers. Although current smokers were younger than former smokers, exacerbation rates were similar, and the prevalence of cardiovascular comorbidities was comparable. This finding differs from other studies reporting improved exacerbation and mortality outcomes in former vs current smokers.[16] However, these prior studies assessed broad COPD populations in contrast to the more specific population in this study (those experiencing frequent moderate/severe exacerbations while receiving inhaled triple therapy), which could explain the difference in results. Overall, findings from this study emphasize the high burden of disease in this COPD population and the need for improved treatment options for all patients at risk of exacerbations, regardless of smoking status.

The heterogeneity of COPD poses a challenge for accurate diagnosis and effective management. While phenotypic classification has been historically used for diagnosis and treatment, the advent of the "treatable traits" approach may enable the implementation of personalized interventions for COPD.[40,41] The patient characteristics identified in this study could add to our understanding of pulmonary, extrapulmonary, and behavioural risk factors in exacerbating COPD, which could help refine the treatment selection to improve clinical outcomes and health-related quality of life for these patients.[40]

Strengths and Limitations

This study is subject to several limitations. First, although the database included a large cohort of people with COPD, those included were primarily insured through Medicare Advantage and may not be generalizable to all patients with COPD in real-world clinical practice. Second, Market Clarity does not capture some clinically relevant data such as disease severity, indicators of medication adherence, socioeconomic status, and other healthcare data, such as access to pulmonary rehabilitation, vaccinations, immunizations, and patient-reported outcomes. Claims data, and use of *ICD-9/10* codes for COPD diagnosis, are also prone to incomplete or miscoded diagnoses, an inherent limitation of claims-based studies, and missing data were not imputed. Mortality rates may have been underestimated, as some patients who died during follow-up may have been recorded as being lost to follow-up; however, substantial morbidity and mortality were still observed among the cohort assessed, emphasizing the disease burden in this population. Smoking status information was available in only one-third of people in the study; however, the baseline characteristics of current and former smokers were very similar to the triple therapy cohort. IRs for mortality and exacerbations were crude unadjusted estimates; nevertheless, results stratified by age and sex suggested an association between age or sex and mortality and exacerbation rates. This study may be considered outdated as it captured data prior to 2019; however, this was done intentionally to assess patient outcomes prior to the COVID-19 pandemic.

Conclusions

This study highlights the considerable clinical and healthcare resource burden of COPD in those who experience frequent moderate or severe exacerbations while receiving inhaled triple therapy, with frequent exposure to add-on COPD therapies that have poor risk/benefit ratios. While air pollution, tobacco use, and lack of timely access to healthcare are known risk factors for COPD exacerbations, identification of other potential risk factors for frequent/severe exacerbations can aid in earlier diagnosis and prompt treatment. While smoking cessation is a key intervention in the management of COPD, the equally high disease burden observed in both current and former smokers highlights an unmet need to improve clinical management for all people with COPD regardless of smoking status.

Abbreviations

CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ER, emergency room; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCRU, healthcare resource utilization; *ICD-9/10, International Classification of Diseases, 9th* or *10th Revision*; ICS, inhaled corticosteroid; IR, incidence rate; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LTRAs, leukotriene receptor antagonists; OCS, oral corticosteroids; PDE4, phosphodiesterase 4; PPY, per patient-years; PY, person-years.

Data Sharing Statement

The data contained in our database contains proprietary elements owned by Optum and, therefore, cannot be broadly disclosed or made publicly available at this time. The disclosure of this data to third party clients assumes certain data security and privacy protocols are in place and that the third party client has executed our standard license agreement, which includes restrictive covenants governing the use of the data.

Ethical Statement

Institutional review board approval or waiver of approval was not required for this study, because the study data were secondary and deidentified in accordance with the United States Department of Health and Human Services Privacy Rule's requirements for deidentification codified at 45 C.F.R. § 164.514(b).

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, and 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 submitted; 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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Disclosure

CN, DC, MF, HM, JAA, and HDG are employees of AstraZeneca and may hold stocks/shares. PSV and TLB are employees of Optum Life Sciences. MCM reports NIH funding; royalties or licenses from UpToDate for authorship and editorial work for pulmonary function testing; consulting fees from Aridis, Boehringer Ingelheim, GlaxoSmithKline, MGC Diagnostics, and ndd Medical Technologies; and payment or honoraria from Talem Health for medical education for asthma and COPD. The authors report no other conflicts of interest in this work.

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