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ORIGINAL RESEARCH

Characteristics of New Users of Single- and Multiple-Inhaler Triple Therapy for COPD in Primary Care in England

Kieran J Rothnie[1], Sandra Joksaite[1], Leah B Sansbury[2], Chris Compton[3], Valentina Di Boscio[4], Afisi S Ismaila[5,6]

[1]Value Evidence and Outcomes, R&D Global Medical, GlaxoSmithKline, London, UK; [2]Value Evidence and Outcomes, R&D Global Medical, GlaxoSmithKline, Research Triangle Park, NC, USA; [3]Global Medical Affairs, GlaxoSmithKline, Middlesex, UK; [4]Global Medical Affairs, GlaxoSmithKline, Ealing, UK; [5]Value Evidence and Outcomes, R&D Global Medical, GlaxoSmithKline, Collegeville, PA, USA; [6]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada

Correspondence: Kieran J Rothnie, Value Evidence and Outcomes, R&D Global Medical, GlaxoSmithKline, London, UK, Tel +44 208 990 3439, Email kieran.j.rothnie@gsk.com

Purpose: Inhaled triple therapy is recommended for patients with chronic obstructive pulmonary disease (COPD) who have poorly controlled symptoms and to reduce the risk of exacerbations. This study assessed the clinical characteristics of new users of single- and multiple-inhaler triple therapy (SITT and MITT) treated in a primary care setting in England.

Patients and Methods: This cross-sectional, observational study used data from an electronic health record database (CPRD Aurum) of COPD patients registered with a primary care practice in England, with linkage to a secondary care database. Patients were required to have initiated a new triple therapy (index) between November 2017 and November 2018 and have ≥12 months of available medical history prior to the index date.

Results: In total, 3536 patients initiated fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) SITT for the first time: 65% had a Medical Research Council (MRC) dyspnea score ≥3, 45% had forced expiratory volume in 1 second (FEV_1)% predicted <50%, and 64% had a moderate or severe exacerbation in the previous 12 months. The majority (83%) of new FF/UMEC/VI users had a history of MITT use. Immediately prior to FF/UMEC/VI initiation, 46% received MITT, 25% received an inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA), 12% received long-acting muscarinic antagonist (LAMA)/LABA, and 14% stepped up directly from LAMA monotherapy. A second cohort of 6540 patients initiated triple therapy (SITT or MITT) for the first time. COPD severity (airflow limitation, exacerbation history) was worse among patients initiating SITT versus MITT. In the 12 months before triple-therapy initiation, ICS/LABA was the most common treatment; a step up from LAMA/LABA was more common among patients initiating FF/UMEC/VI (34%) or beclomethasone/formoterol/glycopyrronium bromide SITT (25%) than MITT (14%).

Conclusion: First-time triple therapy was frequently initiated in patients with COPD inadequately controlled on maintenance therapy. General practitioners in England generally identify appropriate patients who require initiation of triple therapy.

Keywords: chronic obstructive pulmonary disease, multiple-inhaler triple therapy, patient characteristics, single-inhaler triple therapy, triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease, characterized by persistent airflow limitation and increased breathlessness. COPD is a leading cause of morbidity and mortality, and is the third most common cause of death worldwide.[1] The current mainstay pharmacological treatment for COPD includes short- and long-acting muscarinic antagonists (SAMA or LAMA) and short- and long-acting β_2-agonists (SABA or LABA), with the addition of inhaled corticosteroids (ICS) for more severe disease associated with recurrent exacerbations, in order to reduce their frequency.[2] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides treatment

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guidelines for the management of COPD, recommending an incremental approach involving a combination of different drug classes as the disease state worsens.[2]

For patients with COPD whose symptoms remain poorly controlled, inhaled triple therapy is recommended to help reduce symptoms, improve health status, and reduce the risk and frequency of moderate/severe exacerbations.[2] Triple therapy may involve a patient being prescribed multiple inhalers including ICS/LABA+LAMA, LAMA/LABA+ICS, or ICS+LAMA+LABA. A previous study investigating the baseline characteristics of new initiators of multiple-inhaler triple therapy (MITT) in the United Kingdom (UK) found that just over half of patients initiated triple therapy following ICS/LABA therapy, and approximately one third following LAMA monotherapy.[3] Of the new MITT initiators, 41% had a recorded forced expiratory volume in 1 second (FEV_1) <50% and 58% had at least one moderate/severe acute exacerbation of COPD (AECOPD) in the 12 months prior to MITT initiation.

Single-inhaler triple therapy (SITT) with fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) was approved by the European Medicines Agency (EMA) for use in the UK in November 2017, as the first once-daily maintenance treatment for COPD.[4] Two other SITTs are approved for use in the UK: beclomethasone/formoterol/glycopyrronium bromide (BEC/FOR/GLY) was approved in 2017[5] and formoterol/glycopyrronium bromide/budesonide in 2020,[6] both of which require twice-daily dosing. The clinical efficacy of FF/UMEC/VI has been previously demonstrated.[7,8] Compared with MITT, SITT has the advantage of a simpler dosing regimen, which can help reduce medication errors and potentially improve adherence.[9,10] In addition, the INTREPID study recently demonstrated that patients treated with FF/UMEC/VI had a higher likelihood of achieving a clinically relevant improvement in health status, as assessed by the COPD Assessment Test, than those treated with MITT.[11]

A recent study was conducted in the United States to assess patient characteristics of new initiators of FF/UMEC/VI and MITT[12]; however, there are currently limited data on the clinical and demographic characteristics of new initiators of FF/UMEC/VI in the UK.[13] It is also unknown if the characteristics of MITT users have changed since the emergence of SITT. This study aimed to assess the characteristics of new users of FF/UMEC/VI, BEC/FOR/GLY, or MITT, treated in a primary care setting in England.

Materials and Methods

Study Design and Objectives

This cross-sectional, observational study used data from the UK Clinical Practice Research Datalink (CPRD) Aurum, an electronic health record database of anonymized, longitudinal medical records of patients registered with a contributing primary care practice in the UK.[14] CPRD Aurum contains patient registration information and all care events recorded by general practice staff including demographics, medical diagnoses, referrals to specialists, prescriptions, diagnostic testing, and lifestyle information.

CPRD Aurum is linked to the Hospital Episode Statistics (HES) secondary care database, which includes data for a subset of patients registered with participating primary care practices in England only.[15] HES contains information on all inpatient admissions as well as outpatient appointments and accident and emergency attendances at National Health Service (NHS) hospitals in England.

The overall study design is shown in Figure S1. The first objective of the study was to describe the sociodemographic and clinical characteristics of COPD patients who initiated FF/UMEC/VI (index date) for the first time between November 2017 and November 2018 (ie new users of FF/UMEC/VI, irrespective of prior MITT use). The second objective was to describe the characteristics of patients who initiated any inhaled triple therapy for the first time (index date) between November 2017 and November 2018 (ie new first-time users of any triple therapy, with no prior use of any other triple therapy). For this objective, patients with previous use of inhaled triple therapy within 12 months prior to the index date were excluded.

Inhaled triple therapies were defined as SITT (FF/UMEC/VI or BEC/FOR/GLY), as well as MITT. MITT included LAMA combined with a fixed-dose ICS/LABA (administered via two devices), LAMA/LABA combined with an ICS (administered via two devices), or ICS, LABA, and LAMA (administered via three devices).

The index date was the date on which a patient initiated triple therapy. The date of FF/UMEC/VI or BEC/FOR/GLY initiation was defined as the first prescription date of that treatment. The index date for initiation of MITT was defined as the first date of overlapping ICS, LABA, and LAMA therapy. Patients were not followed up after the index date. The study was approved by the CPRD's Independent Scientific Advisory Committee (ISAC protocol number: 19_228).

Study Population

Patients in England were eligible for the study if they were ≥35 years old and had a diagnosis of COPD recorded in CPRD Aurum, with records linked to HES data. Patients were required to have initiated triple therapy (either FF/UMEC/VI, BEC/FOR/GLY, or MITT) for the first time between November 2017 and November 2018. In addition, eligible patients had FEV_1/forced vital capacity <0.7 recorded at any point in their medical history (to confirm COPD diagnosis) and at least 12 months of medical history recorded in CPRD Aurum prior to the index date.

Patients with a recorded code for a medical condition incompatible with COPD diagnosis at any time in their medical history were excluded (this included conditions relating to the lung or bronchial developmental anomalies, degenerative processes, pulmonary resection, or another significant respiratory disorder).

Outcome Variables

The sociodemographic and clinical characteristics assessed included age at the index date, sex, body mass index, smoking status, comorbidities, and asthma diagnosis. Patients were classified (separately for each comorbidity) as having a history of the following comorbidities, if recorded in their CPRD medical history at any time preceding the index date: depression, anxiety, gastroesophageal reflux disease, acute myocardial infarction, congestive heart failure, stroke, bronchiectasis, dementia/cognitive impairment, and rheumatoid/osteoarthritis. Asthma diagnosis was confirmed by the presence of an asthma code in the patients' medical history, using a code list validated by case-note review. A current asthma diagnosis was defined as a diagnosis record in the CPRD within the 24 months prior to the index date; a historical asthma diagnosis was recorded any time in the patients' medical history prior to the index date. Further details on the demographic and comorbidity variables captured in the study are provided in Table S1.

The clinical characteristics of COPD analyzed included Medical Research Council (MRC) dyspnea scale, GOLD grade of airflow limitation, and GOLD stage,[16] with the most recent measurement in the 24 months prior to the index date used. Moderate and severe AECOPDs in the 12 months prior to, and including, the index date were identified from the CPRD Aurum and HES admitted patient care (APC) records based on an algorithm validated against patient notes by two respiratory physicians, involving 8258 potential events and 988 patients.[17] This algorithm had very good accuracy, with a positive predictive value of over 85%. The sensitivity of the algorithm is lower as a result of underestimating exacerbations; it is therefore likely that patients in this study had more exacerbations than were reported. AECOPDs managed in primary care were defined as a record for one of the following: (1) prescription for an antibiotic and oral corticosteroid (5–14 days each); (2) respiratory symptoms (increase in two or more of the following: breathlessness, cough, or sputum volume, and/or purulence recorded on the same date) with prescription for an antibiotic or oral corticosteroid (or both) on the same date; (3) lower respiratory tract infection; and (4) AECOPD-specific medical code.[17] HES data were used to identify AECOPDs that were associated with a hospitalization through the use of International Classification of Diseases (ICD)-10 codes based on a previously validated method.[18] AECOPDs resulting in hospitalization were considered as severe (ie recorded in HES-APC and/or CPRD Aurum), while those managed only in primary care (ie only recorded in CPRD Aurum) were defined as moderate.

Healthcare resource utilization variables included a number of primary and secondary care consultations in the 12 months prior to the index date. Prior COPD maintenance therapy immediately before initiation of triple therapy was recorded, up to 12 months prior to the index date. Blood eosinophil levels in the 12 months prior to the index date, using the record closest to the index date, were captured. Further details on the COPD characteristics captured in the study are provided in Table S2.

Statistical Analyses

Two analytical cohorts were created to address the study objectives. The first cohort included all new users of FF/UMEC/VI on the index date (ie FF/UMEC/VI new users with or without prior use of MITT). The cohort for the second objective comprised new triple-therapy users who initiated triple therapy for the first time on the index date; this included first-time users of FF/UMEC/VI, BEC/FOR/GLY, and MITT, and excluded patients who had received any previous triple therapy (any time in the patients' history as recorded in electronic health record data, and a minimum of 12 months prior to the index date). Analyses were conducted for the overall cohort of new triple-therapy users and stratified by FF/UMEC/VI, BEC/FOR/GLY, and MITT users.

All analyses were descriptive. Demographic characteristics, disease burden, prior COPD treatment use, and healthcare resource utilization were described with count and percentage for categorical variables and mean and standard deviation (SD) for continuous variables. Eosinophil levels were described by geometric mean and SD.

Results

The total cohort of COPD patients initiating FF/UMEC/VI for the first time during the study period (FF/UMEC/VI new users, with or without prior MITT) included 3536 patients. Of these, 610 (17.3%) were first-time triple-therapy users (no prior MITT), and 2926 (82.7%) had previously received MITT. Patient attrition for this cohort is outlined in Figure 1A.

The cohort of patients who initiated triple therapy for the first time (FF/UMEC/VI, BEC/FOR/GLY, or MITT with no prior triple-therapy use) during the study period included 6540 patients. In addition to the 610 new users of FF/UMEC/VI, there were 702 new users of BEC/FOR/GLY and 5228 new users of MITT. Patient attrition is outlined in Figure 1B.

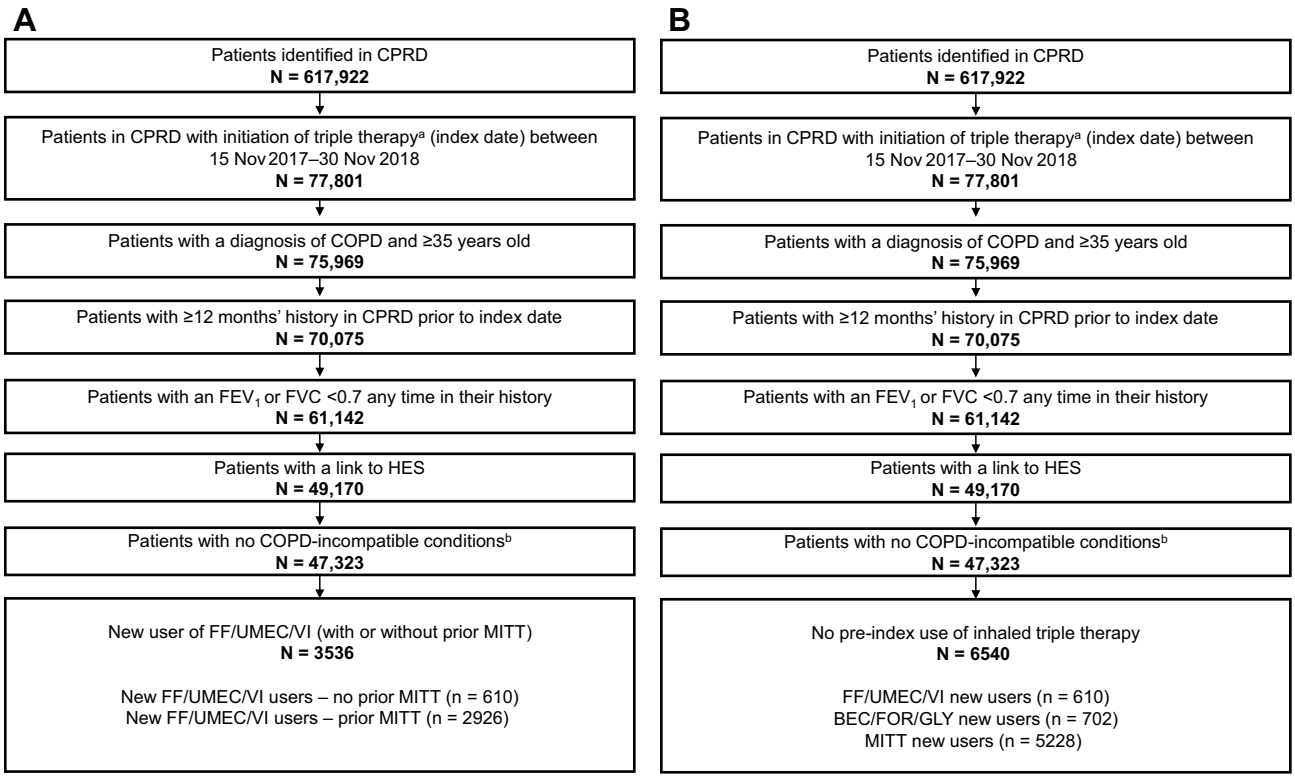

Figure 1 Patient attrition for (**A**) all FF/UMEC/VI users and (**B**) first-time triple-therapy users.

Notes: All FF/UMEC/VI users - objective: to describe the sociodemographic and clinical characteristics of COPD patients who initiate FF/UMEC/VI for the first time (regardless of prior triple-therapy use). First-time triple-therapy users - objective: to describe the sociodemographic and clinical characteristics of COPD patients who initiate inhaled triple therapy for the first time, both overall and stratified by FF/UMEC/VI, BEC/FOR/GLY, or MITT. [a]Including FF/UMEC/VI, BEC/FOR/GLY, or MITT. [b]Including conditions relating to the lung or bronchial developmental anomalies, degenerative processes, pulmonary resection, or other significant respiratory disorders.

Abbreviations: BEC, beclomethasone; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FOR, formoterol; FVC, forced vital capacity; GLY, glycopyrronium bromide; HES, Hospital Episode Statistics; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

FF/UMEC/VI New Users

The patient demographics and clinical characteristics for all FF/UMEC/VI new users (irrespective of prior MITT use) are shown in Table 1. Among the 3536 new users of FF/UMEC/VI, mean patient age was 70.9 years and 1908 (54%) were male. A current asthma diagnosis was recorded in 885 patients (25%). The majority of FF/UMEC/VI new users (99%) had a primary care consultation in the year prior to the index date, with a mean of 12.2 visits. Outpatient attendance for secondary care was recorded in 1609 of the 3536 FF/UMEC/VI new users (46%) in the 3 months prior to the index date, including 564 patients (16%) who attended a respiratory outpatient appointment. Patient characteristics for the FF/UMEC/VI new users with prior MITT use are shown in Table S3.

The proportion of FF/UMEC/VI new users with MRC dyspnea score ≥3 and FEV_1% predicted <50% at their latest assessment prior to the index date is shown in Figure 2A. Among patients with available MRC and FEV_1 data, 65% (2149 of 3330) of all FF/UMEC/VI users had an MRC dyspnea score ≥3 and 44% (1329 of 2975) had FEV_1% predicted <50%. A similar proportion of FF/UMEC/VI users with a history of prior MITT had an MRC dyspnea score ≥3 (67%) and FEV_1% predicted <50% (46%).

The proportion of patients who experienced any moderate or severe AECOPD in the 12 months prior to the initiation of FF/UMEC/VI is shown in Figure 2B. Overall, 2277 of 3536 (64%) patients experienced ≥1 moderate or ≥1 severe AECOPD. In total, 720 patients (20%) had ≥1 severe AECOPD and 204 patients (6%) had ≥1 severe and no moderate AECOPDs. Moderate AECOPDs were experienced by 2073 patients (59%), including 1557 patients (44%) who had only

Table 1 Sociodemographics, Clinical Characteristics, and Healthcare Resource Utilization for All FF/UMEC/VI Users (with and without Prior MITT) and First-Time Triple-Therapy Users by Group

	All FF/UMEC/VI Users N = 3536	First-Time Triple-Therapy Users		
		MITT N = 5228	BEC/FOR/GLY N = 702	FF/UMEC/VI N = 610
Age, mean (SD)	70.9 (10.2)	68.2 (11.0)	70.4 (11.1)	69.7 (11.2)
Male, n (%)	1908 (54)	2745 (53)	368 (52)	365 (60)
Smoking status, n (%)				
Current smoker	1629 (46)	2627 (50)	340 (48)	323 (53)
Ex-smoker	1850 (52)	2411 (46)	350 (50)	278 (46)
Non-smoker	57 (2)	190 (4)	12 (2)	9 (1)
Comorbidities, n (%)				
Current asthma[a]	885 (25)	1752 (34)	167 (24)	154 (25)
Coronary artery bypass graft	93 (3)	114 (2)	21 (3)	19 (3)
Congestive heart failure	310 (9)	321 (6)	61 (9)	47 (8)
Acute myocardial infarction	302 (9)	392 (7)	63 (9)	55 (9)
Stroke	423 (12)	518 (10)	84 (12)	52 (9)
Depression	1598 (45)	2271 (43)	298 (42)	246 (40)
Anxiety	990 (28)	1393 (27)	198 (28)	149 (24)
GERD	744 (21)	949 (18)	121 (17)	118 (19)
Dementia	358 (10)	425 (8)	76 (11)	51 (8)
Rheumatoid/osteoarthritis	1270 (36)	1723 (33)	253 (36)	201 (33)
Bronchiectasis	259 (7)	227 (4)	32 (5)	23 (4)
Eosinophil level prior to index (GI/L), median (IQR)[b]	0.20 (0.1–0.3)	0.20 (0.1–0.3)	0.20 (0.1–0.3)	0.20 (0.1–0.3)
Number of GP attendances in last year, mean (SD)	12.2 (8.7)	11.5 (8.0)	11.6 (7.5)	11.8 (8.2)
Any attendance at secondary-care outpatients in the last 3 months, n (%)	1609 (46)	1866 (36)	272 (39)	196 (32)
Any attendance at secondary-care respiratory outpatients in the last 3 months, n (%)	564 (16)	509 (10)	78 (11)	50 (8)

Notes: [a]Current asthma defined as a diagnosis record in the CPRD within the 24 months prior to index. [b]Latest available assessment to/on index date in the 12 months prior to index.

Abbreviations: BEC, beclomethasone; CPRD, Clinical Practice Research Datalink; FF, fluticasone furoate; FOR, formoterol; GERD, gastroesophageal reflux disease; GLY, glycopyrronium bromide; GP, general practitioner; IQR, interquartile range; MITT, multiple-inhaler triple therapy; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

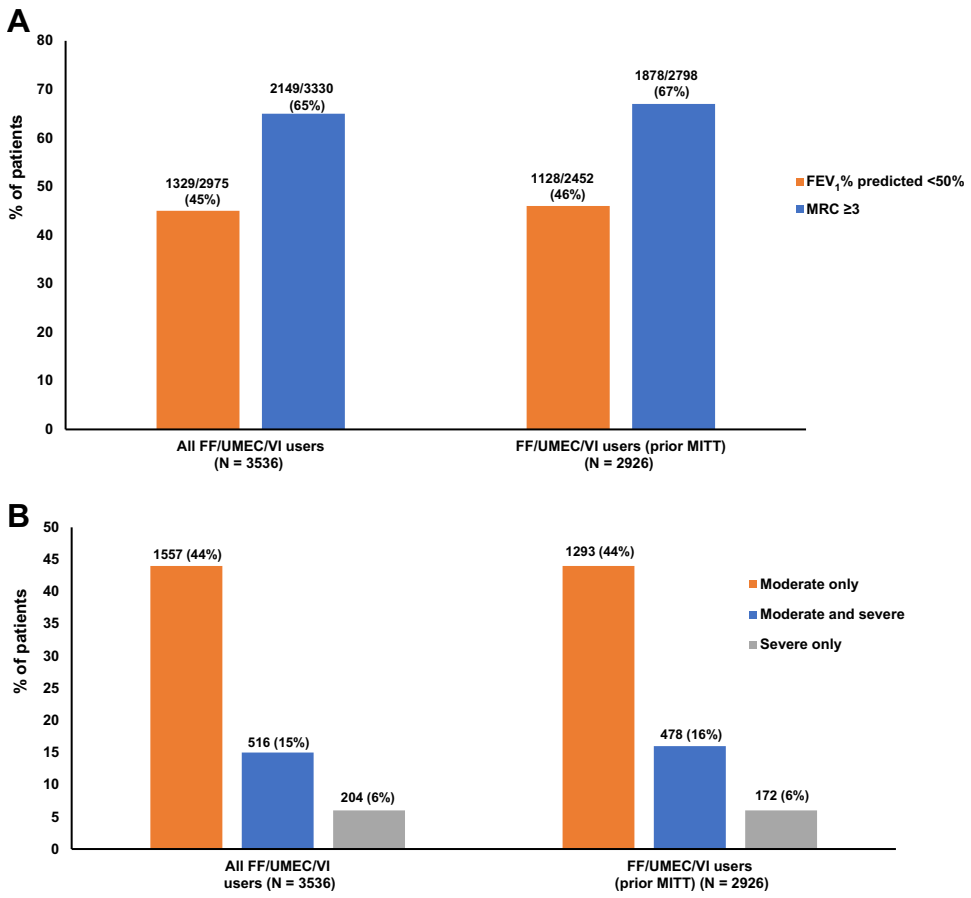

Figure 2 (**A**) Proportion of patients with FEV_1% predicted <50% and MRC dyspnea score ≥3 for all FF/UMEC/VI users, and FF/UMEC/VI (prior MITT) users, and (**B**) patients with ≥1 moderate and/or ≥1 severe AECOPD in the 12 months prior to FF/UMEC/VI initiation for all users of FF/UMEC/VI, and FF/UMEC/VI (prior MITT) users.
Notes: Percentages in panel A are based upon the number of patients with available MRC and FEV_1 data. Moderate and severe AECOPD categories in panel B are not mutually exclusive; patients with both moderate and severe AECOPDs are included in both groups.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; FEV_1%, forced expiratory volume in 1 second as a percentage of forced vital capacity; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; MRC, Medical Research Council; UMEC, umeclidinium; VI, vilanterol.

moderate AECOPDs (with no severe AECOPDs) and 516 patients (15%) who experienced both moderate and severe AECOPDs. One-fifth of patients (720 of the 3536 FF/UMEC/VI users) experienced ≥2 moderate or ≥1 severe AECOPD in the 12 months prior to the index date. A similar pattern of AECOPDs was seen in the FF/UMEC/VI users who had a history of prior MITT use (Figure 2B). Of the FF/UMEC/VI users with prior MITT use, 478 (16%) had both moderate and severe AECOPDs in the previous 12 months, compared with only 38 (6%) of FF/UMEC/VI users without prior MITT use.

Clinical characteristics were compared between FF/UMEC/VI users with comorbid asthma (n = 885; Table S4) and without comorbid asthma (n = 2651; Table S5). No major differences were reported in age, sex, smoking status, or MRC dyspnea score; however, FEV_1% predicted was lower in those without asthma. In addition, the percentage of patients with moderate-to-severe or severe exacerbations in the past year was similar between patients with or without comorbid asthma.

The maintenance treatment received immediately prior to FF/UMEC/VI initiation, for all FF/UMEC/VI users, is shown in Figure 3. In total, 1623 patients (46%) received MITT in the 12 months prior to FF/UMEC/VI initiation. Dual therapy with ICS/LABA or LAMA/LABA was reported in 897 (25%) and 417 (12%) patients, respectively. Initiation of FF/UMEC/VI directly from LAMA monotherapy was recorded in 502 patients (14%). The remaining 97 patients (3%) either did not have a maintenance treatment recorded or were reported as receiving ICS, LABA, or ICS+LAMA in the 12 months prior to the index date. Among the FF/UMEC/VI users with prior MITT use, ICS/LABA, LAMA/LABA, or

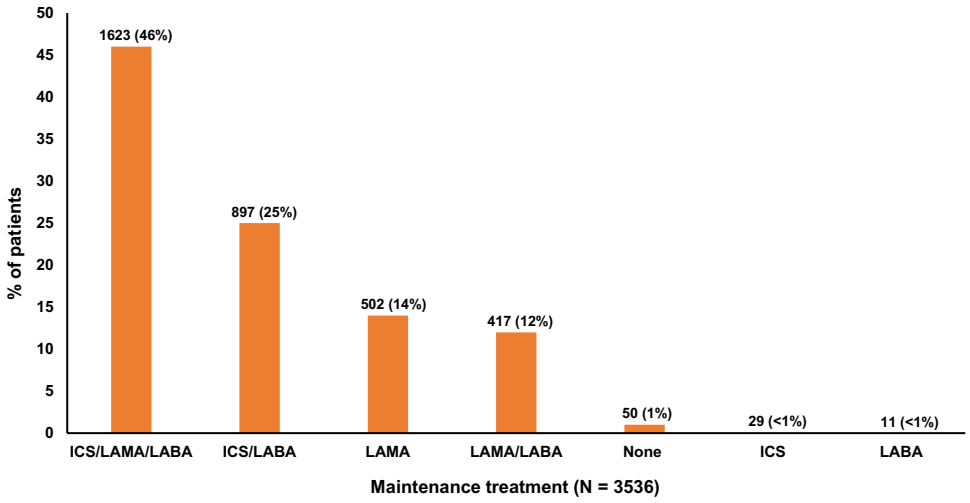

Figure 3 Maintenance treatment immediately prior to initiation of FF/UMEC/VI for all FF/UMEC/VI users.
Notes: Categories are based on the maintenance medication taken on a single day closest to the index date in the 12 months prior to index. "None" indicates that patients did not receive any maintenance therapy in the 12 months prior to initiation of FF/UMEC/VI.
Abbreviations: FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; UMEC, umeclidinium; VI, vilanterol.

LAMA monotherapy in the 12 months prior to FF/UMEC/VI initiation was reported in 645 (22%), 207 (7%), and 422 (14%) patients, respectively.

New Users of Triple Therapy

The patient demographics and clinical characteristics for the 6450 first-time triple-therapy users are shown by group in Table 1. The mean age of the first-time triple-therapy users was 68.6 years and 3478 (53%) were male. In total, 2073 (32%) new users had a concurrent asthma diagnosis, with a higher proportion of patients in the MITT group having current asthma than the BEC/FOR/GLY or FF/UMEC/VI SITT groups. The majority of patients who initiated triple therapy (99%) had a primary care consultation in the year prior to the index date, with a mean of 11.6 visits. Hospital outpatient attendance was recorded in 2334 of the 6540 triple-therapy initiators (36%) in the 3 months prior to the index date, including 637 patients (10%) who attended an outpatient appointment at a respiratory clinic.

Among the patients with a recorded MRC dyspnea score, a higher proportion of FF/UMEC/VI new users had clinically significant breathlessness (MRC score ≥3) compared with MITT new users (271/532 patients [51%] vs 2002/4311 [46%]; Figure 4A). The proportion of patients with an MRC score ≥3 was highest among BEC/FOR/GLY initiators (337/602 patients [56%]). Among patients with recorded FEV_1, the proportion of patients with FEV_1% predicted <50% was higher among FF/UMEC/VI new users compared with MITT new users (201/523 [38%] vs 1453/4548 [32%]; Figure 4B). This proportion was higher still for the BEC/FOR/GLY new users (255/598 [43%]).

The proportion of patients who experienced ≥1 moderate or ≥1 severe AECOPD in the 12 months prior to triple-therapy initiation is shown in Figure 4C. In total, 3377/6540 patients (52%) initiating triple therapy experienced ≥1 moderate or ≥1 severe AECOPD. A slightly higher proportion of patients initiating FF/UMEC/VI (334/610; 55%) had ≥1 moderate or severe AECOPD compared with MITT (2637/5228; 50%). This was slightly higher again for the BEC/FOR/GLY initiators (406/702; 58%). Furthermore, a higher proportion of BEC/FOR/GLY initiators had ≥1 severe AECOPD (118/702; 17%) compared with FF/UMEC/VI (70/610; 11%) and MITT (594/5228; 11%) initiators. The proportion of patients experiencing ≥2 moderate or ≥1 severe AECOPD was also 17% for BEC/FOR/GLY initiators and 11% for both FF/UMEC/VI and MITT initiators.

As above, patient characteristics were compared between first-time triple-therapy users with comorbid asthma (Table S4) and users without comorbid asthma (Table S5). Age, sex, smoking status, and MRC dyspnea score were similar between patients in each treatment group with and without comorbid asthma; however, FEV_1% predicted was lower in those without

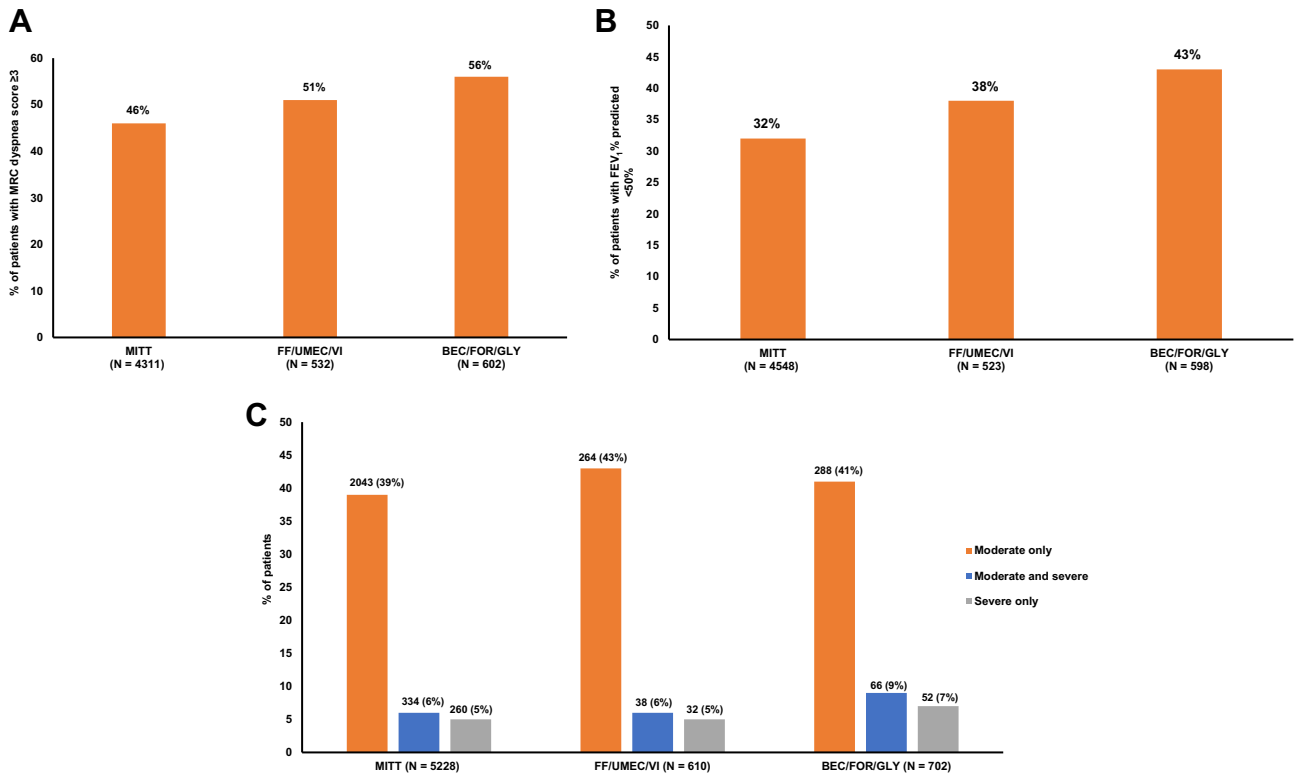

Figure 4 (**A**) Proportion of first-time triple-therapy users with MRC dyspnea score ≥3 by group, (**B**) proportion of first-time triple-therapy users with FEV_1% predicted <50% by group, and (**C**) patients with ≥1 moderate and/or ≥1 severe AECOPD in the 12 months prior to triple-therapy initiation for first-time triple-therapy users.
Note: Percentages in panels A and B are based upon the number of patients with available MRC and FEV_1 data.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BEC, beclomethasone; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FOR, formoterol; GLY, glycopyrronium bromide; MITT, multiple-inhaler triple therapy; MRC, Medical Research Council; UMEC, umeclidinium; VI, vilanterol.

asthma. In addition, no major differences were observed in the proportion of patients experiencing exacerbations between those with and without comorbid asthma.

The maintenance treatment received immediately prior to triple-therapy initiation for the first-time users of triple therapy is shown in Figure 5. A step up from LAMA/LABA was more common among the FF/UMEC/VI new users (210/610; 34%) compared with patients initiating MITT (729/5228; 14%) or BEC/FOR/GLY (175/702; 25%). In total,

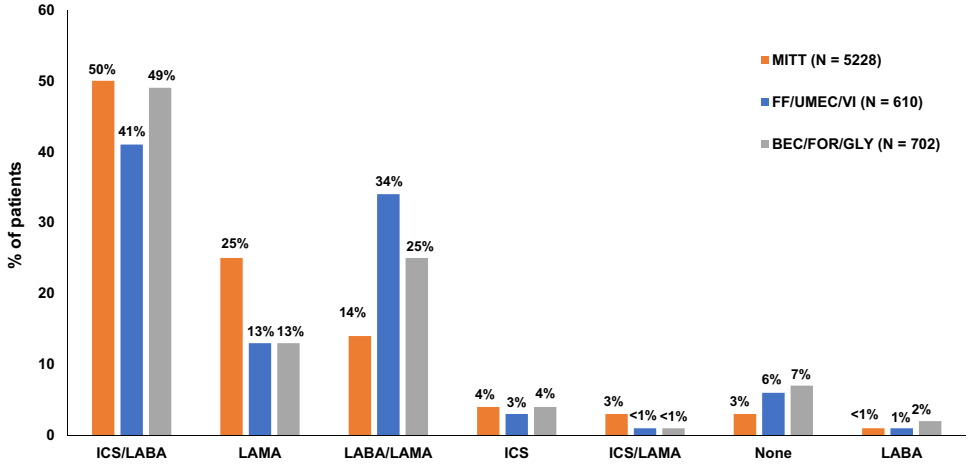

Figure 5 Maintenance treatment immediately prior to initiation of triple therapy for first-time triple-therapy users.
Notes: Categories are based on the maintenance medication taken on a single day closest to the index date in the 12 months prior to index. "None" indicates that patients did not receive any maintenance therapy in the 12 months prior to initiation of triple therapy.
Abbreviations: BEC, beclomethasone; FF, fluticasone furoate; FOR, formoterol; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

260 of the 6540 patients (4%) initiating triple therapy for the first time received no maintenance therapy in the previous 12 months.

Discussion

The purpose of this study was to examine the demographic and clinical characteristics of FF/UMEC/VI users, regardless of prior triple-therapy use, as well as new users of triple therapy (SITT and MITT) in a primary care setting in England.

The results show that in a real-world primary care setting, triple therapy for COPD is frequently initiated after maintenance therapy in patients with a recent exacerbation or a high grade of dyspnea. Our data show that around two-thirds of patients initiating FF/VI/UMEC had clinically significant dyspnea (MRC score ≥3) and had experienced a moderate or severe AECOPD in the 12 months prior to the index date. These symptoms were recorded in around 50% of patients initiating triple therapy for the first time. Many patients appeared to have asthma in addition to COPD, which may have been the reason for initiation of ICS-containing therapy. In the analysis stratifying those with and without comorbid asthma in addition to COPD, we did not find major differences in clinical characteristics between these two groups, with the exception of lower FEV_1% predicted in those without asthma.

Overall, the data support that triple therapy is commonly initiated in patients with COPD inadequately controlled on their current maintenance therapy. Furthermore, few patients (≤16%) had an outpatient appointment at a hospital respiratory clinic recorded within 3 months prior to the index date, indicating that the decision to step up to triple therapy appears to be made in primary care for the majority of patients. The findings on the COPD characteristics associated with triple-therapy initiation are in line with current COPD treatment guidelines,[2] and indicate that general practitioners (GPs) in England are able to appropriately identify the patients who require initiation of triple therapy.

The majority of FF/UMEC/VI users (83%) had previously received MITT, although not always immediately before FF/UMEC/VI initiation. Many patients with a history of MITT use stepped up to FF/UMEC/VI immediately from dual therapy or LAMA monotherapy, suggesting a period of step-down from MITT occurred before the initiation of SITT. Patients initiating FF/UMEC/VI following prior MITT use had more severe COPD compared with those who had not previously received MITT, in terms of airflow limitation (46% vs 38% of patients with FEV_1% predicted <50%, respectively), clinically significant levels of breathlessness (67% vs 51% with MRC score ≥3, respectively), and exacerbation history (16% vs 6% with both moderate and severe AECOPDs in the previous 12 months). Stepping up to triple therapy from dual LAMA/LABA treatment was more common for SITT than for MITT. The severity of COPD (in terms of airflow limitation and exacerbation history) was worse for patients initiating SITT compared with MITT, highlighting an opportunity to address an unmet need in COPD patients with the timely initiation of SITT to prevent worsening of COPD symptoms. It would be interesting to explore patients' compliance with MITT and whether patients found the use of two or three inhalers cumbersome, potentially leading to a step down from MITT to a dual or single therapy that left them at risk of worsening of COPD symptoms. The benefits of SITT compared with MITT have been established in several large-scale clinical trials.[7,8,19] Based on the characteristics of patients receiving triple therapy identified in the current study, patients in the pivotal FF/UMEC/VI trials were closer to those encountered in real-world clinical practice than those in the BEC/FOR/GLY trial, who were required to have ≥1 exacerbation in the previous 12 months and had more severe impairment of airway capacity compared with the FF/UMEC/VI trials.[8,20]

Among the SITT new users, those who initiated BEC/FOR/GLY had more severe COPD in terms of airflow limitation and breathlessness than those who initiated FF/UMEC/VI. The reason for this is unclear; however, Phase III randomized controlled trials for BEC/FOR/GLY registration included only patients with FEV_1% predicted <50%; perhaps the perception of the GPs is that these patients have more severe COPD than patients included in FF/UMEC/VI registration trials, and therefore patients with more severe COPD were more likely to be prescribed BEC/FOR/GLY compared with FF/UMEC/VI. An alternative reason is that patients appear more likely to step up to FF/UMEC/VI from LAMA/LABA compared to ICS/LABA and the reverse for BEC/FOR/GLY. In the UK, ICS/LABA tends to be channelled to sicker patients with more exacerbations and lower FEV_1% predicted.[21] Among the patients who initiated SITT, more patients whose immediate treatment was ICS/LABA were stepped up to BEC/FOR/GLY than to FF/UMEC/VI (and the converse

was true in SITT initiators whose immediate prior treatment was LAMA/LABA). These findings suggest that continuity of device may play a role in treatment decisions for some physicians and patients.

A number of other observational studies have also assessed the characteristics of patients with COPD initiating triple therapy. One large US study characterized patients initiating MITT with ICS/LAMA/LABA in a 2-year period between 2014 and 2016.[22] During a 12-month baseline period, 89% of patients received a short-acting bronchodilator, 50% received ICS/LABA, and only 1% of patients were treated with a LAMA/LABA combination. In total, 10% of patients initiated MITT without prior bronchodilator use or exacerbation history. However, at the time of the study, LAMA/LABA combinations were new to the market and no SITTs were available. A UK study has assessed real-world treatment patterns of MITT (initiated between 2013 and 2015) among patients with COPD (n = 3825) treated in general practice.[3] Most patients prescribed MITT had a history of clinically relevant symptoms and AECOPDs. Eighty-six percent of patients initiated MITT with two inhalers and 14% with three inhalers. Treatment persistence was found to be variable and was probably linked to disease severity. Another US study assessed the characteristics and treatment patterns of more than 20,000 COPD patients enrolled in commercial and Medicare prescription drug plans.[12] The majority of new users to FF/UMEC/VI SITT and MITT had a history of exacerbation or maintenance medication. These findings suggested that triple therapy is used most often as a treatment step up in patients who have persistent symptoms and/or exacerbations despite maintenance treatment with dual therapy (in accordance with treatment guideline recommendations and the licensed indications for SITT in the EU), although approximately 20% of patients receiving either SITT for the first time were stepped-up from mono-bronchodilator or no previous maintenance therapy. The present study provides valuable new insights into real-world treatment patterns following the introduction of SITT as a maintenance treatment for COPD.

There are a number of limitations to the study that should be noted. One consideration is the potential for GPs to misdiagnose asthma as COPD (and vice versa).[23] In order to cover a "real-world" COPD population, we consciously chose not to exclude patients with a recorded asthma diagnosis in addition to their COPD diagnosis, as asthma can co-exist with COPD and may be a factor in initiating patients on ICS-containing therapies.[2] The potential for some misclassification is an inherent risk and would be expected in electronic medical records. There is also a risk that medication use may be misclassified due to our definition of triple therapy (ie 1 day of overlap of all components). There is a possibility that patients switching between different non-MITT regimens may have been classified as MITT users. Previous work undertaken on CPRD to develop this definition indicated that there is little difference in the number of patients classified as MITT users if longer periods of overlap are used. The variables describing MRC score and FEV_1 were missing for 7% and 15% of patients, respectively. Summary data have been presented for complete cases; however, these may be biased if the values for missing patients are larger or smaller than the non-missing data. The potential bias induced is limited by the low proportion of missing cases, particularly with respect to MRC scores.

Conclusions

In this real-world primary care setting, first-time triple therapy was frequently initiated in patients with COPD that was inadequately controlled on maintenance therapy. This study provides valuable insights into the characteristics of new users of SITT in this setting. Characteristics were similar among patients with and without comorbid asthma, with the exception of FEV_1% predicted. Future studies on the impact of adherence to SITT and MITT on the effectiveness of treatment would be of interest.

Abbreviations

AECOPD, acute exacerbation of COPD; APC, admitted patient care; BEC, beclomethasone; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; EMA, European Medicines Agency; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FOR, formoterol; FVC, forced vital capacity; GERD, gastro-esophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; GLY, glycopyrronium bromide; HES, hospital episode statistics; ICD, International Classification of Diseases; ICS, inhaled

corticosteroid; ISAC, Independent Scientific Advisory Committee; IQR, interquartile range; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; MRC, Medical Research Council; NHS, National Health Service; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SITT, single-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

Additional Information

The abstract of this paper was presented at the 2020 European Respiratory Society – 30th Annual Congress as a poster presentation. The poster's abstract was published in the *European Respiratory Journal*. 2020;56(64):2417. Available from: https://erj.ersjournals.com/content/56/suppl_64/2417 DOI: 10.1183/13993003.congress-2020.2417

Data Sharing Statement

The data underlying this study are owned by the UK Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD is a center of the MHRA, and access to individual-level CPRD data is subject to protocol approval by the Independent Scientific Advisory Committee (ISAC). CPRD anonymized data can only be used by bona fide researchers for research to benefit patient and public health. Researchers and their affiliated organizations seeking access to CPRD data may contact CPRD to discuss access.

Ethics Approval and Informed Consent

This study complied with all applicable laws regarding patient privacy. No direct patient contact or primary collection of individual patient data occurred. The study was approved by the CPRD's Independent Scientific Advisory Committee (ISAC study number: 19_228). Following the initial approval of the protocol, a minor amendment was made to also describe the characteristics of all new users of FF/UMEC/VI irrespective of prior triple-therapy use. Generic ethical approval for observational research using the CPRD with approval from ISAC was granted by the Health Research Authority Research Ethics Committee (East Midlands-Derby, REC reference number 05/MRE04/87).

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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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Disclosure

KJR, SJ, CC, VDB, and ASI are employees of and/or hold stocks/shares in GlaxoSmithKline. LBS was an employee of, and held shares in, GlaxoSmithKline, during the time the study was conducted and is currently affiliated with Medical Affairs, Ultragenyx Pharmaceutical Inc., Novato, CA, USA. ASI is also an unpaid part-time professor at McMaster University. The authors report no other conflicts of interest in this work.

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