

Healthcare Resource Utilization, Cost and Clinical Outcomes in Patients Diagnosed with COPD Initiating Tiotropium Bromide/Olodaterol versus Fluticasone Furoate/Umeclidinium/Vilanterol Based on Exacerbation History

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Background: ATS and GOLD guidelines recommend treating low-exacerbation risk COPD patients with dual (LAMA/LABA) agents and reserving triple therapy (TT; LAMA/LABA and inhaled corticosteroids [ICS]) for severe cases with higher-exacerbation risk. However, TT often is prescribed across the COPD spectrum. This study compared COPD exacerbations, pneumonia diagnosis, healthcare resource utilization, and costs for patients initiating tiotropium bromide/olodaterol (TIO/OLO) and a TT, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), stratified by exacerbation history.

Methods: COPD patients who initiated TIO/OLO or FF/UMEC/VI between 06/01/2015–11/30/2019 (index date=first pharmacy fill-date with ≥ 30 consecutive treatment days) were identified from the Optum Research Database. Patients were ≥ 40 years old and continuously enrolled for 12 months during the baseline period and ≥ 30 days during follow-up. Patients were stratified into GOLD A/B (0–1 baseline non-hospitalized exacerbation), No exacerbation (subset of GOLD A/B), and GOLD C/D (≥ 2 non-hospitalized and/or ≥ 1 hospitalized baseline exacerbation). Baseline characteristics were balanced with propensity score matching (1:1). Adjusted risks of exacerbation, pneumonia diagnosis, and COPD and/or pneumonia-related utilization and costs were evaluated.

Results: Adjusted exacerbation risk was similar in GOLD A/B and No exacerbation subgroups, and lower in GOLD C/D for FF/UMEC/VI versus TIO/OLO initiators (hazard ratio: 0.87; 95% CI: 0.78, 0.98, $p=0.020$). Adjusted pneumonia risk was similar between cohorts across the GOLD subgroups. Adjusted COPD and/or pneumonia-related population annualized pharmacy costs were significantly higher for FF/UMEC/VI versus TIO/OLO initiators across subgroups, $p<0.001$. Adjusted COPD and/or pneumonia-related population annualized total healthcare costs were significantly higher for FF/UMEC/VI versus TIO/OLO initiators in the GOLD A/B and No exacerbation, subgroups, $p<0.001$ (cost ratio [95% CI]: 1.25 [1.13, 1.38] and 1.21 [1.09, 1.36], respectively), but similar in the GOLD C/D subgroup.

Conclusion: These real-world results support ATS and GOLD recommendations for treating low-exacerbation risk COPD patients with dual bronchodilators and TT for more severe, higher-exacerbation risk COPD patients.

Keywords: COPD, tiotropium bromide/olodaterol, fluticasone furoate/umeclidinium/vilanterol, exacerbation history, healthcare resource utilization, cost, clinical outcomes

Plain Language Summary

The American Thoracic Society (ATS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend prescribing dual therapy (LAMA/LABA) for COPD patients with low-exacerbation risk and reserving triple therapy (TT) for patients with severe/higher-exacerbation risk COPD. Patients often receive treatment that overlooks this guidance, and lower-risk patients are

treated with TT rather than dual or monotherapy. We assessed COPD exacerbations, pneumonia risk, resource use and costs in insured patients with COPD who started COPD treatment with either a dual therapy TIO/OLO or the TT, FF/UMEC/VI. First, we categorized the patients into subgroups by their exacerbation history: GOLD A/B (0–1 baseline non-hospitalized exacerbation), No exacerbation (a subset of GOLD A/B), and GOLD C/D (≥ 2 non-hospitalized and/or ≥ 1 hospitalized baseline exacerbation). After adjusting for baseline differences between the TIO/OLO and FF/UMEC/VI cohorts, there was no difference in exacerbation risk between the TIO/OLO and the FF/UMEC/VI cohorts in the GOLD A/B and No exacerbation subgroups. In the GOLD C/D subgroup, however, patients in the FF/UMEC/VI cohort had a lower adjusted exacerbation risk than patients in the TIO/OLO cohort. In the GOLD A/B and No exacerbation subgroups, healthcare costs were significantly higher for the FF/UMEC/VI cohort compared to the TIO/OLO cohort but similar between cohorts in the GOLD C/D subgroup. These results support the ATS and GOLD recommendations for treating mild-to-moderate COPD patients with dual therapy, and suggest considerable cost savings could be realized in following them in everyday practice.

Introduction

The American Thoracic Society (ATS) 2020 Clinical Practice Guidelines recommend long-acting muscarinic antagonist/beta₂-agonist (LAMA/LABA) combination therapy versus monotherapy for patients with COPD who experience dyspnea/exercise intolerance. Escalation to triple therapy (TT), with LAMA, LABA and inhaled corticosteroids (ICS), is recommended for patients continuing to experience dyspnea/exercise intolerance, and who had ≥ 1 exacerbation requiring hospitalization and/or treatment with antibiotics/oral steroids in the prior year.¹

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has similar recommendations, and identifies COPD patient exacerbation risk subgroupings based on their prior year history: A/B (low) and C/D (high).² GOLD guidance recommends LAMA/LABA as next-in-line therapy for symptomatic COPD patients on mono-maintenance therapy.² GOLD 2022 recommends consideration of ICS and/or escalating to TT for patients experiencing further exacerbation(s) on dual therapy, after a risk/benefit assessment related to the potential for pneumonia and other side-effects.²

The rationale for our study is that results from randomized clinical trials (RCTs) of fixed dose combination (FDC) TTs, which included a mostly severe COPD subpopulation at higher risk for exacerbations, may not be generalizable to real-world practice. Real-world studies suggest that TT is overprescribed across all COPD severities,^{3–6} especially to patients in low exacerbation risk Groups A and B who comprise the majority of the COPD population.⁷ Other real-world US studies in maintenance-treated COPD patients report that 60–80% of patients were prescribed TT treatment in discordance with GOLD recommendations.^{6,8}

A German DACCORD registry study found that at 1-year follow-up, significantly fewer patients on LABA+LAMA experienced an exacerbation, and at a significantly lower rate versus patients on triple therapy.⁹ Furthermore, an observational study suggested that tiotropium bromide/olodaterol (TIO/OLO) may be associated with improved economic and COPD-related health outcomes, with less pneumonia risk versus TT,⁸ and an economic analysis of a managed care Medicare population reported that COPD-related and all-cause costs were lower for TIO/OLO versus TT.⁶ These studies, however, focused on free-dose TT, reflecting a need for real-world evidence on FDC TT.

The purpose of this study was to compare COPD exacerbations, pneumonia, COPD and/or pneumonia-related and all-cause healthcare resource utilization (HCRU) and costs among patients newly treated with TIO/OLO or fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), stratified by GOLD exacerbation risk.⁵

Methods

Study Design and Data Source

This retrospective observational cohort study included administrative claims data from the Optum Research Database (ORD), a repository of deidentified information for more than 73 million enrollees with commercial or Medicare Advantage with Part D (MAPD) insurance coverage. 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.

Study Population

Inclusion Criteria

Included patients had ≥ 30 consecutive days of TIO/OLO or FF/UMEC/VI treatment initiated during the identification period. The US Food and Drug Administration (FDA) approved Stiolto® Respimat® (TIO/OLO) on 05/21/2015,¹⁰ and Trelegy® Ellipta® (FF/UMEC/VI) on 09/18/2017,¹¹ for COPD. TIO/OLO initiators before and after the launch of FF/UMEC/VI were compared to ensure similar population characteristics before and after FDA's FF/UMEC/VI approval. TIO/OLO initiators were well-balanced on a priori characteristics. The index date was set to the first qualifying pharmacy fill-date between 06/01/2015-11/30/2019. Patients with ≥ 1 facility claim with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and/or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) primary diagnosis for COPD or ≥ 2 professional claims with a COPD diagnosis, on separate service dates during the study period (06/01/2014-12/31/2019), who were ≥ 40 years of age as of the index year and had continuous enrollment with medical and pharmacy coverage for 12 months prior to and including the index date (baseline period) and for ≥ 30 days following the index date were included.

Exclusion Criteria

Patients were excluded if they had ≥ 2 baseline medical claims on separate dates of service with asthma, cystic fibrosis, lung cancer, or interstitial lung disease diagnosis; index date pharmacy claims for both TIO/OLO and FF/UMEC/VI; pharmacy claims for any non-index COPD maintenance medication on the index date (LAMA, LABA, or ICS monotherapy; LABA/ICS or non-TIO/OLO LAMA/LABA FDC); free or FDC LAMA/LABA or TT (defined as ≥ 7 consecutive days of overlapping days' supply with a LAMA and LABA or an ICS, LABA, and LAMA, respectively) during the 6-months prior to and excluding the index date; ≥ 1 medical claim with a procedure code for lung volume reduction during the study period; and unknown age/gender/insurance coverage, or unknown or other geographic region.

GOLD Groups

The GOLD A/B population consisted of patients with 0–1 baseline exacerbation not leading to hospitalization. The No Exacerbation population, a subset of the GOLD A/B, consisted of patients with no baseline exacerbation. The GOLD C/D population included patients with ≥ 2 baseline exacerbations not leading to hospitalization and/or ≥ 1 baseline exacerbation leading to hospitalization.

Baseline Variables

Baseline demographics, clinical characteristics including comorbidity burden, COPD severity score, and baseline medication use were assessed from both pharmacy and medical claims.

Follow-Up and Outcomes

Follow-up continued until the earliest of switch to non-index maintenance COPD medication, discontinuation of index medication, disenrollment from health plan, 12 months post-index date, or end of the study period. All outcomes were assessed during this variable period starting on the day after the index date, with a minimum of 30-days duration up to a maximum of 12 months. Clinical outcomes included COPD exacerbations and pneumonia-related events.

Exacerbations occurring within 14 days of each other were considered a single exacerbation episode and were classified according to the highest severity contributing event. A severe exacerbation was defined as hospitalization/emergency room (ER) visit with a primary COPD diagnosis; or hospitalization/ER visit with a primary acute respiratory failure diagnosis and a COPD diagnosis; or hospitalization/ER visit with a primary acute respiratory failure diagnosis plus hospitalization/ER visit within ± 7 days with a COPD diagnosis. A moderate exacerbation was defined as an office/outpatient visit with a COPD diagnosis plus a pharmacy claim for oral corticosteroids (OCS) and/or antibiotics within ± 7 days.

All-cause HCRU included hospitalizations, ER visits, physician office visits, hospital outpatient visits, other services (including but not limited to independent laboratories, assisted living facilities, and home health providers) and pharmacy claims. All-cause healthcare costs were assessed using plan paid plus patient paid amounts. Total healthcare costs combined pharmacy, and medical costs categorized as hospitalization, ER services, physician office, hospital outpatient,

and other costs. COPD and/or pneumonia-related HCRU and costs were analogous to their respective all-cause outcomes but restricted to utilization with a diagnosis for COPD, pneumonia, or acute bronchitis/bronchiolitis in any position or for a COPD-related treatment including rescue and controller therapies and COPD-guideline recommended antibiotics. Costs were adjusted to 2020 US dollars based on the medical care component of the Consumer Price Index (CPI).¹²

Statistical Analysis

A stratified propensity score match (PSM) was used to 1:1 hard match TIO/OLO and FF/UMEC/VI patients on baseline exacerbation (yes/no), baseline GOLD A/B and C/D status, and baseline maintenance therapy naive status (yes/no). The propensity score model included demographics, baseline comorbidity burden, COPD disease characteristics, use of respiratory medications, and all-cause, COPD-related, and pneumonia-related HCRU and costs. A standardized mean difference (SMD) of $\leq 10\%$ for each measure was deemed acceptable to indicate balance between the cohorts.

Follow-up variables were presented as population annualized averages with Wald 95% confidence intervals using Taylor expansion to estimate the standard error, and were calculated as:

$$\text{Annualized population average} = \left[\frac{\text{Sum of all HCRU or costs for all individuals during the followup period}}{\text{Sum of all followup time in days for all individuals}} \right] \times 365$$

Kaplan-Meier analysis was used to estimate time to first COPD exacerbation and pneumonia diagnosis. To adjust for baseline characteristics that remained imbalanced post-match, multivariable analyses (MVA) were conducted for COPD and/or pneumonia-related total (pharmacy and medical) costs, and hospitalization, any exacerbation, and pneumonia diagnosis. Cost outcomes were modeled with generalized linear models (GLM) using a gamma distribution and log link; except for the GOLD C/D population, where total costs were modeled with inverse Gaussian distribution. Cost ratios were estimated via exponentiated coefficients from a GLM. The average adjusted cost for each cohort was estimated using recycled predictions. Counts of hospitalizations were modeled with negative binomial models, and time to first exacerbation and pneumonia diagnosis with Cox proportional hazard models. All models accounted for clustering within the matched pairs with an a-priori $\alpha=0.05$ for statistical significance. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient Disposition

The analysis included 16,338 patients: approximately 40% initiated TIO/OLO (n=6681) and 60% initiated FF/UMEC/VI (n=9657). SMDs between TIO/OLO initiators before (n=3085; 46.2%) and after FF/UMEC/VI approval (n=3596; 53.8%) were balanced on all a-priori specified characteristics, except insurance type for which imbalances were not meaningful (data not shown). TIO/OLO and FF/UMEC/VI post-match treatment cohorts included 3884, 2552, and 1774 matched pairs for the GOLD A/B, No exacerbation, and GOLD C/D subgroups, respectively ([Supplemental Figure 1](#)).

Baseline Patient Characteristics

Pre-Match

Pre-match patient characteristics provided in [Supplemental Table 1](#).

Baseline Patient Characteristics

Post-Match

Post-match, the TIO/OLO and FF/UMEC/VI cohorts were similar in age, gender, and insurance type; however, some imbalances persisted ([Table 1](#)). Imbalance was frequently observed for other/unknown race/ethnicity, any LAMA, LABA, ICS, and LABA/ICS FDC, and pneumonia-related hospitalization days.

Table I Post-Match Clinical and Demographic Characteristics at Baseline

Characteristics	GOLD A/B			No Exacerbation (Subgroup of GOLD A/B)			GOLD C/D		
	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference
	(N=3884)	(N=3884)		(N=2552)	(N=2552)		(N=1774)	(N=1774)	
Age (continuous), years, mean (SD)	71.68 (8.69)	71.79 (8.66)	-1.26	71.91 (8.73)	71.76 (8.69)	1.72	71.70 (8.69)	71.66 (8.49)	0.54
Age group, n (%)									
40–49	55 (1.42)	40 (1.03)	3.51	34 (1.33)	30 (1.18)	1.41	17 (0.96)	15 (0.85)	1.19
50–59	335 (8.63)	300 (7.72)	3.29	218 (8.54)	199 (7.80)	2.72	148 (8.34)	146 (8.23)	0.41
60–64	320 (8.24)	405 (10.43)	-7.53	208 (8.15)	268 (10.50)	-8.09	195 (10.99)	189 (10.65)	1.09
65–69	716 (18.43)	667 (17.17)	3.30	452 (17.71)	421 (16.50)	3.23	286 (16.12)	316 (17.81)	-4.51
70–74	971 (25.00)	961 (24.74)	0.60	637 (24.96)	633 (24.80)	0.36	445 (25.08)	398 (22.44)	6.23
75+	1487 (38.29)	1511 (38.90)	-1.27	1003 (39.30)	1001 (39.22)	0.16	683 (38.50)	710 (40.02)	-3.12
Gender, n (%)									
Female	1915 (49.30)	1920 (49.43)	-0.26	1203 (47.14)	1238 (48.51)	-2.75	931 (52.48)	946 (53.33)	-1.69
Region, n (%)									
Northeast	517 (13.31)	480 (12.36)	2.85	349 (13.68)	343 (13.44)	0.69	196 (11.05)	221 (12.46)	-4.38
Midwest	858 (22.09)	852 (21.94)	0.37	559 (21.90)	565 (22.14)	-0.57	420 (23.68)	391 (22.04)	3.89
South	2229 (57.39)	2284 (58.81)	-2.87	1444 (56.58)	1467 (57.48)	-1.82	1040 (58.62)	1055 (59.47)	-1.72
West	280 (7.21)	268 (6.90)	1.21	200 (7.84)	177 (6.94)	3.45	118 (6.65)	107 (6.03)	2.54
Resource-scarce area, n (%)^a	844 (21.73)	933 (24.02)	-5.46	548 (21.47)	621 (24.33)	-6.81	421 (23.73)	382 (21.53)	5.26
Insurance type, n (%)									
Commercial	260 (6.69)	252 (6.49)	0.83	191 (7.48)	182 (7.13)	1.36	70 (3.95)	107 (6.03)	-9.59
Medicare Advantage with Part D	3624 (93.31)	3632 (93.51)	-0.83	2361 (92.52)	2370 (92.87)	-1.36	1704 (96.05)	1667 (93.97)	9.59
Race/ethnicity, n (%)									
Non-Hispanic White	2734 (70.39)	2620 (67.46)	6.35	1797 (70.42)	1733 (67.91)	5.43	1281 (72.21)	1195 (67.36)	10.57
Non-Hispanic Black	497 (12.80)	501 (12.90)	-0.31	332 (13.01)	318 (12.46)	1.65	234 (13.19)	239 (13.47)	-0.83
Non-Hispanic Asian	62 (1.60)	36 (0.93)	6.00	37 (1.45)	25 (0.98)	4.29	16 (0.90)	26 (1.47)	-5.21

(Continued)

Table I (Continued).

Characteristics	GOLD A/B			No Exacerbation (Subgroup of GOLD A/B)			GOLD C/D		
	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference
	(N=3884)	(N=3884)		(N=2552)	(N=2552)		(N=1774)	(N=1774)	
Hispanic	218 (5.61)	202 (5.20)	1.82	140 (5.49)	143 (5.60)	−0.51	93 (5.24)	79 (4.45)	3.68
Other/unknown race	373 (9.60)	525 (13.52)	−12.26	246 (9.64)	333 (13.05)	−10.77	150 (8.46)	235 (13.25)	−15.45
Baseline Charlson comorbidity score excluding COPD (continuous), mean (SD) ^b	1.49 (1.74)	1.53 (1.76)	−2.27	1.48 (1.74)	1.51 (1.78)	−1.73	2.26 (2.12)	2.17 (2.00)	4.84
Baseline Elixhauser comorbidity score excluding COPD (continuous), mean (SD) ^c	6.03 (8.33)	6.26 (8.47)	−2.77	6.03 (8.33)	6.10 (8.46)	−0.84	10.98 (10.46)	10.46 (10.41)	4.96
COPD severity score (continuous), mean (SD) ^d	26.87 (6.39)	26.87 (6.23)	−0.07	26.36 (6.10)	26.28 (6.14)	1.38	35.19 (10.98)	34.17 (9.55)	9.94
Baseline comorbidities, n (%)									
Depression	886 (22.81)	1011 (26.03)	−7.50	553 (21.67)	621 (24.33)	−6.33	556 (31.34)	581 (32.75)	−3.02
Dyspnea	2237 (57.60)	2182 (56.18)	2.86	1430 (56.03)	1389 (54.43)	3.23	1408 (79.37)	1392 (78.47)	2.21
Hypertension	3142 (80.90)	3148 (81.05)	−0.39	2074 (81.27)	2051 (80.37)	2.29	1501 (84.61)	1510 (85.12)	−1.42
Ischemic heart disease	1412 (36.35)	1488 (38.31)	−4.05	920 (36.05)	958 (37.54)	−3.09	850 (47.91)	839 (47.29)	1.24
Peptic ulcer/GERD	1198 (30.84)	1205 (31.02)	−0.39	768 (30.09)	748 (29.31)	1.72	777 (43.80)	726 (40.92)	5.82
Pneumonia	348 (8.96)	387 (9.96)	−3.43	157 (6.15)	174 (6.82)	−2.71	673 (37.94)	629 (35.46)	5.15
Tobacco use ^e	2382 (61.33)	2500 (64.37)	−6.29	1501 (58.82)	1570 (61.52)	−5.53	1471 (82.92)	1483 (83.60)	−1.81
Type 2 diabetes	1724 (44.39)	1666 (42.89)	3.01	1155 (45.26)	1099 (43.06)	4.42	814 (45.89)	814 (45.89)	0.00
Baseline respiratory medication use, n (%)									
Long-acting bronchodilator naive ^f	2285 (58.83)	2254 (58.03)	1.62	1521 (59.60)	1511 (59.21)	0.80	886 (49.94)	878 (49.49)	0.90
Maintenance therapy naive ^g	2202 (56.69)	2202 (56.69)	0.00	1476 (57.84)	1476 (57.84)	0.00	823 (46.39)	823 (46.39)	0.00
Nebulized medication delivery	936 (24.10)	955 (24.59)	−1.14	514 (20.14)	502 (19.67)	1.18	987 (55.64)	964 (54.34)	2.61
Pharmacy claims, n (%)									
Controller medications	1681 (43.28)	1695 (43.64)	−0.73	1076 (42.16)	1086 (42.55)	−0.79	956 (53.89)	963 (54.28)	−0.79
LAMA ^h	1021 (26.29)	612 (15.76)	26.06	656 (25.71)	377 (14.77)	27.47	506 (28.52)	354 (19.95)	20.10
LAMA monotherapy	979 (25.21)	539 (13.88)	28.87	628 (24.61)	325 (12.74)	30.83	475 (26.78)	320 (18.04)	21.07
LABA ^h	720 (18.54)	1281 (32.98)	−33.49	460 (18.03)	828 (32.45)	−33.67	512 (28.86)	715 (40.30)	−24.23

ICS ^h	767 (19.75)	1286 (33.11)	-30.66	473 (18.53)	830 (32.52)	-32.50	560 (31.57)	752 (42.39)	-22.56
LABA/ICS combination (fixed dose)	649 (16.71)	1204 (31.00)	-34.01	412 (16.14)	774 (30.33)	-34.07	462 (26.04)	668 (37.66)	-25.12
Rescue medications	2430 (62.56)	2448 (63.03)	-0.96	1478 (57.92)	1482 (58.07)	-0.32	1469 (82.81)	1432 (80.72)	5.40
Oral corticosteroids	1415 (36.43)	1515 (39.01)	-5.31	547 (21.43)	600 (23.51)	-4.98	1422 (80.16)	1503 (84.72)	-12.02
Pharmacy claim count, mean (SD)									
Controller medications	1.92 (3.20)	1.72 (2.80)	6.51	1.90 (3.20)	1.68 (2.76)	7.30	2.45 (3.51)	2.22 (3.15)	6.84
LAMA ^h	1.16 (2.60)	0.50 (1.58)	30.46	1.21 (2.73)	0.47 (1.53)	33.71	1.17 (2.52)	0.54 (1.51)	30.06
LAMA monotherapy	1.14 (2.59)	0.47 (1.55)	31.32	1.20 (2.72)	0.43 (1.51)	34.78	1.13 (2.51)	0.51 (1.49)	30.29
LABA ^h	0.64 (1.88)	1.14 (2.28)	-23.98	0.58 (1.73)	1.14 (2.28)	-27.46	0.95 (2.11)	1.42 (2.48)	-20.30
ICS ^h	0.69 (1.92)	1.18 (2.30)	-22.97	0.62 (1.79)	1.17 (2.31)	-26.53	1.06 (2.24)	1.51 (2.54)	-18.68
LABA/ICS combination (fixed dose)	0.59 (1.81)	1.10 (2.25)	-24.89	0.54 (1.68)	1.09 (2.26)	-27.99	0.88 (2.06)	1.34 (2.46)	-20.63
Rescue medications	2.23 (3.63)	2.19 (3.49)	1.06	2.04 (3.50)	1.96 (3.38)	2.25	4.32 (5.19)	4.11 (5.26)	4.09
Oral corticosteroids	0.64 (1.31)	0.68 (1.24)	-3.70	0.38 (1.06)	0.42 (1.08)	-3.55	2.59 (2.95)	2.61 (2.63)	-0.83
Medical claims, n (%)									
Controller medications	63 (1.62)	42 (1.08)	4.68	39 (1.53)	27 (1.06)	4.16	50 (2.82)	29 (1.63)	8.03
Rescue medications	324 (8.34)	274 (7.05)	4.83	170 (6.66)	134 (5.25)	5.96	266 (14.99)	226 (12.74)	6.53
Medical claim count, mean (SD)									
Controller medications	0.06 (0.81)	0.02 (0.38)	5.60	0.05 (0.63)	0.02 (0.30)	6.01	0.27 (2.22)	0.08 (1.13)	10.46
Rescue medications	0.19 (1.03)	0.13 (0.72)	6.26	0.15 (0.93)	0.11 (0.70)	5.38	0.44 (1.67)	0.32 (1.36)	7.48
Pharmacy and medical claim count, mean (SD)									
Short-acting muscarinic antagonist (SAMA) medications	0.67 (2.22)	0.51 (1.82)	7.94	0.61 (2.17)	0.47 (1.85)	7.06	1.67 (3.28)	1.34 (2.84)	10.50
Any COPD exacerbation, n (%)									
≥ 1 exacerbation	1332 (34.29)	1332 (34.29)	0.00	0 (0.00)	0 (0.00)	-	1774 (100.00)	1774 (100.00)	-
Severe COPD exacerbations, n (%)ⁱ									
≥ 1 exacerbation	150 (3.86)	173 (4.45)	-2.97	0 (0.00)	0 (0.00)	-	1083 (61.05)	1026 (57.84)	6.55

(Continued)

Table I (Continued).

Characteristics	GOLD A/B			No Exacerbation (Subgroup of GOLD A/B)			GOLD C/D		
	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference	TIO/OLO	FF/UMEC/VI	Standardized Mean Difference
	(N=3884)	(N=3884)		(N=2552)	(N=2552)		(N=1774)	(N=1774)	
All-cause utilization, n (%)									
Ambulatory visit	3882 (99.95)	3882 (99.95)	0.00	2550 (99.92)	2550 (99.92)	0.00	1772 (99.89)	1771 (99.83)	1.50
Emergency room visit	1383 (35.61)	1413 (36.38)	−1.61	842 (32.99)	796 (31.19)	3.86	1321 (74.46)	1262 (71.14)	7.48
Hospitalization	529 (13.62)	574 (14.78)	−3.32	348 (13.64)	331 (12.97)	1.96	1032 (58.17)	959 (54.06)	8.30
Acute hospitalization ^l	520 (13.39)	567 (14.60)	−3.49	342 (13.40)	324 (12.70)	2.09	1028 (57.95)	955 (53.83)	8.29
Other medical visits ^k	3361 (86.53)	3382 (87.08)	−1.60	2186 (85.66)	2208 (86.52)	−2.49	1640 (92.45)	1652 (93.12)	−2.61
Pharmacy use	3876 (99.79)	3869 (99.61)	3.32	2544 (99.69)	2537 (99.41)	4.10	1774 (100.00)	1773 (99.94)	3.36
Count of pharmacy claims, mean (SD)	46.66 (34.96)	44.52 (35.16)	6.11	45.14 (35.50)	43.10 (36.21)	5.67	61.57 (41.41)	57.13 (37.51)	11.24
COPD and/or pneumonia-related utilization, n (%) ^l									
Ambulatory visit	3662 (94.28)	3700 (95.26)	−4.40	2332 (91.38)	2380 (93.26)	−7.07	1747 (98.48)	1745 (98.37)	0.90
Emergency room visit	656 (16.89)	654 (16.84)	0.14	337 (13.21)	295 (11.56)	5.00	1006 (56.71)	978 (55.13)	3.18
Hospitalization	379 (9.76)	397 (10.22)	−1.55	233 (9.13)	213 (8.35)	2.78	1013 (57.10)	937 (52.82)	8.62
Acute hospitalization ^l	371 (9.55)	393 (10.12)	−1.90	229 (8.97)	209 (8.19)	2.80	1009 (56.88)	932 (52.54)	8.73
Other medical visits ^k	1263 (32.52)	1314 (33.83)	−2.79	748 (29.31)	787 (30.84)	−3.33	1131 (63.75)	1115 (62.85)	1.87
Pharmacy use	3497 (90.04)	3502 (90.16)	−0.43	2172 (85.11)	2182 (85.50)	−1.11	1756 (98.99)	1760 (99.21)	−2.39
Count of pharmacy claims, mean (SD)	5.98 (5.79)	5.76 (5.48)	3.88	5.12 (5.40)	4.86 (5.22)	4.86	12.51 (9.41)	11.88 (8.63)	6.96
COPD-related utilization, n (%) ^m									
Ambulatory visit	3602 (92.74)	3653 (94.05)	−5.29	2272 (89.03)	2336 (91.54)	−8.47	1739 (98.03)	1739 (98.03)	0.00
Emergency room visit	566 (14.57)	565 (14.55)	0.07	277 (10.85)	256 (10.03)	2.69	921 (51.92)	876 (49.38)	5.08
Hospitalization	334 (8.60)	360 (9.27)	−2.35	207 (8.11)	196 (7.68)	1.60	1004 (56.60)	934 (52.65)	7.93
Acute hospitalization ^l	327 (8.42)	357 (9.19)	−2.73	204 (7.99)	193 (7.56)	1.61	1000 (56.37)	929 (52.37)	8.04
Other medical visits ^k	1193 (30.72)	1246 (32.08)	−2.94	705 (27.63)	751 (29.43)	−3.99	1096 (61.78)	1081 (60.94)	1.74
Pneumonia-related utilization, n (%) ⁿ									
Other medical visit ^k	61 (1.57)	72 (1.85)	−2.18	30 (1.18)	35 (1.37)	−1.75	132 (7.44)	85 (4.79)	11.07

Hospitalization days (among patients with a hospitalization), mean (SD)									
All-cause	9.92 (13.11)	9.71 (11.96)	1.67	10.49 (14.30)	10.89 (13.48)	-2.85	14.26 (20.22)	13.65 (16.64)	3.31
COPD and/or pneumonia-related	9.13 (11.47)	9.69 (12.15)	-4.77	9.39 (12.48)	11.25 (14.04)	-13.99	13.92 (20.06)	13.26 (16.08)	3.59
COPD-related	8.65 (9.63)	9.23 (11.11)	-5.59	8.62 (9.93)	10.99 (13.34)	-20.21	13.86 (19.98)	13.10 (15.81)	4.26
Pneumonia-related	9.62 (11.88)	12.27 (14.83)	-19.75	12.38 (14.27)	14.27 (17.08)	-12.03	14.39 (23.31)	13.75 (16.31)	3.18
COPD and/or pneumonia-attributable	9.88 (12.52)	11.34 (14.64)	-10.72	11.96 (14.49)	13.26 (17.10)	-8.18	13.06 (19.53)	12.03 (14.77)	5.97
Total annual healthcare costs (\$), mean (SD)									
All-cause	16,094 (30,339)	16,448 (28,352)	-1.20	16,274 (34,516)	16,325 (30,893)	-0.16	32,403 (42,136)	30,771 (35,843)	4.17
COPD and/or pneumonia-related	4498 (9583)	4802 (11,610)	-2.85	4168 (9637)	4310 (11,219)	-1.36	19,059 (29,845)	17,644 (23,571)	5.26
COPD-related	4158 (8522)	4463 (9772)	-3.33	3846 (8438)	4014 (8650)	-1.97	18,719 (29,631)	17,338 (23,283)	5.18

Notes: ^aGeographic region designated as resource scarce by the Health Resources and Services Administration because of a shortage of providers to meet the needs of the population. ^bQuan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiology*. 2011; 173 (6): 676–82. ^cWeights are based on the likelihood of hospital mortality from Van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care* 2009;47 (6):626–633. ^dWu EQ, Birnbaum HG, Cifaldi Met al Development of a COPD severity score. *Curr Med Res Opin*. 2006;22 (9):1679–87. ^eBased on diagnosis codes for current or prior tobacco use and pharmacy fills for smoking cessation treatments. ^fNaive to LAMA and LABA during the baseline period. ^gNaive to ICS, LAMA, and LABA during the baseline period. ^hPatients with free or fixed dose LAMA+LABA or ICS+LABA+LAMA maintenance therapy for ≥ 7 consecutive days of overlapping days' supply during the 6-months immediately before the index date were excluded. Patients could have free or fixed dose LAMA+LABA or ICS+LABA+LAMA during months 7–12 prior to the index date. ⁱDefined as a hospitalization or an ER visit with a COPD diagnosis code in the primary position; or a hospitalization or an ER visit with a diagnosis code for acute respiratory failure in the primary position and a COPD diagnosis code in any position; or a hospitalization or an ER visit with a diagnosis code for acute respiratory failure in the primary position + an hospitalization or an ER visit within ±7 days with a COPD diagnosis code in any position. ^jAcute hospitalizations are hospitalizations with at least one claim with a hospital place of service or provider specialty code. ^kOther medical visits may include services like independent laboratory, home health, durable medical equipment, etc. ^lDefined as utilization with a diagnosis for COPD, pneumonia, or acute bronchitis/bronchiolitis in any position or a pharmacy claim for a COPD-related treatment, including COPD-guideline recommended antibiotics. ^mDefined as utilization with a diagnosis for COPD in any position or a pharmacy claim for a COPD-related treatment, including COPD-guideline recommended antibiotics. ⁿDefined as utilization with a diagnosis code for pneumonia in any position. * Variables included in the propensity score model were age, gender, geographic region, insurance type, seasonality, Charlson and Elixhauser scores not including COPD, COPD severity score, count of controller and rescue pharmacy claims, use of nebulized respiratory medications (yes/no), presence of all-cause acute hospitalization (yes/no), COPD-related acute hospitalization (yes/no), pneumonia-related acute hospitalization (yes/no), all-cause ER visit (yes/no), COPD-related ER visit (yes/no), pneumonia-related ER visit (yes/no), all-cause ambulatory visit (yes/no), all-cause ambulatory visit count, COPD-related ambulatory visit count, pneumonia-related ambulatory count, all-cause total costs, COPD-related total costs, pneumonia-related total costs, moderate exacerbation count, severe exacerbation count, spirometry test count, and oxygen therapy (yes/no). **Patients' follow-up was censored at the earliest occurrence of any of the following: switch to non-index maintenance COPD medication, discontinuation of the index medication, disenrollment from health plan, 12 months post-index date, or end of the study period. Switch was defined as a pharmacy fill for ≥30 consecutive days of a non-index regimen containing ICS, LABA, or LAMA, and the switch date as the first date with the new treatment. Discontinuation was defined as a ≥60-day gap in therapy following the runout of medication days' supply, and the discontinuation date as the date of the runout prior to the gap. Patients were censored as of their runout date or if they had <60 days between their last runout date and end of study/disenrollment/1 year of follow-up.

Exacerbation and Pneumonia Diagnosis

GOLD A/B

Time to follow-up for any exacerbation, severe exacerbation, or pneumonia diagnosis was similar for patients in the TIO/OLO and FF/UMEC/VI cohorts. The population annualized count of any COPD exacerbations was also similar. In Kaplan-Meier analysis, 41.4% and 41.6% of patients treated with TIO/OLO and FF/UMEC/VI, respectively, had any COPD exacerbation at one year, sandwich $p=0.916$, while 12.9% and 13.1%, respectively, had a severe exacerbation at one year, sandwich $p\text{-value}=0.731$. Similarly, in Kaplan-Meier analysis, 12.5% and 14.5% of TIO/OLO and FF/UMEC/VI initiators, respectively, had a pneumonia diagnosis at one year, sandwich $p\text{-value}=0.077$. There was no difference in adjusted risks for any exacerbation or pneumonia diagnosis between the FF/UMEC/VI and TIO/OLO initiators. (Figure 1a)

No Exacerbation

No difference was seen between cohorts in time to exacerbation and population annualized count of exacerbations in the No exacerbation subgroup. The time to pneumonia diagnosis, however, was significantly longer among TIO/OLO versus FF/UMEC/VI initiators. In Kaplan-Meier analysis, 36.8% and 38.4% of the TIO/OLO and FF/UMEC/VI cohorts, respectively, had an exacerbation at one year, sandwich $p=0.608$. In addition, 12.1% and 11.2% of the TIO/OLO and

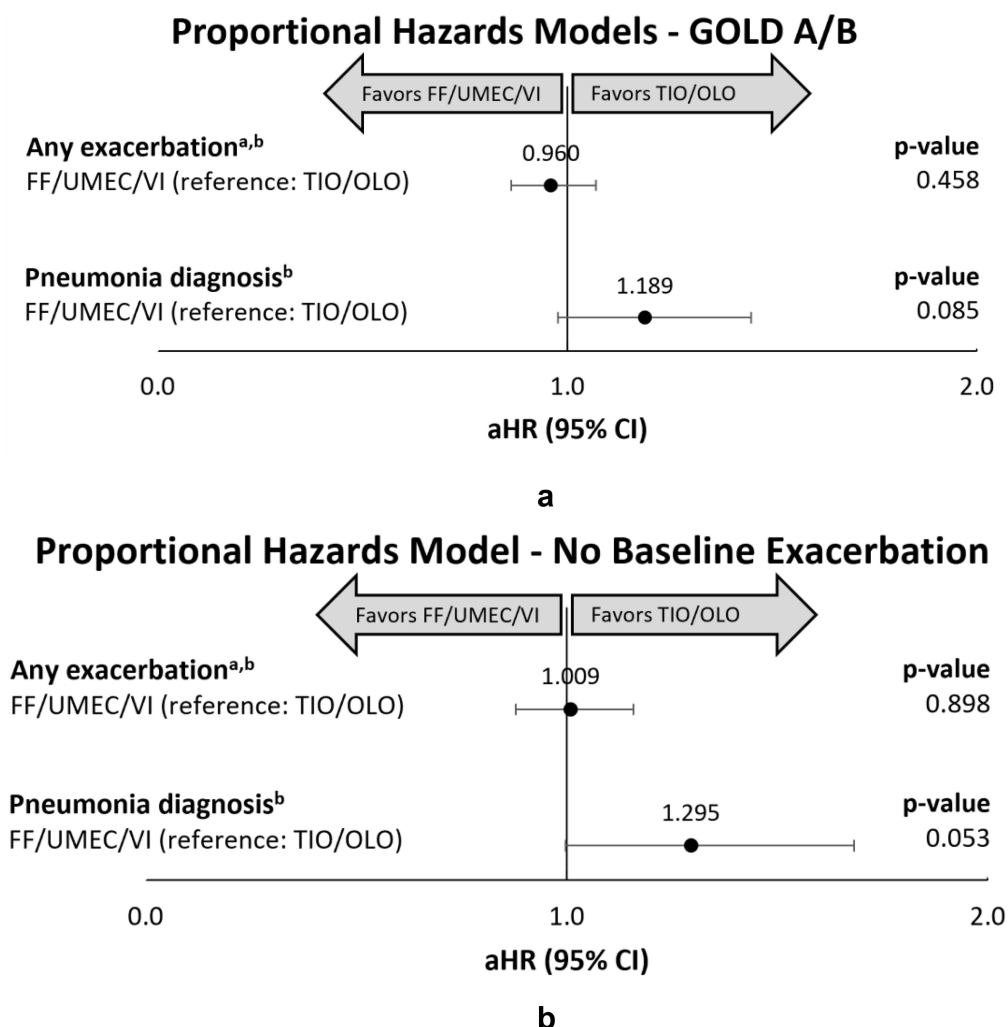


Figure 1 Continued.

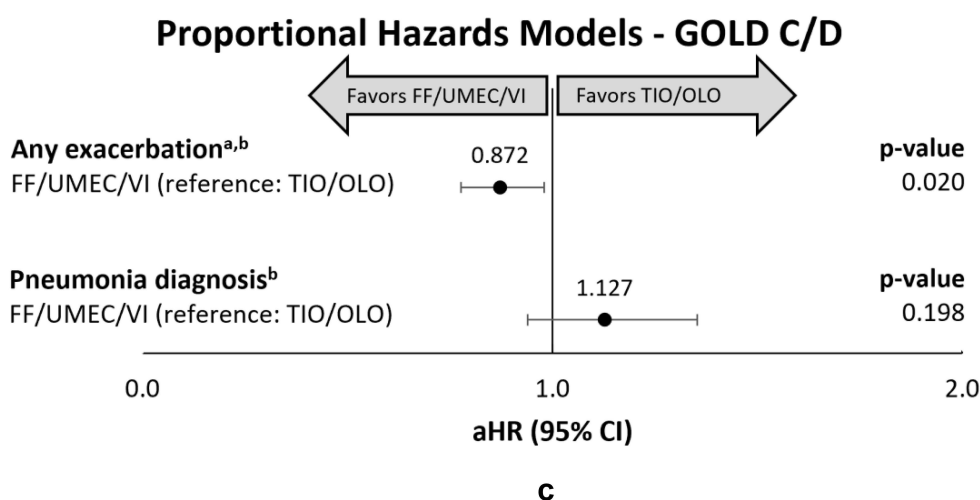


Figure 1 (a) Follow-up exacerbation and pneumonia diagnosis in the GOLD A/B subgroup. (b): Follow-up exacerbation and pneumonia diagnosis in the No Exacerbation subgroup. (c): Follow-up exacerbation and pneumonia diagnosis in the GOLD C/D subgroup.

Notes: (a): ^aA severe exacerbation was defined as a hospitalization or an ER visit with: a COPD diagnosis code in the primary position; a diagnosis code for acute respiratory failure in the primary position and a COPD diagnosis code in any position; or a diagnosis code for acute respiratory failure in the primary position + a hospitalization or an ER visit within ± 7 days with a COPD diagnosis code in any position. A moderate exacerbation was defined as: an ambulatory (office or outpatient) visit with a COPD diagnosis code in any position + a pharmacy claim for an oral corticosteroid (OCS) prescription within ± 7 days of the office/outpatient visit; an office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for COPD-guideline recommended antibiotic prescription within ± 7 days of the office/outpatient visit; or an office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for an OCS + a pharmacy claim for COPD-guideline recommended antibiotic prescription within ± 7 days of the office/outpatient visit. ^bAdjusted for race/ethnicity, baseline LAMA monotherapy pharmacy claims, baseline LABA/ICS pharmacy claims, and baseline length of pneumonia-related hospitalization; p-values account for clustering within matched pairs. (b): ^aA severe exacerbation was defined as a hospitalization or an ER visit with: a COPD diagnosis code in the primary position; a diagnosis code for acute respiratory failure in the primary position and a COPD diagnosis code in any position; or a diagnosis code for acute respiratory failure in the primary position + a hospitalization or an ER visit within ± 7 days with a COPD diagnosis code in any position. A moderate exacerbation was defined as: an ambulatory (office or outpatient) visit with a COPD diagnosis code in any position + a pharmacy claim for an oral corticosteroid (OCS) prescription within ± 7 days of the office/outpatient visit; an office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for COPD-guideline recommended antibiotic prescription within ± 7 days of the office/outpatient visit; or an office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for an OCS + a pharmacy claim for COPD-guideline recommended antibiotic prescription within ± 7 days of the office/outpatient visit. ^bAdjusted for race/ethnicity, baseline LAMA monotherapy pharmacy claims, baseline LABA/ICS pharmacy claims, and baseline length of pneumonia-related hospitalization; p-values account for clustering within matched pairs. (c): ^aA severe exacerbation was defined as a hospitalization or an ER visit with: a COPD diagnosis code in the primary position; a diagnosis code for acute respiratory failure in the primary position and a COPD diagnosis code in any position; or a diagnosis code for acute respiratory failure in the primary position + a hospitalization or an ER visit within ± 7 days with a COPD diagnosis code in any position. A moderate exacerbation was defined as: an ambulatory (office or outpatient) visit with a COPD diagnosis code in any position + a pharmacy claim for an oral corticosteroid (OCS) prescription within ± 7 days of the office/outpatient visit; an office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for COPD-guideline recommended antibiotic prescription within ± 7 days of the office/outpatient visit; or an office or outpatient visit with a COPD diagnosis code in any position + a pharmacy claim for an OCS + a pharmacy claim for COPD-guideline recommended antibiotic prescription within ± 7 days of the office/outpatient visit. ^bAdjusted for race/ethnicity, baseline count of SAMA fills, baseline count of medical claims for controller medications, baseline LAMA monotherapy pharmacy fills, baseline LABA/ICS pharmacy fills, baseline OCS pharmacy fills, baseline pharmacy claim count, and baseline pneumonia-related other medical visits; p-values account for clustering within matched pairs.

FF/UMEC/VI cohorts, respectively, had a severe exacerbation at one year, sandwich p-value=0.559. However, in Kaplan-Meier analysis, 10.0% TIO/OLO and 13.8% FF/UMEC/VI initiators had a pneumonia diagnosis at one year, sandwich p=0.037. There was no difference in adjusted risk of any exacerbation or risk of pneumonia diagnosis between the FF/UMEC/VI and TIO/OLO initiators. (Figure 1b)

GOLD C/D

The population annualized count of any COPD exacerbation was higher among TIO/OLO initiators (1.82; 95% CI: 1.69, 1.95) compared to FF/UMEC/VI (1.59; 95% CI: 1.48, 1.71), p=0.013. In Kaplan-Meier analysis, 71.0% and 70.6% of the TIO/OLO and FF/UMEC/VI cohorts, respectively, had an exacerbation at one year, sandwich p=0.024, and 33.8% and 29.6%, respectively, had a severe exacerbation at one year, sandwich p=0.255. Also, in Kaplan-Meier analysis, 26.6% TIO/OLO and 30.7% FF/UMEC/VI initiators had a pneumonia diagnosis at one year, sandwich p=0.745. In adjusted analyses, FF/UMEC/VI initiators had a lower risk of any exacerbation and a similar risk of pneumonia diagnosis versus TIO/OLO initiators. (Figure 1c)

COPD and/or Pneumonia-Related and All-Cause HCRU (Table 2)

GOLD A/B

Follow-up COPD and/or pneumonia-related HCRU was lower among TIO/OLO initiators compared with FF/UMEC/VI initiators; significant differences were observed for hospitalizations (0.27 vs 0.33; $p=0.022$), ambulatory visits (7.02 vs 7.72; $p=0.036$) and other medical visits (3.10 vs 3.62; $p=0.004$). The adjusted rate of COPD and/or pneumonia-related hospitalizations among FF/UMEC/VI initiators was higher than among TIO/OLO initiators (1.18; 95% CI: 1.00, 1.38; $p=0.048$). All-cause HCRU in the TIO/OLO and FF/UMEC/VI cohorts was similar, except for fewer ER visits among TIO/OLO versus FF/UMEC/VI initiators (0.95 vs 1.10; $p=0.019$), respectively.

No Exacerbation

COPD and/or pneumonia-related HCRU measures were similar between the cohorts with the exception of other medical visits that was lower for the TIO/OLO (2.71; 95% CI: 2.43, 2.99) versus FF/UMEC/VI cohort (3.39; 95% CI: 3.07, 3.71), $p=0.001$. All-cause HCRU measures were similar between the TIO/OLO and FF/UMEC/VI cohorts.

GOLD C/D

COPD and/or pneumonia-related HCRU generally was similar for the TIO/OLO and FF/UMEC/VI cohorts, except for higher outpatient pharmacy fills for TIO/OLO (19.74 vs 18.18; $p<0.001$), respectively. Follow-up all-cause HCRU was similar, except for higher pharmacy fills among TIO/OLO versus FF/UMEC/VI initiators (72.01 vs 65.37; $p<0.001$), respectively.

COPD and/or Pneumonia-Related and All-Cause Healthcare Costs (Figure 2)

GOLD A/B

The population annualized COPD and/or pneumonia-related total costs were significantly lower among TIO/OLO initiators versus FF/UMEC/VI initiators (\$11,521 vs \$14,464; $p<0.001$). Pharmacy costs were significantly lower for TIO/OLO versus FF/UMEC/VI initiators (\$4612 vs \$6484; $p<0.001$). For medical costs, COPD and/or pneumonia-related ER costs were significantly lower among TIO/OLO versus FF/UMEC/VI initiators (\$303 vs \$390; $p=0.031$). Population annualized all-cause total costs (\$23,309 vs \$26,244; $p=0.002$) and pharmacy costs (\$9676 vs \$11,484; $p<0.001$) were significantly lower among TIO/OLO versus FF/UMEC/VI initiators. Adjusted COPD and/or pneumonia-related pharmacy (\$4632 vs \$6455; $p<0.001$) and total healthcare costs (\$11,557 vs \$14,422; $p<0.001$) were significantly lower for TIO/OLO initiators compared to FF/UMEC/VI (Table 3). COPD and/or pneumonia-related medical costs were not significantly different between cohorts.

No Exacerbation

Population annualized COPD and/or pneumonia-related total costs were significantly lower among TIO/OLO initiators (\$11,116) compared with FF/UMEC/VI initiators (\$13,640), $p<0.001$, including significantly lower pharmacy costs (\$4605 vs \$6451; $p<0.001$). All-cause healthcare cost measures were similar between the TIO/OLO and FF/UMEC/VI cohorts, but the population annualized pharmacy costs were significantly lower for TIO/OLO (\$9582 vs \$11,409; $p=0.002$). Adjusted COPD and/or pneumonia-related total (\$11,179 vs \$13,567; $p<0.001$) and pharmacy (\$4631 vs \$6411; $p<0.001$) healthcare costs were significantly lower among TIO/OLO initiators versus FF/UMEC/VI (Table 3); adjusted COPD and/or pneumonia-related medical costs did not statistically differ between cohorts.

GOLD C/D

The only statistically significant difference in COPD and/or pneumonia-related costs was the population annualized pharmacy spending (TIO/OLO: \$5027, vs FF/UMEC/VI: \$6754; $p<0.001$). Adjusted COPD and/or pneumonia-related total or medical healthcare costs were similar for TIO/OLO and FF/UMEC/VI initiators (Table 3). Adjusted COPD and/or pneumonia-related pharmacy costs were significantly lower for TIO/OLO (\$5001) versus FF/UMEC/VI (\$6788) initiators, $p<0.001$. There was no difference in all-cause healthcare costs between cohorts.

Table 2 All-Cause and COPD and/or Pneumonia-Related Healthcare Utilization

	GOLD A/B			No Exacerbation (Subgroup of GOLD A/B)			GOLD C/D		
	TIO/OLO	FF/UMEC/VI	TIO/OLO vs FF/UMEC/VI p-value	TIO/OLO	FF/UMEC/VI	TIO/OLO vs FF/UMEC/VI p-value	TIO/OLO	FF/UMEC/VI	TIO/OLO vs FF/UMEC/VI p-value
	(N=3884)	(N=3884)		(N=2552)	(N=2552)		(N=1774)	(N=1774)	
COPD and/or pneumonia-related utilization counts – population annualized averages^{a,b}	Total Counts/Total Follow up Time (Years) (95% CI)								
Hospitalizations	0.27 (0.24, 0.30)	0.33 (0.29, 0.36)	0.022	0.26 (0.23, 0.30)	0.30 (0.26, 0.34)	0.212	0.73 (0.65, 0.81)	0.74 (0.65, 0.82)	0.927
Hospitalization Days	2.57 (2.13, 3.01)	3.14 (2.64, 3.65)	0.093	2.56 (2.01, 3.11)	2.90 (2.31, 3.49)	0.416	7.56 (6.28, 8.84)	7.52 (6.14, 8.91)	0.968
Emergency Room Visits	0.45 (0.40, 0.50)	0.51 (0.45, 0.57)	0.152	0.41 (0.36, 0.47)	0.41 (0.35, 0.48)	0.956	1.32 (1.14, 1.49)	1.13 (0.99, 1.28)	0.105
Ambulatory visits	7.02 (6.59, 7.46)	7.72 (7.23, 8.22)	0.036	6.51 (6.01, 7.00)	6.95 (6.43, 7.46)	0.222	14.09 (12.89, 15.29)	14.64 (13.41, 15.88)	0.530
Office Visits	3.52 (3.39, 3.65)	3.61 (3.47, 3.75)	0.377	3.22 (3.06, 3.37)	3.37 (3.19, 3.54)	0.206	5.36 (5.07, 5.64)	5.51 (5.21, 5.81)	0.467
Outpatient Visits	3.51 (3.11, 3.91)	4.12 (3.66, 4.59)	0.048	3.30 (2.84, 3.75)	3.59 (3.12, 4.05)	0.379	8.74 (7.60, 9.89)	9.15 (8.00, 10.29)	0.625
Other Medical Visits ^c	3.10 (2.85, 3.35)	3.62 (3.35, 3.89)	0.004	2.71 (2.43, 2.99)	3.39 (3.07, 3.71)	0.001	7.58 (7.01, 8.16)	7.90 (7.34, 8.46)	0.441
Pharmacy Fills	13.81 (13.54, 14.09)	13.70 (13.44, 13.97)	0.577	13.21 (12.89, 13.53)	13.21 (12.89, 13.54)	0.995	19.74 (19.08, 20.40)	18.18 (17.62, 18.74)	<0.001
All-cause utilization counts – population annualized averages^{a,b}									
Hospitalizations	0.32 (0.29, 0.35)	0.36 (0.32, 0.39)	0.157	0.32 (0.28, 0.36)	0.33 (0.28, 0.37)	0.874	0.77 (0.69, 0.86)	0.76 (0.67, 0.85)	0.856
Hospitalization Days	2.91 (2.45, 3.37)	3.35 (2.83, 3.87)	0.219	3.02 (2.43, 3.60)	3.08 (2.48, 3.69)	0.878	7.83 (6.54, 9.11)	7.66 (6.27, 9.06)	0.867
Emergency Room Visits	0.95 (0.87, 1.03)	1.10 (1.00, 1.19)	0.019	0.91 (0.82, 1.00)	0.96 (0.86, 1.07)	0.456	2.05 (1.82, 2.29)	2.06 (1.79, 2.32)	0.997
Ambulatory visits	29.50 (28.31, 30.70)	29.81 (28.65, 30.98)	0.715	28.93 (27.47, 30.40)	28.45 (27.05, 29.86)	0.644	40.29 (37.88, 42.70)	39.86 (37.62, 42.10)	0.798
Office Visits	17.30 (16.62, 17.99)	16.61 (16.06, 17.15)	0.116	16.93 (16.11, 17.76)	15.97 (15.33, 16.62)	0.074	19.07 (18.20, 19.94)	19.73 (18.74, 20.72)	0.328
Outpatient Visits	12.28 (11.42, 13.13)	13.28 (12.34, 14.21)	0.122	12.08 (11.04, 13.12)	12.54 (11.39, 13.70)	0.558	21.31 (19.19, 23.43)	20.23 (18.40, 22.06)	0.454
Other Medical Visits ^c	8.53 (8.11, 8.95)	9.01 (8.54, 9.48)	0.135	8.25 (7.74, 8.77)	8.63 (8.07, 9.19)	0.331	14.08 (13.20, 14.96)	13.79 (13.03, 14.55)	0.628
Pharmacy Fills	54.45 (52.97, 55.93)	53.47 (51.85, 55.09)	0.379	53.80 (51.93, 55.67)	52.29 (50.29, 54.29)	0.281	72.01 (69.26, 74.76)	65.37 (62.81, 67.94)	<0.001

Notes: ^aCounted as one hospitalization per admission (regardless of length of stay), one visit per day for ER visits, and one visit per provider per day for other types of visits. ^bAnnualized population averages are calculated as the ([sum of all utilization for all individuals during the follow-up period] / [sum of follow-up on-treatment time in years (365 days) for all individuals]). ^cOther medical visits may include services like independent laboratory, home health, durable medical equipment, etc. Wald 95% confidence limits for this ratio used the Taylor expansion to estimate the standard error.

All-cause and COPD and/or pneumonia-related health care costs

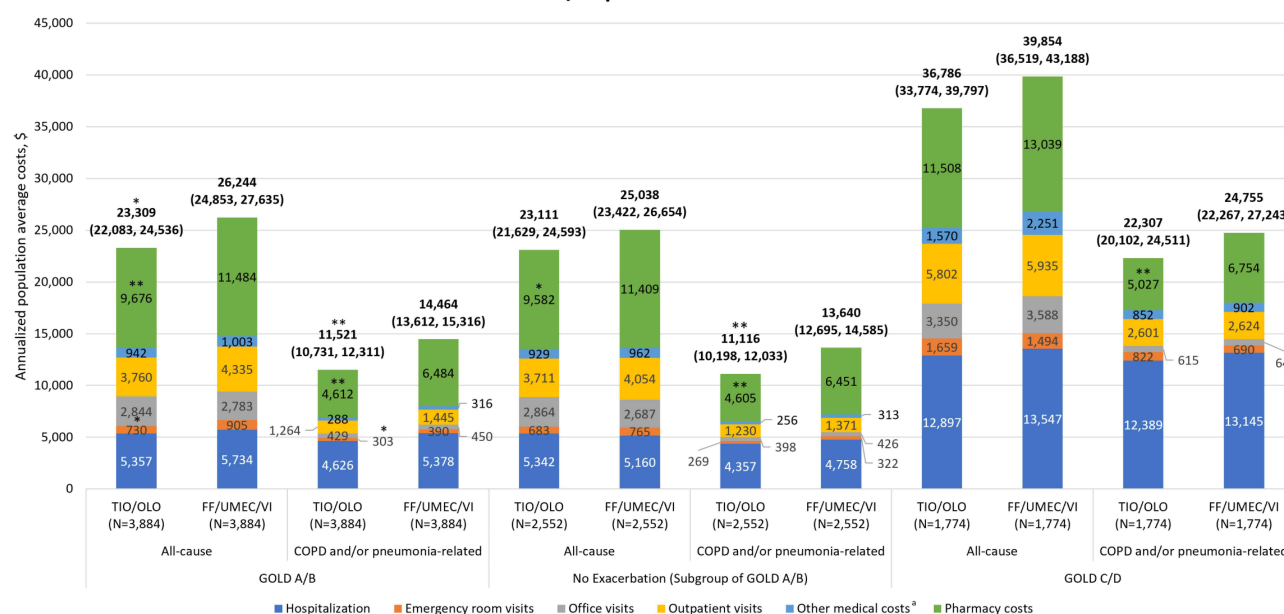


Figure 2 All-cause and COPD and/or pneumonia-related costs by GOLD subgroups.

Notes: *Other costs include service in independent laboratory, home health, durable medical equipment, etc. *p-value <0.05 for comparison of cost for TIO/OLO and FF/UMEC/VI; **p-value <0.001 for comparison of cost for TIO/OLO and FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; TIO/OLO, tiotropium/olodaterol. Annualized population averages are calculated as the ([sum of all costs for all individuals during the follow-up period]/[sum of follow-up on-treatment time in years (365 days) for all individuals]). Wald 95% confidence limits for this ratio used the Taylor expansion to estimate standard error. Patient and insurer paid amounts are combined. Identified during the follow-up period. The index date is included in the baseline period except for the index pharmacy claims, which are included in the follow-up period. Costs are adjusted using the most recent year of the medical care component of the Consumer Price Index (CPI) to reflect inflation to 2020. Retrieved from US Department of Labor, Bureau of Labor Statistics. Consumer Price Index. Medical Care. Series ID: CUUR000SAM. Washington, DC; U.S> Dept. of Labor, Bureau of Labor Statistics, 2012. <http://data.bls.gov/cgi-bin/surveymost?su>. Open Access.¹²

Discussion

In this study, a sizeable proportion of patients initiated treatment on TT contrary to guideline recommendations. While TT provided no clinical benefit such as reduced exacerbations in the GOLD A/B and No exacerbation subgroups, its use resulted in greater HCRU and costs. Results in the GOLD C/D subgroup were consistent with the IMPACT and ETHOS RCTs, which indicated that TT may reduce the risk of exacerbation relative to dual (LAMA/LABA or LABA/ICS)

Table 3 Multivariable Analysis of COPD and/or Pneumonia-Related Costs

Characteristic	HCRU Measure	Statistics	GOLD A/B ^a	No Exacerbation (Subgroup of GOLD A/B) ^b	GOLD C/D ^c
Index medication (cohort): FF/UMEC/VI (reference: TIO/OLO)	Total costs	Cost ratio (95% CI)	1.248 (1.132, 1.376)	1.214 (1.086, 1.356)	1.139 (0.992, 1.307)
		p-value	<0.001	<0.001	0.065
	Medical costs	Cost ratio (95% CI)	1.142 (0.963, 1.353)	1.068 (0.875, 1.303)	1.083 (0.900, 1.305)
		p-value	0.127	0.519	0.398
	Pharmacy costs	Cost ratio (95% CI)	1.394 (1.368, 1.419)	1.384 (1.354, 1.415)	1.357 (1.320, 1.395)
		p-value	<0.001	<0.001	<0.001

Notes: ^aAdjusted for race/ethnicity, baseline LAMA monotherapy pharmacy claims, baseline LABA/ICS pharmacy claims, and baseline length of pneumonia-related hospitalization; p-values account for clustering within matched pairs. ^bAdjusted for race/ethnicity, baseline LAMA monotherapy pharmacy claims, baseline LABA/ICS pharmacy claims, baseline length of COPD-related IP stays, and baseline length of pneumonia-related IP stays; p-values account for clustering within matched pairs. ^cAdjusted for race/ethnicity, baseline count of SAMA fills, baseline count of medical claims for controller medications, baseline LAMA monotherapy pharmacy claims, baseline LABA/ICS pharmacy claims, baseline oral corticosteroids pharmacy claims, baseline pharmacy claim count, and baseline pneumonia-related other medical visits; p-values account for clustering within matched pairs.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; HCRU, healthcare resource utilization; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; SAMA, short-acting muscarinic antagonist; TIO/OLO, tiotropium/olodaterol.

therapy in patients at high exacerbation risk (GOLD C/D).^{13–15} As in the RCTs, the more severe, GOLD C/D, patients in our study who initiated on TT had better exacerbation outcomes.

While the current study cannot accurately classify the patients in the GOLD subgroups, as claims data lack spirometric severity and other clinical characteristics, it is plausible that our GOLD C/D patients were similar to RCT patients, given their exacerbation history, higher COPD severity scores, and comorbidity burden. This is a possible explanation for the similar exacerbation risks observed between cohorts in our GOLD C/D subgroup and in the RCTs, further validating our findings.

Adjusted COPD and/or pneumonia-related total healthcare costs also were significantly lower for TIO/OLO initiators (vs FF/UMEC/VI) in the GOLD A/B and No exacerbation subgroups, driven by significantly lower pharmacy spending in this study. There was no statistically significant difference between the treatment cohorts in medical spending in the GOLD A/B and No exacerbation subgroups. The pattern in the GOLD C/D subgroup, however, was different. The adjusted COPD and/or pneumonia-related total and medical healthcare costs were similar for TIO/OLO and FF/UMEC/VI initiators, despite the significantly lower adjusted pharmacy costs for TIO/OLO. Our study's focus on FDC TT expands upon the findings of Palli et al, which reported average annualized health-plan savings of \$8586 for COPD and/or pneumonia-related costs, when enrollees were treated with TIO/OLO versus mostly free-dose TT.⁶ Consistent with the Palli et al study, our results suggest that adherence to treatment guidelines could result in considerable cost savings.

This study's detailed HCRU and cost findings based on a contemporary COPD population treated with a LAMA/LABA and FDC TT, and stratified by exacerbation risk spectrum, could help to guide future treatment decisions.

Limitations

These results are subject to inherent susceptibilities of administrative claims data repurposed for research, including miscoding and omissions, among others. A claim for a filled prescription does not necessarily mean the medication was used as prescribed or at all, and medicines acquired over the counter or as physicians' samples are not captured in claims data. Moreover, it is not possible to identify the reasons for treatment initiation of the index therapy. Also, largely absent is information on lifestyle behaviors and relevant clinical characteristics such as lung function, smoking status, and symptom burden, among others, that could affect disease progression and study outcomes. Inherent biases from non-randomized patient and treatment selections that are present in observational studies were mitigated with PSM that adequately balanced many baseline characteristics between cohorts and further, post-match residual imbalances between cohorts were addressed with MVA techniques. The on-treatment study design precluded the capture of outcomes occurring right after censoring, including any potentially associated with the index medication. In addition, exacerbations were identified via a claims algorithm. These results may not be generalizable to patients with noncommercial or non-MAPD health insurance.

Conclusions

Initiating maintenance treatment with TIO/OLO rather than FF/UMEC/VI may represent a more cost-effective treatment decision, especially in GOLD A/B and No exacerbation subgroups. Exacerbation risk did not differ between the treatment cohorts in these two subgroups, and the incidence of pneumonia was lower in the No exacerbation subgroup for TIO/OLO versus FF/UMEC/VI. These clinical and economic findings support ATS and GOLD recommendations for treating COPD patients with low exacerbation risk with a LAMA/LABA and those at higher risk with TT.

Ethics Statement

Institutional review board approval or waiver was not sought nor required for this study because no identifiable protected health information was accessed in the conduct of this study 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) data handling rules and were complied with throughout. Hence, no relevant institutional name or other detail is applicable.

Acknowledgments

The authors wish to thank Bernard Tulsi, Sarah Hague and Noah Webb, all of Optum, for writing and editorial support, project management, and preparation of graphic elements, respectively, and Felix Cao, Yiyu Fang, Michael Johnson, and Havisha

Taneja, all of Optum, for dataset programming support. Relevant reviewers from Boehringer Ingelheim Pharmaceuticals, Inc. assessed the contents of the manuscript for medical and scientific accuracy, and for intellectual property considerations. A selection of the study's results have been presented as a poster at the American Thoracic Society International Conference, May 13–18, 2022 with interim findings. The poster's abstract was published in "Poster Abstracts" in *ATS Journal*: Hyperlink: https://www.atsjournals.org/doi/abs/10.1164/ajrcem-conference.2022.205.1_MeetingAbstracts.A5018

Funding

Funding for this study was provided by Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA.

Disclosure

Clark and Shaikh are employees of Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). Palli was employed by BIPI at the time of study. Buysman and Sargent are employees of Optum, which was contracted by BIPI to conduct this study. Bengtson was employed by Optum at the time of study. Sethi of Jacobs School of Medicine and Biomedical Sciences at University at Buffalo and Ferguson of the Department of Medicine, Pulmonary Research Institute of Southeast Michigan are subject matter clinical experts contracted by BIPI for this study. Sethi declares that he has received honoraria/fees for consulting/speaking from AstraZeneca, BIPI, Chiesi, GlaxoSmithKline, Merck and Uptodate. He has received consulting fees for serving on Data safety monitoring boards from Nuvaair, Inc. and Pulmotect, Inc. He has received consulting fees from Apellis Pharmaceuticals and Aerogen Pharma. His institution has received research funds for his participation in Clinical Trials from Regeneron Pharma, Sanofi, Theravance and AstraZeneca. Ferguson reports consulting fees from BIPI, AstraZeneca, DevPro, Syneos Health, GlaxoSmithKline, Teva, Orpheris and Verona Pharma, speaker fees from GlaxoSmithKline and Theravance and is in receipt of research grants from AstraZeneca, Chiesi Novartis International AG, Teva, Galderma, Syneos, PPD, Orpheris, Verona Pharma and GlaxoSmithKline. The authors report no other conflicts of interest in this work.

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