Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial

Running title: cost-effectiveness of tiotropium versus salmeterol

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Abstract

The aim of this study was to perform a 1-year trial-based cost-effectiveness analysis (CEA) of tiotropium versus salmeterol followed by a 5-year model-based CEA. The within-trial CEA, including 7250 patients with moderate-to-very severe COPD, was performed alongside the 1-year international, randomized controlled POET-COPD trial comparing tiotropium with salmeterol regarding the effect on exacerbations. Main endpoints of the trial-based analysis were costs, number of exacerbations and exacerbation days. The model-based analysis was conducted to extrapolate results to 5 years and to calculate quality-adjusted life years (QALYs).

One-year costs per patient from the German Statutory Health Insurance (SHI) perspective and the societal perspective were €126 (95% uncertainty interval (UI):55-195) and €170 (95% UI: 77-260) higher for tiotropium, respectively. The annual number of exacerbations was 0.064 (95% UI: 0.010-0.118) lower for tiotropium, leading to a reduction in exacerbation-related costs of €87 (95% UI: 19-157). The incremental cost-effectiveness ratio (ICER) was €1961 per exacerbation avoided from the SHI perspective and €2647 from the societal perspective. In the model-based analyses, the 5-year costs per QALY for the two perspectives were €3488 and €8141, respectively.

Tiotropium reduced exacerbations and exacerbation-related costs, but increased total costs. The resulting cost-effectiveness ratios were below commonly accepted willingness-to-pay thresholds.

Key words

Chronic Obstructive Pulmonary Disease, costs, exacerbations, model, Quality-adjusted life year, trial
Introduction

The current international guidelines for the treatment of chronic obstructive pulmonary disease (COPD) recommend regular treatment with a long-acting anticholinergic drug (tiotropium) or a long-acting beta-agonist (salmeterol, formoterol, or indacaterol) for patients with moderate to very severe COPD [1]. These bronchodilators have been shown to improve symptoms, health-related quality of life and lung function, and reduce exacerbations and hospitalizations [2-4]. However, guidelines do not give a preference for either drug class. Until the publication of the Prevention Of Exacerbations with Tiotropium (POET-COPD) trial, head-to-head comparisons were limited, had a short duration and/or were underpowered to detect a difference in COPD exacerbations [5,6]. The one-year POET-COPD trial was designed to compare the effects of tiotropium 18 µg once daily or salmeterol 50 µg twice daily on the occurrence of moderate or severe exacerbations in patients with moderate to very severe COPD and a history of at least one exacerbation in the previous year [7]. This clinical trial demonstrated that tiotropium prolonged the time to first exacerbation (HR: 0.83 (95% CI: 0.77-0.90)), the time to first exacerbation leading to hospitalization (HR: 0.72 (95% CI: 0.61-0.85)) and reduced the total number of exacerbations (RR: 0.89 (95% CI: 0.83-0.96)) compared to salmeterol [8].

The question which long-acting bronchodilator to use is especially relevant from a policy and payer’s perspective because of the price difference between tiotropium and salmeterol, and the hypothesis that tiotropium could reduce costs of COPD exacerbations compared to salmeterol by preventing more exacerbations. Hence, a direct comparison of total costs in relation to health outcomes, i.e. a cost-effectiveness analysis between tiotropium and salmeterol would be informative. A recent review showed that there were at least six studies on the cost-effectiveness of tiotropium versus salmeterol in different countries, but all of them were modelling studies using data from studies not powered to investigate COPD exacerbations specifically [9].

The objective of this study was to estimate the cost-effectiveness of tiotropium versus salmeterol. This information could be used for reimbursement decisions and regulations and evidence-based treatment guidelines development. Firstly, a trial-based economic evaluation was performed alongside the POET-COPD trial to estimate the cost-effectiveness in terms of costs per exacerbation avoided and costs per exacerbation day avoided. Secondly, the results of the POET-COPD trial were synthesized with evidence on COPD exacerbations from previous tiotropium studies [5,10,11] and this information was then used as input into a previously published COPD cost-effectiveness model [12-14]. The aim of the model-based analysis was to extrapolate trial results up to five years, to adjust the trial-based COPD severity distribution to a population-based severity distribution and to estimate the costs per quality-adjusted life year (QALY).
Methods

Patients and trial design
The trial-based cost-effectiveness analysis was performed alongside the POET-COPD trial, which was a one-year randomized, double-blind, double-dummy, multinational controlled trial in which patients with moderate to very severe COPD [1] were randomly assigned to tiotropium 18 µg once daily administered via the HandiHaler or salmeterol 50 µg twice daily administered via the metered dose inhaler [8]. Inclusion and exclusion criteria and details about the trial have been described elsewhere [8]. During the one-year treatment period patients were evaluated during six clinical visits at the start of the run-in period (-2 weeks), at baseline and at 2, 4, 8 and 12 months, and during eight scheduled monthly telephone interviews in between. Data on demographics, working status, concomitant disorders and medications as well as health care utilization in the year prior to randomization were collected. During each following visit and each telephone interview, patients were asked to report exacerbation symptoms and/or events as well as exacerbation-related health care utilization, serious adverse events, medication and adverse events leading to study discontinuation using a standardized questionnaire. The study was conducted in 725 centres in 25 different countries, mainly in Europe. The trial-based cost-effectiveness analysis was based on resource utilization and health outcomes of the patients in the trial. The trial-wide resource utilization was multiplied with German unit costs.

Perspective
The trial-based cost-effectiveness study was performed from two different perspectives: 1) the perspective of the Statutory Health Insurance (SHI), which included the costs of study medication, other COPD-related medication and COPD exacerbation-related health care use covered by the SHI, and 2) the societal perspective, which included all COPD-related health care costs covered by the SHI, patient co-payments for hospitalizations, ambulance rides, visits to healthcare providers and medication, costs for travelling and costs of productivity losses due to absence from paid employment.

Health care utilization, productivity losses and unit costs
At all visits and telephone interviews patients were asked about their exacerbation-related health care utilization in terms of number of hospitalizations, dates of admission and discharge, days at intensive care unit (ICU), ambulance transportations, emergency room (ER) visits and contacts with five types of health care providers: study physician, general practitioner, respiratory specialist, non-respiratory specialist and other type of health care provider. Furthermore, patients were asked about the number of days they were unable to
perform paid work. Use of medication was registered by recording the type of medication, total daily dose, start and stop dates, indication or reason to change and whether or not the medication was used to treat a COPD exacerbation. Resource utilization was valued using German unit costs in 2010 € (see supplementary material). The calculation of productivity loss was based on the friction costs approach, which assumes that costs of productivity losses are limited to the period needed to replace a sick worker [15]. The average time to fill a vacancy [16] or the average display of a job offer [17] was estimated to be 75 days in Germany.

Health outcomes
The main outcome parameters in the trial-based economic evaluation were the number of COPD exacerbations and the number of COPD exacerbation days. In line with the definition used in the clinical trial [8], an exacerbation was defined as an increase or new onset of more than one of the following symptoms: cough, sputum, wheezing, shortness of breath or chest tightness with at least one symptom lasting three or more consecutive days and requiring treatment with systemic corticosteroids and/or antibiotics (moderate exacerbation), or hospitalization (severe exacerbation).

Cost-effectiveness
The incremental cost-effectiveness ratio’s (ICERs) were calculated as the difference in mean total costs divided by the difference in mean number of exacerbations or the difference in mean number of exacerbation days between the tiotropium and the salmeterol group resulting in the costs per exacerbation avoided and the costs per exacerbation day avoided, respectively.

Statistical analyses
The analysis was performed according to the intention-to-treat approach. All randomized patients that received at least one dose of study medication and fully completed at least one electronic case report form on exacerbations and health care resource use were included in the trial-based economic evaluation. To account for the costs and effects that were missing because patients prematurely dropped out from the trial or missed a visit or telephone interview the multiple imputation technique was used [18,19]. Each missing value was replaced by ten simulated values using the Monte Carlo Markov Chain (MCMC) method in SAS [20]. Variables included in the final imputation model were sex, age, pack-years, country, centre, employed yes/no, forced expiratory volume in the first second as percentage of the predicted value (FEV1,% predicted) at baseline, total number of co-morbidities, cardiovascular disease yes/no, duration of COPD, number of unscheduled visits to health
care providers in the past year, number of antibiotic prescriptions in the last year and monthly exacerbation numbers and monthly costs in the months prior to the month imputed. Multiple imputation was done separately for each treatment group and costs and effects were imputed simultaneously in order to maintain the association between these two. Results of the ten complete databases were combined to one estimate of the mean effects and costs in both treatment groups using the approach of Rubin et al [21]. Non-parametric bootstrapping was performed to obtain 95% uncertainty intervals around these estimated means. For each of the ten complete datasets 1000 bootstrap replications were done, separately per treatment group. For each of the bootstrap replications, the difference in costs, COPD exacerbations and exacerbation-free days between tiotropium and salmeterol were calculated. The 2.5th and 97.5th percentile of the 10,000 calculated differences in costs and effects between the tiotropium and salmeterol group formed the 95% uncertainty interval (UI). Results of the bootstrap replications were plotted on cost-effectiveness planes (CE-planes) [22]. The information in the CE-planes was summarized in acceptability curves [23], which show the probability that the ICER of tiotropium falls below various threshold values. These threshold values reflect the maximum that decision makers would be willing to invest to avoid one exacerbation or one exacerbation day.

Subgroup analyses
The following subgroup analyses were performed: age (<65 versus ≥65), sex, smoking status (current versus former smokers), COPD severity stage according to GOLD guidelines [1] (mild/moderate versus severe versus very severe COPD), region (Western Europe plus Israel versus Eastern Europe plus Turkey) and use of inhaled corticosteroids (with or without long-acting bronchodilators) at baseline (yes versus no). All subgroups were pre-specified, except for region.

Model-based extrapolation
The exacerbation probabilities and exacerbation-related resource use from the POET-COPD trial were used to inform a model-based analysis that aimed to estimate the costs per QALY of tiotropium versus salmeterol in Germany over a 1-year and 5-year time horizon. First, a Bayesian fixed effects meta-analysis was performed to synthesize the exacerbation probabilities in the tiotropium group of the POET-COPD trial with the exacerbation probabilities in the tiotropium group of six tiotropium trials used to inform a previously published cost-effectiveness model [5,10-13,24]. Also the relative exacerbation risks of salmeterol compared with tiotropium of the POET-COPD trial and the salmeterol-controlled tiotropium trials published by Brusasco et al [5] were combined with this method. To obtain the exacerbation probabilities for salmeterol, the pooled relative risks were then applied to
the pooled exacerbation probabilities for tiotropium. The resulting exacerbation probabilities (Table 1) were entered into a Markov model that was designed to transfer the results to other settings and extrapolate trial-results to up to five years [13]. The exacerbation probabilities were kept constant over time. Additionally, the severity distribution of the POET-COPD trial (49.4% moderate, 42.2% severe, 8.4% very severe COPD) [1] was adjusted to a population-based severity distribution. Due to a lack of German data this distribution was based on Dutch data (73% moderate, 21% severe, 6% very severe COPD [25]). The resource use estimates of the 1105 analyzed German patients in the POET-COPD trial were used to calculate the costs of a moderate and a severe exacerbation and the costs of COPD-related medication use. Unit costs were similar as in the trial-based cost-effectiveness analysis. However, in contrast to the POET-COPD trial, the model also included the costs of COPD maintenance treatment. More details on the costs of maintenance treatment by GOLD stage of COPD severity and the costs of a moderate and severe exacerbation can be found in the supplementary material.

[Table 1]

The model itself has been described in detail previously [12-14]. In short, it is a state-transition Markov model with four states, three COPD severity stages (moderate, severe and very severe) and death. In time intervals of one month patients have a certain probability to move between severity stages or to die. In each COPD severity state patients have a risk to experience a non-severe or severe exacerbation. The risk of experiencing an exacerbation varies by COPD severity state and treatment and was assumed constant over time. Health care resource use, mortality rates, costs, and quality of life (utilities) were assigned to the COPD states and exacerbations and assumed to depend on COPD severity and exacerbation severity, but not on treatment group. With respect to the input parameters of the model, the probabilities to move between states and utility values by COPD severity stage and exacerbation severity remained unchanged and can be found elsewhere [12,26]. Primary outcome of the model-based cost-effectiveness analysis were the costs per QALY gained over a time horizon of one and five years, which is typically the maximum time period for health care budget cycle planning and review. As in the trial-based analysis, the cost-effectiveness was calculated from the perspective of the SHI and the societal perspective. Future effects and costs were discounted by 3% [27]. The model was designed fully probabilistically [12]. The current results were based on 5,000 iterations, which were plotted on cost-effectiveness planes and summarized in cost-effectiveness acceptability curves. In addition to the probabilistic sensitivity analyses several one-way sensitivity analyses were performed.
Results

Patients
A total of 7376 patients were randomized and took at least one dose of study medication, 3707 in the tiotropium and 3669 in the salmeterol group [8]. The proportion of patients that withdrew from the study prematurely was significantly lower in the tiotropium group (15.8%) compared with the salmeterol group (17.7%) (log-rank test: p=0.02). Reasons for drop-out did not differ between the groups. In both treatment groups patients who withdrew from the trial were older, had a worse health status and higher exacerbation rates and health care utilization during their time in the trial compared with patients who completed the trial.

In total 7250 patients had at least one month of data on exacerbations and resource utilization and were, therefore, included in the cost-effectiveness analysis (3649 tiotropium and 3601 salmeterol). Comparison of the baseline characteristics of these patients (table 2) showed that patients in both treatment groups were comparable at baseline with respect to demographics, disease characteristics and resource use in the past year.

[Table 2]

Resource use
Table 3 shows the mean resource use per patient as observed during the trial (before imputation). The mean number of hospital admissions and hospital days was higher in the salmeterol group than in the tiotropium group; the mean length of an in-hospital stay was similar (12.9 days). Mean resource use for the other types of healthcare was comparable between the two treatment groups, except for a slightly higher use of methylxanthines and a higher mean number of days unable to perform paid work in the salmeterol group. Overall, the percentage of missing data due to early withdrawal or missed visits/telephone interviews was 8.9% for the tiotropium and 10.5% for the salmeterol group.

[Table 3]

Costs
Table 4 presents the mean costs per patient for different cost categories and the total costs after multiple imputation. Mean total costs from the SHI perspective were €1089 for the tiotropium group and €963 for the salmeterol group, resulting in a cost difference of €126 (95% UI: 55 -195). From the societal perspective mean total costs in the tiotropium group were also significantly higher than in the salmeterol group due to the higher costs of study medication. Part of the higher costs of study medication were compensated by significantly
lower exacerbation-related costs €87 (95% UI: 19 - 157), costs paid by the patient €5 (95% UI: 1 - 9) and costs due to productivity loss €55 (95% UI: 18 - 94).

[Table 4]

Health outcomes
The mean annual number of exacerbations was 0.644 in the tiotropium group and 0.708 in the salmeterol group, resulting in a significant difference of -0.064 (95% UI: -0.118 - -0.010). The mean number of exacerbation days was 9.0 in the tiotropium compared with 10.1 in the salmeterol group, a difference of -1.1 days (95% UI: -2.04 - -0.09).

Trial-based cost-effectiveness
From a SHI perspective the incremental cost-effectiveness ratio of tiotropium compared with salmeterol were €1961 per exacerbation avoided and €118 per exacerbation day avoided. These ratios were €2647 and €159, respectively, using a societal perspective. The cost-effectiveness planes show that almost all bootstrap replications (99%) fell in the upper right quadrant indicating that tiotropium resulted in higher costs and a lower number of exacerbations and exacerbation days (Supplementary material, figure A1). The acceptability curves presented in figure 1 show that the probability that tiotropium is cost-effective at for example, a willingness-to-pay of €5000 to avoid one exacerbation was 90% using the SHI perspective and 82% using the societal perspective. For a threshold value of for example, €500 to avoid one exacerbation day these probabilities were 93% and 91%, respectively.

[Figure 1]

Subgroup analyses
There was no statistically significant interaction between the effect of treatment in terms of exacerbations and exacerbation days and age, sex, smoking status, COPD severity, region and use of inhaled corticosteroids at baseline. The same applied to the interaction between treatment and costs, with two exceptions. The cost increase due to tiotropium was significantly higher in smokers than in former smokers from the SHI perspective. There was also a significant interaction effect between COPD severity and effect of tiotropium on costs from the societal perspective, i.e. in very severe COPD tiotropium was cost saving versus salmeterol, whereas in moderate COPD tiotropium increased costs.
Model-based cost-effectiveness

Results of the model showed that after one year, the difference in QALYs between tiotropium and salmeterol was 0.012 (95% CI: -0.017 - 0.048). The difference in costs after one year was €116 (95% CI: -32 - 262) from the SHI perspective (table 5). Hence, the costs per QALY gained of using tiotropium instead of salmeterol were €9926. Five-year treatment with tiotropium compared with salmeterol resulted in 0.082 (95% CI: -0.250 - 0.519) QALYs gained. The cost increase was €287 (95% CI: -707 - 1282) from the SHI perspective. Hence, after five years the cost-effectiveness ratio of tiotropium versus salmeterol was €3488 per QALY gained. Corresponding ICERs from the societal perspective were €16771 and €8141 after one and five years, respectively.

Figure 2 shows the acceptability curve for the costs per QALY gained using a five year time horizon. If the maximum willingness to pay for a QALY would be €20000, the probability that tiotropium was cost-effective compared to salmeterol was 62.5%, from the SHI perspective.

[Figure 2]

The one-way sensitivity analyses have been summarized in figure 3 (costs per QALY gained in five-year time horizon, SHI perspective). For all sensitivity analyses the costs per QALY gained remained below €10000.

[Figure 3]

Discussion
In this study the cost-effectiveness of tiotropium versus salmeterol for treatment of patients with moderate to very severe COPD was investigated. The trial-based analysis showed that, from the perspective of the German Statutory Health Insurance, the incremental cost-effectiveness ratios were €1961 per exacerbation avoided and €118 per exacerbation day avoided. The higher costs were due to the higher medication costs of tiotropium (a difference of €213 per patient); they were partly offset by a significant reduction in exacerbation-related costs (€87). When adopting the societal perspective, the statistically significant reduction in the costs paid by the patient (€5) and costs due to productivity loss (€55) were also taken into account. However, despite this, the total costs from the societal perspective were €170 higher when using tiotropium than salmeterol. In the societal perspective the list price of medications without the mandatory discounts that were applied in the SHI perspective were used. This led to a considerable increase in the cost difference between tiotropium and
salmeterol that could not be completely offset by adding both savings in the costs borne by the patients and the costs of productivity loss during an exacerbation.

In the trial-based cost-effectiveness analysis only the exacerbation-related costs and medication costs were included because these are the two main cost drivers in COPD. The trial-based cost-effectiveness analysis did not provide information about the QALYs, the most important outcome for economic evaluations, because it is difficult to capture the impact of short periods of deterioration in quality of life, such as exacerbations, on the QALY when the health-related quality of life is measured at fixed time points.

The model-based analysis yielded costs per QALY gained of €3488 from the SHI perspective and €8141 from the societal perspective. A costs per QALY ratio below €10000 is widely considered as being cost-effective in the international literature, given that thresholds of £20000-30000 (€25000-35000) and $50000 (€40000) are often cited for the maximum willingness to pay [28,29]. The additional value of the model-based analysis was that results were extended to a longer time horizon, results were transferred to the German setting, costs for maintenance treatment for COPD were included and the number of QALYs was calculated allowing for the cost per QALY to be determined in this analysis.

The results from the trial-based cost-effectiveness analysis were quite robust and hardly influenced by the imputation method. The ICERs calculated based on all available data or data from completers only without any further imputation of missing data did not differ much from the base case analysis (data not shown). The model-based cost-effectiveness analysis was also quite robust to changes in input parameters as evidenced by the extensive one-way sensitivity analyses, with all ICERs remaining below €10000. The cost-effectiveness acceptability curves in the trial-based analyses showed that at for example a willingness to pay to avoid an exacerbation of €5000, the probability that tiotropium would be cost-effective compared to salmeterol was 90% (SHI perspective). However, currently there is no basic notion of or general consensus about the maximum willingness to pay to avoid one exacerbation or exacerbation day in Germany or any other country. Using the costs per QALY as outcome as was done in the model-based analysis the probability that tiotropium would be cost-effective compared to salmeterol was 64% at maximum (SHI perspective). The uncertainty around the costs per QALY ratio was greater, because this ratio incorporates more sources of uncertainty (i.e. uncertainty around the transition probabilities, exacerbation probabilities, utilities, utility decrements due to exacerbations and costs estimates).
The POET-COPD trial was a multinational study. Mean resource use in the trial-based cost-effectiveness study was based on patients from all countries (trial-wide resource use) and multiplied with German unit costs. However, health care resources used as well as unit costs are known to vary between different countries due to variation in the organization and financing of health care [30]. The study was not powered to perform trial-based cost-effectiveness analyses per country, but we did perform a subgroup analysis based on region, Western versus Eastern Europe. This analysis showed that effects of tiotropium versus salmeterol on exacerbations and costs were not significantly different between these two regions. Furthermore, in the model-based analysis, we restricted resource use estimates to the subset of German patients (n=1105) and investigated the effect of using the data from all patients in a sensitivity analysis, with little impact on the results. Both these analyses provided confidence that the results of the trial-based analysis were valid for Germany.

A previous version of the model used in the current study has been validated by comparing the model results to the results of the clinical trials, which formed the basis for the clinical model inputs [12]. This approach was repeated here. When the model was filled with the exacerbation probabilities of the POET-COPD trial (before the evidence synthesis), the severity distribution of the trial and the time horizon of the trial, it was possible to reproduce the difference in the total number of exacerbations and the number of severe exacerbations that were found in the POET-COPD trial. The cost-effectiveness ratios from the SHI perspective were also comparable (€1612 compared to €1961 per exacerbation avoided). Results were not expected to be exactly the same, because in the trial the costs were based on trial-wide resource use (based on all patients) whereas in the model the costs were based on German patients only. Moreover, the model included maintenance costs whereas the trial-based analysis did not. However, this model validation provides evidence for the correct calibration of the model, meaning that model outputs are consistent with their underlying data.

Comparison of the results of this study with other studies is difficult because there are few direct comparisons between tiotropium and salmeterol. Most information available is about the cost-effectiveness of tiotropium and salmeterol versus short-acting bronchodilators or placebo. Estimates of the cost-effectiveness of tiotropium versus short-acting bronchodilators or placebo ranged from cost saving to $2341 per exacerbation avoided or $26094 per QALY gained [9]. Estimates of the cost-effectiveness of salmeterol versus short-acting bronchodilators or placebo ranged from cost saving to $10152 per exacerbation avoided or $197000 per QALY gained [9]. Six studies investigated the cost-effectiveness of tiotropium versus salmeterol, all modelling studies [12,13,31-34]. Four studies found that tiotropium was
cost saving in comparison with salmeterol in the Netherlands, Greece, Switzerland and the UK. A study from Naik et al. found the cost-effectiveness ratio to be $1817 per exacerbation avoided in the US [33]. A study from Rutten-van Mölken et al. reported cost-effectiveness ratios of €4118 per QALY gained, €841 per exacerbation avoided and €360 per exacerbation free month gained in the Spanish setting [13]. The current trial-based estimates of the costs per exacerbation avoided and the model-based estimates of the costs per QALY are in line with these previous studies. Few data are available on the cost-effectiveness of tiotropium versus other long-acting beta-agonists. There are no studies on the comparison with formoterol. The only study on the comparison with indacaterol, a model-based study, found indacaterol to be dominant [35]. However, caution is needed when interpreting this finding, as the model input data relied solely on one clinical study in which tiotropium was administered open-label.

In conclusion, treatment with tiotropium resulted in a significantly lower number of exacerbations and exacerbation days compared to salmeterol. Total costs for tiotropium were significantly higher from both the SHI and the societal perspective, because of the higher costs of study medication. Part of these higher costs was compensated by significant reductions in exacerbation-related costs, costs paid by the patient and costs due to productivity loss. In all sensitivity analyses, the five-year costs per QALY remained below €10,000, a threshold that is generally seen as very cost-effective in the international literature.
References


Figure legends

Figure 1: Acceptability curves for cost per exacerbation avoided and cost per exacerbation day avoided, trial-based analysis (grey: SHI perspective, black: societal perspective)
Figure 2: Acceptability curve for cost per QALY gained, model-based analysis, 5-year time horizon (grey: SHI perspective, black: societal perspective)

![Figure 2: Acceptability curve for cost per QALY gained, model-based analysis, 5-year time horizon (grey: SHI perspective, black: societal perspective)](image)

Figure 3: Sensitivity analyses for the model-based analysis of the cost per QALY gained of tiotropium versus salmeterol using a time horizon of five years (SHI perspective). The vertical line indicates the base case cost-effectiveness ratio of €3488/QALY

![Figure 3: Sensitivity analyses for the model-based analysis of the cost per QALY gained of tiotropium versus salmeterol using a time horizon of five years (SHI perspective). The vertical line indicates the base case cost-effectiveness ratio of €3488/QALY](image)
Table 1: Mean (SE) monthly exacerbation probabilities by treatment group after update with data from the POET-COPD trial using Bayesian fixed effects meta-analysis, model-based analysis

<table>
<thead>
<tr>
<th></th>
<th>Probability to experience an exacerbation</th>
<th>Probability that the exacerbation is severe, given an exacerbation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Tiotropium</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>Moderate COPD</td>
<td>.0483 (.002)</td>
<td>.0495 (.004)</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>.0624 (.001)</td>
<td>.0681 (.002)</td>
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<td>Very severe COPD</td>
<td>.0765 (.003)</td>
<td>.0844 (.004)</td>
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Table 2: Baseline characteristics of patients included in the cost-effectiveness study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tiotropium (N=3649)*</th>
<th>Salmeterol (N=3601)*</th>
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<tr>
<td>Male, %</td>
<td>74.7</td>
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<td>Age, years</td>
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<td>62.8 (9.0)</td>
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<td>- Current smoker, %</td>
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<td>- Smoking history, pack-years</td>
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<td>Duration of COPD, years</td>
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<td>7.9 (6.5)</td>
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<td>- LABA §</td>
<td>51.2</td>
<td>51.2</td>
</tr>
<tr>
<td>- ICS †</td>
<td>53.4</td>
<td>53.0</td>
</tr>
<tr>
<td>- LABA + ICS</td>
<td>43.1</td>
<td>43.2</td>
</tr>
<tr>
<td>Resource use in past year:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Scheduled visits to physician</td>
<td>3.9 (3.6)</td>
<td>3.8 (3.3)</td>
</tr>
<tr>
<td>- Unscheduled visits to physician</td>
<td>1.3 (1.4)</td>
<td>1.2 (1.6)</td>
</tr>
<tr>
<td>- ER visit without hospitalization</td>
<td>0.10 (0.6)</td>
<td>0.09 (0.6)</td>
</tr>
<tr>
<td>- ER visit followed by hospitalization</td>
<td>0.11 (0.4)</td>
<td>0.11 (0.4)</td>
</tr>
<tr>
<td>- Direct hospital admission</td>
<td>0.26 (0.6)</td>
<td>0.26 (0.5)</td>
</tr>
</tbody>
</table>

*Data are mean (standard deviation) unless specified otherwise
**23 patients in GOLD stage I (tiotropium 0.2%; salmeterol 0.4%)
§LABA=long-acting beta-agonist. LABA alone or in combination.
†ICS=inhaled corticosteroid. ICS alone or in combination.
Table 3: Use of study medication, exacerbation-related resource use, use of other COPD-related medication and days absent from work per patient as observed during the trial, before imputation, trial-based analysis

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium (n=3649)*</th>
<th>Salmeterol (n=3601)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study medication, days</td>
<td>331 (88)</td>
<td>325 (95)</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>0.096 (0.37)</td>
<td>0.123 (0.42)</td>
</tr>
<tr>
<td>Total hospital days</td>
<td>1.24 (5.53)</td>
<td>1.59 (6.35)</td>
</tr>
<tr>
<td>Total ICU days</td>
<td>0.05 (1.11)</td>
<td>0.11 (1.94)</td>
</tr>
<tr>
<td>Ambulance rides</td>
<td>0.06 (0.35)</td>
<td>0.06 (0.34)</td>
</tr>
<tr>
<td>Visits to emergency department</td>
<td>0.04 (0.25)</td>
<td>0.04 (0.25)</td>
</tr>
<tr>
<td>General practitioner:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Visits to practice</td>
<td>0.33 (1.03)</td>
<td>0.39 (1.06)</td>
</tr>
<tr>
<td>- Home visits</td>
<td>0.04 (0.25)</td>
<td>0.05 (0.36)</td>
</tr>
<tr>
<td>Respiratory specialist:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Visits to clinic</td>
<td>0.37 (1.20)</td>
<td>0.37 (1.18)</td>
</tr>
<tr>
<td>- Home visits</td>
<td>0.007 (0.10)</td>
<td>0.008 (0.12)</td>
</tr>
<tr>
<td>Other non-respiratory specialist:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Visits to clinic</td>
<td>0.03 (0.31)</td>
<td>0.03 (0.32)</td>
</tr>
<tr>
<td>- Home visits</td>
<td>0.003 (0.07)</td>
<td>0.003 (0.07)</td>
</tr>
<tr>
<td>Other health care provider:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Visits to clinic/practice</td>
<td>0.02 (0.58)</td>
<td>0.01 (0.16)</td>
</tr>
<tr>
<td>- Home visits</td>
<td>0.01 (0.27)</td>
<td>0.009 (0.14)</td>
</tr>
<tr>
<td>Systemic corticosteroids, days</td>
<td>14.2 (63.4)</td>
<td>13.6 (58.4)</td>
</tr>
<tr>
<td>Antibiotics, days</td>
<td>8.0 (28.5)</td>
<td>8.6 (29.1)</td>
</tr>
<tr>
<td>Inhaled corticosteroids, days</td>
<td>152 (181)</td>
<td>147 (180)</td>
</tr>
<tr>
<td>Short-acting anticholinergics, days</td>
<td>2.1 (23.6)</td>
<td>1.9 (22.8)</td>
</tr>
<tr>
<td>Short-acting B-agonists, days</td>
<td>7.8 (50.5)</td>
<td>8.6 (54.2)</td>
</tr>
<tr>
<td>Methylxanthines, days</td>
<td>74.4 (144)</td>
<td>66.4 (139)</td>
</tr>
<tr>
<td>Mucolytics, days</td>
<td>12.7 (62.1)</td>
<td>11.6 (59.1)</td>
</tr>
<tr>
<td>Days unable to perform paid work</td>
<td>0.67 (3.98)</td>
<td>0.97 (4.89)</td>
</tr>
</tbody>
</table>

*Data are mean (SD)
Table 4: Mean (95% uncertainty interval) total 1-year costs per patient after imputation and bootstrapping (2010, €), trial-based analysis

<table>
<thead>
<tr>
<th>Costs</th>
<th>Tiotropium</th>
<th>Salmeterol</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statutory Health Insurance perspective</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study medication</td>
<td>581</td>
<td>369</td>
<td>213</td>
</tr>
<tr>
<td>Exacerbation-related healthcare use*</td>
<td>363 (317-411)</td>
<td>450 (400 - 502)</td>
<td>-87 (-157 - -19)</td>
</tr>
<tr>
<td>Other COPD medication</td>
<td>144 (140-149)</td>
<td>144 (139 - 149)</td>
<td>1 (-6 -7)</td>
</tr>
<tr>
<td>Total</td>
<td>1089 (1041-1137)</td>
<td>963 (912 - 1016)</td>
<td>126 (55 -195)</td>
</tr>
<tr>
<td><strong>Societal perspective</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study medication</td>
<td>736</td>
<td>420</td>
<td>316</td>
</tr>
<tr>
<td>Exacerbation-related health care use*</td>
<td>363 (317-411)</td>
<td>450 (400 - 502)</td>
<td>-87 (-157 - -19)</td>
</tr>
<tr>
<td>Other COPD medication</td>
<td>170 (164-176)</td>
<td>170 (164 - 176)</td>
<td>1 (-7 -9)</td>
</tr>
<tr>
<td>Paid by the patient#</td>
<td>24 (22-27)</td>
<td>29 (26 - 32)</td>
<td>-5 (-9 - -1)</td>
</tr>
<tr>
<td>Productivity loss</td>
<td>115 (92-139)</td>
<td>170 (140 - 201)</td>
<td>-55 (-94 - -18)</td>
</tr>
<tr>
<td>Total</td>
<td>1409 (1349-1469)</td>
<td>1239 (1171 - 1310)</td>
<td>170 (77 - 260)</td>
</tr>
</tbody>
</table>

*Includes costs of hospital admissions, ambulance rides, visits to the ER and outpatient contacts to health care providers

#Includes patient co-payments for hospitalization, ambulance rides, contacts with health care providers and travel costs
Table 5: 1-year and 5-year results from the model-based cost-effectiveness analysis (2010, €)

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium*</th>
<th>Salmeterol*</th>
<th>Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One year:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality-adjusted life-years</td>
<td>0.746 (0.726 - 0.762)</td>
<td>0.734 (0.700 - 0.755)</td>
<td>0.012 (-0.017 - 0.048)</td>
</tr>
<tr>
<td>Total costs SHI perspective</td>
<td>1186 (1110 - 1269)</td>
<td>1069 (951 - 1202)</td>
<td>116 (-32 - 262)</td>
</tr>
<tr>
<td>Total costs societal perspective</td>
<td>1570 (1474 - 1668)</td>
<td>1380 (1239 - 1532)</td>
<td>190 (10 - 363)</td>
</tr>
<tr>
<td><strong>Five year:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality-adjusted life-years</td>
<td>3.26 (3.04 - 3.43)</td>
<td>3.18 (2.78 - 3.42)</td>
<td>0.082 (-0.250 - 0.519)</td>
</tr>
<tr>
<td>Total costs SHI perspective</td>
<td>5659 (5135 - 6168)</td>
<td>5372 (4516 - 6222)</td>
<td>287 (-707 - 1282)</td>
</tr>
<tr>
<td>Total costs societal perspective</td>
<td>7520 (6850 - 8138)</td>
<td>6896 (5806 - 7937)</td>
<td>625 (-595 - 1869)</td>
</tr>
</tbody>
</table>

*Data are mean (uncertainty interval)