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External Validation of Health Economic Decision Models for Chronic Obstructive Pulmonary Disease (COPD): Report of the Third COPD Modeling Meeting

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ABSTRACT

Objectives: To validate outcomes of presently available chronic obstructive pulmonary disease (COPD) cost-effectiveness models against results of two large COPD trials—the 3-year TOwards a Revolution in COPD Health (TORCH) trial and the 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial. **Methods:** Participating COPD modeling groups simulated the outcomes for the placebo-treated groups of the TORCH and UPLIFT trials using baseline characteristics of the trial populations as input. Groups then simulated treatment effectiveness by using relative reductions in annual decline in lung function and exacerbation frequency observed in the most intensively treated group compared with placebo as input for the models. Main outcomes were (change in) total/severe exacerbations and mortality. Furthermore, the absolute differences in total exacerbations and quality-adjusted life-years (QALYs) were used to approximate the cost per exacerbation avoided and the cost per QALY gained. **Result:** Of the six participating models, three models reported higher total exacerbation rates than observed in the TORCH trial (1.13/patient-year) (models: 1.22–1.48). Four models reported higher rates than observed in the UPLIFT trial (0.85/patient-year) (models: 1.13–1.52). Two models reported higher mortality rates than in the TORCH trial (15.2%) (models: 20.0% and 30.6%) and the UPLIFT trial (16.3%) (models: 24.8% and 36.0%), whereas one model reported lower rates (9.8% and 12.1%, respectively). Simulation of treatment effectiveness showed that the absolute reduction in total exacerbations, the gain in QALYs, and the cost-effectiveness ratios did not differ from the trials, except for one model. **Conclusions:** Although most of the participating COPD cost-effectiveness models reported higher total exacerbation rates than observed in the trials, estimates of the absolute treatment effect and cost-effectiveness ratios do not seem different from the trials in most models.

Keywords: COPD, cost-effectiveness, external validation, model.

Introduction

Since 2004, several cost-effectiveness models for chronic obstructive pulmonary disease (COPD) have been developed and published [1–13]. Some of these models were specifically built to extrapolate single-trial results to a longer time horizon and support reimbursement decisions for newly developed drugs [4,6,8]. Other models used various data sources as input and are able to evaluate a wide range of different COPD interventions [3,7,10,12]. As a result of differences in data input, the models may refer to different populations of patients with COPD.

Because of their increasing role in decision making, it is very important that these cost-effectiveness models reflect the disease process and disease progression in COPD in an accurate way. Therefore, validation is a crucial part of model development [14]. One of the most important types of validation is external validation, which refers to comparing model outcomes against data from epidemiologic studies, clinical trials, or claims databases, preferably not used to build the model [14].

Since 2011, a worldwide network of researchers involved in COPD modeling (COPD modeling teams, pharmaceutical companies interested in COPD modeling, epidemiologists, clinicians, etc.)

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come together for 1-day annual meetings in Amsterdam to discuss and compare the currently available COPD models, collaborate, and share best practices about COPD modeling. During the second meeting in 2012, the models were cross-validated against each other to assess which differences in model structure, assumptions, and input data had the highest impact on the results of the models [15]. The main topic of the third meeting organized in 2014 was patient heterogeneity in COPD models [16]. Another topic of the third meeting was external validation of the models, which is the focus of this article.

The aim of the present article was to describe the validation of the outcomes of presently available COPD cost-effectiveness models against the results of two large clinical COPD trials and to assess the impact of the observed differences in outcomes on the cost-effectiveness ratio.

Methods

In the spring of 2014, modeling groups that participated in previous meetings as well as new groups were invited to participate in the modeling challenge for the third meeting. The challenge consisted of two components. For the first component, groups were requested to simulate outcomes for the placebo-treated groups of two large clinical COPD trials. For the second component, groups were asked to simulate the treatment effectiveness observed in the same trials. All results of the model simulations were reported in a structured format in Microsoft Excel and sent to the organizers of the meeting 2 weeks in advance. A summary of the combined results was circulated to all participants shortly before the meeting to give them the opportunity to reflect on the outcomes. During the meeting, results were presented and discussed to find possible explanations for deviations of the model outcomes from the trial results.

Clinical Trials

For this validation study, outcomes of two large long-term clinical trials in COPD were used: the TOwards a Revolution in COPD Health (TORCH) trial and the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial [17,18]. In the 3-year TORCH trial, patients were randomly assigned to four treatment groups: 1) placebo, defined as all COPD medications except for long-acting bronchodilators (LABAs) and inhaled corticosteroids (ICSs); 2) salmeterol 50 μg; 3) fluticasone 500 μg; and 4) salmeterol 50 μg plus fluticasone 500 μg. The primary outcome of the trial was all-cause mortality. Secondary outcomes were exacerbations, health status, and lung function decline. The hazard ratio for mortality in the combination-therapy group compared with the placebo group was 0.825 (95% confidence interval [CI] 0.681–1.002) [16]. Compared with placebo the combination-therapy group had a significant reduction in exacerbations (relative reduction [RR] = 0.75; 95% CI 0.69–0.81) and in annual decline in forced expiratory volume in 1 second (FEV_1) (0.9% vs. 1.5% predicted/y; RR = 0.6) [17,19].

In the 4-year UPLIFT trial, patients with COPD were randomly assigned to the placebo group, which was defined as all regular respiratory medication except for inhaled anticholinergics or tiotropium 18 μg plus all regular respiratory medications except other inhaled anticholinergics. Primary outcomes of the trial were the pre- and postbronchodilator yearly rate of decline in FEV_1, whereas secondary outcomes were health-related quality of life, exacerbations, and mortality. No difference was observed between the two groups in the rate of decline in FEV_1 (post-bronchodilator: 40 vs. 42 ml/y; RR = 0.95). The tiotropium group had a lower number of exacerbations (RR = 0.86; 95% CI 0.81–0.91) and less mortality (hazard ratio = 0.87; 95% CI 0.87–0.99) compared with the placebo group [18].

Modeling Challenge

To simulate the outcomes of the two trials, the modeling groups populated their models with the baseline characteristics of the patients in the placebo groups in the trials. Models were adjusted, if possible, for percentage of males, mean age, percentage of present smokers, and mean FEV_1% predicted (or the distribution over the Global initiative for chronic Obstructive Lung Disease [GOLD] severity stages: moderate, severe, and very severe COPD) (Table 1). Other model parameters, such as disease progression, exacerbation probabilities, mortality, and utilities, were left unchanged.

The time horizons of the model simulations were equal to the treatment duration in the trials. Hence, modelers were asked to simulate the outcomes for the placebo group of the 3-year TORCH trial taking into account that patients did not receive LABA or ICS. Furthermore, outcomes for the placebo group of the 4-year UPLIFT trial were simulated taking into account that patients used all regular respiratory medication except other anticholinergics. Outcomes reported and compared with the trial results were total number of exacerbations per patient-year, total number of severe exacerbations per patient-year, and percentage of patients who died (means plus uncertainty intervals). Exacerbations in these analyses were defined as an increase in symptoms requiring treatment with antibiotics and/or systemic corticosteroids (moderate exacerbations) and/or hospitalization (severe exacerbation).

For the second component of the modeling challenge, the modeling groups were asked to simulate the relative treatment effectiveness as observed in the trials. Relative treatment effectiveness was defined as the RR in annual decline in lung function and exacerbations between the most intensively treated group (TORCH: salmeterol/fluticasone; UPLIFT: tiotropium) and the placebo group. The observed RRs in annual decline in lung function and exacerbations were applied to the model input values of these parameters used to simulate the outcomes for the placebo group. This method is regarded as an appropriate

Table 1 – Baseline characteristics of patients in the placebo groups of the TORCH and UPLIFT trials used as starting population of the model simulations [17,18].

Trial	TORCH placebo	UPLIFT placebo
N	1524	3006
Males	76%	74%
Age (y), mean ± SD	65 ± 8	65 ± 9
Current smokers	43%	30%
Post-FEV_1% predicted, mean ± SD	44 ± 12	47 ± 13
Severity distribution		
GOLD II: moderate COPD	35%	45%
GOLD III: severe COPD	50%	44%
GOLD IV: very severe COPD	15%	9%

FEV_1% predicted, forced expiratory volume in 1 s as percentage of the predicted value; GOLD, Global initiative for chronic Obstructive Lung Disease; TORCH, TOwards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.