Effect of tiotropium vs. salmeterol on exacerbations: GOLD II and maintenance therapy naïve patients

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Exacerbations;
GOLD stage II;
Maintenance therapy

Summary
The objective of this study was to investigate the effect of tiotropium compared with salmeterol on exacerbations in patients with moderate (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage II) chronic obstructive pulmonary disease (COPD) and those naïve to maintenance respiratory therapy in the 1-year Prevention Of Exacerbations with Tiotropium in COPD (POET-COPD®) trial (NCT00563381). Time to first exacerbation (primary endpoint) and rates of exacerbations were analyzed using exploratory Cox and Poisson regression (adjusting for time on treatment). Of 7376 randomized patients, 3614 were GOLD stage II (tiotropium n = 1781; salmeterol n = 1833) and 1343 were maintenance therapy naïve (tiotropium n = 672; salmeterol n = 671). Tiotropium significantly increased time to first exacerbation vs. salmeterol in GOLD stage II patients (hazard ratio [HR], 0.88; 95% confidence interval [CI]; 0.79–0.99; p = 0.028) and maintenance therapy naïve patients (HR, 0.79; 95% CI, 0.65–0.97; p = 0.028). Annual exacerbation rates were also significantly lower with tiotropium in the maintenance naïve subgroup compared with salmeterol (rate ratio [RR], 0.77; 95% CI, 0.63–0.94; p = 0.012). In the GOLD stage II subgroup, the rate of hospitalized exacerbations per year was significantly lower with tiotropium than with salmeterol (RR, 0.70; 95% CI, 0.57–0.85; p < 0.001); tiotropium also significantly prolonged time to first hospitalized exacerbation.
exacerbation versus salmeterol in this subgroup (HR, 0.66; 95% CI, 0.48–0.91; \( p = 0.012 \)). In conclusion, results from this prespecified subgroup analysis support the selection of tiotropium as first-choice maintenance therapy for patients with GOLD stage II COPD.

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Introduction

Exacerbations are a key clinical characteristic of chronic obstructive pulmonary disease (COPD) and are strongly associated with disease progression, worsening lung function, dyspnea, deteriorating health status/physical activity, and an increased risk of mortality.\(^1\)\(^-\)\(^5\) Indeed, exacerbations have become a recognized disease-defining feature of COPD in the recent update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee.\(^6\)

Long-term, controlled trials have examined the effect on COPD exacerbations of early bronchodilator maintenance therapy.\(^1\),\(^7\) Previous subgroup analyses of the 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT\(^7\)) trial demonstrated that treatment with tiotropium increased the time to first exacerbation and exacerbations resulting in hospital admission in COPD patients with GOLD stage II disease, compared with control.\(^7\) A reduction in the rate of exacerbations was also noted for patients who were naive to maintenance treatment.\(^8\)

Results have now become available from the Prevention Of Exacerbations with Tiotropium in COPD (POET-COPD\(^9\)) study, a 1-year, randomized, double-blind, double-dummy, parallel-group trial of 7376 patients with moderate to very severe COPD that compared the effect of treatment with the long-acting anticholinergic tiotropium (18 \( \mu \)g via HandiHaler\(^9\) once daily) and the long-acting \( \beta_2 \)-agonist (LABA) salmeterol (50 \( \mu \)g via hydrofluoroalkane-pressurized metered-dose inhaler [HFA-pMDI] twice daily) on the incidence of exacerbations. Compared with salmeterol, tiotropium significantly increased time to first exacerbation \( (p < 0.001) \) and time to first severe exacerbation \( (p < 0.001) \), and reduced annual rates of moderate or severe exacerbations \( (p = 0.002) \) and severe exacerbations \( (p < 0.001) \) in the overall study population.

To explore the relative effects of therapy with tiotropium or salmeterol on exacerbation outcomes further, we conducted prespecified subgroup analyses of the POET-COPD\(^9\) study cohort in patients with moderate (GOLD stage II) disease, and those who were maintenance naive. Results in these populations were considered alongside data from the subgroups of patients in POET-COPD\(^9\) with GOLD stage III and IV disease, and those with prior maintenance therapy experience.

Methods

Study design

POET-COPD\(^9\) was a randomized, double-blind, double-dummy, 1-year trial. The study design has been described in detail elsewhere.\(^9\),\(^10\) Briefly, patients were randomized to tiotropium 18 \( \mu \)g once daily (via HandiHaler\(^9\)) plus placebo twice daily (via HFA-pMDI), or salmeterol 50 \( \mu \)g twice daily (via HFA-pMDI) plus placebo once daily (via HandiHaler\(^10\)). All patients were instructed in the use of HandiHaler\(^9\) and HFA-pMDI devices at visits 1 (screening) and 2 (randomization). Patients who were receiving fixed-dose combinations

![Figure 1](image-url)  
Figure 1   Disposition of GOLD stage II and maintenance naïve patients—prespecified subgroups of the POET-COPD\(^9\) trial. GOLD, Global Initiative for Chronic Obstructive Lung Disease; POET-COPD\(^9\), Prevention Of Exacerbations with Tiotropium in Chronic Obstructive Pulmonary Disease.
of a LABA and an inhaled corticosteroid (ICS) were instructed to switch to ICS monotherapy at the start of randomized treatment. Patients were allowed to continue their usual COPD medication, except for anticholinergics or LABAs, during the double-blind treatment phase. Patients were considered "maintenance naïve" if they were exclusively using short-acting β₂-agonists, or none of the following maintenance medications at baseline: ICS, systemic corticosteroids, xanthines, anticholinergics (short- or long-acting), and LABAs.

The primary endpoint of the trial was time to first moderate or severe exacerbation. Secondary endpoints included the annual rate of moderate or severe exacerbation. Secondary endpoints were grouped with systemic corticosteroids and/or antibiotics (moderate exacerbation) or hospitalization (severe exacerbation).

### Assessments

Patient baseline characteristics were recorded, including demographics, lung function, and pulmonary medication use. Data on exacerbations and medication use/hospitalization for exacerbations were collected using a daily diary card and a questionnaire administered during clinic visits and telephone contacts. An exacerbation was defined as an increase or new onset of more than one symptom (cough, sputum, wheezing, dyspnea, chest tightness), with at least one symptom lasting at least 3 days and requiring treatment with systemic corticosteroids and/or antibiotics (moderate exacerbation) or hospitalization (severe exacerbation).

Serious adverse events, including fatal events, were recorded at each clinic visit.

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### Table 1: Baseline characteristics in GOLD stage II, GOLD stage III and IV, maintenance naïve, and prior maintenance therapy patients.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>GOLD stage II</th>
<th>GOLD stage III and IV</th>
<th>Maintenance therapy naïve</th>
<th>Prior maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tiotropium</td>
<td>Salmeterol</td>
<td>Tiotropium</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>Male, %</td>
<td>(n = 1781)</td>
<td>(n = 1833)</td>
<td>(n = 1726)</td>
<td>(n = 1836)</td>
</tr>
<tr>
<td>Age, years</td>
<td>67.3 ± 9.2</td>
<td>63.2 ± 9.4</td>
<td>62.6 ± 8.8</td>
<td>62.5 ± 8.6</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>60.8 ± 9.4</td>
<td>61.1 ± 9.5</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td></td>
<td></td>
<td>70.8</td>
<td>74.6</td>
</tr>
<tr>
<td>COPD duration, years</td>
<td>7.5 ± 6.6</td>
<td>7.4 ± 6.6</td>
<td>8.5 ± 6.8</td>
<td>8.4 ± 6.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 5.1</td>
<td>27.2 ± 5.0</td>
<td>26.1 ± 5.1</td>
<td>26.0 ± 5.1</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.72 ± 0.40</td>
<td>1.70 ± 0.39</td>
<td>1.12 ± 0.31</td>
<td>1.13 ± 0.30</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>60.7 ± 6.6</td>
<td>60.2 ± 6.7</td>
<td>38.5 ± 8.0</td>
<td>38.5 ± 8.1</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>57.5 ± 8.5</td>
<td>57.5 ± 8.9</td>
<td>47.9 ± 10.5</td>
<td>47.3 ± 11.0</td>
</tr>
</tbody>
</table>

GOLD severity stage, %

- I: — — — 0.7 — 0.9 — 0.1 0.3
- II: — — — 48.2 — 54.1 47.7 48.5
- III: — — — 41.2 — 37.1 43.5 43.2
- IV: 9.8 7.9 8.7 7.9

Pulmonary medicine use, %

- SAAC: 27.5 26.7 31.0 32.5 — — 35.8 36.2
- LAAC: 29.0 29.4 31.9 31.1 — — 37.3 37.0
- SABA: 50.1 49.4 54.7 57.4 44.3 44.0 54.3 55.5
- LABA: 51.0 50.9 52.0 52.2 — — 62.9 63.1
- ICS: 51.1 49.0 55.9 57.6 — — 65.4 65.2
- Xanthines: 20.5 17.7 25.2 24.6 — — 28.0 25.9

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LAAC, long-acting anticholinergic; LABA, long-acting β₂-agonist; SAAC, short-acting anticholinergic; SABA, short-acting β₂-agonist.

*a Twenty-three GOLD stage I patients were included in the GOLD stage II group altogether.

*b Percentages do not total 100% due to rounding. Data are mean ± standard deviation unless specified otherwise.
Figure 2  Kaplan–Meier estimates of probability of first COPD exacerbation for tiotropium and salmeterol in: A) GOLD stage II; B) GOLD stage III and IV; C) maintenance naïve; and D) prior maintenance therapy subgroups. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 1  Subgroup analysis of the primary endpoint “time to first COPD exacerbation” for COPD severity stage (GOLD) and for patients who were maintenance therapy naïve or receiving prior maintenance therapy. Hazard ratios were calculated with the use of Cox regression adjusting for treatment. Horizontal lines represent 95% confidence intervals. Subgroup by treatment interaction p value based on Cox regression adjusted for treatment, subgroup, and subgroup-by-treatment interaction: COPD severity stage (GOLD II/III and IV) p = 0.371; maintenance naïve at baseline (yes/no) p = 0.479. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; n, number of patients with at least one COPD exacerbation; N, number of randomized and treated patients.

Figure 3  Subgroup analysis of the primary endpoint “time to first COPD exacerbation” for COPD severity stage (GOLD) and for patients who were maintenance therapy naïve or receiving prior maintenance therapy. Hazard ratios were calculated with the use of Cox regression adjusting for treatment. Horizontal lines represent 95% confidence intervals. Subgroup by treatment interaction p value based on Cox regression adjusted for treatment, subgroup, and subgroup-by-treatment interaction: COPD severity stage (GOLD II/III and IV) p = 0.371; maintenance naïve at baseline (yes/no) p = 0.479. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; n, number of patients with at least one COPD exacerbation; N, number of randomized and treated patients.
Statistical analyses

All analyses (GOLD stage II, III and IV, maintenance naive, and prior maintenance therapy subgroups) were pre-specified. In line with the primary analysis of the trial, a Cox proportional hazards regression model was used for time-to-event (exacerbation and mortality) analyses. Hazard ratios (HR) and p-values were based on subgroup-restricted 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 analyses.

Results

Baseline characteristics

A total of 7376 patients were randomized and treated in the POET-COPD trial, of whom 3614 were GOLD stage II COPD (tiotropium n = 1781; salmeterol n = 1833); 1343 were maintenance naive (tiotropium n = 672; salmeterol n = 671), whereas 3762 were GOLD stage III and IV (tiotropium n = 1926; salmeterol n = 1836); and 6033 had received prior maintenance therapy at time of randomization (tiotropium n = 3035; salmeterol n = 2998). Patient disposition is detailed in Fig. 1. Baseline characteristics were well balanced between patients receiving tiotropium and salmeterol within each of the four subgroups (Table 1). Mean age was similar across the GOLD stage and maintenance therapy subgroups (ranging from 60.8 to 63.4 years), and a similar proportion of patients at each GOLD stage were within the maintenance therapy naive and prior maintenance therapy subgroups (GOLD stage II, 51.2%–48.1%; GOLD stage III, 39.2%–43.4%; GOLD stage IV, 8.9%–8.3%). An approximately 16% higher proportion of current smokers was noted in the maintenance naive subgroup compared with patients receiving prior maintenance therapy (61% vs. 45%), and fewer than 50% of patients in the naive subgroup were receiving any pulmonary medication (Table 1).

Exacerbation outcomes

Tiotropium significantly prolonged time to first exacerbation in the GOLD stage II subgroup compared with salmeterol (HR 0.88; 95% confidence interval [CI] 0.79–0.99; p = 0.028) (Fig. 2A). This was also true in the GOLD stage III and IV subgroup (HR 0.82; 95% CI 0.74–0.91; p < 0.001). The subgroup-by-treatment interaction p-value for the COPD severity stage category (GOLD stage II, GOLD stage III and IV subgroups) was 0.37.

Tiotropium also significantly prolonged time to first exacerbation in the maintenance naive subgroup compared with salmeterol (HR 0.79; 95% CI 0.65–0.97; p = 0.028) (Fig. 2C). Time to first exacerbation results for the subgroup of patients receiving prior maintenance treatment were also significant in favor of tiotropium (HR 0.86; 95% CI 0.79–0.93; p < 0.001) (Fig. 2D). The subgroup-by-treatment interaction p-value was 0.48 for the maintenance therapy category (maintenance naive and receiving prior maintenance therapy subgroups).

Across all subgroups, an early separation of the tiotropium and salmeterol time curves was observed in the Kaplan–Meier plots (Fig. 2A–D), which was maintained up to the 1-year time-point.

For the GOLD stage II subgroup, the rate of exacerbations per year was numerically lower with tiotropium than with salmeterol (0.55 vs. 0.60; rate ratio [RR] 0.91; 95% CI 0.81–1.01; p = 0.072) (Figs. 3 and 4A). Annual exacerbation rates were significantly lower with tiotropium

Figure 4  A) Exacerbation rates and B) Hospitalized exacerbations rates per patient-year for GOLD stage II, GOLD stage III and IV, maintenance naive, and prior maintenance therapy patients. Subgroup by treatment interaction p-value and rate ratios were calculated as described in the Methods: A) Exacerbations: COPD severity stage (GOLD II/GOLD III and IV), p = 0.617; maintenance naive at baseline (yes/no) p = 0.132; B) Hospitalized exacerbations: COPD severity stage (GOLD II/ GOLD III and IV), p = 0.750; maintenance naive at baseline (yes/no), p = 0.787. CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
compared with salmeterol in the maintenance naïve subgroup (0.38 vs. 0.49; RR 0.77; 95% CI 0.63–0.94; p = 0.012); a similar behavior was also observed in the maintenance therapy and GOLD stage III and IV subgroups (Figs. 3 and 4A).

In the GOLD stage II subgroup, the rate of hospitalized exacerbations per year was significantly lower with tiotropium than with salmeterol (0.05 vs. 0.07; RR 0.70; 95% CI 0.57–0.85; p < 0.001 [Fig. 4B]), while tiotropium also significantly prolonged time to first hospitalized exacerbation compared with salmeterol in this subgroup (HR 0.66; 95% CI 0.48–0.91; p = 0.012 [Fig. 5A]). Both the annual rate of hospitalized exacerbations and time to first hospitalized exacerbation for tiotropium compared with salmeterol did not reach significance for the maintenance naïve subgroup (Figs. 4B and 5C); however, these results were significant for the prior maintenance therapy subgroup (rate of hospitalized exacerbations: 0.10 vs. 0.14; RR 0.73; 95% CI 0.65–0.82; p < 0.001 [Fig. 4B]; time to first hospitalized exacerbation: HR 0.76; 95% CI 0.64–0.90; p = 0.002 [Fig. 5D]).

Safety

The total incidence of serious adverse events was 11.1% in the tiotropium group and 11.7% in the salmeterol group in the GOLD stage II subgroup (RR 0.93; 95% CI 0.77–1.13), and 11.2% and 12.7%, respectively, in the maintenance naïve subgroup (RR 0.87; 95% CI 0.63–1.18). The total incidence of serious adverse events was higher with salmeterol both in the GOLD stage III and IV subgroup (RR 0.81; 95% CI 0.70–0.94) and in the prior maintenance therapy subgroup (RR 0.86; 95% CI 0.76–0.98) (Table 2).

The number of deaths was similar in the tiotropium group compared with the salmeterol group in all subgroups.

Figure 5  Kaplan–Meier estimates of probability of first hospitalized COPD exacerbation for tiotropium and salmeterol in: A) GOLD stage II; B) GOLD stage III and IV; C) Maintenance naïve; and D) Prior maintenance therapy subgroups. Hazard ratios and p-value based on subgroup-restricted Cox regression with treatment as covariate. Interaction p-value based on subgroup-restricted Cox regression with treatment as covariate. Interaction p-value based on Cox regression adjusted for treatment, subgroup, and subgroup-by-treatment interaction: COPD severity stage (GOLD II/GOLD III and IV), p = 0.468; maintenance naïve at baseline (yes/no), p = 0.685. CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
Table 2  Serious adverse event incidence (≥1% in any group) by MedDRA SOC and preferred term: COPD disease stage and maintenance therapy subgroups.

<table>
<thead>
<tr>
<th>SOC/preferred term</th>
<th>GOLD stage II</th>
<th>GOLD stage III and IV</th>
<th>Maintenance therapy naive</th>
<th>Prior maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tiotropium</td>
<td>Salmeterol</td>
<td>Tiotropium</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Total serious adverse events</td>
<td>11.1 (n = 1781)</td>
<td>11.7 (n = 1833)</td>
<td>18.1 (n = 1926)</td>
<td>21.4 (n = 1836)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>2.5</td>
<td>1.3</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>0.7</td>
<td>0.5</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>1.7</td>
<td>2.3</td>
<td>3.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.8</td>
<td>1.4</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Neoplasms, benign malignant, and unspecified (including cysts and polyps)</td>
<td>1.3</td>
<td>1.3</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1.0</td>
<td>0.7</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>4.6</td>
<td>5.8</td>
<td>11.3</td>
<td>14.2</td>
</tr>
<tr>
<td>COPD</td>
<td>3.7</td>
<td>5.2</td>
<td>10.6</td>
<td>13.1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1.2</td>
<td>0.5</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MedDRA, Medical Dictionary for Regulatory Activities (MedDRA v13.0 was used for reporting); SOC, system organ class.

Discussion

The results of these prespecified subgroup analyses of the POET-COPD study showed that tiotropium significantly prolonged time to first exacerbation compared with salmeterol in patients with GOLD stage II disease, and in those who were previously naïve to maintenance respiratory therapy. The Kaplan–Meier plots of time to first exacerbation illustrated an early onset of therapeutic benefit in patients receiving tiotropium compared with salmeterol, and the between-groups separation was maintained over time. A significant lowering of the annual rate of exacerbations was also seen with tiotropium versus salmeterol in the maintenance naïve subgroup.

The present analyses expand on previous subgroup evaluations of patients with moderate COPD from the UPLIFT trial and Towards a Revolution in COPD Health (TORCH) trials, in which a significant reduction in exacerbation risk was observed during long-term treatment with tiotropium or salmeterol/fluticasone propionate, compared with the control groups. Salmeterol appeared to be the best comparator to tiotropium as it possesses the broadest clinical database of all LABAs and has demonstrated consistent efficacy on exacerbations of COPD.

Our subgroup analyses of POET-COPD offer new information, as they suggest that a diminished risk of exacerbations with tiotropium compared with salmeterol is also achievable in patients with less severe disease and in patients with no prior maintenance therapy. While treatment guidelines recommend long-acting bronchodilators to manage symptoms and reduce the risk of exacerbations in patients with moderate to very severe COPD, they do not specify whether a long-acting anticholinergic or LABA is the preferred agent. It is noteworthy that patients in the maintenance naïve subgroup were at least GOLD stage II on enrollment into POET-COPD; according to current guidelines, these patients should have already been receiving long-acting bronchodilator therapy.

In the GOLD stage II subgroup, the annual rate of hospitalized exacerbations was significantly reduced while tiotropium also significantly prolonged time to first severe exacerbation. A trend toward a reduction in the rate of exacerbations with tiotropium was shown in patients at GOLD stage II, as well as a trend toward a reduction in the rate of hospitalized exacerbations in maintenance naïve patients; however there was a lack of a significant effect in both instances. This can be explained by a lack of statistical power and the incidence of fewer exacerbations in these subgroups of less severe disease.

Our serious adverse event results for tiotropium and salmeterol in the prespecified subgroups were consistent with previously published safety profiles, and the GOLD stage II and maintenance naïve subgroups showed an incidence of serious adverse events similar to that in the corresponding groups of patients from the UPLIFT trial. There were no significant differences in mortality between patients receiving tiotropium and salmeterol in any subgroup during the 1-year study period. This finding is consistent with previous study outcomes and can be explained by the study not being designed or powered to show a difference in mortality between two effective long-acting bronchodilators.

The current subgroup analyses of the POET-COPD study were preplanned, and the size of the patient population allows inferences to be drawn about the real effects of treatment on the exacerbation endpoints. However, as with all subanalyses, the results may require confirmation through additional research. The characterization of the
maintenance naïve subgroup also had potential limitations, such as the use of cross-sectional baseline data that did not take into account potential prior prescriptions, the reliance on patient-reported treatment history in many cases, and the possibility of noncompliance in some patients from the subgroup with prior maintenance therapy.

A key strength of the study was that the primary endpoint of the study cohort was time to exacerbation, with a secondary analysis of annual incidence rates; unlike other multicenter studies involving patients with COPD, the POET-COPD study focused on the specific and relevant disease outcome of exacerbations, instead of a wide range of endpoints. It remains unclear whether the superiority of tiotropium can be transferred to other LABAs, including the once-daily LABA indacaterol. However, so far, indacaterol has not been shown to outperform salmeterol or formoterol in reducing exacerbations from direct comparisons.15,16

In conclusion, our subanalyses of the POET-COPD study investigated the effect of tiotropium compared with salmeterol on time to first exacerbation and the rate of exacerbations in patients with moderate (GOLD stage II) COPD and those naïve to maintenance respiratory therapy. Tiotropium significantly increased time to first exacerbation in both of these patient subgroups, and the annual rate of exacerbations in the maintenance naïve subgroup compared to salmeterol. Our results generally support the primary analyses of the POET-COPD trial, and have potential implications for clinicians selecting long-acting bronchodilator therapies, particularly for exacerbation-prone patients with COPD.

Conflict of interest statement

The authors have reported to Respiratory Medicine the following conflicts of interest: Dr Vogelmeier has received honoraria for presentations at symposia sponsored by AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline (GSK), Janssen-Cilag, Novartis, Nycomed, Pfizer, and Taclecris. Dr Vogelmeier has also received fees for consulting from AstraZeneca, Boehringer Ingelheim, GSK, Janssen-Cilag, Mundipharma, Novartis, Nycomed, and Taclecris.

Dr Fabbri has received payment for consultancy from Boehringer Ingelheim, Chiesi Farmaceutici, GSK, Merck Sharp & Dohme (MSD), Novartis, Nycomed, Pearl Therapeutics, SigmaTau, Sterna, Peer Voice Europe, OM Pharma Sa, and TEVA. Dr Fabbri has also received payment for lectures, advisory boards or travel expenses reimbursement from AstraZeneca, Dey Pharma, Novartis, Schering-Plough, SigmaTau, Roche, German Aerospace Center, Mundipharma Int., Genetech Inc, Elevation Pharmaceutical, and the Ferrer Group; and his institution has received grants from Boehringer Ingelheim, Schering-Plough, Pfizer, Nycomed, Menarini Industrie Farmaceutiche, Chiesi Farmaceutici, GSK, MSD, Roche, AstraZeneca, Novartis, SigmaTau, Italian Ministry for University and Research, and the Italian Ministry of Health.

Dr Rabe has consulted for, participated in advisory board meetings with, and received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Pfizer, Novartis, Nycomed, MSD, and GSK; Dr Rabe has also received grants from Novartis, AstraZeneca, Boehringer Ingelheim, Roche, AltanaPharma, and GSK.

Dr Bees has received compensation for organizing or participating in advisory boards for Almirall Hermal, Cytos, Boehringer Ingelheim, AstraZeneca, Novartis, and Revotar Biopharmaceuticals, and has participated as a speaker in scientific meetings or courses supported various pharmaceutical companies (Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, and Takeda) in the past 5 years. Dr Bees has also received consulting fees from Allynx and Apellis Pharmaceuticals. The institution where Dr Bees is currently employed has received compensations for the design, performance, or participation in single or multicenter clinical trials in the past 5 years from several companies, including Almirall, AstraZeneca, Boehringer Ingelheim, Cytox, GSK, Medapharma, Mundipharma, Novartis, Pfizer, and Revotar Biopharmaceuticals.

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