









# Evaluation of Adherence and Persistence to Triple Therapy in Patients with COPD: A German Claims Data Study

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**Purpose:** Triple therapy (long-acting muscarinic antagonist/long-acting  $\beta_2$ -agonist/inhaled corticosteroid) is recommended for patients with chronic obstructive pulmonary disease (COPD) who experience recurrent exacerbations. Multiple-inhaler triple therapy (MITT) is associated with poor adherence and persistence. This study assessed comparative adherence and persistence to single-inhaler triple therapy (SITT) versus MITT among patients with COPD in a real-world setting in Germany.

**Patients and Methods:** This retrospective analysis using the WIG2 benchmark database identified patients with COPD newly initiating triple therapy with MITT or SITT (fluticasone furoate/umeclidinium/vilanterol [FF/UMEC/VI] or formoterol/beclomethasone/glycopyrronium bromide [FOR/BDP/GLY]) November 2017–June 2019. Eligible patients were  $\geq 35$  years with 1 year's continual insurance prior to triple therapy initiation and no previous record of triple therapy. Inverse probability of treatment weighting was used to balance baseline characteristics. Adherence was measured using proportion of days covered (PDC) at 6, 12, and 18 months post-treatment initiation; persistence (time until treatment discontinuation) was measured at 6, 12, and 18 months, with a gap of  $>30$  days used to define non-persistence.

**Results:** Of 5710 patients included in the analysis (mean age 66 years), 71.4% initiated MITT and 28.6% initiated SITT (FF/UMEC/VI: 41.4%; FOR/BDP/GLY: 58.6%). Mean PDC was higher among SITT versus MITT users at all time points; at each time point, mean PDC was highest among FF/UMEC/VI users. During the first 6 months following treatment initiation, higher adherence was exhibited by FF/UMEC/VI (29%) and FOR/BDP/GLY (19%) users versus MITT users. Over the entire observation period, FF/UMEC/VI users had the highest proportion of persistent patients; at 18 months, 16.5% of FF/UMEC/VI users were persistent versus 2.3% of MITT users.

**Conclusion:** Patients initiating SITT in Germany had significantly higher adherence and persistence compared with patients initiating MITT over 6 to 18 months following treatment initiation. Among SITT, FF/UMEC/VI users had the highest proportion of adherence and persistence.

**Keywords:** comparative, multiple- or single-inhaler triple therapy, new-user, proportion of days covered, real-world analysis, treatment discontinuation

## Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, the estimated global prevalence of chronic obstructive pulmonary disease (COPD) was 10.3% in 2019, with Germany being among the top 10 countries with the highest number of COPD cases.<sup>1,2</sup> The World Health Organization estimates that more than

3 million deaths (approximately 6% of all global deaths) in 2019 could be attributed to COPD.<sup>3,4</sup> Treatment for COPD involves inhaled medications that are intended to improve lung function, relieve symptoms, and reduce the frequency of exacerbations.<sup>1</sup> GOLD suggests that triple therapy (inhaled corticosteroid [ICS] + long-acting  $\beta_2$ -agonist [LABA] + long-acting muscarinic antagonist [LAMA]) may be considered as initial maintenance treatment for patients with  $\geq 2$  moderate exacerbations or  $\geq 1$  severe exacerbation in the past year, and elevated blood eosinophil counts ( $\geq 300$  cells/ $\mu$ L); for patients experiencing recurrent exacerbations while receiving mono or dual bronchodilator therapy, an escalation to triple therapy is recommended.<sup>1</sup>

Adherence and persistence to therapy are crucial for achieving optimal clinical outcomes.<sup>5,6</sup> Prior evidence shows that in a real-world setting, adherence and persistence to multiple-inhaler triple therapy (MITT) are low;<sup>7,8</sup> single-inhaler triple therapy (SITT) has the potential to improve adherence and persistence via simplification of the treatment regimen by reducing the number of inhalers required.<sup>9</sup> In 2017, two SITTs were approved for the long-term maintenance treatment of adult patients with COPD in the EU.<sup>10,11</sup> The first comprises fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and requires once-daily dosing;<sup>10</sup> the second comprises formoterol/beclomethasone/glycopyrronium bromide (FOR/BDP/GLY) and requires twice-daily dosing.<sup>11</sup> In December 2020, a third SITT was approved for use in the EU; this comprises formoterol/glycopyrronium bromide/budesonide (FOR/GLY/BUD) and requires twice-daily dosing.<sup>12</sup>

There is limited evidence on the impact of SITT on treatment adherence and persistence among patients with COPD in Germany. The aim of this study was to compare medication adherence and persistence in patients with COPD in Germany initiating triple therapy (MITT or SITT).

## Materials and Methods

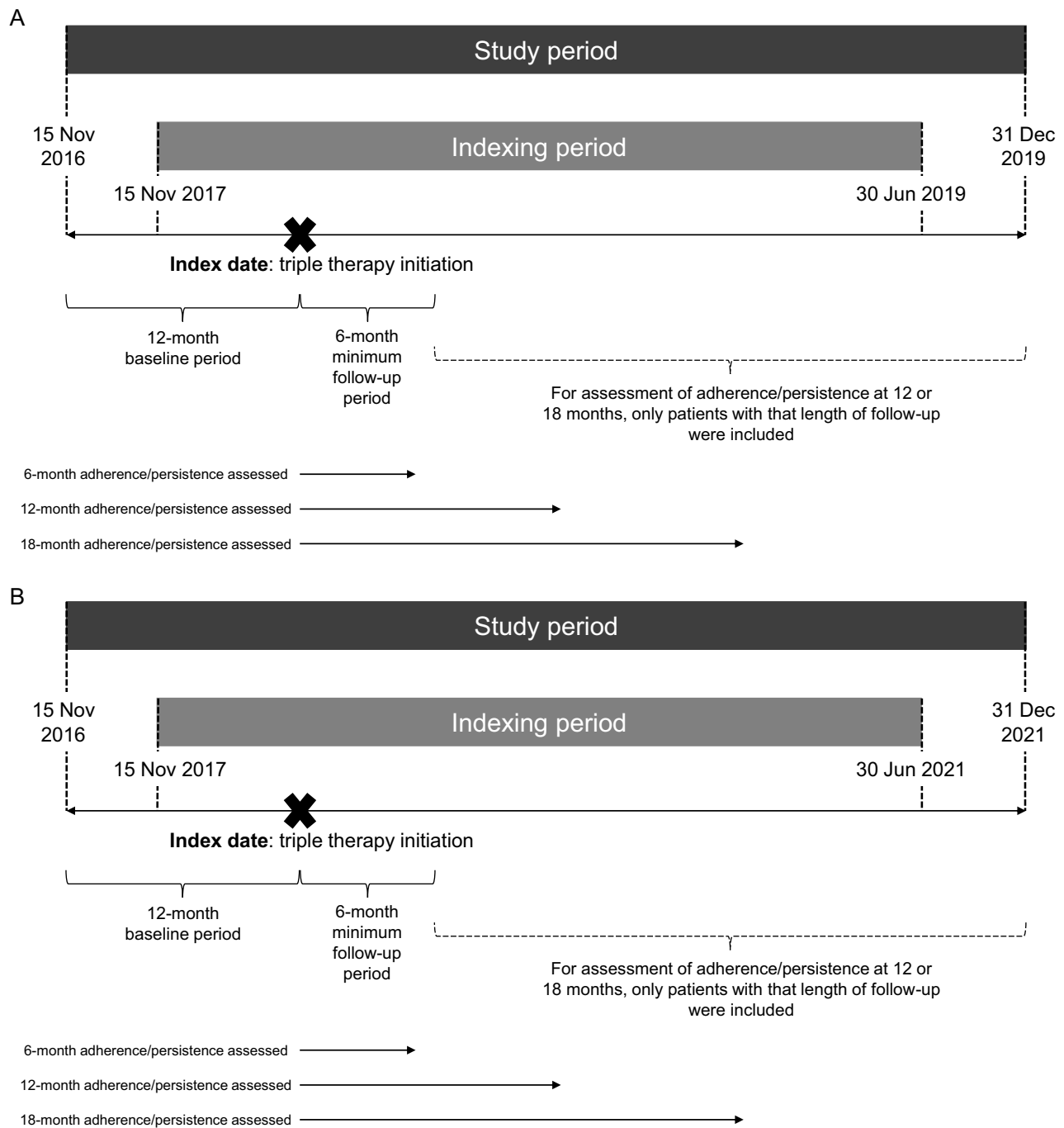
### Study Design and Data Source

This was a new-user, active comparator, retrospective cohort study of patients with COPD initiating triple therapy, identified using the WIG2 (Wissenschaftliches Institut für Gesundheitsökonomie und Gesundheitssystemforschung) benchmark database. The benchmark database is an anonymized healthcare claims database containing longitudinal data on approximately 4.5 million patients from all parts of Germany who are insured within the statutory health insurance (SHI) system.<sup>13</sup> Approximately 88% of the German population is enrolled in an SHI,<sup>14</sup> which provides inpatient, outpatient, and prescription drug coverage. The database is considered representative of the German SHI population.<sup>15</sup>

The study design is shown in [Figure 1A](#). The main study period started on 15 November 2016 and ended on 31 December 2019. The index date was defined as the first date of triple therapy initiation (MITT or SITT [FF/UMEC/VI or FOR/BDP/GLY]) between 15 November 2017 and 30 June 2019. For MITT users, this was defined as the first date of overlapping supply of all three triple therapy components (ICS + LABA + LAMA). The 12-month period prior to index was defined as the baseline period; the follow-up period spanned from the index date until the end of the study period, the end of data availability, or patient death, whichever was earliest. A minimum of 6 months' follow-up was required. An additional analysis was conducted, which included the period covering the COVID-19 pandemic (ie the study period spanned until 31 December 2021; [Figure 1B](#)). Patients initiating SITT with FOR/GLY/BUD were also included in this additional analysis (following the approval for use in Germany in December 2020).

### Study Population

Patients aged  $\geq 35$  years at index (in line with guidance from the National Institute for Health and Care Excellence)<sup>16</sup> with a confirmed COPD diagnosis ( $\geq 1$  inpatient or  $\geq 2$  outpatient; identified via International Statistical Classification of Diseases and Related Health Problems, version 10, German Modification, code J44) at any time during the patient's medical history, and a subsequent prescription for triple therapy (MITT or SITT) during the inclusion period were eligible to be included in the study. A patient was classified as a MITT user if there was a minimum of 30 days' overlap in the treatment supply of all three MITT agents. A 30-day minimum overlap was chosen because both FF/UMEC/VI and FOR/BDP/GLY are available in packs with a supply lasting at least 30 days. Patients were



**Figure 1** Study design: (A) main analysis and (B) exploratory analysis (study period covering the COVID-19 pandemic).

required to have been continuously insured for a minimum of 1 year prior to index and have no record of prior prescriptions for triple therapy. Patients were excluded if they had a record of  $\geq 1$  diagnostic code for any medical condition that can interfere with clinical COPD diagnosis or substantially change the natural history of the disease (ie conditions that are related to lung or bronchial developmental anomalies, degenerative processes [cystic fibrosis, pulmonary fibrosis], pulmonary resection, or other significant respiratory disorders other than COPD). Specific inclusion/exclusion criteria for the different patient cohorts are shown in [Table 1](#).

**Table 1** Specific Eligibility Criteria for the Different Patient Cohorts

Cohort	Eligibility Criteria
<b>Patients initiating MITT (MITT cohort)</b>	<ul style="list-style-type: none"> <li>• At least one inpatient and/or two confirmed outpatient diagnoses of COPD (J44) measured at any time in the patient history prior to index date</li> <li>• At least one prescription for MITT (a combination of ICS, LABA, and LAMA <math>\geq</math>30 overlapping days of supply with all three triple therapy components) from 15 November 2017 to 30 June 2019</li> <li>• No previous prescription for any triple therapy (MITT or SITT) during the study period</li> <li>• At least 35 years of age at the time of therapy initiation (index date)</li> <li>• Continuously insured by their sickness fund for at least 1 year leading up to the index date (therapy initiation) and at least 6 months of follow-up data (with the only exception as death)</li> </ul>
<b>Patients switching from MITT to SITT</b>	<ul style="list-style-type: none"> <li>• Patient satisfies criteria for inclusion in MITT cohort (above)</li> <li>• Patient received a prescription code for SITT (eg FF/UMEC/VI or FOR/BDP/GLY) at least 6 months after the index MITT code</li> <li>• Patient has at least 6 months of post-treatment switch data using SITT (eg FF/UMEC/VI or FOR/BDP/GLY), with the only exception as death</li> <li>• Patient had at least 30 days of MITT supply during the 6-month period leading up to the treatment switch and at least 1 day of MITT supply in the month leading up to the treatment switch</li> </ul>
<b>Patients initiating SITT (SITT cohort)</b>	<ul style="list-style-type: none"> <li>• At least one inpatient and/or two confirmed outpatient diagnoses of COPD (J44) measured at any time in the patient history prior to index date</li> <li>• At least one prescription for SITT (FF/UMEC/VI or FOR/BDP/GLY) from 15 November 2017 to 30 June 2019</li> <li>• No previous prescription for any triple therapy (MITT or SITT) 12 months prior to the index</li> <li>• At least 35 years of age at the time of therapy initiation (index date)</li> <li>• Continuously insured by their sickness fund for at least 1 year leading up to the index date (therapy initiation) and at least 6 months of follow-up data (with the only exception as death)</li> </ul>
<b>Patients initiating FF/UMEC/VI</b>	<ul style="list-style-type: none"> <li>• Patient satisfies criteria for inclusion in SITT cohort (above)</li> <li>• The patient's index triple therapy prescription was for FF/UMEC/VI</li> </ul>
<b>Patients initiating FOR/BDP/GLY</b>	<ul style="list-style-type: none"> <li>• Patient satisfies criteria for inclusion in SITT cohort (above)</li> <li>• The patient's index triple therapy prescription was for FOR/BDP/GLY</li> </ul>

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

## Study Objectives

### Primary Objectives

The primary objective was to describe and compare medication adherence (as measured by proportion of days covered [PDC]  $\geq$ 80%) among patients with COPD initiating MITT or SITT in the 6, 12, and 18 months following index. PDC was described in all patients, without accounting for periods of hospitalization or stockpiling. Outcomes were reported for the MITT versus SITT cohorts overall, and separately by specific SITT (ie MITT vs FF/UMEC/VI and MITT vs FOR/BDP/GLY). The difference in the proportion of adherent patients was also reported between FF/UMEC/VI users and FOR/BDP/GLY users.

The following sensitivity analyses were also conducted using different methods for calculating adherence: 1A) PDC was only reported among patients with  $\geq$ 1 follow-up prescription for the index triple therapy within 2 months of the index date; 1B) PDC was only reported during periods of continuous therapy (ie no discontinuation or treatment switches); 2) stockpiling was permitted (ie treatment supply could be allocated to a later point in the observation period); 3) stockpiling was permitted and periods of hospitalization were considered covered.

### Secondary Objectives

The secondary objective was to compare medication persistence (time until treatment discontinuation, assessed at 6, 12, and 18 months post-index) among patients initiating MITT or SITT (reported among MITT vs SITT overall, MITT vs FF/UMEC/VI, and MITT vs FOR/BDP/GLY).

Other secondary objectives included analyzing the proportion of patients who switched from MITT to SITT and describing the characteristics of patients initiating MITT or SITT. A description of the key baseline variables analyzed is included in [Supplementary Table 1](#).

### Exploratory Objectives

To assess the impact of COVID-19 on medication adherence and persistence, outcomes were assessed among patients initiating MITT or SITT over a prolonged study period (covering the COVID-19 pandemic). Adherence and persistence at 6 months post-index were also assessed among subgroups of patients with and without different comorbidities (cardiovascular disease, lung cancer, dementia/cognitive impairment, or arthritis) recorded during baseline.

### Data Analysis

Patients initiating triple therapy may possess a diverse array of characteristics, which shape their propensity to receive a specific treatment regimen over other options, and patients initiating MITT may possess systematic differences regarding sociodemographic and health characteristics than those initiating SITT. To minimize the impact of confounding on estimated treatment effects, a propensity score method was used to evaluate the study outcomes. Propensity scores were generated separately for each treatment comparison (MITT vs SITT, MITT vs FF/UMEC/VI, and MITT vs FOR/BDP/GLY). Two multivariate logistic regression models were used to assign propensity scores to patients from each cohort. Covariates considered for the model included age, sex, Charlson Comorbidity Index, baseline comorbidities (depression, anxiety, gastroesophageal reflux disease, acute myocardial infarction, congestive heart failure, stroke, bronchiectasis, dementia/cognitive impairment, and rheumatoid/osteo arthritis), asthma history, smoking history, number of visits to a pulmonologist, exacerbation history, and respiratory medication use. An inverse probability of treatment weighting (IPTW) approach was used to estimate the average treatment effect on the entire population of treated and untreated patients. The IPTW designated individual weights based on the propensity scores, creating a pseudo-population whose baseline characteristics were independent of treatment assignment. Standardized mean differences (SMDs) between the adjusted treatment and control groups were calculated, with an SMD <0.1 considered a negligible imbalance between cohorts.

Medication adherence was calculated using PDC (defined as the number of days “covered”/number of days in the period). Days covered by a prescription were calculated based on the quantity of the medication dispensed and the defined daily dosage as formulated by the World Health Organization and the Wissenschaftliches Institut der Ortskrankenkassen (WIdO, Scientific Institute of the General Local Health Insurance Fund, AOK), which serves as a proxy for the prescribed daily dosage.<sup>17</sup> Patients were categorized as adherent (PDC ≥80%) or nonadherent (PDC <80%). Mean (standard deviation [SD]) PDC was also reported for each cohort.

Medication non-persistence (discontinuation) was defined as a gap of >30 days between the end of a SITT prescription and the following refill, or for MITT users, a gap of >30 days between prescriptions in any of the three MITT components. The number and percentage of patients in each cohort who discontinued treatment was reported at 6, 12, and 18 months post-index. Time to treatment discontinuation was calculated using a prescription-based approach using the defined daily dose<sup>17</sup> and Kaplan–Meier estimates. Hazard ratios were calculated to compare outcomes across comparison groups (MITT vs SITT, MITT vs FF/UMEC/VI, and MITT vs FOR/BDP/GLY).

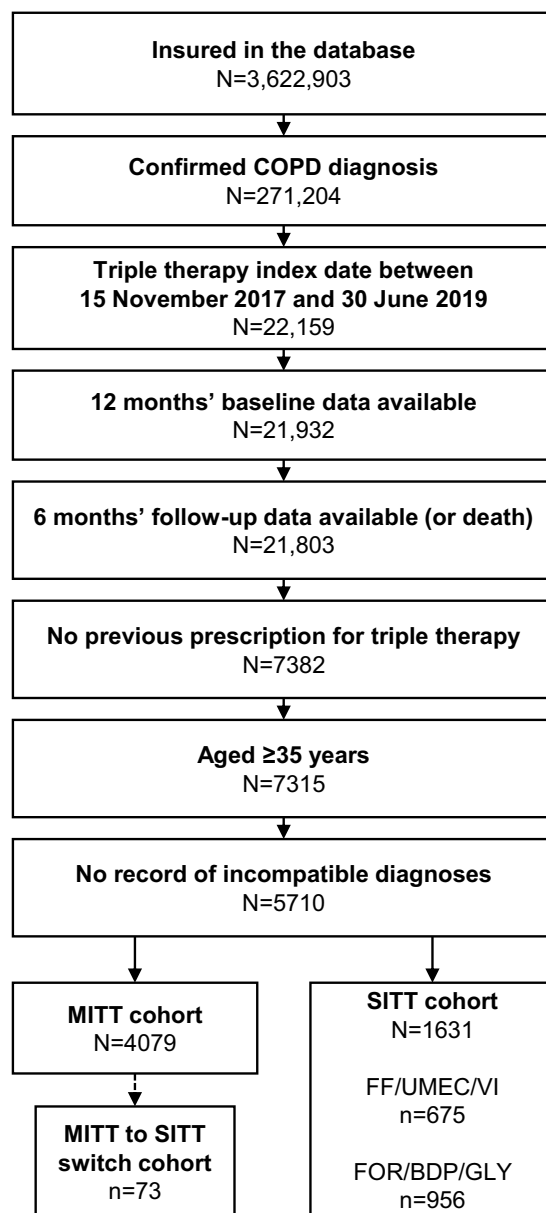
The number and percentage of patients initiating MITT, who later switched to SITT, was descriptively analyzed and reported at 6, 12, and 18 months post-index.

Adherence before and after COVID-19 was analyzed among individuals with ≥6 months of prescription data during the pre- and post-COVID periods. Adherence was also compared between individuals who initiated triple therapy during the pre-COVID period versus following the start of the global pandemic in March 2020.

## Results

### Baseline Characteristics

Overall, 5710 patients met all selection criteria and were included in the main analysis ([Figure 2](#)). Of these, 4079 (71.4%) initiated MITT and 1631 (28.6%) initiated SITT (FF/UMEC/VI: 675 [41.4%]; FOR/BDP/GLY: 956 [58.6%]). A total of 73 patients were included in the MITT to SITT switch analysis.



**Figure 2** Study population.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; FOR/BDP/GLY, formoterol/beclomethasone/glycopyrronium bromide; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.

The mean age was 66 years across all cohorts (Table 2). There was a higher proportion of males among SITT initiators (60.2%) versus MITT initiators (55.1%). The percentage of smokers was higher among FF/UMEC/VI (46.5%) and FOR/BDP/GLY (44.9%) users versus MITT (42.9%) users. Mean (SD) Charlson Comorbidity Index was slightly higher among MITT users (2.32 [1.71]) versus FF/UMEC/VI users (2.19 [1.65]) and FOR/BDP/GLY users (2.19 [1.57]).

## Adherence

Mean PDC was higher among SITT users versus MITT users at all time points (Figure 3). Across all cohorts, mean PDC decreased over time. At each time point, mean PDC was highest among FF/UMEC/VI users; MITT users had the lowest mean PDC at each time point.

Patients treated with SITT had significantly higher adherence than patients treated with MITT. During the first 6 months following index, FF/UMEC/VI users exhibited an adherence which was 29 percentage points higher versus MITT users; FOR/

**Table 2** Baseline Characteristics

	<b>MITT (N=4079)</b>	<b>SITT (N=1631)</b>	<b>FF/UMEC/VI (n=675)</b>	<b>FOR/BDP/GLY (n=956)</b>
<b>Age, years, mean (SD)</b>	66 (11.8)	66 (11.2)	66 (10.9)	66 (11.4)
<b>Male, %</b>	55.1	60.2	60.6	59.8
<b>Index year, %</b>				
2017	9.9	3.9	0	6.7
2018	62.2	54.6	49.3	58.4
2019	27.9	41.5	50.7	34.9
<b>FEV<sub>1</sub> % predicted &lt;50%, %</b>	7.6	7.2	6.1	8.0
<b>Number of prior exacerbations, mean (SD)</b>	0.3 (0.8)	0.2 (0.7)	0.2 (0.6)	0.3 (0.8)
<b>Level of care ≥2, %</b>	15.7	12.9	9.9	15.1
<b>CCI, mean (SD)</b>	2.32 (1.71)	2.19 (1.61)	2.19 (1.65)	2.19 (1.57)
<b>Smoker, %</b>	42.9	45.6	46.5	44.9
<b>Comorbidities, %</b>				
Anxiety	31.3	30.4	27.7	32.3
Arthritis	38.0	37.7	36.3	38.7
Asthma	23.7	13.2	12.9	13.4
Bronchiectasis	2.0	1.8	2.7	1.3
Dementia	8.7	6.6	5.9	7.0
Depression	28.7	25.2	23.3	26.6
Gastroesophageal reflux disease	19.9	18.5	19.4	17.9
Congestive heart failure	9.1	6.9	5.8	7.6
Myocardial infarction	6.4	7.1	5.8	8.0
Stroke	7.6	6.6	6.7	6.6

**Abbreviations:** CCI, Charlson Comorbidity Index; FEV<sub>1</sub>, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; FOR/BDP/GLY, formoterol/beclomethasone/glycopyrronium bromide; MITT, multiple-inhaler triple therapy; SD, standard deviation; SITT, single-inhaler triple therapy.

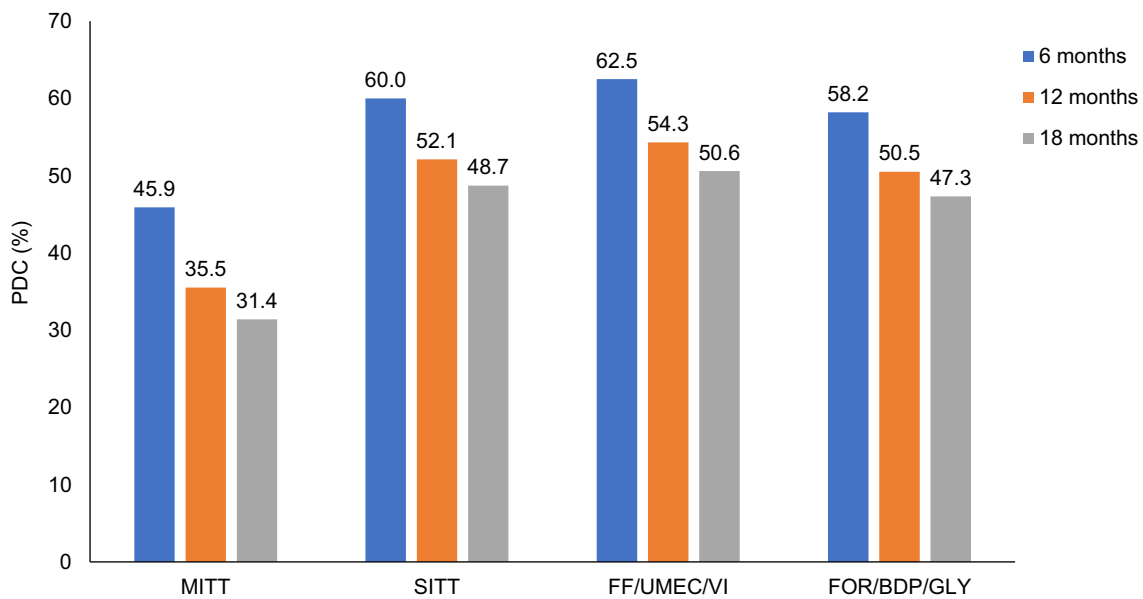
BDP/GLY users exhibited an adherence which was 19 percentage points higher versus MITT users (Figure 4). When comparing patients treated with FF/UMEC/VI and FOR/BDP/GLY, unweighted estimates showed that FF/UMEC/VI users exhibited an adherence which was 10 percentage points higher versus FOR/BDP/GLY users at 6 months and 12 months ( $p=0.0001$  and  $p<0.0001$ , respectively), and 8 percentage points higher at 18 months ( $p=0.0006$ ).

Results were consistent during sensitivity analyses using different methods to calculate adherence (ie 1A, 1B, 2, and 3; [Supplementary Table 2](#) and [Supplementary Figure 1](#)).

## Persistence

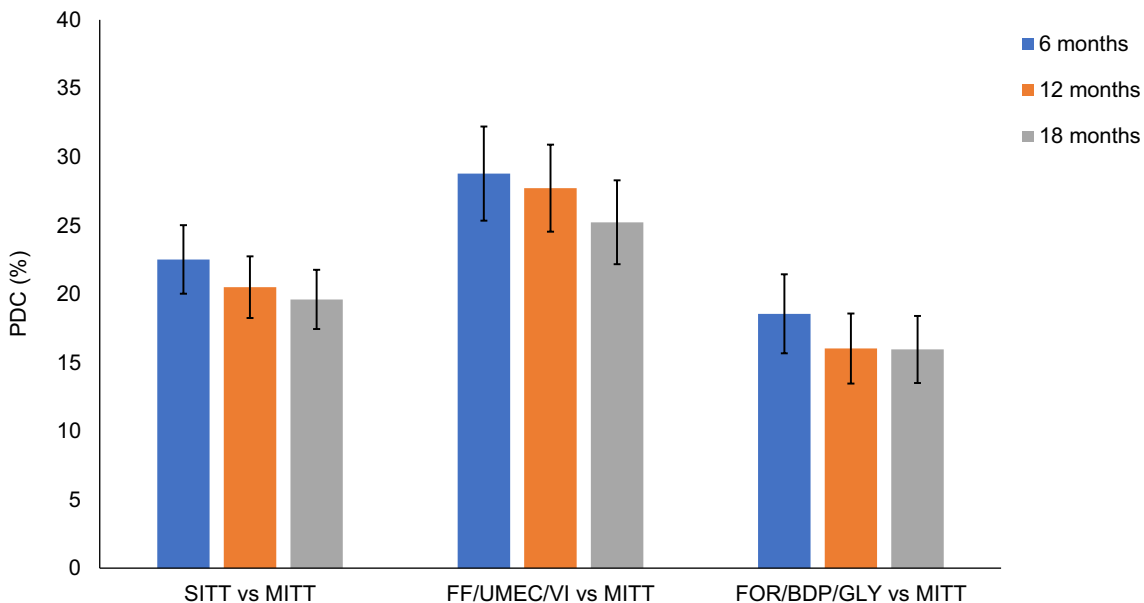
After 30 days, the proportion of persistent patients was approximately equal for MITT and SITT users. After that, FF/UMEC/VI users had a higher persistence versus the other cohorts at 6, 12, and 18 months (Figure 5). The differences were particularly remarkable within the initial 6 months; 36.2% of FF/UMEC/VI users had no gap in





**Figure 3** Mean PDC for MITT, SITT, FF/UMEC/VI, and FOR/BDP/GLY cohorts at 6, 12, and 18 months post-index.

**Abbreviations:** FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; FOR/BDP/GLY, formoterol/beclomethasone/glycopyrronium bromide; MITT, multiple-inhaler triple therapy; PDC, proportion of days covered; SITT, single-inhaler triple therapy.



**Figure 4** Difference in the proportion of adherent patients (PDC  $\geq$ 80%): SITT vs MITT, FF/UMEC/VI vs MITT, and FOR/BDP/GLY vs MITT, IPTW weighted.

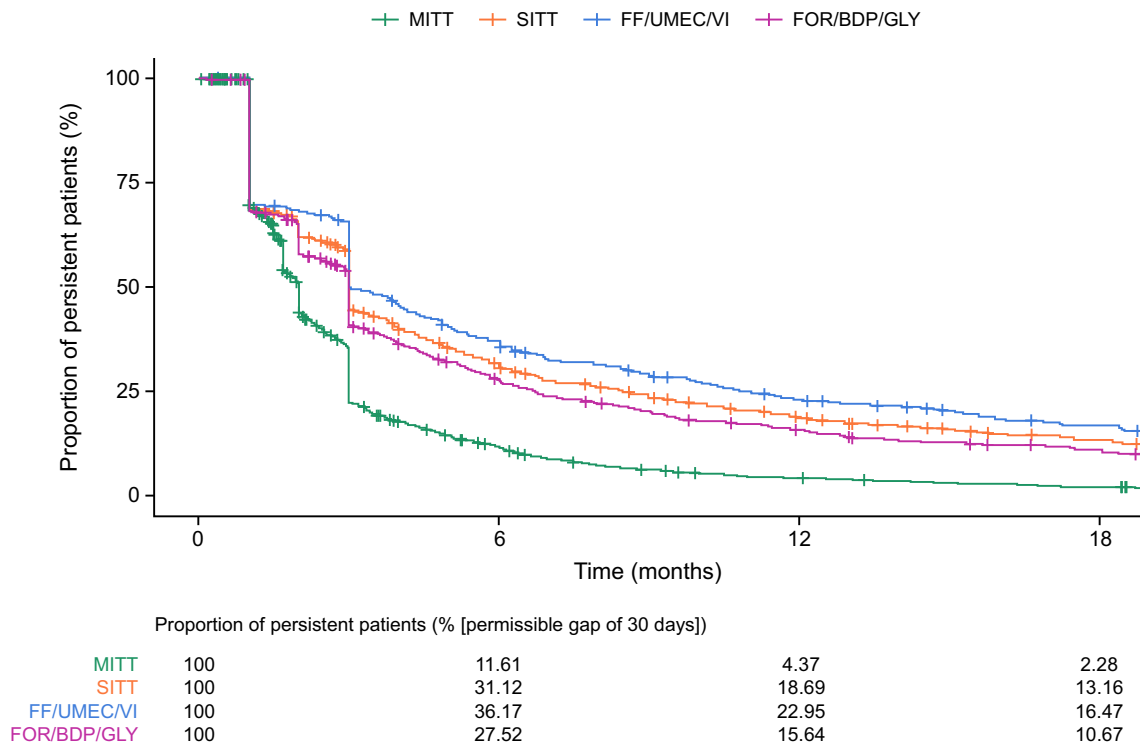
**Abbreviations:** FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; FOR/BDP/GLY, formoterol/beclomethasone/glycopyrronium bromide; IPTW, inverse probability of treatment weighting; MITT, multiple-inhaler triple therapy; PDC, proportion of days covered; SITT, single-inhaler triple therapy.

their supply versus 11.6% of MITT users. At 18 months, 16.5% of FF/UMEC/VI users were persistent versus 2.3% of MITT users.

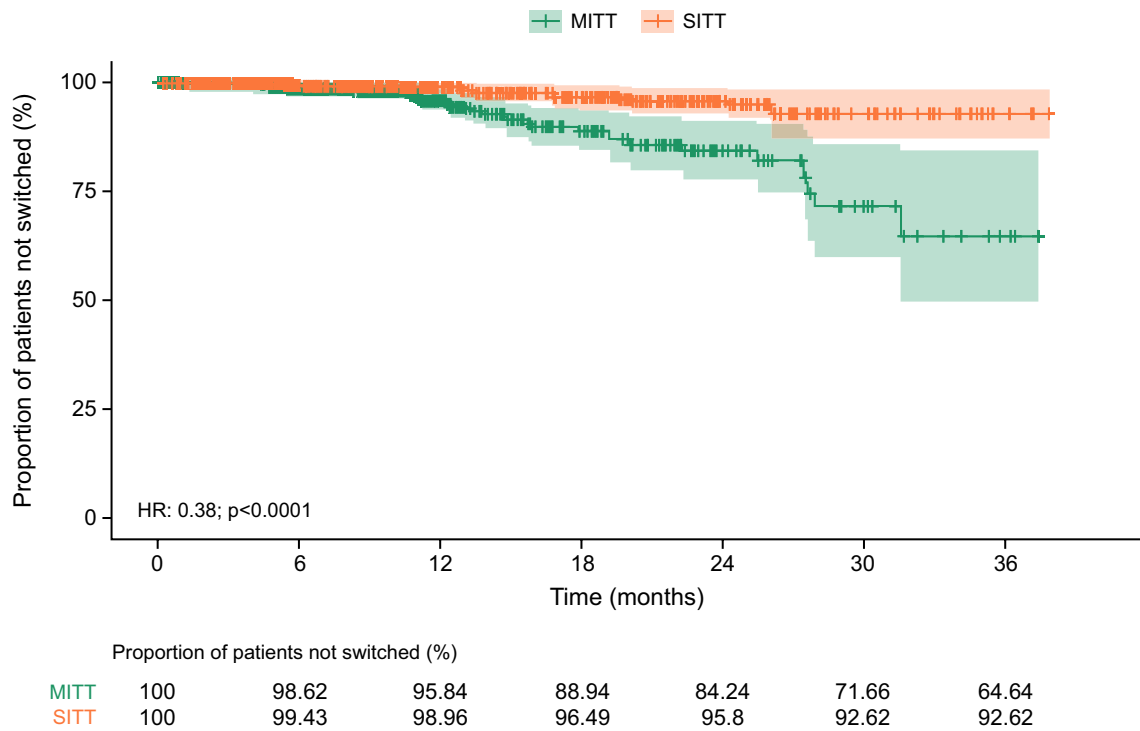
## MITT to SITT Switch

During the first 6 months following index, few patients switched from MITT to SITT (1.4%) and from SITT to MITT or from one SITT to another (0.6%). This proportion increased as the observation period extended; after 36 months, 7.4% of SITT users and 35.4% of MITT users had switched therapy (Figure 6).





**Figure 5** Kaplan–Meier curves of persistence in unweighted MITT, SITT, FF/UMEC/VI, and FOR/BDP/GLY cohorts (permissible gap of 30 days).  
**Abbreviations:** FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; FOR/BDP/GLY, formoterol/beclomethasone/glycopyrronium bromide; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.



**Figure 6** Kaplan–Meier curves of persistence for MITT and SITT cohorts, IPTW weighted (permissible gap of 30 days).  
**Abbreviations:** HR, hazard ratio; IPTW, inverse probability of treatment weighting; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.

## Exploratory Analyses

### Impact of the COVID-19 Pandemic

This exploratory analysis included data from 13,886 patients (MITT: 69.4%; FF/UMEC/VI: 14.1%; FOR/BDP/GLY: 16.2%; FOR/GLY/BUD: 0.3%). Overall, the results were consistent with the main analysis ([Supplementary Figure 2](#)). When focusing on a subgroup of patients who had received  $\geq 1$  prescription for their index therapy within 6 months before and 6 months after the start of the COVID-19 pandemic (n=1843), across all cohorts, adherence rates were higher after the start of the pandemic versus before. MITT users showed the highest rise, with the proportion of adherent patients rising from 16.6% (before pandemic) to 19.9% (after the start of the pandemic).

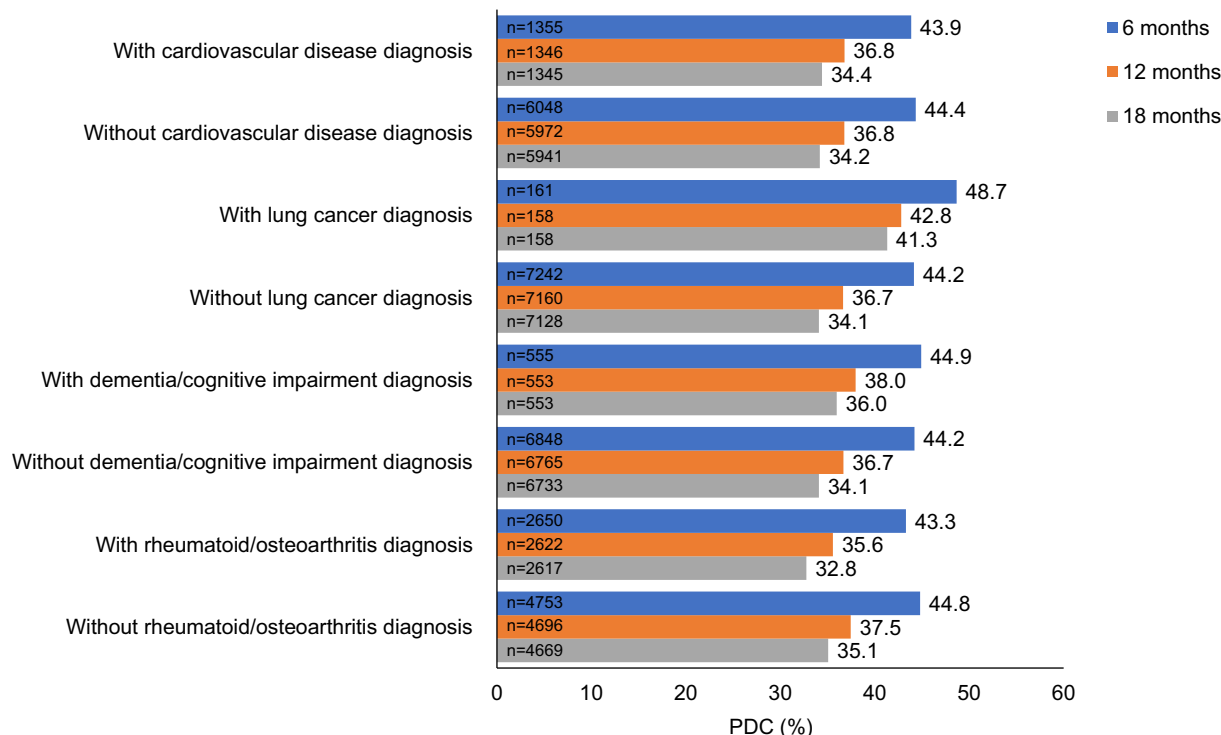
### Comorbidities

For this analysis, patients were stratified based upon pre-existing comorbidities recorded during baseline. No major differences in adherence ([Figure 7](#)) and persistence were observed between comorbidity subgroups. Among all subgroups, the highest persistence was observed among patients with lung cancer; patients with a diagnosis of arthritis showed the lowest proportion of persistent patients.

## Discussion

In this retrospective study using a large German healthcare claims database, patients with COPD newly initiating SITT (FF/UMEC/VI or FOR/BDP/GLY) had consistently greater adherence and persistence compared with patients newly initiating MITT. At 6, 12, and 18 months following treatment initiation, the proportion of adherent patients was consistently higher for patients receiving SITT versus those receiving MITT; patients who received SITT also had a significantly higher persistence versus those treated with MITT during the entire 18-month post-index period.

The findings of the current study are in line with other analyses of adherence and persistence among patients with COPD initiating treatment with SITT in England,<sup>18</sup> US,<sup>19</sup> France,<sup>20</sup> China,<sup>21</sup> and Japan.<sup>22</sup> In a retrospective cohort study conducted using primary and secondary care data in England, a significantly higher proportion of patients initiating SITT



**Figure 7** Proportion of adherent patients (PDC  $\geq 80\%$ ) at 6, 12, and 18 months post-index, stratified by comorbidities.

**Abbreviation:** PDC, proportion of days covered.

with FF/UMEC/VI were adherent to therapy (PDC  $\geq 80\%$ ) versus patients initiating MITT at 6, 12, and 18 months post-index (41.0% vs 18.3%; 34.4% vs 14.9%; 35.5% vs 12.2%, respectively).<sup>18</sup> In a similar US retrospective database analysis, 46.5% of patients initiating SITT FF/UMEC/VI were adherent to therapy at 6 months following treatment initiation versus 22.3% of patients initiating MITT.<sup>19</sup> A recent analysis in Japan also reported that the proportion of patients adherent to therapy was greater for SITT initiators versus MITT initiators at 6, 12, and 18 months post-treatment initiation (19.7% vs 10.2%; 6.0% vs 3.8%; 3.8% vs 1.4%, respectively).<sup>22</sup>

The increased persistence for SITT initiators versus MITT initiators in the current study is also consistent with results from prior studies.<sup>18–22</sup> Higher persistence with SITT has previously been associated with improved health outcomes in patients with COPD. In a retrospective cohort study, Spanish patients with COPD receiving SITT had higher persistence, reduced risk of exacerbations, and lower risk of all-cause mortality compared with patients receiving MITT after 12 and 24 months' follow-up.<sup>23</sup> SITT was also associated with a significant reduction in healthcare resource use, resulting in annual cost savings versus MITT.<sup>23</sup> SITT with FF/UMEC/VI was also associated with significant improvements in health status and lung function when compared with MITT in an effectiveness study conducted in a usual clinical care setting.<sup>24</sup>

When comparing between the different SITT regimens, patients receiving FF/UMEC/VI appeared to show slightly better persistence than patients receiving FOR/BDP/GLY. We also observed that a significantly higher proportion of FF/UMEC/VI users were adherent to therapy at 6, 12, and 18 months post-index versus FOR/BDP/GLY users. However, it should be noted that no statistical comparison for persistence between SITT regimens was performed as this was out of scope for this study, and the adherence analysis reported is unadjusted; as such, the results should be interpreted with caution. These findings could highlight the advantage of once-daily dosing versus twice-daily dosing. Further research comparing adherence and persistence between different SITTs is needed.

The results from this study allow insights into real-world adherence and persistence patterns among patients with COPD in Germany and provide a basis for future research. The findings also highlight possible areas for improved decision-making among practitioners when treating patients with COPD. Taken together, our results indicate that increased utilization of SITT in Germany may lead to reduced treatment discontinuation among patients with COPD. Further investigation is needed to explore the relationship between medication adherence and patient outcomes in Germany.

This analysis has some limitations, which are common to analyses of claims data. There is a possibility that during detection of MITT users (ie patients with an overlap in the prescription of all three components of triple therapy), patients switching between different non-MITT regimens (eg from LAMA to ICS/LABA) may have been misclassified as MITT users. However, using a broad overlap to define MITT use (such as the 30-day overlap used in this study) minimizes the risk of misclassification. Also, some therapies may be prescribed for patients with COPD and comorbid asthma; in these cases, it is impossible to disentangle treatment of COPD from systemic treatment of uncontrolled asthma. As this study uses diagnostic codes recorded for the purpose of reimbursement (ie secondary data), the validity may be impacted. Further to this, dates for diagnoses in the outpatient records are coded as calendar year quarters, therefore the exact timing of these diagnoses is uncertain. Recording of data on medications administered in hospital is limited. In addition, pharmacy claims records do not contain patient counseling (eg number of intakes per day); usage was assumed according to the summary of product characteristics. Although pharmacy claims provide an indirect measurement of adherence, the prescribing of a medication does not guarantee that the patient took the medication as prescribed. Finally, as this study was limited to individuals with SHI, the results may not be generalizable to patients with private health insurance. However, as approximately 88% of the German population is covered by SHI,<sup>14</sup> this is not considered a major limitation.

## Conclusion

In this retrospective study, which used a national claims database, German patients with COPD who initiated SITT with FF/UMEC/VI or FOR/BDP/GLY had significantly higher adherence and persistence compared with patients who initiated MITT over 6 to 18 months following treatment initiation. Among SITT, FF/UMEC/VI users had the highest proportion of adherence and persistence. These data suggest that a reduction in the number of inhalers required may improve adherence and persistence for patients with COPD. These findings support GOLD recommendations and emphasize an overall advantage of SITT in patients with COPD regarding adherence and persistence.

## Abbreviations

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; FOR/BDP/GLY, formoterol/beclomethasone/glycopyrronium bromide; FOR/GLY/BUD, formoterol/glycopyrronium bromide/budesonide; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ICS, inhaled corticosteroid; IPTW, inverse probability of treatment weighting; LABA, long-acting  $\beta$ 2-agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; PDC, proportion of days covered; SD, standard deviation; SHI, statutory health insurance; SITT, single-inhaler triple therapy; SMD, standardized mean difference; WIG2, Wissenschaftliches Institut für Gesundheitsökonomie und Gesundheitssystemforschung.

## Data Sharing Statement

The data analyzed in this manuscript are contained in a database owned by the WIG2 GmbH Scientific Institute for Health Economics and Health Systems Research. All analyses based on WIG2 data are carried out exclusively by WIG2; no transfer of data outside of WIG2 takes place.

## Ethics Approval and Informed Consent

This study complied with all applicable laws regarding patient privacy. No direct patient contact or primary collection of individual human patient data occurred. Study results are in tabular form and presented as aggregate analyses that omit patient identification. 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 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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