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One-year cost-effectiveness of tiotropium *versus* ipratropium to treat chronic obstructive pulmonary disease

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ABSTRACT: The aim of this paper is to assess the health economic consequences of substituting ipratropium with the new, once-daily bronchodilator tiotropium in patients with a diagnosis of chronic obstructive pulmonary disease (COPD).

This prospective cost-effectiveness analysis was performed alongside two 1-yr randomised, double-blind clinical trials in the Netherlands and Belgium. Patients had a diagnosis of COPD and a forced expiratory volume in one second (FEV_1) $\leqslant$65% predicted normal. Patients were randomised to tiotropium (18 µg once daily) or ipratropium (2 puffs of 20 µg administered four times daily) in a ratio of 2:1.

The mean number of exacerbations was reduced from 1.01 in the ipratropium group (n=175) to 0.74 in the tiotropium group (n=344). The percentages of patients with a relevant improvement on the St. George's Respiratory Questionnaire (SGRQ) were 34.6% and 51.2% respectively. Compared to ipratropium, the number of hospital admissions, hospital days and unscheduled visits to healthcare providers was reduced by 46%, 42% and 36% respectively. Mean annual healthcare costs including the acquisition cost of the study drugs were €1721 (SEM 160) in the tiotropium group and €1,541 (SEM 163) in the ipratropium group (difference €180). Incremental cost-effectiveness ratios were €667 per exacerbation avoided and €1084 per patient with a relevant improvement on the SGRQ.

Substituting tiotropium for ipratropium in chronic obstructive pulmonary disease patients offers improved health outcomes and is associated with increased costs of €180 per patient per year.

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Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death and its prevalence is steadily increasing [1]. In the coming decades, general practitioners, respiratory physicians and other healthcare providers will be confronted with an increasing share of their patient population being COPD patients [2]. This is primarily a result of the aging of the population and their smoking behaviour in the past [3]. There is an acute need for more effective treatment options to reduce the burden of this disease for patients, caregivers and society.

Tiotropium is a new inhaled bronchodilator for patients with COPD with a sustained duration of action indicated for once daily dosing [4]. Recent trials showed that tiotropium has superior efficacy compared to ipratropium, salmeterol and placebo [5–7]. Based on the favourable results of these studies, it is suggested that "if the cost is not prohibitive, bronchodilation in moderate COPD could move to once-daily tiotropium" [8].

This paper addresses the health economic aspects of tiotropium as compared to ipratropium. It is the first pharmacoeconomic analysis of tiotropium, conducted to assess whether the benefits of this new therapy are achieved at reasonable costs. Such information is useful to support reimbursement and formulary decision-making and guide the positioning of tiotropium in the treatment spectrum for COPD.

The cost-effectiveness analysis was performed alongside the ipratropium-controlled clinical trials reported by VINCKEN *et al* [5]. These clinical trials showed highly significant differences in the primary outcome measure trough forced expiratory volume in one second (trough FEV_1), defined as the mean of the two predose measurements (*i.e.* 23–24 h after the preceding dose of tiotropium, or 8–9 h after the preceding dose of ipratropium). Trough FEV_1 was improved above baseline by 120 mL after 1 yr for patients receiving tiotropium, whereas it was declined by 30 mL for patients receiving ipratropium. Tiotropium was also found to be more effective in improving dyspnoea, exacerbations and health-related quality of life.

The aim of the cost-effectiveness analysis was to compare tiotropium and ipratropium with respect to healthcare utilisation and costs and to relate the difference in cost to the difference in COPD exacerbations and quality of life over a period of 1 yr. As recommended in current guidelines, a comprehensive societal perspective was adopted [9–11].

Methods

Design of the trials

This cost-effectiveness analysis was performed alongside two randomised controlled, double-blind, double-dummy,

parallel group trials comparing 18 μg tiotropium inhalation capsules administered once daily in the morning *via* the HandiHaler® device with ipratropium 2 puffs of 20 μg administered four times daily *via* the metered dose inhaler (MDI) in patients with airway obstruction due to COPD [5]. All drugs and devises used to administrate the drugs were supplied by Boehringer Ingelheim, Ingelheim am Rhein, Germany. The studies were conducted at 29 centres in the Netherlands and Belgium between October 1996 and June 1998. Since the design of both trials was identical, the cost-effectiveness analysis was based on the combined data. The trials were co-ordinated by Boehringer Ingelheim Pharmaceuticals Inc. in cooperation with the participating centres. Analysis and interpretation of the data and the writing of the manuscript are the sole responsibility of the authors.

Patients

Current or exsmokers with relatively stable COPD and a $FEV_1 \leqslant 65\%$ of predicted normal [12] and $FEV_1 \leqslant 70\%$ of forced vital capacity (FVC) were included. Bronchodilator responsiveness was not an entry criterion. Patients were also required to be aged >40 and to have a smoking history of at least 10 pack-yrs. Patients with a history of asthma, patients requiring regular supplemental oxygen and patients with a recent upper respiratory tract infection or a significant disease other than COPD were excluded. Patients were randomised per centre to either tiotropium or ipratropium in a ratio of 2:1 using a randomisation list with a block size of three. The sample size of the studies was based on the primary clinical outcome parameter trough FEV_1. To detect with 90% power and a type I error of 5% a change of 0.075 L over 1 yr, 240 patients per study were required. The trials were approved by the medical ethics committees of all participating centres and all patients gave written informed consent.

Data collection

Patients were followed for 1 yr. After a 2-week run-in period, patients were seen at baseline (start of study medication) and at weeks 1, 4, 7, 10, 13, 19, 26, 32, 39, 45 and 52 for scheduled regular visits. At all regular visits, data on healthcare utilisation, study drugs, concomitant therapy, and adverse events including COPD exacerbations were recorded in a case report form (CRF). Disease specific quality of life questionnaires were administered at baseline and after 1, 7, 13, 26, 39 and 52 weeks of treatment. All patients who completed at least one scheduled visit after randomisation were included in the cost-effectiveness analysis.

Health outcomes

Prespecified outcomes for the cost-effectiveness analysis were the number of COPD exacerbations and the number of patients with an improvement of at least four units on the St. George's Respiratory Questionnaire (SGRQ). An exacerbation was defined as a complex of respiratory symptoms (*i.e.* new onset or worsening of more than one symptom such as cough, sputum, dyspnoea or wheeze) lasting for $\geqslant 3$ days. The SGRQ is a disease-specific questionnaire designed to measure the impact of chest disease on health-related quality of life and well-being [13]. The questionnaire contained 50 items which can be aggregated into an overall score and three subscores for 'symptoms', 'activity' and 'impact'. An improvement of four units on the total score is considered to be the minimum clinically important difference [14, 15]. The impact of including other thresholds for the minimum clinically important difference is investigated in a sensitivity analysis. Additional outcomes to be considered secondarily in the cost-effectiveness analysis were the proportions of patients with an improvement in trough FEV_1 of at least 12% [16] and the proportion of patients with an improvement of at least one unit on the transitional dyspnoea index (TDI) over 1 yr [17, 18]. The TDI is an interviewer-administered questionnaire designed to improve the clinical evaluation of dyspnoea over time. The TDI consists of three components, *i.e.* functional impairment, magnitude of task and magnitude of effort. A TDI focal score is obtained by adding the scores of the three components and ranges from +9 (indicating a major improvement) to -9 (indicating a major deterioration).

Resource use

All resource use, irrespective of its reason, was recorded prospectively in a detailed pharmaco-economic section of the CRF, which was specifically designed for this study. Resource use included hospital admissions (intensive care unit; ICU and non-ICU days), emergency room visits, unscheduled visits to respiratory physicians, general practitioners and other healthcare providers, pulmonary function tests, imaging tests, laboratory tests, puffs of rescue medication (salbutamol, 1 puff=100 μg), and concomitant medication. In addition, the number of days patients were unable to perform the majority of their usual daily activities was recorded. If hospitalisation continued after the end of the study, the total length of stay included the days after the 1-yr study period. Dates of resource use were recorded to establish a link between resource use and adverse events, which were recorded in another section of the CRF. In the base-case analysis, only the respiratory-related resource use was included. This was defined as resource use related to adverse events that were classified as: 1) COPD and lower airway complaints; 2) upper airway complaints and 3) side effects of study-medication. The impact of including all resource use instead of respiratory-related resource use was investigated in a sensitivity analysis. Except for study medication, all protocol driven resource use was excluded from all analyses.

Costs

In the base-case analysis, costs were calculated by multiplying the respiratory-related resource use of each patient with Dutch 2001 unit costs expressed in Euros (table 1). All costs within the healthcare sector were taken into account, regardless of whether they were borne by government, health insurers or patients. Average unit costs of inpatient hospital days and outpatient visits were obtained from a study that aimed to set standard costs for economic analyses in the Netherlands [19]. This study included seven internal (including pulmonary) wards and five outpatient internal clinics of general and university hospitals. All unit costs included the costs of nursing, materials, hotel costs and the costs of buildings, equipment and overhead. Costs of respiratory physicians were included in the unit costs of inpatient hospital days, emergency room visits and outpatient visits, and were based on average time-estimates of 30 pulmonologists involved in the trials. Costs of pulmonary function tests, imaging tests and laboratory tests were based on charges. Costs of medications were based on list prices and included value added taxes and a mark-up of €6.02 per prescription to cover pharmacist fees. The price of tiotropium was determined assuming the

Table 1. – Unit costs of the most important types of healthcare utilisation in 2001 Euros

	The Netherlands	Belgium*
Day general/pulmonary ward	222	256
Day ICU	1110	769
Visit to pulmonologist	52	52
Visit to GP	17	15
Visit to nurse/physiotherapist	19	14
Visit to emergency room	98	70
Complete spirometry	34	33
Chest radiographs	42	13
Tiotropium (public price per day)	1.57	1.80
Ipratropium (public price per day)[#]	0.33	0.29

GP: general practitioner; ICU; intensive care unit; *: In the base-case analysis, trial-wide resource use is multiplied with Dutch unit costs. As the Belgian unit costs are used in sensitivity analyses, these costs are also reported in this table. [#]: Price of ipratropium based on administration by the metered dose inhaler.

annual use of 1 pack containing 10 units and the device and 11.83 packs with 30 units (refill). The price of ipratropium was based on a pack size of 200 units, administrated *via* the metered dose inhaler, the device used in the trials. Harmonised consumer price indices were used to convert unit costs of previous years to a 2001 price level [20]. Because the period of data collection covered only 1 yr, no discounting was used.

Cost-effectiveness

The prespecified incremental cost-effectiveness ratios were the healthcare costs per exacerbation avoided and the healthcare costs per patient with an improvement of at least four units on the total score of the SGRQ. In addition, the authors calculated the cost per patient with an improvement of at least 12% in trough FEV1 and the cost per patient with an improvement of at least one unit on the TDI.

Missing data

In order to deal with missing data of patients not completing the study, multiple imputation was used. Multiple imputation is a technique that, instead of imputing one value for each missing observation, replaces each missing observation with a set of multiple (in this case 10) plausible values [21, 22]. This resulted in 10 complete data sets for which the overall mean and variance were estimated. The variance between data sets was combined with the variance within data sets and can be considered as the added uncertainty that results from missing values. Imputation within each of the 10 data sets was performed using the propensity score method [23]. In this method, imputed values are drawn at random and with replacement from patients who are comparable on demographic and baseline characteristics and on costs and health outcomes in periods before dropout. Imputation was used for health outcomes and resource use and was performed in both treatment groups separately.

Analysis

Healthcare costs and measures of effectiveness were expressed as the mean (SEM) costs and effects per patient and year. The 95% confidence intervals (CI) of the differences between treatment groups were calculated, taking into account the between variance of the imputed datasets and assuming a normal distribution of the differences. To examine whether the normal distribution assumption held, the authors bootstrapped the major cost items of the individual datasets. This resulted in almost exact replicates of the 95% CIs as obtained with the 'conventional′ method. The incremental cost-effectiveness ratios were calculated as the difference in costs between tiotropium and ipratropium divided by the difference in effects. Due to statistical problems associated with the calculation of CIs for ratios, the uncertainty surrounding the cost-effectiveness ratio is presented graphically on a cost-effectiveness plane [24]. A cost-effectiveness plane is an x- y-axis plot where the horizontal axis shows the difference in effects between the treatment arms (tiotropium minus ipratropium) and the vertical axis shows the difference in costs. The uncertainty around the point-estimate of the difference in costs and effects is surrounded by a 95% elliptical confidence region. The discussion on whether the cost-effectiveness ratio is acceptable depends on the maximum that decision makers are willing to invest to obtain one unit of effect (*e.g.* to avoid one exacerbation). Because the value of this maximum acceptable ratio is unknown, the likelihood that tiotropium is cost-effective at different values of the maximum acceptable ratio is plotted as an acceptability curve [24].

Sensitivity analysis

To investigate the impact of assumptions made during the analysis and to test the robustness of results given variation in the data input, a number of sensitivity analyses were performed. The first sensitivity analysis included all resource use, instead of the respiratory-related resource use only. In the base-case analysis trial-wide resource use was combined with Dutch unit costs. In the second sensitivity analysis resources used by Belgian patients were multiplied with Belgian unit costs and resources used by Dutch patients were multiplied with Dutch unit costs, after which the results were combined. In the third and fourth sensitivity analysis the calculation of costs and health outcomes was based on country-specific unit costs and on the subgroup of patients treated in that particular country. In a fifth sensitivity analysis, the price of ipratropium was set to the average price of the metered dose inhaler (€0.33 per day) and the price of the dry powder inhaler (DPI; €0.97 per day), weighted by the actual use of these devices in the Netherlands (44% MDI versus 56% DPI). In the base case analysis an improvement of four units on the SGRQ total score was defined as a minimum clinically important difference. In a final set of sensitivity analyses (SA6 and SA7) the threshold value for a relevant improvement on the SGRQ was varied and set to six and eight units respectively.

Results

Patients

A total of 535 patients were randomised; 356 in the tiotropium group and 179 in the ipratropium group. About 85% of the patients were enrolled in the Netherlands and 15% in Belgium. A total of 92 patients (18%) withdrew from the study, 54 (15%) in the tiotropium group and 38 (21%) in the ipratropium group. Main reasons for withdrawal were worsening of COPD (11 (3%) in the tiotropium and 11 (6%) in the ipratropium group) and other adverse events (23 (6%) and 8 (4%) respectively). A total of 519 patients completed at least one scheduled clinic visit after the baseline visit and were included in the cost-effectiveness analysis. Lung function

Table 2. – Patient characteristics per treatment group at baseline

	Tiotropium	Ipratropium
Patients n	344	175
Age yrs	64 (8)	65 (8)
Males n(%)	289 (84)	151 (86)
Dutch n(%)	294 (85)	151 (86)
Current smokers n(%)	151 (43.9)	79 (45.1)
Smoking history in pack-yrs	33.8 (17.8)	33.2 (16.7)
Duration of COPD in years	11.3 (10.0)	10.9 (9.7)
FEV1 L	1.21 (0.44)	1.13 (0.38)
FEV1 % of predicted	40.6 (12.8)	38.0 (10.6)
FVC L	2.68 (0.85)	2.52 (0.71)
SGRQ total score	45.5 (16.6)	43.7 (17.6)

All data presented as mean (SD) unless otherwise stated. Reported baseline characteristics are slightly different from those reported in VINCKEN *et al.* [5] because of the different number of patients included for the economic analysis. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire.

parameters of these patients at baseline were slightly higher in the tiotropium group. Other baseline characteristics were comparable across the treatment groups (table 2).

Exacerbations

The mean number of exacerbations per patient was 0.74 (SEM 0.08) in the tiotropium group and 1.01 (SEM 0.10) in the ipratropium group; a difference of 0.27 (95% CI: 0.02; 0.52) or 27%. The percentage of patients with at least one exacerbation was 39.9% (SEM 2.9) in the tiotropium group and 53.5% (SEM 3.9) in the ipratropium group, a difference of 13.6% (95% CI: 4.1%; 23.1%). Approximately 17% of the exacerbations in the tiotropium group and 23% in the ipratropium group were associated with a hospitalisation (Pearson Chi-square: p=0.374).

Quality of life

The percentage of patients with an improvement of at least four units on the SGRQ after 1 yr was 51.2% (SEM 2.8) in the tiotropium group and 34.6% (SEM 3.8) in the ipratropium group; a difference of 16.6% (95% CI: 7.4; 25.9). The percentage of patients with a deterioration of at least four units was 26.0% in the tiotropium group and 33.7% in the ipratropium group, a difference of 7.7% (95% CI: -1.0; 17.0).

Pulmonary function

The percentage of patients with an improvement of at least 12% in FEV1 over 1 year was 47.6% (SEM 2.8) in patients treated with tiotropium and 25.0% (SEM 3.6) in patients treated with ipratropium, a difference of 22.6% (95% CI: 13.8; 31.6).

Dyspnoea

Approximately 30.5% of the patients in the tiotropium group and 16.2% of the patients in the ipratropium group, experienced an improvement of at least one unit on the TDI focal score over 1 yr (difference 14.3, 95% CI: 5.9; 22.7).

Resource use

The mean resource use per patient is presented in table 3. This table shows a consistent pattern of lower resource use in patients treated with tiotropium. The number of hospital admissions in the tiotropium group was reduced from 0.13 to 0.24, a difference of 45% (p=0.03). Approximately 11% of the patients in the tiotropium group and 19% in the ipratropium group had at least one hospital admission (p=0.03). The number of inpatient hospital days was reduced by 42%, from 2.98 (SEM 0.58) in the ipratropium group to 1.72 (SEM 0.37) in the tiotropium group (p=0.07). The number of unscheduled visits was reduced by 36%, from 3.18 (SEM 0.52) in the ipratropium group to 2.04 (SEM 0.16) in the tiotropium group (p=0.04). Only the number of inpatient days in the ICU was 0.08 (SEM 0.12) days higher in the tiotropium group, mainly due to one patient with an ICU stay of 24 days (p=0.37).

Costs

Total costs were €1,721 (SEM 160) in the tiotropium group and €1541 (SEM 163) in the ipratropium group, a difference of

Table 3. – The mean resource use per patient and year

	Tiotropium	Ipratropium	Difference	95% CI
Patients n	344	175		
Hospital admissions	0.13 (0.02)	0.24 (0.05)	-0.11	-0.21–-0.01
Inpatient days in				
General ward	1.62 (0.33)	2.96 (0.58)	-1.34	-2.64–-0.004
ICU	0.10 (0.09)	0.02 (0.02)	0.08	-0.10–0.26
Total	1.72 (0.37)	2.98 (0.58)	-1.26	-2.60–0.09
Unscheduled visits				
Pulmonologist	0.58 (0.06)	0.68 (0.10)	-0.10	-0.33–0.13
GP	1.16 (0.10)	1.48 (0.19)	-0.32	-0.75–0.11
Other HCP	0.25 (0.08)	0.88 (0.39)	-0.63	-1.42–1.52
Emergency room	0.05 (0.01)	0.14 (0.03)	-0.09	-0.16–-0.02
Total	2.04 (0.16)	3.18 (0.52)	-1.14	-2.20–-0.08
Ambulance transports	0.05 (0.02)	0.16 (0.07)	-0.11	-0.25–0.02
Puffs of salbutamol (rescue medication)	605 (42)	714 (68)	-109	-267–47
Inactivity days*	23.98 (2.87)	29.19 (4.03)	- 5.21	-14.92–4.49

All data presented as mean (SEM) unless otherwise stated. CI: confidence intervals; ICU: intensive care unit; GP: general practitioner; HCP: healthcare provider. *: Description in the case report form was "number of days unable to perform the majority of usual daily activities".

Table 4. – The mean healthcare costs per patient and year in 2001 Euros based on Dutch prices

	Tiotropium	Ipratropium	Difference	95% CI
Patients n	344	175		
Inpatient days				
General ward	359 (73)	657 (127)	-298	-586c–-10
ICU	116 (100)	26 (21)	90	-110–291
Total	475 (144)	683 (132)	-208	-591–175
Unscheduled visits: pulmonologist	30 (3)	35 (5)	-5	-17–7
GP	20 (2)	26 (3)	-6	-13–2
Other HCP	5 (2)	17 (8)	-12	-27–3
ER	5 (1)	13 (3)	-8	-15–2
Total	60 (5)	91 (13)	-31	-57–5
Concomitant medication	526 (20)	511 (25)	15	-47–78
Rescue medication (Salbutamol)	16 (1)	19 (2)	-3	-7–1
Diagnostic/prognostic tests	59 (12)	76 (14)	-17	-54–17
Ambulance transport	12 (4)	41 (16)	-29	-60–4
Costs without study medication	1148 (160)	1421 (163)	-273	-721–174
Study medication	573 (0)	120 (0)	453	
Costs including study medication	1721 (160)	1541 (163)	180	-268–627

Data presented as mean (SEM) unless otherwise stated. ICU: intensive care unit; GP: general practitioner; HCP: healthcare provider; ER: emergency room.

€180 (95% CI: -268; 627; table 4). The higher costs of study medication for tiotropium (€453) were partly offset by savings in other types of healthcare resource use (-€273, 95% CI: -721;174), especially inpatient hospital days (-€208, 95% CI: -591; 175). Costs of concomitant medication made up 30% of total costs and were almost the same in both treatment groups, €526 (SEM 20) in the tiotropium group and €511 (SEM 25) in the ipratropium group.

Cost-effectiveness

Because tiotropium was more effective and associated with higher costs, all incremental cost-effectiveness ratios were positive. The cost-effectiveness ratio was €667 per exacerbation avoided and €1,084 per patient with a relevant improvement in disease-specific quality of life. The cost per patient with a relevant improvement in dyspnoea was €1,259 and the cost per patient with a relevant improvement in FEV1 was €796. The uncertainty around the ratios of the two main outcome measures is presented graphically on the cost-effectiveness plane (fig. 1a and 1b). The three ellipses in each figure represent the 5, 50 and 95% confidence areas of the difference in costs and effects. In the cost-effectiveness plane of the costs per exacerbation avoided (fig. 1a), ~ 24% of the surface of the ellipses was situated in the lower-right quadrant, signifying lower costs and less exacerbations in the tiotropium group, whereas 74% was situated in the upper right quadrant signifying a reduction in exacerbations against higher costs. The dotted line from the origin through the point estimate of the difference in costs (€180) and effects (0.27) crosses one exacerbation avoided exactly at €667, the incremental cost-effectiveness ratio. Likewise, in the cost-effectiveness plane of the costs per patient with a relevant improvement in SGRQ total score (fig. 1b), ~25% of the surface of the ellipse was situated in the lower-right quadrant and 75% in the upper right quadrant. Both figs (1a and 1b) show that the uncertainty around the ratio was largely due to the uncertainty around the cost-difference.

The acceptability curves for the two incremental cost-effectiveness ratios are shown in figure 2. The vertical axis shows the percentage of time that tiotropium is cost-effective, given the value of the maximum acceptable ratio on the horizontal axis. If, for instance, the maximum willingness to pay per exacerbation avoided is set at €2,000, then the percentage of time that tiotropium is cost-effective (*i.e.* has a

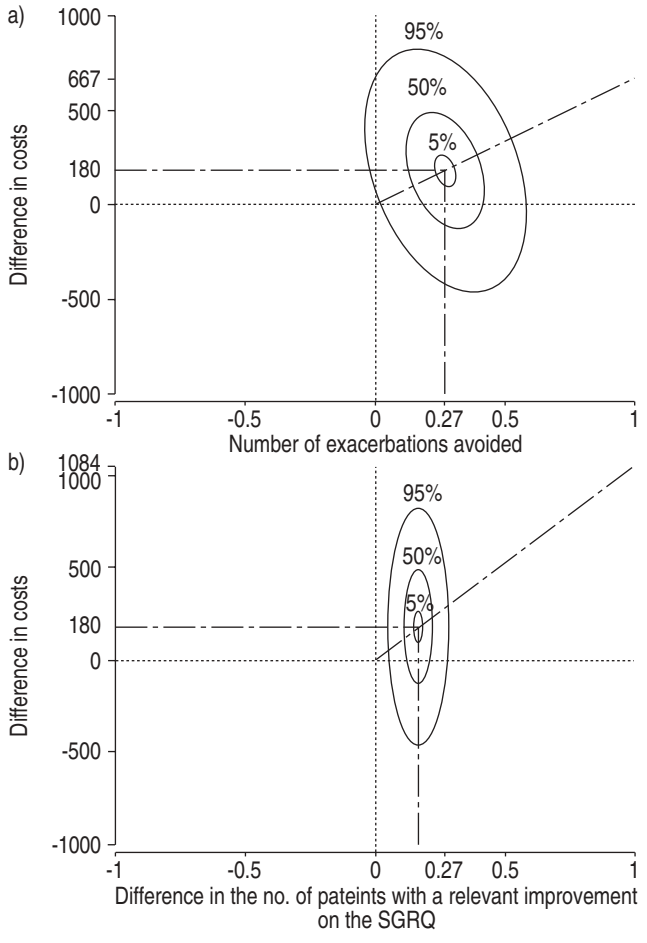

Fig. 1. – Cost-effectiveness planes representing the 5, 50 and 95% confidence areas of a) the incremental healthcare costs per incremental exacerbation avoided and b) the incremental healthcare costs per patient with a relevant improvement on the St. George's Respiratory Questionnaire. – · – (horizontal): point estimate of the difference in costs between tiotropium and ipratropium (€180); – · – (vertical): the point estimate of the difference in effects, 0.27 per exacerbation avoided and 0.17 per patient with a relevant improvement on the St. George's Respiratory Questionnaire; – · – (diagonal): value of the cost-effectiveness ratios of €667 and €1,084 respectively.

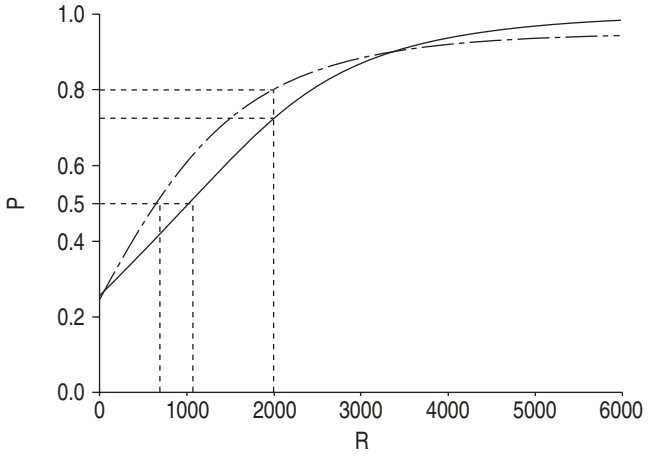

Fig. 2. – Acceptability curves of the cost per exacerbation avoid (– · –) and the cost per patient with a relevant improvement (—) on the St. George's Respiratory Questionnaire. R: the maximum acceptable value of the ratio in Euros; P: CE ratio is acceptable, given R. If the maximum acceptable ratio is set at €2,000, tiotropium will be acceptable 80 and 72% of the time respectively. The curves equal the point estimate of the incremental cost-effectiveness ratios at p=0.5. These are €667 per exacerbation avoided and €1,084 per patient with a relevant improvement in quality of life.

ratio below €2,000) is 80%. Likewise, if the maximum acceptable ratio of the costs per patient with a relevant improvement on the SGRQ is set at €2,000, tiotropium is cost-effective 72% of the time. The reading across the probability of 50% to the curves and down to the horizontal axis gives the point estimate of the incremental cost-effectiveness ratios (€667 and €1084 respectively).

Sensitivity analysis

The results of the sensitivity analysis are presented in table 5. Inclusion of all healthcare resource, use instead of respiratory-related resource use only (sensitivity analysis; SA 1), led to an increase in costs of ~40%, whereas the difference in costs between the two groups was reduced to €111. Valuation based on country-specific unit costs (SA2) or inclusion of Dutch patients only (SA3) had a small impact on the difference in costs and health outcomes. If only the Belgian patients were selected (SA4), the difference in costs hardly changed, whereas the difference in the number of exacerbations increased from 0.27 to 0.43 and the difference in the proportion of patients with a relevant improvement on the SGRQ increased from 16.6% to 33.2%. However, the number of Belgian patients was small: 50 patients in the tiotropium group and 25 patients in the ipratropium group. Changes in the costs of ipratropium had the largest impact on the difference in costs (SA5). When the costs of ipratropium were based on the weighted average of the MDI and DPI price, the difference in costs was decreased to 48 Euro, decreasing the cost-effectiveness ratio to €178 per exacerbation avoided and €289 per patient with a relevant improvement on the SGRQ. Increasing the threshold value of the SGRQ above which a change in health related quality of life was considered to be clinically important, decreased the proportions of patients improved with ~15% when the threshold values was set to 6 units (SA6) and with 30% when this value was set to eight units (SA7). The corresponding differences in the proportion of patients with a relevant improvement decreased to 13.3% and 11.1%, leading to higher cost-effectiveness ratios of €1,353 and €1,622 respectively.

Discussion

This is the first cost-effectiveness study that directly compares the new, once-daily bronchodilator tiotropium to ipratropium. Compared with ipratropium, tiotropium led to a 27% reduction in the mean number of exacerbations and a 17% increase in the number of patients with a relevant improvement on the total score of the SGRQ. In addition, a significantly greater proportion of patients had a clinically relevant improvement in lung function and dyspnoea. These improvements in health outcomes were associated with increased costs of €180 per patient per year. Hence, about 60% of the higher price of tiotropium (€453) was offset by a reduction in the costs of other healthcare resources (€273). These savings were primarily caused by a reduction in the number of hospital admissions and hospitalisation days, which were 45% and 42% lower respectively in patients receiving tiotropium than in patients receiving ipratropium. All other resource items, except concomitant medication, showed the same trend towards reduced costs in patients receiving tiotropium.

This economic evaluation was conducted alongside two

Table 5. – Sensitivity analysis of the differences in costs and health outcomes between tiotropium and ipratropium

	Difference in cost per patient	No of exacerbations avoided	Difference in the proportion of patients improved on the SGRQ %	ICER	
				Cost per exacerbation avoided	Cost per patient improved on the SGRQ
Base-case	180 (228)	0.27 (0.13)	16.6 (0.05)	667	1084
SA 1	111 (277)	0.27 (0.13)	16.6 (0.05)	411	669
SA 2	221 (229)	0.27 (0.13)	16.6 (0.05)	819	1331
SA 3	203 (243)	0.25 (0.12)	13.9 (0.05)	812	1460
SA 4	159 (635)	0.43 (0.51)	33.2 (0.13)	370	479
SA 5	48 (228)	0.27 (0.13)	16.6 (0.05)	178	289
SA 6	180 (228)	0.27 (0.13)	13.3 (0.05)	667	1353
SA 7	180 (228)	0.27 (0.13)	11.1 (0.04)	667	1622

All data presented as mean (SEM) unless otherwise stated. ICER: incremental cost-effectiveness ratio; SGRQ: St George's Respiratory Questionnaire; SA: sensitivity analysis; SA1: inclusion of all resource use; SA2: valuation based on country-specific prices; SA3: Dutch patients only tiotropium n=294, ipratropium n=151; SA4: Belgian patients only, tiotropium n=50, ipratropium n=24; SA5: price ipratropium based on the average of the metered dose inhaler (MDI) and the dry powder inhaler, weighted by the actual use of these devices in the Netherlands (MDI: 44%, DPI:56%); SA6: threshold value of a relevant improvement on the SGRQ set to six units; SA7: threshold value of a relevant improvement on the SGRQ set to eight units.

randomised controlled clinical trials. Hence, all resource use and health outcomes data were fully stochastic and collected prospectively over the 1-yr study period. This is an important strength of the current study as many economic evaluations use modelling often based on indirect data. Another strength of the study is the use of multiple imputation to deal with missing data of patients who dropped out before the scheduled end date after 1 yr. This method imputes values that are sampled from patients who are comparable on demographic and baseline characteristics and on costs and effects in previous periods and makes full use of the costs and effects the withdrawals had during the period they were still in the study. Above all, in contrast with other, more naïve methods, like case deletion, last value carried forward or mean imputation, multiple imputation takes account of the extra uncertainty that results from missing data, by imputing multiple values for each missing value [21]. In additional analyses the authors have shown that the estimates of the difference in costs between tiotropium and ipratropium obtained with multiple imputation were at least as conservative as those obtained with other methods to deal with the data of dropouts [25]. Adopting a complete case analysis would have seriously underestimated the real costs in both treatment groups, as the more severely ill patients were more likely to dropout. In both treatment groups, the mean costs per day of the dropouts during the time they were in the study were approximately four times as high as the mean costs per day of patients who completed the study [25].

This cost-effectiveness analysis was conducted from a societal perspective, which implies that all relevant costs should be taken into account. Hence, in addition to the direct healthcare costs, the authors also studied the indirect costs, *i.e.* the costs associated with absence from work and inability to perform the usual daily activities. Compared to ipratropium, the number of days that patients were unable to perform their usual daily activities including paid work was 18% less in tiotropium, although this difference was not statistically significant. As there is still a lot of discussion on whether and how these days have to be valued, [9, 26, 27] the authors choose not to include these indirect costs in the cost-effectiveness analysis. It is sometimes argued that the calculation of indirect costs is less relevant in a population of moderate and severe COPD patients, because only a small proportion of patients have a paid job. Indeed, in this study, only 9.6% had a paid job. As the proportion of patients with a paid job at baseline differed between the treatment groups (9.3% in the tiotropium group and 10.3% in the ipratropium group), calculating the costs of lost working days would increase the risk of introducing a bias against ipratropium.

Among the disadvantages of an economic evaluation piggybacked to a clinical trial is the occurrence of protocol driven costs. The costs of regular clinic visits were excluded because they were scheduled so frequently that they were not reflective of the treatment pattern in COPD. This may underestimate costs since these visits may have substituted visits that would have occurred if the trial had not taken place. On the other hand, because of the trial situation, patients may have felt less reservation to contact their physician sooner in case of minor complaints. The latter equally affects both treatment groups. The substitution effect however is more likely to occur in the ipratropium group, as the condition of these patients was less well controlled. Therefore, if there is a bias, it is more likely to be a bias against tiotropium. However, the contribution of unscheduled visits on total costs is small and it is unlikely that the difference in costs between treatment groups is largely affected by this bias. Concomitant medication is a more important contributor to total costs. As investigators were instructed to keep the dose of concomitant medication constant, throughout the trial (except in the event of an exacerbation), this study may have obscured changes in the use of concomitant medication. Hence, the costs of concomitant medication were almost the same in both treatment groups and considering the improved health outcomes in the tiotropium group may have led to an underestimation of the actual savings by tiotropium.

The sensitivity analysis showed that the difference in costs between tiotropium and ipratropium was most sensitive to the costs of the device by which ipratropium is administrated, varying from €0.33 per day in the base-case analysis based on the MDI price, to €0.69 per day when the price of ipratropium was based on the weighted average of the MDI (44%) and the DPI (56%). The latter price most accurately reflects the costs of current treatment with ipratropium in the Netherlands. Several papers have shown similar efficacy of the MDI and DPI [28, 29], this sensitivity analysis (SA5) suggests that the cost-effectiveness of tiotropium in daily practice in the Netherlands is probably better than demonstrated in this trial situation. The sensitivity of the results to the choice of the comparator should also be taken into account when reporting on the cost-effectiveness of tiotropium in other countries and is an important issue to consider with regard to the generalisability of cost-effectiveness analyses from one healthcare setting to another.

In other economic evaluations of lung diseases like lung transplantation [30] or lung volume reduction surgery [31] health outcomes have sometimes been measured by a generic quality of life questionnaire that enabled the calculation of quality adjusted life years. As such a questionnaire was not administered in this study, the authors were not able to compare the results with the outcomes of these studies. However, the primary health outcomes that were used in the cost-effectiveness ratios are among the clinical outcome measures most relevant in COPD exacerbations and quality of life (health status) [32]. For reasons of comparison the authors have used the SGRQ, because it is the most frequently used questionnaire in COPD. There is one other economic evaluation by JONES *et al* [33] who calculated the costs per patient with a four-unit improvement on the SGRQ. In this study, salmeterol was compared with placebo over 16 weeks in 189 patients with COPD and an incremental cost-effectiveness ratio was found of £497 (€785). In another economic evaluation, TORRANCE *et al.* [34] compared ciprofloxacin with usual antibacterial treatment for acute exacerbations of chronic bronchitis and reported incremental costs per acute exacerbation-day avoided of $CAN 332 (€217). Considering the average duration of an exacerbation (16 days in this present study) this is considerably higher than the €667 per exacerbation avoided that was found in the current analysis.

The threshold value of four units to identify patients with a minimum clinically relevant improvement on the SGRQ was determined in various studies conducted by the designer of the questionnaire [15] and nearly all studies reporting on the number of patients with a relevant improvement on the SGRQ have used this threshold. However, the authors have assessed the impact of changing the threshold value of the SGRQ on the cost-effectiveness ratio in the sensitivity analysis. This analysis showed that the cost-effectiveness ratio increased to €1353 and €1622 when the threshold value was set to six and eight units respectively, but the difference in the numbers of patients improving was still statistically significant at the 0.05 level.

Assessing the uncertainty around the cost-effectiveness ratios is especially important because many economic evaluations are piggybacked to clinical studies and sample size calculations are based on clinical rather than economic outcomes. Consequently, due to the large variation in costs

between patients, the power of economic evaluations is usually not sufficient to detect statistically significant differences in all economic outcomes. The lack of power in combination with the difficulties related to the interpretation of a ratio statistic, limit the use of classic statistical approaches commonly applied in clinical studies. It is therefore argued as by BRIGGS *et al.* [35] "the goal of economic evaluation should be the estimation of a parameter –incremental cost-effectiveness– with appropriate representation of uncertainty, rather than hypothesis testing". The cost-effectiveness plane and the acceptability curve are two instruments that have been developed to facilitate a visual and straightforward interpretation of the uncertainty around the cost-effectiveness ratios. The cost-effectiveness planes in this study showed that most of the uncertainty around the ratios was associated with the difference in costs between treatment groups. The surface of the ellipses was almost entirely in the upper and lower-right quadrants. Clearly, as long as none of the treatments is dominant (that is when the ellipses fall entirely in the upper left or lower right quadrant), the decision whether to accept a new treatment depends on the maximum willingness to pay for a gain in health. The acceptability curves show the probability that tiotropium is acceptable, given this maximum acceptable ratio. In our study, these figures showed that if the willingness to pay equalled zero, the probability that tiotropium is cost-effective is ~25%. Therefore the probability that tiotropium is cost-saving is about 25%. As the maximum acceptable ratio increases, the probability that tiotropium is cost-effective increases. As the willingness to pay to avoid one exacerbation or to have one additional patient with a relevant improvement on the SGRQ is set at €2,000, the probability that tiotropium is acceptable is 80% and 72% respectively.

In conclusion, tiotropium resulted in significant reductions of chronic obstruction pulmonary disease exacerbations and significant improvements in quality of life, lung function and dyspnoea compared to ipratropium. The additional costs to achieve these favourable outcomes were €180 per patient per year. The higher acquisition costs of tiotropium were offset by 60% through a decrease in other healthcare costs, especially costs of hospitalisations. This is a conservative estimate as tiotropium was compared to the cheapest way of administering ipratropium through the metered dose inhaler.

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