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ORIGINAL RESEARCH

Tiotropium and Salmeterol in COPD Patients at Risk of Exacerbations: A Post Hoc Analysis from POET-COPD®

Claus F. Vogelmeier · Guus M. Asijee · Katrin Kupas · Kai M. Beeh

ABSTRACT

Introduction: Among patients with chronic obstructive pulmonary disease (COPD), the frequency and severity of past exacerbations potentiates future events. The impact of current therapies on exacerbation frequency and severity in patients with different exacerbation risks is not well known.

Methods: A post hoc analysis of patients at low (≤ 1 exacerbation [oral steroids/antibiotics requirement] and no COPD-related hospitalization in the year preceding trial entry) or high (≥ 2 exacerbations [oral steroids/antibiotics requirement] or ≥ 1 COPD-related hospitalization[s] in the year preceding trial entry) exacerbation risk, from the Prevention of Exacerbations with Tiotropium in Chronic Obstructive Pulmonary Disease (POET-COPD®) database.

Results: Compared with salmeterol, tiotropium significantly increased time to first COPD exacerbation (hazard ratio 0.84; 95% confidence interval [CI] 0.76–0.92; $p = 0.0002$) and reduced the number of COPD exacerbations (rate ratio 0.90; 95% CI 0.81–0.99; $p = 0.0383$) in patients at high exacerbation risk. With treatment, the risk of remaining in the high-risk exacerbator subgroup was statistically lower with tiotropium versus salmeterol (risk ratio [RR] 0.89; 95% CI 0.80–1.00; $p = 0.0478$). For low-risk patients, time to first COPD exacerbation and number of COPD exacerbations were numerically lower with tiotropium versus salmeterol. With treatment, the risk of transitioning from a low to a high exacerbation risk was lower with tiotropium versus salmeterol (RR 0.87; 95% CI 0.71–1.07; $p = 0.1968$).

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Discussion: This analysis confirms the higher efficacy of tiotropium versus salmeterol in prolonging time to first COPD exacerbation and reducing number of exacerbations in patients both at low and high exacerbation risk.
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Keywords: COPD; Exacerbations; POET-COPD®; Tiotropium

INTRODUCTION

Exacerbations have a deleterious effect on the morbidity and mortality of patients with chronic obstructive pulmonary disease (COPD) [1] by increasing hospitalization [2], worsening lung function [3] and health-related quality of life, and decreasing survival [4]. As such, the prevention of exacerbations is an important goal of COPD therapy [5], the importance of which is reflected in the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) document on the management of COPD [6].

The frequency of exacerbations increases in parallel with the severity of COPD [7]. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE®) (ClinicalTrials.gov #NCT00292552) observational study of patients with COPD, exacerbation rate was shown to increase with GOLD staging, such that 22% of patients with GOLD Stage II disease had two or more exacerbations during 1 year of follow-up, whereas 47% of patients with GOLD Stage IV disease had frequent exacerbations over the same period. Across all GOLD stages, the single best predictor of future episodes was prior exacerbations [8]. Additionally, the results from the ECLIPSE study suggested that

patients with COPD could be phenotyped according to their exacerbation risk. Those patients who experienced fewer than two exacerbations per year were classified as "infrequent exacerbators"; those experiencing two or more per year were classified as "frequent exacerbators" and considered to be different phenotypes [8]. More recently, the GOLD 2013 guidelines revisited this classification of patients at risk for exacerbations and divided patients into low ($\leq$1 exacerbations; no severe exacerbations) and high ($\geq$2 or $\geq$1 severe exacerbation) risk categories [6]. The critical difference between these classification systems is that, according to the ECLIPSE classification, one hospitalization (severe exacerbation) would suggest an infrequent exacerbator, whereas it would suggest a high-risk exacerbator according to the new GOLD classification [6, 8].

Few studies have investigated the effect of pharmacotherapy on COPD exacerbations in different subsets of exacerbator phenotype patients. The Prevention of Exacerbations with Tiotropium in Chronic Obstructive Pulmonary Disease (POET-COPD®) (ClinicalTrials.gov NCT00563381) study was a 1-year, randomized, double-blind, double-dummy, parallel-group trial that compared the effect of treatment with the long-acting anticholinergic tiotropium (18 µg via the HandiHaler® device once daily) (SPIRIVA®, Boehringer Ingelheim Pharma and Co. KG, Ingelheim, Germany) with that of the long-acting β_2-agonist (LABA) salmeterol (50 µg via a hydrofluoroalkane-pressurized metered-dose inhaler twice daily) on the incidence of moderate and severe exacerbations in 7376 patients with COPD and a history of exacerbations in the preceding year [9]. The POET-COPD trial showed that, among the total patient population, tiotropium as compared with salmeterol (1) increased the time to the first exacerbation, (2) significantly

increased the time to the first severe exacerbation, and (3) reduced the annual number of moderate or severe exacerbations [9]. However, the impact of tiotropium and salmeterol specifically on patients at low or high risk of exacerbations has not been established.

The current study therefore investigated the effect of tiotropium and salmeterol on exacerbations in patients considered to be at a low or high risk for exacerbations (GOLD guidelines 2014 classification) and frequent/infrequent exacerbators (ECLIPSE study criteria) during a 1-year treatment period in a post hoc analysis of patients in the POET-COPD trial.

METHODS

Study Design

POET-COPD was a 1-year, randomized, double-blind, double-dummy, parallel-group trial that analyzed the effect of tiotropium 18 μg once daily or salmeterol 50 μg twice daily on moderate to severe exacerbations in patients with COPD [9]. The primary endpoint of the trial was time to first moderate or severe exacerbation. Secondary and safety endpoints included time to event, number of events, serious adverse events, and mortality. An exacerbation was defined as an increase in, or new onset of, at least two respiratory symptoms (cough, sputum, dyspnea, wheezing, chest tightness) with at least one symptom lasting for ≥ 3 days and leading the patient's attending physician to initiate treatment with systemic corticosteroids and/or antibiotics (moderate exacerbation) or request hospitalization (severe exacerbation) [8, 10]. Patients receiving fixed-dose combinations of LABAs and inhaled corticosteroids (ICS) switched to ICS

monotherapy (on equal ICS dose) at the start of randomized treatment. All COPD medications, except for anticholinergics or LABAs, were permitted during the double-blind treatment phase. Inclusion criteria were age ≥ 40 years, smoking history ≥ 10 pack-years, diagnosis of COPD (post-bronchodilator forced expiratory volume in 1 s [FEV_1] $\leq 70\%$ predicted and FEV_1/forced vital capacity $\leq 70\%$), and at least one exacerbation in the previous year requiring treatment with systemic steroids and/or antibiotics and/or hospitalization.

Statistical Analysis

The statistical tests were designed to test the hypothesis that tiotropium had a greater efficacy than salmeterol in preventing future exacerbations. Post hoc analyses were performed by the subgroups that were low/high risk at baseline and based on collected COPD characteristics, including hospitalization due to an exacerbation and medication use. A Cox proportional hazards regression model was used for time-to-exacerbation analyses. Hazard ratios (HR) and p values were based on stratified Cox regression with treatment as covariate. Poisson regression correcting for overdispersion and adjusting for treatment exposure and with terms for subgroup and treatment-by-subgroup interaction was used for number-of-event (exacerbations) analyses. The probability of a patient being considered at high risk for exacerbations during 1 year of treatment in the POET-COPD study was analyzed using a log-binomial model adjusting for treatment exposure and with terms for subgroup and treatment-by-subgroup interaction. A post hoc subgroup analysis was conducted to compare patients in each study group who were and were not receiving ICS at baseline. Statistical analyses were conducted

using SAS® version 9.2, SAS Institute Inc. 2009, Cary, North Carolina, USA.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

The baseline characteristics of patients stratified according to low/high exacerbation risk is summarized in Table 1. Except for baseline lung function and baseline ICS use, patients in the low-risk ($n = 2610$) and high-risk ($n = 4284$) groups were balanced. Within the risk subgroups, there were no clinically relevant differences in the baseline characteristics of patients in the tiotropium and salmeterol groups (data not shown).

Time to First COPD Exacerbation

Using the GOLD 2013 risk classification for exacerbations, tiotropium reduced the risk of a COPD exacerbation compared with salmeterol in patients classified as being at high risk or low risk for exacerbations (Fig. 1). A similar pattern was obtained when using the frequent/infrequent risk classification definition. Tiotropium also increased the time to first COPD exacerbation compared with salmeterol in patients classified as being at high risk for exacerbations (HR 0.84; 95% confidence interval [CI] 0.76–0.92; $p = 0.0002$) (Table 2).

Table 1 Baseline characteristics of patients in each risk group

	Low risk ($N = 2610$)	High risk ($N = 4284$)
Age, years	63.4 (8.8)	62.7 (9.1)
Male, n (%)	1946 (74.6)	3220 (75.2)
Smoking status, n (%)		
Ex-smoker	1331 (51.0)	2279 (53.2)
Current smoker	1278 (49.0)	2005 (46.8)
Time since diagnosis of COPD, years	7.4 (6.5)	8.3 (6.8)
Spirometry		
FEV_1, L	1.47 (0.47)	1.37 (0.45)
FEV_1, % predicted	51.1 (13.0)	48.0 (13.3)
Respiratory medication taken at baseline, n (%)		
Anticholinergics	1391 (53)	2342 (55)
ICS	1308 (50)	2411 (56)
Other steroids	43 (1.6)	125 (3)
LABA	1355 (52)	2239 (52)
ICS + LABA (free or FDC)	1097 (42)	1929 (45)

Data are mean (SD) unless otherwise specified
COPD chronic obstructive pulmonary disease, *FDC* fixed-dose combination, *FEV₁* forced expiratory volume in 1 s, *ICS* inhaled corticosteroids, *LABA* long-acting β₂-agonist, *SD* standard deviation
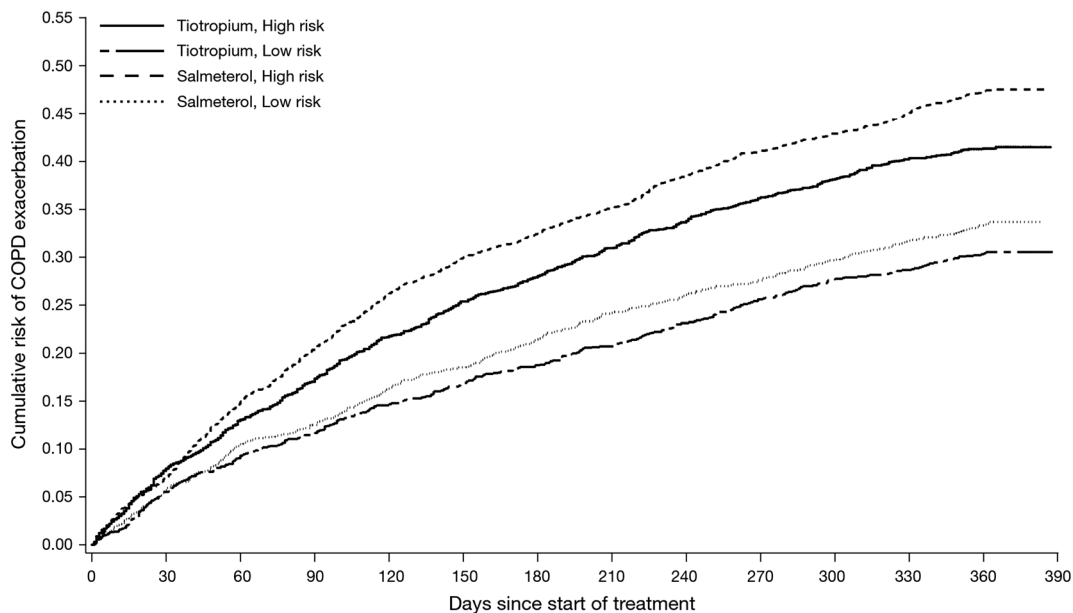
Fig. 1 Cumulative risk of COPD exacerbations on treatment by patient exacerbation risk classification. *COPD* chronic obstructive pulmonary disease

Table 2 Time to first COPD exacerbation by patient exacerbation risk classification

Patient classification	Tiotropium		Salmeterol		Tiotropium vs. salmeterol	
	n	Number of patients with events	*n*	Number of patients with events	HR (95% CI)	*p* value
Low risk	1324	375	1286	402	0.89 (0.77–1.02)	0.1046
High risk	2132	824	2152	993	0.84 (0.76–0.92)	0.0002
Infrequent exacerbator	1531	434	1484	472	0.87 (0.77–0.99)	0.0414
Frequent exacerbator	1878	748	1901	843	0.84 (0.76–0.93)	0.0005

CI confidence interval, *COPD* chronic obstructive pulmonary disease, *HR* hazard ratio

In those patients classified as being at low risk for exacerbations, there was a non-significant increase in time to first COPD exacerbation for tiotropium compared with salmeterol (HR 0.89; 95% CI 0.77–1.02; $p = 0.1046$) (Table 2).

A similar pattern was obtained when using the frequent/infrequent risk classification definition. Tiotropium significantly increased the time to first COPD exacerbation compared with salmeterol in frequent exacerbators (HR 0.84; 95% CI 0.76–0.93; $p = 0.0005$) and

infrequent exacerbators (HR 0.87; 95% CI 0.77–0.99; $p = 0.0414$) (Table 2). Whether or not patients were on background ICS at baseline did not impact these results (Table 3).

Number of COPD Exacerbations (Adjusted Annual Rates)

Tiotropium significantly reduced the number of COPD exacerbations compared with salmeterol in patients classified as being at high risk for

Table 3 Time to first COPD exacerbation by patient exacerbation risk history classification and ICS use at baseline

Patient classification	Tiotropium		Salmeterol		Tiotropium vs. salmeterol	
	n	Number of patients with events	*n*	Number of patients with events	HR (95% CI)	*p* value
Low risk (−ICS)	656	151	646	171	0.85 (0.68–1.06)	0.1415
Low risk (+ICS)	668	224	640	231	0.92 (0.76–1.10)	0.3638
High risk (−ICS)	924	305	949	368	0.81 (0.69–0.94)	0.0054
High risk (+ICS)	1208	519	1203	565	0.85 (0.76–0.96)	0.0086

CI confidence interval, *COPD* chronic obstructive pulmonary disease, *HR* hazard ratio, *ICS* inhaled corticosteroid

exacerbations (rate ratio [RR] 0.90; 95% CI 0.81–0.99; $p = 0.0383$; adjusted annual rates = 0.76 and 0.85 for tiotropium and salmeterol, respectively) (Fig. 2). When using the frequent/infrequent risk classification, there was a borderline significant reduction with tiotropium in the number of COPD exacerbations compared with salmeterol in patients classified as frequent exacerbators (RR 0.90; 95% CI 0.81–1.01; $p = 0.0668$; adjusted annual rates = 0.79 and 0.87 for tiotropium and salmeterol, respectively) and also in the number of COPD exacerbations compared with salmeterol in patients classified as infrequent exacerbators (RR 0.88; 95% CI 0.75–1.02; $p = 0.0881$; adjusted annual rates = 0.48 and 0.55 for tiotropium and salmeterol, respectively) (Fig. 2). In patients classified as being at low risk for exacerbations, there was a borderline significant reduction with tiotropium in the number of COPD exacerbations compared with salmeterol (RR 0.89; 95% CI 0.76–1.05; $p = 0.1768$; adjusted annual rates = 0.48 and 0.54 for tiotropium and salmeterol, respectively) (Fig. 2). The post hoc subgroup analysis comparing both high- and low-risk patients who were or were not receiving ICS at baseline showed similar trends towards tiotropium reducing the number of COPD exacerbations; however, in high-risk

patients receiving ICS at baseline, this was a numerical difference only (Fig. 3).

Treatment-Induced Shifts in Patient Risk Classification

Comparing patients at low versus high risk for exacerbations before and after 1 year's treatment with either tiotropium or salmeterol showed that treatment resulted in a shift in the ratio (low/high exacerbation risk) from 0.62 to 4.98 and from 0.60 to 4.25 for treatment with tiotropium and salmeterol, respectively (Table 4). When using the infrequent versus frequent for exacerbations definition, shifts in the ratio (infrequent/frequent exacerbations) were larger (from 0.82 to 6.44 and from 0.78 to 5.80 for treatment with tiotropium and salmeterol, respectively) (Table 4). The risk of remaining in the high-risk subgroup for exacerbations after 1 year of treatment was statistically lower in the tiotropium group than in the salmeterol group (RR 0.89; 95% CI 0.80–1.00; $p = 0.0478$) (Table 5). The risk of patients who were in the low-risk subgroup for exacerbations in the previous year being considered at high risk for exacerbations after 1 year's treatment was statistically lower in the tiotropium group compared with salmeterol (RR 0.87; 95% CI 0.71–1.07; $p = 0.1968$) (Table 5).
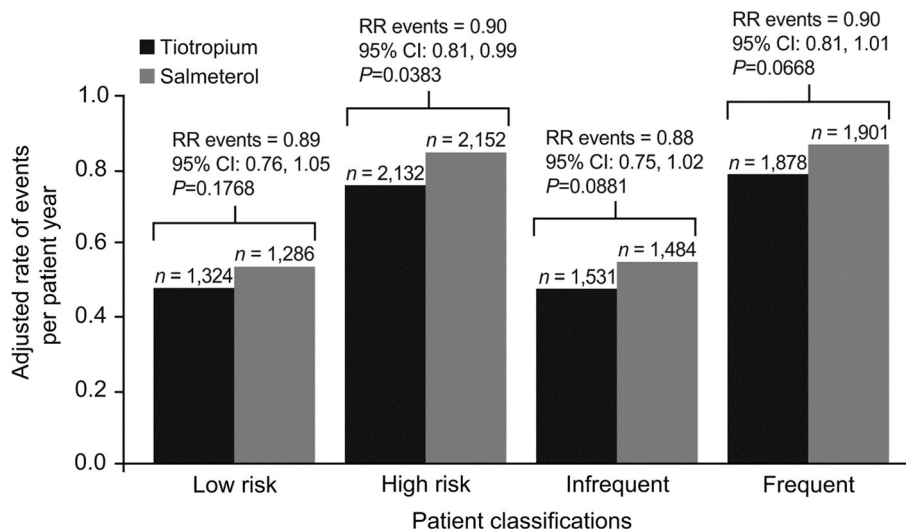
Fig. 2 Number of COPD exacerbations after treatment by patient exacerbation risk classification. *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *RR* risk ratio
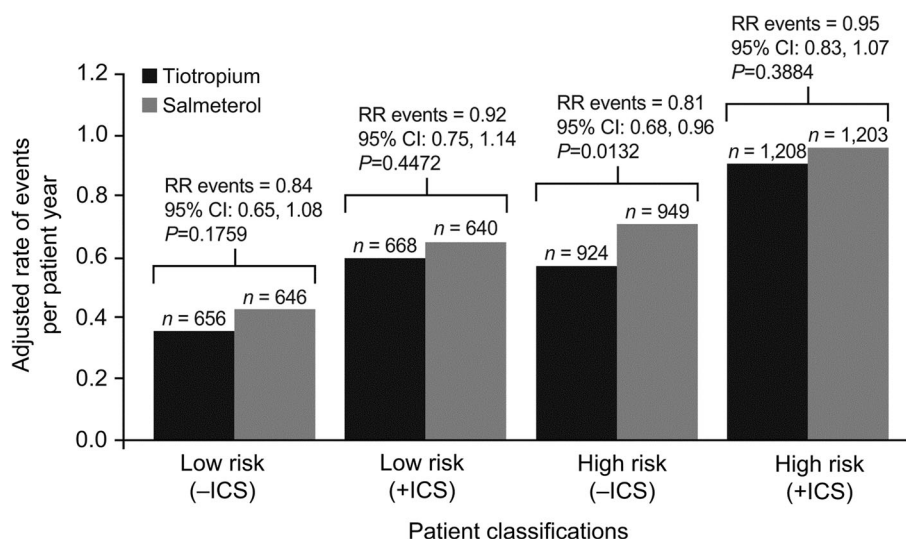

Fig. 3 Number of COPD exacerbations after treatment by patient exacerbation risk classification and ICS use at baseline. *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *ICS* inhaled corticosteroid, *RR* risk ratio

DISCUSSION

This post hoc analysis of the POET-COPD trial, which investigated the effect of tiotropium and salmeterol on exacerbations in patients considered to be at a low or high risk for exacerbations during the 1-year treatment period, had two main findings. First, it confirmed the higher efficacy of tiotropium compared with salmeterol in prolonging the time to first COPD exacerbation and reducing the number of COPD exacerbations in patients considered to be at low risk, as well as in those considered to be at high risk, for exacerbations. Second, our results show that background ICS usage at baseline, or lack thereof, had no impact

Table 4 Comparison of patient classifications before and during treatment

Risk classification	ECLIPSE® exacerbation frequency definition (frequent/ infrequent exacerbator) N = 6794		GOLD 2013/4 risk definition (high risk/ low risk) N = 6894	
	Tiotropium	Salmeterol	Tiotropium	Salmeterol
Before 1 year of treatment (low/infrequent), n^a (%)	1531 (22.5)	1484 (21.8)	1324 (19.2)	1286 (18.7)
During 1 year of treatment (low/infrequent), n^a (%)	2951 (43.4)	2887 (42.5)	3087 (44.8)	2970 (43.1)
Before 1 year of treatment (high/frequent), n^a (%)	1878 (27.6)	1901 (28.0)	2132 (30.9)	2152 (31.2)
During 1 year of treatment (high/frequent), n^a (%)	458 (6.7)	498 (7.3)	620 (9.0)	699 (10.1)
Ratio infrequent (low risk)/frequent (high risk) during 1 year before study	0.82	0.78	0.62	0.60
Ratio infrequent (low risk)/frequent (high risk) on treatment	6.44	5.80	4.98	4.25
Ratio difference (on treatment—before study)	5.62	5.02	4.36	3.65

ECLIPSE® Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, *GOLD* Global Initiative for Chronic Obstructive Lung Disease
[a] Total patient population

Table 5 Probability of shifts to high-risk/frequent exacerbator group with tiotropium and salmeterol treatment

Prior to treatment	On-treatment Exacerbation frequency, n (%)				Probability of shifting to high-risk/ frequent exacerbator category (tiotropium versus salmeterol)	
	Low risk/infrequent		High risk/frequent		RR (95% CI)	p value
	Tiotropium	Salmeterol	Tiotropium	Salmeterol		
Low risk	1172 (88.5)	1117 (86.9)	152 (11.5)	169 (13.1)	0.87 (0.71–1.07)	0.1968
High risk	1692 (79.4)	1654 (76.9)	440 (20.6)	498 (23.1)	0.89 (0.80–1.00)	0.0478
Infrequent exacerbator	1382 (90.3)	1326 (89.4)	149 (9.7)	158 (10.6)	0.91 (0.74–1.13)	0.4065
Frequent exacerbator	1569 (83.5)	1561 (82.1)	309 (16.5)	340 (17.9)	0.92 (0.80–1.06)	0.2436

CI confidence interval, *RR* risk ratio

on tiotropium's efficacy (versus salmeterol) with regard to reducing the exacerbation frequency among patients with COPD, regardless of their risk classification. Although the original trial was not set up to test this, tiotropium, and to a lesser extent salmeterol, appears to shift patients in the high-risk classification group to the low-risk group, suggesting a stabilizing effect on the disease.

The initial observation from the current analysis, that tiotropium had a greater efficacy than salmeterol in prolonging the time to first COPD exacerbation, confirms the primary results among the total patient population for the POET-COPD trial. Additionally, although not formally tested, our results suggest that the impact of tiotropium versus salmeterol on exacerbations was greater among those

patients classified as being at high risk for exacerbations, regardless of whether the ECLIPSE [8] or recent GOLD [6] definitions are applied. In those patients classified as being at low risk for exacerbations, the results were borderline significant in favor of tiotropium, whereas in the high-risk group, this difference was statistically significant in favor of tiotropium. This might be explained by a lower number of exacerbations in the low-risk group.

It is noteworthy that the comparable effect observed from treatment with tiotropium versus salmeterol on COPD exacerbations does not appear to be influenced by the concomitant use of background ICS, although the risk ratio is more favorable for tiotropium when compared with salmeterol in both low- and high-risk exacerbator groups that were not using ICS.

Not only did our results show that treatment with tiotropium or salmeterol resulted in a higher proportion of patients shifting from the high-risk (frequent) to the low-risk (infrequent) exacerbator group, but also that treatment prevented patients at low risk of exacerbations from transitioning into the high-risk group. Many studies have shown that intervention with pharmacotherapy confers benefit to patients with COPD by reducing exacerbations or prolonging the time to first exacerbation [11–14]; however, few have successfully demonstrated that pharmacotherapy can positively influence the future risk of patients experiencing exacerbations [15]. As observed in other interventional trials both in COPD and asthma [13, 16], the overall shift in the exacerbation frequency prior to enrollment versus randomized treatment is remarkable and somehow surprising, particularly in comparison to the relative stability of the phenotype in an observational setting [17]. While insufficient background COPD treatment prior to inclusion may at least partially explain this strong shift, other factors may also be relevant such as the definition and documentation of exacerbations [18] (e.g., post hoc for history of exacerbations vs. prospectively on trials) as well as recall or reporting of exacerbations [19].

We speculate that by intervening early in the disease process, it may therefore be possible to minimize deleterious effects associated with increased frequency and severity of exacerbations in patients with COPD.

A limitation of the current study is that the POET-COPD trial was not designed to evaluate the effect of tiotropium specifically in different exacerbator phenotypes, nor was it designed to evaluate the effect of tiotropium on mitigating future risk for exacerbations. However, the detailed information regarding exacerbation history before enrollment and subsequently recorded over the course of the study, the large number of patients that participated, and the careful attention to study outcomes provides confidence in the results.

CONCLUSION

The results from the current study provide further evidence for intervention with tiotropium as maintenance therapy in COPD patients both at low or high risk for exacerbations.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. Claus F. Vogelmeier gave presentations at symposia and/or served on scientific advisory boards sponsored by Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Janssen, Mundipharma, Novartis, and Takeda. He was responsible for planning and interpretation of data, as well as drafting the manuscript.

The institution where Kai M. Beeh is employed has received compensation for organizing or participating in advisory boards for Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Chiesi, Cytos, Mundipharma, Novartis, and Revotar Biopharmaceuticals and for participation in scientific meetings or courses supported by various pharmaceutical companies (Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, and Takeda) in the past 3 years. His institution has also received consulting fees from Ablynx, Apellis Pharmaceuticals, Chiesi, and Cytos and

compensation for the design, performance, or participation in single- or multicenter clinical trials in the past 3 years from several companies, including Almirall, Boehringer Ingelheim, Cytos, GlaxoSmithKline, Mundipharma, Novartis, Pfizer, Revotar Biopharmaceuticals, Sterna AG, and TEVA. He was responsible for planning and interpretation of data, as well as drafting the manuscript. Guus M. Asijee is an employee of Boehringer Ingelheim and was responsible for planning and interpretation of data, as well as drafting the manuscript. Katrin Kupas is an independent statistician hired by Boehringer Ingelheim and was responsible for statistical analysis, interpretation of data, and drafting the manuscript.

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