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Impact of prompt versus delayed initiation of triple therapy post COPD exacerbation in a US-managed care setting

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ABSTRACT

Background: It is unknown whether there is a benefit to initiating triple therapy (TT; inhaled corticosteroids combined with long-acting β_2-agonists and long-acting muscarinic antagonists) promptly (within 30 days) following a chronic obstructive pulmonary disease (COPD)-related hospitalization or emergency-department (ED) visit compared with delaying treatment (31–180 days).

Methods: This retrospective, observational study (GSK: HO-15-15256) used healthcare claims from a commercial and Medicare claims database (January 1, 2008–December 31, 2015). Patients: ≥40 years of age, diagnosed with COPD and no history of TT 12 months pre-index. Patients experiencing a COPD-related hospitalization or ED visit (index) who initiated TT ≤ 6 months following index were included (January 1, 2009–December 31, 2014). Patients initiating TT ≤ 30 or 31–180 days following index were included in the Prompt or Delayed cohorts, respectively. All-cause and COPD-related costs (total, medical and prescription), and exacerbations (severe and moderate) per patient per year were determined for 12 months post index. Outcomes were adjusted by cohort, weighted for a balanced distribution of baseline covariates between cohorts using inverse probability weights.

Results: Overall, 10,902 patients were identified (Prompt: n = 5701; Delayed: n = 5201). Total, medical and prescription all-cause costs were significantly higher in the Delayed versus Prompt cohorts (percent increase: 18.7%, 22.8% and 8.8%, respectively; all $p < 0.0001$). COPD-related total, medical and prescription costs were 49.3%, 66.3% and 10.3% higher in the Delayed versus Prompt cohorts, respectively (all $p < 0.0001$). Total and severe COPD-related exacerbation rates were 28.2% and 64.7% higher in the Delayed versus Prompt cohorts ($p < 0.0001$).

Conclusion: Prompt use of TT following a COPD-inpatient or ED visit may reduce future costs and subsequent exacerbations compared with delaying the initiation of TT.

1. Introduction

In the United States, chronic obstructive pulmonary disease (COPD) was the third leading cause of death in 2015, according to the American Lung Association [1], and was the second largest cause of reduced disability-adjusted life-years in 2010 [2]. COPD is associated with substantial direct and indirect costs [3], with exacerbations being a major contributor to the total COPD burden on the healthcare system [4]. Currently, treatment options for COPD include long-acting muscarinic antagonists (LAMA), long-acting β_2-agonists (LABA), inhaled corticosteroids (ICS) combined with LABA, and LAMA combined with ICS/LABA (triple therapy [TT]) [4]. For the treatment of exacerbations, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 strategy document recommends that treatment should be aimed at minimizing the impact of the current exacerbation and reducing the risk of future exacerbations [4]. A Phase III study assessing the effect of

Abbreviations: CCI, Charlson comorbidity index; CI, confidence intervals; CM, clinical modification; COPD, chronic obstructive pulmonary disease; ED, emergency department; GOLD, Chronic Obstructive Lung Disease; ICD-9, International Classification of Diseases, Ninth Revision; ICS, inhaled corticosteroids; IPTW, inverse probability of treatment weighting; LABA, long-acting β_2-agonists; LAMA, long-acting muscarinic antagonist; TT, triple therapy; OCS, oral corticosteroids; Rx, prescription; SABA, short-acting β_2-agonists; SAMA, short-acting anti-muscarinic antagonist; SD, standard deviations

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a single inhaler TT on COPD exacerbation risk was recently completed. This study showed that the use of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) TT, combined in a single once-daily inhaler, reduces the rate of moderate or severe exacerbations compared with either UMEC/VI or FF/VI in patients with an exacerbation history [5]. In addition, FF/UMEC/VI was also shown to reduce COPD-related hospitalization compared with UMEC/VI [5]. These results demonstrate the benefit of TT administered in a single device on reduction of severe exacerbations. The administration of long-acting bronchodilators within 30 days of a hospital discharge is currently a quality of care measure in the United States [6]. However, it is unclear whether prompt versus delayed use of TT maintenance treatment post exacerbation has an impact on the number of future exacerbations or the costs associated with the condition. The objectives of this study were to examine all-cause and COPD-related costs (total, medical, prescription [Rx]) for patients initiating TT using multiple inhalers either promptly (≤30 days) or with a delay (31–180 days) following a severe exacerbation. The impact of prompt versus delayed TT initiation on the rate and number of future COPD-related exacerbations was also examined.

2. Materials and methods

2.1. Study design

This was a retrospective, observational, cohort study, using healthcare claims from commercial and Medicare supplemental claims databases between January 1, 2008 and December 31, 2015 (Fig. 1). The Truven Health MarketScan Commercial Claims and Encounters database (commercial) included the annual employer and health plan sourced data, which contained medical and drug claims for over 40 million employees, including their spouses and dependents. The Truven Medicare Supplemental and Coordination of Benefits Database (Medicare) included the annual inpatient and outpatient medical and Rx claims data from approximately 4.3 million Medicare-eligible individuals with supplemental insurance plans offered by their previous employers. Patients from both databases were pooled into a single study population. Patient demographics, baseline characteristics, information on costs, healthcare resource use, and outcomes for inpatient and outpatient services, Rx drug claims and patient enrollment were obtained from both databases.

Patients experiencing their first COPD-related hospitalization or emergency department (ED) visit (index event) were included from January 1, 2009 to December 31, 2014. The index date was defined as the discharge date for COPD-related hospitalizations or as the date of the ED visit for a COPD exacerbation. COPD-related hospitalizations and ED visits were defined with a primary discharge diagnosis or diagnosis code for COPD, respectively. The international Classification of Diseases, Ninth Revision (ICD-9) codes used to confirm a diagnosis of COPD were 490, 491.0, 491.1, 491.2, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.12, 493.22, 493.92, 494.1, 466.0, 496, 518.81, 518.82, 518.84 and 799.1. Patients were included in two cohorts (prompt or delayed), based on when TT was received within the 6 months following the index date. The Prompt cohort included those who had received TT ≤ 30 days after the index date and the Delayed cohort included patients who had received TT 31–180 days after the index date. TT was defined as patients with ≥1 overlapping day(s) supply of LAMA and ICS/LABA Rx, including combination products (Table S1). A baseline assessment was conducted using data 1-year prior to index date (pre-index) and outcomes were assessed during a 1-year follow-up (post index).

2.2. Patient sample

Eligible patients were ≥40 years of age at index date with a diagnosis of COPD defined as the presence of an inpatient or outpatient visit with a diagnosis code for COPD within the baseline period. Patients had a COPD-related hospitalization or ED visit leading to the initiation of TT within 6 months of that event. Patients also had continuous health plan eligibility in the 1-year pre-index and 1-year follow-up periods. Patients were excluded for use of TT for COPD in the 12-month pre-index period, initiation of TT 181–365 days after the index date, use of therapies not approved for COPD including non-approved doses as described in Table S1 (eg, fluticasone propionate/salmeterol 500/50 μg and mometasone/formoterol, respectively), use of ICS monotherapy anytime during the pre-index and follow-up periods, and presence of certain comorbid conditions (Table S2) during the pre-index period.

2.3. Study outcomes

2.3.1. Primary outcomes

The primary outcome was the total annual all-cause and COPD-related costs for patients in the Prompt or Delayed cohort following an exacerbation. Total all-cause cost was defined as the sum of all medical and Rx claims with any diagnosis; total COPD-related cost was defined as the sum of all medical costs for claims with an ICD-9 diagnosis code for COPD in the primary position as well as Rx costs for medications with a national drug code for a COPD-related medication (Table S1).

Costs were assessed using the total gross payment associated with the event. This was the amount eligible for payment after applying pricing guidelines such as fee schedules and discounts, and after applying deductibles, copayments, and coordination of benefits [7]. All costs were standardized to the last year of available data (2015) using the medical component of the Consumer Price Index. Medical costs included inpatient, outpatient and ED costs, and Rx costs included the

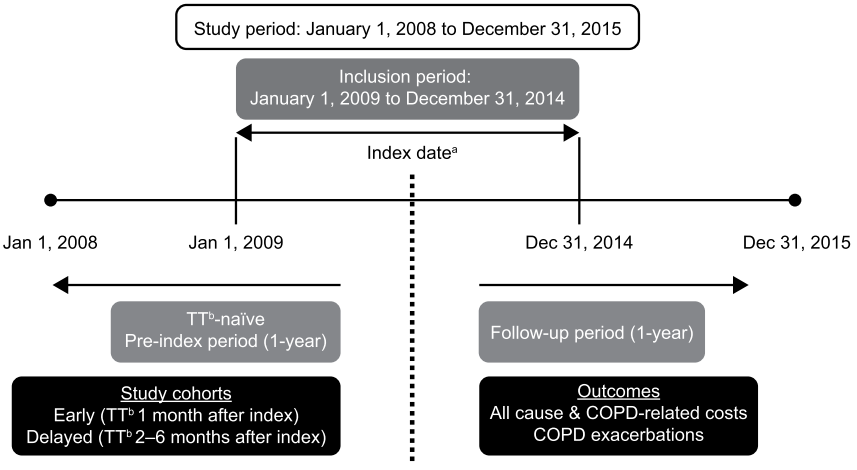

Fig. 1. Study design.
[a]Index date was defined as the discharge date for COPD-related hospitalizations or ED visit due to a COPD exacerbation that was followed by the initiation of TT; [b]TT is defined as treatment with ICS/LABA and LAMA.
COPD, chronic obstructive pulmonary disease; ICS, Inhaled corticosteroids, LABA, long-acting β_2-agonists, LAMA, Long-acting muscarinic antagonist; TT, multiple inhaler triple therapy.

Table 1
Preweighted baseline characteristics.

	Total (N = 10,902)	Prompt (N = 5701)	Delayed (N = 5201)	p-value
Age, years, mean	68.87	67.98 (11.46)	69.84 (11.25)	< 0.0001
Age, > 65%	60.46	56.36	64.95	< 0.0001
Male, %	45.16	44.64	45.72	0.2574
CCI, mean (SD)	2.22	2.15 (1.72)	2.29 (1.82)	< 0.0001
CCI score: 0, %	2.07	2.25	3.46	< 0.0001
CCI score: 1, %	44.38	59.34	54.39	
CCI score: 2–4, %	44.09	32.96	35.42	
CCI score: ≥5, %	9.46	5.46	6.73	
Commercial, %	38.06	42.31	33.4	< 0.0001
Index Season, %				
Fall	21.15	20.72	21.63	0.2572
Spring	27.04	27.82	26.19	
Summer	18.1	18.01	18.19	
Winter	33.71	33.45	33.99	
COPD severity				
SAMA, %	2.95	2.46	3.5	0.0013
SABA, %	30.36	27.56	33.44	< 0.0001
OCS, %	9.74	8.45	11.15	0.0001
Antibiotics, %	46.62	44.15	49.32	< 0.0001
Pre-index all-cause total costs, mean $ (SD)	26,700	23,900 (31,000)	29,800 (49,300)	< 0.0001
Medical costs, mean $ (SD)	23,600	21,200 (30,000)	26,300 (48,800)	< 0.0001
Rx costs, mean $ (SD)	3,070	2,680 (5,130)	3,490 (5,600)	< 0.0001
Pre-index COPD-related total costs, mean $ (SD)	10,600	10,700 (12,800)	10,600 (21,100)	0.7138
Medical costs, mean $ (SD)	9,780	10,000 (12,800)	9,520 (21,100)	0.1283
Rx costs, mean $ (SD)	849	667 (1450)	1,050 (1910)	< 0.0001

All costs data are reported to 3 significant figures; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; OCS, oral corticosteroids; Rx, prescription; SABA, short-acting β_2-agonist; SAMA, short-acting anti-muscarinic agent; SD, standard deviation.

cost of claims for medications.

2.3.2. Secondary outcomes

The secondary outcomes included the number of COPD-related exacerbations per person per year as well as the impact on components (medical and Rx) of all-cause and COPD-related costs in the Prompt versus Delayed cohorts. Severe COPD-related exacerbations were defined as hospitalization with a primary discharge diagnosis code for COPD during the baseline period. Moderate COPD-related exacerbations were defined as either a ED visit with a primary diagnosis of COPD, or an outpatient visit with a primary diagnosis of COPD and receipt of oral corticosteroid (OCS) and/or antibiotic Rx within 5 days of visit (Outpatient + Rx). The exacerbation rates per person per year were calculated separately for each visit type (hospitalization, ED and Outpatient + Rx), as well as for hospitalization and ED visit combined and for total exacerbations (hospitalization, ED visit and Outpatient + Rx combined).

2.3.3. Other outcomes

Other outcomes included the following variables that were used to describe the baseline patient characteristics during the pre-index period or as covariates in the multivariate analyses. Demographic characteristics including age at index, gender, and season of index date (Spring: March–May, Summer: June–August, Fall: September–November, Winter: December–February) were obtained from eligibility files. A Charlson comorbidity index (CCI) score was calculated for each patient in the 1-year pre-index period based on ICD-9 clinical modification (CM) codes, to estimate the presence of comorbidities (Table S3). Higher scores represent a higher burden of comorbidity. In addition, the use of inhaled short-acting β_2-agonists (SABA; pre-index), ipratropium (pre-index), OCS (pre-index) and antibiotics (pre-index), as well as COPD-related exacerbations (follow-up) and COPD-related medical and Rx costs (pre-index) was determined.

2.4. Statistical analyses

A convenience sample of eligible patients was identified from the claims databases. A sample size of 2138 was calculated to estimate an effect size of 0.178 in all-cause total costs with 95% power to detect differences between patients receiving either prompt or delayed TT, assuming an all-cause cost difference between the Prompt and Delayed cohorts of $2,500 and standard deviations (SDs) of $15,000 for the Delayed cohort and $13,000 for the Prompt cohort.

As this is an observational study in which randomization was impossible, observed effects between the cohorts may have been due to group selection rather than the cohorts of interest. To minimize the risk of selection bias, inverse probability of treatment weighting (IPTW) [8,9] was used to balance the treatment cohorts on observed covariates that may be associated with the outcomes of interest. Variables thought to influence outcomes included age, gender, season of index date, CCI, number of SABA canisters, number of OCS Rx, number of ipratropium canisters, use of antibiotics and number of exacerbations.

Baseline demographic, clinical, and healthcare resource utilization characteristics between weighted and unweighted treatment cohorts were compared using paired *t*-tests. Characteristics that remained unbalanced following IPTW, as determined by a p-value of 0.05, were included in the multivariate analysis as independent variables.

Primary and secondary outcomes were reported both as adjusted and unadjusted values. Unadjusted outcomes were analyzed using weighted *t*-tests. Generalized linear models were performed to estimate all-cause and COPD-related costs adjusting for treatment cohort. Adjusted cost outcomes were analyzed using a gamma distribution, log-link transformation and IPTW. In addition to IPTW, medical costs (all-cause and COPD-related) and mean number of exacerbations were adjusted using weighted cohort as the independent variable. All-cause and COPD-related Rx costs were further adjusted for cohort and pre-index Rx costs. Recurrent exacerbations, defined as those occurring after the index date, were analyzed using an unweighted chi square test. Exacerbation rates were then adjusted for baseline covariates using a negative binomial regression (including weights). Statistical significance at the alpha level of 0.05 was evaluated by assessing the 95% confidence intervals (CI) of the adjusted cost difference between cohorts. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). All costs data are reported to 3 significant figures.

3. Results

3.1. Baseline characteristics

Of the 10,902 patients identified for inclusion, 5701 (52.3%) and 5201 (47.7%) patients were included in the Prompt and Delayed cohorts, respectively (Tables 1 and 2). There were significant differences between the cohorts in costs, age, CCI score, the percentage of patients from the commercial database and COPD severity prior to the weighted analysis. The weighted analysis removed the variation between the cohorts for most of the baseline characteristics (Table 2). In weighted analyses, 60.6% of patients were > 65 years of age and 45.3% were male. Most patients had a CCI score of either 1 (44.2%) or 2–4 (44.2%) and patients were identified from across all four index seasons. Treatment with SABA (30.5%) and antibiotics (46.6%) was the most prevalent, compared with short-acting anti-muscarinic antagonists (SAMA) (3.0%) and OCS (9.8%).

After the weighted analyses, variation remained for the mean weighted total COPD-related medical costs, which remained significantly higher in the Delayed cohort ($896) versus the Prompt cohort ($801; p = 0.0034). Total weighted pre-index all-cause costs were $27,500 in the Prompt cohort and $26,900 in the Delayed cohort (p = 0.4648). Weighted pre-index medical costs, all-cause and COPD-related, were much greater than Rx costs in both cohorts (Table 2).

3.2. All-cause costs

After weighting and before adjusting for confounders, there were significant differences between the weighted cohorts in all-cause costs during the follow-up period (p < 0.0001; Table 3). The average total all-cause cost in the Prompt cohort was $24,800 (95% CI: $23,600, $26,000) and $31,000 (95% CI: $29,500, $32,500) in the Delayed cohort. After adjusting for covariates, there were significantly higher all-cause costs recorded in the Delayed cohort ($37,900 [95% CI: $36,900, $39,000]) compared with the Prompt cohort ($32,000 [95% CI: $31,100, $32,900]; difference: $5,960 [95% CI: $5,820, $6,110]; p < 0.0001). In addition, the predicted mean medical and Rx all-cause costs were both significantly higher in the Delayed cohort compared with the Prompt cohort (Fig. 2). The mean difference between Delayed and Prompt cohorts was $5,980 [95% CI: $5,800, $6,160] for medical costs and $636 [95% CI: $617, $656] for Rx costs. The mean percentage increase between the cohorts (Delayed minus Prompt) was 18.7%, 22.8% and 8.8% for all-cause total, medical and Rx costs, respectively, all of which were statistically significant (all p < 0.0001).

Table 2
Weighted baseline characteristics.

	Prompt (N = 5701)	Delayed (N = 5201)	p-value
Age, years mean	68.91 (11.11)	68.91 (11.68)	0.9871
Age, > 65%	60.69	60.48	0.8209
Male, %	45.27	45.31	0.964
CCI, mean (SD)	2.23 (1.74)	2.22 (1.81)	0.8302
CCI score: 0, %	2.05	2.07	0.9975
CCI score: 1, %	44.14	44.32	
CCI score: 2–4, %	44.28	44.11	
CCI score: ≥5, %	9.53	9.5	
Commercial, %	37.93	37.96	0.9761
Index Season, %			
Fall	21.05	21.04	0.9998
Spring	27.23	27.28	
Summer	17.94	17.97	
Winter	33.78	33.7	
COPD severity			
SAMA, %	2.97	2.95	0.9559
SABA, %	30.48	30.49	0.994
OCS, %	9.81	9.83	0.9687
Antibiotics, %	46.57	46.57	0.9997
Pre-Index all-cause total costs, mean $ (SD)	27,500 (42,900)	26,900 (42,700)	0.4648
Medical costs, mean $ (SD)	24,500 (42,100)	23,800 (42,100)	0.4184
Rx costs, mean $ (SD)	3,040 (5,380)	3,090 (5,330)	0.6039
Pre-index COPD-related total costs, $ (SD)	10,700 (13,100)	10,600 (21,700)	0.8929
Medical costs, mean $ (SD)	9,880 (13,100)	9,740 (21,600)	0.6795
Rx costs, mean $ (SD)	801 (1,580)	896 (1,790)	0.0034

All costs data are reported to 3 significant figures; CCI, Charlson comorbidity index; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; OCS, oral corticosteroids; Rx, prescription; SABA, short-acting β_2-agonist; SAMA, short-acting anti-muscarinic antagonist; SD, standard deviation.

3.3. COPD-related medical costs

In unadjusted analyses (Table 3), follow-up COPD-related costs were significantly greater in the Delayed ($9,300 [95% CI: $8,510, $10,100]) versus Prompt cohort ($6,070 [95% CI: $5,690, $6,440]; p < 0.0001). After adjusting for the pre-index covariates, the Delayed cohort was associated with significantly higher predicted mean total COPD-related costs ($13,100 [95% CI: $12,700, $13,500]) compared with the Prompt Cohort ($8,790 [95% CI: $8,510, $9,070]; p < 0.0001), with a mean difference of $4,330 (Fig. 2). This difference was mainly driven by the significantly higher predicted mean medical costs in the Delayed cohort ($10,300 [95% CI: $9,870, $10,800]) versus the Prompt cohort ($6,220 [95% CI: $5,920, $6,530]; difference: $4,120 [95% CI: $3,940, $4,310]; p < 0.0001). The COPD-related Rx costs were $3,770 (95% CI: $3,680, $3,860) and $3,420 (95% CI: $3,340, $3490) in the Delayed and Prompt cohorts, respectively (difference: $352 [95% CI: $342, $362]; p < 0.0001). The mean percentage increase between the cohorts (Delayed minus Prompt) was significantly different between the cohorts for the total (49.3%), medical (66.3%) and Rx (10.3%) costs (all p < 0.0001).

3.4. COPD exacerbation rates

The unadjusted weighted analyses for exacerbations are reported in Table S4. The adjusted analysis (Fig. 3) demonstrated that exacerbation rates were significantly higher (p < 0.0001) for total exacerbations in the Delayed cohort (1.04) compared with the Prompt cohort (0.81). The exacerbation rate following hospitalization or ED visit was significantly lower for prompt (0.31) versus delayed (0.55) TT treatment. Exacerbation rates following ED visits were significantly lower in the Prompt versus Delayed cohort (0.11 vs 0.21, respectively; p < 0.001). In addition, the exacerbation rate following hospitalization was also significantly lower in the Prompt versus Delayed cohort (0.20 vs 0.33, p < 0.001). However, the time at which TT was initiated did not significantly affect the Outpatient + Rx exacerbation rates (Delayed 0.50 vs 0.49 Prompt; p = 0.87).

4. Discussion

As symptoms and exacerbations in COPD are associated with substantial economic burden, initiating TT promptly following a COPD-related hospitalization or ED visit for an exacerbation may be beneficial compared with delaying as it may help to reduce future costs and the frequency, impact, and risk of future exacerbations. TT has been associated with good clinical and health outcomes in patients with COPD. For example, a post hoc analysis of four randomized trials in patients with symptomatic COPD demonstrated that the addition of UMEC as an add-on therapy to ICS/LABA for 12 weeks was associated with significant improvements in lung function, health status, and exacerbation risk compared with placebo plus ICS/LABA [10]. Improvements in health status were also observed at 12 weeks, as measured by COPD assessment test and St Georges Respiratory Questionnaire, compared with baseline [11]. Single inhaler TT has also been shown to reduce the number of exacerbations in COPD compared with ICS/LABA or LAMA

Table 3
Unadjusted COPD costs.

	Prompt, N = 5701 (95% CI)	Delayed, N = 5201 (95% CI)	Change, Delayed − Prompt (95% CI)	Change (%)	p-value
Total all-cause costs, $	24,800 (23,600, 26,000)	31,000 (29,500, 32,500)	6,190 (5,900, 6,490)	24.99	< 0.0001
All-cause Medical costs, $	20,200 (19,000, 21,400)	26,200 (24,700, 27,700)	6,030 (5,730, 6,340)	29.87	< 0.0001
All-cause Rx costs, $	4,580 (4,420, 4,750)	4,740 (4,560, 4,920)	161 (146, 175)	3.50	0.1932
Total COPD-related costs, $	6,070 (5,690, 6,440)	9,300 (8,510, 10,100)	3,230 (2,830, 3,640)	53.28	< 0.0001
COPD-related Medical costs, $	3,910 (3,540, 4,280)	7,030 (6,250, 7,810)	3,120 (2,710, 3,540)	79.88	< 0.0001
COPD-related Rx costs, $	2,160 (2,090, 2,220)	2,260 (2,190, 2,340)	109 (102, 116)	5.04	0.0304

All costs data are reported to 3 significant figures; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; Rx, prescription.

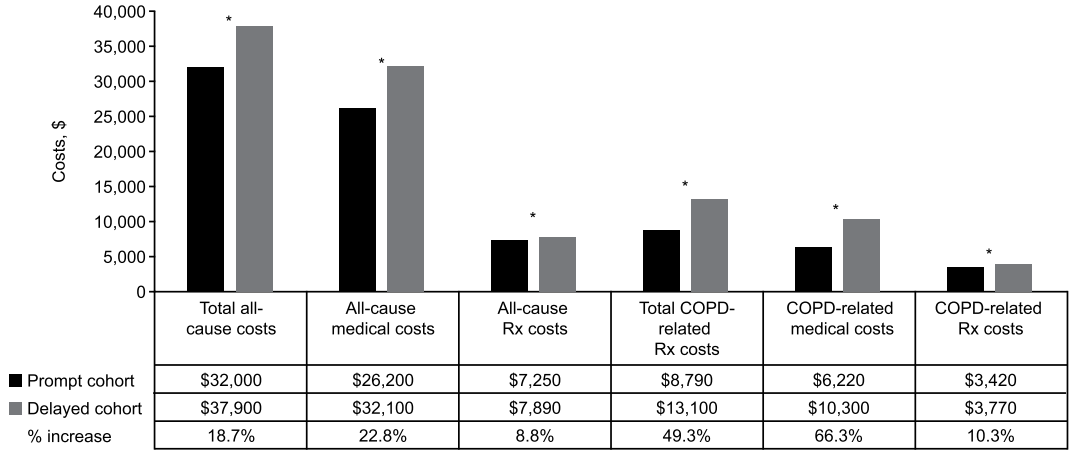

Fig. 2. All-cause and COPD-related costs (adjusted) in the Prompt and Delayed cohorts.
*p < 0.0001; all costs data are reported to 3 significant figures; COPD, chronic obstructive pulmonary disease; Rx, prescription.

[11,12], and two recent trials, the IMPACT and TRIBUTE trials, have demonstrated a reduction in COPD-related exacerbation rates [5,13] and COPD-related hospitalizations [13] with TT in a single inhaler compared with LAMA/LABA therapy. In addition, a retrospective cohort study has shown that treatment with TT reduced all-cause and respiratory-related mortality as well as hospital admissions compared with ICS/LABA [14]. However, the effect of treatment timing on future all-cause and COPD-related costs, and exacerbations following TT initiation has not been previously shown. This study demonstrates that in patients who received triple therapy after a COPD-related hospitalization or ED visit, initiation of TT within 30 days of that event significantly reduced the number of future exacerbations, severe exacerbations (inpatient visits), and all-cause and COPD-related costs, compared with initiating TT within 31–180 days.

Similar to the findings reported here, a previous analysis of published data reported improvements in lung function, symptoms, exacerbations, and quality of life when maintenance therapy was initiated early (when symptoms were mild/moderate) compared with later in the disease (when symptoms were severe) [15]. Although the benefits of initiating maintenance therapy promptly have been previously shown, evidence suggests that many patients with COPD are not prescribed suitable maintenance therapies [15], or worse, do not receive any maintenance therapy [16]. These studies indicate a need to improve the awareness of physicians on COPD treatment pathways, in addition to the importance of initiating prompt maintenance therapy in symptomatic patients with COPD and prompt TT following an exacerbation

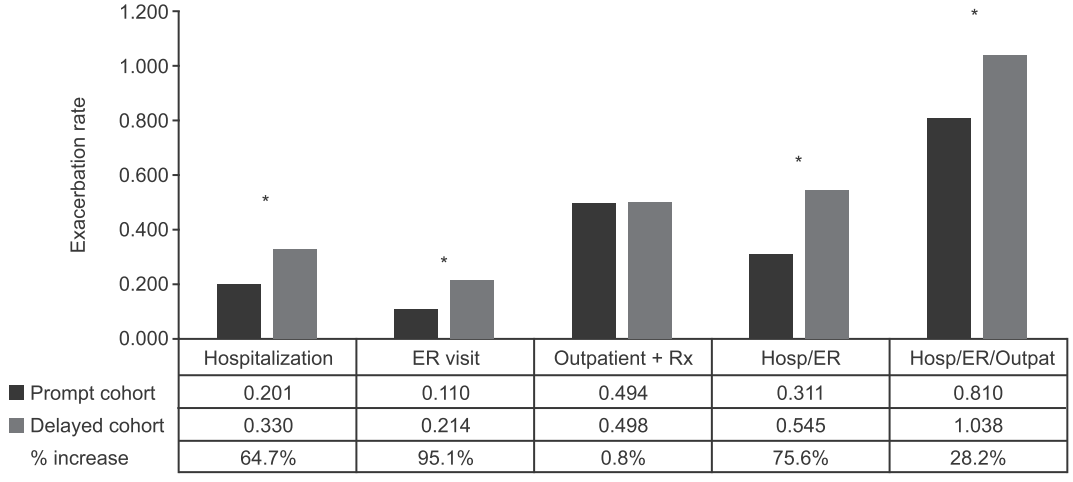

Fig. 3. Exacerbation rates (adjusted) in the Prompt and Delayed cohorts.
*p < 0.0001; all costs data are reported to 3 significant figures; COPD, chronic obstructive pulmonary disease; ER, emergency room, Hosp, hospital; Outpat, outpatient; Rx, prescription.

requiring hospitalization or ED visit, as demonstrated by the present study. In addition, even though dispensing of a bronchodilator within 30 days of an acute inpatient discharge or ED visit for COPD is recommended by the National Committee for Quality Assurance [6] as providing good quality of care, a previous study has shown that fewer than 50% of patients receive a bronchodilator within 45 days of discharge following hospitalization for COPD [16]. Our analysis supports that TT use when indicated, should be initiated within, 30 days of a COPD-related hospitalization or ED visit, similar to the bronchodilator use recommended by the National Committee for Quality Assurance.

Previous reports have demonstrated that COPD is a major cost driver to the US healthcare system [17] and COPD-related hospitalizations make up the largest percentage of COPD-related spending [18]. This is supported by the findings of the present study, which demonstrated high costs and number of exacerbations in the Delayed cohort, and by previous studies showing that increasing exacerbation frequency is associated with an increase in all-cause and/or COPD-related costs [19,20]. One study reported an increase in all-cause costs and COPD-related medical costs from $21,771 and $301, respectively in patients with zero exacerbations to $47,061 and $7,209, respectively in patients with ≥3 exacerbations [19]. In another study, the total COPD-related costs per patient per year increased with each exacerbation, from £1,523 for the first exacerbation to £2,405 for the second and £3,396 for the third [20]. Therefore, a reduction in the number of future COPD-related events, possibly via the initiation of TT promptly following a COPD-related hospitalization or ED visit, could significantly lower the cost burden to the US healthcare system.

This observational study evaluated real-world costs in a large representative sample of patients with COPD. However, this study has several limitations. Firstly, as the classification of cohorts was based on Rx fill date, patients in the Delayed cohort who initiated TT during hospitalization or who may have received free samples may have been misclassified. This misclassification would have reduced the treatment effect leading to a conservative estimate of the impact of prompt initiation of TT. Secondly, claims data can lack clinical and patient characteristics data, and Rx data are based on fill dates. This circumstance can limit the assessment of COPD severity and the accurate initiation of TT by physicians not captured in pharmacy data. Thirdly, although the analyses used IPTW to minimize any selection bias, some residual confounding may be present leading to the possibility that differences in cost and exacerbations are due to underlying differences in the health status of the cohorts rather than to the timing of TT initiation. Nevertheless, if patients with more severe disease are more likely to initiate TT in the first 30 days, the study's results would be expected to be conservative estimates. In addition, as COPD-related costs were defined as costs of claims with a primary diagnosis of COPD, this may have underestimated the costs incurred due to COPD. However, this would have affected both cohorts similarly. As this study was designed to assess costs and effectiveness and not safety, adverse events such as pneumonia and major adverse cardiovascular events were not formally identified a priori to be assessed. Differences in these endpoints between the prompt and delayed cohorts would not be expected to differ. The incidence of these events has been reported in previously published clinical trial data evaluating TT [5,11,13]. Finally, these results can only be generalized to patients with COPD who are TT-naïve, who received TT for the first time after a COPD-related hospitalization or ED visit for an exacerbation and who are insured through employer sponsor plans. Therefore, these data may not be applicable to patients with COPD in Medicare or Medicaid.

5. Conclusions

This retrospective, observational study using claims data suggests that in patients who receive TT after a COPD-related hospitalization/ED visit, prompt initiation may be beneficial compared with delayed initiation by reducing the number of future COPD-related events and the overall economic impact of the condition. Future studies to assess the impact of TT use after a COPD-related event may be warranted.

Clinical relevance statement

Triple therapy (TT) is defined as treatment with an inhaled corticosteroid (ICS) combination with a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), administered using single or separate inhalers. Although TT is the recommended treatment option in patients with chronic obstructive pulmonary disease (COPD) who have persistent symptoms or high exacerbation risk according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 strategy document, the benefit of prompt initiation of TT following a severe COPD exacerbation relative to delayed treatment is unknown. This retrospective, observational study demonstrates that initiating TT early (within 30 days) following a COPD-related hospitalization or emergency department visit may reduce all-cause and COPD-related costs (total, medical and prescription) and subsequent exacerbations compared with delaying therapy.

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Disclosures

The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors. MB and RHS are employees of GSK and own stocks/shares in GSK. MBG was previously a fellow at GSK (employed by University of North Carolina [UNC]) and is now an employee of Ethicon (a subsidiary of Johnson & Johnson). TR is a post-doctoral fellow at GSK and employed by UNC at Chapel Hill. MBG and TR did not receive any direct compensation related to the development of this manuscript.

Author contributions

RHS and MBG contributed to the conception and design of the protocol, MBG and MB contributed to the data acquisition, and all authors contributed to the analysis and interpretation of the data. All authors were involved in preparation and review of the manuscript and approved the final version to be submitted.

Data statement

GSK makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2018.10.013.

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