

# Characteristics of Users and New Initiators of Single- and Multiple-Inhaler Triple Therapy for Chronic Obstructive Pulmonary Disease in Germany

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**Purpose:** To assess patient characteristics of users and new initiators of triple therapy for chronic obstructive pulmonary disease (COPD) in Germany.

**Patients and Methods:** Retrospective cohort study of patients with COPD and  $\geq 1$  prescription for single-inhaler triple therapy (SITT; fluticasone furoate/umeclidinium/vilanterol [FF/UMEC/VI] or beclomethasone dipropionate/glycopyrronium bromide/formoterol [BDP/GLY/FOR]) or multiple-inhaler triple therapy (MITT), using data from the AOK PLUS German sickness fund (1 January 2015–31 December 2019). The index date was the first date of prescription for FF/UMEC/VI or BDP/GLY/FOR (SITT users), or the first date of overlap of inhaled corticosteroid, long-acting  $\beta_2$ -agonist, and long-acting muscarinic antagonist (MITT users). Two cohorts were defined: the prevalent cohort included all identified triple therapy users; the incident cohort included patients newly initiating triple therapy for the first time (no prior use of MITT or SITT in the last 2 years). Patient characteristics and treatment patterns were assessed on the index date and during the 24-month pre-index period.

**Results:** In total, 18,630 patients were identified as prevalent triple therapy users (MITT: 17,945; FF/UMEC/VI: 700; BDP/GLY/FOR: 908; non-mutually exclusive) and 2932 patients were identified as incident triple therapy initiators (MITT: 2246; FF/UMEC/VI: 311; BDP/GLY/FOR: 395; non-mutually exclusive). For both the prevalent and incident cohorts, more than two-thirds of patients experienced  $\geq 1$  moderate/severe exacerbation in the preceding 24 months; in both cohorts more BDP/GLY/FOR users experienced  $\geq 1$  moderate/severe exacerbation, compared with FF/UMEC/VI and MITT users. Overall, 97.9% of prevalent triple therapy users and 86.4% of incident triple therapy initiators received maintenance treatment in the 24-month pre-index period.

**Conclusion:** In a real-world setting in Germany, triple therapy was most frequently used after maintenance therapy in patients with recent exacerbations, in line with current treatment recommendations.

**Plain Language Summary:** Triple therapy (a combination of three different respiratory inhaled medications) is recommended for patients with chronic obstructive pulmonary disease (COPD) who experience repeated short-term symptom flare-ups when taking dual therapy (a combination of two different respiratory medications). Previously, patients had to take triple therapy using two or three separate inhalers. More recently, single-inhaler triple therapies have been developed, meaning patients can take all three different medications at the same time via one single inhaler. This study assessed the characteristics of patients who were already receiving triple therapy, or who started triple therapy (either via multiple inhalers or a single inhaler), in Germany between January 2015 and December 2019.

In total, 18,630 patients who were already receiving triple therapy during the study period, and 2932 patients who newly started using triple therapy were included. The study reported that more than two-thirds of included patients had experienced at least one flare-up of

COPD symptoms in the 2 years before starting triple therapy. Most patients had also received another therapy for COPD before starting triple therapy. A small proportion of patients started taking triple therapy after receiving no other therapy for COPD in the previous 2 years.

The results of the study suggest that triple therapy for COPD in Germany is most often used in accordance with recommendations (patients already receiving therapy and experiencing repeated symptom flare-ups).

**Keywords:** COPD, Germany, MITT, patient characteristics, real-world treatment, SITT

## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality in Germany,<sup>1</sup> and the third most common cause of death worldwide.<sup>2</sup> In 2019, the global prevalence of COPD among individuals aged 30–79 years was estimated as 10.3% (95% confidence interval 8.2 to 12.8), with Germany being among the top 10 countries with the highest number of COPD cases.<sup>3</sup> COPD is also associated with a considerable economic burden, with exacerbations of COPD being a key driver of this cost burden.<sup>4</sup>

Current mainstay pharmacological treatment for COPD includes short- and long-acting muscarinic antagonists (SAMA or LAMA) and short- and long-acting  $\beta_2$ -agonists (SABA or LABA), with the addition of inhaled corticosteroids (ICS) for more severe disease.<sup>5</sup> The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document recommends that for patients who continue to experience exacerbations despite mono or dual bronchodilator maintenance therapy, an escalation to inhaled triple therapy (ICS + LABA + LAMA) should be considered to help reduce symptoms, improve health status, and reduce the risk of further exacerbation.<sup>5</sup>

Triple therapy traditionally required the use of multiple inhalers.<sup>6</sup> Single-inhaler triple therapy (SITT) is a more recent development for the treatment of COPD.<sup>7</sup> SITT with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) was approved by the European Medicines Agency (EMA) in November 2017, as the first once-daily maintenance treatment for COPD.<sup>8</sup> One other SITT was approved at the time of this study: beclomethasone dipropionate/glycopyrronium bromide/formoterol (BDP/GLY/FOR), which requires twice-daily dosing.<sup>9</sup> It should be noted that the product license for both SITTs is broader than the GOLD recommendations and includes all patients who remain uncontrolled despite LABA + LAMA or ICS + LABA maintenance therapy, including patients with persistent symptoms and not just individuals with recurrent exacerbations.<sup>8,9</sup>

Compared with multiple-inhaler triple therapy (MITT), SITT has the advantage of a simpler dosing regimen, thus helping to reduce medication errors and improve patient adherence and persistence.<sup>10–13</sup> A recent retrospective study of patients with COPD in the UK reported that patients initiating SITT with FF/UMEC/VI or BDP/GLY/FOR had significantly better adherence and persistence compared with patients initiating MITT; these improvements persisted for at least 18 months following treatment initiation.<sup>12</sup> In addition, the INTREPID study 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.<sup>7</sup>

Recent studies conducted in the UK, the US, and Japan have assessed characteristics of patients initiating MITT and SITT (Akiyama S, et al. Characteristics of new users of single- and multiple-inhaler triple therapy for COPD in routine clinical practice in Japan: a cross-sectional, observational study [unpublished data]).<sup>14–16</sup> Data from the UK and the US suggest that MITT and SITT are frequently initiated following prior maintenance therapy, and in patients with a recent exacerbation, in line with current clinical guidance.<sup>14–16</sup> However, data from a similar retrospective cohort study conducted in Japan reported that 25% of patients initiating triple therapy had no prior history of ICS, LABA, or LAMA in the past 12 months (Akiyama S, et al. Characteristics of new users of single- and multiple-inhaler triple therapy for COPD in routine clinical practice in Japan: a cross-sectional, observational study [unpublished data]). Similar findings have also been reported in New Zealand.<sup>17</sup>

There are currently limited data on the clinical and demographic characteristics of new initiators of MITT and SITT in Germany, and it is also unknown if the characteristics of MITT users have changed since the emergence of SITT. A better understanding of specific factors more closely linked with MITT or SITT initiation among patients with COPD would be

of value. This study was designed to describe the baseline characteristics, comorbidities, and treatment history of patients with COPD who have received SITT or MITT, based on real-world data derived from Germany.

## Materials and Methods

### Study Design and Objectives

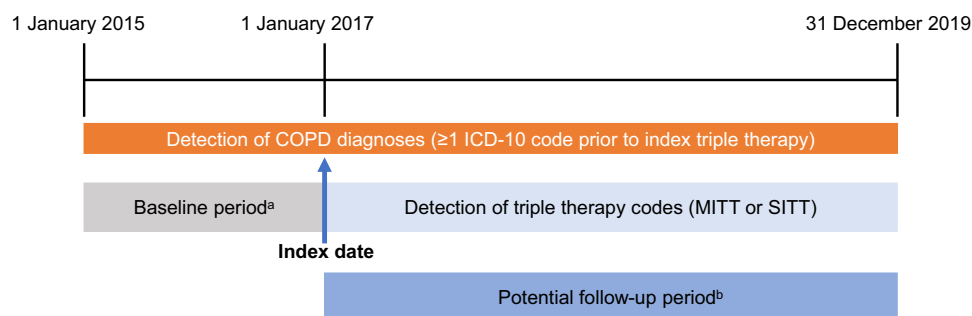
This was a retrospective cohort study of patients with COPD and a prescription for SITT (FF/UMEC/VI or BDP/GLY/FOR) or MITT in Germany based on an analysis of an anonymized claims dataset provided by the AOK PLUS German sickness fund covering the period from 1 January 2015 to 31 December 2019. The study design is shown in [Figure 1](#).

The dataset of AOK PLUS covers approximately 3.1 million insured people in the regions of Saxony and Thuringia in Germany, which is equivalent to approximately 50% of the regional population insured by statutory health insurance and 4.3% of the overall German population insured by statutory health insurance funds.<sup>18</sup> The dataset contains information on patients' demographics and detailed reimbursement claims on outpatient care, inpatient care, pharmaceuticals, therapeutic devices, rehabilitation, and sick leave. For outpatient medication prescriptions, information is available on drug class (according to the Anatomical Therapeutic Chemical [ATC] classification system, see [Table S1](#)), date of prescription/dispensation in the pharmacy, prescribed package size, and defined daily dose according to the World Health Organization and the German AOK Research Institute.<sup>18–20</sup>

The primary objective of the study was to assess the characteristics of all patients with COPD who have used triple therapy (MITT or SITT). The secondary objective was to identify and describe the characteristics of patients newly initiating triple therapy (MITT or SITT) for the first time (ie incident users of triple therapy with no prior use of SITT or MITT).

The date at which a patient initiated triple therapy was defined as the index date ([Figure 1](#)). For SITT users, the index date was the first observed date of prescription of FF/UMEC/VI or BDP/GLY/FOR (1 January 2017–31 December 2019). For MITT users, the index date was the first date of prescription overlap of ICS, LABA, and LAMA therapy (1 January 2017–31 December 2019). To classify a patient as a MITT user, there must have been a minimum of a 1-day overlap of available medication supply of ICS, LABA, and LAMA therapy (as per the defined daily dose). In addition, a sensitivity analysis of the MITT identification strategy was performed using a 14-day period of prescription overlap for identification of MITT patients.

A baseline period of up to 24 months prior to the index date was defined, enabling the description of patient characteristics, including comorbidities and treatment history. The follow-up period started at the index date and ended on 31 December 2019, at the end of continuous insurance period, or upon death, whichever came first ([Figure 1](#)).



**Figure 1** Study design.

**Notes:** Patient characteristics including sociodemographic profile, comorbidities, and treatment history were reported on the date of SITT/MITT initiation or during the 12- or 24-month baseline period. The study population was identified through documented inpatient and/or confirmed outpatient ICD-10 codes for COPD (J44) from 1 January 2015 to 31 December 2019, and subsequent outpatient prescriptions for triple therapy (MITT or SITT) from 1 January 2017 to 31 December 2019. To classify a patient as a MITT user, there must have been a minimum of a 1-day overlap (14-day overlap for the sensitivity analysis) in the treatment supply of all three MITT agents.<sup>a</sup>Including continuous insurance for 24 months pre-index; assessment of baseline characteristics; <sup>b</sup>From the index date of each patient's first observed triple therapy until the end of the study period, continuous insurance period, or death, whichever comes first.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; ICD-10, International statistical Classification of Diseases and related health problems, 10th revision; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.

## Study Population

To be included in the overall (prevalent) cohort of triple therapy users, eligible patients were required to have:  $\geq 1$  inpatient and/or two confirmed outpatient diagnoses of COPD (International Classification of Diseases, 10th revision [ICD-10] code J44) made by a pulmonologist, measured over two quarters from 1 January 2015 to 31 December 2019;  $\geq 1$  prescription for triple therapy, either MITT (ICS/LABA/LAMA via two or three devices) or SITT (FF/UMEC/VI or BDP/GLY/FOR), from 1 January 2017 to 31 December 2019; and  $\geq 1$  diagnosis of COPD before triple therapy initiation. Patients were also required to be aged  $\geq 35$  years at the index date (date of first triple therapy prescription) and have continuous insurance by AOK PLUS for  $\geq 24$  months prior to initiation of SITT or MITT. To be included in the subset of new triple therapy initiators (incident cohort), eligible patients were required to satisfy all the inclusion criteria outlined above for the prevalent cohort of triple therapy users, and in addition, not have a previous prescription for any triple therapy (MITT or SITT) in the 24 months leading up to the index triple therapy prescription.

## Study Endpoints and Statistical Analysis

Patient demographics, characteristics, and comorbidities at baseline were descriptively analyzed for all users of triple therapy and new triple therapy initiators. For continuous variables, summary statistics including mean and standard deviation (SD) were reported. For categorical variables, count and percentage were reported.

Maintenance treatments for COPD, as well as prescriptions for short-acting therapy, were identified using ATC codes (see [Table S1](#) for specific codes per medication class) and were considered within the analysis of treatment history. Moderate/severe exacerbations were identified via outpatient and/or inpatient ICD-10 codes (outpatient J44.1 or a hospitalization with J44).

## Results

In total, 18,630 patients were identified as prevalent users of triple therapy (MITT/SITT). Of these, 17,945 were prevalent MITT users, 700 were prevalent FF/UMEC/VI users, and 908 were prevalent BDP/GLY/FOR users (non-mutually exclusive cohorts). Overall, 2932 patients (15.7%) newly initiated MITT/SITT therapy after a minimum of 2 years without triple therapy (incident cohort). Of these, 2246 were incident MITT users, 311 were incident FF/UMEC/VI users, and 395 were incident BDP/GLY/FOR users (non-mutually exclusive cohorts). The proportion of patients who were new initiators of triple therapy (ie ICS + LABA + LAMA) was 44.4% among users of FF/UMEC/VI and 43.5% among users of BDP/GLY/FOR.

## All Users of Triple Therapy (Prevalent Cohort)

### Patient Demographics and Clinical Characteristics

The patient demographics and clinical characteristics for prevalent triple therapy users are shown in [Table 1](#). Overall, 58.2% of MITT users, 62.3% of FF/UMEC/VI users, and 58.9% of BDP/GLY/FOR users were male. The mean (SD) age of MITT, FF/UMEC/VI, and BDP/GLY/FOR users was 70.4 (11.4), 70.5 (10.6), and 71.0 (11.4) years, respectively. Across the prevalent cohort, more than two-thirds of patients experienced  $\geq 1$  moderate/severe exacerbation in the preceding 24 months. More BDP/GLY/FOR users experienced  $\geq 1$  moderate/severe exacerbation in the preceding 24 months, compared with users of MITT and FF/UMEC/VI (81.1% vs 74.3% and 69.4%, respectively). Overall, 24.8% of MITT users, 19.0% of FF/UMEC/VI users, and 15.8% of BDP/GLY/FOR users also had an asthma diagnosis.

### Patient Comorbidities

The most common comorbidities of interest for prevalent triple therapy users in the last 12 months were rheumatoid/osteoarthritis (41.6%), tobacco use-related comorbidities (mental and behavioral disorders due to tobacco use [28.4%]; toxic effects of tobacco and nicotine [0.1%]), and anxiety (27.6%). There was a lower rate of tobacco use-related psychological or toxic comorbidities and comorbid anxiety among MITT users compared with users of FF/UMEC/VI and BDP/GLY/FOR (tobacco use-related comorbidities: 27.2% vs 34.6% and 37.7%, respectively; comorbid anxiety: 26.3% vs 30.6% and 31.2%, respectively; [Table 2](#)).

**Table I** Demographics and Clinical Characteristics at Baseline for All Users of Triple Therapy (Prevalent Cohort) and New Triple Therapy Initiators (Incident Cohort)

	Prevalent Cohort			Incident Cohort		
	MITT users (n=17,945)	SITT FF/UMEC/VI users (n=700)	SITT BDP/GLY/FOR users (n=908)	MITT users (n=2246)	SITT FF/UMEC/VI users (n=311)	SITT BDP/GLY/FOR users (n=395)
<b>Gender, n (%)</b>						
Male	10,450 (58.2)	436 (62.3)	535 (58.9)	1273 (56.7)	199 (64.0)	234 (59.2)
<b>Age (years) at index, mean (SD)</b>	70.4 (11.4)	70.5 (10.6)	71.0 (11.4)	70.7 (11.8)	70.4 (10.7)	71.0 (12.0)
<b>CCI score, mean (SD)</b>	4.8 (3.1)	4.7 (3.1)	4.9 (3.1)	5.0 (3.2)	4.7 (3.0)	5.0 (3.2)
<b>≥1 visit to lung specialist in prior 24 months, n (%)</b>	12,294 (68.5)	496 (70.9)	626 (68.9)	1382 (61.5)	195 (62.8)	221 (56.0)
<b>Moderate/severe exacerbations, n (%)</b>						
No moderate/severe exacerbations in prior 24 months	4621 (25.8)	214 (30.6)	172 (18.9)	622 (27.7)	116 (37.3)	102 (25.8)
≥1 moderate/severe exacerbation in prior 24 months	13,324 (74.3)	486 (69.4)	736 (81.1)	1624 (72.3)	195 (62.7)	293 (74.2)
≥2 moderate/severe exacerbation in prior 24 months	9563 (53.3)	378 (54.0)	552 (60.8)	1047 (46.6)	147 (47.3)	191 (48.4)
≥3 moderate/severe exacerbation in prior 24 months	7186 (40.0)	296 (42.3)	454 (50.0)	715 (31.8)	118 (37.9)	150 (38.0)
<b>Patients with COPD exacerbations and no visits to a lung specialist, n (%)</b>	4521 (25.2)	144 (20.6)	235 (25.9)	711 (31.7)	75 (24.1)	138 (34.9)
<b>Patients with COPD exacerbations and ≥1 visit to a lung specialist, n (%)</b>	8803 (49.1)	342 (48.9)	501 (55.2)	913 (40.7)	120 (38.6)	155 (39.2)
<b>Asthma diagnosis, n (%)</b>	4453 (24.8)	133 (19.0)	143 (15.8)	560 (24.9)	39 (12.5)	47 (11.9)
<b>FEV<sub>1</sub> predicted, n (%)</b>						
<35%	1107 (6.2)	55 (7.9)	79 (8.7)	114 (5.1)	20 (6.4)	28 (7.1)
≥35% and <50%	987 (5.5)	50 (7.1)	52 (5.7)	97 (4.3)	12 (3.9)	17 (4.3)
≥50% and <70%	832 (4.6)	36 (5.1)	29 (3.2)	113 (5.0)	13 (4.2)	9 (2.3)
≥70%	237 (1.3)	0	17 (1.9)	30 (1.3)	0	10 (2.5)
Not specified	14,782 (82.4)	559 (79.9)	731 (80.5)	1892 (84.2)	266 (85.5)	331 (83.8)
<b>Use of oxygen therapy equipment/device,<sup>a</sup> n (%)</b>	3238 (18.0)	100 (14.3)	207 (22.8)	289 (12.9)	31 (10.0)	68 (17.2)

**Notes:** Treatment groups (MITT, FF/UMEC/VI, BDP/GLY/FOR) are not mutually exclusive. Patient characteristics were reported on the date of SITT/MITT initiation or during the 24-month baseline period. ICD-10-GM codes: asthma J45/J46; FEV<sub>1</sub> predicted values were derived based on codes J44.00, J44.01, J44.02, J44.03, and J44.09.  
<sup>a</sup>Includes prescribed use of compressed gas filling units, compressed and liquid gas, and oxygen concentrators.

**Abbreviations:** BDP/GLY/FOR, beclomethasone dipropionate/glycopyrronium bromide/formoterol; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICD-10-GM, International Statistical Classification of Diseases and related health problems, 10th revision, German Modification; MITT, multiple-inhaler triple therapy; SD, standard deviation; SITT, single-inhaler triple therapy.

## Treatment History

Maintenance treatment received in the 3-, 6-, 12-, and 24-month pre-index period for all patients in the prevalent cohort is shown in [Figure 2](#). Overall, 66.2% of all triple therapy users received COPD maintenance treatment in the 3 months just prior to initiation of triple therapy (MITT users: 67.2%, FF/UMEC/VI users: 48.6%, BDP/GLY/FOR users: 52.8%; [Figure 2A](#)). In the 24 months prior to index, 97.9% of all triple therapy users received maintenance therapy (MITT users: 98.2%, FF/UMEC/VI users: 95.4%, BDP/GLY/FOR users: 93.6%; [Figure 2D](#)).

During the 3-month pre-index period, the most commonly received maintenance therapies across the prevalent cohort were LAMA monotherapy (29.4%), LABA + ICS (29.3%), and LABA + LAMA (16.8%). There was a higher use of LAMA monotherapy and LABA + ICS among MITT users compared with users of FF/UMEC/VI and BDP/GLY/FOR ([Figure 2A](#)). The

**Table 2** Comorbidities of Interest in the Last 12 Months for All Users of Triple Therapy (Prevalent Cohort) and New Triple Therapy Initiators (Incident Cohort)

Patients, n (%)	Prevalent Cohort			Incident Cohort		
	MITT users (n=17,945)	SITT FF/UMEC/VI users (n=700)	SITT BDP/GLY/FOR users (n=908)	MITT users (n=2246)	SITT FF/UMEC/VI users (n=311)	SITT BDP/GLY/FOR users (n=395)
<b>Any comorbidity of interest<sup>a</sup></b>	14,840 (82.7)	590 (84.3)	803 (88.4)	1897 (84.5)	267 (85.9)	344 (87.1)
Depression	4141 (23.1)	147 (21.0)	217 (23.9)	552 (24.6)	55 (17.7)	91 (23.0)
Stroke	1068 (6.0)	42 (6.0)	61 (6.7)	150 (6.7)	19 (6.1)	23 (5.8)
Congestive heart failure	2654 (14.8)	110 (15.7)	153 (16.9)	350 (15.6)	45 (14.5)	67 (17.0)
Gastro-esophageal reflux disease	4179 (23.3)	173 (24.7)	218 (24.0)	531 (23.6)	62 (19.9)	85 (21.5)
Anxiety	4711 (26.3)	214 (30.6)	283 (31.2)	622 (27.7)	105 (33.8)	120 (30.4)
Rheumatoid/osteoarthritis	7194 (40.1)	281 (40.1)	339 (37.3)	935 (41.6)	128 (41.2)	153 (38.7)
Acute myocardial infarction	877 (4.9)	45 (6.4)	44 (4.9)	126 (5.6)	20 (6.4)	21 (5.3)
Dementia/cognitive impairment	2348 (13.1)	85 (12.1)	135 (14.9)	330 (14.7)	41 (13.2)	61 (15.4)
Tobacco use	4882 (27.2)	242 (34.6)	342 (37.7)	645 (28.7)	114 (36.7)	143 (36.2)
Bronchiectasis	749 (4.2)	30 (4.3)	47 (5.2)	65 (3.0)	9 (2.9)	13 (3.3)

**Notes:** ICD-10-GM codes: depression F30–39; stroke I60–64; congestive heart failure I50; gastro-esophageal reflux disease K21; anxiety F40–48; rheumatoid/osteoarthritis M05–06, M15–19; acute myocardial infarction I21; dementia/cognitive impairment F00–09; tobacco use F17, T65.2; bronchiectasis J47. <sup>a</sup>Patients with  $\geq 1$  inpatient or two confirmed outpatient diagnoses.

**Abbreviations:** BDP/GLY/FOR, beclomethasone dipropionate/glycopyrronium bromide/formoterol; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICD-10-GM, International Statistical Classification of Diseases and related health problems, 10th revision, German Modification; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.

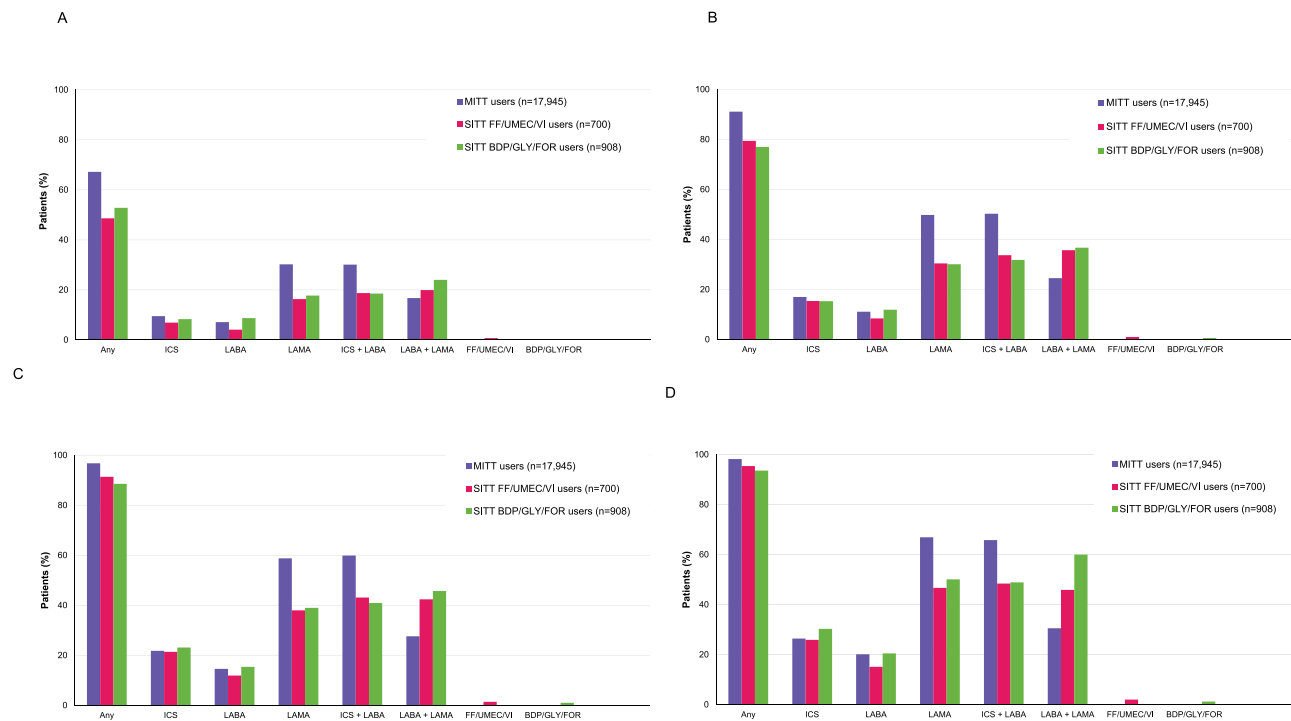
use of LABA + LAMA maintenance therapy was higher among users of FF/UMEC/VI (19.9%) and BDP/GLY/FOR (24.0%) than users of MITT (16.7%). Similar maintenance treatment patterns were observed in the 6-, 12-, and 24-month pre-index periods (Figure 2B–D). During the 24-month pre-index period, LAMA monotherapy (65.4%), LABA + ICS (64.4%), and LABA + LAMA (31.1%) were the most commonly received maintenance therapies. The combinations of different maintenance therapy classes used during the 12- and 24-month pre-index periods across the prevalent cohort are shown in Table S2.

The outpatient prescriptions for short-acting therapy received in the 24-month pre-index period for all patients in the prevalent cohort are shown in Figure 3. The majority of MITT, FF/UMEC/VI, and BDP/GLY/FOR users received short-acting therapy in the 24 months prior to initiation of triple therapy (78.6%, 81.3%, and 83.6%, respectively). The most commonly received short-acting therapies across the prevalent cohort were SABA monotherapy (58.7%) and SABA + SAMA (28.6%).

## New Triple Therapy Initiators (Incident Cohort)

### Patient Demographics and Clinical Characteristics

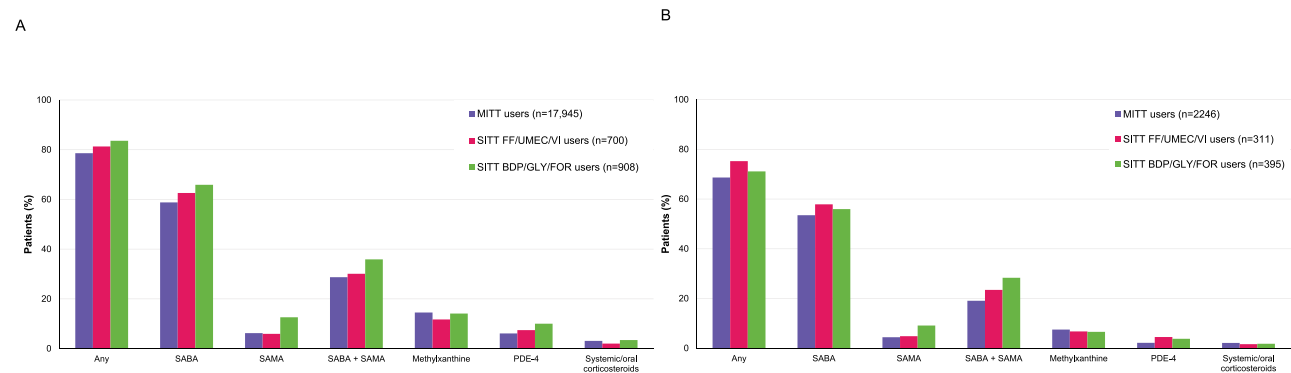
The patient demographics and clinical characteristics for incident triple therapy initiators are shown in Table 1. Overall, 56.7% of MITT initiators, 64.0% of FF/UMEC/VI initiators, and 59.2% of BDP/GLY/FOR initiators were male. The mean (SD) age of incident MITT, FF/UMEC/VI, and BDP/GLY/FOR initiators was 70.7 (11.8), 70.4 (10.7), and 71.0 (12.0) years, respectively. Like the prevalent cohort, more than two-thirds of patients had experienced  $\geq 1$  moderate/severe exacerbation in the preceding 24 months across the incident cohort. More MITT and BDP/GLY/FOR initiators experienced  $\geq 1$  moderate/severe exacerbation in the preceding 24 months, compared with FF/UMEC/VI initiators (72.3% and 74.2% vs 62.7%, respectively). Overall, 24.9% of MITT initiators, 12.5% of FF/UMEC/VI initiators, and 11.9% of BDP/GLY/FOR initiators also had an asthma diagnosis.



**Figure 2** Maintenance COPD therapy used in the 3- (A), 6- (B), 12- (C), and 24- (D) month pre-index period for all users of triple therapy (prevalent cohort).

**Notes:** From patients with at least one prescription.

**Abbreviations:** BDP/GLY/FOR, beclomethasone dipropionate/glycopyrronium bromide/formoterol; COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.



**Figure 3** Outpatient prescriptions for short-acting therapy in the 24-month pre-index period for all users of triple therapy (prevalent cohort) (A), and new triple therapy initiators (incident cohort) (B).

**Notes:** From patients with at least one prescription.

**Abbreviations:** BDP/GLY/FOR, beclomethasone dipropionate/glycopyrronium bromide/formoterol; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; MITT, multiple-inhaler triple therapy; PDE-4, phosphodiesterase type 4; SABA, short-acting  $\beta_2$ -agonist; SAMA, short-acting muscarinic antagonist; SITT, single-inhaler triple therapy.

### Patient Comorbidities

The most common comorbidities of interest for incident triple therapy initiators in the last 12 months were rheumatoid/osteoarthritis (42.7%), tobacco use-related comorbidities (mental and behavioral disorders due to tobacco use [28.6%] and toxic effects of tobacco and nicotine [0.1%]), and anxiety (29.5%). There was a lower rate of tobacco use-related comorbidities and comorbid anxiety in MITT initiators, compared with FF/UMEC/VI and BDP/GLY/FOR initiators

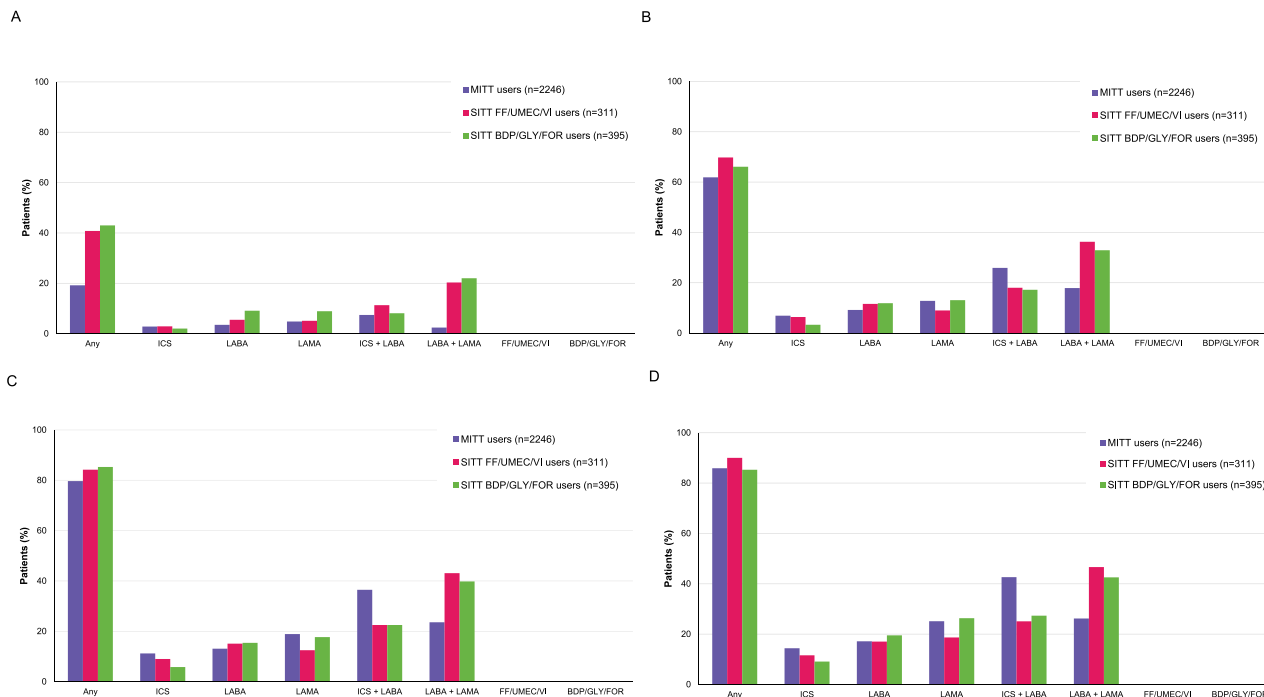
(tobacco use-related comorbidities: 28.7% vs 36.7% and 36.2%, respectively; comorbid anxiety: 27.7% vs 33.8% and 30.4%, respectively; Table 2).

### Treatment History

Maintenance treatment received in the 3-, 6-, 12- and 24-month pre-index periods for triple therapy initiators in the incident cohort is shown in Figure 4. Overall, 24.6% of new MITT, FF/UMEC/VI, and BDP/GLY/FOR initiators received maintenance treatment in the 3 months prior to index (MITT: 19.2%, FF/UMEC/VI: 40.8%, BDP/GLY/FOR: 43.0%; Figure 4A). In the 24 months prior to index, 86.4% of new MITT, FF/UMEC/VI and BDP/GLY/FOR initiators received maintenance treatment (MITT: 85.9%, FF/UMEC/VI: 90.0%, BDP/GLY/FOR: 85.3%; Figure 4D).

During the 3-month pre-index period, the most commonly received maintenance therapies across the incident cohort were LABA + ICS (7.9%) and LABA + LAMA (6.8%). Like the prevalent cohort, the use of LABA + LAMA maintenance therapy was higher among new initiators of FF/UMEC/VI (20.3%) and BDP/GLY/FOR (22.0%) than new initiators of MITT (2.4%). Similar maintenance treatment patterns were observed in the 6-, 12-, and 24-month pre-index periods (Figure 4B–D). During the 24-month pre-index period, LABA + ICS (38.9%), LABA + LAMA (30.5%), and LAMA monotherapy (24.7%) were the most commonly received maintenance therapies. The combinations of different maintenance COPD therapy classes used during the 12- and 24-month pre-index periods across the incident cohort are shown in Table S3.

The outpatient prescriptions for short-acting therapy received in the 24-month pre-index period for new triple therapy initiators are shown in Figure 3. The majority of new MITT, FF/UMEC/VI, and BDP/GLY/FOR initiators received short-acting therapy in the 24 months prior to initiation of triple therapy (68.7%, 75.2%, and 71.1%, respectively). Like the prevalent cohort, the most commonly received short-acting therapies across the incident cohort were SABA monotherapy (54.2%) and the combined usage of SABA/SAMA (20.7%).



**Figure 4** Maintenance COPD therapy used in the 3- (A), 6- (B), 12- (C), and 24- (D) month pre-index period for all new triple therapy initiators (incident cohort).

**Notes:** From patients with at least one prescription.

**Abbreviations:** BDP/GLY/FOR, beclomethasone dipropionate/glycopyrronium bromide/formoterol; COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.



## Sensitivity Analysis

Similar patient demographics and characteristics, comorbidities, and treatment history to those reported above were observed for both the prevalent MITT users and new MITT initiators using a 14-day, rather than 1-day, period of prescription overlap to define MITT use (data not shown).

## Discussion

The results of our study demonstrated that in a real-world setting in Germany, triple therapy (MITT and SITT) for COPD was most frequently used after maintenance therapy in patients with recent exacerbations, in line with current treatment recommendations and label-specific indications that suggest escalation to triple therapy in patients who continue to experience exacerbations or symptoms despite treatment with LABA + LAMA<sup>5</sup> or ICS + LABA.<sup>8,9</sup> Across the different treatment groups, more than two-thirds of patients had experienced  $\geq 1$  moderate/severe exacerbation in the preceding 24 months. In the prevalent and incident cohorts, more BDP/GLY/FOR users experienced  $\geq 1$  moderate/severe exacerbation in the preceding 24 months, compared with users of MITT and FF/UMEC/VI.

These findings are consistent with other recent retrospective analyses from the UK and the US with regard to the baseline characteristics of patients with COPD prior to the initiation of MITT and/or SITT.<sup>14–16</sup> However, it should also be noted that around 15% of MITT and SITT initiators did not have any prescription for an ICS, LABA, or LAMA in the 24 months prior to starting triple therapy, suggesting that a minority of patients received MITT or SITT as a first-line maintenance treatment; GOLD recommendations only suggest triple therapy as initial maintenance treatment for patients with frequent exacerbations ( $\geq 2$  moderate or 1 severe in previous year) and high blood eosinophil count ( $\geq 300$  cells/ $\mu$ L). Over two-thirds of triple therapy initiators received a short-acting therapy in the 24 months prior to index. A direct step-up from no prior maintenance therapy or from a short-acting therapy may be due to a lack of controlled symptoms and/or some physicians' perception that triple therapy may be more effective than dual therapy in relieving symptoms and improving lung function, or preventing disease deterioration, which has previously been observed in the UK, Japan, Italy, and France.<sup>18,21–25</sup> Similar to the findings of Wu et al in the US,<sup>16</sup> the average patient age observed in the current study was  $>70$  years for the MITT and SITT users across both the prevalent and incident cohorts, and the proportion of patients with comorbid conditions was high in both cohorts. It is possible that the high comorbidity rate may have been a factor in the decision to escalate to triple therapy. We observed that in the case of a concurrent asthma diagnosis, MITT initiation was more common than SITT initiation. Approximately 25% of new MITT initiators had an asthma diagnosis (versus approximately 12% of new SITT initiators). GOLD guidelines recommend that for patients with COPD and concurrent asthma, treatment should primarily follow the asthma guideline, in which the use of ICS is mandatory to lower the risk of future exacerbation; triple therapy is recommended for patients whose asthma remains uncontrolled despite medium or high dose ICS + LABA.<sup>5,26</sup>

Since the completion of this study, another twice-daily SITT comprising budesonide/glycopyrronium bromide/formoterol (BUD/GLY/FOR) has been approved by the EMA in 2020.<sup>27</sup> This may have had an impact on the results observed, and further studies with data for BUD/GLY/FOR included may be warranted to investigate the impact of this third approved SITT on the use and initiation of triple therapy in Germany. As the product license for this combination is similar to the existing two SITTs, it is likely that initiation of this therapy among German patients with COPD within the AOK PLUS database would follow a similar pattern to the one observed in this study. However, the availability of more SITT options could also encourage physicians and patients to switch molecules and/or inhalers over the course of their disease management, and it would be interesting to gain information on the characteristics of patients who switch SITTs. In this regard, the ongoing TETRIS (triple therapy in patients with COPD under real live setting) observational study (GSK. Data on file: REF-184782) may help identify some of the drivers of such switches in clinical practice. Studies reporting on the long-term clinical outcomes of patients with COPD initiating SITT would also be of value, as well as studies investigating possible prescribing differences between general practitioners and pulmonologists.

There are several limitations to our study that should be noted. The study uses diagnosis codes recorded for reimbursement purposes, potentially impacting the validity of the data. Another consideration is the 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; however, similar results were observed using both a 1-day and a 14-day overlap (sensitivity analysis) to define MITT use. Similarly, a patient who filled prescriptions for the medications that define MITT may not have used or adhered to all the medications at the same time. Prescribed daily dose or physicians' recommendation on how/when to use each medication were not captured during this study. Further to this, regional differences may exist between different sickness funds in Germany (eg differing prescribing quotas and/or rebate contracts), which may drive prescribing patterns. For example, a practitioner's obligation to fulfil generic prescription quotas may lead to them being more likely to prescribe MITT instead of a SITT. Another potential limitation is that forced expiratory volume in 1 second (FEV<sub>1</sub>) data were obtained via ICD-10 codes. This resulted in a lack of information on symptoms/lung function, with FEV<sub>1</sub> not specified in >80% of all patients. Finally, as the study period occurred before the COVID-19 pandemic, it is possible that the subsequent pandemic may have had an impact on the characteristics and treatment patterns observed.

## Conclusion

The results from our study provide valuable insights into the characteristics, comorbidities, and treatment patterns of patients with COPD using triple therapy (MITT and SITT) in Germany. In a real-world setting, most users and new initiators of MITT and SITT had a history of an exacerbation or maintenance medication. This suggests that triple therapy is used most often in accordance with treatment recommendations/product licenses, as a step-up treatment in patients who have persistent symptoms and/or exacerbations, despite maintenance treatment with dual therapy. However, approximately 15% of patients initiating triple therapy for the first time were stepped up directly from no previous maintenance therapy. These findings suggest that triple therapy is often initiated in patients with COPD whose disease is not adequately controlled.

## Abbreviations

ATC, Anatomical Therapeutic Chemical; BDP/GLY/FOR, beclomethasone dipropionate/glycopyrronium bromide/formoterol; BUD/GLY/FOR, budesonide/glycopyrronium bromide/formoterol; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; EMA, European Medicines Agency; FEV<sub>1</sub>, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD-10, International statistical Classification of Diseases and related health problems, 10th revision; ICD-10-GM, International statistical Classification of Diseases and related health problems, 10th revision, German Modification; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; PDE-4, phosphodiesterase type 4; SABA, short-acting  $\beta_2$ -agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SITT, single-inhaler triple therapy.

## Data Sharing Statement

The data analyzed in this study are derived from the AOK PLUS German sickness fund database. Authors had access to the study data for the purpose of this work only. Therefore, the data cannot be broadly disclosed or made publicly available at this time. Access to the database can be requested via individual application. The interpretation and conclusions contained in this study are those of the authors alone.

## Ethics Approval and Informed Consent

For retrospective analysis of anonymized data there is no requirement for ethical approval and consent to participate according to the German Guidelines for Secondary Data Analysis.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that was 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 manuscript; 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

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