



# Patient and Clinical Demographics of New Users to Single-Inhaler Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease

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## ABSTRACT

**Introduction:** Single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy was approved by the United States Food and Drug Administration in 2017 as a maintenance therapy for chronic obstructive pulmonary disease (COPD). Patient characteristics and treatment patterns prior to initiating FF/UMEC/VI are currently unknown. This study assessed patient characteristics, exacerbation, and medication history in patients with COPD

before the initiation of FF/UMEC/VI or multiple-inhaler triple therapy (MITT).

**Methods:** This was a retrospective study using the Optum Clinformatics® Data Mart. Patients who initiated FF/UMEC/VI triple therapy or MITT (consisting of a long-acting muscarinic antagonist [LAMA], long-acting  $\beta$ 2-agonist [LABA], and inhaled corticosteroid [ICS]) between October 2017 and September 2018, were enrolled in commercial or Medicare Advantage Prescription Drug plans, were aged > 40 years, and had a COPD diagnosis were eligible. Patient characteristics, comorbidities, COPD medication use, exacerbations, and eosinophil counts were assessed in the 12-month baseline period prior to initiation of FF/UMEC/VI triple therapy or MITT.

**Results:** The study population included 3933 FF/UMEC/VI users and 18,244 MITT users. Mean (standard deviation) patient age was 72.2 (8.6) years in FF/UMEC/VI users and 70.7 (9.7) years in MITT users. Prior to initiating triple therapy, the majority of FF/UMEC/VI (89.1%) and MITT (93.8%) users experienced a moderate or severe exacerbation or used a COPD maintenance therapy during the baseline period. In addition, 41.2% of FF/UMEC/VI users received overlapping ICS/LAMA/LABA, 20.3% received ICS/LABA, and 9.7% received LAMA/LABA.

**Conclusion:** In this population of COPD patients, triple therapy was frequently initiated after previous maintenance medication use or

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an exacerbation, in line with treatment guideline recommendations.

**Keywords:** Chronic obstructive pulmonary disease; Exacerbation; Real-world data; Single-inhaler triple therapy; Treatment patterns; Triple therapy

### Key Summary Points

#### *Why carry out this study?*

Triple therapy is recommended for patients with chronic obstructive pulmonary disease (COPD), who remain symptomatic or at risk of exacerbation despite dual therapy. Until recently, triple therapy was delivered via multiple inhalers; in 2017, single-inhaler triple therapy (SITT) with fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) was approved for the long-term maintenance treatment of patients with moderate-to-severe COPD in the United States.

The baseline demographic and clinical characteristics of patients initiating multiple-inhaler triple therapy have previously been assessed; however, the characteristics of patients initiating SITT remain unknown.

This study aimed to assess the characteristics of patients initiating SITT with FF/UMEC/VI.

#### *What was learned from the study?*

The results of this study suggest that SITT with FF/UMEC/VI is frequently initiated as a step-up treatment in patients with COPD who have persistent symptoms or a history of exacerbations, despite dual maintenance therapy.

The results of this study suggest that SITT with FF/UMEC/VI is used most often in accordance with treatment guidelines from the Global Initiative for Chronic Obstructive Lung Disease.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition that is characterized by chronic inflammation of the airways and persistent airflow limitation [1]. COPD symptoms include dyspnea, wheezing, chronic cough, sputum production, and limited exercise capacity [1, 2]. COPD symptoms progressively worsen over time and have a negative impact on patient quality of life and disease prognosis [2]. Many patients with COPD also suffer from comorbidities, which can complicate disease management and contribute to morbidity and mortality [3, 4]. Comorbidities frequently found among COPD patients include cardiovascular disease, osteoporosis, arthritis, asthma, diabetes/metabolic syndrome, and depression [3–5].

COPD was reported to affect 6.4% of adults in the US in 2013, which corresponds to approximately 15.7 million cases [6]. In 2018, chronic lower respiratory diseases (including COPD) were the fourth most common cause of death in the US, following heart disease, cancer, and unintentional injuries [7]. The annual economic burden of COPD in the US was estimated to be US\$50 billion in 2010 [8]. This figure includes direct costs relating to COPD diagnosis, treatment, and hospitalization, and indirect costs (for example, missed days of work) resulting from disease morbidity and mortality [8]. COPD therefore represents a major public health challenge in the US.

Although COPD is an incurable and irreversible disease, pharmacological treatments are used to manage symptoms, reduce the frequency and severity of exacerbations, increase exercise capacity, and improve quality of life [1]. For patients with stable COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend bronchodilator maintenance therapy with an inhaled long-acting  $\beta$ 2-agonist (LABA; e.g., salmeterol, formoterol, or vilanterol) or a long-acting muscarinic antagonist (LAMA; e.g., umeclidinium or tiotropium) [1]. Treatment escalation to dual therapy consisting of LAMA and LABA or LABA plus an inhaled corticosteroid (ICS; e.g.,

fluticasone furoate) is suggested for patients on LABA or LAMA monotherapy who continue to experience exacerbations or have poorly-controlled symptoms. Further treatment escalation to triple therapy with an ICS, LABA, and LAMA is recommended for patients who remain symptomatic or at risk of exacerbations despite the use of dual-therapy regimens [1].

Triple therapy previously involved the use of multiple inhalers. However, in 2017, a once-daily single-inhaler triple therapy (SITT) consisting of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) was approved by the US Food and Drug Administration (FDA) as a long-term maintenance treatment for patients with COPD [9]. The baseline characteristics of COPD patients initiating multiple-inhaler triple therapy (MITT) have previously been assessed [10], however the characteristics of patients who initiate SITT are currently unknown. To determine whether the use of triple therapy for COPD in the US is in accordance with treatment guideline recommendations, this study assesses patient characteristics and exacerbation and medication history in COPD patients prior to initiation of FF/UMEC/VI SITT or MITT.

## METHODS

### Objectives

The primary objective of this study was to describe baseline characteristics of patients with COPD who were new users of FF/UMEC/VI triple therapy. The secondary objective was to describe baseline characteristics in patients who were new users of MITT.

### Study Design

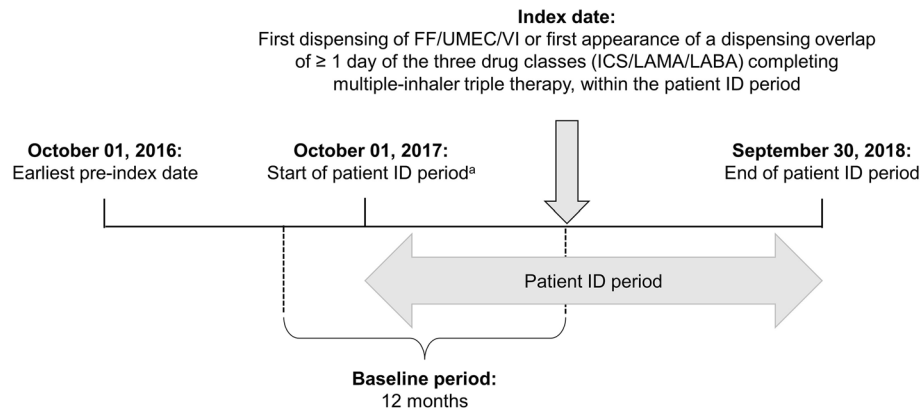
This was a retrospective study of patients enrolled in commercial and Medicare Advantage Prescription Drug (MAPD) plans. The study used Optum's de-identified Clinformatics® Data Mart database, which contains medical and pharmacy healthcare claims, laboratory test results, and linked enrollment information. The analysis included enrollment information and

medical, pharmacy, and laboratory claims data from October 01, 2016 to September 30, 2018.

Ethics committee approval was not required for this study as the results were presented as aggregate analyses that omit patient identification. Patient informed consent was not required as there was no direct patient contact or primary collection of individual patient data. GlaxoSmithKline had permission to access/use the data analyzed in this study through an existing license to the Optum database.

The study design is shown in Fig. 1. Patients were identified between October 01, 2017 and September 30, 2018 (patient identification period). Patients were commercial and MAPD plan enrollees aged > 40 years, with  $\geq 1$  diagnosis code for COPD (International Classification of Disease [ICD]-10-CM: J41-J44) in the previous 12 months. MITT use was defined as a pharmacy dispensing with  $\geq 1$  day overlap for an ICS (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone propionate, fluticasone furoate, mometasone, or triamcinolone), LABA (arformoterol, formoterol, indacaterol, olodaterol, or salmeterol), and LAMA (tiotropium, aclidinium, umeclidinium, or glycopyrrolate), including monotherapies and combination therapies. For patients initiating MITT (MITT users), the index date was defined as the first occurrence of a dispensing overlap of  $\geq 1$  day of an ICS, LABA, and LAMA medicine (considered the initiation of MITT). For patients initiating SITT (FF/UMEC/VI users), the first dispensing date of FF/UMEC/VI was considered the index date. FF/UMEC/VI users could have previously received overlapping ICS, LABA, and LAMA MITT in the 12 months prior to index.

Patients were required to be continually enrolled in the health plan for 12 months prior to the index date; during this 12-month period (baseline period), pre-index characteristics and COPD medication patterns were assessed. The study groups were run independently and were not mutually exclusive. Patients initiating FF/UMEC/VI triple therapy were excluded if they had a dispensing of FF/UMEC/VI in the 12 months prior to index. Patients initiating MITT were excluded if they had a dispensing of an ICS, LABA, and LAMA with  $\geq 1$  day overlap (MITT) in the 12 months prior to index.



**Fig. 1** Study design. *FF* fluticasone furoate, *ICS* inhaled corticosteroid, *ID* identification, *LABA* long-acting  $\beta$ 2-agonist, *LAMA* long-acting muscarinic antagonist, *UMEC* umeclidinium, *VI* vilanterol. <sup>a</sup>FF/UMEC/VI was approved

by the US Food and Drug Administration in September 2017. Patient groups were run in parallel and were not mutually exclusive

## Outcome Measures

The baseline characteristics examined included sociodemographic characteristics, comorbidities, patterns of COPD medication use, exacerbation history, and eosinophil count levels. Patient characteristics included patient age at index year, sex, insurance type, urban/rural area, and US geographic region. Comorbidities were identified using the Clinical Classifications Software managed by the Agency for Healthcare Research and Quality [11]. Separate indicators were created to identify the presence of upper respiratory tract infection, asthma, or pneumonia in the baseline period, based on ICD-9 and ICD-10 diagnosis codes. The Quan-Charlson Comorbidity Index score was calculated based on diagnostic codes in the baseline period and was also categorized into the following groups: 1–2; 3–4;  $\geq 5$ .

COPD medication use in the baseline period was identified by medication class (maintenance or rescue), subclass (ICS, LAMA, LABA, LAMA/LABA, ICS/LABA, ICS/LAMA, ICS/LAMA/LABA, mast cell stabilizers; leukotriene modifiers; methylxanthines; anti-IgE; phosphodiesterase-4 inhibitors; short-acting  $\beta$ -agonists [SABA]; short-acting muscarinic antagonist [SAMA]; SABA/SAMA; and oral systemic corticosteroids), and by individual medication name. For MITT

users, the combination of medications comprising the triple-therapy regimen was also provided by the number of inhalers and medication class.

The number of severe, moderate, and combined moderate and severe exacerbation episodes was determined in the baseline period and used to classify exacerbation history. Exacerbation episodes were defined by COPD-related healthcare visits (exacerbation events). Each episode could consist of single or multiple exacerbation events. An exacerbation episode began on the day of the first exacerbation event and ended when 14 days had passed without any additional events. If another exacerbation event occurred before the episode end date, the episode was extended. The total number of moderate, severe, and combined moderate and severe exacerbation days was determined in the baseline period, inclusive of the start and end days of the episode.

A severe exacerbation event was defined as a COPD-related hospitalization (with a primary COPD diagnosis code or a primary diagnosis code for respiratory failure and secondary COPD diagnosis code). Moderate exacerbation events were defined as a COPD-related emergency department, urgent care, or ambulatory visit (outpatient clinic or physician office) that included treatment with an antibiotic or

systemic corticosteroid (oral or injectable) within 5 days of the visit. Exacerbation episodes that included both moderate and severe events were classified as severe.

Eosinophil values were provided as the first, last, highest, and average results recorded in the baseline period for patients with  $\geq 1$  eosinophil test result. Eosinophil results were provided as counts in cells/ $\mu\text{L}$  and as binary variables ( $< 150$  cells/ $\mu\text{L}$  or  $\geq 150$  cells/ $\mu\text{L}$ ).

### Statistical Analyses

All baseline period variables were analyzed descriptively. Numbers and percentages were provided for dichotomous and polychotomous categorical variables. Mean and standard deviation (SD) were provided for continuous variables.

## RESULTS

In total, 5598 patients initiating FF/UMEC/VI treatment within the patient identification period were identified. After applying the other inclusion and exclusion criteria, a total of 3933 patients remained and were included in the final study population (FF/UMEC/VI users). Overall, 80,201 patients initiating overlapping multiple-inhaler ICS/LAMA/LABA therapy were identified. After the remaining inclusion and exclusion criteria were applied, 18,244 patients were included in the final study population (MITT users).

Patient demographics and clinical characteristics are shown in Table 1. The mean (SD) age of FF/UMEC/VI users was 72.2 (8.6) years and 55.2% were female. The mean (SD) Quan-Charlson Comorbidity Index score was 2.8 (2.0) and 25.4% of patients had concomitant asthma. The mean (SD) age of MITT users was 70.7 (9.7) years and 57.5% were female. The mean (SD) Quan-Charlson Comorbidity Index score was 3.0 (2.1) and 29.4% of patients had concomitant asthma. Aside from respiratory system diseases, the most common comorbidities in both groups were diseases of the circulatory system, endocrine disorders, and mental illnesses (Table 1).

### Medication Use Prior to Initiation of Triple Therapy

The COPD treatments received in the 3 months and 12 months prior to the index date are shown in Fig. 2a and b, respectively. In the 3-month period prior to index, 20.6% of FF/UMEC/VI users received overlapping ICS, LABA, and LAMA therapy and 37.8% received no COPD maintenance medication. Among MITT users, 40.8% received ICS/LABA dual therapy, 7.6% received LAMA/LABA dual therapy, and 22.5% received no COPD medication in the 3 months prior to index. Among FF/UMEC/VI users who experienced an exacerbation in the 12-month baseline period, 23.2% received prior ICS, LABA, and LAMA triple therapy in the 3 months before index, compared with 16.8% of FF/UMEC/VI users who did not have a history of exacerbation (Table 2).

The majority of MITT users (83.9%) started triple therapy using a combined ICS/LABA plus LAMA (Table 3).

### Exacerbation and Maintenance Inhaler History Prior to Initiation of Triple Therapy

During the baseline period, 54.1% of FF/UMEC/VI users and 51.9% of MITT users had at least one moderate and/or severe exacerbation episode (Fig. 3). Among patients who had an exacerbation, the mean (SD) time from the latest exacerbation episode to initiation of triple therapy was 109.3 (95.4) days in FF/UMEC/VI users and 88.2 (95.9) days in MITT users. In total, 11.8% of FF/UMEC/VI users and 10.3% of MITT users experienced both moderate and severe exacerbation episodes during the baseline period.

The majority of FF/UMEC/VI users (89.1%) and MITT users (93.8%) had an exacerbation or used a maintenance therapy during the baseline period (Fig. 4). In total, 46.7% of FF/UMEC/VI users and 45.0% of MITT users had both a history of exacerbation and received maintenance therapy during the baseline period.

**Table 1** Patient demographics and clinical characteristics

	<b>FF/UMEC/VI users (<i>n</i> = 3933)</b>	<b>MITT users (<i>n</i> = 18,244)</b>
Age (years), mean (SD)	72.2 (8.6)	70.7 (9.7)
Age group, <i>n</i> (%)		
40–54 years	111 (2.8)	1008 (5.5)
55–64 years	549 (14)	3592 (19.7)
≥ 65 years	3273 (83.2)	13,644 (74.8)
Sex, <i>n</i> (%)		
Females	2170 (55.2)	10,488 (57.5)
Payer at index, <i>n</i> (%)		
Commercial	139 (3.5)	2496 (13.7)
Commercial/Medicare	1 (0)	11 (0.1)
Medicare	3793 (96.4)	15,737 (86.3)
Quan-Charlson Comorbidity Index score, mean (SD)	2.8 (2)	3 (2.1)
1–2, %	50.7	47.3
3–4, %	31.2	30.9
≥ 5, %	18.1	21.8
Elixhauser Comorbidity Score, mean (SD)	6.1 (3.3)	6.5 (3.6)
Prescriber type, <i>n</i> (%)		
Pulmonologist	1474 (37.2)	3861 (21.2)
Other specialty	2469 (62.8)	14,383 (78.8)
Comorbidities, <i>n</i> (%)		
Asthma	1000 (25.4)	5361 (29.4)
Upper respiratory tract infection	1146 (29.1)	5142 (28.2)
Pneumonia	958 (24.4)	4932 (27)
Most common AHRQ comorbid conditions, <i>n</i> (%)		
Diseases of the respiratory system	3933 (100)	18,244 (100)
Symptoms, signs, and ill-defined conditions and factors influencing health status	3740 (95.1)	17,365 (95.2)
Diseases of the circulatory system	3673 (93.4)	17,020 (93.3)
Endocrine, nutritional, and metabolic diseases and immunity disorders	3685 (93.7)	16,805 (92.1)
Mental illness	3121 (79.4)	14,724 (80.7)

**Table 1** continued

	FF/UMEC/VI users ( <i>n</i> = 3933)	MITT users ( <i>n</i> = 18,244)
Diseases of the musculoskeletal system and connective tissue	3016 (76.7)	14,279 (78.3)

AHRQ Agency for Healthcare Research and Quality, FF fluticasone furoate, MITT multiple-inhaler triple therapy, SD standard deviation, UMEC umeclidinium, VI vilanterol

### Eosinophil Levels Prior to Initiation of Triple Therapy

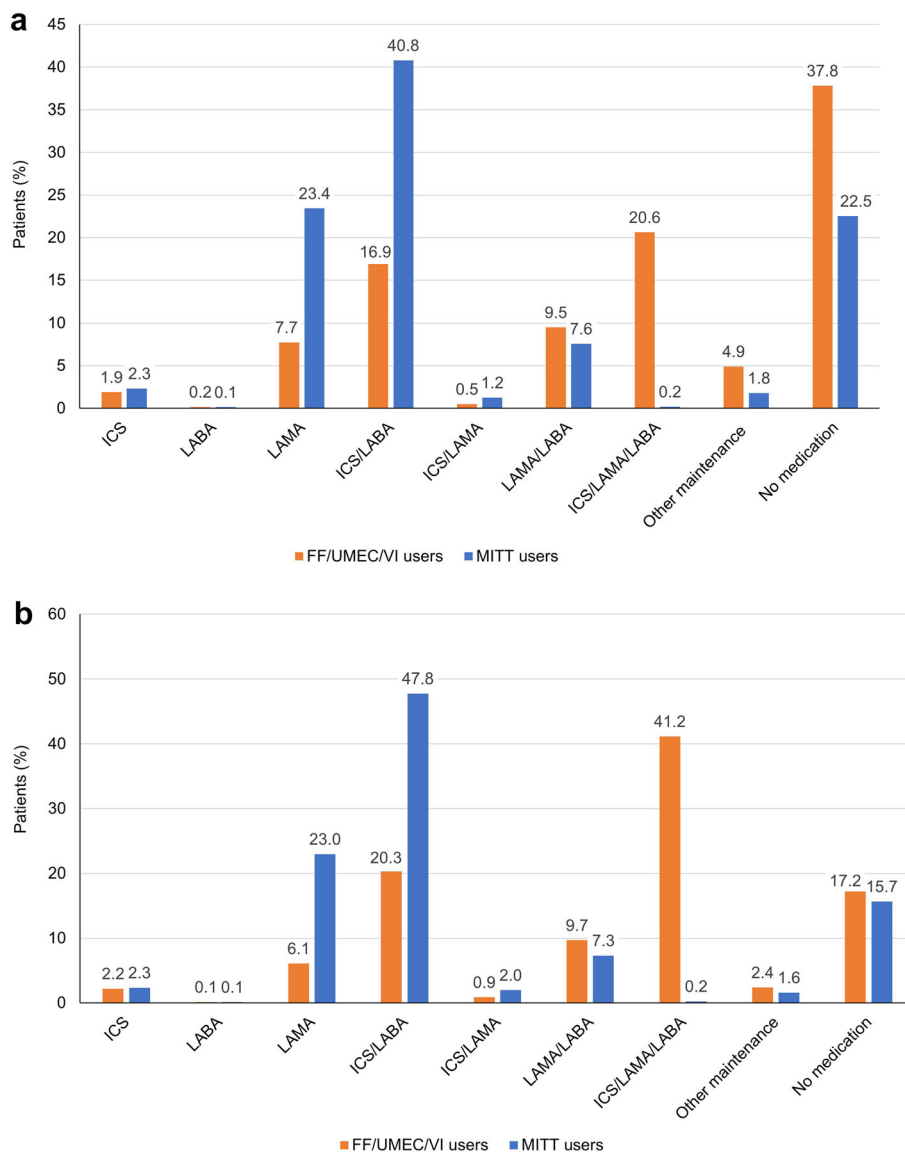
In total, 1401 FF/UMEC/VI users and 5651 MITT users had eosinophil measurements recorded during the baseline period. Among FF/UMEC/VI users, the mean (SD) eosinophil count was 799.6 (17,032.8) cells/ $\mu$ L in the first test and 699.6 (16,559) cells/ $\mu$ L in the last test in the baseline period. In MITT users, the corresponding first and last eosinophil test results were 1267.5 (20,422.6) cells/ $\mu$ L and 592.1 (9777.5) cells/ $\mu$ L, respectively. At the last baseline measurement, 34.5% of FF/UMEC/VI users had eosinophil counts < 150 cells/ $\mu$ L and 65.5% had counts  $\geq$  150 cells/ $\mu$ L. Results were similar in MITT users; 34.9% of patients had counts < 150 cells/ $\mu$ L and 65.1% had counts  $\geq$  150 cells/ $\mu$ L.

## DISCUSSION

This is the first study to assess baseline characteristics, patterns of COPD medication use, and exacerbation history in patients with COPD initiating once-daily FF/UMEC/VI treatment in the US. Our findings indicate that the majority of patients start FF/UMEC/VI triple therapy after receiving previous maintenance therapy, or receiving previous maintenance therapy and experiencing an exacerbation, in line with current GOLD treatment guidelines [1] and treatment recommendations from the COPD Foundation [12]. In the 12 months prior to starting FF/UMEC/VI treatment, approximately 90% of patients had at least one exacerbation or used a maintenance therapy and almost half of patients had both a history of exacerbation and prior maintenance therapy. These findings

suggest that most patients may not have been adequately controlled before initiating triple therapy. In contrast, very few patients (10.9%) started FF/UMEC/VI therapy without a history of exacerbation or previous maintenance therapy. It is possible that these patients switched to triple therapy due to a lack of symptom control, but not at the threshold defined as a moderate or severe exacerbation. Their physician may have opted out of oral steroid treatment and escalated therapy instead. Alternatively, this group of patients could have switched to triple therapy for reasons other than symptom control or exacerbation risk. However, the reasons for treatment decisions were not captured in this study, therefore COPD Assessment Test scores or other patient-reported outcomes would be required to investigate this further.

Similar results were found in patients initiating MITT; the majority of patients (93.8%) had a history of exacerbation or used a maintenance therapy in the previous 12-month period, and only 6.2% started triple therapy without previous maintenance therapy or an exacerbation. Our findings are consistent with another retrospective analysis that examined baseline characteristics of COPD patients prior to the initiation of MITT [10]. This analysis included 13,701 patients enrolled in commercial or MAPD health plans, who had a COPD diagnosis and at least one prescription for a COPD medication between January 2014 and March 2016. This analysis reported that 90.4% of patients started MITT after having an exacerbation or receiving prior maintenance therapy. In total, 81% of patients escalated to triple therapy from LAMA, LABA, ICS/LABA, or LAMA/LABA, and 59.8% of patients had at least one exacerbation prior to initiating MITT [10].



**Fig. 2** COPD maintenance medication use in the **a** 3 months and **b** 12 months prior to the index date. COPD chronic obstructive pulmonary disease, FF fluticasone furoate, ICS inhaled corticosteroid, LABA long-acting

$\beta_2$ -agonist, LAMA long-acting muscarinic antagonist, MITT multiple-inhaler triple therapy, UMEC umeclidinium, VI vilanterol

Only 9.6% of patients started MITT without a history of exacerbation or maintenance therapy, similar to the proportion reported in the current study. Results from our study also revealed that the most frequently prescribed triple therapy among new MITT users was combined ICS/LABA plus LAMA, in line with the previous analysis [10].

The results from this analysis suggest that triple therapy in COPD appears to be used most often as a step up from maintenance therapy or from an event that necessitates further treatment. Current treatment recommendations suggest escalation to ICS/LAMA/LABA triple therapy in patients who have persistent symptoms and/or exacerbations despite treatment



**Table 2** COPD maintenance medications used in the 3 months prior to index by exacerbation status

	FF/UMEC/VI users ( <i>n</i> = 3933)		MITT users ( <i>n</i> = 18,244)	
	≥ 1 exacerbation <sup>a</sup> <i>n</i> (%)	No exacerbation <sup>a</sup> <i>n</i> (%)	≥ 1 exacerbation <sup>a</sup> <i>n</i> (%)	No exacerbation <sup>a</sup> <i>n</i> (%)
Overall, <i>n</i>	2126	1807	9468	8776
ICS	38 (1.8)	35 (1.9)	219 (2.3)	167 (1.9)
LABA	4 (0.2)	2 (0.1)	15 (0.2)	6 (0.1)
LAMA	171 (8.0)	128 (7.1)	1966 (20.8)	1934 (22.0)
ICS/LABA <sup>b</sup>	359 (16.9)	294 (16.3)	3455 (36.5)	3332 (38.0)
ICS/LAMA <sup>b</sup>	13 (0.6)	6 (0.3)	111 (1.2)	97 (1.1)
LAMA/LABA <sup>b</sup>	209 (9.8)	158 (8.7)	665 (7.0)	596 (6.8)
ICS/LAMA/LABA <sup>c</sup>	494 (23.2)	303 (16.8)	16 (0.2)	14 (0.2)
Other maintenance therapy	110 (5.2)	80 (4.4)	168 (1.8)	130 (1.5)
No medication	684 (32.2)	777 (43.0)	1953 (20.6)	1798 (20.5)

COPD chronic obstructive pulmonary disease, FF fluticasone furoate, ICS inhaled corticosteroid, LABA long-acting  $\beta$ 2-agonist, LAMA long-acting muscarinic antagonist, MITT multiple-inhaler triple therapy, UMEC umeclidinium, VI vilanterol

<sup>a</sup>Exacerbation history was determined by the number of exacerbation episodes in the 12-month pre-index period

<sup>b</sup>Medications with a slash (/) indicate combinations, which may be administered via single or multiple devices

<sup>c</sup>Administered via multiple devices

**Table 3** Triple therapy medications at index

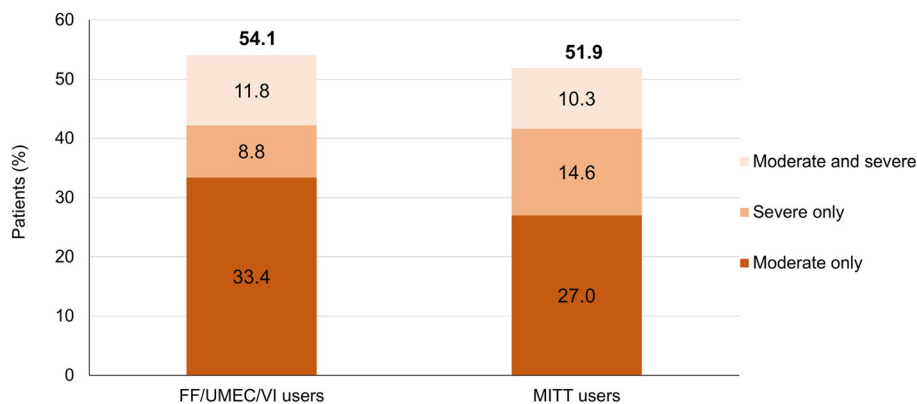
Medication <sup>a</sup>	FF/UMEC/VI users <i>n</i> , %	MITT users <i>n</i> , %
Overall, <i>n</i>	3933 (100)	18,244 (100)
ICS/LABA + LAMA <sup>b</sup>	1 (0.0)	15,298 (83.9)
ICS + LABA + LAMA <sup>b</sup>	0 (0.0)	161 (0.9)
ICS + LAMA/LABA <sup>b</sup>	0 (0.0)	1362 (7.5)
ICS/LABA + LAMA/LABA <sup>b,c</sup>	1 (0.0)	1567 (8.6)
ICS/LAMA/LABA (FF/UMEC/VI) <sup>b</sup>	3933 (100.0)	3 (0.0)

FF fluticasone furoate, ICS inhaled corticosteroid, LABA long-acting  $\beta$ 2-agonist, LAMA long-acting muscarinic antagonist, MITT multiple-inhaler triple therapy, UMEC umeclidinium, VI vilanterol

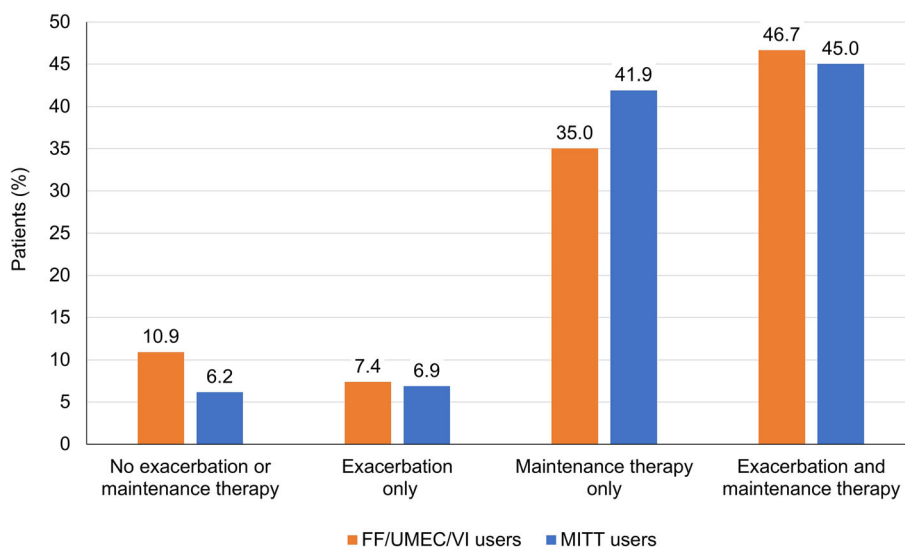
<sup>a</sup>Medication categories are non-mutually exclusive

<sup>b</sup>Classifications with a slash (/) indicate combination medications, a plus (+) indicates simultaneous dispensing medications

<sup>c</sup>Concomitant treatment with ICS/LABA and LAMA/LABA is not advised by current Global Initiative for Chronic Obstructive Lung Disease guidelines



**Fig. 3** Exacerbation history during the 12-month baseline period. *FF* fluticasone furoate, *MITT* multiple-inhaler triple therapy, *UMEC* umeclidinium, *VI* vilanterol



**Fig. 4** Exacerbation and maintenance therapy history during the 12-month baseline period. *FF* fluticasone furoate, *MITT* multiple-inhaler triple therapy, *UMEC* umeclidinium, *VI* vilanterol

with dual-therapy regimens. However, it should also be noted that 37.8% of FF/UMEC/VI users and 22.5% of MITT users did not have a prescription for an ICS, LABA, or LAMA in the 3 months prior to starting triple therapy. In addition, a fifth of FF/UMEC/VI users and almost half of MITT users received ICS/LABA in the 12 months prior to index. Although GOLD guidelines recommend that ICS treatment should be reserved for exacerbating COPD patients, this finding is congruent with previous reports of ICS overutilization [13]. Of note, the average patient age observed in the current

study was 72.2 and 70.7 years for the FF/UMEC/VI and MITT initiators, respectively; potential longer disease duration may have influenced the decision for escalation to triple therapy. Also, the proportion of patients with comorbid conditions was very high in both cohorts, which again may have been a factor in the decision to prescribe triple therapy.

Several recent studies and systematic reviews have demonstrated the efficacy of SITT to provide symptom control, reduce rates of moderate/severe exacerbations, and improve quality of life in patients with moderate-to-severe

COPD [14–18]. In the IMPACT (Informing the Pathway of COPD Treatment) study, over 10,000 symptomatic COPD patients were randomized to FF/UMEC/VI SITT, LAMA/LABA dual therapy (UMEC/VI), or ICS/LABA dual therapy (FF/VI). Over 52 weeks, FF/UMEC/VI SITT significantly decreased the rate of moderate or severe exacerbations, improved lung function, and increased health-related quality of life scores compared with dual-therapy regimens. In addition, patients who received FF/UMEC/VI triple therapy had significantly fewer COPD-related hospitalizations than UMEC/VI-treated patients [16]. A recent systematic review included six randomized controlled trials that assessed SITT and in a collective total of 19,658 patients with COPD. SITT was found to reduce the annual rate of moderate or severe exacerbations by 15% to 52% compared with LAMA/LABA therapy and by 15% to 35% compared with ICS/LABA therapy [14].

Patients receiving SITT have been found to have significantly higher medication adherence and be more likely to persist with their therapy compared with patients receiving MITT [19, 20]. A complicated dosing regimen (i.e., varying frequencies of administration and/or different inhalation techniques between devices) is linked to the low adherence and persistence observed with MITT [21, 22]. Poor adherence to maintenance therapy is also associated with higher healthcare resource utilization rates and costs among patients with COPD [23–25]. SITT with FF/UMEC/VI was shown to result in greater improvements in trough and serial FEV<sub>1</sub> compared with MITT with budesonide/formoterol and tiotropium [26]. A recent real-world evidence study demonstrated the clinical benefits of SITT with FF/UMEC/VI compared with MITT, with patients receiving SITT having greater improvements in lung function and quality of life compared with patients receiving MITT [27].

Following the approval of once-daily FF/UMEC/VI SITT by the US FDA in 2017 [9], the results from our study provide valuable information on patient baseline characteristics and treatment patterns in new users of FF/UMEC/VI in a real-life clinical practice setting. Our findings suggest that triple therapy is most

often initiated in patients who require additional control, either as step up from previous maintenance therapy or due to an exacerbation.

This study has several strengths that should be mentioned, including the use of real-world data from a large and geographically diverse US dataset. The data are reflective of real-world prescribing behavior and therefore validate the latest recommendations for COPD management. One further strength of the study is the inclusion of patients managed by both commercial and MAPD plans.

Our analysis has a number of limitations that should be taken into consideration. Firstly, only patients with continuous use of the health system were included, and therefore patients without continuous membership during the period of evaluation were not included. A potential limitation of the longitudinal data collection should also be mentioned; patients may have received triple therapy before the start of the 12-month baseline period, which would not have been captured in the study. In addition, FF/UMEC/VI users may have previously received MITT prior to index, whereas patients switching from one MITT regimen to another were excluded from the analysis, leading to a potential imbalance of patient types between treatment arms. Furthermore, patient adherence to prescribed medications could not be verified, and the presence of a dispensed medication does not mean that the medication was taken or used as prescribed. For example, a patient who filled prescriptions for the medications that define MITT may not have used all the medications at the same time. Additionally, medications given as samples by the treating physician were not included in the pharmacy data used in the analysis. The inclusion of a diagnosis code on a medical claim may not always confirm the presence of disease; it is possible that, in some cases, the diagnosis code may have been incorrectly coded or included as rule-out criteria rather than a current disease. The results and conclusions from the current analysis may therefore be limited to the patient population studied and may not be generalizable to other commercially insured populations in the US or to other patient populations.

## CONCLUSIONS

The results from our study provide insights into patient characteristics, treatment patterns, and exacerbation history of patients with COPD prior to initiation of FF/UMEC/VI SITT. The majority of new users to FF/UMEC/VI SITT and MITT had a history of an exacerbation or maintenance medication. This suggests that triple therapy is used most often in accordance with treatment guideline recommendations, as a step-up treatment in patients who have persistent symptoms and/or exacerbations, despite maintenance treatment with dual therapy.

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**Data Availability.** The data analyzed in this manuscript are contained in a database owned by Optum Clinformatics<sup>®</sup>, and therefore are not publicly available. Access to the data may be available on license from Optum (optum.com/life-sciences-solutions).

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