Evaluation of clinical outcomes within baseline exacerbation subgroups among patients with COPD initiating combination tiotropium/olodaterol versus triple therapy

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INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is the third-leading cause of death in the US[i] and the only one of the top 6 causes of death that continues to increase in incidence.[ii]
- The estimated total US economic burden of COPD in 2010 was $42.6 billion in direct healthcare expenditures, of which $11.3 billion were for hospital care.[iii]
  - COPD exacerbations account for the majority of the total COPD burden on the healthcare system, with up to 70% of COPD-related healthcare expenditures attributable to acute exacerbations of COPD.
  - Exacerbations of COPD account for approximately 10% of all medical admissions.[iv] COPD was among the most frequent reason for hospital readmissions among Medicare beneficiaries with an all-cause 30-day readmission rate of approximately 23%.[iv]
  - COPD hospital readmissions due to exacerbations account for about $15 billion USD in annual direct costs, and these costs are projected to rise by approximately 53% in the coming years.[v]
- 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations identify dual therapy with long-acting muscarinic antagonists (LAMAs) plus long-acting beta$_2$ agonists (LABAs) for patients who have persistent symptoms and/or exacerbations on LAMA or LABA monotherapy, with escalation to Triple Therapy (TT; LAMA+LABA+inhaled corticosteroids [ICS]) recommended in case of further exacerbation and after assessing the risks/benefits (e.g., pneumonia is one of the adverse events linked to ICS).
- Despite these recommendations, evidence suggests TT is over-prescribed across all COPD severities. This deviation from GOLD recommendations may have an economic and outcomes impact.[v]
- Retrospective observational studies comparing tiotropium+olodaterol (TIO+OLO) - a fixed-dose LAMA+LABA combination inhaler therapy - have shown superior results over TT within intent-to-treat and on-treatment real-world studies.[vi,vii]

Objective: Evaluate occurrence of [1] severe and [2] any (severe or moderate) COPD exacerbation(s) and [3] pneumonia diagnosis among TIO+OLO vs. TT initiators in a US Medicare Advantage Part D (MAPD) population stratified by baseline exacerbation history: none=0 exacerbation; single=1 moderate exacerbation; multiple/severe=≥2 moderate or ≥1 severe exacerbation(s).

METHODS AND MATERIALS

This was a retrospective observational study using the Optum Research Database. Study inclusion requirements were:

- Initiation of COPD treatment (LAMA monotherapy, ICS+LABA, LAMA+LABA [TIO+OLO is a subset], TT – free or fixed dose combinations) with ≥30 days of treatment between 01/01/2014 and 03/31/2018 (identification period)
  - The date of treatment initiation was the index date
- ≥2 diagnoses for COPD on separate dates of service, in any position on the medical claim between 01/01/2013 and 05/31/2018 (study period).
- ≥40 years old as of the index date, complete demographic information
- Continuous medical/pharmacy coverage for 12-months pre-index and for ≥30 days post-index
- MAPD insurance coverage
- No asthma, cystic fibrosis, or lung cancer (identified with ≥2 diagnoses on separate dates of service) during the study period

Exacerbations were defined as:

- Severe - an inpatient admission with a COPD diagnosis code in the primary position on the claim
- Moderate - an emergency department visit with a primary COPD diagnosis code or an office visit with a COPD diagnosis code in any position on the claim plus a pharmacy claim for an oral corticosteroid or COPD-guideline recommended antibiotic within 7 days of the visit

Exacerbation categories were defined according to baseline COPD exacerbation history as follows:

- None - 0 exacerbations
- Single - 1 moderate and no severe exacerbations
- Multiple/severe - ≥2 moderate or ≥1 severe exacerbations

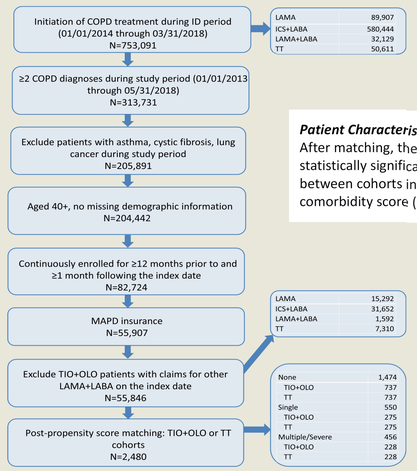
Analysis:

This post-hoc analysis directly matched TIO+OLO and TT cohorts on baseline exacerbation history and maintenance naïve status before being propensity score matched 1:1

Kaplan-Meier log-rank test was applied for all comparisons. Cox proportional hazard models was used adjusting for residual baseline differences

RESULTS

Figure 1. Attrition Diagram



Patient Characteristics

After matching, there were no statistically significant differences between cohorts in age, gender or comorbidity score (see Table 1).

Exacerbation

Kaplan Meier analysis

Occurrence of ≥1 severe exacerbation(s) within 1-year of index date, comparing TIO+OLO vs. TT by baseline exacerbation history category:

- None: 5.92 vs. 13.54% (p=0.002)
- Single: 7.48 vs. 20.04% (p=0.555)
- Multiple/severe: 17.93 vs. 16.64% (p=0.675)

No statistically significant differences were observed for the 'any exacerbation' outcome between cohorts.

Cox proportional hazard model

After adjusting for treatment and additional covariates, the difference in risk for a severe exacerbation was approximately 57% lower for TIO+OLO patients with no exacerbation history, compared to TT patients (see Table 2).

Table 2. Cox proportional hazard models – time to first severe COPD exacerbation[1]

Independent Variables	None (N=1474)		Single (N=550)		Multiple/severe (N=456)	
	hazard ratio	p-value	hazard ratio	p-value	hazard ratio	p-value
Cohort						
TIO+OLO	0.425	0.002	0.785	0.554	1.284	0.444
TT	ref.	–	ref.	–	ref.	–
Age, categorized		0.360		0.893		0.360
<65	0.457	0.154	0.726	0.641	0.450	0.154
65 - <75	0.898	0.689	0.974	0.949	0.926	0.823
75+	ref.	–	ref.	–	ref.	–
Plan type		0.333				0.357
Health maintenance organization (HMO) or Preferred provider organization (PPO)	1.685	0.323			1.982	0.163
Other	ref.	–			ref.	–
Multiple/unknown/missing	1.742	0.140			1.462	0.293
Baseline comorbidities						
Elixhauser comorbidity score[1]			1.034	0.358		
Charlson comorbidity score (categorized)				0.810		
0-1			ref.	–		
2-3			1.314	0.592		
4+			1.578	0.547		
Arrhythmia			0.520	0.410		
Atrial fibrillation (broad definition)			1.711	0.478		
Ischemic heart disease					2.330	0.024
Region						0.281
Northeast					0.252	0.171
Midwest					1.362	0.414
South					ref.	–
West					1.881	0.281
Baseline medical claims						
Any rescue medications (SAMA, SABA, SAMA/SABA)					1.711	0.212
Baseline utilization						
COPD-attributed ambulatory visit					1.645	0.216
COPD-related outpatient visit					1.090	0.819

Time on treatment identified during the follow-up period, including the index date, until the earliest occurrence of index regimen discontinuation (≥60 day gap) or switch, coverage disenrollment, or study end (05/31/2018).

[1]Identified beginning on index date + 1.

Blue p-values indicate statistical significance. Gray cells indicate variables were not included in the model.

Table 1. Patient Demographics by Cohort and Exacerbation Category

Post-match Baseline Characteristics	None				Single				Multiple/severe			
	TIO+OLO (N=737)		TT (N=737)		TIO+OLO (N=275)		TT (N=275)		TIO+OLO (N=228)		TT (N=228)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Age (continuous)	72.20	8.70	72.66	8.41	72.56	8.73	71.88	8.18	72.26	8.35	71.96	8.31
	n	%	n	%	n	%	n	%	n	%	n	%
Female	333	45.18	334	45.32	139	50.55	134	48.73	118	51.75	117	51.32
Charlson comorbidity score categories												
0-1	378	51.29	371	50.34	121	44.00	135	49.09	81	35.53	80	35.09
2-3	214	29.04	226	30.66	102	37.09	88	32.00	71	31.14	75	32.89
4-5	107	14.52	101	13.70	38	13.82	40	14.55	53	23.25	55	24.12
6+	38	5.16	39	5.29	14	5.09	12	4.36	23	10.09	18	7.89
Pneumonia and/or acute bronchitis/bronchiolitis diagnosis	165	22.39	130	17.64	93	33.82	72	26.18	132	57.89	141	61.84
Naïve to LAMA or LABA	696	94.44	696	94.44	253	92.00	254	92.36	201	88.16	201	88.16
Oxygen therapy	118	16.01	117	15.88	52	18.91	59	21.45	93	40.79	104	45.61
	mean	median	mean	median	mean	median	mean	median	mean	median	mean	median
Baseline total costs	$15,023	$5,852	$13,207	$6,433	$12,786	$6,807	$13,572	$6,369	$25,014	$15,017	$27,317	$15,395

Figure 2. Kaplan-Meier curve of severe COPD exacerbation among MAPD patients with no COPD exacerbation history by treatment cohort

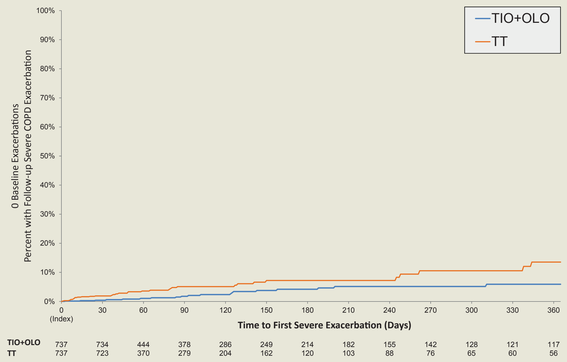
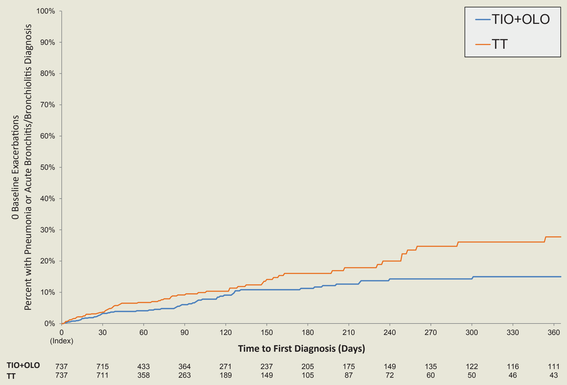


Figure 3. Kaplan-Meier curve of pneumonia or acute bronchitis/bronchiolitis diagnosis among MAPD patients with no COPD exacerbation history by treatment cohort



Pneumonia

Kaplan Meier analysis

Occurrence of pneumonia or acute bronchitis/bronchiolitis within 1 year after index, comparing TIO+OLO vs. TT by baseline exacerbation history category:

- None: 15.00 vs. 27.74% (p=0.015)
- Single: 27.23 vs. 31.02% (p=0.618)
- Multiple/severe: 38.24 vs 32.15% (p=0.667)

Cox proportional hazard model

After adjusting for treatment and other covariates, the difference in risk for pneumonia or acute bronchitis/bronchiolitis was approximately 34% lower for TIO+OLO patient with no exacerbation history, compared to TT (see Table 3).

Table 3. Cox proportional hazard models – time to pneumonia or acute bronchitis/bronchiolitis diagnosis[1]

Independent Variables	None (N=1474)		Single (N=550)		Multiple/severe (N=456)	
	hazard ratio	p-value	hazard ratio	p-value	hazard ratio	p-value
Cohort						
TIO+OLO	0.656	0.018	0.885	0.625	0.946	0.789
TT	ref.	–	ref.	–	ref.	–
Age, categorized		0.168		0.964		0.697
<65	0.570	0.069	0.922	0.815	0.792	0.465
65 - <75	0.839	0.338	0.945	0.833	1.039	0.865
75+	ref.	–	ref.	–	ref.	–
Plan type		0.686				0.544
HMO or PPO	1.291	0.434			0.929	0.812
Other	ref.	–			ref.	–
Multiple/unknown/missing	1.178	0.459			0.790	0.276
Baseline comorbidities						
Elixhauser comorbidity score[1]			1.005	0.851		
Charlson comorbidity score (categorized)				0.438		
0-1			ref.	–		
2-3			0.990	0.976		
4+			1.592	0.310		
Arrhythmia			0.983	0.966		
Atrial fibrillation			0.983	0.971		
Ischemic heart disease					1.292	0.241
Region						0.182
Northeast					1.166	0.677
Midwest					1.426	0.122
South					ref.	–
West					2.067	0.084
Baseline medical claims						
Any rescue medications (SAMA, SABA, SAMA/SABA)					1.564	0.091
Baseline utilization						
COPD-attributed ambulatory visit					0.834	0.448
COPD-related outpatient visit					1.328	0.242

Time on treatment identified during the follow-up period, including the index date, until the earliest occurrence of index regimen discontinuation (≥60 day gap) or switch, coverage disenrollment, or study end (05/31/2018).

[1]Identified beginning on index date + 1. .

Blue p-values indicate statistical significance. Gray cells indicate variables were not included in the model.

Kaplan Meier analysis: Occurrence of ≥1 pneumonia (KM data not shown) within 1-year after index, comparing TIO+OLO vs. TT by baseline exacerbation history category:

- None: 8.74 vs. 16.70% (p=0.016)
- Single: 14.53 vs. 17.35% (p=0.869)
- Multiple/severe: 25.27 vs 27.36% (p=0.377)

LIMITATIONS

- While pharmacy claims demonstrate that a prescription was filled, whether patients actually took the medication as prescribed or used appropriate inhaler technique is unknown.
- 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. However we required ≥2 diagnosis codes for COPD plus ≥1 claim for a long-acting bronchodilator-containing regimen to strengthen the patient selection process.
- The results of this study are based on a population of MAPD enrollees and may not be generalizable to patients with COPD who have other forms of insurance or are uninsured.

CONCLUSIONS

- COPD patients with no history of exacerbations initiating TIO+OLO had significantly lower annual severe exacerbations and pneumonia rates versus those initiating TT.
- Using baseline exacerbation history as a proxy for COPD severity, these real-world findings support GOLD prescribing recommendations restricting TT for the most severe COPD patients.

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