Umeclidinium/Vilanterol Compared with Fluticasone Propionate/Salmeterol, Budesonide/Formoterol, and Tiotropium as Initial Maintenance Therapy in Patients with COPD Who Have High Costs and Comorbidities

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Background: Comorbidities in patients with chronic obstructive pulmonary disease (COPD) are associated with increased medical costs and risk of exacerbations. This study compared COPD-related medical costs and exacerbations in high-cost, high-comorbidity patients with COPD receiving initial maintenance treatment (IMT) with umeclidinium/vilanterol (UMEC/VI) versus fluticasone propionate/salmeterol (FP/SAL), budesonide/formoterol (B/F), or tiotropium (TIO).

Methods: This retrospective, matched cohort study identified patients from Optum's de-identified Clinformatics Data Mart database who initiated UMEC/VI, FP/SAL, B/F, or TIO between January 1, 2014 and December 31, 2018 (index date defined as date of the first fill). Eligibility criteria included age ≥ 40 years at index, ≥ 1 pre-index COPD diagnosis, no pre-index asthma diagnosis, 12 months of continuous insurance coverage pre-index, and high pre-index costs (≥ 80 th percentile of IMT population) and comorbidities (Quan-Charlson comorbidity index ≥ 3). Propensity score matching was used to control for potential confounders. On-treatment COPD-related medical costs (primary endpoint) and exacerbations were evaluated.

Results: Matched cohorts were well balanced on baseline characteristics (UMEC/VI vs FP/SAL: $n=1194$ each; UMEC/VI vs B/F: $n=1441$ each; UMEC/VI vs TIO: $n=1277$ each). Patients receiving UMEC/VI had significantly lower COPD-related medical costs versus FP/SAL (difference: \$6587 per patient per year; $P=0.048$), and numerically lower costs versus B/F and TIO. Patients initiating UMEC/VI had significantly lower risk of COPD-related severe exacerbation versus FP/SAL (hazard ratio [95% CI]: 0.78 [0.62, 0.98]; $P=0.032$), B/F (0.77 [0.63, 0.95]; $P=0.016$), and TIO (0.79 [0.64, 0.98]; $P=0.028$). The rate of COPD-related severe exacerbations was significantly lower with UMEC/VI versus FP/SAL (rate ratio [95% CI]: 0.73 [0.59, 0.91]; $P=0.008$) and B/F (0.73 [0.59, 0.93]; $P=0.012$), and numerically lower versus TIO (0.83 [0.68, 1.04]; $P=0.080$).

Conclusion: These findings suggest that high-cost, high-comorbidity patients with COPD receiving UMEC/VI compared with FP/SAL, B/F, and TIO as IMT may have lower medical costs and exacerbation risk.

Keywords: COPD, LAMA/LABA, medical costs, comorbidities, severe exacerbations

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Plain Language Summary

Why Was the Study Done?

Patients with chronic obstructive pulmonary disease (COPD) who also have other medical conditions have higher COPD-related medical costs and more COPD exacerbations

on average than patients who do not have other medical conditions. More evidence is needed to find out which medicines are most effective at reducing costs and exacerbations in patients with COPD and other medical conditions when prescribed as initial treatment.

What Did the Researchers Do and Find?

We used information from a US healthcare claims database to compare umeclidinium/vilanterol (UMEC/VI) with three other medicines for COPD. These three medicines were fluticasone propionate/salmeterol (FP/SAL), budesonide/formoterol (B/F), and tiotropium (TIO). We specifically looked at patients who had high medical costs and other medical conditions in addition to their COPD. The patients were not receiving regular treatment for their COPD before the start of the study. We found that patients starting treatment with UMEC/VI had lower medical costs related to their COPD than patients starting treatment with FP/SAL, B/F, or TIO. Patients starting treatment with UMEC/VI also had fewer COPD-related exacerbations that led to hospitalization than patients receiving the other medicines.

What Do These Results Mean?

Hospital admissions contribute to high medical costs. UMEC/VI might reduce COPD-related medical costs by reducing the number of exacerbations leading to hospitalization compared with FP/SAL, B/F, or TIO. Our results suggest that starting treatment with UMEC/VI may help reduce medical costs and exacerbations for patients with COPD who also have other medical conditions, compared with FP/SAL, B/F, or TIO.

Introduction

Comorbidities in patients with chronic obstructive pulmonary disease (COPD) are associated with increased healthcare resource use (HCRU), medical costs, and risk of exacerbations.^{1–3} A correlation has been observed between the number of comorbidities and HCRU, such that patients with greater numbers of comorbidities have been shown to have a higher number of emergency room (ER) visits leading to hospitalizations.² Furthermore, comorbidities such as congestive heart failure, myocardial infarction, and cerebrovascular disease predict higher HCRU and costs in patients with COPD.^{3–5} Patients with COPD who have comorbidities therefore represent a vulnerable patient population with considerable unmet needs and high medical costs.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report recommends initial maintenance treatment (IMT) with long-acting muscarinic antagonist (LAMA) or long-acting β_2 -agonist

(LABA) monotherapy for most symptomatic patients with COPD, or LAMA/LABA combination therapy as IMT for patients with severe symptoms.⁶ Clinical trials in patients with COPD have demonstrated greater improvements in lung function, symptoms, and exacerbation rates with LAMA/LABA combination therapy compared with inhaled corticosteroid (ICS)/LABA combinations and LAMA or LABA monotherapy.^{7–17} As a result, the American Thoracic Society (ATS) clinical practice guidelines for the pharmacological management of COPD include a strong recommendation for the use of LAMA/LABA combination therapy over LAMA or LABA monotherapies in patients with COPD and dyspnea or exercise intolerance.¹⁸ However, clinical trial data do not consistently show improvements in exacerbation risk with LAMA/LABA versus ICS/LABA,¹⁰ and real-world evidence in this area is currently lacking.

Exacerbations contribute to the overall disease burden experienced by patients with COPD and are also associated with increased medical costs and HCRU.¹⁹ Severe exacerbations, which require hospitalization, are associated with the greatest increase in economic burden, incurring higher medical costs than moderate exacerbations that do not require inpatient care.^{20,21} Additionally, the onset of exacerbations, particularly those leading to hospitalization, is associated with a substantial increase in the risk of adverse cardiovascular events and death.^{22,23} Identifying first-line maintenance therapies that can reduce the risk of exacerbations in patients with high medical costs, HCRU, and comorbidities is therefore an important goal in improving quality of life and reducing overall cost of treatment.

This study used real-world administrative claims data to evaluate the on-treatment COPD-related medical costs, and time-to-first and rate of on-treatment COPD-related exacerbations among patients with COPD with high costs and comorbidities. These outcomes were compared between patients initiating treatment with the LAMA/LABA umeclidinium/vilanterol (UMEC/VI) and those initiating fluticasone propionate/salmeterol (FP/SAL; ICS/LABA), budesonide/formoterol (B/F; ICS/LABA), or tiotropium (TIO; LAMA).

Materials and Methods

Study Design

Three retrospective matched cohort studies were conducted using medical and pharmacy claims data between January 1,

2013 and December 31, 2018, which were obtained from Optum's de-identified Clinformatics Data Mart database. The three studies each compared UMEC/VI with a different COPD maintenance medication, but were otherwise identical. Patients diagnosed with COPD who had a pharmacy claim for fixed-dose UMEC/VI, FP/SAL, B/F, or TIO as IMT (ie, no other ICS-, LABA-, or LAMA-containing maintenance medications in the 12 months before initiation) between January 1, 2014 and December 31, 2018 were identified (Figure 1). Patients were classified into mutually exclusive cohorts based on their index medication (UMEC/VI, FP/SAL, B/F, or TIO). For each eligible patient, the index date was defined as the date of the first prescription fill and the pre-index period was defined as the 12 months prior to the index date. The on-treatment period spanned from the index date to the first of: a pharmacy fill for a non-index ICS-, LABA-, or LAMA-containing COPD maintenance medication; discontinuation of the index medication; end of continuous enrollment; end of data availability; or death. Discontinuation was defined as a ≥ 45 -day gap in days of supply between the end of a dispensation and the next fill, or between the end of the last dispensation and the end of the on-treatment period. For mail order fills, the discontinuation gap was extended to 115 days. Patient characteristics were assessed during the pre-index period and study outcomes were evaluated during the on-treatment period.

Patients

In addition to the index pharmacy claim, eligible patients had ≥ 1 medical claim with an International Classification of

Diseases 9th Edition Clinical Modification (ICD-9-CM) or 10th Edition Clinical Modification (ICD-10-CM) diagnosis code for COPD (ICD-9-CM: 491.x, 492.x, 496.x; ICD-10-CM: J41–J44; Table S1) in any position during the pre-index period or on the index date, were ≥ 40 years of age on the index date; and had continuous medical and pharmacy coverage throughout the pre-index period. Patients were also required to have high medical costs and a high number of comorbidities in the pre-index period. High-cost patients were defined as those with pre-index all-cause medical costs exceeding the 80th percentile of the cost distribution in the overall IMT COPD population. The overall IMT COPD population included the UMEC/VI, FP/SAL, B/F, and TIO IMT COPD cohorts, as well as patients initiated on other types of COPD IMT during the identification period with no ICS-, LABA- or LAMA-containing maintenance medications within 12 months prior to treatment initiation. High-comorbidity patients were defined as having a pre-index Quan-Charlson comorbidity index (CCI) score ≥ 3 ; higher Quan-CCI scores indicate an increased risk of mortality based on the presence of specific comorbidities.^{24,25}

Patients were excluded from the analysis if they had any pre-index pharmacy claim for ICS-, LABA-, or LAMA-containing maintenance medications; any pharmacy claim for non-index maintenance medication on the index date (including patients with claims for both UMEC/VI and FP/SAL, UMEC/VI and B/F, or UMEC/VI and TIO on the index date); any claim for single- or multiple-inhaler triple therapy (ICS+LAMA+LABA) on the index date; or a medical claim with an ICD-9-CM or ICD-10-CM

Figure 1 Study design.

Abbreviations: B/F, budesonide/formoterol; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

diagnosis code for asthma (ICD-9-CM: 493.xx; ICD-10-CM: J45.3, J45.4, J45.5, J45.9) at any time before or after the index date (Figure 2).

Outcomes

The primary outcome was on-treatment COPD-related medical costs, which were reported per patient per year (PPPY) and defined as costs for medical claims with

a primary or secondary diagnosis of COPD. Total COPD-related medical costs included costs incurred due to hospitalizations, ER visits, outpatient visits, and other visits (such as home services and hospices). Costs were inflation-adjusted to 2019 US dollars based on the medical care component of the Consumer Price Index.

Secondary outcomes included time-to-first and rates per 100 person-days of moderate, severe, and overall

Figure 2 Patient disposition. ^aICD codes for COPD are shown in Table S1. ^bICD codes for asthma included ICD-9-CM: 493.xx; ICD-10-CM: J45.3, J45.4, J45.5, J45.9. ^cHigh-comorbidity patients were defined as having a pre-index Quan-CCI score ≥ 3 . ^dHigh-cost patients were defined as those with pre-index all-cause medical costs exceeding the 80th percentile of the cost distribution in the overall IMT COPD population.

Abbreviations: B/F, budesonide/formoterol; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases; FP/SAL, fluticasone propionate/salmeterol; ICS, inhaled corticosteroid; IMT, initial maintenance treatment; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

COPD-related exacerbations during the on-treatment period. Moderate COPD-related exacerbations were defined as an outpatient or ER visit with a primary COPD-related exacerbation diagnosis code ([Table S1](#)), and ≥ 1 dispensing or administration of a systemic corticosteroid or guideline-recommended antibiotic within 5 days before or after the visit. Severe COPD-related exacerbations were defined as a hospitalization with a primary COPD-related exacerbation diagnosis code. Exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity of the contributing events. Overall COPD-related exacerbations included both moderate and severe exacerbations. Exacerbations with a start date on or before the index date were not included in the outcome measures.

Statistical Analysis

Patients treated with UMEC/VI were matched (1:1) with patients treated with FP/SAL, B/F, or TIO using propensity score (PS) matching with the following baseline covariates: age; sex; region; insurance type; year and quarter of index date; Quan-CCI; respiratory medications; COPD-related HCRU and medical costs; all-cause HCRU and total medical costs; and Elixhauser, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), and COPD-specific comorbidity test (COTE) comorbidities (with a prevalence $\geq 5\%$). Each treatment comparison used a different PS model for matching.

Patient characteristics during the pre-index period were compared between unmatched and matched cohorts, and those with standardized differences $<10\%$ were considered to be balanced between cohorts. COPD-related medical costs were compared between matched cohorts using cost differences and non-parametric bootstrap procedures. Time-to-first on-treatment moderate, severe, and overall COPD-related exacerbation was evaluated using Kaplan–Meier (KM) survival analysis and compared between matched cohorts using hazard ratios (HR) calculated from Cox proportional hazards regression models. Rates of COPD-related severe exacerbations (number of events per 100 person-days in the on-treatment period) were compared between matched cohorts using rate ratios (RR) estimated from Poisson regression models with 95% confidence intervals (CI) and *P*-values generated from non-parametric bootstrap procedures.

Results

Study Population

In total, 684 191 patients who initiated maintenance therapy for COPD between January 1, 2014 and December 31, 2018 were identified. The overall IMT COPD population comprised 116 158 patients and the 80th percentile of the all-cause medical cost distribution (evaluated over the 12-month pre-index period) in this population, which was used to identify high-cost patients, was \$41,254. Of the overall IMT population, 10,261 received UMEC/VI, 22,931 received FP/SAL, 23,164 received B/F, and 30,510 received TIO. Patients who met the high-cost and high-comorbidity eligibility criteria included 1505 receiving UMEC/VI, 3385 receiving FP/SAL, 3470 receiving B/F, and 4089 receiving TIO ([Figure 2](#)).

Following PS matching, the UMEC/VI versus FP/SAL cohorts each included 1194 patients, the UMEC/VI versus B/F cohorts each included 1441 patients, and the UMEC/VI versus TIO cohorts each included 1277 patients. In the matched cohorts, mean on-treatment time was longer for the UMEC/VI versus FP/SAL cohort (144.9 vs 107.5 days), UMEC/VI versus B/F cohort (139.5 vs 102.5 days), and UMEC/VI versus TIO cohort (143.2 vs 130.3 days). All matched cohorts were well balanced on other pre-index patient characteristics (standardized differences $<10\%$). Mean age was similar for the UMEC/VI and FP/SAL cohorts (72.2 vs 72.1 years), the UMEC/VI and B/F cohorts (72.0 vs 71.9 years), and the UMEC/VI and TIO cohorts (72.1 for both cohorts). The proportion of female patients was also comparable for the UMEC/VI and FP/SAL cohorts (46.2% vs 46.3%), the UMEC/VI and B/F cohorts (45.5% vs 44.1%), and the UMEC/VI and TIO cohorts (44.6% vs 43.9%). Similar mean Quan-CCI scores were observed for the UMEC/VI and FP/SAL cohorts (6.2 vs 6.3), the UMEC/VI and B/F cohorts (both 6.1), and the UMEC/VI and TIO cohorts (6.1 vs 6.2; [Table 1](#)). Pre-index characteristics for the unmatched cohorts are shown in [Table S2](#).

Pre-index comorbidities were well balanced between matched cohorts; the most common comorbidities were hypertension, coronary artery disease, and cardiac arrhythmias ([Table S3](#)). Pre-index comorbidities for the unmatched cohorts are shown in [Table S4](#).

COPD-Related Medical Costs

Patients in the UMEC/VI cohort incurred significantly lower on-treatment COPD-related medical costs PPPY compared with the FP/SAL cohort (mean cost difference:

Table 1 Pre-Index Patient Characteristics for UMEC/VI versus FP/SAL, B/F, and TIO Matched Cohorts

Characteristics	UMEC/VI vs FP/SAL			UMEC/VI vs B/F			UMEC/VI vs TIO		
	UMEC/VI (n=1194)	FP/SAL (n=1194)	Std Diff (%)	UMEC/VI (n=1441)	B/F (n=1441)	Std Diff (%)	UMEC/VI (n=1277)	TIO (n=1277)	Std Diff (%)
Post-index eligibility period, days, mean (SD)	389.7 (303.5)	369.7 (291.6)	6.7	364.0 (292.2)	355.7 (296.6)	2.8	379.1 (301.0)	372.8 (305.2)	2.1
On-treatment follow-up period, days, mean (SD)	144.9 (185.3)	107.5 (153.0)	22.0	139.5 (176.9)	102.5 (139.9)	23.2	143.2 (183.3)	130.3 (167.5)	7.3
Age, years, mean (SD)	72.2 (9.4)	72.1 (10.0)	1.3	72.0 (9.4)	71.9 (9.9)	0.9	72.1 (9.4)	72.1 (9.3)	0.9
Female, n (%)	552 (46.2)	553 (46.3)	0.2	656 (45.5)	636 (44.1)	2.8	570 (44.6)	561 (43.9)	1.4
Region, n (%)									
South	638 (53.4)	642 (53.8)	0.7	812 (56.3)	831 (57.7)	2.7	689 (54.0)	667 (52.2)	3.5
West	162 (13.6)	163 (13.7)	0.2	168 (11.7)	160 (11.1)	1.7	169 (13.2)	178 (13.9)	2.1
Midwest	285 (23.9)	280 (23.5)	1.0	331 (23.0)	324 (22.5)	1.2	298 (23.3)	300 (23.5)	0.4
Northeast	108 (9.0)	106 (8.9)	0.6	129 (9.0)	123 (8.5)	1.5	120 (9.4)	131 (10.3)	2.9
Unknown	1 (0.1)	3 (0.3)	4.1	1 (0.1)	3 (0.2)	3.7	1 (0.1)	1 (0.1)	0.0
Insurance plan type, n (%)									
Medicare	1032 (86.4)	1020 (85.4)	2.9	1209 (83.9)	1206 (83.7)	0.6	1075 (84.2)	1083 (84.8)	1.7
Commercial	162 (13.6)	174 (14.6)	2.9	232 (16.1)	235 (16.3)	0.6	202 (15.8)	194 (15.2)	1.7
Quan-CCI, mean (SD)	6.2 (2.5)	6.3 (2.5)	3.6	6.1 (2.5)	6.1 (2.5)	0.9	6.1 (2.5)	6.2 (2.5)	1.6
Number of COPD-related exacerbations, mean (SD)									
Overall	0.88 (1.02)	0.90 (1.02)	1.6	0.87 (1.00)	0.87 (0.98)	0.3	0.88 (1.01)	0.89 (1.04)	1.4
Moderate	0.34 (0.66)	0.36 (0.74)	3.5	0.36 (0.68)	0.37 (0.73)	1.6	0.35 (0.69)	0.37 (0.75)	1.7
Severe	0.55 (0.75)	0.54 (0.72)	1.1	0.51 (0.72)	0.50 (0.68)	1.2	0.52 (0.73)	0.53 (0.68)	0.2
Patients with COPD-related exacerbations, n (%)									
Overall	677 (56.7)	696 (58.3)	3.2	821 (57.0)	833 (57.8)	1.7	725 (56.8)	744 (58.3)	3.0
Moderate	165 (13.8)	182 (15.2)	4.0	234 (16.2)	241 (16.7)	1.3	193 (15.1)	186 (14.6)	1.5
Severe	512 (42.9)	514 (43.0)	0.3	587 (40.7)	592 (41.1)	0.7	532 (41.7)	558 (43.7)	4.1
Respiratory medications, n (%)									
Systemic corticosteroids	719 (60.2)	733 (61.4)	2.4	893 (62.0)	909 (63.1)	2.3	778 (60.9)	781 (61.2)	0.5
SABA	494 (41.4)	488 (40.9)	1.0	618 (42.9)	622 (43.2)	0.6	519 (40.6)	532 (41.7)	2.1
SAMA/SABA	186 (15.6)	198 (16.6)	2.7	221 (15.3)	213 (14.8)	1.6	186 (14.6)	180 (14.1)	1.3
Montelukast	58 (4.9)	56 (4.7)	0.8	68 (4.7)	82 (5.7)	4.4	60 (4.7)	52 (4.1)	3.1
SAMA	38 (3.2)	32 (2.7)	3.0	46 (3.2)	31 (2.2)	6.5	40 (3.1)	21 (1.6)	9.7
Methylxanthines	4 (0.3)	5 (0.4)	1.4	4 (0.3)	2 (0.1)	3.0	3 (0.2)	7 (0.5)	5.0
Chronic antibiotic (≥6 months of continuous use)	6 (0.5)	15 (1.3)	8.1	5 (0.3)	14 (1.0)	7.7	7 (0.5)	9 (0.7)	2.0
N-acetylcysteine	2 (0.2)	6 (0.5)	5.8	2 (0.1)	5 (0.3)	4.2	2 (0.2)	5 (0.4)	4.5
PDE-4 inhibitor	1 (0.1)	1 (0.1)	0.0	1 (0.1)	2 (0.1)	2.2	1 (0.1)	3 (0.2)	4.0

(Continued)

Table 1 (Continued).

Characteristics	UMEC/VI vs FP/SAL			UMEC/VI vs B/F			UMEC/VI vs TIO		
	UMEC/VI (n=1194)	FP/SAL (n=1194)	Std Diff (%)	UMEC/VI (n=1441)	B/F (n=1441)	Std Diff (%)	UMEC/VI (n=1277)	TIO (n=1277)	Std Diff (%)
COPD-related HCRU ^a , mean (SD)									
Hospitalizations	0.95 (1.19)	0.94 (0.96)	1.3	0.87 (1.13)	0.88 (1.01)	0.3	0.92 (1.16)	0.92 (0.94)	0.7
ER visits	0.69 (1.72)	0.74 (1.64)	3.1	0.64 (1.62)	0.71 (1.67)	4.6	0.66 (1.67)	0.72 (1.76)	3.4
Outpatient visits	6.4 (11.6)	5.9 (13.5)	3.7	6.5 (12.8)	6.2 (13.4)	2.3	6.5 (13.3)	5.8 (13.2)	5.1
Other visits ^b	2.0 (5.0)	2.0 (6.6)	1.5	1.9 (5.1)	1.5 (3.8)	9.3	2.0 (5.2)	1.7 (5.1)	4.3
Medical costs ^c , \$, mean (SD)									
COPD-related total	43,731 (55,663)	43,498 (49,066)	0.4	42,350 (54,206)	42,733 (54,732)	0.7	43,911 (55,865)	45,124 (52,941)	2.2
Hospitalizations	31,602 (50,470)	30,902 (42,715)	1.5	29,716 (48,467)	30,175 (46,161)	1.0	31,249 (50,157)	32,170 (47,696)	1.9
ER visits	4491 (15,154)	4678 (17,315)	1.2	4129 (14,129)	4469 (14,830)	2.3	4330 (14,764)	3932 (12,291)	2.9
Outpatient visits	7084 (17,655)	7434 (21,726)	1.8	8002 (20,452)	7692 (28,620)	1.2	7798 (20,584)	8444 (23,415)	2.9
Other visits ^b	554 (5577)	483 (2754)	1.6	503 (5183)	396 (3354)	2.4	534 (5400)	578 (5001)	0.9
All-cause total	113,558 (112,537)	113,968 (106,298)	0.4	113,440 (113,914)	112,781 (107,329)	0.6	111,970 (106,109)	110,769 (104,920)	1.1

Notes: ^aCOPD-related HCRU and costs were defined as claims with a primary or secondary diagnosis of COPD. ^bIncluded visits such as home services and hospice. ^cMedical costs are inflated to 2019 US dollars using the US Medical Care consumer price index from the Bureau of Labor Statistics, US Department of Labor.

Abbreviations: B/F, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; ER, emergency room; FP/SAL, fluticasone propionate/salmeterol; HCRU, healthcare resource use; PDE-4, phosphodiesterase-4; Quan-CCI, Quan-Charlson comorbidity index; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; Std diff, standardized difference; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

\$6587; $P=0.048$). This difference was mainly driven by numerically lower hospitalization costs (UMEC/VI: \$14,961 vs FP/SAL: \$18,793) and ER visit costs (UMEC/VI: \$3719 vs FP/SAL: \$6580). COPD-related medical costs were lower for patients receiving UMEC/VI compared with those receiving B/F (mean cost difference: \$4633) and TIO (mean cost difference: \$5559), although the differences were not statistically significant (Table 2). Differences between treatment groups in all-cause medical costs were directionally similar to those observed for COPD-related costs, with patients in the UMEC/VI cohorts incurring numerically lower all-cause medical costs compared with the FP/SAL, B/F and TIO cohorts, but did not reach statistical significance (Table 2).

COPD-Related Exacerbations

The risk of on-treatment COPD-related severe exacerbation was significantly lower with UMEC/VI compared with FP/SAL (25.3% vs 32.6%; HR [95% CI]: 0.78 [0.62, 0.98]; $P=0.032$), B/F (26.7% vs 31.8%; HR [95%

CI]: 0.77 [0.63, 0.95]; $P=0.016$), and TIO (27.0% vs 30.8%; HR [95% CI]: 0.79 [0.64, 0.98]; $P=0.028$) (Figure 3; Table S5). Risk of COPD-related moderate exacerbation was similar in patients receiving UMEC/VI versus FP/SAL (33.2% vs 38.9%; HR [95% CI]: 0.94 [0.76, 1.17]), B/F (32.0% vs 37.4%; HR [95% CI]: 0.94 [0.77, 1.15]), and TIO (33.0% vs 31.2%; HR [95% CI]: 1.05 [0.85, 1.29]) (Table S6). Patients initiating treatment with UMEC/VI had a numerically lower risk of overall COPD-related exacerbations compared with FP/SAL (46.2% vs 55.7%; HR [95% CI]: 0.86 [0.73, 1.02]), B/F (46.8% vs 54.8%; HR [95% CI]: 0.87 [0.75, 1.01]), and TIO (47.2% vs 53.0%; HR [95% CI]: 0.90 [0.77, 1.05]), although these differences were not statistically significant (Table S7).

The rate of COPD-related severe exacerbations was significantly lower with UMEC/VI compared with FP/SAL (UMEC/VI: 0.10, FP/SAL: 0.13; RR [95% CI]: 0.73 [0.59, 0.91]; $P=0.008$) and B/F (UMEC/VI: 0.10, B/F: 0.14; RR [95% CI]: 0.73 [0.59, 0.93]; $P=0.012$).

Table 2 On-Treatment Medical Costs PPPY for UMEC/VI versus FP/SAL, B/F, and TIO Matched Cohorts

	Medical Costs, \$ ^b PPPY, Mean (SD)		Cost Difference (95% CI)	P-value
	UMEC/VI (N=1194)	FP/SAL (N=1194)		
Total COPD-related ^a medical costs	28,823 (65,220)	35,411 (92,590)	-6587 (-13,661, -21)	0.048
Hospitalizations	14,961 (47,032)	18,793 (54,422)	-3832 (-8183, 613)	0.072
ER visits	3719 (30,675)	6580 (62,666)	-2862 (-6775, 387)	0.100
Outpatient visits	9360 (28,210)	9254 (35,078)	106 (-3181, 2759)	0.942
Other visits	784 (2849)	784 (2916)	0 (-342, 314)	0.998
Total all-cause medical costs	79,603 (127 705)	94,312 (166 284)	-14,709 (-29,239, 724)	0.060
	UMEC/VI (N=1441)	B/F (N=1441)	-	-
Total COPD-related ^a medical costs	30,104 (66,821)	34,737 (80,979)	-4633 (-11,354, 1554)	0.156
Hospitalizations	15,745 (47,196)	18,631 (55,724)	-2887 (-7361, 1685)	0.188
ER visits	3466 (28,689)	4077 (29,383)	-610 (-2106, 1130)	0.401
Outpatient visits	10,141 (31,466)	10,242 (38,813)	-102 (-4191, 3122)	0.906
Other visits	752 (2769)	1787 (28,994)	-1035 (-3148, 167)	0.216
Total all-cause medical costs	87,463 (144 600)	102 158 (186 293)	-14,695 (34,688, 3098)	0.128
	UMEC/VI (N=1277)	TIO (N=1277)	-	-
Total COPD-related ^a medical costs	30,022 (66,372)	35,581 (73,944)	-5559 (-11,541, 670)	0.080
Hospitalizations	15,750 (48,130)	20,890 (59,541)	-5140 (-9838, 35)	0.052
ER visits	3619 (29,892)	4411 (17,246)	-793 (-2314, 857)	0.301
Outpatient visits	9866 (28,961)	9598 (33,649)	268 (-2351, 2663)	0.878
Other visits	787 (2879)	681 (3043)	106 (-201, 407)	0.481
All-cause total	85,819 (138,079)	91,161 (156,275)	-5342 (-20,926, 8996)	0.501

Notes: ^aCOPD-related costs were defined as claims with a primary or secondary diagnosis of COPD. ^bMedical costs are inflated to US dollars 2019 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor.

Abbreviations: B/F, budesonide/formoterol; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; FP/SAL, fluticasone propionate/salmeterol; PPPY, per patient per year; SD, standard deviation; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

Patients initiating treatment with UMEC/VI experienced lower rates of COPD-related severe exacerbations compared with patients receiving TIO, although this difference did not reach statistical significance (UMEC/VI: 0.10, TIO: 0.12; RR [95% CI]: 0.83 [0.68, 1.04]; [Table 3](#)). The rate of COPD-related moderate exacerbations was numerically lower with UMEC/VI compared with FP/SAL (UMEC/VI: 0.13, FP/SAL: 0.14; RR [95% CI]: 0.89 [0.73, 1.08]) and B/F (UMEC/VI: 0.13, B/F: 0.16; RR [95% CI]: 0.84 [0.69, 1.04]). Similar rates of COPD-related moderate exacerbations were experienced by patients receiving UMEC/VI versus TIO (UMEC/VI: 0.13, TIO: 0.14; RR [95% CI]: 0.99 [0.81, 1.22]; [Table S8](#)). Patients initiating treatment with UMEC/VI experienced significantly lower rates of overall COPD-related exacerbations compared with patients receiving FP/SAL (UMEC/VI: 0.22, FP/SAL: 0.28; RR [95% CI]: 0.81 [0.70, 0.95]; $P=0.004$) and B/F (UMEC/VI: 0.23, B/F: 0.30; RR

[95% CI]: 0.79 [0.68, 0.93]; $P<0.001$). The rate of overall COPD-related exacerbations was similar for patients receiving UMEC/VI compared with TIO (UMEC/VI: 0.24, TIO: 0.26; RR [95% CI]: 0.91 [0.79, 1.06]; [Table S8](#)).

Discussion

This study compared on-treatment COPD-related medical costs and exacerbations in patients with COPD who had high costs and comorbidities. Patients initiating therapy with UMEC/VI had significantly lower COPD-related and all-cause medical costs compared with patients initiating FP/SAL, and numerically lower costs compared with B/F and TIO, which were primarily driven by reductions in hospitalization costs. This is consistent with previous studies, which have shown hospitalizations to be a key driver of costs in patients with COPD,^{20,26} and may be related to reductions in severe exacerbations.

Figure 3 Kaplan–Meier curves for time-to-first severe exacerbation during the on-treatment period for (A) UMEC/VI versus FP/SAL, (B) UMEC/VI versus B/F, and (C) UMEC/VI versus TIO matched cohorts. ^aNumber of patients still observed at the specific point in time. ^bSevere COPD-related exacerbation defined as an inpatient hospitalization with a diagnosis code for COPD in the primary position.

Abbreviations: B/F, budesonide/formoterol; CI, confidence interval; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

Table 3 Rate of on-Treatment COPD-Related Severe Exacerbations for UMEC/VI versus FP/SAL, B/F, and TIO and Matched Cohorts

	Number of Events		Rate (per 100 Person Days)		Rate Ratio (95% CI)	P-value
	UMEC/VI (N=1194)	FP/SAL (N=1194)	UMEC/VI (N=1194)	FP/SAL (N=1194)	–	–
On-treatment period, mean (SD)	144.9 (185.3)	107.5 (153.0)	–	–	–	–
Total person-days	173,045	128,367	–	–	–	–
Severe exacerbations	170	172	0.10	0.13	0.73 (0.59, 0.91)	0.008
	UMEC/VI (N=1441)	B/F (N=1441)	UMEC/VI (N=1441)	B/F (N=1441)	–	–
	UMEC/VI (N=1441)	B/F (N=1441)	UMEC/VI (N=1441)	B/F (N=1441)	–	–
On-treatment period, mean (SD)	139.5 (176.9)	102.5 (139.9)	–	–	–	–
Total person-days	201,019	147,676	–	–	–	–
Severe exacerbations	203	203	0.10	0.14	0.73 (0.59, 0.93)	0.012
	UMEC/VI (N=1277)	TIO (N=1277)	UMEC/VI (N=1277)	TIO (N=1277)	–	–
	UMEC/VI (N=1277)	TIO (N=1277)	UMEC/VI (N=1277)	TIO (N=1277)	–	–
On-treatment period, mean (SD)	143.2 (183.3)	130.3 (167.5)	–	–	–	–
Total person-days	182,822	166,413	–	–	–	–
Severe exacerbations	186	205	0.10	0.12	0.83 (0.68, 1.04)	0.080

Abbreviations: B/F, budesonide/formoterol; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

In this study, IMT with UMEC/VI was associated with a significantly lower risk and rate of COPD-related severe exacerbations compared with FP/SAL, B/F, or TIO. This is consistent with the results of a previous claims-based study, which also demonstrated a reduced risk of moderate/severe exacerbation with UMEC/VI versus FP/SAL.²⁷ Interestingly, the rate of on-treatment COPD-related severe exacerbations among patients receiving UMEC/VI was significantly lower compared with those receiving FP/SAL and B/F, while the difference compared with TIO did not reach statistical significance. There is evidence to suggest that LAMA-containing maintenance treatments are more effective at reducing exacerbations than other maintenance medication classes; a network meta-analysis of 21 studies found that LAMA and LABA/LAMA therapies were ranked higher than ICS/LABA and LABA for reducing moderate/severe exacerbations in patients with COPD.²⁸ Other studies have also found evidence that LAMA/LABA combinations modestly reduce exacerbations compared with

LAMA monotherapy.^{16,29,30} This difference between treatment classes could explain the larger differences in the rate of on-treatment COPD exacerbations observed with UMEC/VI versus FP/SAL and B/F than with UMEC/VI versus TIO.

The reductions in severe exacerbations observed in the present study among patients treated with UMEC/VI compared with FP/SAL, B/F, and TIO may have contributed to the reductions in COPD-related medical costs, since previous studies have shown that patients with frequent exacerbations have higher average medical costs than patients who experience exacerbations less frequently.^{19,20} Furthermore, severe exacerbations have been associated with greater increases in medical costs than exacerbations that do not necessitate hospitalization.²¹ The high-cost, high-comorbidity patients included within this study have a higher average rate of hospitalizations compared with the overall patient population,^{2,4} and as such reducing their risk of severe exacerbations is likely to have a large impact on COPD-related medical costs.

In this study, the mean on-treatment time was longer in the UMEC/VI cohort compared with the FP/SAL, B/F, and TIO cohorts. Improvements in adherence with UMEC/VI versus FP/SAL, B/F, and TIO, which have been demonstrated in previous studies,^{27,31} may have contributed to this difference and to the reduced medical costs and exacerbation risk observed in the current study.

Some limitations of this investigation should be considered. For instance, although PS matching on observed pre-index variables was used to account for potential differences between the UMEC/VI and FP/SAL, B/F, and TIO cohorts, the possibility of unmeasured confounding cannot be excluded. As a result, physicians prescribing IMT for patients with COPD may consider factors in their decision-making process that are not accounted for by the PS matching approach used in this study. The results may also have limited generalizability to the uninsured US population, patients with other types of public insurance such as Medicaid, or patients outside of the US. It should also be noted that the analysis was vulnerable to coding inaccuracies; the presence of a diagnosis code may not demonstrate presence of the disease. Finally, this study did not compare UMEC/VI with other LAMA/LABA combinations. Nevertheless, key strengths of this study should also be highlighted. To our knowledge this is the first study using real-world data to evaluate the on-treatment costs and outcomes with UMEC/VI, FP/SAL, B/F, and TIO in patients with COPD (and without asthma) who have high costs and comorbidities. Data were extracted from the Optum Clinformatics Data Mart database, a large database representing a geographically diverse sample of the US population, enabling a comprehensive evaluation of patient demographics, clinical characteristics, medical costs, and COPD-related exacerbations.

Conclusion

In this retrospective claims-based study, patients with COPD who had high costs and comorbidities incurred significantly lower COPD-related medical costs after initiating maintenance therapy with UMEC/VI compared with FP/SAL, and numerically lower costs compared with B/F and TIO. Furthermore, the rate of severe exacerbations was significantly lower among patients receiving UMEC/VI compared with FP/SAL and B/F, and was numerically lower versus TIO. These findings highlight the potential benefits of UMEC/VI compared with three alternative maintenance medications as IMT in patients

with COPD who have high costs and comorbidities, and could provide information for physicians considering treatment options for patients newly diagnosed with COPD.

Abbreviations

B/F, budesonide/formoterol; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COTE, COPD-specific comorbidity test; ER, emergency room; FP/SAL, fluticasone propionate/salmeterol; GOLD, Global Initiative for Chronic Lung Disease; HCRU, healthcare resource use; ICD, International Classification of Diseases; ICS, inhaled corticosteroid; IMT, initial maintenance treatment; KM, Kaplan–Meier; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; PDE, phosphodiesterase; PPPY, per patient per year; PS, propensity score; Quan-CCI, Quan-Charlson comorbidity index; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SITT, single-inhaler triple therapy; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

Data Sharing Statement

Information on GlaxoSmithKline's (GSK) data sharing commitments and requesting access to anonymized individual participant data and associated documents from GSK-sponsored studies can be found at www.clinicalstudydatarequest.com. The data reported in this publication are contained in a database owned by Optum and contain proprietary elements. Therefore, it cannot be broadly disclosed or made publicly available at this time. The disclosure of this data to third-party clients assumes certain data security and privacy protocols are in place and that the third-party client has executed Optum's standard license agreement, which includes restrictive covenants governing the use of the data.

Ethics Approval and Informed Consent

The study was designed and conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. The study used fully de-identified retrospective claims data, which were compliant with the patient requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and as such was not classified as research involving human participants. Therefore, institutional review board approval was not required.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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References

- Halpin DM, Miravitlles M, Metzendorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2891–2908. doi:10.2147/COPD.S139470
- Mannino DM, Higuchi K, Yu TC, et al. Economic burden of COPD in the presence of comorbidities. *Chest*. 2015;148(1):138–150. doi:10.1378/chest.14-2434
- Schwab P, Dhamane AD, Hopson SD, et al. Impact of comorbid conditions in COPD patients on health care resource utilization and costs in a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis*. 2017;12:735–744. doi:10.2147/COPD.S112256
- Lin PJ, Shaya FT, Scharf SM. Economic implications of comorbid conditions among Medicaid beneficiaries with COPD. *Respir Med*. 2010;104(5):697–704. doi:10.1016/j.rmed.2009.11.009
- Simon-Tuval T, Scharf SM, Maimon N, Bernhard-Scharf BJ, Reuveni H, Tarasiuk A. Determinants of elevated healthcare utilization in patients with COPD. *Respir Res*. 2011;12(1):7. doi:10.1186/1465-9921-12-7
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of Chronic Obstructive Pulmonary Disease (2020 report). Available from: <https://goldcopd.org/>. Accessed January 2020.
- Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med*. 2014;2(6):472–486. doi:10.1016/S2213-2600(14)70065-7
- Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med*. 2015;109(7):870–881. doi:10.1016/j.rmed.2015.04.018
- Kerwin EM, Kalberg CJ, Galkin DV, et al. Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderate COPD: a randomized, parallel-group, 12-week study. *Int J Chron Obstruct Pulmon Dis*. 2017;12:745–755. doi:10.2147/COPD.S119032
- Lipson DA, Barnhart F, Boucot I, et al. Comparison of LAMA/LABA vs ICS/LABA in high risk COPD patients: pre-specified analysis on lung function and health status from the IMPACT trial. *Eur Respir J*. 2018;52(suppl 62):PA4385.
- Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A. Efficacy and safety of umeclidinium/vilanterol 62.5/25mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med*. 2014;108(12):1752–1760. doi:10.1016/j.rmed.2014.10.002
- Maltais F, Bjerner L, Kerwin EM, et al. Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: the EMAX randomised trial. *Respir Res*. 2019;20(1):238. doi:10.1186/s12931-019-1193-9
- Singh D, Jones PW, Bateman ED, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med*. 2014;14(1):178. doi:10.1186/1471-2466-14-178
- Singh D, Worsley S, Zhu CQ, Hardaker L, Church A. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. *BMC Pulm Med*. 2015;15(1):91. doi:10.1186/s12890-015-0092-1
- Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med*. 2016;374(23):2222–2234. doi:10.1056/NEJMoa1516385
- Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med*. 2013;1(3):199–209. doi:10.1016/S2213-2600(13)70052-3

17. Zhong N, Wang C, Zhou X, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1015–1026. doi:10.2147/COPD.S84436
18. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of Chronic Obstructive Pulmonary Disease. An official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;201(9):e56–e69. doi:10.1164/rccm.202003-0625ST
19. Dhamane AD, Moretz C, Zhou Y, et al. COPD exacerbation frequency and its association with health care resource utilization and costs. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2609–2618. doi:10.2147/COPD.S90148
20. Iheanacho I, Zhang S, King D, Rizzo M, Ismaila AS. Economic burden of Chronic Obstructive Pulmonary Disease (COPD): a Systematic Literature Review. *Int J Chron Obstruct Pulmon Dis*. 2020;15:439–460. doi:10.2147/COPD.S234942
21. Pasquale MK, Sun SX, Song F, Hartnett HJ, Stemkowski SA. Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis*. 2012;7:757–764. doi:10.2147/COPD.S36997
22. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of Chronic Obstructive Pulmonary Disease and cardiac events. A post hoc cohort analysis from the SUMMIT Randomized Clinical Trial. *Am J Respir Crit Care Med*. 2018;198(1):51–57. doi:10.1164/rccm.201711-2239OC
23. Reilev M, Pottegård A, Lykkegaard J, Søndergaard J, Ingebrigtsen TS, Hallas J. Increased risk of major adverse cardiac events following the onset of acute exacerbations of COPD. *Respirology*. 2019;24(12):1183–1190. doi:10.1111/resp.13620
24. Echave-Sustaeta JM, Comeche Casanova L, Cosio BG, Soler-Cataluña JJ, Garcia-Lujan R, Ribera X. Comorbidity in chronic obstructive pulmonary disease. Related to disease severity? *Int J Chron Obstruct Pulmon Dis*. 2014;9:1307–1314. doi:10.2147/COPD.S71849
25. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130–1139. doi:10.1097/01.mlr.0000182534.19832.83
26. Dalal AA, Christensen L, Liu F, Riedel AA. Direct costs of chronic obstructive pulmonary disease among managed care patients. *Int J Chron Obstruct Pulmon Dis*. 2010;5:341–349. doi:10.2147/COPD.S13771
27. Moretz C, Sharpsten L, Bengtson LG, et al. Real-world effectiveness of umeclidinium/vilanterol versus fluticasone propionate/salmeterol as initial maintenance therapy for chronic obstructive pulmonary disease (COPD): a retrospective cohort study. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1721–1737. doi:10.2147/COPD.S204649
28. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2018;12(12):Cd012620. doi:10.1002/14651858.CD012620.pub2
29. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6(5):337–344. doi:10.1016/S2213-2600(18)30102-4
30. Mathioudakis AG, Vestbo J, Singh D. Long-acting bronchodilators for chronic obstructive pulmonary disease: Which One(S), How, and When? *Clin Chest Med*. 2020;41(3):463–474. doi:10.1016/j.ccm.2020.05.005
31. Slade D, Ray R, Moretz C, et al. Medication adherence and COPD-related costs among patients with COPD treated with Umeclidinium/Vilanterol (UMEC/VI) vs Tiotropium (Tio). Paper presented at: CHEST Annual Meeting; 2020. Virtual conference.

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