

# Cost-Effectiveness of Salmeterol, Fluticasone, and Combination Therapy for COPD

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**Objective:** To assess the incremental cost-effectiveness of inhaled medication use in chronic obstructive pulmonary disease (COPD).

**Study Design:** A Markov model was constructed to estimate the incremental quality-adjusted life-years (QALYs) gained of the alternative treatment arms used in the Towards a Revolution in COPD Health (TORCH) study (ie, salmeterol-fluticasone propionate combination [SFC], salmeterol, fluticasone, and placebo).

**Methods:** The cycle length for the model was set to 3 months, and the maximum time horizon was set to 3 years. The cost-effective analysis was conducted from a third-party payer's perspective in the US healthcare system. Future costs and effects were discounted at 3%. Multiple 1-way sensitivity analyses and a probabilistic sensitivity analysis using Monte Carlo simulation were performed to handle uncertainty.

**Results:** The most cost-effective strategies are placebo (as-needed short-acting bronchodilator use with no maintenance therapy) when willingness to pay (WTP) is less than \$52,800/QALY gained and SFC when WTP exceeds that threshold. When no maintenance therapy is not an acceptable option, the most cost-effective strategies are treatment with salmeterol when WTP is less than \$49,500/QALY gained and treatment with SFC when WTP exceeds that threshold. The base-case analysis showed that incremental cost-effectiveness ratios of salmeterol, fluticasone, and SFC relative to placebo were \$56,519, \$62,833, and \$52,046/QALY gained, respectively.

**Conclusions:** The most cost-effective strategy in moderate-to-severe COPD depends on how much society is willing to pay to achieve health improvements. When treatment with as-needed short-acting bronchodilator use does not provide adequate control, salmeterol or SFC would be the drug of choice depending on WTP.

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In 2003, 10.7 million US adults were estimated to have chronic obstructive pulmonary disease (COPD).<sup>1</sup> Healthcare costs for COPD have continued to increase with the increased prevalence of the disease. The total cost of COPD in 2004 was \$37.2 billion, including \$20.9 billion in direct healthcare expenditures, \$7.4 billion in indirect morbidity costs, and \$8.9 billion in indirect mortality costs.<sup>2</sup>

The Towards a Revolution in COPD Health (TORCH) trial<sup>3</sup> is a large multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Approximately 6200 patients with moderate-to-severe COPD were randomly assigned to twice-daily treatment with salmeterol-fluticasone propionate combination (SFC) (50 µg and 500 µg, respectively), fluticasone propionate (500 µg), salmeterol (50 µg), or placebo for 3 years. In that study, treatment with SFC was associated with a 2.6% reduction in mortality, which failed to reach statistical significance. In several outcomes, salmeterol alone seemed superior to fluticasone alone. How to apply these results to clinical practice has been debated.<sup>4,5</sup>

Given the comparable therapeutic efficacies and adverse event rates among the inhaled medications used in the TORCH study, cost-effectiveness may have an important role in the decision as to which is the agent of choice in moderate-to-severe COPD. The objective of this study was to assess the cost-effectiveness of these inhaled medications.

## METHODS

### Analytic Overview

A Markov model was constructed with 4 mutually exclusive disease states for patients with moderate-to-severe COPD. The disease states include stable, exacerbation requiring a physician visit, severe exacerbation requiring hospitalization, and death. The cycle length for the model was set to 3 months to fully incorporate the effect of an exacerbation on quality of life,<sup>6</sup> and the maximum time horizon was set to 3 years to match the duration of the TORCH study. The cost-effectiveness of 4 strategies used in the TORCH study (ie, salmeterol, fluticasone, SFC, and placebo) was compared. An incremental cost-effectiveness ratio (ICER) of each strategy was calculated. A discount rate of 3% was applied to costs and health benefits based on international recommendations.<sup>7</sup> The effect of changes in the discount rate ranging

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from 0% to 7% was examined by 1-way sensitivity analysis. A half-cycle correction was applied in each period to allow for the fact that transitions between health states could take place at any time during the modeled 3-month intervals.<sup>8</sup> Decision analyses were performed using TreeAge Pro (TreeAge Software, Inc, Williamstown, MA) and Excel 2000 (Microsoft, Redmond, WA).

### Input Data

Efficacy data were derived from the TORCH study. Efficacy data incorporated in the present model were frequency of exacerbation requiring a physician visit, hospitalization rate, all-cause mortality rate, and changes in health status of each treatment arm. It was assumed that moderate exacerbations requiring treatment with systemic corticosteroids required a visit to a physician's office or an emergency department.

Utility weights were estimated by converting St George's Respiratory Questionnaire (SGRQ) scores measured in the TORCH study to EuroQoL Five-dimension Questionnaire (EQ5D) scores. The EQ5D is a generic health-related quality-of-life measure with scores ranging from 0 to 1 (where 1 represents a perfect state) and allows measurement of utility weights. The following equation was formulated based on data from a study by Ståhl et al<sup>9</sup>:

$$\text{EQ5D Index} = (1.102 - 0.01083) \times \text{SGRQ Score (correlation coefficient, } -0.9851)^{10}$$

Transition probabilities were calculated and applied as follows. The quarterly mortality rate associated with each arm was calculated using an exponential approximation described by Beck et al<sup>11</sup> and incorporated in the Markov model. Study subjects who died during each 3-month period were excluded from further analysis. Physician visit and hospitalization rates observed in the TORCH study were adjusted for the cycle length of 3 months and incorporated in the model as transition probabilities. The survivors of each 3-month cycle continued through another cycle, and a similar set of probabilities for death, hospitalization, and exacerbation was applied. These nonfatal event rates were also used between exacerbation states because such information was not provided in the TORCH study. Twelve 3-month cycles translated into 36 months of follow-up.

The cost-effective analysis was conducted from a third-party payer's perspective in the US healthcare system; hence, only direct costs were included in this analysis. Costs for medications related to respiratory disease were determined on the basis of the mean wholesale price for 2006<sup>12</sup> discounted by 15% to adjust for typical retail acquisition costs, with a \$2.50 dispensing fee added for each 30-day period.<sup>13</sup> The following assumptions were made to estimate the costs of exacerbations:

(1) Ten percent of unscheduled physician visits occurred in emergency departments.<sup>14,15</sup> (2) A 7-day course of prednisone (40 mg/d) and antibiotics was used for outpatient treatment of COPD exacerbations. (3) The mean length of hospital stay for COPD exacerbation was 4.9 days.<sup>16</sup> The mean cost of hospitalization because of COPD exacerbation was quoted from Solucient's Medicare database,<sup>16</sup> which was based on the Medicare Provider Analysis and Review File. Actual costs rather than reimbursement were used because the reimbursement per discharge was lower than the mean actual costs. The cost of a physician visit was based on the mean reimbursement of the *Current Procedural Terminology-4* code 99214 for a visit made by an established patient to a general practitioner.<sup>17</sup> Costs for inpatient physician visit and emergency department visit for COPD exacerbations were based on data by Wilson et al.<sup>18</sup> The cost of antibiotic treatment was based on data by Sin et al.<sup>19</sup> All costs are reported in 2006 US dollars (adjusted when necessary) using the Consumer Price Index inflation calculator provided by the US Department of Labor.<sup>20</sup> The baseline values used in the present model for all variables are listed in **eAppendix Table 1** (available at [www.ajmc.com](http://www.ajmc.com)).

### Sensitivity Analyses

Variability was assessed by multiple 1-way sensitivity analyses. The value of each variable was placed in the decision model with its upper and lower limits, while holding all other values constant (eAppendix Table 1). For efficacy variables, these limits were derived from the 95% confidence intervals of relative risks for each variable, comparing each active arm with placebo results reported in the TORCH study. For cost variables, these limits were decided as follows. The limits of medication costs were derived from the highest and lowest costs listed in the *Drug Topics 2006 Red Book*.<sup>12</sup> The limits of hospitalization cost were derived from the 25th percentile and 75th percentile of the mean cost listed in the Medicare database.<sup>16</sup> The limits of minor exacerbation costs were set at -20% and 20% of the base value<sup>21</sup> because variances were not found in the literature. Threshold analyses identified the value of each variable across its range (if any) at which the ICER of another strategy exceeds that of the most cost-effective strategy. Monte Carlo simulation was used in the model to handle the uncertainty probabilistically, with distributions assigned to multiple parameters to reflect the second-order uncertainty.<sup>22,23</sup> Probability distributions of exacerbation rates, hospitalization rates, all-cause mortality rates, quality-of-life utility weights, and costs of the medications were incorporated in the model. Efficacy parameters were assigned beta distributions, and unit cost parameters were assigned gamma distributions.<sup>24</sup> The present analysis was based on 10,000 simulations. The uncertainty in costs and effects was illustrated as a cost-benefit acceptability curve.<sup>25</sup>

## RESULTS

At baseline, the patient population analyzed in the present model was 76% male and comprised 43% current smokers and had the following mean (SD) values: age of 65 (8.3) years, prebronchodilator forced expiratory volume in the first second of expiration (FEV<sub>1</sub>) of 1.1 (0.4) L, predicted FEV<sub>1</sub> percentage of 44.0% (12.4%), and baseline SGRQ score of 49.3 (17.1). **Table 1** summarizes the results of the base-case analysis. The ICERs of salmeterol, fluticasone, and SFC relative to placebo were \$56,519, \$62,833, and \$52,046/QALY gained, respectively. No treatment arms were clearly dominated by any other arm (ie, no strategies have higher cost and lower effectiveness than some other options). The salmeterol and fluticasone strategies were each dominated by the principle of extended dominance by a blend of the SFC and placebo strategies. Multiple 1-way sensitivity analyses revealed that the incremental cost-effectiveness among the alternative treatment arms was sensitive to several variables, including costs of SFC and salmeterol, all-cause mortality rate with each treatment arm, hospitalization rate with salmeterol, and utility weight with each treatment arm during a stable phase of the disease. The results of comparative cost-effectiveness were robust over reasonable parameter uncertainty with other variables (eAppendix Table 1).

**Figure 1** shows a selection of the 1-way sensitivity analyses (tornado diagram) for the salmeterol arm. The dotted vertical line represents the base-case incremental cost-effectiveness estimate (\$56,519/QALY gained). In the graph, a horizontal bar was generated for each selected variable being analyzed. Expected value is displayed on the horizontal axis, so each bar represents the range of expected values generated by varying the related variable. A wide bar indicates that the associated variable has a large potential effect on the expected value of the present model. Most notable among these variables

were the utility weight and the mortality rate. As the utility rate was varied from 0.569 to 0.591, the ICER ranged from \$37,522 to \$117,396/QALY gained, whereas the ICER ranged from \$42,204 to \$93,120/QALY gained when the quarterly mortality rate was varied from 0.97% to 1.46%. The variables that significantly affected the cost-effectiveness and the magnitudes of effects of their ranges on the cost-effectiveness in the SFC and fluticasone arms were similar to those in the salmeterol arm.

A sensitivity analysis using different data sets to estimate utility weights was also performed. Rutten-van Mülken et al<sup>26</sup> examined the correlation between EQ5D utility scores and SGRQ scores. Assuming a linear correlation between EQ5D and SGRQ scores and using the EQ5D scores calculated with the United Kingdom value set (also known as the MVH A1 value set), the following equation was formulated to estimate utility weights. EQ5D Index = (1.173 – 0.009160) × SGRQ Score. Then, ICERs for salmeterol, fluticasone, and SFC were \$53,873, \$68,175, and \$52,785/QALY gained, respectively. These results were similar to those of the present base-case analysis. However, when the EQ5D scores calculated with the US value set<sup>27</sup> were used, ICERs for salmeterol, fluticasone, and SFC relative to placebo were \$58,149, \$85,806, and \$60,159/QALY gained, respectively. The fluticasone strategy was dominated by the salmeterol strategy. The SFC strategy was still the most effective but also the most costly. The ICER for SFC relative to salmeterol was \$62,604/QALY gained.

The **eAppendix Figure** (available at [www.ajmc.com](http://www.ajmc.com)) shows the uncertainty around the costs and health benefits on a cost-effectiveness plane. Each dot represents 1 of 10,000 model simulations. Data points from the Monte Carlo simulation illustrate that SFC is generally associated with a gain in QALYs at the expense of higher costs compared with other inhaled medications. **Figure 2** shows a net benefits acceptability

■ **Table 1.** Discounted Absolute and Incremental Costs and Effectiveness and Incremental Cost-Effectiveness Ratios in the Base-Case Analysis<sup>a</sup>

Strategy	Total (Medication/Hospitalization/Mild Exacerbation and Physician Visit) Cost, \$	Total Effectiveness, QALYs Gained	Incremental Cost, \$ <sup>b</sup>	Incremental Effectiveness, QALYs Gained <sup>b</sup>	Incremental Cost-Effectiveness Ratio, \$/QALY Gained <sup>b</sup>
Placebo	2780 (0/2509/271)	1.444	—	—	—
Salmeterol propionate	5832 (3484/2130/218)	1.498	3052	0.054	56,345 <sup>c</sup>
Fluticasone	6927 (4516/2236/175)	1.510	1095	0.013	87,600 <sup>c</sup>
SFC	9598 (7300/2140/158)	1.575	2671	0.065	41,092

QALY indicates quality-adjusted life-year; SFC, salmeterol–fluticasone propionate combination.

<sup>a</sup>All costs are in 2006 US dollars.

<sup>b</sup>Relative to the next less costly or less effective strategy. Values are rounded.

<sup>c</sup>Dominated by extended dominance.

curve that represents, at each level of willingness to pay (WTP), the percentage of the simulations for which each strategy is cost-effective relative to the others. The placebo arm (as-needed short-acting bronchodilator use with no maintenance therapy) was the most cost-effective strategy when WTP was less than \$52,800/QALY gained. The SFC arm became the most cost-effective strategy when WTP exceeded that threshold. Among the active arms, salmeterol had the highest likelihood of being the most cost-effective when WTP was less than \$49,500/QALY gained, and the SFC strategy became the most cost-effective when WTP exceeded that threshold.

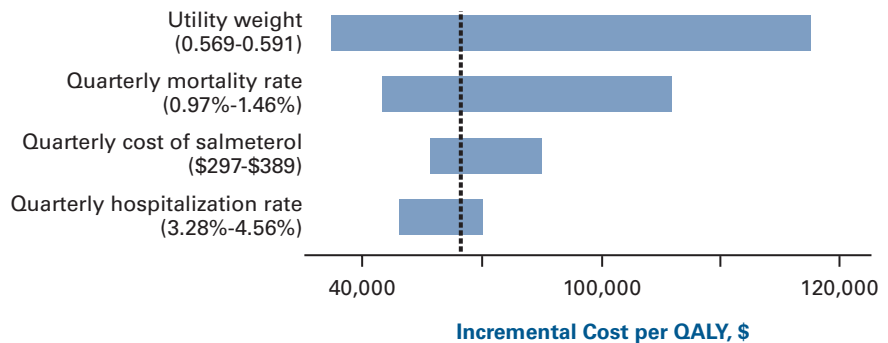
## DISCUSSION

To my knowledge, this is the first published study that compares the cost-effectiveness of an inhaled corticosteroid (ICS), a long-acting  $\beta_2$ -agonist (LABA), and a combination of both from a US healthcare payer's perspective. The cost-effectiveness ratios of the inhaled medications analyzed in this study were comparable to those of other therapies commonly used in clinical practice.<sup>28</sup> Although the reduction in all-cause mortality with either strategy did not reach statistical significance in the TORCH study, the increase in QALYs gained was significantly better with all active treatments compared with placebo, especially with the combination therapy (eAppendix Figure). The effect of fluticasone on QALYs gained was also positive because of significant improvement in quality of life, despite the fact that it had a trend toward increased all-cause mortality and increased risk of pneumonia.

The SFC therapy seemed to be the most cost-effective in the base-case analysis. However, the results were sensitive to WTP and to changes in several variables (eAppendix Table 1).

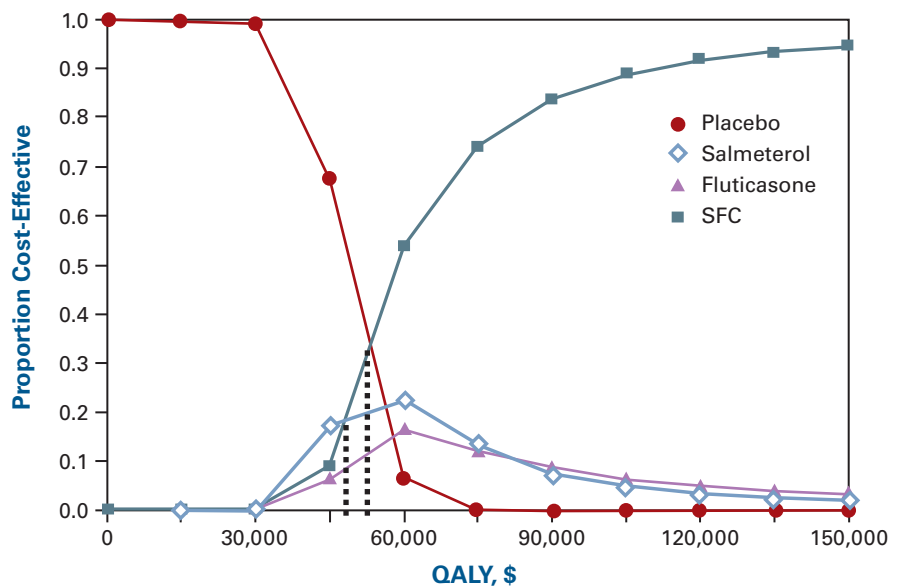
The present study differs in some respects from a recent Canadian study.<sup>29</sup> In that study, the cost of the combination therapy

**Figure 1.** Tornado Diagram Showing a Series of 1-Way Sensitivity Analyses for the Salmeterol Arm



The dotted line represents the base-case incremental cost-effectiveness estimate (\$56,519 per quality-adjusted life-year [QALY] gained).

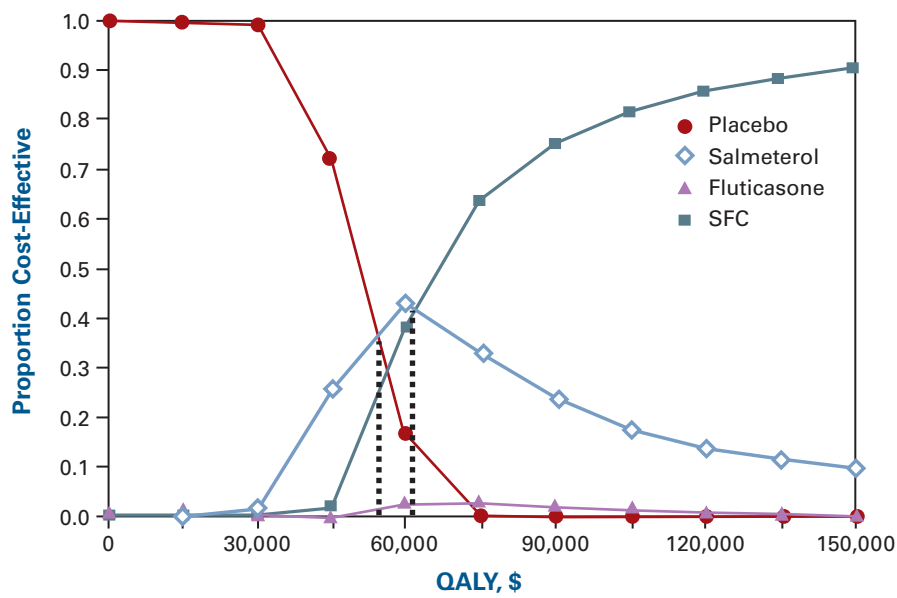
**Figure 2.** Net Benefits Acceptability Curve of Alternative Strategies



QALY indicates quality-adjusted life-year; SFC, salmeterol-fluticasone propionate combination. The dotted lines represent threshold levels of \$49,500 and \$52,800, at which the cost-effectiveness between 2 strategies changes.

per QALY gained was consistently higher than that of LABA (ie, LABA was consistently more cost-effective than the combination therapy), while the present study showed comparable cost-effectiveness between SFC and salmeterol. A possible explanation for this discrepancy is that the greater improvement in quality of life among the combination group during a stable phase of the disease was not considered in the Canadian study, which could have led to underestimation of the incremental effectiveness in the combination group. When the incremental QALYs gained of SFC during the stable phase of the disease, relative to salmeterol, were eliminated from the present model, the cost-effectiveness ratio of SFC increased from \$52,046 to \$95,136/

■ **Figure 3.** Net Benefits Acceptability Curve of Alternative Strategies Using Pooled Data



QALY indicates quality-adjusted life-year; SFC, salmeterol–fluticasone propionate combination. The dotted lines represent threshold levels of \$55,200 and \$62,400, at which the most cost-effective strategy changes.

QALY gained, and SFC became less cost-effective than salmeterol (\$56,519/QALY gained), as the Canadian study noted. After the adjustment described, the difference in cost-effectiveness ratios between the combination therapy and LABA became strikingly similar.

The ICERs were also calculated using key variables from a recently published systematic review<sup>30</sup> to assure the robustness of the baseline analysis. The ICERs for salmeterol, fluticasone, and SFC relative to placebo were \$53,911, \$81,900, and \$56,466/QALY gained, respectively. The ICERs relative to the next less costly or less effective strategy are given in eAppendix Table 2 (available at [www.ajmc.com](http://www.ajmc.com)). Fluticasone was dominated by salmeterol (ie, fluticasone was more expensive but less effective than salmeterol). A net benefits acceptability curve is shown in Figure 3. The most cost-effective strategies were placebo (as-needed short-acting bronchodilator use only) when WTP was less than \$55,200/QALY gained, salmeterol when WTP was between \$55,200 and \$62,400/QALY gained, and SFC when WTP was more than \$62,400/QALY gained. The variables incorporated in the model were relative risks for death (0.91, 1.00, and 0.82 for LABA, ICS, and combined LABA-ICS vs placebo, respectively); differences in COPD-related hospitalizations<sup>31</sup> (−0.01, −0.02, and −0.03/patient-year for LABA, ICS, and combined LABA-ICS vs placebo, respectively); changes in SGRQ scores (−1.59, −1.54, and −3.10 for salmeterol, ICS, and combined LABA-ICS, respectively), which were converted to EQ5D scores using the same method; and relative risks for

COPD exacerbations (0.87, 0.85, and 0.77 for LABA, ICS, and combined LABA-ICS, respectively).

There are several limitations in this analysis. First, the results should be interpreted cautiously given the magnitude in the uncertainty of incremental costs and effectiveness. The efficacy data may have been affected by the differences in healthcare system and hospitalization criteria in different countries, as the TORCH study was an international trial. Other confounding factors include high and inconsistent drop-out rates (34%-44%) in each arm of the TORCH study, as well as the effect of cointerventions in a real-world setting and their interactions with the study drugs.

Second, the utility values were estimated by converting SGRQ scores to EQ5D scores. In general, utility values derived from choice-based methods such as the standard gamble and the time trade-off are thought to be the most robust and to have the greatest theoretical validity and acceptable levels of reliability.<sup>32</sup> However, to my knowledge, there are no established standards for how to estimate or measure utility weights in a cost-effectiveness analysis for patients with COPD, as summarized in Table 2. Although there is a paucity of data on the precision of the utility estimates used in this study, the uncertainty of those estimates was assessed in the sensitivity analyses. The cost-effectiveness ratio of fluticasone was always inferior to that of the other arms, and the cost-effectiveness ratio between salmeterol and SFC was comparable regardless of the method used. A change in the utility weights associated with each arm resulted in large changes in the cost-effectiveness outcomes in the present study. This may mean that the parameter has to be determined very accurately or that an alternative has to be redesigned for low sensitivity. The method used to estimate the utility values needs further validation in future studies.

Third, the present model was limited to a 3-year time horizon and to patients with moderate-to-severe COPD. The cost-effectiveness of the medications beyond 3 years was not studied because it is unclear that the clinical efficacies and potencies of the inhaled medications remain the same beyond that point. Furthermore, there have been many controversies about the long-term adverse effects of ICS (such as cataract and osteo-

■ **Table 2.** Estimation of Utility Weights in Previous COPD Studies

Source and Characteristics and Classifications of Patients	Utility Weight	Method
<b>Smith and Pesce,<sup>33</sup> 1994</b> Lifelong high supportive care needs and poor functional status	0.4 (range, 0.2-0.8)	Assumed
<b>Borg et al,<sup>34</sup> 2004, FEV<sub>1</sub> %</b>	<b>Mean (SD)</b>	
>80	0.8971 (0.1117)	Measured using EQ5D and then modified using a previous study <sup>9</sup>
>50-80	0.7551 (0.2747)	
30-50	0.7481 (0.2991)	
<30	0.5493 (0.3129)	
<b>Ramsey et al,<sup>35</sup> 2003</b> FEV <sub>1</sub> 26.7% of predicted and SGRQ score of 53.6 <sup>a</sup>	0.57 (0.11) <sup>a</sup>	Measured using Quality of Well-being Scale
<b>Sin et al,<sup>19</sup> 2004, FEV<sub>1</sub> %</b>		
>50	1.0	Assumed based on values measured using Index of Health-Related Quality of Life in a previous study <sup>36</sup>
35-50	0.92	
<35	0.84	
<b>Spencer et al,<sup>6</sup> 2005, FEV<sub>1</sub> %</b>	<b>Mean (SE)</b>	
>50	0.81 (0.02)	Assumed based on values measured using EQ5D in a previous study <sup>37</sup>
35-50	0.72 (0.03)	
<35	0.67 (0.05)	
<b>Rutten-van Mólken et al,<sup>26</sup> 2006, FEV<sub>1</sub> %<sup>b</sup></b>	<b>Value (95% CI)</b>	
>50-80	0.832 (0.821-0.843)	Measured using EQ5D
30-50	0.803 (0.790-0.816)	
<30	0.731 (0.699-0.762)	

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; EQ5D, EuroQoL Five-dimension Questionnaire; FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; SGRQ, St George's Respiratory Questionnaire.  
<sup>a</sup>Mean value for the medical therapy group.  
<sup>b</sup>Calculated using the US value set by Shaw et al.<sup>27</sup>

porosis) as to whether they cause such adverse effects or if it is merely an association,<sup>37,38</sup> as well as about the safety profile of LABAs as to whether they increase deaths in patients with asthma and COPD.<sup>39-41</sup> The costs of these potential adverse events were not included in this study because it was thought to be unlikely that these events would occur in the 3-year time frame. The present study was also compared with another Canadian study by Sin et al.<sup>19</sup> They reported that the cost per QALY gained with the use of ICS in patients with stage 2 or 3 disease when no mortality benefits were assumed was \$34,100 at a discount rate of 3% under a 3-year time horizon. When adjusted for inflation and for the differences in the costs of the medication and hospitalization between Canada and the United States, the cost per QALY gained with the use of ICS using the present model was \$41,028 in 2004 US dollars at a discount rate of 3% under a 3-year time horizon, which is comparable to the estimate in the

study by Sin et al. Despite all these limitations, the results of the present study were comparable to the Canadian studies<sup>19,29</sup> after making the necessary adjustments.

In conclusion, this analysis showed that the most cost-effective strategy in moderate-to-severe COPD depends on how much society is willing to pay to achieve health improvements. The most cost-effective strategies are placebo (as-needed short-acting bronchodilator use with no maintenance therapy) when WTP is less than \$52,800/QALY gained and SFC when WTP exceeds that threshold. When treatment with as-needed short-acting bronchodilator use does not provide adequate control or

**Take-Away Points**

The most cost-effective strategy in moderate-to-severe chronic obstructive pulmonary disease depends on willingness to pay (WTP).

- The most cost-effective strategy is no maintenance therapy (as-needed short-acting bronchodilator use only) when WTP is less than \$52,800 per quality-adjusted life-year (QALY) gained.
- When no maintenance therapy is not an acceptable option, the most cost-effective strategies are treatment with salmeterol when WTP is less than \$49,500/QALY gained and combination treatment with salmeterol-fluticasone propionate when WTP exceeds that threshold.

is not an acceptable option, the most cost-effective strategies are salmeterol when WTP is less than \$49,500/QALY gained and SFC when WTP exceeds that threshold. These results may assist clinicians and healthcare policy makers to make informed decisions as to which therapy for moderate-to-severe COPD would be optimal in the US healthcare system.

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