Bronchodilators are central to the symptomatic management of patients with COPD. Current management guidelines recommend the use of monotherapy using either long-acting inhaled muscarinic antagonists or long-acting inhaled β₂-agonists (LABAs) for patients with moderate or more severe disease on the basis of long-term improvements that can be achieved in clinical outcomes, such as dyspnea, health status, and exacerbations. Currently available long-acting inhaled bronchodilators include once-daily tiotropium and the bid LABA (TD-LABA) formoterol and salmeterol. Tiotropium is widely used and has generally been shown to provide better bronchodilation and clinical outcomes than TD-LABA. More recently, indacaterol, an inhaled ultra-LABA (24 h) with a rapid onset of action, was approved in many countries at different doses (75 to 300 μg once daily) for the treatment of patients with COPD. A once-daily LABA could not only simplify disease management but has the potential to improve adherence and compliance. Accordingly, a published study found that adherence was strongly correlated with dosing frequency. Additionally, randomized, controlled phase 3 COPD trials have shown that indacaterol improved numerous clinical outcomes over placebo, including dyspnea, health status, and pulmonary function.

For editorial comment see page 1082
FEV₁, symptom control, health status, and exacerbations, with a safety and tolerability profile similar to placebo. The objective of this systematic review was to explore the efficacy and safety of inhaled indacaterol in comparison with tiotropium or TD-LABA in moderate to severe COPD.

Materials and Methods

We adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this systematic review. A protocol was prospectively developed detailing the study objectives, primary and secondary outcomes, criteria for study selection, approach to assessing study quality, data synthe-
sis, and statistical analysis. This study was registered with the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO) as CRD42011001539.

Search and Selection Criteria

We identified published studies from MEDLINE, EMBASE (December 2011), and the Cochrane Controlled Trials Register (CENTRAL) (December 2011) database using the terms "indacaterol," "QAB-149," "long-acting β-2-agonists," "salmeterol," "formoterol," "long-acting antimuscarinic agents," "tiotropium," and "chronic obstructive pulmonary disease." Also, we performed a search of relevant files from the Novartis Pharma AG (http://www.novcrtd.com/ctrWebApp/cclinicaltrialrepository/public/login.jsp) and US Food and Drug Administration (www.fda.gov) databases. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet all the following criteria: (1) randomized (parallel group or crossover) controlled trials without language restriction of >4 weeks of duration; (2) inclusion of adult patients aged ≥40 years with stable moderate to severe COPD satisfying American Thoracic Society/European Respiratory Society or GOLD (Global Initiative for Chronic Obstructive Lung Disease) diagnostic criteria; (3) comparison of inhaled indacaterol with tiotropium, salmeterol, or formoterol monotherapy; and (4) report at least one of the following outcomes: trough (2-h postdose) FEV₁ at the end of treatment (primary variable), use of rescue medications, health status assessed with the St. George's Respiratory Questionnaire (SGRQ), dyspnea assessed with the transitional dyspnea index (TDI), COPD exacerbations, all-cause mortality, withdrawals during treatment period, adverse effects (AEs), and severe adverse effects (SAEs), ECG data including Fridericia correction of QT interval (QTc interval), and the incidence of clinically notable laboratory values, including reduced serum potassium level (<3.5 mmol/L) and elevated blood glucose level (>9.99 mmol/L) (secondary variables). A serious adverse event was defined as any untoward medical occurrence that sometimes results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability/incapacity.

Data Abstraction and Assessment of Risk of Bias

Titles, abstracts, and citations were independently analyzed by the two authors (G. J. R. and H. N.). From full text, they independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. The authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The latter was assessed according to recommendations outlined in the Cochrane Handbook for the following items: (1) adequacy of sequence generation, (2) allocation concealment, (3) blinding of participants and investigators, (4) reporting of withdrawals and loss to follow up, and (5) reporting of adverse outcomes. Disagreements were resolved by group consensus (G. J. R. and H. N.). In case of multiple published or unpublished reports, data from the most recent version were extracted.

Data Analysis

Analysis was by intention to treat and included all participants to minimize bias. Outcomes were pooled using weighted mean differences (WMDs) or Mantel-Haenszel ORs. The precision of the mean estimates was quantified by the 95% CIs. When effect estimates were significantly different between groups, the number needed to treat for benefit (NNTB) or for harm was obtained. Heterogeneity was measured by the I² test (<40%, unimportant; 40%-60%, moderate; and 60%-100%, substantial). Because selected studies differed in the mixes of participants and interventions, a random-effects meta-analysis was performed to address this variation across studies for all outcomes. Publication bias of primary outcomes was evaluated by visual inspection of funnel plots. In trials that had more than two intervention groups, we preserved randomization but collapsed the multiple intervention arms (eg, indacaterol 150 µg and 300 µg once daily) into single treatment arms. As a priori subgroup analysis, we explored the influence of the type of TD-LABA (formoterol or salmeterol vs indacaterol) and length of treatment (<24 weeks vs ≥24 weeks). Subgroups were compared using the interaction test. P ≤ .05 (two-tailed test) was considered significant. Predefined sensitivity analysis was done to explore the influence of the statistical model (fixed vs random effects) on the effect size. Meta-analysis was performed with the Review Manager 5.1.6 software.

Results

Five randomized controlled trials enrolling 5,920 subjects (3,377 in the indacaterol arms and 2,543 in the comparators arms) met the entry criteria (Fig 1). Participants were symptomatic at baseline with moderate to severe airflow obstruction. All studies were multicenter, randomized, parallel groups and were sponsored by a single pharmaceutical company (Table 1). Two studies compared indacaterol with tiotropium, and three compared indacaterol with a TD-LABA (salmeterol or formoterol). All medications were administered via dry powder inhalers. Two studies included two indacaterol arms. The mean age of patients was 63 years (71% were men).
trials reported complete outcome data and information on the AEs.

**Primary Outcome**

The analysis of two studies comparing indacaterol with tiotropium showed no statistical difference in mean trough FEV₁ (at the end of treatment or in change from baseline) (Table 2). The first outcome showed statistical heterogeneity. In contrast, data from three studies comparing indacaterol with TD-LABA showed that mean trough FEV₁ at the end of treatment was 70 mL higher with indacaterol than TD-LABA ($P < .0001$) (Table 3). Also, as change from baseline, trough FEV₁ significantly increased by 80 mL with indacaterol compared with TD-LABA ($P < .0001$). Sensitivity analyses showed similar results to those of the primary analysis. Post hoc subgroup analysis was not performed due to the small number of trials.

**Secondary Outcomes**

On the basis of two trials including 2,840 subjects with COPD (1,626 in the indacaterol arm and 1,214 in the tiotropium arm), significant reductions in the use of rescue medication ($-2.02$ puffs/d, $P < .0001$) (Table 2) and dyspnea were reported with inhaled indacaterol therapy.

Compared with tiotropium, indacaterol arm subjects showed a $43\%$ greater likelihood of experiencing a minimal clinically important difference (MCID) in TDI (≥1 point) (62% of indacaterol arm patients vs 52% of tiotropium arm patients, $P < .0001$). The NNTB was 10 (95% CI, 7-16) (Fig 2). Also, the final mean SGRQ total score was significantly lower with indacaterol than tiotropium ($-2.02$ units, $P < .0008$). Most importantly, the percentage of patients receiving indacaterol with an MCID in the SGRQ (≥4 units of total score) was significantly higher compared with those receiving tiotropium (57% vs 46%, $P < .0001$) (Fig 2). The NNTB was 10 (95% CI, 7-15). On the other hand, the duration of treatment ranged from 12 weeks to 52 weeks. Overall, the five studies were judged to have a low risk of bias. All studies presented adequate sequence generation and concealment. One study had an open-label design for tiotropium. Finally, all studies included subjects with COPD (1,626 in the indacaterol arm and 1,214 in the tiotropium arm).

Table 1—Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration, wk</th>
<th>No. of Subjects</th>
<th>Men,%</th>
<th>Mean Age, y</th>
<th>Mean Baseline FEV₁, % Predicted</th>
<th>Smoking History, pack-y</th>
<th>Drug and Dose</th>
<th>Main Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donohue et al¹⁸</td>
<td>12</td>
<td>416</td>
<td>63</td>
<td>63</td>
<td>55</td>
<td>50</td>
<td>Ind 150 µg OD</td>
<td>Trough FEV₁</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>416</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Ind 300 µg OD</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>415</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Tio 18 µg OD</td>
<td>...</td>
</tr>
<tr>
<td>Buhl et al¹⁹</td>
<td>12</td>
<td>794</td>
<td>68</td>
<td>63</td>
<td>54</td>
<td>43</td>
<td>Ind 150 µg OD</td>
<td>Trough FEV₁</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>799</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Tio 18 µg OD</td>
<td>...</td>
</tr>
<tr>
<td>Dahl et al²⁰</td>
<td>52</td>
<td>437</td>
<td>79</td>
<td>64</td>
<td>52</td>
<td>41</td>
<td>Ind 300 µg OD</td>
<td>Trough FEV₁</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>425</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Ind 600 µg OD</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>434</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Form 12 µg bid</td>
<td>...</td>
</tr>
<tr>
<td>Kormann et al²¹</td>
<td>26</td>
<td>330</td>
<td>73</td>
<td>63</td>
<td>54</td>
<td>40</td>
<td>Ind 150 µg OD</td>
<td>Trough FEV₁</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>333</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Salm 50 µg bid</td>
<td>...</td>
</tr>
<tr>
<td>Korn et al²²</td>
<td>12</td>
<td>569</td>
<td>70</td>
<td>63</td>
<td>51</td>
<td>45</td>
<td>Ind 150 µg OD</td>
<td>Area under curve of FEV₁</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>562</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Salm 50 µg TD</td>
<td>...</td>
</tr>
</tbody>
</table>

Form = formoterol; Ind = indacaterol; OD = once daily; Salm = salmeterol; Tio = tiotropium.
Table 2—Effect of Indacaterol vs Tiotropium Monotherapy on Different COPD Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No.</th>
<th>Estimate</th>
<th>Effect (95% CI)</th>
<th>I², %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final trough FEV₁, L</td>
<td>2,565</td>
<td>WMD</td>
<td>0.07 (0.20 to −0.06)</td>
<td>92</td>
<td>.27</td>
</tr>
<tr>
<td>Change from baseline of trough FEV₁, L</td>
<td>2,422</td>
<td>WMD</td>
<td>0.01 (0.03 to −0.01)</td>
<td>0</td>
<td>.27</td>
</tr>
<tr>
<td>Mean change in rescue medication, puffs/24 h</td>
<td>2,734</td>
<td>WMD</td>
<td>−0.57 (−0.37 to −0.77)</td>
<td>0</td>
<td>.00001</td>
</tr>
<tr>
<td>Final SGRQ total score</td>
<td>2,840</td>
<td>WMD</td>
<td>−2.02 (−3.19 to −0.84)</td>
<td>0</td>
<td>.0008</td>
</tr>
<tr>
<td>Final change in SGRQ total score</td>
<td>2,656</td>
<td>WMD</td>
<td>−2.14 (−3.05 to −1.22)</td>
<td>0</td>
<td>.00001</td>
</tr>
<tr>
<td>Patients with SGRQ decrease ≥ 4 units, %</td>
<td>2,612</td>
<td>OR</td>
<td>1.43 (1.22 to 1.66)</td>
<td>0</td>
<td>.00001</td>
</tr>
<tr>
<td>Final TDI score</td>
<td>2,638</td>
<td>WMD</td>
<td>−0.34 (−0.70 to 0.02)</td>
<td>41</td>
<td>.06</td>
</tr>
<tr>
<td>Patients with TDI increase ≥ 1 point, %</td>
<td>2,713</td>
<td>OR</td>
<td>1.43 (1.22 to 1.67)</td>
<td>0</td>
<td>.00001</td>
</tr>
<tr>
<td>COPD exacerbations</td>
<td>2,840</td>
<td>OR</td>
<td>0.97 (0.79 to 1.21)</td>
<td>0</td>
<td>.81</td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>2,840</td>
<td>OR</td>
<td>0.97 (0.77 to 1.21)</td>
<td>0</td>
<td>.78</td>
</tr>
<tr>
<td>Withdrawals due to treatment failure</td>
<td>2,840</td>
<td>OR</td>
<td>0.65 (0.29 to 1.45)</td>
<td>0</td>
<td>.29</td>
</tr>
<tr>
<td>Withdrawals due to adverse effects</td>
<td>2,840</td>
<td>OR</td>
<td>1.37 (0.94 to 2.01)</td>
<td>0</td>
<td>.10</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>2,840</td>
<td>OR</td>
<td>1.05 (0.89 to 1.22)</td>
<td>0</td>
<td>.58</td>
</tr>
<tr>
<td>Serious adverse effects</td>
<td>2,840</td>
<td>OR</td>
<td>0.88 (0.63 to 1.24)</td>
<td>0</td>
<td>.46</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2,840</td>
<td>OR</td>
<td>0.23 (0.03 to 1.51)</td>
<td>0</td>
<td>.13</td>
</tr>
<tr>
<td>Patients with glucose &gt; 9.99 mmol/L, %</td>
<td>2,801</td>
<td>OR</td>
<td>1.22 (0.86 to 1.73)</td>
<td>0</td>
<td>.27</td>
</tr>
<tr>
<td>QTc &gt; 60 ms</td>
<td>2,819</td>
<td>OR</td>
<td>1.20 (0.13 to 11.40)</td>
<td>40</td>
<td>.88</td>
</tr>
<tr>
<td>Nonacuate cough</td>
<td>2,840</td>
<td>OR</td>
<td>1.27 (0.90 to 1.79)</td>
<td>0</td>
<td>.60</td>
</tr>
</tbody>
</table>

Data based on Donohue et al.18 and Buhl et al.19 I² = measure of heterogeneity; QTc = Fridericia correction of QT interval; SGRQ = St. George’s Respiratory Questionnaire; TDI = transitional dyspnea index; WMD = weighted mean difference.

hand, there were nonsignificant differences in the rate of COPD exacerbations (15.1% vs 14.6%), withdrawals (14.2% vs 12.3%), AEs (53% vs 48%), SAEs (5.4% vs 5.2%), all-cause mortality (0.06% vs 0.32%), percent of patients with blood glucose level >9.99 mmol/L (6.0% vs 4.2%), and serum potassium level < 3.0 mmol/L (0.24% vs 0.16%). The rate of nonacute cough as an adverse event did not differ across the treatment groups (4.6% vs 3.3%). However, in one study,18 investigators recorded any instances of acute cough occurring within 5 min of drug administration, finding in the indacaterol 150- and 300-mg arms and in 0.8% of the tiotropium group. This cough typically started within 15 s of inhalation and had a median duration of 6 s. It was not associated with bronchospasm or with increased study discontinuation rates.

The assessment of three trials20–22 with 3,080 patients (1,449 in the indacaterol arms and 1,329 in TD-LABA arms) showed that indacaterol significantly improved clinical outcomes and health status more than did therapy with TD-LABA. It reported significant reductions in the use of rescue medication (−0.22 puffs/d, P = .03) (Table 3) and dyspnea (a significant improvement in mean TDI score and a significant increase in the percentage of patients achieving an MCID in

Table 3—Effect of Indacaterol vs bid Long-Acting β-Agonist Monotherapy on Different COPD Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No.</th>
<th>Estimate</th>
<th>Effect (95% CI)</th>
<th>I², %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final trough FEV₁, L</td>
<td>2,552</td>
<td>WMD</td>
<td>0.07 (0.04 to 0.09)</td>
<td>0</td>
<td>.00001</td>
</tr>
<tr>
<td>Change from baseline of trough FEV₁, L</td>
<td>2,639</td>
<td>WMD</td>
<td>0.08 (0.06 to 0.09)</td>
<td>75</td>
<td>.00001</td>
</tr>
<tr>
<td>Mean change in rescue medication, puffs/24 h</td>
<td>3,080</td>
<td>WMD</td>
<td>−0.22 (−0.42 to −0.02)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Final SGRQ total score</td>
<td>1,959</td>
<td>WMD</td>
<td>−1.20 (−2.72 to 0.32)</td>
<td>10</td>
<td>.12</td>
</tr>
<tr>
<td>Final change in SGRQ total score</td>
<td>1,862</td>
<td>WMD</td>
<td>−0.41 (−1.56 to 0.73)</td>
<td>0</td>
<td>.48</td>
</tr>
<tr>
<td>Patients with SGRQ decrease ≥ 4 units, %</td>
<td>1,949</td>
<td>OR</td>
<td>1.21 (1.01 to 1.45)</td>
<td>0</td>
<td>.04</td>
</tr>
<tr>
<td>Final TDI score</td>
<td>2,003</td>
<td>WMD</td>
<td>0.42 (0.23 to 0.62)</td>
<td>22</td>
<td>.00001</td>
</tr>
<tr>
<td>Patients with TDI increase ≥ 1 point, %</td>
<td>3,080</td>
<td>OR</td>
<td>1.61 (1.13 to 2.28)</td>
<td>81</td>
<td>.008</td>
</tr>
<tr>
<td>COPD exacerbations</td>
<td>3,080</td>
<td>OR</td>
<td>1.01 (0.83 to 1.23)</td>
<td>0</td>
<td>.93</td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>3,080</td>
<td>OR</td>
<td>0.95 (0.77 to 1.16)</td>
<td>4</td>
<td>.60</td>
</tr>
<tr>
<td>Withdrawals due to treatment failure</td>
<td>3,080</td>
<td>OR</td>
<td>0.86 (0.45 to 1.64)</td>
<td>0</td>
<td>.64</td>
</tr>
<tr>
<td>Withdrawals due to adverse effects</td>
<td>3,080</td>
<td>OR</td>
<td>1.05 (0.63 to 1.75)</td>
<td>54</td>
<td>.67</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>3,080</td>
<td>OR</td>
<td>1.11 (0.96 to 1.30)</td>
<td>0</td>
<td>.16</td>
</tr>
<tr>
<td>Serious adverse effects</td>
<td>3,080</td>
<td>OR</td>
<td>1.10 (0.70 to 1.72)</td>
<td>55</td>
<td>.67</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3,080</td>
<td>OR</td>
<td>0.54 (0.13 to 2.23)</td>
<td>35</td>
<td>.86</td>
</tr>
<tr>
<td>Patients with glucose &gt; 9.99 mmol/L, %</td>
<td>3,080</td>
<td>OR</td>
<td>0.79 (0.43 to 1.44)</td>
<td>72</td>
<td>.44</td>
</tr>
<tr>
<td>QTc &gt; 60 ms</td>
<td>3,080</td>
<td>OR</td>
<td>0.77 (0.16 to 3.74)</td>
<td>0</td>
<td>.76</td>
</tr>
<tr>
<td>Patients with K⁺ &lt; 3 mmol/L, %</td>
<td>3,080</td>
<td>OR</td>
<td>1.27 (0.25 to 6.43)</td>
<td>0</td>
<td>.78</td>
</tr>
<tr>
<td>Nonacuate cough</td>
<td>1,959</td>
<td>OR</td>
<td>1.43 (0.75 to 2.73)</td>
<td>35</td>
<td>.28</td>
</tr>
</tbody>
</table>

K⁺ = serum potassium. See Table 2 legend for expansion of other abbreviations.
drug administration during clinic visits. They observed an average of 18% in the indacaterol groups against 0.9% in the TD-LABA groups. This cough of short duration (few seconds) was not associated with bronchospasm or withdrawals.

Discussion

Indacaterol is a novel inhaled LABA providing 24-h bronchodilation on once-daily dosing recently approved in many countries for the treatment of patients with COPD. Previous data have shown that inhaled indacaterol improved numerous clinical outcomes over placebo, with a similar safety and tolerability profile. This review has found a similar efficacy

![Figure 2](http://journal.publications.chestnet.org/)

![Figure 3](http://journal.publications.chestnet.org/)
between indacaterol (150-300 μg/d) and tiotropium (18 μg/d) on trough FEV\textsubscript{1} after 12 to 26 weeks of treatment. Since the relationship between spirometry, symptoms, and health status appears to be poor, measures of lung physiology alone may not adequately describe both the social impact of COPD and the effectiveness of therapeutic interventions.\textsuperscript{22} Thus, indacaterol produced statistically significantly better results in clinical outcomes of dyspnea, use of as-needed salbutamol, and health status, compared with tiotropium. Dyspnea is the primary reason for patients seeking medical care, and its measure may provide an insight into the practical effects of treatment on everyday life, reflecting whether patients perceive an improvement in this primary symptom of COPD. Patients treated with indacaterol had a greater likelihood of experiencing an MCID in TDI\textsuperscript{23} compared with those receiving tiotropium. The NNTB was 10, indicating that one of every 10 patients treated with indacaterol obtained this benefit. Additionally, we found statistically significant improvements in total SGRQ score; however, the clinical relevance of these findings remains unclear, because they did not reach the MCID of 4 units. However, the interpretation of this remains unclear, because MCID differences were derived on the basis of differences vs placebo or changes from baseline rather than differences between two active treatments.\textsuperscript{23} Even so, compared with tiotropium, indacaterol-treated patients had a greater likelihood of achieving an MCID improvement in health status with an NNTB of 10. In addition, patients taking indacaterol required significantly less rescue medication (more than one-half puff per day) reflecting the effectiveness of treatment in achieving clinical control. Finally, indacaterol-related and tiotropium-related events, like COPD exacerbations and withdrawals, did not differ from each other.

Our data also indicated that indacaterol (150-600 μg) was more effective than TD-LABA (salmeterol 50 μg bid or formoterol 12 μg bid) for several outcomes. Thus, trough FEV\textsubscript{1} was significantly higher with indacaterol than TD-LABA (P < .0001), after 12 to 52 weeks of treatment. The difference in trough effect with indacaterol of 70 to 80 mL relative to TD-LABA did not exceed the prespecified 100-mL MCID. However, the clinical interpretation is unclear, since reported MCID differences were derived on the basis of differences vs placebo.\textsuperscript{23} This bronchodilator effect of indacaterol was associated with a significant but small increase in \textbeta\textsubscript{2}-mediated effects relative to tiotropium and TD-LABA. Thus, the class-related side effects of \textbeta\textsubscript{2}-agonists (hyperglycemia, hypokalemia, or prolonged QTc interval) were low. Although the rate of nonacute cough did not differ across the treatment groups, different studies have reported acute cough immediately following indacaterol inhalation. Although these events occurred with some frequency (15%-20% of subjects), they did not decrease the effectiveness of indacaterol and did not produce bronchoconstriction or study withdrawal.

This study met most of the methodologic criteria suggested for systematic reviews.\textsuperscript{7} Inclusion criteria were clearly defined. Several relevant databases were searched for published and unpublished articles in any language. Attempts were made to minimize error and bias in the process of study selection, data extraction and quality assessment. Trial quality was formally assessed, and the results were clearly reported. Its assessment showed a high methodologic quality of studies. Overall, the effect sizes were consistent, and only 10% of outcomes explored showed evidence of substantial heterogeneity. Although the small number of included trials can be considered a limitation of this review, they included a significant sample of nearly 6,000 subjects.

In November 2009, indacaterol was approved for the maintenance treatment of COPD in the European Union at a recommended dose of 150 μg once daily and a maximum dose of 300 μg once daily. Although the same doses of indacaterol are used almost worldwide, the Federal Drug Administration decreed a few months ago that the only available dosage for US physicians would be 75 μg per day. Although the use of indacaterol 75 μg per day in patients with COPD shows statistical and clinical benefits compared with placebo,\textsuperscript{24,25} most studies have used 150 to 300 μg per day. In fact, all the studies included in this review used a dose of ≥ 150 μg per day.

In summary, this systematic review suggests that indacaterol has better effects than once-daily tiotropium or TD-LABA, with a favorable safety profile. This evidence from a limited number of studies suggests that patients with moderate to severe COPD treated with indacaterol have better clinical outcomes.
(dyspnea and health status) than those treated with tiotropium. Similarly, indacaterol may be a useful alternative to TD-LABA due to its effects on pulmonary function, health status, and dyspnea. These effects are statistically and clinically significant in both comparisons.

**ACKNOWLEDGMENTS**

**Author contributions:** Dr Rodrigo, contributed to study conception and design; acquisition, analysis, and interpretation of data; drafting the submitted article and revising it critically for important intellectual content; and providing final approval of the version to be published.

Dr Neffen: contributed to study conception and design, interpretation of data, revising the article critically for important intellectual content, and providing final approval of the version to be published.

**Financial/nonfinancial disclosures:** The authors have reported to CHEST the following conflicts of interest: Dr Rodrigo has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Boehringer Ingelheim GmbH, GlaxoSmithKline plc, AstraZeneca, Dr. Esteve SA, Merck Sharp & Dohme Corp, and Admiral. Dr Neffen has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Merck & Co, Inc, GlaxoSmithKline plc, Novartis AG, and AstraZeneca.

**Role of sponsors:** The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

**REFERENCES**


