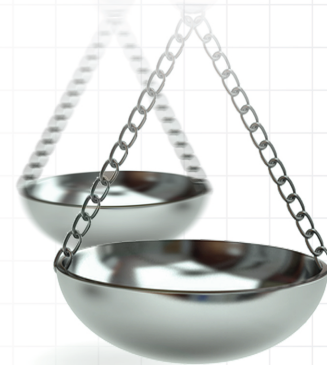




Costs, exacerbations and pneumonia after initiating combination tiotropium olodaterol versus triple therapy for chronic obstructive pulmonary disease

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Aim: To compare health plan-paid costs, exacerbations and pneumonia outcomes for patients with chronic obstructive pulmonary disease (COPD) initiating combination tiotropium olodaterol (TIO + OLO) versus triple therapy (TT: long-acting muscarinic antagonist + long-acting β_2 agonists + inhaled corticosteroid). **Patients & methods:** COPD patients initiating TIO + OLO or TT between 1 January 2014 and 30 June 2016 were identified from a managed care Medicare database and balanced for baseline characteristics using inverse probability of treatment weighting before assessment of outcomes. **Results:** Annual COPD-related and all-cause costs were US\$4118 (35%) and US\$5384 (23%) lower for TIO + OLO versus TT (both $p \leq 0.001$). TIO + OLO patients had nearly half the severe exacerbations (8.3 vs 15.5%; $p = 0.014$) and pneumonia was also less common (18.9 vs 30.9%; $p < 0.001$). **Conclusion:** TIO + OLO was associated with improved economic and COPD health outcomes versus TT.

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Keywords: COPD exacerbation • healthcare resource use • healthcare costs • pneumonia • tiotropium olodaterol • triple therapy

Chronic obstructive pulmonary disease (COPD) affects approximately 24 million adults in USA and is a leading cause of disability and mortality [1–4]. The economic burden is also substantial; the direct medical costs of managing COPD are projected to reach US\$49 billion by 2020 [5]. The disease is characterized by chronic airflow limitation, commonly manifesting as shortness of breath, coughing and/or sputum production [6]. COPD exacerbations represent an acute worsening of symptoms that require treatment, ranging from outpatient care to hospitalization, and are the major driver of COPD-related healthcare costs [7–9]. The 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations provide first and second line pharmacologic treatment algorithms for patients with COPD, grouping them according to their severity, as measured by their exacerbation risk and symptom burden [6]. Groups A and B are characterized by low risk of exacerbation while Groups C and D are at high exacerbation risk [6]. Symptom burden differentiates Group A and C (low) and Groups B and D (high). Accordingly, Group A is the least severe (low exacerbation risk/symptom burden) while Group D represents the most severe (high exacerbation risk/symptom burden).

Inhaled long-acting bronchodilators, namely long-acting muscarinic antagonists (LAMAs) and long-acting β_2 agonists (LABAs), are the mainstays of maintenance therapy for patients in Groups B–D [6]. When treatment with a LAMA or LABA, as monotherapy, does not achieve adequate symptom control [10], and symptoms or exacerbations persist, escalation from monotherapy to LAMA + LABA is the preferred treatment pathway for patients in Groups B and C, although escalation to LABA + inhaled corticosteroids (ICS) may also be considered for patients in Group C [6]. Triple therapy (TT; LAMA + LABA + ICS) is recommended only for the most severe patients: those in Group D who experience further exacerbations after escalation to dual therapy [6]. Although the 2018 GOLD recommendations reserved ICS-containing regimens for a select group of patients in Groups C and D,

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use of these regimens among patients in Groups A and B is reportedly widespread in clinical practice [11–14]. TT specifically has been widely reported among patients with mild or moderate disease [15–20]. However, ICS-containing regimens, including TT, require a risk–benefit assessment given the risk of pneumonia and other potential long-term complications (cataracts, diabetes progression and osteoporosis) associated with regular use of ICS [6,21–25], which in turn results in higher symptom burden, healthcare resource use (HCRU) and costs. Use of ICS-containing regimens early in the patient journey may not only unnecessarily expose patients to an elevated risk of these complications but has also been shown to accelerate the pathway to TT [16].

Overuse of TT has been well documented [15–20]. However, there has been limited comparison of economic and COPD health outcomes for TT versus other therapies, particularly LAMA + LABA, in a real-world setting. Researchers in Germany found that patients treated with LAMA + LABA in primary and secondary care experienced exacerbations at roughly half the rate of their counterparts on TT [26]. Two recent claims-based studies in USA compared tiotropium olodaterol (TIO + OLO) [27,28] – a fixed-dose combination of LAMA (TIO) plus LABA (OLO) in a single inhaler – with TT and found that patients initiating TIO + OLO incurred 27–53% lower COPD-related costs than patients initiating TT in the first year of therapy [29,30]. Besides being conducted in populations with mixed forms of insurance, both these studies employed traditional regression modeling methods to evaluate these treatments. These methodological limitations therefore necessitate additional research to corroborate their findings. Further still, no study to date has accounted for the impact of pneumonia burden. Therefore, the primary objective of this study was to compare HCRU, associated costs (all-cause, COPD-related and non-COPD pneumonia-related), as well as incident COPD exacerbations and occurrences of pneumonia among patients initiating TIO + OLO versus TT in a real-world setting. A secondary analysis compared patients initiating any LAMA + LABA regimen (including TIO + OLO) with TT for the same outcomes. Since Medicare is the primary payer for COPD-related costs in USA [31–33], this study was conducted among a population of managed Medicare beneficiaries with prescription drug coverage, who were diagnosed with COPD.

Methods

Design & data source

This retrospective, observational study used an administrative claims database from the Optum Research Database (ORD). The ORD contains enrollment information and administrative claims for all medical and pharmacy services submitted to each patient's health plan(s) for reimbursement. Medical claims include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes and site of service codes. Pharmacy claims include National Drug Codes for medications dispensed with quantity, dose and days' supply. The ORD is geographically diverse in coverage and represented approximately 17% (~3.2 million individuals) of the US population with Medicare Advantage with Part D prescription drug coverage (MAPD) benefits in 2016.

No identifiable protected health information was extracted or accessed during the course of the study. All data were accessed in compliance with the Health Insurance Portability and Accountability Act's rules so Institutional Review Board approval or waiver of authorization was not required.

Patient selection & cohort assignment

The initial population comprised patients diagnosed with COPD as confirmed by the presence of ICD-9-CM (491.xx, 492.xx, 493.2x and 496.xx) and/or ICD-10-CM (J41-J44) codes on ≥ 2 medical claims on separate dates of service between 1 January 2013 and 30 June 2017 (study period). The first observed long-acting bronchodilator-containing regimen (LAMA, LABA + ICS, LAMA + LABA or TT) with ≥ 30 consecutive days of therapy between 1 January 2014 and 30 June 2016 (identification period) was defined as the index regimen. The start date of the regimen was set as the index date. For example, for patients initiating TIO + OLO, the index date was the first pharmacy claim for TIO + OLO. For regimens comprised of multiple inhalers, the index date was the fill date for the pharmacy claim commencing ≥ 30 consecutive days of concurrent therapy for all medications in the regimen. Patients were excluded if they were < 40 years on their index date, had incomplete demographic information or had ≥ 2 medical claims on separate dates of service with a diagnosis of asthma, lung cancer or cystic fibrosis during the study period (Supplementary Table 1 for diagnostic codes). All remaining patients were required to have continuous medical and pharmacy enrollment in a MAPD health plan during the 12-month pre-index (baseline) and 12-month postindex (follow-up) periods; this criterion ensured that all patients had full data for both the 12-month baseline and follow-up periods. The sample was limited to patients who were naive to the index regimen

as of the index date. Patients initiating treatment with TIO + OLO or TT, the main therapies of interest, were retained as the final study population for the primary analysis and all other regimens (i.e., LAMA, LABA + ICS and LAMA + LABA other than TIO + OLO) were excluded. The secondary analysis retained the TT cohort and patients initiating any LAMA + LABA regimen (free or fixed-dose combinations, including TIO + OLO). This study used an intent-to-treat approach, with all outcomes during follow-up attributed to the index regimen.

Measures

Patient characteristics

Demographic and clinical characteristics were determined during the baseline period. Comorbidity burden was determined by the Quan–Charlson Comorbidity Index score [34] and the Elixhauser score [35]. Baseline COPD medication use was captured along with any occurrence of severe or moderate COPD exacerbations. Severe exacerbations were defined as an inpatient admission with a COPD diagnosis code in the primary position. Moderate exacerbations were defined as either an emergency department (ED) visit with a COPD diagnosis in the primary position, or an office visit with a COPD diagnosis code in any position plus a pharmacy claim for an oral corticosteroid or COPD-guideline recommended antibiotic prescription within 7 days of the ED or office visit. Exacerbations occurring within 14 days of each other were considered a single exacerbation episode and classified according to the highest severity contributing event.

Outcomes

HCRU and costs were assessed during the follow-up period and further stratified by setting, in other words, acute inpatient stays, ED visits, ambulatory (office and outpatient) visits and other services (e.g., durable medical equipment, home health visits, independent laboratory tests, long-term care). All-cause resource use included all claims for medical services and all-cause total costs were the sum of all medical costs plus outpatient pharmacy costs. COPD-related resource use was defined as medical claims with a diagnosis of COPD in any position and COPD-related total costs comprised COPD-related medical costs and outpatient pharmacy claims for COPD medications. COPD-attributable resource use was defined as medical claims with a diagnosis of COPD in the primary position on the claim and their corresponding costs together with outpatient COPD pharmacy claims were considered as COPD-attributable costs. Similarly, pneumonia-related resource use included medical claims with a diagnosis code for pneumonia and/or acute bronchitis/bronchiolitis in any position (codes shown in Supplementary Table 1). Since it was possible for COPD and pneumonia/acute bronchitis/bronchiolitis diagnoses to occur on the same claim, non-COPD pneumonia-related costs, in other words, pneumonia-related claims without a concurrent COPD diagnosis on the same claim, were computed. COPD/pneumonia total costs were then calculated by summing total COPD-related costs and the non-COPD pneumonia-related medical costs. All costs measures were computed from a payer perspective and defined as health-plan paid costs, with inflation adjustment to 2017 US dollars [36]. Additional outcomes including occurrence and time to exacerbations (as defined above) and pneumonia diagnosis were assessed starting on the day after the index date.

Statistical analysis

Prior to assessing the outcomes between the TIO + OLO versus TT (primary) and LAMA + LABA versus TT (secondary) cohorts, the cohorts were balanced using inverse probability of treatment weighting (IPTW). IPTW is an established method to minimize or eliminate potential confounding factors in observational studies before assessment of treatment effect [37]. Given the large number of clinically relevant patient baseline characteristics that could potentially influence outcomes, an iterative process was used to identify the logistic regression model that provided the best balance in characteristics (i.e., model covariates) between cohorts. For each potential model, the propensity score (PS) – the conditional probability that the patient would receive TIO + OLO (or LAMA + LABA) treatment, given the observed covariates (defined below) – for each patient was estimated. The weights were computed as the inverse of the conditional probability that the patient would receive the treatment they actually received (i.e., for the TIO + OLO cohort, $1/PS$ and for the TT cohort, $1/([1-PS])$). The distribution of these scores was reviewed to assess the amount of overlap between cohorts, and patients with extreme weights (i.e. >10) [38] were removed. Several candidate models were evaluated by adding/removing covariates until a model that provided the best balance between cohorts across the maximum number of covariates was identified. Balance was assessed postweighting by examining standardized differences between cohorts for each covariate. Standardized

differences of less than 20% were considered adequate [39]. The weights were then normalized within each cohort to sum to the total sample size for the cohort.

Covariates selected for the final IPTW model included health plan type, US census region, index regimen prescriber specialty and baseline characteristics including pneumonia and/or acute bronchitis/bronchiolitis diagnosis, severe COPD exacerbation, COPD medication use, resource use and COPD-related medical cost quartiles. Cohort differences in unweighted baseline characteristics were analyzed by Pearson χ^2 test (categorical variables) and two-sample t-test (continuous measures); when comparing cohorts after weighting, statistical testing was done using a Z-test with robust standard errors. The weighted difference in time to first COPD (any, severe) exacerbation was estimated by the Kaplan–Meier method and analyzed by the log-rank test. Weighted COPD-related and weighted all-cause cost outcomes were modeled using Manning and Mullahy's formulation [40], using a generalized linear model with a γ -distribution and log link and adjusted for any residual imbalances between cohorts. Covariates selected for inclusion in the cost models were based on clinical relevance with an emphasis on characteristics with a standardized difference $\geq 10\%$ after weighting. Separate models were constructed for total costs, medical costs and pharmacy costs. After adjustment, predicted costs were computed for each cohort using recycled predictions [41]. A secondary analysis was also conducted to compare LAMA + LABA and TT cohorts using the same primary analysis methodology.

Results

Patient identification & baseline characteristics

Among 844,551 patients diagnosed with COPD during the study period, 179,790 were ≥ 40 years of age and initiating a long-acting bronchodilator-containing regimen during the identification period (Figure 1). Of these patients, 3580 met all remaining inclusion criteria and were assigned to the TIO + OLO ($n = 348$) or TT ($n = 3232$) cohort. After examination of the PS distribution between study cohorts, one patient in the TIO + OLO cohort with an extreme weight was removed, leaving 347 patients in the final TIO + OLO cohort.

Baseline demographic and clinical characteristics before and after IPTW are shown in Table 1. Prior to IPTW, the TIO + OLO cohort was similar to the TT cohort with respect to mean age (72.6 vs 72.2 years), the proportion of men (52.9 vs 48.8%) and mean Quan–Charlson Comorbidity Index score (2.1 vs 2.3). However, there were differences in other characteristics between cohorts including a smaller percentage of TIO + OLO patients with severe exacerbations (5.5 vs 23.9%), pneumonia (13.5 vs 24.4%), controller and rescue medication usage and a larger proportion of maintenance naive patients prior to index (80.2 vs 55.0%). After IPTW, the standardized mean difference for nearly all baseline characteristics was below 20%, a cutoff considered to represent small imbalances [39]. Only four baseline characteristics had standardized mean differences that were marginally higher than 20% (21.09–22.89%) after IPTW.

Outcomes

COPD-related & all-cause HCRU & costs

Annual medical resource use during follow-up is shown in Table 2. Compared with the TT cohort, significantly lower percentage of TIO + OLO patients had ≥ 1 COPD-related acute inpatient stays (16.8 vs 28.7%; $p < 0.001$), ED visits (22.0 vs 30.0%; $p = 0.045$) and/or outpatient visits (36.1 vs 54.0%; $p < 0.001$). The TIO + OLO cohort also had fewer mean acute inpatient stays (0.3 vs 0.5; $p = 0.006$), inpatient days (1.9 vs 3.2 days; $p = 0.018$) and ED visits (0.3 vs 0.6; $p = 0.002$). This pattern observed for COPD-related HCRU was also evident for all-cause HCRU: mean counts of acute inpatient stays, ED visits and outpatient visits were lower in the TIO + OLO cohort and a smaller share of TIO + OLO patients utilized these services.

Annual weighted mean COPD-related costs, before and after multivariable adjustment for baseline characteristics, are shown in Figure 2. Pre-adjustment, total mean weighted COPD-related costs were US\$4834 lower for TIO + OLO versus TT (US\$7076 vs US\$11,910; $p < 0.001$). Acute inpatient costs were the largest contributor (43.5–45.6%) to the total costs in both cohorts and were also the driver (–US\$2353) behind the observed weighted difference. Multivariable adjustment of residual baseline imbalances provided a more conservative estimate of the weighted cohort difference: adjusted total costs averaged US\$7794 for TIO + OLO versus US\$11,912 for TT and were 35% lower (US\$4118) for TIO + OLO (cost ratio [CR] = 0.65; 95% CI = 0.54–0.80). This difference was primarily driven by medical cost differences for TIO + OLO versus TT (US\$3103). Specifically, the adjusted COPD-related medical and pharmacy costs were lower for TIO + OLO by approximately 36 and 39%, respectively.

A similar pattern of cost savings for the TIO + OLO cohort was documented for all-cause costs (Figure 3).

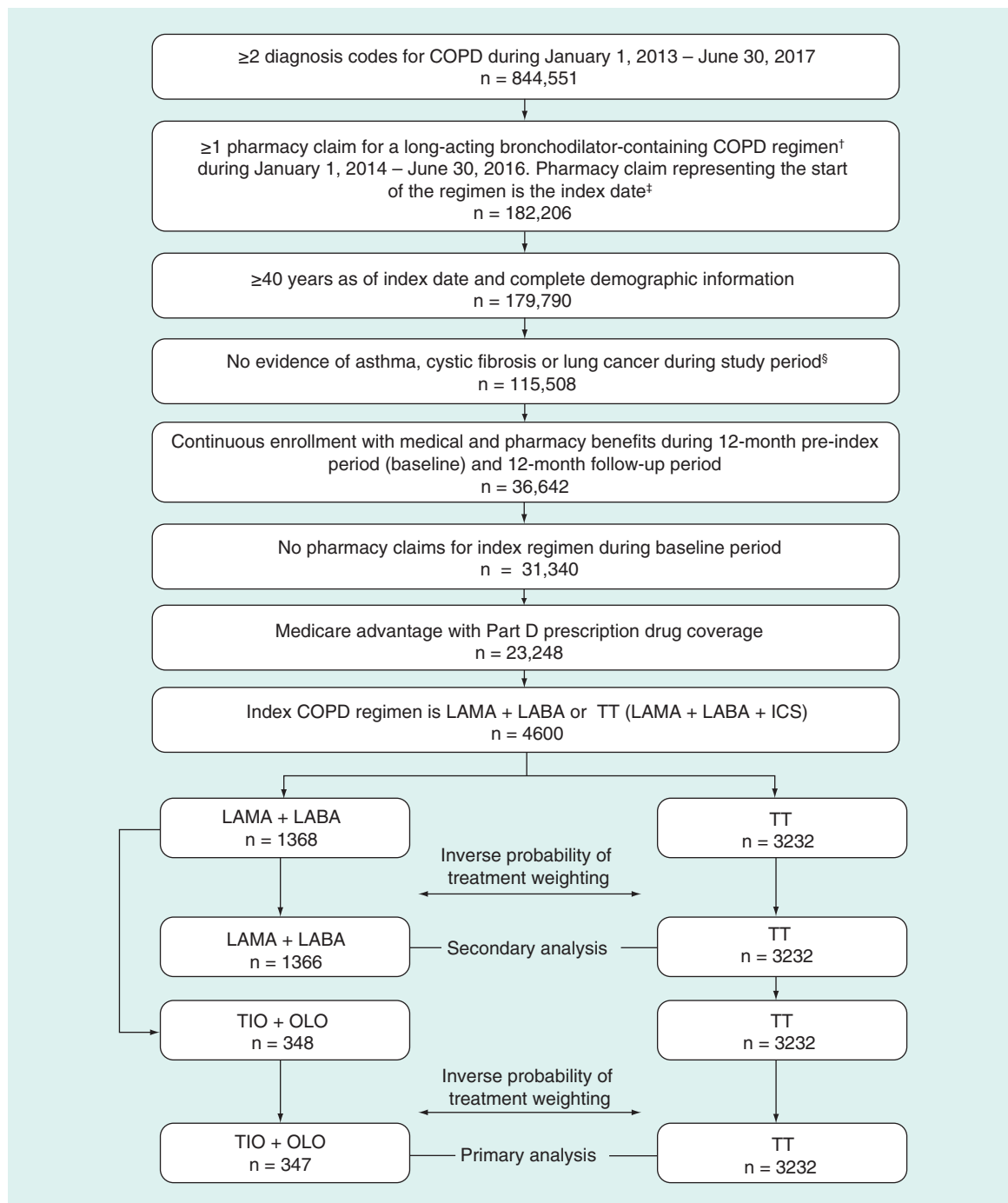


Table 1. Baseline demographic and clinical characteristics before and after inverse probability of treatment weighting[†].

Characteristic	Before IPTW				After IPTW			
	TIO + OLO (n = 348)	TT (n = 3232)	STD DIFF %	p-value	TIO + OLO (n = 347)	TT (n = 3232)	STD DIFF %	p-value
Age, years, mean (SD) [‡]	72.6 (8.6)	72.2 (8.4)	−4.10	0.463	72.5 (8.4)	72.2 (8.4)	−4.61	0.549
Age group, years, n (%)								
– 40–64	56 (16.1)	498 (15.4)	−1.88	0.738	59 (17.1)	506 (15.6)	−3.90	0.637
– 65–74	146 (42.0)	1486 (46.0)	8.11	0.152	145 (41.8)	1488 (46.0)	8.55	0.299
– ≥75	146 (42.0)	1248 (38.6)	−6.81	0.225	143 (41.3)	1239 (38.3)	−5.72	0.485
Male, n (%)	184 (52.9)	1577 (48.8)	−8.17	0.148	180 (52.0)	1593 (49.3)	−5.41	0.510
US Census region, n (%)								
– Northeast	60 (17.2)	733 (22.7)	13.64	0.020	68 (19.5)	716 (22.1)	6.50	0.427
– Midwest	85 (24.4)	1,022 (31.0)	14.73	0.011	101 (29.0)	981 (30.3)	2.95	0.731
– South	184 (52.9)	1221 (37.8)	−30.68	<0.001	145 (41.7)	1270 (39.3)	−4.95	0.534
– West	19 (5.5)	276 (8.5)	12.09	0.047	34 (9.8)	266 (8.2)	−5.43	0.582
Quan–Charlson comorbidity Index score, mean (SD)	2.1 (1.7)	2.3 (1.7)	8.41	0.141	2.2 (1.6)	2.3 (1.7)	4.88	0.500
Quan–Charlson Comorbidity Index score categories, n (%)								
– 0–1	173 (49.7)	1600 (49.5)	−0.42	0.941	170 (48.9)	1681 (50.1)	2.30	0.780
– 2–3	118 (33.9)	981 (30.4)	−7.62	0.172	118 (34.0)	973 (30.1)	−8.32	0.306
– 4–5	39 (11.2)	510 (15.8)	13.41	0.024	44 (12.6)	503 (15.6)	8.69	0.280
– ≥6	18 (5.2)	141 (4.4)	−3.80	0.486	16 (4.6)	138 (4.3)	−1.41	0.852
Elixhauser comorbidity score, mean (SD)	8.0 (7.8)	9.4 (8.6)	17.72	0.001	8.2 (7.6)	9.2 (8.5)	13.13	0.070
Pneumonia diagnosis, n (%)	47 (13.5)	787 (24.4)	27.95	<0.001	50 (14.5)	755 (23.4)	22.89	0.013
Pneumonia and/or acute bronchitis/bronchiolitis diagnosis, n (%)	96 (27.6)	1178 (36.5)	19.08	0.001	98 (28.3)	1147 (35.5)	15.43	0.076
COPD medications, n (%)								
– Naive to LAMA or LABA [§]	279 (80.2)	1776 (55.0)	−55.94	<0.001	210 (60.5)	1857 (57.5)	−6.12	0.492
– Any LAMA [¶]	48 (13.8)	746 (23.1)	24.13	<0.001	91 (26.1)	717 (22.2)	−9.15	0.314
– Any LABA [¶]	22 (6.3)	779 (24.1)	51.10	<0.001	59 (16.9)	721 (22.3)	13.68	0.222
– Any ICS [¶]	24 (6.9)	928 (28.7)	59.50	<0.001	62 (17.7)	872 (27.0)	22.34	0.048
– LABA + ICS [#]	17 (4.9)	745 (23.1)	54.30	<0.001	56 (16.0)	687 (21.3)	13.49	0.240
– Any SABA [¶]	189 (54.3)	1890 (58.5)	8.41	0.134	214 (61.6)	1870 (57.9)	−7.64	0.334
– Any SAMA [¶]	49 (14.1)	667 (20.6)	17.38	0.004	59 (17.1)	654 (20.3)	8.21	0.416
– SABA + SAMA [#]	45 (12.9)	596 (18.4)	15.19	0.011	52 (15.1)	584 (18.1)	8.00	0.439
– Methlyxanthines	2 (0.6)	50 (1.6)	9.50	0.150	5 (1.4)	49 (1.5)	1.25	0.910
– Phosphodiesterase-4 inhibitors	2 (0.6)	26 (0.8)	2.78	0.644	11 (3.2)	26 (0.8)	−17.43	0.062
– Oral corticosteroids	131 (37.6)	1427 (44.2)	13.27	0.020	165 (47.5)	1413 (43.7)	−7.61	0.358
Oxygen therapy, n (%)	77 (22.1)	1047 (32.4)	23.21	<0.001	104 (29.9)	1014 (31.4)	3.11	0.727
Annual exacerbations								
Severe								
– n (%)	19 (5.5)	772 (23.9)	53.94	<0.001	56 (16.3)	713 (22.1)	14.76	0.185
– Count, mean (SD)	0.06 (0.28)	0.28 (0.57)	49.37	<0.001	0.19 (0.46)	0.26 (0.55)	14.10	0.174

[†] Weighted results were computed from propensity scores derived from a logistic regression model adjusted for health plan type (health maintenance organization, preferred provider organization, other, missing), US census region (northeast, midwest, south, west), index regimen prescriber specialty (pulmonology, all others) and baseline characteristics including pneumonia and/or acute bronchitis/bronchiolitis diagnosis, severe COPD exacerbation, COPD medication use (any LAMA [free dose or combination inhaler], LABA/ICS [single combination inhaler]), HCRU (COPD-attributable ED visit, number of COPD-related ambulatory visits, other COPD-related medical resource use, pneumonia-related ambulatory visit) and COPD-related medical cost quartile group (<US\$1450; US\$1450 – <US\$8700; US\$8700 – <US\$21,000; ≥US\$21,000).

[‡] As of index date.

[§] Based on medical and pharmacy claims.

[¶] Free dose or combination inhaler.

[#] Single combination inhaler.

^{††} ≥2 moderate exacerbations or ≥1 severe exacerbation.

COPD: Chronic obstructive pulmonary disease; ED: Emergency department; GOLD: Global initiative for chronic obstructive lung disease; HCRU: Healthcare resource use; ICS: Inhaled corticosteroid; IPTW: Inverse probability of treatment weighting; LABA: Long-acting β_2 agonist; LAMA: Long-acting muscarinic antagonist; SABA: Short-acting β_2 agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; STD DIFF: Standardized difference; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

Table 1. Baseline demographic and clinical characteristics before and after inverse probability of treatment weighting[†] (cont.).

Characteristic	Before IPTW				After IPTW			
	TIO + OLO (n = 348)	TT (n = 3232)	STD DIFF %	p-value	TIO + OLO (n = 347)	TT (n = 3232)	STD DIFF %	p-value
Moderate								
– n (%)	130 (37.4)	1376 (42.6)	10.67	0.061	162 (46.6)	1362 (42.1)	-9.09	0.271
– Count, mean (SD)	0.55 (0.90)	0.70 (1.07)	14.41	0.006	0.77 (1.06)	0.69 (1.06)	-7.67	0.443
GOLD high risk group classification, n (%) ^{††}	58 (16.7)	1162 (36.0)	44.89	<0.001	107 (30.7)	1101 (34.1)	7.18	0.444
Annual acute inpatient utilization, n (%)								
– COPD-related	53 (15.2)	1196 (37.0)	51.17	<0.001	99 (28.5)	1125 (34.8)	13.58	0.156
– Pneumonia-related	23 (6.6)	613 (19.0)	37.65	<0.001	45 (12.9)	579 (17.9)	14.06	0.195
– All-cause	74 (21.3)	1340 (41.5)	44.60	<0.001	112 (32.2)	1278 (40.0)	15.29	0.095
Annual health plan-paid costs, US\$, mean (SD)								
– COPD-related total cost	3603 (7890)	9693 (17,939)	43.95	<0.001	6108 (10,070)	9157 (17,451)	21.41	<0.001
– Pneumonia-related medical cost	1011 (5437)	3593 (13,506)	25.09	<0.001	1331 (4,508)	3395 (13,090)	21.09	<0.001
– All-cause total cost	14,215 (20,470)	18,802 (26,440)	19.40	<0.001	14,674 (17,214)	18,330 (26,062)	16.55	0.003

[†]Weighted results were computed from propensity scores derived from a logistic regression model adjusted for health plan type (health maintenance organization, preferred provider organization, other, missing), US census region (northeast, midwest, south, west), index regimen prescriber specialty (pulmonology, all others) and baseline characteristics including pneumonia and/or acute bronchitis/bronchiolitis diagnosis, severe COPD exacerbation, COPD medication use (any LAMA [free dose or combination inhaler], LABA/ICS [single combination inhaler]), HCRU (COPD-attributable ED visit, number of COPD-related ambulatory visits, other COPD-related medical resource use, pneumonia-related ambulatory visit) and COPD-related medical cost quartile group (<US\$1450; US\$1450 – <US\$8700; US\$8700 – <US\$21,000; ≥US\$21,000).

[‡]As of index date.

[§]Based on medical and pharmacy claims.

[¶]Free dose or combination inhaler.

^{*}Single combination inhaler.

^{††}≥2 moderate exacerbations or ≥1 severe exacerbation.

COPD: Chronic obstructive pulmonary disease; ED: Emergency department; GOLD: Global initiative for chronic obstructive lung disease; HCRU: Healthcare resource use; ICS: Inhaled corticosteroid; IPTW: Inverse probability of treatment weighting; LABA: Long-acting β_2 agonist; LAMA: Long-acting muscarinic antagonist; SABA: Short-acting β_2 agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; STD DIFF: Standardized difference; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

Annual weighted all-cause total costs were US\$6274 lower for TIO + OLO versus TT (US\$15,758 vs US\$22,031; $p < 0.001$); after adjustment, weighted costs were 23% lower (US\$5384) for TIO + OLO versus TT (US\$17,504 vs US\$22,887; CR: 0.77; 95% CI: 0.65–0.90). Consistent with the COPD-related cost results, the TIO + OLO cohort's lower costs were driven primarily by lower (US\$4652) adjusted all-cause medical costs (US\$11,130 vs US\$15,782; $p < 0.001$).

COPD exacerbations

Severe exacerbations were significantly less common during follow-up in the TIO + OLO cohort, with 8.3% experiencing them compared with 15.5% of TT patients ($p = 0.014$; Table 3). Kaplan–Meier estimates of the distribution of severe exacerbations over time were consistent with these results ($p = 0.018$; Figure 4A). The percentage of patients with any exacerbation (i.e., moderate or severe) and the corresponding Kaplan–Meier distribution (Figure 4B) did not differ significantly between cohorts.

Pneumonia-related outcomes

Pneumonia or acute bronchitis/bronchiolitis was significantly less common for patients in the TIO + OLO cohort compared with the TT cohort (18.9 vs 30.9%; $p < 0.001$; Table 4). A smaller percentage of TIO + OLO patients had pneumonia-related acute inpatient stays, and utilization of pneumonia-related ED and outpatient visits was also lower. Total annual pneumonia-related medical costs were lower for TIO + OLO, averaging US\$1566 versus US\$2897 for TT ($p = 0.045$). Acute inpatient costs accounted for more than 85% of total pneumonia-related medical costs in both cohorts and the difference between cohorts (US\$1138) also appeared to drive the observed medical cost differences. Non-COPD pneumonia-related medical costs averaged US\$1223 for the TIO + OLO cohort (78.1% of pneumonia-related medical costs) and US\$2058 for the TT cohort (71.0% of pneumonia-related medical costs; $p = 0.104$). COPD/pneumonia costs were thus calculated to be US\$8299 (i.e., US\$7076 [COPD]

Table 2. Annual weighted medical resource use postinitiation of tiotropium olodaterol versus triple therapy.

Medical resource use category	TIO + OLO (n = 347)	TT (n = 3232)	p-value
COPD-related			
Acute inpatient stay			
– n (%)	58 (16.8)	927 (28.7)	<0.001
– Count, mean (SD)	0.28 (0.77)	0.46 (0.92)	0.006
– Length of stay, days, mean (SD)	1.9 (6.7)	3.2 (8.8)	0.018
Emergency department visit			
– n (%)	76 (22.0)	968 (30.0)	0.045
– Count, mean (SD)	0.33 (0.73)	0.57 (1.34)	0.002
Office visit			
– n (%)	310 (89.4)	2692 (83.3)	0.052
– Count, mean (SD)	4.09 (3.23)	3.85 (3.86)	0.440
Outpatient visit			
– n (%)	125 (36.1)	1746 (54.0)	<0.001
– Count, mean (SD)	1.66 (3.69)	2.55 (4.63)	0.008
Other			
– n (%)	164 (47.2)	1805 (55.8)	0.037
– Count, mean (SD)	4.36 (7.82)	6.75 (13.80)	<0.001
All-cause			
Acute inpatient stay			
– n (%)	80 (22.9)	1042 (32.2)	0.009
– Count, mean (SD)	0.35 (0.81)	0.55 (1.05)	0.003
– Length of stay, days, mean (SD)	2.4 (8.9)	3.8 (9.7)	0.018
Emergency department visit			
– n (%)	139 (40.0)	1559 (48.2)	0.043
– Count, mean (SD)	0.88 (1.62)	1.38 (2.84)	<0.001
Office visit			
– n (%)	338 (97.4)	3106 (96.1)	0.571
– Count, mean (SD)	16.49 (13.98)	14.98 (12.35)	0.205
Outpatient visit			
– n (%)	246 (70.9)	2648 (81.9)	0.001
– Count, mean (SD)	7.29 (11.23)	9.90 (12.69)	0.001
Other			
– n (%)	297 (85.5)	2853 (88.3)	0.334
– Count, mean (SD)	9.84 (11.10)	13.93 (20.87)	<0.001

COPD: Chronic obstructive pulmonary disease; SD: Standard deviation; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

Table 3. Annual weighted chronic obstructive pulmonary disease exacerbations postinitiation of tiotropium olodaterol versus triple therapy.

COPD exacerbation	TIO + OLO (n = 347)	TT (n = 3232)	p-value
Severe			
– n (%)	29 (8.3)	502 (15.5)	0.014
– Count, mean (SD)	0.13 (0.49)	0.20 (0.54)	0.109
Moderate			
– n (%)	143 (41.3)	1331 (41.2)	0.986
– Count, mean (SD)	0.75 (1.31)	0.74 (1.16)	0.903
Any (moderate or severe)			
– n (%)	162 (46.8)	1549 (47.9)	0.776
– Count, mean (SD)	0.89 (1.38)	0.94 (1.37)	0.736

COPD: Chronic obstructive pulmonary disease; SD: Standard deviation; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

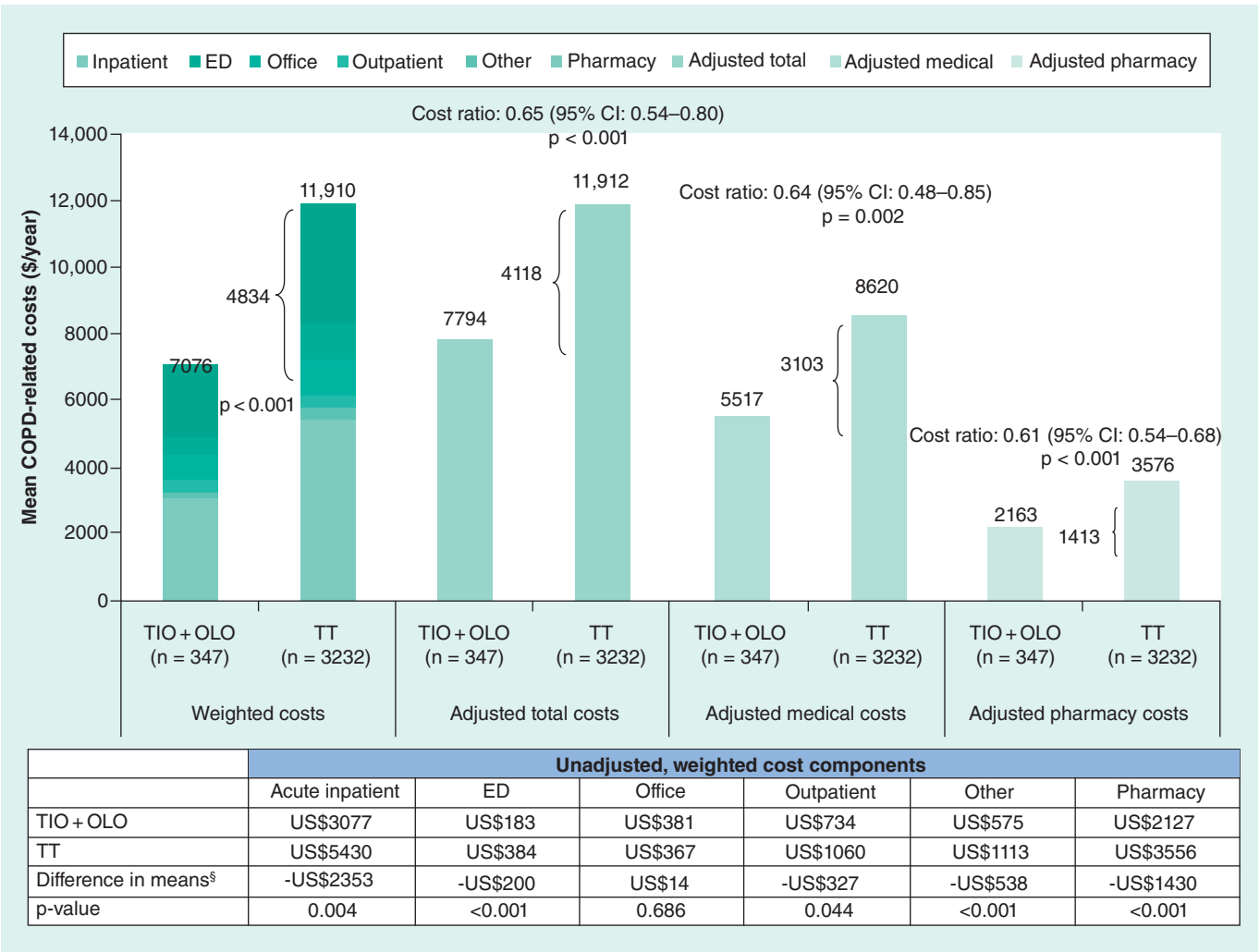


Figure 2. Annual weighted and adjusted[†] weighted chronic obstructive pulmonary disease-related costs[‡] postinitiation of tiotropium olodaterol versus triple therapy.
[†]COPD-related total, medical and pharmacy adjusted costs were computed using a generalized linear model adjusted for age (<65, 65–<75, 75+), gender, US census region (northeast, midwest, south, west, other), index season (winter, spring, summer, fall), index prescribing provider specialty (pulmonology, internal medicine, cardiology, other), baseline comorbidities (arrhythmia, pneumonia or acute bronchitis/bronchiolitis, pneumonia) and the following baseline characteristics: total days' supply of any LABA [free dose or combination], ICS (free dose or combination) use, count of oral corticosteroids fills, oxygen therapy, all-cause utilization (count of ambulatory visits, ≥1 office visit, count of office visits, ≥1 ED visit, count of ED visits, ≥1 acute inpatient stay, count of acute inpatient stays, count of other medical visits), all-cause costs (other medical, medical), COPD-attributable count of ED visits and costs, COPD-related utilization (acute inpatient stays [days], ≥1 ambulatory visit), COPD-related costs (ED, other medical visits, pharmacy) and pneumonia-related count of other medical visits. Park test estimate for model = 1.498.
[‡]Values are health plan-paid costs.
[§]Mean costs for TIO + OLO cohort minus mean costs for TT cohort.
COPD: Chronic obstructive pulmonary disease; ED: Emergency department; ICS: Inhaled corticosteroid; LABA: Long-acting bronchodilator agents; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

+US\$1223 [non-COPD pneumonia]) and US\$13,968 (i.e., US\$11,910 + US\$2058) for the TIO + OLO and TT cohorts respectively, yielding a total difference of US\$5669 favoring TIO + OLO.

Secondary analysis

For the LAMA + LABA versus TT cohort comparison, out of the initial 1368 LAMA + LABA patients, 1366 were well matched to the TT cohort (n = 3232) and retained in the final post-IPTW cohort (Figure 1). COPD-related and all-cause cost outcomes are shown in Supplementary Figures 1 & 2, respectively. Consistent with the primary

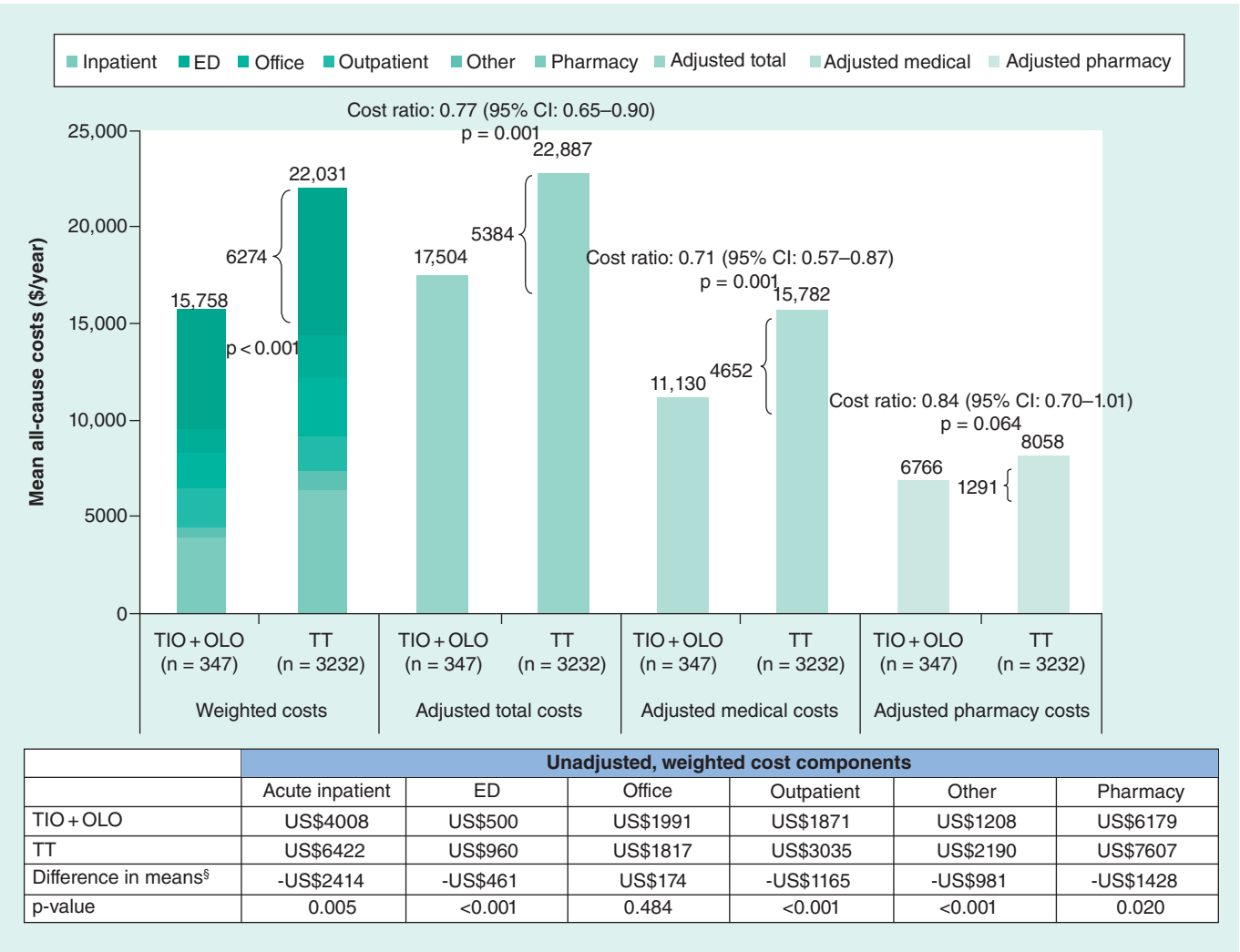
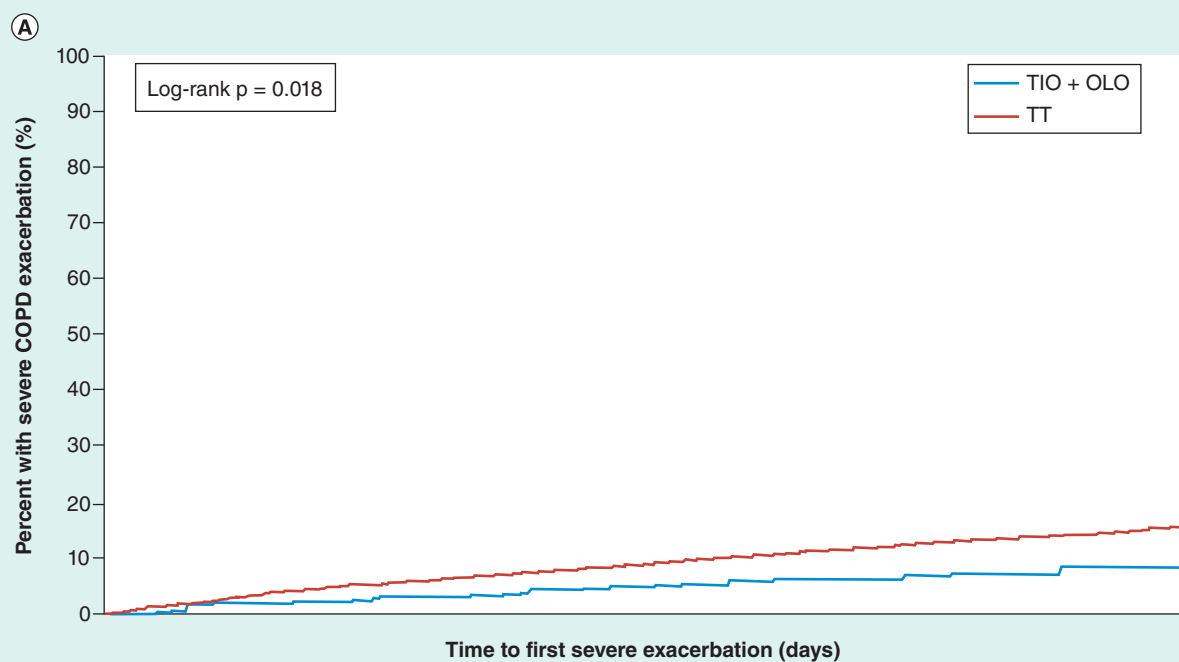
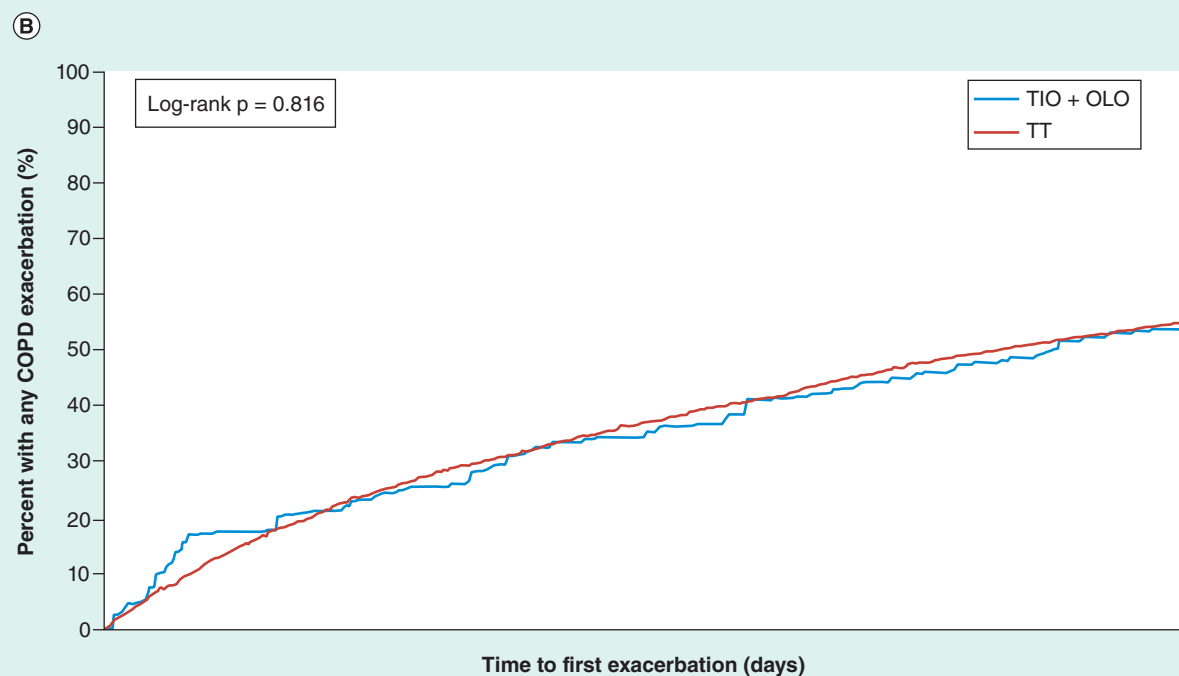


Figure 3. Annual weighted and adjusted[†] weighted all-cause costs[‡] postinitiation of tiotropium olodaterol versus triple therapy.
[†]All-cause total, medical and pharmacy adjusted costs were computed using a generalized linear model adjusted for age (<65, 65–<75, 75+), gender, US census region (northeast, midwest, south, west, other), index season (winter, spring, summer, fall), index prescribing provider specialty (pulmonology, internal medicine, cardiology, other), baseline comorbidities (arrhythmia, pneumonia or acute bronchitis/bronchiolitis, pneumonia) and the following baseline characteristics: total days' supply of any LABA [free dose or combination]), ICS (free dose or combination) use, count of oral corticosteroids fills, oxygen therapy, all-cause utilization (count of ambulatory visits, ≥1 office visit, count of office visits, ≥1 ED visit, count of ED visits, ≥1 acute inpatient stay, count of acute inpatient stays, count of other medical visits), all-cause costs (other medical, medical), COPD-attributable count of ED visits and costs, COPD-related utilization (acute inpatient stays [days], ≥1 ambulatory visit), COPD-related costs (ED, other medical visits, pharmacy) and pneumonia-related count of other medical visits. Park test estimate for model = 1.536.
[‡]Values are health plan-paid costs.
[§]Mean costs for TIO + OLO cohort minus mean costs for TT cohort.
COPD: Chronic obstructive pulmonary disease; ED: Emergency department; ICS: Inhaled corticosteroid; LABA: Long-acting bronchodilator agent; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

analysis, adjusted mean annual COPD-related total costs were lower by 25% for LAMA + LABA versus TT (US\$8971 vs US\$11,985; CR: 0.75; 95% CI: 0.67–0.84; $p < 0.001$). Total annual all-cause costs followed a similar pattern (US\$19,872 vs US\$23,055; CR: 0.86; 95% CI: 0.78–0.95; $p = 0.002$). However, there were no significant differences between cohorts for exacerbation or pneumonia outcomes (complete results shown in the Supplementary Material). Different inhaler combinations within the LAMA + LABA group were not analyzed.



Patients with severe COPD exacerbation (%)		Days after index date													
	Cohort	30	45	60	90	120	150	180	210	240	270	300	330	365	
	TIO + OLO	1.8	2.0	2.0	2.6	3.2	4.5	4.8	5.3	6.2	6.2	7.1	8.3	8.3	
	TT	2.0	3.1	4.1	5.3	6.6	7.8	8.8	10.2	11.4	12.5	13.4	14.3	15.5	



Patients with any COPD exacerbation (%)		Days after index date													
	Cohort	30	45	60	90	120	150	180	210	240	270	300	330	365	
	TIO + OLO	14.6	15.1	17.7	20.4	22.7	28.3	30.0	32.8	36.9	39.2	41.8	45.1	46.8	
	TT	9.0	12.8	15.9	21.1	25.5	28.8	32.0	35.0	38.0	41.0	43.4	45.6	47.9	

Figure 4. Kaplan-Meier probability of time to first weighted chronic obstructive pulmonary disease exacerbation postinitiation of tiotropium olodaterol versus triple therapy. (A) Severe COPD exacerbation. (B) COPD exacerbation (any severity).

COPD: Chronic obstructive pulmonary disease; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

Table 4. Annual weighted pneumonia occurrence and weighted pneumonia-related medical resource use and costs postinitiation of tiotropium olodaterol versus triple therapy.

Pneumonia outcomes	TIO + OLO (n = 347)	TT (n = 3,232)	p-value
Pneumonia diagnosis, n (%)	46 (13.3)	720 (22.3)	0.007
Pneumonia and/or acute bronchitis/bronchiolitis diagnosis, n (%)	66 (18.9)	999 (30.9)	<0.001
Pneumonia-related medical resource use			
Acute inpatient stay	46 (13.3)	720 (22.3)	0.007
– n (%)	23 (6.6)	405 (12.5)	0.014
– Count, mean (SD)	0.10 (0.46)	0.16 (0.49)	0.062
– Length of stay, days, mean (SD)	0.9 (4.5)	1.5 (6.5)	0.105
Emergency department visit			
– n (%)	23 (6.8)	338 (10.4)	0.095
– Count, mean (SD)	0.08 (0.31)	0.13 (0.44)	0.015
Office visit			
– n (%)	52 (15.0)	569 (17.6)	0.367
– Count, mean (SD)	0.23 (0.71)	0.31 (0.86)	0.115
Outpatient visit			
– n (%)	15 (4.4)	302 (9.3)	<0.001
– Count, mean (SD)	0.12 (0.96)	0.26 (1.20)	0.002
Other			
– n (%)	20 (5.8)	281 (8.7)	0.152
– Count, mean (SD)	0.17 (1.11)	0.41 (2.33)	0.001
Pneumonia-related medical costs, US\$, mean (SD) [†]			
– Total medical	1566 (7351)	2897 (14,202)	0.045
– Acute inpatient stay	1360 (6541)	2498 (13,428)	0.054
– Emergency department	28 (175)	45 (222)	0.064
– Office	22 (66)	27 (80)	0.258
– Outpatient	30 (292)	80 (473)	0.001
– Other	126 (1015)	247 (2064)	0.154

[†]Values are health plan-paid costs for medical claims with a diagnosis of pneumonia and/or acute bronchitis/bronchiolitis. SD: Standard deviation; TIO + OLO: Tiotropium olodaterol; TT: Triple therapy.

Discussion

To our knowledge, this is the first study comparing resource use, cost, COPD exacerbations and pneumonia after initiating TIO + OLO versus TT within a large real-world MAPD population with COPD. We used IPTW methodology to provide a robust comparison of cohorts [37]. Our findings support economic and COPD health benefit of TIO + OLO versus TT, with lower COPD-related, pneumonia-related and all-cause resource use and costs among patients treated with TIO + OLO, and a smaller percentage of patients experiencing severe exacerbations and pneumonia with TIO + OLO.

Annual COPD-related health plan-paid total costs were 35% lower (–US\$4118) for TIO + OLO versus TT, reflecting lower costs in both medical service (–US\$3103) and pharmacy (–US\$1413) settings. Lower pharmacy costs for TIO + OLO were plausible because TIO + OLO was provided as a single inhaler whereas TT regimens in this study required the use of multiple inhalers. However, cohort differences in COPD-related total costs were primarily driven by medical expenditures, particularly the difference in acute inpatient costs (US\$2353). Our results are supported by two previous studies in mixed populations of commercial and managed Medicare enrollees, which found patients initiating TIO + OLO incurred COPD-related costs that were 27–53% lower than their counterparts initiating TT, resulting in annual health plan cost savings of US\$3361–US\$6765 [29,30]. The COPD-related cost savings observed in the TIO + OLO cohort contributed to lower all-cause costs (23% lower or US\$5384 vs TT). The savings in all-cause costs are also consistent with a health and economic modeling study [42] based on efficacy and safety endpoints from the recent IMPACT clinical trial [43] in which total costs were estimated for patients treated with a single LAMA + LABA combination inhaler versus a single combination TT inhaler. In addition, across all phenotypic subgroups examined, annual cost savings with LAMA + LABA ranged

from approximately 5–20% [42]. Our secondary analysis comparing treatment with any LAMA + LABA regimen versus the TT cohort found results consistent with the primary analysis; however, the magnitude of the cost savings was lower (US\$3013 for COPD-related and US\$3183 for all-cause), than what was observed for TIO + OLO versus TT.

Resource use and cost results are consistent with COPD exacerbation and pneumonia outcome results. Acute inpatient costs accounted for 48.7% of the difference in mean COPD-related costs between cohorts. COPD exacerbations have historically been a major driver of COPD burden [7–9], particularly severe exacerbations which, by our definition, required an acute inpatient stay with an admission diagnosis of COPD. In our study, we found that the percentage of patients experiencing severe exacerbations in the TIO + OLO cohort was roughly half that of the TT cohort (8.3 vs 15.5%); moderate exacerbations were more common and nearly identical between cohorts (41.3 vs 41.2%). One plausible interpretation is that there was a larger shift from more severe to less severe exacerbations for TIO + OLO versus TT patients, but this hypothesis remains to be confirmed. Respiratory infections such as pneumonia are a frequent trigger of COPD exacerbations [44] and the increased rate of severe exacerbations in the TT cohort can be potentially explained by the higher rate of pneumonia that we observed in this group of patients. Accounting for pneumonia as part of COPD-related burden further widens the gap between TIO + OLO (or LAMA + LABA) and TT. In the TIO + OLO cohort, 18.9% of patients were diagnosed with pneumonia or acute bronchitis/bronchiolitis compared with 30.9% of patients in the TT cohort. The recent IMPACT clinical trial also observed a 53% increased risk of pneumonia with TT compared with LAMA + LABA [43]. However, the results of IMPACT [43], as well as the recent TRIBUTE clinical trial [45] which compared a single LAMA + LABA combination inhaler with a single combination TT inhaler (albeit with different LAMA, LABA and ICS components than IMPACT), did show a lower rate of moderate-to-severe exacerbations among patients with COPD who were treated with TT versus LAMA + LABA. The difference between our results and these two studies likely reflects multiple factors. First, our study population represents patients with COPD treated in a real-world setting rather than the relatively restrictive selection of patients required for clinical trial participation. For example, patients in both the IMPACT and TRIBUTE trials were likely to have more severe COPD than our population because inclusion in the trial required a history of exacerbations [43,45]. Second, neither clinical trial used TIO + OLO as the LAMA + LABA comparator. Last, the IMPACT study did not exclude patients with asthma; and a majority of patients had previous exposure to ICS, which was then abruptly withdrawn from those randomized to the LAMA + LABA treatment arm. This in turn, may have triggered exacerbations, in particular for those patients with comorbid asthma. The inclusion of patients with asthma and abrupt withdrawal of ICS have been widely criticized for the potential to skew results in favor of the TT arm [46–48].

While it is possible that our resource utilization-based definition of exacerbations underestimated the incidence of milder exacerbations (e.g., patients who did not seek medical treatment), our findings corroborate prior reports that TT is commonly prescribed for patients with less severe symptoms and/or exacerbation risk [15–20] thereby indicating that this GOLD inconsistent prescribing pattern is persisting. Although symptom burden could not be measured in this study, a little over a third (34.1%) of patients in the TT cohort would be classified in Groups C or D based on their exacerbation history (≥ 1 inpatient or ≥ 2 outpatient exacerbations). Even conservatively assuming that all TT patients with a high baseline risk of exacerbations also had high symptom burden (i.e., Group D), our results are consistent with most study findings that less severe patients are frequently treated with TT [15–20]. Nevertheless, these results contradict a recent study conclusion that overprescribing of TT is limited to roughly 10% of patients in USA [49]. However, that study considered any history of moderate or severe exacerbation or treatment with a COPD maintenance medication (ICS, LAMA or LABA) – not just high risk of future exacerbation – as a criterion for TT appropriateness. While we cannot know the clinical rationale for prescribing either TIO + OLO (or LAMA + LABA) or TT in our study and we excluded patients diagnosed with asthma, in general practice, COPD may be misdiagnosed as asthma, leading to inappropriate use of ICS in COPD [50,51]. It has also been suggested that some clinicians may initiate care with TT to provide maximum treatment for their patients at the outset [52]; however, this approach is incongruent with the preferred GOLD treatment pathway which recommends TT only as an escalation step, and not as an initial therapy [6]. Notably, 57.5% of TT patients in our study had no exposure to a LAMA or a LABA at baseline, suggesting that the recommended escalation pathway to TT per the 2018 GOLD guidelines was uncommon in our study. Shortly after the results of this study were finalized, the 2019 GOLD guidelines were released [53]. The 2019 guidelines maintain the initial approach to therapy for Groups A–D, but follow-up management, while still based on symptoms and exacerbations, are not dependent on GOLD group classification [53]. Nevertheless, the recommendation for TT only as an escalation step after therapy

with LAMA + LABA (or LABA + ICS) has been retained. Thus, efforts either through policies or education or both are needed to encourage guideline-compliant prescribing.

Our study provides novel insights into the real-world impact of patients initiating TIO + OLO (or LAMA + LABA) versus TT. While TT is indicated for a subset of patients with severe COPD [6], use of TT in less severe patients may have negative economic, COPD exacerbation and pneumonia consequences. The risk of pneumonia is an important consideration; pneumonia increases the risk of hospitalization and represents an unnecessary and avoidable expense [54]. Careful assessment of the risks and benefits of ICS therapy as well as inhaler type is needed to identify patients for whom TT should be considered.

Limitations

The results of this study should be interpreted in the context of certain limitations. First, the study used administrative claims data which have inherent limitations. The presence of a diagnosis code on a medical claim is not positive proof of disease, but may have been incorrectly coded or included as rule-out criteria. Nevertheless, we required ≥ 2 diagnosis codes for COPD (on separate dates of service) plus ≥ 1 claim for a long-acting bronchodilator-containing regimen, strengthening the patient selection process. Also, while pharmacy claims demonstrate that a prescription was filled, whether patients took the medication as prescribed is unknown. Further, although we were able to capture exacerbation risk using GOLD criteria and included the presence of severe exacerbation(s) as an adjustment variable in the IPTW model, symptom burden as measured by the COPD assessment test (CATTM) or modified British Medical Research Council (mMRC) questionnaire [55] scores per GOLD recommendations, were not available and thus, were not accounted for by IPTW, which may have resulted in undetectable, residual imbalances in COPD severity between cohorts. The same limitation applies to other clinically relevant but claims unobservable characteristics (e.g., tobacco history, spirometry results, COPD phenotype, blood eosinophil count and other clinical markers) and residual imbalance in these characteristics may also have influenced outcomes. Second, because no single TT inhaler was available during the study, the TT cohort required use of multiple inhalers (unlike TIO + OLO) which may be less convenient for patients and could potentially impact adherence and ultimately outcomes. However, treatment with TT administered by a single versus two inhalers did not impact exacerbation outcomes in a clinical trial setting [56]. Third, we used an intent-to-treat approach which assigns outcomes to the index treatment and did not control for medication exposures. Although inclusion required ≥ 30 days of concurrent therapy with the index regimen, it is possible that patients subsequently discontinued or switched their index regimen and differential rates of persistence or adherence to index therapy among cohorts during follow-up may have affected outcomes. An on-treatment analysis is currently being conducted as a follow-up. Fourth, unlike TIO + OLO, TT and LAMA + LABA regimens included in this study contained a mix of different LAMA and LABA (and ICS for TT) components and inhalers and the potential impact of this mix on outcomes is unknown; assessing their differential impact on the outcomes was not the objective of this study. Fifth, all patients in the study were required to have 12 months of follow-up. This may have led to selection of healthier patients into both cohorts, and may limit the generalizability of our results. Further, if a treatment is associated with survival, the requirement of a fixed follow-up period may have increased the bias, and the planned on-treatment analysis will address this limitation. Lastly, the results of this study are based on a population of Medicare Advantage beneficiaries and may not be generalizable to patients with COPD who have other forms of insurance or the uninsured.

Conclusion

This study concluded that health plans can incur annual per patient cost savings for patients initiating TIO + OLO (or LAMA + LABA) versus TT. Consistent with these cost savings, the percentage of patients experiencing severe exacerbations, as well as pneumonia and acute bronchitis/bronchiolitis, was significantly lower for TIO + OLO compared with TT. These findings provide an important economic and clinical real-world perspective to the GOLD recommendations for LAMA + LABA, and specifically TIO + OLO therapy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/ce-2019-0101

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Summary points

- The Global Initiative for Chronic Obstructive Lung Disease recommends dual therapy with long-acting muscarinic agents/long-acting β_2 -agonists (LAMA + LABA) for patients who have persistent symptoms and/or exacerbations on LABA or LAMA monotherapy; triple therapy (TT) with LAMA + LABA + inhaled corticosteroids is reserved for the most severe patients such as those experiencing exacerbations after LAMA + LABA treatment.
- Use of TT must be balanced with the risk/benefit profile given the substantially higher risk of pneumonia and other complications with regular inhaled corticosteroids use; nevertheless, contrary to Global Initiative for Chronic Obstructive Lung Disease recommendations, TT is commonly overprescribed to patients with mild or moderate disease which may impact clinical and economic outcomes.
- This retrospective based study compared chronic obstructive pulmonary disease (COPD)-related resource use and health plan-paid costs, COPD exacerbations and pneumonia outcomes among patients initiating tiotropium + olodaterol (TIO + OLO) – a LAMA + LABA fixed-dose combination inhaler – versus TT in a real-world US population of managed Medicare insurees; a secondary analysis compared any LAMA + LABA combination (including TIO + OLO) versus TT.
- The final study cohorts represented patients diagnosed with COPD initiating TIO + OLO or TT between January 2014 and June 2016; cohorts were balanced for baseline characteristics using inverse probability of treatment weighting prior to statistical comparison of outcomes.
- The TIO + OLO (n = 347) cohort incurred US\$4118 (35%) lower annual COPD-related costs and US\$5384 (23% lower annual all-cause than the TT cohort (n = 3232) in the first year after therapy initiation.
- A lesser percentage of patients in the TIO + OLO versus TT cohort experienced severe exacerbations (8.3 vs 15.5%; p = 0.014) and pneumonia diagnoses (18.9 vs 30.9%; p < 0.001).
- When the TIO + OLO cohort was expanded to include any LAMA + LABA combination, significant (p < 0.01) but lower cost savings were evident for LAMA + LABA versus TT (COPD-related: 25%; all-cause: 14%).
- The results of this study support improved economic and COPD health outcomes for TIO + OLO relative to TT in a real-world setting.

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