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Role of Tiotropium in Reducing Exacerbations of Chronic Obstructive Pulmonary Disease When Combined With Long-Acting β_2-Agonists and Inhaled Corticosteroids: The OUTPUL Study

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Abstract

Combined inhaled therapy in chronic obstructive pulmonary disease (COPD) is commonly used, but its benefits remain controversial. We assessed the effect of tiotropium in reducing COPD exacerbations when combined with long-acting β_2 agonists (LABA) and/or inhaled corticosteroids (ICS). This new-user cohort study is based on administrative data from 3 Italian regions. We identified adults hospitalized for COPD from 2006 to 2009 who were newly prescribed a fixed LABA/ICS combination (double therapy). We classified patients according to whether tiotropium was also prescribed (triple therapy), using both intention-to-treat and as-treated approaches, and followed them for 1 year. COPD exacerbations were measured as outcomes. Multivariate and propensity score-adjusted hazard ratios (HRs, 95%CI) were calculated with Cox regression models. We identified 5717 new users of LABA/ICS of which 31.9% initiated triple therapy. In the intention-to-treat analysis, the multivariate adjusted HR for moderate, severe, and any exacerbations were 1.02 (95%CI 0.89-1.16), 0.92 (95%CI 0.76-1.12), and 1.08 (95%CI 0.91-1.28), respectively. The propensity score adjustment produced similar results. In the subcohort of patients with previous exacerbations, triple therapy was significantly associated with reduced risk of moderate exacerbations, compared to double therapy (HR 0.68, 95%CI 0.48-0.98 in intention-to-treat approach). In conclusion, the addition of tiotropium to LABA/ICS did not reduce COPD exacerbations compared to LABA/ICS alone. A protective role for moderate exacerbations was found in patients at risk of frequent exacerbations. Given the impact of exacerbations on health status and prognosis, it is crucial to target COPD patients for optimal treatment.

Keywords

chronic obstructive pulmonary disease, exacerbation, tiotropium, comparative effectiveness, inhaled therapy

For patients with chronic obstructive pulmonary disease (COPD), guidelines suggest a stepwise treatment approach using a combination of long-acting β_2 agonists (LABA) and inhaled corticosteroids (ICS). This approach is shown to improve lung function and quality of life and to reduce the risk of exacerbations.[1–5] For patients with severe COPD, guidelines recommend the use of an additional long-acting bronchodilator with the LABA/ICS treatment. Tiotropium, a long-acting muscarinic receptor antagonist, was shown to reduce exacerbations and improve quality of life and lung function compared to a placebo.[6]

Triple therapy (tiotropium plus LABA/ICS) is widely used by physicians to manage COPD, but this practice has limited scientific support. Although the benefits of tiotropium, LABA, and ICS have been extensively studied independently, the short- and long-term effects of the triple combination therapy on disease outcomes are not well established. Clinical trials assessing the efficacy of triple therapy compared

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to control groups show controversial results.[7–9] Recently, systematic reviews have indicated the need for longer-term studies to provide stronger evidence of the benefits of triple therapy.[10–12] Although this aim can be readily addressed with observational studies, methodological issues (including patient selection, adjustment methods, and study design) must be considered to avoid potential biases that can affect internal validity.[13] In particular, time-related biases may amplify the observed benefits of a drug.[14]

Recently, patients with frequent exacerbations have been recognized as a distinct clinical subgroup, the "frequent exacerbator" phenotype, that is associated with poorer health outcomes.[15] Due to the complexity of the pathophysiology underlying the frequent exacerbator phenotype, this subgroup is a priority for research and treatment.[16]

To our knowledge, only 1 observational study has assessed the effectiveness of tiotropium added to LABA/ICS in patients with COPD. Triple therapy was found to reduce all-cause mortality and exacerbations; however, as stated by the authors, this finding should be treated with caution.[17] The aims of the present study are (1) to evaluate the role of tiotropium in reducing exacerbations in a large cohort of patients with COPD treated with LABA/ICS and (2) to test the hypothesis of an effect modification of the history of previous COPD exacerbations. To strengthen the validity of results, multiple analytical strategies and several sensitivity analyses were applied.

Methods

Sources of Data

Regional health information systems from 3 large regions in Italy, Emilia Romagna, Lombardia, and Lazio (about 19 million residents), were used for this study: Hospital Information Systems (HIS) (ICD-9-CM codes of the International Classification of Diseases), Drug Registers (PHARM), and Mortality Registers. For Lazio region, information from the Emergency Information System (EIS) was also available. Details on these data sets have been described elsewhere.[18] Drugs dispensed to patients, which are reimbursable by the National Health Service, the Italian universal coverage healthcare system, are identified by the national drug register code, accordant with the international Anatomical Therapeutic Chemical (ATC) classification. The following information was available for each prescription: patient identification number, ATC code, number of packs, number of units per pack, dosage, unit cost per pack, and prescription date. In compliance with the national law on privacy, records were linked using an anonymous key.

Population

A standardized algorithm was used to identify patients aged ≥45 years who were discharged with a diagnosis of acute exacerbation of COPD between 2006 and 2009 from the HIS of the 3 regions in Italy.[19,20] We selected hospital discharges with COPD as the main diagnosis (ICD 9 CM codes 490, 491, 492, 494, 496) or secondary diagnosis with a main diagnosis of acute respiratory failure (ICD 9 CM codes 518.81-518.84), dyspnea (786.0), cough (786.2), or abnormal sputum (786.4). In cases with multiple COPD admissions, the first admission was used. Patients were enrolled who received at least 1 prescription of a fixed LABA/ICS combination (ATC code R03AK06, R03AK07) within 6 months of discharge.

Only new users, those patients without a previous prescription for LABA, ICS, or tiotropium (ATC code R03BB04), were included, with a washout period of 6 months. The definition of "new users" and ATC codes can be found in Supplementary Table S1.

Study Design and Exposure Definition

Two analytical approaches were used to assess the role of tiotropium in reducing COPD-exacerbations (Figure 1). In the intention-to-treat (ITT) approach, patients were classified as receiving triple or double therapy (ie, LABA/ICS with or without tiotropium, respectively), based on index date exposure (ie, date of the first fixed LABA/ICS prescription). In the as-treated approach, the exposure was classified at the index date and tracked throughout the follow-up period. Drug exposure was measured in terms of defined daily doses (DDD). The number of DDD was converted to the number of days the patient was treated, counting 1 DDD per day and distributing all available DDDs to days of follow-up (including the days covered by the last prescription). At the end of the exposure period (ie, when all available DDDs were expired), a renewal time of 30 days (ie, grace time) was applied during which the patient was considered "exposed" without being censored for discontinuation.[20,21] In the case of switching, a 7-day grace time was used to limit the potential misclassification of exposure accounting for the 5- to 6-day half-life of tiotropium terminal elimination.[22]

Demographic and Clinical Characteristics

The following patient characteristics were assessed: (1) proxy of COPD severity based on 12 months of information from HIS and PHARM registries, (2) concomitant respiratory disease based on 24 months of HIS data, (3) comorbidities based on 24 months of HIS information, and (4) prescriptions of respiratory and nonrespiratory drugs based on 6 months of

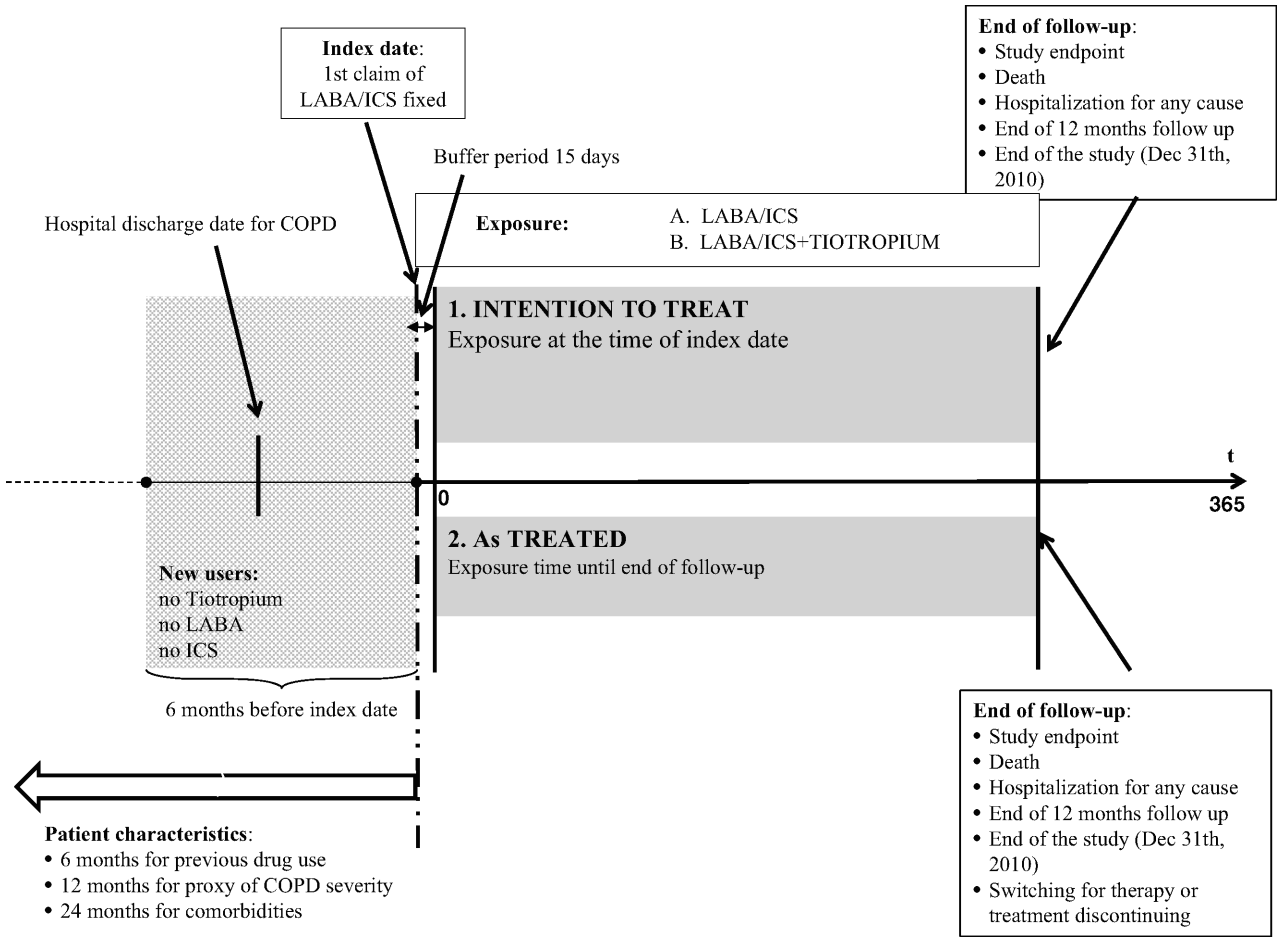

Figure 1. Study designs: (1) intention-to-treat and (2) as-treated approaches. LABA, Long acting beta 2 agonists; ICS, Inhaled corticosteroids.

PHARM information. Details on codes are reported in Supplementary Tables S2-S5.

Endpoints and Follow-Up

COPD-related acute exacerbations were defined as events that require acute pharmacological treatment (ie, oral corticosteroid and antibiotics) or a hospital admission.[7,23–26] The study endpoint, the first observed COPD-related acute event, was recorded and classified as follows:

1. "Moderate COPD exacerbation" refers to an event that requires both oral corticosteroids and antibiotics. (ATC codes H02AB and J01), prescribed within 15 days of the event.
2. "Severe COPD exacerbation" refers to a COPD hospitalization assessed with the criteria used for case identification.
3. "Any exacerbation" means moderate or severe exacerbation.

We started counting the person-years on the 15th day of follow-up (buffer period) to allow for the biologic action of the medication to occur (Figure 1). In the ITT approach, each patient was followed for 12 months after the index date until a study endpoint was observed, death or the end of the study (December 31, 2010), whichever came first. In the as-treated approach, censoring was applied if there was a switch or discontinuation of the index medication. In both analytical approaches, a lack of information on drug exposure during the first hospitalization (for any reason) resulted in the interruption of follow-up. Details on the as-treated approach are reported in Supplementary Figure S1.

Statistical Analysis

The incidence rate for the first episode of moderate, severe, or any exacerbation was calculated as the number of patients who experienced an event divided by the person-years at risk. To develop the predictive model, each variable measured at baseline in a backward stepwise procedure was included, discarding variables not associated with the outcome.

To balance measured risk factors for the outcome between drug user groups, the propensity scores of

initiating triple vs double therapy were estimated with a logistic regression model, including all characteristics potentially associated with the exposure: sociodemographic factors, proxies of COPD severity, concomitant respiratory diseases, comorbidities, and previous use of respiratory and nonrespiratory drugs.[27,28]

To test the role of tiotropium in reducing exacerbations, multivariate analysis with Cox proportional hazard models was performed to determine the hazard ratio (HR) and 95% confidence interval (95%CI). The models were run separately, adjusting for (1) characteristics resulting from the predictive model and (2) indicators of propensity score quintiles following standardized techniques.[13,28,29]

After testing a potential interaction between drug exposure and proxies of COPD severity, an analysis was conducted among the subcohort of COPD patients with previous 12-month exacerbations (both moderate or severe). Statistical significance was set at $P < .05$ for main effects and $P < .10$ for interactions.

Sensitivity Analysis

Several sensitivity analyses were performed. First, the ITT analyses were rerun with an exposure definition based on the information collected on the index day and the 4 subsequent days to account for drugs that are not readily available in pharmacies. Second, 2 different intervals, 7 and 15 days, were considered as grace time for treatment discontinuation in the as-treated approach.[30,31] Third, the analysis for the subcohort of patients in the Lazio region was rerun using (1) a broader definition of the outcome "any exacerbation" by including information (COPD related ICD-9-CM codes at emergency visits) registered in the EIS (available only in the Lazio region), and (2) a broader definition of COPD severity by including the variable "use of liquid oxygen" (available only in the Lazio region).

Statistical analyses were performed using SAS 9.2.

Results

From January 1, 2006 to December 31, 2009, we selected 68,795 patients with COPD hospital discharges. Of these, 26,197 (38.1%) had at least 1 prescription of fixed LABA/ICS combinations, and 5717 (21.8%) were classified as new users.

The demographic characteristics of the study population, stratified by treatment regimen, are shown in Table 1. Most patients were male (56.5%) and residents of the Lombardia region (46.8%). The mean age of the population was 73.8 (SD = 10.7) years, and 31.9% (n = 1821) had received triple therapy.

Univariate analyses showed that the double- and triple-therapy groups were similar in the proxy of COPD severity variables except for the diagnosis of respiratory failure and the concomitant use of oral corticosteroids and antibiotics. In general, patients with double therapy were more likely than those with triple therapy to have comorbidities, particularly ischemic heart disease, cerebrovascular disease, and psychiatric diseases. Use of respiratory drugs was comparable between the 2 groups, except for xanthines. Patients with triple therapy appeared to receive fewer treatments than those with double therapy for nonrespiratory diseases such as cardiac therapies, antiplatelets, and antihypertensives. For each patient, we calculated the expected probability of being treated with triple therapy, adjusting for all characteristics measured at baseline. There was a reasonably large overlap in the distribution of propensity scores between treatment groups. Box plots displaying the expected probability of being treated with triple therapy can be found in Supplementary Figure S2. The adjusted *P*-values are reported in Table 1.

The predictive model for any exacerbation, calculated according to the ITT approach, providing the HR and relative 95%CI for each condition, is shown in Figure 2. As expected, variables defined as a proxy of COPD severity were most highly associated with the outcome. The only variable with a protective effect was the use of antihypertensive drugs in the previous 6 months. When we considered severe and moderate exacerbations separately, other variables were identified in the predictive model. In particular, severe exacerbations were positively associated with the use of cardiac drugs and statins, previous hospitalization for heart failure, and other chronic heart diseases. For moderate exacerbations, treatment with antidiabetic drugs had a protective effect (data not shown).

Table 2 shows each study outcome rate and HR for patients who received triple therapy vs double therapy. The overall rates of moderate, severe, and any exacerbations were 13.7, 13.4, and 26.3, per 100 person-years, respectively. The rates did not differ considerably between the 2 treatment regimens. In the ITT analysis the adjusted HRs for moderate, severe, and any exacerbations were: 0.92 (95%CI 0.76-1.12), 1.08 (95%CI 0.91-1.28), and 1.02 (95%CI 0.89-1.16), respectively. The as-treated analysis produced consistent results. In particular, for moderate exacerbations HR 0.93 (95%CI 0.98-1.29), severe exacerbations HR 1.13 (95%CI 0.82-1.55), and any exacerbation HR 0.95 (95%CI 0.74-1.22). For both the ITT and as-treated approaches, the adjustments based on propensity scores led to similar results.

Table 3 shows each study outcome rate and HR for patients who received triple therapy vs those who received double therapy in the subcohort of patients with a history of 12 months previous exacerbations

Table 1. Characteristics of the Study Population According to Therapy (Double and Triple): OUTPUL Study 2006-2009

	Long-Acting β_2 Agonists and Inhaled Corticosteroids[a] (n = 3896)	Long-Acting β_2 Agonists and Inhaled Corticosteroids[a] Plus Tiotropium (n = 1821)	*P*-Value	Adjusted *P*-Value[b]
Residence (region)				
Lazio	26.3	29.2	0.077	0.930
Emilia Romagna	29.1	19.2		
Lombardia	44.6	51.6		
Age (years)				
45-54	5.1	5.5	<.001	.748
55-64	13.2	17.5		
65-74	26.3	31.1		
75-84	37.6	33.8		
85+	17.8	12.0		
Sex				
Male	54.3	61.1	<.001	.725
Female	45.7	38.9		
Proxy of COPD severity (previous 12 months)				
Previous COPD hospitalization	7.8	7.7	.880	.588
Concomitant use of oral corticosteroids and antibiotics	10.5	8.5	.018	.100
Diagnosis of respiratory failure	42.1	51.9	<.001	.506
Invasive respiratory procedures	2.9	2.9	.925	.340
Staying in intensive care unit during a COPD hospitalization	3.0	3.6	.235	.737
Oxygen therapy (gas)	5.3	4.3	.135	.151
Concomitant respiratory diseases (previous 24 months)				
Asthma	1.8	1.3	.166	.153
Chronic respiratory disease other than COPD	3.4	3.3	.901	.588
Pulmonary infections	11.3	12.3	.281	.446
Acute pulmonary symptoms	3.4	3.2	.654	.614
Apnea	2.1	2.9	.061	.545
Comorbidities (previous 24 months)				
Diabetes	17.4	18.9	.143	.113
Hypertension	39.8	39.2	.637	.150
Ischemic heart disease	17.0	14.8	.035	.321
Heart failure/pulmonary heart disease	18.2	18.2	.994	.701
Other chronic heart diseases	10.0	8.4	.057	.090
Arrythmia	15.6	13.8	.081	.927
Cerebrovascular diseases	11.3	9.2	.015	.288
Peripheral vascular diseases	5.7	5.4	.574	.650
Obesity, dyslipidemia	9.4	11.8	.005	.714
Liver disease	4.3	3.7	.349	.950
Other chronic digestive disease	1.3	1.5	.598	.678
Chronic renal diseases	7.9	7.4	.471	.934
Neurological and muscle disease	2.8	2.5	.556	.874
Anemia and coagulation disorders	4.7	3.4	.028	.161
Thyroid disease	5.3	4.8	.421	.748
Depression	3.2	2.1	.032	.149
Psychiatric disease	4.4	2.3	<.001	.457
Peptic ulcer/esophageal reflux	1.4	1.2	.638	.410
Rheumatologic/diffuse disease of connective tissue	1.2	0.5	.023	.078
Prescriptions of respiratory drugs (previous 6 months)				
Short-acting β_2 agonists	7.7	6.3	.065	.118
Short-acting anticholinergics	3.3	2.6	.125	.236
Xanthines	13.6	10.9	.004	.889
Prescriptions of nonrespiratory drugs (previous 6 months)				
Cardiac therapies	27.5	22.6	<.001	.247
Antidiabetic drugs	16.6	16.6	.995	.802
Antiplatelets	37.4	32.2	<.001	.856
Antihypertensives	71.1	64.6	<.001	.784
Statins	15.6	16.9	.218	.128

[a] Fixed combination.

[b] Adjusted for the quintiles of the propensity score.

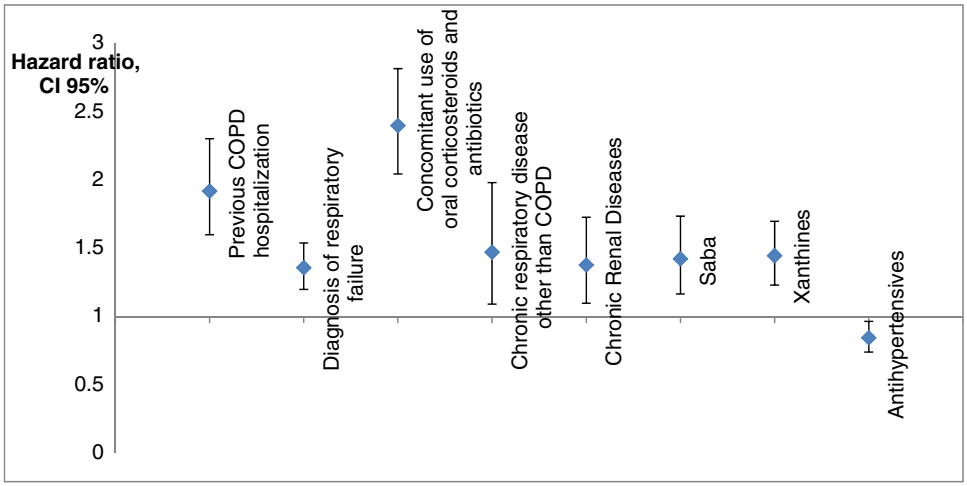

Figure 2. Predictive model for any exacerbation calculated with the intention-to-treat approach.

Table 2. Rates and Hazard Ratios (HRs, CI95%) for Moderate, Severe, and Any Exacerbations in COPD Patients with Triple Therapy vs Those With Double Therapy, Using 2 Different Study Designs[a]

	Intention to Treat									As Treated								
				Adjusted With Predictive Model			Adjusted With Propensity Score Index						Adjusted With Predictive Model			Adjusted With Propensity Score Index		
	N	Person Years	Rate per 100 PY[b]	HR	95%CI		HR	95%CI		N	Person Years	Rate per 100 PY[b]	HR	95%CI		HR	95%CI	
Moderate exacerbation	533	3878	13.7							185	1154	16.0						
Fixed LABA/ICS[c]	385	2668	14.4	1.00	-	-	1.00	-	-	146	857	17.0	1.00	-	-	1.00	-	-
Fixed LABA/ICS plus tiotropium	148	1209	12.2	0.92	0.76	1.12	0.92	0.76	1.12	39	297	13.1	0.93	0.98	1.29	0.98	0.71	1.36
Severe exacerbation	598	4476	13.4							190	1296	14.7						
Fixed LABA/ICS[c]	388	3054	12.7	1.00	-	-	1.00	-	-	135	957	14.1	1.00	-	-	1.00	-	-
Fixed LABA/ICS plus tiotropium	210	1421	14.8	1.08	0.91	1.28	1.11	0.93	1.31	55	338	16.3	1.13	0.82	1.55	1.11	0.80	1.53
Any exacerbation	1020	3878	26.3							342	1154	29.6						
Fixed LABA/ICS[c]	696	2668	26.1	1.00	-	-	1.00	-	-	257	857	30.0	1.00	-	-	1.00	-	-
Fixed LABA/ICS plus tiotropium	324	1209	26.8	1.02	0.89	1.16	1.04	0.91	1.19	85	297	28.6	0.95	0.74	1.22	0.99	0.77	1.27

[a]OUTPUL study 2006-2009 (n = 5717).
[b]PY, person years.
[c]LABA, long-acting β_2 agonists; ICS, inhaled corticosteroids.

(n = 945). The overall rates of moderate, severe, and any exacerbation were 35.4, 23.8, and 58.0 per 100 person-years, respectively. Triple therapy was significantly associated with reduced risk of moderate exacerbations compared to double therapy (HR 0.68, 95%CI 0.48-0.983 for ITT approach; HR 0.46, 95%CI 0.23-0.93 for as-treated approach).

In the first sensitivity analysis, we used a 4-day time window (instead of only the index day) to define drug exposure in the ITT approach. This analysis produced results consistent with those mentioned above. The second analysis, applying 7- and 15-day grace time for drug discontinuation in the as-treated approach, showed similar association patterns. However, the numbers of person years (drug exposure) and of outcome events were smaller than in the main analysis, and no statistically significant results were found (Supplementary Tables S6 and S7). Third, an analysis of the subcohort of the Lazio region produced a higher overall rate of any exacerbation (33.4%), but it did not modify the HR (1.09, 95%CI 0.86-1.37). For this analysis, emergency department visits were added to the definition of exacerbation events. In the last sensitivity analysis, the effect of liquid oxygen as a predictive

Table 3. Rates and Hazard Ratios (HRs, 95%CI) for Moderate, Severe, and Any Exacerbations in COPD Patients With Triple Treatment, Those With Double Therapy, Using 2 Different Study Designs[a]

	Intention to Treat									As Treated								
				Adjusted With Predictive Model			Adjusted With Propensity Score Index						Adjusted With Predictive Model			Adjusted With Propensity Score Index		
	N	Person Years	Rate per 100 PY[b]	HR	95%CI		HR	95%CI		N	Person Years	Rate per 100 PY[b]	HR	95%CI		HR	95%CI	
Moderate exacerbation	185	522	35.4							73	183	39.9						
Fixed LABA/ICS[c]	144	361	39.9	1.00	-	-	1.00	-	-	63	135	46.7	1.00	-	-	1.00	-	-
Fixed LABA/ICS plus tiotropium	41	161	22.5	0.68	0.48	0.98	0.65	0.46	0.93	10	48	20.8	0.46	0.23	0.93	0.47	0.24	0.93
Severe exacerbation	158	664	23.8							58	217	26.7						
Fixed LABA/ICS[c]	107	461	23.2	1.00	-	-	1.00	-	-	42	161	26.1	1.00	-	-	1.00	-	-
Fixed LABA/ICS plus tiotropium	51	203	25.1	0.99	0.70	1.40	0.97	0.69	1.37	16	56	28.6	1.14	0.63	2.09	1.14	0.63	2.06
Any exacerbation	303	522	58.0							118	183	64.5						
Fixed LABA/ICS[c]	223	361	61.8	1.00	-	-	1.00	-	-	96	135	71.1	1.00	-	-	1.00	-	-
Fixed LABA/ICS plus tiotropium	80	161	49.7	0.79	0.60	1.03	0.78	0.60	1.02	22	48	45.8	0.63	0.39	1.02	0.67	0.50	1.09

[a]Subcohort of patients with previous COPD exacerbations (n = 945).

[b]PY, person years.

[c]LABA, long-acting β_2 agonists; ICS, inhaled corticosteroids.

variable for exacerbation was tested. This variable was found to be highly associated with any exacerbation. Its inclusion in the predictive model produced a reduction of the effects of the other variables considered to be proxies of COPD severity without modifying the HR of triple therapy vs double therapy for any exacerbation (1.06, 95%CI 0.81-1.38).

Discussion

This study included a large cohort of individuals discharged with a diagnosis of COPD exacerbation to represent patients with moderate to severe COPD and evaluated the effect of tiotropium on COPD exacerbations over the following 12 months. Consistently, no evidence was found of increased benefit associated with its addition to the fixed combination of LABA/ICS. Analyses suggest a protective role for moderate exacerbation in the subgroup of COPD patients with a history of 12 months of previous exacerbations.

COPD exacerbations are episodes in the natural course of the disease characterized by worsening of respiratory symptoms.[1,32] These events are indicative of the health status in COPD patients and are independent predictors of disease progression and mortality.[32,33] In most cases, exacerbations are triggered by viral infections, especially rhinovirus, the cause of the common cold. Therefore, preventing COPD exacerbations is crucial for disease management.[1,32] Anti-inflammatory drugs, including inhaled corticosteroids, have proven effective in reducing the frequency and severity of exacerbations, while bronchodilators reduce dynamic hyperinflation.[34] Tiotropium, a long-acting, specific, muscarinic receptor antagonist or anticholinergic drug was approved by the Food and Drug Administration in 2004 as an anticholinergic bronchodilator. It has been widely used in clinical practice over the last decade and is considered a first-line agent for COPD patients.[1] In the large UPLIFT trial, tiotropium was found to be associated with a reduction in exacerbation risk.[8] In the POET-COPD trial, tiotropium was more effective than salmeterol in preventing exacerbation.[35] The lack of evidence on the impact of tiotropium when added to LABA/ICS, a treatment previously proven to be effective, highlights the need to assess its role in real practice.[10–12] LABA and tiotropium are known to have distinct bronchodilator mechanisms and have exhibited a synergistic action in reducing bronchial tone.[36,37] The beneficial bronchodilator effect of this combination compared to tiotropium alone or LABA/ICS alone has also been demonstrated in recent large clinical trials.[38,39] However, these studies only assessed pulmonary function (ie, forced expiratory flow in the first second, FEV_1) and did not measure any patient-centered outcomes.

In our study, the addition of tiotropium to LABA/ICS did not affect the risk of new exacerbations in comparison to fixed LABA/ICS among patients with

moderate or severe COPD in the 12 months following discharge. This finding supports the hypothesis of the importance of anti-inflammatory treatments, such as ICS combined with LABA, and a lack of an increased effect of the double therapy with the addition of the antimuscarinic or anticholinergic action of tiotropium. A distinct group of COPD patients has been recognized as more susceptible to exacerbations ("frequent exacerbator phenotype"). However, the complex pathophysiology is not fully understood.[15] Our study suggests a major effect of LABA/ICS with tiotropium, in comparison to double therapy, for preventing moderate exacerbations among patients with a history of frequent exacerbations. This finding contributes to the complex ongoing debate on this COPD subgroup. The lack of evidence of a higher effect of triple therapy in comparison to LABA/ICS on severe exacerbations (ie, those requiring hospitalization) can be attributed to the large heterogeneity of COPD exacerbations involving multiple interacting factors. For example, cardiovascular comorbidity and environmental pollution may play a role in worsening COPD symptoms and subsequent hospitalizations through mechanisms that remain unclear.[40,41]

To the best of our knowledge, only one retrospective study measured patient-centered outcomes with electronic healthcare data bases, demonstrating a beneficial effect of tiotropium in conjunction with ICS plus LABA on the COPD exacerbation rate.[17] However, Short et al highlight a number of limitations that may have affected their results. Most importantly, the absence of an accurate definition of exposure, essential for the research topic, can produce time-related biases that can lead to an overestimation of the drug's beneficial effect.[14,17]

In the present study the risk influence of previous treatments on the outcome was minimized by restricting the cohort to new users.[42] Moreover, 2 adjustment techniques were applied to control for confounding; each provided information about the association between the treatment and a COPD exacerbation. In the predictive model, adjustments were performed for the factors most strongly associated with the outcome. The propensity score was used to balance factors that could influence the treatment choice.

Patients taking other respiratory drugs, such as short-acting β agonists and xanthines, were used as a proxy for increased disease severity and were found to have the highest risk of COPD exacerbation. In accordance with results of previous studies, the use of antihypertensive drugs was protective, but their role remains unclear.[23,43] For moderate exacerbations, antidiabetics showed a protective effect. In this case the effect could be explained by an underestimation of the outcome due to the contraindicated use of oral corticosteroids in patients with diabetes.[44] To apply the propensity score adjustment, we calculated the distribution of the probability of receiving a given treatment. Unexpectedly, this analysis did not identify any factors, even for variables related to COPD severity, which are strong predictors of treatment choice. This result may reflect the absence of an indication bias. Alternatively, despite our testing of variables used in previous studies, some variables associated with treatment choice that correlated with patient characteristics and physician preferences may have been omitted. Nevertheless, when information on the use of liquid oxygen for the subcohort of Lazio region was included as a proxy for COPD severity, the results were consistent with those obtained in our main analysis.

The comparability between the 2 treatment groups in terms of COPD severity is critical in this type of study. In theory, triple therapy should be given only when double therapy is no longer effective. Guidelines for COPD management suggest a stepwise treatment approach, which accounts for disease progression.[1] Patients in a stable clinical condition with no previous use of respiratory drugs are not expected to benefit from the addition of tiotropium to LABA/ICS compared to LABA/ICS alone. In the present study the 2 treatment groups were not substantially different in terms of COPD severity. Therefore, a possible interpretation of our results could be that the choice of triple or double therapy might have been random, based on the physician's preferences. Alternatively, it may have been based on clinical criteria that we are unable to measure. Testing the added value of a drug in a cohort of patients who are currently in treatment remains a challenge in pharmacoepidemiology due to the difficulty of measuring a possible carryover effect.

To avoid misclassification of exposure, a typical issue in observational studies, we tested 2 different approaches. The number of days in which the patient was treated was measured on the basis of DDDs with potential misclassification of exposure because the pharmaceutical data base used in this study does not include information on prescribed daily doses.[45] The ITT approach measures the exposure at the index date; thus, all outcomes that occur in the follow-up period are associated with the index date. The as-treated approach accounts for switching therapy and therapy discontinuation during the follow-up period. However, both switching and discontinuation might be predictors of adverse health outcomes due to drug intolerance or treatment failure, which may have led to informative censoring.[20,21] To limit this potential bias, a 30-day grace period for drug discontinuation was applied, according to previous studies.[21,28] Sensitivity analyses for varying lengths of grace periods (7 or 15 days) were also performed; it is worthy of note that lower grace

time intervals lead to smaller exposure time and lower number of outcome events and may limit the statistical power in the detection of an effect.

Another limitation of this study was the difficulty in measuring the outcome. Exacerbations may require hospitalizations, but in less severe cases, they may not require any use of health resources, which may have underestimated the number of moderate exacerbations. However, a previously used event-based definition of COPD exacerbation was used for this study.[7,23–26] When drug prescriptions were used to define the outcome, we attempted to define the prescriptions as specifically as possible, including only combined prescriptions of antibiotics and oral corticosteroids filled within 15 days of the event. Nevertheless, this definition did not account for patients who might have stored drugs at home as a stand-by therapy, in which case there would be no need to fill the prescription in case of an acute exacerbation. Furthermore, for the subcohort in the Lazio region, emergency department visits for COPD were used to assess the "any exacerbation" outcome. The sensitivity analysis showed that this inclusion did not change the results compared to the main analysis.

In conclusion, our results suggested that tiotropium added to fixed a LABA/ICS combination did not reduce COPD exacerbations within a 1-year follow-up period compared to LABA/ICS alone among patients discharged after a COPD exacerbation. Among those with a history of frequent exacerbations, LABA/ICS in conjunction with tiotropium shows a greater effect in preventing moderate exacerbations compared to double therapy. Findings from this type of observational study could have an impact on the management of patients with COPD in current clinical practice. Given the complex pathophysiology of exacerbations and their role on prognosis, targeting COPD patients for appropriate therapy is crucial.

Declaration of Conflicting Interests

The authors report no conflicting interests.

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Author Contributions

N.A. and R.P. conceived the idea for the study and designed the study in collaboration with E.F. and V.B. V.B., M.D.M., G.F., and S.C. were responsible for acquiring the data. V.B. was responsible for the data analysis, tables, and graphs with input from N.A., S.C., U.K., M.D.M., and D.F. R.P., E.P., M.D., G.F., and C.A.P. contributed to the interpretation of the results. The initial draft of the manuscript was prepared by E.F., V.B., and N.A. and then circulated repeatedly among all authors for critical revision.

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