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

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ABSTRACT: The aim of this study was to perform a 1-yr trial-based cost-effectiveness analysis (CEA) of tiotropium *versus* salmeterol followed by a 5-yr model-based CEA.

The within-trial CEA, including 7,250 patients with moderate to very severe chronic obstructive pulmonary disease (COPD), was performed alongside the 1-yr international randomised controlled Prevention of Exacerbations with Tiotropium (POET)-COPD trial comparing tiotropium with salmeterol regarding the effect on exacerbations. Main end-points of the trial-based analysis were costs, number of exacerbations and exacerbation days. The model-based analysis was conducted to extrapolate results to 5 yrs and to calculate quality-adjusted life years (QALYs).

1-yr 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 was €1,961 per exacerbation avoided from the SHI perspective and €2,647 from the societal perspective. In the model-based analyses, the 5-yr costs per QALY were €3,488 from the SHI perspective and €8,141 from the societal perspective.

Tiotropium reduced exacerbations and exacerbation-related costs, but increased total costs. Tiotropium can be considered cost-effective as the resulting cost-effectiveness ratios were below commonly accepted willingness-to-pay thresholds.

KEYWORDS: Chronic obstructive pulmonary disease, costs, exacerbations, model, quality-adjusted life year, trial

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 β-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 hospitalisations [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 1-yr 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 least one exacerbation in the previous year [7]. This clinical trial demonstrated that tiotropium prolonged the time to first exacerbation (hazard ratio (HR) 0.83, 95% CI 0.77–0.90) and the time to first exacerbation leading to hospitalisation (HR 0.72, 95% CI 0.61–0.85), and reduced the total number of exacerbations (relative risk 0.89, 95% CI 0.83–0.96) compared to salmeterol [8].

The question of 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

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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. First, 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. Second, the results of the POET-COPD trial were synthesised 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 5 yrs, 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 1-yr, randomised, 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 (Boehringer Ingelheim, Ingelheim am Rhein, Germany) 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 1-yr treatment period, patients were evaluated at 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 healthcare utilisation in the year prior to randomisation were collected. During each following visit and each telephone interview, a standardised questionnaire was used and patients were asked to report exacerbation symptoms and/or events as well as exacerbation-related healthcare utilisation, serious adverse events, medication and adverse events leading to study discontinuation. The study was conducted in 725 centres in 25 different countries, mainly in Europe. The trial-based cost-effectiveness analysis was based on resource utilisation and health outcomes of the patients in the trial. The trial-wide resource utilisation was multiplied with German unit costs.

Perspective

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

Healthcare utilisation, productivity losses and unit costs

At all visits and telephone interviews patients were asked about their exacerbation-related healthcare utilisation in terms of number of hospitalisations, dates of admission and discharge, days at intensive care unit, ambulance transportations, emergency room visits and contact with five types of healthcare providers: study physician, general practitioner, respiratory specialist, non-respiratory specialist and other type of healthcare 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 utilisation was valued using German unit costs in 2010 € (see online 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 $\geqslant 3$ consecutive days and requiring treatment with systemic corticosteroids and/or antibiotics (moderate exacerbation), or hospitalisation (severe exacerbation).

Cost-effectiveness

The incremental cost-effectiveness ratios (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 randomised patients that received at least one dose of study medication and fully completed at least one electronic case report form on exacerbations and healthcare 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 10 simulated values using the Markov chain Monte Carlo method in SAS (SAS Institute Inc., Cary, NC, USA) [20]. Variables included in the final imputation model

were sex, age, pack-yrs, country, centre, employed (yes/no), forced expiratory volume in 1 s as a percentage of the predicted value at baseline, total number of comorbidities, cardiovascular disease (yes/no), duration of COPD, number of unscheduled visits to healthcare 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 performed separately for each treatment group and costs and effects were imputed simultaneously in order to maintain the association between these two. Results of the 10 complete databases were combined to form one estimate of the mean effects and costs in both treatment groups using the approach of RUBIN [21]. Non-parametric bootstrapping was performed to obtain 95% uncertainty intervals around these estimated means. For each of the 10 complete datasets, 1,000 bootstrap replications were performed, separately per treatment group. For each of the bootstrap replications, the differences 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 groups formed the 95% uncertainty interval (UI). Results of the bootstrap replications were plotted on cost-effectiveness planes [22]. The information in the cost-effectiveness planes was summarised 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 yrs *versus* ⩾65 yrs), sex, smoking status (current *versus* former smokers), COPD severity stage according to Global Initiative for Chronic Obstructive Lung Disease (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 1-yr and 5-yr time horizons.

First, a Bayesian fixed-effects meta-analysis was performed to synthesise 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]. 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 5 yrs [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 1,105 German patients analysed 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 online supplementary material.

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 1 month patients have a certain probability of moving between severity stages or to die. In each COPD severity state, patients have a risk of experiencing a non-severe or severe exacerbation. The risk of experiencing an exacerbation varies by COPD severity state and treatment and was assumed to be constant over time. Healthcare resource use, mortality rates, costs and quality of life (utilities) were assigned to the COPD states and exacerbations, and were 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 of moving between states and utility values by COPD severity stage and exacerbation severity remained unchanged and can be found elsewhere [12, 26].

TABLE 1 Monthly exacerbation probabilities by treatment group

	Probability of an exacerbation		Probability that the exacerbation is severe	
	Tiotropium	Salmeterol	Tiotropium	Salmeterol
Moderate COPD	0.0483±0.002	0.0495±0.004	0.1098±0.014	0.1093±0.026
Severe COPD	0.0624±0.001	0.0681±0.002	0.1697±0.010	0.1776±0.015
Very severe COPD	0.0765±0.003	0.0844±0.004	0.2439±0.017	0.2738±0.028

Data presented are the exacerbation probabilities resulting from Bayesian fixed-effects meta-analysis combining exacerbation data from the Prevention of Exacerbations with Tiotropium (POET) trial and exacerbation data from [5, 10–13, 24]. Data are presented as mean±SE. COPD: chronic obstructive pulmonary disease.

Primary outcomes of the model-based cost-effectiveness analysis were the costs per QALY gained over time horizons of 1 and 5 yrs, which is typically the maximum time period for healthcare 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 summarised in cost-effectiveness acceptability curves. In addition to the probabilistic sensitivity analyses, several one-way sensitivity analyses were performed.

RESULTS

Patients

A total of 7,376 patients were randomised and took at least one dose of study medication; 3,707 in the tiotropium group and 3,669 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 healthcare utilisation during their time in the trial compared with patients who completed the trial.

In total, 7,250 patients had ⩾1 month of data on exacerbations and resource utilisation and were, therefore, included in the cost-effectiveness analysis (3,649 tiotropium and 3,601 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.

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

TABLE 2 Baseline characteristics of patients included in the cost-effectiveness study

	Tiotropium	Salmeterol
Subjects n	3649	3601
Male	74.7	75.1
Age yrs	62.9±8.9	62.8±9.0
Smoking status		
Current smoker	48.1	48.6
Smoking history pack-yrs	38.8±20.0	37.8±19.2
Patients in paid employment	27.5	28.4
Duration of COPD yrs	8.0±6.7	7.9±6.5
GOLD stage#		
II	48	50
III	43	42
IV	9	8
Post-bronchodilator FEV_1 % pred	49.2±13.3	49.4±13.1
Pulmonary medications		
Tiotropium	30.4	30.0
Short-acting anticholinergic drug	29.5	29.4
LABA¶	51.2	51.2
ICS+	53.4	53.0
LABA + ICS	43.1	43.2
Resource use in past year		
Scheduled visits to physician	3.9±3.6	3.8±3.3
Unscheduled visits to physician	1.3±1.4	1.2±1.6
ER visit without hospitalisation	0.10±0.6	0.09±0.6
ER visit followed by hospitalisation	0.11±0.4	0.11±0.4
Direct hospital admission	0.26±0.6	0.26±0.5

Data are presented as % or mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstrucive Lung Disease; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; LABA: long-acting β-agonist; ICS: inhaled corticosteroid; ER: emergency room. #: 23 patients were in GOLD stage I (tiotropium 0.2%; salmeterol 0.4%); ¶: LABA alone or in combination; +: ICS alone or in combination.

TABLE 3 Medication and exacerbation-related resource use, and absence from work

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

Data presented are per patient as observed during the trial, before imputation; trial-based analysis. Data are presented as mean±SD, unless otherwise stated. ICU: intensive care unit.

TABLE 4 Total 1-yr costs per patient after imputation and bootstrapping, trial-based analysis

	Tiotropium	Salmeterol	Difference
SHI perspective			
Study medication	581	369	213
Exacerbation-related healthcare use#	363 (317–411)	450 (400–502)	-87 (-157–-19)
Other COPD medication	144 (140–149)	144 (139–149)	1 (-6–7)
Total	1089 (1041–1137)	963 (912–1016)	126 (55–195)
Societal perspective			
Study medication	736	420	316
Exacerbation-related healthcare use#	363 (317–411)	450 (400–502)	-87 (-157–-19)
Other COPD medication	170 (164–176)	170 (164–176)	1 (-7–9)
Paid by the patient¶	24 (22–27)	29 (26–32)	-5 (-9–-1)
Productivity loss	115 (92–139)	170 (140–201)	-55 (-94–-18)
Total	1409 (1349–1469)	1239 (1171–1310)	170 (77–260)

Costs are presented as 2010 €. Data are presented as n or mean (95% uncertainty interval). SHI: statutory health insurance; COPD: chronic obstructive pulmonary disease. #: includes costs of hospital admissions, ambulance rides, visits to the emergency room and outpatient contacts to healthcare providers; ¶: includes patient co-payments for hospitalisation, ambulance rides, contacts with healthcare providers and travel costs.

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 in the tiotropium group 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.

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 €1,089 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 the study medication. Part of the higher costs of the study medication was 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 losses (€55, 95% UI €18–94).

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 days).

Trial-based cost-effectiveness

From a SHI perspective, the ICER of tiotropium compared with salmeterol was €1,961 per exacerbation avoided and €118 per exacerbation day avoided. These ratios were €2,647 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 (see online supplementary figure S1). The acceptability curves presented in figure 1 show that the probability that tiotropium is cost-effective at, for example, a willingness-to-pay of €5,000 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 1 exacerbation day, these probabilities were 93% and 91%, respectively.

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 tiotropium effect 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 1 yr, the difference in QALYs between tiotropium and salmeterol was 0.012 (95% UI -0.017–0.048). The difference in costs after 1 yr was €116 (95% UI €-32–262) from the SHI perspective (table 5). Hence, the costs per QALY gained of using tiotropium instead of salmeterol were €9,926. 5-yr treatment with tiotropium compared with salmeterol resulted in 0.082 QALYs (95% UI -0.250–0.519) gained. The cost increase was €287 (95% UI €-707–1282) from the SHI perspective. Hence, after 5 yrs the cost-effectiveness ratio of tiotropium *versus* salmeterol was €3,488 per QALY gained. Corresponding ICERs from the societal perspective were €16,771 and €8,141 after 1 and 5 yrs, respectively.

Figure 2 shows the acceptability curve for the costs per QALY gained using a 5-yr time horizon. If the maximum

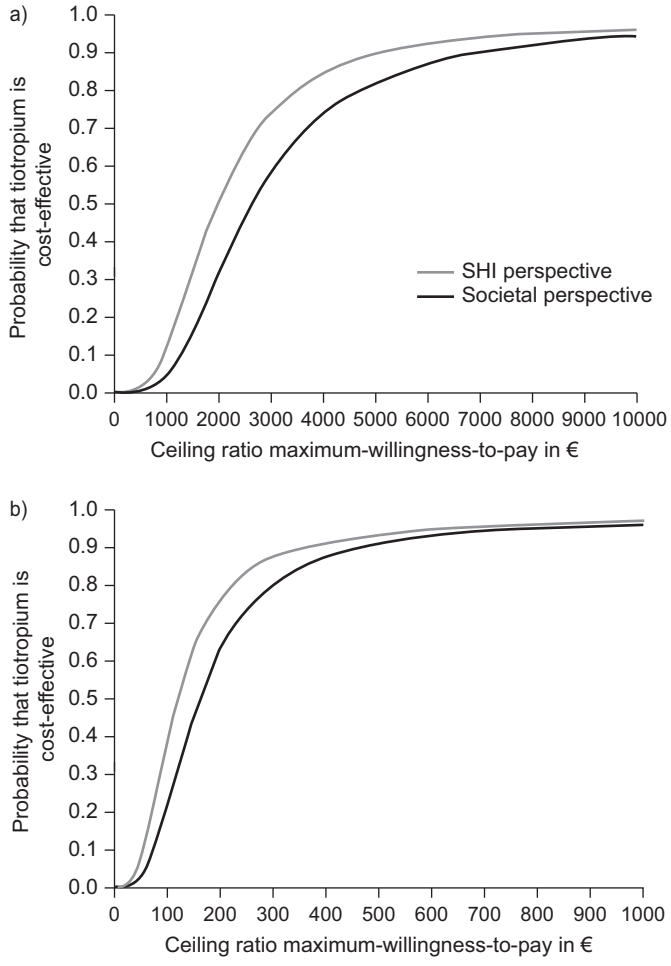

FIGURE 1. Acceptability curves for a) cost per exacerbation avoided and b) cost per exacerbation day avoided; trial-based analysis. SHI: statutory healthcare insurance.

willingness-to-pay for a QALY were €20,000, the probability that tiotropium was cost-effective compared to salmeterol was 62.5%, from the SHI perspective.

The one-way sensitivity analyses have been summarised in figure 3. For all sensitivity analyses the costs per QALY gained remained <€10,000.

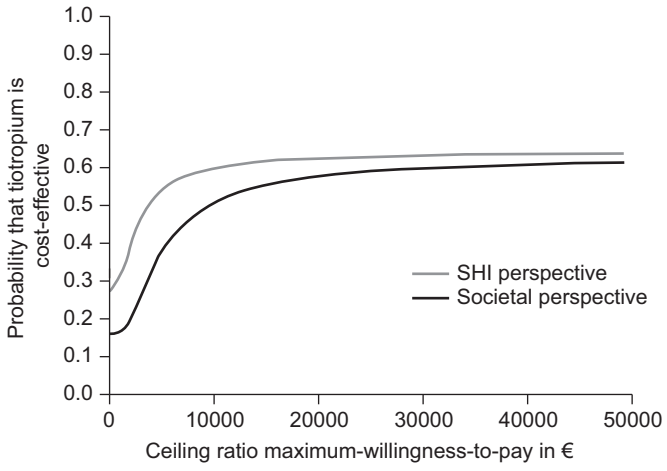

FIGURE 2. Acceptability curve for cost per quality-adjusted life year gained. Model-based analysis, 5-yr time horizon. SHI: statutory healthcare insurance.

DISCUSSION

In this study, the cost-effectiveness of tiotropium *versus* salmeterol for the treatment of patients with moderate to very severe COPD was investigated. The trial-based analysis showed that, from the perspective of the German SHI, the incremental cost-effectiveness ratios were €1,961 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 the 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. From the societal perspective, the list price of medications without the mandatory discounts that were applied in the SHI perspective was 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

TABLE 5 1- and 5-yr results from the model-based cost-effectiveness analysis

	Tiotropium	Salmeterol	Difference
1 yr			
QALYs	0.746 (0.726–0.762)	0.734 (0.700–0.755)	0.012 (-0.017–0.048)
Total costs SHI perspective	1186 (1110–1269)	1069 (951–1202)	116 (-32–262)
Total costs societal perspective	1570 (1474–1668)	1380 (1239–1532)	190 (10–363)
5 yrs			
QALYs	3.26 (3.04–3.43)	3.18 (2.78–3.42)	0.082 (-0.250–0.519)
Total costs SHI perspective	5659 (5135–6168)	5372 (4516–6222)	287 (-707–1282)
Total costs societal perspective	7520 (6850–8138)	6896 (5806–7937)	625 (-595–1869)

Data are presented as mean (95% uncertainty interval). QALYs: quality-adjusted life years; SHI: statutory healthcare insurance.

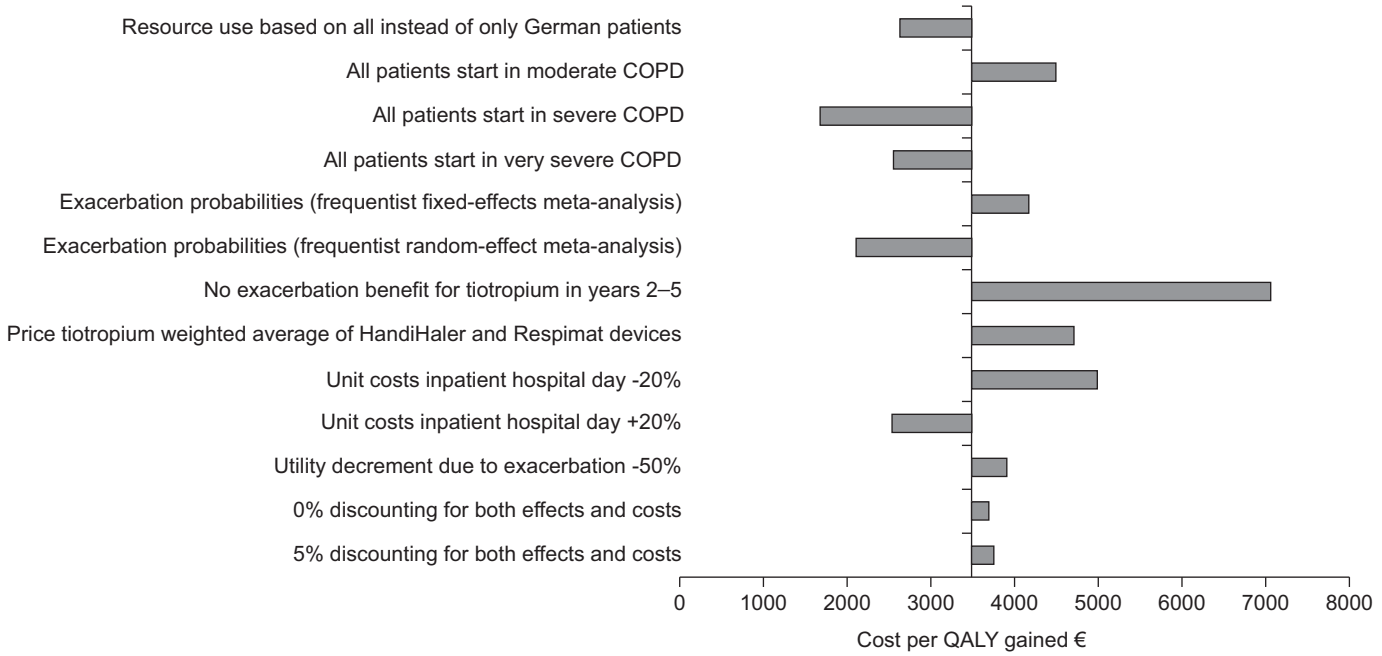

FIGURE 3. Sensitivity analyses for the model-based analysis of the cost per quality-adjusted life year (QALY) gained from tiotropium *versus* salmeterol using a time horizon of 5 yrs (statutory healthcare insurance perspective). The vertical line indicates the base case cost-effectiveness ratio of €3,488 per QALY gained. Handihaler is manufactured by Boehringer Ingelheim (Ingelheim am Rhein, Germany). Respimat is manufactured by Boehringer Ingelheim microParts GmbH (Dortmund, Germany). COPD: chronic obstructive pulmonary disease.

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 QALY when the health-related quality of life is measured at fixed time-points.

The model-based analysis yielded costs per QALY gained of €3,488 from the SHI perspective and €8,141 from the societal perspective. A costs per QALY ratio <€10,000 is widely considered as being cost-effective in the international literature, given that thresholds of £20,000–30,000 (€25,000–35,000) and US$50,000 (€40,000) 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 <€10,000. The cost-effectiveness acceptability curves in the trial-based analyses showed that at, for example, a willingness-to-pay to avoid an exacerbation of €5,000, 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, healthcare resources used, as well as unit costs, are known to vary between different countries due to variation in the organisation and financing of healthcare [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 the two regions. Furthermore, in the model-based analysis, we restricted resource-use estimates to the subset of German patients (n=1,105) 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 was found in the POET-COPD trial. The cost-effectiveness ratios from the SHI perspective were also comparable (€1,612 compared to €1,961 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 focuses on 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 $2,341 per exacerbation avoided or $26,094 per QALY gained [9]. Estimates of the cost-effectiveness of salmeterol *versus* short-acting bronchodilators or placebo ranged from cost savings of $10,152 per exacerbation avoided or $197,000 per QALY gained [9]. Six modelling studies investigated the cost-effectiveness of tiotropium *versus* salmeterol [12, 13, 31–34]. Four studies found that tiotropium was cost saving in comparison with salmeterol in the Netherlands, Greece, Switzerland and the UK [12, 31, 32, 34]. A study from NAIK *et al*. [33] found the cost-effectiveness ratio to be $1,817 per exacerbation avoided in USA. A study from RUTTEN-VAN MÖLKEN *et al*. [13] reported cost-effectiveness ratios of €4,118 per QALY gained, €841 per exacerbation avoided and €360 per exacerbation-free month gained in the Spanish setting. 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 β-agonists. There are no studies on the comparison with formoterol. The only study (model-based) on the comparison with indacaterol 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 on an open-label basis.

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. These higher costs were partly compensated by significant reductions in exacerbation-related costs, costs paid by the patient and costs due to productivity loss. In all sensitivity analyses, the 5-yr costs per QALY remained <€10,000, a threshold that is generally seen as very cost-effective in the international literature.

STATEMENT OF INTEREST

Statements of interest for M. Hoogendoorn, M.J. Al, K-M. Beeh, J.M. Graf von der Schulenburg, J. Lungershausen, B.U. Monz, H. Schmidt, C. Vogelmeier and M.P.M.H. Rutten-van Mölken, and for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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