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

Martine Hoogendoorn ,[1] Isaac Corro Ramos,[1] Stéphane Soulard,[2] Jennifer Cook,[3] Erkki Soini,[4] Emma Paulsson,[5] Maureen Rutten-van Mölken [1,6]

To cite: Hoogendoorn M, Corro Ramos I, Soulard S, *et al*. 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. *BMJ Open* 2021;**11**:e049675. doi:10.1136/bmjopen-2021-049675

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online. (http://dx.doi.org/10.1136/bmjopen-2021-049675).

Received 02 February 2021
Accepted 20 July 2021

For numbered affiliations see end of article.

Correspondence to
Dr Martine Hoogendoorn; hoogendoorn@imta.eur.nl

ABSTRACT

Objectives Chronic obstructive pulmonary disease (COPD) guidelines advocate treatment with combinations of long-acting bronchodilators for patients with COPD who 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 1 s (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 €6200/QALY and dominant, respectively (societal perspective). The Dutch ICERs were €14 400 and €9200, respectively (societal perspective). The probability that tiotropium/olodaterol was cost-effective compared with 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 with 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 (ie, dominant) in comparison with LABA/ICS.

Strengths and limitations of this study

- A validated comprehensive health economic model built with patient-level data of 35 000 patients with chronic obstructive pulmonary disease (COPD) 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 long-acting β2 agonist/inhaled corticosteroid was used by comparing both treatment options to tiotropium monotherapy.
- The model and efficacy data were based on data from patients with COPD 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 with 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 patients with COPD 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 patients with COPD in Europe is currently still treated with combinations of a bronchodilator plus ICS. In both Sweden and the Netherlands, around 60% of the patients with COPD 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 with tiotropium monotherapy.[13–15] Tiotropium/olodaterol has also been shown to be a cost-effective treatment option compared with 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 Tiotropium Olodaterol for COPD trial (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 optimise healthcare expenditures. Therefore, this study aimed to estimate the cost-effectiveness of the fixed dose combination tiotropium/olodaterol versus two treatment options, that is, 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 5 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 1 s (FEV_1), total number of (severe) exacerbations and total number of pneumonias. For the literature search on efficacy data, the following prioritisation 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*.[23] The efficacy of LABA/ICS versus tiotropium was obtained from an NMA of Oba *et al*.[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 interpreted as rate ratios (RR), 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.

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

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

	Tiotropium/olodaterol	LABA/ICS
Trough FEV_1 in litre, mean difference (95% CI)	+0.05 (0.03 to 0.09)[23]	Not available, assumed zero*
Total exacerbations, ratio (95% CI)	RR=0.89 (0.84 to 0.95)[20]	HR=1.03 (0.91 to 1.17)[24]
Severe exacerbations, ratio (95% CI)	RR=0.86 (0.75 to 0.99)[20]	HR=1.25 (0.86 to 1.85)[24]
Total pneumonias†, ratio (95% CI)	RR=1.02 (0.86 to 1.21)[13 15]	OR=2.02 (1.16 to 3.72)[24]

*To be conservative we assumed the difference to be zero.
†No distinction could be made between moderate and severe pneumonias.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonists; RR, rate ratio.

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 patient population at baseline in the five previously mentioned COPD trials, that is, about 35 000 patients. For the analyses, results of 2000 randomly sampled patients were combined to estimate the average number of QALYs and healthcare costs for each treatment option. Simulating 2000 patients was shown to provide stable results.

Relative efficacy of tiotropium/olodaterol and LABA/ICS compared with 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 modelled by adding the mean difference in FEV_1 between tiotropium/olodaterol and tiotropium, 0.05 L (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 with the annual exacerbation rate with tiotropium was equal to rate ratio (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 with 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 HRs for LABA/ICS presented in the literature were interpreted as rate ratios, because this assumption resulted in more conservative results than interpreting the HRs 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 healthcare costs and patient copayments (value added tax (VAT) excluded) related to COPD.[29] For Sweden, a societal perspective was applied including all direct medical healthcare 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

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[37 38]	€1.00[39 40]	€1.41[41]
Tiotropium/olodaterol	Per day	€1.81[37 38]	€1.32[39 40]	€1.72[41]
LABA/ICS	Per day	€1.28[37 38]	€1.22[39 40]	€1.31[41]
COPD-related annual maintenance treatment*				
General practitioner	Visits Unit cost	1.73[42] €120[43]	2.74[44]† €160[45]	3.64[46 47] €38.88[48]
Respiratory specialist	Visits Unit cost	0.82[49] €305[43]	1.78[44] €239[45]	1.36[46 47] €103.19[48]
Spirometry test	Tests Unit cost	0.77[50] €52.38[43]	0.64[51]‡ €76[45]	0.72[46 52] €17.95[48]
Influenza vaccination	Vaccination Unit cost	0.52[53] €51.28[43]	0.52[54] €65[45]	0.52[55] €15.75[48]
Informal care§	Hours Unit cost	Not applicable	Not applicable	270[56] €14.95[48]
Costs related to COPD exacerbations				
Moderate exacerbation	Per event	€220[33 50 57]	€634/€289*¶[21 40 45 58]	€637/€124*¶[21 41 48]
Severe exacerbation (=hospitalisation)	Per event	€4390[43 50 57]	€4028/€3067*¶[21 40 45 58 59]	€5612/€4182*¶[21 41 48 60]
Costs for treating pneumonias				
Without hospitalisation	Per event	€225[43]	€584/€239*[45 58]	€637/€124*[21 41 48]
With hospitalisation	Per event	€4498[33 43 57]	€5813/€4851*[45 58 59]	€5142/€3711*[48 60]
Average retirement	Age in years	Not applicable	65[58]	65[48]

Exchange rate for Sweden 1 Swedish krona=€0.095 (May 2020).
*Costs below retirement age including short-term productivity costs/costs above retirement age without productivity costs.
†Incremental number of primary care visits for COPD 5.17[44] of which 53% was with physician.[44]
‡Weighted average for primary care and secondary care patients.[51]
§Unpaid care provided to a patient by family or friends.
¶Bottom-up estimate of healthcare use for a moderate and severe exacerbation[21] and country-specific unit costs and duration of a hospitalisation for COPD.
COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist.

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, that is, 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 hospitalisation) or a severe exacerbation or pneumonia (with hospitalisation). Short-term productivity costs related to exacerbations and pneumonias were estimated using the average number of working days lost 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 V.3.0.[32]

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 (eg, tiotropium), the guidelines recommend follow-up treatment for patients with persistent dyspnoea or exacerbations, with either LABA/LAMA (eg, tiotropium/olodaterol) or LABA/ICS (for subgroup with high blood eosinophil levels). Based on these recommendations, incremental cost-effectiveness ratios (ICERs) were calculated for the following treatment comparisons: tiotropium/olodaterol versus tiotropium monotherapy, LABA/ICS versus tiotropium monotherapy and tiotropium/olodaterol versus 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 HRs 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 5000 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 33] was run including the base case costs (direct payer costs, patient copayments) (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 (PSAs) were performed to assess the joint uncertainty around input parameters. The PSAs 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 planes and cost-effectiveness acceptability curves were constructed showing the uncertainty around the difference in QALYs and costs and the probability that one treatment is cost-effective compared with 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 SEK500 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.[34]

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 online supplemental table S1. Of the 2000 simulated patients, about one-quarter were female, the average age was 64 years and the mean FEV_1 was 1.4 L (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 supplemental 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 with 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 with tiotropium, but these higher costs were partly outweighed by a reduction in exacerbation costs (online supplemental figure S1). 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, €6200 for Sweden and €14 400 for the Netherlands (table 3).

Treatment with LABA/ICS compared with tiotropium resulted in fewer QALYs (−0.141) and higher costs (+€1587–€2161) for Finland and Sweden and less QALYs (−0.171) and less costs (−€1006) for the Netherlands.

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

Country	) Outcome	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	€1011	€1587	-€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	€2161	-€1736
	Incremental cost-effectiveness ratio				€6193	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	€1591	-€1006	€2597
	Incremental cost-effectiveness ratio				€14 398	€5,902‡	€9243

*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.
ICER, incremental cost-effectiveness ratio; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; QALY, quality-adjusted life year.

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 with LABA/ICS, the higher treatment costs for tiotropium/olodaterol were completely outweighed by a reduction in exacerbation and pneumonia costs for Finland and Sweden (online supplemental figure S1), resulting in tiotropium/olodaterol being the dominant treatment option, that is, better health effects and less costs. For the Netherlands, the net total costs increase versus LABA/ICS was €2597, and the cost-effectiveness ratio was €9200/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 €9200 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 with LABA/ICS.

Cost-effectiveness planes are shown in the online supplemental figures S2–S4. Cost-effectiveness acceptability curves (figure 1) showed that the probability that treatment with tiotropium/olodaterol is cost-effective compared with 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 with tiotropium. Compared with 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 with 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 with 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 with LABA/ICS was €9200 per

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*	€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
	5000 simulated patients	€10 203	Dominated	Dominant
	No discounting	€9726	Dominated	Dominant
	Limited societal perspective	Dominant	Dominated	Dominant
Sweden	Base case§	€6193	Dominated	Dominant
	Effect on: FEV_1 only	€36 165	NA	NA
	Effect on: exacerbations only	€7977	Dominated	Dominant
	Effect on: exacerbations+FEV_1	€5610	Dominated	Dominant
	Hazard rates interpreted as risk ratios	NA	Dominated	Dominant
	5000 simulated patients	€5662	Dominated	Dominant
	No discounting	€6531	Dominated	Dominant
	Healthcare perspective	€7130	Dominated	Dominant
The Netherlands	Base case¶	€14 398	€5902**	€9243
	Effect on: FEV_1 only	€38 401	NA	NA
	Effect on: exacerbations only	€15 849	€9211**	€12 319
	Effect on: exacerbations+FEV_1	€14 176	€9211**	€12 319
	Hazard rates interpreted as risk ratios	NA	€4732**	€8248
	5000 simulated patients	€13 898	€6229**	€9296
	No discounting	€18 674	€10 168**	€13 513
	Healthcare perspective	€3638	Dominated	Dominant
	Societal perspective without unrelated medical costs in life years gained	€6715	Dominated	€754

*Payer perspective, 2000 simulated patients, discount rate 3%, and effect on FEV_1, exacerbations and pneumonias.
†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.
§Societal perspective, 2000 simulated patients, discount rate 3% and effect on FEV_1, exacerbations and pneumonias.
¶Societal perspective, 2000 simulated patients, discount rate 1.5% for effects and 4% for costs and effect on FEV_1, exacerbations and pneumonias.
**ICER should be interpreted as cost saved per QALY lost.
FEV_1, forced expiratory volume in 1 s; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

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 with the patient population using dual therapy considered in this study.

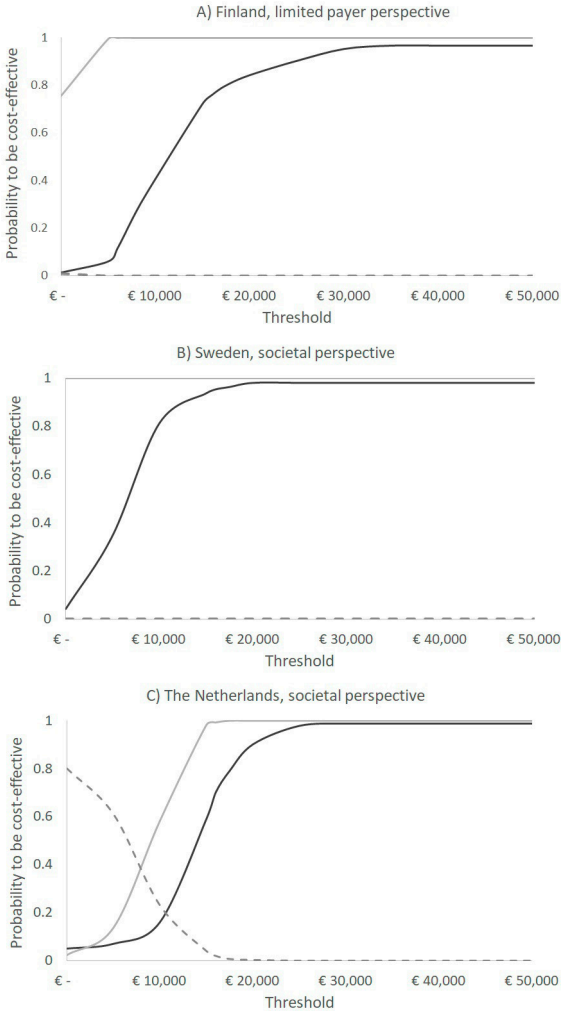

Figure 1 Acceptability curves for tiotropium/olodaterol versus tiotropium (black), tiotropium/olodaterol versus LABA/ICS (grey) and LABA/ICS versus tiotropium (dashed) for (A) Finland, (B) Sweden and (C) the Netherlands. ICS, inhaled corticosteroids; LABA, long-acting β2 agonist.

We acknowledge, however, that because of different recommendations in the past, a substantial proportion of the patients with COPD 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 are 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 favourable for Sweden, which can mainly be explained by the smaller difference in daily costs between tiotropium/olodaterol versus tiotropium and versus LABA/ICS compared with 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.[33] In addition, Finland has a costly pharmaceutical pricing scheme, which explains quite high margins (ie, relative high retail costs excluding VAT in comparison with 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 with 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 with 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 with tiotropium of €2900 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 NMAs and a post hoc analysis of two trials and efficacy was modelled as an impact on multiple parameters (trough FEV1, exacerbations and pneumonias), which explains the difference in QALYs gained in the current study compared with the French study.[16] A previous Dutch study found an ICER of €7000 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 Selya-Hammer *et al*[18] reported an ICER of €7500 per QALY for tiotropium/olodaterol compared with tiotropium in Italy. Tebboth *et al*[19] explored the cost-effectiveness of tiotropium/olodaterol compared with other LABA/LAMA combinations in the UK and concluded that the ICER for tiotropium/olodaterol was acceptable, that is, within the range considered cost-effective and comparable with the ICERs for the other LABA/LAMA combinations. None of the earlier published studies compared tiotropium/olodaterol with LABA/ICS or included Finland or Sweden.

A key strength of this 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 patients with COPD. 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.[35] 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 HRs. 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 10 studies reported that LABA/LAMA combinations resulted in fewer exacerbations, a larger improvement in FEV_1 and lower risk of pneumonia compared with 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 FEV_1 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 to 0.85) and fewer pneumonias (HR: 0.74 (95% CI 0.57 to 0.97).[36] Using these data in the model would have resulted in a comparable ICER for tiotropium/olodaterol versus LABA/ICS for the Netherlands (€9600/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 with 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 with tiotropium, tiotropium/olodaterol can be considered a cost-effective treatment option in all three countries with low ICERs varying between €6200 and €14 400 per QALY. The model outcomes were robust within most of the sensitivity analyses that were performed.

Author affiliations
[1]institute for Medical Technology Assessment (iMTA), Erasmus University Rotterdam, Rotterdam, The Netherlands
[2]Boehringer Ingelheim The Netherlands, Amsterdam, The Netherlands
[3]Boehringer Ingelheim International GmbH, Ingelheim, Rheinland-Pfalz, Germany
[4]ESiOR Oy, Kuopio, Finland
[5]Quantify Research AB, Stockholm, Sweden
[6]Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, Zuid-Holland, The Netherlands

Contributors 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. MR-vM 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.

Funding This work was financially supported by Boehringer Ingelheim the Netherlands and Boehringer Ingelheim GmbH. Award/grant number is not applicable.

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

Competing interests MH reports grants from Boehringer Ingelheim, during the conduct of the study. 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 chronic obstructive pulmonary disease), food industry, diagnostics and device companies, hospitals, consultancies, projects and academic institutions. EP reports grants from Institute for Medical Technology Assessment, Erasmus University Rotterdam, during the conduct of the study; personal fees and other from Quantify Research AB, outside the submitted work. MR-vM reports grants from Boehringer Ingelheim during the conduct of the study.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Martine Hoogendoorn http://orcid.org/0000-0002-7122-9780
Maureen Rutten-van Mölken http://orcid.org/0000-0001-8706-3159

REFERENCES

1 Blanco I, Diego I, Bueno P, *et al*. Geographical distribution of COPD prevalence in Europe, estimated by an inverse distance weighting interpolation technique. *Int J Chron Obstruct Pulmon Dis* 2018;13:57–67.
2 Rehman AU, Hassali MAA, Muhammad SA, *et al*. The economic burden of chronic obstructive pulmonary disease (COPD) in Europe: results from a systematic review of the literature. *Eur J Health Econ* 2020;21:181-194.
3 Global Strategy for the Diagnosis. Management and prevention of COPD, global initiative for chronic obstructive lung disease (gold) report 2020, 2020. Available: http://goldcopd.org [Accessed 24 Jan 2020].
4 Global Strategy for the Diagnosis. *Management and prevention of COPD, global initiative for chronic obstructive lung disease (gold) report*, 2015.
5 Cheng S-L. Blood eosinophils and inhaled corticosteroids in patients with COPD: systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2018;13:2775–84.
6 Finney L, Berry M, Singanayagam A, *et al*. Inhaled corticosteroids and pneumonia in chronic obstructive pulmonary disease. *Lancet Respir Med* 2014;2:919–32.
7 Beeh K-M, Derom E, Echave-Sustaeta J, *et al*. The lung function profile of once-daily tiotropium and olodaterol via Respimat(®) is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler(®) (ENERGITO(®) study). *Int J Chron Obstruct Pulmon Dis* 2016;11:193–205.
8 Horita N, Goto A, Shibata Y, *et al*. Long-Acting muscarinic antagonist (Lama) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2017;2:CD012066.
9 Rodrigo GJ, Price D, Anzueto A, *et al*. LABA/LAMA combinations versus Lama monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2017;12:907–22.
10 Wedzicha JA, Banerji D, Chapman KR, *et al*. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med* 2016;374:2222–34.
11 Johansson G, Mushnikov V, Bäckström T, *et al*. Exacerbations and healthcare resource utilization among COPD patients in a Swedish registry-based nation-wide study. *BMC Pulm Med* 2018;18:17.
12 Fens T, van der Pol S, Kocks JWH, *et al*. Economic impact of reducing inappropriate inhaled corticosteroids use in patients with chronic obstructive pulmonary disease: ISPOR's guidance on budget impact in practice. *Value Health* 2019;22:1092–101.
13 Buhl R, Maltais F, Abrahams R, *et al*. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (gold 2-4). *Eur Respir J* 2015;45:969–79.
14 Singh D, Ferguson GT, Bolitschek J, *et al*. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respir Med* 2015;109:1312–9.
15 Calverley PMA, Anzueto AR, Carter K, *et al*. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med* 2018;6:337–44.
16 Hoogendoorn M, Corro Ramos I, Baldwin M, *et al*. Long-Term cost-effectiveness of the fixed-dose combination of tiotropium plus olodaterol based on the DYNAGITO trial results. *Int J Chron Obstruct Pulmon Dis* 2019;14:447–56.
17 van Boven JF, Kocks JW, Postma MJ. Cost-Effectiveness and budget impact of the fixed-dose dual bronchodilator combination tiotropium-olodaterol for patients with COPD in the Netherlands. *Int J Chron Obstruct Pulmon Dis* 2016;11:2191–201.
18 Selya-Hammer C, Gonzalez-Rojas Guix N, Baldwin M, *et al*. Development of an enhanced health-economic model and cost-effectiveness analysis of tiotropium + olodaterol Respimat® fixed-dose combination for chronic obstructive pulmonary disease patients in Italy. *Ther Adv Respir Dis* 2016;10:391–401.
19 Tebboth A, Ternouth A, Gonzalez-Rojas N. UK-specific cost-effectiveness of tiotropium + olodaterol fixed-dose combination versus other Lama + LABA combinations in patients with COPD. *Clinicoecon Outcomes Res* 2016;8:667–74.
20 Wedzicha J, Buhl R, De La Hoz A. The effect of tiotropium/olodaterol versus tiotropium on COPD exacerbation rates in patients with/without frequent exacerbation history. *Eur Respir J* 2019;54:OA5351.
21 Hoogendoorn M, Corro Ramos I, Baldwin M, *et al*. Broadening the perspective of cost-effectiveness modeling in chronic obstructive pulmonary disease: a new patient-level simulation model suitable to evaluate stratified medicine. *Value Health* 2019;22:313–21.
22 Corro Ramos I, Hoogendoorn M, Rutten-van Mölken MPMH. How to address uncertainty in health economic Discrete-Event simulation models: an illustration for chronic obstructive pulmonary disease. *Med Decis Making* 2020;40:619–32.
23 Aziz MIA, Tan LE, Wu DB-C, *et al*. Comparative efficacy of inhaled medications (ICS/LABA, Lama, LAMA/LABA and SAMA) for COPD: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2018;13:3203–31.
24 Oba Y, Keeney E, Ghatehorde N, *et al*. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2018;12:CD012620.
25 Tashkin DP, Celli B, Senn S, *et al*. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–54.
26 Cooper CB, Celli BR, Jardim JR, *et al*. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. *Chest* 2013;144:490–7.
27 Vogelmeier C, Hederer B, Glaab T, *et al*. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093–103.
28 Wise RA, Anzueto A, Cotton D, *et al*. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013;369:1491–501.
29 Preparing a health economic evaluation to be attached to the application for reimbursement status and Wholesale price for a medicinal product. Application instructions (2019) for Finland. Available: https://www.hila.fi/content/uploads/2020/01/Instructions_TTS_2019.pdf [Accessed Mar 2020].
30 Sweden: general guidelines for economic evaluations from the dental and pharmaceutical benefits agency (updated 2017). Available: https://www.tlv.se/om-oss/om-tlv/regelverk/allmanna-rad.html [Accessed Mar 2020].
31 Dutch guidelines: guideline for the conduct of economic evaluations in health care (Dutch version February 2016). Available: https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg
32 van Baal PHM, Wong A, Slobbe LCJ, *et al*. Standardizing the inclusion of indirect medical costs in economic evaluations. *Pharmacoeconomics* 2011;29:175–87.
33 Mankinen P, Soini E, Linna M. Terveysteknologioiden taloudellisen arvioinnin tuloksiin – esimerkkinä iäkkäiden pneumokokkirokottaminen. perspective affects economic assessment of health technologies – using the elderly pneumococcal vaccination as example. *Dosis* 2019;35:118–35.
34 Versteegh MM, Ramos IC, Buyukkaramikli NC, *et al*. Severity-Adjusted probability of being cost effective. *Pharmacoeconomics* 2019;37:1155–63.
35 Kruis AL, Ställberg B, Jones RCM, *et al*. Primary care COPD patients compared with large pharmaceutically-sponsored COPD studies: an unlock validation study. *PLoS One* 2014;9:e90145.
36 Quint JK, Montonen J, Esposito D. Copd maintenance therapy with tiotropium/olodaterol versus LABA/ICS: an assessment of the risk of treatment escalation and adverse outcomes in over 40,000 patients. *Am J Respir Crit Care Med* 2020;201:A5072.
37 Drug prices 12/2019. Helsinki: pharmaceuticals pricing board 2020.
38 Official statistics of Finland: Reimbursements of medicine expenses: number of recipients and prescription data. Helsinki: Kela 2020.
39 FASS. Swedish webpage containing information about all accepted drugs and related dosing information to indications. Available: https://www.fass.se/LIF/startpage
40 Medprice document, medical product prices downloaded from Swedish TLV – the standard for medical evaluations in Sweden. Available: https://www.tlv.se/in-english/prices-in-our-database.html [Accessed Apr 2020].

41 Costs and reimbursement of drugs in the Netherlands (may 2020). Zorginstituut Nederland. Available: www.medicijnkosten.nl [Accessed Apr 2020].
42 Herse F, Kiljander T, Lehtimäki L. Annual costs of chronic obstructive pulmonary disease in Finland during 1996-2006 and a prediction model for 2007-2030. *NPJ Prim Care Respir Med* 2015;25:15015.
43 Kapiainen S, Väisänen A, Haula T. *Terveyden- JA sosiaalihuollon yksikkökustannukset Suomessa vuonna 2011. health and social care unit cost in Finland in 2011*, 2014.
44 Lisspers K, Larsson K, Johansson G, *et al*. Economic burden of COPD in a Swedish cohort: the Arctic study. *Int J Chron Obstruct Pulmon Dis* 2018;13:275–85.
45 South Health Care Region, Sweden. Regionala priser och ersättningar för södra sjukvårdsregionen 2020, 2020. Available: https://sodrasjukvardsregionen.se/verksamhet/avtal-priser/ [Accessed Apr 2020].
46 Nivel. *Leven Met EEN longziekte in Nederland Cijfers en trends over de zorg- en leefsituatie van mensen Met EEN longziekte 2018*, 2019.
47 Transparante ketenzorg. Rapportage 2018. Zorggroepen diabetes mellitus, VRM, COPD en astma. Ineen 2019.
48 Hakkaart-van Roijen L, Van der Linden N, Bouwmans CAM. *Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. (Dutch costing manual) Zorginstituut Nederland. Geactualiseerde versie*, 2015.
49 Viinanen A, Lassenius MI, Toppila I, *et al*. The burden of chronic obstructive pulmonary disease (COPD) in Finland: impact of disease severity and eosinophil count on healthcare resource utilization. *Int J Chron Obstruct Pulmon Dis* 2019;14:2409–21.
50 Katajisto M, Laitinen T. Estimating the effectiveness of pulmonary rehabilitation for COPD exacerbations: reduction of hospital inpatient days during the following year. *Int J Chron Obstruct Pulmon Dis* 2017;12:2763–9.
51 Löfdahl C-G, Tilling B, Ekström T, *et al*. COPD health care in Sweden - A study in primary and secondary care. *Respir Med* 2010;104:404–11.
52 Zorgstandaard COPD 2019. Long Alliantie Nederland.
53 Influenssarokotuskattavus, Kausi 2018-2019 : 65 v täyttäneet. Influenza vaccination allowance, Season 2018-2019 : 65 years of age. RokottaminenRokotusrekisteri. 2020.
54 Andel AV befolkningen ≥65 år vaccinerad mot influensa, säsong 2018–2019. proportion of the population ≥65 years vaccinated against influenza, season 2018-2019. Available: https://www.folkhalsomyndigheten.se/contentassets/fd95add32f77479bac3ca61934527008/vaccinationstackningen-influensa-2018-2019.pdf [Accessed Apr 2020].
55 Monitor Vaccinatiegraad Nationaal Programma Griepppreventie 2018.
56 Brouwer WBF, van Exel NJA, van den Berg B, *et al*. Process utility from providing informal care: the benefit of caring. *Health Policy* 2005;74:85–99.
57 Heinonen J, Koskela TH, Soini E, *et al*. Primary-care-based episodes of care and their costs in a three-month follow-up in Finland. *Scand J Prim Health Care* 2015;33:283–90.
58 Average monthly wages in 2018, for those who worked. statistics Sweden, 2018.
59 Average number of inpatient days by ICD-10 code. statistics Sweden, 2018.
60 Hospital admissions by ICD-10 code. statistics Netherlands 2017.