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ORIGINAL RESEARCH

Clinical and Economic Evaluation of Fluticasone Furoate/Umeclidinium/Vilanterol Versus Tiotropium/Olodaterol Therapy in Maintenance Treatment–Naive Patients with COPD in the US

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Purpose: Long-acting bronchodilator (LABD) therapy is recommended for maintenance treatment in most patients with chronic obstructive pulmonary disease (COPD). However, triple therapy (TT; dual LABDs + inhaled corticosteroid [ICS]) is often used as first-line maintenance treatment. The benefits of TT versus dual LABDs as first-line treatments are unknown, necessitating an evaluation of its effectiveness and costs versus non-ICS alternatives.

Patients and Methods: This retrospective study assessed administrative claims of maintenance treatment–naive patients in the United States with COPD aged ≥40 years initiating single-inhaler fluticasone furoate+umeclidinium+vilanterol (FF+UMEC+VI) or tiotropium+olodaterol (TIO+OLO). Patients were propensity score–matched (1:1) and followed for up to 12 months. The primary outcome was time to first COPD exacerbation. Secondary outcomes included time to first pneumonia diagnosis, pneumonia-related hospitalization, healthcare resource utilization (HCRU), and costs. COPD exacerbation and pneumonia risk were assessed using Cox proportional hazards regression.

Results: A total of 5,121 and 3,996 patients met the eligibility criteria for the FF+UMEC+VI and TIO+OLO groups, respectively. Outcomes were assessed among 2,951 matched pairs. The risk of moderate or severe COPD exacerbation was not significantly different between FF+UMEC+VI and TIO+OLO groups (hazard ratio [HR] [95% confidence interval {CI}]: 1.13 [0.99–1.29]; P=0.064). The risks of pneumonia (HR [95% CI]: 1.04 [0.85–1.27]; P=0.723) and pneumonia-related hospitalization (HR [95% CI]: 1.18 [0.78–1.79]; P=0.429) were also not significantly different between the groups. There were no significant differences in HCRU events or all-cause costs; however, FF+UMEC+VI initiators incurred greater COPD- and/or pneumonia-related pharmacy costs than TIO+OLO initiators (FF+UMEC+VI: $2,934 [$2,827–$3,041], TIO+OLO: $1,994 [$1,915–$2,073]; P<0.001).

Conclusion: In maintenance treatment–naive patients, FF+UMEC+VI offered no reduction in COPD exacerbation risk over TIO+OLO and resulted in higher pharmacy costs related to COPD and/or pneumonia treatment. These results support treatment recommendations for LAMA+LABA as initial maintenance therapy.

Trial Registration: ClinicalTrials.gov identifier - NCT05169424.

Plain Language Summary: Chronic obstructive pulmonary disease (COPD) is a disease affecting the lungs, which causes symptoms such as shortness of breath, cough, and phlegm. The goal of COPD management is to control the symptoms and reduce the risk of flare-ups (exacerbations). COPD maintenance treatments include medications called inhaled corticosteroids (ICS) that reduce airway inflammation and bronchodilators that either prevent the closing of airways (eg, long-acting muscarinic antagonists [LAMAs]), or keep them open longer (eg, long-acting beta2-agonists [LABAs]). National and international guidelines recommend triple therapy (ICS+LAMA+LABA) for symptomatic patients who continue to have frequent exacerbations despite LAMA+LABA dual therapy. However, the use of triple therapy as the first treatment choice is common in everyday clinical practice, even in patients who have not received any long-acting bronchodilators in the past (maintenance treatment–naive patients). Therefore, our study compared the clinical and economic outcomes in maintenance

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treatment–naive patients who were given single-inhaler triple therapy (LAMA+LABA+ICS) with those who were given dual therapy (LAMA+LABA). In our study, the risk of COPD flare-up, pneumonia, and hospitalization due to pneumonia was not different between patients who received triple and dual therapy, indicating no significant benefit of triple therapy over dual therapy. Additionally, triple therapy resulted in higher pharmacy costs. We conclude that for patients with COPD starting maintenance treatment, dual therapy was not only as effective as triple therapy in managing COPD but also had economic benefits.

Keywords: dual bronchodilator therapy, exacerbation risk, health outcomes, maintenance treatment–naive, treatment initiation, triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is ranked as one of the top three causes of mortality worldwide and is associated with progressive and partially reversible airflow obstruction.[1,2] Exacerbations, particularly those resulting in hospitalization, contribute to approximately 50% of direct costs and 70% of COPD-related costs of the total healthcare expenditure associated with COPD and lead to a decline in the quality of life.[3,4] To manage symptoms and reduce exacerbation risk, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 report recommends long-acting bronchodilator (LABD) therapy at treatment initiation. Dual therapy with a long-acting muscarinic antagonist (LAMA) plus a long-acting beta2-agonist (LABA) is preferred over a single LABD. Triple therapy (TT) comprising a LAMA, LABA, and an inhaled corticosteroid (ICS) is recommended as the initial therapy only for patients with concomitant asthma or frequent/severe exacerbations and elevated blood eosinophil levels (≥300 cells/μL).[5]

Although multiple randomized controlled trials have compared the efficacy of TT with that of dual LABD therapy, there are concerns regarding the study design and applicability of the results to a broader COPD patient population, warranting additional research in different COPD populations.[6–8] For instance, the IMPACT and ETHOS trials investigated the annualized rate of moderate or severe COPD exacerbations over 1 year with TT use compared to LAMA plus LABA use.[7,8] The populations studied in these trials were considered high-risk, with lower lung function and a history of exacerbations in the previous year. A total of 62% of the IMPACT population had COPD for ≥5 years at screening, whereas the mean duration of COPD in ETHOS was >8 years.[7,8] Approximately 40% of the IMPACT and 46% of the ETHOS populations received TT, and over two-thirds had received ICS before entering the study.[7,8] The KRONOS trial compared the efficacy of TT versus LAMA plus LABA among symptomatic patients with moderate-to-very severe COPD without the need for prior COPD exacerbations within the preceding year.[9] However, the enrolled patients received ≥2 inhaled maintenance therapies for at ≥6 weeks prior to screening.[9]

Routine clinical practice data suggest that 85.5% of patients with COPD receiving maintenance therapy are categorized (according to GOLD 2022 criteria) as GOLD A/B, 4.1% as GOLD C, and 10.4% as GOLD D.[10] However, all three trials (IMPACT, ETHOS, and KRONOS) recruited patients with persistent symptoms despite receiving ≥2 maintenance therapies.[6–8] By design, the patients and their previous treatment patterns included in these trials differed from those in routine clinical practice.[11] Therefore, the treatment benefit of initiating or re-initiating TT in a routine clinical setting in a maintenance treatment–naive population at low risk of exacerbations should not be extrapolated from existing trials of TT.[6–8]

Despite the availability of recommendations built upon a synthesis of the available evidence, in clinical practice, TT is often prescribed as first-line maintenance therapy and up to 37.6% of patients with COPD who are prescribed single-inhaler TT are maintenance treatment–naive.[12] Although recommendations for treatment algorithms have changed over time, GOLD has consistently not endorsed the use of TT in patient populations with low exacerbation history,[5] and there could be a greater risk of pneumonia with TT overuse, potential for higher costs and healthcare resource utilization (HCRU), and other possible long-term risks linked to ICS use.[13–15] GOLD 2024 also recommends fixed-dose combination (FDC) LAMA plus LABA therapy as the preferred choice for initial maintenance therapy in patients with COPD with increased symptoms and moderate-to-severe exacerbations (GOLD 2024 group B and group E with eosinophil count <300/μL). Conversely, TT should be prescribed only for patients in group E with eosinophil count ≥300/μL.[5] Consequently, assessing the clinical effectiveness and cost implications of TT compared with FDC LAMA plus LABA as initial therapy in COPD patient populations is important. This study aimed to assess COPD exacerbations, pneumonia

diagnosis and pneumonia-related hospitalization, HCRU, and costs in maintenance treatment–naive patients with COPD initiating first-line treatment with TT: fluticasone furoate plus umeclidinium plus vilanterol (FF+UMEC+VI), compared with those initiating dual therapy: tiotropium bromide plus olodaterol (TIO+OLO).

Materials and Methods

Study Design

This was a retrospective, observational, new user design study, conducted using real-world data from administrative claims of commercial insurance and Medicare Advantage with Part D (MAPD) prescription drug coverage beneficiaries for the period between September 15, 2016, and March 31, 2020 (ClinicalTrials.gov ID: NCT05169424).

Medical and pharmacy claim records were sourced from the IQVIA PharMetrics® Plus database (previously known as IMS PharMetrics) containing administrative insurance data and enrollment information of approximately 150 million patients who were commercially insured or had Medicare, covering 90% of the United States (US) hospitals compliant with the Health Insurance Portability and Accountability Act.

Considering the availability of tiotropium+olodaterol (TIO+OLO) since May 2015 and that of fluticasone furoate+umeclidinium+vilanterol (FF+UMEC+VI) since September 2017, prescription claims between September 15, 2017, and February 29, 2020, were analyzed to identify the initiation of maintenance therapy. The index date was the date of the first claim for FDC of FF+UMEC+VI (100/62.5/25 µg) or TIO+OLO (5/5 µg). The baseline period was defined as the 12 months preceding the index date. Eligible patients were required to be enrolled continuously in a health plan during the 12-month baseline period and on the index date. Patients aged ≥40 years with two separate medical claims (≥1 claim on or before the index date in the baseline period) with a COPD diagnosis code (International Classification of Diseases [ICD] Tenth Revision, Clinical Modification J41–J44) in any position on unique dates during the study period and ≥1 pharmacy claim (Supplemental Table S1) initiating single-inhaler FF+UMEC+VI or TIO+OLO were included. Patients with ≥2 medical claims for asthma, cystic fibrosis, interstitial lung disease, or lung cancer during the study period were not eligible for inclusion in the study. Patients who were not on any maintenance treatment for 6 months prior to the index date were considered treatment-naive. The exclusion criteria included the use of biologics, LAMA, LABA, or ICS monotherapy; free or FDC ICS+LABA, LAMA+LABA, and ICS+LAMA+LABA therapy in the 6 months before the index date; and pharmacy claims for >1 index medication on the index date.

Patients were followed up from the index date onward for no longer than 12 months. Follow-up was censored for any of the following reasons (whichever occurred first): switch in index treatment, discontinuation of index treatment, end of the study period (March 31, 2020), or end of continuous health plan enrollment.

Outcomes and Assessments

Demographic and clinical characteristics of the groups at baseline (Table 1), respiratory medications used, and all-cause and disease-related HCRU and costs were assessed 12 months prior to the index date (inclusive).

Table 1 Baseline Demographic and Clinical Characteristics of a Maintenance Treatment–Naive Population Initiating TIO+OLO or FF+UMEC+VI Before and After PSM

	Pre-PSM			Post-PSM		
	FF+UMEC+VI (n=5,121)	TIO+OLO (n=3,996)	SMD	FF+UMEC+VI (n=2,951)	TIO+OLO (n=2,951)	SMD
Age, years, mean (SD)	60.9 (7.87)	61.7 (8.37)	0.097	61.2 (8.17)	61.4 (8.16)	0.031
Sex, n (%)						
Female	2,368 (46)	1,894 (47)	−0.023	1,363 (46)	1,406 (48)	−0.029
Male	2,753 (54)	2,102 (53)		1,588 (54)	1,545 (52)	
Charlson Comorbidity Index score, mean (SD)	1.7 (1.71)	1.7 (1.75)	0.013	1.7 (1.69)	1.7 (1.76)	0.021

(*Continued*)

Table 1 (Continued).

	Pre-PSM			Post-PSM		
	FF+UMEC+VI (n=5,121)	**TIO+OLO (n=3,996)**	**SMD**	**FF+UMEC+VI (n=2,951)**	**TIO+OLO (n=2,951)**	**SMD**
Region, n (%)						
Northeast	630 (12)	574 (14)	0.213	389 (13)	403 (14)	0.0258
Midwest	1,129 (22)	1,147 (29)		784 (27)	756 (26)	
South	3,096 (60)	2,001 (50)		1,597 (54)	1,602 (54)	
West	264 (5)	272 (7)		180 (6)	189 (6)	
Unknown	2 (<1)	2 (<1)		1 (<1)	1 (<1)	
Insurance type, n (%)						
Commercial	3,771 (74)	2,695 (67)	0.196	2,078 (70)	2,060 (70)	0.03
Medicare	367 (7)	512 (13)		296 (10)	323 (11)	
Medicaid	19 (<1)	16 (<1)		12 (<1)	12 (<1)	
Self/Other/Unknown	964 (19)	773 (19)		565 (19)	556 (19)	
Year of cohort entry, n (%)						
2017	12 (<1)	519 (13)	0.686	12 (<1)	12 (<1)	0.021
2018	1,273 (25)	1,529 (38)		1,016 (34)	1,017 (34)	
2019	2,993 (58)	1,608 (40)		1,564 (53)	1,582 (54)	
2020	843 (16)	340 (9)		359 (12)	340 (12)	
Season (index date), n (%)						
Spring	998 (19)	835 (21)	0.118	633 (21)	629 (21)	0.023
Summer	1,079 (21)	758 (19)		666 (23)	693 (23)	
Fall	1,127 (22)	1,047 (26)		613 (21)	612 (21)	
Winter	1,917 (37)	1,356 (34)		1,039 (35)	1,017 (34)	
Severe exacerbations, n (%)						
0	4,551 (89)	3,639 (91)	0.088	2,664 (90)	2,677 (91)	0.061
1	497 (10)	320 (8)		251 (9)	252 (9)	
≥2	73 (1)	37 (1)		36 (1)	22 (1)	
Moderate/severe exacerbations, n (%)						
0	3,529 (69)	2,946 (74)	0.119	2,114 (72)	2,128 (72)	0.064
1	1,350 (26)	912 (23)		715 (24)	724 (25)	
≥2	242 (5)	138 (3)		122 (4)	99 (3)	

(*Continued*)

Table 1 (Continued).

	Pre-PSM			Post-PSM		
	FF+UMEC+VI (n=5,121)	**TIO+OLO (n=3,996)**	**SMD**	**FF+UMEC+VI (n=2,951)**	**TIO+OLO (n=2,951)**	**SMD**
Hospitalizations, n (%)						
Yes	810 (16)	596 (15)	−0.025	437 (15)	453 (15)	0.015
No	4,311 (84)	3,400 (85)		2,514 (85)	2,498 (85)	
ED visits, n (%)						
Yes	1,023 (20)	820 (21)	0.013	580 (20)	609 (21)	0.024
No	4,098 (80)	3,176 (79)		2,371 (80)	2,342 (79)	
OP visits, n (%)						
Yes	4,716 (92)	3,745 (94)	0.063	2,736 (93)	2,757 (93)	0.028
No	405 (8)	251 (6)		215 (7)	194 (7)	
Total IP costs[a], USD, mean (SD)	4,640 (21,394)	4,752 (22,174)	0.005	4,294 (21,372)	4,815 (22,532)	0.024
Total ED costs[a], USD, mean (SD)	304 (1,668)	282 (1,479)	−0.014	280 (1,683)	291 (1,440)	0.007
Total OP costs[a], USD, mean (SD)	4,078 (10,892)	4,023 (10,413)	−0.005	3,927 (10,269)	4,043 (10,599)	0.011
Any LAMA use, n (%)	527 (10)	269 (7)	−0.128	195 (7)	209 (7)	0.0188
Any LABA use, n (%)	2 (<1)	2 (<1)	0.005	1 (<1)	1 (<1)	0
Any ICS use, n (%)	60 (1)	27 (1)	−0.0519	36 (1)	18 (1)	−0.064
ICS/LABA use, n (%)	428 (8)	130 (3)	−0.219	93 (3)	99 (3)	0.011
Any SABA use, n (%)	2,507 (49)	1,918 (48)	−0.019	1,417 (48)	1,438 (49)	0.014
Any SAMA use, n (%)	6 (<1)	1 (<1)	−0.03	4 (<1)	1 (<1)	−0.035
Methylxanthine use, n (%)	31 (<1)	15 (<1)	−0.033	18 (<1)	9 (<1)	−0.045
OCS, n (%)	2,337 (46)	1,519 (38)	−0.155	1,173 (40)	1,188 (40)	0.01
Antibiotics, n (%)	2,801 (55)	2,051 (51)	−0.067	1,537 (52)	1,551 (53)	0.009
Azithromycin, n (%)	1,300 (25)	931 (23)	−0.049	685 (23)	669 (23)	−0.013
Tobacco counseling, n (%)	820 (16)	621 (16)	−0.013	472 (16)	445 (15)	−0.025
Pulmonary rehabilitation, n (%)	34 (1)	13 (<1)	−0.048	7 (<1)	8 (<1)	0.007
Oxygen therapy, n (%)	795 (16)	551 (14)	−0.049	432 (15)	396 (13)	−0.035
Cardiovascular disease, n (%)	1,429 (28)	1,137 (28)	0.012	822 (28)	836 (28)	0.011
Diabetes, n (%)	920 (18)	733 (18)	0.009	518 (18)	526 (18)	0.007
Renal failure, n (%)	368 (7)	309 (8)	0.021	209 (7)	222 (8)	0.017
GERD, n (%)	987 (19)	733 (18)	−0.024	547 (19)	538 (18)	−0.007
Arthritis, n (%)	711 (14)	561 (14)	0.004	403 (14)	407 (14)	0.004
Osteoporosis, n (%)	160 (3)	132 (3)	0.01	103 (3)	88 (3)	−0.029

(*Continued*)

Table 1 (Continued).

	Pre-PSM			Post-PSM		
	FF+UMEC+VI (n=5,121)	**TIO+OLO (n=3,996)**	**SMD**	**FF+UMEC+VI (n=2,951)**	**TIO+OLO (n=2,951)**	**SMD**
Cancer, n (%)	278 (5)	227 (6)	0.011	162 (5)	171 (6)	0.013
Pneumonia, n (%)	590 (12)	437 (11)	−0.018	307 (10)	332 (11)	0.027
Acute bronchitis, n (%)	831 (16)	557 (14)	−0.064	456 (15)	423 (14)	−0.031
Dyspnea, n (%)	1,860 (36)	1,502 (38)	0.026	1,059 (36)	1,123 (38)	0.045
Obesity, n (%)	713 (14)	502 (13)	−0.04	378 (13)	375 (13)	−0.003
Alcohol dependence, n (%)	187 (4)	140 (4)	−0.008	114 (4)	103 (3)	−0.0198
Smoking dependence, n (%)	1,910 (37)	1,516 (38)	0.013	1,142 (39)	1,142 (39)	0

Notes: [a]Total costs include medical and pharmacy costs. The patient and insurer's paid amounts were combined. All the costs were identified during the baseline period. The index date was included in the baseline period, except for the index pharmacy claims, which were included in the follow-up period. Costs were adjusted using the medical care component of the Consumer Price Index to reflect inflation between the date of the claim and 2019. US Department of Labor, Bureau of Labor Statistics. Consumer Price Index. Medical Care. Series ID: CUUR0000SAM. Washington, DC, 2012. https://data.bls.gov/cgi-bin/surveymost?cu.

Abbreviations: ED, emergency department; FF+UMEC+VI, fluticasone furoate+umeclidinium+vilanterol; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids; IP, inpatient; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids; OP, outpatient; PSM, propensity score matching; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SMD, standardized mean difference; TIO+OLO, tiotropium+olodaterol; USD, United States dollar.

The primary outcome was the time from the index date to the first moderate or severe COPD exacerbation. Severe exacerbation was defined as: an inpatient admission or an emergency department (ED) visit with a primary COPD diagnosis code; an inpatient admission or an ED visit with a primary acute respiratory failure (ARF) diagnosis code and a diagnosis code for COPD in any position; or an inpatient admission or an ED visit with a primary ARF diagnosis code and an inpatient admission or an ED visit within ±7 days with a diagnosis code for COPD in any position. Moderate exacerbation was defined as an ambulatory (office/outpatient [OP]) visit with a diagnosis code for COPD in any position and an oral corticosteroid (OCS) pharmacy claim and/or a COPD guideline–recommended antibiotic prescription within ±7 days of the ambulatory visit. Multiple exacerbations occurring within a period of 14 days of each other were designated as a single exacerbation and were classified according to the exacerbation episode contributing to the highest severity.

Secondary outcomes included the time to first pneumonia diagnosis, time to first pneumonia-related hospitalization, HCRU, and associated costs. A pneumonia diagnosis was identified by medical claims for any diagnosis of pneumonia (ICD-10 codes J10.0, J11.0, J12–J18, J22, J69, J85.0, J85.1, and J86). Pneumonia-related hospitalization was defined as hospitalization involving a pneumonia diagnosis in the primary position. The HCRU included hospitalizations, ED visits, and OP visits. HCRU that was COPD- and/or pneumonia-related was restricted to medical claims with a COPD or pneumonia diagnosis in any position and pharmacy claims for treatment that was COPD-related (bronchodilators and ICS), as well as antibiotics recommended in COPD guidelines. Healthcare costs were computed as the sum of the actual amount paid to the provider by the health plan and patient-paid copay and/or coinsurance amounts. The costs were adjusted to 2021 US dollars according to the then-available medical care component of the consumer price index.

Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics. Matched groups of FF+UMEC+VI and TIO+OLO initiators were obtained using propensity score matching (PSM), involving a 1:1 nearest neighbor–matching approach with a caliper of 0.2. Demographic characteristics, baseline medication use, comorbidities, healthcare costs, COPD exacerbations, and covariates such as region, type of insurance, year of cohort entry, and seasonality that affect treatment availability and accessibility were also included while performing PSM to reduce potential confounding factors. A standardized mean difference of ≤10% for a variable was designated as an acceptable threshold indicating balance of characteristics between the treatment groups, and if patients' propensity scores were within ±0.1, they were matched without replacement.

The Cox proportional hazards model–derived hazard ratio (HR) and 95% confidence interval (CI) were used to assess differences in the primary objective of COPD exacerbation risk between the matched FF+UMEC+VI and TIO+OLO groups as well as to assess secondary outcomes, that is, the risk of pneumonia-related hospitalization and pneumonia diagnosis. Follow-up COPD exacerbations, HCRU, and costs were expressed as annualized population averages with Wald 95% CIs using Taylor series expansion for standard error estimation and were calculated as the sum of events or costs for the cohort divided by the sum of patient-years of follow-up for the cohort. As sensitivity analysis, patient-level costs were modeled for the selected outcomes (total costs, medical costs, and pharmacy costs [COPD- and/or pneumonia-related for each]) using zero-inflated negative binomial regression with a log link, with an offset for patient follow-up time. All data analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA). The conventional significance level α=0.05 was set a priori to determine statistical significance.

Compliance with Ethics Guidelines

The data source used for this study was private data, proprietary to IQVIA. Institutional review board and informed consent procedures were not sought nor required for this study, which accessed no identifiable protected health information in accordance with the United States Department of Health and Human Services Privacy Rule requirements for de-identification codified at 45 C.F.R. § 164.514 (b). Patient privacy was preserved, and Health Insurance Portability and Accountability Act (HIPAA) rules were complied with throughout.

Results

Patient Identification and Baseline Characteristics

From a starting population of patients initiating FF+UMEC+VI (n=28,405) or TIO+OLO (n=13,331) between September 15, 2017, and February 29, 2020, a total of 5,121 and 3,996 maintenance treatment–naive patients met the study eligibility criteria, respectively. Before matching, baseline characteristics, including age, region, type of insurance, year of cohort entry, season of index date, previous moderate or severe exacerbations, use of ICS/LABA, use of OCS, and use of LAMA, varied significantly between the FF+UMEC+VI and TIO+OLO groups (Table 1 and Supplementary Table S2). After matching, the FF+UMEC +VI and TIO+OLO groups comprised 2,951 patients each. The baseline characteristics of the matched groups, including COPD pharmacotherapy, were well balanced (Figure S1). During the baseline period, 90% of patients in the FF+UMEC+VI group and 91% of patients in the TIO/OLO group did not experience severe exacerbations. Only 1% of the patients in each group experienced ≥2 severe exacerbations during the baseline period. Additionally, 72% of the patients in each group did not experience any moderate/severe exacerbations, whereas 24% of the patients in the FF+UMEC+VI group and 25% in the TIO/OLO group had a single moderate/severe exacerbation, and 4% and 3%, respectively, had ≥2 moderate/severe exacerbations. The mean follow-up time was 225 days (standard deviation [SD]: 135.91) for the FF+UMEC+VI group and 211 days (SD: 138.26) for the TIO+OLO group.

COPD Exacerbations

The risk of first moderate or severe COPD exacerbation was not significantly different between the FF+UMEC+VI and TIO+OLO initiators (HR [95% CI]: 1.13 [0.99–1.29]; *P*=0.064; Figure 1).

The average count (population-annualized) of COPD exacerbations was significantly greater among the FF+UMEC +VI initiators than among the TIO+OLO initiators (0.32 versus 0.28 per patient-year, *P*=0.032).

Pneumonia Events

The risks of pneumonia diagnosis (HR [95% CI]: 1.04 [0.85–1.27]; *P*=0.723) and pneumonia-related hospitalization (HR [95% CI]: 1.18 [0.78–1.79]; *P*=0.429) were not significantly different between FF+UMEC+VI initiators and TIO+OLO initiators (Figure 1).

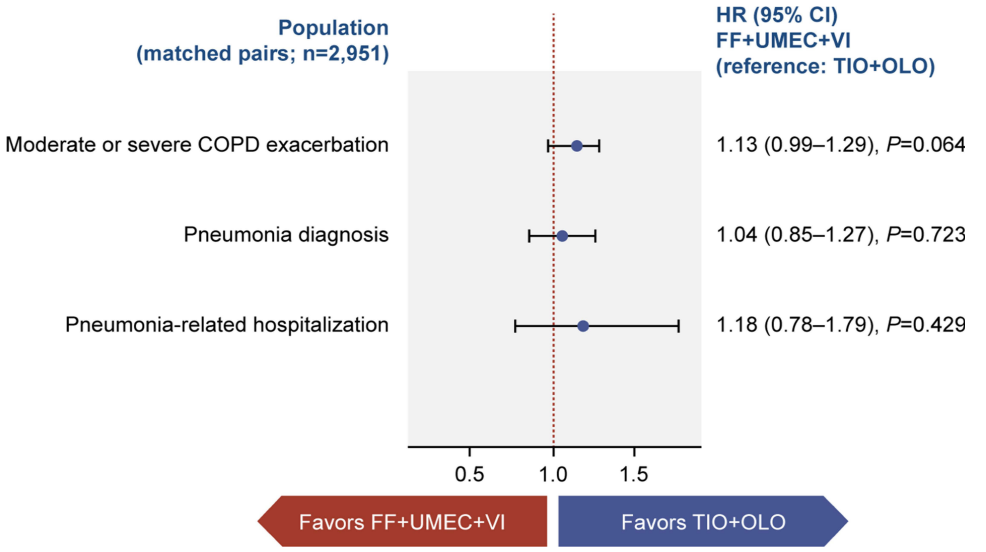


Figure 1 Cox proportional hazards model of follow-up of moderate or severe COPD exacerbations, pneumonia diagnosis, and pneumonia-related hospitalizations for matched maintenance treatment–naive patients initiating FF+UMEC+VI versus those initiating TIO+OLO.
Abbreviations: COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; OLO, olodaterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

All-Cause and COPD- and/or Pneumonia-Related Healthcare Events and Costs

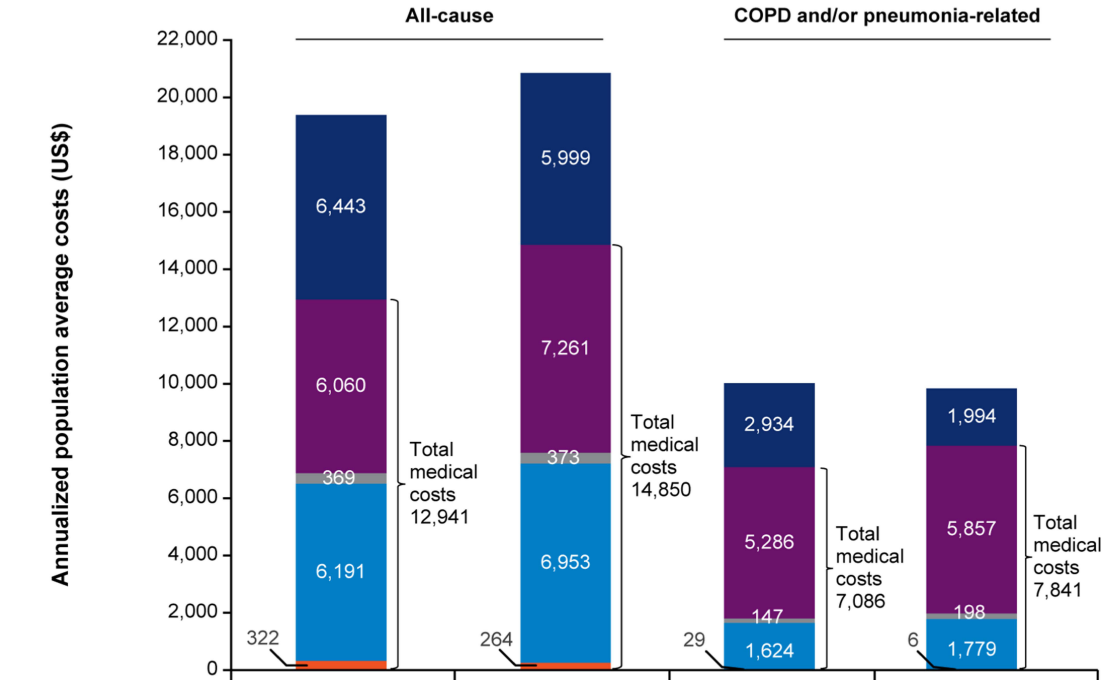
The population-annualized average counts of HCRU events (all-cause and COPD- and/or pneumonia-related) were not significantly different between the FF+UMEC+VI and TIO+OLO groups (Table 2). No significant differences were observed between the groups in the population-annualized average all-cause total (medical+pharmacy) costs incurred by patients (FF+UMEC+VI: $19,384 [$17,282–$21,487], TIO+OLO: $20,849 [$18,803–$22,896]; *P*=0.328; Figure 2). Similarly, the all-cause medical (including OP, ED, and hospitalization) and pharmacy costs for patients receiving either FF+UMEC+VI and TIO+OLO were not significantly different (*P*>0.05).

There were no significant differences in the population-annualized average COPD- and/or pneumonia-related costs between the FF+UMEC+VI and TIO+OLO groups, except for significantly higher pharmacy costs among FF+UMEC +VI initiators (FF+UMEC+VI: $2,934 [$2,827–$3,041], TIO+OLO: $1,994 [$1,915–$2,073]; *P*<0.001; Figure 2).

Table 2 Population-Annualized HCRU Events

Event	FF+UMEC+VI		TIO+OLO		*P* value
	Annualized Count	95% CI	Annualized Count	95% CI	
All-cause medical	15.58	14.84–16.32	15.61	14.95–16.28	0.946
All-cause hospitalization	0.22	0.19–0.25	0.24	0.21–0.27	0.359
All-cause ED visit	0.41	0.36–0.45	0.39	0.35–0.44	0.745
All-cause OP visit	15.17	14.45–15.90	15.15	14.51–15.79	0.961
COPD- and/or pneumonia-related medical	3.44	3.27–3.61	3.31	3.11–3.51	0.312
COPD- and/or pneumonia-related hospitalization	0.18	0.15–0.20	0.18	0.16–0.21	0.854
COPD- and/or pneumonia-related ED visit	0.10	0.08–0.12	0.10	0.08–0.12	0.900
COPD- and/or pneumonia-related OP visit	3.19	3.03–3.34	3.03	2.85–3.22	0.206

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; FF+UMEC+VI, fluticasone furoate+umeclidinium+vilanterol; HCRU, healthcare resource utilization; OP, outpatient; TIO+OLO, tiotropium+olodaterol.



	FF+UMEC+VI	TIO+OLO	FF+UMEC+VI	TIO+OLO
Pharmacy costs[a]	$6,443	$5,999	$2,934	$1,994
Hospitalization costs	$6,060	$7,261	$5,286	$5,857
ED visit costs	$369	$373	$147	$198
OP visit costs	$6,191	$6,953	$1,624	$1,779
Other medical costs	$322	$264	$29	$6
Total costs	$19,384	$20,849	$10,020	$9,835

Figure 2 Post-matching annualized population average all-cause and COPD and/or pneumonia-related costs during follow-up with FF+UMEC+VI versus TIO+OLO in the matched maintenance treatment–naive populations.

Notes: Annualized population averages were calculated as [sum of the outcomes of interest for all individuals during the follow-up period]+[sum of the follow-up on treatment time for all individuals]×365 days. Costs were adjusted to [date] US dollars using the medical care component of the Consumer Price Index to reflect inflation between the month of the claim and the most recent complete year for which this index was available. The total medical cost is the sum of the costs of hospitalization, ED visits, OP visits, and all other medical costs. [a]$P<0.001$ for COPD- and/or pneumonia-related costs.

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; FF+UMEC+VI, fluticasone furoate+umeclidinium+vilanterol; OP, outpatient; TIO+OLO, tiotropium+olodaterol.

Sensitivity analysis modeling patient-level costs found that FF+UMEC+VI was associated with a 53% significantly greater COPD-related pharmacy cost (cost ratio [95% CI]: 1.53 [1.43–1.64]; $P<0.001$) than TIO+OLO, consistent with the population-annualized result (Table 3). No significant difference was observed in COPD- and/or pneumonia-related

Table 3 Comparison of Total[a], Medical, and Pharmacy Costs Between FF+UMEC+VI and TIO+OLO

	Predicted Mean Costs		Cost Ratio (95% CI) FF+UMEC+VI (reference: TIO+OLO)	*P* value
	FF+UMEC+VI	TIO+OLO		
COPD- and/or pneumonia-related total costs	$8,099	$7,230	1.12 (1.03–1.22)	0.01*
COPD- and/or pneumonia-related medical costs	$5,632	$5,648	0.97 (0.85–1.11)	0.636
COPD-related pharmacy costs	$2,467	$1,582	1.53 (1.43–1.64)	<0.001*

Notes: [a]Total costs include medical and pharmacy costs. The patient and insurer's paid amounts were combined. *Significant at $P<0.05$.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF+UMEC+VI, fluticasone furoate+umeclidinium+vilanterol; TIO+OLO, tiotropium+olodaterol.

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medical costs (cost ratio [95% CI]: 0.97 [0.85–1.11]; *P*=0.636). FF+UMEC+VI was associated with 12% greater COPD- and/or pneumonia-related total costs (cost ratio [95% CI]: 1.12 [1.03–1.22]; *P*=0.01) than TIO+OLO.

Discussion

This retrospective study provides real-world evidence of the clinical and economic outcomes associated with the prescription of FF+UMEC+VI versus TIO+OLO in a commercially insured and MAPD-insured maintenance treatment–naive COPD patient population with a primarily low exacerbator phenotype (two or fewer baseline exacerbations). Our study found that TT with FF+UMEC+VI showed no benefit over dual LABD therapy, specifically TIO+OLO, in lowering the risk of exacerbations in maintenance treatment–naive patients with COPD. Pneumonia risk and total annualized costs (all-cause and COPD- and/or pneumonia-related) were not significantly different between the FF +UMEC+VI and TIO+OLO initiators. However, exacerbation risk and pneumonia hospitalization risk were higher by 13% (HR [95% CI]: 1.13 [0.99–1.29]; *P*=0.064) and 18% (1.18 [0.78–1.79]; *P*=0.429), respectively, in patients receiving FF+UMEC+VI versus TIO+OLO, although these differences were not statistically significant. FF+UMEC+VI initiators also incurred significantly higher COPD- and/or pneumonia-related pharmacy costs than TIO+OLO initiators.

Overall, the occurrence of exacerbations during follow-up was low, which is consistent with the exacerbation history criteria for the GOLD A/B classification.[5] This finding is in line with the results of previous reports in which mean (SD) exacerbations per year were 0.3 (0.5) and 0.4 (0.5) in the GOLD Groups A and B, respectively.[16] This study showed that treatment with TIO+OLO effectively controlled potential exacerbations and may be a suitable option for maintenance treatment–naive patients.

Our results align with those of an administrative-claims-based retrospective observational study by Sethi et al, of a primarily MAPD-insured population of patients with COPD initiating treatment with FF+UMEC+VI or TIO+OLO.[17] They identified no additional benefit of TT in controlling exacerbations in the post-PSM matched maintenance treatment–naive population (adjusted HR [95% CI]: 0.99 [0.88–1.10]) compared with TIO+OLO.[17] Additionally, FF+UMEC+VI users exhibited significantly higher COPD- and/or pneumonia-related adjusted total annualized costs than TIO+OLO in the maintenance treatment–naive population.[17] Our study expands upon these findings in a population that was 70% commercially insured, 10 years younger on average, and had a lower history of exacerbations.

Palli et al conducted a retrospective analysis that compared outcomes of TIO+OLO versus single- or multiple-inhaler TT among patients newly initiating COPD maintenance therapy in a US MAPD-insured population.[18] Notably, approximately 90% of the included patients were bronchodilator-naive. The findings showed no statistically significant difference in the time to first moderate or severe exacerbation between the treatment cohorts.[18] Furthermore, in comparison with the TT cohort, in the TIO+OLO cohort, mean COPD-related total costs were lower by 41.1% ($10,094 versus $17,135; *P*<0.001) and pharmacy costs were lower by 51.9% ($3,646 versus $7,020; *P*<0.001).[18] However, over 99% of TT regimens consisted of multiple inhalers, which may have contributed to the difference in pharmacy costs.

Another study by Suissa et al compared the outcomes among new users of single-inhaler TT and LAMA+LABA, identified from the United Kingdom's Clinical Practice Research Datalink, who were treated between 2017 and 2020.[19] Among the subset of maintenance treatment–naive patients, no significant difference was observed in the incidence of moderate or severe COPD exacerbation (adjusted HR [95% CI]: 1.12 [0.99–1.28]) between TT and dual LABD therapy.

Another retrospective cohort study analyzed data from the US HealthCore Integrated Research Database to compare among patients initiating maintenance therapy with TT and TIO+OLO, the time to the first hospitalization for community-acquired pneumonia and the time to the first COPD exacerbation.[20] The study found no advantage of TT over TIO+OLO in reducing exacerbation risk, including among treatment-naive patients, while also indicating a potentially lower risk of pneumonia with TIO+OLO.[20]

These real-world studies have consistently suggested that dual LABD therapy is as effective as TT in controlling COPD exacerbations in maintenance treatment–naive patients. These findings are also in accordance with the current treatment guidelines from a clinical perspective. The GOLD 2024 report and American Thoracic Society 2020 guidelines recommend considering TT in patients with a high risk of exacerbations and elevated blood eosinophil levels (≥300 cells/μL).[5,21] Notably, one study assessed treatment adherence to GOLD recommendations and highlighted the prevalence of

exacerbation-discordant patients with maintenance treatment–naive individuals.[12] Furthermore, prescriptions of GOLD-compliant regimens were observed more frequently (58.9%) in patients with a higher exacerbation risk.[10]

Considering the price differential of approximately $169 in the wholesale acquisition costs of FF+UMEC+VI ($638.52)[22] and TIO+OLO ($469.60) inhalers (as of October 2023),[23] opting for TIO+OLO can reduce the additional medication expenditure for a payor managing their maintenance treatment–naive COPD population. This consideration is especially pertinent because of the comparable treatment benefits offered by both TT and dual LABD in patients with a low risk of exacerbation. Given the chronic nature of COPD that necessitates long-term maintenance therapy, assessing the cost implications of initiating TIO+OLO versus FF+UMEC+VI within the context of clinical practice in the US is of substantial importance. As such, our study findings, which show that compared with FF+UMEC+VI initiators, lower annualized COPD- and/or pneumonia-related pharmacy costs were observed for maintenance treatment–naive TIO+OLO initiators, are especially relevant. These findings are consistent with those of a retrospective study using the Optum Research Database, which reported 35% lower total costs and 39% lower pharmacy costs for TIO+OLO initiators than for TT initiators.[13] This is also in agreement with the study by Sethi et al, where a statistically significant relative increase of 26.8% in COPD- and/or pneumonia-related adjusted total annualized costs was observed for the FF+UMEC+VI cohort versus the TIO+OLO cohort in maintenance treatment–naive patients, with significantly higher pharmacy costs with FF+UMEC+VI versus TIO+OLO (39.8% relative increase).[17] Therefore, adhering to practice guidelines and initiating LAMA+LABA therapy can enhance real-world economic outcomes in maintenance treatment–naive populations.

In contrast to other studies assessing ICS-containing treatment,[15,18] the risks of pneumonia and pneumonia-related HCRU events were not markedly elevated in patients initiating TT or dual LABD therapy. Notably, the point estimates in the current study reflected a trend in alignment with findings from real-world evidence, which may suggest that regimens containing ICS are associated with an elevated pneumonia risk.[24] However, it is crucial to acknowledge that the study participants were new to the maintenance treatment and were not observed over a prolonged timeframe.

Limitations of this study include its retrospective nature, unavailability of data on lung function, possibility of patient misclassification, missing data, and lack of objective and reliable measurements of patient outcomes, detailed information regarding patient clinical history, or clinical status during the study timeframe. Furthermore, blood eosinophil counts were not included. Although the data of 9,117 patients (5,121 FF+UMEC+VI initiators and 3,996 TIO+OLO initiators) were acquired, data for 35% of the patients were lost owing to the matching of groups on 46 variables, thereby reducing the cohort sizes. Underreporting of pneumonia in primary care due to overlap with exacerbations and misclassification arising from errors in coding and clinical diagnosis[3,25] may also explain the low incidence and risk of pneumonia observed in patients treated with TT versus dual therapy. Symptom evaluation based on scales such as the modified Medical Research Council (mMRC) and/or COPD assessment test (CAT) was not conducted due to unavailability of these measures in the source data, which may have led to an underestimation of the benefits of TT versus dual therapy as the rate of exacerbations was already low in the populations studied. However, it should be noted that GOLD does not recommend the use of TT for dyspnea in patients without exacerbations.[5] As the study population was selected from US insurance databases, the results may not be generalizable to individuals without a commercial or Medicare insurance coverage. The strength of this study lies in its focus on maintenance treatment–naive patients who initiated FF+UMEC+VI or TIO+OLO therapy, the wide range of insurers covered, and a large, well-matched patient population reflective of patients commonly seen in primary care practice.

Conclusion

In patients with COPD, who were maintenance treatment–naive, initiating treatment with FF+UMEC+VI did not demonstrate an advantage over TIO+OLO in terms of reducing COPD exacerbation risk. FF+UMEC+VI initiators also incurred higher treatment-related pharmacy costs. These findings are in support of current GOLD clinical practice recommendations for LAMA+LABA as an initial treatment for patients with COPD. These data may be used to assist HCPs in clinical decision-making and to determine appropriate efficacious interventions that can be individualized for different patient populations.

Abbreviations

ARF, Acute respiratory failure; CAT, COPD Assessment Test; COPD, Chronic obstructive pulmonary disease; CI, Confidence interval; ED, Emergency department; FDC, fixed-dose combination; FF, Fluticasone furoate; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; HR, Hazard ratio; HCRU, Healthcare resource utilization; ICS, Inhaled corticosteroid; ICD, International Classification of Diseases; LABA, Long-acting beta2-agonist; LABD, Long-acting bronchodilator; LAMA, Long-acting muscarinic antagonist; MAPD, Medicare Advantage with Part D; mMRC, modified Medical Research Council; OCS, Oral corticosteroid; OLO, Olodaterol; OP, Outpatient; PSM, Propensity score matching; SD, Standard deviation; TIO, Tiotropium; TT, Triple therapy; UMEC, Umeclidinium; US, United States; VI, Vilanterol.

Data Sharing Statement

The raw dataset and the datasets generated and/or analyzed during the study are not publicly available because they are part of the proprietary IQVIA PharMetrics® Plus database licensed per signed agreement between Boehringer Ingelheim, eMAX Health, and IQVIA Inc.

Ethics Approval

The data source used for this study was private data, proprietary to IQVIA. Institutional review board and informed consent procedures were not sought nor required for this study, which accessed no identifiable protected health information in accordance with the United States Department of Health and Human Services Privacy Rule requirements for de-identification codified at 45 C.F.R. § 164.514 (b). Patient privacy was preserved, and Health Insurance Portability and Accountability Act (HIPAA) rules were complied with throughout.

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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 the final approval of the version to be published; have agreed on the journal to which this article has been submitted; and agree to be accountable for all aspects of this work.

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