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Cost-effectiveness of the fixed-dose combination tiotropium/olodaterol versus tiotropium monotherapy or a fixed-dose combination of long-acting β2-agonist/inhaled corticosteroid for COPD in Finland, Sweden, and The Netherlands, a model-based study

Martine Hoogendoorn [1]

Isaac Corro Ramos [1]

Stéphane Soulard [2]

Jennifer Cook [3]

Erkki Soini [4]

Emma Paulsson [5]

Maureen P.M.H. Rutten-van Mölken [1,6]

1. Institute for Medical Technology Assessment (iMTA), Erasmus University Rotterdam, Rotterdam, The Netherlands

2. Boehringer Ingelheim The Netherlands, Amsterdam, The Netherlands

3. Boehringer Ingelheim GmbH, Ingelheim, Germany

4. ESiOR, Kuopio, Finland

5. Quantify Research, Stockholm Sweden

6 Erasmus School of Health Policy & Management (ESHPM), Erasmus University Rotterdam, Rotterdam, The Netherlands

Correspondence:

Martine Hoogendoorn

Institute for Medical Technology Assessment

Erasmus University Rotterdam

Burgemeester Oudlaan 50

3062 PA Rotterdam, The Netherlands

Phone: *31 10 4088871

Email: hoogendoorn@imta.eur.nl

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Abstract

Objectives: Chronic obstructive pulmonary disease (COPD) guidelines advocate treatment with combinations of long-acting bronchodilators for COPD patients that have persistent symptoms or continue to have exacerbations while using a single bronchodilator. This study assessed the cost-utility of the fixed dose combination of the bronchodilators tiotropium and olodaterol versus two comparators, tiotropium monotherapy and long-acting β2 agonist/ inhaled corticosteroid (LABA/ICS) combinations, in three European countries: Finland, Sweden, and The Netherlands.

Methods: A previously published COPD patient-level discrete event simulation model was updated with most recent evidence to estimate lifetime quality-adjusted life-years (QALYs) and costs for COPD patients receiving either tiotropium/olodaterol, tiotropium monotherapy or LABA/ICS. Treatment efficacy covered impact on trough forced expiratory volume in one second (FEV_1), total and severe exacerbations, and pneumonias. The unit costs of medication, maintenance treatment, exacerbations and pneumonias were obtained for each country. The country-specific analyses adhered to the Finnish, Swedish and Dutch pharmacoeconomic guidelines, respectively.

Results: Treatment with tiotropium/olodaterol gained QALYs ranging from 0.09 (Finland and Sweden) to 0.11 (The Netherlands) versus tiotropium and 0.23 (Finland and Sweden) to 0.28 (The Netherlands) versus LABA/ICS. The Finnish payer's incremental cost-effectiveness ratio (ICER) of tiotropium/olodaterol was €11,000/QALY versus tiotropium and dominant versus LABA/ICS. The Swedish ICERs were €6,200/QALY and dominant, respectively (societal perspective). The Dutch ICERs were €14,400 and €9,200, respectively (societal perspective). The probability that tiotropium/olodaterol was cost-effective compared to tiotropium at the country-specific (unofficial) threshold values for the maximum willingness to pay for a QALY was 84% for Finland, 98% for Sweden and 99% for The Netherlands. Compared to LABA/ICS this probability was 100% for all three countries.

Conclusions: Based on the simulations, tiotropium/olodaterol is a cost-effective treatment option versus tiotropium or LABA/ICS in all three countries. In both Finland and Sweden, tiotropium/olodaterol is more effective and cost saving (i.e. dominant) in comparison to LABA/ICS.

Keywords: COPD, cost-effectiveness, tiotropium/olodaterol, decision model, QALYs, costs

Strengths and limitations of this study

- A validated comprehensive health economic model built with patient-level data of 35,000 COPD patients was used for the analysis.
- This study is one of the first studies including effects and costs of adverse events related to COPD treatment.
- Indirect evidence for the comparison of tiotropium/olodaterol versus LABA/ICS was used by comparing both treatment options to tiotropium monotherapy.
- The model and efficacy data were based on data from COPD patients participating in clinical trials, which might limit extrapolation of the results to the COPD population as a whole.

Introduction

Chronic obstructive pulmonary disease (COPD) is a large and increasing health problem in Europe and associated with a high economic burden [1,2]. Pharmacological therapy to treat stable COPD mainly focuses on reducing symptoms, improving health status and reducing the risk for exacerbations. The most important types of medication available for COPD are long-acting β2 agonists (LABAs), long-acting anticholinergics (LAMAs) and inhaled corticosteroids (ICS) [3]. Older versions of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance advocated the use of LABA/ICS combinations for patients with severe airflow obstruction and frequent exacerbations [4]. More recent studies have shown that treatment response to ICS is variable across patients. High blood eosinophil levels are found to be a good predictor for treatment response for ICS, while the added value of ICS in patients with low eosinophil levels, patients with low symptoms and patients with a low exacerbation history seems limited [5]. In addition, the use of ICS is associated with an increased risk of pneumonia [3,6]. Several recent studies have found improvements in lung function, exacerbation and pneumonia rates with LABA/LAMA combinations compared to LABA/ICS [7-10]. Based on all these findings, the latest GOLD COPD guidelines recommend treatment with combinations of different types of long-acting bronchodilators (LABA/LAMA) for COPD patients who have persistent symptoms or exercise intolerance while using a single bronchodilator, and for patients with frequent exacerbations and a low blood eosinophil count [3]. However, because of the recommendations in the past, a substantial proportion of the COPD patients in Europe is currently still treated with combinations of a bronchodilator plus ICS. In both Sweden and The Netherlands around 60% of the COPD patients are using ICS for maintenance treatment [11,12], although for some of them LABA/LAMA combinations would be the preferred option according to the current GOLD guidance [3].

The fixed-dose LABA/LAMA combination tiotropium/olodaterol has been shown to improve lung function, decrease exacerbation risk and increase quality of life compared to tiotropium monotherapy [13-15]. Tiotropium/olodaterol has also been shown to be a cost-effective treatment option compared to tiotropium monotherapy in France, The Netherlands, Italy and the UK [16-19]. However, all these studies used efficacy data from one either the TONADO or the DYNAGITO trial [13,15]. A recent study provided new efficacy data based on a post-hoc analysis of both trials combined [20]. Moreover, the previously performed Dutch cost-effectiveness study was not performed from a societal perspective as recommended in the guidelines. The cost-effectiveness in Northern European countries, such as Sweden and Finland, and the cost-effectiveness versus other comparators than tiotropium, such as LABA/ICS, are currently unknown. Information on long-term effects, and costs of tiotropium/olodaterol are needed to guide clinical practice and optimize healthcare expenditures. Therefore, the current study aimed to estimate the cost-effectiveness of the fixed dose combination tiotropium/olodaterol versus two treatment options, i.e. tiotropium and LABA/ICS for Finland, Sweden and The Netherlands.

Methods

The study consisted of two steps. First, a literature search was performed to identify studies published in the past five years to obtain recent estimates for the efficacy of tiotropium/olodaterol versus tiotropium and LABA/ICS. Second, the efficacy data were used in a recently developed and published COPD patient-level discrete event simulation model to estimate the lifetime effects, costs and cost-effectiveness for tiotropium/olodaterol [16, 21, 22].

<ins>Efficacy data</ins>

Treatment efficacy was implemented using four relevant clinical parameters: trough forced expiratory volume in one second (FEV_1), total number of (severe) exacerbations and total number of pneumonias.

For the literature search on efficacy data the following prioritization of inclusion into the model was used. Efficacy data from a network meta-analysis (NMA) had the highest priority, followed by efficacy data from a pairwise meta-analysis, and efficacy data from single studies. To be able to compare the different treatment options with each other, the efficacy of all treatment options was defined relative to tiotropium, because that is the base-case in the health economic model. Consequently, a literature search was performed to obtain efficacy data for tiotropium/olodaterol versus tiotropium and LABA/ICS versus tiotropium. The efficacy of tiotropium/olodaterol versus tiotropium monotherapy with respect to exacerbations was based on a post-hoc analysis of the combined patient-level data of the TONADO and DYNAGITO trial [20]. The effect on trough FEV_1 was obtained from an NMA by Aziz et al (2018) [23]. The efficacy of LABA/ICS versus tiotropium was obtained from an NMA of Oba et al (2018) [24]. Because this NMA considered all types of LABA/ICS combined into one class, no specification in type of LABA/ICS was made for the current analyses. All efficacy data obtained from the literature used as input for the cost-effectiveness model are shown in Table 1. For pneumonias, efficacy data were only available for total pneumonias, and specification between moderate and severe pneumonias was not possible.

<u>Health-economic model</u>

A recently developed COPD patient-level discrete event simulation model was used to estimate the lifetime effects and costs for all the different treatment options. The model has been previously published and described in detail elsewhere [16,21,22]. In summary, the model is a discrete event simulation model that links a series of regression equations that predict intermediate and final outcomes at time t using a wide variety of patient characteristics and intermediate outcomes at time t-1. The intermediate outcome measures include three types of events (exacerbations, pneumonias and death), lung function, physical activity, symptoms and disease-specific quality of life. Final outcome measures are mortality, the number of quality-adjusted life-years (QALYs) and COPD-related healthcare costs. The regression equations were estimated using data from patients in the tiotropium treatment groups of five large COPD trials (TONADO, UPLIFT, EXACTT, POET, and TIOSPIR) [13,25-28]. Hence, tiotropium is the comparator group and the base case in the model.

The starting population of the model consists of the total patient population at baseline in the above-mentioned COPD trials, i.e. about 35,000 patients. For the current analyses, results of 2,000 randomly sampled patients were combined to estimate the average number of QALYs and health care costs for each treatment option. Simulating 2,000 patients was shown to provide stable results.

Relative efficacy of tiotropium/olodaterol and LABA/ICS compared to tiotropium was modelled by adjusting the base case outcomes of the regression equations for FEV_1, time to any exacerbation, probability that an exacerbation is severe, and time to pneumonia. Using tiotropium/olodaterol as example, the effect on FEV_1 (relative to tiotropium) is modeled by adding the mean difference in FEV_1 between tiotropium/olodaterol and tiotropium, 0.05 liter (Table 1) to the outcome of the standard equation for FEV_1 representative for tiotropium. The effect on exacerbations and pneumonias could not directly be applied because the regression equations for these outcomes predicted time to event and not event rates or proportion of patients with an event. Therefore, the outcome of the time to exacerbation equation was calibrated in such a way that the rate ratio for the annual exacerbation rate for exacerbations with tiotropium/olodaterol compared to the annual exacerbation rate with tiotropium was equal to RR=0.89 (Table 1). This approach was also applied for severe exacerbations. The time to pneumonia equation was calibrated such that the rate ratio for pneumonias for patients using tiotropium/olodaterol compared to patients using tiotropium was equal to RR=1.02 (Table 1). The same method was used to model the efficacy for LABA/ICS. In the base case analysis the hazard ratios for LABA/ICS presented in the literature were interpreted as rate ratios, because this assumption resulted in more conservative results than interpreting the hazard ratios as risk ratios. Treatment effects were assumed constant over the simulated lifetime horizon.

Cost-effectiveness analyses

The cost-effectiveness study was performed for three different countries: Finland, Sweden, and The Netherlands using the country-specific pharmacoeconomic guidelines to specify the base case analysis [29-31]. For Finland, a limited payer perspective was used including all direct health care costs and patient co-payments (value added tax excluded) related to COPD [29]. For Sweden, a societal perspective was applied including all direct medical health care costs related to COPD and costs of productivity loss [30]. Finnish and Swedish effects and costs were discounted by 3% per year [29,30]. For The Netherlands, a societal perspective was used including all direct medical costs related to COPD, unrelated medical costs in life-years gained, travel costs, costs of informal care and costs of productivity loss. Health effects were discounted by 1.5%, while costs were discounted by 4% per year [31].

Health outcomes

Intermediate health outcomes relevant for the current analysis were the annual total exacerbation rate, the annual severe exacerbation rate, the annual pneumonia rate and life-expectancy. The final health outcome for the cost-effectiveness analysis was the number of QALYs for each treatment option as predicted by the model. The regression equations to predict health outcomes were based on the international patient population included in the COPD trials and were assumed to be representative for Finland, Sweden and The Netherlands.

Costs

The model predicted costs for the following categories: study medication, maintenance treatment, and for treating exacerbations and pneumonias. The model was adjusted to the Finnish, Swedish and Dutch setting by using country-specific input data for all cost categories. All costs were valued in 2019 Euros. Costs were indexed to 2019 based on official indices if needed. The medication costs were calculated using official list prices (May 2020) of the three countries. If applicable, a weighted average was calculated using the market shares of the products. The total costs for study medication were calculated as the number of days alive multiplied with the daily medication costs (Table 2). Costs for maintenance treatment included the costs for visits to a general practitioner or respiratory specialist, spirometries, influenza vaccination and informal care, i.e. costs for unpaid care provided to a patient by family or friends. In the model the annual number of visits to a general practitioner and respiratory specialist was predicted by regression equations [21,22] using all patient characteristics and intermediate outcomes as predictors. To make the resulting number of visits representative for the specific countries, the outcome of the equations was multiplied with a correction factor that was calculated as the average annual number of COPD-related visits to a general practitioner or respiratory specialist in Finland, Sweden or The Netherlands (see Table 2) divided by the average number of visits predicted by the equation. The use of spirometries, influenza vaccination and informal care was assumed the same across patients (Table 2). For exacerbations and pneumonias, a distinction was made between costs for a moderate (no hospitalization), or a severe exacerbation or pneumonia (with hospitalization). Short-term productivity costs related to exacerbations and pneumonias were estimated using the average number of working days lost for per event estimated in the POET trial (moderate: 1.73 days, severe: 4.82 days) [21,27] multiplied by an estimate of the productivity costs per hour. For The Netherlands, unrelated medical costs in life-years gained were estimated using the PAID tool version 3.0 [57].

Incremental cost-effectiveness ratios

The model outcomes on QALYs and costs were used to calculate the difference in the total average number of QALYs and the total average lifetime costs per patient between two treatment options. Instead of performing a full hierarchical analysis as is common in cost-effectiveness analyses with multiple treatments, the choice of treatment comparisons was based on the current COPD guidelines [3].

After initial treatment with one long-acting bronchodilator (for example tiotropium), the guidelines recommend follow-up treatment for patients that remain having dyspnea or exacerbations, which is either LABA/LAMA (for example tiotropium/olodaterol) or LABA/ICS (for subgroup with high blood eosinophil levels). Based on these recommendations, incremental cost-effectiveness ratios (ICER) were calculated for the following treatment comparisons: tiotropium/olodaterol versus tiotropium monotherapy, LABA/ICS versus tiotropium monotherapy and tiotropium/olodaterol vs LABA/ICS. The ICERs were calculated as the difference in costs between two treatment options divided by the difference in QALYs.

Sensitivity and scenario analyses

Several scenario analyses were performed on the efficacy data, number of simulated patients, discount rate, and the perspective used for each country. In the base case analyses, the treatments were assumed to have an impact on FEV_1 and the exacerbation and pneumonia rates. Three scenario analyses were run assuming impact of treatment on FEV_1 only, exacerbations only, and FEV_1 plus exacerbations. Another scenario analysis was performed for LABA/ICS in which hazard ratios presented in the literature were interpreted as risk ratios instead of rate ratios as was done in the base-case analysis. A scenario analysis with 5,000 patients was performed to show the impact of the number of simulated patients on the results. The impact of discounting was explored for all countries, while in addition some country-specific scenario analyses were performed on the analytical perspective of the analysis. For Finland an analysis with a limited societal perspective [39] was run including the base case costs (direct payer costs, patient co-payments) (Table 2) as well as social services, travel costs and productivity costs, while for Sweden the impact of using a healthcare perspective only including direct medical costs was explored. For The Netherlands, an analysis from the healthcare perspective was performed as well as an analysis from the societal perspective without unrelated medical costs in life-years gained.

Finally, probabilistic sensitivity analyses (PSA) were performed to assess the joint uncertainty. The PSA were based on 300 sets of randomly drawn input parameters (outer loop) with a sample size of 100 patients per set (inner loop). Further details about the PSA have been published previously [21]. Based on the PSA results cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEAC) were constructed showing the uncertainty around the difference in QALYs and costs and the probability that one treatment is cost-effective compared to another treatment option at different values of the maximum willingness to pay values for a QALY in Finland, Sweden and The Netherlands, respectively. To assess whether a treatment was cost-effective the country-specific threshold values for the maximum willingness to pay for a QALY were taken into account. For Finland the low and unofficial threshold value of €20,000 per QALY was applied, while for Sweden an unofficial threshold value of SEK 500,000 (~€47,500) was used assuming that COPD was considered a disease with moderate severity. For The Netherlands the burden of disease was estimated to be 0.56, which corresponds with a threshold value of €50,000 per QALY [58].

Patient and public involvement

Clinical COPD experts were involved in the development of the health-economic model by providing their input on the model structure and input parameters and relevance of outcomes. This research was performed without patient involvement.

Results

The baseline characteristics of the patient population in the model at start of the simulation are shown in Table S1 In the Online Supplementary data. Of the 2000 simulated patients, about one quarter were female, the average age was 64 years and the mean FEV_1 was 1.4 liter (49% of the predicted value). Almost 60% of the patients had a history of exacerbations in the past year.

Base case cost-effectiveness analyses

Table 3 shows the annual exacerbation rates, the predicted average life-expectancy, and lifetime number of QALYs, and costs for tiotropium monotherapy, tiotropium/olodaterol, and LABA/ICS. In comparison with Finland and Sweden, the costs for all treatment options were much higher for The Netherlands as a result of the inclusion of costs for informal care and unrelated medical costs in life-years gained. Compared to tiotropium, treatment with tiotropium/olodaterol resulted in a gain in discounted QALYs of 0.092 for Finland and Sweden, and 0.111 for The Netherlands. For all countries, tiotropium/olodaterol was associated with an increase in medication costs compared to tiotropium, but these higher costs were partly outweighed by a reduction in exacerbation costs (Figure S1, Online Supplementary data). As a result, treatment with tiotropium/olodaterol was associated with an increase in net total costs, resulting in a cost-effectiveness ratio of €11,000/QALY gained for Finland, €6,200 for Sweden, and €14,400 for The Netherlands (Table 3).

Treatment with LABA/ICS compared to tiotropium resulted in fewer QALYs (-0.141) and higher costs (+€ 1,587-€2,161) for Finland and Sweden, and less QALYs (-0.171) and less costs (-€1,006) for The Netherlands.

For the comparison tiotropium/olodaterol versus LABA/ICS, the gain in discounted QALYs was 0.233 for Finland and Sweden, and 0.281 for The Netherlands. Compared to LABA/ICS, the higher treatment costs for tiotropium/olodaterol were completely outweighed by a reduction in exacerbation and pneumonia costs for Finland and Sweden (Figure S1, Online Supplementary data), resulting in tiotropium/olodaterol being the dominant treatment option, i.e. better health effects and less costs. For The Netherlands, the net total costs increase versus LABA/ICS was €2,597 and the cost-effectiveness ratio was €9,200/QALY.

Scenario analyses

The results of the scenario analyses showed that, for the comparison tiotropium/olodaterol versus tiotropium, a scenario assuming a treatment effect on lung function only (and not on exacerbations) had the highest impact on the ICERs. Assuming an effect on exacerbations only (no effect on pneumonias) in the comparison to LABA/ICS, increased the ICER from €9,200 to €12,300 for The Netherlands, while for Finland it would become €250/QALY instead of tiotropium/olodaterol being dominant. Using the limited societal perspective in Finland resulted in savings in costs for tiotropium/olodaterol versus both tiotropium and LABA/ICS, while using a healthcare perspective in The Netherlands resulted in tiotropium/olodaterol being dominant compared to LABA/ICS.

Cost-effectiveness planes are shown in the Online supplementary data (Figure S2-S4). Cost-effectiveness acceptability curves (Figure 1) showed that the probability that treatment with tiotropium/olodaterol is cost-effective compared to tiotropium at the country-specific (unofficial) willingness to pay thresholds was 84% for Finland, 98% for Sweden and 99% for The Netherlands. LABA/ICS had a probability of almost 0% of being cost-effective compared to tiotropium. Compared to LABA/ICS, the probability of tiotropium/olodaterol to be cost-effective was 100% for all three countries.

Discussion

The current study aimed to estimate the cost-effectiveness of tiotropium/olodaterol versus different comparators in three European countries, Finland, Sweden, and The Netherlands. The results showed that, compared to tiotropium, treatment with tiotropium/olodaterol resulted in a gain in QALYs and higher total costs. The resulting ICERs were below €14,400 per QALY for all three countries, resulting in tiotropium/olodaterol being a cost-effective treatment considering the country-specific thresholds for the maximum willingness to pay for a QALY. Compared to LABA/ICS, tiotropium/olodaterol resulted in a gain in QALYs and net savings in costs for Finland and Sweden. For The Netherlands, the ICER of tiotropium/olodaterol compared to LABA/ICS was €9,200 per QALY. Scenario analyses showed that the ICERs were robust to changes in general assumptions on discount rate, number of patients simulated, and interpretation of hazard rates. Using the unrealistic assumption that treatment with tiotropium/olodaterol only had an impact on lung function and not on exacerbations resulted in an increase in the ICERs and tiotropium/olodaterol being not cost-effective for Finland. Using a different analytical perspective reduced the ICERs substantially for Finland and The Netherlands.

Because the same efficacy data is used for all three countries, differences in the cost-effectiveness of tiotropium/olodaterol between the three countries can mainly be explained by discount rates, the unit costs and the perspective of the economic evaluation. The gains in QALYs varied between the countries due to the discount rate for health effects, 3% for Finland and Sweden and 1.5% for The Netherlands. ICERs were most favorable for Sweden, which can mainly be explained by the smaller difference in daily costs between tiotropium/olodaterol versus tiotropium and versus LABA/ICS compared to the other countries. Therefore, the incremental lifetime medication costs associated with tiotropium/olodaterol were lower for Sweden, which made it more likely that these costs could be compensated by reductions in exacerbation and pneumonia costs. The ICERs for Finland were generally between Swedish and Dutch ICERs. The Finnish base case analyses apply direct cost perspectives in health economic evaluations [29], which potentially miss two thirds of costs paid by society [39]. In addition, Finland has a costly pharmaceutical pricing scheme, which explains quite high margins (i.e. relative high retail costs excluding VAT in comparison to the generally affordable Finnish wholesale prices). The ICERs were highest for The Netherlands, because of the inclusion of informal care costs and unrelated medical costs in life-years gained as required by the guidelines for pharmacoeconomic evaluations [31]. Inclusion of these costs resulted in higher incremental costs for tiotropium/olodaterol, because these costs were mainly dependent on being alive and tiotropium/olodaterol increased the life-expectancy compared to the other two treatment options. Medication costs for The Netherlands were derived from list prices of May 2020. New list prices resulting from a change in reference countries were published in October 2020; they were in general lower, but the relative decrease in price was larger in tiotropium/olodaterol and tiotropium than in LABA/ICS. Using the most recent prices would have further reduced the ICER compared to LABA/ICS.

The results of the current study were in line with previous published cost-effectiveness studies for tiotropium/olodaterol [16-19]. A study for France reported an ICER for tiotropium/olodaterol compared to tiotropium of €2,900 per QALY using a societal perspective [16]. This study used the same health-economic model as used in the current study. However, the efficacy for tiotropium/olodaterol versus tiotropium in the previous study was based on one trial and only defined as the impact on exacerbations. In the current study efficacy was based on all available evidence combined using data from an NMAs and a post-hoc analysis of two trials and efficacy was modelled as an impact on multiple parameters (trough FEV1, exacerbations, pneumonias), which explains the difference in QALYs gained in the current study compared to the French study [16]. A previous Dutch study found an ICER of €7,000 per QALY for tiotropium/olodaterol versus tiotropium [17], which was lower than the ICER in the current study, €14,400 per QALY. This might be explained because the earlier study did not include costs for informal care and unrelated medical costs in life-years gained, which were shown to have a substantial impact on the ICER (as shown in sensitivity analyses). A study from Seyla-Hammer reported an ICER of €7,500 per QALY for tiotropium/olodaterol compared to tiotropium in Italy [18]. Tebboth et al. explored the cost-effectiveness of tiotropium/olodaterol compared to other LABA/LAMA combinations in the UK and concluded that the ICER for tiotropium/olodaterol was acceptable and comparable with the ICERs for the other LABA/LAMA combinations [19]. None of the earlier published studies compared tiotropium/olodaterol with LABA/ICS or included Finland or Sweden.

A key strength of the current study was that a comprehensive health-economic model for COPD was used to simulate the long-term outcomes. The model has been validated and previously used for cost-effectiveness analyses [16,21,22] and has been built with patient-level data of 35,000 COPD patients. The current study is also one of the first studies including the effects and costs of adverse events related to the treatment. LABA/ICS is associated with an increased risk for pneumonias [3,6], which is however, often not included in cost-effectiveness models.

A limitation of the current study was that the efficacy data found in the literature were expressed in different ways and sourced from different studies. Efficacy for tiotropium/olodaterol versus tiotropium was expressed as rate ratios, while efficacy for LABA/ICS was reported as hazard ratios. The model has the option to apply treatment efficacy as rate ratios or risk ratios. For this study we took a conservative approach and interpreted all reported results as rate ratios for the base case and risk ratios in a scenario analysis. A second limitation was that indirect evidence for the comparison of tiotropium/olodaterol versus LABA/ICS was used by comparing both treatments to tiotropium, which was in line with how the model has been built. Several studies have compared LABA/LAMA and LABA/ICS combinations directly [7-10]. Yet, evidence supports our approach. A Cochrane review from 2017 including ten studies reported that LABA/LAMA combinations resulted in fewer exacerbations, a larger improvement in FEV1 and lower risk of pneumonia compared to LABA/ICS, although the evidence was of low or moderate quality, in general [8]. Another meta-analysis from 2017 including 18 studies found a significant improvement in trough FEV1 and lower annual exacerbation rates and pneumonia risks for LABA/LAMA versus LABA/ICS [9]. A recent real-life study comparing treatment with tiotropium/olodaterol and LABA/ICS directly found that tiotropium/olodaterol resulted in fewer exacerbations (HR: 0.74 (95%: 0.68-0.85) and fewer pneumonias (HR: 0.74 (95% CI: 0.57-0.97) [59]. Using these data in the model would have resulted in a comparable ICER for tiotropium/olodaterol versus LABA/ICS for The Netherlands,

(€9,600/QALY), while tiotropium/olodaterol would also have been the dominant treatment option for Finland and Sweden resulting in more effects and lower costs.

In conclusion, this model-based health economic evaluation showed that treatment with the fixed-dose combination of tiotropium/olodaterol resulted in a gain in QALYs compared to tiotropium monotherapy and LABA/ICS. Compared with LABA/ICS, tiotropium/olodaterol resulted in savings in costs in Finland and Sweden and a low cost per QALY gained for The Netherlands. Compared to tiotropium, tiotropium/olodaterol can be considered a cost-effective treatment option in all three countries with low ICERs varying between €6,200 and €14,400 per QALY. The model outcomes were robust within most of the sensitivity analyses that were performed.

Contributorship statement

MH developed the health-economic model, designed the study, collected input data, performed the modelling analysis and wrote the first version of the manuscript

ICR developed the health-economic model, designed the study and performed part of the modelling analysis and contributed to drafting and critical review of the manuscript

SS provided data to develop the model, supervised the design of the study and interpretation of the results and contributed to drafting and review of the manuscript

JC provided data to develop the model, supervised the design of the study and interpretation of the results and contributed to drafting and review of the manuscript

ES: collected input data and contributed to interpretation of the results and to drafting and critical review of the manuscript

EP: collected input data and contributed to interpretation of the results and to drafting and critical review of the manuscript

MRM: developed the health-economic model, designed the study, collected input data and contributed to the analysis and interpretation of the results and to drafting and critical review of the manuscript

All authors approved the final version for publication.

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Competing interests

MH reports grants from Boehringer Ingelheim, during the conduct of the study.

ICR has nothing to disclose

SS is an employee of Boehringer Ingelheim

JC is an employee of Boehringer Ingelheim

ES is a partner, employee and CEO of ESiOR Oy, Kuopio, Finland. ESiOR Oy carries out studies, statistical analysis, consultancy, education, reporting and health economic evaluations for several pharmaceutical (including companies producing and marketing treatments for COPD), food industry, diagnostics and device companies, hospitals, consultancies, projects and academic institutions.

EP reports grants from Institute for Medical Technology Assessment (iMTA), Erasmus University Rotterdam, during the conduct of the study; personal fees and other from Quantify Research AB, outside the submitted work

MRM reports grants from Boehringer Ingelheim, during the conduct of the study.

Patient consent for publication:

Not required

Ethics approval:

Ethical approval was not required, because the economic evaluation was based on a mathematical model analysis.

Data sharing management

Data are available upon reasonable request.

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Table 1: Efficacy for COPD treatment options compared to tiotropium used as input for the cost-effectiveness model

	Tiotropium/olodaterol	LABA/ICS
Trough FEV1 in liter, mean difference (95% CI)	+0.05 (0.03; 0.09) [23]	Not available, assumed zero*
Total exacerbations, ratio (95% CI)	RR=0.89 (0.84; 0.95) [20]	HR=1.03 (0.91; 1.17) [24]
Severe exacerbations, ratio (95% CI)	RR=0.86 (0.75; 0.99) [20]	HR=1.25 (0.86; 1.85) [24]
Total pneumonias#, ratio (95% CI)	RR=1.02 (0.86; 1.21) [13,15]	HR=2.02 (1.16; 3.72) [24]

No distinction could be made between moderate and severe pneumonias.

*To be conservative we assumed the difference to be zero.

LABA=long-acting beta-2 agonists (LABA's), ICS=inhaled corticosteroids (ICS), CI=confidence interval, RR=rate ratio, HR=hazard ratio

Table 2: Country-specific input data for healthcare use and costs (price level 2019)

Cost item	Unit	Finland (Market share weighted retail, VAT excluded)	Sweden (societal perspective)	The Netherlands (societal perspective)
Medication costs				
Tiotropium	Per day	€1.32 [32,33]	€1.00 [41,42]	€1.41 [49]
Tiotropium/olodaterol	Per day	€1.81 [32,33]	€1.32 [41,42]	€1.72 [49]
LABA/ICS	Per day	€1.28 [32,33]	€1.22 [41,42]	€1.31 [49]
COPD-related annual maintenance treatment*				
General practitioner	Visits Unit cost	1.73 [34] €120 [35]	2.74 [43][a] €160 [44]	3.64 [50,51] €38.88 [52]
Respiratory specialist	Visits Unit cost	0.82 [36] €305 [35]	1.78 [43] €239 [44]	1.36 [50,51] €103.19 [52]
Spirometry test	Tests Unit cost	0.77 [37] €52.38 [35]	0.64 [45] [b] €76 [44]	0.72 [50,53] €17.95 [52]
Influenza vaccination	Vaccination Unit cost	0.52 [38] €51.28 [35]	0.52 [46] €65 [44]	0.52 [54] €15.75 [52]
Informal care#	Hours Unit cost	Not applicable	Not applicable	270 [55] €14.95 [52]
Costs related to COPD exacerbations				
Moderate exacerbation	Per event	€220 [37,39,40]	€634 / €289*^ [21,42,44,47]	€637 / €124*^ [21,49,52]
Severe exacerbation (=hospitalization)	Per event	€4390 [35,37,40]	€4028 / €3067*^ [21,42,44,47,48]	€5612 / €4182*^ [21,49,52,56]
Costs for treating pneumonias				
Without hospitalization	Per event	€225 [35]	€584 / €239* [44,47]	€637 / €124* [21,49,52]

With hospitalization	Per event	€4498 [35,39,40]	€5813 / €4851* [44,47,48]	€5142 / €3711* [52,56]
Average retirement	Age in years	Not applicable	65 [47]	65 [52]

*Costs below retirement age including short-term productivity costs / costs above retirement age without productivity costs,

Exchange rate for Sweden 1 SEK = €0.095 (May 2020)

Unpaid care provided to a patient by family or friends

[a] Incremental number of primary care visits for COPD 5.17 [43] of which 53% was with physician [43]

[b] Weighted average for primary care and secondary care patients [45]

^Bottom-up estimate of healthcare use for a moderate and severe exacerbation [21] and country-specific unit costs and duration of a hospitalization for COPD

Table 3: Lifetime model results and cost-effectiveness results

	Treatment option:	Tiotropium/ olodaterol	Tiotropium	LABA/ICS	Tiotropium/olodaterol versus tiotropium	LABA/ICS versus tiotropium	Tiotropium/olodaterol versus LABA/ICS
Equal across countries	Annual total exacerbation rate	0.592	0.664	0.679	-0.072	+0.015	-0.087
	Annual severe exacerbation rate	0.128	0.148	0.184	-0.020	+0.036	-0.056
	Annual pneumonia rate	0.035	0.035	0.071	0.001	+0.036	-0.035
	Life-expectancy (years)	11.75	11.54	11.16	+0.21	-0.38	+0.59
Finland	Discounted QALYs	6.159	6.067	5.926	0.092	-0.141	0.233
	Discounted lifetime costs	16,921	15,910	17,497	€1,011	€1,587	-€576
	Incremental cost-effectiveness ratio				€11,013	Dominated*	Dominant**
Sweden	Discounted QALYs	6.159	6.067	5.926	0.092	-0.141	0.233
	Discounted lifetime costs	18,916	18,348	20,509	€568	€2,161	-€1,736
	Incremental cost-effectiveness ratio				€6,193	Dominated*	Dominant**
The Netherlands	Discounted QALYs	6.832	6.722	6.551	0.111	-0.171	0.281
	Discounted lifetime costs	137,253	135,662	134,656	€1,591	-€1,006	€2,597
	Incremental cost-effectiveness ratio				€14,398	€5,902***	€9,243

*A treatment is dominated by the comparator, when the treatment results in less health effects and higher costs. **A treatment is dominant versus a comparator when the treatment results in better health effects and savings in costs. ***ICER should be interpreted as cost saved per QALY lost

Table 4: Scenario analyses; impact on the incremental cost-effectiveness ratios (ICERs)

Country	Scenario	ICER tiotropium/olodaterol versus tiotropium	ICER LABA/ICS versus tiotropium	ICER tiotropium/olodaterol versus LABA/ICS
Finland	Base-case [a]	€11,013	Dominated*	Dominant**
	Effect on: FEV_1 only	€52,438	NA	NA
	Effect on: Exacerbations only	€16,225	Dominated	€251
	Effect on: Exacerbations + FEV_1	€10,265	Dominated	€251
	Hazard rates interpreted as risk ratios	NA	Dominated	Dominant
	5,000 simulated patients	€10,203	Dominated	Dominant
	No discounting	€9,726	Dominated	Dominant
	Limited societal perspective	Dominant	Dominated	Dominant
Sweden	Base-case [b]	€6,193	Dominated	Dominant
	Effect on: FEV_1 only	€36,165	NA	NA
	Effect on: Exacerbations only	€7,977	Dominated	Dominant
	Effect on: Exacerbations + FEV_1	€5,610	Dominated	Dominant
	Hazard rates interpreted as risk ratios	NA	Dominated	Dominant
	5,000 simulated patients	€5,662	Dominated	Dominant
	No discounting	€6,531	Dominated	Dominant
	Healthcare perspective	€7,130	Dominated	Dominant
The Netherlands	Base-case [c]	€14,398	€5,902***	€9,243
	Effect on: FEV_1 only	€38,401	NA	NA
	Effect on: Exacerbations only	€15,849	€9,211***	€12,319
	Effect on: Exacerbations + FEV_1	€14,176	€9,211***	€12,319
	Hazard rates interpreted as risk ratios	NA	€4,732***	€8,248
	5,000 simulated patients	€13,898	€6,229***	€9,296
	No discounting	€18,674	€10,168***	€13,513
	Healthcare perspective	€3,638	Dominated	Dominant
	Societal perspective without unrelated medical costs in life-years gained	€6,715	Dominated	€754

[a] Payer perspective, 2000 simulated patients, discount rate 3%, and effect on FEV1, exacerbations and pneumonias, [b] Societal perspective, 2000 simulated patients, discount rate 3% and effect on FEV1, exacerbations and pneumonias, [c] Societal perspective, 2000 simulated patients, discount rate 1.5% for effects and 4% for costs

and effect on FEV1, exacerbations and pneumonias, NA=not applicable, *A treatment is dominated by the comparator, when the treatment results in less health effects and higher costs. **A treatment is dominant versus a comparator when the treatment results in better health effects and savings in costs. ***ICER should be interpreted as cost saved per QALY lost

Figure legends

Figure 1: Acceptability curves for tiotropium/olodaterol versus tiotropium (black), tiotropium/olodaterol versus LABA/ICS (grey) and LABA/ICS versus tiotropium (dashed) for A) Finland, B) Sweden and C) The Netherlands

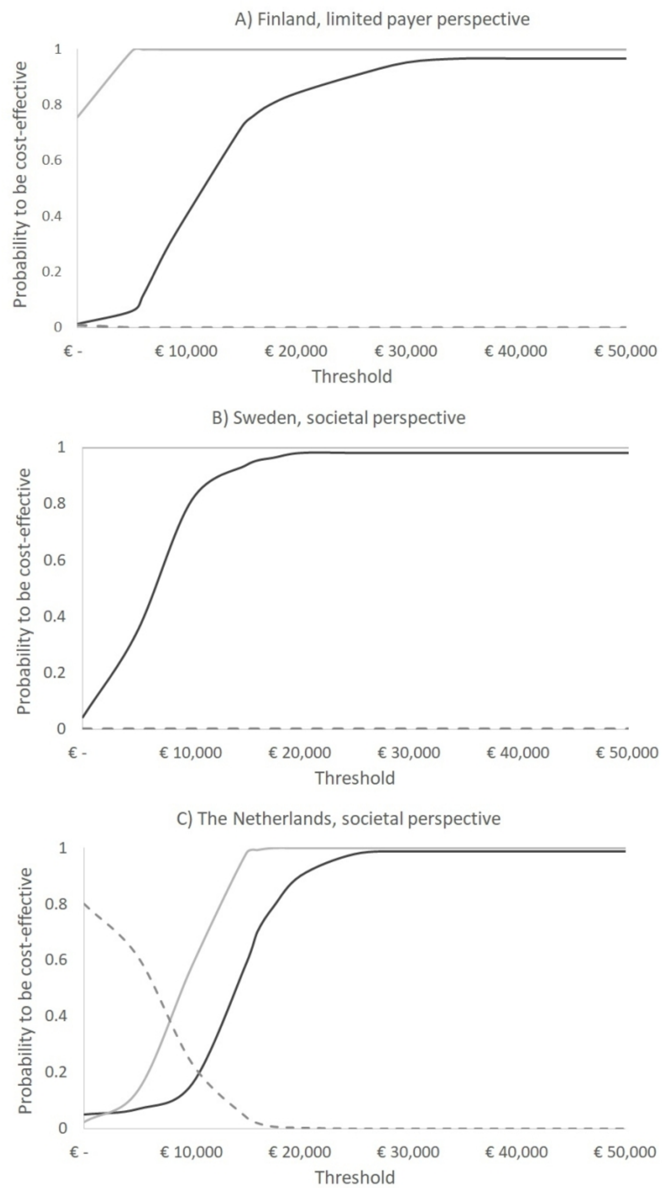

Figure 1: Acceptability curves for tiotropium/olodaterol versus tiotropium (black), tiotropium/olodaterol versus LABA/ICS (grey) and LABA/ICS versus tiotropium (dashed) for A) Finland, B) Sweden and C) The Netherlands

76x135mm (300 x 300 DPI)

Online supplementary data for manuscript:

"Cost-effectiveness of the fixed-dose combination tiotropium/olodaterol versus tiotropium monotherapy or a fixed-dose combination of long-acting β2-agonist/inhaled corticosteroid for COPD in Finland, Sweden, and The Netherlands, a model-based study"

Table S1: Baseline characteristics of the 2,000 simulated patients

Characteristic	Total population
Total number of patients available in the model population	35,341
Female, %	26
Age (years)	64
FEV_1 (L)	1.4
FEV_1% predicted, %	49
Low BMI (<21 kg/m^2), %	15
Smoking, %	38
Pack-years (years)	44
Emphysema, %	49
Asthma, %	6
Heart failure, %	5
Other CVD, %	13
Depression, %	8
Diabetes, %	11
High eosinophils, %	24
Bronchodilator responsiveness (%)	23
Previous exacerbations, %	59
Previous severe exacerbations, %	16
Exercise capacity (seconds)	347
Physical activity, SGRQ activity score (points)	59
Presence cough/sputum, %	67
Presence breathlessness, %	63
Disease-specific quality of life, SGRQ total score (points)	44

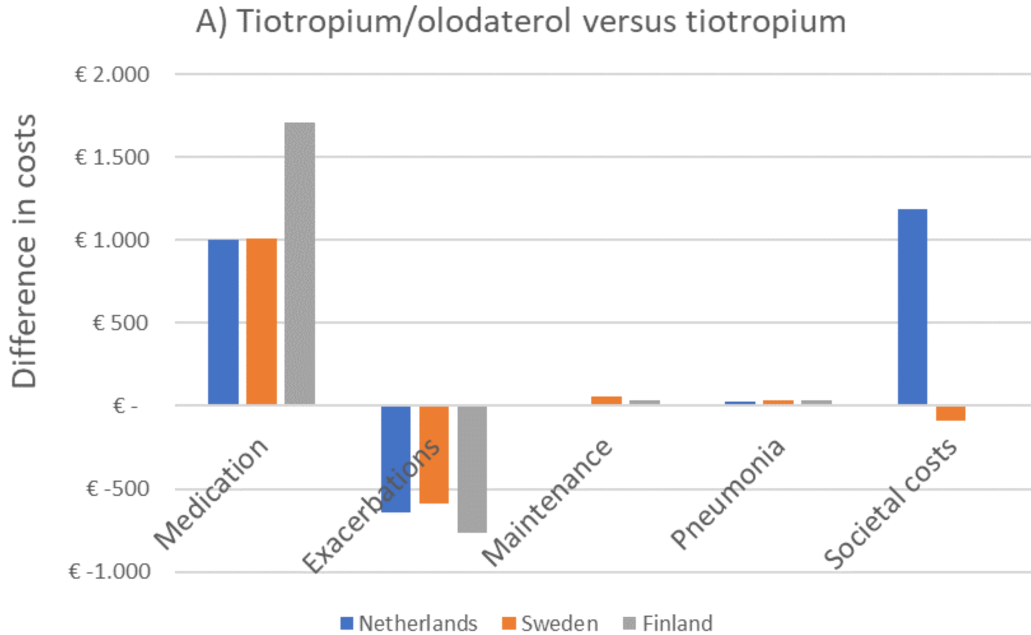

Figure S1A: Difference in costs between tiotropium/olodaterol and tiotropium specified by type of costs

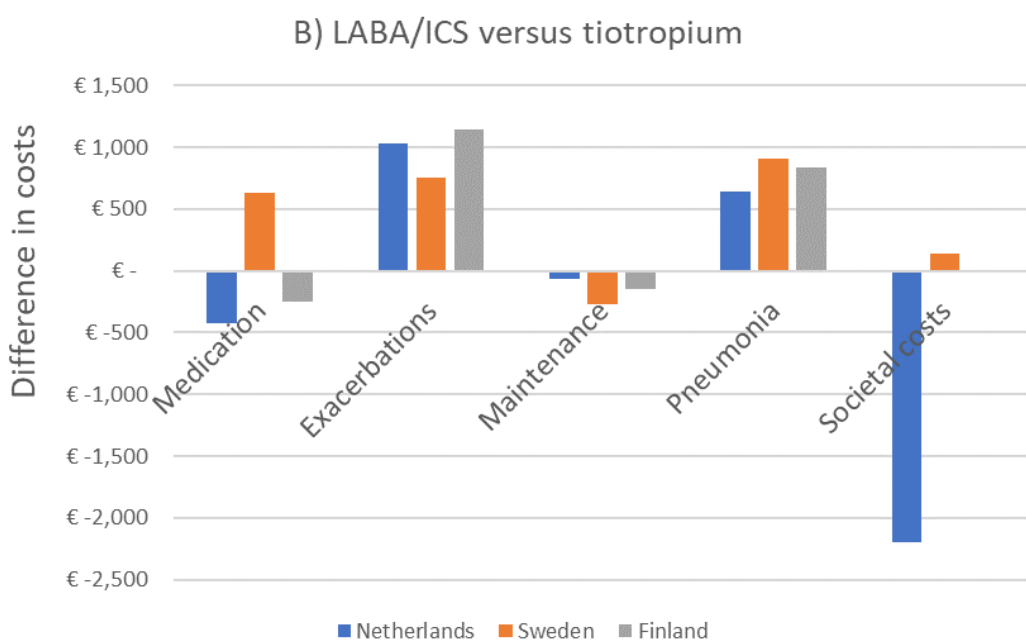

Figure S1B: Difference in costs between LABA/ICS versus tiotropium specified by type of costs

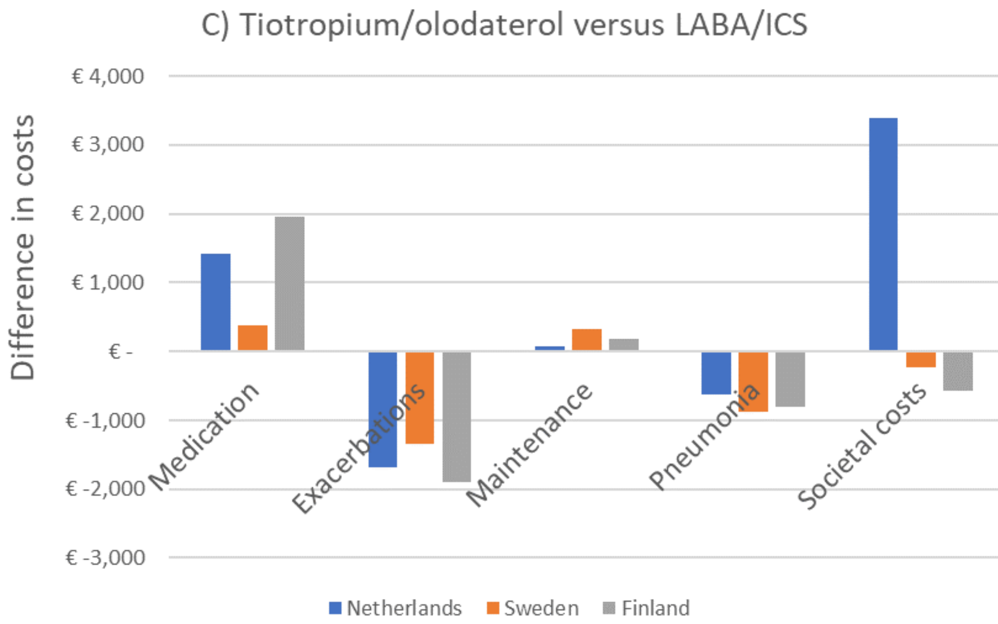

Figure S1C: Difference in costs between tiotropium/olodaterol and LABA/ICS specified by type of costs

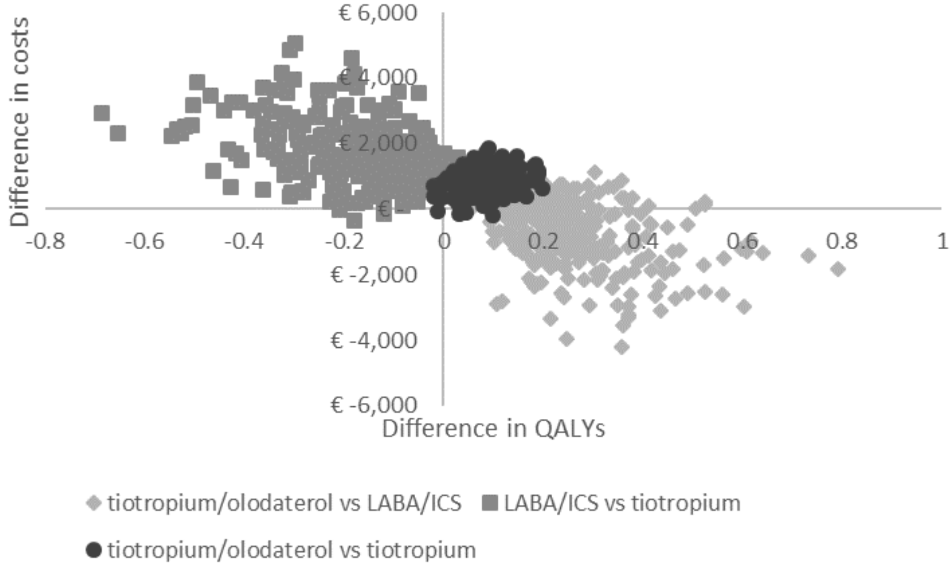

Figure S2: Cost-effectiveness plane for tiotropium/olodaterol versus tiotropium (Black), LABA/ICS versus tiotropium (dark grey) and tiotropium/olodaterol versus LABA/ICS (light grey) for Finland using a limited payer perspective

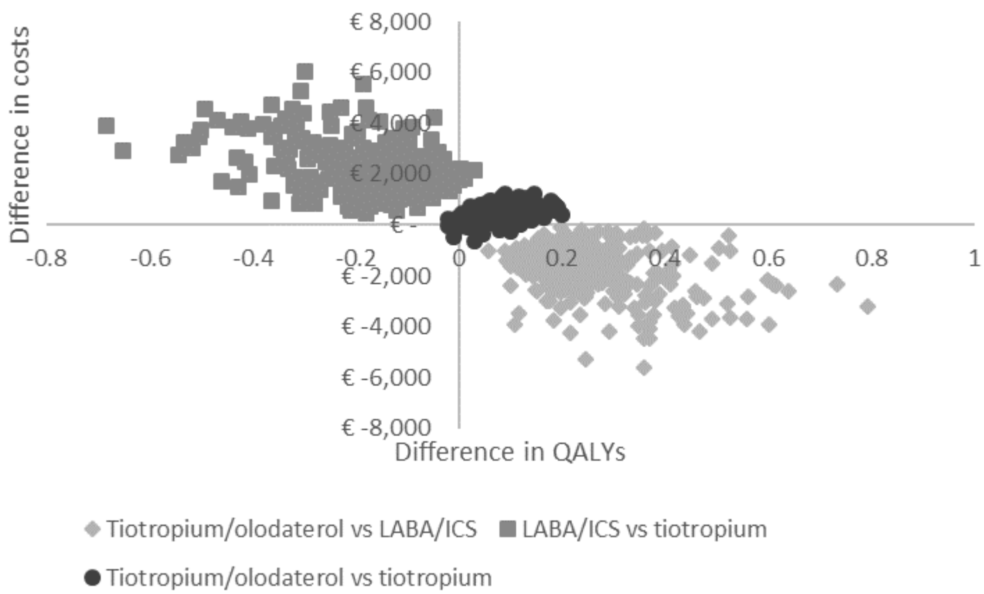

Figure S3: Cost-effectiveness plane for tiotropium/olodaterol versus tiotropium (Black), LABA/ICS versus tiotropium (dark grey) and tiotropium/olodaterol versus LABA/ICS (light grey) for Sweden using a societal perspective

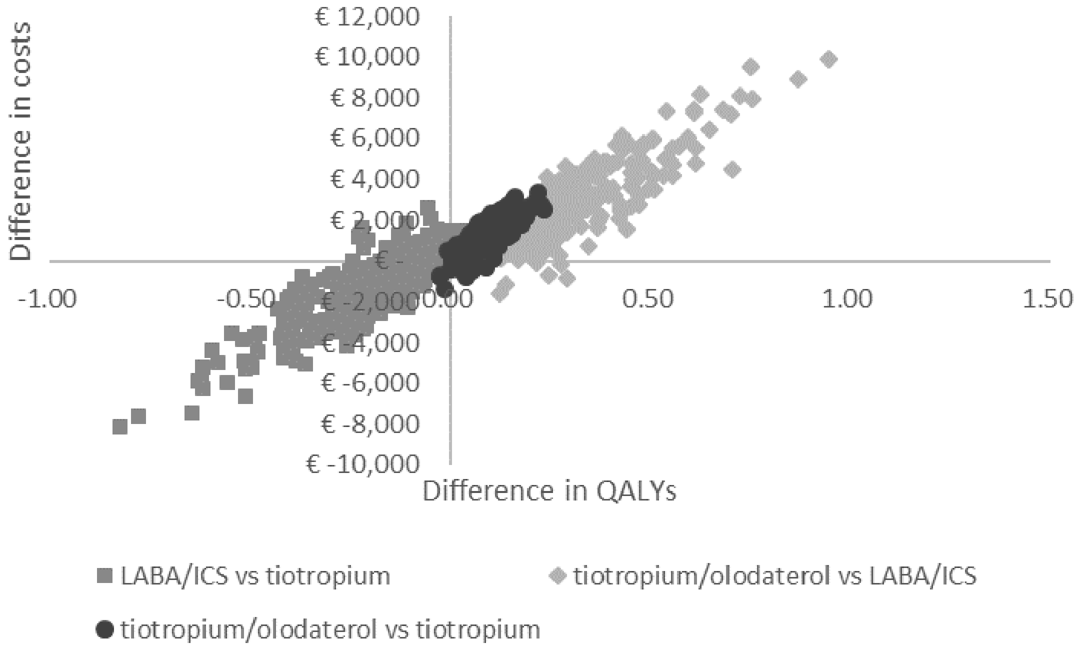

Figure S4: Cost-effectiveness plane for tiotropium/olodaterol versus tiotropium (Black), LABA/ICS versus tiotropium (dark grey) and tiotropium/olodaterol versus LABA/ICS (light grey) for The Netherlands using a societal perspective

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1, title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 4
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 6
		Present the study question and its relevance for health policy or practice decisions.	Page 7
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 9 Table S1 supplementary data
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 10
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 10
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page7/8 Page 11/12
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 9
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 10
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not applicable
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 8
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Page 10/11

Section/item	Item No	Recommendation	Reported on page No/ line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 10/11 Table 2
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 8/9, model figure and full details in reference
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 8/9
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Original publication of the model, page 11/12 sensitivity and scenario analyses
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Original publication of the mode Table 2,
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 4 and Figure 1
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Table 4, SA on number of patients
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 15-18

Section/item	Item No	Recommendation	Reported on page No/ line No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Submission system and page20
onflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Submission system and page 21

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

Cost-effectiveness of the fixed-dose combination tiotropium/olodaterol versus tiotropium monotherapy or a fixed-dose combination of long-acting β2-agonist/inhaled corticosteroid for COPD in Finland, Sweden, and the Netherlands, a model-based study

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Cost-effectiveness of the fixed-dose combination tiotropium/olodaterol versus tiotropium monotherapy or a fixed-dose combination of long-acting β2-agonist/inhaled corticosteroid for COPD in Finland, Sweden, and the Netherlands, a model-based study

Martine Hoogendoorn [1]

Isaac Corro Ramos [1]

Stéphane Soulard [2]

Jennifer Cook [3]

Erkki Soini [4]

Emma Paulsson [5]

Maureen P.M.H. Rutten-van Mölken [1,6]

1. Institute for Medical Technology Assessment (iMTA), Erasmus University Rotterdam, Rotterdam, the Netherlands

2. Boehringer Ingelheim the Netherlands, Amsterdam, the Netherlands

3. Boehringer Ingelheim GmbH, Ingelheim, Germany

4. ESiOR, Kuopio, Finland

5. Quantify Research, Stockholm Sweden

6 Erasmus School of Health Policy & Management (ESHPM), Erasmus University Rotterdam, Rotterdam, the Netherlands

Correspondence:

Martine Hoogendoorn

Institute for Medical Technology Assessment

Erasmus University Rotterdam

Burgemeester Oudlaan 50

3062 PA Rotterdam, the Netherlands

Phone: *31 10 4088871

Email: hoogendoorn@imta.eur.nl

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Figures: 1

Abstract

Objectives: Chronic obstructive pulmonary disease (COPD) guidelines advocate treatment with combinations of long-acting bronchodilators for COPD patients that have persistent symptoms or continue to have exacerbations while using a single bronchodilator. This study assessed the cost-utility of the fixed dose combination of the bronchodilators tiotropium and olodaterol versus two comparators, tiotropium monotherapy and long-acting β2 agonist/ inhaled corticosteroid (LABA/ICS) combinations, in three European countries: Finland, Sweden, and the Netherlands.

Methods: A previously published COPD patient-level discrete event simulation model was updated with most recent evidence to estimate lifetime quality-adjusted life-years (QALYs) and costs for COPD patients receiving either tiotropium/olodaterol, tiotropium monotherapy or LABA/ICS. Treatment efficacy covered impact on trough forced expiratory volume in one second (FEV_1), total and severe exacerbations, and pneumonias. The unit costs of medication, maintenance treatment, exacerbations and pneumonias were obtained for each country. The country-specific analyses adhered to the Finnish, Swedish and Dutch pharmacoeconomic guidelines, respectively.

Results: Treatment with tiotropium/olodaterol gained QALYs ranging from 0.09 (Finland and Sweden) to 0.11 (the Netherlands) versus tiotropium and 0.23 (Finland and Sweden) to 0.28 (the Netherlands) versus LABA/ICS. The Finnish payer's incremental cost-effectiveness ratio (ICER) of tiotropium/olodaterol was €11,000/QALY versus tiotropium and dominant versus LABA/ICS. The Swedish ICERs were €6,200/QALY and dominant, respectively (societal perspective). The Dutch ICERs were €14,400 and €9,200, respectively (societal perspective). The probability that tiotropium/olodaterol was cost-effective compared to tiotropium at the country-specific (unofficial) threshold values for the maximum willingness to pay for a QALY was 84% for Finland, 98% for Sweden and 99% for the Netherlands. Compared to LABA/ICS this probability was 100% for all three countries.

Conclusions: Based on the simulations, tiotropium/olodaterol is a cost-effective treatment option versus tiotropium or LABA/ICS in all three countries. In both Finland and Sweden, tiotropium/olodaterol is more effective and cost saving (i.e. dominant) in comparison to LABA/ICS.

Keywords: COPD, cost-effectiveness, tiotropium/olodaterol, decision model, QALYs, costs

Strengths and limitations of this study

- A validated comprehensive health economic model built with patient-level data of 35,000 COPD patients was used for the analysis.
- This study is one of the first studies including effects and costs of adverse events related to COPD treatment.
- Indirect evidence for the comparison of tiotropium/olodaterol versus LABA/ICS was used by comparing both treatment options to tiotropium monotherapy.
- The model and efficacy data were based on data from COPD patients participating in clinical trials, which might limit extrapolation of the results to the COPD population as a whole.

Introduction

Chronic obstructive pulmonary disease (COPD) is a large and increasing health problem in Europe and associated with a high economic burden [1,2]. Pharmacological therapy to treat stable COPD mainly focuses on reducing symptoms, improving health status and reducing the risk for exacerbations. The most important types of medication available for COPD are long-acting β2 agonists (LABAs), long-acting anticholinergics (LAMAs) and inhaled corticosteroids (ICS) [3]. Older versions of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance advocated the use of LABA/ICS combinations for patients with severe airflow obstruction and frequent exacerbations [4]. More recent studies have shown that treatment response to ICS varied across patients. High blood eosinophil levels are found to be a good predictor for treatment response for ICS, while the added value of ICS in patients with low eosinophil levels, low symptoms and a low exacerbation history seems limited [5]. In addition, the use of ICS is associated with an increased risk of pneumonia [3,6]. Several recent studies have found improvements in lung function, exacerbation and pneumonia rates with LABA/LAMA combinations compared to LABA/ICS [7-10]. Based on all these findings, the latest GOLD COPD guidelines recommend treatment with combinations of different types of long-acting bronchodilators (LABA/LAMA) for COPD patients who have persistent symptoms or exercise intolerance while using a single bronchodilator, and for patients with frequent exacerbations and a low blood eosinophil count [3]. However, because of the recommendations in the past, a substantial proportion of the COPD patients in Europe is currently still treated with combinations of a bronchodilator plus ICS. In both Sweden and the Netherlands around 60% of the COPD patients are using ICS for maintenance treatment [11,12], although for some of them LABA/LAMA combinations would be the preferred option according to the current GOLD guidance [3].

The fixed-dose LABA/LAMA combination tiotropium/olodaterol has been shown to improve lung function, decrease exacerbation risk and increase quality of life compared to tiotropium monotherapy

[13-15]. Tiotropium/olodaterol has also been shown to be a cost-effective treatment option compared to tiotropium monotherapy in France, the Netherlands, Italy and the UK [16-19]. Three of these studies used efficacy data on long function obtained from the TONADO trial [13]. The relevance of exacerbations in cost-effectiveness is significant as these events are important drivers of quality of life and costs. Only one cost-effectiveness study included efficacy data on exacerbations obtained from the DYNAGITO trial [15]. A recent study provided new efficacy data on exacerbations based on a post-hoc analysis of both the TONADO and DYNAGITO trial combined [20]. Moreover, the previously performed Dutch cost-effectiveness study was not performed from a societal perspective as recommended in the guidelines. The cost-effectiveness in Northern European countries, such as Sweden and Finland, and the cost-effectiveness versus other comparators than tiotropium, such as LABA/ICS, are currently unknown. Information on long-term effects, and costs of tiotropium/olodaterol are needed to guide clinical practice and optimize healthcare expenditures. Therefore, the this study aimed to estimate the cost-effectiveness of the fixed dose combination tiotropium/olodaterol versus two treatment options, i.e. tiotropium and LABA/ICS for Finland, Sweden and the Netherlands.

Methods

The study consisted of two steps. First, a literature search was performed to identify studies published in the past five years to obtain recent estimates for the efficacy of tiotropium/olodaterol versus tiotropium and LABA/ICS. Second, the efficacy data were used in a recently developed and published COPD patient-level discrete event simulation model to estimate the lifetime effects, costs and cost-effectiveness for tiotropium/olodaterol [16, 21, 22].

Efficacy data

Treatment efficacy was implemented in the model using four relevant clinical outcomes: trough forced expiratory volume in one second (FEV_1), total number of (severe) exacerbations and total number of pneumonias. For the literature search on efficacy data the following prioritization of inclusion into the model was used. Efficacy data from a network meta-analysis (NMA) had the highest priority, followed by efficacy data from a pairwise meta-analysis, and efficacy data from single studies. To be able to compare different treatment options, the efficacy of all treatment options was defined relative to tiotropium, given that is the base-case in the health economic model. Consequently, a literature search was performed to obtain efficacy data for tiotropium/olodaterol versus tiotropium and LABA/ICS versus tiotropium. The efficacy of tiotropium/olodaterol versus tiotropium monotherapy with respect to exacerbations was based on a post-hoc analysis of the combined patient-level data of the TONADO and DYNAGITO trial [20]. The effect on trough FEV_1 was obtained from an NMA by Aziz et al (2018) [23]. The efficacy of LABA/ICS versus tiotropium was obtained from an NMA of Oba et al (2018) [24]. Because this NMA considered all types of LABA/ICS combined into one class, no specification in type of LABA/ICS was made for the analyses. All efficacy data obtained from the literature used as input for the cost-effectiveness model are shown in Table 1. For the base case analysis all different ratios in Table 1 were interpretated as rate ratios, because this was found to be most conservative. For pneumonias, efficacy data were only available for total pneumonias, and specification between moderate and severe pneumonias was not reported.

Table 1: Efficacy for COPD treatment options compared to tiotropium used as input for the cost-effectiveness model

	Tiotropium/olodaterol	LABA/ICS
Trough FEV1 in liter, mean difference (95% CI)	+0.05 (0.03; 0.09) [23]	Not available, assumed zero*
Total exacerbations, ratio (95% CI)	Rate Ratio=0.89 (0.84; 0.95) [20]	Hazard Ratio=1.03 (0.91; 1.17) [24]
Severe exacerbations, ratio (95% CI)	Rate Ratio=0.86 (0.75; 0.99) [20]	Hazard Ratio=1.25 (0.86; 1.85) [24]
Total pneumonias#, ratio (95% CI)	Risk Ratio=1.02 (0.86; 1.21) [13,15]	OR=2.02 (1.16; 3.72) [24]

No distinction could be made between moderate and severe pneumonias.

*To be conservative we assumed the difference to be zero.

LABA=long-acting beta-2 agonists (LABA's), ICS=inhaled corticosteroids (ICS), CI=confidence interval, RR=rate ratio, HR=hazard ratio, OR=odds ratio

Health-economic model

A recently developed COPD patient-level discrete event simulation model was used to estimate the lifetime effects and costs for all the different treatment options. The model has been previously published and described in detail elsewhere [16,21,22]. In summary, the model is a discrete event simulation model that links a series of regression equations that predict intermediate and final outcomes at time t using a wide variety of patient characteristics and intermediate outcomes at time t-1. The intermediate outcome measures include three types of events (exacerbations, pneumonias and death), lung function, physical activity, symptoms and disease-specific quality of life. Final outcome measures are mortality, the number of quality-adjusted life-years (QALYs) and COPD-related healthcare costs. The regression equations were estimated using data from patients in the tiotropium treatment groups of five large COPD trials (TONADO, UPLIFT, EXACTT, POET, and TIOSPIR) [13,25-28]. Hence, tiotropium is the comparator group and the base case in the model.

The starting population of the model consist of the patient population at baseline in the above-mentioned COPD trials, i.e. about 35,000 patients. For the analyses, results of 2,000 randomly sampled patients were combined to estimate the average number of QALYs and health care costs for each treatment option. Simulating 2,000 patients was shown to provide stable results.

Relative efficacy of tiotropium/olodaterol and LABA/ICS compared to tiotropium was modelled by adjusting the base case outcomes of the regression equations for FEV_1, time to any exacerbation, probability that an exacerbation is severe, and time to pneumonia. Using tiotropium/olodaterol as example, the effect on FEV_1 (relative to tiotropium) is modeled by adding the mean difference in FEV_1 between tiotropium/olodaterol and tiotropium, 0.05 liter (Table 1) to the outcome of the standard equation for FEV_1 representative for tiotropium. The effect on exacerbations and pneumonias could not directly be applied because the regression equations for these outcomes predicted time to event and not event rates or proportion of patients with an event. Therefore, the outcome of the time to exacerbation equation was calibrated in such a way that the rate ratio for the annual exacerbation rate for exacerbations with tiotropium/olodaterol compared to the annual exacerbation rate with tiotropium was equal to RR=0.89 (Table 1). This approach was also applied for severe exacerbations. The time to pneumonia equation was calibrated such that the rate ratio for pneumonias for patients using tiotropium/olodaterol compared to patients using tiotropium was equal to RR=1.02 (Table 1). The same method was used to model the efficacy for LABA/ICS. In the base case analysis the hazard ratios for LABA/ICS presented in the literature were interpreted as rate ratios, because this assumption resulted in more conservative results than interpreting the hazard ratios as risk ratios. Treatment effects were assumed constant over the simulated lifetime horizon.

Cost-effectiveness analyses

The cost-effectiveness study was performed for three different countries: Finland, Sweden, and the Netherlands using the country-specific pharmacoeconomic guidelines to specify the base case analysis [29-31]. For Finland, a limited payer perspective was used including all direct health care costs and patient co-payments (value added tax excluded) related to COPD [29]. For Sweden, a societal perspective was applied including all direct medical health care costs related to COPD and costs of productivity loss [30]. Finnish and Swedish effects and costs were discounted by 3% per year [29,30]. For the Netherlands, a societal perspective was used including all direct medical costs related to COPD, unrelated medical costs in life-years gained, travel costs, costs of informal care and costs of productivity loss. Health effects were discounted by 1.5%, while costs were discounted by 4% per year [31].

Health outcomes

Intermediate health outcomes relevant for the analysis were the annual total exacerbation rate, the annual severe exacerbation rate, the annual pneumonia rate and life-expectancy. The final health outcome for the cost-effectiveness analysis was the number of QALYs for each treatment option as predicted by the model. The regression equations to predict health outcomes were based on the international patient population included in the COPD trials and were assumed to be representative for Finland, Sweden and the Netherlands.

Costs

The model predicted costs for the following categories: study medication, maintenance treatment, and for treating exacerbations and pneumonias. The model was adjusted to the Finnish, Swedish and Dutch setting by using country-specific input data for all cost categories. All costs were valued in 2019 Euros. Costs were indexed to 2019 based on official indices if needed. The medication costs were calculated using official list prices (May 2020) of the three countries. If applicable, a weighted average was calculated using the market shares of the products. The total costs for study medication were calculated as the number of days alive multiplied with the daily medication costs (Table 2). Costs for maintenance treatment included the costs for visits to a general practitioner or respiratory specialist, spirometries, influenza vaccination and informal care, i.e. costs for unpaid care provided to a patient by family or friends. In the model the annual number of visits to a general practitioner and respiratory specialist was predicted by regression equations [21,22] using all patient characteristics and intermediate outcomes as predictors. To make the resulting number of visits representative for the specific countries, the outcome of the equations was multiplied with a correction factor that was calculated as the average annual number of COPD-related visits to a general practitioner or respiratory specialist in Finland, Sweden or the Netherlands (see Table 2) divided by the average number of visits predicted by the equation. The use of spirometries, influenza vaccination and informal care was assumed the same across patients (Table 2).

Table 2: Country-specific input data for healthcare use and costs (price level 2019)

Cost item	Unit	Finland (Market share weighted retail, VAT excluded)	Sweden (societal perspective)	The Netherlands (societal perspective)
Medication costs				
Tiotropium	Per day	€1.32 [32,33]	€1.00 [34,35]	€1.41 [36]
Tiotropium/olodaterol	Per day	€1.81 [32,33]	€1.32 [34,35]	€1.72 [36]
LABA/ICS	Per day	€1.28 [32,33]	€1.22 [34,35]	€1.31 [36]
COPD-related annual maintenance treatment*				
General practitioner	Visits Unit cost	1.73 [37] €120 [38]	2.74 [39][a] €160 [40]	3.64 [41,42] €38.88 [43]
Respiratory specialist	Visits Unit cost	0.82 [44] €305 [38]	1.78 [39] €239 [40]	1.36 [41,42] €103.19 [43]
Spirometry test	Tests Unit cost	0.77 [45] €52.38 [38]	0.64 [46] [b] €76 [40]	0.72 [41,47] €17.95 [43]
Influenza vaccination	Vaccination Unit cost	0.52 [48] €51.28 [38]	0.52 [49] €65 [40]	0.52 [50] €15.75 [43]
Informal care#	Hours Unit cost	Not applicable	Not applicable	270 [51] €14.95 [43]
Costs related to COPD exacerbations				
Moderate exacerbation	Per event	€220 [45,52,53]	€634 / €289*^ [21,35,40,54]	€637 / €124*^ [21,36,43]
Severe exacerbation (=hospitalization)	Per event	€4390 [38,45,53]	€4028 / €3067*^ [21,35,40,54,55]	€5612 / €4182*^ [21,36,43,56]
Costs for treating pneumonias				

Without hospitalization	Per event	€225 [38]	€584 / €239* [40,54]	€637 / €124* [21,36,43]
With hospitalization	Per event	€4498 [38,52,53]	€5813 / €4851* [40,54,55]	€5142 / €3711* [43,56]
Average retirement	Age in years	Not applicable	65 [54]	65 [43]

*Costs below retirement age including short-term productivity costs / costs above retirement age without productivity costs,

Exchange rate for Sweden 1 SEK = €0.095 (May 2020)

Unpaid care provided to a patient by family or friends

[a] Incremental number of primary care visits for COPD 5.17 [39] of which 53% was with physician [39]

[b] Weighted average for primary care and secondary care patients [46]

^Bottom-up estimate of healthcare use for a moderate and severe exacerbation [21] and country-specific unit costs and duration of a hospitalization for COPD

For exacerbations and pneumonias, a distinction was made between costs for a moderate (no hospitalization), or a severe exacerbation or pneumonia (with hospitalization). Short-term productivity costs related to exacerbations and pneumonias were estimated using the average number of working days lost for per event estimated in the POET trial (moderate: 1.73 days, severe: 4.82 days) [21,27] multiplied by an estimate of the productivity costs per hour. For the Netherlands, unrelated medical costs in life-years gained were estimated using the PAID tool version 3.0 [57].

<u>Incremental cost-effectiveness ratios</u>

The model outcomes on QALYs and costs were used to calculate the difference in the total average number of QALYs and the total average lifetime costs per patient between two treatment options. Instead of performing a full hierarchical analysis as is common in cost-effectiveness analyses with multiple treatments, the choice of treatment comparisons was based on the current COPD guidelines [3]. After initial treatment with one long-acting bronchodilator (for example tiotropium), the guidelines recommend follow-up treatment for patients with persistent dyspnea or exacerbations, with either LABA/LAMA (for example tiotropium/olodaterol) or LABA/ICS (for subgroup with high blood eosinophil levels). Based on these recommendations, incremental cost-effectiveness ratios (ICER) were calculated for the following treatment comparisons: tiotropium/olodaterol versus tiotropium monotherapy, LABA/ICS versus tiotropium monotherapy and tiotropium/olodaterol vs LABA/ICS. The ICERs were calculated as the difference in costs between two treatment options divided by the difference in QALYs.

Sensitivity and scenario analyses

Several scenario analyses were performed on the efficacy data, number of simulated patients, discount rate, and the perspective used for each country. In the base case analyses, the treatments were assumed to have an impact on FEV_1 and the exacerbation and pneumonia rates. Three scenario analyses were run assuming impact of treatment on FEV_1 only, exacerbations only, and FEV_1 plus exacerbations. Another scenario analysis was performed for LABA/ICS in which hazard ratios presented in the literature were interpreted as risk ratios instead of rate ratios as was done in the base-case analysis. A scenario analysis with 5,000 patients was performed to show the impact of the number of simulated patients on the results. The impact of discounting was explored for all countries, while in addition some country-specific scenario analyses were performed on the analytical perspective of the analysis. For Finland an analysis with a limited societal perspective [29,52] was run including the base case costs (direct payer costs, patient co-payments) (Table 2) as well as social services, travel costs and productivity costs, while for Sweden the impact of using a healthcare perspective only including direct medical costs was explored. For the Netherlands, an analysis from the healthcare perspective was performed as well as an analysis from the societal perspective without unrelated medical costs in life-years gained.

Finally, probabilistic sensitivity analyses (PSA) were performed to assess the joint uncertainty. The PSA were based on 300 sets of randomly drawn input parameters (outer loop) with a sample size of 100 patients per set (inner loop). Further details about the PSA have been published previously [21]. Based on the PSA results cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEAC) were constructed showing the uncertainty around the difference in QALYs and costs and the probability that one treatment is cost-effective compared to another treatment option at different values of the maximum willingness to pay values for a QALY in Finland, Sweden and the Netherlands, respectively. To assess whether a treatment was cost-effective the country-specific threshold values for the maximum willingness to pay for a QALY were taken into account. For Finland the low and unofficial threshold value of €20,000 per QALY was applied, while for Sweden an unofficial threshold value of SEK 500,000 (~€47,500) was used assuming that COPD was considered a disease with moderate severity. For the Netherlands the burden of disease was estimated to be 0.56, which corresponds with a threshold value of €50,000 per QALY [58].

<u>Patient and public involvement</u>

Clinical COPD experts were involved in the development of the health-economic model by providing their input on the model structure and input parameters and relevance of outcomes. This research was performed without patient involvement.

Results

The baseline characteristics of the patient population in the model at start of the simulation are shown in Table S1 In the Online Supplementary data. Of the 2000 simulated patients, about one quarter were female, the average age was 64 years and the mean FEV_1 was 1.4 liter (49% of the predicted value). Almost 60% of the patients had a history of exacerbations in the past year.

Base case cost-effectiveness analyses

Table 3 shows the annual exacerbation rates, the predicted average life-expectancy, and lifetime number of QALYs, and costs for tiotropium monotherapy, tiotropium/olodaterol, and LABA/ICS. PSA results for QALYs and costs including uncertainty are shown in the Online Supplementary data. In comparison with Finland and Sweden, the costs for all treatment options were much higher for the Netherlands as a result of the inclusion of costs for informal care and unrelated medical costs in life-years gained. Compared to tiotropium, treatment with tiotropium/olodaterol resulted in a gain in discounted QALYs of 0.092 for Finland and Sweden, and 0.111 for the Netherlands. For all countries, tiotropium/olodaterol was associated with an increase in medication costs compared to tiotropium, but these higher costs were partly outweighed by a reduction in exacerbation costs (Figure S1, Online Supplementary data). As a result, treatment with tiotropium/olodaterol was associated with an increase in net total costs, resulting in a cost-effectiveness ratio of €11,000/QALY gained for Finland, €6,200 for Sweden, and €14,400 for the Netherlands (Table 3).

Table 3: Lifetime model results (per patient) and cost-effectiveness results

	Treatment option:	Tiotropium/ olodaterol	Tiotropium	LABA/ICS	Tiotropium/olodaterol versus tiotropium	LABA/ICS versus tiotropium	Tiotropium/olodaterol versus LABA/ICS
Equal across countries	Annual total exacerbation rate	0.592	0.664	0.679	-0.072	+0.015	-0.087
	Annual severe exacerbation rate	0.128	0.148	0.184	-0.020	+0.036	-0.056
	Annual pneumonia rate	0.035	0.035	0.071	0.001	+0.036	-0.035
	Life-expectancy (years)	11.75	11.54	11.16	+0.21	-0.38	+0.59
Finland	Discounted QALYs	6.159	6.067	5.926	0.092	-0.141	0.233
	Discounted lifetime costs	16,921	15,910	17,497	€1,011	€1,587	-€576
	Incremental cost-effectiveness ratio				€11,013	Dominated*	Dominant**
Sweden	Discounted QALYs	6.159	6.067	5.926	0.092	-0.141	0.233
	Discounted lifetime costs	18,916	18,348	20,509	€568	€2,161	-€1,736
	Incremental cost-effectiveness ratio				€6,193	Dominated*	Dominant**
The Netherlands	Discounted QALYs	6.832	6.722	6.551	0.111	-0.171	0.281
	Discounted lifetime costs	137,253	135,662	134,656	€1,591	-€1,006	€2,597
	Incremental cost-effectiveness ratio				€14,398	€5,902***	€9,243

*A treatment is dominated by the comparator, when the treatment results in less health effects and higher costs. **A treatment is dominant versus a comparator when the treatment results in better health effects and savings in costs. ***ICER should be interpreted as cost saved per QALY lost

Treatment with LABA/ICS compared to tiotropium resulted in fewer QALYs (-0.141) and higher costs (+€ 1,587-€2,161) for Finland and Sweden, and less QALYs (-0.171) and less costs (-€1,006) for the Netherlands.

For the comparison tiotropium/olodaterol versus LABA/ICS, the gain in discounted QALYs was 0.233 for Finland and Sweden, and 0.281 for the Netherlands. Compared to LABA/ICS, the higher treatment costs for tiotropium/olodaterol were completely outweighed by a reduction in exacerbation and pneumonia costs for Finland and Sweden (Figure S1, Online Supplementary data), resulting in tiotropium/olodaterol being the dominant treatment option, i.e. better health effects and less costs. For the Netherlands, the net total costs increase versus LABA/ICS was €2,597 and the cost-effectiveness ratio was €9,200/QALY.

Scenario analyses

The results of the scenario analyses (Table 4) showed that, for the comparison tiotropium/olodaterol versus tiotropium, a scenario assuming a treatment effect on lung function only (and not on exacerbations) had the highest impact on the ICERs. Assuming an effect on exacerbations only (no effect on pneumonias) in the analysis tiotropium/olodaterol versus LABA/ICS, increased the ICER from €9,200 to €12,300 for the Netherlands, while for Finland it would become €250/QALY instead of tiotropium/olodaterol being dominant. Using the limited societal perspective in Finland resulted in savings in costs for tiotropium/olodaterol versus both tiotropium and LABA/ICS, while using a healthcare perspective in the Netherlands resulted in tiotropium/olodaterol being dominant compared to LABA/ICS.

Table 4: Scenario analyses; impact on the incremental cost-effectiveness ratios (ICERs)

Country	Scenario	ICER tiotropium/olodaterol versus tiotropium	ICER LABA/ICS versus tiotropium	ICER tiotropium/olodaterol versus LABA/ICS
Finland	Base-case [a]	€11,013	Dominated*	Dominant**
	Effect on: FEV_1 only	€52,438	NA	NA
	Effect on: Exacerbations only	€16,225	Dominated	€251
	Effect on: Exacerbations + FEV_1	€10,265	Dominated	€251
	Hazard rates interpreted as risk ratios	NA	Dominated	Dominant
	5,000 simulated patients	€10,203	Dominated	Dominant
	No discounting	€9,726	Dominated	Dominant
	Limited societal perspective	Dominant	Dominated	Dominant
Sweden	Base-case [b]	€6,193	Dominated	Dominant
	Effect on: FEV_1 only	€36,165	NA	NA
	Effect on: Exacerbations only	€7,977	Dominated	Dominant
	Effect on: Exacerbations + FEV_1	€5,610	Dominated	Dominant
	Hazard rates interpreted as risk ratios	NA	Dominated	Dominant
	5,000 simulated patients	€5,662	Dominated	Dominant
	No discounting	€6,531	Dominated	Dominant
	Healthcare perspective	€7,130	Dominated	Dominant
The Netherlands	Base-case [c]	€14,398	€5,902***	€9,243
	Effect on: FEV_1 only	€38,401	NA	NA
	Effect on: Exacerbations only	€15,849	€9,211***	€12,319
	Effect on: Exacerbations + FEV_1	€14,176	€9,211***	€12,319
	Hazard rates interpreted as risk ratios	NA	€4,732***	€8,248
	5,000 simulated patients	€13,898	€6,229***	€9,296
	No discounting	€18,674	€10,168***	€13,513
	Healthcare perspective	€3,638	Dominated	Dominant
	Societal perspective without unrelated medical costs in life-years gained	€6,715	Dominated	€754

[a] Payer perspective, 2000 simulated patients, discount rate 3%, and effect on FEV1, exacerbations and pneumonias, [b] Societal perspective, 2000 simulated patients, discount rate 3% and effect on FEV1, exacerbations

and pneumonias, [c] Societal perspective, 2000 simulated patients, discount rate 1.5% for effects and 4% for costs and effect on FEV1, exacerbations and pneumonias, NA=not applicable, *A treatment is dominated by the comparator, when the treatment results in less health effects and higher costs. **A treatment is dominant versus a comparator when the treatment results in better health effects and savings in costs. ***ICER should be interpreted as cost saved per QALY lost

Cost-effectiveness planes are shown in the Online supplementary data (Figure S2-S4). Cost-effectiveness acceptability curves (Figure 1) showed that the probability that treatment with tiotropium/olodaterol is cost-effective compared to tiotropium at the country-specific (unofficial) willingness to pay thresholds was 84% for Finland, 98% for Sweden and 99% for the Netherlands. LABA/ICS had a probability of almost 0% of being cost-effective compared to tiotropium. Compared to LABA/ICS, the probability of tiotropium/olodaterol to be cost-effective was 100% for all three countries.

Discussion

This study aimed to estimate the cost-effectiveness of tiotropium/olodaterol versus different comparators in three European countries, Finland, Sweden, and the Netherlands. The results showed that, compared to tiotropium, treatment with tiotropium/olodaterol resulted in a gain in QALYs and higher total costs. The resulting ICERs were below €14,400 per QALY for all three countries, resulting in tiotropium/olodaterol being a cost-effective treatment considering the country-specific thresholds for the maximum willingness to pay for a QALY. Compared to LABA/ICS, tiotropium/olodaterol resulted in a gain in QALYs and net savings in costs for Finland and Sweden. For the Netherlands, the ICER of tiotropium/olodaterol compared to LABA/ICS was €9,200 per QALY. Scenario analyses showed that the ICERs were robust to changes in general assumptions on discount rate, number of patients simulated, and interpretation of hazard rates. Using the assumption that treatment with tiotropium/olodaterol only had an impact on lung function and not on exacerbations resulted in an increase in the ICERs and tiotropium/olodaterol being not cost-effective for Finland. Using a different analytical perspective reduced the ICERs substantially for Finland and the Netherlands. All cost-effectiveness results were calculated using the overall patient population in the model, which was in line with the population from which the efficacy data were obtained. Results for subgroups of patients might differ. In the subgroup of patients with a history of exacerbations in the previous year for example, the ICERs for tiotropium/olodaterol versus tiotropium were somewhat lower, while the ICERs for tiotropium/olodaterol versus LABA/ICS were slightly higher. Triple therapy is not considered in the current study, because according to the guidelines the target population for triple therapy is a high-risk population not comparable to the patient population using dual therapy considered in this study. We acknowledge however, that because of different recommendations in the past, a substantial proportion of the COPD patients is currently still treated with LAMA+ LABA/ICS or even triple therapy fixed dose combinations.

Because the same patient population and the same efficacy data is used for all three countries, differences in the cost-effectiveness of tiotropium/olodaterol between the three countries can mainly be explained by discount rates, the unit costs and the perspective of the economic evaluation. The gains in QALYs varied between the countries due to the discount rate for health effects, 3% for Finland and Sweden and 1.5% for the Netherlands. ICERs were most favorable for Sweden, which can mainly be explained by the smaller difference in daily costs between tiotropium/olodaterol versus tiotropium and versus LABA/ICS compared to the other countries. Therefore, the incremental lifetime medication costs associated with tiotropium/olodaterol were lower for Sweden, which made it more likely that these costs could be compensated by reductions in exacerbation and pneumonia costs. The ICERs for Finland were generally between Swedish and Dutch ICERs. The Finnish base case analyses apply direct cost perspectives in health economic evaluations [29], which potentially miss two thirds of costs paid by society [52]. In addition, Finland has a costly pharmaceutical pricing scheme, which explains quite high margins (i.e. relative high retail costs excluding value added tax (VAT) in comparison to the generally affordable Finnish wholesale prices). The ICERs were highest for the Netherlands, because of the inclusion of informal care costs and unrelated medical costs in life-years gained as required by the guidelines for pharmacoeconomic evaluations [31]. Inclusion of these costs resulted in higher incremental costs for tiotropium/olodaterol, because these costs were mainly dependent on being alive and tiotropium/olodaterol increased the life-expectancy compared to the other two treatment options. Medication costs for the Netherlands were derived from list prices of May 2020. New list prices resulting from a change in reference countries were published in October 2020; they were in general lower, but the relative decrease in price was larger in tiotropium/olodaterol and tiotropium than in LABA/ICS. Using the most recent prices would have further reduced the ICER compared to LABA/ICS.

The results of the study were in line with previous published cost-effectiveness studies for tiotropium/olodaterol [16-19]. A study for France reported an ICER for tiotropium/olodaterol compared to tiotropium of €2,900 per QALY using a societal perspective [16]. This study used the same health-economic model as used in the current study. However, the efficacy for tiotropium/olodaterol versus tiotropium in the previous study was based on one trial and only defined as the impact on exacerbations. In the current study efficacy was based on all available evidence combined using data from an NMAs and a post-hoc analysis of two trials and efficacy was modelled as an impact on multiple parameters (trough FEV1, exacerbations, pneumonias), which explains the difference in QALYs gained in the current study compared to the French study [16]. A previous Dutch study found an ICER of €7,000 per QALY for tiotropium/olodaterol versus tiotropium [17], which was lower than the ICER in the current study, €14,400 per QALY. This might be explained by the fact that the earlier study did not include costs for informal care and unrelated medical costs in life-years gained, which were shown to have a substantial impact on the ICER (as shown in sensitivity analyses). A study from Seyla-Hammer reported an ICER of €7,500 per QALY for tiotropium/olodaterol compared to tiotropium in Italy [18]. Tebboth et al. explored the cost-effectiveness of tiotropium/olodaterol compared to other LABA/LAMA combinations in the UK and concluded that the ICER for tiotropium/olodaterol was acceptable, i.e. within the range considered cost-effective and comparable with the ICERs for the other LABA/LAMA combinations [19]. None of the earlier published studies compared tiotropium/olodaterol with LABA/ICS or included Finland or Sweden.

A key strength of thisstudy was that a comprehensive health-economic model for COPD was used to simulate the long-term outcomes. The model has been validated and previously used for cost-effectiveness analyses [16,21,22] and has been built with patient-level data of 35,000 COPD patients. The study is also one of the first studies including the effects and costs of adverse events related to the treatment. LABA/ICS is associated with an increased risk for pneumonias [3,6].

A limitation of the study was that the patient population in the model did not vary by country. The five large COPD trials used to build the model were multinational trials, but the number of patients per country were too small to sample patients from one specific country. In addition, patients participating in large clinical trials are mainly secondary care patients with moderate to severe airflow obstruction and no other life-treating diseases. Although it is very common to use clinical trial data for cost-effectiveness analyses, this could limit the extrapolation of the results to the total COPD population [59]. A second limitation was that the efficacy data found in the literature were expressed in different ways and sourced from different studies. Efficacy for tiotropium/olodaterol versus tiotropium was expressed as rate ratios, while efficacy for LABA/ICS was reported as hazard ratios. The model has the option to apply treatment efficacy as rate ratios or risk ratios. For this study we took a conservative approach and interpreted all reported results as rate ratios for the base case and risk ratios in a scenario analysis. Finally, indirect evidence for the comparison of tiotropium/olodaterol versus LABA/ICS was used by comparing both treatments to tiotropium, which was in line with how the model has been built. Several studies have compared LABA/LAMA and LABA/ICS combinations directly [7-10]. Yet, evidence supports our approach. A Cochrane review from 2017 including ten studies reported that LABA/LAMA combinations resulted in fewer exacerbations, a larger improvement in FEV1 and lower risk of pneumonia compared to LABA/ICS, although the evidence was of low or moderate quality, in general [8]. Another meta-analysis from 2017 including 18 studies found a significant improvement in trough FEV1 and lower annual exacerbation rates and pneumonia risks for LABA/LAMA versus LABA/ICS [9]. A recent real-life study comparing treatment with tiotropium/olodaterol and LABA/ICS directly found that tiotropium/olodaterol resulted in fewer exacerbations (HR: 0.74 (95%: 0.68-0.85) and fewer pneumonias (HR: 0.74 (95% CI: 0.57-0.97) [60]. Using these data in the model would have resulted in a comparable ICER for tiotropium/olodaterol versus LABA/ICS for the Netherlands, (€9,600/QALY), while tiotropium/olodaterol would also have been the dominant treatment option for Finland and Sweden resulting in more effects and lower costs.

In conclusion, this model-based health economic evaluation showed that treatment with the fixed-dose combination of tiotropium/olodaterol resulted in a gain in QALYs compared to tiotropium monotherapy and LABA/ICS. Compared with LABA/ICS, tiotropium/olodaterol resulted in savings in costs in Finland and Sweden and a low cost per QALY gained for the Netherlands. Compared to tiotropium, tiotropium/olodaterol can be considered a cost-effective treatment option in all three countries with low ICERs varying between €6,200 and €14,400 per QALY. The model outcomes were robust within most of the sensitivity analyses that were performed.

Contributorship statement

MH developed the health-economic model, designed the study, collected input data, performed the modelling analysis and wrote the first version of the manuscript

ICR developed the health-economic model, designed the study and performed part of the modelling analysis and contributed to drafting and critical review of the manuscript

SS provided data to develop the model, supervised the design of the study and interpretation of the results and contributed to drafting and review of the manuscript

JC provided data to develop the model, supervised the design of the study and interpretation of the results and contributed to drafting and review of the manuscript

ES: collected input data and contributed to interpretation of the results and to drafting and critical review of the manuscript

EP: collected input data and contributed to interpretation of the results and to drafting and critical review of the manuscript

MRM: developed the health-economic model, designed the study, collected input data and contributed to the analysis and interpretation of the results and to drafting and critical review of the manuscript

All authors approved the final version for publication.

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Competing interests

MH reports grants from Boehringer Ingelheim, during the conduct of the study.

ICR has nothing to disclose

SS is an employee of Boehringer Ingelheim

JC is an employee of Boehringer Ingelheim

ES is a partner, employee and CEO of ESiOR Oy, Kuopio, Finland. ESiOR Oy carries out studies, statistical analysis, consultancy, education, reporting and health economic evaluations for several pharmaceutical (including companies producing and marketing treatments for COPD), food industry, diagnostics and device companies, hospitals, consultancies, projects and academic institutions.

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Patient consent for publication:

Not required

Ethics approval:

Ethical approval was not required, because the economic evaluation was based on a mathematical model analysis.

Data sharing management

Data are available upon reasonable request.

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Figure legends

Figure 1: Acceptability curves for tiotropium/olodaterol versus tiotropium (black), tiotropium/olodaterol versus LABA/ICS (grey) and LABA/ICS versus tiotropium (dashed) for A) Finland, B) Sweden and C) the Netherlands

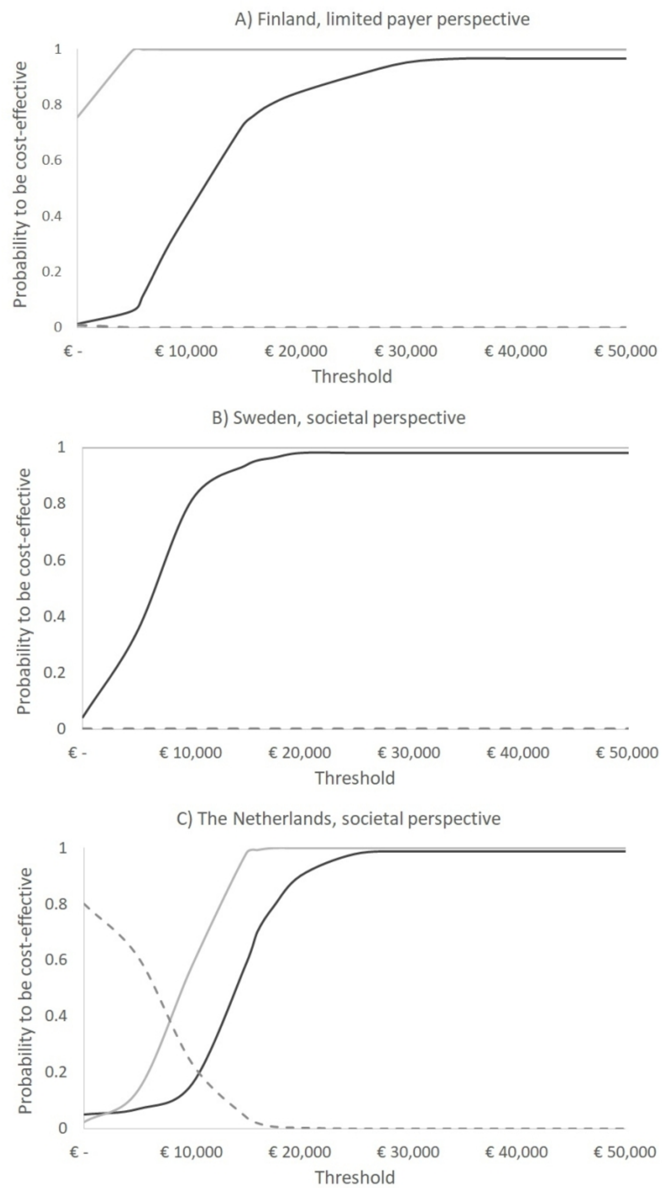

Figure 1: Acceptability curves for tiotropium/olodaterol versus tiotropium (black), tiotropium/olodaterol versus LABA/ICS (grey) and LABA/ICS versus tiotropium (dashed) for A) Finland, B) Sweden and C) The Netherlands

76x135mm (300 x 300 DPI)

Online supplementary data for manuscript:

"Cost-effectiveness of the fixed-dose combination tiotropium/olodaterol versus tiotropium monotherapy or a fixed-dose combination of long-acting β2-agonist/inhaled corticosteroid for COPD in Finland, Sweden, and The Netherlands, a model-based study"

Table S1: Baseline characteristics of the 2,000 simulated patients

Characteristic	Total population
Total number of patients available in the model population	35,341
Female, %	26
Age (years)	64
FEV_1 (L)	1.4
FEV_1% predicted, %	49
Low BMI (<21 kg/m^2), %	15
Smoking, %	38
Pack-years (years)	44
Emphysema, %	49
Asthma, %	6
Heart failure, %	5
Other CVD, %	13
Depression, %	8
Diabetes, %	11
High eosinophils (≥4%), %	24
Bronchodilator responsiveness, post-bronchodilator FEV_1/pre-bronchodilator FEV_1 (%)	23
History ≥1 exacerbation in previous year, %	59
History ≥1 severe exacerbation in previous year, %	16
Exercise capacity, treadmill test (seconds)	347
Physical activity, SGRQ activity score (points)	59
Presence cough/sputum (most or several days/week), %	67
Presence breathlessness (most or several days/week), %	63
Disease-specific quality of life, SGRQ total score (points)	44

Table S2: Lifetime model results (per patient) based on PSA, mean (95% uncertainty interval)

	Treatment option:	Tiotropium/olodaterol versus tiotropium	LABA/ICS versus tiotropium	Tiotropium/olodaterol versus LABA/ICS
Finland	Discounted QALYs	0.087 (0.015; 0.167)	-0.174 (-0.498; -0.017)	0.261 (0.107; 0.566)
	Discounted lifetime costs	€931 (€232; €1439)	€1680 (€230; €3790)	-€749 (-€2979; €713)
Sweden	Discounted QALYs	0.087 (0.015; 0.167)	-0.174 (-0.498; -0.017)	0.261 (0.107; 0.566)
	Discounted lifetime costs	€522 (-€138; €978)	€2258 (€843; €4523)	-€1736 (-€4021; -€326)
The Netherlands	Discounted QALYs	0.104 (0.017; 0.194)	-0.207 (-0.587; -0.021)	0.311 (0.126; 0.666)
	Discounted lifetime costs	€1439 (-€346; €2754)	-€1428 (-€5634; €1227)	-€2867 (€97; €7377)

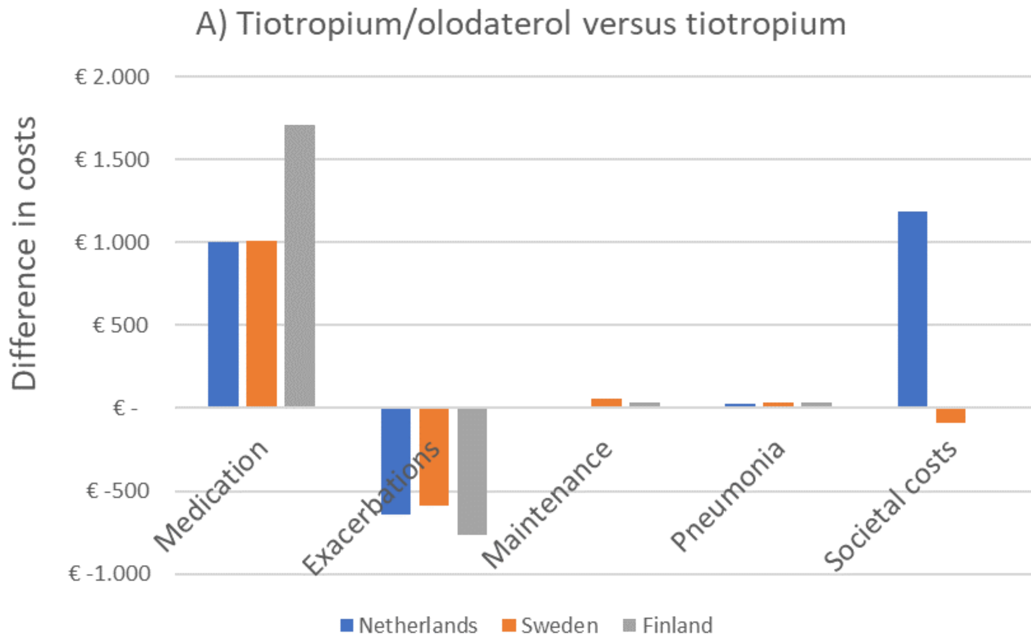

Figure S1A: Difference in costs between tiotropium/olodaterol and tiotropium specified by type of costs

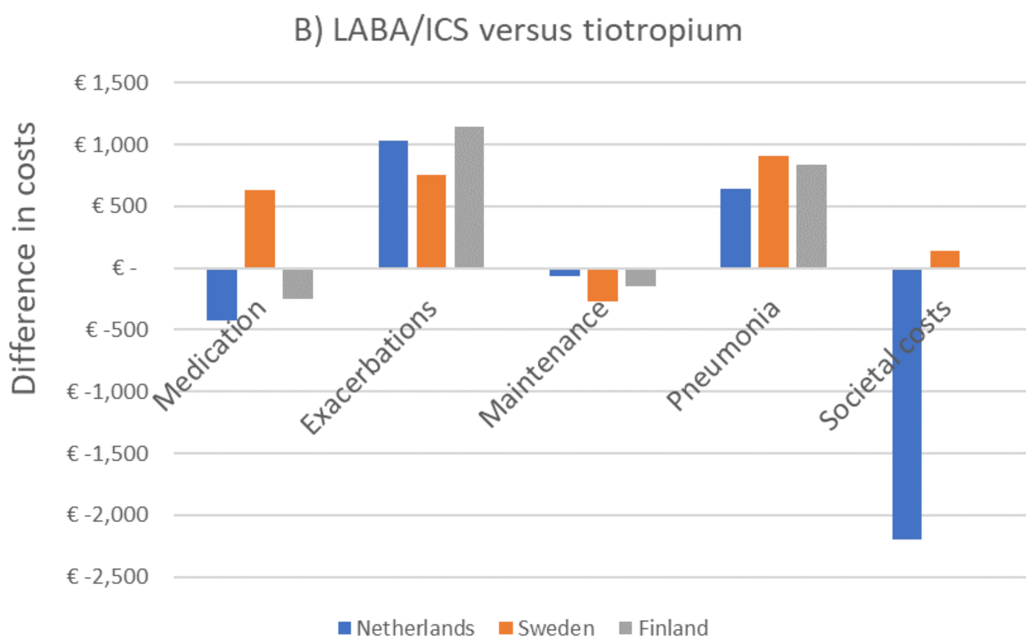

Figure S1B: Difference in costs between LABA/ICS versus tiotropium specified by type of costs

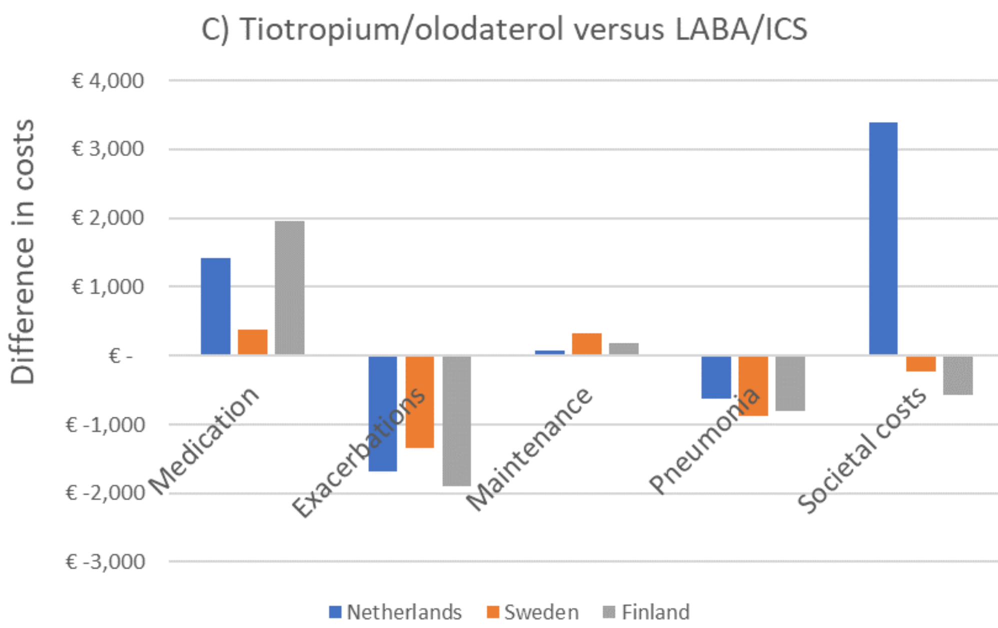

Figure S1C: Difference in costs between tiotropium/olodaterol and LABA/ICS specified by type of costs

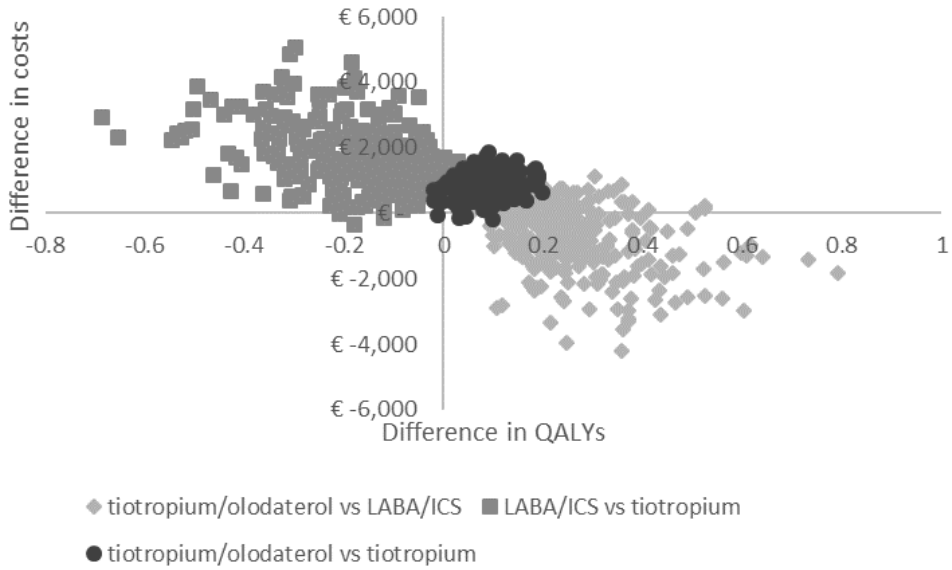

Figure S2: Cost-effectiveness plane for tiotropium/olodaterol versus tiotropium (Black), LABA/ICS versus tiotropium (dark grey) and tiotropium/olodaterol versus LABA/ICS (light grey) for Finland using a limited payer perspective

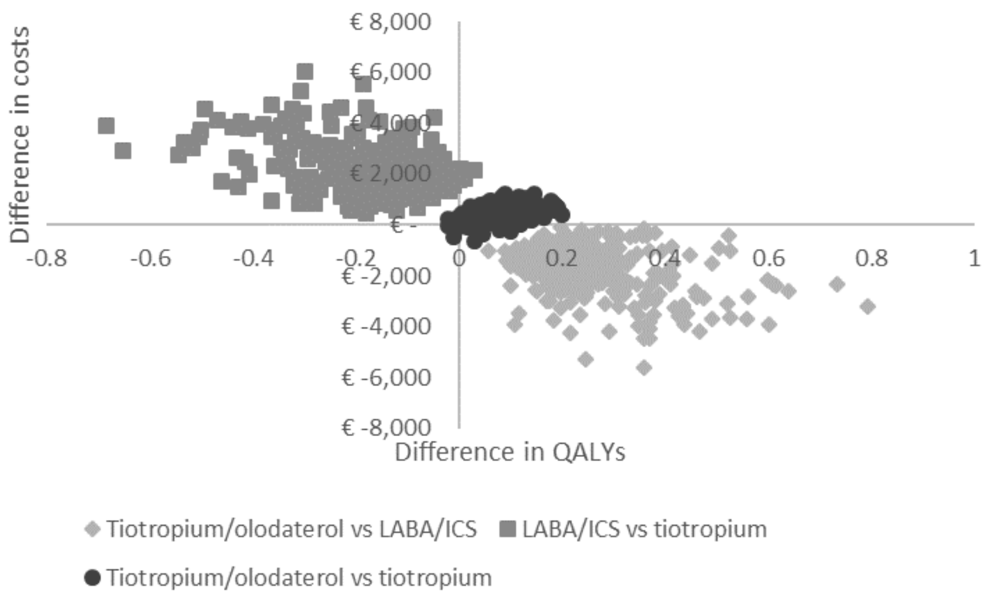

Figure S3: Cost-effectiveness plane for tiotropium/olodaterol versus tiotropium (Black), LABA/ICS versus tiotropium (dark grey) and tiotropium/olodaterol versus LABA/ICS (light grey) for Sweden using a societal perspective

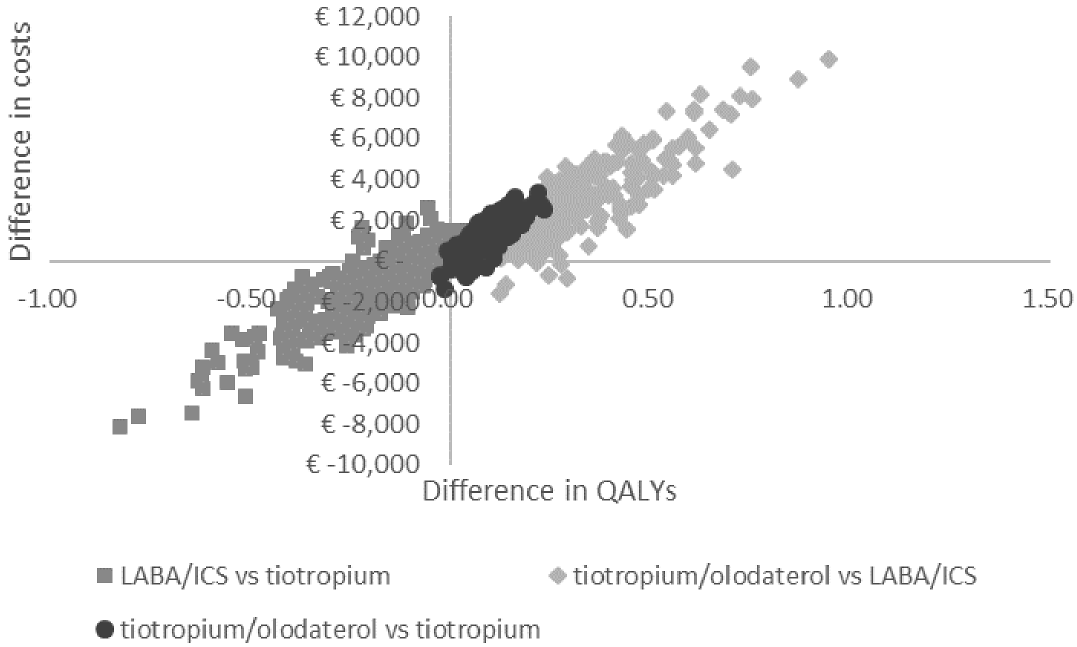

Figure S4: Cost-effectiveness plane for tiotropium/olodaterol versus tiotropium (Black), LABA/ICS versus tiotropium (dark grey) and tiotropium/olodaterol versus LABA/ICS (light grey) for The Netherlands using a societal perspective

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1, title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 4
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 6
		Present the study question and its relevance for health policy or practice decisions.	Page 7
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 9 Table S1 supplementary data
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 10
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 10
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page7/8 Page 11/12
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 9
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 10
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not applicable
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 8
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Page 10/11

Section/item	Item No	Recommendation	Reported on page No/ line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 10/11 Table 2
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 8/9, model figure and full details in reference
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 8/9
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Original publication of the model, page 11/12 sensitivity and scenario analyses
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Original publication of the mode Table 2,
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 4 and Figure 1
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Table 4, SA on number of patients
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 15-18

Section/item	Item No	Recommendation	Reported on page No/ line No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Submission system and page20
onflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Submission system and page 21

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist