Efficacy and safety of formoterol for the treatment of chronic obstructive pulmonary disease

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Summary
Formoterol is a selective long-acting β2-adrenergic receptor agonist (LABA) that provides significant and sustained bronchodilatory effect for up to 12 h following a single dose. The onset of effect is significantly faster with formoterol compared with an alternative LABA, salmeterol, although both have a similar duration of action. The overall efficacy of formoterol in improving lung function and controlling symptoms of chronic obstructive pulmonary disease (COPD) is comparable to that of salmeterol and potentially superior to that of ipratropium or theophylline. Formoterol provides additional benefit when administered in combination with other bronchodilators or inhaled corticosteroids. In clinical studies, formoterol was well tolerated and had an adverse-event profile similar to that of other β2-adrenergic receptor agonists. Formoterol is a rapidly acting, well-tolerated, effective β2-adrenergic receptor agonist that can be regularly used as a long-acting bronchodilator for patients with moderate to severe COPD, as per recommendations of the current treatment guidelines.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airflow limitation that is not fully reversible and accompanied by pathologic changes in the lung. The airflow limitation, which is characteristic of COPD, results from a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) secondary to inflammation. Although cigarette smoking is the most common COPD risk factor, air pollution, history of childhood respiratory illness, exposure to secondhand smoke, occupational exposure to chemicals, dust, and heredity have also been implicated.

More than 122,000 Americans died from this disease in 2003, making COPD both the nation’s fourth leading cause of death and one of the few major diseases associated with rising mortality rates. In the United States, an estimated 16 million adults are diagnosed with the disease and an additional 14 million may have undiagnosed COPD. In 2004, 11.4 million US adults were estimated to have COPD, which accounted for $37.2 billion in total healthcare expenditures; $20.9 billion were attributable to direct medical costs. Improvement in lung function with formoterol accounted for $37.2 billion in total healthcare expenditures; 11.4 million US adults were estimated to have COPD, which treatment of COPD do not modify the progressive decline in pulmonary hypertension, and cor pulmonale. Spirometry pulmonary hyperinflation, gas exchange abnormalities, characteristic physiologic changes include mucus hypersecretion, ciliary dysfunction, chronic airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale. Spirometry provides the most reliable quantitative assessment of airflow function and is an essential tool in the diagnosis, monitoring, and management of COPD. Forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) are key spirometric indices. A decrease in the FEV₁/FVC ratio often signals the development of increasing airflow limitation.

Pharmacologic agents that are currently approved for the treatment of COPD do not modify the progressive decline in lung function, a hallmark of COPD. Moreover, airflow limitation in patients with COPD is only partially reversible. Therefore, the goal of pharmacotherapy is to treat the reversible components of COPD and improve patient-centered outcomes such as symptoms, use of rescue bronchodilator, and quality of life as measured by St. Georges Respiratory Questionnaire (SGRQ). Thus anticholinergics, β₂-adrenergic receptor agonists, and methylxanthine-type bronchodilators have a critical role in management of the disease. Inhaled agents are generally preferred over systemic agents because of their lower potential for adverse events. Treatment regimens vary with disease severity. As-needed use of a short-acting bronchodilator may be sufficient for patients with mild disease (Stage I), whereas regularly scheduled treatment with a long-acting bronchodilator or a combination may be necessary in moderate to severe disease (Stages II–IV).

Formoterol and salmeterol are two inhaled long-acting β₂-adrenergic receptor agonists (LABAs). Formoterol is available in a capsule dosage form containing a dry-powder formulation for oral inhalation and is approved for long-term, twice-daily maintenance treatment of bronchoconstriction in patients with COPD. Consistent with its drug class effects, formoterol stimulates β₂-adrenergic receptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction. Affinity of formoterol is highly selective for the β₂-receptor with minimal affinity for β₁- and α-adrenergic receptors.

There are two important differences between formoterol and salmeterol. The first difference is the relative degree of β₂-receptor activation. Results from methacholine-challenge studies have shown that formoterol elicits a dose-dependent protective response, whereas salmeterol is associated with both a flatter dose–response curve and significantly weaker protection against bronchoconstriction. These results suggest that salmeterol exerts partial...
\( \beta_2 \)-agonism, whereas formoterol seems to be a highly selective \( \beta_2 \)-agonist.\(^9\)\(^{-11}\) The greater peak bronchodilatory effect with formoterol compared with salmeterol\(^9\) appears consistent with this finding. The second difference between the two LABAs is that the onset of action with formoterol is significantly faster than with salmeterol.\(^{12}\) This review summarizes the key findings from several clinical studies that investigated the clinical topics related to use of formoterol in patients with COPD.

### Onset of action and duration of effect with formoterol

Thirteen crossover trials have evaluated the effects of formoterol in patients meeting the diagnostic criteria for moderate to severe COPD (Table 1).\(^{12,24}\) All but three of these trials included a placebo arm and all but one included an active comparator arm. The results of these studies strongly support the conclusion that the onset of action with formoterol is faster than that with anticholinergic agents or salmeterol and similar to that of short-acting \( \beta_2 \)-adrenergic receptor agonists (SABAs), such as albuterol. These studies also confirm that the duration of action of both formoterol and salmeterol (\( \geq 12 \) h) is consistent with the twice-daily dosing schedule approved for these agents.

### Formoterol versus placebo

The only study in the series that did not incorporate an active comparator was conducted by Maesen and coworkers\(^{13}\) in 12 patients with poorly reversible COPD (FEV\(_1\) increase \(-9\%\) predicted following inhalation of 1 mg terbutaline) of at least moderate severity (FEV\(_1\) 30–60% predicted). In this early pilot study, once-daily formoterol 6 or 24 \( \mu \)g produced modest, but rapid increases in FEV\(_1\) within 10 min of administration. The mean increases in FEV\(_1\) were below the threshold of reversibility (3.4% and 6.8% with formoterol 6 and 24 \( \mu \)g, respectively). However, formoterol 24 \( \mu \)g produced greater increase in FEV\(_1\) than formoterol 6 \( \mu \)g or placebo (\( P = 0.002 \)). Maximum increase in FEV\(_1\) of 7.4% and 10.0% was achieved 2 h after administration of formoterol 6 and 24 \( \mu \)g, respectively, versus 3.6% with placebo. The mean increase in FEV\(_1\) over 12 h was not statistically different between treatments (formoterol 6 \( \mu \)g (0.12 L), 24 \( \mu \)g (0.23 L), and placebo (0.05 L)). However, formoterol 6 and 24 \( \mu \)g significantly reduced the mean work of breathing (\( P = 0.0007 \)) and airway resistance (\( P = 0.003 \)) 10 min post-treatment and significantly reduced the 12-h area under the curve (AUC\(_{0-12 \text{h}}\)) for work of breathing (\( P = 0.03 \)) versus placebo. The authors concluded that formoterol is effective in the management of COPD even in patients with poorly reversible airway obstruction.

### Formoterol versus salmeterol

The effects of single-dose formoterol and salmeterol were examined in three crossover studies and one subset analyses.\(^{14}\) The results from all of these studies demonstrated that the onset of bronchodilation with formoterol was faster than salmeterol. The largest (\( n = 47 \)) and most recent of these studies was a multicenter trial conducted by Kottakis and associates.\(^{14}\) Patients received formoterol (12 and 24 \( \mu \)g) or salmeterol (50 and 100 \( \mu \)g). The FEV\(_1\) AUC during the first hour post-treatment (AUC\(_{0-1 \text{h}}\)) and the percentage change from baseline in FEV\(_1\) were greater with formoterol (12 \( \mu \)g) than salmeterol (50 \( \mu \)g (\( P = 0.0044 \)) and 0.0021, respectively). Similarly, formoterol 24 \( \mu \)g induced greater improvement than salmeterol 100 \( \mu \)g (\( P = 0.0001 \)) and 0.0001, respectively). Formoterol 24 \( \mu \)g, but not formoterol 12 \( \mu \)g, produced a greater peak bronchodilatory effect than salmeterol 50 \( \mu \)g (\( P = 0.0004 \)). Both doses of formoterol resulted in a more rapid onset of action than the corresponding doses of salmeterol and placebo. The median time to a 15% increase in FEV\(_1\) above maximum predose level was 5 min in both doses of formoterol compared with 15 and 10 min with salmeterol 50 and 100 \( \mu \)g, respectively. A 15% increase in FEV\(_1\) above maximum predose level within 5 min of dosing was achieved by approximately three times as many patients receiving formoterol as those receiving salmeterol. The authors concluded that formoterol 12 and 24 \( \mu \)g provided a faster onset of bronchodilation than the corresponding doses of salmeterol.

Bourou and coworkers\(^{12}\) performed a post hoc analysis of lung function data from the above study, to evaluate the mean change in inspiratory capacity (IC) with formoterol 12 \( \mu \)g versus salmeterol 50 \( \mu \)g. The result showed that treatment with formoterol 12 \( \mu \)g led to a greater improvement in IC values at 5 and 10 min post-treatment than salmeterol 50 \( \mu \)g (\( P = 0.0024 \)) and 0.0033, respectively). Between-treatment differences persisted throughout the first 60 min post-treatment. Formoterol 24 \( \mu \)g also provided a greater improvement in IC (AUC\(_{0-1 \text{h}}\)) than salmeterol 100 \( \mu \)g (\( P = 0.0043 \)).

Similarly, Celik and coworkers\(^{15}\) showed that treatment with formoterol 12 \( \mu \)g resulted in a faster onset of action than salmeterol 50 \( \mu \)g. The baseline spirometric values for formoterol, salmeterol, and placebo groups were comparable. The mean increase from baseline in FEV\(_1\) 10 min post-treatment was significantly greater with formoterol (0.2 L; 18%) than with placebo (0.04 L; 3.9%; \( P < 0.05 \)) and salmeterol (0.11 L; 9%). Twenty min post-treatment, the mean increase from baseline in FEV\(_1\) was significantly greater with both formoterol and salmeterol than placebo. The mean peak bronchodilation occurred faster with formoterol (60 min) than salmeterol (120 min); however, increases in FEV\(_1\) throughout the 12-h monitoring period was similar with both drugs and significantly greater than placebo (\( P < 0.05 \)).

Cazzola and colleagues\(^{25}\) compared the effects of once-daily formoterol (12, 24, or 36 \( \mu \)g) or salmeterol (25, 50, or 75 \( \mu \)g) administered on nonconsecutive days to patients with severe COPD. Peak bronchodilation (mean maximum increase in FEV\(_1\)) occurred 1 h earlier with all three doses of formoterol than the corresponding doses of salmeterol. Both agents consistently improved spirometry indices over the 12-h monitoring period (\( P < 0.01 \), both drugs versus placebo); however, the mean FEV\(_1\) AUC was greater with salmeterol 50 \( \mu \)g compared with formoterol 12 and 24 \( \mu \)g, but not with formoterol 36 \( \mu \)g. Formoterol was associated with a dose-dependent increase in FEV\(_1\), FVC, and forced expiratory flow at 50% of FVC (FEF\(_{50%}\)). In contrast, salmeterol 75 \( \mu \)g provided no additional benefit over salmeterol 50 \( \mu \)g.
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<th>Author</th>
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<td>Benhamou et al., 18</td>
<td>24</td>
<td>61.6</td>
<td>Single-dose: FORM 24 μg; ALB 400 μg</td>
<td>R, DB*, PC, 3-way xvr</td>
<td>Drugs similar to each other, significantly different from placebo in 0–30 min post-treatment increase in FEV&lt;sub&gt;1&lt;/sub&gt; AUC versus baseline</td>
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<td>Bouros et al., 12</td>
<td>47</td>
<td>63.5</td>
<td>Single-dose: FORM 12 μg; FORM 24 μg; SAL 50 μg; SAL 100 μg</td>
<td>R, DB, PC, DD, MC, 5-way xvr</td>
<td>FORM 12 and 24 μg produced statistically greater increase in IC than both SAL 50 and 100 μg at all time points during first 60 min post-treatment (P&lt;0.0431)</td>
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<td>Cazzola et al., 21</td>
<td>20</td>
<td>70.7</td>
<td>Single-dose: FORM 12 μg; TIO 18 μg; FORM 12 μg+TIO 18 μg</td>
<td>R, DB, DD, 3-way xvr</td>
<td>FORM, FORM/TIO showed significantly faster onset, trends to greater FEV&lt;sub&gt;1&lt;/sub&gt; improvement versus TIO alone. TIO, FORM/TIO associated with greater FEV&lt;sub&gt;1&lt;/sub&gt; 24 h post-treatment versus baseline (P = 0.003 and 0.045, resp.) FORM versus baseline (NS)</td>
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<td>Cazzola et al., 16</td>
<td>20</td>
<td>60.6</td>
<td>Group A Single-dose: FORM 9 μg; ALB 100 μg Group B Single dose: FORM 18 μg; ALB 200 μg</td>
<td>R, DB,DD, 2-way xvr</td>
<td>Onset of effect with FORM similar to that with ALB as measured by FEV&lt;sub&gt;1&lt;/sub&gt; 5 and 15 min post-treatment</td>
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<td>Cazzola et al., 17</td>
<td>16</td>
<td>65.6</td>
<td>Single-dose: FORM 12 μg; FORM 24 μg; ALB 400 μg; ALB 800 μg</td>
<td>R, DB,PC DD, 5-way xvr</td>
<td>No significant between-treatment differences in time to ≥15% increase in FEV&lt;sub&gt;1&lt;/sub&gt; versus baseline or time to ≥200 mL absolute increase in FEV&lt;sub&gt;1&lt;/sub&gt; versus baseline</td>
</tr>
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<td>Cazzola et al., 19</td>
<td>16</td>
<td>64.3</td>
<td>Single-dose: FORM 24 μg; SAL 50 μg; ALB 200 μg</td>
<td>R, SB, PC, 4-way xvr</td>
<td>ALB onset faster than FORM or SAL as determined by time to ≥15% FEV&lt;sub&gt;1&lt;/sub&gt; increase versus baseline (both P&lt;0.05). FORM onset more rapid than SAL in 9/16 patients, overall mean values NS</td>
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<tr>
<td>Celik et al., 15</td>
<td>22</td>
<td>57.3</td>
<td>Single-dose: FORM 12 μg; SAL 50 μg</td>
<td>R, DB, PC, 3-way xvr</td>
<td>Significant increase in FEV&lt;sub&gt;1&lt;/sub&gt; 10 min post-treatment with FORM (200 mL), not SAL (40 mL), versus PB and baseline. FORM, SAL effects on FEV&lt;sub&gt;1&lt;/sub&gt; (250 mL and 200 mL, resp.) significantly different from PB, baseline 20 min post-treatment. FORM, SAL peak effects attained at 60 and 120 min resp. Both drugs superior to PB 12 h post-treatment</td>
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<td>Chhabra et al., 23</td>
<td>44</td>
<td>56.2</td>
<td>Single-dose: FORM 12 μg; IPRA 40 μg</td>
<td>R, DB, PC, 3-way xvr</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; change over baseline 5 min post-treatment greater with FORM compared with IPRA (P&lt;0.01). Effects equivalent 30 min post-treatment. Overall absolute increase in FEV&lt;sub&gt;1&lt;/sub&gt;, FVC with FORM and IPRA similar</td>
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Formoterol versus albuterol

Albuterol has a very rapid onset of effect, which makes it particularly useful as a rescue medication in patients with COPD or asthma who experience symptom exacerbations. Formoterol, demonstrated to have a rapid onset of action, was compared with albuterol in three small crossover studies as both a rescue and maintenance medication in patients with COPD.\textsuperscript{16-18} The results of these studies suggest that formoterol has a rapid onset of action similar to albuterol.

**Table 1 (continued)**

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<th>Key findings</th>
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<td>Di Marco et al.,\textsuperscript{22}</td>
<td>20</td>
<td>65</td>
<td>Single-dose: FORM 12(\mu)g; SAL 50(\mu)g; ALB 200(\mu)g; OXIT 200(\mu)g</td>
<td>R, DB, PC, 5-way xvr</td>
<td>All active therapies associated with improvements in FEV(_1) and IC versus baseline (all (P &lt; 0.05)). FORM effects on FEV(_1) superior to SAL at 30 min ((P = 0.01)), all (\beta)-agonists superior to OXIT at 30, 60, 120 min. FORM effects on IC superior to SAL at 30 min, superior to OXIT at 15, 30 min</td>
</tr>
<tr>
<td>Kottakis et al.,\textsuperscript{14}</td>
<td>47</td>
<td>63.5</td>
<td>Single-dose: FORM 12(\mu)g; FORM 24(\mu)g; SAL 50(\mu)g; SAL 100(\mu)g</td>
<td>R, DB, PC, DD, MC, 5-way xvr</td>
<td>FORM 12 and 24(\mu)g superior to corresponding SAL 50 and 100(\mu)g doses on primary endpoint of FEV(<em>1) (\text{AUC}</em>{0-1\text{h}}). FORM 24(\mu)g produced highest mean peak FEV(<em>1) (1.63L), followed by FORM 12(\mu)g (1.58L). FORM superior to SAL for all pair contrasts of FVC mean treatment differences in (\text{AUC}</em>{0-1\text{h}})</td>
</tr>
<tr>
<td>Maesen et al.,\textsuperscript{13}</td>
<td>12\textsuperscript{z}</td>
<td>61</td>
<td>Single-dose: FORM 6(\mu)g; FORM 24(\mu)g</td>
<td>R, DB, PC, 3-way xvr</td>
<td>Compared with placebo, FORM (both doses) produced statistically, clinically relevant improvement in work of breathing and airway resistance within 10 min post-treatment and persisting 12 h post-treatment. FEV(_1) improvement limited</td>
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<tr>
<td>Richter et al.,\textsuperscript{24}</td>
<td>38</td>
<td>64</td>
<td>Multiple-dose: FORM 12(\mu)g, BID x 7 d; TIO 18(\mu)g QD x 7 d</td>
<td>R, OL, MC, 2-way xvr</td>
<td>Primary endpoint of FEV (\text{AUC}_{10-120\text{min}}) greater with FORM versus TIO. Between-treatment difference in per protocol population 124 mL after first dose (day 1) ((P = 0.016)), 80 mL after last dose (day 7) ((P = 0.036)). FEV(<em>1) (\text{AUC}</em>{0-12\text{h}}), similar with both drugs</td>
</tr>
<tr>
<td>Sichleditis et al.,\textsuperscript{20}</td>
<td>27</td>
<td>64.7</td>
<td>Single-dose: FORM 12(\mu)g; FORM 24(\mu)g; IPRA 40(\mu)g; IPRA 80(\mu)g; FORM 12(\mu)g+IPRA 40(\mu)g</td>
<td>R, SB, PC, 6-way xvr</td>
<td>Combination produced significantly greater FEV(_1) improvement versus IPRA 40 and 80(\mu)g (both (P &lt; 0.05)), but not FORM 12 or 24(\mu)g (NS). Mean peak change in FEV(_1) with all drugs/doses significantly greater versus placebo</td>
</tr>
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</table>

\(\text{ALB} = \) albuterol; \(\text{DB} = \) double-blind; \(\text{AUC} = \) area under the curve; \(\text{DD} = \) double-dummy; \(\text{FEV}_1 = \) forced expiratory volume at 1 second; \(\text{FORM} = \) formoterol; \(\text{FVC} = \) forced vital capacity; \(\text{IPRA} = \) ipratropium; \(\text{MC} = \) multicenter; \(\text{NS} = \) non significant; \(\text{OL} = \) open-label; \(\text{OXIT} = \) oxisetropium; \(\text{PC} = \) placebo-controlled; \(\text{QD} = \) once-daily; \(\text{R} = \) randomized; \(\text{SAL} = \) salmeterol; \(\text{SB} = \) single-blind; \(\text{TIO} = \) tiotropium; \(\text{xvr} = \) crossover.

\*Single-blind with albuterol.
\textsuperscript{y}Population also included patients with intrinsic asthma.
\textsuperscript{z}”Poorly reversible” COPD patients as defined by <9% of predicted FEV\(_1\) increase following inhalation of terbutaline 1 mg.
Benhamou and colleagues\textsuperscript{18} compared the onset of action of formoterol 24\,\mu g with albuterol 400\,\mu g. The mean increase in FEV\textsubscript{1} AUC\textsubscript{0–30 min} (the primary efficacy variable) was similar between formoterol (5.89\,L/min) and albuterol (6.06\,L/min), but significantly greater than placebo (–0.32\,L/min; both $P < 0.0001$). Improvement in FEV\textsubscript{1} from 5\,min to 3\,h post-treatment was also similar with formoterol and albuterol. Both drugs induced almost maximal bronchodilatation by 30\,min post-treatment, with 80\% of maximal effect occurring within 5\,min.

Cazzola and coworkers\textsuperscript{16,17} also compared the onset of action of formoterol with albuterol in two crossover trials. One study compared once-daily formoterol (9 and 18\,\mu g) with once-daily albuterol (100 and 200\,\mu g) in 20 patients with intrinsic asthma or COPD.\textsuperscript{16} Improvement in FEV\textsubscript{1} at 5- and 15-\,min intervals after inhalation of formoterol 9 and 18\,\mu g was similar to albuterol 100 and 200\,\mu g ($P = 0.704$ and 0.260, respectively). The mean time to response, defined as a 15\% increase in FEV\textsubscript{1} above baseline, ranged from 5\,min with albuterol 200\,\mu g to 17.5\,min with formoterol 9\,\mu g. The onset of action of both agents was similar when the bronchodilating effect in responders was expressed either as a percentage of maximum response attained within 5\,min post-treatment or as the time required for achieving a 15\% increase in FEV\textsubscript{1} versus baseline. The authors concluded that formoterol is a useful alternative to SABAs for as-needed use. The other study compared formoterol 12 and 24\,\mu g with albuterol 400 and 800\,\mu g, which are higher than normal clinical doses of albuterol.\textsuperscript{17} The mean time required to achieve a 15\% increase in FEV\textsubscript{1} over baseline was 15.2 and 15.1\,min with formoterol 12 and 24\,\mu g, respectively, and 13.6 and 14.5\,min with albuterol 400 and 800\,\mu g, respectively. The mean time to increase in FEV\textsubscript{1} $\geq 200$\,mL was also similar between the two treatments.

Formoterol versus salmeterol and albuterol

Cazzola and associates\textsuperscript{19} compared the onset of action of formoterol 24\,\mu g, salmeterol 50\,\mu g, and albuterol 200\,\mu g in a small ($n = 16$) study population. The mean time to 15\% increase in FEV\textsubscript{1} from baseline was shorter with albuterol (4\,min) compared with formoterol (11\,min) and salmeterol (10\,min) ($P < 0.05$). Time to maximum increase in FEV\textsubscript{1} with albuterol, formoterol, and salmeterol was 1, 4, and 5\,h, respectively. These results differ markedly from results reported earlier by this same group\textsuperscript{16,17} and by Benhamou and colleagues.\textsuperscript{18}

Formoterol versus ipratropium

Two crossover studies demonstrated that formoterol has a faster onset of effect than the short-acting anticholinergic bronchodilator, ipratropium. Sichletidis and colleagues\textsuperscript{20} evaluated the bronchodilatory effects of formoterol 12 and 24\,\mu g, ipratropium 40 and 80\,\mu g, and a combination of formoterol 12\,\mu g with ipratropium 40\,\mu g in 27 patients who were receiving a SABA, ipratropium, and an inhaled corticosteroid (ICS) at entry into the study. The mean increase in peak FEV\textsubscript{1} with formoterol 12\,\mu g and ipratropium 40\,\mu g combination was greater than that with either dose of ipratropium (40\,\mu g, $P = 0.0025$ or 80\,\mu g, $P = 0.01$) alone, but not formoterol alone ($P = \text{NS}$ for both 12 and 24\,\mu g). A mean increase of 15\% in FEV\textsubscript{1} from baseline occurred at 10\,min after both doses of formoterol, 15\,min after combination therapy, and at 30 and 60\,min after ipratropium 40 and 80\,\mu g, respectively. The mean FEV\textsubscript{1} AUC\textsubscript{0–6 h}, AUC\textsubscript{0–12 h}, and AUC\textsubscript{0–24 h} values with combination therapy were significantly greater than those with ipratropium 40\,\mu g ($P = 0.0023$, $P < 0.0005$, and $P < 0.0005$, respectively) and 80\,\mu g ($P = 0.003$, $P < 0.0005$, and $P = 0.0003$, respectively), but not formoterol. These results suggest that addition of ipratropium to formoterol does not result in additional benefit in patients with stable COPD.

Chhabra and coworkers\textsuperscript{23} compared the onset of action of formoterol 12\,\mu g with ipratropium 40\,\mu g. Formoterol elicited a greater improvement in FEV\textsubscript{1} within 5\,min post-treatment compared with ipratropium (18.1\% versus 13.9\%, respectively; $P < 0.01$). Other indices of lung function, including FVC, functional residual capacity, residual volume, slow vital capacity, and total lung capacity, assessed at 5, 30, and 60\,min post-treatment were similar between active drugs and significantly different from placebo. The authors concluded that formoterol is associated with a faster onset of action than ipratropium; however, both agents were equally effective in improving lung function.

Formoterol versus tiotropium

Two studies compared formoterol with the long-acting anticholinergic bronchodilator tiotropium.\textsuperscript{21,24} Similar to the results of the comparison with ipratropium, formoterol has a faster onset of action than tiotropium.

Richter and coworkers\textsuperscript{24} compared treatment with formoterol 12\,\mu g twice-daily (BID) and tiotropium 18\,\mu g once daily (QD) over 7 days in 38 patients. Data obtained after the first and last doses demonstrated that treatment with formoterol resulted in a greater FEV\textsubscript{1} AUC\textsubscript{0–24 h} at both time points compared with tiotropium ($P = 0.016$ and 0.036, respectively). In the per-protocol study population ($n = 34$), the between-treatment difference was 0.124 L after the first dose and 0.08 L after 7 days of treatment in favor of formoterol. Between-treatment differences in mean FEV\textsubscript{1} AUC\textsubscript{0–720 min} values, use of rescue medication, and other secondary outcomes were not significant.

Cazzola and coworkers\textsuperscript{21} studied formoterol 12\,\mu g and tiotropium 18\,\mu g alone and in combination in a small ($n = 20$) trial. At 10\,min post-treatment, the mean change in FEV\textsubscript{1} with formoterol/tiotropium combination was greater than with tiotropium alone (0.085 versus 0.039 L, respectively; $P = 0.016$) but not greater than with formoterol alone (0.085 versus 0.088 L, respectively; $P = \text{NS}$). Similarly, the mean maximal increase in FEV\textsubscript{1} with combination therapy (0.21 L) exceeded that with tiotropium alone (0.18 L) more than that with formoterol alone (0.19 L). The mean increases in FEV\textsubscript{1} AUC\textsubscript{0–12 h} and AUC\textsubscript{0–24 h} showed only nonsignificant trends favoring the combination. In all three treatment arms, mean FEV\textsubscript{1} values were significantly higher than baseline levels at 12 and 24\,h post-treatment. The two agents were considered complementary in that formoterol provided faster onset of action and greater maximal response, whereas tiotropium provided a longer duration of action.
Formoterol versus albuterol, salmeterol, and oxitropium

Di Marco and coworkers\textsuperscript{22} assessed treatment with single doses of formoterol 12 \( \mu \)g, albuterol 200 \( \mu \)g, salmeterol 50 \( \mu \)g, and oxitropium 200 \( \mu \)g in 20 patients with COPD. Increase in FEV\(_1\) at 5 min post-treatment was observed in all active treatment groups. Treatment with formoterol and albuterol resulted in increased IC levels at 5 min whereas treatment with salmeterol and oxitropium resulted in IC levels at 15 and 30 min, respectively. Among patients with reduced IC at baseline, significantly greater improvements in IC were observed only in patients receiving formoterol. Increases in FEV\(_1\) at 5 and 15 min after treatment with formoterol were comparable to those with albuterol and greater than those achieved with salmeterol. Improvements in FEV\(_1\) 30 min post-treatment were also greater with formoterol than salmeterol (\( P = 0.01 \)). At 30, 60, and 120 min post-treatment, increases in FEV\(_1\) with formoterol, albuterol, and salmeterol exceeded those with oxitropium. Maximum increases in IC and FEV\(_1\) were attained 30 min after inhalation of each bronchodilator, with no additional improvement at either 60 or 120 min. The authors concluded that at standard dosages, formoterol elicited a greater average increase in IC than salmeterol or oxitropium.

Efficacy of formoterol in randomized controlled trials

Four large, placebo-controlled clinical trials evaluated the efficacy of treatment with formoterol for up to 12 months in patients with COPD (Table 2).\textsuperscript{26–29} Outcome variables included spirometric indices, use of rescue medication, and other measures of symptom control. Three of the four trials included an active comparator. Overall findings demonstrate that the efficacy with formoterol is sustained over periods of up to 12 months of continuous use and is comparable, and in some instances superior, to that associated with other bronchodilators.

Improvement in lung function with formoterol

A 12-week dose-ranging study (\( n = 692 \)) conducted by Aalbers and coworkers\textsuperscript{26} demonstrated that twice-daily treatment with formoterol 4.5, 9, and 18 \( \mu \)g resulted in increased FEV\(_1\) levels compared with placebo (\( P = 0.010, 0.039 \) and 0.001, respectively). Although a graded dose-dependent response was evident in the FEV\(_1\) data, a confirmatory statistical analysis of the data was not conducted.

Similar improvements in lung function were reported by Dahl and colleagues\textsuperscript{27} in a 3-month study (\( n = 780 \)) of formoterol 12 or 24 \( \mu \)g BID and ipratropium 40 \( \mu \)g four times daily (QID). Treatment with either dose of formoterol resulted in greater mean FEV\(_1\) AUC\(_{0-12h}\) values than treatment with ipratropium (both \( P \leq 0.024 \)) or placebo (both \( P < 0.001 \)). Furthermore, increase in FEV\(_1\) with either dose of formoterol was clinically relevant (i.e. \( \geq 0.120 \) L) at all post-treatment time points from 5 min through 12 h on both the first and last study days. Treatment with either dose of formoterol also resulted in superior improvement in FEV\(_1\), over the first 6 h post-treatment compared with ipratropium. The authors concluded that formoterol was more effective than ipratropium for the treatment of patients with COPD.

Campbell and associates\textsuperscript{29} evaluated the suitability of formoterol for both maintenance and as-needed (rescue) therapy. Patients (\( n = 657 \)) with an FEV\(_1\) 40–70% predicted received formoterol 9 \( \mu \)g BID plus formoterol 4.5 \( \mu \)g as-needed (PRN) (Group A), formoterol 9 \( \mu \)g BID plus terbutaline 0.5 mg prn (Group B), or placebo plus terbutaline 0.5 mg PRN (Group C) for a period of 6 months. Patients receiving formoterol achieved greater increase in mean FEV\(_1\) 0.5–2 h post-treatment (5.0% Group A, 10.2% Group B) than patients in Group C (−1.4%; \( P < 0.01 \) versus placebo). Patients receiving formoterol also achieved greater morning peak expiratory flow (PEF) rates compared with patients in Group C (Group A = 17%; Group B = 23%; Group C = 2%; \( P < 0.001 \) both comparisons).

Rossi and colleagues\textsuperscript{28} extended these findings by showing that formoterol 12 or 24 \( \mu \)g BID maintained improvement in lung function over 12 months in a population of 854 patients. Both doses of formoterol were superior to placebo, as assessed by FEV\(_1\) AUC\(_{0-12h}\) values at 3 and 12 months. The differences in FEV\(_1\) AUC values in the formoterol treatment arms were > 0.120L at all time points and statistically significantly higher than those in the placebo group (\( P < 0.001 \)). Furthermore, improvements in PEF rates were significantly greater at all time points in patients receiving formoterol than in patients receiving placebo (\( P < 0.001 \)).

Improvement in symptoms and the need for rescue medication with formoterol

The formoterol efficacy studies described previously assessed symptom control and reduction in the use of rescue medication.\textsuperscript{26–29} Formoterol treatment was associated with overall consistent and favorable results. Aalbers and coworkers\textsuperscript{26} observed that doses of formoterol as low as 4.5 \( \mu \)g BID improved symptom scores for breathlessness, cough, chest tightness, and sleep disturbance. Total symptom scores improved by 6% and 8%, with formoterol 4.5 and 9 \( \mu \)g BID (\( P = 0.05 \), respectively, and by 13% with formoterol 18 \( \mu \)g BID (\( P = 0.002 \)). Treatment with formoterol 9 and 18 \( \mu \)g also resulted in more symptom-free days (11.3% and 12.3%, respectively) than treatment with placebo (6.6%; \( P < 0.025 \), both comparisons).

Dahl and coworkers\textsuperscript{27} corroborated these findings by demonstrating that formoterol 12 and 24 \( \mu \)g BID were superior to placebo in lowering total symptom scores (perform usual daily activity, breathlessness on rising and over each 24-h period, waking at night due to respiratory symptoms, cough, and sputum production) (\( P < 0.001 \) and \( P = 0.007 \), respectively). Treatment with either dose of formoterol also resulted in a significant reduction in the use of rescue medication (\( P < 0.001 \) versus placebo).

Similarly, Campbell and associates\textsuperscript{29} found that total scores for COPD-related symptoms improved with formoterol 9 \( \mu \)g BID compared with placebo (\( P < 0.05 \)). Treatment with formoterol also resulted in a reduction in the use of rescue medication during the day and at night and an
increase in the percentage of rescue medication-free days (all P < 0.05 versus placebo).

In contrast, Rossi and coworkers\textsuperscript{28} reported only modest, nonsignificant improvements in COPD-related symptom scores with formoterol 12 or 24 μg BID after 12 months of treatment. However, treatment with either dose of formoterol reduced the frequency of mild COPD exacerbations (P ≤ 0.008) and rescue medication use (P ≤ 0.003) compared with placebo. Treatment with formoterol 24 μg also resulted in a reduction in COPD exacerbations of moderate severity (P = 0.043). Notably, only 4.7% (10/211) of patients receiving formoterol 12 μg and 2.3% (5/214) of patients receiving formoterol 24 μg required hospitalization for severe COPD exacerbations compared with 9.1% (20/220) of patients receiving placebo.

### Efficacy of formoterol versus other bronchodilators

#### Formoterol versus salmeterol

Vervloet and colleagues\textsuperscript{30} conducted a 6-month study in 482 patients with COPD regularly using ICSs (Table 2). Patients received either formoterol 12 μg BID or salmeterol 50 μg BID. Improvements in morning predose PEF rates, COPD-related

| Table 2: Controlled Studies of Formoterol With/Without an Active Comparator. |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Author                            | N               | Mean age (yr)   | Study drugs     | Study design/duration | Key findings                                      |
| Aalbers et al.,\textsuperscript{26} | 692             | 62.4            | FORM 4.5 μg, 9 μg, 18 μg BID | R, DB, PC, PG, MC/12 wk | FORM improved lung function at all doses. FORM 9, 18 μg reduced selected symptom scores, relief medication use, increased symptom-free days. Only 18 μg dose associated with significantly improved TSS, TDI |
| Dahl et al.,\textsuperscript{27}   | 780             | 63.7            | FORM 12 μg, 24 μg BID; IPRA 40 μg QID | R, DB, PC, PG, MC/12 wk | Both FORM 12, 24 μg superior to IPRA in terms of FEV\textsubscript{1} AUC \textsubscript{0-12 h} primary efficacy variable as well as rescue medication use. FORM 12 μg, but not 24 μg, superior to IPRA in reducing TSS |
| Campbell et al.,\textsuperscript{29} | 657             | 60              | FORM 9 μg BID+TER 0.5 mg prn; FORM 9 μg BID + FORM 4.5 μg prn; P+TER 0.5 mg prn | R, DB, PC, PG, MC/6 mo | Both FORM regimens significantly increased FEV\textsubscript{1} values, decreased CSS, and prn medication use versus P. FORM 9/4.5 μg provided significantly better FEV\textsubscript{1} improvement versus FORM 9 μg/TER 0.5 mg (P < 0.05) |
| Rossi et al.,\textsuperscript{28}  | 854             | 63              | FORM 12 μg, 24 μg BID; THEO 200-300 mg BID | R, DB, PC, PG, MC/12 mo | All active treatments associated with clinically relevant increases in FEV\textsubscript{1}; AUC at months 3 and 12. FORM 12 μg superior to THEO at months 3 and 12, FORM 24 μg only at month 3. Median TSS similar among active drugs |
| Vervloet et al.,\textsuperscript{30} | 482             | 48              | FORM 12 μg BID; SAL 50 μg BID | R, OL, PG, MC/6 mo | Active drugs had similar effect on primary endpoint of mean morning pre-dose PEF, mean rescue medication use, RSS. FORM produced superior improvements in evening predose PEF at months 2-4 (P < 0.05) |

AUC = area under the curve; BID = twice-daily; CSS = combined symptom score; FORM = formoterol; IPRA = ipratropium; MC = multicenter; OL = open-label; P = placebo; PC = placebo-controlled; PEF = peak expiratory flow; PG = parallel group; QID = four times daily; R = randomized; RSS = respiratory symptom score; SAL = salmeterol; TDI = transitional dyspnea index; TER = terbutaline; THEO = theophylline; TSS = total symptom score.
symptoms, and the use of rescue medication were similar in both groups. Patients receiving formoterol experienced superior improvements in evening predose PEF rates at months 2, 3, and 4 (P < 0.05 versus salmeterol).

**Formoterol versus inhaled anticholinergics**

The effectiveness of formoterol monotherapy has been compared with that of ipratropium or tiotropium monotherapy in two trials.27,31

**Ipratropium**

A 12-week comparison of formoterol (12 or 24 μg BID) and ipratropium (40 μg QID) by Dahl and coworkers27 demonstrated that formoterol was superior to ipratropium in improving lung function and controlling COPD symptoms (Table 2). Although treatment with either agent resulted in improving lung function and controlling COPD symptoms, the improvements with formoterol were significantly better than those with ipratropium (P < 0.024). COPD symptoms improved significantly with formoterol 12 and 24 μg than placebo (P < 0.001 and P = 0.007, respectively). Formoterol 12 μg was also superior to ipratropium in improving COPD symptoms (P = 0.009). Treatment with either dose of formoterol resulted in a significant reduction in the use of rescue medication compared with ipratropium (both P < 0.014) and placebo (both P < 0.001).

**Tiotropium**

The efficacy of formoterol 12 μg BID and tiotropium 18 μg QD was compared in an 18-week crossover trial conducted by van Noord and colleagues (Table 3).31 Treatment with tiotropium resulted in greater average daytime FEV1 levels over 12 h than formoterol (P < 0.03). The differences in FEV1 levels between the two treatment groups were most noticeable at 8–12 h after the morning dose of formoterol (P < 0.002), whereas no significant between-treatment differences in FEV1 occurred following the evening dosing of formoterol, except for a higher 24-h (trough) FEV1 level with tiotropium (P < 0.05). Patterns of improvements in FVC were similar to those for FEV1 and favored tiotropium. Nighttime use of rescue medication was comparable between the two treatment groups.

**Formoterol versus theophylline**

Rossi and associates28 compared the efficacy of formoterol 12 or 24 μg BID with that of theophylline in a large-scale (n = 854), 12-month, placebo-controlled, parallel-group trial (Table 2). FEV1, AUC_{0-12h} levels at months 3 and 12 with either dose of formoterol or theophylline were superior to placebo (P < 0.001 and P < 0.007, respectively). Moreover, treatment with either dose of formoterol was superior to treatment with theophylline at month 3 (P < 0.016 for both doses) and treatment with formoterol 12 μg was superior to theophylline at month 12 (P = 0.026). Whereas morning PEF improved significantly in all three active treatment arms (P < 0.001 for both doses of formoterol versus placebo, P = 0.007 for theophylline versus placebo), improvements were significantly better with either dose of formoterol than theophylline (all P ≤ 0.020). The mean percentage of days with mild COPD exacerbations was also lower in both formoterol arms than in the theophylline arm (both P < 0.035; P = NS for theophylline versus placebo). The mean percentage of days with moderate COPD exacerbations was lower in both the formoterol 24 μg arm and theophylline arm than placebo arm (P = 0.043 and 0.019, respectively).

**Effectiveness of formoterol in combination therapies**

The effects of formoterol combination therapy on lung function and COPD exacerbations were evaluated in 4 crossover and 2 parallel-group studies (Table 3).31–36 The results of these studies support the hypothesis that combination therapy of LABA, such as formoterol with other bronchodilators such as anticholinergic agents or theophyllines result in additional benefits in patients with COPD. The current treatment guidelines recommend addition of one or more long-acting bronchodilators in patients with moderate to severe COPD.37

**Formoterol plus long-acting bronchodilators**

Van Noord and colleagues31 compared monotherapy with formoterol 12 μg BID or tiotropium 18 μg QD with once-daily combination therapy with these two agents. Morning administration of formoterol/tiotropium combination resulted in FEV1 values that were higher at each time point and over 24 h than those with formoterol BID and tiotropium QD (all P < 0.0001). Combination therapy also resulted in higher morning and evening PEF values versus monotherapy with either agent (both P < 0.02) and reduced daytime, but not nighttime, use of rescue medication (both P < 0.01). The authors concluded that once-daily combination treatment with formoterol/tiotropium provided additive and sustained 24-h activity that was superior to that with monotherapy with either agent.

A second crossover study by the van Noord group33 investigated the effects of adding once-daily or twice-daily treatment with formoterol 12 μg to standard treatment with tiotropium 18 μg QD. Addition of formoterol in the morning resulted in increased AUC_{0-12h}, and AUC_{0-24h} levels for FEV1, FVC, and IC compared with tiotropium alone (all P < 0.05). Addition of twice-daily dosing with formoterol resulted in additional increases in AUC_{12-24h} levels for FEV1 and FVC compared with tiotropium alone or formoterol alone once daily (P < 0.05). Combination therapy with once-daily or twice-daily formoterol also resulted in a significant reduction in the use of rescue medication during the daytime versus treatment with tiotropium alone (P < 0.01). The authors concluded that addition of either once-daily or twice-daily formoterol offered multiple benefits versus treatment with tiotropium alone.

Di Marco and associates34 conducted a pilot crossover study with formoterol 12 μg and tiotropium 18 μg alone and in combination in 21 patients with acute exacerbations of COPD. Unlike the previous trial, patients only received formoterol once daily. Combined therapy resulted in greater AUC_{0-12h} and AUC_{0-24h} levels for FEV1, FVC and IC than...
Table 3  Studies of Formoterol in Combination Use.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Mean age (yr)</th>
<th>Study drugs</th>
<th>Study design/duration</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calverley et al., 40</td>
<td>1022</td>
<td>a</td>
<td>BUD 200 μg BID; FORM 4.5 μg BID; BUD 160 μg BID + FORM 4.5 μg BID</td>
<td>R, DB, PC, PG, MC/12 mo</td>
<td>Combination superior to BUD and FORM (P&lt;0.001 and 0.002, resp.) in maintaining FEV₁ achieved during steroid run-in period. Combination prolonged time to first exacerbation versus both comparators (P&lt;0.05), also reduced reliever medication use (P&lt;0.001 and P&lt;0.05, BUD and FORM resp.)</td>
</tr>
<tr>
<td>Cazzola et al., 38</td>
<td>16</td>
<td>67.1</td>
<td>FORM 12 μg + BUD 400 μg × 1; SAL 50 μg + FLU 250 μg × 1</td>
<td>R, SB, 2-way xvr/4 d (2 × 2 d)</td>
<td>FORM/BUD combination effects on FEV₁ greater at 120 and 360 min (both P&lt;0.05). AUC₀₋₁₂ h and effects on IC similar between groups</td>
</tr>
<tr>
<td>Celik et al., 35</td>
<td>117^b</td>
<td>65.7^c</td>
<td>IPRA 40 μg QID + FORM 12 μg BID; IPRA 40 μg QID + FORM 12 μg BID + MKT 10 mg hs</td>
<td>R, SB, PG/2 mo</td>
<td>Addition of MKT resulted in greater improvements in FEV₁, FVC, PEF and SGRQ versus non-MKT combination (all P&lt;0.05). No significant changes versus baseline noted in IPRA/FORM combination group</td>
</tr>
<tr>
<td>Di Marco et al., 34</td>
<td>21</td>
<td>72</td>
<td>FORM 12 μg BID; TIO 18 μg QID; FORM 12 μg BID + TIO 18 μg QID</td>
<td>R, DB, DD, 3-way xvr 3 d (3 × 1d)</td>
<td>Mean FEV₁, FVC, IC AUC₀₋₁₂ h and AUC₀₋₂₄ h greater with FORM/TIO versus either monotherapy (P&lt;0.01). Maximum FEV₁ greater with FORM/TIO versus either monotherapy (P&lt;0.01). FORM alone superior to TIO alone (P&lt;0.05)</td>
</tr>
<tr>
<td>D’Urzo et al., 32</td>
<td>172</td>
<td>65</td>
<td>IPRA 40 μg QID + FORM 12 μg BID; IPRA 40 μg QID + ALB 200 μg QID</td>
<td>R, DB, DD, MC, 2-way xvr/6 wk (3 wk × 2)</td>
<td>Morning PEF, FEV₁ AUC higher with IPRA/FORM than IPRA/ALB (P = 0.0003 and P&lt;0.0001, resp). IPRA/FORM associated with lower mean TSS (P = 0.0042)</td>
</tr>
<tr>
<td>Szafranski et al., 39</td>
<td>812</td>
<td>64</td>
<td>BUD 200 μg BID; FORM 4.5 μg BID; BUD 160 μg BID + FORM 4.5 μg BID</td>
<td>R, DB, PC, PG, MC/12 mo</td>
<td>BUD/FORM produced greater FEV₁ increase than BUD alone (P&lt;0.001), but not FORM alone. Fewer severe exacerbations with combination versus FORM (P&lt;0.001) but not BUD. Superior PEF with combination versus BUD, FORM, P</td>
</tr>
<tr>
<td>Van Noord et al., 33</td>
<td>95</td>
<td>64</td>
<td>TIO 18 μg QD; TIO 18 μg QD + FORM 12 μg QD; TIO 18 μg QD + FORM 12 μg BID</td>
<td>R, OL, MC, 3-way xvr/6 wk (2 wk × 3)</td>
<td>Addition of morning FORM resulted in improved FEV₁, FVC, and IC versus TIO alone. Addition of evening FORM resulted in further FEV₁ improvement for &gt;12 h but FVC and IC increases lasted &lt;12 h. Addition of morning and morning-evening FORM produced corresponding decreases in rescue medication use versus TIO alone</td>
</tr>
</tbody>
</table>
FEV1 AUCs were greater with formoterol/ipratropium than ipratropium (2 versus 1 h, respectively), the peak levels and slowly with formoterol/ipratropium than with albuterol/ 

Formoterol plus short-acting bronchodilators

In a crossover trial, D’Urzo and coworkers compared formoterol 12 µg BID plus ipratropium 40 µg QID with albuterol 200 µg QID plus ipratropium 40 µg QID over a 6-week period. Both regimens were effective in terms of improvements in the primary efficacy variable, mean morning PEF, but formoterol/ipratropium was superior to albuterol/ipratropium (P = 0.0003). Predose FEV1 increased with formoterol/ipratropium, but decreased with albuterol/ipratropium (P < 0.0001). FEV1 levels were also greater with formoterol/ipratropium at all post-treatment time points through 6 h. Although peak FEV1 levels were reached more slowly with formoterol/ipratropium than with albuterol/ipratropium (2 versus 1 h, respectively), the peak levels and FEV1 AUCs were greater with formoterol/ipratropium than with albuterol/ipratropium (both P < 0.0001). The proportions of patients without COPD exacerbations and proportions with “bad days” were similar between the two treatment groups.

More recently, the results of a 3-month study examining the effects of combination bronchodilator therapy on quality of life, assessed using the SGRQ, for patients with COPD were reported by Yildiz and coworkers. Treatment consisted of formoterol 12 µg BID plus oral theophylline (200 mg BID), ipratropium 40 µg QID plus theophylline, or formoterol plus ipratropium. Overall scores improved significantly in all treatment groups compared with baseline. However, no significant differences were observed between treatments. The formoterol/ipratropium combination was associated with significant improvement in FEV1 and FVC from baseline after 3 months. The differences between groups were not statistically significant. Increases in FEV1 correlated with improvements in health-related quality of life. All three treatments resulted in a similar proportion of patients reporting clinically significant improvements in total symptom scores (range: 66–68%).

Finally, Celik and colleagues examined the effect of adding on montelukast, a leukotriene receptor antagonist, to formoterol 12 µg BID plus ipratropium 40 µg QID treatment regimen over a 2-month period in COPD patients with nonreversible airway obstruction. The addition of montelukast 10 mg at bedtime resulted in significant improvements in FEV1, FVC, and PEF levels compared with baseline levels (P < 0.05). Similarly, symptom, activity, impact, sensation of dyspnea, and total SGRQ scores were improved in the montelukast group (all P < 0.05 versus baseline). The authors
concluded that adding montelukast to formoterol/ipratropium combination therapy results in additional benefits on spirometric and quality-of-life measures.

**Effectiveness of formoterol in combination with ICS in COPD treatment**

The current COPD management guidelines recommend addition of an ICS to bronchodilator therapy for patients with an FEV1 < 50% predicted who experience repeated exacerbations. Three trials have examined the effects of adding formoterol to the ICS budesonide and reported favorable results (Table 3). In a crossover study among 16 patients with moderate to severe COPD on regular LABA therapy, Cazzola and colleagues compared the effects of single doses of formoterol 12 μg plus budesonide 400 μg with those of salmeterol 50 μg plus fluticasone 250 μg over 12 h. FEV1 levels improved to a similar extent with both regimens, as assessed by AUC_{0–12 h} levels (both P < 0.001 versus baseline). Treatment with formoterol/budesonide resulted in faster onset of action and superior improvements in FEV1 levels compared with salmeterol/fluticasone at both 2 and 6 h post-treatment (P < 0.05).

Two placebo-controlled studies compared treatment with formoterol 9 μg plus budesonide 320 μg BID administered via a single inhaler and treatment with formoterol 9 μg and budesonide 200 or 400 μg BID administered alone. In a 12-month trial involving 812 patients with COPD, Szafranski scores compared with placebo (salmeterol/fluticasone at both 2 and 6 h post-treatment). Formoterol has been well tolerated in placebo-controlled trials, demonstrating a safety profile similar to placebo. Aalbers and colleagues reported that deterioration of COPD and respiratory infection were the most frequent AEs observed in all treatment groups in a 3-month dose-ranging trial of formoterol 4.5, 9 or 18 μg BID. The incidence, type, and severity of serious AEs in the 3 formoterol groups were similar between groups treated with formoterol. Furthermore, there was no significant difference in patient withdrawals (16–19%) across the four groups.

**Safety of formoterol in the treatment of COPD**

Many of the adverse events (AEs) associated with β2-adrenergic receptor agonists are pharmacologically predictable (ie, related to α- and β-adrenergic receptor stimulation). Treatment with SABAs or LABAs can result in tachycardia, arrhythmia, other cardiac AEs (e.g. ischemia, heart failure, cardiomyopathy), tremor, and metabolic imbalances, such as decreased serum potassium levels or increased glucose levels. However, these events are generally less pronounced with LABAs than with SABAs. It should be noted that a recent large-scale, placebo-controlled, observational study of salmeterol in 26,355 patients with asthma was terminated prematurely because of a small but statistically significant increase in respiratory-related deaths that occurred primarily in African-American patients. This has resulted in a "black-box warning" in the prescribing information for both salmeterol and formoterol regarding the potential increased risk for asthma-related deaths. Furthermore, the prescribing information for both formoterol and salmeterol indicate that the use of SABAs on a regular basis should be discontinued in patients with asthma when initiating treatment with LABAs, and that SABAs should only be used on an as-needed basis in these patients because of possible cross tolerance. However, no studies have been conducted to date that evaluated the association of deaths with the use of LABAs in patients with COPD. The current guidelines for COPD do not suggest any restriction on the use of SABAs and LABAs in patients with COPD.
headache. Gastrointestinal events (dyspepsia, abdominal pain, nausea, vomiting) were reported more frequently in theophylline-treated patients than by other groups. A greater percentage of theophylline-treated patients also experienced drug-related AEs (32%), compared with formoterol 12 μg BID (9%), 24 μg BID (8%), and placebo groups (8%). Patients receiving theophylline were 2 or 4 times more likely to discontinue treatment because of AEs than patients taking placebo or formoterol, respectively. The incidence of serious cardiac AEs among the groups was similar: 2% formoterol 12 μg, 0% formoterol 24 μg, 2% theophylline, and 1% placebo.

In studies reporting on the safety of salmeterol, heart rates were increased by 2–5 beats per min with doses of salmeterol up to 100 μg compared with placebo. Salmeterol 100 μg has been associated with a higher-than-normal rate of premature ventricular beats and palpitations. Salmeterol also appears to affect the QTc interval to a greater extent than albuterol. However, high-dose (90 μg) formoterol has minimal effect on heart rate and serum potassium compared with terbutaline 10 μg. Although tremor associated with salmeterol is dose related, the incidence is less than that with albuterol. Salmeterol is also associated with dose-related decreases in serum potassium levels. Similar decreases have been seen with formoterol. However, decreases with formoterol have occurred only at very high doses and have not been considered clinically significant.

Small increases in airway hyperresponsiveness (AHR) have been associated with regular or frequent use of SABAs. Formoterol and salmeterol have not been shown to increase AHR in adults following challenge with specific or nonspecific stimuli. Furthermore, neither drug has been associated with rebound AHR, although tolerance to the bronchoprotective effects of both has been shown. Salmeterol has been associated with AHR and deterioration of lung function in children. Results of a 6-month safety and efficacy comparison of formoterol and salmeterol conducted by Vervloet and coworkers indicated that both drugs were well tolerated and that AEs were reported by similar proportions of patients in both treatment groups. As in other studies, viral infection, exacerbation of obstructive airway disease, headache, rhinitis, and chest infection were the most common AEs. Headache was the most frequently reported drug-related AE. The incidences of AEs considered to be drug-related were similar between groups.

Adverse-event profiles reported in studies of formoterol used in combination therapy regimens were similar to those in placebo-controlled trials. In the 3-month study comparing combination therapy of formoterol/ipratropium with albuterol/ipratropium, D’Urzo and coworkers found that dyspnea, COPD exacerbation, and pharyngitis were the most frequently reported AEs in both groups during the study. The AEs occurred more frequently in patients treated with the albuterol/ipratropium combination than with formoterol/ipratropium combination. Albuterol/ipratropium was also associated with a higher proportion of severe AEs. Moreover, a larger proportion of drug-related AEs were reported with albuterol/ipratropium than with formoterol/ipratropium. The most commonly reported drug-related AEs were hypertension, dry mouth, and leg cramps in patients taking formoterol/ipratropium and pharyngitis, dyspnea, dizziness, tremor, leg cramps, coughing, and exacerbation of obstructive airway disease in the albuterol/ipratropium group.

In two 12-month studies that compared monotherapy with formoterol, or budesonide, or placebo with combination therapy of formoterol/budesonide, AEs with combination therapy were similar to those reported with monotherapy with each component or with placebo. Frequencies of event-related study withdrawals were similar among all groups in one study by Szafranski and coworkers, and slightly lower in the placebo group in the second trial conducted by Calverley and colleagues.

In a 3-week crossover comparison of formoterol 12 μg BID, tiotropium 18 μg QD, and combination therapy with both drugs, van Noord and coworkers found that all regimens were well tolerated and that there were no relevant between-treatment differences in AE rates. Nasopharyngitis, headache, and exacerbations of COPD and dyspnea were the most commonly reported events.

Few AEs were reported in noncontrolled, single-dose, or dose-response studies of formoterol. The AEs reported were primarily either known class effects of β2-adrenergic receptor agonists such as muscle cramps, tremor, and palpitations, or were considered unrelated to formoterol treatment. No clinically important changes in laboratory tests, heart rate, or electrocardiography measurements (including QTc), were associated with the use of formoterol, regardless of dose or treatment duration.

Discussion
Bronchodilators are the mainstay of pharmacologic management for patients with moderate to severe COPD. Among agents approved for the treatment of COPD in the United States, the LABA formoterol is characterized by rapid onset and long duration of action. Inhalational therapy with formoterol can produce a significant bronchodilatory effect within 5 min and maximal FEV1 increase within 30–60 min. In placebo-controlled trials, formoterol significantly improved lung function and maintained beneficial bronchodilatory effects for up to 12 months. Formoterol also significantly reduced daytime and nighttime symptoms of COPD, use of rescue medication, acute exacerbations of COPD, and exacerbation-related hospitalizations.

The efficacy of formoterol 12 μg BID is comparable to salmeterol 50 μg BID and superior to ipratropium 40 μg QID in improving lung function, controlling COPD symptoms, and reducing the need for rescue medications. The bronchodilatory effect of twice-daily formoterol was similar to that of once-daily tiotropium over a 24-h dosing period. Compared with theophylline, formoterol was more effective in improving lung function, reducing exacerbations of COPD of any severity, and increasing the number of days in which rescue medication was unnecessary. Formoterol was also better tolerated and associated with fewer AEs than theophylline.

Formoterol also improves lung function and symptom control when administered in combination with other bronchodilators. Albuterol/ipratropium combination therapy resulted in improvements in FEV1, a more rapid
attainment of peak effect, and a reduction in the frequency of COPD exacerbations than combination therapy with formoterol/ipratropium. Similary, combination therapy with formoterol and budesonide resulted in improvements in total symptom scores, longer time to first exacerbation, and reduction in the number of exacerbations and use of rescue medications compared with formoterol or budesonide alone. The decrease in airway obstruction reported with combined formoterol/budesonide treatment was comparable to that seen with the salmeterol/fluticasone propionate combination.

Formoterol is also effective when used as a rescue medication for acute exacerbations of COPD in patients already using an inhaled LABA (including formoterol) as maintenance therapy for COPD. Additional doses of formoterol can be used safely to control symptoms. Onset of effect with formoterol is similar to that with albuterol, but has a significantly longer duration.

In clinical trials, formoterol was better tolerated than theophylline and at least as well-tolerated as budesonide, salmeterol, albuterol, ipratropium, and tiotropium, regardless of administration as monotherapy or combination therapy.

Conclusions

Formoterol is a LABA that is effective and well tolerated in management of COPD. Unlike other LABAs, formoterol offers the benefit of rapid onset of action. Formoterol is effective as monotherapy and in combination with other bronchodilators or ICSs. The current guidelines for the management of COPD recommend the use of inhaled long-acting bronchodilators as maintenance therapy in patients with moderate to severe COPD. The rapid onset and prolonged duration of action of formoterol makes it an ideal therapeutic option for patients with this moderate to severe COPD.

Conflict of interest statement

Dr. Berger has served as a consultant, participated in Advisory Boards and Speaker’s Bureaus, and has been the recipient of honoraria and research grants from the following companies: Alcon, Altana, Aplieron, AstraZeneca, Dey, Genentech, GlaxoSmithKline, Medpointe, Novartis, Sanofi-Aventis, Schering-Plough, Sepacor, and Teva. Dr. Nadel has no conflict of interest.

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